付録 2.7.4- 80　　臨床検査値の Grade がベースラインより悪化した患者の要約

010 試験（安全性解析対象集団）（PD-L1 発現陽性）

Laboratory Test	Docetaxel 75 mg/m2 Q3W (N=309)	MK-3475 2 mg/kg Q3W (N=339)	MK-3475 10 mg/kg Q3W (N=343)
APTT Increased			
Improved from baseline	1 (0.3)	0 (0.0)	0 (0.0)
Worsened from baseline	4 (1.3)	7 (2.1)	4 (1.2)
Clinically meaningful† worsened from baseline	1 (0.3)	0 (0.0)	1 (0.3)
Alanine Aminotransferase Increased			
Improved from baseline	0 (0.0)	0 (0.0)	1 (0.3)
Worsened from baseline	29 (9.4)	77 (22.7)	69 (20.1)
Clinically meaningful† worsened from baseline	2 (0.6)	16 (4.7)	15 (4.4)
Albumin Decreased			
Improved from baseline	1 (0.3)	1 (0.3)	3 (0.9)
Worsened from baseline	98 (31.7)	108 (31.9)	116 (33.8)
Clinically meaningful† worsened from baseline	25 (8.1)	33 (9.7)	30 (8.7)
Alkaline Phosphatase Increased			
Improved from baseline	1 (0.3)	1 (0.3)	2 (0.6)
Worsened from baseline	50 (16.2)	87 (25.7)	101 (29.4)
Clinically meaningful† worsened from baseline	3 (1.0)	17 (5.0)	18 (5.2)
Amylase Increased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	0 (0.0)	2 (0.6)	2 (0.6)
Clinically meaningful† worsened from baseline	0 (0.0)	2 (0.6)	2 (0.6)
Aspartate Aminotransferase Increased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)

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Summary of Worsening in Laboratory CTCAE Grades from Baseline to Worst Value Post-baseline
APaT Population (TPS ≥1%)

Laboratory Test	Docetaxel 75 mg/m2 Q3W (N=309)	MK-3475 2 mg/kg Q3W (N=339)	MK-3475 10 mg/kg Q3W (N=343)
Aspartate Aminotransferase Increased			
Worsened from baseline	36 (11.7)	86 (25.4)	84 (24.5)
Clinically meaningful† worsened from baseline	4 (1.3)	15 (4.4)	15 (4.4)
Bilirubinn Increased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	11 (3.6)	24 (7.1)	20 (5.8)
Clinically meaningful† worsened from baseline	4 (1.3)	9 (2.7)	9 (2.6)
Calcium Decreased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	57 (18.4)	65 (19.2)	66 (19.2)
Clinically meaningful† worsened from baseline	11 (3.6)	14 (4.1)	16 (4.7)
Calcium Increased			
Improved from baseline	0 (0.0)	1 (0.3)	0 (0.0)
Worsened from baseline	22 (7.1)	33 (9.7)	39 (11.4)
Clinically meaningful† worsened from baseline	3 (1.0)	6 (1.8)	11 (3.2)
Cholesterol			
Improved from baseline	2 (0.6)	0 (0.0)	1 (0.3)
Worsened from baseline	61 (19.7)	63 (18.6)	75 (21.9)
Clinically meaningful† worsened from baseline	5 (1.6)	2 (0.6)	10 (2.9)
Creatine Kinase			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	0 (0.0)	3 (0.9)	0 (0.0)

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Summary of Worsening in Laboratory CTCAE Grades from Baseline to Worst Value Post-baseline
APaT Population (TPS ≥1%)

Laboratory Test	Docetaxel 75 mg/m2 Q3W (N=309)	MK-3475 2 mg/kg Q3W (N=339)	MK-3475 10 mg/kg Q3W (N=343)
Creatine Kinase			
Clinically meaningful† worsened from baseline	0 (0.0)	1 (0.3)	0 (0.0)
Creatinine Increased			
Improved from baseline	3 (1.0)	0 (0.0)	0 (0.0)
Worsened from baseline	28 (9.1)	57 (16.8)	63 (18.4)
Clinically meaningful† worsened from baseline	4 (1.3)	9 (2.7)	8 (2.3)
Gamma Glutamyl Transferase Increased			
Improved from baseline	0 (0.0)	0 (0.0)	1 (0.3)
Worsened from baseline	2 (0.6)	3 (0.9)	7 (2.0)
Clinically meaningful† worsened from baseline	2 (0.6)	3 (0.9)	6 (1.7)
Glucose Decreased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	8 (2.6)	27 (8.0)	26 (7.6)
Clinically meaningful† worsened from baseline	2 (0.6)	6 (1.8)	5 (1.5)
Glucose Increased			
Improved from baseline	4 (1.3)	4 (1.2)	2 (0.6)
Worsened from baseline	150 (48.5)	132 (38.9)	157 (45.8)
Clinically meaningful† worsened from baseline	48 (15.5)	27 (8.0)	32 (9.3)
Hemoglobin Decreased			
Improved from baseline	2 (0.6)	0 (0.0)	7 (2.0)
Worsened from baseline	170 (55.0)	128 (37.8)	121 (35.3)
Clinically meaningful† worsened from baseline	28 (9.1)	24 (7.1)	15 (4.4)

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Summary of Worsening in Laboratory CTCAE Grades from Baseline to Worst Value Post-baseline
APaT Population (TPS ≥1%)

Laboratory Test	Docetaxel 75 mg/m2 Q3W (N=309)	MK-3475 2 mg/kg Q3W (N=339)	MK-3475 10 mg/kg Q3W (N=343)
Hemoglobin Increased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	0 (0.0)	1 (0.3)	0 (0.0)
Clinically meaningful† worsened from baseline	0 (0.0)	1 (0.3)	0 (0.0)
Leukocytes Decreased			
Improved from baseline	0 (0.0)	0 (0.0)	1 (0.3)
Worsened from baseline	73 (23.6)	18 (5.3)	25 (7.3)
Clinically meaningful† worsened from baseline	58 (18.8)	4 (1.2)	5 (1.5)
Leukocytes Increased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	0 (0.0)	0 (0.0)	2 (0.6)
Clinically meaningful† worsened from baseline	0 (0.0)	0 (0.0)	2 (0.6)
Lymphocytes Decreased			
Improved from baseline	2 (0.6)	9 (2.7)	3 (0.9)
Worsened from baseline	122 (39.5)	103 (30.4)	111 (32.4)
Clinically meaningful† worsened from baseline	73 (23.6)	57 (16.8)	65 (19.0)
Lymphocytes Increased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	11 (3.6)	0 (0.0)	0 (0.0)
Clinically meaningful† worsened from baseline	8 (2.6)	0 (0.0)	0 (0.0)
Magnesium Decreased			
Improved from baseline	1 (0.3)	0 (0.0)	0 (0.0)

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Summary of Worsening in Laboratory CTCAE Grades from Baseline to Worst Value Post-baseline
APaT Population (TPS ≥1%)

Laboratory Test	Docetaxel 75 mg/m2 Q3W (N=309)	MK-3475 2 mg/kg Q3W (N=339)	MK-3475 10 mg/kg Q3W (N=343)
Magnesium Decreased			
Worsened from baseline	40 (12.9)	67 (19.8)	64 (18.7)
Clinically meaningful† worsened from baseline	6 (1.9)	9 (2.7)	10 (2.9)
Magnesium Increased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	8 (2.6)	13 (3.8)	18 (5.2)
Clinically meaningful† worsened from baseline	1 (0.3)	2 (0.6)	3 (0.9)
Neutrophils Decreased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	73 (23.6)	14 (4.1)	24 (7.0)
Clinically meaningful† worsened from baseline	65 (21.0)	6 (1.8)	10 (2.9)
Neutrophils Increased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	4 (1.3)	1 (0.3)	0 (0.0)
Clinically meaningful† worsened from baseline	4 (1.3)	1 (0.3)	0 (0.0)
Phosphate Decreased			
Improved from baseline	0 (0.0)	3 (0.9)	1 (0.3)
Worsened from baseline	54 (17.5)	50 (14.7)	69 (20.1)
Clinically meaningful† worsened from baseline	46 (14.9)	38 (11.2)	62 (18.1)
Platelet Decreased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	24 (7.8)	35 (10.3)	39 (11.4)

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Summary of Worsening in Laboratory CTCAE Grades from Baseline to Worst Value Post-baseline
APaT Population (TPS ≥1%)

Laboratory Test	Docetaxel 75 mg/m2 Q3W (N=309)	MK-3475 2 mg/kg Q3W (N=339)	MK-3475 10 mg/kg Q3W (N=343)
Platelet Decreased			
Clinically meaningful† worsened from baseline	6 (1.9)	9 (2.7)	7 (2.0)
Platelet Increased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	0 (0.0)	0 (0.0)	1 (0.3)
Clinically meaningful† worsened from baseline	0 (0.0)	0 (0.0)	1 (0.3)
Potassium Decreased			
Improved from baseline	0 (0.0)	1 (0.3)	0 (0.0)
Worsened from baseline	24 (7.8)	42 (12.4)	27 (7.9)
Clinically meaningful† worsened from baseline	6 (1.9)	7 (2.1)	4 (1.2)
Potassium Increased			
Improved from baseline	2 (0.6)	0 (0.0)	2 (0.6)
Worsened from baseline	47 (15.2)	60 (17.7)	56 (16.3)
Clinically meaningful† worsened from baseline	8 (2.6)	15 (4.4)	19 (5.5)
Prothrombin Intl. Normalized Ratio Incre			
Improved from baseline	1 (0.3)	0 (0.0)	0 (0.0)
Worsened from baseline	5 (1.6)	6 (1.8)	3 (0.9)
Clinically meaningful† worsened from baseline	0 (0.0)	1 (0.3)	1 (0.3)
Sodium Decreased			
Improved from baseline	1 (0.3)	1 (0.3)	0 (0.0)
Worsened from baseline	77 (24.9)	99 (29.2)	115 (33.5)
Clinically meaningful† worsened from baseline	8 (2.6)	28 (8.3)	29 (8.5)

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Summary of Worsening in Laboratory CTCAE Grades from Baseline to Worst Value Post-baseline
APaT Population (TPS ≥1%)

Laboratory Test	Docetaxel 75 mg/m2 Q3W (N=309)	MK-3475 2 mg/kg Q3W (N=339)	MK-3475 10 mg/kg Q3W (N=343)
Sodium Increased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	6 (1.9)	16 (4.7)	16 (4.7)
Clinically meaningful[†] worsened from baseline	1 (0.3)	1 (0.3)	1 (0.3)
Triacylglycerol Lipase Increased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	0 (0.0)	1 (0.3)	0 (0.0)
Clinically meaningful[†] worsened from baseline	0 (0.0)	1 (0.3)	0 (0.0)
Triglycerides			
Improved from baseline	2 (0.6)	4 (1.2)	1 (0.3)
Worsened from baseline	89 (28.8)	96 (28.3)	120 (35.0)
Clinically meaningful[†] worsened from baseline	11 (3.6)	10 (2.9)	21 (6.1)

A missing baseline value was set to Grade 0.
[†] A clinically meaningful worsening in CTCAE grade was defined as a shift from less than Grade 3 to Grade 3 , 4 or 5 or a shift from Grade 0 to Grade 2.
(Database Cutoff Date: 30SEP2015)

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付録 2.7.4- 81　　臨床検査値の Grade がベースラインより悪化した患者での臨床検査値異常の最大 Grade の要約

001 試験＋002 試験＋006 試験＋010 試験

MK-3475 を投与された悪性黒色腫及び非小細胞肺癌患者（安全性解析対象集団）

Laboratory Test	P010 (N=682)	PN001 Lung, PN010 (N=1232)	PN001 Mel, PN002, PN006 (N=1567)	PN001,PN002, PN006, PN010 (N=2799)
APTT Increased				
Toxicity Grade 1	8 (1.2)	25 (2.0)	28 (1.8)	53 (1.9)
Toxicity Grade 2	2 (0.3)	5 (0.4)	5 (0.3)	10 (0.4)
Toxicity Grade 3	0 (0.0)	3 (0.2)	4 (0.3)	7 (0.3)
Toxicity Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Alanine Aminotransferase Increased				
Toxicity Grade 1	103 (15.1	185 (15.0	295 (18.8	480 (17.1
Toxicity Grade 2	16 (2.3)	28 (2.3)	43 (2.7)	71 (2.5)
Toxicity Grade 3	12 (1.8)	16 (1.3)	25 (1.6)	41 (1.5)
Toxicity Grade 4	2 (0.3)	2 (0.2)	5 (0.3)	7 (0.3)
Albumin Decreased				
Toxicity Grade 1	118 (17.3	243 (19.7	278 (17.7	521 (18.6
Toxicity Grade 2	83 (12.2)	136 (11.0	194 (12.4	330 (11.8
Toxicity Grade 3	9 (1.3)	12 (1.0)	25 (1.6)	37 (1.3)
Toxicity Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Alkaline Phosphatase Increased				
Toxicity Grade 1	133 (19.5	237 (19.2	243 (15.5	480 (17.1
Toxicity Grade 2	30 (4.4)	66 (5.4)	73 (4.7)	139 (5.0
Toxicity Grade 3	19 (2.8)	24 (1.9)	28 (1.8)	52 (1.9)
Toxicity Grade 4	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)
Amylase Increased				
Toxicity Grade 1	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)
Toxicity Grade 2	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)
Toxicity Grade 3	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.1)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Patients that Worsened from Baseline PN001, PN002, PN006 and PN010 Subjects Treated with MK-3475 (APaT Population)

Laboratory Test	P010 (N=682)	PN001 Lung, PN010 (N=1232)	PN001 Mel, PN002, PN006 (N=1567)	PN001,PN002, PN006, PN010 (N=2799)
Toxicity Grade 4	2 (0.3)	2 (0.2)	1 (0.1)	3 (0.1)
Aspartate Aminotransferase Increased				
Toxicity Grade 1	128 (18.8	220 (17.9	336 (21.4	556 (19.9
Toxicity Grade 2	23 (3.4)	41 (3.3)	60 (3.8)	101 (3.6
Toxicity Grade 3	9 (1.3)	12 (1.0)	28 (1.8)	40 (1.4)
Toxicity Grade 4	1 (0.1)	2 (0.2)	9 (0.6)	11 (0.4)
Bicarbonate Decreased				
Toxicity Grade 1	0 (0.0)	34 (2.8)	105 (6.7	139 (5.0
Toxicity Grade 2	0 (0.0)	0 (0.0)	3 (0.2)	3 (0.1)
Toxicity Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bilirubinn Increased				
Toxicity Grade 1	27 (4.0)	44 (3.6)	88 (5.6)	132 (4.7
Toxicity Grade 2	6 (0.9)	22 (1.8)	46 (2.9)	68 (2.4)
Toxicity Grade 3	6 (0.9)	10 (0.8)	20 (1.3)	30 (1.1)
Toxicity Grade 4	1 (0.1)	1 (0.1)	5 (0.3)	6 (0.2)
Calcium Decreased				
Toxicity Grade 1	93 (13.6)	182 (14.8	288 (18.4	470 (16.8
Toxicity Grade 2	23 (3.4)	38 (3.1)	53 (3.4)	91 (3.3)
Toxicity Grade 3	2 (0.3)	6 (0.5)	10 (0.6)	16 (0.6)
Toxicity Grade 4	2 (0.3)	6 (0.5)	7 (0.4)	13 (0.5)
Calcium Increased				
Toxicity Grade 1	50 (7.3)	74 (6.0)	99 (6.3)	173 (6.2
Toxicity Grade 2	6 (0.9)	9 (0.7)	1 (0.1)	10 (0.4)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Patients that Worsened from Baseline PN001, PN002, PN006 and PN010 Subjects Treated with MK-3475 (APaT Population)

Laboratory Test	P010 (N=682)	PN001 Lung, PN010 (N=1232)	PN001 Mel, PN002, PN006 (N=1567)	PN001,PN002, PN006, PN010 (N=2799)
Toxicity Grade 3	6 (0.9)	7 (0.6)	2 (0.1)	9 (0.3)
Toxicity Grade 4	5 (0.7)	5 (0.4)	13 (0.8)	18 (0.6)
Cholesterol				
Toxicity Grade 1	106 (15.5	201 (16.3	285 (18.2	486 (17.4
Toxicity Grade 2	22 (3.2)	36 (2.9)	46 (2.9)	82 (2.9)
Toxicity Grade 3	2 (0.3)	7 (0.6)	5 (0.3)	12 (0.4)
Toxicity Grade 4	2 (0.3)	5 (0.4)	7 (0.4)	12 (0.4)
Creatine Kinase				
Toxicity Grade 1	2 (0.3)	2 (0.2)	4 (0.3)	6 (0.2)
Toxicity Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)	2 (0.1)	2 (0.1)
Toxicity Grade 4	1 (0.1)	1 (0.1)	0 (0.0)	1 (0.0)
Creatinine Increased				
Toxicity Grade 1	87 (12.8)	139 (11.3	197 (12.6	336 (12.0
Toxicity Grade 2	23 (3.4)	33 (2.7)	34 (2.2)	67 (2.4)
Toxicity Grade 3	5 (0.7)	6 (0.5)	5 (0.3)	11 (0.4)
Toxicity Grade 4	1 (0.1)	2 (0.2)	4 (0.3)	6 (0.2)
Gamma Glutamyl Transferase Increased				
Toxicity Grade 1	1 (0.1)	1 (0.1)	8 (0.5)	9 (0.3)
Toxicity Grade 2	4 (0.6)	4 (0.3)	4 (0.3)	8 (0.3)
Toxicity Grade 3	2 (0.3)	2 (0.2)	5 (0.3)	7 (0.3)
Toxicity Grade 4	2 (0.3)	2 (0.2)	2 (0.1)	4 (0.1)
Glucose Decreased				
Toxicity Grade 1	40 (5.9)	61 (5.0)	120 (7.7	181 (6.5

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Patients that Worsened from Baseline PN001, PN002, PN006 and PN010 Subjects Treated with MK-3475 (APaT Population)

Laboratory Test	P010 (N=682)	PN001 Lung, PN010 (N=1232)	PN001 Mel, PN002, PN006 (N=1567)	PN001,PN002, PN006, PN010 (N=2799)
Toxicity Grade 2	10 (1.5)	12 (1.0)	20 (1.3)	32 (1.1)
Toxicity Grade 3	1 (0.1)	1 (0.1)	2 (0.1)	3 (0.1)
Toxicity Grade 4	1 (0.1)	2 (0.2)	5 (0.3)	7 (0.3)
Glucose Increased				
Toxicity Grade 1	192 (28.2	364 (29.5	486 (31.0	850 (30.4
Toxicity Grade 2	67 (9.8)	152 (12.3	165 (10.5	317 (11.3
Toxicity Grade 3	19 (2.8)	30 (2.4)	65 (4.1)	95 (3.4)
Toxicity Grade 4	4 (0.6)	9 (0.7)	5 (0.3)	14 (0.5)
Hemoglobin Decreased				
Toxicity Grade 1	119 (17.4	224 (18.2	393 (25.1	617 (22.0
Toxicity Grade 2	98 (14.4)	178 (14.4	184 (11.7	362 (12.9
Toxicity Grade 3	22 (3.2)	33 (2.7)	71 (4.5)	104 (3.7
Toxicity Grade 4	0 (0.0)	1 (0.1)	8 (0.5)	9 (0.3)
Leukocytes Decreased				
Toxicity Grade 1	33 (4.8)	67 (5.4)	173 (11.0	240 (8.6
Toxicity Grade 2	5 (0.7)	18 (1.5)	48 (3.1)	66 (2.4)
Toxicity Grade 3	1 (0.1)	2 (0.2)	2 (0.1)	4 (0.1)
Toxicity Grade 4	3 (0.4)	5 (0.4)	0 (0.0)	5 (0.2)
Leukocytes Increased				
Toxicity Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Toxicity Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Toxicity Grade 4	2 (0.3)	2 (0.2)	0 (0.0)	2 (0.1)
Lymphocytes Decreased				

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Patients that Worsened from Baseline PN001, PN002, PN006 and PN010 Subjects Treated with MK-3475 (APaT Population)

Laboratory Test	P010 (N=682)	PN001 Lung, PN010 (N=1232)	PN001 Mel, PN002, PN006 (N=1567)	PN001,PN002, PN006, PN010 (N=2799)
Toxicity Grade 1	63 (9.2)	93 (7.5)	200 (12.8	293 (10.5
Toxicity Grade 2	92 (13.5)	138 (11.2	213 (13.6	351 (12.5
Toxicity Grade 3	32 (4.7)	54 (4.4)	89 (5.7)	143 (5.1
Toxicity Grade 4	9 (1.3)	11 (0.9)	25 (1.6)	36 (1.3)
Lymphocytes Increased				
Toxicity Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Toxicity Grade 2	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Magnesium Decreased				
Toxicity Grade 1	99 (14.5)	172 (14.0	181 (11.6	353 (12.6
Toxicity Grade 2	27 (4.0)	32 (2.6)	20 (1.3)	52 (1.9)
Toxicity Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Toxicity Grade 4	1 (0.1)	2 (0.2)	3 (0.2)	5 (0.2)
Magnesium Increased				
Toxicity Grade 1	26 (3.8)	61 (5.0)	88 (5.6)	149 (5.3
Toxicity Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Toxicity Grade 3	3 (0.4)	4 (0.3)	10 (0.6)	14 (0.5)
Toxicity Grade 4	2 (0.3)	3 (0.2)	7 (0.4)	10 (0.4)
Neutrophils Decreased				
Toxicity Grade 1	19 (2.8)	25 (2.0)	57 (3.6)	82 (2.9)
Toxicity Grade 2	11 (1.6)	14 (1.1)	40 (2.6)	54 (1.9)
Toxicity Grade 3	0 (0.0)	1 (0.1)	11 (0.7)	12 (0.4)
Toxicity Grade 4	6 (0.9)	7 (0.6)	15 (1.0)	22 (0.8)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Patients that Worsened from Baseline
PN001, PN002, PN006 and PN010 Subjects Treated with MK-3475
(APaT Population)

Laboratory Test	P010 (N=682)	PN001 Lung, PN010 (N=1232)	PN001 Mel, PN002, PN006 (N=1567)	PN001,PN002, PN006, PN010 (N=2799)
Neutrophils Increased				
Toxicity Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Toxicity Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Toxicity Grade 4	1 (0.1)	1 (0.1)	0 (0.0)	1 (0.0)
Phosphate Decreased				
Toxicity Grade 1	16 (2.3)	32 (2.6)	20 (1.3)	52 (1.9)
Toxicity Grade 2	65 (9.5)	127 (10.3	205 (13.1	332 (11.9
Toxicity Grade 3	28 (4.1)	49 (4.0)	71 (4.5)	120 (4.3
Toxicity Grade 4	4 (0.6)	4 (0.3)	2 (0.1)	6 (0.2)
Platelet Decreased				
Toxicity Grade 1	54 (7.9)	94 (7.6)	155 (9.9	249 (8.9
Toxicity Grade 2	5 (0.7)	7 (0.6)	9 (0.6)	16 (0.6)
Toxicity Grade 3	4 (0.6)	4 (0.3)	5 (0.3)	9 (0.3)
Toxicity Grade 4	4 (0.6)	13 (1.1)	8 (0.5)	21 (0.8)
Platelet Increased				
Toxicity Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Toxicity Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Toxicity Grade 4	1 (0.1)	1 (0.1)	0 (0.0)	1 (0.0)
Potassium Decreased				
Toxicity Grade 1	54 (7.9)	103 (8.4	166 (10.6	269 (9.6
Toxicity Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Toxicity Grade 3	7 (1.0)	14 (1.1)	24 (1.5)	38 (1.4)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Patients that Worsened from Baseline PN001, PN002, PN006 and PN010 Subjects Treated with MK-3475 (APaT Population)

Laboratory Test	P010 (N=682)	PN001 Lung, PN010 (N=1232)	PN001 Mel, PN002, PN006 (N=1567)	PN001,PN002, PN006, PN010 (N=2799)
Toxicity Grade 4	3 (0.4)	4 (0.3)	5 (0.3)	9 (0.3)
Potassium Increased				
Toxicity Grade 1	77 (11.3)	125 (10.1	179 (11.4	304 (10.9
Toxicity Grade 2	21 (3.1)	32 (2.6)	43 (2.7)	75 (2.7)
Toxicity Grade 3	4 (0.6)	6 (0.5)	10 (0.6)	16 (0.6)
Toxicity Grade 4	9 (1.3)	9 (0.7)	11 (0.7)	20 (0.7)
Prothrombin Intl. Normalized Ratio Incre				
Toxicity Grade 1	6 (0.9)	22 (1.8)	27 (1.7)	49 (1.8)
Toxicity Grade 2	0 (0.0)	1 (0.1)	6 (0.4)	7 (0.3)
Toxicity Grade 3	2 (0.3)	5 (0.4)	16 (1.0)	21 (0.8)
Toxicity Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sodium Decreased				
Toxicity Grade 1	148 (21.7	322 (26.1	426 (27.2	748 (26.7
Toxicity Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Toxicity Grade 3	41 (6.0)	74 (6.0)	65 (4.1)	139 (5.0
Toxicity Grade 4	14 (2.1)	15 (1.2)	23 (1.5)	38 (1.4)
Sodium Increased				
Toxicity Grade 1	30 (4.4)	41 (3.3)	96 (6.1)	137 (4.9
Toxicity Grade 2	1 (0.1)	1 (0.1)	0 (0.0)	1 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Toxicity Grade 4	1 (0.1)	1 (0.1)	2 (0.1)	3 (0.1)
Triacylglycerol Lipase Increased				
Toxicity Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Toxicity Grade 2	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Patients that Worsened from Baseline PN001, PN002, PN006 and PN010 Subjects Treated with MK-3475 (APaT Population)

Laboratory Test	P010 (N=682)	PN001 Lung, PN010 (N=1232)	PN001 Mel, PN002, PN006 (N=1567)	PN001,PN002, PN006, PN010 (N=2799)
Toxicity Grade 3	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)
Toxicity Grade 4	1 (0.1)	1 (0.1)	2 (0.1)	3 (0.1)
Triglycerides				
Toxicity Grade 1	157 (23.0	275 (22.3	466 (29.7	741 (26.5
Toxicity Grade 2	39 (5.7)	52 (4.2)	98 (6.3)	150 (5.4
Toxicity Grade 3	10 (1.5)	11 (0.9)	22 (1.4)	33 (1.2)
Toxicity Grade 4	4 (0.6)	4 (0.3)	2 (0.1)	6 (0.2)

If a patient had more than one graded abnormalities for a lab test, only the hightest grade is counted.
Grades are based on NCI CTCAE version 4.
(MK-3475 PN001 Database Cutoff Date for MEL: [redacted]).
(MK-3475 PN001 Database Cutoff Date for Lung: [redacted]).
(MK-3475 PN002 Database Cutoff Date: [redacted]).
(MK-3475 PN006 Database Cutoff Date: 03MAR2015).
(MK-3475 PN010 Database Cutoff Date: 30SEP2015).

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付録 2.7.4- 82　　投与状況の要約

010 試験（日本人安全性解析対象集団）（PD-L1 高発現）

Summary of Drug Exposure
Subject with TPS ≥ 50%
APaT Japan Population

	Docetaxel 75 mg/m2 Q3W	MK-3475 2 mg/kg Q3W	MK-3475 10 mg/kg Q3W
	N=11	N=10	N=13
Study Days On-Therapy (days)			
Mean	113.55	144.30	134.62
Median	106.00	147.00	70.00
SD	97.47	84.45	147.12
Range	1.00 to 349.00	1.00 to 259.00	24.00 to 485.00
Number of Administrations			
Mean	6.09	7.50	6.62
Median	6.00	7.00	4.00
SD	4.53	3.87	6.32
Range	1.00 to 17.00	1.00 to 13.00	2.00 to 23.00
Database Cutoff Date: 30SEP2015			

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付録 2.7.4- 83　　投与期間の分布

010 試験（日本人安全性解析対象集団）（PD-L1 高発現）

Exposure by Duration
Subjects with TPS ≥ 50%
APaT Japan Population

Duration of Exposure	Docetaxel 75 mg/m2 Q3W (N=11)		MK-3475 2 mg/kg Q3W (N=10)		MK-3475 10 mg/kg Q3W (N=13)	
	n	Patient Years	n	Patient Years	n	Patient Years
> 0 m	11	3.4	10	4.0	13	4.8
≥ 1 m	9	3.3	9	3.9	12	4.7
≥ 3 m	6	2.9	8	3.8	6	3.9
≥ 6 m	2	1.5	5	3.0	3	3.0
≥ 12 m	0	0	0	0	0	0

Each subject is counted once on each applicable duration category row.
Duration of Exposure is calculated as last dose date - first dose date +1.
(Database Cutoff Date: 30SEP2015).

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付録 2.7.4- 84　　投与状況の要約

010 試験（日本人安全性解析対象集団）（PD-L1 低発現）

Summary of Drug Exposure
Subject with 1% ≤ TPS < 50%
APaT Japan Population

	Docetaxel 75 mg/m2 Q3W	MK-3475 2 mg/kg Q3W	MK-3475 10 mg/kg Q3W
	N=16	N=18	N=21
Study Days On-Therapy (days)			
Mean	89.94	127.33	130.95
Median	47.00	107.50	126.00
SD	91.91	85.06	119.22
Range	1.00 to 273.00	1.00 to 316.00	1.00 to 454.00
Number of Administrations			
Mean	4.81	6.67	6.76
Median	3.00	6.00	6.00
SD	3.78	3.87	5.26
Range	1.00 to 12.00	1.00 to 16.00	1.00 to 22.00
Database Cutoff Date: 30SEP2015			

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付録 2.7.4- 85　　投与期間の分布

010 試験（日本人安全性解析対象集団）（PD-L1 低発現）

Exposure by Duration
Subjects with 1% ≤ TPS < 50%
APaT Japan Population

Duration of Exposure	Docetaxel 75 mg/m2 Q3W (N=16)		MK-3475 2 mg/kg Q3W (N=18)		MK-3475 10 mg/kg Q3W (N=21)	
	n	Patient Years	n	Patient Years	n	Patient Years
> 0 m	16	3.9	18	6.3	21	7.5
≥ 1 m	10	3.8	16	6.2	16	7.3
≥ 3 m	7	3.4	9	4.8	12	6.7
≥ 6 m	4	2.5	6	3.7	5	4.2
≥ 12 m	0	0	0	0	0	0

Each subject is counted once on each applicable duration category row.
Duration of Exposure is calculated as last dose date - first dose date +1.
(Database Cutoff Date: 30SEP2015).

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付録 2.7.4- 86　　患者の特性

010 試験（日本人安全性解析対象集団）（PD-L1 発現陽性）
Subject Characteristics
APaT Japan Population (TPS ≥ 1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	27		28		34		89	
Gender								
Male	21	(77.8)	17	(60.7)	20	(58.8)	58	(65.2)
Female	6	(22.2)	11	(39.3)	14	(41.2)	31	(34.8)
Age (Years)								
<65	13	(48.1)	11	(39.3)	15	(44.1)	39	(43.8)
>=65	14	(51.9)	17	(60.7)	19	(55.9)	50	(56.2)
Mean	61.3		63.9		63.9		63.1	
SD	13.8		10.7		10.7		11.6	
Median	66.0		65.5		66.0		66.0	
Range	34 to 77		30 to 79		38 to 78		30 to 79	
Race								
Asian	27	(100.0)	28	(100.0)	34	(100.0)	89	(100.0)
Ethnicity								
Not Hispanic Or Latino	27	(100.0)	27	(96.4)	33	(97.1)	87	(97.8)
Not Reported	0	(0.0)	0	(0.0)	1	(2.9)	1	(1.1)
Unknown	0	(0.0)	1	(3.6)	0	(0.0)	1	(1.1)
Race								
East Asian	27	(100.0)	28	(100.0)	34	(100.0)	89	(100.0)
Geographic Region								
EX US	27	(100.0)	28	(100.0)	34	(100.0)	89	(100.0)

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Subject Characteristics
APaT Japan Population (TPS ≥ 1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Region								
East Asian	27	(100.0)	28	(100.0)	34	(100.0)	89	(100.0)
Smoker								
Never Smoker	5	(18.5)	9	(32.1)	13	(38.2)	27	(30.3)
Current/Ex Smoker	22	(81.5)	19	(67.9)	21	(61.8)	62	(69.7)
ECOG								
0	12	(44.4)	14	(50.0)	15	(44.1)	41	(46.1)
1	15	(55.6)	14	(50.0)	19	(55.9)	48	(53.9)
Cancer Stage								
IIIB	5	(18.5)	3	(10.7)	7	(20.6)	15	(16.9)
IV	22	(81.5)	25	(89.3)	27	(79.4)	74	(83.1)
Metastatic Staging								
M0	5	(18.5)	3	(10.7)	7	(20.6)	15	(16.9)
M1	1	(3.7)	0	(0.0)	4	(11.8)	5	(5.6)
M1A	8	(29.6)	8	(28.6)	10	(29.4)	26	(29.2)
M1B	13	(48.1)	17	(60.7)	13	(38.2)	43	(48.3)
Baseline Tumor Size (mm)								
Subjects with data	27		27		33		87	
Mean	95.3		64.9		78.5		79.5	
SD	49.4		43.6		42.8		46.3	
Median	88.0		47.0		74.0		71.0	
Range	21 to 221		12 to 173		23 to 202		12 to 221	

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Subject Characteristics
APaT Japan Population (TPS ≥ 1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Brain Metastasis								
Yes	4	(14.8)	6	(21.4)	6	(17.6)	16	(18.0)
No	23	(85.2)	22	(78.6)	28	(82.4)	73	(82.0)
Non-small Cell Histology								
SQUAMOUS	9	(33.3)	6	(21.4)	3	(8.8)	18	(20.2)
NON-SQUAMOUS	16	(59.3)	21	(75.0)	29	(85.3)	66	(74.2)
UNKNOWN	2	(7.4)	1	(3.6)	2	(5.9)	5	(5.6)
PD-L1 Status								
WEAKLY POSITIVE	16	(59.3)	18	(64.3)	21	(61.8)	55	(61.8)
STRONGLY POSITIVE	11	(40.7)	10	(35.7)	13	(38.2)	34	(38.2)
EGFR Mutation								
MUTANT	3	(11.1)	7	(25.0)	11	(32.4)	21	(23.6)
WILD TYPE	23	(85.2)	18	(64.3)	22	(64.7)	63	(70.8)
UNDETERMINED	0	(0.0)	2	(7.1)	0	(0.0)	2	(2.2)
Missing	1	(3.7)	1	(3.6)	1	(2.9)	3	(3.4)
ALK Translocation Status								
MUTANT	0	(0.0)	1	(3.6)	1	(2.9)	2	(2.2)
WILD TYPE	22	(81.5)	23	(82.1)	25	(73.5)	70	(78.7)
UNDETERMINED	2	(7.4)	3	(10.7)	5	(14.7)	10	(11.2)
Missing	3	(11.1)	1	(3.6)	3	(8.8)	7	(7.9)
Prior Lines of Systemic Therapy								
FIRST LINE	16	(59.3)	16	(57.1)	17	(50.0)	49	(55.1)

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Subject Characteristics
APaT Japan Population (TPS ≥ 1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Prior Lines of Systemic Therapy								
SECOND LINE	6	(22.2)	8	(28.6)	10	(29.4)	24	(27.0)
THIRD LINE	4	(14.8)	3	(10.7)	5	(14.7)	12	(13.5)
FOURTH LINE	1	(3.7)	0	(0.0)	0	(0.0)	1	(1.1)
FIFTH LINE OR GREATER	0	(0.0)	1	(3.6)	2	(5.9)	3	(3.4)
Prior Adjuvant/Neo-adjuvant Therapy								
Y	1	(3.7)	3	(10.7)	2	(5.9)	6	(6.7)
N	26	(96.3)	25	(89.3)	32	(94.1)	83	(93.3)
Prior Chemotherapy[†]								
Y	27	(100.0)	28	(100.0)	34	(100.0)	89	(100.0)
Prior Immunotherapy[†]								
Y	1	(3.7)	0	(0.0)	0	(0.0)	1	(1.1)
N	26	(96.3)	28	(100.0)	34	(100.0)	88	(98.9)
Prior EGFR TKI Therapy[†]								
Y	5	(18.5)	8	(28.6)	12	(35.3)	25	(28.1)
N	22	(81.5)	20	(71.4)	22	(64.7)	64	(71.9)
Prior ALK inhibitor Therapy[†]								
Y	0	(0.0)	1	(3.6)	1	(2.9)	2	(2.2)

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Subject Characteristics
APaT Japan Population (TPS ≥ 1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Prior ALK inhibitor Therapy[†]								
N	27	(100.0)	27	(96.4)	33	(97.1)	87	(97.8)

[†]Prior systemic therapy
(Database Cutoff Date: 30SEP2015).

Data Source:　[16.4]

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付録 2.7.4- 87　　患者の特性

010 試験（日本人安全性解析対象集団）（PD-L1 高発現）
Subject Characteristics
TPS≥50%, APaT Japan Population

	Docetaxel 75 mg/m2 Q3W		MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	11		10		13		34	
Gender								
Male	10	(90.9)	5	(50.0)	9	(69.2)	24	(70.6)
Female	1	(9.1)	5	(50.0)	4	(30.8)	10	(29.4)
Age (Years)								
<65	6	(54.5)	4	(40.0)	6	(46.2)	16	(47.1)
>=65	5	(45.5)	6	(60.0)	7	(53.8)	18	(52.9)
Mean	60.7		61.8		64.5		62.5	
SD	13.5		12.7		8.3		11.3	
Median	64.0		65.0		67.0		65.0	
Range	34 to 77		30 to 78		45 to 74		30 to 78	
Race								
Asian	11	(100.0)	10	(100.0)	13	(100.0)	34	(100.0)
Ethnicity								
Not Hispanic Or Latino	11	(100.0)	10	(100.0)	13	(100.0)	34	(100.0)
Race								
East Asian	11	(100.0)	10	(100.0)	13	(100.0)	34	(100.0)
Geographic Region								
EX US	11	(100.0)	10	(100.0)	13	(100.0)	34	(100.0)
Region								

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Subject Characteristics
TPS≥50%, APaT Japan Population

	Docetaxel 75 mg/m2 Q3W		MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Region								
East Asian	11	(100.0)	10	(100.0)	13	(100.0)	34	(100.0)
Smoker								
Never Smoker	2	(18.2)	3	(30.0)	4	(30.8)	9	(26.5)
Current/Ex Smoker	9	(81.8)	7	(70.0)	9	(69.2)	25	(73.5)
ECOG								
0	5	(45.5)	4	(40.0)	4	(30.8)	13	(38.2)
1	6	(54.5)	6	(60.0)	9	(69.2)	21	(61.8)
Cancer Stage								
IIIB	3	(27.3)	1	(10.0)	1	(7.7)	5	(14.7)
IV	8	(72.7)	9	(90.0)	12	(92.3)	29	(85.3)
Metastatic Staging								
M0	3	(27.3)	1	(10.0)	1	(7.7)	5	(14.7)
M1A	2	(18.2)	2	(20.0)	4	(30.8)	8	(23.5)
M1B	6	(54.5)	7	(70.0)	8	(61.5)	21	(61.8)
Baseline Tumor Size (mm)								
Subjects with data	11		10		13		34	
Mean	95.6		69.8		79.8		82.0	
SD	48.7		22.7		50.9		43.7	
Median	89.0		68.0		78.0		78.5	
Range	21 to 221		41 to 113		23 to 202		21 to 221	

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Subject Characteristics
TPS≥50%, APaT Japan Population

	Docetaxel 75 mg/m2 Q3W		MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Brain Metastasis								
Yes	2	(18.2)	2	(20.0)	3	(23.1)	7	(20.6)
No	9	(81.8)	8	(80.0)	10	(76.9)	27	(79.4)
Non-small Cell Histology								
SQUAMOUS	4	(36.4)	0	(0.0)	2	(15.4)	6	(17.6)
NON-SQUAMOUS	6	(54.5)	9	(90.0)	9	(69.2)	24	(70.6)
UNKNOWN	1	(9.1)	1	(10.0)	2	(15.4)	4	(11.8)
PD-L1 Status								
STRONGLY POSITIVE	11	(100.0)	10	(100.0)	13	(100.0)	34	(100.0)
EGFR Mutation								
MUTANT	1	(9.1)	1	(10.0)	6	(46.2)	8	(23.5)
WILD TYPE	9	(81.8)	9	(90.0)	6	(46.2)	24	(70.6)
Missing	1	(9.1)	0	(0.0)	1	(7.7)	2	(5.9)
ALK Translocation Status								
MUTANT	0	(0.0)	1	(10.0)	0	(0.0)	1	(2.9)
WILD TYPE	8	(72.7)	9	(90.0)	7	(53.8)	24	(70.6)
UNDETERMINED	0	(0.0)	0	(0.0)	3	(23.1)	3	(8.8)
Missing	3	(27.3)	0	(0.0)	3	(23.1)	6	(17.6)
Prior Lines of Systemic Therapy								
FIRST LINE	8	(72.7)	6	(60.0)	7	(53.8)	21	(61.8)
SECOND LINE	1	(9.1)	3	(30.0)	3	(23.1)	7	(20.6)
THIRD LINE	2	(18.2)	1	(10.0)	2	(15.4)	5	(14.7)

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Subject Characteristics
TPS≥50%, APaT Japan Population

	Docetaxel 75 mg/m2 Q3W		MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Prior Lines of Systemic Therapy								
FIFTH LINE OR GREATER	0	(0.0)	0	(0.0)	1	(7.7)	1	(2.9)
Prior Adjuvant/Neo-adjuvant Therapy								
N	11	(100.0)	10	(100.0)	13	(100.0)	34	(100.0)
Prior Chemotherapy[†]								
Y	11	(100.0)	10	(100.0)	13	(100.0)	34	(100.0)
Prior Immunotherapy[†]								
N	11	(100.0)	10	(100.0)	13	(100.0)	34	(100.0)
Prior EGFR TKI Therapy[†]								
Y	1	(9.1)	2	(20.0)	6	(46.2)	9	(26.5)
N	10	(90.9)	8	(80.0)	7	(53.8)	25	(73.5)
Prior ALK inhibitor Therapy[†]								
Y	0	(0.0)	1	(10.0)	0	(0.0)	1	(2.9)
N	11	(100.0)	9	(90.0)	13	(100.0)	33	(97.1)

[†]Prior systemic therapy
(Database Cutoff Date: 30SEP2015).

Data Source:　[16.4]

Confidential

付録 2.7.4- 88　　患者の特性

010 試験（日本人安全性解析対象集団）（PD-L1 低発現）
Subject Characteristics
Subjects with 1%≤ TPS<50%, APaT Japan Population

	Docetaxel 75 mg/m2 Q3W		MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	16		18		21		55	
Gender								
Male	11	(68.8)	12	(66.7)	11	(52.4)	34	(61.8)
Female	5	(31.3)	6	(33.3)	10	(47.6)	21	(38.2)
Age (Years)								
<65	7	(43.8)	7	(38.9)	9	(42.9)	23	(41.8)
>=65	9	(56.3)	11	(61.1)	12	(57.1)	32	(58.2)
Mean	61.7		65.1		63.6		63.5	
SD	14.5		9.6		12.1		12.0	
Median	66.0		66.5		65.0		66.0	
Range	35 to 76		48 to 79		38 to 78		35 to 79	
Race								
Asian	16	(100.0)	18	(100.0)	21	(100.0)	55	(100.0)
Ethnicity								
Not Hispanic Or Latino	16	(100.0)	17	(94.4)	20	(95.2)	53	(96.4)
Not Reported	0	(0.0)	0	(0.0)	1	(4.8)	1	(1.8)
Unknown	0	(0.0)	1	(5.6)	0	(0.0)	1	(1.8)
Race								
East Asian	16	(100.0)	18	(100.0)	21	(100.0)	55	(100.0)
Geographic Region								
EX US	16	(100.0)	18	(100.0)	21	(100.0)	55	(100.0)

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Subject Characteristics
Subjects with 1%≤ TPS<50%, APaT Japan Population

	Docetaxel 75 mg/m2 Q3W		MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Region								
East Asian	16	(100.0)	18	(100.0)	21	(100.0)	55	(100.0)
Smoker								
Never Smoker	3	(18.8)	6	(33.3)	9	(42.9)	18	(32.7)
Current/Ex Smoker	13	(81.3)	12	(66.7)	12	(57.1)	37	(67.3)
ECOG								
0	7	(43.8)	10	(55.6)	11	(52.4)	28	(50.9)
1	9	(56.3)	8	(44.4)	10	(47.6)	27	(49.1)
Cancer Stage								
IIIB	2	(12.5)	2	(11.1)	6	(28.6)	10	(18.2)
IV	14	(87.5)	16	(88.9)	15	(71.4)	45	(81.8)
Metastatic Staging								
M0	2	(12.5)	2	(11.1)	6	(28.6)	10	(18.2)
M1	1	(6.3)	0	(0.0)	4	(19.0)	5	(9.1)
M1A	6	(37.5)	6	(33.3)	6	(28.6)	18	(32.7)
M1B	7	(43.8)	10	(55.6)	5	(23.8)	22	(40.0)
Baseline Tumor Size (mm)								
Subjects with data	16		17		20		53	
Mean	95.0		62.0		77.6		77.8	
SD	51.6		52.7		38.1		48.2	
Median	83.0		43.0		71.0		68.0	
Range	26 to 200		12 to 173		25 to 139		12 to 200	

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Subject Characteristics
Subjects with 1%≤ TPS<50%, APaT Japan Population

	Docetaxel 75 mg/m2 Q3W		MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Brain Metastasis								
Yes	2	(12.5)	4	(22.2)	3	(14.3)	9	(16.4)
No	14	(87.5)	14	(77.8)	18	(85.7)	46	(83.6)
Non-small Cell Histology								
SQUAMOUS	5	(31.3)	6	(33.3)	1	(4.8)	12	(21.8)
NON-SQUAMOUS	10	(62.5)	12	(66.7)	20	(95.2)	42	(76.4)
UNKNOWN	1	(6.3)	0	(0.0)	0	(0.0)	1	(1.8)
PD-L1 Status								
WEAKLY POSITIVE	16	(100.0)	18	(100.0)	21	(100.0)	55	(100.0)
EGFR Mutation								
MUTANT	2	(12.5)	6	(33.3)	5	(23.8)	13	(23.6)
WILD TYPE	14	(87.5)	9	(50.0)	16	(76.2)	39	(70.9)
UNDETERMINED	0	(0.0)	2	(11.1)	0	(0.0)	2	(3.6)
Missing	0	(0.0)	1	(5.6)	0	(0.0)	1	(1.8)
ALK Translocation Status								
MUTANT	0	(0.0)	0	(0.0)	1	(4.8)	1	(1.8)
WILD TYPE	14	(87.5)	14	(77.8)	18	(85.7)	46	(83.6)
UNDETERMINED	2	(12.5)	3	(16.7)	2	(9.5)	7	(12.7)
Missing	0	(0.0)	1	(5.6)	0	(0.0)	1	(1.8)
Prior Lines of Systemic Therapy								
FIRST LINE	8	(50.0)	10	(55.6)	10	(47.6)	28	(50.9)
SECOND LINE	5	(31.3)	5	(27.8)	7	(33.3)	17	(30.9)

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Subject Characteristics
Subjects with 1%≤ TPS<50%, APaT Japan Population

	Docetaxel 75 mg/m2 Q3W		MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Prior Lines of Systemic Therapy								
THIRD LINE	2	(12.5)	2	(11.1)	3	(14.3)	7	(12.7)
FOURTH LINE	1	(6.3)	0	(0.0)	0	(0.0)	1	(1.8)
FIFTH LINE OR GREATER	0	(0.0)	1	(5.6)	1	(4.8)	2	(3.6)
Prior Adjuvant/Neo-adjuvant Therapy								
Y	1	(6.3)	3	(16.7)	2	(9.5)	6	(10.9)
N	15	(93.8)	15	(83.3)	19	(90.5)	49	(89.1)
Prior Chemotherapy[†]								
Y	16	(100.0)	18	(100.0)	21	(100.0)	55	(100.0)
Prior Immunotherapy[†]								
Y	1	(6.3)	0	(0.0)	0	(0.0)	1	(1.8)
N	15	(93.8)	18	(100.0)	21	(100.0)	54	(98.2)
Prior EGFR TKI Therapy[†]								
Y	4	(25.0)	6	(33.3)	6	(28.6)	16	(29.1)
N	12	(75.0)	12	(66.7)	15	(71.4)	39	(70.9)
Prior ALK inhibitor Therapy[†]								
Y	0	(0.0)	0	(0.0)	1	(4.8)	1	(1.8)
N	16	(100.0)	18	(100.0)	20	(95.2)	54	(98.2)

[†]Prior systemic therapy
(Database Cutoff Date: 30SEP2015).

Data Source:　[16.4]

Confidential

付録 2.7.4- 89　　有害事象（いずれかの投与群で発現割合 0%超）

011 試験（パート A）（安全性解析対象集団）

	MK-3475 2 mg/kg Q2W		MK-3475 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	3		7		10	
with one or more adverse events	3	(100.0)	7	(100.0)	10	(100.0)
Grade 1	1	(33.3)	1	(14.3)	2	(20.0)
Grade 2	1	(33.3)	3	(42.9)	4	(40.0)
Grade 3	1	(33.3)	1	(14.3)	2	(20.0)
Grade 4	0	(0.0)	2	(28.6)	2	(20.0)
with no adverse events	0	(0.0)	0	(0.0)	0	(0.0)
Blood and lymphatic system disorders	0	(0.0)	3	(42.9)	3	(30.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)
Grade 3	0	(0.0)	1	(14.3)	1	(10.0)
Anaemia	0	(0.0)	2	(28.6)	2	(20.0)
Grade 2	0	(0.0)	2	(28.6)	2	(20.0)
Lymphopenia	0	(0.0)	1	(14.3)	1	(10.0)
Grade 3	0	(0.0)	1	(14.3)	1	(10.0)
Neutropenia	0	(0.0)	1	(14.3)	1	(10.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Thrombocytopenia	0	(0.0)	1	(14.3)	1	(10.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Gastrointestinal disorders	1	(33.3)	4	(57.1)	5	(50.0)
Grade 1	1	(33.3)	4	(57.1)	5	(50.0)
Abdominal distension	0	(0.0)	1	(14.3)	1	(10.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Abdominal pain lower	0	(0.0)	1	(14.3)	1	(10.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Constipation	1	(33.3)	0	(0.0)	1	(10.0)
Grade 1	1	(33.3)	0	(0.0)	1	(10.0)
Diarrhoea	0	(0.0)	2	(28.6)	2	(20.0)
Grade 1	0	(0.0)	2	(28.6)	2	(20.0)
Nausea	1	(33.3)	1	(14.3)	2	(20.0)
Grade 1	1	(33.3)	1	(14.3)	2	(20.0)
Vomiting	0	(0.0)	1	(14.3)	1	(10.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
General disorders and administration site conditions	2	(66.7)	4	(57.1)	6	(60.0)
Grade 1	2	(66.7)	1	(14.3)	3	(30.0)
Grade 2	0	(0.0)	2	(28.6)	2	(20.0)
Grade 3	0	(0.0)	1	(14.3)	1	(10.0)
Fatigue	1	(33.3)	3	(42.9)	4	(40.0)
Grade 1	1	(33.3)	1	(14.3)	2	(20.0)
Grade 2	0	(0.0)	2	(28.6)	2	(20.0)
Gait disturbance	0	(0.0)	1	(14.3)	1	(10.0)
Grade 3	0	(0.0)	1	(14.3)	1	(10.0)
Malaise	1	(33.3)	1	(14.3)	2	(20.0)
Grade 1	1	(33.3)	1	(14.3)	2	(20.0)
Oedema peripheral	0	(0.0)	3	(42.9)	3	(30.0)
Grade 1	0	(0.0)	2	(28.6)	2	(20.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)

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付録 2.7.4- 89　　有害事象（いずれかの投与群で発現割合 0%超）

011 試験（パート A）（安全性解析対象集団）（続き）

	MK-3475 2 mg/kg Q2W		MK-3475 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)
Pyrexia	1	(33.3)	2	(28.6)	3	(30.0)
Grade 1	1	(33.3)	2	(28.6)	3	(30.0)
Hepatobiliary disorders	0	(0.0)	1	(14.3)	1	(10.0)
Grade 3	0	(0.0)	1	(14.3)	1	(10.0)
Hyperbilirubinaemia	0	(0.0)	1	(14.3)	1	(10.0)
Grade 3	0	(0.0)	1	(14.3)	1	(10.0)
Infections and infestations	2	(66.7)	2	(28.6)	4	(40.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Grade 2	1	(33.3)	1	(14.3)	2	(20.0)
Grade 3	1	(33.3)	0	(0.0)	1	(10.0)
Infection	0	(0.0)	1	(14.3)	1	(10.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)
Pneumonia	1	(33.3)	1	(14.3)	2	(20.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Grade 3	1	(33.3)	0	(0.0)	1	(10.0)
Wound infection	1	(33.3)	0	(0.0)	1	(10.0)
Grade 2	1	(33.3)	0	(0.0)	1	(10.0)
Injury, poisoning and procedural complications	0	(0.0)	1	(14.3)	1	(10.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Breast injury	0	(0.0)	1	(14.3)	1	(10.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Investigations	1	(33.3)	5	(71.4)	6	(60.0)
Grade 1	1	(33.3)	1	(14.3)	2	(20.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)
Grade 3	0	(0.0)	3	(42.9)	3	(30.0)
Alanine aminotransferase increased	0	(0.0)	2	(28.6)	2	(20.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Grade 3	0	(0.0)	1	(14.3)	1	(10.0)
Aspartate aminotransferase increased	0	(0.0)	2	(28.6)	2	(20.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Grade 3	0	(0.0)	1	(14.3)	1	(10.0)
Blood alkaline phosphatase increased	0	(0.0)	1	(14.3)	1	(10.0)
Grade 3	0	(0.0)	1	(14.3)	1	(10.0)
Blood cholesterol increased	1	(33.3)	0	(0.0)	1	(10.0)
Grade 1	1	(33.3)	0	(0.0)	1	(10.0)
Blood thyroid stimulating hormone increased	0	(0.0)	2	(28.6)	2	(20.0)
Grade 1	0	(0.0)	2	(28.6)	2	(20.0)
Gamma-glutamyltransferase increased	0	(0.0)	1	(14.3)	1	(10.0)
Grade 3	0	(0.0)	1	(14.3)	1	(10.0)
Lymphocyte count decreased	0	(0.0)	2	(28.6)	2	(20.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)
Grade 3	0	(0.0)	1	(14.3)	1	(10.0)
Platelet count decreased	0	(0.0)	2	(28.6)	2	(20.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Grade 3	0	(0.0)	1	(14.3)	1	(10.0)
QRS axis abnormal	0	(0.0)	1	(14.3)	1	(10.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)

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付録 2.7.4- 89　　有害事象（いずれかの投与群で発現割合 0%超）
011 試験（パート A）（安全性解析対象集団）（続き）

	MK-3475 2 mg/kg Q2W		MK-3475 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)
Weight decreased	0	(0.0)	2	(28.6)	2	(20.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)
Metabolism and nutrition disorders	1	(33.3)	5	(71.4)	6	(60.0)
Grade 1	1	(33.3)	1	(14.3)	2	(20.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)
Grade 3	0	(0.0)	2	(28.6)	2	(20.0)
Grade 4	0	(0.0)	1	(14.3)	1	(10.0)
Decreased appetite	0	(0.0)	3	(42.9)	3	(30.0)
Grade 1	0	(0.0)	2	(28.6)	2	(20.0)
Grade 3	0	(0.0)	1	(14.3)	1	(10.0)
Dehydration	0	(0.0)	1	(14.3)	1	(10.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)
Hypercalcaemia	0	(0.0)	2	(28.6)	2	(20.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)
Grade 3	0	(0.0)	1	(14.3)	1	(10.0)
Hyperglycaemia	0	(0.0)	1	(14.3)	1	(10.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)
Hyperkalaemia	0	(0.0)	2	(28.6)	2	(20.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)
Hypermagnesaemia	0	(0.0)	2	(28.6)	2	(20.0)
Grade 1	0	(0.0)	2	(28.6)	2	(20.0)
Hypertriglyceridaemia	1	(33.3)	0	(0.0)	1	(10.0)
Grade 1	1	(33.3)	0	(0.0)	1	(10.0)
Hyperuricaemia	0	(0.0)	1	(14.3)	1	(10.0)
Grade 4	0	(0.0)	1	(14.3)	1	(10.0)
Hypoalbuminaemia	0	(0.0)	2	(28.6)	2	(20.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)
Hypokalaemia	0	(0.0)	1	(14.3)	1	(10.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)
Hyponatraemia	0	(0.0)	3	(42.9)	3	(30.0)
Grade 3	0	(0.0)	3	(42.9)	3	(30.0)
Hypophosphataemia	0	(0.0)	2	(28.6)	2	(20.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)
Grade 3	0	(0.0)	1	(14.3)	1	(10.0)
Musculoskeletal and connective tissue disorders	1	(33.3)	0	(0.0)	1	(10.0)
Grade 1	1	(33.3)	0	(0.0)	1	(10.0)
Temporomandibular joint syndrome	1	(33.3)	0	(0.0)	1	(10.0)
Grade 1	1	(33.3)	0	(0.0)	1	(10.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	(0.0)	2	(28.6)	2	(20.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)
Cancer pain	0	(0.0)	2	(28.6)	2	(20.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)

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付録 2.7.4- 89　　有害事象（いずれかの投与群で発現割合 0%超）

011 試験（パート A）（安全性解析対象集団）（続き）

	MK-3475 2 mg/kg Q2W		MK-3475 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)
Nervous system disorders	0	(0.0)	2	(28.6)	2	(20.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Grade 4	0	(0.0)	1	(14.3)	1	(10.0)
Cerebral infarction	0	(0.0)	1	(14.3)	1	(10.0)
Grade 4	0	(0.0)	1	(14.3)	1	(10.0)
Hypersomnia	0	(0.0)	1	(14.3)	1	(10.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Respiratory, thoracic and mediastinal disorders	1	(33.3)	4	(57.1)	5	(50.0)
Grade 1	1	(33.3)	2	(28.6)	3	(30.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)
Grade 3	0	(0.0)	1	(14.3)	1	(10.0)
Dyspnoea	1	(33.3)	2	(28.6)	3	(30.0)
Grade 1	1	(33.3)	0	(0.0)	1	(10.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)
Grade 3	0	(0.0)	1	(14.3)	1	(10.0)
Dyspnoea exertional	0	(0.0)	1	(14.3)	1	(10.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Hypoxia	0	(0.0)	1	(14.3)	1	(10.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)
Pneumonitis	0	(0.0)	1	(14.3)	1	(10.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Skin and subcutaneous tissue disorders	0	(0.0)	6	(85.7)	6	(60.0)
Grade 1	0	(0.0)	5	(71.4)	5	(50.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)
Drug eruption	0	(0.0)	1	(14.3)	1	(10.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Dry skin	0	(0.0)	1	(14.3)	1	(10.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Rash	0	(0.0)	2	(28.6)	2	(20.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)
Rash maculo-papular	0	(0.0)	2	(28.6)	2	(20.0)
Grade 1	0	(0.0)	2	(28.6)	2	(20.0)
Urticaria	0	(0.0)	1	(14.3)	1	(10.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Vascular disorders	0	(0.0)	1	(14.3)	1	(10.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Embolism	0	(0.0)	1	(14.3)	1	(10.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)

Every patient is counted a single time for each applicable specific adverse event.　A patient with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title.
Only the highest reported grade of a given adverse event is counted for the individual patient.
Grades are based on CTCAE Version 4.0.
MedDRA preferred terms 'Malignant neoplasm progression' not related to the drug are excluded.

C Confidential

付録 2.7.4- 90　　副作用（いずれかの投与群で発現割合 0%超）

011 試験（パート A）（安全性解析対象集団）

	MK-3475 2 mg/kg Q2W		MK-3475 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	3		7		10	
with one or more adverse events	2	(66.7)	6	(85.7)	8	(80.0)
Grade 1	2	(66.7)	3	(42.9)	5	(50.0)
Grade 2	0	(0.0)	2	(28.6)	2	(20.0)
Grade 3	0	(0.0)	1	(14.3)	1	(10.0)
with no adverse events	1	(33.3)	1	(14.3)	2	(20.0)
Blood and lymphatic system disorders	0	(0.0)	2	(28.6)	2	(20.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)
Anaemia	0	(0.0)	1	(14.3)	1	(10.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)
Neutropenia	0	(0.0)	1	(14.3)	1	(10.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Thrombocytopenia	0	(0.0)	1	(14.3)	1	(10.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Gastrointestinal disorders	1	(33.3)	1	(14.3)	2	(20.0)
Grade 1	1	(33.3)	1	(14.3)	2	(20.0)
Nausea	1	(33.3)	1	(14.3)	2	(20.0)
Grade 1	1	(33.3)	1	(14.3)	2	(20.0)
General disorders and administration site conditions	2	(66.7)	2	(28.6)	4	(40.0)
Grade 1	2	(66.7)	2	(28.6)	4	(40.0)
Fatigue	1	(33.3)	0	(0.0)	1	(10.0)
Grade 1	1	(33.3)	0	(0.0)	1	(10.0)
Malaise	1	(33.3)	1	(14.3)	2	(20.0)
Grade 1	1	(33.3)	1	(14.3)	2	(20.0)
Pyrexia	1	(33.3)	1	(14.3)	2	(20.0)
Grade 1	1	(33.3)	1	(14.3)	2	(20.0)
Infections and infestations	0	(0.0)	1	(14.3)	1	(10.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)
Infection	0	(0.0)	1	(14.3)	1	(10.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)
Investigations	1	(33.3)	2	(28.6)	3	(30.0)
Grade 1	1	(33.3)	1	(14.3)	2	(20.0)
Grade 3	0	(0.0)	1	(14.3)	1	(10.0)

C Confidential

付録 2.7.4- 90　　副作用（いずれかの投与群で発現割合 0%超）
011 試験（パート A）（安全性解析対象集団）（続き）

	MK-3475 2 mg/kg Q2W		MK-3475 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)
Alanine aminotransferase increased	0	(0.0)	2	(28.6)	2	(20.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Grade 3	0	(0.0)	1	(14.3)	1	(10.0)
Aspartate aminotransferase increased	0	(0.0)	2	(28.6)	2	(20.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Grade 3	0	(0.0)	1	(14.3)	1	(10.0)
Blood cholesterol increased	1	(33.3)	0	(0.0)	1	(10.0)
Grade 1	1	(33.3)	0	(0.0)	1	(10.0)
Blood thyroid stimulating hormone increased	0	(0.0)	1	(14.3)	1	(10.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Weight decreased	0	(0.0)	1	(14.3)	1	(10.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)
Metabolism and nutrition disorders	1	(33.3)	2	(28.6)	3	(30.0)
Grade 1	1	(33.3)	0	(0.0)	1	(10.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)
Grade 3	0	(0.0)	1	(14.3)	1	(10.0)
Dehydration	0	(0.0)	1	(14.3)	1	(10.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)
Hyperglycaemia	0	(0.0)	1	(14.3)	1	(10.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)
Hyperkalaemia	0	(0.0)	1	(14.3)	1	(10.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)
Hypertriglyceridaemia	1	(33.3)	0	(0.0)	1	(10.0)
Grade 1	1	(33.3)	0	(0.0)	1	(10.0)
Hypokalaemia	0	(0.0)	1	(14.3)	1	(10.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)
Hyponatraemia	0	(0.0)	1	(14.3)	1	(10.0)
Grade 3	0	(0.0)	1	(14.3)	1	(10.0)
Respiratory, thoracic and mediastinal disorders	0	(0.0)	2	(28.6)	2	(20.0)
Grade 1	0	(0.0)	2	(28.6)	2	(20.0)
Dyspnoea exertional	0	(0.0)	1	(14.3)	1	(10.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Pneumonitis	0	(0.0)	1	(14.3)	1	(10.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Skin and subcutaneous tissue disorders	0	(0.0)	3	(42.9)	3	(30.0)
Grade 1	0	(0.0)	2	(28.6)	2	(20.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)
Drug eruption	0	(0.0)	1	(14.3)	1	(10.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)
Rash	0	(0.0)	1	(14.3)	1	(10.0)
Grade 2	0	(0.0)	1	(14.3)	1	(10.0)
Urticaria	0	(0.0)	1	(14.3)	1	(10.0)
Grade 1	0	(0.0)	1	(14.3)	1	(10.0)

Every patient is counted a single time for each applicable specific adverse event.　A patient with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title.
Only the highest reported grade of a given adverse event is counted for the individual patient.
Grades are based on CTCAE Version 4.0.

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付録 2.7.4- 91　　有害事象の要約

025 試験（安全性解析対象集団）（PD-L1 高発現）

Adverse Event Summary

Strongly Positive PD-L1 Subjects

(All Treated Set Population)

	MK-3475 10mg/kg Q3W	
	n	(%)
Subjects in population	12	
with one or more adverse events	12	(100.0)
with no adverse event	0	(0.0)
with drug-related† adverse events	9	(75.0)
with Grade 3- 5 adverse events	6	(50.0)
with Grade 3- 5 drug-related adverse events	3	(25.0)
with serious adverse events	3	(25.0)
with serious drug-related adverse events	3	(25.0)
who died	0	(0.0)
with drug-related death	0	(0.0)
discontinued‡ due to an adverse event	0	(0.0)
discontinued due to a drug-related adverse event	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
Grades are based on NCI CTCAE version 4.0.
MedDRA preferred terms 'Neoplasm Progression', 'Malignant Neoplasm Progression' and 'Disease Progression' not related to the drug is excluded.

Confidential

付録 2.7.4- 92　　有害事象（発現割合 0%超）

025 試験（安全性解析対象集団）（PD-L1 高発現）

Subjects With Adverse Events by All Toxicity Grades vs. Grades 3 – 5

(Incidence > 0%)

Strongly Positive PD-L1 Subjects

(All Treated Set Population)

	MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5	
	n	(%)	n	(%)
Subjects in population	12		12	
with one or more adverse events	12	(100.0)	6	(50.0)
with no adverse events	0	(0.0)	6	(50.0)
			0	(0.0)
Blood and lymphatic system disorders	**1**	**(8.3)**	**0**	**(0.0)**
Anaemia	1	(8.3)	0	(0.0)
Cardiac disorders	**1**	**(8.3)**	**0**	**(0.0)**
Sinus tachycardia	1	(8.3)	0	(0.0)
Ear and labyrinth disorders	**2**	**(16.7)**	**0**	**(0.0)**
Ear discomfort	1	(8.3)	0	(0.0)
Tinnitus	1	(8.3)	0	(0.0)
Endocrine disorders	**1**	**(8.3)**	**0**	**(0.0)**
Hyperparathyroidism	1	(8.3)	0	(0.0)
Eye disorders	**1**	**(8.3)**	**0**	**(0.0)**
Vitreous floaters	1	(8.3)	0	(0.0)
Gastrointestinal disorders	**4**	**(33.3)**	**1**	**(8.3)**
Abdominal pain	1	(8.3)	0	(0.0)
Abdominal pain upper	1	(8.3)	0	(0.0)
Colitis	1	(8.3)	0	(0.0)
Constipation	1	(8.3)	0	(0.0)
Diarrhoea	2	(16.7)	1	(8.3)
Dyspepsia	1	(8.3)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3 – 5
(Incidence > 0%)
Strongly Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5	
	n	(%)	n	(%)
Nausea	2	(16.7)	0	(0.0)
Stomatitis	1	(8.3)	0	(0.0)
Vomiting	1	(8.3)	0	(0.0)
General disorders and administration site conditions	**8**	**(66.7)**	**0**	**(0.0)**
Fatigue	1	(8.3)	0	(0.0)
Injection site reaction	1	(8.3)	0	(0.0)
Malaise	4	(33.3)	0	(0.0)
Oedema peripheral	1	(8.3)	0	(0.0)
Pyrexia	4	(33.3)	0	(0.0)
Thirst	1	(8.3)	0	(0.0)
Hepatobiliary disorders	**1**	**(8.3)**	**0**	**(0.0)**
Liver disorder	1	(8.3)	0	(0.0)
Infections and infestations	**7**	**(58.3)**	**0**	**(0.0)**
Bronchitis	1	(8.3)	0	(0.0)
Diverticulitis	1	(8.3)	0	(0.0)
Enterocolitis infectious	1	(8.3)	0	(0.0)
Influenza	1	(8.3)	0	(0.0)
Lung infection	1	(8.3)	0	(0.0)
Nasopharyngitis	1	(8.3)	0	(0.0)
Rhinitis	1	(8.3)	0	(0.0)
Upper respiratory tract infection	1	(8.3)	0	(0.0)
Urinary tract infection	1	(8.3)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3 – 5
(Incidence > 0%)
Strongly Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5	
	n	(%)	n	(%)
Investigations	**5**	**(41.7)**	**3**	**(25.0)**
Alanine aminotransferase increased	3	(25.0)	1	(8.3)
Aspartate aminotransferase increased	3	(25.0)	1	(8.3)
Blood alkaline phosphatase increased	1	(8.3)	0	(0.0)
Blood lactate dehydrogenase increased	1	(8.3)	0	(0.0)
Blood phosphorus decreased	1	(8.3)	1	(8.3)
Blood phosphorus increased	1	(8.3)	0	(0.0)
Blood triglycerides increased	1	(8.3)	1	(8.3)
Gamma-glutamyltransferase increased	1	(8.3)	1	(8.3)
Weight decreased	3	(25.0)	0	(0.0)
White blood cell count decreased	1	(8.3)	0	(0.0)
Metabolism and nutrition disorders	**5**	**(41.7)**	**1**	**(8.3)**
Decreased appetite	4	(33.3)	0	(0.0)
Hypercalcaemia	1	(8.3)	1	(8.3)
Hyperkalaemia	1	(8.3)	0	(0.0)
Hyponatraemia	1	(8.3)	0	(0.0)
Musculoskeletal and connective tissue disorders	**1**	**(8.3)**	**0**	**(0.0)**
Arthritis	1	(8.3)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts	**2**	**(16.7)**	**1**	**(8.3)**
Lung neoplasm malignant	1	(8.3)	0	(0.0)
Oesophageal carcinoma	1	(8.3)	1	(8.3)
Nervous system disorders	**5**	**(41.7)**	**0**	**(0.0)**

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3 – 5
(Incidence > 0%)
Strongly Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5	
	n	(%)	n	(%)
Cerebrovascular accident	1	(8.3)	0	(0.0)
Dizziness	1	(8.3)	0	(0.0)
Dysgeusia	1	(8.3)	0	(0.0)
Headache	2	(16.7)	0	(0.0)
Nervous system disorder	1	(8.3)	0	(0.0)
Sciatica	1	(8.3)	0	(0.0)
Psychiatric disorders	**2**	**(16.7)**	**0**	**(0.0)**
Anxiety	1	(8.3)	0	(0.0)
Nervousness	1	(8.3)	0	(0.0)
Renal and urinary disorders	**3**	**(25.0)**	**0**	**(0.0)**
Haemoglobinuria	1	(8.3)	0	(0.0)
Hypertonic bladder	1	(8.3)	0	(0.0)
Proteinuria	1	(8.3)	0	(0.0)
Renal impairment	1	(8.3)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**3**	**(25.0)**	**1**	**(8.3)**
Atelectasis	1	(8.3)	1	(8.3)
Dyspnoea	2	(16.7)	0	(0.0)
Haemoptysis	1	(8.3)	0	(0.0)
Pleural effusion	1	(8.3)	0	(0.0)
Skin and subcutaneous tissue disorders	**5**	**(41.7)**	**0**	**(0.0)**
Dermatitis acneiform	2	(16.7)	0	(0.0)
Dry skin	1	(8.3)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3 – 5
(Incidence > 0%)
Strongly Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5	
	n	(%)	n	(%)
Pruritus	2	(16.7)	0	(0.0)
Rash	2	(16.7)	0	(0.0)
Vascular disorders	**4**	**(33.3)**	**0**	**(0.0)**
Hypertension	2	(16.7)	0	(0.0)
Hypotension	1	(8.3)	0	(0.0)
Phlebitis	1	(8.3)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
Percentage is based on the number of subjects in population.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Grades are based on NCI CTCAE version 4.0.
MedDRA preferred terms ‘Neoplasm Progression’, 'Malignant Neoplasm Progression' and ‘Disease Progression’ not related to the drug is excluded.

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付録 2.7.4- 93　　副作用（発現割合 0%超）

025 試験（安全性解析対象集団）（PD-L1 高発現）

Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3 – 5

(Incidence > 0%)

Strongly Positive PD-L1 Subjects

(All Treated Set Population)

	MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5	
	n	(%)	n	(%)
Subjects in population	12		12	
with one or more adverse events	9	(75.0)	3	(25.0)
with no adverse events	3	(25.0)	9	(75.0)
			0	(0.0)
Cardiac disorders	**1**	**(8.3)**	**0**	**(0.0)**
Sinus tachycardia	1	(8.3)	0	(0.0)
Ear and labyrinth disorders	**1**	**(8.3)**	**0**	**(0.0)**
Tinnitus	1	(8.3)	0	(0.0)
Endocrine disorders	**1**	**(8.3)**	**0**	**(0.0)**
Hyperparathyroidism	1	(8.3)	0	(0.0)
Eye disorders	**1**	**(8.3)**	**0**	**(0.0)**
Vitreous floaters	1	(8.3)	0	(0.0)
Gastrointestinal disorders	**2**	**(16.7)**	**1**	**(8.3)**
Colitis	1	(8.3)	0	(0.0)
Diarrhoea	1	(8.3)	1	(8.3)
Dyspepsia	1	(8.3)	0	(0.0)
Nausea	1	(8.3)	0	(0.0)
General disorders and administration site conditions	**3**	**(25.0)**	**0**	**(0.0)**
Malaise	3	(25.0)	0	(0.0)
Pyrexia	1	(8.3)	0	(0.0)
Hepatobiliary disorders	**1**	**(8.3)**	**0**	**(0.0)**
Liver disorder	1	(8.3)	0	(0.0)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3 – 5
(Incidence > 0%)
Strongly Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5	
	n	(%)	n	(%)
Infections and infestations	**3**	**(25.0)**	**0**	**(0.0)**
Diverticulitis	1	(8.3)	0	(0.0)
Enterocolitis infectious	1	(8.3)	0	(0.0)
Rhinitis	1	(8.3)	0	(0.0)
Upper respiratory tract infection	1	(8.3)	0	(0.0)
Investigations	**3**	**(25.0)**	**2**	**(16.7)**
Alanine aminotransferase increased	2	(16.7)	1	(8.3)
Aspartate aminotransferase increased	2	(16.7)	1	(8.3)
Blood lactate dehydrogenase increased	1	(8.3)	0	(0.0)
Blood phosphorus decreased	1	(8.3)	1	(8.3)
Blood phosphorus increased	1	(8.3)	0	(0.0)
Weight decreased	2	(16.7)	0	(0.0)
White blood cell count decreased	1	(8.3)	0	(0.0)
Metabolism and nutrition disorders	**2**	**(16.7)**	**0**	**(0.0)**
Decreased appetite	1	(8.3)	0	(0.0)
Hyponatraemia	1	(8.3)	0	(0.0)
Musculoskeletal and connective tissue disorders	**1**	**(8.3)**	**0**	**(0.0)**
Arthritis	1	(8.3)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts	**1**	**(8.3)**	**1**	**(8.3)**
Oesophageal carcinoma	1	(8.3)	1	(8.3)
Nervous system disorders	**1**	**(8.3)**	**0**	**(0.0)**
Cerebrovascular accident	1	(8.3)	0	(0.0)

C Confidential

Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3 – 5
(Incidence > 0%)
Strongly Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5	
	n	(%)	n	(%)
Psychiatric disorders	**1**	**(8.3)**	**0**	**(0.0)**
Nervousness	1	(8.3)	0	(0.0)
Renal and urinary disorders	**2**	**(16.7)**	**0**	**(0.0)**
Haemoglobinuria	1	(8.3)	0	(0.0)
Proteinuria	1	(8.3)	0	(0.0)
Renal impairment	1	(8.3)	0	(0.0)
Skin and subcutaneous tissue disorders	**5**	**(41.7)**	**0**	**(0.0)**
Dermatitis acneiform	2	(16.7)	0	(0.0)
Pruritus	2	(16.7)	0	(0.0)
Rash	2	(16.7)	0	(0.0)
Vascular disorders	**2**	**(16.7)**	**0**	**(0.0)**
Hypertension	1	(8.3)	0	(0.0)
Hypotension	1	(8.3)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
Percentage is based on the number of subjects in population.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Grades are based on NCI CTCAE version 4.0.
MedDRA preferred terms ‘Neoplasm Progression’, 'Malignant Neoplasm Progression' and ‘Disease Progression’ not related to the drug is excluded.

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付録 2.7.4- 94　　有害事象の要約

010 試験（日本人安全性解析対象集団）（PD-L1 高発現）

Adverse Event Summary
Subjects with TPS ≥ 50%
APaT Japan Population

	Docetaxel 75 mg/m2 Q3W		MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W	
	n	(%)	n	(%)	n	(%)
Subjects in population	11		10		13	
with one or more adverse events	10	(90.9)	10	(100.0)	13	(100.0)
with no adverse event	1	(9.1)	0	(0.0)	0	(0.0)
with drug-related† adverse events	10	(90.9)	9	(90.0)	11	(84.6)
with toxicity grade 3-5 adverse events	10	(90.9)	5	(50.0)	8	(61.5)
with toxicity grade 3-5 drug-related adverse events	10	(90.9)	2	(20.0)	5	(38.5)
with serious adverse events	5	(45.5)	3	(30.0)	8	(61.5)
with serious drug-related adverse events	2	(18.2)	2	(20.0)	4	(30.8)
who died	2	(18.2)	0	(0.0)	1	(7.7)
who died due to a drug-related adverse event	1	(9.1)	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	2	(18.2)	0	(0.0)	1	(7.7)
discontinued due to a drug-related adverse event	2	(18.2)	0	(0.0)	1	(7.7)
discontinued due to a serious adverse event	2	(18.2)	0	(0.0)	1	(7.7)
discontinued due to a serious drug-related adverse event	2	(18.2)	0	(0.0)	1	(7.7)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
MedDRA preferred terms 'Neoplasm Progression' ,'Malignant Neoplasm Progression'　and 'Disease Progression' not related to the drug are excluded.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 30SEP2015)

Data Source:　[16.4]

C Confidential

付録 2.7.4- 95　　有害事象の要約

010 試験（MK-3475 併合、日本人安全性解析対象集団）（PD-L1 高発現）

Adverse Event Summary
MK-3475 Treatment Groups Pooled
Subjects with TPS ≥ 50%
APaT Japan Population

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled	
	n	(%)	n	(%)
Subjects in population	11		23	
with one or more adverse events	10	(90.9)	23	(100.0)
with no adverse event	1	(9.1)	0	(0.0)
with drug-related† adverse events	10	(90.9)	20	(87.0)
with toxicity grade 3-5 adverse events	10	(90.9)	13	(56.5)
with toxicity grade 3-5 drug-related adverse events	10	(90.9)	7	(30.4)
with serious adverse events	5	(45.5)	11	(47.8)
with serious drug-related adverse events	2	(18.2)	6	(26.1)
who died	2	(18.2)	1	(4.3)
who died due to a drug-related adverse event	1	(9.1)	0	(0.0)
discontinued‡ due to an adverse event	2	(18.2)	1	(4.3)
discontinued due to a drug-related adverse event	2	(18.2)	1	(4.3)
discontinued due to a serious adverse event	2	(18.2)	1	(4.3)
discontinued due to a serious drug-related adverse event	2	(18.2)	1	(4.3)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
MedDRA preferred terms 'Neoplasm Progression' ,'Malignant Neoplasm Progression'　and 'Disease Progression' not related to the drug are excluded.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 30SEP2015)

Data Source:　[16.4]

Confidential

付録 2.7.4- 96　　有害事象の要約

010 試験（日本人安全性解析対象集団）（PD-L1 低発現）

Adverse Event Summary
Subjects with 1% ≤ TPS < 50%
APaT Japan Population

	Docetaxel 75 mg/m2 Q3W		MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W	
	n	(%)	n	(%)	n	(%)
Subjects in population	16		18		21	
with one or more adverse events	16	(100.0)	18	(100.0)	21	(100.0)
with no adverse event	0	(0.0)	0	(0.0)	0	(0.0)
with drug-related† adverse events	16	(100.0)	13	(72.2)	19	(90.5)
with toxicity grade 3-5 adverse events	13	(81.3)	7	(38.9)	8	(38.1)
with toxicity grade 3-5 drug-related adverse events	13	(81.3)	2	(11.1)	5	(23.8)
with serious adverse events	2	(12.5)	4	(22.2)	7	(33.3)
with serious drug-related adverse events	2	(12.5)	3	(16.7)	5	(23.8)
who died	1	(6.3)	0	(0.0)	1	(4.8)
who died due to a drug-related adverse event	1	(6.3)	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	4	(25.0)	1	(5.6)	2	(9.5)
discontinued due to a drug-related adverse event	4	(25.0)	0	(0.0)	1	(4.8)
discontinued due to a serious adverse event	0	(0.0)	1	(5.6)	1	(4.8)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	1	(4.8)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
MedDRA preferred terms 'Neoplasm Progression' ,'Malignant Neoplasm Progression'　and 'Disease Progression' not related to the drug are excluded.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 30SEP2015)

Data Source:　[16.4]

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付録 2.7.4- 97　　有害事象（いずれかの投与群で発現割合 0%超）

010 試験（日本人安全性解析対象集団）（PD-L1 発現陽性）

Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	27				28				34			
with one or more adverse events	26	(96.3)	23	(85.2)	28	(100.0)	12	(42.9)	34	(100.0)	16	(47.1)
with no adverse events	1	(3.7)	4	(14.8)	0	(0.0)	16	(57.1)	0	(0.0)	18	(52.9)
Blood and lymphatic system disorders	**18**	**(66.7)**	**13**	**(48.1)**	**1**	**(3.6)**	**0**	**(0.0)**	**5**	**(14.7)**	**2**	**(5.9)**
Anaemia	6	(22.2)	1	(3.7)	1	(3.6)	0	(0.0)	4	(11.8)	2	(5.9)
Febrile neutropenia	3	(11.1)	3	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Leukopenia	2	(7.4)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Lymphopenia	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	2	(5.9)	0	(0.0)
Neutropenia	11	(40.7)	11	(40.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiac disorders	**3**	**(11.1)**	**2**	**(7.4)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(2.9)**	**1**	**(2.9)**
Atrial fibrillation	2	(7.4)	2	(7.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Atrioventricular block complete	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	1	(2.9)
Cardiac failure acute	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Supraventricular tachycardia	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Ear and labyrinth disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(2.9)**	**0**	**(0.0)**
Vertigo	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Endocrine disorders	**0**	**(0.0)**	**0**	**(0.0)**	**5**	**(17.9)**	**1**	**(3.6)**	**3**	**(8.8)**	**2**	**(5.9)**

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Endocrine disorders	**0**	**(0.0)**	**0**	**(0.0)**	**5**	**(17.9)**	**1**	**(3.6)**	**3**	**(8.8)**	**2**	**(5.9)**
Adrenal insufficiency	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	1	(2.9)	1	(2.9)
Hyperthyroidism	0	(0.0)	0	(0.0)	2	(7.1)	0	(0.0)	0	(0.0)	0	(0.0)
Hypopituitarism	0	(0.0)	0	(0.0)	1	(3.6)	1	(3.6)	1	(2.9)	1	(2.9)
Hypothalamo-pituitary disorder	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hypothyroidism	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	2	(5.9)	0	(0.0)
Eye disorders	**2**	**(7.4)**	**0**	**(0.0)**	**3**	**(10.7)**	**0**	**(0.0)**	**1**	**(2.9)**	**0**	**(0.0)**
Cataract	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Dry eye	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	1	(2.9)	0	(0.0)
Lacrimation increased	2	(7.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Vitreous floaters	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Gastrointestinal disorders	**15**	**(55.6)**	**2**	**(7.4)**	**18**	**(64.3)**	**2**	**(7.1)**	**17**	**(50.0)**	**3**	**(8.8)**
Abdominal distension	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Abdominal pain lower	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Abdominal pain upper	0	(0.0)	0	(0.0)	2	(7.1)	0	(0.0)	1	(2.9)	0	(0.0)
Colitis	0	(0.0)	0	(0.0)	1	(3.6)	1	(3.6)	1	(2.9)	1	(2.9)
Constipation	2	(7.4)	0	(0.0)	4	(14.3)	0	(0.0)	3	(8.8)	1	(2.9)
Diarrhoea	5	(18.5)	1	(3.7)	2	(7.1)	0	(0.0)	8	(23.5)	0	(0.0)
Dyspepsia	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Faecaloma	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Gastritis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Ileus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	1	(2.9)
Nausea	6	(22.2)	0	(0.0)	5	(17.9)	0	(0.0)	6	(17.6)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Gastrointestinal disorders	**15**	**(55.6)**	**2**	**(7.4)**	**18**	**(64.3)**	**2**	**(7.1)**	**17**	**(50.0)**	**3**	**(8.8)**
Pancreatitis	0	(0.0)	0	(0.0)	1	(3.6)	1	(3.6)	0	(0.0)	0	(0.0)
Periodontal disease	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Stomatitis	7	(25.9)	1	(3.7)	6	(21.4)	0	(0.0)	2	(5.9)	0	(0.0)
Toothache	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Vomiting	1	(3.7)	0	(0.0)	2	(7.1)	0	(0.0)	3	(8.8)	0	(0.0)
General disorders and administration site conditions	**21**	**(77.8)**	**2**	**(7.4)**	**11**	**(39.3)**	**0**	**(0.0)**	**19**	**(55.9)**	**0**	**(0.0)**
Chest pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(5.9)	0	(0.0)
Chills	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Fatigue	6	(22.2)	1	(3.7)	3	(10.7)	0	(0.0)	3	(8.8)	0	(0.0)
Infusion site vasculitis	2	(7.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Malaise	7	(25.9)	0	(0.0)	6	(21.4)	0	(0.0)	10	(29.4)	0	(0.0)
Non-cardiac chest pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Oedema	3	(11.1)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Oedema peripheral	4	(14.8)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pyrexia	6	(22.2)	0	(0.0)	4	(14.3)	0	(0.0)	6	(17.6)	0	(0.0)
Hepatobiliary disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(2.9)**	**0**	**(0.0)**
Hepatic function abnormal	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Infections and infestations	**14**	**(51.9)**	**4**	**(14.8)**	**6**	**(21.4)**	**1**	**(3.6)**	**11**	**(32.4)**	**5**	**(14.7)**
Bacteraemia	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Bronchitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Infections and infestations	**14**	**(51.9)**	**4**	**(14.8)**	**6**	**(21.4)**	**1**	**(3.6)**	**11**	**(32.4)**	**5**	**(14.7)**
Clostridium difficile infection	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Conjunctivitis	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
External ear cellulitis	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Herpes simplex	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Herpes zoster	1	(3.7)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Infected dermal cyst	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Influenza	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Lung infection	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Nail infection	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nasopharyngitis	4	(14.8)	1	(3.7)	1	(3.6)	0	(0.0)	2	(5.9)	0	(0.0)
Onychomycosis	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Oral candidiasis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Osteomyelitis	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)	1	(2.9)	1	(2.9)
Otitis media acute	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Periodontitis	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pharyngitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Pneumonia	1	(3.7)	0	(0.0)	1	(3.6)	1	(3.6)	2	(5.9)	2	(5.9)
Pneumonia bacterial	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)	1	(2.9)	1	(2.9)
Pneumonia pneumococcal	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	1	(2.9)
Septic shock	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Staphylococcal infection	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Tracheitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Trichophytosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Infections and infestations	**14**	**(51.9)**	**4**	**(14.8)**	**6**	**(21.4)**	**1**	**(3.6)**	**11**	**(32.4)**	**5**	**(14.7)**
Upper respiratory tract infection	2	(7.4)	0	(0.0)	2	(7.1)	0	(0.0)	1	(2.9)	0	(0.0)
Injury, poisoning and procedural complications	**3**	**(11.1)**	**1**	**(3.7)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(8.8)**	**0**	**(0.0)**
Arthropod bite	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Contusion	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(5.9)	0	(0.0)
Skin abrasion	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Traumatic intracranial haemorrhage	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Investigations	**18**	**(66.7)**	**15**	**(55.6)**	**10**	**(35.7)**	**2**	**(7.1)**	**14**	**(41.2)**	**2**	**(5.9)**
Alanine aminotransferase increased	2	(7.4)	0	(0.0)	4	(14.3)	0	(0.0)	2	(5.9)	0	(0.0)
Aspartate aminotransferase increased	1	(3.7)	0	(0.0)	3	(10.7)	0	(0.0)	0	(0.0)	0	(0.0)
Blood alkaline phosphatase increased	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	2	(5.9)	0	(0.0)
Blood bilirubin increased	1	(3.7)	0	(0.0)	1	(3.6)	0	(0.0)	1	(2.9)	0	(0.0)
Blood creatine phosphokinase increased	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Blood creatinine increased	1	(3.7)	0	(0.0)	1	(3.6)	0	(0.0)	4	(11.8)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**18**	**(66.7)**	**15**	**(55.6)**	**10**	**(35.7)**	**2**	**(7.1)**	**14**	**(41.2)**	**2**	**(5.9)**
Blood thyroid stimulating hormone increased	0	(0.0)	0	(0.0)	2	(7.1)	0	(0.0)	1	(2.9)	0	(0.0)
Blood urea increased	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Blood uric acid increased	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
C-reactive protein increased	1	(3.7)	0	(0.0)	1	(3.6)	0	(0.0)	1	(2.9)	0	(0.0)
Computerised tomogram thorax abnormal	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Eosinophil count increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Gamma-glutamyltransferase increased	0	(0.0)	0	(0.0)	2	(7.1)	1	(3.6)	2	(5.9)	0	(0.0)
Lymphocyte count decreased	2	(7.4)	1	(3.7)	1	(3.6)	1	(3.6)	3	(8.8)	2	(5.9)
Neutrophil count decreased	11	(40.7)	10	(37.0)	1	(3.6)	0	(0.0)	2	(5.9)	0	(0.0)
Platelet count decreased	1	(3.7)	1	(3.7)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Thyroxine free increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Tri-iodothyronine decreased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Weight decreased	2	(7.4)	0	(0.0)	2	(7.1)	0	(0.0)	3	(8.8)	0	(0.0)
White blood cell count decreased	15	(55.6)	10	(37.0)	0	(0.0)	0	(0.0)	2	(5.9)	0	(0.0)
White blood cell count increased	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Metabolism and nutrition disorders	**14**	**(51.9)**	**5**	**(18.5)**	**12**	**(42.9)**	**4**	**(14.3)**	**8**	**(23.5)**	**3**	**(8.8)**
Decreased appetite	9	(33.3)	3	(11.1)	7	(25.0)	2	(7.1)	7	(20.6)	0	(0.0)
Dehydration	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)	2	(5.9)	0	(0.0)
Diabetes mellitus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(5.9)	1	(2.9)
Hypercalcaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Hyperglycaemia	0	(0.0)	0	(0.0)	1	(3.6)	1	(3.6)	0	(0.0)	0	(0.0)
Hyperkalaemia	1	(3.7)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hyperlipidaemia	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hypernatraemia	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hypertriglyceridaemia	1	(3.7)	1	(3.7)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hyperuricaemia	2	(7.4)	0	(0.0)	1	(3.6)	0	(0.0)	1	(2.9)	0	(0.0)
Hypoalbuminaemia	1	(3.7)	0	(0.0)	2	(7.1)	0	(0.0)	2	(5.9)	0	(0.0)
Hypocalcaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	1	(2.9)
Hypokalaemia	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Hyponatraemia	1	(3.7)	0	(0.0)	1	(3.6)	1	(3.6)	1	(2.9)	1	(2.9)
Hypophosphataemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	1	(2.9)
Musculoskeletal and connective tissue disorders	**13**	**(48.1)**	**0**	**(0.0)**	**6**	**(21.4)**	**0**	**(0.0)**	**4**	**(11.8)**	**0**	**(0.0)**
Arthralgia	7	(25.9)	0	(0.0)	2	(7.1)	0	(0.0)	0	(0.0)	0	(0.0)
Arthritis	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Back pain	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	2	(5.9)	0	(0.0)
Flank pain	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Muscle spasms	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Musculoskeletal and connective tissue disorders	**13**	**(48.1)**	**0**	**(0.0)**	**6**	**(21.4)**	**0**	**(0.0)**	**4**	**(11.8)**	**0**	**(0.0)**
Musculoskeletal pain	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Musculoskeletal stiffness	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Myalgia	5	(18.5)	0	(0.0)	2	(7.1)	0	(0.0)	1	(2.9)	0	(0.0)
Pain in extremity	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Periarthritis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Synovial cyst	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1**	**(3.7)**	**0**	**(0.0)**	**3**	**(10.7)**	**3**	**(10.7)**	**3**	**(8.8)**	**1**	**(2.9)**
Cancer pain	0	(0.0)	0	(0.0)	1	(3.6)	1	(3.6)	1	(2.9)	1	(2.9)
Gastric cancer	0	(0.0)	0	(0.0)	1	(3.6)	1	(3.6)	0	(0.0)	0	(0.0)
Malignant pleural effusion	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Tumour pain	1	(3.7)	0	(0.0)	1	(3.6)	1	(3.6)	2	(5.9)	0	(0.0)
Nervous system disorders	**13**	**(48.1)**	**0**	**(0.0)**	**3**	**(10.7)**	**0**	**(0.0)**	**10**	**(29.4)**	**0**	**(0.0)**
Cerebral ischaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Dizziness	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dysarthria	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dysgeusia	7	(25.9)	0	(0.0)	0	(0.0)	0	(0.0)	4	(11.8)	0	(0.0)
Headache	1	(3.7)	0	(0.0)	3	(10.7)	0	(0.0)	3	(8.8)	0	(0.0)
Hypoaesthesia	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Nervous system disorders	**13**	**(48.1)**	**0**	**(0.0)**	**3**	**(10.7)**	**0**	**(0.0)**	**10**	**(29.4)**	**0**	**(0.0)**
Neuropathy peripheral	4	(14.8)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Peripheral motor neuropathy	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral sensory neuropathy	3	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Post herpetic neuralgia	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Sciatica	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Psychiatric disorders	**3**	**(11.1)**	**0**	**(0.0)**	**1**	**(3.6)**	**0**	**(0.0)**	**4**	**(11.8)**	**1**	**(2.9)**
Completed suicide	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	1	(2.9)
Delirium	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Insomnia	2	(7.4)	0	(0.0)	1	(3.6)	0	(0.0)	3	(8.8)	0	(0.0)
Renal and urinary disorders	**1**	**(3.7)**	**1**	**(3.7)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(5.9)**	**0**	**(0.0)**
Acute kidney injury	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Proteinuria	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Renal impairment	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**13**	**(48.1)**	**3**	**(11.1)**	**9**	**(32.1)**	**1**	**(3.6)**	**10**	**(29.4)**	**2**	**(5.9)**
Bronchostenosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	1	(2.9)
Chronic obstructive pulmonary disease	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Cough	1	(3.7)	0	(0.0)	2	(7.1)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Respiratory, thoracic and mediastinal disorders	**13**	**(48.1)**	**3**	**(11.1)**	**9**	**(32.1)**	**1**	**(3.6)**	**10**	**(29.4)**	**2**	**(5.9)**
Dyspnoea	5	(18.5)	2	(7.4)	1	(3.6)	1	(3.6)	3	(8.8)	0	(0.0)
Epistaxis	1	(3.7)	0	(0.0)	2	(7.1)	0	(0.0)	0	(0.0)	0	(0.0)
Haemoptysis	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	2	(5.9)	0	(0.0)
Hiccups	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Interstitial lung disease	2	(7.4)	1	(3.7)	1	(3.6)	0	(0.0)	1	(2.9)	0	(0.0)
Nasal discomfort	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Oropharyngeal pain	0	(0.0)	0	(0.0)	2	(7.1)	0	(0.0)	0	(0.0)	0	(0.0)
Pleural effusion	1	(3.7)	0	(0.0)	1	(3.6)	0	(0.0)	1	(2.9)	0	(0.0)
Pneumonia aspiration	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonitis	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	1	(2.9)
Productive cough	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Pulmonary haemorrhage	2	(7.4)	1	(3.7)	0	(0.0)	0	(0.0)	1	(2.9)	1	(2.9)
Respiratory failure	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Rhinitis allergic	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(5.9)	0	(0.0)
Upper respiratory tract inflammation	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	1	(2.9)	0	(0.0)
Skin and subcutaneous tissue disorders	**18**	**(66.7)**	**1**	**(3.7)**	**14**	**(50.0)**	**0**	**(0.0)**	**17**	**(50.0)**	**2**	**(5.9)**
Alopecia	12	(44.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dermatitis bullous	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Drug eruption	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	1	(2.9)
Dry skin	2	(7.4)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Eczema	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**18**	**(66.7)**	**1**	**(3.7)**	**14**	**(50.0)**	**0**	**(0.0)**	**17**	**(50.0)**	**2**	**(5.9)**
Erythema multiforme	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Nail discolouration	2	(7.4)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Nail disorder	2	(7.4)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Nail ridging	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Night sweats	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Onychomadesis	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Palmar-plantar erythrodysaesthesia syndrome	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pruritus	2	(7.4)	1	(3.7)	4	(14.3)	0	(0.0)	7	(20.6)	0	(0.0)
Rash	6	(22.2)	0	(0.0)	7	(25.0)	0	(0.0)	9	(26.5)	0	(0.0)
Rash maculo-papular	0	(0.0)	0	(0.0)	2	(7.1)	0	(0.0)	2	(5.9)	0	(0.0)
Skin fissures	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Skin hyperpigmentation	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Skin induration	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Skin ulcer	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Urticaria	3	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	1	(2.9)
Xeroderma	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Vascular disorders	**2**	**(7.4)**	**0**	**(0.0)**	**1**	**(3.6)**	**0**	**(0.0)**	**4**	**(11.8)**	**2**	**(5.9)**
Hypertension	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	2	(5.9)	1	(2.9)
Hypotension	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral ischaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	1	(2.9)
Phlebitis	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Vascular disorders	**2**	**(7.4)**	**0**	**(0.0)**	**1**	**(3.6)**	**0**	**(0.0)**	**4**	**(11.8)**	**2**	**(5.9)**
Venous thrombosis limb	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
Adverse event terms are from MedDRA Version 18.0.
(Database Cutoff Date: &cutoff).

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付録 2.7.4- 98　　有害事象（いずれかの投与群で発現割合 0%超）

010 試験（MK-3475 併合、日本人安全性解析対象集団）（PD-L1 発現陽性）
Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	27				62			
with one or more adverse events	26	(96.3)	23	(85.2)	62	(100.0)	28	(45.2)
with no adverse events	1	(3.7)	4	(14.8)	0	(0.0)	34	(54.8)
Blood and lymphatic system disorders	**18**	**(66.7)**	**13**	**(48.1)**	**6**	**(9.7)**	**2**	**(3.2)**
Anaemia	6	(22.2)	1	(3.7)	5	(8.1)	2	(3.2)
Febrile neutropenia	3	(11.1)	3	(11.1)	0	(0.0)	0	(0.0)
Leukopenia	2	(7.4)	1	(3.7)	0	(0.0)	0	(0.0)
Lymphopenia	1	(3.7)	0	(0.0)	2	(3.2)	0	(0.0)
Neutropenia	11	(40.7)	11	(40.7)	0	(0.0)	0	(0.0)
Cardiac disorders	**3**	**(11.1)**	**2**	**(7.4)**	**1**	**(1.6)**	**1**	**(1.6)**
Atrial fibrillation	2	(7.4)	2	(7.4)	0	(0.0)	0	(0.0)
Atrioventricular block complete	0	(0.0)	0	(0.0)	1	(1.6)	1	(1.6)
Cardiac failure acute	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)
Supraventricular tachycardia	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Ear and labyrinth disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(1.6)**	**0**	**(0.0)**
Vertigo	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Endocrine disorders	**0**	**(0.0)**	**0**	**(0.0)**	**8**	**(12.9)**	**3**	**(4.8)**
Adrenal insufficiency	0	(0.0)	0	(0.0)	2	(3.2)	1	(1.6)
Hyperthyroidism	0	(0.0)	0	(0.0)	2	(3.2)	0	(0.0)
Hypopituitarism	0	(0.0)	0	(0.0)	2	(3.2)	2	(3.2)
Hypothalamo-pituitary disorder	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Hypothyroidism	0	(0.0)	0	(0.0)	3	(4.8)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Eye disorders	**2**	**(7.4)**	**0**	**(0.0)**	**4**	**(6.5)**	**0**	**(0.0)**
Cataract	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Dry eye	0	(0.0)	0	(0.0)	2	(3.2)	0	(0.0)
Lacrimation increased	2	(7.4)	0	(0.0)	0	(0.0)	0	(0.0)
Vitreous floaters	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Gastrointestinal disorders	**15**	**(55.6)**	**2**	**(7.4)**	**35**	**(56.5)**	**5**	**(8.1)**
Abdominal distension	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Abdominal pain lower	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Abdominal pain upper	0	(0.0)	0	(0.0)	3	(4.8)	0	(0.0)
Colitis	0	(0.0)	0	(0.0)	2	(3.2)	2	(3.2)
Constipation	2	(7.4)	0	(0.0)	7	(11.3)	1	(1.6)
Diarrhoea	5	(18.5)	1	(3.7)	10	(16.1)	0	(0.0)
Dyspepsia	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Faecaloma	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Gastritis	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Ileus	0	(0.0)	0	(0.0)	1	(1.6)	1	(1.6)
Nausea	6	(22.2)	0	(0.0)	11	(17.7)	0	(0.0)
Pancreatitis	0	(0.0)	0	(0.0)	1	(1.6)	1	(1.6)
Periodontal disease	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Stomatitis	7	(25.9)	1	(3.7)	8	(12.9)	0	(0.0)
Toothache	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Vomiting	1	(3.7)	0	(0.0)	5	(8.1)	0	(0.0)
General disorders and administration site conditions	**21**	**(77.8)**	**2**	**(7.4)**	**30**	**(48.4)**	**0**	**(0.0)**

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
General disorders and administration site conditions	**21**	**(77.8)**	**2**	**(7.4)**	**30**	**(48.4)**	**0**	**(0.0)**
Chest pain	0	(0.0)	0	(0.0)	2	(3.2)	0	(0.0)
Chills	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Fatigue	6	(22.2)	1	(3.7)	6	(9.7)	0	(0.0)
Infusion site vasculitis	2	(7.4)	0	(0.0)	0	(0.0)	0	(0.0)
Malaise	7	(25.9)	0	(0.0)	16	(25.8)	0	(0.0)
Non-cardiac chest pain	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Oedema	3	(11.1)	1	(3.7)	0	(0.0)	0	(0.0)
Oedema peripheral	4	(14.8)	0	(0.0)	0	(0.0)	0	(0.0)
Pyrexia	6	(22.2)	0	(0.0)	10	(16.1)	0	(0.0)
Hepatobiliary disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(1.6)**	**0**	**(0.0)**
Hepatic function abnormal	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Infections and infestations	**14**	**(51.9)**	**4**	**(14.8)**	**17**	**(27.4)**	**6**	**(9.7)**
Bacteraemia	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)
Bronchitis	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Clostridium difficile infection	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)
Conjunctivitis	1	(3.7)	0	(0.0)	1	(1.6)	0	(0.0)
External ear cellulitis	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)
Herpes simplex	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Herpes zoster	1	(3.7)	0	(0.0)	1	(1.6)	0	(0.0)
Infected dermal cyst	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Influenza	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Lung infection	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Infections and infestations	**14**	**(51.9)**	**4**	**(14.8)**	**17**	**(27.4)**	**6**	**(9.7)**
Nail infection	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Nasopharyngitis	4	(14.8)	1	(3.7)	3	(4.8)	0	(0.0)
Onychomycosis	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Oral candidiasis	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Osteomyelitis	1	(3.7)	1	(3.7)	1	(1.6)	1	(1.6)
Otitis media acute	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Periodontitis	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Pharyngitis	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Pneumonia	1	(3.7)	0	(0.0)	3	(4.8)	3	(4.8)
Pneumonia bacterial	1	(3.7)	1	(3.7)	1	(1.6)	1	(1.6)
Pneumonia pneumococcal	0	(0.0)	0	(0.0)	1	(1.6)	1	(1.6)
Septic shock	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)
Staphylococcal infection	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)
Tracheitis	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Trichophytosis	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Upper respiratory tract infection	2	(7.4)	0	(0.0)	3	(4.8)	0	(0.0)
Injury, poisoning and procedural complications	**3**	**(11.1)**	**1**	**(3.7)**	**3**	**(4.8)**	**0**	**(0.0)**
Arthropod bite	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Contusion	0	(0.0)	0	(0.0)	2	(3.2)	0	(0.0)
Skin abrasion	1	(3.7)	0	(0.0)	1	(1.6)	0	(0.0)
Traumatic intracranial haemorrhage	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)
Investigations	**18**	**(66.7)**	**15**	**(55.6)**	**24**	**(38.7)**	**4**	**(6.5)**

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**18**	**(66.7)**	**15**	**(55.6)**	**24**	**(38.7)**	**4**	**(6.5)**
Alanine aminotransferase increased	2	(7.4)	0	(0.0)	6	(9.7)	0	(0.0)
Aspartate aminotransferase increased	1	(3.7)	0	(0.0)	3	(4.8)	0	(0.0)
Blood alkaline phosphatase increased	0	(0.0)	0	(0.0)	3	(4.8)	0	(0.0)
Blood bilirubin increased	1	(3.7)	0	(0.0)	2	(3.2)	0	(0.0)
Blood creatine phosphokinase increased	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Blood creatinine increased	1	(3.7)	0	(0.0)	5	(8.1)	0	(0.0)
Blood thyroid stimulating hormone increased	0	(0.0)	0	(0.0)	3	(4.8)	0	(0.0)
Blood urea increased	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Blood uric acid increased	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
C-reactive protein increased	1	(3.7)	0	(0.0)	2	(3.2)	0	(0.0)
Computerised tomogram thorax abnormal	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Eosinophil count increased	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Gamma-glutamyltransferase increased	0	(0.0)	0	(0.0)	4	(6.5)	1	(1.6)
Lymphocyte count decreased	2	(7.4)	1	(3.7)	4	(6.5)	3	(4.8)
Neutrophil count decreased	11	(40.7)	10	(37.0)	3	(4.8)	0	(0.0)
Platelet count decreased	1	(3.7)	1	(3.7)	1	(1.6)	0	(0.0)
Thyroxine free increased	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Tri-iodothyronine decreased	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Weight decreased	2	(7.4)	0	(0.0)	5	(8.1)	0	(0.0)
White blood cell count decreased	15	(55.6)	10	(37.0)	2	(3.2)	0	(0.0)
White blood cell count increased	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Metabolism and nutrition disorders	**14**	**(51.9)**	**5**	**(18.5)**	**20**	**(32.3)**	**7**	**(11.3)**
Decreased appetite	9	(33.3)	3	(11.1)	14	(22.6)	2	(3.2)
Dehydration	1	(3.7)	1	(3.7)	2	(3.2)	0	(0.0)
Diabetes mellitus	0	(0.0)	0	(0.0)	2	(3.2)	1	(1.6)
Hypercalcaemia	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Hyperglycaemia	0	(0.0)	0	(0.0)	1	(1.6)	1	(1.6)
Hyperkalaemia	1	(3.7)	0	(0.0)	1	(1.6)	0	(0.0)
Hyperlipidaemia	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Hypernatraemia	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Hypertriglyceridaemia	1	(3.7)	1	(3.7)	1	(1.6)	0	(0.0)
Hyperuricaemia	2	(7.4)	0	(0.0)	2	(3.2)	0	(0.0)
Hypoalbuminaemia	1	(3.7)	0	(0.0)	4	(6.5)	0	(0.0)
Hypocalcaemia	0	(0.0)	0	(0.0)	1	(1.6)	1	(1.6)
Hypokalaemia	1	(3.7)	1	(3.7)	1	(1.6)	0	(0.0)
Hyponatraemia	1	(3.7)	0	(0.0)	2	(3.2)	2	(3.2)
Hypophosphataemia	0	(0.0)	0	(0.0)	1	(1.6)	1	(1.6)
Musculoskeletal and connective tissue disorders	**13**	**(48.1)**	**0**	**(0.0)**	**10**	**(16.1)**	**0**	**(0.0)**
Arthralgia	7	(25.9)	0	(0.0)	2	(3.2)	0	(0.0)
Arthritis	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Back pain	0	(0.0)	0	(0.0)	3	(4.8)	0	(0.0)
Flank pain	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Muscle spasms	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Musculoskeletal pain	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Musculoskeletal stiffness	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Musculoskeletal and connective tissue disorders	**13**	**(48.1)**	**0**	**(0.0)**	**10**	**(16.1)**	**0**	**(0.0)**
Myalgia	5	(18.5)	0	(0.0)	3	(4.8)	0	(0.0)
Pain in extremity	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Periarthritis	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Synovial cyst	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1**	**(3.7)**	**0**	**(0.0)**	**6**	**(9.7)**	**4**	**(6.5)**
Cancer pain	0	(0.0)	0	(0.0)	2	(3.2)	2	(3.2)
Gastric cancer	0	(0.0)	0	(0.0)	1	(1.6)	1	(1.6)
Malignant pleural effusion	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Tumour pain	1	(3.7)	0	(0.0)	3	(4.8)	1	(1.6)
Nervous system disorders	**13**	**(48.1)**	**0**	**(0.0)**	**13**	**(21.0)**	**0**	**(0.0)**
Cerebral ischaemia	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Dizziness	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Dysarthria	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Dysgeusia	7	(25.9)	0	(0.0)	4	(6.5)	0	(0.0)
Headache	1	(3.7)	0	(0.0)	6	(9.7)	0	(0.0)
Hypoaesthesia	1	(3.7)	0	(0.0)	1	(1.6)	0	(0.0)
Neuropathy peripheral	4	(14.8)	0	(0.0)	1	(1.6)	0	(0.0)
Peripheral motor neuropathy	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral sensory neuropathy	3	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
Post herpetic neuralgia	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Sciatica	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Psychiatric disorders	**3**	**(11.1)**	**0**	**(0.0)**	**5**	**(8.1)**	**1**	**(1.6)**
Completed suicide	0	(0.0)	0	(0.0)	1	(1.6)	1	(1.6)
Delirium	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Insomnia	2	(7.4)	0	(0.0)	4	(6.5)	0	(0.0)
Renal and urinary disorders	**1**	**(3.7)**	**1**	**(3.7)**	**2**	**(3.2)**	**0**	**(0.0)**
Acute kidney injury	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)
Proteinuria	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Renal impairment	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**13**	**(48.1)**	**3**	**(11.1)**	**19**	**(30.6)**	**3**	**(4.8)**
Bronchostenosis	0	(0.0)	0	(0.0)	1	(1.6)	1	(1.6)
Chronic obstructive pulmonary disease	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Cough	1	(3.7)	0	(0.0)	2	(3.2)	0	(0.0)
Dyspnoea	5	(18.5)	2	(7.4)	4	(6.5)	1	(1.6)
Epistaxis	1	(3.7)	0	(0.0)	2	(3.2)	0	(0.0)
Haemoptysis	1	(3.7)	0	(0.0)	2	(3.2)	0	(0.0)
Hiccups	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Interstitial lung disease	2	(7.4)	1	(3.7)	2	(3.2)	0	(0.0)
Nasal discomfort	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Oropharyngeal pain	0	(0.0)	0	(0.0)	2	(3.2)	0	(0.0)
Pleural effusion	1	(3.7)	0	(0.0)	2	(3.2)	0	(0.0)
Pneumonia aspiration	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)
Pneumonitis	1	(3.7)	0	(0.0)	1	(1.6)	1	(1.6)
Productive cough	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Respiratory, thoracic and mediastinal disorders	**13**	**(48.1)**	**3**	**(11.1)**	**19**	**(30.6)**	**3**	**(4.8)**
Pulmonary haemorrhage	2	(7.4)	1	(3.7)	1	(1.6)	1	(1.6)
Respiratory failure	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)
Rhinitis allergic	0	(0.0)	0	(0.0)	2	(3.2)	0	(0.0)
Upper respiratory tract inflammation	0	(0.0)	0	(0.0)	2	(3.2)	0	(0.0)
Skin and subcutaneous tissue disorders	**18**	**(66.7)**	**1**	**(3.7)**	**31**	**(50.0)**	**2**	**(3.2)**
Alopecia	12	(44.4)	0	(0.0)	0	(0.0)	0	(0.0)
Dermatitis bullous	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Drug eruption	0	(0.0)	0	(0.0)	1	(1.6)	1	(1.6)
Dry skin	2	(7.4)	0	(0.0)	1	(1.6)	0	(0.0)
Eczema	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Erythema multiforme	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Nail discolouration	2	(7.4)	0	(0.0)	1	(1.6)	0	(0.0)
Nail disorder	2	(7.4)	0	(0.0)	1	(1.6)	0	(0.0)
Nail ridging	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Night sweats	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Onychomadesis	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Palmar-plantar erythrodysaesthesia syndrome	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Pruritus	2	(7.4)	1	(3.7)	11	(17.7)	0	(0.0)
Rash	6	(22.2)	0	(0.0)	16	(25.8)	0	(0.0)
Rash maculo-papular	0	(0.0)	0	(0.0)	4	(6.5)	0	(0.0)
Skin fissures	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**18**	**(66.7)**	**1**	**(3.7)**	**31**	**(50.0)**	**2**	**(3.2)**
Skin hyperpigmentation	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Skin induration	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Skin ulcer	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Urticaria	3	(11.1)	0	(0.0)	1	(1.6)	1	(1.6)
Xeroderma	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Vascular disorders	**2**	**(7.4)**	**0**	**(0.0)**	**5**	**(8.1)**	**2**	**(3.2)**
Hypertension	0	(0.0)	0	(0.0)	3	(4.8)	1	(1.6)
Hypotension	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral ischaemia	0	(0.0)	0	(0.0)	1	(1.6)	1	(1.6)
Phlebitis	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Venous thrombosis limb	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
Adverse event terms are from MedDRA Version 18.0.
(Database Cutoff Date: &cutoff).

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付録 2.7.4- 99　　有害事象（いずれかの投与群で発現割合 10%以上）

010 試験（日本人安全性解析対象集団）（PD-L1 高発現）

Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence ≥ 10% in One or More Treatment Groups)
APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	11				10				13			
with one or more adverse events	10	(90.9)	10	(90.9)	10	(100.0)	5	(50.0)	13	(100.0)	8	(61.5)
with no adverse events	1	(9.1)	1	(9.1)	0	(0.0)	5	(50.0)	0	(0.0)	5	(38.5)
Blood and lymphatic system disorders	**8**	**(72.7)**	**6**	**(54.5)**	**1**	**(10.0)**	**0**	**(0.0)**	**4**	**(30.8)**	**2**	**(15.4)**
Anaemia	3	(27.3)	1	(9.1)	1	(10.0)	0	(0.0)	3	(23.1)	2	(15.4)
Neutropenia	5	(45.5)	5	(45.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiac disorders	**2**	**(18.2)**	**1**	**(9.1)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Endocrine disorders	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(20.0)**	**1**	**(10.0)**	**2**	**(15.4)**	**1**	**(7.7)**
Adrenal insufficiency	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	1	(7.7)	1	(7.7)
Hypopituitarism	0	(0.0)	0	(0.0)	1	(10.0)	1	(10.0)	0	(0.0)	0	(0.0)
Hypothalamo-pituitary disorder	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Gastrointestinal disorders	**8**	**(72.7)**	**1**	**(9.1)**	**8**	**(80.0)**	**1**	**(10.0)**	**6**	**(46.2)**	**2**	**(15.4)**
Constipation	1	(9.1)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Diarrhoea	5	(45.5)	1	(9.1)	1	(10.0)	0	(0.0)	1	(7.7)	0	(0.0)
Nausea	4	(36.4)	0	(0.0)	2	(20.0)	0	(0.0)	2	(15.4)	0	(0.0)
Pancreatitis	0	(0.0)	0	(0.0)	1	(10.0)	1	(10.0)	0	(0.0)	0	(0.0)
Periodontal disease	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Stomatitis	2	(18.2)	0	(0.0)	5	(50.0)	0	(0.0)	0	(0.0)	0	(0.0)
Vomiting	1	(9.1)	0	(0.0)	1	(10.0)	0	(0.0)	2	(15.4)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence ≥ 10% in One or More Treatment Groups)
APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
General disorders and administration site conditions	**8**	**(72.7)**	**1**	**(9.1)**	**5**	**(50.0)**	**0**	**(0.0)**	**7**	**(53.8)**	**0**	**(0.0)**
Fatigue	5	(45.5)	1	(9.1)	2	(20.0)	0	(0.0)	0	(0.0)	0	(0.0)
Malaise	2	(18.2)	0	(0.0)	3	(30.0)	0	(0.0)	4	(30.8)	0	(0.0)
Oedema peripheral	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pyrexia	1	(9.1)	0	(0.0)	2	(20.0)	0	(0.0)	4	(30.8)	0	(0.0)
Infections and infestations	**7**	**(63.6)**	**3**	**(27.3)**	**1**	**(10.0)**	**0**	**(0.0)**	**5**	**(38.5)**	**4**	**(30.8)**
Upper respiratory tract infection	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	1	(7.7)	0	(0.0)
Injury, poisoning and procedural complications	**2**	**(18.2)**	**1**	**(9.1)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(7.7)**	**0**	**(0.0)**
Investigations	**10**	**(90.9)**	**8**	**(72.7)**	**3**	**(30.0)**	**0**	**(0.0)**	**6**	**(46.2)**	**2**	**(15.4)**
Alanine aminotransferase increased	1	(9.1)	0	(0.0)	1	(10.0)	0	(0.0)	2	(15.4)	0	(0.0)
Aspartate aminotransferase increased	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Blood bilirubin increased	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	1	(7.7)	0	(0.0)
Blood creatine phosphokinase increased	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence ≥ 10% in One or More Treatment Groups)
APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**10**	**(90.9)**	**8**	**(72.7)**	**3**	**(30.0)**	**0**	**(0.0)**	**6**	**(46.2)**	**2**	**(15.4)**
Gamma-glutamyltransferase increased	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	2	(15.4)	0	(0.0)
Lymphocyte count decreased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(15.4)	2	(15.4)
Neutrophil count decreased	4	(36.4)	4	(36.4)	1	(10.0)	0	(0.0)	2	(15.4)	0	(0.0)
White blood cell count decreased	7	(63.6)	5	(45.5)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Metabolism and nutrition disorders	**9**	**(81.8)**	**4**	**(36.4)**	**7**	**(70.0)**	**3**	**(30.0)**	**4**	**(30.8)**	**3**	**(23.1)**
Decreased appetite	6	(54.5)	2	(18.2)	5	(50.0)	2	(20.0)	3	(23.1)	0	(0.0)
Diabetes mellitus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(15.4)	1	(7.7)
Hyperglycaemia	0	(0.0)	0	(0.0)	1	(10.0)	1	(10.0)	0	(0.0)	0	(0.0)
Hypoalbuminaemia	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	2	(15.4)	0	(0.0)
Musculoskeletal and connective tissue disorders	**7**	**(63.6)**	**0**	**(0.0)**	**3**	**(30.0)**	**0**	**(0.0)**	**1**	**(7.7)**	**0**	**(0.0)**
Arthralgia	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Myalgia	3	(27.3)	0	(0.0)	2	(20.0)	0	(0.0)	1	(7.7)	0	(0.0)
Pain in extremity	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Synovial cyst	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence ≥ 10% in One or More Treatment Groups)
APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(10.0)**	**1**	**(10.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Cancer pain	0	(0.0)	0	(0.0)	1	(10.0)	1	(10.0)	0	(0.0)	0	(0.0)
Nervous system disorders	**5**	**(45.5)**	**0**	**(0.0)**	**1**	**(10.0)**	**0**	**(0.0)**	**4**	**(30.8)**	**0**	**(0.0)**
Dysgeusia	3	(27.3)	0	(0.0)	0	(0.0)	0	(0.0)	2	(15.4)	0	(0.0)
Headache	1	(9.1)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral sensory neuropathy	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Psychiatric disorders	**2**	**(18.2)**	**0**	**(0.0)**	**1**	**(10.0)**	**0**	**(0.0)**	**1**	**(7.7)**	**0**	**(0.0)**
Insomnia	1	(9.1)	0	(0.0)	1	(10.0)	0	(0.0)	1	(7.7)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**7**	**(63.6)**	**3**	**(27.3)**	**3**	**(30.0)**	**0**	**(0.0)**	**2**	**(15.4)**	**0**	**(0.0)**
Dyspnoea	2	(18.2)	2	(18.2)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Epistaxis	1	(9.1)	0	(0.0)	2	(20.0)	0	(0.0)	0	(0.0)	0	(0.0)
Oropharyngeal pain	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pulmonary haemorrhage	2	(18.2)	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Skin and subcutaneous tissue disorders	**8**	**(72.7)**	**1**	**(9.1)**	**6**	**(60.0)**	**0**	**(0.0)**	**7**	**(53.8)**	**0**	**(0.0)**
Alopecia	4	(36.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Onychomadesis	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence ≥ 10% in One or More Treatment Groups)
APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**8**	**(72.7)**	**1**	**(9.1)**	**6**	**(60.0)**	**0**	**(0.0)**	**7**	**(53.8)**	**0**	**(0.0)**
Pruritus	2	(18.2)	1	(9.1)	3	(30.0)	0	(0.0)	3	(23.1)	0	(0.0)
Rash	3	(27.3)	0	(0.0)	3	(30.0)	0	(0.0)	3	(23.1)	0	(0.0)
Rash maculo-papular	0	(0.0)	0	(0.0)	2	(20.0)	0	(0.0)	2	(15.4)	0	(0.0)
Urticaria	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
Adverse event terms are from MedDRA Version 18.0.
(Database Cutoff Date: &cutoff).

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付録 2.7.4- 100　有害事象（いずれかの投与群で発現割合 10%以上）

010 試験（MK-3475 併合、日本人安全性解析対象集団）（PD-L1 高発現）

Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence ≥ 10% in One or More Treatment Groups)
APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	11				23			
with one or more adverse events	10	(90.9)	10	(90.9)	23	(100.0)	13	(56.5)
with no adverse events	1	(9.1)	1	(9.1)	0	(0.0)	10	(43.5)
Blood and lymphatic system disorders	**8**	**(72.7)**	**6**	**(54.5)**	**5**	**(21.7)**	**2**	**(8.7)**
Anaemia	3	(27.3)	1	(9.1)	4	(17.4)	2	(8.7)
Neutropenia	5	(45.5)	5	(45.5)	0	(0.0)	0	(0.0)
Cardiac disorders	**2**	**(18.2)**	**1**	**(9.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Endocrine disorders	**0**	**(0.0)**	**0**	**(0.0)**	**4**	**(17.4)**	**2**	**(8.7)**
Gastrointestinal disorders	**8**	**(72.7)**	**1**	**(9.1)**	**14**	**(60.9)**	**3**	**(13.0)**
Diarrhoea	5	(45.5)	1	(9.1)	2	(8.7)	0	(0.0)
Nausea	4	(36.4)	0	(0.0)	4	(17.4)	0	(0.0)
Stomatitis	2	(18.2)	0	(0.0)	5	(21.7)	0	(0.0)
Vomiting	1	(9.1)	0	(0.0)	3	(13.0)	0	(0.0)
General disorders and administration site conditions	**8**	**(72.7)**	**1**	**(9.1)**	**12**	**(52.2)**	**0**	**(0.0)**
Fatigue	5	(45.5)	1	(9.1)	2	(8.7)	0	(0.0)
Malaise	2	(18.2)	0	(0.0)	7	(30.4)	0	(0.0)
Oedema peripheral	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)
Pyrexia	1	(9.1)	0	(0.0)	6	(26.1)	0	(0.0)
Infections and infestations	**7**	**(63.6)**	**3**	**(27.3)**	**6**	**(26.1)**	**4**	**(17.4)**

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence ≥ 10% in One or More Treatment Groups)
APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Injury, poisoning and procedural complications	**2**	**(18.2)**	**1**	**(9.1)**	**1**	**(4.3)**	**0**	**(0.0)**
Investigations	**10**	**(90.9)**	**8**	**(72.7)**	**9**	**(39.1)**	**2**	**(8.7)**
Alanine aminotransferase increased	1	(9.1)	0	(0.0)	3	(13.0)	0	(0.0)
Gamma-glutamyltransferase increased	0	(0.0)	0	(0.0)	3	(13.0)	0	(0.0)
Neutrophil count decreased	4	(36.4)	4	(36.4)	3	(13.0)	0	(0.0)
White blood cell count decreased	7	(63.6)	5	(45.5)	1	(4.3)	0	(0.0)
Metabolism and nutrition disorders	**9**	**(81.8)**	**4**	**(36.4)**	**11**	**(47.8)**	**6**	**(26.1)**
Decreased appetite	6	(54.5)	2	(18.2)	8	(34.8)	2	(8.7)
Hypoalbuminaemia	0	(0.0)	0	(0.0)	3	(13.0)	0	(0.0)
Musculoskeletal and connective tissue disorders	**7**	**(63.6)**	**0**	**(0.0)**	**4**	**(17.4)**	**0**	**(0.0)**
Arthralgia	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)
Myalgia	3	(27.3)	0	(0.0)	3	(13.0)	0	(0.0)
Nervous system disorders	**5**	**(45.5)**	**0**	**(0.0)**	**5**	**(21.7)**	**0**	**(0.0)**
Dysgeusia	3	(27.3)	0	(0.0)	2	(8.7)	0	(0.0)
Peripheral sensory neuropathy	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)
Psychiatric disorders	**2**	**(18.2)**	**0**	**(0.0)**	**2**	**(8.7)**	**0**	**(0.0)**
Respiratory, thoracic and mediastinal disorders	**7**	**(63.6)**	**3**	**(27.3)**	**5**	**(21.7)**	**0**	**(0.0)**

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence ≥ 10% in One or More Treatment Groups)
APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Respiratory, thoracic and mediastinal disorders	**7**	**(63.6)**	**3**	**(27.3)**	**5**	**(21.7)**	**0**	**(0.0)**
Dyspnoea	2	(18.2)	2	(18.2)	1	(4.3)	0	(0.0)
Pulmonary haemorrhage	2	(18.2)	1	(9.1)	0	(0.0)	0	(0.0)
Skin and subcutaneous tissue disorders	**8**	**(72.7)**	**1**	**(9.1)**	**13**	**(56.5)**	**0**	**(0.0)**
Alopecia	4	(36.4)	0	(0.0)	0	(0.0)	0	(0.0)
Pruritus	2	(18.2)	1	(9.1)	6	(26.1)	0	(0.0)
Rash	3	(27.3)	0	(0.0)	6	(26.1)	0	(0.0)
Rash maculo-papular	0	(0.0)	0	(0.0)	4	(17.4)	0	(0.0)
Urticaria	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
Adverse event terms are from MedDRA Version 18.0.
(Database Cutoff Date: &cutoff).

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付録 2.7.4- 101　有害事象（いずれかの投与群で発現割合 10%以上）

010 試験（日本人安全性解析対象集団）（PD-L1 低発現）

Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence ≥ 10% in One or More Treatment Groups)
APaT Japan Population (1% ≤ TPS < 50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	16				18				21			
with one or more adverse events	16	(100.0)	13	(81.3)	18	(100.0)	7	(38.9)	21	(100.0)	8	(38.1)
with no adverse events	0	(0.0)	3	(18.8)	0	(0.0)	11	(61.1)	0	(0.0)	13	(61.9)
Blood and lymphatic system disorders	**10**	**(62.5)**	**7**	**(43.8)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(4.8)**	**0**	**(0.0)**
Anaemia	3	(18.8)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Febrile neutropenia	2	(12.5)	2	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Leukopenia	2	(12.5)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Neutropenia	6	(37.5)	6	(37.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Endocrine disorders	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(16.7)**	**0**	**(0.0)**	**1**	**(4.8)**	**1**	**(4.8)**
Hyperthyroidism	0	(0.0)	0	(0.0)	2	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
Eye disorders	**1**	**(6.3)**	**0**	**(0.0)**	**3**	**(16.7)**	**0**	**(0.0)**	**1**	**(4.8)**	**0**	**(0.0)**
Gastrointestinal disorders	**7**	**(43.8)**	**1**	**(6.3)**	**10**	**(55.6)**	**1**	**(5.6)**	**11**	**(52.4)**	**1**	**(4.8)**
Abdominal pain upper	0	(0.0)	0	(0.0)	2	(11.1)	0	(0.0)	1	(4.8)	0	(0.0)
Constipation	1	(6.3)	0	(0.0)	3	(16.7)	0	(0.0)	3	(14.3)	1	(4.8)
Diarrhoea	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	7	(33.3)	0	(0.0)
Nausea	2	(12.5)	0	(0.0)	3	(16.7)	0	(0.0)	4	(19.0)	0	(0.0)
Stomatitis	5	(31.3)	1	(6.3)	1	(5.6)	0	(0.0)	2	(9.5)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence ≥ 10% in One or More Treatment Groups)
APaT Japan Population (1% ≤ TPS < 50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
General disorders and administration site conditions	**13**	**(81.3)**	**1**	**(6.3)**	**6**	**(33.3)**	**0**	**(0.0)**	**12**	**(57.1)**	**0**	**(0.0)**
Fatigue	1	(6.3)	0	(0.0)	1	(5.6)	0	(0.0)	3	(14.3)	0	(0.0)
Malaise	5	(31.3)	0	(0.0)	3	(16.7)	0	(0.0)	6	(28.6)	0	(0.0)
Oedema	2	(12.5)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Oedema peripheral	2	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pyrexia	5	(31.3)	0	(0.0)	2	(11.1)	0	(0.0)	2	(9.5)	0	(0.0)
Infections and infestations	**7**	**(43.8)**	**1**	**(6.3)**	**5**	**(27.8)**	**1**	**(5.6)**	**6**	**(28.6)**	**1**	**(4.8)**
Nasopharyngitis	3	(18.8)	0	(0.0)	1	(5.6)	0	(0.0)	2	(9.5)	0	(0.0)
Upper respiratory tract infection	2	(12.5)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Investigations	**8**	**(50.0)**	**7**	**(43.8)**	**7**	**(38.9)**	**2**	**(11.1)**	**8**	**(38.1)**	**0**	**(0.0)**
Alanine aminotransferase increased	1	(6.3)	0	(0.0)	3	(16.7)	0	(0.0)	0	(0.0)	0	(0.0)
Aspartate aminotransferase increased	1	(6.3)	0	(0.0)	2	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
Blood creatinine increased	1	(6.3)	0	(0.0)	1	(5.6)	0	(0.0)	3	(14.3)	0	(0.0)
Blood thyroid stimulating hormone increased	0	(0.0)	0	(0.0)	2	(11.1)	0	(0.0)	1	(4.8)	0	(0.0)
Lymphocyte count decreased	2	(12.5)	1	(6.3)	1	(5.6)	1	(5.6)	1	(4.8)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence ≥ 10% in One or More Treatment Groups)
APaT Japan Population (1% ≤ TPS < 50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**8**	**(50.0)**	**7**	**(43.8)**	**7**	**(38.9)**	**2**	**(11.1)**	**8**	**(38.1)**	**0**	**(0.0)**
Neutrophil count decreased	7	(43.8)	6	(37.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Weight decreased	1	(6.3)	0	(0.0)	2	(11.1)	0	(0.0)	2	(9.5)	0	(0.0)
White blood cell count decreased	8	(50.0)	5	(31.3)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Metabolism and nutrition disorders	**5**	**(31.3)**	**1**	**(6.3)**	**5**	**(27.8)**	**1**	**(5.6)**	**4**	**(19.0)**	**0**	**(0.0)**
Decreased appetite	3	(18.8)	1	(6.3)	2	(11.1)	0	(0.0)	4	(19.0)	0	(0.0)
Musculoskeletal and connective tissue disorders	**6**	**(37.5)**	**0**	**(0.0)**	**3**	**(16.7)**	**0**	**(0.0)**	**3**	**(14.3)**	**0**	**(0.0)**
Arthralgia	5	(31.3)	0	(0.0)	2	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
Myalgia	2	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1**	**(6.3)**	**0**	**(0.0)**	**2**	**(11.1)**	**2**	**(11.1)**	**3**	**(14.3)**	**1**	**(4.8)**
Nervous system disorders	**8**	**(50.0)**	**0**	**(0.0)**	**2**	**(11.1)**	**0**	**(0.0)**	**6**	**(28.6)**	**0**	**(0.0)**
Dysgeusia	4	(25.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(9.5)	0	(0.0)
Headache	0	(0.0)	0	(0.0)	2	(11.1)	0	(0.0)	3	(14.3)	0	(0.0)
Neuropathy peripheral	4	(25.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence ≥ 10% in One or More Treatment Groups)
APaT Japan Population (1% ≤ TPS < 50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Psychiatric disorders	**1**	**(6.3)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(14.3)**	**1**	**(4.8)**
Respiratory, thoracic and mediastinal disorders	**6**	**(37.5)**	**0**	**(0.0)**	**6**	**(33.3)**	**1**	**(5.6)**	**8**	**(38.1)**	**2**	**(9.5)**
Cough	1	(6.3)	0	(0.0)	2	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
Dyspnoea	3	(18.8)	0	(0.0)	1	(5.6)	1	(5.6)	2	(9.5)	0	(0.0)
Skin and subcutaneous tissue disorders	**10**	**(62.5)**	**0**	**(0.0)**	**8**	**(44.4)**	**0**	**(0.0)**	**10**	**(47.6)**	**2**	**(9.5)**
Alopecia	8	(50.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dry skin	2	(12.5)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Pruritus	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	4	(19.0)	0	(0.0)
Rash	3	(18.8)	0	(0.0)	4	(22.2)	0	(0.0)	6	(28.6)	0	(0.0)
Vascular disorders	**1**	**(6.3)**	**0**	**(0.0)**	**1**	**(5.6)**	**0**	**(0.0)**	**3**	**(14.3)**	**1**	**(4.8)**

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
Adverse event terms are from MedDRA Version 18.0.
(Database Cutoff Date: 30SEP2015).

C Confidential

付録 2.7.4- 102　有害事象（いずれかの投与群で発現割合 0%超）

010 試験（日本人安全性解析対象集団）（PD-L1 高発現）

Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	11				10				13			
with one or more adverse events	10	(90.9)	10	(90.9)	10	(100.0)	5	(50.0)	13	(100.0)	8	(61.5)
with no adverse events	1	(9.1)	1	(9.1)	0	(0.0)	5	(50.0)	0	(0.0)	5	(38.5)
Blood and lymphatic system disorders	**8**	**(72.7)**	**6**	**(54.5)**	**1**	**(10.0)**	**0**	**(0.0)**	**4**	**(30.8)**	**2**	**(15.4)**
Anaemia	3	(27.3)	1	(9.1)	1	(10.0)	0	(0.0)	3	(23.1)	2	(15.4)
Febrile neutropenia	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Lymphopenia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Neutropenia	5	(45.5)	5	(45.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiac disorders	**2**	**(18.2)**	**1**	**(9.1)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Atrial fibrillation	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Supraventricular tachycardia	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Endocrine disorders	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(20.0)**	**1**	**(10.0)**	**2**	**(15.4)**	**1**	**(7.7)**
Adrenal insufficiency	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	1	(7.7)	1	(7.7)
Hypopituitarism	0	(0.0)	0	(0.0)	1	(10.0)	1	(10.0)	0	(0.0)	0	(0.0)
Hypothalamo-pituitary disorder	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hypothyroidism	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Eye disorders	**1**	**(9.1)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Lacrimation increased	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Gastrointestinal disorders	**8**	**(72.7)**	**1**	**(9.1)**	**8**	**(80.0)**	**1**	**(10.0)**	**6**	**(46.2)**	**2**	**(15.4)**
Abdominal distension	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Abdominal pain lower	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Colitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	1	(7.7)
Constipation	1	(9.1)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Diarrhoea	5	(45.5)	1	(9.1)	1	(10.0)	0	(0.0)	1	(7.7)	0	(0.0)
Dyspepsia	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Gastritis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Ileus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	1	(7.7)
Nausea	4	(36.4)	0	(0.0)	2	(20.0)	0	(0.0)	2	(15.4)	0	(0.0)
Pancreatitis	0	(0.0)	0	(0.0)	1	(10.0)	1	(10.0)	0	(0.0)	0	(0.0)
Periodontal disease	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Stomatitis	2	(18.2)	0	(0.0)	5	(50.0)	0	(0.0)	0	(0.0)	0	(0.0)
Vomiting	1	(9.1)	0	(0.0)	1	(10.0)	0	(0.0)	2	(15.4)	0	(0.0)
General disorders and administration site conditions	**8**	**(72.7)**	**1**	**(9.1)**	**5**	**(50.0)**	**0**	**(0.0)**	**7**	**(53.8)**	**0**	**(0.0)**
Fatigue	5	(45.5)	1	(9.1)	2	(20.0)	0	(0.0)	0	(0.0)	0	(0.0)
Infusion site vasculitis	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Malaise	2	(18.2)	0	(0.0)	3	(30.0)	0	(0.0)	4	(30.8)	0	(0.0)
Non-cardiac chest pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Oedema	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Oedema peripheral	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pyrexia	1	(9.1)	0	(0.0)	2	(20.0)	0	(0.0)	4	(30.8)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Infections and infestations	**7**	**(63.6)**	**3**	**(27.3)**	**1**	**(10.0)**	**0**	**(0.0)**	**5**	**(38.5)**	**4**	**(30.8)**
Bacteraemia	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Clostridium difficile infection	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Conjunctivitis	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
External ear cellulitis	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Herpes simplex	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Influenza	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nasopharyngitis	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Onychomycosis	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Oral candidiasis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Osteomyelitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	1	(7.7)
Periodontitis	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	1	(7.7)
Pneumonia bacterial	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)	1	(7.7)	1	(7.7)
Pneumonia pneumococcal	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	1	(7.7)
Septic shock	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Staphylococcal infection	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Tracheitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Upper respiratory tract infection	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	1	(7.7)	0	(0.0)
Injury, poisoning and procedural complications	**2**	**(18.2)**	**1**	**(9.1)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(7.7)**	**0**	**(0.0)**
Arthropod bite	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Injury, poisoning and procedural complications	**2**	**(18.2)**	**1**	**(9.1)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(7.7)**	**0**	**(0.0)**
Contusion	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Traumatic intracranial haemorrhage	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Investigations	**10**	**(90.9)**	**8**	**(72.7)**	**3**	**(30.0)**	**0**	**(0.0)**	**6**	**(46.2)**	**2**	**(15.4)**
Alanine aminotransferase increased	1	(9.1)	0	(0.0)	1	(10.0)	0	(0.0)	2	(15.4)	0	(0.0)
Aspartate aminotransferase increased	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Blood alkaline phosphatase increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Blood bilirubin increased	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	1	(7.7)	0	(0.0)
Blood creatine phosphokinase increased	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Blood creatinine increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Gamma-glutamyltransferase increased	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	2	(15.4)	0	(0.0)
Lymphocyte count decreased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(15.4)	2	(15.4)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**10**	**(90.9)**	**8**	**(72.7)**	**3**	**(30.0)**	**0**	**(0.0)**	**6**	**(46.2)**	**2**	**(15.4)**
Neutrophil count decreased	4	(36.4)	4	(36.4)	1	(10.0)	0	(0.0)	2	(15.4)	0	(0.0)
Platelet count decreased	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Weight decreased	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
White blood cell count decreased	7	(63.6)	5	(45.5)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Metabolism and nutrition disorders	**9**	**(81.8)**	**4**	**(36.4)**	**7**	**(70.0)**	**3**	**(30.0)**	**4**	**(30.8)**	**3**	**(23.1)**
Decreased appetite	6	(54.5)	2	(18.2)	5	(50.0)	2	(20.0)	3	(23.1)	0	(0.0)
Diabetes mellitus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(15.4)	1	(7.7)
Hypercalcaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Hyperglycaemia	0	(0.0)	0	(0.0)	1	(10.0)	1	(10.0)	0	(0.0)	0	(0.0)
Hyperkalaemia	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hypertriglyceridaemia	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hyperuricaemia	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hypoalbuminaemia	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	2	(15.4)	0	(0.0)
Hypocalcaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	1	(7.7)
Hypokalaemia	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hyponatraemia	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	1	(7.7)
Hypophosphataemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	1	(7.7)
Musculoskeletal and connective tissue disorders	**7**	**(63.6)**	**0**	**(0.0)**	**3**	**(30.0)**	**0**	**(0.0)**	**1**	**(7.7)**	**0**	**(0.0)**

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Musculoskeletal and connective tissue disorders	**7**	**(63.6)**	**0**	**(0.0)**	**3**	**(30.0)**	**0**	**(0.0)**	**1**	**(7.7)**	**0**	**(0.0)**
Arthralgia	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Musculoskeletal pain	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Musculoskeletal stiffness	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Myalgia	3	(27.3)	0	(0.0)	2	(20.0)	0	(0.0)	1	(7.7)	0	(0.0)
Pain in extremity	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Synovial cyst	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(10.0)**	**1**	**(10.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Cancer pain	0	(0.0)	0	(0.0)	1	(10.0)	1	(10.0)	0	(0.0)	0	(0.0)
Nervous system disorders	**5**	**(45.5)**	**0**	**(0.0)**	**1**	**(10.0)**	**0**	**(0.0)**	**4**	**(30.8)**	**0**	**(0.0)**
Cerebral ischaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Dizziness	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dysgeusia	3	(27.3)	0	(0.0)	0	(0.0)	0	(0.0)	2	(15.4)	0	(0.0)
Headache	1	(9.1)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hypoaesthesia	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Peripheral sensory neuropathy	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Sciatica	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Psychiatric disorders	**2**	**(18.2)**	**0**	**(0.0)**	**1**	**(10.0)**	**0**	**(0.0)**	**1**	**(7.7)**	**0**	**(0.0)**
Delirium	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Insomnia	1	(9.1)	0	(0.0)	1	(10.0)	0	(0.0)	1	(7.7)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**7**	**(63.6)**	**3**	**(27.3)**	**3**	**(30.0)**	**0**	**(0.0)**	**2**	**(15.4)**	**0**	**(0.0)**
Dyspnoea	2	(18.2)	2	(18.2)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Epistaxis	1	(9.1)	0	(0.0)	2	(20.0)	0	(0.0)	0	(0.0)	0	(0.0)
Haemoptysis	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hiccups	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Interstitial lung disease	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Nasal discomfort	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Oropharyngeal pain	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pleural effusion	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonia aspiration	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pulmonary haemorrhage	2	(18.2)	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Respiratory failure	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Rhinitis allergic	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Skin and subcutaneous tissue disorders	**8**	**(72.7)**	**1**	**(9.1)**	**6**	**(60.0)**	**0**	**(0.0)**	**7**	**(53.8)**	**0**	**(0.0)**
Alopecia	4	(36.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nail discolouration	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Nail disorder	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Night sweats	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Onychomadesis	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**8**	**(72.7)**	**1**	**(9.1)**	**6**	**(60.0)**	**0**	**(0.0)**	**7**	**(53.8)**	**0**	**(0.0)**
Pruritus	2	(18.2)	1	(9.1)	3	(30.0)	0	(0.0)	3	(23.1)	0	(0.0)
Rash	3	(27.3)	0	(0.0)	3	(30.0)	0	(0.0)	3	(23.1)	0	(0.0)
Rash maculo-papular	0	(0.0)	0	(0.0)	2	(20.0)	0	(0.0)	2	(15.4)	0	(0.0)
Skin fissures	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Skin hyperpigmentation	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Skin ulcer	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Urticaria	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Xeroderma	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Vascular disorders	**1**	**(9.1)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(7.7)**	**1**	**(7.7)**
Peripheral ischaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	1	(7.7)
Phlebitis	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
Adverse event terms are from MedDRA Version 18.0.
(Database Cutoff Date: &cutoff).

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付録 2.7.4- 103　有害事象（いずれかの投与群で発現割合 0%超）

010 試験（MK-3475 併合、日本人安全性解析対象集団）（PD-L1 高発現）
Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	11				23			
with one or more adverse events	10	(90.9)	10	(90.9)	23	(100.0)	13	(56.5)
with no adverse events	1	(9.1)	1	(9.1)	0	(0.0)	10	(43.5)
Blood and lymphatic system disorders	**8**	**(72.7)**	**6**	**(54.5)**	**5**	**(21.7)**	**2**	**(8.7)**
Anaemia	3	(27.3)	1	(9.1)	4	(17.4)	2	(8.7)
Febrile neutropenia	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)
Lymphopenia	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Neutropenia	5	(45.5)	5	(45.5)	0	(0.0)	0	(0.0)
Cardiac disorders	**2**	**(18.2)**	**1**	**(9.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Atrial fibrillation	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)
Supraventricular tachycardia	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Endocrine disorders	**0**	**(0.0)**	**0**	**(0.0)**	**4**	**(17.4)**	**2**	**(8.7)**
Adrenal insufficiency	0	(0.0)	0	(0.0)	2	(8.7)	1	(4.3)
Hypopituitarism	0	(0.0)	0	(0.0)	1	(4.3)	1	(4.3)
Hypothalamo-pituitary disorder	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Hypothyroidism	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Eye disorders	**1**	**(9.1)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Lacrimation increased	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Gastrointestinal disorders	**8**	**(72.7)**	**1**	**(9.1)**	**14**	**(60.9)**	**3**	**(13.0)**
Abdominal distension	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Abdominal pain lower	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Gastrointestinal disorders	**8**	**(72.7)**	**1**	**(9.1)**	**14**	**(60.9)**	**3**	**(13.0)**
Colitis	0	(0.0)	0	(0.0)	1	(4.3)	1	(4.3)
Constipation	1	(9.1)	0	(0.0)	1	(4.3)	0	(0.0)
Diarrhoea	5	(45.5)	1	(9.1)	2	(8.7)	0	(0.0)
Dyspepsia	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Gastritis	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Ileus	0	(0.0)	0	(0.0)	1	(4.3)	1	(4.3)
Nausea	4	(36.4)	0	(0.0)	4	(17.4)	0	(0.0)
Pancreatitis	0	(0.0)	0	(0.0)	1	(4.3)	1	(4.3)
Periodontal disease	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Stomatitis	2	(18.2)	0	(0.0)	5	(21.7)	0	(0.0)
Vomiting	1	(9.1)	0	(0.0)	3	(13.0)	0	(0.0)
General disorders and administration site conditions	**8**	**(72.7)**	**1**	**(9.1)**	**12**	**(52.2)**	**0**	**(0.0)**
Fatigue	5	(45.5)	1	(9.1)	2	(8.7)	0	(0.0)
Infusion site vasculitis	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Malaise	2	(18.2)	0	(0.0)	7	(30.4)	0	(0.0)
Non-cardiac chest pain	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Oedema	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Oedema peripheral	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)
Pyrexia	1	(9.1)	0	(0.0)	6	(26.1)	0	(0.0)
Infections and infestations	**7**	**(63.6)**	**3**	**(27.3)**	**6**	**(26.1)**	**4**	**(17.4)**
Bacteraemia	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)
Clostridium difficile infection	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Infections and infestations	**7**	**(63.6)**	**3**	**(27.3)**	**6**	**(26.1)**	**4**	**(17.4)**
Conjunctivitis	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
External ear cellulitis	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)
Herpes simplex	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Influenza	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Nasopharyngitis	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)
Onychomycosis	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Oral candidiasis	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Osteomyelitis	0	(0.0)	0	(0.0)	1	(4.3)	1	(4.3)
Periodontitis	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonia	0	(0.0)	0	(0.0)	1	(4.3)	1	(4.3)
Pneumonia bacterial	1	(9.1)	1	(9.1)	1	(4.3)	1	(4.3)
Pneumonia pneumococcal	0	(0.0)	0	(0.0)	1	(4.3)	1	(4.3)
Septic shock	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)
Staphylococcal infection	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)
Tracheitis	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Upper respiratory tract infection	0	(0.0)	0	(0.0)	2	(8.7)	0	(0.0)
Injury, poisoning and procedural complications	**2**	**(18.2)**	**1**	**(9.1)**	**1**	**(4.3)**	**0**	**(0.0)**
Arthropod bite	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Contusion	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Traumatic intracranial haemorrhage	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)
Investigations	**10**	**(90.9)**	**8**	**(72.7)**	**9**	**(39.1)**	**2**	**(8.7)**
Alanine aminotransferase increased	1	(9.1)	0	(0.0)	3	(13.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**10**	**(90.9)**	**8**	**(72.7)**	**9**	**(39.1)**	**2**	**(8.7)**
Aspartate aminotransferase increased	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Blood alkaline phosphatase increased	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Blood bilirubin increased	0	(0.0)	0	(0.0)	2	(8.7)	0	(0.0)
Blood creatine phosphokinase increased	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Blood creatinine increased	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Gamma-glutamyltransferase increased	0	(0.0)	0	(0.0)	3	(13.0)	0	(0.0)
Lymphocyte count decreased	0	(0.0)	0	(0.0)	2	(8.7)	2	(8.7)
Neutrophil count decreased	4	(36.4)	4	(36.4)	3	(13.0)	0	(0.0)
Platelet count decreased	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)
Weight decreased	1	(9.1)	0	(0.0)	1	(4.3)	0	(0.0)
White blood cell count decreased	7	(63.6)	5	(45.5)	1	(4.3)	0	(0.0)
Metabolism and nutrition disorders	**9**	**(81.8)**	**4**	**(36.4)**	**11**	**(47.8)**	**6**	**(26.1)**
Decreased appetite	6	(54.5)	2	(18.2)	8	(34.8)	2	(8.7)
Diabetes mellitus	0	(0.0)	0	(0.0)	2	(8.7)	1	(4.3)
Hypercalcaemia	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Hyperglycaemia	0	(0.0)	0	(0.0)	1	(4.3)	1	(4.3)
Hyperkalaemia	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Hypertriglyceridaemia	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)
Hyperuricaemia	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Hypoalbuminaemia	0	(0.0)	0	(0.0)	3	(13.0)	0	(0.0)
Hypocalcaemia	0	(0.0)	0	(0.0)	1	(4.3)	1	(4.3)
Hypokalaemia	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)
Hyponatraemia	1	(9.1)	0	(0.0)	1	(4.3)	1	(4.3)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Metabolism and nutrition disorders	**9**	**(81.8)**	**4**	**(36.4)**	**11**	**(47.8)**	**6**	**(26.1)**
Hypophosphataemia	0	(0.0)	0	(0.0)	1	(4.3)	1	(4.3)
Musculoskeletal and connective tissue disorders	**7**	**(63.6)**	**0**	**(0.0)**	**4**	**(17.4)**	**0**	**(0.0)**
Arthralgia	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)
Musculoskeletal pain	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Musculoskeletal stiffness	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Myalgia	3	(27.3)	0	(0.0)	3	(13.0)	0	(0.0)
Pain in extremity	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Synovial cyst	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(4.3)**	**1**	**(4.3)**
Cancer pain	0	(0.0)	0	(0.0)	1	(4.3)	1	(4.3)
Nervous system disorders	**5**	**(45.5)**	**0**	**(0.0)**	**5**	**(21.7)**	**0**	**(0.0)**
Cerebral ischaemia	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Dizziness	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Dysgeusia	3	(27.3)	0	(0.0)	2	(8.7)	0	(0.0)
Headache	1	(9.1)	0	(0.0)	1	(4.3)	0	(0.0)
Hypoaesthesia	1	(9.1)	0	(0.0)	1	(4.3)	0	(0.0)
Peripheral sensory neuropathy	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)
Sciatica	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Psychiatric disorders	**2**	**(18.2)**	**0**	**(0.0)**	**2**	**(8.7)**	**0**	**(0.0)**

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Psychiatric disorders	**2**	**(18.2)**	**0**	**(0.0)**	**2**	**(8.7)**	**0**	**(0.0)**
Delirium	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Insomnia	1	(9.1)	0	(0.0)	2	(8.7)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**7**	**(63.6)**	**3**	**(27.3)**	**5**	**(21.7)**	**0**	**(0.0)**
Dyspnoea	2	(18.2)	2	(18.2)	1	(4.3)	0	(0.0)
Epistaxis	1	(9.1)	0	(0.0)	2	(8.7)	0	(0.0)
Haemoptysis	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Hiccups	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Interstitial lung disease	1	(9.1)	1	(9.1)	1	(4.3)	0	(0.0)
Nasal discomfort	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Oropharyngeal pain	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Pleural effusion	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonia aspiration	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)
Pulmonary haemorrhage	2	(18.2)	1	(9.1)	0	(0.0)	0	(0.0)
Respiratory failure	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)
Rhinitis allergic	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Skin and subcutaneous tissue disorders	**8**	**(72.7)**	**1**	**(9.1)**	**13**	**(56.5)**	**0**	**(0.0)**
Alopecia	4	(36.4)	0	(0.0)	0	(0.0)	0	(0.0)
Nail discolouration	1	(9.1)	0	(0.0)	1	(4.3)	0	(0.0)
Nail disorder	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Night sweats	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Onychomadesis	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**8**	**(72.7)**	**1**	**(9.1)**	**13**	**(56.5)**	**0**	**(0.0)**
Pruritus	2	(18.2)	1	(9.1)	6	(26.1)	0	(0.0)
Rash	3	(27.3)	0	(0.0)	6	(26.1)	0	(0.0)
Rash maculo-papular	0	(0.0)	0	(0.0)	4	(17.4)	0	(0.0)
Skin fissures	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Skin hyperpigmentation	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Skin ulcer	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Urticaria	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)
Xeroderma	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Vascular disorders	**1**	**(9.1)**	**0**	**(0.0)**	**1**	**(4.3)**	**1**	**(4.3)**
Peripheral ischaemia	0	(0.0)	0	(0.0)	1	(4.3)	1	(4.3)
Phlebitis	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
Adverse event terms are from MedDRA Version 18.0.
(Database Cutoff Date: &cutoff).

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付録 2.7.4- 104　有害事象（いずれかの投与群で発現割合 0%超）

010 試験（日本人安全性解析対象集団）（PD-L1 低発現）

Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (1% ≤ TPS < 50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	16				18				21			
with one or more adverse events	16	(100.0)	13	(81.3)	18	(100.0)	7	(38.9)	21	(100.0)	8	(38.1)
with no adverse events	0	(0.0)	3	(18.8)	0	(0.0)	11	(61.1)	0	(0.0)	13	(61.9)
Blood and lymphatic system disorders	**10**	**(62.5)**	**7**	**(43.8)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(4.8)**	**0**	**(0.0)**
Anaemia	3	(18.8)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Febrile neutropenia	2	(12.5)	2	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Leukopenia	2	(12.5)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Lymphopenia	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Neutropenia	6	(37.5)	6	(37.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiac disorders	**1**	**(6.3)**	**1**	**(6.3)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(4.8)**	**1**	**(4.8)**
Atrial fibrillation	1	(6.3)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Atrioventricular block complete	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	1	(4.8)
Cardiac failure acute	1	(6.3)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Ear and labyrinth disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(4.8)**	**0**	**(0.0)**
Vertigo	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Endocrine disorders	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(16.7)**	**0**	**(0.0)**	**1**	**(4.8)**	**1**	**(4.8)**
Hyperthyroidism	0	(0.0)	0	(0.0)	2	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
Hypopituitarism	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	1	(4.8)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (1% ≤ TPS < 50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Endocrine disorders	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(16.7)**	**0**	**(0.0)**	**1**	**(4.8)**	**1**	**(4.8)**
Hypothyroidism	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	1	(4.8)	0	(0.0)
Eye disorders	**1**	**(6.3)**	**0**	**(0.0)**	**3**	**(16.7)**	**0**	**(0.0)**	**1**	**(4.8)**	**0**	**(0.0)**
Cataract	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Dry eye	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	1	(4.8)	0	(0.0)
Lacrimation increased	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Vitreous floaters	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Gastrointestinal disorders	**7**	**(43.8)**	**1**	**(6.3)**	**10**	**(55.6)**	**1**	**(5.6)**	**11**	**(52.4)**	**1**	**(4.8)**
Abdominal pain upper	0	(0.0)	0	(0.0)	2	(11.1)	0	(0.0)	1	(4.8)	0	(0.0)
Colitis	0	(0.0)	0	(0.0)	1	(5.6)	1	(5.6)	0	(0.0)	0	(0.0)
Constipation	1	(6.3)	0	(0.0)	3	(16.7)	0	(0.0)	3	(14.3)	1	(4.8)
Diarrhoea	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	7	(33.3)	0	(0.0)
Faecaloma	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nausea	2	(12.5)	0	(0.0)	3	(16.7)	0	(0.0)	4	(19.0)	0	(0.0)
Stomatitis	5	(31.3)	1	(6.3)	1	(5.6)	0	(0.0)	2	(9.5)	0	(0.0)
Toothache	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Vomiting	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	1	(4.8)	0	(0.0)
General disorders and administration site conditions	**13**	**(81.3)**	**1**	**(6.3)**	**6**	**(33.3)**	**0**	**(0.0)**	**12**	**(57.1)**	**0**	**(0.0)**
Chest pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(9.5)	0	(0.0)
Chills	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Fatigue	1	(6.3)	0	(0.0)	1	(5.6)	0	(0.0)	3	(14.3)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (1% ≤ TPS < 50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
General disorders and administration site conditions	**13**	**(81.3)**	**1**	**(6.3)**	**6**	**(33.3)**	**0**	**(0.0)**	**12**	**(57.1)**	**0**	**(0.0)**
Infusion site vasculitis	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Malaise	5	(31.3)	0	(0.0)	3	(16.7)	0	(0.0)	6	(28.6)	0	(0.0)
Oedema	2	(12.5)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Oedema peripheral	2	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pyrexia	5	(31.3)	0	(0.0)	2	(11.1)	0	(0.0)	2	(9.5)	0	(0.0)
Hepatobiliary disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(4.8)**	**0**	**(0.0)**
Hepatic function abnormal	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Infections and infestations	**7**	**(43.8)**	**1**	**(6.3)**	**5**	**(27.8)**	**1**	**(5.6)**	**6**	**(28.6)**	**1**	**(4.8)**
Bronchitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Conjunctivitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Herpes zoster	1	(6.3)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Infected dermal cyst	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Lung infection	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Nail infection	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nasopharyngitis	3	(18.8)	0	(0.0)	1	(5.6)	0	(0.0)	2	(9.5)	0	(0.0)
Osteomyelitis	1	(6.3)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Otitis media acute	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Pharyngitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Pneumonia	1	(6.3)	0	(0.0)	1	(5.6)	1	(5.6)	1	(4.8)	1	(4.8)
Trichophytosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (1% ≤ TPS < 50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Infections and infestations	**7**	**(43.8)**	**1**	**(6.3)**	**5**	**(27.8)**	**1**	**(5.6)**	**6**	**(28.6)**	**1**	**(4.8)**
Upper respiratory tract infection	2	(12.5)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Injury, poisoning and procedural complications	**1**	**(6.3)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(9.5)**	**0**	**(0.0)**
Contusion	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Skin abrasion	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Investigations	**8**	**(50.0)**	**7**	**(43.8)**	**7**	**(38.9)**	**2**	**(11.1)**	**8**	**(38.1)**	**0**	**(0.0)**
Alanine aminotransferase increased	1	(6.3)	0	(0.0)	3	(16.7)	0	(0.0)	0	(0.0)	0	(0.0)
Aspartate aminotransferase increased	1	(6.3)	0	(0.0)	2	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
Blood alkaline phosphatase increased	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	1	(4.8)	0	(0.0)
Blood bilirubin increased	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Blood creatinine increased	1	(6.3)	0	(0.0)	1	(5.6)	0	(0.0)	3	(14.3)	0	(0.0)
Blood thyroid stimulating hormone increased	0	(0.0)	0	(0.0)	2	(11.1)	0	(0.0)	1	(4.8)	0	(0.0)
Blood urea increased	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Blood uric acid increased	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
C-reactive protein increased	1	(6.3)	0	(0.0)	1	(5.6)	0	(0.0)	1	(4.8)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (1% ≤ TPS < 50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**8**	**(50.0)**	**7**	**(43.8)**	**7**	**(38.9)**	**2**	**(11.1)**	**8**	**(38.1)**	**0**	**(0.0)**
Computerised tomogram thorax abnormal	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Eosinophil count increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Gamma-glutamyltransferase increased	0	(0.0)	0	(0.0)	1	(5.6)	1	(5.6)	0	(0.0)	0	(0.0)
Lymphocyte count decreased	2	(12.5)	1	(6.3)	1	(5.6)	1	(5.6)	1	(4.8)	0	(0.0)
Neutrophil count decreased	7	(43.8)	6	(37.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Platelet count decreased	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Thyroxine free increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Tri-iodothyronine decreased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Weight decreased	1	(6.3)	0	(0.0)	2	(11.1)	0	(0.0)	2	(9.5)	0	(0.0)
White blood cell count decreased	8	(50.0)	5	(31.3)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
White blood cell count increased	1	(6.3)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Metabolism and nutrition disorders	**5**	**(31.3)**	**1**	**(6.3)**	**5**	**(27.8)**	**1**	**(5.6)**	**4**	**(19.0)**	**0**	**(0.0)**
Decreased appetite	3	(18.8)	1	(6.3)	2	(11.1)	0	(0.0)	4	(19.0)	0	(0.0)
Dehydration	1	(6.3)	1	(6.3)	0	(0.0)	0	(0.0)	2	(9.5)	0	(0.0)
Hyperkalaemia	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (1% ≤ TPS < 50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Metabolism and nutrition disorders	**5**	**(31.3)**	**1**	**(6.3)**	**5**	**(27.8)**	**1**	**(5.6)**	**4**	**(19.0)**	**0**	**(0.0)**
Hyperlipidaemia	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hypernatraemia	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hypertriglyceridaemia	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hyperuricaemia	1	(6.3)	0	(0.0)	1	(5.6)	0	(0.0)	1	(4.8)	0	(0.0)
Hypoalbuminaemia	1	(6.3)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hypokalaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Hyponatraemia	0	(0.0)	0	(0.0)	1	(5.6)	1	(5.6)	0	(0.0)	0	(0.0)
Musculoskeletal and connective tissue disorders	**6**	**(37.5)**	**0**	**(0.0)**	**3**	**(16.7)**	**0**	**(0.0)**	**3**	**(14.3)**	**0**	**(0.0)**
Arthralgia	5	(31.3)	0	(0.0)	2	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
Arthritis	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Back pain	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	2	(9.5)	0	(0.0)
Flank pain	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Muscle spasms	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Myalgia	2	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Periarthritis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1**	**(6.3)**	**0**	**(0.0)**	**2**	**(11.1)**	**2**	**(11.1)**	**3**	**(14.3)**	**1**	**(4.8)**
Cancer pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	1	(4.8)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (1% ≤ TPS < 50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1**	**(6.3)**	**0**	**(0.0)**	**2**	**(11.1)**	**2**	**(11.1)**	**3**	**(14.3)**	**1**	**(4.8)**
Gastric cancer	0	(0.0)	0	(0.0)	1	(5.6)	1	(5.6)	0	(0.0)	0	(0.0)
Malignant pleural effusion	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Tumour pain	1	(6.3)	0	(0.0)	1	(5.6)	1	(5.6)	2	(9.5)	0	(0.0)
Nervous system disorders	**8**	**(50.0)**	**0**	**(0.0)**	**2**	**(11.1)**	**0**	**(0.0)**	**6**	**(28.6)**	**0**	**(0.0)**
Dysarthria	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dysgeusia	4	(25.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(9.5)	0	(0.0)
Headache	0	(0.0)	0	(0.0)	2	(11.1)	0	(0.0)	3	(14.3)	0	(0.0)
Neuropathy peripheral	4	(25.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Peripheral motor neuropathy	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral sensory neuropathy	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Post herpetic neuralgia	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Psychiatric disorders	**1**	**(6.3)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(14.3)**	**1**	**(4.8)**
Completed suicide	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	1	(4.8)
Insomnia	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	2	(9.5)	0	(0.0)
Renal and urinary disorders	**1**	**(6.3)**	**1**	**(6.3)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(9.5)**	**0**	**(0.0)**
Acute kidney injury	1	(6.3)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (1% ≤ TPS < 50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Renal and urinary disorders	**1**	**(6.3)**	**1**	**(6.3)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(9.5)**	**0**	**(0.0)**
Proteinuria	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Renal impairment	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**6**	**(37.5)**	**0**	**(0.0)**	**6**	**(33.3)**	**1**	**(5.6)**	**8**	**(38.1)**	**2**	**(9.5)**
Bronchostenosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	1	(4.8)
Chronic obstructive pulmonary disease	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Cough	1	(6.3)	0	(0.0)	2	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
Dyspnoea	3	(18.8)	0	(0.0)	1	(5.6)	1	(5.6)	2	(9.5)	0	(0.0)
Haemoptysis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(9.5)	0	(0.0)
Interstitial lung disease	1	(6.3)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Oropharyngeal pain	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Pleural effusion	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	1	(4.8)	0	(0.0)
Pneumonitis	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	1	(4.8)
Productive cough	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Pulmonary haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	1	(4.8)
Rhinitis allergic	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Upper respiratory tract inflammation	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	1	(4.8)	0	(0.0)
Skin and subcutaneous tissue disorders	**10**	**(62.5)**	**0**	**(0.0)**	**8**	**(44.4)**	**0**	**(0.0)**	**10**	**(47.6)**	**2**	**(9.5)**
Alopecia	8	(50.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (1% ≤ TPS < 50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**10**	**(62.5)**	**0**	**(0.0)**	**8**	**(44.4)**	**0**	**(0.0)**	**10**	**(47.6)**	**2**	**(9.5)**
Dermatitis bullous	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Drug eruption	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	1	(4.8)
Dry skin	2	(12.5)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Eczema	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Erythema multiforme	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Nail discolouration	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nail disorder	1	(6.3)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Nail ridging	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Palmar-plantar erythrodysaesthesia syndrome	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pruritus	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	4	(19.0)	0	(0.0)
Rash	3	(18.8)	0	(0.0)	4	(22.2)	0	(0.0)	6	(28.6)	0	(0.0)
Skin induration	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Urticaria	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	1	(4.8)
Vascular disorders	**1**	**(6.3)**	**0**	**(0.0)**	**1**	**(5.6)**	**0**	**(0.0)**	**3**	**(14.3)**	**1**	**(4.8)**
Hypertension	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	2	(9.5)	1	(4.8)
Hypotension	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (1% ≤ TPS < 50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Vascular disorders	**1**	**(6.3)**	**0**	**(0.0)**	**1**	**(5.6)**	**0**	**(0.0)**	**3**	**(14.3)**	**1**	**(4.8)**
Venous thrombosis limb	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
Adverse event terms are from MedDRA Version 18.0.
(Database Cutoff Date: 30SEP2015).

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付録 2.7.4- 105　副作用（いずれかの投与群で発現割合 0%超）

010 試験（日本人安全性解析対象集団）（PD-L1 発現陽性）

Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)

APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	27				28				34			
with one or more adverse events	26	(96.3)	23	(85.2)	22	(78.6)	4	(14.3)	30	(88.2)	10	(29.4)
with no adverse events	1	(3.7)	4	(14.8)	6	(21.4)	24	(85.7)	4	(11.8)	24	(70.6)
Blood and lymphatic system disorders	**17**	**(63.0)**	**13**	**(48.1)**	**1**	**(3.6)**	**0**	**(0.0)**	**2**	**(5.9)**	**0**	**(0.0)**
Anaemia	5	(18.5)	1	(3.7)	1	(3.6)	0	(0.0)	1	(2.9)	0	(0.0)
Febrile neutropenia	3	(11.1)	3	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Leukopenia	2	(7.4)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Lymphopenia	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	2	(5.9)	0	(0.0)
Neutropenia	11	(40.7)	11	(40.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiac disorders	**2**	**(7.4)**	**2**	**(7.4)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(2.9)**	**1**	**(2.9)**
Atrial fibrillation	2	(7.4)	2	(7.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Atrioventricular block complete	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	1	(2.9)
Cardiac failure acute	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Ear and labyrinth disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(2.9)**	**0**	**(0.0)**
Vertigo	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Endocrine disorders	**0**	**(0.0)**	**0**	**(0.0)**	**5**	**(17.9)**	**1**	**(3.6)**	**3**	**(8.8)**	**2**	**(5.9)**
Adrenal insufficiency	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	1	(2.9)	1	(2.9)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Endocrine disorders	**0**	**(0.0)**	**0**	**(0.0)**	**5**	**(17.9)**	**1**	**(3.6)**	**3**	**(8.8)**	**2**	**(5.9)**
Hyperthyroidism	0	(0.0)	0	(0.0)	2	(7.1)	0	(0.0)	0	(0.0)	0	(0.0)
Hypopituitarism	0	(0.0)	0	(0.0)	1	(3.6)	1	(3.6)	1	(2.9)	1	(2.9)
Hypothalamo-pituitary disorder	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hypothyroidism	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	2	(5.9)	0	(0.0)
Eye disorders	**1**	**(3.7)**	**0**	**(0.0)**	**1**	**(3.6)**	**0**	**(0.0)**	**1**	**(2.9)**	**0**	**(0.0)**
Dry eye	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	1	(2.9)	0	(0.0)
Lacrimation increased	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Gastrointestinal disorders	**13**	**(48.1)**	**2**	**(7.4)**	**12**	**(42.9)**	**1**	**(3.6)**	**8**	**(23.5)**	**1**	**(2.9)**
Abdominal pain lower	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Colitis	0	(0.0)	0	(0.0)	1	(3.6)	1	(3.6)	1	(2.9)	1	(2.9)
Constipation	2	(7.4)	0	(0.0)	2	(7.1)	0	(0.0)	1	(2.9)	0	(0.0)
Diarrhoea	4	(14.8)	1	(3.7)	2	(7.1)	0	(0.0)	5	(14.7)	0	(0.0)
Dyspepsia	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Faecaloma	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Gastritis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Nausea	6	(22.2)	0	(0.0)	3	(10.7)	0	(0.0)	2	(5.9)	0	(0.0)
Stomatitis	7	(25.9)	1	(3.7)	6	(21.4)	0	(0.0)	2	(5.9)	0	(0.0)
Vomiting	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
General disorders and administration site conditions	**20**	**(74.1)**	**2**	**(7.4)**	**6**	**(21.4)**	**0**	**(0.0)**	**16**	**(47.1)**	**0**	**(0.0)**
Chest pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Chills	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Fatigue	6	(22.2)	1	(3.7)	1	(3.6)	0	(0.0)	3	(8.8)	0	(0.0)
Infusion site vasculitis	2	(7.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Malaise	6	(22.2)	0	(0.0)	4	(14.3)	0	(0.0)	9	(26.5)	0	(0.0)
Oedema	3	(11.1)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Oedema peripheral	4	(14.8)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pyrexia	5	(18.5)	0	(0.0)	3	(10.7)	0	(0.0)	4	(11.8)	0	(0.0)
Hepatobiliary disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(2.9)**	**0**	**(0.0)**
Hepatic function abnormal	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Infections and infestations	**7**	**(25.9)**	**2**	**(7.4)**	**1**	**(3.6)**	**1**	**(3.6)**	**3**	**(8.8)**	**1**	**(2.9)**
Herpes zoster	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nail infection	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nasopharyngitis	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Oral candidiasis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Otitis media acute	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Pneumonia	1	(3.7)	0	(0.0)	1	(3.6)	1	(3.6)	1	(2.9)	1	(2.9)
Pneumonia bacterial	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Septic shock	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Infections and infestations	**7**	**(25.9)**	**2**	**(7.4)**	**1**	**(3.6)**	**1**	**(3.6)**	**3**	**(8.8)**	**1**	**(2.9)**
Upper respiratory tract infection	2	(7.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Injury, poisoning and procedural complications	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(2.9)**	**0**	**(0.0)**
Skin abrasion	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Investigations	**17**	**(63.0)**	**15**	**(55.6)**	**6**	**(21.4)**	**0**	**(0.0)**	**10**	**(29.4)**	**2**	**(5.9)**
Alanine aminotransferase increased	2	(7.4)	0	(0.0)	3	(10.7)	0	(0.0)	1	(2.9)	0	(0.0)
Aspartate aminotransferase increased	1	(3.7)	0	(0.0)	2	(7.1)	0	(0.0)	0	(0.0)	0	(0.0)
Blood alkaline phosphatase increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Blood bilirubin increased	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	1	(2.9)	0	(0.0)
Blood creatinine increased	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	1	(2.9)	0	(0.0)
Blood thyroid stimulating hormone increased	0	(0.0)	0	(0.0)	2	(7.1)	0	(0.0)	1	(2.9)	0	(0.0)
Blood urea increased	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Blood uric acid increased	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
C-reactive protein increased	1	(3.7)	0	(0.0)	1	(3.6)	0	(0.0)	1	(2.9)	0	(0.0)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**17**	**(63.0)**	**15**	**(55.6)**	**6**	**(21.4)**	**0**	**(0.0)**	**10**	**(29.4)**	**2**	**(5.9)**
Eosinophil count increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Gamma-glutamyltransferase increased	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Lymphocyte count decreased	2	(7.4)	1	(3.7)	0	(0.0)	0	(0.0)	3	(8.8)	2	(5.9)
Neutrophil count decreased	11	(40.7)	10	(37.0)	0	(0.0)	0	(0.0)	2	(5.9)	0	(0.0)
Platelet count decreased	1	(3.7)	1	(3.7)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Thyroxine free increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Tri-iodothyronine decreased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Weight decreased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
White blood cell count decreased	15	(55.6)	10	(37.0)	0	(0.0)	0	(0.0)	2	(5.9)	0	(0.0)
White blood cell count increased	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Metabolism and nutrition disorders	**10**	**(37.0)**	**2**	**(7.4)**	**6**	**(21.4)**	**1**	**(3.6)**	**6**	**(17.6)**	**1**	**(2.9)**
Decreased appetite	8	(29.6)	2	(7.4)	4	(14.3)	1	(3.6)	5	(14.7)	0	(0.0)
Dehydration	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Diabetes mellitus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	1	(2.9)
Hyperuricaemia	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Metabolism and nutrition disorders	**10**	**(37.0)**	**2**	**(7.4)**	**6**	**(21.4)**	**1**	**(3.6)**	**6**	**(17.6)**	**1**	**(2.9)**
Hypoalbuminaemia	1	(3.7)	0	(0.0)	2	(7.1)	0	(0.0)	1	(2.9)	0	(0.0)
Hypokalaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Hyponatraemia	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Musculoskeletal and connective tissue disorders	**9**	**(33.3)**	**0**	**(0.0)**	**4**	**(14.3)**	**0**	**(0.0)**	**2**	**(5.9)**	**0**	**(0.0)**
Arthralgia	7	(25.9)	0	(0.0)	2	(7.1)	0	(0.0)	0	(0.0)	0	(0.0)
Arthritis	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Back pain	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Muscle spasms	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Myalgia	3	(11.1)	0	(0.0)	1	(3.6)	0	(0.0)	1	(2.9)	0	(0.0)
Pain in extremity	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Periarthritis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Nervous system disorders	**11**	**(40.7)**	**0**	**(0.0)**	**2**	**(7.1)**	**0**	**(0.0)**	**6**	**(17.6)**	**0**	**(0.0)**
Dysgeusia	7	(25.9)	0	(0.0)	0	(0.0)	0	(0.0)	4	(11.8)	0	(0.0)
Headache	1	(3.7)	0	(0.0)	2	(7.1)	0	(0.0)	2	(5.9)	0	(0.0)
Hypoaesthesia	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Neuropathy peripheral	4	(14.8)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral motor neuropathy	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Nervous system disorders	**11**	**(40.7)**	**0**	**(0.0)**	**2**	**(7.1)**	**0**	**(0.0)**	**6**	**(17.6)**	**0**	**(0.0)**
Peripheral sensory neuropathy	3	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Psychiatric disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(2.9)**	**0**	**(0.0)**
Insomnia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Renal and urinary disorders	**1**	**(3.7)**	**1**	**(3.7)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(5.9)**	**0**	**(0.0)**
Acute kidney injury	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Proteinuria	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Renal impairment	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**8**	**(29.6)**	**3**	**(11.1)**	**3**	**(10.7)**	**0**	**(0.0)**	**3**	**(8.8)**	**0**	**(0.0)**
Dyspnoea	2	(7.4)	2	(7.4)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Hiccups	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Interstitial lung disease	2	(7.4)	1	(3.7)	1	(3.6)	0	(0.0)	1	(2.9)	0	(0.0)
Nasal discomfort	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Oropharyngeal pain	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Pleural effusion	1	(3.7)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonia aspiration	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonitis	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Rhinitis allergic	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**15**	**(55.6)**	**1**	**(3.7)**	**11**	**(39.3)**	**0**	**(0.0)**	**16**	**(47.1)**	**1**	**(2.9)**
Alopecia	12	(44.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dermatitis bullous	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Drug eruption	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	1	(2.9)
Dry skin	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nail discolouration	2	(7.4)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	0	(0.0)
Nail disorder	2	(7.4)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Nail ridging	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Onychomadesis	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Palmar-plantar erythrodysaesthesia syndrome	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pruritus	2	(7.4)	1	(3.7)	3	(10.7)	0	(0.0)	7	(20.6)	0	(0.0)
Rash	4	(14.8)	0	(0.0)	6	(21.4)	0	(0.0)	9	(26.5)	0	(0.0)
Rash maculo-papular	0	(0.0)	0	(0.0)	2	(7.1)	0	(0.0)	2	(5.9)	0	(0.0)
Skin fissures	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Skin hyperpigmentation	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Skin induration	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Urticaria	3	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Vascular disorders	**1**	**(3.7)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(5.9)**	**2**	**(5.9)**
Hypertension	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	1	(2.9)
Peripheral ischaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)	1	(2.9)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Vascular disorders	**1**	**(3.7)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(5.9)**	**2**	**(5.9)**
Phlebitis	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Grades are based on NCI CTCAE version 4.0.
Adverse event terms are from MedDRA Version 18.0.
(Database Cutoff Date: &cutoff).

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付録 2.7.4- 106　副作用（いずれかの投与群で発現割合 0%超）

010 試験（MK-3475 併合、日本人安全性解析対象集団）（PD-L1 発現陽性）

Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	27				62			
with one or more adverse events	26	(96.3)	23	(85.2)	52	(83.9)	14	(22.6)
with no adverse events	1	(3.7)	4	(14.8)	10	(16.1)	48	(77.4)
Blood and lymphatic system disorders	**17**	**(63.0)**	**13**	**(48.1)**	**3**	**(4.8)**	**0**	**(0.0)**
Anaemia	5	(18.5)	1	(3.7)	2	(3.2)	0	(0.0)
Febrile neutropenia	3	(11.1)	3	(11.1)	0	(0.0)	0	(0.0)
Leukopenia	2	(7.4)	1	(3.7)	0	(0.0)	0	(0.0)
Lymphopenia	1	(3.7)	0	(0.0)	2	(3.2)	0	(0.0)
Neutropenia	11	(40.7)	11	(40.7)	0	(0.0)	0	(0.0)
Cardiac disorders	**2**	**(7.4)**	**2**	**(7.4)**	**1**	**(1.6)**	**1**	**(1.6)**
Atrial fibrillation	2	(7.4)	2	(7.4)	0	(0.0)	0	(0.0)
Atrioventricular block complete	0	(0.0)	0	(0.0)	1	(1.6)	1	(1.6)
Cardiac failure acute	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)
Ear and labyrinth disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(1.6)**	**0**	**(0.0)**
Vertigo	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Endocrine disorders	**0**	**(0.0)**	**0**	**(0.0)**	**8**	**(12.9)**	**3**	**(4.8)**
Adrenal insufficiency	0	(0.0)	0	(0.0)	2	(3.2)	1	(1.6)
Hyperthyroidism	0	(0.0)	0	(0.0)	2	(3.2)	0	(0.0)
Hypopituitarism	0	(0.0)	0	(0.0)	2	(3.2)	2	(3.2)
Hypothalamo-pituitary disorder	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Hypothyroidism	0	(0.0)	0	(0.0)	3	(4.8)	0	(0.0)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Eye disorders	**1**	**(3.7)**	**0**	**(0.0)**	**2**	**(3.2)**	**0**	**(0.0)**
Dry eye	0	(0.0)	0	(0.0)	2	(3.2)	0	(0.0)
Lacrimation increased	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Gastrointestinal disorders	**13**	**(48.1)**	**2**	**(7.4)**	**20**	**(32.3)**	**2**	**(3.2)**
Abdominal pain lower	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Colitis	0	(0.0)	0	(0.0)	2	(3.2)	2	(3.2)
Constipation	2	(7.4)	0	(0.0)	3	(4.8)	0	(0.0)
Diarrhoea	4	(14.8)	1	(3.7)	7	(11.3)	0	(0.0)
Dyspepsia	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Faecaloma	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Gastritis	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Nausea	6	(22.2)	0	(0.0)	5	(8.1)	0	(0.0)
Stomatitis	7	(25.9)	1	(3.7)	8	(12.9)	0	(0.0)
Vomiting	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
General disorders and administration site conditions	**20**	**(74.1)**	**2**	**(7.4)**	**22**	**(35.5)**	**0**	**(0.0)**
Chest pain	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Chills	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Fatigue	6	(22.2)	1	(3.7)	4	(6.5)	0	(0.0)
Infusion site vasculitis	2	(7.4)	0	(0.0)	0	(0.0)	0	(0.0)
Malaise	6	(22.2)	0	(0.0)	13	(21.0)	0	(0.0)
Oedema	3	(11.1)	1	(3.7)	0	(0.0)	0	(0.0)
Oedema peripheral	4	(14.8)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
General disorders and administration site conditions	**20**	**(74.1)**	**2**	**(7.4)**	**22**	**(35.5)**	**0**	**(0.0)**
Pyrexia	5	(18.5)	0	(0.0)	7	(11.3)	0	(0.0)
Hepatobiliary disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(1.6)**	**0**	**(0.0)**
Hepatic function abnormal	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Infections and infestations	**7**	**(25.9)**	**2**	**(7.4)**	**4**	**(6.5)**	**2**	**(3.2)**
Herpes zoster	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Nail infection	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Nasopharyngitis	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Oral candidiasis	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Otitis media acute	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Pneumonia	1	(3.7)	0	(0.0)	2	(3.2)	2	(3.2)
Pneumonia bacterial	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)
Septic shock	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)
Upper respiratory tract infection	2	(7.4)	0	(0.0)	0	(0.0)	0	(0.0)
Injury, poisoning and procedural complications	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(1.6)**	**0**	**(0.0)**
Skin abrasion	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Investigations	**17**	**(63.0)**	**15**	**(55.6)**	**16**	**(25.8)**	**2**	**(3.2)**
Alanine aminotransferase increased	2	(7.4)	0	(0.0)	4	(6.5)	0	(0.0)
Aspartate aminotransferase increased	1	(3.7)	0	(0.0)	2	(3.2)	0	(0.0)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**17**	**(63.0)**	**15**	**(55.6)**	**16**	**(25.8)**	**2**	**(3.2)**
Blood alkaline phosphatase increased	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Blood bilirubin increased	0	(0.0)	0	(0.0)	2	(3.2)	0	(0.0)
Blood creatinine increased	0	(0.0)	0	(0.0)	2	(3.2)	0	(0.0)
Blood thyroid stimulating hormone increased	0	(0.0)	0	(0.0)	3	(4.8)	0	(0.0)
Blood urea increased	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Blood uric acid increased	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
C-reactive protein increased	1	(3.7)	0	(0.0)	2	(3.2)	0	(0.0)
Eosinophil count increased	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Gamma-glutamyltransferase increased	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Lymphocyte count decreased	2	(7.4)	1	(3.7)	3	(4.8)	2	(3.2)
Neutrophil count decreased	11	(40.7)	10	(37.0)	2	(3.2)	0	(0.0)
Platelet count decreased	1	(3.7)	1	(3.7)	1	(1.6)	0	(0.0)
Thyroxine free increased	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Tri-iodothyronine decreased	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Weight decreased	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
White blood cell count decreased	15	(55.6)	10	(37.0)	2	(3.2)	0	(0.0)
White blood cell count increased	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)
Metabolism and nutrition disorders	**10**	**(37.0)**	**2**	**(7.4)**	**12**	**(19.4)**	**2**	**(3.2)**
Decreased appetite	8	(29.6)	2	(7.4)	9	(14.5)	1	(1.6)
Dehydration	1	(3.7)	1	(3.7)	1	(1.6)	0	(0.0)
Diabetes mellitus	0	(0.0)	0	(0.0)	1	(1.6)	1	(1.6)
Hyperuricaemia	1	(3.7)	0	(0.0)	1	(1.6)	0	(0.0)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Metabolism and nutrition disorders	**10**	**(37.0)**	**2**	**(7.4)**	**12**	**(19.4)**	**2**	**(3.2)**
Hypoalbuminaemia	1	(3.7)	0	(0.0)	3	(4.8)	0	(0.0)
Hypokalaemia	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Hyponatraemia	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Musculoskeletal and connective tissue disorders	**9**	**(33.3)**	**0**	**(0.0)**	**6**	**(9.7)**	**0**	**(0.0)**
Arthralgia	7	(25.9)	0	(0.0)	2	(3.2)	0	(0.0)
Arthritis	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Back pain	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Muscle spasms	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Myalgia	3	(11.1)	0	(0.0)	2	(3.2)	0	(0.0)
Pain in extremity	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Periarthritis	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Nervous system disorders	**11**	**(40.7)**	**0**	**(0.0)**	**8**	**(12.9)**	**0**	**(0.0)**
Dysgeusia	7	(25.9)	0	(0.0)	4	(6.5)	0	(0.0)
Headache	1	(3.7)	0	(0.0)	4	(6.5)	0	(0.0)
Hypoaesthesia	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Neuropathy peripheral	4	(14.8)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral motor neuropathy	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral sensory neuropathy	3	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
Psychiatric disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(1.6)**	**0**	**(0.0)**
Insomnia	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Renal and urinary disorders	**1**	**(3.7)**	**1**	**(3.7)**	**2**	**(3.2)**	**0**	**(0.0)**
Acute kidney injury	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)
Proteinuria	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Renal impairment	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**8**	**(29.6)**	**3**	**(11.1)**	**6**	**(9.7)**	**0**	**(0.0)**
Dyspnoea	2	(7.4)	2	(7.4)	1	(1.6)	0	(0.0)
Hiccups	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Interstitial lung disease	2	(7.4)	1	(3.7)	2	(3.2)	0	(0.0)
Nasal discomfort	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Oropharyngeal pain	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Pleural effusion	1	(3.7)	0	(0.0)	1	(1.6)	0	(0.0)
Pneumonia aspiration	1	(3.7)	1	(3.7)	0	(0.0)	0	(0.0)
Pneumonitis	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Rhinitis allergic	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Skin and subcutaneous tissue disorders	**15**	**(55.6)**	**1**	**(3.7)**	**27**	**(43.5)**	**1**	**(1.6)**
Alopecia	12	(44.4)	0	(0.0)	0	(0.0)	0	(0.0)
Dermatitis bullous	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Drug eruption	0	(0.0)	0	(0.0)	1	(1.6)	1	(1.6)
Dry skin	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Nail discolouration	2	(7.4)	0	(0.0)	1	(1.6)	0	(0.0)
Nail disorder	2	(7.4)	0	(0.0)	1	(1.6)	0	(0.0)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**15**	**(55.6)**	**1**	**(3.7)**	**27**	**(43.5)**	**1**	**(1.6)**
Nail ridging	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Onychomadesis	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
Palmar-plantar erythrodysaesthesia syndrome	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Pruritus	2	(7.4)	1	(3.7)	10	(16.1)	0	(0.0)
Rash	4	(14.8)	0	(0.0)	15	(24.2)	0	(0.0)
Rash maculo-papular	0	(0.0)	0	(0.0)	4	(6.5)	0	(0.0)
Skin fissures	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Skin hyperpigmentation	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Skin induration	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
Urticaria	3	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
Vascular disorders	**1**	**(3.7)**	**0**	**(0.0)**	**2**	**(3.2)**	**2**	**(3.2)**
Hypertension	0	(0.0)	0	(0.0)	1	(1.6)	1	(1.6)
Peripheral ischaemia	0	(0.0)	0	(0.0)	1	(1.6)	1	(1.6)
Phlebitis	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Grades are based on NCI CTCAE version 4.0.
Adverse event terms are from MedDRA Version 18.0.
(Database Cutoff Date: &cutoff).

Confidential

付録 2.7.4- 107　副作用（いずれかの投与群で発現割合 5%以上）

010 試験（日本人安全性解析対象集団）（PD-L1 高発現）

Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence ≥ 5% in One or More Treatment Groups) APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	11				10				13			
with one or more adverse events	10	(90.9)	10	(90.9)	9	(90.0)	2	(20.0)	11	(84.6)	5	(38.5)
with no adverse events	1	(9.1)	1	(9.1)	1	(10.0)	8	(80.0)	2	(15.4)	8	(61.5)
Blood and lymphatic system disorders	**7**	**(63.6)**	**6**	**(54.5)**	**1**	**(10.0)**	**0**	**(0.0)**	**1**	**(7.7)**	**0**	**(0.0)**
Anaemia	2	(18.2)	1	(9.1)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Febrile neutropenia	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Lymphopenia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Neutropenia	5	(45.5)	5	(45.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiac disorders	**1**	**(9.1)**	**1**	**(9.1)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Atrial fibrillation	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Endocrine disorders	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(20.0)**	**1**	**(10.0)**	**2**	**(15.4)**	**1**	**(7.7)**
Adrenal insufficiency	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	1	(7.7)	1	(7.7)
Hypopituitarism	0	(0.0)	0	(0.0)	1	(10.0)	1	(10.0)	0	(0.0)	0	(0.0)
Hypothalamo-pituitary disorder	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hypothyroidism	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Gastrointestinal disorders	**7**	**(63.6)**	**1**	**(9.1)**	**7**	**(70.0)**	**0**	**(0.0)**	**3**	**(23.1)**	**1**	**(7.7)**
Abdominal pain lower	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Colitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	1	(7.7)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence ≥ 5% in One or More Treatment Groups) APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Gastrointestinal disorders	**7**	**(63.6)**	**1**	**(9.1)**	**7**	**(70.0)**	**0**	**(0.0)**	**3**	**(23.1)**	**1**	**(7.7)**
Constipation	1	(9.1)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Diarrhoea	4	(36.4)	1	(9.1)	1	(10.0)	0	(0.0)	1	(7.7)	0	(0.0)
Dyspepsia	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Gastritis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Nausea	4	(36.4)	0	(0.0)	2	(20.0)	0	(0.0)	0	(0.0)	0	(0.0)
Stomatitis	2	(18.2)	0	(0.0)	5	(50.0)	0	(0.0)	0	(0.0)	0	(0.0)
Vomiting	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
General disorders and administration site conditions	**8**	**(72.7)**	**1**	**(9.1)**	**4**	**(40.0)**	**0**	**(0.0)**	**5**	**(38.5)**	**0**	**(0.0)**
Fatigue	5	(45.5)	1	(9.1)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Infusion site vasculitis	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Malaise	2	(18.2)	0	(0.0)	3	(30.0)	0	(0.0)	4	(30.8)	0	(0.0)
Oedema	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Oedema peripheral	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pyrexia	0	(0.0)	0	(0.0)	2	(20.0)	0	(0.0)	3	(23.1)	0	(0.0)
Infections and infestations	**2**	**(18.2)**	**2**	**(18.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(7.7)**	**0**	**(0.0)**
Oral candidiasis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Pneumonia bacterial	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Septic shock	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Investigations	**9**	**(81.8)**	**8**	**(72.7)**	**1**	**(10.0)**	**0**	**(0.0)**	**6**	**(46.2)**	**2**	**(15.4)**

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence ≥ 5% in One or More Treatment Groups) APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**9**	**(81.8)**	**8**	**(72.7)**	**1**	**(10.0)**	**0**	**(0.0)**	**6**	**(46.2)**	**2**	**(15.4)**
Alanine aminotransferase increased	1	(9.1)	0	(0.0)	1	(10.0)	0	(0.0)	1	(7.7)	0	(0.0)
Aspartate aminotransferase increased	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Blood bilirubin increased	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	1	(7.7)	0	(0.0)
Gamma-glutamyltransferase increased	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Lymphocyte count decreased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(15.4)	2	(15.4)
Neutrophil count decreased	4	(36.4)	4	(36.4)	0	(0.0)	0	(0.0)	2	(15.4)	0	(0.0)
Platelet count decreased	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
White blood cell count decreased	7	(63.6)	5	(45.5)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Metabolism and nutrition disorders	**5**	**(45.5)**	**1**	**(9.1)**	**4**	**(40.0)**	**1**	**(10.0)**	**3**	**(23.1)**	**1**	**(7.7)**
Decreased appetite	5	(45.5)	1	(9.1)	3	(30.0)	1	(10.0)	2	(15.4)	0	(0.0)
Diabetes mellitus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	1	(7.7)
Hypoalbuminaemia	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	1	(7.7)	0	(0.0)
Hyponatraemia	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence ≥ 5% in One or More Treatment Groups)
APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Musculoskeletal and connective tissue disorders	**3**	**(27.3)**	**0**	**(0.0)**	**2**	**(20.0)**	**0**	**(0.0)**	**1**	**(7.7)**	**0**	**(0.0)**
Arthralgia	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Myalgia	1	(9.1)	0	(0.0)	1	(10.0)	0	(0.0)	1	(7.7)	0	(0.0)
Pain in extremity	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nervous system disorders	**3**	**(27.3)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(15.4)**	**0**	**(0.0)**
Dysgeusia	3	(27.3)	0	(0.0)	0	(0.0)	0	(0.0)	2	(15.4)	0	(0.0)
Headache	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hypoaesthesia	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral sensory neuropathy	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**6**	**(54.5)**	**3**	**(27.3)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(15.4)**	**0**	**(0.0)**
Dyspnoea	2	(18.2)	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hiccups	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Interstitial lung disease	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Nasal discomfort	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pleural effusion	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonia aspiration	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Rhinitis allergic	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence ≥ 5% in One or More Treatment Groups) APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**5**	**(45.5)**	**1**	**(9.1)**	**6**	**(60.0)**	**0**	**(0.0)**	**7**	**(53.8)**	**0**	**(0.0)**
Alopecia	4	(36.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nail discolouration	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Nail disorder	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Onychomadesis	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pruritus	2	(18.2)	1	(9.1)	2	(20.0)	0	(0.0)	3	(23.1)	0	(0.0)
Rash	1	(9.1)	0	(0.0)	3	(30.0)	0	(0.0)	3	(23.1)	0	(0.0)
Rash maculo-papular	0	(0.0)	0	(0.0)	2	(20.0)	0	(0.0)	2	(15.4)	0	(0.0)
Skin fissures	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Skin hyperpigmentation	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Urticaria	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Vascular disorders	**1**	**(9.1)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(7.7)**	**1**	**(7.7)**
Peripheral ischaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	1	(7.7)
Phlebitis	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Grades are based on NCI CTCAE version 4.0.
Adverse event terms are from MedDRA Version 18.0.
(Database Cutoff Date: &cutoff).

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付録 2.7.4- 108　副作用（いずれかの投与群で発現割合 5%以上）

010 試験（MK-3475 併合、日本人安全性解析対象集団）（PD-L1 高発現）

Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence ≥ 5% in One or More Treatment Groups)
APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	11				23			
with one or more adverse events	10	(90.9)	10	(90.9)	20	(87.0)	7	(30.4)
with no adverse events	1	(9.1)	1	(9.1)	3	(13.0)	16	(69.6)
Blood and lymphatic system disorders	**7**	**(63.6)**	**6**	**(54.5)**	**2**	**(8.7)**	**0**	**(0.0)**
Anaemia	2	(18.2)	1	(9.1)	1	(4.3)	0	(0.0)
Febrile neutropenia	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)
Neutropenia	5	(45.5)	5	(45.5)	0	(0.0)	0	(0.0)
Cardiac disorders	**1**	**(9.1)**	**1**	**(9.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Atrial fibrillation	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)
Endocrine disorders	**0**	**(0.0)**	**0**	**(0.0)**	**4**	**(17.4)**	**2**	**(8.7)**
Adrenal insufficiency	0	(0.0)	0	(0.0)	2	(8.7)	1	(4.3)
Gastrointestinal disorders	**7**	**(63.6)**	**1**	**(9.1)**	**10**	**(43.5)**	**1**	**(4.3)**
Constipation	1	(9.1)	0	(0.0)	1	(4.3)	0	(0.0)
Diarrhoea	4	(36.4)	1	(9.1)	2	(8.7)	0	(0.0)
Dyspepsia	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Nausea	4	(36.4)	0	(0.0)	2	(8.7)	0	(0.0)
Stomatitis	2	(18.2)	0	(0.0)	5	(21.7)	0	(0.0)
Vomiting	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
General disorders and administration site conditions	**8**	**(72.7)**	**1**	**(9.1)**	**9**	**(39.1)**	**0**	**(0.0)**

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence ≥ 5% in One or More Treatment Groups)
APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
General disorders and administration site conditions	**8**	**(72.7)**	**1**	**(9.1)**	**9**	**(39.1)**	**0**	**(0.0)**
Fatigue	5	(45.5)	1	(9.1)	1	(4.3)	0	(0.0)
Infusion site vasculitis	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Malaise	2	(18.2)	0	(0.0)	7	(30.4)	0	(0.0)
Oedema	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Oedema peripheral	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)
Pyrexia	0	(0.0)	0	(0.0)	5	(21.7)	0	(0.0)
Infections and infestations	**2**	**(18.2)**	**2**	**(18.2)**	**1**	**(4.3)**	**0**	**(0.0)**
Pneumonia bacterial	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)
Septic shock	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)
Investigations	**9**	**(81.8)**	**8**	**(72.7)**	**7**	**(30.4)**	**2**	**(8.7)**
Alanine aminotransferase increased	1	(9.1)	0	(0.0)	2	(8.7)	0	(0.0)
Blood bilirubin increased	0	(0.0)	0	(0.0)	2	(8.7)	0	(0.0)
Lymphocyte count decreased	0	(0.0)	0	(0.0)	2	(8.7)	2	(8.7)
Neutrophil count decreased	4	(36.4)	4	(36.4)	2	(8.7)	0	(0.0)
Platelet count decreased	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)
White blood cell count decreased	7	(63.6)	5	(45.5)	1	(4.3)	0	(0.0)
Metabolism and nutrition disorders	**5**	**(45.5)**	**1**	**(9.1)**	**7**	**(30.4)**	**2**	**(8.7)**
Decreased appetite	5	(45.5)	1	(9.1)	5	(21.7)	1	(4.3)
Hypoalbuminaemia	0	(0.0)	0	(0.0)	2	(8.7)	0	(0.0)
Hyponatraemia	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence ≥ 5% in One or More Treatment Groups) APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Musculoskeletal and connective tissue disorders	**3**	**(27.3)**	**0**	**(0.0)**	**3**	**(13.0)**	**0**	**(0.0)**
Arthralgia	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)
Myalgia	1	(9.1)	0	(0.0)	2	(8.7)	0	(0.0)
Nervous system disorders	**3**	**(27.3)**	**0**	**(0.0)**	**2**	**(8.7)**	**0**	**(0.0)**
Dysgeusia	3	(27.3)	0	(0.0)	2	(8.7)	0	(0.0)
Headache	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Hypoaesthesia	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral sensory neuropathy	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**6**	**(54.5)**	**3**	**(27.3)**	**2**	**(8.7)**	**0**	**(0.0)**
Dyspnoea	2	(18.2)	2	(18.2)	0	(0.0)	0	(0.0)
Hiccups	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Interstitial lung disease	1	(9.1)	1	(9.1)	1	(4.3)	0	(0.0)
Nasal discomfort	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Pleural effusion	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonia aspiration	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)
Skin and subcutaneous tissue disorders	**5**	**(45.5)**	**1**	**(9.1)**	**13**	**(56.5)**	**0**	**(0.0)**
Alopecia	4	(36.4)	0	(0.0)	0	(0.0)	0	(0.0)
Nail discolouration	1	(9.1)	0	(0.0)	1	(4.3)	0	(0.0)
Nail disorder	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence ≥ 5% in One or More Treatment Groups)
APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**5**	**(45.5)**	**1**	**(9.1)**	**13**	**(56.5)**	**0**	**(0.0)**
Pruritus	2	(18.2)	1	(9.1)	5	(21.7)	0	(0.0)
Rash	1	(9.1)	0	(0.0)	6	(26.1)	0	(0.0)
Rash maculo-papular	0	(0.0)	0	(0.0)	4	(17.4)	0	(0.0)
Skin fissures	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Skin hyperpigmentation	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Urticaria	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)
Vascular disorders	**1**	**(9.1)**	**0**	**(0.0)**	**1**	**(4.3)**	**1**	**(4.3)**
Phlebitis	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Grades are based on NCI CTCAE version 4.0.
Adverse event terms are from MedDRA Version 18.0.
(Database Cutoff Date: &cutoff).

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付録 2.7.4- 109　副作用（いずれかの投与群で発現割合 5%以上）

010 試験（日本人安全性解析対象集団）（PD-L1 低発現）

Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence ≥ 5% in One or More Treatment Groups)
APaT Japan Population (1% ≤ TPS < 50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	16				18				21			
with one or more adverse events	16	(100.0)	13	(81.3)	13	(72.2)	2	(11.1)	19	(90.5)	5	(23.8)
with no adverse events	0	(0.0)	3	(18.8)	5	(27.8)	16	(88.9)	2	(9.5)	16	(76.2)
Blood and lymphatic system disorders	**10**	**(62.5)**	**7**	**(43.8)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(4.8)**	**0**	**(0.0)**
Anaemia	3	(18.8)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Febrile neutropenia	2	(12.5)	2	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Leukopenia	2	(12.5)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Lymphopenia	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Neutropenia	6	(37.5)	6	(37.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiac disorders	**1**	**(6.3)**	**1**	**(6.3)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(4.8)**	**1**	**(4.8)**
Atrial fibrillation	1	(6.3)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiac failure acute	1	(6.3)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Endocrine disorders	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(16.7)**	**0**	**(0.0)**	**1**	**(4.8)**	**1**	**(4.8)**
Hyperthyroidism	0	(0.0)	0	(0.0)	2	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
Hypothyroidism	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	1	(4.8)	0	(0.0)
Eye disorders	**1**	**(6.3)**	**0**	**(0.0)**	**1**	**(5.6)**	**0**	**(0.0)**	**1**	**(4.8)**	**0**	**(0.0)**
Dry eye	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	1	(4.8)	0	(0.0)
Lacrimation increased	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence ≥ 5% in One or More Treatment Groups)
APaT Japan Population (1% ≤ TPS < 50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Gastrointestinal disorders	**6**	**(37.5)**	**1**	**(6.3)**	**5**	**(27.8)**	**1**	**(5.6)**	**5**	**(23.8)**	**0**	**(0.0)**
Colitis	0	(0.0)	0	(0.0)	1	(5.6)	1	(5.6)	0	(0.0)	0	(0.0)
Constipation	1	(6.3)	0	(0.0)	1	(5.6)	0	(0.0)	1	(4.8)	0	(0.0)
Diarrhoea	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	4	(19.0)	0	(0.0)
Faecaloma	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nausea	2	(12.5)	0	(0.0)	1	(5.6)	0	(0.0)	2	(9.5)	0	(0.0)
Stomatitis	5	(31.3)	1	(6.3)	1	(5.6)	0	(0.0)	2	(9.5)	0	(0.0)
General disorders and administration site conditions	**12**	**(75.0)**	**1**	**(6.3)**	**2**	**(11.1)**	**0**	**(0.0)**	**11**	**(52.4)**	**0**	**(0.0)**
Fatigue	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	3	(14.3)	0	(0.0)
Infusion site vasculitis	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Malaise	4	(25.0)	0	(0.0)	1	(5.6)	0	(0.0)	5	(23.8)	0	(0.0)
Oedema	2	(12.5)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Oedema peripheral	2	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pyrexia	5	(31.3)	0	(0.0)	1	(5.6)	0	(0.0)	1	(4.8)	0	(0.0)
Infections and infestations	**5**	**(31.3)**	**0**	**(0.0)**	**1**	**(5.6)**	**1**	**(5.6)**	**2**	**(9.5)**	**1**	**(4.8)**
Herpes zoster	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nail infection	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nasopharyngitis	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonia	1	(6.3)	0	(0.0)	1	(5.6)	1	(5.6)	1	(4.8)	1	(4.8)
Upper respiratory tract infection	2	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence ≥ 5% in One or More Treatment Groups)
APaT Japan Population (1% ≤ TPS < 50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**8**	**(50.0)**	**7**	**(43.8)**	**5**	**(27.8)**	**0**	**(0.0)**	**4**	**(19.0)**	**0**	**(0.0)**
Alanine aminotransferase increased	1	(6.3)	0	(0.0)	2	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
Aspartate aminotransferase increased	1	(6.3)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Blood creatinine increased	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	1	(4.8)	0	(0.0)
Blood thyroid stimulating hormone increased	0	(0.0)	0	(0.0)	2	(11.1)	0	(0.0)	1	(4.8)	0	(0.0)
Blood urea increased	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Blood uric acid increased	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
C-reactive protein increased	1	(6.3)	0	(0.0)	1	(5.6)	0	(0.0)	1	(4.8)	0	(0.0)
Lymphocyte count decreased	2	(12.5)	1	(6.3)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Neutrophil count decreased	7	(43.8)	6	(37.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Platelet count decreased	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
White blood cell count decreased	8	(50.0)	5	(31.3)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
White blood cell count increased	1	(6.3)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Metabolism and nutrition disorders	**5**	**(31.3)**	**1**	**(6.3)**	**2**	**(11.1)**	**0**	**(0.0)**	**3**	**(14.3)**	**0**	**(0.0)**

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence ≥ 5% in One or More Treatment Groups)
APaT Japan Population (1% ≤ TPS < 50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Metabolism and nutrition disorders	**5**	**(31.3)**	**1**	**(6.3)**	**2**	**(11.1)**	**0**	**(0.0)**	**3**	**(14.3)**	**0**	**(0.0)**
Decreased appetite	3	(18.8)	1	(6.3)	1	(5.6)	0	(0.0)	3	(14.3)	0	(0.0)
Dehydration	1	(6.3)	1	(6.3)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Hyperuricaemia	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Hypoalbuminaemia	1	(6.3)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Musculoskeletal and connective tissue disorders	**6**	**(37.5)**	**0**	**(0.0)**	**2**	**(11.1)**	**0**	**(0.0)**	**1**	**(4.8)**	**0**	**(0.0)**
Arthralgia	5	(31.3)	0	(0.0)	2	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
Arthritis	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Back pain	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Myalgia	2	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nervous system disorders	**8**	**(50.0)**	**0**	**(0.0)**	**2**	**(11.1)**	**0**	**(0.0)**	**4**	**(19.0)**	**0**	**(0.0)**
Dysgeusia	4	(25.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(9.5)	0	(0.0)
Headache	0	(0.0)	0	(0.0)	2	(11.1)	0	(0.0)	2	(9.5)	0	(0.0)
Neuropathy peripheral	4	(25.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral motor neuropathy	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral sensory neuropathy	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence ≥ 5% in One or More Treatment Groups) APaT Japan Population (1% ≤ TPS < 50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Renal and urinary disorders	**1**	**(6.3)**	**1**	**(6.3)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(9.5)**	**0**	**(0.0)**
Acute kidney injury	1	(6.3)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**2**	**(12.5)**	**0**	**(0.0)**	**3**	**(16.7)**	**0**	**(0.0)**	**1**	**(4.8)**	**0**	**(0.0)**
Interstitial lung disease	1	(6.3)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Oropharyngeal pain	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Pleural effusion	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonitis	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Skin and subcutaneous tissue disorders	**10**	**(62.5)**	**0**	**(0.0)**	**5**	**(27.8)**	**0**	**(0.0)**	**9**	**(42.9)**	**1**	**(4.8)**
Alopecia	8	(50.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dry skin	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nail discolouration	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nail disorder	1	(6.3)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Nail ridging	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Palmar-plantar erythrodysaesthesia syndrome	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pruritus	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	4	(19.0)	0	(0.0)
Rash	3	(18.8)	0	(0.0)	3	(16.7)	0	(0.0)	6	(28.6)	0	(0.0)
Skin induration	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence ≥ 5% in One or More Treatment Groups)
APaT Japan Population (1% ≤ TPS < 50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**10**	**(62.5)**	**0**	**(0.0)**	**5**	**(27.8)**	**0**	**(0.0)**	**9**	**(42.9)**	**1**	**(4.8)**
Urticaria	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Grades are based on NCI CTCAE version 4.0.
Adverse event terms are from MedDRA Version 18.0.
(Database Cutoff Date: 30SEP2015).

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付録 2.7.4- 110　副作用（いずれかの投与群で発現割合 0%超）

010 試験（日本人安全性解析対象集団）（PD-L1 高発現）

Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	11				10				13			
with one or more adverse events	10	(90.9)	10	(90.9)	9	(90.0)	2	(20.0)	11	(84.6)	5	(38.5)
with no adverse events	1	(9.1)	1	(9.1)	1	(10.0)	8	(80.0)	2	(15.4)	8	(61.5)
Blood and lymphatic system disorders	**7**	**(63.6)**	**6**	**(54.5)**	**1**	**(10.0)**	**0**	**(0.0)**	**1**	**(7.7)**	**0**	**(0.0)**
Anaemia	2	(18.2)	1	(9.1)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Febrile neutropenia	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Lymphopenia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Neutropenia	5	(45.5)	5	(45.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiac disorders	**1**	**(9.1)**	**1**	**(9.1)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Atrial fibrillation	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Endocrine disorders	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(20.0)**	**1**	**(10.0)**	**2**	**(15.4)**	**1**	**(7.7)**
Adrenal insufficiency	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	1	(7.7)	1	(7.7)
Hypopituitarism	0	(0.0)	0	(0.0)	1	(10.0)	1	(10.0)	0	(0.0)	0	(0.0)
Hypothalamo-pituitary disorder	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hypothyroidism	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Gastrointestinal disorders	**7**	**(63.6)**	**1**	**(9.1)**	**7**	**(70.0)**	**0**	**(0.0)**	**3**	**(23.1)**	**1**	**(7.7)**
Abdominal pain lower	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Colitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	1	(7.7)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Gastrointestinal disorders	**7**	**(63.6)**	**1**	**(9.1)**	**7**	**(70.0)**	**0**	**(0.0)**	**3**	**(23.1)**	**1**	**(7.7)**
Constipation	1	(9.1)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Diarrhoea	4	(36.4)	1	(9.1)	1	(10.0)	0	(0.0)	1	(7.7)	0	(0.0)
Dyspepsia	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Gastritis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Nausea	4	(36.4)	0	(0.0)	2	(20.0)	0	(0.0)	0	(0.0)	0	(0.0)
Stomatitis	2	(18.2)	0	(0.0)	5	(50.0)	0	(0.0)	0	(0.0)	0	(0.0)
Vomiting	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
General disorders and administration site conditions	**8**	**(72.7)**	**1**	**(9.1)**	**4**	**(40.0)**	**0**	**(0.0)**	**5**	**(38.5)**	**0**	**(0.0)**
Fatigue	5	(45.5)	1	(9.1)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Infusion site vasculitis	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Malaise	2	(18.2)	0	(0.0)	3	(30.0)	0	(0.0)	4	(30.8)	0	(0.0)
Oedema	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Oedema peripheral	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pyrexia	0	(0.0)	0	(0.0)	2	(20.0)	0	(0.0)	3	(23.1)	0	(0.0)
Infections and infestations	**2**	**(18.2)**	**2**	**(18.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(7.7)**	**0**	**(0.0)**
Oral candidiasis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Pneumonia bacterial	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Septic shock	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Investigations	**9**	**(81.8)**	**8**	**(72.7)**	**1**	**(10.0)**	**0**	**(0.0)**	**6**	**(46.2)**	**2**	**(15.4)**

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**9**	**(81.8)**	**8**	**(72.7)**	**1**	**(10.0)**	**0**	**(0.0)**	**6**	**(46.2)**	**2**	**(15.4)**
Alanine aminotransferase increased	1	(9.1)	0	(0.0)	1	(10.0)	0	(0.0)	1	(7.7)	0	(0.0)
Aspartate aminotransferase increased	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Blood bilirubin increased	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	1	(7.7)	0	(0.0)
Gamma-glutamyltransferase increased	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Lymphocyte count decreased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(15.4)	2	(15.4)
Neutrophil count decreased	4	(36.4)	4	(36.4)	0	(0.0)	0	(0.0)	2	(15.4)	0	(0.0)
Platelet count decreased	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
White blood cell count decreased	7	(63.6)	5	(45.5)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Metabolism and nutrition disorders	**5**	**(45.5)**	**1**	**(9.1)**	**4**	**(40.0)**	**1**	**(10.0)**	**3**	**(23.1)**	**1**	**(7.7)**
Decreased appetite	5	(45.5)	1	(9.1)	3	(30.0)	1	(10.0)	2	(15.4)	0	(0.0)
Diabetes mellitus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	1	(7.7)
Hypoalbuminaemia	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	1	(7.7)	0	(0.0)
Hyponatraemia	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Musculoskeletal and connective tissue disorders	**3**	**(27.3)**	**0**	**(0.0)**	**2**	**(20.0)**	**0**	**(0.0)**	**1**	**(7.7)**	**0**	**(0.0)**
Arthralgia	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Myalgia	1	(9.1)	0	(0.0)	1	(10.0)	0	(0.0)	1	(7.7)	0	(0.0)
Pain in extremity	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nervous system disorders	**3**	**(27.3)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(15.4)**	**0**	**(0.0)**
Dysgeusia	3	(27.3)	0	(0.0)	0	(0.0)	0	(0.0)	2	(15.4)	0	(0.0)
Headache	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hypoaesthesia	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral sensory neuropathy	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**6**	**(54.5)**	**3**	**(27.3)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(15.4)**	**0**	**(0.0)**
Dyspnoea	2	(18.2)	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hiccups	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Interstitial lung disease	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Nasal discomfort	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pleural effusion	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonia aspiration	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Rhinitis allergic	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**5**	**(45.5)**	**1**	**(9.1)**	**6**	**(60.0)**	**0**	**(0.0)**	**7**	**(53.8)**	**0**	**(0.0)**
Alopecia	4	(36.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nail discolouration	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)
Nail disorder	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Onychomadesis	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pruritus	2	(18.2)	1	(9.1)	2	(20.0)	0	(0.0)	3	(23.1)	0	(0.0)
Rash	1	(9.1)	0	(0.0)	3	(30.0)	0	(0.0)	3	(23.1)	0	(0.0)
Rash maculo-papular	0	(0.0)	0	(0.0)	2	(20.0)	0	(0.0)	2	(15.4)	0	(0.0)
Skin fissures	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Skin hyperpigmentation	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Urticaria	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Vascular disorders	**1**	**(9.1)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(7.7)**	**1**	**(7.7)**
Peripheral ischaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	1	(7.7)
Phlebitis	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Grades are based on NCI CTCAE version 4.0.
Adverse event terms are from MedDRA Version 18.0.
(Database Cutoff Date: &cutoff).

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付録 2.7.4- 111　副作用（いずれかの投与群で発現割合 0%超）

010 試験（MK-3475 併合、日本人安全性解析対象集団）（PD-L1 高発現）

Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	11				23			
with one or more adverse events	10	(90.9)	10	(90.9)	20	(87.0)	7	(30.4)
with no adverse events	1	(9.1)	1	(9.1)	3	(13.0)	16	(69.6)
Blood and lymphatic system disorders	**7**	**(63.6)**	**6**	**(54.5)**	**2**	**(8.7)**	**0**	**(0.0)**
Anaemia	2	(18.2)	1	(9.1)	1	(4.3)	0	(0.0)
Febrile neutropenia	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)
Lymphopenia	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Neutropenia	5	(45.5)	5	(45.5)	0	(0.0)	0	(0.0)
Cardiac disorders	**1**	**(9.1)**	**1**	**(9.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Atrial fibrillation	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)
Endocrine disorders	**0**	**(0.0)**	**0**	**(0.0)**	**4**	**(17.4)**	**2**	**(8.7)**
Adrenal insufficiency	0	(0.0)	0	(0.0)	2	(8.7)	1	(4.3)
Hypopituitarism	0	(0.0)	0	(0.0)	1	(4.3)	1	(4.3)
Hypothalamo-pituitary disorder	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Hypothyroidism	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Gastrointestinal disorders	**7**	**(63.6)**	**1**	**(9.1)**	**10**	**(43.5)**	**1**	**(4.3)**
Abdominal pain lower	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Colitis	0	(0.0)	0	(0.0)	1	(4.3)	1	(4.3)
Constipation	1	(9.1)	0	(0.0)	1	(4.3)	0	(0.0)
Diarrhoea	4	(36.4)	1	(9.1)	2	(8.7)	0	(0.0)
Dyspepsia	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Gastrointestinal disorders	**7**	**(63.6)**	**1**	**(9.1)**	**10**	**(43.5)**	**1**	**(4.3)**
Gastritis	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Nausea	4	(36.4)	0	(0.0)	2	(8.7)	0	(0.0)
Stomatitis	2	(18.2)	0	(0.0)	5	(21.7)	0	(0.0)
Vomiting	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
General disorders and administration site conditions	**8**	**(72.7)**	**1**	**(9.1)**	**9**	**(39.1)**	**0**	**(0.0)**
Fatigue	5	(45.5)	1	(9.1)	1	(4.3)	0	(0.0)
Infusion site vasculitis	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Malaise	2	(18.2)	0	(0.0)	7	(30.4)	0	(0.0)
Oedema	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Oedema peripheral	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)
Pyrexia	0	(0.0)	0	(0.0)	5	(21.7)	0	(0.0)
Infections and infestations	**2**	**(18.2)**	**2**	**(18.2)**	**1**	**(4.3)**	**0**	**(0.0)**
Oral candidiasis	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Pneumonia bacterial	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)
Septic shock	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)
Investigations	**9**	**(81.8)**	**8**	**(72.7)**	**7**	**(30.4)**	**2**	**(8.7)**
Alanine aminotransferase increased	1	(9.1)	0	(0.0)	2	(8.7)	0	(0.0)
Aspartate aminotransferase increased	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Blood bilirubin increased	0	(0.0)	0	(0.0)	2	(8.7)	0	(0.0)
Gamma-glutamyltransferase increased	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**9**	**(81.8)**	**8**	**(72.7)**	**7**	**(30.4)**	**2**	**(8.7)**
Lymphocyte count decreased	0	(0.0)	0	(0.0)	2	(8.7)	2	(8.7)
Neutrophil count decreased	4	(36.4)	4	(36.4)	2	(8.7)	0	(0.0)
Platelet count decreased	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)
White blood cell count decreased	7	(63.6)	5	(45.5)	1	(4.3)	0	(0.0)
Metabolism and nutrition disorders	**5**	**(45.5)**	**1**	**(9.1)**	**7**	**(30.4)**	**2**	**(8.7)**
Decreased appetite	5	(45.5)	1	(9.1)	5	(21.7)	1	(4.3)
Diabetes mellitus	0	(0.0)	0	(0.0)	1	(4.3)	1	(4.3)
Hypoalbuminaemia	0	(0.0)	0	(0.0)	2	(8.7)	0	(0.0)
Hyponatraemia	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Musculoskeletal and connective tissue disorders	**3**	**(27.3)**	**0**	**(0.0)**	**3**	**(13.0)**	**0**	**(0.0)**
Arthralgia	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)
Myalgia	1	(9.1)	0	(0.0)	2	(8.7)	0	(0.0)
Pain in extremity	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Nervous system disorders	**3**	**(27.3)**	**0**	**(0.0)**	**2**	**(8.7)**	**0**	**(0.0)**
Dysgeusia	3	(27.3)	0	(0.0)	2	(8.7)	0	(0.0)
Headache	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Hypoaesthesia	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral sensory neuropathy	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Respiratory, thoracic and mediastinal disorders	**6**	**(54.5)**	**3**	**(27.3)**	**2**	**(8.7)**	**0**	**(0.0)**
Dyspnoea	2	(18.2)	2	(18.2)	0	(0.0)	0	(0.0)
Hiccups	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Interstitial lung disease	1	(9.1)	1	(9.1)	1	(4.3)	0	(0.0)
Nasal discomfort	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Pleural effusion	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonia aspiration	1	(9.1)	1	(9.1)	0	(0.0)	0	(0.0)
Rhinitis allergic	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Skin and subcutaneous tissue disorders	**5**	**(45.5)**	**1**	**(9.1)**	**13**	**(56.5)**	**0**	**(0.0)**
Alopecia	4	(36.4)	0	(0.0)	0	(0.0)	0	(0.0)
Nail discolouration	1	(9.1)	0	(0.0)	1	(4.3)	0	(0.0)
Nail disorder	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Onychomadesis	0	(0.0)	0	(0.0)	1	(4.3)	0	(0.0)
Pruritus	2	(18.2)	1	(9.1)	5	(21.7)	0	(0.0)
Rash	1	(9.1)	0	(0.0)	6	(26.1)	0	(0.0)
Rash maculo-papular	0	(0.0)	0	(0.0)	4	(17.4)	0	(0.0)
Skin fissures	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Skin hyperpigmentation	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Urticaria	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)
Vascular disorders	**1**	**(9.1)**	**0**	**(0.0)**	**1**	**(4.3)**	**1**	**(4.3)**
Peripheral ischaemia	0	(0.0)	0	(0.0)	1	(4.3)	1	(4.3)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) APaT Japan Population (TPS ≥50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 Pooled			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Vascular disorders	**1**	**(9.1)**	**0**	**(0.0)**	**1**	**(4.3)**	**1**	**(4.3)**
Phlebitis	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Grades are based on NCI CTCAE version 4.0.
Adverse event terms are from MedDRA Version 18.0.
(Database Cutoff Date: &cutoff).

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付録 2.7.4- 112　副作用（いずれかの投与群で発現割合 0%超）

010 試験（日本人安全性解析対象集団）（PD-L1 低発現）

Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (1% ≤ TPS < 50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	16				18				21			
with one or more adverse events	16	(100.0)	13	(81.3)	13	(72.2)	2	(11.1)	19	(90.5)	5	(23.8)
with no adverse events	0	(0.0)	3	(18.8)	5	(27.8)	16	(88.9)	2	(9.5)	16	(76.2)
Blood and lymphatic system disorders	**10**	**(62.5)**	**7**	**(43.8)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(4.8)**	**0**	**(0.0)**
Anaemia	3	(18.8)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Febrile neutropenia	2	(12.5)	2	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Leukopenia	2	(12.5)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Lymphopenia	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Neutropenia	6	(37.5)	6	(37.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiac disorders	**1**	**(6.3)**	**1**	**(6.3)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(4.8)**	**1**	**(4.8)**
Atrial fibrillation	1	(6.3)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Atrioventricular block complete	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	1	(4.8)
Cardiac failure acute	1	(6.3)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Ear and labyrinth disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(4.8)**	**0**	**(0.0)**
Vertigo	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Endocrine disorders	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(16.7)**	**0**	**(0.0)**	**1**	**(4.8)**	**1**	**(4.8)**
Hyperthyroidism	0	(0.0)	0	(0.0)	2	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (1% ≤ TPS < 50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Endocrine disorders	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(16.7)**	**0**	**(0.0)**	**1**	**(4.8)**	**1**	**(4.8)**
Hypopituitarism	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	1	(4.8)
Hypothyroidism	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	1	(4.8)	0	(0.0)
Eye disorders	**1**	**(6.3)**	**0**	**(0.0)**	**1**	**(5.6)**	**0**	**(0.0)**	**1**	**(4.8)**	**0**	**(0.0)**
Dry eye	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	1	(4.8)	0	(0.0)
Lacrimation increased	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Gastrointestinal disorders	**6**	**(37.5)**	**1**	**(6.3)**	**5**	**(27.8)**	**1**	**(5.6)**	**5**	**(23.8)**	**0**	**(0.0)**
Colitis	0	(0.0)	0	(0.0)	1	(5.6)	1	(5.6)	0	(0.0)	0	(0.0)
Constipation	1	(6.3)	0	(0.0)	1	(5.6)	0	(0.0)	1	(4.8)	0	(0.0)
Diarrhoea	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	4	(19.0)	0	(0.0)
Faecaloma	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nausea	2	(12.5)	0	(0.0)	1	(5.6)	0	(0.0)	2	(9.5)	0	(0.0)
Stomatitis	5	(31.3)	1	(6.3)	1	(5.6)	0	(0.0)	2	(9.5)	0	(0.0)
General disorders and administration site conditions	**12**	**(75.0)**	**1**	**(6.3)**	**2**	**(11.1)**	**0**	**(0.0)**	**11**	**(52.4)**	**0**	**(0.0)**
Chest pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Chills	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Fatigue	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	3	(14.3)	0	(0.0)
Infusion site vasculitis	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Malaise	4	(25.0)	0	(0.0)	1	(5.6)	0	(0.0)	5	(23.8)	0	(0.0)
Oedema	2	(12.5)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (1% ≤ TPS < 50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
General disorders and administration site conditions	**12**	**(75.0)**	**1**	**(6.3)**	**2**	**(11.1)**	**0**	**(0.0)**	**11**	**(52.4)**	**0**	**(0.0)**
Oedema peripheral	2	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pyrexia	5	(31.3)	0	(0.0)	1	(5.6)	0	(0.0)	1	(4.8)	0	(0.0)
Hepatobiliary disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(4.8)**	**0**	**(0.0)**
Hepatic function abnormal	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Infections and infestations	**5**	**(31.3)**	**0**	**(0.0)**	**1**	**(5.6)**	**1**	**(5.6)**	**2**	**(9.5)**	**1**	**(4.8)**
Herpes zoster	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nail infection	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nasopharyngitis	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Otitis media acute	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Pneumonia	1	(6.3)	0	(0.0)	1	(5.6)	1	(5.6)	1	(4.8)	1	(4.8)
Upper respiratory tract infection	2	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Injury, poisoning and procedural complications	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(4.8)**	**0**	**(0.0)**
Skin abrasion	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Investigations	**8**	**(50.0)**	**7**	**(43.8)**	**5**	**(27.8)**	**0**	**(0.0)**	**4**	**(19.0)**	**0**	**(0.0)**

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) APaT Japan Population (1% ≤ TPS < 50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**8**	**(50.0)**	**7**	**(43.8)**	**5**	**(27.8)**	**0**	**(0.0)**	**4**	**(19.0)**	**0**	**(0.0)**
Alanine aminotransferase increased	1	(6.3)	0	(0.0)	2	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
Aspartate aminotransferase increased	1	(6.3)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Blood alkaline phosphatase increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Blood creatinine increased	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	1	(4.8)	0	(0.0)
Blood thyroid stimulating hormone increased	0	(0.0)	0	(0.0)	2	(11.1)	0	(0.0)	1	(4.8)	0	(0.0)
Blood urea increased	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Blood uric acid increased	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
C-reactive protein increased	1	(6.3)	0	(0.0)	1	(5.6)	0	(0.0)	1	(4.8)	0	(0.0)
Eosinophil count increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Lymphocyte count decreased	2	(12.5)	1	(6.3)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Neutrophil count decreased	7	(43.8)	6	(37.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Platelet count decreased	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Thyroxine free increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Tri-iodothyronine decreased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Weight decreased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (1% ≤ TPS < 50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**8**	**(50.0)**	**7**	**(43.8)**	**5**	**(27.8)**	**0**	**(0.0)**	**4**	**(19.0)**	**0**	**(0.0)**
White blood cell count decreased	8	(50.0)	5	(31.3)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
White blood cell count increased	1	(6.3)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Metabolism and nutrition disorders	**5**	**(31.3)**	**1**	**(6.3)**	**2**	**(11.1)**	**0**	**(0.0)**	**3**	**(14.3)**	**0**	**(0.0)**
Decreased appetite	3	(18.8)	1	(6.3)	1	(5.6)	0	(0.0)	3	(14.3)	0	(0.0)
Dehydration	1	(6.3)	1	(6.3)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Hyperuricaemia	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Hypoalbuminaemia	1	(6.3)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hypokalaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Musculoskeletal and connective tissue disorders	**6**	**(37.5)**	**0**	**(0.0)**	**2**	**(11.1)**	**0**	**(0.0)**	**1**	**(4.8)**	**0**	**(0.0)**
Arthralgia	5	(31.3)	0	(0.0)	2	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
Arthritis	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Back pain	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Muscle spasms	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Myalgia	2	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Periarthritis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Nervous system disorders	**8**	**(50.0)**	**0**	**(0.0)**	**2**	**(11.1)**	**0**	**(0.0)**	**4**	**(19.0)**	**0**	**(0.0)**

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (1% ≤ TPS < 50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Nervous system disorders	**8**	**(50.0)**	**0**	**(0.0)**	**2**	**(11.1)**	**0**	**(0.0)**	**4**	**(19.0)**	**0**	**(0.0)**
Dysgeusia	4	(25.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(9.5)	0	(0.0)
Headache	0	(0.0)	0	(0.0)	2	(11.1)	0	(0.0)	2	(9.5)	0	(0.0)
Neuropathy peripheral	4	(25.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral motor neuropathy	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral sensory neuropathy	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Psychiatric disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(4.8)**	**0**	**(0.0)**
Insomnia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Renal and urinary disorders	**1**	**(6.3)**	**1**	**(6.3)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(9.5)**	**0**	**(0.0)**
Acute kidney injury	1	(6.3)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Proteinuria	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Renal impairment	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**2**	**(12.5)**	**0**	**(0.0)**	**3**	**(16.7)**	**0**	**(0.0)**	**1**	**(4.8)**	**0**	**(0.0)**
Dyspnoea	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Interstitial lung disease	1	(6.3)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Oropharyngeal pain	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Pleural effusion	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonitis	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Drug-Related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (1% ≤ TPS < 50%)

	Docetaxel 75 mg/m2 Q3W				MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**10**	**(62.5)**	**0**	**(0.0)**	**5**	**(27.8)**	**0**	**(0.0)**	**9**	**(42.9)**	**1**	**(4.8)**
Alopecia	8	(50.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dermatitis bullous	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)
Drug eruption	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	1	(4.8)
Dry skin	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nail discolouration	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nail disorder	1	(6.3)	0	(0.0)	1	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Nail ridging	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Palmar-plantar erythrodysaesthesia syndrome	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pruritus	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	4	(19.0)	0	(0.0)
Rash	3	(18.8)	0	(0.0)	3	(16.7)	0	(0.0)	6	(28.6)	0	(0.0)
Skin induration	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Urticaria	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Vascular disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(4.8)**	**1**	**(4.8)**
Hypertension	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	1	(4.8)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Grades are based on NCI CTCAE version 4.0.
Adverse event terms are from MedDRA Version 18.0.
(Database Cutoff Date: 30SEP2015).

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付録 2.7.4- 113　最終投与後 90 日までに発現した重篤な有害事象
（発現割合 0%超）
025 試験（安全性解析対象集団）
Subjects With Serious Adverse Events Up to 90 Days after Last Dose
(Incidence > 0%)
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10mg/kg Q3W	
	n	(%)
Subjects in population	38	
with one or more adverse events	11	(28.9)
with no adverse events	27	(71.1)
Gastrointestinal disorders	**1**	**(2.6)**
Inguinal hernia	1	(2.6)
Infections and infestations	**1**	**(2.6)**
Diverticulitis	1	(2.6)
Metabolism and nutrition disorders	**1**	**(2.6)**
Decreased appetite	1	(2.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1**	**(2.6)**
Oesophageal carcinoma	1	(2.6)
Nervous system disorders	**2**	**(5.3)**
Cerebrovascular accident	1	(2.6)
Optic neuritis	1	(2.6)
Respiratory, thoracic and mediastinal disorders	**4**	**(10.5)**
Interstitial lung disease	2	(5.3)
Organising pneumonia	1	(2.6)
Pneumonia aspiration	1	(2.6)
Pulmonary embolism	1	(2.6)
Vascular disorders	**1**	**(2.6)**
Pelvic venous thrombosis	1	(2.6)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms 'Neoplasm Progression', 'Malignant Neoplasm Progression' and 'Disease Progression' not related to the drug is excluded.

C Confidential

付録 2.7.4- 114　最終投与後 90 日までに発現した重篤な副作用
（発現割合 0%超）
025 試験（安全性解析対象集団）

Subjects With Drug-Related Serious Adverse Events Up to 90 Days after Last Dose
(Incidence > 0%)
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10mg/kg Q3W	
	n	(%)
Subjects in population	38	
with one or more adverse events	8	(21.1)
with no adverse events	30	(78.9)
Infections and infestations	**1**	**(2.6)**
Diverticulitis	1	(2.6)
Metabolism and nutrition disorders	**1**	**(2.6)**
Decreased appetite	1	(2.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1**	**(2.6)**
Oesophageal carcinoma	1	(2.6)
Nervous system disorders	**2**	**(5.3)**
Cerebrovascular accident	1	(2.6)
Optic neuritis	1	(2.6)
Respiratory, thoracic and mediastinal disorders	**3**	**(7.9)**
Interstitial lung disease	2	(5.3)
Organising pneumonia	1	(2.6)
Pneumonia aspiration	1	(2.6)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms 'Neoplasm Progression', 'Malignant Neoplasm Progression' and 'Disease Progression' not related to the drug is excluded.

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付録 2.7.4- 115　最終投与後 90 日までに発現した重篤な有害事象
（いずれかの投与群で発現割合 0%超）
010 試験（MK-3475 併合、日本人安全性解析対象集団）（PD-L1 発現陽性）
Subjects With Serious Adverse Events Up to 90 Days After Last Dose (Incidence > 0% in One or More Treatment Groups) MK-3475 Treatment Groups Pooled APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled	
	n	(%)	n	(%)
Subjects in population	27		62	
with one or more adverse events	7	(25.9)	22	(35.5)
with no adverse events	20	(74.1)	40	(64.5)
Blood and lymphatic system disorders	**0**	**(0.0)**	**1**	**(1.6)**
Anaemia	0	(0.0)	1	(1.6)
Cardiac disorders	**1**	**(3.7)**	**1**	**(1.6)**
Atrial fibrillation	1	(3.7)	0	(0.0)
Atrioventricular block complete	0	(0.0)	1	(1.6)
Cardiac failure acute	1	(3.7)	0	(0.0)
Endocrine disorders	**0**	**(0.0)**	**3**	**(4.8)**
Adrenal insufficiency	0	(0.0)	1	(1.6)
Hypopituitarism	0	(0.0)	2	(3.2)
Gastrointestinal disorders	**0**	**(0.0)**	**3**	**(4.8)**
Colitis	0	(0.0)	1	(1.6)
Ileus	0	(0.0)	1	(1.6)
Pancreatitis	0	(0.0)	1	(1.6)
General disorders and administration site conditions	**1**	**(3.7)**	**0**	**(0.0)**
Pyrexia	1	(3.7)	0	(0.0)
Infections and infestations	**3**	**(11.1)**	**6**	**(9.7)**
External ear cellulitis	1	(3.7)	0	(0.0)
Nasopharyngitis	1	(3.7)	0	(0.0)
Osteomyelitis	0	(0.0)	1	(1.6)
Pneumonia	0	(0.0)	3	(4.8)
Pneumonia bacterial	1	(3.7)	1	(1.6)
Pneumonia pneumococcal	0	(0.0)	1	(1.6)
Septic shock	1	(3.7)	0	(0.0)
Staphylococcal infection	1	(3.7)	0	(0.0)
Injury, poisoning and procedural complications	**1**	**(3.7)**	**0**	**(0.0)**
Traumatic intracranial haemorrhage	1	(3.7)	0	(0.0)
Metabolism and nutrition disorders	**2**	**(7.4)**	**2**	**(3.2)**
Decreased appetite	1	(3.7)	1	(1.6)
Dehydration	1	(3.7)	0	(0.0)
Diabetes mellitus	0	(0.0)	1	(1.6)

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Subjects With Serious Adverse Events Up to 90 Days After Last Dose (Incidence > 0% in One or More Treatment Groups) MK-3475 Treatment Groups Pooled APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled	
	n	(%)	n	(%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**(0.0)**	**1**	**(1.6)**
Gastric cancer	0	(0.0)	1	(1.6)
Nervous system disorders	**0**	**(0.0)**	**1**	**(1.6)**
Cerebral ischaemia	0	(0.0)	1	(1.6)
Psychiatric disorders	**0**	**(0.0)**	**1**	**(1.6)**
Completed suicide	0	(0.0)	1	(1.6)
Renal and urinary disorders	**1**	**(3.7)**	**0**	**(0.0)**
Acute kidney injury	1	(3.7)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**3**	**(11.1)**	**5**	**(8.1)**
Dyspnoea	1	(3.7)	1	(1.6)
Interstitial lung disease	1	(3.7)	1	(1.6)
Pleural effusion	0	(0.0)	1	(1.6)
Pneumonia aspiration	1	(3.7)	0	(0.0)
Pneumonitis	0	(0.0)	1	(1.6)
Pulmonary haemorrhage	1	(3.7)	1	(1.6)
Respiratory failure	1	(3.7)	0	(0.0)
Skin and subcutaneous tissue disorders	**0**	**(0.0)**	**1**	**(1.6)**
Drug eruption	0	(0.0)	1	(1.6)
Vascular disorders	**0**	**(0.0)**	**1**	**(1.6)**
Peripheral ischaemia	0	(0.0)	1	(1.6)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms 'Neoplasm Progression' ,'Malignant Neoplasm Progression' and 'Disease Progression' not related to the drug are excluded.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 30SEP2015)

Data Source:　[16.4]

C Confidential

付録 2.7.4- 116　最終投与後 90 日までに発現した重篤な副作用

（いずれかの投与群で発現割合 0%超）

010 試験（MK-3475 併合、日本人安全性解析対象集団）（PD-L1 発現陽性）

Subjects With Drug-Related Serious Adverse Events Up to 90 Days After Last Dose (Incidence > 0% in One or More Treatment Groups)
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled	
	n	(%)	n	(%)
Subjects in population	27		62	
with one or more adverse events	4	(14.8)	14	(22.6)
with no adverse events	23	(85.2)	48	(77.4)
Cardiac disorders	**1**	**(3.7)**	**1**	**(1.6)**
Atrial fibrillation	1	(3.7)	0	(0.0)
Atrioventricular block complete	0	(0.0)	1	(1.6)
Cardiac failure acute	1	(3.7)	0	(0.0)
Endocrine disorders	**0**	**(0.0)**	**3**	**(4.8)**
Adrenal insufficiency	0	(0.0)	1	(1.6)
Hypopituitarism	0	(0.0)	2	(3.2)
Gastrointestinal disorders	**0**	**(0.0)**	**1**	**(1.6)**
Colitis	0	(0.0)	1	(1.6)
Infections and infestations	**2**	**(7.4)**	**2**	**(3.2)**
Pneumonia	0	(0.0)	2	(3.2)
Pneumonia bacterial	1	(3.7)	0	(0.0)
Septic shock	1	(3.7)	0	(0.0)
Metabolism and nutrition disorders	**2**	**(7.4)**	**2**	**(3.2)**
Decreased appetite	1	(3.7)	1	(1.6)
Dehydration	1	(3.7)	0	(0.0)
Diabetes mellitus	0	(0.0)	1	(1.6)

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Subjects With Drug-Related Serious Adverse Events Up to 90 Days After Last Dose (Incidence > 0% in One or More Treatment Groups)
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled	
	n	(%)	n	(%)
Renal and urinary disorders	**1**	**(3.7)**	**0**	**(0.0)**
Acute kidney injury	1	(3.7)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**2**	**(7.4)**	**3**	**(4.8)**
Dyspnoea	1	(3.7)	1	(1.6)
Interstitial lung disease	1	(3.7)	1	(1.6)
Pleural effusion	0	(0.0)	1	(1.6)
Pneumonia aspiration	1	(3.7)	0	(0.0)
Skin and subcutaneous tissue disorders	**0**	**(0.0)**	**1**	**(1.6)**
Drug eruption	0	(0.0)	1	(1.6)
Vascular disorders	**0**	**(0.0)**	**1**	**(1.6)**
Peripheral ischaemia	0	(0.0)	1	(1.6)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 30SEP2015).

Data Source:　[16.4]

Confidential

付録 2.7.4- 117　治験薬の投与中止に至った有害事象

（いずれかの投与群で発現割合 0%超）

010 試験（MK-3475 併合、日本人安全性解析対象集団）（PD-L1 発現陽性）

Subjects With Adverse Events Resulting in Discontinuation (Incidence > 0% in One or More Treatment Groups)
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled	
	n	(%)	n	(%)
Subjects in population	27		62	
with one or more adverse events	6	(22.2)	4	(6.5)
with no adverse events	21	(77.8)	58	(93.5)
Cardiac disorders	**0**	**(0.0)**	**1**	**(1.6)**
Atrioventricular block complete	0	(0.0)	1	(1.6)
Infections and infestations	**1**	**(3.7)**	**0**	**(0.0)**
Septic shock	1	(3.7)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**(0.0)**	**1**	**(1.6)**
Gastric cancer	0	(0.0)	1	(1.6)
Respiratory, thoracic and mediastinal disorders	**3**	**(11.1)**	**1**	**(1.6)**
Bronchostenosis	0	(0.0)	1	(1.6)
Interstitial lung disease	2	(7.4)	0	(0.0)
Pneumonitis	1	(3.7)	0	(0.0)
Skin and subcutaneous tissue disorders	**2**	**(7.4)**	**0**	**(0.0)**
Alopecia	1	(3.7)	0	(0.0)
Rash	1	(3.7)	0	(0.0)
Vascular disorders	**0**	**(0.0)**	**1**	**(1.6)**

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Subjects With Adverse Events Resulting in Discontinuation (Incidence > 0% in One or More Treatment Groups)
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled	
	n	(%)	n	(%)
Vascular disorders	**0**	**(0.0)**	**1**	**(1.6)**
Peripheral ischaemia	0	(0.0)	1	(1.6)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms 'Neoplasm Progression' ,'Malignant Neoplasm Progression'　and 'Disease Progression' not related to the drug are excluded.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 30SEP2015)

Data Source:　[16.4]

Confidential

付録 2.7.4- 118　治験薬の投与中止に至った副作用

（いずれかの投与群で発現割合 0%超）

010 試験（日本人安全性解析対象集団）（PD-L1 発現陽性）

Subjects With Drug-Related Adverse Events Resulting in Discontinuation (Incidence > 0% in One or More Treatment Groups)
APaT Japan Population (TPS ≥ 1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W	
	n	(%)	n	(%)	n	(%)
Subjects in population	27		28		34	
with one or more adverse events	6	(22.2)	0	(0.0)	2	(5.9)
with no adverse events	21	(77.8)	28	(100.0)	32	(94.1)
Cardiac disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(2.9)**
Atrioventricular block complete	0	(0.0)	0	(0.0)	1	(2.9)
Infections and infestations	**1**	**(3.7)**	**0**	**(0.0)**	**0**	**(0.0)**
Septic shock	1	(3.7)	0	(0.0)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**3**	**(11.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Interstitial lung disease	2	(7.4)	0	(0.0)	0	(0.0)
Pneumonitis	1	(3.7)	0	(0.0)	0	(0.0)
Skin and subcutaneous tissue disorders	**2**	**(7.4)**	**0**	**(0.0)**	**0**	**(0.0)**
Alopecia	1	(3.7)	0	(0.0)	0	(0.0)
Rash	1	(3.7)	0	(0.0)	0	(0.0)
Vascular disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(2.9)**
Peripheral ischaemia	0	(0.0)	0	(0.0)	1	(2.9)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 30SEP2015)

Data Source:　[16.4]

Confidential

付録 2.7.4- 119　休薬に至った有害事象

（いずれかの投与群で発現割合 0%超）

010 試験（MK-3475 併合、日本人安全性解析対象集団）（PD-L1 発現陽性）

Subjects With Adverse Events Resulting in Treatment Interruption
(Incidence > 0% in One or More Treatment Groups)
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled	
	n	(%)	n	(%)
Subjects in population	27		62	
with one or more adverse events	7	(25.9)	16	(25.8)
with no adverse events	20	(74.1)	46	(74.2)
Blood and lymphatic system disorders	**1**	**(3.7)**	**1**	**(1.6)**
Anaemia	0	(0.0)	1	(1.6)
Febrile neutropenia	1	(3.7)	0	(0.0)
Endocrine disorders	**0**	**(0.0)**	**3**	**(4.8)**
Adrenal insufficiency	0	(0.0)	2	(3.2)
Hypopituitarism	0	(0.0)	1	(1.6)
Hypothalamo-pituitary disorder	0	(0.0)	1	(1.6)
Gastrointestinal disorders	**0**	**(0.0)**	**2**	**(3.2)**
Colitis	0	(0.0)	2	(3.2)
General disorders and administration site conditions	**3**	**(11.1)**	**2**	**(3.2)**
Malaise	0	(0.0)	2	(3.2)
Oedema	2	(7.4)	0	(0.0)
Oedema peripheral	1	(3.7)	0	(0.0)
Hepatobiliary disorders	**0**	**(0.0)**	**1**	**(1.6)**
Hepatic function abnormal	0	(0.0)	1	(1.6)
Infections and infestations	**3**	**(11.1)**	**4**	**(6.5)**
Infected dermal cyst	0	(0.0)	1	(1.6)
Nail infection	1	(3.7)	0	(0.0)
Pneumonia	0	(0.0)	2	(3.2)
Pneumonia pneumococcal	0	(0.0)	1	(1.6)
Staphylococcal infection	1	(3.7)	0	(0.0)
Upper respiratory tract infection	1	(3.7)	1	(1.6)
Investigations	**0**	**(0.0)**	**2**	**(3.2)**
Alanine aminotransferase increased	0	(0.0)	1	(1.6)
Aspartate aminotransferase increased	0	(0.0)	1	(1.6)
C-reactive protein increased	0	(0.0)	1	(1.6)
Metabolism and nutrition disorders	**1**	**(3.7)**	**1**	**(1.6)**
Decreased appetite	1	(3.7)	1	(1.6)
Musculoskeletal and connective tissue disorders	**0**	**(0.0)**	**3**	**(4.8)**

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Subjects With Adverse Events Resulting in Treatment Interruption
(Incidence > 0% in One or More Treatment Groups)
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled	
	n	(%)	n	(%)
Musculoskeletal and connective tissue disorders	**0**	**(0.0)**	**3**	**(4.8)**
Arthralgia	0	(0.0)	2	(3.2)
Myalgia	0	(0.0)	1	(1.6)
Nervous system disorders	**0**	**(0.0)**	**1**	**(1.6)**
Cerebral ischaemia	0	(0.0)	1	(1.6)
Respiratory, thoracic and mediastinal disorders	**2**	**(7.4)**	**1**	**(1.6)**
Dyspnoea	1	(3.7)	0	(0.0)
Interstitial lung disease	0	(0.0)	1	(1.6)
Pleural effusion	1	(3.7)	0	(0.0)
Skin and subcutaneous tissue disorders	**0**	**(0.0)**	**2**	**(3.2)**
Drug eruption	0	(0.0)	1	(1.6)
Rash	0	(0.0)	1	(1.6)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms 'Neoplasm Progression' ,'Malignant Neoplasm Progression' and 'Disease Progression' not related to the drug are excluded.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 30SEP2015)

Data Source:　[16.4]

Confidential

付録 2.7.4- 120　免疫関連の肺臓炎の AEOSI 解析
025 試験（安全性解析対象集団）

Adverse Event Summary
AEOSI - Pneumonitis
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10mg/kg Q3W	
	n	(%)
Subjects in population	38	
with one or more adverse events	4	(10.5)
with no adverse event	34	(89.5)
with drug-related† adverse events	4	(10.5)
with Grade 3- 5 adverse events	1	(2.6)
with Grade 3- 5 immune-related adverse events	1	(2.6)
with Grade 3- 5 drug-related adverse events	1	(2.6)
with serious adverse events	3	(7.9)
with serious drug-related adverse events	3	(7.9)
who died	1	(2.6)
with drug-related death	1	(2.6)
discontinued‡ due to an adverse event	2	(5.3)
discontinued due to a drug-related adverse event	2	(5.3)
discontinued due to a serious adverse event	2	(5.3)
discontinued due to a serious drug-related adverse event	2	(5.3)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
Acute interstitial pneumonitis, Interstitial lung disease, Pneumonitis, Idiopathic pneumonia syndrome, and Organising pneumonia were counted as Pneumonitis.
Grades are based on NCI CTCAE version 4.0.
MedDRA preferred terms 'Neoplasm Progression', 'Malignant Neoplasm Progression' and 'Disease Progression' not related to the drug is excluded.

C Confidential

Summary of AEOSI - Pneumonitis
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10 mg/kg Q3W
Subjects in population	38
Subjects with Pneumonitis	4 (10.5)
Time to Onset of First Pneumonitis† (days)	
Mean (SD)	30.5 (23.2)
Median (Range)	22.0 (14, 64)
Total episodes of Pneumonitis	4
Average Episodes per Subject	1.00
Episode duration‡ (days)	
Mean (SD)	87.5 (54.4)
Median (Range)	86.0 (30, 148)

(%) = Number of patients with Pneumonitis / Number of patients in population.
† Time to onset statistics are based on number of patients with Pneumonitis.
‡ Episode duration is based on a time-to-event analysis. If an adverse event is not resolved at the time of analysis or the patient died without adverse event resolved, the duration is censored at either date of last contact or date of death, whichever occurred first.

C Confidential

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0%)
AEOSI - Pneumonitis
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10mg/kg Q3W	
	n	(%)
Subjects in population	38	
with one or more adverse events	4	(10.5)
Grade 2	3	(7.9)
Grade 5	1	(2.6)
with no adverse events	34	(89.5)
Respiratory, thoracic and mediastinal disorders	**4**	**(10.5)**
Grade 2	3	(7.9)
Grade 5	1	(2.6)
Interstitial lung disease	2	(5.3)
Grade 2	1	(2.6)
Grade 5	1	(2.6)
Organising pneumonia	1	(2.6)
Grade 2	1	(2.6)
Pneumonitis	1	(2.6)
Grade 2	1	(2.6)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.0.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

C Confidential

Subjects With Concomitant Corticosteroid Use for AEOSI - Pneumonitis
(Incidence > 0%)
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10mg/kg Q3W (N=38)	
	n	%
Subjects with one or more Pneumonitis events	4	
Treated with systemic corticosteroid	4	100.0

The number of Subjects with one or more Pneumonitis events is used as the denominator for the percentage calculation.

Summary of Concomitant Corticosteroid Use for AEOSI - Pneumonitis
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10 mg/kg Q3W
Subjects in population	38
Number of Subjects with Pneumonitis	4
Total Pneumonitis Episodes	4
High Starting Dose (%) †, n (%)	**2 (50.0)**
Starting dose (mg/day)	
Mean (SD)	650 (849)
Median (Range)	650 (50-1250)
Duration‡ (days)	
Mean (SD)	4 (4)
Median (Range)	4 (1-7)
Low Starting Dose (%) †, n (%)	**2 (50.0)**
Starting dose (mg/day)	
Mean (SD)	18 (11)
Median (Range)	18 (10-25)
Duration‡ (days)	
Mean (SD)	70 (88)
Median (Range)	70 (8-132)
Not Treated with Systemic Corticosteroid, n (%)	**0 (0.0)**

(%) = Number of specific episodes / Number of total Pneumonitis episodes.
† High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent, Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
‡ Ongoing corticosteroid treatment is censored at the either date of last contact or date of death, whichever occurred first. Product-limit (Kaplan-Meier) method is applied for censored data.

Confidential

Listing of Subjects With AEOSI - Pneumonitis Adverse Events
All Positive PD-L1 Subjects
(All Treated Set Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Intensity	Toxicity Grade	Ser-ious	Related	Action Taken	Outcome
MK-3475 10mg/kg Q3W										
Trial Number=3475-025, Site Number=0003, Subject ID=025031, Gender=M, Race=Asian, Age=61 Years, Rel Day of Last Recorded Dose of Study Medication=22										
025031	Safety Follow-up	28	Interstitial lung disease	4.29 Weeks		5	Y	Y	Discontinued	Fatal
Trial Number=3475-025, Site Number=0009, Subject ID=025097, Gender=M, Race=Asian, Age=66 Years, Rel Day of Last Recorded Dose of Study Medication=82										
025097	Treatment Cycle 1	14	Organising pneumonia	1.81 Months		2	Y	Y	Interrupted	Resolved
Trial Number=3475-025, Site Number=0013, Subject ID=025131, Gender=M, Race=Asian, Age=71 Years, Rel Day of Last Recorded Dose of Study Medication=352										
025131	Treatment Cycle 3	64	Pneumonitis	4.86 Months		2	N	Y	Interrupted	Resolved
Trial Number=3475-025, Site Number=0013, Subject ID=025132, Gender=M, Race=Asian, Age=75 Years, Rel Day of Last Recorded Dose of Study Medication=1										
025132	Safety Follow-up	16	Interstitial lung disease	3.84 Months		2	Y	Y	Discontinued	Resolved

Action Taken: None = DOSE NOT CHANGED, Reduced = DOSE REDUCED, Interrupted = DRUG INTERRUPTED, Discontinued = DRUG WITHDRAWN, Increased = DOSE INCREASED, N/A = NOT APPLICABLE.
Outcome: Resolved = RECOVERED/RESOLVED, Resolving = RECOVERING/RESOLVING, Sequelae = RECOVERED/RESOLVED WITH SEQUELAE, Not resolved = NOT RECOVERED/NOT RESOLVED.
Related: Investigator-assessed relationship of the adverse event to study medication.
Grades are based on NCI CTCAE version 4.0.

Confidential

Listing of Concomitant Systemic Corticosteroid Use for Adverse Events AEOSI - Pneumonitis
(All Treated Set Population)

Subject ID	Med. Start Day	Med. Duration (Days)	Med. Name	Total Daily Dose	Frequency	Route	Prednisone Equiv.† (mg)	Adverse Event for Use	AE Start Day	AE End Day	AE Toxicity Grade
MK-3475 10mg/kg Q3W											
Trial Number=3475-025, Site Number=0003, Subject ID=025031, Gender=M, Race=Asian, Age=61 Years, Rel Day of Study Medication Discontinuance‡=22											
025031	28	1	Methylprednisolone Sodium Succinate	1000	QD	Intravenous	1250.00	Interstitial lung disease	28	57	5
	29	2	Methylprednisolone Sodium Succinate	1000	BID	Intravenous	1250.00	Interstitial lung disease	28	57	5
	47	1	Methylprednisolone Sodium Succinate	1000	QD	Intravenous	1250.00	Interstitial lung disease	28	57	5
	48	2	Methylprednisolone Sodium Succinate	1000	BID	Intravenous	1250.00	Interstitial lung disease	28	57	5
	31	7	Prednisolone	60	QD	Intravenous	60.00	Interstitial lung disease	28	57	5
	38	6	Prednisolone	50	QD	Intravenous	50.00	Interstitial lung disease	28	57	5
	44	4	Prednisolone	40	QD	Oral	40.00	Interstitial lung disease	28	57	5
	50	7	Prednisolone	60	QD	Intravenous	60.00	Interstitial lung disease	28	57	5
Trial Number=3475-025, Site Number=0009, Subject ID=025097, Gender=M, Race=Asian, Age=66 Years, Rel Day of Study Medication Discontinuance‡=82											
025097	36	8	Prednisolone	25	QD	Oral	25.00	Organising pneumonia	14	68	2
	44	10	Prednisolone	15	QD	Oral	15.00	Organising pneumonia	14	68	2
	54	8	Prednisolone	10	QD	Oral	10.00	Organising pneumonia	14	68	2
	62	7	Prednisolone	5	QD	Oral	5.00	Organising pneumonia	14	68	2
Trial Number=3475-025, Site Number=0013, Subject ID=025131, Gender=M, Race=Asian, Age=71 Years, Rel Day of Study Medication Discontinuance‡=											
025131	79	132	Prednisolone	10	QD	Oral	10.00	Pneumonitis	64	211	2
Trial Number=3475-025, Site Number=0013, Subject ID=025132, Gender=M, Race=Asian, Age=75 Years, Rel Day of Study Medication Discontinuance‡=1											

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Listing of Concomitant Systemic Corticosteroid Use for Adverse Events AEOSI - Pneumonitis
(All Treated Set Population)

Subject ID	Med. Start Day	Med. Duration (Days)	Med. Name	Total Daily Dose	Frequency	Route	Prednisone Equiv.† (mg)	Adverse Event for Use	AE Start Day	AE End Day	AE Toxicity Grade
025132	21	7	Prednisolone	50	QD	Oral	50.00	Interstitial lung disease	16	132	2
	28	7	Prednisolone	40	QD	Oral	40.00	Interstitial lung disease	16	132	2
	35	7	Prednisolone	30	QD	Oral	30.00	Interstitial lung disease	16	132	2
	42	7	Prednisolone	20	QD	Oral	20.00	Interstitial lung disease	16	132	2
	49	7	Prednisolone	15	QD	Oral	15.00	Interstitial lung disease	16	132	2
	56	.	Prednisolone	10	QD	Oral	10.00	Interstitial lung disease	16	132	2

Med.: Medication.
Equiv.: Equivalent.
AE: Adverse Event.
†: Prednisone equivalent total daily dose.
‡Relative Day of Study Medication Discontinuance is defined as the day of the last recorded dose of study medication for the subject relative to the start of study medication.
AE start date is defined as the start day of the adverse event for the subject relative to the start of study medication.
Grades are based on NCI CTCAE version 4.0.
(Data Cutoff Date: 09JUL2015).

C Confidential

付録 2.7.4- 121　免疫関連の大腸炎の AEOSI 解析
025 試験（安全性解析対象集団）

Adverse Event Summary
AEOSI - Colitis
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10mg/kg Q3W	
	n	(%)
Subjects in population	38	
with one or more adverse events	2	(5.3)
with no adverse event	36	(94.7)
with drug-related† adverse events	2	(5.3)
with Grade 3- 5 adverse events	0	(0.0)
with Grade 3- 5 immune-related adverse events	0	(0.0)
with Grade 3- 5 drug-related adverse events	0	(0.0)
with serious adverse events	0	(0.0)
with serious drug-related adverse events	0	(0.0)
who died	0	(0.0)
with drug-related death	0	(0.0)
discontinued‡ due to an adverse event	0	(0.0)
discontinued due to a drug-related adverse event	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
Colitis, Colitis microscopic, Enterocolitis, Enterocolitis haemorrhagic, Necrotising colitis and Colitis erosive were counted regarded as Colitis.
Grades are based on NCI CTCAE version 4.0.
MedDRA preferred terms 'Neoplasm Progression', 'Malignant Neoplasm Progression' and 'Disease Progression' not related to the drug is excluded.

C Confidential

Summary of AEOSI - Colitis
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10 mg/kg Q3W
Subjects in population	38
Subjects with Colitis	2 (5.3)
Time to Onset of First Colitis† (days)	
Mean (SD)	142.0 (55.2)
Median (Range)	142.0 (103, 181)
Total episodes of Colitis	2
Average Episodes per Subject	1.00
Episode duration‡ (days)	
Mean (SD)	219.0 (121.6)
Median (Range)	219.0 (133, 305)

(%) = Number of patients with Colitis / Number of patients in population.
† Time to onset statistics are based on number of patients with Colitis.
‡ Episode duration is based on a time-to-event analysis. If an adverse event is not resolved at the time of analysis or the patient died without adverse event resolved, the duration is censored at either date of last contact or date of death, whichever occurred first.

C Confidential

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0%)
AEOSI - Colitis
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10mg/kg Q3W	
	n	(%)
Subjects in population	38	
with one or more adverse events	2	(5.3)
Grade 1	1	(2.6)
Grade 2	1	(2.6)
with no adverse events	36	(94.7)
Gastrointestinal disorders	**2**	**(5.3)**
Grade 1	1	(2.6)
Grade 2	1	(2.6)
Colitis	1	(2.6)
Grade 2	1	(2.6)
Enterocolitis	1	(2.6)
Grade 1	1	(2.6)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.0.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

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Subjects With Concomitant Corticosteroid Use for AEOSI - Colitis
(Incidence > 0%)
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10mg/kg Q3W (N=38)	
	n	%
Subjects with one or more Colitis events	2	
Treated with systemic corticosteroid	2	100.0
The number of Subjects with one or more Colitis events is used as the denominator for the percentage calculation.		

Summary of Concomitant Corticosteroid Use for AEOSI - Colitis
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10 mg/kg Q3W
Subjects in population	38
Number of Subjects with Colitis	2
Total Colitis Episodes	2
High Starting Dose (%) †, n (%)	**0 (0.0)**
Low Starting Dose (%) †, n (%)	**2 (100.0)**
Starting dose (mg/day)	
Mean (SD)	18 (11)
Median (Range)	18 (10-25)
Duration‡ (days)	
Mean (SD)	11 (11)
Median (Range)	11 (3-18)
Not Treated with Systemic Corticosteroid, n (%)	**0 (0.0)**

(%) = Number of specific episodes / Number of total Colitis episodes.
† High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent, Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
‡ Ongoing corticosteroid treatment is censored at the either date of last contact or date of death, whichever occurred first. Product-limit (Kaplan-Meier) method is applied for censored data.

Confidential

Listing of Subjects With AEOSI - Colitis Adverse Events
All Positive PD-L1 Subjects
(All Treated Set Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Intensity	Toxicity Grade	Ser-ious	Related	Action Taken	Outcome
MK-3475 10mg/kg Q3W										
Trial Number=3475-025, Site Number=0003, Subject ID=025033, Gender=M, Race=Asian, Age=67 Years, Rel Day of Last Recorded Dose of Study Medication=308										
025033	Treatment Cycle 9	181	Enterocolitis	Continuing		1	N	Y	None	Not Resolved
Trial Number=3475-025, Site Number=0010, Subject ID=025101, Gender=F, Race=Asian, Age=66 Years, Rel Day of Last Recorded Dose of Study Medication=407										
025101	Treatment Cycle 5	103	Colitis	Continuing		2	N	Y	Interrupted	Not Resolved

Action Taken: None = DOSE NOT CHANGED, Reduced = DOSE REDUCED, Interrupted = DRUG INTERRUPTED, Discontinued = DRUG WITHDRAWN, Increased = DOSE INCREASED, N/A = NOT APPLICABLE.
Outcome: Resolved = RECOVERED/RESOLVED, Resolving = RECOVERING/RESOLVING, Sequelae = RECOVERED/RESOLVED WITH SEQUELAE, Not resolved = NOT RECOVERED/NOT RESOLVED.
Related: Investigator-assessed relationship of the adverse event to study medication.
Grades are based on NCI CTCAE version 4.0.

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Listing of Concomitant Systemic Corticosteroid Use for Adverse Events AEOSI - Colitis
(All Treated Set Population)

Subject ID	Med. Start Day	Med. Duration (Days)	Med. Name	Total Daily Dose	Frequency	Route	Prednisone Equiv.† (mg)	Adverse Event for Use	AE Start Day	AE End Day	AE Toxicity Grade
MK-3475 10mg/kg Q3W											
Trial Number=3475-025, Site Number=0003, Subject ID=025033, Gender=M, Race=Asian, Age=67 Years											
025033	208	3	Prednisolone	10	QD	Oral	10.00	Enterocolitis	181	.	1
	211	2	Prednisolone	5	QD	Oral	5.00	Enterocolitis	181	.	1
	213	6	Prednisolone	3	QD	Oral	2.50	Enterocolitis	181	.	1
	231	2	Prednisolone	10	QD	Oral	10.00	Enterocolitis	181	.	1
	233	4	Prednisolone	5	QD	Oral	5.00	Enterocolitis	181	.	1
	237	2	Prednisolone	3	QD	Oral	2.50	Enterocolitis	181	.	1
	254	1	Prednisolone	10	QD	Oral	10.00	Enterocolitis	181	.	1
	255	2	Prednisolone	5	QD	Oral	5.00	Enterocolitis	181	.	1
	257	3	Prednisolone	3	QD	Oral	2.50	Enterocolitis	181	.	1
	261	1	Prednisolone	10	QD	Oral	10.00	Enterocolitis	181	.	1
	262	2	Prednisolone	5	QD	Oral	5.00	Enterocolitis	181	.	1
	264	3	Prednisolone	3	QD	Oral	2.50	Enterocolitis	181	.	1
	275	1	Prednisolone	10	QD	Oral	10.00	Enterocolitis	181	.	1
	276	2	Prednisolone	5	QD	Oral	5.00	Enterocolitis	181	.	1
	278	10	Prednisolone	3	QD	Oral	2.50	Enterocolitis	181	.	1
	294	1	Prednisolone	10	QD	Oral	10.00	Enterocolitis	181	.	1

Confidential

Listing of Concomitant Systemic Corticosteroid Use for Adverse Events AEOSI - Colitis
(All Treated Set Population)

Subject ID	Med. Start Day	Med. Duration (Days)	Med. Name	Total Daily Dose	Frequency	Route	Prednisone Equiv.† (mg)	Adverse Event for Use	AE Start Day	AE End Day	AE Toxicity Grade
	295	2	Prednisolone	5	QD	Oral	5.00	Enterocolitis	181	.	1
	297	3	Prednisolone	3	QD	Oral	2.50	Enterocolitis	181	.	1
Trial Number=3475-025, Site Number=0010, Subject ID=025101, Gender=F, Race=Asian, Age=66 Years											
025101	103	18	Prednisolone	25	QD	Oral	25.00	Colitis	103	.	2
	121	7	Prednisolone	50	QD	Oral	50.00	Colitis	103	.	2
	128	6	Prednisolone	40	QD	Oral	40.00	Colitis	103	.	2
	134	8	Prednisolone	30	QD	Oral	30.00	Colitis	103	.	2
	142	7	Prednisolone	20	QD	Oral	20.00	Colitis	103	.	2
	149	7	Prednisolone	15	QD	Oral	15.00	Colitis	103	.	2
	156	21	Prednisolone	10	QD	Oral	10.00	Colitis	103	.	2

Confidential

Listing of Concomitant Systemic Corticosteroid Use for Adverse Events AEOSI - Colitis
(All Treated Set Population)

Subject ID	Med. Start Day	Med. Duration (Days)	Med. Name	Total Daily Dose	Frequency	Route	Prednisone Equiv.† (mg)	Adverse Event for Use	AE Start Day	AE End Day	AE Toxicity Grade
	177	28	Prednisolone	8	QD	Oral	7.50	Colitis	103	.	2
	205	.	Prednisolone	5	QD	Oral	5.00	Colitis	103	.	2

Med.: Medication.
Equiv.: Equivalent.
AE: Adverse Event.
†: Prednisone equivalent total daily dose.
‡Relative Day of Study Medication Discontinuance is defined as the day of the last recorded dose of study medication for the subject relative to the start of study medication.
AE start date is defined as the start day of the adverse event for the subject relative to the start of study medication.
Grades are based on NCI CTCAE version 4.0.
(Data Cutoff Date: 09JUL2015).

Confidential

付録 2.7.4- 122　免疫関連の甲状腺機能障害（甲状腺機能低下症及び甲状腺機能亢進症）の AEOSI 解析

025 試験（安全性解析対象集団）

Adverse Event Summary
AEOSI - Hypothyroidism
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10mg/kg Q3W	
	n	(%)
Subjects in population	38	
with one or more adverse events	2	(5.3)
with no adverse event	36	(94.7)
with drug-related† adverse events	2	(5.3)
with Grade 3- 5 adverse events	0	(0.0)
with Grade 3- 5 immune-related adverse events	0	(0.0)
with Grade 3- 5 drug-related adverse events	0	(0.0)
with serious adverse events	0	(0.0)
with serious drug-related adverse events	0	(0.0)
who died	0	(0.0)
with drug-related death	0	(0.0)
discontinued‡ due to an adverse event	0	(0.0)
discontinued due to a drug-related adverse event	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
Hypothyroidism, Hypothyroidic goitre, Myxoedema, Myxoedema coma and Primary hypothyroidism were counted regarded as Hypothyroidism.
Grades are based on NCI CTCAE version 4.0.
MedDRA preferred terms 'Neoplasm Progression', 'Malignant Neoplasm Progression' and 'Disease Progression' not related to the drug is excluded.

C Confidential

Summary of AEOSI - Hypothyroidism
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10 mg/kg Q3W
Subjects in population	38
Subjects with Hypothyroidism	2 (5.3)
Time to Onset of First Hypothyroidism† (days)	
Mean (SD)	35.0 (41.0)
Median (Range)	35.0 (6, 64)
Total episodes of Hypothyroidism	3
Average Episodes per Subject	1.50
Episode duration‡ (days)	
Mean (SD)	136.0 (209.6)
Median (Range)	20.0 (10, 378)

(%) = Number of patients with Hypothyroidism / Number of patients in population.
† Time to onset statistics are based on number of patients with Hypothyroidism.
‡ Episode duration is based on a time-to-event analysis. If an adverse event is not resolved at the time of analysis or the patient died without adverse event resolved, the duration is censored at either date of last contact or date of death, whichever occurred first.

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0%)
AEOSI - Hypothyroidism
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10mg/kg Q3W	
	n	(%)
Subjects in population	38	
with one or more adverse events	2	(5.3)
Grade 1	2	(5.3)
with no adverse events	36	(94.7)
Endocrine disorders	**2**	**(5.3)**
Grade 1	2	(5.3)
Hypothyroidism	2	(5.3)
Grade 1	2	(5.3)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.0.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

Confidential

Subjects With Concomitant Corticosteroid Use for AEOSI - Hypothyroidism
(Incidence > 0%)
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10mg/kg Q3W (N=38)	
	n	%
Subjects with one or more Hypothyroidism events	2	
Not treated with systemic corticosteroid	2	100.0
The number of Subjects with one or more Hypothyroidism events is used as the denominator for the percentage calculation.		

Summary of Concomitant Corticosteroid Use for AEOSI - Hypothyroidism
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10 mg/kg Q3W
Subjects in population	38
Number of Subjects with Hypothyroidism	2
Total Hypothyroidism Episodes	3
High Starting Dose (%) †, n (%)	**0 (0.0)**
Low Starting Dose (%) †, n (%)	**0 (0.0)**
Not Treated with Systemic Corticosteroid, n (%)	**3 (100.0)**
(%) = Number of specific episodes / Number of total Hypothyroidism episodes. † High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent, Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent. ‡ Ongoing corticosteroid treatment is censored at the either date of last contact or date of death, whichever occurred first. Product-limit (Kaplan-Meier) method is applied for censored data.	

Confidential

Listing of Subjects With AEOSI - Hypothyroidism Adverse Events
All Positive PD-L1 Subjects
(All Treated Set Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Intensity	Toxicity Grade	Ser-ious	Related	Action Taken	Outcome
MK-3475 10mg/kg Q3W										
Trial Number=3475-025, Site Number=0001, Subject ID=025011, Gender=M, Race=Asian, Age=57 Years, Rel Day of Last Recorded Dose of Study Medication=435										
025011	Treatment Cycle 4	64	Hypothyroidism	Continuing		1	N	Y	None	Not Resolved
Trial Number=3475-025, Site Number=0012, Subject ID=025122, Gender=F, Race=Asian, Age=68 Years, Rel Day of Last Recorded Dose of Study Medication=105										
025122	Treatment Cycle 1	6	Hypothyroidism	1.43 Weeks		1	N	Y	None	Resolved
	Treatment Cycle 6	105	Hypothyroidism	2.86 Weeks		1	N	Y	None	Resolved

Action Taken: None = DOSE NOT CHANGED, Reduced = DOSE REDUCED, Interrupted = DRUG INTERRUPTED, Discontinued = DRUG WITHDRAWN, Increased = DOSE INCREASED, N/A = NOT APPLICABLE.
Outcome: Resolved = RECOVERED/RESOLVED, Resolving = RECOVERING/RESOLVING, Sequelae = RECOVERED/RESOLVED WITH SEQUELAE, Not resolved = NOT RECOVERED/NOT RESOLVED.
Related: Investigator-assessed relationship of the adverse event to study medication.
Grades are based on NCI CTCAE version 4.0.

C Confidential

Adverse Event Summary
AEOSI - Hyperthyroidism
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10mg/kg Q3W	
	n	(%)
Subjects in population	38	
with one or more adverse events	1	(2.6)
with no adverse event	37	(97.4)
with drug-related† adverse events	1	(2.6)
with Grade 3- 5 adverse events	0	(0.0)
with Grade 3- 5 immune-related adverse events	0	(0.0)
with Grade 3- 5 drug-related adverse events	0	(0.0)
with serious adverse events	0	(0.0)
with serious drug-related adverse events	0	(0.0)
who died	0	(0.0)
with drug-related death	0	(0.0)
discontinued‡ due to an adverse event	0	(0.0)
discontinued due to a drug-related adverse event	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
Hyperthyroidism, Basedow's disease and Thyrotoxic crisis were counted as Hyperthyroidism.
Grades are based on NCI CTCAE version 4.0.
MedDRA preferred terms 'Neoplasm Progression', 'Malignant Neoplasm Progression' and 'Disease Progression' not related to the drug is excluded.

C Confidential

Summary of AEOSI - Hyperthyroidism
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10 mg/kg Q3W
Subjects in population	38
Subjects with Hyperthyroidism	1 (2.6)
Time to Onset of First Hyperthyroidism† (days)	
Mean (SD)	22.0
Median (Range)	22.0 (22, 22)
Total episodes of Hyperthyroidism	1
Average Episodes per Subject	1.00
Episode duration‡ (days)	
Mean (SD)	211.0
Median (Range)	211.0 (211, 211)

(%) = Number of patients with Hyperthyroidism / Number of patients in population.
† Time to onset statistics are based on number of patients with Hyperthyroidism.
‡ Episode duration is based on a time-to-event analysis. If an adverse event is not resolved at the time of analysis or the patient died without adverse event resolved, the duration is censored at either date of last contact or date of death, whichever occurred first.

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0%)
AEOSI - Hyperthyroidism
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10mg/kg Q3W	
	n	(%)
Subjects in population	38	
with one or more adverse events	1	(2.6)
Grade 2	1	(2.6)
with no adverse events	37	(97.4)
Endocrine disorders	**1**	**(2.6)**
Grade 2	1	(2.6)
Hyperthyroidism	1	(2.6)
Grade 2	1	(2.6)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.0.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

Confidential

Subjects With Concomitant Corticosteroid Use for AEOSI - Hyperthyroidism
(Incidence > 0%)
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10mg/kg Q3W (N=38)	
	n	%
Subjects with one or more Hyperthyroidism events	1	
Treated with systemic corticosteroid	1	100.0

The number of Subjects with one or more Hyperthyroidism events is used as the denominator for the percentage calculation.

Summary of Concomitant Corticosteroid Use for AEOSI - Hyperthyroidism
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10 mg/kg Q3W
Subjects in population	38
Number of Subjects with Hyperthyroidism	1
Total Hyperthyroidism Episodes	1
High Starting Dose (%) †, n (%)	**0 (0.0)**
Low Starting Dose (%) †, n (%)	**1 (100.0)**
Starting dose (mg/day)	
Mean (SD)	10
Median (Range)	10 (10-10)
Duration‡ (days)	
Mean (SD)	169
Median (Range)	169 (169-169)
Not Treated with Systemic Corticosteroid, n (%)	**0 (0.0)**

(%) = Number of specific episodes / Number of total Hyperthyroidism episodes.
† High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent, Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
‡ Ongoing corticosteroid treatment is censored at the either date of last contact or date of death, whichever occurred first. Product-limit (Kaplan-Meier) method is applied for censored data.

Confidential

Listing of Subjects With AEOSI - Hyperthyroidism Adverse Events
All Positive PD-L1 Subjects
(All Treated Set Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Intensity	Toxicity Grade	Ser-ious	Related	Action Taken	Outcome
MK-3475 10mg/kg Q3W										
Trial Number=3475-025, Site Number=0013, Subject ID=025133, Gender=F, Race=Asian, Age=66 Years, Rel Day of Last Recorded Dose of Study Medication=106										
025133	Treatment Cycle 2	22	Hyperthyroidism	Continuing		2	N	Y	Interrupted	Not Resolved

Action Taken: None = DOSE NOT CHANGED, Reduced = DOSE REDUCED, Interrupted = DRUG INTERRUPTED, Discontinued = DRUG WITHDRAWN, Increased = DOSE INCREASED, N/A = NOT APPLICABLE.
Outcome: Resolved = RECOVERED/RESOLVED, Resolving = RECOVERING/RESOLVING, Sequelae = RECOVERED/RESOLVED WITH SEQUELAE, Not resolved = NOT RECOVERED/NOT RESOLVED.
Related: Investigator-assessed relationship of the adverse event to study medication.
Grades are based on NCI CTCAE version 4.0.

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Listing of Concomitant Systemic Corticosteroid Use for Adverse Events AEOSI - Hyperthyroidism
(All Treated Set Population)

Subject ID	Med. Start Day	Med. Duration (Days)	Med. Name	Total Daily Dose	Frequency	Route	Prednisone Equiv.† (mg)	Adverse Event for Use	AE Start Day	AE End Day	AE Toxicity Grade
MK-3475 10mg/kg Q3W											
Trial Number=3475-025, Site Number=0013, Subject ID=025133, Gender=F, Race=Asian, Age=66 Years, Rel Day of Study Medication Discontinuance‡=106											
025133	64	.	Prednisolone	10	QD	Oral	10.00	Hyperthyroidism	22	.	2

Med.: Medication.
Equiv.: Equivalent.
AE: Adverse Event.
†: Prednisone equivalent total daily dose.
‡Relative Day of Study Medication Discontinuance is defined as the day of the last recorded dose of study medication for the subject relative to the start of study medication.
AE start date is defined as the start day of the adverse event for the subject relative to the start of study medication.
Grades are based on NCI CTCAE version 4.0.
(Data Cutoff Date: 09JUL2015).

Confidential

付録 2.7.4- 123　免疫関連のぶどう膜炎の AEOSI 解析
025 試験（安全性解析対象集団）

Adverse Event Summary
AEOSI - Uveitis
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10mg/kg Q3W	
	n	(%)
Subjects in population	38	
with one or more adverse events	1	(2.6)
with no adverse event	37	(97.4)
with drug-related† adverse events	1	(2.6)
with Grade 3- 5 adverse events	0	(0.0)
with Grade 3- 5 immune-related adverse events	0	(0.0)
with Grade 3- 5 drug-related adverse events	0	(0.0)
with serious adverse events	0	(0.0)
with serious drug-related adverse events	0	(0.0)
who died	0	(0.0)
with drug-related death	0	(0.0)
discontinued‡ due to an adverse event	0	(0.0)
discontinued due to a drug-related adverse event	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
Iritis, Uveitis, Cyclitis, Intermediate uveitis and Iridocyclitis were counted as Uveitis.
Grades are based on NCI CTCAE version 4.0.
MedDRA preferred terms 'Neoplasm Progression', 'Malignant Neoplasm Progression' and 'Disease Progression' not related to the drug is excluded.

C Confidential

Summary of AEOSI - Uveitis
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10 mg/kg Q3W
Subjects in population	38
Subjects with Uveitis	1 (2.6)
Time to Onset of First Uveitis† (days)	
Mean (SD)	43.0
Median (Range)	43.0 (43, 43)
Total episodes of Uveitis	1
Average Episodes per Subject	1.00
Episode duration‡ (days)	
Mean (SD)	162.0
Median (Range)	162.0 (162, 162)

(%) = Number of patients with Uveitis / Number of patients in population.
† Time to onset statistics are based on number of patients with Uveitis.
‡ Episode duration is based on a time-to-event analysis. If an adverse event is not resolved at the time of analysis or the patient died without adverse event resolved, the duration is censored at either date of last contact or date of death, whichever occurred first.

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0%)
AEOSI - Uveitis
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10mg/kg Q3W	
	n	(%)
Subjects in population	38	
with one or more adverse events	1	(2.6)
Grade 2	1	(2.6)
with no adverse events	37	(97.4)
Eye disorders	**1**	**(2.6)**
Grade 2	1	(2.6)
Uveitis	1	(2.6)
Grade 2	1	(2.6)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.0.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

C Confidential

Subjects With Concomitant Corticosteroid Use for AEOSI - Uveitis
(Incidence > 0%)
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10mg/kg Q3W (N=38)	
	n	%
Subjects with one or more Uveitis events	1	
Not treated with systemic corticosteroid	1	100.0
The number of Subjects with one or more Uveitis events is used as the denominator for the percentage calculation.		

Summary of Concomitant Corticosteroid Use for AEOSI - Uveitis
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10 mg/kg Q3W
Subjects in population	38
Number of Subjects with Uveitis	1
Total Uveitis Episodes	1
High Starting Dose (%) [†], n (%)	**0 (0.0)**
Low Starting Dose (%) [†], n (%)	**0 (0.0)**
Not Treated with Systemic Corticosteroid, n (%)	**1 (100.0)**
(%) = Number of specific episodes / Number of total Uveitis episodes. [†] High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent, Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent. [‡] Ongoing corticosteroid treatment is censored at the either date of last contact or date of death, whichever occurred first. Product-limit (Kaplan-Meier) method is applied for censored data.	

Confidential

Listing of Subjects With AEOSI - Uveitis Adverse Events
All Positive PD-L1 Subjects
(All Treated Set Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Intensity	Toxicity Grade	Ser-ious	Related	Action Taken	Outcome
MK-3475 10mg/kg Q3W										
Trial Number=3475-025, Site Number=0010, Subject ID=025102, Gender=M, Race=Asian, Age=64 Years, Rel Day of Last Recorded Dose of Study Medication=149										
025102	Treatment Cycle 3	43	Uveitis	5.32 Months		2	N	Y	None	Resolved

Action Taken: None = DOSE NOT CHANGED, Reduced = DOSE REDUCED, Interrupted = DRUG INTERRUPTED, Discontinued = DRUG WITHDRAWN, Increased = DOSE INCREASED, N/A = NOT APPLICABLE.
Outcome: Resolved = RECOVERED/RESOLVED, Resolving = RECOVERING/RESOLVING, Sequelae = RECOVERED/RESOLVED WITH SEQUELAE, Not resolved = NOT RECOVERED/NOT RESOLVED.
Related: Investigator-assessed relationship of the adverse event to study medication.
Grades are based on NCI CTCAE version 4.0.

Confidential

付録 2.7.4- 124　Infusion Reaction の AEOSI 解析
025 試験（安全性解析対象集団）

Adverse Event Summary
AEOSI - Infusion Reactions
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10mg/kg Q3W	
	n	(%)
Subjects in population	38	
with one or more adverse events	1	(2.6)
with no adverse event	37	(97.4)
with drug-related† adverse events	0	(0.0)
with Grade 3- 5 adverse events	0	(0.0)
with Grade 3- 5 immune-related adverse events	0	(0.0)
with Grade 3- 5 drug-related adverse events	0	(0.0)
with serious adverse events	0	(0.0)
with serious drug-related adverse events	0	(0.0)
who died	0	(0.0)
with drug-related death	0	(0.0)
discontinued‡ due to an adverse event	0	(0.0)
discontinued due to a drug-related adverse event	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
Hypersensitivity, Drug hypersensitivity, Anaphylactic reaction, Cytokine release syndrome, Serum sickness, Serum sickness-like reaction and Infusion related reaction were counted regarded as Infusion Reactions.
Grades are based on NCI CTCAE version 4.0.
MedDRA preferred terms 'Neoplasm Progression', 'Malignant Neoplasm Progression' and 'Disease Progression' not related to the drug is excluded.

Confidential

Summary of AEOSI - Infusion Reactions
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10 mg/kg Q3W
Subjects in population	38
Subjects with Infusion Reactions	1 (2.6)
Time to Onset of First Infusion Reactions† (days)	
Mean (SD)	122.0
Median (Range)	122.0 (122, 122)
Total episodes of Infusion Reactions	1
Average Episodes per Subject	1.00
Episode duration‡ (days)	
Mean (SD)	2.0
Median (Range)	2.0 (2, 2)

(%) = Number of patients with Infusion Reactions / Number of patients in population.
† Time to onset statistics are based on number of patients with Infusion Reactions.
‡ Episode duration is based on a time-to-event analysis. If an adverse event is not resolved at the time of analysis or the patient died without adverse event resolved, the duration is censored at either date of last contact or date of death, whichever occurred first.

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0%)
AEOSI - Infusion Reactions
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10mg/kg Q3W	
	n	(%)
Subjects in population	38	
with one or more adverse events	1	(2.6)
Grade 1	1	(2.6)
with no adverse events	37	(97.4)
Immune system disorders	**1**	**(2.6)**
Grade 1	1	(2.6)
Hypersensitivity	1	(2.6)
Grade 1	1	(2.6)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.0.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

C Confidential

Subjects With Concomitant Corticosteroid Use for AEOSI - Infusion Reactions
(Incidence > 0%)
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10mg/kg Q3W (N=38)	
	n	%
Subjects with one or more Infusion Reactions events	1	
Not treated with systemic corticosteroid	1	100.0
The number of Subjects with one or more Infusion Reactions events is used as the denominator for the percentage calculation.		

Summary of Concomitant Corticosteroid Use for AEOSI - Infusion Reactions
All Positive PD-L1 Subjects
(All Treated Set Population)

	MK-3475 10 mg/kg Q3W
Subjects in population	38
Number of Subjects with Infusion Reactions	1
Total Infusion Reactions Episodes	1
High Starting Dose (%) †, n (%)	**0 (0.0)**
Low Starting Dose (%) †, n (%)	**0 (0.0)**
Not Treated with Systemic Corticosteroid, n (%)	**1 (100.0)**
(%) = Number of specific episodes / Number of total Infusion Reactions episodes. † High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent, Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent. ‡ Ongoing corticosteroid treatment is censored at the either date of last contact or date of death, whichever occurred first. Product-limit (Kaplan-Meier) method is applied for censored data.	

Confidential

Listing of Subjects With AEOSI - Infusion Reactions Adverse Events
All Positive PD-L1 Subjects
(All Treated Set Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Intensity	Toxicity Grade	Ser-ious	Related	Action Taken	Outcome
MK-3475 10mg/kg Q3W										
Trial Number=3475-025, Site Number=0010, Subject ID=025102, Gender=M, Race=Asian, Age=64 Years, Rel Day of Last Recorded Dose of Study Medication=149										
025102	Treatment Cycle 6	122	Hypersensitivity	2 Days		1	N	N	None	Resolved

Action Taken: None = DOSE NOT CHANGED, Reduced = DOSE REDUCED, Interrupted = DRUG INTERRUPTED, Discontinued = DRUG WITHDRAWN, Increased = DOSE INCREASED, N/A = NOT APPLICABLE.
Outcome: Resolved = RECOVERED/RESOLVED, Resolving = RECOVERING/RESOLVING, Sequelae = RECOVERED/RESOLVED WITH SEQUELAE, Not resolved = NOT RECOVERED/NOT RESOLVED.
Related: Investigator-assessed relationship of the adverse event to study medication.
Grades are based on NCI CTCAE version 4.0.

Confidential

付録 2.7.4- 125　免疫関連の肺臓炎の AEOSI 解析

010 試験（MK-3475 併合、日本人安全性解析対象集団）（PD-L1 発現陽性）

Adverse Event Summary
AEOSI - Pneumonitis
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled	
	n	(%)	n	(%)
Subjects in population	27		62	
with one or more adverse events	3	(11.1)	3	(4.8)
with no adverse event	24	(88.9)	59	(95.2)
with drug-related† adverse events	3	(11.1)	2	(3.2)
with toxicity grade 3-5 adverse events	1	(3.7)	1	(1.6)
with toxicity grade 3-5 drug-related adverse events	1	(3.7)	0	(0.0)
with serious adverse events	1	(3.7)	2	(3.2)
with serious drug-related adverse events	1	(3.7)	1	(1.6)
who died	1	(3.7)	0	(0.0)
who died due to a drug-related adverse event	1	(3.7)	0	(0.0)
discontinued‡ due to an adverse event	3	(11.1)	0	(0.0)
discontinued due to a drug-related adverse event	3	(11.1)	0	(0.0)
discontinued due to a serious adverse event	1	(3.7)	0	(0.0)
discontinued due to a serious drug-related adverse event	1	(3.7)	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
AE of clinical interest reported by investigator.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 30SEP2015)

Data Source:　[16.4]

Confidential

Summary of AEOSI - Pneumonitis
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥ 1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	27		62		89	
Subjects with Pneumonitis	3	(11.1)	3	(4.8)	6	(6.7)
Time to Onset of First Pneumonitis (days)†						
Mean (Std)	63.0 (56.3)		114.3 (71.3)		88.7 (64.0)	
Median	41.0		102.0		76.0	
Range	21 to 127		50 to 191		21 to 191	
Total episodes of Pneumonitis	3		3		6	
Average Episodes per patient	1.00		1.00		1.00	
Episode duration (days)‡						
Median	Not reached		Not reached		Not reached	
Range	13+ to 384+		7+ to 101+		7+ to 384+	

(%) = Number of subjects with Pneumonitis / Number of subjects in population.
† Time to onset statistics are based on number of subjects with Pneumonitis.
‡ From product-limit (Kaplan-Meier) method for censored data. If an adverse event is not resolved at the time of analysis or the subject died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.
+ indicates the AE episode is not recovered/resolved by the time of the cutoff date or date of death.
Std = Standard Deviation.
Grades are based on NCI CTCAE version 4.0.
Database Cutoff Date: 30SEP2015

Data Source:　[16.4]

Confidential

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Pneumonitis
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥ 1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled	
	n	(%)	n	(%)
Subjects in population	27		62	
with one or more adverse events	3	(11.1)	3	(4.8)
with no adverse events	24	(88.9)	59	(95.2)
Respiratory, thoracic and mediastinal disorders	**3**	**(11.1)**	**3**	**(4.8)**
Interstitial lung disease	2	(7.4)	2	(3.2)
Grade 1	1	(3.7)	1	(1.6)
Grade 2	0	(0.0)	1	(1.6)
Grade 5	1	(3.7)	0	(0.0)
Pneumonitis	1	(3.7)	1	(1.6)
Grade 2	1	(3.7)	0	(0.0)
Grade 3	0	(0.0)	1	(1.6)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.0.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose
(Database Cutoff Date: 30SEP2015).

Data Source: [16.4]

C Confidential

Summary of Concomitant Corticosteroid Use for AEOSI - Pneumonitis
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W (N=27)		MK-3475 Pooled (N=62)		Total (N=89)	
	n	%	n	%	n	%
Patients with one or more Pneumonitis events	3		3		6	
Treated with systemic corticosteroid	1	33.3	2	66.7	3	50.0
Not treated with systemic corticosteroid	2	66.7	1	33.3	3	50.0

The number of Patients with one or more Pneumonitis events is used as the denominator for the percentage calculation.
Database Cutoff Date: 30SEP2015

Data Source:　[16.4]

Summary of Concomitant Corticosteroid Use for Pneumonitis Episodes
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W	MK-3475 Pooled	Total
Total Episodes	3	3	6
High Starting Dose (%) †	**1 (33.3)**	**1 (33.3)**	**2 (33.3)**
Starting dose (mg/day)			
Mean (Std)	1250 (.)	1250 (.)	1250 (0)
Median (Range)	1250 (1250-1250)	1250 (1250-1250)	1250 (1250-1250)
Duration (days)§			
Mean (Std)	3 (.)	3 (.)	3 (0)
Median (Range)	3 (3-3)	3 (3-3)	3 (3-3)
Low Starting Dose (%) ‡	**0 (0.0)**	**1 (33.3)**	**1 (16.7)**
Starting dose (mg/day)			
Mean (Std)	0 (0)	30 (.)	30 (.)
Median (Range)	0 (0-0)	30 (30-30)	30 (30-30)
Duration (days)§			
Mean (Std)	0 (0)	14 (.)	14 (.)
Median (Range)	0 (0-0)	14 (14-14)	14 (14-14)
Not Treated with Systemic Corticosteroid (%)	**2 (66.7)**	**1 (33.3)**	**3 (50.0)**

† High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
§ Ongoing corticosteroid treatment is censored at the cutoff date or date of death, whichever occurs first.
Database Cutoff Date: 30SEP2015

Data Source: [16.4]

C Confidential

Listing of Subjects With Adverse Events
AEOSI - Pneumonitis
APaT Japan Population (TPS ≥1%)

AN	Epoch	Rel Day of Onset	Adverse Event	Duration	Ser-ious	Related	Action Taken	Outcome
Docetaxel 75 mg/m2 Q3W								
Study Number=3475-010, Site Number=1403, AN=309360, Gender=M, Race=Asian, Age=68 Years, Rel Day of Study Medication Discontinuance†=30								
309360	Safety Follow-up	41	Interstitial lung disease	1.86 Weeks	Y	Y	Discontinued	Fatal
Study Number=3475-010, Site Number=1406, AN=308153, Gender=M, Race=Asian, Age=40 Years, Rel Day of Study Medication Discontinuance†=109								
308153	Safety Follow-up	127	Interstitial lung disease	Continuing	N	Y	Discontinued	Not Resolved
Study Number=3475-010, Site Number=1429, AN=308116, Gender=F, Race=Asian, Age=76 Years, Rel Day of Study Medication Discontinuance†=1								
308116	Safety Follow-up	21	Pneumonitis	1.35 Months	N	Y	Discontinued	Resolved
MK-3475 2 mg/kg Q3W								
Study Number=3475-010, Site Number=1422, AN=308873, Gender=M, Race=Asian, Age=70 Years, Rel Day of Study Medication Discontinuance†=								
308873	Treatment Cycle 9	191	Interstitial lung disease	Continuing	N	Y	None	Not Resolved
MK-3475 10 mg/kg Q3W								
Study Number=3475-010, Site Number=1401, AN=311426, Gender=F, Race=Asian, Age=74 Years, Rel Day of Study Medication Discontinuance†=1								
311426	Extended Safety Follow-up	50	Pneumonitis	1.87 Months	Y	N	N/A	Sequelae
Study Number=3475-010, Site Number=1410, AN=307796, Gender=M, Race=Asian, Age=69 Years, Rel Day of Study Medication Discontinuance†=								

C Confidential

Listing of Subjects With Adverse Events
AEOSI - Pneumonitis
APaT Japan Population (TPS ≥1%)

AN	Epoch	Rel Day of Onset	Adverse Event	Duration	Ser-ious	Related	Action Taken	Outcome
MK-3475 10 mg/kg Q3W								
Study Number=3475-010, Site Number=1410, AN=307796, Gender=M, Race=Asian, Age=69 Years, Rel Day of Study Medication Discontinuance†=								
307796	Treatment Cycle 4	102	Interstitial lung disease	Continuing	Y	Y	Interrupted	Not Resolved

†Relative Day of Study Medication Discontinuance is defined as the day of the last recorded dose of study medication for the subject relative to the start of study medication.

Action Taken: None = DOSE NOT CHANGED, Reduced = DOSE REDUCED, Interrupted = DRUG INTERRUPTED, Discontinued = DRUG WITHDRAWN, Increased = DOSE INCREASED, N/A = NOT APPLICABLE.

Outcome: Resolved = RECOVERED/RESOLVED, Resolving = RECOVERING/RESOLVING, Sequelae = RECOVERED/RESOLVED WITH SEQUELAE, Not resolved = NOT RECOVERED/NOT RESOLVED.

Related: Investigator-assessed relationship of the adverse event to study medication.

AE of clinical interest reported by investigator

After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 30SEP2015).

Data Source:　[16.4]

C Confidential

Listing of Concomitant Systemic Corticosteroid Use for Adverse Events AEOSI - Pneumonitis
APaT Japan Population (TPS ≥1%)

Subject ID	Med. Start Day	Med. Duration (Days)	Med. Name	Total Daily Dose	Frequency	Route	Prednisone Equiv.† (mg)	Adverse Event for Use	AE Start Day	AE End Day	AE Toxicity Grade
Docetaxel 75 mg/m2 Q3W											
Trial Number=3475-010, Site Number=1403, Subject ID=309360, Gender=M, Race=Asian, Age=68 Years, Rel Day of Study Medication Discontinuance‡=30											
309360	-1	1	Dexamethasone	8	QD	Oral	53.36	Interstitial lung disease	41	53	5
	41	3	Methylprednisolone Sodium Succinate	1000	QD	Intravenous	1250.00	Interstitial lung disease	41	53	5
	44	7	Methylprednisolone Sodium Succinate	500	OTHER	Intravenous	625.00	Interstitial lung disease	41	53	5
	51	3	Methylprednisolone Sodium Succinate	250	OTHER	Intravenous	312.50	Interstitial lung disease	41	53	5
MK-3475 10 mg/kg Q3W											
Trial Number=3475-010, Site Number=1401, Subject ID=311426, Gender=F, Race=Asian, Age=74 Years, Rel Day of Study Medication Discontinuance‡=1											
311426	50	3	Methylprednisolone Sodium Succinate	1000	BID	Intravenous	1250.00	Pneumonitis	50	106	3

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Listing of Concomitant Systemic Corticosteroid Use for Adverse Events AEOSI - Pneumonitis
APaT Japan Population (TPS ≥1%)

Subject ID	Med. Start Day	Med. Duration (Days)	Med. Name	Total Daily Dose	Frequency	Route	Prednisone Equiv.† (mg)	Adverse Event for Use	AE Start Day	AE End Day	AE Toxicity Grade
	65	16	Prednisolone	30	QD	Oral	30.00	Pneumonitis	50	106	3
	53	12	Prednisone	40	UNKNOWN	Intravenous	40.00	Pneumonitis	50	106	3
	81	21	Prednisone	25	QD	Oral	25.00	Pneumonitis	50	106	3
Trial Number=3475-010, Site Number=1410, Subject ID=307796, Gender=M, Race=Asian, Age=69 Years, Rel Day of Study Medication Discontinuance‡=											
307796	104	14	Prednisolone	30	QD	Oral	30.00	Interstitial lung disease	102	.	2
	118	14	Prednisolone	20	QD	Oral	20.00	Interstitial lung disease	102	.	2
	132	.	Prednisolone	10	QD	Oral	10.00	Interstitial lung disease	102	.	2

Med.: Medication.
Equiv.: Equivalent.
AE: Adverse Event.
†: Prednisone equivalent total daily dose.
‡Relative Day of Study Medication Discontinuance is defined as the day of the last recorded dose of study medication for the subject relative to the start of study medication.
AE start date is defined as the start day of the adverse event for the subject relative to the start of study medication.
Grades are based on NCI CTCAE version 4.0.
(Database Cutoff Date: 30SEP2015).

Data Source:　[16.4]

Confidential

付録 2.7.4- 126　免疫関連の大腸炎の AEOSI 解析

010 試験（MK-3475 併合、日本人安全性解析対象集団）（PD-L1 発現陽性）

Adverse Event Summary
AEOSI - Colitis
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled	
	n	(%)	n	(%)
Subjects in population	27		62	
with one or more adverse events	0	(0.0)	2	(3.2)
with no adverse event	27	(100.0)	60	(96.8)
with drug-related† adverse events	0	(0.0)	2	(3.2)
with toxicity grade 3-5 adverse events	0	(0.0)	2	(3.2)
with toxicity grade 3-5 drug-related adverse events	0	(0.0)	2	(3.2)
with serious adverse events	0	(0.0)	1	(1.6)
with serious drug-related adverse events	0	(0.0)	1	(1.6)
who died	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	0	(0.0)	0	(0.0)
discontinued due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
AE of clinical interest reported by investigator.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 30SEP2015)

Data Source:　[16.4]

Confidential

Summary of AEOSI - Colitis
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥ 1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	27		62		89	
Subjects with Colitis	0		2	(3.2)	2	(2.2)
Time to Onset of First Colitis (days)†						
Mean (Std)	0		67.0 (72.1)		67.0 (72.1)	
Median	0.0		67.0		67.0	
Range	0 to 0		16 to 118		16 to 118	
Total episodes of Colitis	0		2		2	
Average Episodes per patient	0		1.00		1.00	
Episode duration (days)‡						
Median			Not reached		Not reached	
Range			55 to 106+		55 to 106+	

(%) = Number of subjects with Colitis / Number of subjects in population.
† Time to onset statistics are based on number of subjects with Colitis.
‡ From product-limit (Kaplan-Meier) method for censored data. If an adverse event is not resolved at the time of analysis or the subject died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.
+ indicates the AE episode is not recovered/resolved by the time of the cutoff date or date of death.
Std = Standard Deviation.
Grades are based on NCI CTCAE version 4.0.
Database Cutoff Date: 30SEP2015

Data Source:　[16.4]

Confidential

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Colitis
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥ 1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled	
	n	(%)	n	(%)
Subjects in population	27		62	
with one or more adverse events	0	(0.0)	2	(3.2)
with no adverse events	27	(100.0)	60	(96.8)
Gastrointestinal disorders	**0**	**(0.0)**	**2**	**(3.2)**
Colitis	0	(0.0)	2	(3.2)
Grade 3	0	(0.0)	2	(3.2)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.0.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose
(Database Cutoff Date: 30SEP2015).

Data Source: [16.4]

Confidential

Summary of Concomitant Corticosteroid Use for AEOSI - Colitis
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W (N=27)		MK-3475 Pooled (N=62)		Total (N=89)	
	n	%	n	%	n	%
Patients with one or more Colitis events	0		2		2	
Treated with systemic corticosteroid	0	0	2	100.0	2	100.0
Not treated with systemic corticosteroid	0	0	0	0	0	0

The number of Patients with one or more Colitis events is used as the denominator for the percentage calculation.
Database Cutoff Date: 30SEP2015

Data Source:　[16.4]

Summary of Concomitant Corticosteroid Use for Colitis Episodes
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W	MK-3475 Pooled	Total
Total Episodes	0	2	2
High Starting Dose (%) †	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Low Starting Dose (%) ‡	**0 (0.0)**	**2 (100.0)**	**2 (100.0)**
Starting dose (mg/day)			
Mean (Std)	0 (0)	30 (0)	30 (0)
Median (Range)	0 (0-0)	30 (30-30)	30 (30-30)
Duration (days)§			
Mean (Std)	0 (0)	3 (0)	3 (0)
Median (Range)	0 (0-0)	3 (3-3)	3 (3-3)
Not Treated with Systemic Corticosteroid (%)	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**

† High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
§ Ongoing corticosteroid treatment is censored at the cutoff date or date of death, whichever occurs first.
Database Cutoff Date: 30SEP2015

Data Source: [16.4]

C Confidential

Listing of Subjects With Adverse Events
AEOSI - Colitis
APaT Japan Population (TPS ≥1%)

AN	Epoch	Rel Day of Onset	Adverse Event	Duration	Ser-ious	Related	Action Taken	Outcome
MK-3475 2 mg/kg Q3W								
Study Number=3475-010, Site Number=1405, AN=304574, Gender=M, Race=Asian, Age=66 Years, Rel Day of Study Medication Discontinuance†=								
304574	Treatment Cycle 4	118	Colitis	Continuing	Y	Y	Interrupted	Resolving
MK-3475 10 mg/kg Q3W								
Study Number=3475-010, Site Number=1405, AN=312141, Gender=M, Race=Asian, Age=74 Years, Rel Day of Study Medication Discontinuance†=40								
312141	Treatment Cycle 1	16	Colitis	1.81 Months	N	Y	Interrupted	Resolved

†Relative Day of Study Medication Discontinuance is defined as the day of the last recorded dose of study medication for the subject relative to the start of study medication.
Action Taken: None = DOSE NOT CHANGED, Reduced = DOSE REDUCED, Interrupted = DRUG INTERRUPTED, Discontinued = DRUG WITHDRAWN, Increased = DOSE INCREASED, N/A = NOT APPLICABLE.
Outcome: Resolved = RECOVERED/RESOLVED, Resolving = RECOVERING/RESOLVING, Sequelae = RECOVERED/RESOLVED WITH SEQUELAE, Not resolved = NOT RECOVERED/NOT RESOLVED.
Related: Investigator-assessed relationship of the adverse event to study medication.
AE of clinical interest reported by investigator
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 30SEP2015).

Data Source:　[16.4]

C Confidential

Listing of Concomitant Systemic Corticosteroid Use for Adverse Events AEOSI - Colitis
APaT Japan Population (TPS ≥1%)

Subject ID	Med. Start Day	Med. Duration (Days)	Med. Name	Total Daily Dose	Frequency	Route	Prednisone Equiv.† (mg)	Adverse Event for Use	AE Start Day	AE End Day	AE Toxicity Grade
MK-3475 2 mg/kg Q3W											
Trial Number=3475-010, Site Number=1405, Subject ID=304574, Gender=M, Race=Asian, Age=66 Years, Rel Day of Study Medication Discontinuance‡=											
304574	118	3	Prednisolone	30	QD	Intravenous	30.00	Colitis	118	.	3
	121	10	Prednisolone	30	BID	Oral	30.00	Colitis	118	.	3
	131	14	Prednisolone	20	QD	Oral	20.00	Colitis	118	.	3
	145	11	Prednisolone	15	QD	Oral	15.00	Colitis	118	.	3
	156	38	Prednisolone	10	QD	Oral	10.00	Colitis	118	.	3
	194	.	Prednisolone	5	QD	Oral	5.00	Colitis	118	.	3
MK-3475 10 mg/kg Q3W											

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Listing of Concomitant Systemic Corticosteroid Use for Adverse Events AEOSI - Colitis
APaT Japan Population (TPS ≥1%)

Subject ID	Med. Start Day	Med. Duration (Days)	Med. Name	Total Daily Dose	Frequency	Route	Prednisone Equiv.† (mg)	Adverse Event for Use	AE Start Day	AE End Day	AE Toxicity Grade
Trial Number=3475-010, Site Number=1405, Subject ID=312141, Gender=M, Race=Asian, Age=74 Years, Rel Day of Study Medication Discontinuance‡=40											
312141	16	3	Prednisolone	30	QD	Intravenous	30.00	Colitis	16	70	3
	19	3	Prednisolone	30	BID	Oral	30.00	Colitis	16	70	3
	23	7	Prednisolone	20	BID	Oral	20.00	Colitis	16	70	3
	30	17	Prednisolone	10	BID	Oral	10.00	Colitis	16	70	3
	47	19	Prednisolone	30	BID	Oral	30.00	Colitis	16	70	3

Med.: Medication.
Equiv.: Equivalent.
AE: Adverse Event.
†: Prednisone equivalent total daily dose.
‡Relative Day of Study Medication Discontinuance is defined as the day of the last recorded dose of study medication for the subject relative to the start of study medication.
AE start date is defined as the start day of the adverse event for the subject relative to the start of study medication.
Grades are based on NCI CTCAE version 4.0.
(Database Cutoff Date: 30SEP2015).

Data Source:　[16.4]

Confidential

付録 2.7.4- 127　免疫関連の下垂体炎（下垂体機能低下症及び続発性副腎機能不全を含む）の AEOSI 解析

010 試験（MK-3475 併合、日本人安全性解析対象集団）（PD-L1 発現陽性）

Adverse Event Summary
AEOSI - Hypophysitis
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled	
	n	(%)	n	(%)
Subjects in population	27		62	
with one or more adverse events	0	(0.0)	2	(3.2)
with no adverse event	27	(100.0)	60	(96.8)
with drug-related† adverse events	0	(0.0)	2	(3.2)
with toxicity grade 3-5 adverse events	0	(0.0)	2	(3.2)
with toxicity grade 3-5 drug-related adverse events	0	(0.0)	2	(3.2)
with serious adverse events	0	(0.0)	2	(3.2)
with serious drug-related adverse events	0	(0.0)	2	(3.2)
who died	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	0	(0.0)	0	(0.0)
discontinued due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
AE of clinical interest reported by investigator.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 30SEP2015)

Data Source:　[16.4]

Confidential

Summary of AEOSI - Hypophysitis
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥ 1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	27		62		89	
Subjects with Hypophysitis	0		2	(3.2)	2	(2.2)
Time to Onset of First Hypophysitis (days)†						
Mean (Std)	0		192.0 (121.6)		192.0 (121.6)	
Median	0.0		192.0		192.0	
Range	0 to 0		106 to 278		106 to 278	
Total episodes of Hypophysitis	0		2		2	
Average Episodes per patient	0		1.00		1.00	
Episode duration (days)‡						
Median			Not reached		Not reached	
Range			94+ to 97+		94+ to 97+	

(%) = Number of subjects with Hypophysitis / Number of subjects in population.
† Time to onset statistics are based on number of subjects with Hypophysitis.
‡ From product-limit (Kaplan-Meier) method for censored data. If an adverse event is not resolved at the time of analysis or the subject died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.
+ indicates the AE episode is not recovered/resolved by the time of the cutoff date or date of death.
Std = Standard Deviation.
Grades are based on NCI CTCAE version 4.0.
Database Cutoff Date: 30SEP2015

Data Source:　[16.4]

Confidential

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Hypophysitis
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥ 1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled	
	n	(%)	n	(%)
Subjects in population	27		62	
with one or more adverse events	0	(0.0)	2	(3.2)
with no adverse events	27	(100.0)	60	(96.8)
Endocrine disorders	**0**	**(0.0)**	**2**	**(3.2)**
Hypopituitarism	0	(0.0)	2	(3.2)
Grade 3	0	(0.0)	2	(3.2)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.0.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose
(Database Cutoff Date: 30SEP2015).

Data Source: [16.4]

C Confidential

Summary of Concomitant Corticosteroid Use for AEOSI - Hypophysitis
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W (N=27)		MK-3475 Pooled (N=62)		Total (N=89)	
	n	%	n	%	n	%
Patients with one or more Hypophysitis events	0		2		2	
Treated with systemic corticosteroid	0	0	2	100.0	2	100.0
Not treated with systemic corticosteroid	0	0	0	0	0	0

The number of Patients with one or more Hypophysitis events is used as the denominator for the percentage calculation.
Database Cutoff Date: 30SEP2015

Data Source:　[16.4]

Summary of Concomitant Corticosteroid Use for Hypophysitis Episodes
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W	MK-3475 Pooled	Total
Total Episodes	0	2	2
High Starting Dose (%) †	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Low Starting Dose (%) ‡	**0 (0.0)**	**2 (100.0)**	**2 (100.0)**
Starting dose (mg/day)			
Mean (Std)	0 (0)	14 (15)	14 (15)
Median (Range)	0 (0-0)	14 (4-25)	14 (4-25)
Duration (days)§			
Mean (Std)	0 (0)	44 (60)	44 (60)
Median (Range)	0 (0-0)	44 (1-86)	44 (1-86)
Not Treated with Systemic Corticosteroid (%)	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**

† High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
§ Ongoing corticosteroid treatment is censored at the cutoff date or date of death, whichever occurs first.
Database Cutoff Date: 30SEP2015

Data Source: [16.4]

C Confidential

Listing of Subjects With Adverse Events
AEOSI - Hypophysitis
APaT Japan Population (TPS ≥1%)

AN	Epoch	Rel Day of Onset	Adverse Event	Duration	Ser-ious	Related	Action Taken	Outcome
MK-3475 2 mg/kg Q3W								
Study Number=3475-010, Site Number=1403, AN=301594, Gender=M, Race=Asian, Age=78 Years								
301594	Treatment Cycle 5	106	Hypopituitarism	Continuing	Y	Y	Reduced	Not Resolved
MK-3475 10 mg/kg Q3W								
Study Number=3475-010, Site Number=1421, AN=311479, Gender=M, Race=Asian, Age=49 Years								
311479	Treatment Cycle 11	278	Hypopituitarism	Continuing	Y	Y	Interrupted	Not Resolved

Action Taken: None = DOSE NOT CHANGED, Reduced = DOSE REDUCED, Interrupted = DRUG INTERRUPTED, Discontinued = DRUG WITHDRAWN, Increased = DOSE INCREASED, N/A = NOT APPLICABLE.

Outcome: Resolved = RECOVERED/RESOLVED, Resolving = RECOVERING/RESOLVING, Sequelae = RECOVERED/RESOLVED WITH SEQUELAE, Not resolved = NOT RECOVERED/NOT RESOLVED.

Related: Investigator-assessed relationship of the adverse event to study medication.

AE of clinical interest reported by investigator

After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 30SEP2015).

Data Source:　[16.4]

Confidential

Listing of Concomitant Systemic Corticosteroid Use for Adverse Events AEOSI - Hypophysitis
APaT Japan Population (TPS ≥1%)

Subject ID	Med. Start Day	Med. Duration (Days)	Med. Name	Total Daily Dose	Frequency	Route	Prednisone Equiv.† (mg)	Adverse Event for Use	AE Start Day	AE End Day	AE Toxicity Grade
MK-3475 2 mg/kg Q3W											
Trial Number=3475-010, Site Number=1403, Subject ID=301594, Gender=M, Race=Asian, Age=78 Years											
301594	106	1	Hydrocortisone Sodium Succinate	100	QD	Intravenous	25.00	Hypopituitarism	106	.	3
MK-3475 10 mg/kg Q3W											
Trial Number=3475-010, Site Number=1421, Subject ID=311479, Gender=M, Race=Asian, Age=49 Years											
311479	286	.	Hydrocortisone	15	BID	Oral	3.75	Hypopituitarism	278	.	3

Med.: Medication.
Equiv.: Equivalent.
AE: Adverse Event.
†: Prednisone equivalent total daily dose.
‡Relative Day of Study Medication Discontinuance is defined as the day of the last recorded dose of study medication for the subject relative to the start of study medication.
AE start date is defined as the start day of the adverse event for the subject relative to the start of study medication.
Grades are based on NCI CTCAE version 4.0.
(Database Cutoff Date: 30SEP2015).

Data Source:　[16.4]

Confidential

Adverse Event Summary
AEOSI - Adrenal
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled	
	n	(%)	n	(%)
Subjects in population	27		62	
with one or more adverse events	0	(0.0)	2	(3.2)
with no adverse event	27	(100.0)	60	(96.8)
with drug-related† adverse events	0	(0.0)	2	(3.2)
with toxicity grade 3-5 adverse events	0	(0.0)	1	(1.6)
with toxicity grade 3-5 drug-related adverse events	0	(0.0)	1	(1.6)
with serious adverse events	0	(0.0)	1	(1.6)
with serious drug-related adverse events	0	(0.0)	1	(1.6)
who died	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	0	(0.0)	0	(0.0)
discontinued due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
AE of clinical interest reported by investigator.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 30SEP2015)

Data Source:　[16.4]

C Confidential

Summary of AEOSI - Adrenal Insufficiency
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥ 1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	27		62		89	
Subjects with Adrenal Insufficiency	0		2	(3.2)	2	(2.2)
Time to Onset of First Adrenal Insufficiency (days)†						
Mean (Std)	0		298.0 (35.4)		298.0 (35.4)	
Median	0.0		298.0		298.0	
Range	0 to 0		273 to 323		273 to 323	
Total episodes of Adrenal Insufficiency	0		2		2	
Average Episodes per patient	0		1.00		1.00	
Episode duration (days)‡						
Median			Not reached		Not reached	
Range			56+ to 120+		56+ to 120+	

(%) = Number of subjects with Adrenal Insufficiency / Number of subjects in population.
† Time to onset statistics are based on number of subjects with Adrenal Insufficiency.
‡ From product-limit (Kaplan-Meier) method for censored data. If an adverse event is not resolved at the time of analysis or the subject died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.
+ indicates the AE episode is not recovered/resolved by the time of the cutoff date or date of death.
Std = Standard Deviation.
Grades are based on NCI CTCAE version 4.0.
Database Cutoff Date: 30SEP2015

Data Source:　[16.4]

Confidential

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Adrenal Insufficiency
APaT Japan Population (TPS ≥ 1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W	
	n	(%)	n	(%)	n	(%)
Subjects in population	27		28		34	
with one or more adverse events	0	(0.0)	1	(3.6)	1	(2.9)
with no adverse events	27	(100.0)	27	(96.4)	33	(97.1)
Endocrine disorders	**0**	**(0.0)**	**1**	**(3.6)**	**1**	**(2.9)**
Adrenal insufficiency	0	(0.0)	1	(3.6)	1	(2.9)
Grade 1	0	(0.0)	1	(3.6)	0	(0.0)
Grade 3	0	(0.0)	0	(0.0)	1	(2.9)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.0.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose
(Database Cutoff Date: 30SEP2015).

Data Source: [16.4]

Confidential

Summary of Concomitant Corticosteroid Use for AEOSI -Adrenal Insufficiency
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W (N=27)		MK-3475 Pooled (N=62)		Total (N=89)	
	n	%	n	%	n	%
Patients with one or more Adrenal Insufficiency events	0		2		2	
Treated with systemic corticosteroid	0	0	1	50.0	1	50.0
Not treated with systemic corticosteroid	0	0	1	50.0	1	50.0

The number of Patients with one or more Adrenal Insufficiency events is used as the denominator for the percentage calculation.
Database Cutoff Date: 30SEP2015

Data Source:　[16.4]

Summary of Concomitant Corticosteroid Use for Adrenal Insufficiency Episodes
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W	MK-3475 Pooled	Total
Total Episodes	0	2	2
High Starting Dose (%) †	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Low Starting Dose (%) ‡	**0 (0.0)**	**1 (50.0)**	**1 (50.0)**
Starting dose (mg/day)			
Mean (Std)	0 (0)	1 (.)	1 (.)
Median (Range)	0 (0-0)	1 (1-1)	1 (1-1)
Duration (days)§			
Mean (Std)	0 (0)	1 (.)	1 (.)
Median (Range)	0 (0-0)	1 (1-1)	1 (1-1)
Not Treated with Systemic Corticosteroid (%)	**0 (0.0)**	**1 (50.0)**	**1 (50.0)**

† High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
§ Ongoing corticosteroid treatment is censored at the cutoff date or date of death, whichever occurs first.
Database Cutoff Date: 30SEP2015

Data Source: [16.4]

C Confidential

Listing of Subjects With Adverse Events
AEOSI - Adrenal
APaT Japan Population (TPS ≥1%)

AN	Epoch	Rel Day of Onset	Adverse Event	Duration	Ser-ious	Related	Action Taken	Outcome
MK-3475 2 mg/kg Q3W								
Study Number=3475-010, Site Number=1438, AN=312992, Gender=F, Race=Asian, Age=65 Years, Rel Day of Study Medication Discontinuance†=259								
312992	Safety Follow-up	273	Adrenal insufficiency	Continuing	N	Y	Interrupted	Not Resolved
MK-3475 10 mg/kg Q3W								
Study Number=3475-010, Site Number=1424, AN=301369, Gender=F, Race=Asian, Age=74 Years, Rel Day of Study Medication Discontinuance†=								
301369	Treatment Cycle 16	323	Adrenal insufficiency	Continuing	Y	Y	Interrupted	Not Resolved

†Relative Day of Study Medication Discontinuance is defined as the day of the last recorded dose of study medication for the subject relative to the start of study medication.

Action Taken: None = DOSE NOT CHANGED, Reduced = DOSE REDUCED, Interrupted = DRUG INTERRUPTED, Discontinued = DRUG WITHDRAWN, Increased = DOSE INCREASED, N/A = NOT APPLICABLE.

Outcome: Resolved = RECOVERED/RESOLVED, Resolving = RECOVERING/RESOLVING, Sequelae = RECOVERED/RESOLVED WITH SEQUELAE, Not resolved = NOT RECOVERED/NOT RESOLVED.

Related: Investigator-assessed relationship of the adverse event to study medication.

AE of clinical interest reported by investigator

After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 30SEP2015).

Data Source:　[16.4]

C Confidential

Listing of Concomitant Systemic Corticosteroid Use for Adverse Events AEOSI - Adrenal
APaT Japan Population (TPS ≥1%)

Subject ID	Med. Start Day	Med. Duration (Days)	Med. Name	Total Daily Dose	Frequency	Route	Prednisone Equiv.† (mg)	Adverse Event for Use	AE Start Day	AE End Day	AE Toxicity Grade
MK-3475 10 mg/kg Q3W											
Trial Number=3475-010, Site Number=1424, Subject ID=301369, Gender=F, Race=Asian, Age=74 Years											
301369	353	1	Hydrocortisone	5	QD	Oral	1.25	Adrenal insufficiency	323	.	3
	354	3	Hydrocortisone	10	QD	Oral	2.50	Adrenal insufficiency	323	.	3
	356	2	Prednisolone	40	QD	Oral	40.00	Adrenal insufficiency	323	.	3
	358	15	Prednisolone	35	QD	Oral	35.00	Adrenal insufficiency	323	.	3
	373	13	Prednisolone	30	QD	Oral	30.00	Adrenal insufficiency	323	.	3
	386	14	Prednisolone	20	QD	Oral	20.00	Adrenal insufficiency	323	.	3
	400	13	Prednisolone	10	QD	Oral	10.00	Adrenal insufficiency	323	.	3

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Listing of Concomitant Systemic Corticosteroid Use for Adverse Events AEOSI - Adrenal
APaT Japan Population (TPS ≥1%)

Subject ID	Med. Start Day	Med. Duration (Days)	Med. Name	Total Daily Dose	Frequency	Route	Prednisone Equiv.† (mg)	Adverse Event for Use	AE Start Day	AE End Day	AE Toxicity Grade
	414	7	Prednisolone	30	QD	Oral	30.00	Adrenal insufficiency	323	.	3
	421	8	Prednisolone	18	QD	Oral	17.50	Adrenal insufficiency	323	.	3
	435	7	Prednisolone	15	QD	Oral	15.00	Adrenal insufficiency	323	.	3
	442	7	Prednisolone	10	QD	Oral	10.00	Adrenal insufficiency	323	.	3
	442	7	Prednisolone	4	QD	Oral	3.50	Adrenal insufficiency	323	.	3

Med.: Medication.
Equiv.: Equivalent.
AE: Adverse Event.
†: Prednisone equivalent total daily dose.
‡Relative Day of Study Medication Discontinuance is defined as the day of the last recorded dose of study medication for the subject relative to the start of study medication.
AE start date is defined as the start day of the adverse event for the subject relative to the start of study medication.
Grades are based on NCI CTCAE version 4.0.
(Database Cutoff Date: 30SEP2015).

Data Source:　[16.4]

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付録 2.7.4- 128　免疫関連の甲状腺機能障害（甲状腺機能低下症及び甲状腺機能亢進症）の AEOSI 解析

010 試験（MK-3475 併合、日本人安全性解析対象集団）（PD-L1 発現陽性）

Adverse Event Summary
AEOSI - Hypothyroidism
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled	
	n	(%)	n	(%)
Subjects in population	27		62	
with one or more adverse events	0	(0.0)	3	(4.8)
with no adverse event	27	(100.0)	59	(95.2)
with drug-related† adverse events	0	(0.0)	3	(4.8)
with toxicity grade 3-5 adverse events	0	(0.0)	0	(0.0)
with toxicity grade 3-5 drug-related adverse events	0	(0.0)	0	(0.0)
with serious adverse events	0	(0.0)	0	(0.0)
with serious drug-related adverse events	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	0	(0.0)	0	(0.0)
discontinued due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
AE of clinical interest reported by investigator.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 30SEP2015)

Data Source:　[16.4]

C Confidential

Summary of AEOSI - Hypothyroidism
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥ 1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	27		62		89	
Subjects with Hypothyroidism	0		3	(4.8)	3	(3.4)
Time to Onset of First Hypothyroidism (days)†						
Mean (Std)	0		71.7 (9.3)		71.7 (9.3)	
Median	0.0		69.0		69.0	
Range	0 to 0		64 to 82		64 to 82	
Total episodes of Hypothyroidism	0		3		3	
Average Episodes per patient	0		1.00		1.00	
Episode duration (days)‡						
Median			Not reached		Not reached	
Range			6+ to 308+		6+ to 308+	

(%) = Number of subjects with Hypothyroidism / Number of subjects in population.
† Time to onset statistics are based on number of subjects with Hypothyroidism.
‡ From product-limit (Kaplan-Meier) method for censored data. If an adverse event is not resolved at the time of analysis or the subject died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.
+ indicates the AE episode is not recovered/resolved by the time of the cutoff date or date of death.
Std = Standard Deviation.
Grades are based on NCI CTCAE version 4.0.
Database Cutoff Date: 30SEP2015

Data Source:　[16.4]

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Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Hypothyroidism
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥ 1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled	
	n	(%)	n	(%)
Subjects in population	27		62	
with one or more adverse events	0	(0.0)	3	(4.8)
with no adverse events	27	(100.0)	59	(95.2)
Endocrine disorders	**0**	**(0.0)**	**3**	**(4.8)**
Hypothyroidism	0	(0.0)	3	(4.8)
Grade 1	0	(0.0)	1	(1.6)
Grade 2	0	(0.0)	2	(3.2)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.0.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose
(Database Cutoff Date: 30SEP2015).

Data Source: [16.4]

Confidential

Summary of Concomitant Corticosteroid Use for AEOSI - Hypothyroidism
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W (N=27)		MK-3475 Pooled (N=62)		Total (N=89)	
	n	%	n	%	n	%
Patients with one or more Hypothyroidism events	0		3		3	
Treated with systemic corticosteroid	0	0	0	0	0	0
Not treated with systemic corticosteroid	0	0	3	100.0	3	100.0

The number of Patients with one or more Hypothyroidism events is used as the denominator for the percentage calculation.
Database Cutoff Date: 30SEP2015

Data Source:　[16.4]

Summary of Concomitant Corticosteroid Use for Hypothyroidism Episodes
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W	MK-3475 Pooled	Total
Total Episodes	0	3	3
High Starting Dose (%) †	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Low Starting Dose (%) ‡	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Not Treated with Systemic Corticosteroid (%)	**0 (0.0)**	**3 (100.0)**	**3 (100.0)**

† High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
§ Ongoing corticosteroid treatment is censored at the cutoff date or date of death, whichever occurs first.
Database Cutoff Date: 30SEP2015

Data Source: [16.4]

C Confidential

Listing of Subjects With Adverse Events
AEOSI - Hypothyroidism
APaT Japan Population (TPS ≥1%)

AN	Epoch	Rel Day of Onset	Adverse Event	Duration	Ser-ious	Related	Action Taken	Outcome
MK-3475 2 mg/kg Q3W								
Study Number=3475-010, Site Number=1411, AN=301875, Gender=M, Race=Asian, Age=70 Years, Rel Day of Study Medication Discontinuance†=64								
301875	Safety Follow-up	82	Hypothyroidism	Continuing	N	Y	None	Not Resolved
MK-3475 10 mg/kg Q3W								
Study Number=3475-010, Site Number=1405, AN=312141, Gender=M, Race=Asian, Age=74 Years, Rel Day of Study Medication Discontinuance†=40								
312141	Safety Follow-up	69	Hypothyroidism	Continuing	N	Y	None	Not Resolved
Study Number=3475-010, Site Number=1421, AN=311479, Gender=M, Race=Asian, Age=49 Years, Rel Day of Study Medication Discontinuance†=								
311479	Treatment Cycle 3	64	Hypothyroidism	Continuing	N	Y	None	Not Resolved

†Relative Day of Study Medication Discontinuance is defined as the day of the last recorded dose of study medication for the subject relative to the start of study medication.

Action Taken: None = DOSE NOT CHANGED, Reduced = DOSE REDUCED, Interrupted = DRUG INTERRUPTED, Discontinued = DRUG WITHDRAWN, Increased = DOSE INCREASED, N/A = NOT APPLICABLE.

Outcome: Resolved = RECOVERED/RESOLVED, Resolving = RECOVERING/RESOLVING, Sequelae = RECOVERED/RESOLVED WITH SEQUELAE, Not resolved = NOT RECOVERED/NOT RESOLVED.

Related: Investigator-assessed relationship of the adverse event to study medication.

AE of clinical interest reported by investigator

After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 30SEP2015).

Data Source:　[16.4]

Confidential

Adverse Event Summary
AEOSI - Hyperthyroidism
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled	
	n	(%)	n	(%)
Subjects in population	27		62	
with one or more adverse events	0	(0.0)	2	(3.2)
with no adverse event	27	(100.0)	60	(96.8)
with drug-related† adverse events	0	(0.0)	2	(3.2)
with toxicity grade 3-5 adverse events	0	(0.0)	0	(0.0)
with toxicity grade 3-5 drug-related adverse events	0	(0.0)	0	(0.0)
with serious adverse events	0	(0.0)	0	(0.0)
with serious drug-related adverse events	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	0	(0.0)	0	(0.0)
discontinued due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
AE of clinical interest reported by investigator.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 30SEP2015)

Data Source:　[16.4]

Confidential

Summary of AEOSI - Hyperthyroidism
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥ 1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	27		62		89	
Subjects with Hyperthyroidism	0		2	(3.2)	2	(2.2)
Time to Onset of First Hyperthyroidism (days)†						
Mean (Std)	0		32.0 (15.6)		32.0 (15.6)	
Median	0.0		32.0		32.0	
Range	0 to 0		21 to 43		21 to 43	
Total episodes of Hyperthyroidism	0		2		2	
Average Episodes per patient	0		1.00		1.00	
Episode duration (days)‡						
Median			56.5		56.5	
Range			43 to 70		43 to 70	

(%) = Number of subjects with Hyperthyroidism / Number of subjects in population.
† Time to onset statistics are based on number of subjects with Hyperthyroidism.
‡ From product-limit (Kaplan-Meier) method for censored data. If an adverse event is not resolved at the time of analysis or the subject died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.
+ indicates the AE episode is not recovered/resolved by the time of the cutoff date or date of death.
Std = Standard Deviation.
Grades are based on NCI CTCAE version 4.0.
Database Cutoff Date: 30SEP2015

Data Source:　[16.4]

Confidential

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Hyperthyroidism
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥ 1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled	
	n	(%)	n	(%)
Subjects in population	27		62	
with one or more adverse events	0	(0.0)	2	(3.2)
with no adverse events	27	(100.0)	60	(96.8)
Endocrine disorders	**0**	**(0.0)**	**2**	**(3.2)**
Hyperthyroidism	0	(0.0)	2	(3.2)
Grade 1	0	(0.0)	2	(3.2)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.0.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose
(Database Cutoff Date: 30SEP2015).

Data Source: [16.4]

C Confidential

Summary of Concomitant Corticosteroid Use for AEOSI - Hyperthyroidism
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W (N=27)		MK-3475 Pooled (N=62)		Total (N=89)	
	n	%	n	%	n	%
Patients with one or more Hyperthyroidism events	0		2		2	
Treated with systemic corticosteroid	0	0	0	0	0	0
Not treated with systemic corticosteroid	0	0	2	100.0	2	100.0

The number of Patients with one or more Hyperthyroidism events is used as the denominator for the percentage calculation.
Database Cutoff Date: 30SEP2015

Data Source:　[16.4]

Summary of Concomitant Corticosteroid Use for Hyperthyroidism Episodes
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W	MK-3475 Pooled	Total
Total Episodes	0	2	2
High Starting Dose (%) †	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Low Starting Dose (%) ‡	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Not Treated with Systemic Corticosteroid (%)	**0 (0.0)**	**2 (100.0)**	**2 (100.0)**

† High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
§ Ongoing corticosteroid treatment is censored at the cutoff date or date of death, whichever occurs first.
Database Cutoff Date: 30SEP2015

Data Source: [16.4]

Confidential

Listing of Subjects With Adverse Events
AEOSI - Hyperthyroidism
APaT Japan Population (TPS ≥1%)

AN	Epoch	Rel Day of Onset	Adverse Event	Duration	Ser-ious	Related	Action Taken	Outcome
MK-3475 2 mg/kg Q3W								
Study Number=3475-010, Site Number=1420, AN=302578, Gender=F, Race=Asian, Age=48 Years, Rel Day of Study Medication Discontinuance†=90								
302578	Treatment Cycle 2	43	Hyperthyroidism	2.3 Months	N	Y	None	Resolved
Study Number=3475-010, Site Number=1428, AN=307204, Gender=F, Race=Asian, Age=78 Years, Rel Day of Study Medication Discontinuance†=								
307204	Treatment Cycle 1	21	Hyperthyroidism	1.41 Months	N	Y	None	Resolved

†Relative Day of Study Medication Discontinuance is defined as the day of the last recorded dose of study medication for the subject relative to the start of study medication.

Action Taken: None = DOSE NOT CHANGED, Reduced = DOSE REDUCED, Interrupted = DRUG INTERRUPTED, Discontinued = DRUG WITHDRAWN, Increased = DOSE INCREASED, N/A = NOT APPLICABLE.

Outcome: Resolved = RECOVERED/RESOLVED, Resolving = RECOVERING/RESOLVING, Sequelae = RECOVERED/RESOLVED WITH SEQUELAE, Not resolved = NOT RECOVERED/NOT RESOLVED.

Related: Investigator-assessed relationship of the adverse event to study medication.

AE of clinical interest reported by investigator

After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 30SEP2015).

Data Source:　[16.4]

C Confidential

付録 2.7.4- 129　免疫関連の膵炎の AEOSI 解析

010 試験（MK-3475 併合、日本人安全性解析対象集団）（PD-L1 発現陽性）

Adverse Event Summary
AEOSI - Pancreatitis
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled	
	n	(%)	n	(%)
Subjects in population	27		62	
with one or more adverse events	0	(0.0)	1	(1.6)
with no adverse event	27	(100.0)	61	(98.4)
with drug-related[†] adverse events	0	(0.0)	0	(0.0)
with toxicity grade 3-5 adverse events	0	(0.0)	1	(1.6)
with toxicity grade 3-5 drug-related adverse events	0	(0.0)	0	(0.0)
with serious adverse events	0	(0.0)	1	(1.6)
with serious drug-related adverse events	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued[‡] due to an adverse event	0	(0.0)	0	(0.0)
discontinued due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)

[†] Determined by the investigator to be related to the drug.
[‡] Study medication withdrawn.
AE of clinical interest reported by investigator.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 30SEP2015)

Data Source:　[16.4]

Confidential

Summary of AEOSI - Pancreatitis
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥ 1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	27		62		89	
Subjects with Pancreatitis	0		1	(1.6)	1	(1.1)
Time to Onset of First Pancreatitis (days)†						
Mean (Std)	0		149.0		149.0	
Median	0.0		149.0		149.0	
Range	0 to 0		149 to 149		149 to 149	
Total episodes of Pancreatitis	0		1		1	
Average Episodes per patient	0		1.00		1.00	
Episode duration (days)‡						
Median			55.0		55.0	
Range			55 to 55		55 to 55	

(%) = Number of subjects with Pancreatitis / Number of subjects in population.
† Time to onset statistics are based on number of subjects with Pancreatitis.
‡ From product-limit (Kaplan-Meier) method for censored data. If an adverse event is not resolved at the time of analysis or the subject died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.
+ indicates the AE episode is not recovered/resolved by the time of the cutoff date or date of death.
Std = Standard Deviation.
Grades are based on NCI CTCAE version 4.0.
Database Cutoff Date: 30SEP2015

Data Source:　[16.4]

Confidential

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Pancreatitis
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥ 1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled	
	n	(%)	n	(%)
Subjects in population	27		62	
with one or more adverse events	0	(0.0)	1	(1.6)
with no adverse events	27	(100.0)	61	(98.4)
Gastrointestinal disorders	**0**	**(0.0)**	**1**	**(1.6)**
Pancreatitis	0	(0.0)	1	(1.6)
Grade 3	0	(0.0)	1	(1.6)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.0.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose
(Database Cutoff Date: 30SEP2015).

Data Source: [16.4]

Confidential

Summary of Concomitant Corticosteroid Use for AEOSI - Pancreatitis
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W (N=27)		MK-3475 Pooled (N=62)		Total (N=89)	
	n	%	n	%	n	%
Patients with one or more Pancreatitis events	0		1		1	
Treated with systemic corticosteroid	0	0	0	0	0	0
Not treated with systemic corticosteroid	0	0	1	100.0	1	100.0

The number of Patients with one or more Pancreatitis events is used as the denominator for the percentage calculation.
Database Cutoff Date: 30SEP2015

Data Source:　[16.4]

Summary of Concomitant Corticosteroid Use for Pancreatitis Episodes
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W	MK-3475 Pooled	Total
Total Episodes	0	1	1
High Starting Dose (%) †	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Low Starting Dose (%) ‡	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Not Treated with Systemic Corticosteroid (%)	**0 (0.0)**	**1 (100.0)**	**1 (100.0)**

† High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
§ Ongoing corticosteroid treatment is censored at the cutoff date or date of death, whichever occurs first.
Database Cutoff Date: 30SEP2015

Data Source: [16.4]

C Confidential

Listing of Subjects With Adverse Events
AEOSI - Pancreatitis
APaT Japan Population (TPS ≥1%)

AN	Epoch	Rel Day of Onset	Adverse Event	Duration	Ser-ious	Related	Action Taken	Outcome
MK-3475 2 mg/kg Q3W								
Study Number=3475-010, Site Number=1417, AN=309855, Gender=M, Race=Asian, Age=64 Years, Rel Day of Study Medication Discontinuance†=110								
309855	Extended Safety Follow-up	149	Pancreatitis	1.81 Months	Y	N	N/A	Resolved

†Relative Day of Study Medication Discontinuance is defined as the day of the last recorded dose of study medication for the subject relative to the start of study medication.

Action Taken: None = DOSE NOT CHANGED, Reduced = DOSE REDUCED, Interrupted = DRUG INTERRUPTED, Discontinued = DRUG WITHDRAWN, Increased = DOSE INCREASED, N/A = NOT APPLICABLE.

Outcome: Resolved = RECOVERED/RESOLVED, Resolving = RECOVERING/RESOLVING, Sequelae = RECOVERED/RESOLVED WITH SEQUELAE, Not resolved = NOT RECOVERED/NOT RESOLVED.

Related: Investigator-assessed relationship of the adverse event to study medication.

AE of clinical interest reported by investigator

After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 30SEP2015).

Data Source:　[16.4]

Confidential

付録 2.7.4- 130　免疫関連の重度の皮膚反応の AEOSI 解析
010 試験（MK-3475 併合、日本人安全性解析対象集団）（PD-L1 発現陽性）

Adverse Event Summary
AEOSI - Skin
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled	
	n	(%)	n	(%)
Subjects in population	27		62	
with one or more adverse events	1	(3.7)	3	(4.8)
with no adverse event	26	(96.3)	59	(95.2)
with drug-related† adverse events	1	(3.7)	2	(3.2)
with toxicity grade 3-5 adverse events	1	(3.7)	1	(1.6)
with toxicity grade 3-5 drug-related adverse events	1	(3.7)	1	(1.6)
with serious adverse events	0	(0.0)	1	(1.6)
with serious drug-related adverse events	0	(0.0)	1	(1.6)
who died	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	0	(0.0)	0	(0.0)
discontinued due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
AE of clinical interest reported by investigator.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 30SEP2015)

Data Source:　[16.4]

Confidential

Summary of AEOSI - Skin
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥ 1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	27		62		89	
Subjects with Skin	1	(3.7)	3	(4.8)	4	(4.5)
Time to Onset of First Skin (days)†						
Mean (Std)	15.0		91.0 (51.1)		72.0 (56.4)	
Median	15.0		100.0		68.0	
Range	15 to 15		36 to 137		15 to 137	
Total episodes of Skin	1		3		4	
Average Episodes per patient	1.00		1.00		1.00	
Episode duration (days)‡						
Median	18.0		134.0		76.0	
Range	18 to 18		8 to 134		8 to 134	

(%) = Number of subjects with Skin / Number of subjects in population.
† Time to onset statistics are based on number of subjects with Skin.
‡ From product-limit (Kaplan-Meier) method for censored data. If an adverse event is not resolved at the time of analysis or the subject died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.
+ indicates the AE episode is not recovered/resolved by the time of the cutoff date or date of death.
Std = Standard Deviation.
Grades are based on NCI CTCAE version 4.0.
Database Cutoff Date: 30SEP2015

Data Source:　[16.4]

Confidential

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Skin
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥ 1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 Pooled	
	n	(%)	n	(%)
Subjects in population	27		62	
with one or more adverse events	1	(3.7)	3	(4.8)
with no adverse events	26	(96.3)	59	(95.2)
Skin and subcutaneous tissue disorders	**1**	**(3.7)**	**3**	**(4.8)**
Dermatitis bullous	0	(0.0)	1	(1.6)
Grade 2	0	(0.0)	1	(1.6)
Drug eruption	0	(0.0)	1	(1.6)
Grade 3	0	(0.0)	1	(1.6)
Erythema multiforme	0	(0.0)	1	(1.6)
Grade 2	0	(0.0)	1	(1.6)
Pruritus	1	(3.7)	0	(0.0)
Grade 3	1	(3.7)	0	(0.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.0.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose
(Database Cutoff Date: 30SEP2015).

Data Source: [16.4]

C Confidential

Summary of Concomitant Corticosteroid Use for AEOSI - Skin
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W (N=27)		MK-3475 Pooled (N=62)		Total (N=89)	
	n	%	n	%	n	%
Patients with one or more Skin events	1		3		4	
Treated with systemic corticosteroid	0	0	1	33.3	1	25.0
Not treated with systemic corticosteroid	1	100.0	2	66.7	3	75.0

The number of Patients with one or more Skin events is used as the denominator for the percentage calculation.
Database Cutoff Date: 30SEP2015

Data Source:　[16.4]

Summary of Concomitant Corticosteroid Use for Skin Episodes
MK-3475 Treatment Groups Pooled
APaT Japan Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W	MK-3475 Pooled	Total
Total Episodes	1	3	4
High Starting Dose (%) †	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Low Starting Dose (%) ‡	**0 (0.0)**	**1 (33.3)**	**1 (25.0)**
Starting dose (mg/day)			
Mean (Std)	0 (0)	25 (.)	25 (.)
Median (Range)	0 (0-0)	25 (25-25)	25 (25-25)
Duration (days)§			
Mean (Std)	0 (0)	4 (.)	4 (.)
Median (Range)	0 (0-0)	4 (4-4)	4 (4-4)
Not Treated with Systemic Corticosteroid (%)	**1 (100.0)**	**2 (66.7)**	**3 (75.0)**

† High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
§ Ongoing corticosteroid treatment is censored at the cutoff date or date of death, whichever occurs first.
Database Cutoff Date: 30SEP2015

Data Source: [16.4]

Confidential

Listing of Subjects With Adverse Events
AEOSI - Skin
APaT Japan Population (TPS ≥1%)

AN	Epoch	Rel Day of Onset	Adverse Event	Duration	Ser-ious	Related	Action Taken	Outcome
Docetaxel 75 mg/m2 Q3W								
Study Number=3475-010, Site Number=1417, AN=309461, Gender=M, Race=Asian, Age=61 Years, Rel Day of Study Medication Discontinuance†=349								
309461	Treatment Cycle 1	15	Pruritus	2.57 Weeks	N	Y	Reduced	Resolved
MK-3475 2 mg/kg Q3W								
Study Number=3475-010, Site Number=1405, AN=304574, Gender=M, Race=Asian, Age=66 Years, Rel Day of Study Medication Discontinuance†=								
304574	Treatment Cycle 4	137	Erythema multiforme	1.14 Weeks	N	N	N/A	Resolved
MK-3475 10 mg/kg Q3W								
Study Number=3475-010, Site Number=1411, AN=300216, Gender=M, Race=Asian, Age=60 Years, Rel Day of Study Medication Discontinuance†=								
300216	Treatment Cycle 5	100	Dermatitis bullous	4.4 Months	N	Y	None	Resolved
Study Number=3475-010, Site Number=1430, AN=304201, Gender=F, Race=Asian, Age=54 Years, Rel Day of Study Medication Discontinuance†=29								

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Listing of Subjects With Adverse Events
AEOSI - Skin
APaT Japan Population (TPS ≥1%)

AN	Epoch	Rel Day of Onset	Adverse Event	Duration	Ser-ious	Related	Action Taken	Outcome
MK-3475 10 mg/kg Q3W								
Study Number=3475-010, Site Number=1430, AN=304201, Gender=F, Race=Asian, Age=54 Years, Rel Day of Study Medication Discontinuance†=29								
304201	Safety Follow-up	36	Drug eruption	Continuing	Y	Y	Interrupted	Resolving

†Relative Day of Study Medication Discontinuance is defined as the day of the last recorded dose of study medication for the subject relative to the start of study medication.

Action Taken: None = DOSE NOT CHANGED, Reduced = DOSE REDUCED, Interrupted = DRUG INTERRUPTED, Discontinued = DRUG WITHDRAWN, Increased = DOSE INCREASED, N/A = NOT APPLICABLE.

Outcome: Resolved = RECOVERED/RESOLVED, Resolving = RECOVERING/RESOLVING, Sequelae = RECOVERED/RESOLVED WITH SEQUELAE, Not resolved = NOT RECOVERED/NOT RESOLVED.

Related: Investigator-assessed relationship of the adverse event to study medication.

AE of clinical interest reported by investigator

After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 30SEP2015).

Data Source:　[16.4]

Confidential

Listing of Concomitant Systemic Corticosteroid Use for Adverse Events AEOSI - Skin
APaT Japan Population (TPS ≥1%)

Subject ID	Med. Start Day	Med. Duration (Days)	Med. Name	Total Daily Dose	Frequency	Route	Prednisone Equiv.† (mg)	Adverse Event for Use	AE Start Day	AE End Day	AE Toxicity Grade
MK-3475 10 mg/kg Q3W											
Trial Number=3475-010, Site Number=1430, Subject ID=304201, Gender=F, Race=Asian, Age=54 Years, Rel Day of Study Medication Discontinuance‡=29											
304201	52	3	Methylprednisolone	500	UNKNOWN	Intravenous	625.00	Drug eruption	36	.	3
	48	4	Prednisolone	25	UNKNOWN	Oral	25.00	Drug eruption	36	.	3
	55	3	Prednisolone	40	UNKNOWN	Oral	40.00	Drug eruption	36	.	3
	58	4	Prednisolone	30	UNKNOWN	Oral	30.00	Drug eruption	36	.	3
	62	4	Prednisolone	20	UNKNOWN	Oral	20.00	Drug eruption	36	.	3
	66	4	Prednisolone	15	UNKNOWN	Oral	15.00	Drug eruption	36	.	3
	70	4	Prednisolone	10	UNKNOWN	Oral	10.00	Drug eruption	36	.	3

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Listing of Concomitant Systemic Corticosteroid Use for Adverse Events AEOSI - Skin
APaT Japan Population (TPS ≥1%)

Subject ID	Med. Start Day	Med. Duration (Days)	Med. Name	Total Daily Dose	Frequency	Route	Prednisone Equiv.† (mg)	Adverse Event for Use	AE Start Day	AE End Day	AE Toxicity Grade
	74	4	Prednisolone	5	UNKNOWN	Oral	5.00	Drug eruption	36	.	3

Med.: Medication.
Equiv.: Equivalent.
AE: Adverse Event.
†: Prednisone equivalent total daily dose.
‡Relative Day of Study Medication Discontinuance is defined as the day of the last recorded dose of study medication for the subject relative to the start of study medication.
AE start date is defined as the start day of the adverse event for the subject relative to the start of study medication.
Grades are based on NCI CTCAE version 4.0.
(Database Cutoff Date: 30SEP2015).

Data Source:　[16.4]

Confidential

付録 2.7.4- 131　臨床検査値の Grade がベースラインより悪化した患者の要約

025 試験（安全性解析対象集団）

Summary of Worsening in Laboratory CTCAE Grades from Baseline to Worst Value Post-baseline

All Positive PD-L1 Subjects

(All Subjects as Treated)

Laboratory Test	MK-3475 10mg/kg Q3W (N=38)
Alanine Aminotransferase Increased	
Improved from baseline	0 (0.0)
Worsened from baseline	10 (26.3)
Clinically meaningful† worsened from baseline	2 (5.3)
Albumin Decreased	
Improved from baseline	0 (0.0)
Worsened from baseline	25 (65.8)
Clinically meaningful† worsened from baseline	7 (18.4)
Alkaline Phosphatase Increased	
Improved from baseline	0 (0.0)
Worsened from baseline	20 (52.6)
Clinically meaningful† worsened from baseline	2 (5.3)
Aspartate Aminotransferase Increased	
Improved from baseline	0 (0.0)
Worsened from baseline	14 (36.8)
Clinically meaningful† worsened from baseline	2 (5.3)
Bilirubinn Increased	
Improved from baseline	0 (0.0)
Worsened from baseline	4 (10.5)
Clinically meaningful† worsened from baseline	1 (2.6)
Calcium Decreased	

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Summary of Worsening in Laboratory CTCAE Grades from Baseline to Worst Value Post-baseline
All Positive PD-L1 Subjects
(All Subjects as Treated)

Laboratory Test	MK-3475 10mg/kg Q3W (N=38)
Calcium Decreased	
Improved from baseline	0 (0.0)
Worsened from baseline	9 (23.7)
Clinically meaningful† worsened from baseline	2 (5.3)
Calcium Increased	
Improved from baseline	0 (0.0)
Worsened from baseline	3 (7.9)
Clinically meaningful† worsened from baseline	2 (5.3)
Creatinine Increased	
Improved from baseline	0 (0.0)
Worsened from baseline	10 (26.3)
Clinically meaningful† worsened from baseline	1 (2.6)
Glucose Increased	
Improved from baseline	0 (0.0)
Worsened from baseline	30 (78.9)
Clinically meaningful† worsened from baseline	3 (7.9)
Hemoglobin Decreased	
Improved from baseline	1 (2.6)
Worsened from baseline	12 (31.6)
Clinically meaningful† worsened from baseline	1 (2.6)
Leukocytes Decreased	

C Confidential

Summary of Worsening in Laboratory CTCAE Grades from Baseline to Worst Value Post-baseline
All Positive PD-L1 Subjects
(All Subjects as Treated)

Laboratory Test	MK-3475 10mg/kg Q3W (N=38)
Leukocytes Decreased	
Improved from baseline	0 (0.0)
Worsened from baseline	2 (5.3)
Clinically meaningful† worsened from baseline	1 (2.6)
Lymphocytes Decreased	
Improved from baseline	0 (0.0)
Worsened from baseline	4 (10.5)
Clinically meaningful† worsened from baseline	2 (5.3)
Magnesium Decreased	
Improved from baseline	0 (0.0)
Worsened from baseline	9 (23.7)
Clinically meaningful† worsened from baseline	1 (2.6)
Neutrophils Decreased	
Improved from baseline	0 (0.0)
Worsened from baseline	1 (2.6)
Clinically meaningful† worsened from baseline	1 (2.6)
Phosphate Decreased	
Improved from baseline	0 (0.0)
Worsened from baseline	12 (31.6)
Clinically meaningful† worsened from baseline	11 (28.9)
Triglycerides	

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Summary of Worsening in Laboratory CTCAE Grades from Baseline to Worst Value Post-baseline
All Positive PD-L1 Subjects
(All Subjects as Treated)

Laboratory Test	MK-3475 10mg/kg Q3W (N=38)
Triglycerides	
Improved from baseline	2 (5.3)
Worsened from baseline	19 (50.0)
Clinically meaningful† worsened from baseline	1 (2.6)

A missing baseline value was set to Grade 0.
† A clinically meaningful worsening in CTCAE grade was defined as a shift from less than Grade 3 to Grade 3 , 4 or 5 or a shift from Grade 0 to Grade 2.
(Database Cutoff Date: 09JUL2015).

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付録 2.7.4- 132　臨床検査値の Grade がベースラインより悪化した患者の要約

010 試験（日本人安全性解析対象集団）（PD-L1 発現陽性）
Summary of Worsening in Laboratory CTCAE Grades from Baseline to Worst Value Post-baseline
APaT Japan Population (TPS ≥1%)

Laboratory Test	Docetaxel 75 mg/m2 Q3W (N=27)	MK-3475 2 mg/kg Q3W (N=28)	MK-3475 10 mg/kg Q3W (N=34)
APTT Increased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	2 (7.4)	0 (0.0)	0 (0.0)
Clinically meaningful† worsened from baseline	1 (3.7)	0 (0.0)	0 (0.0)
Alanine Aminotransferase Increased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	2 (7.4)	5 (17.9)	5 (14.7)
Clinically meaningful† worsened from baseline	0 (0.0)	1 (3.6)	0 (0.0)
Albumin Decreased			
Improved from baseline	0 (0.0)	0 (0.0)	1 (2.9)
Worsened from baseline	11 (40.7)	14 (50.0)	15 (44.1)
Clinically meaningful† worsened from baseline	2 (7.4)	1 (3.6)	3 (8.8)
Alkaline Phosphatase Increased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	2 (7.4)	6 (21.4)	11 (32.4)
Clinically meaningful† worsened from baseline	0 (0.0)	2 (7.1)	0 (0.0)
Amylase Increased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	0 (0.0)	1 (3.6)	0 (0.0)
Clinically meaningful† worsened from baseline	0 (0.0)	1 (3.6)	0 (0.0)
Aspartate Aminotransferase Increased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)

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Summary of Worsening in Laboratory CTCAE Grades from Baseline to Worst Value Post-baseline APaT Japan Population (TPS ≥1%)

Laboratory Test	Docetaxel 75 mg/m2 Q3W (N=27)	MK-3475 2 mg/kg Q3W (N=28)	MK-3475 10 mg/kg Q3W (N=34)
Aspartate Aminotransferase Increased			
Worsened from baseline	4 (14.8)	7 (25.0)	6 (17.6)
Clinically meaningful† worsened from baseline	0 (0.0)	3 (10.7)	2 (5.9)
Bilirubinn Increased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	3 (11.1)	3 (10.7)	1 (2.9)
Clinically meaningful† worsened from baseline	1 (3.7)	1 (3.6)	0 (0.0)
Calcium Decreased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	12 (44.4)	5 (17.9)	5 (14.7)
Clinically meaningful† worsened from baseline	3 (11.1)	0 (0.0)	2 (5.9)
Cholesterol			
Improved from baseline	1 (3.7)	0 (0.0)	0 (0.0)
Worsened from baseline	4 (14.8)	5 (17.9)	6 (17.6)
Clinically meaningful† worsened from baseline	0 (0.0)	0 (0.0)	1 (2.9)
Creatinine Increased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	4 (14.8)	4 (14.3)	7 (20.6)
Clinically meaningful† worsened from baseline	1 (3.7)	0 (0.0)	0 (0.0)
Gamma Glutamyl Transferase Increased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	0 (0.0)	1 (3.6)	3 (8.8)

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Summary of Worsening in Laboratory CTCAE Grades from Baseline to Worst Value Post-baseline APaT Japan Population (TPS ≥1%)

Laboratory Test	Docetaxel 75 mg/m2 Q3W (N=27)	MK-3475 2 mg/kg Q3W (N=28)	MK-3475 10 mg/kg Q3W (N=34)
Gamma Glutamyl Transferase Increased			
Clinically meaningful† worsened from baseline	0 (0.0)	1 (3.6)	2 (5.9)
Glucose Increased			
Improved from baseline	1 (3.7)	0 (0.0)	0 (0.0)
Worsened from baseline	12 (44.4)	15 (53.6)	13 (38.2)
Clinically meaningful† worsened from baseline	1 (3.7)	4 (14.3)	2 (5.9)
Hemoglobin Decreased			
Improved from baseline	0 (0.0)	0 (0.0)	3 (8.8)
Worsened from baseline	18 (66.7)	11 (39.3)	13 (38.2)
Clinically meaningful† worsened from baseline	2 (7.4)	1 (3.6)	3 (8.8)
Leukocytes Decreased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	19 (70.4)	1 (3.6)	2 (5.9)
Clinically meaningful† worsened from baseline	18 (66.7)	0 (0.0)	2 (5.9)
Lymphocytes Decreased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	11 (40.7)	5 (17.9)	11 (32.4)
Clinically meaningful† worsened from baseline	6 (22.2)	4 (14.3)	9 (26.5)
Lymphocytes Increased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	4 (14.8)	0 (0.0)	0 (0.0)
Clinically meaningful† worsened from baseline	2 (7.4)	0 (0.0)	0 (0.0)

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Summary of Worsening in Laboratory CTCAE Grades from Baseline to Worst Value Post-baseline APaT Japan Population (TPS ≥1%)

Laboratory Test	Docetaxel 75 mg/m2 Q3W (N=27)	MK-3475 2 mg/kg Q3W (N=28)	MK-3475 10 mg/kg Q3W (N=34)
Magnesium Decreased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	6 (22.2)	6 (21.4)	8 (23.5)
Clinically meaningful† worsened from baseline	1 (3.7)	1 (3.6)	0 (0.0)
Magnesium Increased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	0 (0.0)	2 (7.1)	3 (8.8)
Clinically meaningful† worsened from baseline	0 (0.0)	0 (0.0)	1 (2.9)
Neutrophils Decreased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	19 (70.4)	1 (3.6)	1 (2.9)
Clinically meaningful† worsened from baseline	19 (70.4)	1 (3.6)	0 (0.0)
Neutrophils Increased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	1 (3.7)	0 (0.0)	0 (0.0)
Clinically meaningful† worsened from baseline	1 (3.7)	0 (0.0)	0 (0.0)
Phosphate Decreased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	7 (25.9)	5 (17.9)	5 (14.7)
Clinically meaningful† worsened from baseline	4 (14.8)	3 (10.7)	4 (11.8)
Platelet Decreased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)

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Summary of Worsening in Laboratory CTCAE Grades from Baseline to Worst Value Post-baseline APaT Japan Population (TPS ≥1%)

Laboratory Test	Docetaxel 75 mg/m2 Q3W (N=27)	MK-3475 2 mg/kg Q3W (N=28)	MK-3475 10 mg/kg Q3W (N=34)
Platelet Decreased			
Worsened from baseline	3 (11.1)	5 (17.9)	5 (14.7)
Clinically meaningful† worsened from baseline	1 (3.7)	0 (0.0)	0 (0.0)
Potassium Decreased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	2 (7.4)	2 (7.1)	2 (5.9)
Clinically meaningful† worsened from baseline	2 (7.4)	0 (0.0)	0 (0.0)
Potassium Increased			
Improved from baseline	1 (3.7)	0 (0.0)	0 (0.0)
Worsened from baseline	8 (29.6)	3 (10.7)	5 (14.7)
Clinically meaningful† worsened from baseline	2 (7.4)	0 (0.0)	0 (0.0)
Sodium Decreased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	6 (22.2)	8 (28.6)	13 (38.2)
Clinically meaningful† worsened from baseline	1 (3.7)	1 (3.6)	1 (2.9)
Sodium Increased			
Improved from baseline	0 (0.0)	0 (0.0)	0 (0.0)
Worsened from baseline	1 (3.7)	2 (7.1)	0 (0.0)
Clinically meaningful† worsened from baseline	1 (3.7)	0 (0.0)	0 (0.0)
Triglycerides			
Improved from baseline	0 (0.0)	2 (7.1)	0 (0.0)
Worsened from baseline	10 (37.0)	9 (32.1)	12 (35.3)

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Summary of Worsening in Laboratory CTCAE Grades from Baseline to Worst Value Post-baseline
APaT Japan Population (TPS ≥1%)

Laboratory Test	Docetaxel 75 mg/m2 Q3W (N=27)	MK-3475 2 mg/kg Q3W (N=28)	MK-3475 10 mg/kg Q3W (N=34)
Triglycerides			
Clinically meaningful† worsened from baseline	1 (3.7)	2 (7.1)	2 (5.9)

A missing baseline value was set to Grade 0.
† A clinically meaningful worsening in CTCAE grade was defined as a shift from less than Grade 3 to Grade 3 , 4 or 5 or a shift from Grade 0 to Grade 2.
(Database Cutoff Date: 30SEP2015)

Data Source:　[16.4]

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付録 2.7.4- 133　副作用の基本語（PT）一覧

器官別大分類（SOC）	基本語（PT）	重篤	非重篤	合計
血液およびリンパ系障害	抗第ＶＩＩＩ因子、抗第ＸＩ因子、または抗第ＸＩＩＩ因子を有する後天性血友病	1	0	1
	貧血	2	5	7
	溶血性貧血	1	0	1
	鉄欠乏性貧血	1	0	1
	白血球減少症	0	1	1
	リンパ節症	1	1	2
	リンパ球増加症	0	1	1
	好中球減少症	0	2	2
	汎血球減少症	1	0	1
	血小板減少症	0	4	4
血液およびリンパ系障害　合計		7	14	21
心臓障害	不整脈	1	0	1
	心房細動	1	0	1
	心停止	2	0	2
	心障害	0	1	1
	心筋梗塞	1	0	1
	心筋炎	0	1	1
	動悸	0	1	1
心臓障害　合計		5	3	8
耳および迷路障害	難聴	1	0	1
耳および迷路障害　合計		1	0	1
内分泌障害	副腎機能不全	0	1	1
	内分泌障害	0	1	1
	悪性腫瘍に伴う高カルシウム血症	1	0	1
	甲状腺機能亢進症	1	3	4
	男性性腺機能低下	1	0	1
	下垂体炎	0	3	3
	下垂体機能低下症	0	2	2
	甲状腺機能低下症	1	5	6
	原発性副腎機能不全	0	1	1
	続発性副腎皮質機能不全	1	0	1

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付録 2.7.4- 133　副作用の基本語（PT）一覧（続き）

器官別大分類（SOC）	基本語（PT）	重篤	非重篤	合計
内分泌障害	甲状腺障害	0	1	1
	甲状腺炎	1	0	1
内分泌障害　合計		6	17	23
眼障害	複視	0	1	1
	眼瞼下垂	1	0	1
	黄斑症	1	0	1
	網膜剥離	0	1	1
	網膜出血	0	1	1
	網膜下液	1	0	1
	ぶどう膜炎	1	1	2
	霧視	0	3	3
	視力障害	1	2	3
眼障害　合計		5	9	14
胃腸障害	腹部不快感	0	1	1
	腹部膨満	1	0	1
	腹痛	1	3	4
	上腹部痛	2	0	2
	腹水	1	0	1
	便通不規則	0	1	1
	口唇炎	0	1	1
	慢性胃炎	1	0	1
	大腸炎	0	3	3
	顕微鏡的大腸炎	0	1	1
	便秘	0	2	2
	下痢	1	9	10
	口内乾燥	0	4	4
	消化不良	0	2	2
	嚥下障害	2	1	3
	変色便	0	1	1
	放屁	0	1	1
	排便回数増加	0	1	1
	胃炎	0	1	1

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付録 2.7.4- 133　副作用の基本語（PT）一覧（続き）

器官別大分類（SOC）	基本語（PT）	重篤	非重篤	合計
胃腸障害	血便排泄	0	1	1
	腸閉塞	2	0	2
	悪心	5	8	13
	膵炎	3	0	3
	急性膵炎	1	0	1
	舌変色	0	1	1
	嘔吐	2	4	6
胃腸障害　合計		22	46	68
一般・全身障害および投与部位の状態	歩行不能	1	0	1
	有害事象	7	7	14
	無力症	2	5	7
	胸部不快感	1	1	2
	胸痛	1	3	4
	悪寒	0	5	5
	状態悪化	0	1	1
	死亡	33	0	33
	疾患合併症	1	0	1
	疾患進行	2	6	8
	薬効欠如	0	8	8
	疲労	5	20	25
	異常感	0	3	3
	歩行障害	2	0	2
	全身健康状態低下	2	0	2
	注入部位血管外漏出	0	1	1
	注入部位反応	0	1	1
	注射部位紅斑	0	1	1
	注射部位硬結	0	1	1
	注射部位炎症	0	1	1
	注射部位腫瘤	0	1	1
	注射部位発疹	0	1	1
	注射部位反応	0	1	1
	限局性浮腫	1	0	1

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付録 2.7.4- 133　副作用の基本語（PT）一覧（続き）

器官別大分類（SOC）	基本語（PT）	重篤	非重篤	合計
一般･全身障害および投与部位の状態	倦怠感	4	4	8
	粘膜の炎症	0	1	1
	有害事象なし	0	22	22
	治療効果なし	0	1	1
	末梢性浮腫	0	2	2
	疼痛	2	10	12
	末梢腫脹	0	1	1
	製品品質の問題	0	1	1
	発熱	2	10	12
	腫脹	1	0	1
	圧痛	0	1	1
	終末期状態	1	0	1
	予想外の治療反応	0	7	7
	治療レスポンダー	0	1	1
一般・全身障害および投与部位の状態　合計		68	128	196
肝胆道系障害	自己免疫性肝炎	1	1	2
	胆汁うっ滞	1	0	1
	胆汁うっ滞性肝損傷	1	0	1
	肝不全	1	0	1
	急性肝炎	1	0	1
	高ビリルビン血症	0	1	1
	黄疸	1	0	1
肝胆道系障害　合計		6	2	8
免疫系障害	自己免疫障害	0	2	2
	サイトカインストーム	0	1	1
	免疫反応	1	0	1
	季節性アレルギー	0	1	1
免疫系障害　合計		1	4	5
感染症および寄生虫症	細菌感染	1	1	2
	クロストリジウム性大腸炎	0	1	1
	クロストリジウム・ディフィシレ大腸炎	1	0	1
	結腸膿瘍	1	0	1

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付録 2.7.4- 133　副作用の基本語（PT）一覧（続き）

器官別大分類（SOC）	基本語（PT）	重篤	非重篤	合計
感染症および寄生虫症	憩室炎	1	0	1
	歯肉炎	0	1	1
	帯状疱疹	0	2	2
	感染	3	0	3
	鼻咽頭炎	0	1	1
	口腔感染	0	1	1
	肺炎	2	1	3
	敗血症	4	0	4
	副鼻腔炎	0	1	1
	尿路感染	2	1	3
感染症および寄生虫症　合計		15	10	25
傷害、中毒および処置合併症	偶発的製品曝露	0	1	1
	禁忌薬剤投与	0	1	1
	薬剤誤投与	0	6	6
	投薬欠落	0	6	6
	処方過誤	0	4	4
	焼痂	0	1	1
	転倒	1	0	1
	大腿骨骨折	1	0	1
	不適切な薬剤投与計画	0	4	4
	誤った投与期間	0	1	1
	製品の誤った保存	0	2	2
	誤った投与経路	0	2	2
	回避された薬剤処方過誤	0	1	1
	適応外使用	1	56	57
	品質不良薬剤の投与	0	1	1
	処置後出血	1	0	1
	製品使用の問題	0	3	3
	腱断裂	0	1	1
	創部分泌	1	0	1
	製品使用過程における誤った技法	0	6	6
傷害、中毒および処置合併症　合計		5	96	101

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付録 2.7.4- 133　副作用の基本語（PT）一覧（続き）

器官別大分類（SOC）	基本語（PT）	重篤	非重篤	合計
臨床検査	アラニンアミノトランスフェラーゼ異常	1	0	1
	アラニンアミノトランスフェラーゼ増加	0	1	1
	アミラーゼ増加	0	1	1
	アスパラギン酸アミノトランスフェラーゼ増加	0	1	1
	血中ビリルビン増加	2	2	4
	血中コレステロール増加	0	1	1
	血中クレアチンホスホキナーゼ MB 増加	0	1	1
	血中クレアチニン増加	2	0	2
	血中ブドウ糖増加	1	0	1
	血中乳酸脱水素酵素減少	0	1	1
	血中乳酸脱水素酵素増加	1	2	3
	血中カリウム減少	0	1	1
	収縮期血圧上昇	1	0	1
	血中甲状腺刺激ホルモン増加	0	1	1
	血中尿素増加	0	1	1
	C-反応性蛋白異常	0	1	1
	駆出率減少	0	1	1
	ヘモグロビン減少	0	1	1
	心拍数増加	1	0	1
	肝酵素上昇	3	7	10
	リパーゼ増加	0	3	3
	肝機能検査異常	1	1	2
	心筋壊死マーカー上昇	0	1	1
	好中球数増加	0	1	1
	PO2低下	1	0	1
	血小板数異常	0	2	2
	血小板数減少	1	0	1
	ブドウ球菌検査陽性	0	1	1
	サイログロブリン増加	0	1	1
	甲状腺ホルモン増加	0	1	1
	トランスアミナーゼ上昇	1	0	1

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付録 2.7.4- 133　副作用の基本語（PT）一覧（続き）

器官別大分類（SOC）	基本語（PT）	重篤	非重篤	合計
臨床検査	体重減少	3	4	7
	体重増加	0	1	1
	白血球数増加	0	1	1
臨床検査　合計		19	40	59
代謝および栄養障害	食欲減退	3	5	8
	脱水	1	0	1
	糖尿病	0	1	1
	糖尿病性ケトアシドーシス	2	0	2
	成長障害	1	0	1
	栄養補給障害	0	2	2
	高カルシウム血症	1	0	1
	高血糖	1	2	3
	低カリウム血症	1	0	1
	低ナトリウム血症	2	1	3
	低リン酸血症	1	0	1
	ケトアシドーシス	1	0	1
	代謝性アシドーシス	1	0	1
	腫瘍崩壊症候群	1	1	2
代謝および栄養障害　合計		16	12	28
筋骨格系および結合組織障害	関節痛	1	11	12
	腋窩腫瘤	0	1	1
	背部痛	0	1	1
	骨痛	0	1	1
	側腹部痛	0	1	1
	関節硬直	0	1	1
	関節腫脹	0	2	2
	筋力低下	1	4	5
	筋骨格痛	0	1	1
	筋骨格硬直	0	1	1
	筋肉痛	2	6	8
	四肢痛	0	1	1
	関節リウマチ	1	0	1
	軟部組織壊死	1	0	1
筋骨格系および結合組織障害　合計		6	31	37

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付録 2.7.4- 133　副作用の基本語（PT）一覧（続き）

器官別大分類（SOC）	基本語（PT）	重篤	非重篤	合計
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	骨新生物	0	1	1
	脳の悪性新生物	1	0	1
	乳癌	1	0	1
	癌、寛解期	0	1	1
	癌疼痛	1	1	2
	遠隔転移を伴う肝癌	1	0	1
	悪性黒色腫	1	0	1
	悪性黒色腫第4期	1	0	1
	悪性新生物進行	37	1	38
	中枢神経系転移	2	0	2
	遠隔転移を伴う悪性黒色腫	6	0	6
	遠隔転移を伴う眼球黒色腫	1	0	1
	新生物	1	0	1
	新生物進行	1	0	1
	非小細胞肺癌	1	0	1
	皮膚有棘細胞癌	1	0	1
	腫瘍フレア	0	1	1
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）　合計		56	5	61
神経系障害	健忘	0	1	1
	平衡障害	1	1	2
	脳浮腫	2	0	2
	灼熱感	0	1	1
	中枢神経系出血	1	0	1
	中枢神経系病変	0	1	1
	脳出血	3	0	3
	脳血管発作	1	0	1
	認知障害	0	1	1
	浮動性めまい	2	0	2

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付録 2.7.4- 133　副作用の基本語（PT）一覧（続き）

器官別大分類（SOC）	基本語（PT）	重篤	非重篤	合計
神経系障害	統合運動障害	0	1	1
	起立障害	0	1	1
	顔面不全麻痺	0	1	1
	頭痛	1	5	6
	片頭痛	0	1	1
	重症筋無力症	2	0	2
	重症筋無力症クリーゼ	1	0	1
	筋無力症候群	1	0	1
	神経系障害	2	0	2
	視神経炎	0	1	1
	部分発作	0	1	1
	痙攣発作	3	0	3
	会話障害	0	1	1
	振戦	1	1	2
	刺激無反応	1	0	1
神経系障害　合計		22	18	40
精神障害	異常行動	0	1	1
	激越	1	0	1
	錯乱状態	1	1	2
	譫妄	2	0	2
	うつ病	0	1	1
	恐怖	0	1	1
	感情の平板化	0	1	1
	落ち着きのなさ	1	0	1
精神障害　合計		5	5	10
腎および尿路障害	急性腎不全	2	0	2
	慢性腎臓病	1	0	1
	腎炎	1	2	3
	頻尿	0	1	1
	尿閉	2	0	2
腎および尿路障害　合計		6	3	9
生殖系および乳房障害	精巣腫脹	0	1	1
生殖系および乳房障害　合計		0	1	1

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付録 2.7.4- 133　副作用の基本語（PT）一覧（続き）

器官別大分類（SOC）	基本語（PT）	重篤	非重篤	合計
呼吸器、胸郭および縦隔障害	慢性閉塞性肺疾患	0	2	2
	咳嗽	0	2	2
	発声障害	0	1	1
	呼吸困難	5	3	8
	労作性呼吸困難	0	2	2
	肺気腫	0	1	1
	間質性肺疾患	0	1	1
	肺障害	1	1	2
	鼻閉	0	1	1
	閉塞性気道障害	1	0	1
	起坐呼吸	0	1	1
	胸水	2	1	3
	肺臓炎	2	7	9
	湿性咳嗽	0	1	1
	肺塞栓症	1	0	1
	呼吸障害	2	0	2
	鼻漏	0	1	1
呼吸器、胸郭および縦隔障害　合計		14	25	39
皮膚および皮下組織障害	脱毛症	0	1	1
	水疱	0	2	2
	冷汗	0	1	1
	皮膚炎	0	1	1
	剥脱性皮膚炎	0	1	1
	皮膚乾燥	0	1	1
	紅斑	1	4	5
	毛髪変色	0	3	3
	類天疱瘡	1	0	1
	光線過敏性反応	0	1	1
	そう痒症	0	6	6
	全身性そう痒症	0	3	3
	乾癬	0	1	1
	発疹	1	10	11

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付録 2.7.4- 133　副作用の基本語（PT）一覧（続き）

器官別大分類（SOC）	基本語（PT）	重篤	非重篤	合計
皮膚および皮下組織障害	紅斑性皮疹	0	1	1
	全身性皮疹	1	3	4
	斑状丘疹状皮疹	0	1	1
	そう痒性皮疹	0	1	1
	痂皮	0	1	1
	皮膚変色	2	0	2
	皮膚障害	0	1	1
	皮膚剥脱	0	1	1
	皮膚病変	0	1	1
	皮膚熱感	0	1	1
	蕁麻疹	0	3	3
	尋常性白斑	0	3	3
皮膚および皮下組織障害　合計		6	52	58
外科および内科処置	胆嚢切除	1	0	1
	透析	1	0	1
	入院	1	0	1
	血小板輸血	0	1	1
	治療的塞栓術	1	0	1
	輸血	0	2	2
外科および内科処置　合計		4	3	7
血管障害	深部静脈血栓症	1	0	1
	出血	0	1	1
	ほてり	1	0	1
	高血圧	0	1	1
	低血圧	1	0	1
	リンパ浮腫	1	0	1
	起立性低血圧	0	1	1
	血栓症	1	0	1
血管障害　合計		5	3	8
合計		300	527	827

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付録 2.7.4- 134 患者の特性
024 試験（安全性解析対象集団）

Subject Characteristics
(ITT Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	154		151	
Gender				
Male	92	(59.7)	95	(62.9)
Female	62	(40.3)	56	(37.1)
Age (Years)				
< 65	77	(50.0)	64	(42.4)
>= 65	77	(50.0)	87	(57.6)
Mean	63.9		64.6	
SD	10.1		9.5	
Median	64.5		66.0	
Range	33 to 90		38 to 85	
Race				
American Indian Or Alaska Native	0	(0.0)	1	(0.7)
Asian	25	(16.2)	21	(13.9)
Black Or African American	2	(1.3)	2	(1.3)
Native Hawaiian Or Other Pacific Islander	0	(0.0)	1	(0.7)
White	125	(81.2)	126	(83.4)
Missing	2	(1.3)	0	(0.0)
Ethnicity				
Hispanic Or Latino	1	(0.6)	5	(3.3)
Not Hispanic Or Latino	147	(95.5)	135	(89.4)
Not Reported	4	(2.6)	6	(4.0)
Unknown	2	(1.3)	5	(3.3)
ECOG				
0	54	(35.1)	53	(35.1)
1	99	(64.3)	98	(64.9)
2	1	(0.6)	0	(0.0)
Cancer Stage at Screening				
IIIB	1	(0.6)	1	(0.7)
IV	153	(99.4)	150	(99.3)
Geographic Region of Enrolling Site				
Non-East Asia	133	(86.4)	132	(87.4)
East Asia	21	(13.6)	19	(12.6)
Histology				
ADENOCARCINOMA	104	(67.5)	108	(71.5)
ADENOSQUAMOUS	2	(1.3)	2	(1.3)

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Subject Characteristics
(ITT Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Histology				
LARGE CELL CARCINOMA	2	(1.3)	2	(1.3)
NON-SQUAMOUS CELL CARCINOMA	5	(3.2)	7	(4.6)
POORLY DIFFERENTIATED	9	(5.8)	3	(2.0)
SARCOMATOID	3	(1.9)	2	(1.3)
SQUAMOUS CELL CARCINOMA	29	(18.8)	26	(17.2)
POORLY DIFFERENTIATED SQUAMOUS CELL CARCINOMA	0	(0.0)	1	(0.7)
Smoking Status				
Current	34	(22.1)	31	(20.5)
Former	115	(74.7)	101	(66.9)
Never	5	(3.2)	19	(12.6)
Brain Metastasis Status at Baseline				
Y	18	(11.7)	10	(6.6)
N	136	(88.3)	141	(93.4)
Baseline Tumor Size (mm)				
Subjects with data	151		150	
Mean	90.9		99.8	
SD	53.4		63.4	
Median	82		84	
Range	14 to 322		14 to 369	
Baseline Weight (kg)				
Subjects with data	154		151	
Mean	68.8		72.7	
SD	13.7		17.2	
Median	69		70	
Range	38 to 110		39 to 132	
Prior Adjuvant Therapy				
Yes	6	(3.9)	3	(2.0)
No	148	(96.1)	148	(98.0)
Prior Neo-adjuvant Therapy				
Yes	3	(1.9)	1	(0.7)
No	151	(98.1)	150	(99.3)
(Database Cutoff Date: 09MAY2016).				

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付録 2.7.4- 135 有害事象（いずれかの投与群で発現割合 0%超）
024 試験（安全性解析対象集団）

Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) (ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	154				150			
with one or more adverse events	148	(96.1)	82	(53.2)	145	(96.7)	109	(72.7)
with no adverse events	6	(3.9)	72	(46.8)	5	(3.3)	41	(27.3)
Blood and lymphatic system disorders	**28**	**(18.2)**	**7**	**(4.5)**	**100**	**(66.7)**	**56**	**(37.3)**
Anaemia	20	(13.0)	7	(4.5)	79	(52.7)	35	(23.3)
Anaemia of malignant disease	0	(0.0)	0	(0.0)	2	(1.3)	0	(0.0)
Eosinophilia	3	(1.9)	0	(0.0)	0	(0.0)	0	(0.0)
Febrile neutropenia	0	(0.0)	0	(0.0)	3	(2.0)	3	(2.0)
Leukocytosis	1	(0.6)	0	(0.0)	5	(3.3)	2	(1.3)
Leukopenia	1	(0.6)	0	(0.0)	10	(6.7)	2	(1.3)
Lymph node pain	0	(0.0)	0	(0.0)	2	(1.3)	0	(0.0)
Lymphopenia	3	(1.9)	0	(0.0)	0	(0.0)	0	(0.0)
Neutropenia	2	(1.3)	0	(0.0)	36	(24.0)	21	(14.0)
Neutrophilia	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Pancytopenia	0	(0.0)	0	(0.0)	3	(2.0)	3	(2.0)
Pernicious anaemia	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Splenic infarction	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Thrombocytopenia	2	(1.3)	0	(0.0)	20	(13.3)	9	(6.0)
Thrombocytosis	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Cardiac disorders	**14**	**(9.1)**	**6**	**(3.9)**	**19**	**(12.7)**	**10**	**(6.7)**
Angina pectoris	0	(0.0)	0	(0.0)	2	(1.3)	1	(0.7)
Atrial fibrillation	2	(1.3)	0	(0.0)	3	(2.0)	3	(2.0)
Bradycardia	1	(0.6)	0	(0.0)	2	(1.3)	0	(0.0)
Cardiac arrest	1	(0.6)	1	(0.6)	1	(0.7)	1	(0.7)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) (ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Cardiac disorders	**14**	**(9.1)**	**6**	**(3.9)**	**19**	**(12.7)**	**10**	**(6.7)**
Cardiac failure	1	(0.6)	1	(0.6)	3	(2.0)	2	(1.3)
Cardio-respiratory arrest	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Coronary artery disease	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Ischaemic cardiomyopathy	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Palpitations	2	(1.3)	0	(0.0)	1	(0.7)	0	(0.0)
Pericardial effusion	4	(2.6)	2	(1.3)	1	(0.7)	1	(0.7)
Pericarditis	2	(1.3)	1	(0.6)	0	(0.0)	0	(0.0)
Right ventricular failure	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Sinus tachycardia	1	(0.6)	0	(0.0)	3	(2.0)	0	(0.0)
Supraventricular tachycardia	1	(0.6)	1	(0.6)	1	(0.7)	0	(0.0)
Tachycardia	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Ear and labyrinth disorders	**4**	**(2.6)**	**0**	**(0.0)**	**6**	**(4.0)**	**0**	**(0.0)**
Cerumen impaction	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Ear pain	1	(0.6)	0	(0.0)	2	(1.3)	0	(0.0)
Hypoacusis	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Tinnitus	1	(0.6)	0	(0.0)	2	(1.3)	0	(0.0)
Vertigo	2	(1.3)	0	(0.0)	1	(0.7)	0	(0.0)
Endocrine disorders	**24**	**(15.6)**	**1**	**(0.6)**	**4**	**(2.7)**	**0**	**(0.0)**
Autoimmune thyroiditis	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Euthyroid sick syndrome	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hyperparathyroidism	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hyperthyroidism	12	(7.8)	0	(0.0)	2	(1.3)	0	(0.0)
Hypophysitis	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Endocrine disorders	**24**	**(15.6)**	**1**	**(0.6)**	**4**	**(2.7)**	**0**	**(0.0)**
Hypothyroidism	14	(9.1)	0	(0.0)	2	(1.3)	0	(0.0)
Thyroiditis	3	(1.9)	0	(0.0)	0	(0.0)	0	(0.0)
Eye disorders	**7**	**(4.5)**	**0**	**(0.0)**	**17**	**(11.3)**	**0**	**(0.0)**
Abnormal sensation in eye	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Cataract	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Diplopia	2	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)
Dry eye	2	(1.3)	0	(0.0)	6	(4.0)	0	(0.0)
Eye oedema	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Eye pain	2	(1.3)	0	(0.0)	3	(2.0)	0	(0.0)
Eye pruritus	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Keratitis	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Lacrimation increased	0	(0.0)	0	(0.0)	5	(3.3)	0	(0.0)
Periorbital oedema	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Vision blurred	1	(0.6)	0	(0.0)	3	(2.0)	0	(0.0)
Gastrointestinal disorders	**80**	**(51.9)**	**12**	**(7.8)**	**107**	**(71.3)**	**15**	**(10.0)**
Abdominal discomfort	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Abdominal distension	3	(1.9)	0	(0.0)	1	(0.7)	0	(0.0)
Abdominal pain	10	(6.5)	1	(0.6)	10	(6.7)	0	(0.0)
Abdominal pain lower	2	(1.3)	0	(0.0)	1	(0.7)	0	(0.0)
Abdominal pain upper	6	(3.9)	0	(0.0)	7	(4.7)	1	(0.7)
Abdominal tenderness	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Anal fissure	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Anal haemorrhage	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Gastrointestinal disorders	**80**	**(51.9)**	**12**	**(7.8)**	**107**	**(71.3)**	**15**	**(10.0)**
Anal incontinence	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Aphthous ulcer	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Ascites	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Coating in mouth	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Colitis	2	(1.3)	2	(1.3)	0	(0.0)	0	(0.0)
Constipation	32	(20.8)	1	(0.6)	34	(22.7)	1	(0.7)
Dental caries	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Diarrhoea	32	(20.8)	6	(3.9)	33	(22.0)	3	(2.0)
Dry mouth	5	(3.2)	0	(0.0)	5	(3.3)	0	(0.0)
Dyspepsia	5	(3.2)	0	(0.0)	9	(6.0)	0	(0.0)
Dysphagia	2	(1.3)	0	(0.0)	6	(4.0)	2	(1.3)
Enterocolitis	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Faecaloma	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Gastric disorder	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Gastric ulcer	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Gastritis	2	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)
Gastritis erosive	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Gastrointestinal motility disorder	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Gastrooesophageal reflux disease	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Gingival bleeding	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Gingival pain	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Haematemesis	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Haemorrhoidal haemorrhage	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Inguinal hernia	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Intestinal obstruction	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Gastrointestinal disorders	**80**	**(51.9)**	**12**	**(7.8)**	**107**	**(71.3)**	**15**	**(10.0)**
Large intestine polyp	2	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)
Lip dry	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Lip pain	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Nausea	30	(19.5)	0	(0.0)	70	(46.7)	4	(2.7)
Odynophagia	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Oesophageal stenosis	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Oesophagitis	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Oral mucosal erythema	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Oral pain	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Painful defaecation	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Pancreatitis	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Paraesthesia oral	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Salivary hypersecretion	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Small intestinal obstruction	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Stomatitis	7	(4.5)	0	(0.0)	18	(12.0)	2	(1.3)
Tooth impacted	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Toothache	2	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)
Vomiting	12	(7.8)	1	(0.6)	36	(24.0)	3	(2.0)
General disorders and administration site conditions	**91**	**(59.1)**	**8**	**(5.2)**	**96**	**(64.0)**	**15**	**(10.0)**
Asthenia	10	(6.5)	1	(0.6)	16	(10.7)	4	(2.7)
Catheter site pain	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Catheter site swelling	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Chest discomfort	3	(1.9)	0	(0.0)	1	(0.7)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
General disorders and administration site conditions	**91**	**(59.1)**	**8**	**(5.2)**	**96**	**(64.0)**	**15**	**(10.0)**
Chest pain	12	(7.8)	0	(0.0)	14	(9.3)	2	(1.3)
Chills	4	(2.6)	0	(0.0)	1	(0.7)	0	(0.0)
Death	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Drug intolerance	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Enanthema	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Extravasation	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Face oedema	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Fatigue	32	(20.8)	2	(1.3)	53	(35.3)	7	(4.7)
Feeling cold	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Gait disturbance	1	(0.6)	0	(0.0)	2	(1.3)	1	(0.7)
General physical health deterioration	1	(0.6)	1	(0.6)	2	(1.3)	0	(0.0)
Gravitational oedema	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Hyperpyrexia	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Influenza like illness	2	(1.3)	0	(0.0)	2	(1.3)	0	(0.0)
Infusion site extravasation	0	(0.0)	0	(0.0)	2	(1.3)	0	(0.0)
Local swelling	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Localised oedema	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Malaise	4	(2.6)	0	(0.0)	12	(8.0)	0	(0.0)
Multiple organ dysfunction syndrome	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Non-cardiac chest pain	0	(0.0)	0	(0.0)	3	(2.0)	0	(0.0)
Oedema	5	(3.2)	0	(0.0)	3	(2.0)	0	(0.0)
Oedema peripheral	16	(10.4)	1	(0.6)	15	(10.0)	0	(0.0)
Pain	5	(3.2)	0	(0.0)	5	(3.3)	1	(0.7)
Peripheral swelling	2	(1.3)	0	(0.0)	2	(1.3)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
General disorders and administration site conditions	**91**	**(59.1)**	**8**	**(5.2)**	**96**	**(64.0)**	**15**	**(10.0)**
Puncture site pain	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Pyrexia	24	(15.6)	0	(0.0)	14	(9.3)	0	(0.0)
Sudden death	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Suprapubic pain	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Swelling	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Thirst	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Xerosis	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hepatobiliary disorders	**3**	**(1.9)**	**1**	**(0.6)**	**1**	**(0.7)**	**0**	**(0.0)**
Acute hepatic failure	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Cholestasis	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hepatic function abnormal	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hepatotoxicity	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Immune system disorders	**6**	**(3.9)**	**1**	**(0.6)**	**1**	**(0.7)**	**0**	**(0.0)**
Anaphylactic shock	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Contrast media allergy	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Drug hypersensitivity	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Hypersensitivity	4	(2.6)	0	(0.0)	0	(0.0)	0	(0.0)
Infections and infestations	**57**	**(37.0)**	**19**	**(12.3)**	**66**	**(44.0)**	**28**	**(18.7)**
Angular cheilitis	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Appendicitis	1	(0.6)	1	(0.6)	1	(0.7)	1	(0.7)
Asymptomatic bacteriuria	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Infections and infestations	**57**	**(37.0)**	**19**	**(12.3)**	**66**	**(44.0)**	**28**	**(18.7)**
Bacteraemia	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Balanitis candida	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Bronchitis	5	(3.2)	0	(0.0)	4	(2.7)	0	(0.0)
Candida infection	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Catheter site infection	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Cellulitis	1	(0.6)	1	(0.6)	2	(1.3)	1	(0.7)
Chronic sinusitis	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Clostridium difficile colitis	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Conjunctivitis	1	(0.6)	0	(0.0)	4	(2.7)	0	(0.0)
Device related infection	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Diverticulitis	0	(0.0)	0	(0.0)	2	(1.3)	1	(0.7)
Escherichia urinary tract infection	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Eye infection	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Folliculitis	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Fungal infection	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Fungal skin infection	2	(1.3)	0	(0.0)	1	(0.7)	0	(0.0)
Gastroenteritis viral	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Gingivitis	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Herpes zoster	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Implant site infection	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Infected dermal cyst	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Infection	1	(0.6)	1	(0.6)	1	(0.7)	0	(0.0)
Infection susceptibility increased	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Infectious pleural effusion	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) (ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Infections and infestations	**57**	**(37.0)**	**19**	**(12.3)**	**66**	**(44.0)**	**28**	**(18.7)**
Infective exacerbation of chronic obstructive airways disease	0	(0.0)	0	(0.0)	2	(1.3)	1	(0.7)
Influenza	2	(1.3)	0	(0.0)	2	(1.3)	0	(0.0)
Laryngitis	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Localised infection	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Lower respiratory tract infection	5	(3.2)	2	(1.3)	5	(3.3)	3	(2.0)
Lung infection	3	(1.9)	3	(1.9)	2	(1.3)	2	(1.3)
Nasopharyngitis	16	(10.4)	0	(0.0)	2	(1.3)	0	(0.0)
Neutropenic sepsis	1	(0.6)	1	(0.6)	2	(1.3)	2	(1.3)
Oesophageal candidiasis	0	(0.0)	0	(0.0)	2	(1.3)	0	(0.0)
Oral candidiasis	5	(3.2)	0	(0.0)	6	(4.0)	0	(0.0)
Oral herpes	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Peritonsillar abscess	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Pharyngitis	0	(0.0)	0	(0.0)	2	(1.3)	0	(0.0)
Pneumonia	4	(2.6)	3	(1.9)	14	(9.3)	11	(7.3)
Pneumonia bacterial	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Pneumonia streptococcal	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Pulmonary sepsis	0	(0.0)	0	(0.0)	2	(1.3)	2	(1.3)
Pulpitis dental	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Respiratory tract infection	3	(1.9)	2	(1.3)	4	(2.7)	1	(0.7)
Rhinitis	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Sepsis	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Septic shock	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Sialoadenitis	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Sinusitis	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) (ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Infections and infestations	**57**	**(37.0)**	**19**	**(12.3)**	**66**	**(44.0)**	**28**	**(18.7)**
Skin infection	2	(1.3)	0	(0.0)	1	(0.7)	1	(0.7)
Splenic abscess	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Subcutaneous abscess	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Tinea pedis	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Tonsillitis	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Tooth abscess	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Tooth infection	1	(0.6)	0	(0.0)	2	(1.3)	0	(0.0)
Tracheobronchitis	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Upper respiratory tract infection	9	(5.8)	0	(0.0)	5	(3.3)	0	(0.0)
Urinary tract infection	8	(5.2)	1	(0.6)	7	(4.7)	2	(1.3)
Urosepsis	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Viral infection	2	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)
Viral rhinitis	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Viral upper respiratory tract infection	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Vulvovaginal candidiasis	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Injury, poisoning and procedural complications	**21**	**(13.6)**	**0**	**(0.0)**	**16**	**(10.7)**	**3**	**(2.0)**
Accidental overdose	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Arthropod bite	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Bone contusion	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Concussion	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Contrast media reaction	2	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)
Contusion	2	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)
Facial bones fracture	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) (ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Injury, poisoning and procedural complications	**21**	**(13.6)**	**0**	**(0.0)**	**16**	**(10.7)**	**3**	**(2.0)**
Fall	6	(3.9)	0	(0.0)	3	(2.0)	0	(0.0)
Foot fracture	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Fractured ischium	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Infusion related reaction	3	(1.9)	0	(0.0)	1	(0.7)	0	(0.0)
Joint injury	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Ligament sprain	2	(1.3)	0	(0.0)	1	(0.7)	0	(0.0)
Limb injury	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Muscle injury	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Muscle strain	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Procedural pain	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Pubis fracture	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Pulmonary radiation injury	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Radiation myelopathy	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Radiation oesophagitis	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Rib fracture	0	(0.0)	0	(0.0)	2	(1.3)	1	(0.7)
Skin abrasion	2	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)
Spinal fracture	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Subdural haematoma	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Thermal burn	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Thoracic vertebral fracture	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Tooth fracture	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Toxicity to various agents	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Wound complication	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) (ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**62**	**(40.3)**	**12**	**(7.8)**	**72**	**(48.0)**	**18**	**(12.0)**
Adjusted calcium decreased	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Alanine aminotransferase increased	17	(11.0)	2	(1.3)	11	(7.3)	0	(0.0)
Amylase increased	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Aspartate aminotransferase increased	13	(8.4)	2	(1.3)	7	(4.7)	0	(0.0)
Bilirubin conjugated increased	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Blood 25-hydroxycholecalciferol decreased	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Blood albumin decreased	2	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)
Blood alkaline phosphatase increased	10	(6.5)	1	(0.6)	4	(2.7)	0	(0.0)
Blood bilirubin increased	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Blood calcium decreased	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Blood chloride decreased	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Blood creatine increased	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Blood creatine phosphokinase increased	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Blood creatinine decreased	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Blood creatinine increased	10	(6.5)	0	(0.0)	20	(13.3)	1	(0.7)
Blood glucose increased	2	(1.3)	0	(0.0)	2	(1.3)	1	(0.7)
Blood lactate dehydrogenase increased	2	(1.3)	0	(0.0)	2	(1.3)	0	(0.0)
Blood magnesium decreased	2	(1.3)	0	(0.0)	4	(2.7)	0	(0.0)
Blood potassium decreased	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Blood potassium increased	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Blood sodium decreased	2	(1.3)	0	(0.0)	1	(0.7)	0	(0.0)
Blood thyroid stimulating hormone decreased	4	(2.6)	0	(0.0)	1	(0.7)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) (ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**62**	**(40.3)**	**12**	**(7.8)**	**72**	**(48.0)**	**18**	**(12.0)**
Blood thyroid stimulating hormone increased	6	(3.9)	0	(0.0)	0	(0.0)	0	(0.0)
Blood urea increased	2	(1.3)	0	(0.0)	1	(0.7)	0	(0.0)
Blood uric acid increased	4	(2.6)	0	(0.0)	0	(0.0)	0	(0.0)
C-reactive protein increased	1	(0.6)	1	(0.6)	1	(0.7)	0	(0.0)
Creatinine renal clearance decreased	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Enterococcus test positive	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Fungal test positive	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Gamma-glutamyltransferase increased	5	(3.2)	1	(0.6)	6	(4.0)	0	(0.0)
Haemoglobin decreased	0	(0.0)	0	(0.0)	6	(4.0)	1	(0.7)
Hepatic enzyme increased	2	(1.3)	1	(0.6)	0	(0.0)	0	(0.0)
Inspiratory capacity decreased	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
International normalised ratio increased	2	(1.3)	1	(0.6)	1	(0.7)	0	(0.0)
Lymphocyte count decreased	1	(0.6)	1	(0.6)	4	(2.7)	3	(2.0)
Neutrophil count decreased	1	(0.6)	0	(0.0)	20	(13.3)	6	(4.0)
Neutrophil count increased	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Platelet count decreased	1	(0.6)	0	(0.0)	19	(12.7)	9	(6.0)
Procalcitonin increased	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Protein total decreased	2	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)
Red blood cell sedimentation rate increased	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Respiratory rate decreased	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Thyroxine decreased	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Thyroxine free decreased	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**62**	**(40.3)**	**12**	**(7.8)**	**72**	**(48.0)**	**18**	**(12.0)**
Thyroxine free increased	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Thyroxine increased	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Transaminases increased	3	(1.9)	2	(1.3)	0	(0.0)	0	(0.0)
Tri-iodothyronine decreased	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Tri-iodothyronine free decreased	2	(1.3)	0	(0.0)	1	(0.7)	0	(0.0)
Tri-iodothyronine free increased	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Troponin I increased	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Troponin increased	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Weight decreased	13	(8.4)	0	(0.0)	11	(7.3)	0	(0.0)
Weight increased	4	(2.6)	0	(0.0)	1	(0.7)	0	(0.0)
White blood cell count decreased	1	(0.6)	0	(0.0)	16	(10.7)	3	(2.0)
White blood cell count increased	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Metabolism and nutrition disorders	**61**	**(39.6)**	**16**	**(10.4)**	**82**	**(54.7)**	**22**	**(14.7)**
Decreased appetite	31	(20.1)	2	(1.3)	49	(32.7)	5	(3.3)
Dehydration	4	(2.6)	2	(1.3)	4	(2.7)	0	(0.0)
Diabetes mellitus	2	(1.3)	2	(1.3)	0	(0.0)	0	(0.0)
Diabetic ketoacidosis	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Dyslipidaemia	2	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)
Gout	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Hypercalcaemia	5	(3.2)	0	(0.0)	4	(2.7)	2	(1.3)
Hyperchloraemia	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hypercholesterolaemia	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Hyperglycaemia	11	(7.1)	4	(2.6)	9	(6.0)	1	(0.7)
Hyperkalaemia	7	(4.5)	2	(1.3)	6	(4.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Metabolism and nutrition disorders	**61**	**(39.6)**	**16**	**(10.4)**	**82**	**(54.7)**	**22**	**(14.7)**
Hypermagnesaemia	2	(1.3)	1	(0.6)	1	(0.7)	0	(0.0)
Hypernatraemia	2	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)
Hypertriglyceridaemia	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hyperuricaemia	5	(3.2)	0	(0.0)	1	(0.7)	1	(0.7)
Hypoalbuminaemia	7	(4.5)	2	(1.3)	7	(4.7)	3	(2.0)
Hypocalcaemia	2	(1.3)	0	(0.0)	4	(2.7)	1	(0.7)
Hypochloraemia	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hypoglycaemia	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Hypokalaemia	4	(2.6)	2	(1.3)	5	(3.3)	2	(1.3)
Hypomagnesaemia	2	(1.3)	0	(0.0)	13	(8.7)	0	(0.0)
Hyponatraemia	11	(7.1)	5	(3.2)	12	(8.0)	7	(4.7)
Hypophagia	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Hypophosphataemia	5	(3.2)	0	(0.0)	4	(2.7)	4	(2.7)
Hypovolaemia	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Malnutrition	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Type 2 diabetes mellitus	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Vitamin D deficiency	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Musculoskeletal and connective tissue disorders	**67**	**(43.5)**	**5**	**(3.2)**	**61**	**(40.7)**	**11**	**(7.3)**
Arthralgia	24	(15.6)	0	(0.0)	15	(10.0)	1	(0.7)
Arthritis	3	(1.9)	0	(0.0)	1	(0.7)	0	(0.0)
Back pain	20	(13.0)	2	(1.3)	21	(14.0)	5	(3.3)
Bone pain	4	(2.6)	0	(0.0)	3	(2.0)	2	(1.3)
Bursitis	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Musculoskeletal and connective tissue disorders	**67**	**(43.5)**	**5**	**(3.2)**	**61**	**(40.7)**	**11**	**(7.3)**
Fistula	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Flank pain	3	(1.9)	0	(0.0)	2	(1.3)	0	(0.0)
Groin pain	6	(3.9)	0	(0.0)	0	(0.0)	0	(0.0)
Hypercreatinaemia	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Joint effusion	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Joint range of motion decreased	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Joint swelling	0	(0.0)	0	(0.0)	2	(1.3)	0	(0.0)
Limb deformity	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Muscle atrophy	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Muscle haemorrhage	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Muscle spasms	8	(5.2)	0	(0.0)	2	(1.3)	0	(0.0)
Muscular weakness	4	(2.6)	1	(0.6)	4	(2.7)	0	(0.0)
Musculoskeletal chest pain	5	(3.2)	0	(0.0)	2	(1.3)	0	(0.0)
Musculoskeletal discomfort	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Musculoskeletal pain	11	(7.1)	1	(0.6)	8	(5.3)	1	(0.7)
Musculoskeletal stiffness	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Myalgia	7	(4.5)	0	(0.0)	2	(1.3)	0	(0.0)
Myalgia intercostal	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Myopathy	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Myositis	2	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)
Neck pain	4	(2.6)	0	(0.0)	4	(2.7)	0	(0.0)
Osteolysis	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Osteopenia	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Osteoporosis	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Musculoskeletal and connective tissue disorders	**67**	**(43.5)**	**5**	**(3.2)**	**61**	**(40.7)**	**11**	**(7.3)**
Pain in extremity	6	(3.9)	1	(0.6)	10	(6.7)	0	(0.0)
Pathological fracture	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Spinal pain	1	(0.6)	1	(0.6)	2	(1.3)	1	(0.7)
Tendon disorder	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**4**	**(2.6)**	**3**	**(1.9)**	**4**	**(2.7)**	**4**	**(2.7)**
Bladder neoplasm	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Cancer pain	0	(0.0)	0	(0.0)	2	(1.3)	2	(1.3)
Gastrointestinal carcinoma	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Infected neoplasm	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Malignant neoplasm progression	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Metastases to meninges	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Tumour pain	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Nervous system disorders	**42**	**(27.3)**	**3**	**(1.9)**	**57**	**(38.0)**	**7**	**(4.7)**
Ageusia	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Amnesia	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Aphasia	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Brain oedema	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Cerebral infarction	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Cerebrovascular accident	1	(0.6)	1	(0.6)	1	(0.7)	1	(0.7)
Clonus	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Dizziness	16	(10.4)	1	(0.6)	12	(8.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Nervous system disorders	**42**	**(27.3)**	**3**	**(1.9)**	**57**	**(38.0)**	**7**	**(4.7)**
Dysarthria	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Dysgeusia	3	(1.9)	0	(0.0)	18	(12.0)	0	(0.0)
Haemorrhagic stroke	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Headache	9	(5.8)	0	(0.0)	7	(4.7)	0	(0.0)
Hypoaesthesia	2	(1.3)	0	(0.0)	3	(2.0)	0	(0.0)
Ischaemic stroke	1	(0.6)	0	(0.0)	1	(0.7)	1	(0.7)
Lethargy	5	(3.2)	0	(0.0)	3	(2.0)	0	(0.0)
Memory impairment	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Migraine	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Myoclonus	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Neurological symptom	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Neuropathy peripheral	2	(1.3)	0	(0.0)	10	(6.7)	1	(0.7)
Paraesthesia	3	(1.9)	0	(0.0)	3	(2.0)	0	(0.0)
Parosmia	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral motor neuropathy	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Peripheral sensory neuropathy	0	(0.0)	0	(0.0)	6	(4.0)	1	(0.7)
Polyneuropathy	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Sciatica	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Sinus headache	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Somnolence	0	(0.0)	0	(0.0)	2	(1.3)	0	(0.0)
Syncope	0	(0.0)	0	(0.0)	3	(2.0)	2	(1.3)
Tension headache	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Transient ischaemic attack	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Tremor	2	(1.3)	0	(0.0)	2	(1.3)	0	(0.0)
Vocal cord paralysis	1	(0.6)	0	(0.0)	1	(0.7)	1	(0.7)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Product issues	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.7)**	**1**	**(0.7)**
Device dislocation	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Psychiatric disorders	**25**	**(16.2)**	**1**	**(0.6)**	**22**	**(14.7)**	**1**	**(0.7)**
Abulia	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Agitation	2	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)
Anxiety	4	(2.6)	0	(0.0)	5	(3.3)	0	(0.0)
Bradyphrenia	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Confusional state	3	(1.9)	0	(0.0)	2	(1.3)	1	(0.7)
Delirium	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Delusion	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Depressed mood	1	(0.6)	0	(0.0)	2	(1.3)	0	(0.0)
Depression	2	(1.3)	0	(0.0)	3	(2.0)	0	(0.0)
Disorientation	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Dissociation	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Insomnia	13	(8.4)	0	(0.0)	10	(6.7)	0	(0.0)
Panic attack	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Personality change	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Restlessness	0	(0.0)	0	(0.0)	3	(2.0)	0	(0.0)
Renal and urinary disorders	**11**	**(7.1)**	**1**	**(0.6)**	**18**	**(12.0)**	**3**	**(2.0)**
Acute kidney injury	1	(0.6)	0	(0.0)	3	(2.0)	2	(1.3)
Chromaturia	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Chronic kidney disease	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Dysuria	4	(2.6)	0	(0.0)	3	(2.0)	0	(0.0)
Haematuria	1	(0.6)	0	(0.0)	3	(2.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Renal and urinary disorders	**11**	**(7.1)**	**1**	**(0.6)**	**18**	**(12.0)**	**3**	**(2.0)**
Hypertensive nephropathy	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Leukocyturia	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Nephrolithiasis	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Pollakiuria	1	(0.6)	0	(0.0)	2	(1.3)	0	(0.0)
Proteinuria	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Renal disorder	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Renal failure	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Renal impairment	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Renal infarct	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Tubulointerstitial nephritis	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Urinary tract pain	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Reproductive system and breast disorders	**6**	**(3.9)**	**3**	**(1.9)**	**2**	**(1.3)**	**0**	**(0.0)**
Benign prostatic hyperplasia	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Breast pain	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Genital rash	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Ovarian haemorrhage	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Pelvic pain	2	(1.3)	2	(1.3)	0	(0.0)	0	(0.0)
Vaginal haemorrhage	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Vulvovaginal dryness	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**77**	**(50.0)**	**25**	**(16.2)**	**72**	**(48.0)**	**21**	**(14.0)**
Acute respiratory failure	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Respiratory, thoracic and mediastinal disorders	**77**	**(50.0)**	**25**	**(16.2)**	**72**	**(48.0)**	**21**	**(14.0)**
Atelectasis	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Bronchial obstruction	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Chronic obstructive pulmonary disease	8	(5.2)	6	(3.9)	1	(0.7)	1	(0.7)
Cough	26	(16.9)	0	(0.0)	21	(14.0)	0	(0.0)
Dysphonia	3	(1.9)	0	(0.0)	3	(2.0)	1	(0.7)
Dyspnoea	34	(22.1)	3	(1.9)	24	(16.0)	4	(2.7)
Dyspnoea exertional	2	(1.3)	0	(0.0)	2	(1.3)	0	(0.0)
Epistaxis	1	(0.6)	0	(0.0)	9	(6.0)	2	(1.3)
Haemoptysis	11	(7.1)	1	(0.6)	5	(3.3)	1	(0.7)
Haemothorax	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hiccups	2	(1.3)	0	(0.0)	10	(6.7)	0	(0.0)
Hypoxia	2	(1.3)	1	(0.6)	1	(0.7)	0	(0.0)
Interstitial lung disease	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Lower respiratory tract inflammation	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Lung infiltration	2	(1.3)	0	(0.0)	1	(0.7)	0	(0.0)
Nasal congestion	1	(0.6)	0	(0.0)	2	(1.3)	0	(0.0)
Organising pneumonia	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Oropharyngeal pain	2	(1.3)	0	(0.0)	5	(3.3)	0	(0.0)
Painful respiration	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Pleural effusion	8	(5.2)	6	(3.9)	6	(4.0)	4	(2.7)
Pleuritic pain	2	(1.3)	0	(0.0)	2	(1.3)	1	(0.7)
Pneumonitis	8	(5.2)	4	(2.6)	1	(0.7)	1	(0.7)
Pneumothorax	1	(0.6)	1	(0.6)	1	(0.7)	1	(0.7)
Productive cough	6	(3.9)	0	(0.0)	5	(3.3)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) (ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Respiratory, thoracic and mediastinal disorders	**77**	**(50.0)**	**25**	**(16.2)**	**72**	**(48.0)**	**21**	**(14.0)**
Pulmonary alveolar haemorrhage	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Pulmonary embolism	5	(3.2)	4	(2.6)	4	(2.7)	4	(2.7)
Pulmonary fibrosis	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Pulmonary hypertension	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Pulmonary oedema	0	(0.0)	0	(0.0)	2	(1.3)	2	(1.3)
Rales	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Respiratory failure	1	(0.6)	1	(0.6)	1	(0.7)	1	(0.7)
Respiratory tract congestion	3	(1.9)	0	(0.0)	0	(0.0)	0	(0.0)
Rhinitis allergic	0	(0.0)	0	(0.0)	2	(1.3)	0	(0.0)
Rhinorrhoea	2	(1.3)	0	(0.0)	2	(1.3)	0	(0.0)
Sneezing	2	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)
Tachypnoea	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Upper respiratory tract congestion	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Upper respiratory tract inflammation	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Upper-airway cough syndrome	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Wheezing	3	(1.9)	0	(0.0)	2	(1.3)	0	(0.0)
Skin and subcutaneous tissue disorders	**70**	**(45.5)**	**7**	**(4.5)**	**32**	**(21.3)**	**0**	**(0.0)**
Alopecia	2	(1.3)	0	(0.0)	13	(8.7)	0	(0.0)
Asteatosis	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Decubitus ulcer	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Dermatitis	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Dermatitis acneiform	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) (ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**70**	**(45.5)**	**7**	**(4.5)**	**32**	**(21.3)**	**0**	**(0.0)**
Dermatitis allergic	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Drug eruption	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Dry skin	13	(8.4)	0	(0.0)	1	(0.7)	0	(0.0)
Eczema	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Erythema	4	(2.6)	0	(0.0)	1	(0.7)	0	(0.0)
Hyperhidrosis	3	(1.9)	0	(0.0)	2	(1.3)	0	(0.0)
Hyperkeratosis	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Lichen sclerosus	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Lichenoid keratosis	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Night sweats	5	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Onycholysis	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Petechiae	2	(1.3)	0	(0.0)	1	(0.7)	0	(0.0)
Pruritus	23	(14.9)	0	(0.0)	5	(3.3)	0	(0.0)
Pruritus generalised	3	(1.9)	0	(0.0)	1	(0.7)	0	(0.0)
Psoriasis	3	(1.9)	1	(0.6)	0	(0.0)	0	(0.0)
Rash	22	(14.3)	2	(1.3)	6	(4.0)	0	(0.0)
Rash erythematous	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Rash generalised	1	(0.6)	1	(0.6)	2	(1.3)	0	(0.0)
Rash maculo-papular	6	(3.9)	1	(0.6)	1	(0.7)	0	(0.0)
Rash pruritic	3	(1.9)	0	(0.0)	1	(0.7)	0	(0.0)
Rash vesicular	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Seborrhoeic dermatitis	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Skin exfoliation	3	(1.9)	0	(0.0)	0	(0.0)	0	(0.0)
Skin lesion	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**70**	**(45.5)**	**7**	**(4.5)**	**32**	**(21.3)**	**0**	**(0.0)**
Skin mass	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Solar dermatitis	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Stasis dermatitis	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Swelling face	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Toxic skin eruption	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Urticaria	3	(1.9)	0	(0.0)	1	(0.7)	0	(0.0)
Vitiligo	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Social circumstances	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.7)**	**0**	**(0.0)**
Menopause	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Vascular disorders	**15**	**(9.7)**	**2**	**(1.3)**	**14**	**(9.3)**	**2**	**(1.3)**
Deep vein thrombosis	2	(1.3)	0	(0.0)	2	(1.3)	0	(0.0)
Embolism	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Flushing	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Hot flush	2	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)
Hypertension	6	(3.9)	2	(1.3)	4	(2.7)	1	(0.7)
Hypertensive crisis	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hypotension	2	(1.3)	0	(0.0)	4	(2.7)	0	(0.0)
Lymphoedema	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Pallor	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Peripheral coldness	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Peripheral embolism	1	(0.6)	0	(0.0)	1	(0.7)	1	(0.7)
Phlebitis	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) (ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Vascular disorders	**15**	**(9.7)**	**2**	**(1.3)**	**14**	**(9.3)**	**2**	**(1.3)**
Thrombosis	0	(0.0)	0	(0.0)	2	(1.3)	0	(0.0)
Vasospasm	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Vena cava thrombosis	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.
Adverse event terms are from MedDRA Version 18.0.
(Database Cutoff Date: 09MAY2016).

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付録 2.7.4- 136 すべての副作用（いずれかの投与群で発現割合 0%超）
024 試験（安全性解析対象集団）

Subjects With Drug-related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	154				150			
with one or more adverse events	113	(73.4)	41	(26.6)	135	(90.0)	80	(53.3)
with no adverse events	41	(26.6)	113	(73.4)	15	(10.0)	70	(46.7)
Blood and lymphatic system disorders	**13**	**(8.4)**	**3**	**(1.9)**	**86**	**(57.3)**	**50**	**(33.3)**
Anaemia	8	(5.2)	3	(1.9)	66	(44.0)	29	(19.3)
Anaemia of malignant disease	0	(0.0)	0	(0.0)	2	(1.3)	0	(0.0)
Eosinophilia	3	(1.9)	0	(0.0)	0	(0.0)	0	(0.0)
Febrile neutropenia	0	(0.0)	0	(0.0)	3	(2.0)	3	(2.0)
Leukocytosis	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Leukopenia	1	(0.6)	0	(0.0)	8	(5.3)	2	(1.3)
Lymph node pain	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Lymphopenia	2	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)
Neutropenia	1	(0.6)	0	(0.0)	34	(22.7)	20	(13.3)
Pancytopenia	0	(0.0)	0	(0.0)	3	(2.0)	3	(2.0)
Thrombocytopenia	0	(0.0)	0	(0.0)	17	(11.3)	8	(5.3)
Cardiac disorders	**2**	**(1.3)**	**1**	**(0.6)**	**1**	**(0.7)**	**0**	**(0.0)**
Angina pectoris	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Pericardial effusion	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Pericarditis	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Sinus tachycardia	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Ear and labyrinth disorders	**0**	**(0.0)**	**0**	**(0.0)**	**5**	**(3.3)**	**0**	**(0.0)**
Ear pain	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)

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Subjects With Drug-related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Ear and labyrinth disorders	**0**	**(0.0)**	**0**	**(0.0)**	**5**	**(3.3)**	**0**	**(0.0)**
Hypoacusis	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Tinnitus	0	(0.0)	0	(0.0)	2	(1.3)	0	(0.0)
Vertigo	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Endocrine disorders	**22**	**(14.3)**	**1**	**(0.6)**	**1**	**(0.7)**	**0**	**(0.0)**
Autoimmune thyroiditis	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Euthyroid sick syndrome	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hyperthyroidism	11	(7.1)	0	(0.0)	0	(0.0)	0	(0.0)
Hypophysitis	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Hypothyroidism	12	(7.8)	0	(0.0)	1	(0.7)	0	(0.0)
Thyroiditis	3	(1.9)	0	(0.0)	0	(0.0)	0	(0.0)
Eye disorders	**3**	**(1.9)**	**0**	**(0.0)**	**12**	**(8.0)**	**0**	**(0.0)**
Abnormal sensation in eye	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Cataract	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Diplopia	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Dry eye	1	(0.6)	0	(0.0)	6	(4.0)	0	(0.0)
Eye pain	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Keratitis	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Lacrimation increased	0	(0.0)	0	(0.0)	4	(2.7)	0	(0.0)
Vision blurred	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Gastrointestinal disorders	**46**	**(29.9)**	**10**	**(6.5)**	**90**	**(60.0)**	7	**(4.7)**
Abdominal discomfort	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)

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Subjects With Drug-related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) (ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Gastrointestinal disorders	**46**	**(29.9)**	**10**	**(6.5)**	**90**	**(60.0)**	7	**(4.7)**
Abdominal distension	2	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)
Abdominal pain	4	(2.6)	0	(0.0)	3	(2.0)	0	(0.0)
Abdominal pain lower	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Abdominal pain upper	0	(0.0)	0	(0.0)	5	(3.3)	0	(0.0)
Aphthous ulcer	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Colitis	2	(1.3)	2	(1.3)	0	(0.0)	0	(0.0)
Constipation	6	(3.9)	0	(0.0)	17	(11.3)	0	(0.0)
Diarrhoea	22	(14.3)	6	(3.9)	20	(13.3)	2	(1.3)
Dry mouth	1	(0.6)	0	(0.0)	3	(2.0)	0	(0.0)
Dyspepsia	2	(1.3)	0	(0.0)	4	(2.7)	0	(0.0)
Dysphagia	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Enterocolitis	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Gastric ulcer	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Gastritis	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Gingival pain	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Lip dry	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Lip pain	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Nausea	15	(9.7)	0	(0.0)	65	(43.3)	3	(2.0)
Oral pain	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Pancreatitis	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Paraesthesia oral	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Stomatitis	4	(2.6)	0	(0.0)	18	(12.0)	2	(1.3)
Vomiting	4	(2.6)	1	(0.6)	30	(20.0)	1	(0.7)

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Subjects With Drug-related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
General disorders and administration site conditions	**45**	**(29.2)**	**5**	**(3.2)**	**73**	**(48.7)**	**9**	**(6.0)**
Asthenia	5	(3.2)	1	(0.6)	11	(7.3)	2	(1.3)
Chest pain	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Chills	3	(1.9)	0	(0.0)	0	(0.0)	0	(0.0)
Death	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Enanthema	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Extravasation	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Face oedema	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Fatigue	16	(10.4)	2	(1.3)	43	(28.7)	5	(3.3)
Gait disturbance	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
General physical health deterioration	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Influenza like illness	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Infusion site extravasation	0	(0.0)	0	(0.0)	2	(1.3)	0	(0.0)
Malaise	1	(0.6)	0	(0.0)	9	(6.0)	0	(0.0)
Oedema	2	(1.3)	0	(0.0)	2	(1.3)	0	(0.0)
Oedema peripheral	4	(2.6)	1	(0.6)	6	(4.0)	0	(0.0)
Pain	1	(0.6)	0	(0.0)	2	(1.3)	0	(0.0)
Pyrexia	16	(10.4)	0	(0.0)	8	(5.3)	0	(0.0)
Sudden death	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Suprapubic pain	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Swelling	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Xerosis	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hepatobiliary disorders	**1**	**(0.6)**	**1**	**(0.6)**	**0**	**(0.0)**	**0**	**(0.0)**

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Subjects With Drug-related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) (ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Hepatobiliary disorders	**1**	**(0.6)**	**1**	**(0.6)**	**0**	**(0.0)**	**0**	**(0.0)**
Acute hepatic failure	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Immune system disorders	**1**	**(0.6)**	**0**	**(0.0)**	**1**	**(0.7)**	**0**	**(0.0)**
Drug hypersensitivity	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Hypersensitivity	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Infections and infestations	7	**(4.5)**	**2**	**(1.3)**	**22**	**(14.7)**	**12**	**(8.0)**
Angular cheilitis	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Bronchitis	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Cellulitis	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Chronic sinusitis	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Conjunctivitis	1	(0.6)	0	(0.0)	3	(2.0)	0	(0.0)
Diverticulitis	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Eye infection	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Fungal skin infection	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Infected dermal cyst	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Localised infection	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Lower respiratory tract infection	2	(1.3)	2	(1.3)	0	(0.0)	0	(0.0)
Lung infection	0	(0.0)	0	(0.0)	2	(1.3)	2	(1.3)
Nasopharyngitis	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Neutropenic sepsis	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Oral candidiasis	1	(0.6)	0	(0.0)	3	(2.0)	0	(0.0)
Oral herpes	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Pneumonia	0	(0.0)	0	(0.0)	3	(2.0)	3	(2.0)

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Subjects With Drug-related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Infections and infestations	7	**(4.5)**	**2**	**(1.3)**	**22**	**(14.7)**	**12**	**(8.0)**
Pulmonary sepsis	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Respiratory tract infection	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Skin infection	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Tinea pedis	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Tracheobronchitis	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Upper respiratory tract infection	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Urinary tract infection	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Vulvovaginal candidiasis	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Injury, poisoning and procedural complications	**3**	**(1.9)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Infusion related reaction	3	(1.9)	0	(0.0)	0	(0.0)	0	(0.0)
Investigations	**31**	**(20.1)**	**6**	**(3.9)**	**55**	**(36.7)**	**16**	**(10.7)**
Alanine aminotransferase increased	10	(6.5)	0	(0.0)	7	(4.7)	0	(0.0)
Aspartate aminotransferase increased	8	(5.2)	2	(1.3)	5	(3.3)	0	(0.0)
Bilirubin conjugated increased	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Blood alkaline phosphatase increased	1	(0.6)	0	(0.0)	3	(2.0)	0	(0.0)
Blood bilirubin increased	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Blood creatine increased	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Blood creatinine decreased	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Blood creatinine increased	3	(1.9)	0	(0.0)	15	(10.0)	1	(0.7)
Blood lactate dehydrogenase increased	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Blood magnesium decreased	0	(0.0)	0	(0.0)	2	(1.3)	0	(0.0)

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Subjects With Drug-related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**31**	**(20.1)**	**6**	**(3.9)**	**55**	**(36.7)**	**16**	**(10.7)**
Blood sodium decreased	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Blood thyroid stimulating hormone decreased	4	(2.6)	0	(0.0)	0	(0.0)	0	(0.0)
Blood thyroid stimulating hormone increased	5	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Blood urea increased	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Blood uric acid increased	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Creatinine renal clearance decreased	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Gamma-glutamyltransferase increased	3	(1.9)	1	(0.6)	4	(2.7)	0	(0.0)
Haemoglobin decreased	0	(0.0)	0	(0.0)	5	(3.3)	1	(0.7)
Hepatic enzyme increased	2	(1.3)	1	(0.6)	0	(0.0)	0	(0.0)
Lymphocyte count decreased	0	(0.0)	0	(0.0)	3	(2.0)	3	(2.0)
Neutrophil count decreased	0	(0.0)	0	(0.0)	20	(13.3)	6	(4.0)
Neutrophil count increased	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Platelet count decreased	0	(0.0)	0	(0.0)	18	(12.0)	9	(6.0)
Thyroxine free decreased	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Thyroxine free increased	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Thyroxine increased	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Transaminases increased	3	(1.9)	2	(1.3)	0	(0.0)	0	(0.0)
Weight decreased	5	(3.2)	0	(0.0)	4	(2.7)	0	(0.0)
White blood cell count decreased	1	(0.6)	0	(0.0)	16	(10.7)	3	(2.0)
White blood cell count increased	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Metabolism and nutrition disorders	**25**	**(16.2)**	**4**	**(2.6)**	**52**	**(34.7)**	**6**	**(4.0)**

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Subjects With Drug-related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Metabolism and nutrition disorders	**25**	**(16.2)**	**4**	**(2.6)**	**52**	**(34.7)**	**6**	**(4.0)**
Decreased appetite	14	(9.1)	0	(0.0)	39	(26.0)	4	(2.7)
Dehydration	0	(0.0)	0	(0.0)	3	(2.0)	0	(0.0)
Diabetes mellitus	2	(1.3)	2	(1.3)	0	(0.0)	0	(0.0)
Diabetic ketoacidosis	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Dyslipidaemia	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hyperchloraemia	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hypercholesterolaemia	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Hyperglycaemia	2	(1.3)	1	(0.6)	2	(1.3)	0	(0.0)
Hyperkalaemia	3	(1.9)	0	(0.0)	1	(0.7)	0	(0.0)
Hypernatraemia	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hypoalbuminaemia	3	(1.9)	2	(1.3)	4	(2.7)	2	(1.3)
Hypocalcaemia	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Hypokalaemia	0	(0.0)	0	(0.0)	2	(1.3)	0	(0.0)
Hypomagnesaemia	1	(0.6)	0	(0.0)	9	(6.0)	0	(0.0)
Hyponatraemia	5	(3.2)	0	(0.0)	2	(1.3)	1	(0.7)
Hypophosphataemia	1	(0.6)	0	(0.0)	1	(0.7)	1	(0.7)
Hypovolaemia	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Musculoskeletal and connective tissue disorders	**24**	**(15.6)**	**1**	**(0.6)**	**12**	**(8.0)**	**0**	**(0.0)**
Arthralgia	13	(8.4)	0	(0.0)	4	(2.7)	0	(0.0)
Arthritis	2	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)
Back pain	2	(1.3)	0	(0.0)	1	(0.7)	0	(0.0)
Bone pain	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Drug-related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) (ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Musculoskeletal and connective tissue disorders	**24**	**(15.6)**	**1**	**(0.6)**	**12**	**(8.0)**	**0**	**(0.0)**
Flank pain	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Hypercreatinaemia	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Joint effusion	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Joint swelling	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Muscle atrophy	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Muscle spasms	1	(0.6)	0	(0.0)	2	(1.3)	0	(0.0)
Muscular weakness	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Musculoskeletal pain	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Musculoskeletal stiffness	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Myalgia	3	(1.9)	0	(0.0)	1	(0.7)	0	(0.0)
Myositis	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Pain in extremity	0	(0.0)	0	(0.0)	3	(2.0)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.7)**	**1**	**(0.7)**
Malignant neoplasm progression	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Nervous system disorders	**12**	**(7.8)**	**1**	**(0.6)**	**35**	**(23.3)**	**2**	**(1.3)**
Cerebrovascular accident	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Dizziness	2	(1.3)	0	(0.0)	3	(2.0)	0	(0.0)
Dysgeusia	1	(0.6)	0	(0.0)	15	(10.0)	0	(0.0)
Headache	1	(0.6)	0	(0.0)	2	(1.3)	0	(0.0)
Hypoaesthesia	0	(0.0)	0	(0.0)	3	(2.0)	0	(0.0)

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Subjects With Drug-related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Nervous system disorders	**12**	**(7.8)**	**1**	**(0.6)**	**35**	**(23.3)**	**2**	**(1.3)**
Lethargy	1	(0.6)	0	(0.0)	3	(2.0)	0	(0.0)
Neuropathy peripheral	2	(1.3)	0	(0.0)	9	(6.0)	1	(0.7)
Paraesthesia	2	(1.3)	0	(0.0)	2	(1.3)	0	(0.0)
Parosmia	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral sensory neuropathy	0	(0.0)	0	(0.0)	6	(4.0)	1	(0.7)
Polyneuropathy	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Tension headache	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Tremor	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Psychiatric disorders	**4**	**(2.6)**	**0**	**(0.0)**	**1**	**(0.7)**	**0**	**(0.0)**
Abulia	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Agitation	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Anxiety	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Depressed mood	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Insomnia	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Renal and urinary disorders	**3**	**(1.9)**	**1**	**(0.6)**	7	**(4.7)**	**2**	**(1.3)**
Acute kidney injury	0	(0.0)	0	(0.0)	2	(1.3)	2	(1.3)
Chromaturia	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Chronic kidney disease	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Dysuria	2	(1.3)	0	(0.0)	1	(0.7)	0	(0.0)
Leukocyturia	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Pollakiuria	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Renal disorder	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)

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Subjects With Drug-related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Renal and urinary disorders	**3**	**(1.9)**	**1**	**(0.6)**	7	**(4.7)**	**2**	**(1.3)**
Renal impairment	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Tubulointerstitial nephritis	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Reproductive system and breast disorders	**1**	**(0.6)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Breast pain	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**20**	**(13.0)**	**6**	**(3.9)**	**21**	**(14.0)**	7	**(4.7)**
Cough	5	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Dysphonia	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Dyspnoea	4	(2.6)	1	(0.6)	5	(3.3)	1	(0.7)
Epistaxis	0	(0.0)	0	(0.0)	6	(4.0)	2	(1.3)
Haemoptysis	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Hiccups	2	(1.3)	0	(0.0)	7	(4.7)	0	(0.0)
Hypoxia	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Interstitial lung disease	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Lower respiratory tract inflammation	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Organising pneumonia	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Pleural effusion	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Pleuritic pain	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonitis	8	(5.2)	4	(2.6)	1	(0.7)	1	(0.7)
Productive cough	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Pulmonary alveolar haemorrhage	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)

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Subjects With Drug-related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) (ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Respiratory, thoracic and mediastinal disorders	**20**	**(13.0)**	**6**	**(3.9)**	**21**	**(14.0)**	7	**(4.7)**
Pulmonary embolism	1	(0.6)	1	(0.6)	1	(0.7)	1	(0.7)
Pulmonary fibrosis	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
Rhinorrhoea	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Wheezing	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Skin and subcutaneous tissue disorders	**43**	**(27.9)**	**5**	**(3.2)**	**22**	**(14.7)**	**0**	**(0.0)**
Alopecia	0	(0.0)	0	(0.0)	12	(8.0)	0	(0.0)
Dermatitis acneiform	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Dry skin	8	(5.2)	0	(0.0)	1	(0.7)	0	(0.0)
Eczema	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Erythema	3	(1.9)	0	(0.0)	0	(0.0)	0	(0.0)
Hyperhidrosis	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Lichenoid keratosis	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Night sweats	3	(1.9)	0	(0.0)	0	(0.0)	0	(0.0)
Onycholysis	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Petechiae	1	(0.6)	0	(0.0)	1	(0.7)	0	(0.0)
Pruritus	12	(7.8)	0	(0.0)	3	(2.0)	0	(0.0)
Pruritus generalised	3	(1.9)	0	(0.0)	1	(0.7)	0	(0.0)
Psoriasis	2	(1.3)	1	(0.6)	0	(0.0)	0	(0.0)
Rash	11	(7.1)	1	(0.6)	3	(2.0)	0	(0.0)
Rash erythematous	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Rash generalised	1	(0.6)	1	(0.6)	1	(0.7)	0	(0.0)

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Subjects With Drug-related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**43**	**(27.9)**	**5**	**(3.2)**	**22**	**(14.7)**	**0**	**(0.0)**
Rash maculo-papular	5	(3.2)	1	(0.6)	1	(0.7)	0	(0.0)
Rash pruritic	2	(1.3)	0	(0.0)	1	(0.7)	0	(0.0)
Seborrhoeic dermatitis	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Skin exfoliation	2	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)
Skin lesion	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Urticaria	2	(1.3)	0	(0.0)	1	(0.7)	0	(0.0)
Vitiligo	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Vascular disorders	**4**	**(2.6)**	**0**	**(0.0)**	**5**	**(3.3)**	**0**	**(0.0)**
Deep vein thrombosis	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Flushing	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Hot flush	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hypertension	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hypotension	0	(0.0)	0	(0.0)	3	(2.0)	0	(0.0)
Lymphoedema	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Phlebitis	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Thrombosis	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)

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Subjects With Drug-related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) (ASaT Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Vascular disorders	**4**	**(2.6)**	**0**	**(0.0)**	**5**	**(3.3)**	**0**	**(0.0)**
Vasospasm	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.
Adverse event terms are from MedDRA Version 18.0.
(Database Cutoff Date: 09MAY2016).

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付録 2.7.4- 137 最終投与後 90 日までに発現した重篤な有害事象
（いずれかの投与群で発現割合 0%超）
024 試験（安全性解析対象集団）

Subjects With Serious Adverse Events by Decreasing Incidence
(Incidence >0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	154		150		304	
with one or more adverse events	68	(44.2)	66	(44.0)	134	(44.1)
with no adverse events	86	(55.8)	84	(56.0)	170	(55.9)
Pneumonia	3	(1.9)	9	(6.0)	12	(3.9)
Pleural effusion	5	(3.2)	3	(2.0)	8	(2.6)
Pneumonitis	7	(4.5)	1	(0.7)	8	(2.6)
Anaemia	2	(1.3)	5	(3.3)	7	(2.3)
Chronic obstructive pulmonary disease	4	(2.6)	1	(0.7)	5	(1.6)
Back pain	1	(0.6)	3	(2.0)	4	(1.3)
Diarrhoea	3	(1.9)	1	(0.7)	4	(1.3)
Hyponatraemia	4	(2.6)	0	(0.0)	4	(1.3)
Lower respiratory tract infection	2	(1.3)	2	(1.3)	4	(1.3)
Lung infection	2	(1.3)	2	(1.3)	4	(1.3)
Pulmonary embolism	2	(1.3)	2	(1.3)	4	(1.3)
Acute kidney injury	0	(0.0)	3	(2.0)	3	(1.0)
Cardiac failure	1	(0.6)	2	(1.3)	3	(1.0)
Febrile neutropenia	0	(0.0)	3	(2.0)	3	(1.0)
Hypercalcaemia	0	(0.0)	3	(2.0)	3	(1.0)
Hyperglycaemia	3	(1.9)	0	(0.0)	3	(1.0)
Pancytopenia	0	(0.0)	3	(2.0)	3	(1.0)
Pyrexia	2	(1.3)	1	(0.7)	3	(1.0)
Thrombocytopenia	0	(0.0)	3	(2.0)	3	(1.0)
Urinary tract infection	1	(0.6)	2	(1.3)	3	(1.0)
Alanine aminotransferase increased	2	(1.3)	0	(0.0)	2	(0.7)
Atrial fibrillation	0	(0.0)	2	(1.3)	2	(0.7)
Cardiac arrest	1	(0.6)	1	(0.7)	2	(0.7)
Cellulitis	1	(0.6)	1	(0.7)	2	(0.7)
Cerebrovascular accident	1	(0.6)	1	(0.7)	2	(0.7)
Colitis	2	(1.3)	0	(0.0)	2	(0.7)
Diabetes mellitus	2	(1.3)	0	(0.0)	2	(0.7)
Epistaxis	0	(0.0)	2	(1.3)	2	(0.7)
Haemoptysis	2	(1.3)	0	(0.0)	2	(0.7)
Ischaemic stroke	1	(0.6)	1	(0.7)	2	(0.7)
Musculoskeletal pain	1	(0.6)	1	(0.7)	2	(0.7)
Nausea	0	(0.0)	2	(1.3)	2	(0.7)
Neutropenic sepsis	1	(0.6)	1	(0.7)	2	(0.7)
Pericardial effusion	1	(0.6)	1	(0.7)	2	(0.7)
Pneumothorax	1	(0.6)	1	(0.7)	2	(0.7)
Pulmonary oedema	0	(0.0)	2	(1.3)	2	(0.7)
Pulmonary sepsis	0	(0.0)	2	(1.3)	2	(0.7)
Respiratory tract infection	0	(0.0)	2	(1.3)	2	(0.7)
Supraventricular tachycardia	1	(0.6)	1	(0.7)	2	(0.7)
Abdominal pain	1	(0.6)	0	(0.0)	1	(0.3)
Acute hepatic failure	1	(0.6)	0	(0.0)	1	(0.3)

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Subjects With Serious Adverse Events by Decreasing Incidence (Incidence >0% in One or More Treatment Groups) (ASaT Population)

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Acute respiratory failure	1	(0.6)	0	(0.0)	1	(0.3)
Anaphylactic shock	1	(0.6)	0	(0.0)	1	(0.3)
Angina pectoris	0	(0.0)	1	(0.7)	1	(0.3)
Appendicitis	1	(0.6)	0	(0.0)	1	(0.3)
Arthralgia	0	(0.0)	1	(0.7)	1	(0.3)
Aspartate aminotransferase increased	1	(0.6)	0	(0.0)	1	(0.3)
Atelectasis	1	(0.6)	0	(0.0)	1	(0.3)
Bilirubin conjugated increased	1	(0.6)	0	(0.0)	1	(0.3)
Bladder neoplasm	0	(0.0)	1	(0.7)	1	(0.3)
Bradycardia	0	(0.0)	1	(0.7)	1	(0.3)
Bronchial obstruction	0	(0.0)	1	(0.7)	1	(0.3)
Bronchitis	1	(0.6)	0	(0.0)	1	(0.3)
Cancer pain	0	(0.0)	1	(0.7)	1	(0.3)
Cardio-respiratory arrest	0	(0.0)	1	(0.7)	1	(0.3)
Cerebral infarction	0	(0.0)	1	(0.7)	1	(0.3)
Chest pain	0	(0.0)	1	(0.7)	1	(0.3)
Clostridium difficile colitis	0	(0.0)	1	(0.7)	1	(0.3)
Constipation	0	(0.0)	1	(0.7)	1	(0.3)
Coronary artery disease	0	(0.0)	1	(0.7)	1	(0.3)
Death	0	(0.0)	1	(0.7)	1	(0.3)
Decreased appetite	1	(0.6)	0	(0.0)	1	(0.3)
Dehydration	1	(0.6)	0	(0.0)	1	(0.3)
Device dislocation	0	(0.0)	1	(0.7)	1	(0.3)
Device related infection	1	(0.6)	0	(0.0)	1	(0.3)
Diabetic ketoacidosis	1	(0.6)	0	(0.0)	1	(0.3)
Enterocolitis	1	(0.6)	0	(0.0)	1	(0.3)
Face oedema	1	(0.6)	0	(0.0)	1	(0.3)
Faecaloma	0	(0.0)	1	(0.7)	1	(0.3)
Fatigue	1	(0.6)	0	(0.0)	1	(0.3)
Gait disturbance	0	(0.0)	1	(0.7)	1	(0.3)
Gastric ulcer	1	(0.6)	0	(0.0)	1	(0.3)
Gastritis erosive	1	(0.6)	0	(0.0)	1	(0.3)
Gastroenteritis viral	1	(0.6)	0	(0.0)	1	(0.3)
Gastrointestinal carcinoma	1	(0.6)	0	(0.0)	1	(0.3)
General physical health deterioration	1	(0.6)	0	(0.0)	1	(0.3)
Haemorrhagic stroke	1	(0.6)	0	(0.0)	1	(0.3)
Hepatic enzyme increased	1	(0.6)	0	(0.0)	1	(0.3)
Hypersensitivity	1	(0.6)	0	(0.0)	1	(0.3)
Hypertensive nephropathy	0	(0.0)	1	(0.7)	1	(0.3)
Hyperthyroidism	1	(0.6)	0	(0.0)	1	(0.3)
Hypocalcaemia	0	(0.0)	1	(0.7)	1	(0.3)
Hypophysitis	1	(0.6)	0	(0.0)	1	(0.3)
Hypovolaemia	1	(0.6)	0	(0.0)	1	(0.3)
Infected neoplasm	1	(0.6)	0	(0.0)	1	(0.3)
Infectious pleural effusion	1	(0.6)	0	(0.0)	1	(0.3)

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Subjects With Serious Adverse Events by Decreasing Incidence (Incidence >0% in One or More Treatment Groups) (ASaT Population)

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Infective exacerbation of chronic obstructive airways disease	0	(0.0)	1	(0.7)	1	(0.3)
Infusion related reaction	1	(0.6)	0	(0.0)	1	(0.3)
Insomnia	0	(0.0)	1	(0.7)	1	(0.3)
Ischaemic cardiomyopathy	0	(0.0)	1	(0.7)	1	(0.3)
Leukocytosis	0	(0.0)	1	(0.7)	1	(0.3)
Lichenoid keratosis	1	(0.6)	0	(0.0)	1	(0.3)
Malignant neoplasm progression	0	(0.0)	1	(0.7)	1	(0.3)
Metastases to meninges	1	(0.6)	0	(0.0)	1	(0.3)
Multiple organ dysfunction syndrome	1	(0.6)	0	(0.0)	1	(0.3)
Muscle haemorrhage	0	(0.0)	1	(0.7)	1	(0.3)
Oedema peripheral	1	(0.6)	0	(0.0)	1	(0.3)
Oral candidiasis	1	(0.6)	0	(0.0)	1	(0.3)
Organising pneumonia	1	(0.6)	0	(0.0)	1	(0.3)
Osteolysis	1	(0.6)	0	(0.0)	1	(0.3)
Ovarian haemorrhage	1	(0.6)	0	(0.0)	1	(0.3)
Painful respiration	1	(0.6)	0	(0.0)	1	(0.3)
Pancreatitis	1	(0.6)	0	(0.0)	1	(0.3)
Pericarditis	1	(0.6)	0	(0.0)	1	(0.3)
Peripheral embolism	0	(0.0)	1	(0.7)	1	(0.3)
Peritonsillar abscess	0	(0.0)	1	(0.7)	1	(0.3)
Platelet count decreased	0	(0.0)	1	(0.7)	1	(0.3)
Pneumonia streptococcal	1	(0.6)	0	(0.0)	1	(0.3)
Pulmonary alveolar haemorrhage	0	(0.0)	1	(0.7)	1	(0.3)
Pulmonary radiation injury	0	(0.0)	1	(0.7)	1	(0.3)
Radiation oesophagitis	0	(0.0)	1	(0.7)	1	(0.3)
Rash	1	(0.6)	0	(0.0)	1	(0.3)
Respiratory failure	1	(0.6)	0	(0.0)	1	(0.3)
Restlessness	0	(0.0)	1	(0.7)	1	(0.3)
Rib fracture	0	(0.0)	1	(0.7)	1	(0.3)
Right ventricular failure	0	(0.0)	1	(0.7)	1	(0.3)
Sepsis	0	(0.0)	1	(0.7)	1	(0.3)
Septic shock	0	(0.0)	1	(0.7)	1	(0.3)
Skin infection	0	(0.0)	1	(0.7)	1	(0.3)
Small intestinal obstruction	0	(0.0)	1	(0.7)	1	(0.3)
Spinal pain	1	(0.6)	0	(0.0)	1	(0.3)
Splenic abscess	1	(0.6)	0	(0.0)	1	(0.3)
Stomatitis	0	(0.0)	1	(0.7)	1	(0.3)
Sudden death	1	(0.6)	0	(0.0)	1	(0.3)
Toxicity to various agents	0	(0.0)	1	(0.7)	1	(0.3)
Transaminases increased	1	(0.6)	0	(0.0)	1	(0.3)
Transient ischaemic attack	0	(0.0)	1	(0.7)	1	(0.3)
Tubulointerstitial nephritis	1	(0.6)	0	(0.0)	1	(0.3)
Urosepsis	1	(0.6)	0	(0.0)	1	(0.3)
Vasospasm	0	(0.0)	1	(0.7)	1	(0.3)

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Subjects With Serious Adverse Events by Decreasing Incidence
(Incidence >0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Vomiting	1	(0.6)	0	(0.0)	1	(0.3)

Every subject is counted a single time for each applicable specific adverse event.
A system organ class appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
MedDRA preferred terms "Neoplasm Progression" and "Malignant Neoplasm Progression" not related to the drug are excluded.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

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付録 2.7.4- 138 最終投与後 90 日までに発現した重篤な有害事象の一覧
024 試験（安全性解析対象集団）

Listing of Subjects With Serious Adverse Events
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
Pembrolizumab									
Trial Number=3475-024, Site Number=0004, Subject ID=244828, Gender=F, Race=White, Age=59 Years, Rel Day of Last Recorded Dose of Study Medication=266									
244828	Treatment Cycle 7	159	Haemoptysis	5 Days	3	Y	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0005, Subject ID=245205, Gender=F, Race=White, Age=60 Years, Rel Day of Last Recorded Dose of Study Medication=257									
245205	Treatment Cycle 2	44	Hepatic enzyme increased	2.33 Months	3	Y	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0007, Subject ID=244216, Gender=M, Race=White, Age=43 Years, Rel Day of Last Recorded Dose of Study Medication=232									
244216	Treatment Cycle 4	83	Diabetes mellitus	2.17 Months	3	Y	Y	Interrupted	Sequelae
		83	Diabetic ketoacidosis	2 Days	4	Y	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0007, Subject ID=244837, Gender=M, Race=Asian, Age=80 Years, Rel Day of Last Recorded Dose of Study Medication=162									
244837	Treatment Cycle 1	8	Lichenoid keratosis	Continuing	3	Y	Y	Interrupted	Resolving
	Treatment Cycle 7	197	Hypophysitis	Unknown	3	Y	Y	Interrupted	Unknown
Trial Number=3475-024, Site Number=0007, Subject ID=245120, Gender=M, Race=White, Age=68 Years, Rel Day of Last Recorded Dose of Study Medication=472									
245120	Treatment Cycle 13	267	Chronic obstructive pulmonary disease	2 Weeks	3	Y	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0007, Subject ID=245150, Gender=F, Race=White, Age=67 Years, Rel Day of Last Recorded Dose of Study Medication=253									
245150	Treatment Cycle 3	63	Pyrexia	5 Days	2	Y	N	None	Resolved
Trial Number=3475-024, Site Number=0039, Subject ID=245154, Gender=F, Race=White, Age=62 Years, Rel Day of Last Recorded Dose of Study Medication=385									
245154	Treatment Cycle 8	148	Osteolysis	4.21 Months	2	Y	N	None	Resolved
Trial Number=3475-024, Site Number=0044, Subject ID=244829, Gender=M, Race=White, Age=64 Years, Rel Day of Last Recorded Dose of Study Medication=253									

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Listing of Subjects With Serious Adverse Events
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
Pembrolizumab									
Trial Number=3475-024, Site Number=0044, Subject ID=244829, Gender=M, Race=White, Age=64 Years, Rel Day of Last Recorded Dose of Study Medication=253									
244829	Treatment Cycle 2	22	Hyperglycaemia	5 Days	4	Y	N	None	Resolved
Trial Number=3475-024, Site Number=0044, Subject ID=244835, Gender=M, Race=White, Age=63 Years, Rel Day of Last Recorded Dose of Study Medication=20									
244835	Treatment Cycle 1	7	Colitis	Continuing	3	Y	Y	N/A	Not Resolved
	Safety Follow-up	36	Acute hepatic failure	Continuing	4	Y	Y	N/A	Not Resolved
Trial Number=3475-024, Site Number=0044, Subject ID=245161, Gender=M, Race=White, Age=65 Years, Rel Day of Last Recorded Dose of Study Medication=349									
245161	Treatment Cycle 2	26	Gastritis erosive	4 Days	2	Y	N	None	Resolved
	Treatment Cycle 6	106	Anaemia	1.14 Weeks	3	Y	N	None	Resolved
	Treatment Cycle 13	251	Anaemia	3 Days	3	Y	Y	None	Resolved
	Treatment Cycle 16	314	Gastrointestinal carcinoma	3.14 Weeks	3	Y	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0045, Subject ID=244518, Gender=F, Race=White, Age=68 Years, Rel Day of Last Recorded Dose of Study Medication=21									
244518	Treatment Cycle 1	11	Pneumonitis	Continuing	2	Y	Y	Discontinued	Not Resolved
Trial Number=3475-024, Site Number=0048, Subject ID=244540, Gender=F, Race=White, Age=50 Years, Rel Day of Last Recorded Dose of Study Medication=106									
244540	Safety Follow-up	127	Pneumonia	5 Days	5	Y	N	Discontinued	Fatal
Trial Number=3475-024, Site Number=0048, Subject ID=244541, Gender=M, Race=White, Age=55 Years, Rel Day of Last Recorded Dose of Study Medication=306									
244541	Treatment Cycle 1	4	Pleural effusion	1.71 Weeks	3	Y	N	None	Resolved
	Treatment Cycle 2	34	Splenic abscess	2.29 Weeks	3	Y	N	None	Resolved
	Treatment Cycle 6	110	Pneumonia	2 Weeks	3	Y	N	None	Resolved

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Listing of Subjects With Serious Adverse Events
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
Pembrolizumab									
Trial Number=3475-024, Site Number=0064, Subject ID=245110, Gender=F, Race=White, Age=70 Years, Rel Day of Last Recorded Dose of Study Medication=1									
245110	Safety Follow-up	3	Vomiting	1.57 Weeks	3	Y	Y	Discontinued	Resolved
Trial Number=3475-024, Site Number=0064, Subject ID=245192, Gender=F, Race=White, Age=77 Years, Rel Day of Last Recorded Dose of Study Medication=293									
245192	Treatment Cycle 2	41	Diabetes mellitus	2.29 Weeks	3	Y	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0065, Subject ID=244566, Gender=M, Race=White, Age=58 Years, Rel Day of Last Recorded Dose of Study Medication=227									
244566	Treatment Cycle 2	44	Alanine aminotransferase increased	3.86 Weeks	1	Y	Y	Interrupted	Resolved
		44	Aspartate aminotransferase increased	5 Days	3	Y	Y	None	Resolved
		44	Bilirubin conjugated increased	5 Days	2	Y	Y	Interrupted	Resolved
	Treatment Cycle 8	175	Hyponatraemia	3 Days	4	Y	N	Interrupted	Resolved
	Treatment Cycle 10	219	Hyponatraemia	2 Days	3	Y	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0065, Subject ID=244819, Gender=F, Race=White, Age=69 Years, Rel Day of Last Recorded Dose of Study Medication=23									
244819	Safety Follow-up	43	Hyponatraemia	1.57 Weeks	4	Y	N	N/A	Resolved
Trial Number=3475-024, Site Number=0065, Subject ID=245206, Gender=M, Race=White, Age=62 Years, Rel Day of Last Recorded Dose of Study Medication=190									
245206	Safety Follow-up	193	Cardiac arrest	2 Hours	5	Y	N	Discontinued	Fatal
Trial Number=3475-024, Site Number=0067, Subject ID=245230, Gender=F, Race=White, Age=58 Years, Rel Day of Last Recorded Dose of Study Medication=198									
245230	Treatment Cycle 1	9	Abdominal pain	1.29 Weeks	3	Y	N	None	Resolved
		9	Spinal pain	1.29 Weeks	3	Y	N	None	Resolved
Trial Number=3475-024, Site Number=0069, Subject ID=244504, Gender=F, Race=White, Age=49 Years, Rel Day of Last Recorded Dose of Study Medication=425									

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Listing of Subjects With Serious Adverse Events
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
Pembrolizumab									
Trial Number=3475-024, Site Number=0069, Subject ID=244504, Gender=F, Race=White, Age=49 Years, Rel Day of Last Recorded Dose of Study Medication=425									
244504	Treatment Cycle 2	22	Hyperthyroidism	4.34 Months	2	Y	Y	None	Resolved
Trial Number=3475-024, Site Number=0081, Subject ID=244508, Gender=F, Race=White, Age=76 Years, Rel Day of Last Recorded Dose of Study Medication=133									
244508	Treatment Cycle 5	100	Transaminases increased	3.86 Weeks	3	Y	Y	Interrupted	Resolved
	Safety Follow-up	137	Transaminases increased	1.05 Months	3	Y	Y	Discontinued	Resolved
Trial Number=3475-024, Site Number=0081, Subject ID=244539, Gender=M, Race=White, Age=33 Years, Rel Day of Last Recorded Dose of Study Medication=1									
244539	Safety Follow-up	8	Pancreatitis	1.15 Months	3	Y	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0081, Subject ID=245186, Gender=M, Race=White, Age=66 Years, Rel Day of Last Recorded Dose of Study Medication=310									
245186	Treatment Cycle 1	2	Haemoptysis	1 Weeks	2	Y	N	None	Resolved
	Treatment Cycle 10	238	Pyrexia	4 Days	2	Y	N	None	Resolved
Trial Number=3475-024, Site Number=0086, Subject ID=245108, Gender=M, Race=White, Age=65 Years, Rel Day of Last Recorded Dose of Study Medication=1									
245108	Safety Follow-up	19	Pneumonitis	1.57 Weeks	2	Y	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0092, Subject ID=244550, Gender=F, Race=White, Age=68 Years, Rel Day of Last Recorded Dose of Study Medication=41									
244550	Treatment Cycle 1	10	Pleural effusion	3.57 Weeks	4	Y	N	None	Sequelae
		26	Pericardial effusion	1.29 Weeks	3	Y	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0092, Subject ID=245227, Gender=F, Race=White, Age=58 Years, Rel Day of Last Recorded Dose of Study Medication=41									
245227	Extended Safety Follow-up	75	Acute respiratory failure	1.14 Weeks	5	Y	N	None	Fatal

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Listing of Subjects With Serious Adverse Events
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
Pembrolizumab									
Trial Number=3475-024, Site Number=0093, Subject ID=244571, Gender=F, Race=White, Age=71 Years, Rel Day of Last Recorded Dose of Study Medication=196									
244571	Treatment Cycle 2	41	Diarrhoea	4.17 Months	2	Y	Y	Interrupted	Resolved
	Treatment Cycle 4	168	Diarrhoea	1.43 Weeks	3	Y	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0100, Subject ID=244824, Gender=M, Race=White, Age=87 Years, Rel Day of Last Recorded Dose of Study Medication=106									
244824	Treatment Cycle 4	82	Musculoskeletal pain	Continuing	3	Y	Y	None	Resolving
	Safety Follow-up	113	Pneumonia streptococcal	6 Days	5	Y	N	N/A	Fatal
		115	Multiple organ dysfunction syndrome	4 Days	5	Y	N	N/A	Fatal
Trial Number=3475-024, Site Number=0100, Subject ID=245115, Gender=M, Race=White, Age=60 Years, Rel Day of Last Recorded Dose of Study Medication=477									
245115	Treatment Cycle 3	58	Bronchitis	5 Days	2	Y	N	None	Resolved
Trial Number=3475-024, Site Number=0123, Subject ID=244210, Gender=M, Race=White, Age=73 Years, Rel Day of Last Recorded Dose of Study Medication=209									
244210	Treatment Cycle 7	141	Pneumonitis	2.27 Months	2	Y	Y	Interrupted	Resolved
	Extended Safety Follow-up	268	Infectious pleural effusion	3 Weeks	3	Y	N	N/A	Resolved
		294	Infectious pleural effusion	2.86 Weeks	3	Y	N	N/A	Resolved
Trial Number=3475-024, Site Number=0123, Subject ID=244565, Gender=M, Race=White, Age=59 Years, Rel Day of Last Recorded Dose of Study Medication=226									
244565	Treatment Cycle 8	150	Tubulointerstitial nephritis	1.84 Months	3	Y	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0123, Subject ID=244802, Gender=M, Race=White, Age=77 Years, Rel Day of Last Recorded Dose of Study Medication=468									
244802	Treatment Cycle 1	15	Chronic obstructive pulmonary disease	1.86 Weeks	3	Y	N	None	Sequelae

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Listing of Subjects With Serious Adverse Events
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
Pembrolizumab									
Trial Number=3475-024, Site Number=0123, Subject ID=244810, Gender=M, Race=White, Age=62 Years, Rel Day of Last Recorded Dose of Study Medication=388									
244810	Treatment Cycle 9	180	Diarrhoea	1.71 Weeks	3	Y	Y	Interrupted	Resolved
		187	Hyponatraemia	4 Days	3	Y	N	None	Resolved
	Treatment Cycle 12	255	Cerebrovascular accident	1.43 Weeks	4	Y	Y	None	Resolved
		268	Gastric ulcer	2.63 Months	3	Y	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0123, Subject ID=244823, Gender=F, Race=White, Age=53 Years, Rel Day of Last Recorded Dose of Study Medication=57									
244823	Treatment Cycle 1	33	Device related infection	1.71 Weeks	3	Y	N	Interrupted	Resolved
	Safety Follow-up	59	Cellulitis	1.08 Months	3	Y	N	N/A	Resolved
Trial Number=3475-024, Site Number=0123, Subject ID=245107, Gender=M, Race=White, Age=70 Years, Rel Day of Last Recorded Dose of Study Medication=379									
245107	Treatment Cycle 19	379	Hyponatraemia	Continuing	3	Y	N	N/A	Not Resolved
	Safety Follow-up	402	Urosepsis	Continuing	4	Y	N	N/A	Not Resolved
		404	General physical health deterioration	3 Days	5	Y	N	N/A	Fatal
		404	Hyperglycaemia	Continuing	3	Y	N	N/A	Not Resolved
Trial Number=3475-024, Site Number=0123, Subject ID=245118, Gender=M, Race=White, Age=66 Years, Rel Day of Last Recorded Dose of Study Medication=173									
245118	Safety Follow-up	190	Pleural effusion	1 Weeks	3	Y	N	N/A	Resolved
	Extended Safety Follow-up	204	Respiratory failure	2 Days	5	Y	N	N/A	Fatal
Trial Number=3475-024, Site Number=0123, Subject ID=245122, Gender=M, Race=White, Age=46 Years, Rel Day of Last Recorded Dose of Study Medication=1									
245122	Safety Follow-up	7	Haemorrhagic stroke	4 Days	5	Y	N	Discontinued	Fatal

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Listing of Subjects With Serious Adverse Events
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
Pembrolizumab									
Trial Number=3475-024, Site Number=0126, Subject ID=245147, Gender=M, Race=White, Age=57 Years, Rel Day of Last Recorded Dose of Study Medication=169									
245147	Treatment Cycle 4	70	Atelectasis	1.14 Weeks	3	Y	N	None	Resolved
Trial Number=3475-024, Site Number=0126, Subject ID=245182, Gender=F, Race=White, Age=64 Years, Rel Day of Last Recorded Dose of Study Medication=322									
245182	Treatment Cycle 11	230	Appendicitis	4 Days	3	Y	N	None	Resolved
Trial Number=3475-024, Site Number=0127, Subject ID=244555, Gender=M, Race=White, Age=66 Years, Rel Day of Last Recorded Dose of Study Medication=1									
244555	Safety Follow-up	21	Anaphylactic shock	2 Days	4	Y	N	N/A	Resolved
Trial Number=3475-024, Site Number=0130, Subject ID=244215, Gender=M, Race=White, Age=58 Years, Rel Day of Last Recorded Dose of Study Medication=133									
244215	Treatment Cycle 5	106	Rash	3.02 Months	3	Y	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0132, Subject ID=245145, Gender=M, Race=White, Age=66 Years, Rel Day of Last Recorded Dose of Study Medication=44									
245145	Extended Safety Follow-up	92	Neutropenic sepsis	3 Days	5	Y	N	N/A	Fatal
Trial Number=3475-024, Site Number=0132, Subject ID=245163, Gender=F, Race=White, Age=76 Years, Rel Day of Last Recorded Dose of Study Medication=75									
245163	Safety Follow-up	79	Urinary tract infection	1.86 Weeks	3	Y	N	None	Resolved
		82	Lower respiratory tract infection	1.43 Weeks	3	Y	Y	None	Resolved
		83	Oral candidiasis	1.29 Weeks	2	Y	N	None	Resolved
		102	Alanine aminotransferase increased	2.57 Weeks	1	Y	Y	Discontinued	Resolved
Trial Number=3475-024, Site Number=0132, Subject ID=245167, Gender=F, Race=White, Age=59 Years, Rel Day of Last Recorded Dose of Study Medication=134									
245167	Treatment Cycle 6	114	Lower respiratory tract infection	1.43 Weeks	3	Y	Y	None	Resolved

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Listing of Subjects With Serious Adverse Events
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
Pembrolizumab									
Trial Number=3475-024, Site Number=0134, Subject ID=244209, Gender=M, Race=White, Age=71 Years, Rel Day of Last Recorded Dose of Study Medication=22									
244209	Safety Follow-up	31	Oedema peripheral	Continuing	3	Y	Y	N/A	Not Resolved
Trial Number=3475-024, Site Number=0136, Subject ID=245136, Gender=M, Race=White, Age=71 Years, Rel Day of Last Recorded Dose of Study Medication=407									
245136	Treatment Cycle 1	7	Pleural effusion	1.48 Months	3	Y	N	Interrupted	Sequelae
Trial Number=3475-024, Site Number=0142, Subject ID=244501, Gender=M, Race=White, Age=69 Years, Rel Day of Last Recorded Dose of Study Medication=1									
244501	Safety Follow-up	18	Pneumonia	3.57 Weeks	3	Y	N	Interrupted	Resolved
		18	Pneumonitis	3.42 Months	4	Y	Y	Discontinued	Resolved
	Extended Safety Follow-up	57	Pneumonia	2.14 Weeks	3	Y	N	N/A	Resolved
Trial Number=3475-024, Site Number=0155, Subject ID=244574, Gender=F, Race=Black Or African American, Age=79 Years, Rel Day of Last Recorded Dose of Study Medication=43									
244574	Extended Safety Follow-up	91	Colitis	1.86 Weeks	3	Y	Y	None	Resolved
Trial Number=3475-024, Site Number=0168, Subject ID=245121, Gender=M, Race=White, Age=80 Years, Rel Day of Last Recorded Dose of Study Medication=154									
245121	Treatment Cycle 1	5	Ischaemic stroke	1 Weeks	2	Y	N	None	Sequelae
	Treatment Cycle 2	28	Pulmonary embolism	1.14 Weeks	3	Y	N	None	Resolved
		28	Supraventricular tachycardia	1.14 Weeks	3	Y	N	None	Resolved
Trial Number=3475-024, Site Number=0168, Subject ID=245133, Gender=F, Race=White, Age=74 Years, Rel Day of Last Recorded Dose of Study Medication=60									
245133	Treatment Cycle 1	10	Chronic obstructive pulmonary disease	3 Days	3	Y	N	None	Resolved

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Listing of Subjects With Serious Adverse Events
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
Pembrolizumab									
Trial Number=3475-024, Site Number=0174, Subject ID=244807, Gender=F, Race=White, Age=77 Years, Rel Day of Last Recorded Dose of Study Medication=1									
244807	Safety Follow-up	11	Pneumonitis	1.14 Weeks	3	Y	Y	Discontinued	Resolved
Trial Number=3475-024, Site Number=0176, Subject ID=245193, Gender=F, Race=Black Or African American, Age=65 Years, Rel Day of Last Recorded Dose of Study Medication=1									
245193	Safety Follow-up	2	Sudden death	1 Days	5	Y	Y	Discontinued	Fatal
Trial Number=3475-024, Site Number=0192, Subject ID=245129, Gender=M, Race=White, Age=76 Years, Rel Day of Last Recorded Dose of Study Medication=370									
245129	Treatment Cycle 2	37	Pulmonary embolism	4 Days	3	Y	Y	None	Resolved
	Treatment Cycle 3	43	Lung infection	1.58 Months	3	Y	N	None	Resolved
Trial Number=3475-024, Site Number=0201, Subject ID=244803, Gender=M, Race=Asian, Age=57 Years, Rel Day of Last Recorded Dose of Study Medication=1									
244803	Safety Follow-up	9	Dehydration	6 Days	3	Y	N	N/A	Resolved
		9	Pneumothorax	3 Days	3	Y	N	N/A	Resolved
		21	Anaemia	3 Days	3	Y	N	N/A	Resolved
		21	Dehydration	Continuing	3	Y	N	N/A	Not Resolved
Trial Number=3475-024, Site Number=0202, Subject ID=244521, Gender=F, Race=White, Age=53 Years, Rel Day of Last Recorded Dose of Study Medication=296									
244521	Safety Follow-up	303	Pneumonitis	2.1 Months	3	Y	Y	Discontinued	Resolved
	Extended Safety Follow-up	351	Lung infection	2.29 Weeks	3	Y	N	None	Resolved
Trial Number=3475-024, Site Number=0202, Subject ID=245198, Gender=F, Race=White, Age=51 Years, Rel Day of Last Recorded Dose of Study Medication=274									
245198	Treatment Cycle 4	77	Hypersensitivity	30 Minutes	2	Y	N	None	Resolved

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Listing of Subjects With Serious Adverse Events
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
Pembrolizumab									
Trial Number=3475-024, Site Number=0210, Subject ID=244556, Gender=M, Race=White, Age=61 Years, Rel Day of Last Recorded Dose of Study Medication=212									
244556	Safety Follow-up	227	Back pain	5 Days	3	Y	N	None	Resolved
		233	Metastases to meninges	4.14 Weeks	3	Y	N	None	Resolved
Trial Number=3475-024, Site Number=0252, Subject ID=243913, Gender=M, Race=Asian, Age=58 Years, Rel Day of Last Recorded Dose of Study Medication=1									
243913	Safety Follow-up	7	Pneumonitis	Continuing	4	Y	Y	Discontinued	Not Resolved
Trial Number=3475-024, Site Number=0252, Subject ID=243915, Gender=M, Race=Asian, Age=64 Years, Rel Day of Last Recorded Dose of Study Medication=33									
243915	Safety Follow-up	40	Hypovolaemia	Continuing	2	Y	Y	None	Not Resolved
		43	Face oedema	Continuing	2	Y	Y	None	Not Resolved
		43	Pericarditis	Continuing	4	Y	Y	None	Not Resolved
Trial Number=3475-024, Site Number=0252, Subject ID=243919, Gender=M, Race=Asian, Age=70 Years, Rel Day of Last Recorded Dose of Study Medication=253									
243919	Treatment Cycle 2	50	Infected neoplasm	1.43 Weeks	3	Y	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0257, Subject ID=243003, Gender=M, Race=Asian, Age=66 Years, Rel Day of Last Recorded Dose of Study Medication=231									
243003	Treatment Cycle 2	43	Decreased appetite	3 Weeks	3	Y	N	Interrupted	Resolved
	Treatment Cycle 5	174	Painful respiration	1.22 Months	3	Y	N	Interrupted	Resolved
		175	Cardiac failure	Continuing	3	Y	N	Interrupted	Resolving
Trial Number=3475-024, Site Number=0258, Subject ID=243312, Gender=F, Race=Asian, Age=40 Years, Rel Day of Last Recorded Dose of Study Medication=217									
243312	Treatment Cycle 9	189	Ovarian haemorrhage	Continuing	3	Y	N	None	Not Resolved
Trial Number=3475-024, Site Number=0260, Subject ID=243902, Gender=F, Race=Asian, Age=71 Years, Rel Day of Last Recorded Dose of Study Medication=188									

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Listing of Subjects With Serious Adverse Events
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
Pembrolizumab									
Trial Number=3475-024, Site Number=0260, Subject ID=243902, Gender=F, Race=Asian, Age=71 Years, Rel Day of Last Recorded Dose of Study Medication=188									
243902	Treatment Cycle 6	104	Fatigue	Continuing	3	Y	Y	Discontinued	Not Resolved
Trial Number=3475-024, Site Number=0270, Subject ID=244576, Gender=M, Race=White, Age=62 Years, Rel Day of Last Recorded Dose of Study Medication=169									
244576	Treatment Cycle 9	181	Organising pneumonia	Continuing	3	Y	Y	Interrupted	Not Resolved
Trial Number=3475-024, Site Number=0301, Subject ID=244525, Gender=M, Race=White, Age=80 Years, Rel Day of Last Recorded Dose of Study Medication=245									
244525	Treatment Cycle 9	186	Chronic obstructive pulmonary disease	1.57 Weeks	3	Y	N	Interrupted	Resolved
	Treatment Cycle 10	242	Chronic obstructive pulmonary disease	1.29 Weeks	3	Y	N	None	Resolved
Trial Number=3475-024, Site Number=0330, Subject ID=244517, Gender=F, Race=White, Age=56 Years, Rel Day of Last Recorded Dose of Study Medication=219									
244517	Treatment Cycle 6	114	Gastroenteritis viral	6 Days	3	Y	N	None	Resolved
	Safety Follow-up	231	Hyperglycaemia	2.86 Weeks	4	Y	N	N/A	Resolved
Trial Number=3475-024, Site Number=0330, Subject ID=245170, Gender=F, Race=White, Age=73 Years, Rel Day of Last Recorded Dose of Study Medication=170									
245170	Extended Safety Follow-up	221	Pleural effusion	1.86 Weeks	3	Y	N	N/A	Sequelae
Trial Number=3475-024, Site Number=0335, Subject ID=243909, Gender=M, Race=Asian, Age=65 Years, Rel Day of Last Recorded Dose of Study Medication=337									
243909	Treatment Cycle 1	1	Infusion related reaction	3.25 Hours	2	Y	Y	None	Resolved
	Treatment Cycle 15	311	Diarrhoea	3.86 Weeks	3	Y	Y	None	Resolved
		311	Enterocolitis	3.86 Weeks	2	Y	Y	None	Resolved
SOC									

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Listing of Subjects With Serious Adverse Events
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
SOC									
Trial Number=3475-024, Site Number=0003, Subject ID=245208, Gender=M, Race=White, Age=72 Years, Rel Day of Last Recorded Dose of Study Medication=165									
245208	Chemotherapy Washout	92	Pneumonia	2 Weeks	3	Y	Y	N/A	Resolved
		112	Malignant neoplasm progression	1.86 Weeks	3	Y	Y	N/A	Sequelae
		112	Pericardial effusion	1.86 Weeks	3	Y	N	N/A	Sequelae
		155	Lower respiratory tract infection	1 Weeks	3	Y	N	N/A	Sequelae
Trial Number=3475-024, Site Number=0006, Subject ID=244516, Gender=F, Race=Native Hawaiian Or Other Pacific Islander, Age=56 Years, Rel Day of Last Recorded Dose of Study Medication=1									
244516	Safety Follow-up	3	Musculoskeletal pain	3 Days	3	Y	N	N/A	Resolved
Trial Number=3475-024, Site Number=0007, Subject ID=244512, Gender=M, Race=White, Age=66 Years, Rel Day of Last Recorded Dose of Study Medication=372									
244512	Treatment Cycle 3	54	Urinary tract infection	1.05 Months	3	Y	N	Reduced	Resolved
Trial Number=3475-024, Site Number=0007, Subject ID=245119, Gender=F, Race=White, Age=73 Years, Rel Day of Last Recorded Dose of Study Medication=127									
245119	Treatment Cycle 1	15	Pleural effusion	Continuing	3	Y	N	Interrupted	Not Resolved
Trial Number=3475-024, Site Number=0007, Subject ID=245178, Gender=M, Race=White, Age=60 Years, Rel Day of Last Recorded Dose of Study Medication=209									
245178	Safety Follow-up	210	Cerebrovascular accident	2.43 Weeks	3	Y	N	N/A	Sequelae
Trial Number=3475-024, Site Number=0011, Subject ID=245189, Gender=M, Race=White, Age=58 Years, Rel Day of Last Recorded Dose of Study Medication=1									
245189	Safety Follow-up	15	Acute kidney injury	1.29 Weeks	3	Y	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0011, Subject ID=245204, Gender=M, Race=White, Age=79 Years, Rel Day of Last Recorded Dose of Study Medication=259									
245204	Treatment Cycle 5	91	Skin infection	1.61 Months	3	Y	Y	Interrupted	Resolved

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Listing of Subjects With Serious Adverse Events
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
SOC									
Trial Number=3475-024, Site Number=0011, Subject ID=245204, Gender=M, Race=White, Age=79 Years, Rel Day of Last Recorded Dose of Study Medication=259									
245204	Study Medication Completion Follow-up	119	Muscle haemorrhage	3.14 Weeks	3	Y	N	N/A	Resolved
Trial Number=3475-024, Site Number=0030, Subject ID=244801, Gender=M, Race=White, Age=73 Years, Rel Day of Last Recorded Dose of Study Medication=1									
244801	Safety Follow-up	7	Pneumonia	3.86 Weeks	3	Y	N	Discontinued	Resolved
		16	Febrile neutropenia	2 Days	3	Y	Y	N/A	Resolved
Trial Number=3475-024, Site Number=0030, Subject ID=245166, Gender=M, Race=White, Age=61 Years, Rel Day of Last Recorded Dose of Study Medication=350									
245166	Study Medication Completion Follow-up	155	Vasospasm	1.84 Months	2	Y	Y	N/A	Resolved
Trial Number=3475-024, Site Number=0035, Subject ID=244563, Gender=M, Race=White, Age=53 Years, Rel Day of Last Recorded Dose of Study Medication=141									
244563	Treatment Cycle 5	111	Acute kidney injury	Continuing	3	Y	Y	Discontinued	Not Resolved
Trial Number=3475-024, Site Number=0044, Subject ID=245140, Gender=M, Race=White, Age=50 Years, Rel Day of Last Recorded Dose of Study Medication=232									
245140	Treatment Cycle 8	155	Back pain	2.63 Months	3	Y	N	N/A	Resolved
Trial Number=3475-024, Site Number=0044, Subject ID=245148, Gender=F, Race=White, Age=60 Years, Rel Day of Last Recorded Dose of Study Medication=389									
245148	Treatment Cycle 1	17	Atrial fibrillation	2 Days	3	Y	N	None	Resolved
	Chemotherapy	38	Faecaloma	2.57 Weeks	3	Y	N	N/A	Resolved
	Washout	61	Transient ischaemic attack	23 Hours	2	Y	N	N/A	Resolved

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Listing of Subjects With Serious Adverse Events
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
SOC									
Trial Number=3475-024, Site Number=0044, Subject ID=245209, Gender=M, Race=White, Age=70 Years, Rel Day of Last Recorded Dose of Study Medication=241									
245209	Treatment Cycle 1	3	Nausea	1.08 Months	3	Y	Y	Reduced	Resolved
	Treatment Cycle 3	58	Coronary artery disease	3 Days	3	Y	N	Discontinued	Resolved
	Treatment Cycle 4	85	Angina pectoris	4 Days	3	Y	N	None	Resolved
Trial Number=3475-024, Site Number=0045, Subject ID=245215, Gender=F, Race=White, Age=75 Years, Rel Day of Last Recorded Dose of Study Medication=234									
245215	Treatment Cycle 1	8	Stomatitis	1.14 Weeks	3	Y	Y	Reduced	Resolved
Trial Number=3475-024, Site Number=0045, Subject ID=245226, Gender=M, Race=White, Age=73 Years, Rel Day of Last Recorded Dose of Study Medication=43									
245226	Treatment Cycle 1	4	Nausea	Continuing	3	Y	N	None	Resolving
		8	Right ventricular failure	1.18 Months	3	Y	N	None	Resolved
	Safety Follow-up	48	Back pain	Continuing	3	Y	N	N/A	Not Resolved
Trial Number=3475-024, Site Number=0046, Subject ID=244531, Gender=F, Race=White, Age=76 Years, Rel Day of Last Recorded Dose of Study Medication=120									
244531	Treatment Cycle 2	35	Pneumonia	1.71 Weeks	4	Y	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0048, Subject ID=244205, Gender=M, Race=White, Age=54 Years, Rel Day of Last Recorded Dose of Study Medication=392									
244205	Treatment Cycle 1	8	Pneumonia	2.14 Weeks	3	Y	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0048, Subject ID=244211, Gender=M, Race=White, Age=63 Years, Rel Day of Last Recorded Dose of Study Medication=303									
244211	Treatment Cycle 1	13	Febrile neutropenia	4 Days	3	Y	Y	Discontinued	Resolved
Trial Number=3475-024, Site Number=0048, Subject ID=244568, Gender=M, Race=White, Age=76 Years, Rel Day of Last Recorded Dose of Study Medication=7									
244568	Safety Follow-up	19	Pulmonary sepsis	1 Weeks	5	Y	Y	Discontinued	Fatal

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Listing of Subjects With Serious Adverse Events
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
SOC									
Trial Number=3475-024, Site Number=0062, Subject ID=245128, Gender=M, Race=White, Age=52 Years, Rel Day of Last Recorded Dose of Study Medication=136									
245128	Chemotherapy Washout	115	Pneumothorax	Continuing	3	Y	N	N/A	Not Resolved
Trial Number=3475-024, Site Number=0064, Subject ID=245168, Gender=M, Race=White, Age=59 Years, Rel Day of Last Recorded Dose of Study Medication=50									
245168	Safety Follow-up	64	Pulmonary embolism	23 Hours	5	Y	N	Discontinued	Fatal
Trial Number=3475-024, Site Number=0065, Subject ID=244821, Gender=F, Race=White, Age=67 Years, Rel Day of Last Recorded Dose of Study Medication=115									
244821	Treatment Cycle 2	35	Device dislocation	1.14 Weeks	3	Y	N	None	Resolved
Trial Number=3475-024, Site Number=0065, Subject ID=245194, Gender=M, Race=White, Age=69 Years, Rel Day of Last Recorded Dose of Study Medication=43									
245194	Safety Follow-up	58	Clostridium difficile colitis	4 Days	3	Y	N	N/A	Resolved
		61	Cardiac failure	5 Hours	5	Y	N	N/A	Fatal
Trial Number=3475-024, Site Number=0070, Subject ID=244533, Gender=M, Race=White, Age=69 Years, Rel Day of Last Recorded Dose of Study Medication=21									
244533	Treatment Cycle 1	19	Hypertensive nephropathy	Continuing	3	Y	N	None	Not Resolved
	Treatment Cycle 2	21	Ischaemic cardiomyopathy	1 Weeks	3	Y	N	None	Resolved
	Safety Follow-up	29	Ischaemic cardiomyopathy	Continuing	3	Y	N	N/A	Not Resolved
Trial Number=3475-024, Site Number=0074, Subject ID=244814, Gender=F, Race=White, Age=77 Years, Rel Day of Last Recorded Dose of Study Medication=247									
244814	Chemotherapy Washout	204	Infective exacerbation of chronic obstructive airways disease	1.57 Weeks	3	Y	N	N/A	Resolved
Trial Number=3475-024, Site Number=0074, Subject ID=245195, Gender=M, Race=White, Age=54 Years, Rel Day of Last Recorded Dose of Study Medication=22									

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Listing of Subjects With Serious Adverse Events
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
SOC									
Trial Number=3475-024, Site Number=0074, Subject ID=245195, Gender=M, Race=White, Age=54 Years, Rel Day of Last Recorded Dose of Study Medication=22									
245195	Extended Safety Follow-up	56	Hypercalcaemia	4 Days	3	Y	N	N/A	Resolved
Trial Number=3475-024, Site Number=0075, Subject ID=244214, Gender=M, Race=White, Age=44 Years, Rel Day of Last Recorded Dose of Study Medication=135									
244214	Treatment Cycle 1	19	Radiation oesophagitis	1.71 Weeks	2	Y	N	Interrupted	Resolved
	Chemotherapy Washout	70	Pulmonary radiation injury	Continuing	3	Y	N	N/A	Not Resolved
Trial Number=3475-024, Site Number=0076, Subject ID=245222, Gender=M, Race=White, Age=66 Years, Rel Day of Last Recorded Dose of Study Medication=1									
245222	Safety Follow-up	4	Pulmonary embolism	6 Days	4	Y	N	N/A	Resolved
		16	Cancer pain	2 Days	3	Y	N	N/A	Resolved
		20	Toxicity to various agents	1.43 Weeks	3	Y	N	N/A	Resolved
	Extended Safety Follow-up	39	Insomnia	Continuing	2	Y	N	N/A	Not Resolved
		39	Restlessness	Continuing	2	Y	N	N/A	Not Resolved
		40	Arthralgia	Continuing	2	Y	N	N/A	Not Resolved
		40	Chest pain	Continuing	3	Y	N	N/A	Not Resolved
Trial Number=3475-024, Site Number=0081, Subject ID=245160, Gender=M, Race=White, Age=66 Years, Rel Day of Last Recorded Dose of Study Medication=100									
245160	Treatment Cycle 2	45	Anaemia	5 Days	3	Y	Y	None	Resolved
	Chemotherapy Washout	59	Pancytopenia	1.71 Weeks	3	Y	Y	N/A	Resolved

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Listing of Subjects With Serious Adverse Events
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
SOC									
Trial Number=3475-024, Site Number=0081, Subject ID=245228, Gender=F, Race=White, Age=78 Years, Rel Day of Last Recorded Dose of Study Medication=1									
245228	Safety Follow-up	10	Pancytopenia	Continuing	4	Y	Y	N/A	Not Resolved
Trial Number=3475-024, Site Number=0082, Subject ID=245132, Gender=M, Race=White, Age=49 Years, Rel Day of Last Recorded Dose of Study Medication=428									
245132	Treatment Cycle 2	32	Pneumonia	1.71 Weeks	3	Y	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0085, Subject ID=244507, Gender=F, Race=White, Age=79 Years, Rel Day of Last Recorded Dose of Study Medication=365									
244507	Treatment Cycle 6	108	Pulmonary oedema	2 Days	3	Y	N	None	Resolved
	Treatment Cycle 8	158	Peritonsillar abscess	5 Days	3	Y	N	None	Resolved
Trial Number=3475-024, Site Number=0085, Subject ID=244515, Gender=F, Race=White, Age=69 Years, Rel Day of Last Recorded Dose of Study Medication=79									
244515	Treatment Cycle 3	58	Chronic obstructive pulmonary disease	1.14 Weeks	3	Y	N	None	Resolved
	Extended Safety Follow-up	141	Chronic obstructive pulmonary disease	6 Days	3	Y	N	N/A	Resolved
Trial Number=3475-024, Site Number=0096, Subject ID=245142, Gender=M, Race=White, Age=57 Years, Rel Day of Last Recorded Dose of Study Medication=1									
245142	Safety Follow-up	21	Pneumonia	Continuing	3	Y	N	N/A	Not Resolved
Trial Number=3475-024, Site Number=0097, Subject ID=245127, Gender=M, Race=White, Age=74 Years, Rel Day of Last Recorded Dose of Study Medication=1									
245127	Safety Follow-up	31	Gait disturbance	Continuing	3	Y	Y	Discontinued	Not Resolved
	Extended Safety Follow-up	59	Bradycardia	5 Days	2	Y	N	N/A	Resolved
Trial Number=3475-024, Site Number=0098, Subject ID=244520, Gender=F, Race=White, Age=77 Years, Rel Day of Last Recorded Dose of Study Medication=354									

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Listing of Subjects With Serious Adverse Events
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
SOC									
Trial Number=3475-024, Site Number=0098, Subject ID=244520, Gender=F, Race=White, Age=77 Years, Rel Day of Last Recorded Dose of Study Medication=354									
244520	Treatment Cycle 4	87	Thrombocytopenia	2.71 Weeks	4	Y	Y	None	Resolved
Trial Number=3475-024, Site Number=0098, Subject ID=245162, Gender=M, Race=White, Age=73 Years, Rel Day of Last Recorded Dose of Study Medication=121									
245162	Treatment Cycle 1	17	Back pain	1.86 Weeks	3	Y	N	None	Resolved
Trial Number=3475-024, Site Number=0099, Subject ID=245143, Gender=M, Race=White, Age=65 Years, Rel Day of Last Recorded Dose of Study Medication=174									
245143	Treatment Cycle 1	4	Hypocalcaemia	1.29 Weeks	3	Y	N	None	Resolved
Trial Number=3475-024, Site Number=0100, Subject ID=244820, Gender=M, Race=White, Age=57 Years, Rel Day of Last Recorded Dose of Study Medication=1									
244820	Safety Follow-up	8	Death	23 Hours	5	Y	Y	N/A	Fatal
Trial Number=3475-024, Site Number=0100, Subject ID=245169, Gender=F, Race=White, Age=52 Years, Rel Day of Last Recorded Dose of Study Medication=1									
245169	Safety Follow-up	5	Anaemia	Continuing	3	Y	Y	N/A	Not Resolved
		22	Leukocytosis	Continuing	3	Y	Y	Discontinued	Not Resolved
Trial Number=3475-024, Site Number=0121, Subject ID=245113, Gender=M, Race=White, Age=78 Years, Rel Day of Last Recorded Dose of Study Medication=123									
245113	Chemotherapy Washout	58	Lower respiratory tract infection	2.29 Weeks	3	Y	N	N/A	Resolved
Trial Number=3475-024, Site Number=0123, Subject ID=245207, Gender=F, Race=White, Age=43 Years, Rel Day of Last Recorded Dose of Study Medication=1									
245207	Safety Follow-up	7	Ischaemic stroke	Continuing	4	Y	N	N/A	Not Resolved
Trial Number=3475-024, Site Number=0127, Subject ID=244547, Gender=F, Race=White, Age=47 Years, Rel Day of Last Recorded Dose of Study Medication=244									

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Listing of Subjects With Serious Adverse Events
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
SOC									
Trial Number=3475-024, Site Number=0127, Subject ID=244547, Gender=F, Race=White, Age=47 Years, Rel Day of Last Recorded Dose of Study Medication=244									
244547	Chemotherapy Washout	201	Hypercalcaemia	1.18 Months	3	Y	N	N/A	Resolved
Trial Number=3475-024, Site Number=0127, Subject ID=244559, Gender=M, Race=White, Age=67 Years, Rel Day of Last Recorded Dose of Study Medication=213									
244559	Treatment Cycle 6	119	Septic shock	2.71 Weeks	4	Y	N	Interrupted	Resolved
	Treatment Cycle 8	180	Respiratory tract infection	5 Days	3	Y	Y	Discontinued	Resolved
Trial Number=3475-024, Site Number=0130, Subject ID=244832, Gender=M, Race=White, Age=60 Years, Rel Day of Last Recorded Dose of Study Medication=219									
244832	Treatment Cycle 1	12	Respiratory tract infection	2.71 Weeks	2	Y	N	Interrupted	Resolved
	Treatment Cycle 2	39	Pyrexia	5 Days	2	Y	Y	None	Resolved
Trial Number=3475-024, Site Number=0131, Subject ID=245117, Gender=M, Race=White, Age=76 Years, Rel Day of Last Recorded Dose of Study Medication=8									
245117	Safety Follow-up	12	Epistaxis	2.29 Weeks	3	Y	Y	N/A	Resolved
		12	Pancytopenia	Continuing	4	Y	Y	N/A	Resolving
		12	Pulmonary sepsis	2.29 Weeks	4	Y	N	N/A	Resolved
		14	Pleural effusion	Continuing	3	Y	N	N/A	Not Resolved
Trial Number=3475-024, Site Number=0132, Subject ID=245131, Gender=F, Race=Black Or African American, Age=56 Years, Rel Day of Last Recorded Dose of Study Medication=58									
245131	Safety Follow-up	88	Anaemia	Continuing	3	Y	N	N/A	Not Resolved
Trial Number=3475-024, Site Number=0136, Subject ID=244554, Gender=F, Race=White, Age=70 Years, Rel Day of Last Recorded Dose of Study Medication=260									
244554	Safety Follow-up	273	Cerebral infarction	3 Days	2	Y	N	Discontinued	Resolved

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Listing of Subjects With Serious Adverse Events
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
SOC									
Trial Number=3475-024, Site Number=0136, Subject ID=244831, Gender=F, Race=White, Age=68 Years, Rel Day of Last Recorded Dose of Study Medication=51									
244831	Treatment Cycle 1	5	Urinary tract infection	4 Days	3	Y	Y	Interrupted	Resolved
	Treatment Cycle 2	27	Rib fracture	2.57 Weeks	3	Y	N	None	Resolved
	Treatment Cycle 3	48	Constipation	3 Days	2	Y	N	None	Resolved
	Safety Follow-up	57	Thrombocytopenia	Continuing	4	Y	Y	N/A	Not Resolved
Trial Number=3475-024, Site Number=0136, Subject ID=245213, Gender=M, Race=White, Age=85 Years, Rel Day of Last Recorded Dose of Study Medication=182									
245213	Treatment Cycle 1	10	Febrile neutropenia	1.57 Weeks	3	Y	Y	Reduced	Resolved
	Treatment Cycle 2	31	Neutropenic sepsis	1.57 Weeks	4	Y	Y	None	Resolved
	Safety Follow-up	194	Pneumonia	5 Days	3	Y	N	Interrupted	Sequelae
	Extended Safety Follow-up	221	Cardiac arrest	23 Hours	5	Y	N	None	Fatal
Trial Number=3475-024, Site Number=0138, Subject ID=245101, Gender=M, Race=White, Age=68 Years, Rel Day of Last Recorded Dose of Study Medication=1									
245101	Safety Follow-up	8	Pleural effusion	Continuing	3	Y	N	N/A	Not Resolved
		26	Sepsis	Continuing	4	Y	N	N/A	Not Resolved
Trial Number=3475-024, Site Number=0152, Subject ID=244818, Gender=M, Race=White, Age=72 Years, Rel Day of Last Recorded Dose of Study Medication=114									
244818	Extended Safety Follow-up	166	Hypercalcaemia	2.57 Weeks	2	Y	N	N/A	Resolved
Trial Number=3475-024, Site Number=0155, Subject ID=244502, Gender=F, Race=White, Age=68 Years, Rel Day of Last Recorded Dose of Study Medication=511									
244502	Treatment Cycle 22	458	Small intestinal obstruction	6 Days	3	Y	N	None	Resolved

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Listing of Subjects With Serious Adverse Events
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
SOC									
Trial Number=3475-024, Site Number=0168, Subject ID=244804, Gender=F, Race=White, Age=73 Years, Rel Day of Last Recorded Dose of Study Medication=191									
244804	Treatment Cycle 1	8	Diarrhoea	2 Days	3	Y	Y	None	Resolved
Trial Number=3475-024, Site Number=0174, Subject ID=245218, Gender=F, Race=White, Age=64 Years, Rel Day of Last Recorded Dose of Study Medication=22									
245218	Safety Follow-up	29	Bronchial obstruction	4 Days	3	Y	N	N/A	Resolved
		51	Supraventricular tachycardia	3 Days	2	Y	N	N/A	Resolved
Trial Number=3475-024, Site Number=0202, Subject ID=245202, Gender=M, Race=White, Age=74 Years, Rel Day of Last Recorded Dose of Study Medication=33									
245202	Treatment Cycle 1	1	Anaemia	Continuing	3	Y	Y	Interrupted	Not Resolved
	Treatment Cycle 2	33	Thrombocytopenia	3.14 Weeks	3	Y	Y	None	Resolved
	Safety Follow-up	43	Epistaxis	2 Days	3	Y	Y	N/A	Resolved
		54	Acute kidney injury	6 Days	2	Y	N	Interrupted	Resolved
		54	Atrial fibrillation	6 Days	4	Y	N	Interrupted	Resolved
		54	Cardiac failure	6 Days	3	Y	N	Interrupted	Resolved
		54	Pulmonary oedema	6 Days	4	Y	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0256, Subject ID=243916, Gender=M, Race=Asian, Age=68 Years, Rel Day of Last Recorded Dose of Study Medication=93									
243916	Safety Follow-up	109	Pulmonary alveolar haemorrhage	4 Days	5	Y	Y	Discontinued	Fatal
Trial Number=3475-024, Site Number=0258, Subject ID=243904, Gender=M, Race=Asian, Age=66 Years, Rel Day of Last Recorded Dose of Study Medication=371									
243904	Study Medication Completion Follow-up	114	Pneumonia	5.72 Months	3	Y	N	N/A	Resolved
Trial Number=3475-024, Site Number=0258, Subject ID=243922, Gender=M, Race=Asian, Age=68 Years, Rel Day of Last Recorded Dose of Study Medication=117									

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Listing of Subjects With Serious Adverse Events
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
SOC									
Trial Number=3475-024, Site Number=0258, Subject ID=243922, Gender=M, Race=Asian, Age=68 Years, Rel Day of Last Recorded Dose of Study Medication=117									
243922	Treatment Cycle 4	92	Lung infection	1.77 Months	3	Y	Y	Interrupted	Resolved
		92	Platelet count decreased	2.71 Weeks	3	Y	Y	None	Resolved
Trial Number=3475-024, Site Number=0260, Subject ID=243906, Gender=M, Race=Asian, Age=61 Years, Rel Day of Last Recorded Dose of Study Medication=25									
243906	Extended Safety Follow-up	61	Pneumonitis	Continuing	3	Y	Y	N/A	Not Resolved
Trial Number=3475-024, Site Number=0330, Subject ID=245114, Gender=F, Race=White, Age=74 Years, Rel Day of Last Recorded Dose of Study Medication=381									
245114	Treatment Cycle 2	31	Peripheral embolism	4 Days	3	Y	N	None	Resolved
	Treatment Cycle 18	375	Bladder neoplasm	1.12 Months	3	Y	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0331, Subject ID=243921, Gender=M, Race=Asian, Age=77 Years, Rel Day of Last Recorded Dose of Study Medication=1									
243921	Safety Follow-up	21	Cellulitis	2.29 Weeks	3	Y	Y	N/A	Resolved
Trial Number=3475-024, Site Number=0333, Subject ID=243905, Gender=M, Race=Asian, Age=66 Years, Rel Day of Last Recorded Dose of Study Medication=22									
243905	Safety Follow-up	28	Lung infection	Continuing	3	Y	Y	N/A	Resolving
Trial Number=3475-024, Site Number=0340, Subject ID=243901, Gender=M, Race=Asian, Age=67 Years, Rel Day of Last Recorded Dose of Study Medication=22									
243901	Safety Follow-up	41	Cardio-respiratory arrest	2.5 Hours	5	Y	N	N/A	Fatal
Trial Number=3475-024, Site Number=0351, Subject ID=244822, Gender=M, Race=White, Age=56 Years, Rel Day of Last Recorded Dose of Study Medication=169									
244822	Treatment Cycle 2	33	Anaemia	5 Days	3	Y	Y	Reduced	Resolved
	Treatment Cycle 3	64	Anaemia	1.14 Weeks	2	Y	Y	Reduced	Resolved

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Listing of Subjects With Serious Adverse Events
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
SOC									
Trial Number=3475-024, Site Number=0352, Subject ID=244203, Gender=M, Race=White, Age=71 Years, Rel Day of Last Recorded Dose of Study Medication=280									
244203	Chemotherapy Washout	162	Pneumonia	1.57 Weeks	3	Y	N	N/A	Resolved

Toxicity Grade: NCI CTCAE version 4.03.

Related: Investigator-assessed relationship of the adverse event to study medication. Y = RELATED, N = NOT RELATED

Action Taken: Discontinued = DRUG WITHDRAWN, Interrupted = DRUG INTERRUPTED, Reduced = DOSE REDUCED, Increased = DOSE INCREASED, None = DOSE NOT CHANGED, N/A = NOT APPLICABLE.

Outcome: Resolved = RECOVERED/RESOLVED, Resolving = RECOVERING/RESOLVING, Sequelae = RECOVERED/RESOLVED WITH SEQUELAE, Not resolved = NOT RECOVERED/NOT RESOLVED.

MedDRA preferred terms "Neoplasm Progression" and "Malignant Neoplasm Progression" not related to the drug are excluded.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

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付録 2.7.4- 139 最終投与後 90 日までに発現した重篤な副作用
（いずれかの投与群で発現割合 0%超）
024 試験（安全性解析対象集団）

Subjects With Drug-Related Serious Adverse Events by Decreasing Incidence
(Incidence >0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	154		150		304	
with one or more adverse events	33	(21.4)	31	(20.7)	64	(21.1)
with no adverse events	121	(78.6)	119	(79.3)	240	(78.9)
Pneumonitis	7	(4.5)	1	(0.7)	8	(2.6)
Anaemia	1	(0.6)	4	(2.7)	5	(1.6)
Diarrhoea	3	(1.9)	1	(0.7)	4	(1.3)
Febrile neutropenia	0	(0.0)	3	(2.0)	3	(1.0)
Pancytopenia	0	(0.0)	3	(2.0)	3	(1.0)
Pneumonia	0	(0.0)	3	(2.0)	3	(1.0)
Thrombocytopenia	0	(0.0)	3	(2.0)	3	(1.0)
Acute kidney injury	0	(0.0)	2	(1.3)	2	(0.7)
Alanine aminotransferase increased	2	(1.3)	0	(0.0)	2	(0.7)
Colitis	2	(1.3)	0	(0.0)	2	(0.7)
Diabetes mellitus	2	(1.3)	0	(0.0)	2	(0.7)
Epistaxis	0	(0.0)	2	(1.3)	2	(0.7)
Lower respiratory tract infection	2	(1.3)	0	(0.0)	2	(0.7)
Lung infection	0	(0.0)	2	(1.3)	2	(0.7)
Acute hepatic failure	1	(0.6)	0	(0.0)	1	(0.3)
Aspartate aminotransferase increased	1	(0.6)	0	(0.0)	1	(0.3)
Bilirubin conjugated increased	1	(0.6)	0	(0.0)	1	(0.3)
Cellulitis	0	(0.0)	1	(0.7)	1	(0.3)
Cerebrovascular accident	1	(0.6)	0	(0.0)	1	(0.3)
Death	0	(0.0)	1	(0.7)	1	(0.3)
Diabetic ketoacidosis	1	(0.6)	0	(0.0)	1	(0.3)
Enterocolitis	1	(0.6)	0	(0.0)	1	(0.3)
Face oedema	1	(0.6)	0	(0.0)	1	(0.3)
Fatigue	1	(0.6)	0	(0.0)	1	(0.3)
Gait disturbance	0	(0.0)	1	(0.7)	1	(0.3)
Gastric ulcer	1	(0.6)	0	(0.0)	1	(0.3)
Hepatic enzyme increased	1	(0.6)	0	(0.0)	1	(0.3)
Hyperthyroidism	1	(0.6)	0	(0.0)	1	(0.3)
Hypophysitis	1	(0.6)	0	(0.0)	1	(0.3)
Hypovolaemia	1	(0.6)	0	(0.0)	1	(0.3)
Infusion related reaction	1	(0.6)	0	(0.0)	1	(0.3)
Leukocytosis	0	(0.0)	1	(0.7)	1	(0.3)
Lichenoid keratosis	1	(0.6)	0	(0.0)	1	(0.3)
Malignant neoplasm progression	0	(0.0)	1	(0.7)	1	(0.3)
Musculoskeletal pain	1	(0.6)	0	(0.0)	1	(0.3)
Nausea	0	(0.0)	1	(0.7)	1	(0.3)
Neutropenic sepsis	0	(0.0)	1	(0.7)	1	(0.3)
Oedema peripheral	1	(0.6)	0	(0.0)	1	(0.3)
Organising pneumonia	1	(0.6)	0	(0.0)	1	(0.3)
Pancreatitis	1	(0.6)	0	(0.0)	1	(0.3)
Pericarditis	1	(0.6)	0	(0.0)	1	(0.3)

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Subjects With Drug-Related Serious Adverse Events by Decreasing Incidence (Incidence >0% in One or More Treatment Groups) (ASaT Population)

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Platelet count decreased	0	(0.0)	1	(0.7)	1	(0.3)
Pulmonary alveolar haemorrhage	0	(0.0)	1	(0.7)	1	(0.3)
Pulmonary embolism	1	(0.6)	0	(0.0)	1	(0.3)
Pulmonary sepsis	0	(0.0)	1	(0.7)	1	(0.3)
Pyrexia	0	(0.0)	1	(0.7)	1	(0.3)
Rash	1	(0.6)	0	(0.0)	1	(0.3)
Respiratory tract infection	0	(0.0)	1	(0.7)	1	(0.3)
Skin infection	0	(0.0)	1	(0.7)	1	(0.3)
Stomatitis	0	(0.0)	1	(0.7)	1	(0.3)
Sudden death	1	(0.6)	0	(0.0)	1	(0.3)
Transaminases increased	1	(0.6)	0	(0.0)	1	(0.3)
Tubulointerstitial nephritis	1	(0.6)	0	(0.0)	1	(0.3)
Urinary tract infection	0	(0.0)	1	(0.7)	1	(0.3)
Vasospasm	0	(0.0)	1	(0.7)	1	(0.3)
Vomiting	1	(0.6)	0	(0.0)	1	(0.3)

Every subject is counted a single time for each applicable specific adverse event.
A system organ class appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
MedDRA preferred terms "Neoplasm Progression" and "Malignant Neoplasm Progression" not related to the drug are excluded.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

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付録 2.7.4- 140 治験薬の投与中止に至った副作用
いずれかの投与群で発現割合 0%超）
024 試験（安全性解析対象集団）

Subjects With Drug-Related Adverse Events Resulting in Treatment Discontinuation by Decreasing Incidence
(Incidence >0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	154		150		304	
with one or more adverse events	11	(7.1)	16	(10.7)	27	(8.9)
with no adverse events	143	(92.9)	134	(89.3)	277	(91.1)
Pneumonitis	6	(3.9)	0	(0.0)	6	(2.0)
Fatigue	1	(0.6)	2	(1.3)	3	(1.0)
Blood creatinine increased	0	(0.0)	2	(1.3)	2	(0.7)
Vomiting	1	(0.6)	1	(0.7)	2	(0.7)
Acute kidney injury	0	(0.0)	1	(0.7)	1	(0.3)
Alanine aminotransferase increased	1	(0.6)	0	(0.0)	1	(0.3)
Blood creatine increased	0	(0.0)	1	(0.7)	1	(0.3)
Creatinine renal clearance decreased	0	(0.0)	1	(0.7)	1	(0.3)
Decreased appetite	0	(0.0)	1	(0.7)	1	(0.3)
Enanthema	0	(0.0)	1	(0.7)	1	(0.3)
Febrile neutropenia	0	(0.0)	1	(0.7)	1	(0.3)
Gait disturbance	0	(0.0)	1	(0.7)	1	(0.3)
Hypoacusis	0	(0.0)	1	(0.7)	1	(0.3)
Hypoxia	0	(0.0)	1	(0.7)	1	(0.3)
Lethargy	0	(0.0)	1	(0.7)	1	(0.3)
Leukocytosis	0	(0.0)	1	(0.7)	1	(0.3)
Nausea	0	(0.0)	1	(0.7)	1	(0.3)
Peripheral sensory neuropathy	0	(0.0)	1	(0.7)	1	(0.3)
Platelet count decreased	0	(0.0)	1	(0.7)	1	(0.3)
Pulmonary alveolar haemorrhage	0	(0.0)	1	(0.7)	1	(0.3)
Pulmonary sepsis	0	(0.0)	1	(0.7)	1	(0.3)
Respiratory tract infection	0	(0.0)	1	(0.7)	1	(0.3)
Sudden death	1	(0.6)	0	(0.0)	1	(0.3)
Transaminases increased	1	(0.6)	0	(0.0)	1	(0.3)

Every subject is counted a single time for each applicable specific adverse event.
A system organ class appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
MedDRA preferred terms "Neoplasm Progression" and "Malignant Neoplasm Progression" not related to the drug are excluded.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

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付録 2.7.4- 141 治験薬の投与中止に至った有害事象の一覧
024 試験（安全性解析対象集団）

Listing of Subjects With Adverse Events Resulting in Treatment Discontinuation
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
Pembrolizumab									
Trial Number=3475-024, Site Number=0045, Subject ID=244518, Gender=F, Race=White, Age=68 Years, Rel Day of Last Recorded Dose of Study Medication=21									
244518	Treatment Cycle 1	11	Pneumonitis	Continuing	2	Y	Y	Discontinued	Not Resolved
Trial Number=3475-024, Site Number=0048, Subject ID=244540, Gender=F, Race=White, Age=50 Years, Rel Day of Last Recorded Dose of Study Medication=106									
244540	Safety Follow-up	127	Pneumonia	5 Days	5	Y	N	Discontinued	Fatal
Trial Number=3475-024, Site Number=0064, Subject ID=245110, Gender=F, Race=White, Age=70 Years, Rel Day of Last Recorded Dose of Study Medication=1									
245110	Safety Follow-up	3	Vomiting	1.57 Weeks	3	Y	Y	Discontinued	Resolved
Trial Number=3475-024, Site Number=0065, Subject ID=245206, Gender=M, Race=White, Age=62 Years, Rel Day of Last Recorded Dose of Study Medication=190									
245206	Safety Follow-up	193	Cardiac arrest	2 Hours	5	Y	N	Discontinued	Fatal
Trial Number=3475-024, Site Number=0081, Subject ID=244508, Gender=F, Race=White, Age=76 Years, Rel Day of Last Recorded Dose of Study Medication=133									
244508	Safety Follow-up	137	Transaminases increased	1.05 Months	3	Y	Y	Discontinued	Resolved
Trial Number=3475-024, Site Number=0123, Subject ID=244210, Gender=M, Race=White, Age=73 Years, Rel Day of Last Recorded Dose of Study Medication=209									
244210	Safety Follow-up	230	Pneumonitis	4.14 Weeks	2	N	Y	Discontinued	Resolved
Trial Number=3475-024, Site Number=0123, Subject ID=245122, Gender=M, Race=White, Age=46 Years, Rel Day of Last Recorded Dose of Study Medication=1									
245122	Safety Follow-up	7	Haemorrhagic stroke	4 Days	5	Y	N	Discontinued	Fatal
Trial Number=3475-024, Site Number=0132, Subject ID=245163, Gender=F, Race=White, Age=76 Years, Rel Day of Last Recorded Dose of Study Medication=75									
245163	Safety Follow-up	102	Alanine aminotransferase increased	2.57 Weeks	1	Y	Y	Discontinued	Resolved

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Listing of Subjects With Adverse Events Resulting in Treatment Discontinuation (ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
Pembrolizumab									
Trial Number=3475-024, Site Number=0142, Subject ID=244501, Gender=M, Race=White, Age=69 Years, Rel Day of Last Recorded Dose of Study Medication=1									
244501	Safety Follow-up	18	Pneumonitis	3.42 Months	4	Y	Y	Discontinued	Resolved
Trial Number=3475-024, Site Number=0174, Subject ID=244807, Gender=F, Race=White, Age=77 Years, Rel Day of Last Recorded Dose of Study Medication=1									
244807	Safety Follow-up	11	Pneumonitis	1.14 Weeks	3	Y	Y	Discontinued	Resolved
Trial Number=3475-024, Site Number=0176, Subject ID=245193, Gender=F, Race=Black Or African American, Age=65 Years, Rel Day of Last Recorded Dose of Study Medication=1									
245193	Safety Follow-up	2	Sudden death	1 Days	5	Y	Y	Discontinued	Fatal
Trial Number=3475-024, Site Number=0202, Subject ID=244521, Gender=F, Race=White, Age=53 Years, Rel Day of Last Recorded Dose of Study Medication=296									
244521	Safety Follow-up	303	Pneumonitis	2.1 Months	3	Y	Y	Discontinued	Resolved
Trial Number=3475-024, Site Number=0252, Subject ID=243913, Gender=M, Race=Asian, Age=58 Years, Rel Day of Last Recorded Dose of Study Medication=1									
243913	Safety Follow-up	7	Pneumonitis	Continuing	4	Y	Y	Discontinued	Not Resolved
Trial Number=3475-024, Site Number=0260, Subject ID=243902, Gender=F, Race=Asian, Age=71 Years, Rel Day of Last Recorded Dose of Study Medication=188									
243902	Treatment Cycle 6	104	Fatigue	Continuing	3	Y	Y	Discontinued	Not Resolved
SOC									
Trial Number=3475-024, Site Number=0005, Subject ID=245200, Gender=F, Race=White, Age=57 Years, Rel Day of Last Recorded Dose of Study Medication=274									
245200	Treatment Cycle 5	87	Fatigue	2 Weeks	3	N	Y	Discontinued	Resolved
Trial Number=3475-024, Site Number=0030, Subject ID=244801, Gender=M, Race=White, Age=73 Years, Rel Day of Last Recorded Dose of Study Medication=1									

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Listing of Subjects With Adverse Events Resulting in Treatment Discontinuation
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
SOC									
Trial Number=3475-024, Site Number=0030, Subject ID=244801, Gender=M, Race=White, Age=73 Years, Rel Day of Last Recorded Dose of Study Medication=1									
244801	Safety Follow-up	7	Pneumonia	3.86 Weeks	3	Y	N	Discontinued	Resolved
Trial Number=3475-024, Site Number=0030, Subject ID=245219, Gender=M, Race=White, Age=80 Years, Rel Day of Last Recorded Dose of Study Medication=210									
245219	Safety Follow-up	116	Lethargy	1.12 Months	2	N	Y	Discontinued	Resolved
Trial Number=3475-024, Site Number=0035, Subject ID=244563, Gender=M, Race=White, Age=53 Years, Rel Day of Last Recorded Dose of Study Medication=141									
244563	Treatment Cycle 5	111	Acute kidney injury	Continuing	3	Y	Y	Discontinued	Not Resolved
Trial Number=3475-024, Site Number=0035, Subject ID=245135, Gender=F, Race=White, Age=50 Years, Rel Day of Last Recorded Dose of Study Medication=416									
245135	Safety Follow-up	151	Vomiting	1.57 Weeks	2	N	Y	Discontinued	Resolved
Trial Number=3475-024, Site Number=0044, Subject ID=245148, Gender=F, Race=White, Age=60 Years, Rel Day of Last Recorded Dose of Study Medication=389									
245148	Treatment Cycle 1	9	Hypoacusis	2.73 Months	2	N	Y	Discontinued	Resolved
Trial Number=3475-024, Site Number=0044, Subject ID=245209, Gender=M, Race=White, Age=70 Years, Rel Day of Last Recorded Dose of Study Medication=241									
245209	Treatment Cycle 3	58	Coronary artery disease	3 Days	3	Y	N	Discontinued	Resolved
Trial Number=3475-024, Site Number=0045, Subject ID=244567, Gender=M, Race=White, Age=71 Years, Rel Day of Last Recorded Dose of Study Medication=1									
244567	Safety Follow-up	7	Blood creatinine increased	2.14 Weeks	1	N	Y	Discontinued	Resolved
		7	Peripheral sensory neuropathy	Continuing	2	N	Y	Discontinued	Resolving
		8	Enanthema	3.14 Weeks	2	N	Y	Discontinued	Resolved
Trial Number=3475-024, Site Number=0048, Subject ID=244211, Gender=M, Race=White, Age=63 Years, Rel Day of Last Recorded Dose of Study Medication=303									

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Listing of Subjects With Adverse Events Resulting in Treatment Discontinuation
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
SOC									
Trial Number=3475-024, Site Number=0048, Subject ID=244211, Gender=M, Race=White, Age=63 Years, Rel Day of Last Recorded Dose of Study Medication=303									
244211	Treatment Cycle 1	13	Febrile neutropenia	4 Days	3	Y	Y	Discontinued	Resolved
Trial Number=3475-024, Site Number=0048, Subject ID=244568, Gender=M, Race=White, Age=76 Years, Rel Day of Last Recorded Dose of Study Medication=7									
244568	Safety Follow-up	19	Pulmonary sepsis	1 Weeks	5	Y	Y	Discontinued	Fatal
Trial Number=3475-024, Site Number=0064, Subject ID=245112, Gender=M, Race=White, Age=59 Years, Rel Day of Last Recorded Dose of Study Medication=50									
245112	Treatment Cycle 3	50	Decreased appetite	3 Weeks	2	N	Y	Discontinued	Resolved
		50	Nausea	2.71 Weeks	2	N	Y	Discontinued	Resolved
Trial Number=3475-024, Site Number=0064, Subject ID=245168, Gender=M, Race=White, Age=59 Years, Rel Day of Last Recorded Dose of Study Medication=50									
245168	Safety Follow-up	64	Pulmonary embolism	23 Hours	5	Y	N	Discontinued	Fatal
Trial Number=3475-024, Site Number=0083, Subject ID=245231, Gender=M, Race=White, Age=77 Years, Rel Day of Last Recorded Dose of Study Medication=138									
245231	Treatment Cycle 4	86	Platelet count decreased	4 Weeks	2	N	Y	Discontinued	Resolved
Trial Number=3475-024, Site Number=0097, Subject ID=245127, Gender=M, Race=White, Age=74 Years, Rel Day of Last Recorded Dose of Study Medication=1									
245127	Safety Follow-up	31	Gait disturbance	Continuing	3	Y	Y	Discontinued	Not Resolved
Trial Number=3475-024, Site Number=0100, Subject ID=245169, Gender=F, Race=White, Age=52 Years, Rel Day of Last Recorded Dose of Study Medication=1									
245169	Safety Follow-up	22	C-reactive protein increased	Continuing	2	N	N	Discontinued	Not Resolved
		22	Leukocytosis	Continuing	3	Y	Y	Discontinued	Not Resolved
Trial Number=3475-024, Site Number=0127, Subject ID=244559, Gender=M, Race=White, Age=67 Years, Rel Day of Last Recorded Dose of Study Medication=213									

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Listing of Subjects With Adverse Events Resulting in Treatment Discontinuation
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
SOC									
Trial Number=3475-024, Site Number=0127, Subject ID=244559, Gender=M, Race=White, Age=67 Years, Rel Day of Last Recorded Dose of Study Medication=213									
244559	Treatment Cycle 8	180	Respiratory tract infection	5 Days	3	Y	Y	Discontinued	Resolved
Trial Number=3475-024, Site Number=0132, Subject ID=245106, Gender=F, Race=White, Age=60 Years, Rel Day of Last Recorded Dose of Study Medication=134									
245106	Treatment Cycle 4	64	Fatigue	2.71 Weeks	2	N	Y	Discontinued	Resolved
	Treatment Cycle 6	133	Blood creatine increased	Continuing	1	N	Y	Discontinued	Not Resolved
Trial Number=3475-024, Site Number=0136, Subject ID=244554, Gender=F, Race=White, Age=70 Years, Rel Day of Last Recorded Dose of Study Medication=260									
244554	Safety Follow-up	273	Cerebral infarction	3 Days	2	Y	N	Discontinued	Resolved
Trial Number=3475-024, Site Number=0162, Subject ID=244535, Gender=M, Race=White, Age=71 Years, Rel Day of Last Recorded Dose of Study Medication=92									
244535	Treatment Cycle 4	85	Fatigue	1.18 Months	2	N	N	Discontinued	Resolved
Trial Number=3475-024, Site Number=0256, Subject ID=243916, Gender=M, Race=Asian, Age=68 Years, Rel Day of Last Recorded Dose of Study Medication=93									
243916	Treatment Cycle 3	46	Hypoxia	2.3 Hours	2	N	Y	Discontinued	Resolved
	Safety Follow-up	109	Pulmonary alveolar haemorrhage	4 Days	5	Y	Y	Discontinued	Fatal
Trial Number=3475-024, Site Number=0386, Subject ID=244548, Gender=M, Race=White, Age=56 Years, Rel Day of Last Recorded Dose of Study Medication=275									
244548	Treatment Cycle 1	8	Blood creatinine increased	2.14 Weeks	3	N	Y	Discontinued	Resolved

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Listing of Subjects With Adverse Events Resulting in Treatment Discontinuation
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
SOC									
Trial Number=3475-024, Site Number=0386, Subject ID=244548, Gender=M, Race=White, Age=56 Years, Rel Day of Last Recorded Dose of Study Medication=275									
244548	Treatment Cycle 1	8	Creatinine renal clearance decreased	3.43 Weeks	3	N	Y	Discontinued	Resolved

Toxicity Grade: NCI CTCAE version 4.03.

Related: Investigator-assessed relationship of the adverse event to study medication. Y = RELATED, N = NOT RELATED

Action Taken: Discontinued = DRUG WITHDRAWN, Interrupted = DRUG INTERRUPTED, Reduced = DOSE REDUCED, Increased = DOSE INCREASED, None = DOSE NOT CHANGED, N/A = NOT APPLICABLE.

Outcome: Resolved = RECOVERED/RESOLVED, Resolving = RECOVERING/RESOLVING, Sequelae = RECOVERED/RESOLVED WITH SEQUELAE, Not resolved = NOT RECOVERED/NOT RESOLVED.

MedDRA preferred terms "Neoplasm Progression" and "Malignant Neoplasm Progression" not related to the drug are excluded.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

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付録 2.7.4- 142 治験薬の休薬に至った有害事象
（いずれかの投与群で発現割合 0%超）
024 試験（安全性解析対象集団）

Subjects With Adverse Events Resulting in Treatment Interruption by Decreasing Incidence (Incidence >0% in One or More Treatment Groups) (ASaT Population)

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	154		150		304	
with one or more adverse events	53	(34.4)	51	(34.0)	104	(34.2)
with no adverse events	101	(65.6)	99	(66.0)	200	(65.8)
Anaemia	2	(1.3)	10	(6.7)	12	(3.9)
Neutropenia	0	(0.0)	12	(8.0)	12	(3.9)
Neutrophil count decreased	0	(0.0)	11	(7.3)	11	(3.6)
Diarrhoea	7	(4.5)	0	(0.0)	7	(2.3)
Dyspnoea	5	(3.2)	1	(0.7)	6	(2.0)
Platelet count decreased	0	(0.0)	6	(4.0)	6	(2.0)
Pneumonia	1	(0.6)	4	(2.7)	5	(1.6)
Pleural effusion	2	(1.3)	2	(1.3)	4	(1.3)
White blood cell count decreased	0	(0.0)	4	(2.7)	4	(1.3)
Alanine aminotransferase increased	3	(1.9)	0	(0.0)	3	(1.0)
Asthenia	1	(0.6)	2	(1.3)	3	(1.0)
Chronic obstructive pulmonary disease	3	(1.9)	0	(0.0)	3	(1.0)
Fatigue	1	(0.6)	2	(1.3)	3	(1.0)
Thrombocytopenia	0	(0.0)	3	(2.0)	3	(1.0)
Transaminases increased	3	(1.9)	0	(0.0)	3	(1.0)
Acute kidney injury	0	(0.0)	2	(1.3)	2	(0.7)
Aspartate aminotransferase increased	2	(1.3)	0	(0.0)	2	(0.7)
Blood creatinine increased	0	(0.0)	2	(1.3)	2	(0.7)
Cardiac failure	1	(0.6)	1	(0.7)	2	(0.7)
Cough	1	(0.6)	1	(0.7)	2	(0.7)
Decreased appetite	2	(1.3)	0	(0.0)	2	(0.7)
Diabetes mellitus	2	(1.3)	0	(0.0)	2	(0.7)
Hyponatraemia	2	(1.3)	0	(0.0)	2	(0.7)
Hypothyroidism	2	(1.3)	0	(0.0)	2	(0.7)
Leukopenia	0	(0.0)	2	(1.3)	2	(0.7)
Oedema peripheral	1	(0.6)	1	(0.7)	2	(0.7)
Pericardial effusion	2	(1.3)	0	(0.0)	2	(0.7)
Pneumonitis	2	(1.3)	0	(0.0)	2	(0.7)
Rash	2	(1.3)	0	(0.0)	2	(0.7)
Respiratory tract infection	1	(0.6)	1	(0.7)	2	(0.7)
Urticaria	2	(1.3)	0	(0.0)	2	(0.7)
Amylase increased	1	(0.6)	0	(0.0)	1	(0.3)
Appendicitis	0	(0.0)	1	(0.7)	1	(0.3)
Arthralgia	1	(0.6)	0	(0.0)	1	(0.3)
Asymptomatic bacteriuria	1	(0.6)	0	(0.0)	1	(0.3)
Atrial fibrillation	0	(0.0)	1	(0.7)	1	(0.3)
Bilirubin conjugated increased	1	(0.6)	0	(0.0)	1	(0.3)
Bladder neoplasm	0	(0.0)	1	(0.7)	1	(0.3)
Blood alkaline phosphatase increased	1	(0.6)	0	(0.0)	1	(0.3)
Concussion	0	(0.0)	1	(0.7)	1	(0.3)

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Subjects With Adverse Events Resulting in Treatment Interruption by Decreasing Incidence (Incidence >0% in One or More Treatment Groups) (ASaT Population)

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Device related infection	1	(0.6)	0	(0.0)	1	(0.3)
Diabetic ketoacidosis	1	(0.6)	0	(0.0)	1	(0.3)
Dizziness	1	(0.6)	0	(0.0)	1	(0.3)
Dysphagia	0	(0.0)	1	(0.7)	1	(0.3)
Eye pain	0	(0.0)	1	(0.7)	1	(0.3)
Facial bones fracture	0	(0.0)	1	(0.7)	1	(0.3)
Gait disturbance	0	(0.0)	1	(0.7)	1	(0.3)
Gamma-glutamyltransferase increased	1	(0.6)	0	(0.0)	1	(0.3)
Gastric ulcer	1	(0.6)	0	(0.0)	1	(0.3)
Gastrointestinal carcinoma	1	(0.6)	0	(0.0)	1	(0.3)
General physical health deterioration	0	(0.0)	1	(0.7)	1	(0.3)
Haematemesis	1	(0.6)	0	(0.0)	1	(0.3)
Haemoptysis	1	(0.6)	0	(0.0)	1	(0.3)
Hepatic enzyme increased	1	(0.6)	0	(0.0)	1	(0.3)
Hypertension	1	(0.6)	0	(0.0)	1	(0.3)
Hypoalbuminaemia	1	(0.6)	0	(0.0)	1	(0.3)
Hypophysitis	1	(0.6)	0	(0.0)	1	(0.3)
Infected neoplasm	1	(0.6)	0	(0.0)	1	(0.3)
Infection	0	(0.0)	1	(0.7)	1	(0.3)
Infusion related reaction	0	(0.0)	1	(0.7)	1	(0.3)
Infusion site extravasation	0	(0.0)	1	(0.7)	1	(0.3)
Lichenoid keratosis	1	(0.6)	0	(0.0)	1	(0.3)
Lower respiratory tract infection	0	(0.0)	1	(0.7)	1	(0.3)
Lower respiratory tract inflammation	1	(0.6)	0	(0.0)	1	(0.3)
Lung infection	0	(0.0)	1	(0.7)	1	(0.3)
Lymphoedema	1	(0.6)	0	(0.0)	1	(0.3)
Malaise	0	(0.0)	1	(0.7)	1	(0.3)
Muscular weakness	1	(0.6)	0	(0.0)	1	(0.3)
Musculoskeletal pain	1	(0.6)	0	(0.0)	1	(0.3)
Myositis	1	(0.6)	0	(0.0)	1	(0.3)
Nausea	0	(0.0)	1	(0.7)	1	(0.3)
Neuropathy peripheral	0	(0.0)	1	(0.7)	1	(0.3)
Organising pneumonia	1	(0.6)	0	(0.0)	1	(0.3)
Oropharyngeal pain	0	(0.0)	1	(0.7)	1	(0.3)
Painful respiration	1	(0.6)	0	(0.0)	1	(0.3)
Pancreatitis	1	(0.6)	0	(0.0)	1	(0.3)
Pericarditis	1	(0.6)	0	(0.0)	1	(0.3)
Pneumonia bacterial	1	(0.6)	0	(0.0)	1	(0.3)
Psoriasis	1	(0.6)	0	(0.0)	1	(0.3)
Pulmonary oedema	0	(0.0)	1	(0.7)	1	(0.3)
Radiation oesophagitis	0	(0.0)	1	(0.7)	1	(0.3)
Rash generalised	0	(0.0)	1	(0.7)	1	(0.3)
Rash maculo-papular	1	(0.6)	0	(0.0)	1	(0.3)
Renal impairment	1	(0.6)	0	(0.0)	1	(0.3)

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Subjects With Adverse Events Resulting in Treatment Interruption by Decreasing Incidence (Incidence >0% in One or More Treatment Groups) (ASaT Population)

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Septic shock	0	(0.0)	1	(0.7)	1	(0.3)
Sialoadenitis	1	(0.6)	0	(0.0)	1	(0.3)
Skin infection	0	(0.0)	1	(0.7)	1	(0.3)
Tachycardia	1	(0.6)	0	(0.0)	1	(0.3)
Thoracic vertebral fracture	1	(0.6)	0	(0.0)	1	(0.3)
Thyroiditis	1	(0.6)	0	(0.0)	1	(0.3)
Toxic skin eruption	1	(0.6)	0	(0.0)	1	(0.3)
Tubulointerstitial nephritis	1	(0.6)	0	(0.0)	1	(0.3)
Upper respiratory tract infection	1	(0.6)	0	(0.0)	1	(0.3)
Upper respiratory tract inflammation	0	(0.0)	1	(0.7)	1	(0.3)
Urinary tract infection	0	(0.0)	1	(0.7)	1	(0.3)
Vocal cord paralysis	1	(0.6)	0	(0.0)	1	(0.3)
Vomiting	0	(0.0)	1	(0.7)	1	(0.3)

Every subject is counted a single time for each applicable specific adverse event.
A system organ class appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
MedDRA preferred terms "Neoplasm Progression" and "Malignant Neoplasm Progression" not related to the drug are excluded.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

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付録 2.7.4- 143 治験薬の休薬に至った有害事象の一覧
024 試験（安全性解析対象集団）

Listing of Subjects With Adverse Events Resulting in Treatment Interruption
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
Pembrolizumab									
Trial Number=3475-024, Site Number=0002, Subject ID=245144, Gender=F, Race=White, Age=66 Years, Rel Day of Last Recorded Dose of Study Medication=395									
245144	Treatment Cycle 2	39	Diarrhoea	1.02 Months	3	N	Y	Interrupted	Resolved
	Treatment Cycle 3	73	Diarrhoea	1 Weeks	2	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0004, Subject ID=244572, Gender=M, Race=White, Age=53 Years, Rel Day of Last Recorded Dose of Study Medication=169									
244572	Treatment Cycle 8	167	Myositis	Continuing	2	N	Y	Interrupted	Resolving
Trial Number=3475-024, Site Number=0004, Subject ID=244828, Gender=F, Race=White, Age=59 Years, Rel Day of Last Recorded Dose of Study Medication=266									
244828	Treatment Cycle 4	83	Hypothyroidism	Continuing	2	N	Y	Interrupted	Not Resolved
		83	Transaminases increased	1.41 Months	3	N	Y	Interrupted	Resolved
	Treatment Cycle 7	159	Haemoptysis	5 Days	3	Y	N	Interrupted	Resolved
	Treatment Cycle 8	217	Lymphoedema	2.57 Weeks	2	N	Y	Interrupted	Resolved
	Treatment Cycle 9	236	Transaminases increased	Continuing	2	N	Y	Interrupted	Resolving
Trial Number=3475-024, Site Number=0005, Subject ID=244207, Gender=M, Race=White, Age=68 Years, Rel Day of Last Recorded Dose of Study Medication=321									
244207	Treatment Cycle 8	165	Sialoadenitis	3.57 Weeks	3	N	N	Interrupted	Resolved
	Treatment Cycle 15	325	Diarrhoea	Continuing	3	N	Y	Interrupted	Not Resolved
Trial Number=3475-024, Site Number=0005, Subject ID=245125, Gender=F, Race=White, Age=46 Years, Rel Day of Last Recorded Dose of Study Medication=443									
245125	Treatment Cycle 19	419	Upper respiratory tract infection	3.57 Weeks	2	N	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0005, Subject ID=245205, Gender=F, Race=White, Age=60 Years, Rel Day of Last Recorded Dose of Study Medication=257									
245205	Treatment Cycle 2	44	Hepatic enzyme increased	2.33 Months	3	Y	Y	Interrupted	Resolved

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Listing of Subjects With Adverse Events Resulting in Treatment Interruption
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
Pembrolizumab									
Trial Number=3475-024, Site Number=0007, Subject ID=244216, Gender=M, Race=White, Age=43 Years, Rel Day of Last Recorded Dose of Study Medication=232									
244216	Treatment Cycle 4	83	Diabetes mellitus	2.17 Months	3	Y	Y	Interrupted	Sequelae
		83	Diabetic ketoacidosis	2 Days	4	Y	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0007, Subject ID=244837, Gender=M, Race=Asian, Age=80 Years, Rel Day of Last Recorded Dose of Study Medication=162									
244837	Treatment Cycle 1	8	Lichenoid keratosis	Continuing	3	Y	Y	Interrupted	Resolving
	Treatment Cycle 7	182	Chronic obstructive pulmonary disease	Unknown	1	N	N	Interrupted	Unknown
		197	Hypophysitis	Unknown	3	Y	Y	Interrupted	Unknown
Trial Number=3475-024, Site Number=0007, Subject ID=245120, Gender=M, Race=White, Age=68 Years, Rel Day of Last Recorded Dose of Study Medication=472									
245120	Treatment Cycle 13	267	Chronic obstructive pulmonary disease	2 Weeks	3	Y	N	Interrupted	Resolved
		275	Thoracic vertebral fracture	Continuing	2	N	N	Interrupted	Not Resolved
Trial Number=3475-024, Site Number=0007, Subject ID=245141, Gender=M, Race=Asian, Age=36 Years, Rel Day of Last Recorded Dose of Study Medication=210									
245141	Treatment Cycle 6	143	Arthralgia	Continuing	2	N	N	Interrupted	Not Resolved
Trial Number=3475-024, Site Number=0028, Subject ID=245220, Gender=M, Race=Asian, Age=69 Years, Rel Day of Last Recorded Dose of Study Medication=102									
245220	Treatment Cycle 3	55	Tachycardia	6 Hours	1	N	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0030, Subject ID=244543, Gender=F, Race=White, Age=63 Years, Rel Day of Last Recorded Dose of Study Medication=298									
244543	Treatment Cycle 6	130	Cough	1.02 Months	2	N	N	Interrupted	Resolved
		130	Dyspnoea	1.02 Months	2	N	N	Interrupted	Sequelae
Trial Number=3475-024, Site Number=0030, Subject ID=245180, Gender=M, Race=White, Age=63 Years, Rel Day of Last Recorded Dose of Study Medication=326									

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Listing of Subjects With Adverse Events Resulting in Treatment Interruption
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
Pembrolizumab									
Trial Number=3475-024, Site Number=0030, Subject ID=245180, Gender=M, Race=White, Age=63 Years, Rel Day of Last Recorded Dose of Study Medication=326									
245180	Treatment Cycle 13	276	Diarrhoea	3.57 Weeks	2	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0039, Subject ID=245221, Gender=M, Race=White, Age=78 Years, Rel Day of Last Recorded Dose of Study Medication=37									
245221	Treatment Cycle 1	2	Asthenia	2.33 Months	3	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0044, Subject ID=245161, Gender=M, Race=White, Age=65 Years, Rel Day of Last Recorded Dose of Study Medication=349									
245161	Treatment Cycle 16	314	Gastrointestinal carcinoma	3.14 Weeks	3	Y	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0048, Subject ID=244541, Gender=M, Race=White, Age=55 Years, Rel Day of Last Recorded Dose of Study Medication=306									
244541	Treatment Cycle 12	252	Gamma-glutamyltransferase increased	Continuing	3	N	Y	Interrupted	Not Resolved
Trial Number=3475-024, Site Number=0064, Subject ID=245192, Gender=F, Race=White, Age=77 Years, Rel Day of Last Recorded Dose of Study Medication=293									
245192	Treatment Cycle 2	41	Diabetes mellitus	2.29 Weeks	3	Y	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0065, Subject ID=244566, Gender=M, Race=White, Age=58 Years, Rel Day of Last Recorded Dose of Study Medication=227									
244566	Treatment Cycle 2	44	Alanine aminotransferase increased	3.86 Weeks	1	Y	Y	Interrupted	Resolved
		44	Bilirubin conjugated increased	5 Days	2	Y	Y	Interrupted	Resolved
	Treatment Cycle 8	175	Hyponatraemia	3 Days	4	Y	N	Interrupted	Resolved
	Treatment Cycle 10	219	Hyponatraemia	2 Days	3	Y	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0081, Subject ID=244508, Gender=F, Race=White, Age=76 Years, Rel Day of Last Recorded Dose of Study Medication=133									
244508	Treatment Cycle 4	84	Transaminases increased	1 Weeks	3	N	Y	Interrupted	Resolved
	Treatment Cycle 5	100	Transaminases increased	3.86 Weeks	3	Y	Y	Interrupted	Resolved

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Listing of Subjects With Adverse Events Resulting in Treatment Interruption
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
Pembrolizumab									
Trial Number=3475-024, Site Number=0081, Subject ID=244539, Gender=M, Race=White, Age=33 Years, Rel Day of Last Recorded Dose of Study Medication=1									
244539	Safety Follow-up	8	Pancreatitis	1.15 Months	3	Y	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0081, Subject ID=245186, Gender=M, Race=White, Age=66 Years, Rel Day of Last Recorded Dose of Study Medication=310									
245186	Treatment Cycle 2	43	Thyroiditis	Continuing	2	N	Y	Interrupted	Not Resolved
	Treatment Cycle 4	115	Amylase increased	6 Days	4	N	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0082, Subject ID=244805, Gender=M, Race=White, Age=77 Years, Rel Day of Last Recorded Dose of Study Medication=435									
244805	Treatment Cycle 12	259	Muscular weakness	1.54 Months	1	N	N	Interrupted	Resolved
	Treatment Cycle 13	266	Musculoskeletal pain	Continuing	2	N	N	Interrupted	Resolving
Trial Number=3475-024, Site Number=0084, Subject ID=244201, Gender=M, Race=White, Age=63 Years, Rel Day of Last Recorded Dose of Study Medication=427									
244201	Treatment Cycle 5	111	Vocal cord paralysis	Continuing	2	N	N	Interrupted	Resolving
Trial Number=3475-024, Site Number=0086, Subject ID=245108, Gender=M, Race=White, Age=65 Years, Rel Day of Last Recorded Dose of Study Medication=1									
245108	Safety Follow-up	19	Pneumonitis	1.57 Weeks	2	Y	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0092, Subject ID=244550, Gender=F, Race=White, Age=68 Years, Rel Day of Last Recorded Dose of Study Medication=41									
244550	Treatment Cycle 1	26	Pericardial effusion	1.29 Weeks	3	Y	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0093, Subject ID=244571, Gender=F, Race=White, Age=71 Years, Rel Day of Last Recorded Dose of Study Medication=196									
244571	Treatment Cycle 2	41	Diarrhoea	4.17 Months	2	Y	Y	Interrupted	Resolved
	Treatment Cycle 4	168	Diarrhoea	1.43 Weeks	3	Y	Y	Interrupted	Resolved
		178	Diarrhoea	Continuing	1	N	Y	Interrupted	Not Resolved

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Listing of Subjects With Adverse Events Resulting in Treatment Interruption
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
Pembrolizumab									
Trial Number=3475-024, Site Number=0100, Subject ID=245115, Gender=M, Race=White, Age=60 Years, Rel Day of Last Recorded Dose of Study Medication=477									
245115	Treatment Cycle 20	400	Alanine aminotransferase increased	1.81 Months	2	N	Y	Interrupted	Resolved
		400	Aspartate aminotransferase increased	1.61 Months	2	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0123, Subject ID=244210, Gender=M, Race=White, Age=73 Years, Rel Day of Last Recorded Dose of Study Medication=209									
244210	Treatment Cycle 7	141	Pneumonitis	2.27 Months	2	Y	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0123, Subject ID=244565, Gender=M, Race=White, Age=59 Years, Rel Day of Last Recorded Dose of Study Medication=226									
244565	Treatment Cycle 8	150	Tubulointerstitial nephritis	1.84 Months	3	Y	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0123, Subject ID=244802, Gender=M, Race=White, Age=77 Years, Rel Day of Last Recorded Dose of Study Medication=468									
244802	Treatment Cycle 21	438	Dyspnoea	1.29 Weeks	2	N	N	Interrupted	Resolved
		438	Respiratory tract infection	1.29 Weeks	2	N	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0123, Subject ID=244810, Gender=M, Race=White, Age=62 Years, Rel Day of Last Recorded Dose of Study Medication=388									
244810	Treatment Cycle 9	180	Diarrhoea	1.71 Weeks	3	Y	Y	Interrupted	Resolved
	Treatment Cycle 12	268	Gastric ulcer	2.63 Months	3	Y	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0123, Subject ID=244823, Gender=F, Race=White, Age=53 Years, Rel Day of Last Recorded Dose of Study Medication=57									
244823	Treatment Cycle 1	22	Anaemia	Continuing	2	N	N	Interrupted	Resolving
		22	Asymptomatic bacteriuria	1.29 Weeks	2	N	N	Interrupted	Resolved
		22	Hyponatraemia	1.14 Weeks	1	N	Y	Interrupted	Resolved
		22	Toxic skin eruption	1.15 Months	3	N	N	Interrupted	Resolved
		33	Device related infection	1.71 Weeks	3	Y	N	Interrupted	Resolved

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Listing of Subjects With Adverse Events Resulting in Treatment Interruption
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
Pembrolizumab									
Trial Number=3475-024, Site Number=0126, Subject ID=245104, Gender=M, Race=White, Age=67 Years, Rel Day of Last Recorded Dose of Study Medication=561									
245104	Treatment Cycle 26	549	Rash	Continuing	2	N	Y	Interrupted	Resolving
Trial Number=3475-024, Site Number=0130, Subject ID=244215, Gender=M, Race=White, Age=58 Years, Rel Day of Last Recorded Dose of Study Medication=133									
244215	Treatment Cycle 5	106	Rash	3.02 Months	3	Y	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0132, Subject ID=245163, Gender=F, Race=White, Age=76 Years, Rel Day of Last Recorded Dose of Study Medication=75									
245163	Treatment Cycle 3	67	Hypothyroidism	2.1 Months	2	N	Y	Interrupted	Resolved
	Safety Follow-up	81	Fatigue	2.33 Months	2	N	Y	Interrupted	Resolved
		92	Diarrhoea	4 Weeks	2	N	Y	Interrupted	Resolved
		102	Decreased appetite	1.51 Months	1	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0132, Subject ID=245167, Gender=F, Race=White, Age=59 Years, Rel Day of Last Recorded Dose of Study Medication=134									
245167	Treatment Cycle 2	30	Psoriasis	Continuing	2	N	Y	Interrupted	Resolving
Trial Number=3475-024, Site Number=0136, Subject ID=245136, Gender=M, Race=White, Age=71 Years, Rel Day of Last Recorded Dose of Study Medication=407									
245136	Treatment Cycle 1	7	Pleural effusion	1.48 Months	3	Y	N	Interrupted	Sequelae
Trial Number=3475-024, Site Number=0142, Subject ID=244501, Gender=M, Race=White, Age=69 Years, Rel Day of Last Recorded Dose of Study Medication=1									
244501	Safety Follow-up	18	Pneumonia	3.57 Weeks	3	Y	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0168, Subject ID=245121, Gender=M, Race=White, Age=80 Years, Rel Day of Last Recorded Dose of Study Medication=154									
245121	Treatment Cycle 1	21	Alanine aminotransferase increased	4.14 Weeks	3	N	N	Interrupted	Resolved
		21	Aspartate aminotransferase increased	4.14 Weeks	2	N	N	Interrupted	Resolved

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Listing of Subjects With Adverse Events Resulting in Treatment Interruption
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
Pembrolizumab									
Trial Number=3475-024, Site Number=0168, Subject ID=245133, Gender=F, Race=White, Age=74 Years, Rel Day of Last Recorded Dose of Study Medication=60									
245133	Treatment Cycle 1	2	Dyspnoea	1.91 Months	2	N	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0174, Subject ID=245187, Gender=M, Race=White, Age=86 Years, Rel Day of Last Recorded Dose of Study Medication=130									
245187	Treatment Cycle 4	88	Blood alkaline phosphatase increased	1.41 Months	3	N	N	Interrupted	Resolved
	Safety Follow-up	150	Anaemia	Continuing	3	N	Y	Interrupted	Not Resolved
Trial Number=3475-024, Site Number=0180, Subject ID=245177, Gender=F, Race=White, Age=56 Years, Rel Day of Last Recorded Dose of Study Medication=323									
245177	Treatment Cycle 7	145	Dizziness	1.05 Months	2	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0252, Subject ID=243915, Gender=M, Race=Asian, Age=64 Years, Rel Day of Last Recorded Dose of Study Medication=33									
243915	Treatment Cycle 1	8	Pericardial effusion	3 Weeks	2	N	Y	Interrupted	Resolved
		8	Pericarditis	3.14 Weeks	2	N	Y	Interrupted	Resolved
		8	Pleural effusion	Continuing	2	N	Y	Interrupted	Not Resolved
		11	Oedema peripheral	Continuing	2	N	Y	Interrupted	Not Resolved
Trial Number=3475-024, Site Number=0252, Subject ID=243919, Gender=M, Race=Asian, Age=70 Years, Rel Day of Last Recorded Dose of Study Medication=253									
243919	Treatment Cycle 1	13	Urticaria	Continuing	2	N	Y	Interrupted	Resolving
	Treatment Cycle 2	50	Infected neoplasm	1.43 Weeks	3	Y	N	Interrupted	Resolved
	Treatment Cycle 9	206	Infected neoplasm	2.14 Weeks	2	N	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0256, Subject ID=243309, Gender=M, Race=Asian, Age=71 Years, Rel Day of Last Recorded Dose of Study Medication=289									
243309	Treatment Cycle 1	10	Pneumonia bacterial	1.43 Weeks	3	N	N	Interrupted	Resolved
	Treatment Cycle 11	228	Haematemesis	5 Days	1	N	N	Interrupted	Resolved

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Listing of Subjects With Adverse Events Resulting in Treatment Interruption
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
Pembrolizumab									
Trial Number=3475-024, Site Number=0257, Subject ID=243003, Gender=M, Race=Asian, Age=66 Years, Rel Day of Last Recorded Dose of Study Medication=231									
243003	Treatment Cycle 2	43	Decreased appetite	3 Weeks	3	Y	N	Interrupted	Resolved
		50	Renal impairment	1 Weeks	1	N	N	Interrupted	Resolved
	Treatment Cycle 4	112	Hypoalbuminaemia	Continuing	3	N	Y	Interrupted	Not Resolved
	Treatment Cycle 5	158	Dyspnoea	1.74 Months	2	N	N	Interrupted	Resolved
		174	Painful respiration	1.22 Months	3	Y	N	Interrupted	Resolved
		175	Cardiac failure	Continuing	3	Y	N	Interrupted	Resolving
Trial Number=3475-024, Site Number=0258, Subject ID=243312, Gender=F, Race=Asian, Age=40 Years, Rel Day of Last Recorded Dose of Study Medication=217									
243312	Treatment Cycle 2	36	Rash maculo-papular	Continuing	3	N	Y	Interrupted	Not Resolved
	Treatment Cycle 3	63	Urticaria	2.95 Hours	2	N	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0270, Subject ID=244576, Gender=M, Race=White, Age=62 Years, Rel Day of Last Recorded Dose of Study Medication=169									
244576	Treatment Cycle 9	181	Organising pneumonia	Continuing	3	Y	Y	Interrupted	Not Resolved
Trial Number=3475-024, Site Number=0301, Subject ID=244523, Gender=F, Race=White, Age=54 Years, Rel Day of Last Recorded Dose of Study Medication=317									
244523	Treatment Cycle 1	1	Hypertension	30 Minutes	1	N	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0301, Subject ID=244525, Gender=M, Race=White, Age=80 Years, Rel Day of Last Recorded Dose of Study Medication=245									
244525	Treatment Cycle 9	186	Chronic obstructive pulmonary disease	1.57 Weeks	3	Y	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0311, Subject ID=245203, Gender=F, Race=White, Age=54 Years, Rel Day of Last Recorded Dose of Study Medication=260									
245203	Treatment Cycle 9	189	Transaminases increased	4.14 Weeks	2	N	Y	Interrupted	Resolved

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Listing of Subjects With Adverse Events Resulting in Treatment Interruption
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
Pembrolizumab									
Trial Number=3475-024, Site Number=0330, Subject ID=245171, Gender=F, Race=White, Age=71 Years, Rel Day of Last Recorded Dose of Study Medication=338									
245171	Treatment Cycle 12	248	Lower respiratory tract inflammation	2.1 Months	1	N	Y	Interrupted	Resolved
		274	Dyspnoea	Continuing	2	N	N	Interrupted	Not Resolved
Trial Number=3475-024, Site Number=0338, Subject ID=243911, Gender=M, Race=Asian, Age=48 Years, Rel Day of Last Recorded Dose of Study Medication=298									
243911	Treatment Cycle 10	208	Diarrhoea	1.14 Weeks	1	N	Y	Interrupted	Resolved
SOC									
Trial Number=3475-024, Site Number=0005, Subject ID=245183, Gender=F, Race=White, Age=68 Years, Rel Day of Last Recorded Dose of Study Medication=221									
245183	Treatment Cycle 1	21	Neutropenia	1.14 Weeks	3	N	Y	Interrupted	Resolved
	Treatment Cycle 4	98	Neutrophil count decreased	3 Days	2	N	Y	Interrupted	Resolved
	Treatment Cycle 5	122	Neutropenia	5 Days	2	N	Y	Interrupted	Resolved
	Treatment Cycle 8	190	Pleural effusion	2.3 Months	2	N	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0006, Subject ID=244553, Gender=M, Race=White, Age=66 Years, Rel Day of Last Recorded Dose of Study Medication=176									
244553	Treatment Cycle 2	42	Neutropenia	1.29 Weeks	2	N	Y	Interrupted	Resolved
		42	White blood cell count decreased	1.29 Weeks	2	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0007, Subject ID=245119, Gender=F, Race=White, Age=73 Years, Rel Day of Last Recorded Dose of Study Medication=127									
245119	Treatment Cycle 1	15	Pleural effusion	Continuing	3	Y	N	Interrupted	Not Resolved
Trial Number=3475-024, Site Number=0011, Subject ID=245189, Gender=M, Race=White, Age=58 Years, Rel Day of Last Recorded Dose of Study Medication=1									
245189	Safety Follow-up	15	Acute kidney injury	1.29 Weeks	3	Y	Y	Interrupted	Resolved

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Listing of Subjects With Adverse Events Resulting in Treatment Interruption
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
SOC									
Trial Number=3475-024, Site Number=0011, Subject ID=245204, Gender=M, Race=White, Age=79 Years, Rel Day of Last Recorded Dose of Study Medication=259									
245204	Treatment Cycle 5	91	Skin infection	1.61 Months	3	Y	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0030, Subject ID=244811, Gender=M, Race=White, Age=80 Years, Rel Day of Last Recorded Dose of Study Medication=384									
244811	Treatment Cycle 2	42	Thrombocytopenia	1.29 Weeks	1	N	Y	Interrupted	Resolved
	Treatment Cycle 3	64	Dyspnoea	1.29 Weeks	2	N	Y	Interrupted	Resolved
		70	Thrombocytopenia	1.14 Weeks	1	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0030, Subject ID=245166, Gender=M, Race=White, Age=61 Years, Rel Day of Last Recorded Dose of Study Medication=350									
245166	Treatment Cycle 1	21	Neutropenia	2.14 Weeks	3	N	Y	Interrupted	Resolved
	Treatment Cycle 2	54	Thrombocytopenia	1.43 Weeks	1	N	Y	Interrupted	Resolved
	Treatment Cycle 3	98	Neutropenia	1.14 Weeks	3	N	Y	Interrupted	Resolved
	Treatment Cycle 5	134	Neutropenia	2 Weeks	3	N	Y	Interrupted	Resolved
	Study Medication Completion Follow-up	155	Thrombocytopenia	3 Weeks	1	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0030, Subject ID=245219, Gender=M, Race=White, Age=80 Years, Rel Day of Last Recorded Dose of Study Medication=210									
245219	Treatment Cycle 2	25	Fatigue	4.11 Months	3	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0035, Subject ID=245135, Gender=F, Race=White, Age=50 Years, Rel Day of Last Recorded Dose of Study Medication=416									
245135	Treatment Cycle 4	89	Neutropenia	1.57 Weeks	2	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0044, Subject ID=244218, Gender=M, Race=White, Age=38 Years, Rel Day of Last Recorded Dose of Study Medication=43									
244218	Treatment Cycle 2	29	Nausea	Continuing	3	N	Y	Interrupted	Not Resolved

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Listing of Subjects With Adverse Events Resulting in Treatment Interruption
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
SOC									
Trial Number=3475-024, Site Number=0044, Subject ID=245148, Gender=F, Race=White, Age=60 Years, Rel Day of Last Recorded Dose of Study Medication=389									
245148	Treatment Cycle 1	24	General physical health deterioration	1 Weeks	2	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0044, Subject ID=245188, Gender=F, Race=White, Age=67 Years, Rel Day of Last Recorded Dose of Study Medication=308									
245188	Treatment Cycle 1	23	Leukopenia	1 Weeks	2	N	Y	Interrupted	Resolved
		23	Neutropenia	1 Weeks	2	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0045, Subject ID=245215, Gender=F, Race=White, Age=75 Years, Rel Day of Last Recorded Dose of Study Medication=234									
245215	Treatment Cycle 3	61	Neutrophil count decreased	1 Weeks	2	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0046, Subject ID=244531, Gender=F, Race=White, Age=76 Years, Rel Day of Last Recorded Dose of Study Medication=120									
244531	Treatment Cycle 2	35	Pneumonia	1.71 Weeks	4	Y	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0048, Subject ID=244205, Gender=M, Race=White, Age=54 Years, Rel Day of Last Recorded Dose of Study Medication=392									
244205	Treatment Cycle 1	8	Pneumonia	2.14 Weeks	3	Y	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0048, Subject ID=244211, Gender=M, Race=White, Age=63 Years, Rel Day of Last Recorded Dose of Study Medication=303									
244211	Treatment Cycle 5	107	Infection	1 Weeks	2	N	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0075, Subject ID=244214, Gender=M, Race=White, Age=44 Years, Rel Day of Last Recorded Dose of Study Medication=135									
244214	Treatment Cycle 1	19	Radiation oesophagitis	1.71 Weeks	2	Y	N	Interrupted	Resolved
		24	Anaemia	2 Days	2	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0081, Subject ID=245134, Gender=M, Race=White, Age=70 Years, Rel Day of Last Recorded Dose of Study Medication=157									

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Listing of Subjects With Adverse Events Resulting in Treatment Interruption
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
SOC									
Trial Number=3475-024, Site Number=0081, Subject ID=245134, Gender=M, Race=White, Age=70 Years, Rel Day of Last Recorded Dose of Study Medication=157									
245134	Treatment Cycle 2	43	Neutrophil count decreased	1.14 Weeks	2	N	Y	Interrupted	Resolved
	Treatment Cycle 3	72	Anaemia	1.14 Weeks	2	N	Y	Interrupted	Resolved
		72	Neutrophil count decreased	1.14 Weeks	3	N	Y	Interrupted	Resolved
	Treatment Cycle 4	106	Neutrophil count decreased	1.14 Weeks	2	N	Y	Interrupted	Resolved
	Treatment Cycle 5	134	Anaemia	3 Days	2	N	Y	Interrupted	Resolved
		134	Neutrophil count decreased	3 Days	2	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0082, Subject ID=245132, Gender=M, Race=White, Age=49 Years, Rel Day of Last Recorded Dose of Study Medication=428									
245132	Treatment Cycle 2	32	Pneumonia	1.71 Weeks	3	Y	Y	Interrupted	Resolved
		39	Fatigue	1.64 Months	1	N	N	Interrupted	Resolved
	Treatment Cycle 3	59	Anaemia	Continuing	3	N	N	Interrupted	Resolving
	Treatment Cycle 6	151	Blood creatinine increased	3.65 Months	1	N	N	Interrupted	Resolved
	Treatment Cycle 14	316	Concussion	Continuing	1	N	N	Interrupted	Resolving
		316	Facial bones fracture	Continuing	1	N	N	Interrupted	Resolving
	Treatment Cycle 18	414	Blood creatinine increased	2.14 Weeks	1	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0086, Subject ID=244542, Gender=F, Race=White, Age=56 Years, Rel Day of Last Recorded Dose of Study Medication=316									
244542	Treatment Cycle 11	219	Dysphagia	1.15 Months	1	N	Y	Interrupted	Resolved
		219	Eye pain	1.15 Months	1	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0086, Subject ID=245146, Gender=M, Race=White, Age=62 Years, Rel Day of Last Recorded Dose of Study Medication=390									
245146	Treatment Cycle 1	5	Vomiting	3 Days	2	N	Y	Interrupted	Resolved

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Listing of Subjects With Adverse Events Resulting in Treatment Interruption
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
SOC									
Trial Number=3475-024, Site Number=0092, Subject ID=244833, Gender=M, Race=White, Age=76 Years, Rel Day of Last Recorded Dose of Study Medication=125									
244833	Treatment Cycle 2	21	Anaemia	Continuing	3	N	Y	Interrupted	Not Resolved
	Treatment Cycle 3	57	Appendicitis	2 Weeks	3	N	N	Interrupted	Resolved
	Treatment Cycle 5	105	Neutrophil count decreased	3 Weeks	3	N	Y	Interrupted	Resolved
		112	Platelet count decreased	2 Weeks	3	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0096, Subject ID=245176, Gender=F, Race=White, Age=57 Years, Rel Day of Last Recorded Dose of Study Medication=334									
245176	Treatment Cycle 3	70	Neutropenia	1.14 Weeks	2	N	Y	Interrupted	Resolved
	Treatment Cycle 4	98	Neutropenia	1.14 Weeks	2	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0098, Subject ID=244520, Gender=F, Race=White, Age=77 Years, Rel Day of Last Recorded Dose of Study Medication=354									
244520	Treatment Cycle 3	52	Anaemia	23 Hours	3	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0123, Subject ID=244836, Gender=M, Race=White, Age=54 Years, Rel Day of Last Recorded Dose of Study Medication=221									
244836	Treatment Cycle 4	85	Neutropenia	1.14 Weeks	2	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0127, Subject ID=244208, Gender=M, Race=White, Age=60 Years, Rel Day of Last Recorded Dose of Study Medication=320									
244208	Treatment Cycle 1	20	Neutrophil count decreased	2 Days	1	N	Y	Interrupted	Resolved
	Treatment Cycle 3	62	Neutropenia	1.08 Months	1	N	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0127, Subject ID=244559, Gender=M, Race=White, Age=67 Years, Rel Day of Last Recorded Dose of Study Medication=213									
244559	Treatment Cycle 6	119	Septic shock	2.71 Weeks	4	Y	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0130, Subject ID=244832, Gender=M, Race=White, Age=60 Years, Rel Day of Last Recorded Dose of Study Medication=219									

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Listing of Subjects With Adverse Events Resulting in Treatment Interruption
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
SOC									
Trial Number=3475-024, Site Number=0130, Subject ID=244832, Gender=M, Race=White, Age=60 Years, Rel Day of Last Recorded Dose of Study Medication=219									
244832	Treatment Cycle 1	12	Respiratory tract infection	2.71 Weeks	2	Y	N	Interrupted	Resolved
	Treatment Cycle 3	78	Neutropenia	1.22 Months	3	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0131, Subject ID=244522, Gender=F, Race=White, Age=53 Years, Rel Day of Last Recorded Dose of Study Medication=393									
244522	Treatment Cycle 17	352	Oropharyngeal pain	3.29 Weeks	1	N	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0131, Subject ID=245179, Gender=M, Race=White, Age=53 Years, Rel Day of Last Recorded Dose of Study Medication=323									
245179	Treatment Cycle 9	204	Lower respiratory tract infection	1.14 Weeks	1	N	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0133, Subject ID=244511, Gender=M, Race=White, Age=58 Years, Rel Day of Last Recorded Dose of Study Medication=192									
244511	Treatment Cycle 2	43	Neutrophil count decreased	1.29 Weeks	1	N	Y	Interrupted	Resolved
	Treatment Cycle 4	79	Infusion site extravasation	3 Days	1	N	Y	Interrupted	Resolved
		100	Neutrophil count decreased	1.14 Weeks	1	N	Y	Interrupted	Resolved
	Treatment Cycle 5	135	Blood creatinine increased	Continuing	1	N	Y	Interrupted	Resolving
		136	Neutropenia	Continuing	3	N	Y	Interrupted	Resolving
Trial Number=3475-024, Site Number=0136, Subject ID=244831, Gender=F, Race=White, Age=68 Years, Rel Day of Last Recorded Dose of Study Medication=51									
244831	Treatment Cycle 1	5	Urinary tract infection	4 Days	3	Y	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0136, Subject ID=245213, Gender=M, Race=White, Age=85 Years, Rel Day of Last Recorded Dose of Study Medication=182									
245213	Safety Follow-up	194	Pneumonia	5 Days	3	Y	N	Interrupted	Sequelae
Trial Number=3475-024, Site Number=0139, Subject ID=245181, Gender=F, Race=White, Age=65 Years, Rel Day of Last Recorded Dose of Study Medication=232									

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Listing of Subjects With Adverse Events Resulting in Treatment Interruption
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
SOC									
Trial Number=3475-024, Site Number=0139, Subject ID=245181, Gender=F, Race=White, Age=65 Years, Rel Day of Last Recorded Dose of Study Medication=232									
245181	Treatment Cycle 3	63	Anaemia	3.14 Weeks	2	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0155, Subject ID=244502, Gender=F, Race=White, Age=68 Years, Rel Day of Last Recorded Dose of Study Medication=511									
244502	Treatment Cycle 3	63	Platelet count decreased	1.22 Months	2	N	Y	Interrupted	Resolved
	Treatment Cycle 4	89	Neutrophil count decreased	1.57 Weeks	3	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0155, Subject ID=244560, Gender=F, Race=White, Age=55 Years, Rel Day of Last Recorded Dose of Study Medication=231									
244560	Treatment Cycle 4	82	Neutrophil count decreased	1.43 Weeks	2	N	Y	Interrupted	Resolved
		82	Platelet count decreased	1.43 Weeks	1	N	Y	Interrupted	Resolved
	Treatment Cycle 5	109	Neutrophil count decreased	1.29 Weeks	1	N	Y	Interrupted	Resolved
		109	Platelet count decreased	2.57 Weeks	2	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0166, Subject ID=245224, Gender=F, Race=White, Age=68 Years, Rel Day of Last Recorded Dose of Study Medication=205									
245224	Treatment Cycle 1	1	Infusion related reaction	40 Minutes	2	N	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0168, Subject ID=244804, Gender=F, Race=White, Age=73 Years, Rel Day of Last Recorded Dose of Study Medication=191									
244804	Treatment Cycle 1	9	Anaemia	Continuing	3	N	Y	Interrupted	Not Resolved
Trial Number=3475-024, Site Number=0202, Subject ID=245202, Gender=M, Race=White, Age=74 Years, Rel Day of Last Recorded Dose of Study Medication=33									
245202	Treatment Cycle 1	1	Anaemia	Continuing	3	Y	Y	Interrupted	Not Resolved
		11	Neutropenia	2.43 Weeks	4	N	Y	Interrupted	Resolved
		11	White blood cell count decreased	2.43 Weeks	3	N	Y	Interrupted	Resolved
		27	Gait disturbance	1 Weeks	1	N	N	Interrupted	Resolved

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Listing of Subjects With Adverse Events Resulting in Treatment Interruption
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
SOC									
Trial Number=3475-024, Site Number=0202, Subject ID=245202, Gender=M, Race=White, Age=74 Years, Rel Day of Last Recorded Dose of Study Medication=33									
245202	Safety Follow-up	54	Acute kidney injury	6 Days	2	Y	N	Interrupted	Resolved
		54	Atrial fibrillation	6 Days	4	Y	N	Interrupted	Resolved
		54	Cardiac failure	6 Days	3	Y	N	Interrupted	Resolved
		54	Pulmonary oedema	6 Days	4	Y	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0204, Subject ID=245175, Gender=F, Race=American Indian Or Alaska Native, Age=71 Years, Rel Day of Last Recorded Dose of Study Medication=206									
245175	Treatment Cycle 3	43	Neuropathy peripheral	3.81 Months	3	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0258, Subject ID=243922, Gender=M, Race=Asian, Age=68 Years, Rel Day of Last Recorded Dose of Study Medication=117									
243922	Treatment Cycle 1	9	Platelet count decreased	3 Weeks	2	N	Y	Interrupted	Resolved
		20	Neutrophil count decreased	1.43 Weeks	2	N	Y	Interrupted	Resolved
	Treatment Cycle 2	50	Malaise	5 Days	2	N	Y	Interrupted	Resolved
	Treatment Cycle 3	75	Anaemia	1.18 Months	3	N	Y	Interrupted	Resolved
		75	Neutrophil count decreased	1.14 Weeks	2	N	Y	Interrupted	Resolved
	Treatment Cycle 4	92	Lung infection	1.77 Months	3	Y	Y	Interrupted	Resolved
		110	Neutrophil count decreased	1.14 Weeks	2	N	Y	Interrupted	Resolved
	Safety Follow-up	145	Lung infection	2.56 Months	2	N	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0270, Subject ID=244530, Gender=F, Race=White, Age=62 Years, Rel Day of Last Recorded Dose of Study Medication=203									
244530	Treatment Cycle 1	12	Neutrophil count decreased	1.43 Weeks	2	N	Y	Interrupted	Resolved
		12	White blood cell count decreased	3 Weeks	2	N	Y	Interrupted	Resolved
	Treatment Cycle 3	72	Platelet count decreased	6 Days	2	N	N	Interrupted	Resolved
		78	Neutrophil count decreased	5 Days	1	N	Y	Interrupted	Resolved

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Listing of Subjects With Adverse Events Resulting in Treatment Interruption
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
SOC									
Trial Number=3475-024, Site Number=0323, Subject ID=244809, Gender=M, Race=White, Age=71 Years, Rel Day of Last Recorded Dose of Study Medication=34									
244809	Treatment Cycle 1	8	Thrombocytopenia	2.86 Weeks	4	N	Y	Interrupted	Resolved
		14	Leukopenia	4 Weeks	4	N	Y	Interrupted	Resolved
		14	Neutropenia	2.86 Weeks	4	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0330, Subject ID=244816, Gender=F, Race=White, Age=70 Years, Rel Day of Last Recorded Dose of Study Medication=351									
244816	Treatment Cycle 2	43	Neutrophil count decreased	6 Days	2	N	Y	Interrupted	Resolved
	Treatment Cycle 3	70	Neutrophil count decreased	1 Weeks	2	N	Y	Interrupted	Resolved
	Treatment Cycle 5	99	Oedema peripheral	3.55 Months	2	N	N	Interrupted	Resolved
	Treatment Cycle 6	133	Rash generalised	1.48 Months	2	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0330, Subject ID=245114, Gender=F, Race=White, Age=74 Years, Rel Day of Last Recorded Dose of Study Medication=381									
245114	Treatment Cycle 18	375	Bladder neoplasm	1.12 Months	3	Y	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0331, Subject ID=243308, Gender=M, Race=Asian, Age=69 Years, Rel Day of Last Recorded Dose of Study Medication=237									
243308	Treatment Cycle 1	12	Platelet count decreased	2.14 Weeks	1	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0331, Subject ID=243921, Gender=M, Race=Asian, Age=77 Years, Rel Day of Last Recorded Dose of Study Medication=1									
243921	Safety Follow-up	20	White blood cell count decreased	3 Days	3	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0335, Subject ID=243307, Gender=M, Race=Asian, Age=68 Years, Rel Day of Last Recorded Dose of Study Medication=274									
243307	Treatment Cycle 3	59	Upper respiratory tract inflammation	2.86 Weeks	2	N	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0340, Subject ID=243302, Gender=F, Race=Asian, Age=57 Years, Rel Day of Last Recorded Dose of Study Medication=483									

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Listing of Subjects With Adverse Events Resulting in Treatment Interruption
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
SOC									
Trial Number=3475-024, Site Number=0340, Subject ID=243302, Gender=F, Race=Asian, Age=57 Years, Rel Day of Last Recorded Dose of Study Medication=483									
243302	Treatment Cycle 11	227	Cough	Continuing	2	N	N	Interrupted	Not Resolved
Trial Number=3475-024, Site Number=0352, Subject ID=244203, Gender=M, Race=White, Age=71 Years, Rel Day of Last Recorded Dose of Study Medication=280									
244203	Treatment Cycle 3	44	Anaemia	Continuing	2	N	Y	Interrupted	Not Resolved
		65	Asthenia	4.14 Weeks	2	N	Y	Interrupted	Sequelae
Trial Number=3475-024, Site Number=0390, Subject ID=244212, Gender=M, Race=White, Age=67 Years, Rel Day of Last Recorded Dose of Study Medication=278									
244212	Treatment Cycle 5	106	Asthenia	2.14 Weeks	3	N	Y	Interrupted	Unknown

Toxicity Grade: NCI CTCAE version 4.03.

Related: Investigator-assessed relationship of the adverse event to study medication. Y = RELATED, N = NOT RELATED

Action Taken: Discontinued = DRUG WITHDRAWN, Interrupted = DRUG INTERRUPTED, Reduced = DOSE REDUCED, Increased = DOSE INCREASED, None = DOSE NOT CHANGED, N/A = NOT APPLICABLE.

Outcome: Resolved = RECOVERED/RESOLVED, Resolving = RECOVERING/RESOLVING, Sequelae = RECOVERED/RESOLVED WITH SEQUELAE, Not resolved = NOT RECOVERED/NOT RESOLVED.

MedDRA preferred terms "Neoplasm Progression" and "Malignant Neoplasm Progression" not related to the drug are excluded.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

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付録 2.7.4- 144 AEOSI に該当する有害事象のリスト（2016 年 5 月 2 日時点）

MK-3475
AEOSI Preferred Terms, Core RMST Approved List v 10.2
(02-May-2016)

This list is based on MedDRA version 19.0

Important Identified Risks

Pneumonitis
Acute interstitial pneumonitis, Interstitial lung disease, Pneumonitis, Idiopathic pneumonia syndrome

Colitis
Colitis, Colitis microscopic, Enterocolitis, Enterocolitis haemorrhagic, Necrotising colitis, Colitis erosive

Hepatitis
Hepatitis, Autoimmune hepatitis, Hepatitis acute, Hepatitis fulminant, Drug-induced liver injury

Nephritis
Nephritis, Autoimmune nephritis, Chronic autoimmune glomerulonephritis, Fibrillary glomerulonephritis, Focal segmental glomerulosclerosis, Glomerulonephritis, Glomerulonephritis acute, Glomerulonephritis membranoproliferative, Glomerulonephritis membranous, Glomerulonephritis minimal lesion, Glomerulonephritis proliferative, Glomerulonephritis rapidly progressive, Mesangioproliferative glomerulonephritis, Nephritis haemorrhagic, Tubulointerstitial nephritis, Nephrotic syndrome

Endocrine Disorders

Adrenal Insufficiency
Adrenal insufficiency, Adrenocortical insufficiency acute, Secondary adrenocortical insufficiency

Hypophysitis
Hypophysitis, Hypopituitarism, Lymphocytic hypophysitis

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Hyperthyroidism
Hyperthyroidism, Basedow's disease, Thyrotoxic crisis

Hypothyroidism
Hypothyroidism, Hypothyroidic goitre, Myxoedema, Myxoedema coma, Primary hypothyroidism

Thyroiditis
Thyroid disorder, Thyroiditis, Autoimmune thyroiditis, Thyroiditis acute

Type 1 Diabetes Mellitus
Diabetic ketoacidosis, Diabetic ketoacidotic hyperglycaemic coma, Fulminant type 1 diabetes mellitus, Latent autoimmune diabetes in adults, Type 1 diabetes mellitus

Other Immune-mediated Events:

Uveitis
Iritis, Uveitis, Cyclitis, Autoimmune uveitis, Iridocyclitis,

Pancreatitis
Pancreatitis, Autoimmune pancreatitis, Pancreatitis acute, Pancreatitis haemorrhagic, Pancreatitis necrotising

Myositis
Myositis, Necrotising myositis, Polymyositis, Immune-mediated necrotising myopathy, Rhabdomyolysis, Myopathy

Guillain-Barre Syndrome
Demyelinating polyneuropathy, Guillain-Barre syndrome, Axonal neuropathy, Multifocal motor neuropathy, Polyneuropathy idiopathic progressive, Miller Fisher syndrome

Severe Skin Reactions
Any grade from Severe cutaneous reactions SMQ narrow: Acute generalised exanthematous pustulosis, Cutaneous vasculitis, Dermatitis bullous, Dermatitis exfoliative, Dermatitis exfoliative generalised, Drug reaction with eosinophilia and systemic symptoms, Epidermal necrosis, Erythema multiforme, Exfoliative rash, Oculomucocutaneous syndrome,

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Skin necrosis, Stevens-Johnson syndrome, Toxic epidermal necrolysis and Toxic skin eruption;

If grade 3 or higher: Any event from the Epidermal and dermal conditions HLGT of the Skin and subcutaneous tissue disorders SOC.

Infusion Reactions
Hypersensitivity, Drug hypersensitivity, Anaphylactic reaction, Cytokine release syndrome, Serum sickness, Serum sickness-like reaction, Infusion related reaction,

Important Potential Risk(s)

Myasthenic Syndrome
Myasthenic syndrome, Myasthenia gravis, Myasthenia gravis crisis, Ocular myasthenia

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付録 2.7.4- 145 AEOSI の要約

024 試験（安全性解析対象集団）

Adverse Event Summary
AEOSI
(ASaT Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	154		150	
with one or more adverse events	45	(29.2)	7	(4.7)
with no adverse event	109	(70.8)	143	(95.3)
with drug-related† adverse events	39	(25.3)	3	(2.0)
with toxicity grade 3-5 adverse events	15	(9.7)	1	(0.7)
with toxicity grade 3-5 drug-related adverse events	13	(8.4)	1	(0.7)
with serious adverse events	17	(11.0)	1	(0.7)
with serious drug-related adverse events	16	(10.4)	1	(0.7)
who died	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	6	(3.9)	0	(0.0)
discontinued due to a drug-related adverse event	6	(3.9)	0	(0.0)
discontinued due to a serious adverse event	5	(3.2)	0	(0.0)
discontinued due to a serious drug-related adverse event	5	(3.2)	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

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付録 2.7.4- 146 Grade 3 以上の AEOSI

024 試験（安全性解析対象集団）

Subjects With Grade 3-5 Adverse Events by Decreasing Incidence
(Incidence >0% in One or More Treatment Groups)
AEOSI
(ASaT Population)

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	154		150		304	
with one or more adverse events	15	(9.7)	1	(0.7)	16	(5.3)
with no adverse events	139	(90.3)	149	(99.3)	288	(94.7)
Pneumonitis	4	(2.6)	1	(0.7)	5	(1.6)
Skin-A	5	(3.2)	0	(0.0)	5	(1.6)
Colitis	2	(1.3)	0	(0.0)	2	(0.7)
Hypophysitis	1	(0.6)	0	(0.0)	1	(0.3)
Nephritis	1	(0.6)	0	(0.0)	1	(0.3)
Pancreatitis	1	(0.6)	0	(0.0)	1	(0.3)
Skin-B	1	(0.6)	0	(0.0)	1	(0.3)
Type 1 Diabetes Mellitus	1	(0.6)	0	(0.0)	1	(0.3)

Every subject is counted a single time for each applicable specific adverse event.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

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付録 2.7.4- 147 AEOSI を発現した患者の一覧

024 試験（安全性解析対象集団）

Listing of Subjects With Adverse Events
AEOSI
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
Pembrolizumab									
Trial Number=3475-024, Site Number=0004, Subject ID=244572, Gender=M, Race=White, Age=53 Years, Rel Day of Last Recorded Dose of Study Medication=169									
244572	Treatment Cycle 8	167	Myositis	Continuing	2	N	Y	Interrupted	Resolving
Trial Number=3475-024, Site Number=0004, Subject ID=244828, Gender=F, Race=White, Age=59 Years, Rel Day of Last Recorded Dose of Study Medication=266									
244828	Treatment Cycle 2	27	Hyperthyroidism	1.87 Months	2	N	Y	None	Resolved
	Treatment Cycle 4	83	Hypothyroidism	Continuing	2	N	Y	Interrupted	Not Resolved
Trial Number=3475-024, Site Number=0007, Subject ID=244216, Gender=M, Race=White, Age=43 Years, Rel Day of Last Recorded Dose of Study Medication=232									
244216	Treatment Cycle 1	16	Hypothyroidism	Continuing	2	N	Y	None	Not Resolved
	Treatment Cycle 4	83	Diabetic ketoacidosis	2 Days	4	Y	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0007, Subject ID=244837, Gender=M, Race=Asian, Age=80 Years, Rel Day of Last Recorded Dose of Study Medication=162									
244837	Treatment Cycle 3	62	Hyperthyroidism	1.64 Months	1	N	Y	None	Resolved
	Treatment Cycle 4	112	Hypothyroidism	Unknown	2	N	N	None	Unknown
	Treatment Cycle 7	197	Hypophysitis	Unknown	3	Y	Y	Interrupted	Unknown
Trial Number=3475-024, Site Number=0007, Subject ID=245150, Gender=F, Race=White, Age=67 Years, Rel Day of Last Recorded Dose of Study Medication=253									
245150	Treatment Cycle 11	246	Myopathy	Continuing	1	N	N	None	Not Resolved
Trial Number=3475-024, Site Number=0028, Subject ID=245220, Gender=M, Race=Asian, Age=69 Years, Rel Day of Last Recorded Dose of Study Medication=102									
245220	Treatment Cycle 1	14	Rash	6 Days	3	N	N	None	Resolved
Trial Number=3475-024, Site Number=0030, Subject ID=244543, Gender=F, Race=White, Age=63 Years, Rel Day of Last Recorded Dose of Study Medication=298									

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Listing of Subjects With Adverse Events
AEOSI
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
Pembrolizumab									
Trial Number=3475-024, Site Number=0030, Subject ID=244543, Gender=F, Race=White, Age=63 Years, Rel Day of Last Recorded Dose of Study Medication=298									
244543	Treatment Cycle 14	307	Hypersensitivity	1.14 Weeks	2	N	N	None	Resolved
Trial Number=3475-024, Site Number=0030, Subject ID=245180, Gender=M, Race=White, Age=63 Years, Rel Day of Last Recorded Dose of Study Medication=326									
245180	Treatment Cycle 5	108	Hypothyroidism	Continuing	1	N	Y	None	Not Resolved
Trial Number=3475-024, Site Number=0039, Subject ID=245154, Gender=F, Race=White, Age=62 Years, Rel Day of Last Recorded Dose of Study Medication=385									
245154	Treatment Cycle 17	360	Myositis	Continuing	2	N	N	None	Not Resolved
Trial Number=3475-024, Site Number=0044, Subject ID=244835, Gender=M, Race=White, Age=63 Years, Rel Day of Last Recorded Dose of Study Medication=20									
244835	Treatment Cycle 1	7	Colitis	Continuing	3	Y	Y	N/A	Not Resolved
Trial Number=3475-024, Site Number=0045, Subject ID=244518, Gender=F, Race=White, Age=68 Years, Rel Day of Last Recorded Dose of Study Medication=21									
244518	Treatment Cycle 1	11	Pneumonitis	Continuing	2	Y	Y	Discontinued	Not Resolved
Trial Number=3475-024, Site Number=0046, Subject ID=244557, Gender=M, Race=White, Age=61 Years, Rel Day of Last Recorded Dose of Study Medication=253									
244557	Treatment Cycle 1	1	Hypersensitivity	1 Hours	1	N	Y	None	Resolved
	Treatment Cycle 3	59	Pneumonitis	1.97 Months	1	N	Y	None	Resolved
Trial Number=3475-024, Site Number=0064, Subject ID=245138, Gender=F, Race=White, Age=57 Years, Rel Day of Last Recorded Dose of Study Medication=421									
245138	Treatment Cycle 6	106	Hyperthyroidism	1.41 Months	1	N	Y	None	Resolved
	Treatment Cycle 8	148	Hypothyroidism	Continuing	1	N	Y	None	Resolving

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Listing of Subjects With Adverse Events
AEOSI
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
Pembrolizumab									
Trial Number=3475-024, Site Number=0065, Subject ID=245206, Gender=M, Race=White, Age=62 Years, Rel Day of Last Recorded Dose of Study Medication=190									
245206	Treatment Cycle 1	21	Hyperthyroidism	1.38 Months	1	N	Y	None	Resolved
	Treatment Cycle 3	63	Hypothyroidism	Continuing	1	N	Y	None	Not Resolved
Trial Number=3475-024, Site Number=0069, Subject ID=244504, Gender=F, Race=White, Age=49 Years, Rel Day of Last Recorded Dose of Study Medication=425									
244504	Treatment Cycle 2	22	Hyperthyroidism	4.34 Months	2	Y	Y	None	Resolved
Trial Number=3475-024, Site Number=0074, Subject ID=245139, Gender=F, Race=White, Age=59 Years, Rel Day of Last Recorded Dose of Study Medication=401									
245139	Treatment Cycle 4	85	Hyperthyroidism	Continuing	2	N	Y	None	Not Resolved
		85	Thyroiditis	Continuing	2	N	Y	None	Not Resolved
Trial Number=3475-024, Site Number=0081, Subject ID=244508, Gender=F, Race=White, Age=76 Years, Rel Day of Last Recorded Dose of Study Medication=133									
244508	Treatment Cycle 4	63	Hyperthyroidism	1.15 Months	1	N	Y	None	Resolved
Trial Number=3475-024, Site Number=0081, Subject ID=244539, Gender=M, Race=White, Age=33 Years, Rel Day of Last Recorded Dose of Study Medication=1									
244539	Safety Follow-up	8	Pancreatitis	1.15 Months	3	Y	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0081, Subject ID=245186, Gender=M, Race=White, Age=66 Years, Rel Day of Last Recorded Dose of Study Medication=310									
245186	Treatment Cycle 2	43	Thyroiditis	Continuing	2	N	Y	Interrupted	Not Resolved
Trial Number=3475-024, Site Number=0082, Subject ID=244514, Gender=M, Race=White, Age=68 Years, Rel Day of Last Recorded Dose of Study Medication=422									
244514	Treatment Cycle 3	64	Thyroiditis	2.79 Months	1	N	Y	None	Resolved

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Listing of Subjects With Adverse Events
AEOSI
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
Pembrolizumab									
Trial Number=3475-024, Site Number=0086, Subject ID=245108, Gender=M, Race=White, Age=65 Years, Rel Day of Last Recorded Dose of Study Medication=1									
245108	Safety Follow-up	19	Pneumonitis	1.57 Weeks	2	Y	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0096, Subject ID=245214, Gender=F, Race=White, Age=67 Years, Rel Day of Last Recorded Dose of Study Medication=43									
245214	Treatment Cycle 1	21	Hypothyroidism	Continuing	1	N	Y	None	Not Resolved
Trial Number=3475-024, Site Number=0123, Subject ID=244210, Gender=M, Race=White, Age=73 Years, Rel Day of Last Recorded Dose of Study Medication=209									
244210	Treatment Cycle 7	141	Pneumonitis	2.27 Months	2	Y	Y	Interrupted	Resolved
	Safety Follow-up	230	Pneumonitis	4.14 Weeks	2	N	Y	Discontinued	Resolved
Trial Number=3475-024, Site Number=0123, Subject ID=244565, Gender=M, Race=White, Age=59 Years, Rel Day of Last Recorded Dose of Study Medication=226									
244565	Treatment Cycle 8	150	Tubulointerstitial nephritis	1.84 Months	3	Y	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0123, Subject ID=244823, Gender=F, Race=White, Age=53 Years, Rel Day of Last Recorded Dose of Study Medication=57									
244823	Treatment Cycle 1	22	Toxic skin eruption	1.15 Months	3	N	N	Interrupted	Resolved
Trial Number=3475-024, Site Number=0123, Subject ID=245107, Gender=M, Race=White, Age=70 Years, Rel Day of Last Recorded Dose of Study Medication=379									
245107	Treatment Cycle 2	23	Hyperthyroidism	2.04 Months	1	N	N	None	Resolved
	Treatment Cycle 6	106	Hypothyroidism	5.52 Months	2	N	Y	None	Resolved
Trial Number=3475-024, Site Number=0126, Subject ID=245104, Gender=M, Race=White, Age=67 Years, Rel Day of Last Recorded Dose of Study Medication=561									
245104	Treatment Cycle 2	22	Psoriasis	Continuing	3	N	Y	None	Resolving

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Listing of Subjects With Adverse Events
AEOSI
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
Pembrolizumab									
Trial Number=3475-024, Site Number=0130, Subject ID=244215, Gender=M, Race=White, Age=58 Years, Rel Day of Last Recorded Dose of Study Medication=133									
244215	Treatment Cycle 5	106	Rash	3.02 Months	3	Y	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0132, Subject ID=245163, Gender=F, Race=White, Age=76 Years, Rel Day of Last Recorded Dose of Study Medication=75									
245163	Treatment Cycle 3	67	Hypothyroidism	2.1 Months	2	N	Y	Interrupted	Resolved
Trial Number=3475-024, Site Number=0133, Subject ID=244217, Gender=M, Race=White, Age=71 Years, Rel Day of Last Recorded Dose of Study Medication=233									
244217	Treatment Cycle 8	147	Hypothyroidism	Continuing	2	N	N	None	Resolving
Trial Number=3475-024, Site Number=0134, Subject ID=244204, Gender=F, Race=White, Age=70 Years, Rel Day of Last Recorded Dose of Study Medication=399									
244204	Treatment Cycle 3	62	Hyperthyroidism	2.79 Months	1	N	Y	None	Resolved
Trial Number=3475-024, Site Number=0142, Subject ID=244501, Gender=M, Race=White, Age=69 Years, Rel Day of Last Recorded Dose of Study Medication=1									
244501	Safety Follow-up	18	Pneumonitis	3.42 Months	4	Y	Y	Discontinued	Resolved
		21	Rash generalised	1.29 Weeks	3	N	Y	N/A	Resolved
Trial Number=3475-024, Site Number=0155, Subject ID=244574, Gender=F, Race=Black Or African American, Age=79 Years, Rel Day of Last Recorded Dose of Study Medication=43									
244574	Extended Safety Follow-up	91	Colitis	1.86 Weeks	3	Y	Y	None	Resolved
Trial Number=3475-024, Site Number=0174, Subject ID=244807, Gender=F, Race=White, Age=77 Years, Rel Day of Last Recorded Dose of Study Medication=1									
244807	Safety Follow-up	11	Pneumonitis	1.14 Weeks	3	Y	Y	Discontinued	Resolved

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Listing of Subjects With Adverse Events
AEOSI
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
Pembrolizumab									
Trial Number=3475-024, Site Number=0202, Subject ID=244521, Gender=F, Race=White, Age=53 Years, Rel Day of Last Recorded Dose of Study Medication=296									
244521	Treatment Cycle 4	64	Hyperthyroidism	2.79 Months	1	N	Y	None	Resolved
	Safety Follow-up	303	Pneumonitis	2.1 Months	3	Y	Y	Discontinued	Resolved
Trial Number=3475-024, Site Number=0202, Subject ID=245198, Gender=F, Race=White, Age=51 Years, Rel Day of Last Recorded Dose of Study Medication=274									
245198	Treatment Cycle 2	22	Hyperthyroidism	1.41 Months	1	N	Y	None	Resolved
	Treatment Cycle 4	64	Hypothyroidism	Continuing	2	N	Y	None	Not Resolved
		77	Hypersensitivity	30 Minutes	2	Y	N	None	Resolved
Trial Number=3475-024, Site Number=0252, Subject ID=243913, Gender=M, Race=Asian, Age=58 Years, Rel Day of Last Recorded Dose of Study Medication=1									
243913	Safety Follow-up	7	Pneumonitis	Continuing	4	Y	Y	Discontinued	Not Resolved
Trial Number=3475-024, Site Number=0254, Subject ID=243920, Gender=M, Race=Asian, Age=52 Years, Rel Day of Last Recorded Dose of Study Medication=232									
243920	Treatment Cycle 3	45	Hyperthyroidism	1.41 Months	2	N	Y	None	Resolved
	Treatment Cycle 5	87	Hypothyroidism	Continuing	1	N	Y	None	Not Resolved
Trial Number=3475-024, Site Number=0255, Subject ID=243304, Gender=F, Race=Asian, Age=51 Years, Rel Day of Last Recorded Dose of Study Medication=381									
243304	Treatment Cycle 8	150	Autoimmune thyroiditis	Continuing	2	N	Y	None	Not Resolved
	Treatment Cycle 16	318	Hypersensitivity	2 Days	1	N	N	None	Resolved
Trial Number=3475-024, Site Number=0258, Subject ID=243312, Gender=F, Race=Asian, Age=40 Years, Rel Day of Last Recorded Dose of Study Medication=217									
243312	Treatment Cycle 2	21	Infusion related reaction	2 Days	2	N	Y	None	Resolved
		36	Rash maculo-papular	Continuing	3	N	Y	Interrupted	Not Resolved

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Listing of Subjects With Adverse Events
AEOSI
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
Pembrolizumab									
Trial Number=3475-024, Site Number=0259, Subject ID=243601, Gender=M, Race=Asian, Age=67 Years, Rel Day of Last Recorded Dose of Study Medication=295									
243601	Safety Follow-up	314	Interstitial lung disease	Continuing	2	N	Y	None	Resolving
Trial Number=3475-024, Site Number=0259, Subject ID=243908, Gender=F, Race=Asian, Age=70 Years, Rel Day of Last Recorded Dose of Study Medication=231									
243908	Treatment Cycle 4	64	Hypothyroidism	3.48 Months	1	N	Y	None	Resolved
Trial Number=3475-024, Site Number=0335, Subject ID=243909, Gender=M, Race=Asian, Age=65 Years, Rel Day of Last Recorded Dose of Study Medication=337									
243909	Treatment Cycle 1	1	Infusion related reaction	3.25 Hours	2	Y	Y	None	Resolved
	Treatment Cycle 15	311	Enterocolitis	3.86 Weeks	2	Y	Y	None	Resolved
Trial Number=3475-024, Site Number=0336, Subject ID=243305, Gender=M, Race=Asian, Age=80 Years, Rel Day of Last Recorded Dose of Study Medication=344									
243305	Treatment Cycle 1	1	Infusion related reaction	2 Days	2	N	Y	None	Resolved
Trial Number=3475-024, Site Number=0342, Subject ID=243001, Gender=M, Race=Asian, Age=73 Years, Rel Day of Last Recorded Dose of Study Medication=274									
243001	Treatment Cycle 9	169	Hypothyroidism	Continuing	2	N	Y	None	Not Resolved
SOC									
Trial Number=3475-024, Site Number=0030, Subject ID=244526, Gender=F, Race=White, Age=52 Years, Rel Day of Last Recorded Dose of Study Medication=236									
244526	Treatment Cycle 3	62	Hypothyroidism	Continuing	1	N	N	N/A	Not Resolved
Trial Number=3475-024, Site Number=0035, Subject ID=244563, Gender=M, Race=White, Age=53 Years, Rel Day of Last Recorded Dose of Study Medication=141									
244563	Treatment Cycle 3	68	Hypothyroidism	3.29 Weeks	1	N	Y	None	Resolved

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Listing of Subjects With Adverse Events
AEOSI
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
SOC									
Trial Number=3475-024, Site Number=0086, Subject ID=245146, Gender=M, Race=White, Age=62 Years, Rel Day of Last Recorded Dose of Study Medication=390									
245146	Treatment Cycle 1	1	Drug hypersensitivity	15 Minutes	1	N	Y	None	Resolved
Trial Number=3475-024, Site Number=0131, Subject ID=245179, Gender=M, Race=White, Age=53 Years, Rel Day of Last Recorded Dose of Study Medication=323									
245179	Treatment Cycle 9	204	Hyperthyroidism	2.33 Months	1	N	N	None	Resolved
Trial Number=3475-024, Site Number=0166, Subject ID=245224, Gender=F, Race=White, Age=68 Years, Rel Day of Last Recorded Dose of Study Medication=205									
245224	Treatment Cycle 1	1	Infusion related reaction	40 Minutes	2	N	N	Interrupted	Resolved
	Treatment Cycle 2	22	Infusion related reaction	40 Minutes	2	N	N	None	Resolved
Trial Number=3475-024, Site Number=0204, Subject ID=245175, Gender=F, Race=American Indian Or Alaska Native, Age=71 Years, Rel Day of Last Recorded Dose of Study Medication=206									
245175	Treatment Cycle 2	23	Hyperthyroidism	3 Weeks	1	N	N	None	Resolved
	Chemotherapy Washout	106	Hyperthyroidism	4.14 Weeks	1	N	N	N/A	Resolved
Trial Number=3475-024, Site Number=0260, Subject ID=243906, Gender=M, Race=Asian, Age=61 Years, Rel Day of Last Recorded Dose of Study Medication=25									

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Listing of Subjects With Adverse Events
AEOSI
(ASaT Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
SOC									
Trial Number=3475-024, Site Number=0260, Subject ID=243906, Gender=M, Race=Asian, Age=61 Years, Rel Day of Last Recorded Dose of Study Medication=25									
243906	Extended Safety Follow-up	61	Pneumonitis	Continuing	3	Y	Y	N/A	Not Resolved

Toxicity Grade: NCI CTCAE version 4.03.

Related: Investigator-assessed relationship of the adverse event to study medication. Y = RELATED, N = NOT RELATED

Action Taken: Discontinued = DRUG WITHDRAWN, Interrupted = DRUG INTERRUPTED, Reduced = DOSE REDUCED, Increased = DOSE INCREASED, None = DOSE NOT CHANGED, N/A = NOT APPLICABLE.

Outcome: Resolved = RECOVERED/RESOLVED, Resolving = RECOVERING/RESOLVING, Sequelae = RECOVERED/RESOLVED WITH SEQUELAE, Not resolved = NOT RECOVERED/NOT RESOLVED.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

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付録 2.7.4- 148 各 AEOSI に対する副腎皮質ホルモン剤の使用の要約 024 試験（安全性解析対象集団）

Summary of Concomitant Corticosteroid Use for AEOSI - Colitis (ASaT Population)

	Pembrolizumab (N=154)		SOC (N=150)	
	n	%	n	%
Subjects with one or more Colitis events	3		0	
Treated with systemic corticosteroid	2	66.7	0	0
High starting dose†	2	66.7	0	0
Low starting dose‡	0	0	0	0
Not treated with systemic corticosteroid	1	33.3	0	0

The number of Subjects with one or more Colitis events is used as the denominator for the percentage calculation.
† High starting dose corticosteroid treatment is defined as >= 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

Summary of Concomitant Corticosteroid Use for AEOSI - Hyperthyroidism (ASaT Population)

	Pembrolizumab (N=154)		SOC (N=150)	
	n	%	n	%
Subjects with one or more Hyperthyroidism events	12		2	
Treated with systemic corticosteroid	0	0	0	0
High starting dose†	0	0	0	0
Low starting dose‡	0	0	0	0
Not treated with systemic corticosteroid	12	100.0	2	100.0

The number of Subjects with one or more Hyperthyroidism events is used as the denominator for the percentage calculation.
† High starting dose corticosteroid treatment is defined as >= 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

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Summary of Concomitant Corticosteroid Use for AEOSI - Hypophysitis (ASaT Population)

	Pembrolizumab (N=154)		SOC (N=150)	
	n	%	n	%
Subjects with one or more Hypophysitis events	1		0	
Treated with systemic corticosteroid	0	0	0	0
High starting dose†	0	0	0	0
Low starting dose‡	0	0	0	0
Not treated with systemic corticosteroid	1	100.0	0	0

The number of Subjects with one or more Hypophysitis events is used as the denominator for the percentage calculation.
† High starting dose corticosteroid treatment is defined as >= 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

Summary of Concomitant Corticosteroid Use for AEOSI - Hypothyroidism (ASaT Population)

	Pembrolizumab (N=154)		SOC (N=150)	
	n	%	n	%
Subjects with one or more Hypothyroidism events	14		2	
Treated with systemic corticosteroid	0	0	0	0
High starting dose†	0	0	0	0
Low starting dose‡	0	0	0	0
Not treated with systemic corticosteroid	14	100.0	2	100.0

The number of Subjects with one or more Hypothyroidism events is used as the denominator for the percentage calculation.
† High starting dose corticosteroid treatment is defined as >= 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

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Summary of Concomitant Corticosteroid Use for AEOSI - Infusion Reactions (ASaT Population)

	Pembrolizumab (N=154)		SOC (N=150)	
	n	%	n	%
Subjects with one or more Infusion Reactions events	7		2	
Treated with systemic corticosteroid	1	14.3	1	50.0
High starting dose†	1	14.3	1	50.0
Low starting dose‡	0	0	0	0
Not treated with systemic corticosteroid	6	85.7	1	50.0

The number of Subjects with one or more Infusion Reactions events is used as the denominator for the percentage calculation.
† High starting dose corticosteroid treatment is defined as >= 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

Summary of Concomitant Corticosteroid Use for AEOSI - Myositis (ASaT Population)

	Pembrolizumab (N=154)		SOC (N=150)	
	n	%	n	%
Subjects with one or more Myositis events	3		0	
Treated with systemic corticosteroid	2	66.7	0	0
High starting dose†	2	66.7	0	0
Low starting dose‡	0	0	0	0
Not treated with systemic corticosteroid	1	33.3	0	0

The number of Subjects with one or more Myositis events is used as the denominator for the percentage calculation.
† High starting dose corticosteroid treatment is defined as >= 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

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Summary of Concomitant Corticosteroid Use for AEOSI - Nephritis (ASaT Population)

	Pembrolizumab (N=154)		SOC (N=150)	
	n	%	n	%
Subjects with one or more Nephritis events	1		0	
Treated with systemic corticosteroid	1	100.0	0	0
High starting dose†	1	100.0	0	0
Low starting dose‡	0	0	0	0
Not treated with systemic corticosteroid	0	0	0	0

The number of Subjects with one or more Nephritis events is used as the denominator for the percentage calculation.
† High starting dose corticosteroid treatment is defined as >= 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

Summary of Concomitant Corticosteroid Use for AEOSI - Pancreatitis (ASaT Population)

	Pembrolizumab (N=154)		SOC (N=150)	
	n	%	n	%
Subjects with one or more Pancreatitis events	1		0	
Treated with systemic corticosteroid	1	100.0	0	0
High starting dose†	1	100.0	0	0
Low starting dose‡	0	0	0	0
Not treated with systemic corticosteroid	0	0	0	0

The number of Subjects with one or more Pancreatitis events is used as the denominator for the percentage calculation.
† High starting dose corticosteroid treatment is defined as >= 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

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Summary of Concomitant Corticosteroid Use for AEOSI - Pneumonitis (ASaT Population)

	Pembrolizumab (N=154)		SOC (N=150)	
	n	%	n	%
Subjects with one or more Pneumonitis events	9		1	
Treated with systemic corticosteroid	8	88.9	1	100.0
High starting dose†	7	77.8	1	100.0
Low starting dose‡	0	0	0	0
Not treated with systemic corticosteroid	1	11.1	0	0

The number of Subjects with one or more Pneumonitis events is used as the denominator for the percentage calculation.
† High starting dose corticosteroid treatment is defined as >= 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

Summary of Concomitant Corticosteroid Use for AEOSI - Skin (ASaT Population)

	Pembrolizumab (N=154)		SOC (N=150)	
	n	%	n	%
Subjects with one or more Skin events	6		0	
Treated with systemic corticosteroid	1	16.7	0	0
High starting dose†	1	16.7	0	0
Low starting dose‡	0	0	0	0
Not treated with systemic corticosteroid	5	83.3	0	0

The number of Subjects with one or more Skin events is used as the denominator for the percentage calculation.
† High starting dose corticosteroid treatment is defined as >= 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

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Summary of Concomitant Corticosteroid Use for AEOSI - Thyroiditis (ASaT Population)

	Pembrolizumab (N=154)		SOC (N=150)	
	n	%	n	%
Subjects with one or more Thyroiditis events	4		0	
Treated with systemic corticosteroid	0	0	0	0
High starting dose†	0	0	0	0
Low starting dose‡	0	0	0	0
Not treated with systemic corticosteroid	4	100.0	0	0

The number of Subjects with one or more Thyroiditis events is used as the denominator for the percentage calculation.
† High starting dose corticosteroid treatment is defined as >= 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

Summary of Concomitant Corticosteroid Use for AEOSI - Type 1 Diabetes Mellitus (ASaT Population)

	Pembrolizumab (N=154)		SOC (N=150)	
	n	%	n	%
Subjects with one or more Type 1 Diabetes Mellitus events	1		0	
Treated with systemic corticosteroid	0	0	0	0
High starting dose†	0	0	0	0
Low starting dose‡	0	0	0	0
Not treated with systemic corticosteroid	1	100.0	0	0

The number of Subjects with one or more Type 1 Diabetes Mellitus events is used as the denominator for the percentage calculation.
† High starting dose corticosteroid treatment is defined as >= 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

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Summary of Concomitant Corticosteroid Use for AEOSI Episodes - Colitis
(ASaT Population)

	Pembrolizumab	SOC
Total Episodes	3	0
High Starting Dose (%) †	**2 (66.7)**	**0 (0.0)**
Starting dose (mg/day)		
Mean (Std)	281 (309)	0 (0)
Median (Range)	281 (63-500)	0 (0-0)
Duration (days)§		
Mean (Std)	1 (0)	0 (0)
Median (Range)	1 (1-1)	0 (0-0)
Low Starting Dose (%) ‡	**0 (0.0)**	**0 (0.0)**
Not Treated with Systemic Corticosteroid (%)	**1 (33.3)**	**0 (0.0)**

† High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
§ Ongoing corticosteroid treatment is censored at the cutoff date or date of death, whichever occurs first.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

Summary of Concomitant Corticosteroid Use for AEOSI Episodes - Hyperthyroidism
(ASaT Population)

	Pembrolizumab	SOC
Total Episodes	12	3
High Starting Dose (%) †	**0 (0.0)**	**0 (0.0)**
Low Starting Dose (%) ‡	**0 (0.0)**	**0 (0.0)**
Not Treated with Systemic Corticosteroid (%)	**12 (100.0)**	**3 (100.0)**

† High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
§ Ongoing corticosteroid treatment is censored at the cutoff date or date of death, whichever occurs first.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

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Summary of Concomitant Corticosteroid Use for AEOSI Episodes - Hypophysitis (ASaT Population)

	Pembrolizumab	SOC
Total Episodes	1	0
High Starting Dose (%) †	**0 (0.0)**	**0 (0.0)**
Low Starting Dose (%) ‡	**0 (0.0)**	**0 (0.0)**
Not Treated with Systemic Corticosteroid (%)	**1 (100.0)**	**0 (0.0)**

† High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
§ Ongoing corticosteroid treatment is censored at the cutoff date or date of death, whichever occurs first.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

Summary of Concomitant Corticosteroid Use for AEOSI Episodes - Hypothyroidism (ASaT Population)

	Pembrolizumab	SOC
Total Episodes	14	2
High Starting Dose (%) †	**0 (0.0)**	**0 (0.0)**
Low Starting Dose (%) ‡	**0 (0.0)**	**0 (0.0)**
Not Treated with Systemic Corticosteroid (%)	**14 (100.0)**	**2 (100.0)**

† High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
§ Ongoing corticosteroid treatment is censored at the cutoff date or date of death, whichever occurs first.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

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Summary of Concomitant Corticosteroid Use for AEOSI Episodes - Infusion Reactions (ASaT Population)

	Pembrolizumab	SOC
Total Episodes	7	3
High Starting Dose (%) †	**1 (14.3)**	**2 (66.7)**
Starting dose (mg/day)		
Mean (Std)	75 (.)	178 (31)
Median (Range)	75 (75-75)	178 (156-200)
Duration (days)§		
Mean (Std)	1 (.)	1 (0)
Median (Range)	1 (1-1)	1 (1-1)
Low Starting Dose (%) ‡	**0 (0.0)**	**0 (0.0)**
Not Treated with Systemic Corticosteroid (%)	**6 (85.7)**	**1 (33.3)**

† High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
§ Ongoing corticosteroid treatment is censored at the cutoff date or date of death, whichever occurs first.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

Summary of Concomitant Corticosteroid Use for AEOSI Episodes - Myositis (ASaT Population)

	Pembrolizumab	SOC
Total Episodes	3	0
High Starting Dose (%) †	**2 (66.7)**	**0 (0.0)**
Starting dose (mg/day)		
Mean (Std)	80 (28)	0 (0)
Median (Range)	80 (60-100)	0 (0-0)
Duration (days)§		
Mean (Std)	13 (11)	0 (0)
Median (Range)	13 (5-20)	0 (0-0)
Low Starting Dose (%) ‡	**0 (0.0)**	**0 (0.0)**
Not Treated with Systemic Corticosteroid (%)	**1 (33.3)**	**0 (0.0)**

† High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
§ Ongoing corticosteroid treatment is censored at the cutoff date or date of death, whichever occurs first.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

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Summary of Concomitant Corticosteroid Use for AEOSI Episodes - Nephritis
(ASaT Population)

	Pembrolizumab	SOC
Total Episodes	1	0
High Starting Dose (%) †	**1 (100.0)**	**0 (0.0)**
Starting dose (mg/day)		
Mean (Std)	75 (.)	0 (0)
Median (Range)	75 (75-75)	0 (0-0)
Duration (days)§		
Mean (Std)	11 (.)	0 (0)
Median (Range)	11 (11-11)	0 (0-0)
Low Starting Dose (%) ‡	**0 (0.0)**	**0 (0.0)**
Not Treated with Systemic Corticosteroid (%)	**0 (0.0)**	**0 (0.0)**

† High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
§ Ongoing corticosteroid treatment is censored at the cutoff date or date of death, whichever occurs first.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

Summary of Concomitant Corticosteroid Use for AEOSI Episodes - Pancreatitis
(ASaT Population)

	Pembrolizumab	SOC
Total Episodes	1	0
High Starting Dose (%) †	**1 (100.0)**	**0 (0.0)**
Starting dose (mg/day)		
Mean (Std)	100 (.)	0 (0)
Median (Range)	100 (100-100)	0 (0-0)
Duration (days)§		
Mean (Std)	8 (.)	0 (0)
Median (Range)	8 (8-8)	0 (0-0)
Low Starting Dose (%) ‡	**0 (0.0)**	**0 (0.0)**
Not Treated with Systemic Corticosteroid (%)	**0 (0.0)**	**0 (0.0)**

† High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
§ Ongoing corticosteroid treatment is censored at the cutoff date or date of death, whichever occurs first.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

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Summary of Concomitant Corticosteroid Use for AEOSI Episodes - Pneumonitis
(ASaT Population)

	Pembrolizumab	SOC
Total Episodes	10	1
High Starting Dose (%) †	**7 (70.0)**	**1 (100.0)**
Starting dose (mg/day)		
Mean (Std)	195 (206)	50 (.)
Median (Range)	100 (60-625)	50 (50-50)
Duration (days)§		
Mean (Std)	6 (6)	7 (.)
Median (Range)	4 (1-19)	7 (7-7)
Low Starting Dose (%) ‡	**2 (20.0)**	**0 (0.0)**
Starting dose (mg/day)		
Mean (Std)	30 (0)	0 (0)
Median (Range)	30 (30-30)	0 (0-0)
Duration (days)§		
Mean (Std)	5 (4)	0 (0)
Median (Range)	5 (2-7)	0 (0-0)
Not Treated with Systemic Corticosteroid (%)	**1 (10.0)**	**0 (0.0)**

† High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
§ Ongoing corticosteroid treatment is censored at the cutoff date or date of death, whichever occurs first.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

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Summary of Concomitant Corticosteroid Use for AEOSI Episodes - Skin
(ASaT Population)

	Pembrolizumab	SOC
Total Episodes	6	0
High Starting Dose (%) †	**1 (16.7)**	**0 (0.0)**
Starting dose (mg/day)		
Mean (Std)	50 (.)	0 (0)
Median (Range)	50 (50-50)	0 (0-0)
Duration (days)§		
Mean (Std)	3 (.)	0 (0)
Median (Range)	3 (3-3)	0 (0-0)
Low Starting Dose (%) ‡	**0 (0.0)**	**0 (0.0)**
Not Treated with Systemic Corticosteroid (%)	**5 (83.3)**	**0 (0.0)**

† High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
§ Ongoing corticosteroid treatment is censored at the cutoff date or date of death, whichever occurs first.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

Summary of Concomitant Corticosteroid Use for AEOSI Episodes - Thyroiditis
(ASaT Population)

	Pembrolizumab	SOC
Total Episodes	4	0
High Starting Dose (%) †	**0 (0.0)**	**0 (0.0)**
Low Starting Dose (%) ‡	**0 (0.0)**	**0 (0.0)**
Not Treated with Systemic Corticosteroid (%)	**4 (100.0)**	**0 (0.0)**

† High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
§ Ongoing corticosteroid treatment is censored at the cutoff date or date of death, whichever occurs first.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

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Summary of Concomitant Corticosteroid Use for AEOSI Episodes - Type 1 Diabetes Mellitus
(ASaT Population)

	Pembrolizumab	SOC
Total Episodes	1	0
High Starting Dose (%) †	**0 (0.0)**	**0 (0.0)**
Low Starting Dose (%) ‡	**0 (0.0)**	**0 (0.0)**
Not Treated with Systemic Corticosteroid (%)	**1 (100.0)**	**0 (0.0)**

† High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
§ Ongoing corticosteroid treatment is censored at the cutoff date or date of death, whichever occurs first.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

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付録 2.7.4- 149 各 AEOSI の Grade 別有害事象

024 試験（安全性解析対象集団）

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Adrenal Insufficiency
(ASaT Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	154		150	
with one or more adverse events	0	(0.0)	0	(0.0)
with no adverse events	154	(100.0)	150	(100.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.03.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Colitis
(ASaT Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	154		150	
with one or more adverse events	3	(1.9)	0	(0.0)
Grade 2	1	(0.6)	0	(0.0)
Grade 3	2	(1.3)	0	(0.0)
with no adverse events	151	(98.1)	150	(100.0)
Gastrointestinal disorders	**3**	**(1.9)**	**0**	**(0.0)**
Colitis	2	(1.3)	0	(0.0)
Grade 3	2	(1.3)	0	(0.0)
Enterocolitis	1	(0.6)	0	(0.0)
Grade 2	1	(0.6)	0	(0.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.03.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

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Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Guillain-Barre Syndrome
(ASaT Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	154		150	
with one or more adverse events	0	(0.0)	0	(0.0)
with no adverse events	154	(100.0)	150	(100.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.

Only the highest reported grade of a given adverse event is counted for the individual subject.

Grades are based on NCI CTCAE version 4.03.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Hepatitis
(ASaT Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	154		150	
with one or more adverse events	0	(0.0)	0	(0.0)
with no adverse events	154	(100.0)	150	(100.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.

Only the highest reported grade of a given adverse event is counted for the individual subject.

Grades are based on NCI CTCAE version 4.03.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

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Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Hyperthyroidism
(ASaT Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	154		150	
with one or more adverse events	12	(7.8)	2	(1.3)
Grade 1	8	(5.2)	2	(1.3)
Grade 2	4	(2.6)	0	(0.0)
with no adverse events	142	(92.2)	148	(98.7)
Endocrine disorders	**12**	**(7.8)**	**2**	**(1.3)**
Hyperthyroidism	12	(7.8)	2	(1.3)
Grade 1	8	(5.2)	2	(1.3)
Grade 2	4	(2.6)	0	(0.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.03.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Hypophysitis
(ASaT Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	154		150	
with one or more adverse events	1	(0.6)	0	(0.0)
Grade 3	1	(0.6)	0	(0.0)
with no adverse events	153	(99.4)	150	(100.0)
Endocrine disorders	**1**	**(0.6)**	**0**	**(0.0)**
Hypophysitis	1	(0.6)	0	(0.0)
Grade 3	1	(0.6)	0	(0.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.03.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

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Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Hypothyroidism
(ASaT Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	154		150	
with one or more adverse events	14	(9.1)	2	(1.3)
Grade 1	6	(3.9)	2	(1.3)
Grade 2	8	(5.2)	0	(0.0)
with no adverse events	140	(90.9)	148	(98.7)
Endocrine disorders	**14**	**(9.1)**	**2**	**(1.3)**
Hypothyroidism	14	(9.1)	2	(1.3)
Grade 1	6	(3.9)	2	(1.3)
Grade 2	8	(5.2)	0	(0.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.03.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Infusion Reactions
(ASaT Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	154		150	
with one or more adverse events	7	(4.5)	2	(1.3)
Grade 1	2	(1.3)	1	(0.7)
Grade 2	5	(3.2)	1	(0.7)
with no adverse events	147	(95.5)	148	(98.7)
Immune system disorders	**4**	**(2.6)**	**1**	**(0.7)**
Drug hypersensitivity	0	(0.0)	1	(0.7)
Grade 1	0	(0.0)	1	(0.7)
Hypersensitivity	4	(2.6)	0	(0.0)
Grade 1	2	(1.3)	0	(0.0)
Grade 2	2	(1.3)	0	(0.0)
Injury, poisoning and procedural complications	**3**	**(1.9)**	**1**	**(0.7)**
Infusion related reaction	3	(1.9)	1	(0.7)
Grade 2	3	(1.9)	1	(0.7)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
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Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.03.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

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Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Myasthenic Syndrome
(ASaT Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	154		150	
with one or more adverse events	0	(0.0)	0	(0.0)
with no adverse events	154	(100.0)	150	(100.0)

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A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.03.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Myositis
(ASaT Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	154		150	
with one or more adverse events	3	(1.9)	0	(0.0)
Grade 1	1	(0.6)	0	(0.0)
Grade 2	2	(1.3)	0	(0.0)
with no adverse events	151	(98.1)	150	(100.0)
Musculoskeletal and connective tissue disorders	**3**	**(1.9)**	**0**	**(0.0)**
Myopathy	1	(0.6)	0	(0.0)
Grade 1	1	(0.6)	0	(0.0)
Myositis	2	(1.3)	0	(0.0)
Grade 2	2	(1.3)	0	(0.0)

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A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.03.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

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Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Nephritis
(ASaT Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	154		150	
with one or more adverse events	1	(0.6)	0	(0.0)
Grade 3	1	(0.6)	0	(0.0)
with no adverse events	153	(99.4)	150	(100.0)
Renal and urinary disorders	**1**	**(0.6)**	**0**	**(0.0)**
Tubulointerstitial nephritis	1	(0.6)	0	(0.0)
Grade 3	1	(0.6)	0	(0.0)

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A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.03.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Pancreatitis
(ASaT Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	154		150	
with one or more adverse events	1	(0.6)	0	(0.0)
Grade 3	1	(0.6)	0	(0.0)
with no adverse events	153	(99.4)	150	(100.0)
Gastrointestinal disorders	**1**	**(0.6)**	**0**	**(0.0)**
Pancreatitis	1	(0.6)	0	(0.0)
Grade 3	1	(0.6)	0	(0.0)

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A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.03.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

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Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Pneumonitis
(ASaT Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	154		150	
with one or more adverse events	9	(5.8)	1	(0.7)
Grade 1	1	(0.6)	0	(0.0)
Grade 2	4	(2.6)	0	(0.0)
Grade 3	2	(1.3)	1	(0.7)
Grade 4	2	(1.3)	0	(0.0)
with no adverse events	145	(94.2)	149	(99.3)
Respiratory, thoracic and mediastinal disorders	**9**	**(5.8)**	**1**	**(0.7)**
Interstitial lung disease	1	(0.6)	0	(0.0)
Grade 2	1	(0.6)	0	(0.0)
Pneumonitis	8	(5.2)	1	(0.7)
Grade 1	1	(0.6)	0	(0.0)
Grade 2	3	(1.9)	0	(0.0)
Grade 3	2	(1.3)	1	(0.7)
Grade 4	2	(1.3)	0	(0.0)

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A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.03.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

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Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Skin
(ASaT Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	154		150	
with one or more adverse events	6	(3.9)	0	(0.0)
Grade 3	6	(3.9)	0	(0.0)
with no adverse events	148	(96.1)	150	(100.0)
Skin and subcutaneous tissue disorders	**6**	**(3.9)**	**0**	**(0.0)**
Psoriasis	1	(0.6)	0	(0.0)
Grade 3	1	(0.6)	0	(0.0)
Rash	2	(1.3)	0	(0.0)
Grade 3	2	(1.3)	0	(0.0)
Rash generalised	1	(0.6)	0	(0.0)
Grade 3	1	(0.6)	0	(0.0)
Rash maculo-papular	1	(0.6)	0	(0.0)
Grade 3	1	(0.6)	0	(0.0)
Toxic skin eruption	1	(0.6)	0	(0.0)
Grade 3	1	(0.6)	0	(0.0)

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A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.03.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

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Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Thyroiditis
(ASaT Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	154		150	
with one or more adverse events	4	(2.6)	0	(0.0)
Grade 1	1	(0.6)	0	(0.0)
Grade 2	3	(1.9)	0	(0.0)
with no adverse events	150	(97.4)	150	(100.0)
Endocrine disorders	**4**	**(2.6)**	**0**	**(0.0)**
Autoimmune thyroiditis	1	(0.6)	0	(0.0)
Grade 2	1	(0.6)	0	(0.0)
Thyroiditis	3	(1.9)	0	(0.0)
Grade 1	1	(0.6)	0	(0.0)
Grade 2	2	(1.3)	0	(0.0)

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A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.03.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Type 1 Diabetes Mellitus
(ASaT Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	154		150	
with one or more adverse events	1	(0.6)	0	(0.0)
Grade 4	1	(0.6)	0	(0.0)
with no adverse events	153	(99.4)	150	(100.0)
Metabolism and nutrition disorders	**1**	**(0.6)**	**0**	**(0.0)**
Diabetic ketoacidosis	1	(0.6)	0	(0.0)
Grade 4	1	(0.6)	0	(0.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.03.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

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Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Uveitis
(ASaT Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	154		150	
with one or more adverse events	0	(0.0)	0	(0.0)
with no adverse events	154	(100.0)	150	(100.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.

Only the highest reported grade of a given adverse event is counted for the individual subject.

Grades are based on NCI CTCAE version 4.03.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

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付録 2.7.4- 150 臨床検査値の Grade がベースラインより悪化した患者での臨床検査値異常の最大 Grade の要約
（ベースライン及びベースライン後の測定がある患者）
024 試験（安全性解析対象集団）

Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline
(Subjects with Both Baseline and Post-baseline Measurements)

Laboratory Test	Pembrolizumab (N=154)	SOC (N=150)
APTT Increased		
Subjects with Baseline and Post-Baseline Measurements	8	4
Toxicity Grade 1	0 (0.0)	0 (0.0)
Toxicity Grade 2	0 (0.0)	1 (25.0)
Toxicity Grade 3	1 (12.5)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	1 (12.5)	0 (0.0)
All Grades	1 (12.5)	1 (25.0)
Alanine Aminotransferase Increased		
Subjects with Baseline and Post-Baseline Measurements	2	4
Toxicity Grade 1	0 (0.0)	0 (0.0)
Toxicity Grade 2	0 (0.0)	1 (25.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	0 (0.0)	0 (0.0)
All Grades	0 (0.0)	1 (25.0)
Albumin Decreased		
Subjects with Baseline and Post-Baseline Measurements	36	27
Toxicity Grade 1	0 (0.0)	0 (0.0)
Toxicity Grade 2	10 (27.8)	6 (22.2)
Toxicity Grade 3	2 (5.6)	2 (7.4)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline
(Subjects with Both Baseline and Post-baseline Measurements)

Laboratory Test	Pembrolizumab (N=154)	SOC (N=150)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	2 (5.6)	2 (7.4)
All Grades	12 (33.3)	8 (29.6)
Alkaline Phosphatase Increased		
Subjects with Baseline and Post-Baseline Measurements	38	26
Toxicity Grade 1	0 (0.0)	0 (0.0)
Toxicity Grade 2	2 (5.3)	3 (11.5)
Toxicity Grade 3	4 (10.5)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	4 (10.5)	0 (0.0)
All Grades	6 (15.8)	3 (11.5)
Aspartate Aminotransferase Increased		
Subjects with Baseline and Post-Baseline Measurements	5	2
Toxicity Grade 1	0 (0.0)	0 (0.0)
Toxicity Grade 2	0 (0.0)	1 (50.0)
Toxicity Grade 3	1 (20.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	1 (20.0)	0 (0.0)
All Grades	1 (20.0)	1 (50.0)
Calcium Decreased		
Subjects with Baseline and Post-Baseline Measurements	10	7

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline
(Subjects with Both Baseline and Post-baseline Measurements)

Laboratory Test	Pembrolizumab (N=154)	SOC (N=150)
Toxicity Grade 1	0 (0.0)	0 (0.0)
Toxicity Grade 2	3 (30.0)	1 (14.3)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	0 (0.0)	0 (0.0)
All Grades	3 (30.0)	1 (14.3)
Calcium Increased		
Subjects with Baseline and Post-Baseline Measurements	5	6
Toxicity Grade 1	0 (0.0)	0 (0.0)
Toxicity Grade 2	0 (0.0)	2 (33.3)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	0 (0.0)	0 (0.0)
All Grades	0 (0.0)	2 (33.3)
Creatinine Increased		
Subjects with Baseline and Post-Baseline Measurements	8	10
Toxicity Grade 1	0 (0.0)	0 (0.0)
Toxicity Grade 2	1 (12.5)	2 (20.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	0 (0.0)	0 (0.0)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline
(Subjects with Both Baseline and Post-baseline Measurements)

Laboratory Test	Pembrolizumab (N=154)	SOC (N=150)
All Grades	1 (12.5)	2 (20.0)
Glucose Increased		
Subjects with Baseline and Post-Baseline Measurements	39	44
Toxicity Grade 1	0 (0.0)	0 (0.0)
Toxicity Grade 2	7 (17.9)	16 (36.4)
Toxicity Grade 3	5 (12.8)	7 (15.9)
Toxicity Grade 4	2 (5.1)	0 (0.0)
Grade 3-4	7 (17.9)	7 (15.9)
All Grades	14 (35.9)	23 (52.3)
Hemoglobin Decreased		
Subjects with Baseline and Post-Baseline Measurements	63	69
Toxicity Grade 1	0 (0.0)	0 (0.0)
Toxicity Grade 2	14 (22.2)	27 (39.1)
Toxicity Grade 3	6 (9.5)	24 (34.8)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	6 (9.5)	24 (34.8)
All Grades	20 (31.7)	51 (73.9)
Leukocytes Decreased		
Subjects with Baseline and Post-Baseline Measurements	1	5
Toxicity Grade 1	0 (0.0)	0 (0.0)
Toxicity Grade 2	0 (0.0)	2 (40.0)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline
(Subjects with Both Baseline and Post-baseline Measurements)

Laboratory Test	Pembrolizumab (N=154)	SOC (N=150)
Toxicity Grade 3	0 (0.0)	2 (40.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	0 (0.0)	2 (40.0)
All Grades	0 (0.0)	4 (80.0)
Lymphocytes Decreased		
Subjects with Baseline and Post-Baseline Measurements	53	59
Toxicity Grade 1	4 (7.5)	6 (10.2)
Toxicity Grade 2	8 (15.1)	12 (20.3)
Toxicity Grade 3	7 (13.2)	10 (16.9)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	7 (13.2)	10 (16.9)
All Grades	19 (35.8)	28 (47.5)
Magnesium Decreased		
Subjects with Baseline and Post-Baseline Measurements	12	9
Toxicity Grade 1	0 (0.0)	0 (0.0)
Toxicity Grade 2	4 (33.3)	2 (22.2)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	1 (8.3)	0 (0.0)
Grade 3-4	1 (8.3)	0 (0.0)
All Grades	5 (41.7)	2 (22.2)
Neutrophils Decreased		

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline
(Subjects with Both Baseline and Post-baseline Measurements)

Laboratory Test	Pembrolizumab (N=154)	SOC (N=150)
Subjects with Baseline and Post-Baseline Measurements	1	3
Toxicity Grade 1	0 (0.0)	0 (0.0)
Toxicity Grade 2	0 (0.0)	0 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	1 (33.3)
Grade 3-4	0 (0.0)	1 (33.3)
All Grades	0 (0.0)	1 (33.3)
Neutrophils Increased		
Subjects with Baseline and Post-Baseline Measurements	47	52
Toxicity Grade 1	0 (0.0)	0 (0.0)
Toxicity Grade 2	0 (0.0)	0 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	1 (2.1)	0 (0.0)
Grade 3-4	1 (2.1)	0 (0.0)
All Grades	1 (2.1)	0 (0.0)
Phosphate Decreased		
Subjects with Baseline and Post-Baseline Measurements	6	7
Toxicity Grade 1	0 (0.0)	0 (0.0)
Toxicity Grade 2	1 (16.7)	1 (14.3)
Toxicity Grade 3	1 (16.7)	2 (28.6)
Toxicity Grade 4	0 (0.0)	0 (0.0)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline
(Subjects with Both Baseline and Post-baseline Measurements)

Laboratory Test	Pembrolizumab (N=154)	SOC (N=150)
Grade 3-4	1 (16.7)	2 (28.6)
All Grades	2 (33.3)	3 (42.9)
Platelet Decreased		
Subjects with Baseline and Post-Baseline Measurements	1	4
Toxicity Grade 1	0 (0.0)	0 (0.0)
Toxicity Grade 2	0 (0.0)	1 (25.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	0 (0.0)	0 (0.0)
All Grades	0 (0.0)	1 (25.0)
Potassium Increased		
Subjects with Baseline and Post-Baseline Measurements	4	4
Toxicity Grade 1	0 (0.0)	0 (0.0)
Toxicity Grade 2	0 (0.0)	0 (0.0)
Toxicity Grade 3	1 (25.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	1 (25.0)	0 (0.0)
All Grades	1 (25.0)	0 (0.0)
Prothrombin Intl. Normalized Ratio Increased		
Subjects with Baseline and Post-Baseline Measurements	9	5
Toxicity Grade 1	0 (0.0)	0 (0.0)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline (Subjects with Both Baseline and Post-baseline Measurements)

Laboratory Test	Pembrolizumab (N=154)	SOC (N=150)
Toxicity Grade 2	0 (0.0)	0 (0.0)
Toxicity Grade 3	1 (11.1)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	1 (11.1)	0 (0.0)
All Grades	1 (11.1)	0 (0.0)
Sodium Decreased		
Subjects with Baseline and Post-Baseline Measurements	21	16
Toxicity Grade 1	0 (0.0)	0 (0.0)
Toxicity Grade 2	0 (0.0)	0 (0.0)
Toxicity Grade 3	6 (28.6)	4 (25.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	6 (28.6)	4 (25.0)
All Grades	6 (28.6)	4 (25.0)
If a subject had more than one graded abnormalities for a lab test, only the highest grade is counted. Grades are based on NCI CTCAE version 4.03. (Database Cutoff Date: 09MAY2016)		

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付録 2.7.4- 151 臨床検査値の Grade がベースラインより悪化した患者での臨床検査値異常の最大 Grade の要約
024 試験（安全性解析対象集団）

Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline (ASaT Population)

Laboratory Test	Pembrolizumab (N=154)	SOC (N=150)
APTT Increased		
All Grades	16 (10.4)	12 (8.0)
Toxicity Grade 1	11 (7.1)	11 (7.3)
Toxicity Grade 2	2 (1.3)	1 (0.7)
Toxicity Grade 3	3 (1.9)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Alanine Aminotransferase Increased		
All Grades	47 (30.5)	46 (30.7)
Toxicity Grade 1	34 (22.1)	44 (29.3)
Toxicity Grade 2	6 (3.9)	2 (1.3)
Toxicity Grade 3	6 (3.9)	0 (0.0)
Toxicity Grade 4	1 (0.6)	0 (0.0)
Albumin Decreased		
All Grades	51 (33.1)	54 (36.0)
Toxicity Grade 1	23 (14.9)	30 (20.0)
Toxicity Grade 2	25 (16.2)	20 (13.3)
Toxicity Grade 3	3 (1.9)	4 (2.7)
Toxicity Grade 4	0 (0.0)	0 (0.0)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline
(ASaT Population)

Laboratory Test	Pembrolizumab (N=154)	SOC (N=150)
Toxicity Grade 2	4 (2.6)	3 (2.0)
Toxicity Grade 3	4 (2.6)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Amylase Increased		
All Grades	3 (1.9)	0 (0.0)
Toxicity Grade 1	1 (0.6)	0 (0.0)
Toxicity Grade 2	0 (0.0)	0 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	2 (1.3)	0 (0.0)
Aspartate Aminotransferase Increased		
All Grades	38 (24.7)	49 (32.7)
Toxicity Grade 1	29 (18.8)	46 (30.7)
Toxicity Grade 2	3 (1.9)	3 (2.0)
Toxicity Grade 3	5 (3.2)	0 (0.0)
Toxicity Grade 4	1 (0.6)	0 (0.0)
Bilirubin Increased		
All Grades	15 (9.7)	2 (1.3)
Toxicity Grade 1	11 (7.1)	2 (1.3)
Toxicity Grade 2	3 (1.9)	0 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	1 (0.6)	0 (0.0)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline
(ASaT Population)

Laboratory Test	Pembrolizumab (N=154)	SOC (N=150)
Calcium Decreased		
All Grades	39 (25.3)	30 (20.0)
Toxicity Grade 1	29 (18.8)	28 (18.7)
Toxicity Grade 2	10 (6.5)	2 (1.3)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Calcium Increased		
All Grades	9 (5.8)	17 (11.3)
Toxicity Grade 1	9 (5.8)	14 (9.3)
Toxicity Grade 2	0 (0.0)	3 (2.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Creatinine Increased		
All Grades	27 (17.5)	43 (28.7)
Toxicity Grade 1	23 (14.9)	32 (21.3)
Toxicity Grade 2	4 (2.6)	9 (6.0)
Toxicity Grade 3	0 (0.0)	2 (1.3)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Gamma Glutamyl Transferase Increased		
All Grades	7 (4.5)	3 (2.0)
Toxicity Grade 1	1 (0.6)	2 (1.3)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline
(ASaT Population)

Laboratory Test	Pembrolizumab (N=154)	SOC (N=150)
Toxicity Grade 2	2 (1.3)	1 (0.7)
Toxicity Grade 3	3 (1.9)	0 (0.0)
Toxicity Grade 4	1 (0.6)	0 (0.0)
Glucose Decreased		
All Grades	13 (8.4)	10 (6.7)
Toxicity Grade 1	13 (8.4)	9 (6.0)
Toxicity Grade 2	0 (0.0)	1 (0.7)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Glucose Increased		
All Grades	80 (51.9)	69 (46.0)
Toxicity Grade 1	52 (33.8)	31 (20.7)
Toxicity Grade 2	16 (10.4)	29 (19.3)
Toxicity Grade 3	9 (5.8)	8 (5.3)
Toxicity Grade 4	3 (1.9)	1 (0.7)
Hemoglobin Decreased		
All Grades	62 (40.3)	122 (81.3
Toxicity Grade 1	35 (22.7)	33 (22.0)
Toxicity Grade 2	21 (13.6)	53 (35.3)
Toxicity Grade 3	6 (3.9)	36 (24.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline
(ASaT Population)

Laboratory Test	Pembrolizumab (N=154)	SOC (N=150)
Leukocytes Decreased		
All Grades	11 (7.1)	80 (53.3)
Toxicity Grade 1	9 (5.8)	27 (18.0)
Toxicity Grade 2	1 (0.6)	34 (22.7)
Toxicity Grade 3	1 (0.6)	14 (9.3)
Toxicity Grade 4	0 (0.0)	5 (3.3)
Lymphocytes Decreased		
All Grades	37 (24.0)	65 (43.3)
Toxicity Grade 1	14 (9.1)	18 (12.0)
Toxicity Grade 2	13 (8.4)	27 (18.0)
Toxicity Grade 3	9 (5.8)	18 (12.0)
Toxicity Grade 4	1 (0.6)	2 (1.3)
Lymphocytes Increased		
All Grades	0 (0.0)	2 (1.3)
Toxicity Grade 1	0 (0.0)	0 (0.0)
Toxicity Grade 2	0 (0.0)	1 (0.7)
Toxicity Grade 3	0 (0.0)	1 (0.7)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Magnesium Decreased		
All Grades	25 (16.2)	47 (31.3)
Toxicity Grade 1	19 (12.3)	25 (16.7)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline
(ASaT Population)

Laboratory Test	Pembrolizumab (N=154)	SOC (N=150)
Toxicity Grade 2	5 (3.2)	22 (14.7)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	1 (0.6)	0 (0.0)
Magnesium Increased		
All Grades	8 (5.2)	7 (4.7)
Toxicity Grade 1	8 (5.2)	6 (4.0)
Toxicity Grade 2	0 (0.0)	0 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	1 (0.7)
Neutrophils Decreased		
All Grades	7 (4.5)	74 (49.3)
Toxicity Grade 1	6 (3.9)	18 (12.0)
Toxicity Grade 2	0 (0.0)	25 (16.7)
Toxicity Grade 3	1 (0.6)	19 (12.7)
Toxicity Grade 4	0 (0.0)	12 (8.0)
Neutrophils Increased		
All Grades	1 (0.6)	0 (0.0)
Toxicity Grade 1	0 (0.0)	0 (0.0)
Toxicity Grade 2	0 (0.0)	0 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	1 (0.6)	0 (0.0)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline
(ASaT Population)

Laboratory Test	Pembrolizumab (N=154)	SOC (N=150)
Phosphate Decreased		
All Grades	23 (14.9)	31 (20.7)
Toxicity Grade 1	3 (1.9)	2 (1.3)
Toxicity Grade 2	16 (10.4)	18 (12.0)
Toxicity Grade 3	4 (2.6)	11 (7.3)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Platelet Decreased		
All Grades	6 (3.9)	57 (38.0)
Toxicity Grade 1	3 (1.9)	27 (18.0)
Toxicity Grade 2	3 (1.9)	11 (7.3)
Toxicity Grade 3	0 (0.0)	8 (5.3)
Toxicity Grade 4	0 (0.0)	11 (7.3)
Potassium Decreased		
All Grades	15 (9.7)	11 (7.3)
Toxicity Grade 1	10 (6.5)	8 (5.3)
Toxicity Grade 2	0 (0.0)	0 (0.0)
Toxicity Grade 3	5 (3.2)	3 (2.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Potassium Increased		
All Grades	33 (21.4)	38 (25.3)
Toxicity Grade 1	19 (12.3)	26 (17.3)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline
(ASaT Population)

Laboratory Test	Pembrolizumab (N=154)	SOC (N=150)
Toxicity Grade 2	11 (7.1)	9 (6.0)
Toxicity Grade 3	2 (1.3)	3 (2.0)
Toxicity Grade 4	1 (0.6)	0 (0.0)
Prothrombin Intl. Normalized Ratio Increased		
All Grades	11 (7.1)	7 (4.7)
Toxicity Grade 1	9 (5.8)	5 (3.3)
Toxicity Grade 2	0 (0.0)	2 (1.3)
Toxicity Grade 3	2 (1.3)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Sodium Decreased		
All Grades	52 (33.8)	48 (32.0)
Toxicity Grade 1	38 (24.7)	37 (24.7)
Toxicity Grade 2	0 (0.0)	0 (0.0)
Toxicity Grade 3	13 (8.4)	11 (7.3)
Toxicity Grade 4	1 (0.6)	0 (0.0)
Sodium Increased		
All Grades	3 (1.9)	4 (2.7)
Toxicity Grade 1	3 (1.9)	4 (2.7)
Toxicity Grade 2	0 (0.0)	0 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline (ASaT Population)

Laboratory Test	Pembrolizumab (N=154)	SOC (N=150)
Triacylglycerol Lipase Increased		
All Grades	1 (0.6)	0 (0.0)
Toxicity Grade 1	0 (0.0)	0 (0.0)
Toxicity Grade 2	0 (0.0)	0 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	1 (0.6)	0 (0.0)
Triglycerides		
All Grades	0 (0.0)	1 (0.7)
Toxicity Grade 1	0 (0.0)	0 (0.0)
Toxicity Grade 2	0 (0.0)	1 (0.7)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
If a subject had more than one graded abnormalities for a lab test, only the highest grade is counted. Grades are based on NCI CTCAE version 4.03. (Database Cutoff Date: 09MAY2016)		

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付録 2.7.4- 152 患者の特性

024 試験（日本人安全性解析対象集団）

Subject Characteristics
(ITT Japan Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	21		19	
Gender				
Male	16	(76.2)	18	(94.7)
Female	5	(23.8)	1	(5.3)
Age (Years)				
< 65	9	(42.9)	6	(31.6)
>= 65	12	(57.1)	13	(68.4)
Mean	63.9		65.9	
SD	9.8		6.8	
Median	66.0		67.0	
Range	40 to 80		53 to 77	
Race				
Asian	21	(100.0)	19	(100.0)
Ethnicity				
Not Hispanic Or Latino	21	(100.0)	18	(94.7)
Not Reported	0	(0.0)	1	(5.3)
ECOG				
0	7	(33.3)	8	(42.1)
1	14	(66.7)	11	(57.9)
Cancer Stage at Screening				
IV	21	(100.0)	19	(100.0)
Geographic Region of Enrolling Site				
East Asia	21	(100.0)	19	(100.0)
Histology				
ADENOCARCINOMA	14	(66.7)	16	(84.2)
NON-SQUAMOUS CELL CARCINOMA	3	(14.3)	1	(5.3)
POORLY DIFFERENTIATED	1	(4.8)	1	(5.3)
SQUAMOUS CELL CARCINOMA	3	(14.3)	1	(5.3)
Smoking Status				
Current	0	(0.0)	1	(5.3)
Former	20	(95.2)	18	(94.7)
Never	1	(4.8)	0	(0.0)
Brain Metastasis Status at Baseline				
Y	1	(4.8)	1	(5.3)

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Subject Characteristics
(ITT Japan Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Brain Metastasis Status at Baseline				
N	20	(95.2)	18	(94.7)
Baseline Tumor Size (mm)				
Subjects with data	20		19	
Mean	81.7		88.6	
SD	55.5		72.4	
Median	68		77	
Range	20 to 245		15 to 251	
Baseline Weight (kg)				
Subjects with data	21		19	
Mean	58.4		63.6	
SD	8.4		11.1	
Median	58		64	
Range	38 to 69		47 to 86	
Prior Adjuvant Therapy				
No	21	(100.0)	19	(100.0)
Prior Neo-adjuvant Therapy				
No	21	(100.0)	19	(100.0)
(Database Cutoff Date: 09MAY2016).				

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付録 2.7.4- 153 有害事象（いずれかの投与群で発現割合 0%超）
024 試験（日本人安全性解析対象集団）

Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) (ASaT Japan Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	21				19			
with one or more adverse events	21	(100.0)	10	(47.6)	18	(94.7)	12	(63.2)
with no adverse events	0	(0.0)	11	(52.4)	1	(5.3)	7	(36.8)
Blood and lymphatic system disorders	**4**	**(19.0)**	**1**	**(4.8)**	**11**	**(57.9)**	**6**	**(31.6)**
Anaemia	2	(9.5)	1	(4.8)	10	(52.6)	6	(31.6)
Eosinophilia	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Leukopenia	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Lymphopenia	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Neutropenia	0	(0.0)	0	(0.0)	2	(10.5)	1	(5.3)
Cardiac disorders	**2**	**(9.5)**	**2**	**(9.5)**	**1**	**(5.3)**	**1**	**(5.3)**
Cardiac failure	1	(4.8)	1	(4.8)	0	(0.0)	0	(0.0)
Cardio-respiratory arrest	0	(0.0)	0	(0.0)	1	(5.3)	1	(5.3)
Pericardial effusion	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Pericarditis	1	(4.8)	1	(4.8)	0	(0.0)	0	(0.0)
Endocrine disorders	**4**	**(19.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Autoimmune thyroiditis	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Hyperthyroidism	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Hypothyroidism	3	(14.3)	0	(0.0)	0	(0.0)	0	(0.0)
Eye disorders	**1**	**(4.8)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Dry eye	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Gastrointestinal disorders	**11**	**(52.4)**	**1**	**(4.8)**	**16**	**(84.2)**	**0**	**(0.0)**

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
(ASaT Japan Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Gastrointestinal disorders	**11**	**(52.4)**	**1**	**(4.8)**	**16**	**(84.2)**	**0**	**(0.0)**
Abdominal pain upper	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Constipation	4	(19.0)	0	(0.0)	6	(31.6)	0	(0.0)
Dental caries	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Diarrhoea	5	(23.8)	1	(4.8)	7	(36.8)	0	(0.0)
Dyspepsia	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Enterocolitis	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Gastritis	2	(9.5)	0	(0.0)	0	(0.0)	0	(0.0)
Gingival pain	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Haematemesis	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Large intestine polyp	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Lip pain	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Nausea	1	(4.8)	0	(0.0)	12	(63.2)	0	(0.0)
Stomatitis	4	(19.0)	0	(0.0)	1	(5.3)	0	(0.0)
Tooth impacted	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Vomiting	2	(9.5)	0	(0.0)	2	(10.5)	0	(0.0)
General disorders and administration site conditions	**12**	**(57.1)**	**1**	**(4.8)**	**14**	**(73.7)**	**0**	**(0.0)**
Chest pain	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Face oedema	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Fatigue	2	(9.5)	1	(4.8)	2	(10.5)	0	(0.0)
Malaise	3	(14.3)	0	(0.0)	9	(47.4)	0	(0.0)
Oedema	0	(0.0)	0	(0.0)	2	(10.5)	0	(0.0)
Oedema peripheral	2	(9.5)	0	(0.0)	1	(5.3)	0	(0.0)
Pyrexia	7	(33.3)	0	(0.0)	4	(21.1)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
(ASaT Japan Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Hepatobiliary disorders	**1**	**(4.8)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Hepatic function abnormal	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Immune system disorders	**1**	**(4.8)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Hypersensitivity	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Infections and infestations	**4**	**(19.0)**	**2**	**(9.5)**	**8**	**(42.1)**	**5**	**(26.3)**
Bacteraemia	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Cellulitis	0	(0.0)	0	(0.0)	1	(5.3)	1	(5.3)
Conjunctivitis	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Infected dermal cyst	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Influenza	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Lung infection	1	(4.8)	1	(4.8)	2	(10.5)	2	(10.5)
Nasopharyngitis	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Oesophageal candidiasis	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Oral candidiasis	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Pneumonia	0	(0.0)	0	(0.0)	3	(15.8)	2	(10.5)
Pneumonia bacterial	1	(4.8)	1	(4.8)	0	(0.0)	0	(0.0)
Tinea pedis	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Tonsillitis	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Upper respiratory tract infection	2	(9.5)	0	(0.0)	0	(0.0)	0	(0.0)
Injury, poisoning and procedural complications	**4**	**(19.0)**	**0**	**(0.0)**	**2**	**(10.5)**	**0**	**(0.0)**
Fall	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Infusion related reaction	3	(14.3)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) (ASaT Japan Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Injury, poisoning and procedural complications	**4**	**(19.0)**	**0**	**(0.0)**	**2**	**(10.5)**	**0**	**(0.0)**
Subdural haematoma	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Thermal burn	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Tooth fracture	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Investigations	**11**	**(52.4)**	**1**	**(4.8)**	**13**	**(68.4)**	**3**	**(15.8)**
Alanine aminotransferase increased	4	(19.0)	0	(0.0)	2	(10.5)	0	(0.0)
Aspartate aminotransferase increased	2	(9.5)	0	(0.0)	1	(5.3)	0	(0.0)
Blood alkaline phosphatase increased	2	(9.5)	0	(0.0)	0	(0.0)	0	(0.0)
Blood bilirubin increased	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Blood chloride decreased	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Blood creatine phosphokinase increased	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Blood creatinine increased	2	(9.5)	0	(0.0)	1	(5.3)	0	(0.0)
Blood glucose increased	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Blood lactate dehydrogenase increased	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Blood potassium increased	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Blood sodium decreased	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Blood thyroid stimulating hormone decreased	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Blood thyroid stimulating hormone increased	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Blood urea increased	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Gamma-glutamyltransferase increased	1	(4.8)	0	(0.0)	1	(5.3)	0	(0.0)
Haemoglobin decreased	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) (ASaT Japan Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**11**	**(52.4)**	**1**	**(4.8)**	**13**	**(68.4)**	**3**	**(15.8)**
Lymphocyte count decreased	1	(4.8)	1	(4.8)	1	(5.3)	1	(5.3)
Neutrophil count decreased	0	(0.0)	0	(0.0)	4	(21.1)	1	(5.3)
Platelet count decreased	0	(0.0)	0	(0.0)	8	(42.1)	3	(15.8)
Weight decreased	1	(4.8)	0	(0.0)	2	(10.5)	0	(0.0)
Weight increased	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
White blood cell count decreased	0	(0.0)	0	(0.0)	8	(42.1)	1	(5.3)
Metabolism and nutrition disorders	**7**	**(33.3)**	**4**	**(19.0)**	**15**	**(78.9)**	**4**	**(21.1)**
Decreased appetite	4	(19.0)	1	(4.8)	12	(63.2)	2	(10.5)
Dyslipidaemia	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Hyperglycaemia	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Hyperkalaemia	2	(9.5)	1	(4.8)	1	(5.3)	0	(0.0)
Hypoalbuminaemia	2	(9.5)	2	(9.5)	5	(26.3)	2	(10.5)
Hyponatraemia	1	(4.8)	1	(4.8)	1	(5.3)	1	(5.3)
Hypophosphataemia	1	(4.8)	0	(0.0)	1	(5.3)	1	(5.3)
Hypovolaemia	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Musculoskeletal and connective tissue disorders	**7**	**(33.3)**	**0**	**(0.0)**	**3**	**(15.8)**	**0**	**(0.0)**
Arthralgia	3	(14.3)	0	(0.0)	2	(10.5)	0	(0.0)
Arthritis	2	(9.5)	0	(0.0)	0	(0.0)	0	(0.0)
Back pain	2	(9.5)	0	(0.0)	0	(0.0)	0	(0.0)
Muscle spasms	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Myalgia	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Myalgia intercostal	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) (ASaT Japan Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2**	**(9.5)**	**1**	**(4.8)**	**0**	**(0.0)**	**0**	**(0.0)**
Infected neoplasm	1	(4.8)	1	(4.8)	0	(0.0)	0	(0.0)
Tumour pain	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Nervous system disorders	**2**	**(9.5)**	**0**	**(0.0)**	**6**	**(31.6)**	**0**	**(0.0)**
Dizziness	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Dysgeusia	0	(0.0)	0	(0.0)	3	(15.8)	0	(0.0)
Headache	2	(9.5)	0	(0.0)	0	(0.0)	0	(0.0)
Hypoaesthesia	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Peripheral sensory neuropathy	0	(0.0)	0	(0.0)	3	(15.8)	0	(0.0)
Psychiatric disorders	**2**	**(9.5)**	**0**	**(0.0)**	**2**	**(10.5)**	**0**	**(0.0)**
Abulia	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Delusion	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Insomnia	1	(4.8)	0	(0.0)	2	(10.5)	0	(0.0)
Renal and urinary disorders	**1**	**(4.8)**	**0**	**(0.0)**	**3**	**(15.8)**	**0**	**(0.0)**
Chronic kidney disease	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Renal disorder	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Renal impairment	1	(4.8)	0	(0.0)	1	(5.3)	0	(0.0)
Reproductive system and breast disorders	**1**	**(4.8)**	**1**	**(4.8)**	**0**	**(0.0)**	**0**	**(0.0)**
Ovarian haemorrhage	1	(4.8)	1	(4.8)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
(ASaT Japan Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Respiratory, thoracic and mediastinal disorders	**6**	**(28.6)**	**2**	**(9.5)**	**10**	**(52.6)**	**2**	**(10.5)**
Cough	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Dyspnoea	2	(9.5)	0	(0.0)	0	(0.0)	0	(0.0)
Haemoptysis	3	(14.3)	0	(0.0)	0	(0.0)	0	(0.0)
Hiccups	1	(4.8)	0	(0.0)	8	(42.1)	0	(0.0)
Hypoxia	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Interstitial lung disease	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Painful respiration	1	(4.8)	1	(4.8)	0	(0.0)	0	(0.0)
Pleural effusion	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonitis	1	(4.8)	1	(4.8)	1	(5.3)	1	(5.3)
Pulmonary alveolar haemorrhage	0	(0.0)	0	(0.0)	1	(5.3)	1	(5.3)
Rhinitis allergic	0	(0.0)	0	(0.0)	2	(10.5)	0	(0.0)
Upper respiratory tract inflammation	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Skin and subcutaneous tissue disorders	**15**	**(71.4)**	**1**	**(4.8)**	**5**	**(26.3)**	**0**	**(0.0)**
Alopecia	0	(0.0)	0	(0.0)	2	(10.5)	0	(0.0)
Asteatosis	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Decubitus ulcer	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Dry skin	3	(14.3)	0	(0.0)	0	(0.0)	0	(0.0)
Eczema	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Erythema	2	(9.5)	0	(0.0)	0	(0.0)	0	(0.0)
Pruritus	3	(14.3)	0	(0.0)	0	(0.0)	0	(0.0)
Rash	4	(19.0)	0	(0.0)	0	(0.0)	0	(0.0)
Rash maculo-papular	3	(14.3)	1	(4.8)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) (ASaT Japan Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**15**	**(71.4)**	**1**	**(4.8)**	**5**	**(26.3)**	**0**	**(0.0)**
Urticaria	3	(14.3)	0	(0.0)	1	(5.3)	0	(0.0)
Vascular disorders	**2**	**(9.5)**	**1**	**(4.8)**	**0**	**(0.0)**	**0**	**(0.0)**
Hypertension	2	(9.5)	1	(4.8)	0	(0.0)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.
Adverse event terms are from MedDRA Version 18.0.
(Database Cutoff Date: 09MAY2016).

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付録 2.7.4- 154 副作用（いずれかの投与群で発現割合 0%超）
024 試験（日本人安全性解析対象集団）

Subjects With Drug-related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) (ASaT Japan Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	21				19			
with one or more adverse events	20	(95.2)	7	(33.3)	18	(94.7)	9	(47.4)
with no adverse events	1	(4.8)	14	(66.7)	1	(5.3)	10	(52.6)
Blood and lymphatic system disorders	**4**	**(19.0)**	**1**	**(4.8)**	**10**	**(52.6)**	**5**	**(26.3)**
Anaemia	2	(9.5)	1	(4.8)	9	(47.4)	5	(26.3)
Eosinophilia	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Leukopenia	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Lymphopenia	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Neutropenia	0	(0.0)	0	(0.0)	2	(10.5)	1	(5.3)
Cardiac disorders	**1**	**(4.8)**	**1**	**(4.8)**	**0**	**(0.0)**	**0**	**(0.0)**
Pericardial effusion	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Pericarditis	1	(4.8)	1	(4.8)	0	(0.0)	0	(0.0)
Endocrine disorders	**4**	**(19.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Autoimmune thyroiditis	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Hyperthyroidism	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Hypothyroidism	3	(14.3)	0	(0.0)	0	(0.0)	0	(0.0)
Eye disorders	**1**	**(4.8)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Dry eye	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Gastrointestinal disorders	**8**	**(38.1)**	**1**	**(4.8)**	**15**	**(78.9)**	**0**	**(0.0)**
Abdominal pain upper	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)

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Subjects With Drug-related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
(ASaT Japan Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Gastrointestinal disorders	**8**	**(38.1)**	**1**	**(4.8)**	**15**	**(78.9)**	**0**	**(0.0)**
Constipation	1	(4.8)	0	(0.0)	5	(26.3)	0	(0.0)
Diarrhoea	4	(19.0)	1	(4.8)	3	(15.8)	0	(0.0)
Dyspepsia	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Enterocolitis	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Gastritis	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Gingival pain	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Lip pain	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Nausea	0	(0.0)	0	(0.0)	11	(57.9)	0	(0.0)
Stomatitis	3	(14.3)	0	(0.0)	1	(5.3)	0	(0.0)
Vomiting	0	(0.0)	0	(0.0)	2	(10.5)	0	(0.0)
General disorders and administration site conditions	**9**	**(42.9)**	**1**	**(4.8)**	**11**	**(57.9)**	**0**	**(0.0)**
Face oedema	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Fatigue	2	(9.5)	1	(4.8)	2	(10.5)	0	(0.0)
Malaise	1	(4.8)	0	(0.0)	8	(42.1)	0	(0.0)
Oedema	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Oedema peripheral	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Pyrexia	5	(23.8)	0	(0.0)	2	(10.5)	0	(0.0)
Infections and infestations	**1**	**(4.8)**	**0**	**(0.0)**	**4**	**(21.1)**	**3**	**(15.8)**
Cellulitis	0	(0.0)	0	(0.0)	1	(5.3)	1	(5.3)
Infected dermal cyst	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Lung infection	0	(0.0)	0	(0.0)	2	(10.5)	2	(10.5)

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Subjects With Drug-related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) (ASaT Japan Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Infections and infestations	**1**	**(4.8)**	**0**	**(0.0)**	**4**	**(21.1)**	**3**	**(15.8)**
Nasopharyngitis	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Oral candidiasis	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Tinea pedis	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Upper respiratory tract infection	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Injury, poisoning and procedural complications	**3**	**(14.3)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Infusion related reaction	3	(14.3)	0	(0.0)	0	(0.0)	0	(0.0)
Investigations	**6**	**(28.6)**	**0**	**(0.0)**	**13**	**(68.4)**	**3**	**(15.8)**
Alanine aminotransferase increased	2	(9.5)	0	(0.0)	2	(10.5)	0	(0.0)
Aspartate aminotransferase increased	1	(4.8)	0	(0.0)	1	(5.3)	0	(0.0)
Blood bilirubin increased	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Blood creatinine increased	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Blood thyroid stimulating hormone decreased	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Blood thyroid stimulating hormone increased	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Blood urea increased	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Gamma-glutamyltransferase increased	1	(4.8)	0	(0.0)	1	(5.3)	0	(0.0)
Haemoglobin decreased	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Lymphocyte count decreased	0	(0.0)	0	(0.0)	1	(5.3)	1	(5.3)
Neutrophil count decreased	0	(0.0)	0	(0.0)	4	(21.1)	1	(5.3)
Platelet count decreased	0	(0.0)	0	(0.0)	8	(42.1)	3	(15.8)

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Subjects With Drug-related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) (ASaT Japan Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**6**	**(28.6)**	**0**	**(0.0)**	**13**	**(68.4)**	**3**	**(15.8)**
Weight decreased	1	(4.8)	0	(0.0)	1	(5.3)	0	(0.0)
White blood cell count decreased	0	(0.0)	0	(0.0)	8	(42.1)	1	(5.3)
Metabolism and nutrition disorders	**5**	**(23.8)**	**2**	**(9.5)**	**12**	**(63.2)**	**3**	**(15.8)**
Decreased appetite	3	(14.3)	0	(0.0)	12	(63.2)	2	(10.5)
Dyslipidaemia	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Hyperkalaemia	1	(4.8)	0	(0.0)	1	(5.3)	0	(0.0)
Hypoalbuminaemia	2	(9.5)	2	(9.5)	4	(21.1)	2	(10.5)
Hyponatraemia	0	(0.0)	0	(0.0)	1	(5.3)	1	(5.3)
Hypovolaemia	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Musculoskeletal and connective tissue disorders	**3**	**(14.3)**	**0**	**(0.0)**	**2**	**(10.5)**	**0**	**(0.0)**
Arthralgia	2	(9.5)	0	(0.0)	2	(10.5)	0	(0.0)
Arthritis	2	(9.5)	0	(0.0)	0	(0.0)	0	(0.0)
Nervous system disorders	**0**	**(0.0)**	**0**	**(0.0)**	**6**	**(31.6)**	**0**	**(0.0)**
Dysgeusia	0	(0.0)	0	(0.0)	2	(10.5)	0	(0.0)
Hypoaesthesia	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Peripheral sensory neuropathy	0	(0.0)	0	(0.0)	3	(15.8)	0	(0.0)
Psychiatric disorders	**1**	**(4.8)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Abulia	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Drug-related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups)
(ASaT Japan Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Renal and urinary disorders	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(15.8)**	**0**	**(0.0)**
Chronic kidney disease	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Renal disorder	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Renal impairment	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**4**	**(19.0)**	**1**	**(4.8)**	**6**	**(31.6)**	**2**	**(10.5)**
Dyspnoea	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Hiccups	1	(4.8)	0	(0.0)	6	(31.6)	0	(0.0)
Hypoxia	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)
Interstitial lung disease	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Pleural effusion	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonitis	1	(4.8)	1	(4.8)	1	(5.3)	1	(5.3)
Pulmonary alveolar haemorrhage	0	(0.0)	0	(0.0)	1	(5.3)	1	(5.3)
Skin and subcutaneous tissue disorders	**12**	**(57.1)**	**1**	**(4.8)**	**3**	**(15.8)**	**0**	**(0.0)**
Alopecia	0	(0.0)	0	(0.0)	2	(10.5)	0	(0.0)
Dry skin	2	(9.5)	0	(0.0)	0	(0.0)	0	(0.0)
Eczema	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Erythema	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Pruritus	2	(9.5)	0	(0.0)	0	(0.0)	0	(0.0)
Rash	3	(14.3)	0	(0.0)	0	(0.0)	0	(0.0)
Rash maculo-papular	3	(14.3)	1	(4.8)	0	(0.0)	0	(0.0)
Urticaria	2	(9.5)	0	(0.0)	1	(5.3)	0	(0.0)

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Subjects With Drug-related Adverse Events by All Toxicity Grades vs. Grades 3-5 (Incidence > 0% in One or More Treatment Groups) (ASaT Japan Population)

	Pembrolizumab				SOC			
	All Grades		Grades 3 – 5		All Grades		Grades 3 – 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Vascular disorders	**1**	**(4.8)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Hypertension	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.
Adverse event terms are from MedDRA Version 18.0.
(Database Cutoff Date: 09MAY2016).

Confidential

付録 2.7.4- 155 最終投与後 90 日までに発現した重篤な有害事象
（いずれかの投与群で発現割合 0%超）
024 試験（日本人安全性解析対象集団）

Subjects With Serious Adverse Events by Decreasing Incidence
(Incidence >0% in One or More Treatment Groups)
(ASaT Japan Population)

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	21		19		40	
with one or more adverse events	7	(33.3)	7	(36.8)	14	(35.0)
with no adverse events	14	(66.7)	12	(63.2)	26	(65.0)
Lung infection	0	(0.0)	2	(10.5)	2	(5.0)
Pneumonitis	1	(4.8)	1	(5.3)	2	(5.0)
Cardiac failure	1	(4.8)	0	(0.0)	1	(2.5)
Cardio-respiratory arrest	0	(0.0)	1	(5.3)	1	(2.5)
Cellulitis	0	(0.0)	1	(5.3)	1	(2.5)
Decreased appetite	1	(4.8)	0	(0.0)	1	(2.5)
Diarrhoea	1	(4.8)	0	(0.0)	1	(2.5)
Enterocolitis	1	(4.8)	0	(0.0)	1	(2.5)
Face oedema	1	(4.8)	0	(0.0)	1	(2.5)
Fatigue	1	(4.8)	0	(0.0)	1	(2.5)
Hypovolaemia	1	(4.8)	0	(0.0)	1	(2.5)
Infected neoplasm	1	(4.8)	0	(0.0)	1	(2.5)
Infusion related reaction	1	(4.8)	0	(0.0)	1	(2.5)
Ovarian haemorrhage	1	(4.8)	0	(0.0)	1	(2.5)
Painful respiration	1	(4.8)	0	(0.0)	1	(2.5)
Pericarditis	1	(4.8)	0	(0.0)	1	(2.5)
Platelet count decreased	0	(0.0)	1	(5.3)	1	(2.5)
Pneumonia	0	(0.0)	1	(5.3)	1	(2.5)
Pulmonary alveolar haemorrhage	0	(0.0)	1	(5.3)	1	(2.5)

Every subject is counted a single time for each applicable specific adverse event.

A system organ class appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.

MedDRA preferred terms "Neoplasm Progression" and "Malignant Neoplasm Progression" not related to the drug are excluded.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

C Confidential

付録 2.7.4- 156 最終投与後 90 日までに発現した重篤な副作用
（いずれかの投与群で発現割合 0%超）
024 試験（日本人安全性解析対象集団）

Subjects With Drug-Related Serious Adverse Events by Decreasing Incidence
(Incidence >0% in One or More Treatment Groups)
(ASaT Japan Population)

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	21		19		40	
with one or more adverse events	4	(19.0)	5	(26.3)	9	(22.5)
with no adverse events	17	(81.0)	14	(73.7)	31	(77.5)
Lung infection	0	(0.0)	2	(10.5)	2	(5.0)
Pneumonitis	1	(4.8)	1	(5.3)	2	(5.0)
Cellulitis	0	(0.0)	1	(5.3)	1	(2.5)
Diarrhoea	1	(4.8)	0	(0.0)	1	(2.5)
Enterocolitis	1	(4.8)	0	(0.0)	1	(2.5)
Face oedema	1	(4.8)	0	(0.0)	1	(2.5)
Fatigue	1	(4.8)	0	(0.0)	1	(2.5)
Hypovolaemia	1	(4.8)	0	(0.0)	1	(2.5)
Infusion related reaction	1	(4.8)	0	(0.0)	1	(2.5)
Pericarditis	1	(4.8)	0	(0.0)	1	(2.5)
Platelet count decreased	0	(0.0)	1	(5.3)	1	(2.5)
Pulmonary alveolar haemorrhage	0	(0.0)	1	(5.3)	1	(2.5)

Every subject is counted a single time for each applicable specific adverse event.

A system organ class appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.

MedDRA preferred terms "Neoplasm Progression" and "Malignant Neoplasm Progression" not related to the drug are excluded.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

C Confidential

付録 2.7.4- 157 治験薬の休薬に至った有害事象
（いずれかの投与群で発現割合 0%超）
024 試験（日本人安全性解析対象集団）

Subjects With Adverse Events Resulting in Treatment Interruption by Decreasing Incidence (Incidence >0% in One or More Treatment Groups) (ASaT Japan Population)

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	21		19		40	
with one or more adverse events	6	(28.6)	5	(26.3)	11	(27.5)
with no adverse events	15	(71.4)	14	(73.7)	29	(72.5)
Platelet count decreased	0	(0.0)	2	(10.5)	2	(5.0)
Urticaria	2	(9.5)	0	(0.0)	2	(5.0)
Anaemia	0	(0.0)	1	(5.3)	1	(2.5)
Cardiac failure	1	(4.8)	0	(0.0)	1	(2.5)
Cough	0	(0.0)	1	(5.3)	1	(2.5)
Decreased appetite	1	(4.8)	0	(0.0)	1	(2.5)
Diarrhoea	1	(4.8)	0	(0.0)	1	(2.5)
Dyspnoea	1	(4.8)	0	(0.0)	1	(2.5)
Haematemesis	1	(4.8)	0	(0.0)	1	(2.5)
Hypoalbuminaemia	1	(4.8)	0	(0.0)	1	(2.5)
Infected neoplasm	1	(4.8)	0	(0.0)	1	(2.5)
Lung infection	0	(0.0)	1	(5.3)	1	(2.5)
Malaise	0	(0.0)	1	(5.3)	1	(2.5)
Neutrophil count decreased	0	(0.0)	1	(5.3)	1	(2.5)
Oedema peripheral	1	(4.8)	0	(0.0)	1	(2.5)
Painful respiration	1	(4.8)	0	(0.0)	1	(2.5)
Pericardial effusion	1	(4.8)	0	(0.0)	1	(2.5)
Pericarditis	1	(4.8)	0	(0.0)	1	(2.5)
Pleural effusion	1	(4.8)	0	(0.0)	1	(2.5)
Pneumonia bacterial	1	(4.8)	0	(0.0)	1	(2.5)
Rash maculo-papular	1	(4.8)	0	(0.0)	1	(2.5)
Renal impairment	1	(4.8)	0	(0.0)	1	(2.5)
Upper respiratory tract inflammation	0	(0.0)	1	(5.3)	1	(2.5)
White blood cell count decreased	0	(0.0)	1	(5.3)	1	(2.5)

Every subject is counted a single time for each applicable specific adverse event.

A system organ class appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.

MedDRA preferred terms "Neoplasm Progression" and "Malignant Neoplasm Progression" not related to the drug are excluded.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

C Confidential

付録 2.7.4- 158 AEOSI を発現した患者の一覧
024 試験（日本人安全性解析対象集団）

Listing of Subjects With Adverse Events
AEOSI
(ASaT Japan Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
Pembrolizumab									
Trial Number=3475-024, Site Number=0252, Subject ID=243913, Gender=M, Race=Asian, Age=58 Years, Rel Day of Last Recorded Dose of Study Medication=1									
243913	Safety Follow-up	7	Pneumonitis	Continuing	4	Y	Y	Discontinued	Not Resolved
Trial Number=3475-024, Site Number=0254, Subject ID=243920, Gender=M, Race=Asian, Age=52 Years, Rel Day of Last Recorded Dose of Study Medication=232									
243920	Treatment Cycle 3	45	Hyperthyroidism	1.41 Months	2	N	Y	None	Resolved
	Treatment Cycle 5	87	Hypothyroidism	Continuing	1	N	Y	None	Not Resolved
Trial Number=3475-024, Site Number=0255, Subject ID=243304, Gender=F, Race=Asian, Age=51 Years, Rel Day of Last Recorded Dose of Study Medication=381									
243304	Treatment Cycle 8	150	Autoimmune thyroiditis	Continuing	2	N	Y	None	Not Resolved
	Treatment Cycle 16	318	Hypersensitivity	2 Days	1	N	N	None	Resolved
Trial Number=3475-024, Site Number=0258, Subject ID=243312, Gender=F, Race=Asian, Age=40 Years, Rel Day of Last Recorded Dose of Study Medication=217									
243312	Treatment Cycle 2	21	Infusion related reaction	2 Days	2	N	Y	None	Resolved
		36	Rash maculo-papular	Continuing	3	N	Y	Interrupted	Not Resolved
Trial Number=3475-024, Site Number=0259, Subject ID=243601, Gender=M, Race=Asian, Age=67 Years, Rel Day of Last Recorded Dose of Study Medication=295									
243601	Safety Follow-up	314	Interstitial lung disease	Continuing	2	N	Y	None	Resolving
Trial Number=3475-024, Site Number=0259, Subject ID=243908, Gender=F, Race=Asian, Age=70 Years, Rel Day of Last Recorded Dose of Study Medication=231									
243908	Treatment Cycle 4	64	Hypothyroidism	3.48 Months	1	N	Y	None	Resolved
Trial Number=3475-024, Site Number=0335, Subject ID=243909, Gender=M, Race=Asian, Age=65 Years, Rel Day of Last Recorded Dose of Study Medication=337									
243909	Treatment Cycle 1	1	Infusion related reaction	3.25 Hours	2	Y	Y	None	Resolved

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Listing of Subjects With Adverse Events
AEOSI
(ASaT Japan Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
Pembrolizumab									
Trial Number=3475-024, Site Number=0335, Subject ID=243909, Gender=M, Race=Asian, Age=65 Years, Rel Day of Last Recorded Dose of Study Medication=337									
243909	Treatment Cycle 15	311	Enterocolitis	3.86 Weeks	2	Y	Y	None	Resolved
Trial Number=3475-024, Site Number=0336, Subject ID=243305, Gender=M, Race=Asian, Age=80 Years, Rel Day of Last Recorded Dose of Study Medication=344									
243305	Treatment Cycle 1	1	Infusion related reaction	2 Days	2	N	Y	None	Resolved
Trial Number=3475-024, Site Number=0342, Subject ID=243001, Gender=M, Race=Asian, Age=73 Years, Rel Day of Last Recorded Dose of Study Medication=274									
243001	Treatment Cycle 9	169	Hypothyroidism	Continuing	2	N	Y	None	Not Resolved
SOC									
Trial Number=3475-024, Site Number=0260, Subject ID=243906, Gender=M, Race=Asian, Age=61 Years, Rel Day of Last Recorded Dose of Study Medication=25									

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Listing of Subjects With Adverse Events
AEOSI
(ASaT Japan Population)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Toxicity Grade	Serious	Related	Action Taken	Outcome
SOC									
Trial Number=3475-024, Site Number=0260, Subject ID=243906, Gender=M, Race=Asian, Age=61 Years, Rel Day of Last Recorded Dose of Study Medication=25									
243906	Extended Safety Follow-up	61	Pneumonitis	Continuing	3	Y	Y	N/A	Not Resolved

Toxicity Grade: NCI CTCAE version 4.03.

Related: Investigator-assessed relationship of the adverse event to study medication. Y = RELATED, N = NOT RELATED

Action Taken: Discontinued = DRUG WITHDRAWN, Interrupted = DRUG INTERRUPTED, Reduced = DOSE REDUCED, Increased = DOSE INCREASED, None = DOSE NOT CHANGED, N/A = NOT APPLICABLE.

Outcome: Resolved = RECOVERED/RESOLVED, Resolving = RECOVERING/RESOLVING, Sequelae = RECOVERED/RESOLVED WITH SEQUELAE, Not resolved = NOT RECOVERED/NOT RESOLVED.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

Confidential

付録 2.7.4- 159 各 AEOSI に対する副腎皮質ホルモン剤の使用の要約
024 試験（日本人安全性解析対象集団）

Summary of Concomitant Corticosteroid Use for AEOSI - Colitis
(ASaT Japan Population)

	Pembrolizumab (N=21)		SOC (N=19)	
	n	%	n	%
Subjects with one or more Colitis events	1		0	
Treated with systemic corticosteroid	0	0	0	0
High starting dose†	0	0	0	0
Low starting dose‡	0	0	0	0
Not treated with systemic corticosteroid	1	100.0	0	0

The number of Subjects with one or more Colitis events is used as the denominator for the percentage calculation.

† High starting dose corticosteroid treatment is defined as >= 40 mg/day prednisone or equivalent.

‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

Summary of Concomitant Corticosteroid Use for AEOSI - Hyperthyroidism
(ASaT Japan Population)

	Pembrolizumab (N=21)		SOC (N=19)	
	n	%	n	%
Subjects with one or more Hyperthyroidism events	1		0	
Treated with systemic corticosteroid	0	0	0	0
High starting dose†	0	0	0	0
Low starting dose‡	0	0	0	0
Not treated with systemic corticosteroid	1	100.0	0	0

The number of Subjects with one or more Hyperthyroidism events is used as the denominator for the percentage calculation.

† High starting dose corticosteroid treatment is defined as >= 40 mg/day prednisone or equivalent.

‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

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Summary of Concomitant Corticosteroid Use for AEOSI - Hypothyroidism (ASaT Japan Population)

	Pembrolizumab (N=21)		SOC (N=19)	
	n	%	n	%
Subjects with one or more Hypothyroidism events	3		0	
Treated with systemic corticosteroid	0	0	0	0
High starting dose†	0	0	0	0
Low starting dose‡	0	0	0	0
Not treated with systemic corticosteroid	3	100.0	0	0

The number of Subjects with one or more Hypothyroidism events is used as the denominator for the percentage calculation.

† High starting dose corticosteroid treatment is defined as >= 40 mg/day prednisone or equivalent.

‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

Summary of Concomitant Corticosteroid Use for AEOSI - Infusion Reactions (ASaT Japan Population)

	Pembrolizumab (N=21)		SOC (N=19)	
	n	%	n	%
Subjects with one or more Infusion Reactions events	4		0	
Treated with systemic corticosteroid	1	25.0	0	0
High starting dose†	1	25.0	0	0
Low starting dose‡	0	0	0	0
Not treated with systemic corticosteroid	3	75.0	0	0

The number of Subjects with one or more Infusion Reactions events is used as the denominator for the percentage calculation.

† High starting dose corticosteroid treatment is defined as >= 40 mg/day prednisone or equivalent.

‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

Confidential

Summary of Concomitant Corticosteroid Use for AEOSI - Pneumonitis (ASaT Japan Population)

	Pembrolizumab (N=21)		SOC (N=19)	
	n	%	n	%
Subjects with one or more Pneumonitis events	2		1	
Treated with systemic corticosteroid	2	100.0	1	100.0
High starting dose†	1	50.0	1	100.0
Low starting dose‡	0	0	0	0
Not treated with systemic corticosteroid	0	0	0	0

The number of Subjects with one or more Pneumonitis events is used as the denominator for the percentage calculation.

† High starting dose corticosteroid treatment is defined as >= 40 mg/day prednisone or equivalent.

‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

Summary of Concomitant Corticosteroid Use for AEOSI - Skin (ASaT Japan Population)

	Pembrolizumab (N=21)		SOC (N=19)	
	n	%	n	%
Subjects with one or more Skin events	1		0	
Treated with systemic corticosteroid	0	0	0	0
High starting dose†	0	0	0	0
Low starting dose‡	0	0	0	0
Not treated with systemic corticosteroid	1	100.0	0	0

The number of Subjects with one or more Skin events is used as the denominator for the percentage calculation.

† High starting dose corticosteroid treatment is defined as >= 40 mg/day prednisone or equivalent.

‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

Confidential

Summary of Concomitant Corticosteroid Use for AEOSI - Thyroiditis (ASaT Japan Population)

	Pembrolizumab (N=21)		SOC (N=19)	
	n	%	n	%
Subjects with one or more Thyroiditis events	1		0	
Treated with systemic corticosteroid	0	0	0	0
High starting dose†	0	0	0	0
Low starting dose‡	0	0	0	0
Not treated with systemic corticosteroid	1	100.0	0	0

The number of Subjects with one or more Thyroiditis events is used as the denominator for the percentage calculation.

† High starting dose corticosteroid treatment is defined as >= 40 mg/day prednisone or equivalent.

‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

Confidential

Summary of Concomitant Corticosteroid Use for AEOSI Episodes - Colitis
(ASaT Japan Population)

	Pembrolizumab	SOC
Total Episodes	1	0
High Starting Dose (%) †	**0 (0.0)**	**0 (0.0)**
Low Starting Dose (%) ‡	**0 (0.0)**	**0 (0.0)**
Not Treated with Systemic Corticosteroid (%)	**1 (100.0)**	**0 (0.0)**

† High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
§ Ongoing corticosteroid treatment is censored at the cutoff date or date of death, whichever occurs first.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

Summary of Concomitant Corticosteroid Use for AEOSI Episodes - Hyperthyroidism
(ASaT Japan Population)

	Pembrolizumab	SOC
Total Episodes	1	0
High Starting Dose (%) †	**0 (0.0)**	**0 (0.0)**
Low Starting Dose (%) ‡	**0 (0.0)**	**0 (0.0)**
Not Treated with Systemic Corticosteroid (%)	**1 (100.0)**	**0 (0.0)**

† High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
§ Ongoing corticosteroid treatment is censored at the cutoff date or date of death, whichever occurs first.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

Confidential

Summary of Concomitant Corticosteroid Use for AEOSI Episodes - Hypothyroidism (ASaT Japan Population)

	Pembrolizumab	SOC
Total Episodes	3	0
High Starting Dose (%) †	**0 (0.0)**	**0 (0.0)**
Low Starting Dose (%) ‡	**0 (0.0)**	**0 (0.0)**
Not Treated with Systemic Corticosteroid (%)	**3 (100.0)**	**0 (0.0)**

† High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
§ Ongoing corticosteroid treatment is censored at the cutoff date or date of death, whichever occurs first.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

Summary of Concomitant Corticosteroid Use for AEOSI Episodes - Infusion Reactions (ASaT Japan Population)

	Pembrolizumab	SOC
Total Episodes	4	0
High Starting Dose (%) †	**1 (25.0)**	**0 (0.0)**
Starting dose (mg/day)		
Mean (Std)	75 (.)	0 (0)
Median (Range)	75 (75-75)	0 (0-0)
Duration (days)§		
Mean (Std)	1 (.)	0 (0)
Median (Range)	1 (1-1)	0 (0-0)
Low Starting Dose (%) ‡	**0 (0.0)**	**0 (0.0)**
Not Treated with Systemic Corticosteroid (%)	**3 (75.0)**	**0 (0.0)**

† High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
§ Ongoing corticosteroid treatment is censored at the cutoff date or date of death, whichever occurs first.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

Confidential

Summary of Concomitant Corticosteroid Use for AEOSI Episodes - Pneumonitis
(ASaT Japan Population)

	Pembrolizumab	SOC
Total Episodes	2	1
High Starting Dose (%) †	**0 (0.0)**	**1 (100.0)**
Starting dose (mg/day)		
Mean (Std)	0 (0)	50 (.)
Median (Range)	0 (0-0)	50 (50-50)
Duration (days)§		
Mean (Std)	0 (0)	7 (.)
Median (Range)	0 (0-0)	7 (7-7)
Low Starting Dose (%) ‡	**2 (100.0)**	**0 (0.0)**
Starting dose (mg/day)		
Mean (Std)	30 (0)	0 (0)
Median (Range)	30 (30-30)	0 (0-0)
Duration (days)§		
Mean (Std)	5 (4)	0 (0)
Median (Range)	5 (2-7)	0 (0-0)
Not Treated with Systemic Corticosteroid (%)	**0 (0.0)**	**0 (0.0)**

† High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
§ Ongoing corticosteroid treatment is censored at the cutoff date or date of death, whichever occurs first.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

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Summary of Concomitant Corticosteroid Use for AEOSI Episodes - Skin
(ASaT Japan Population)

	Pembrolizumab	SOC
Total Episodes	1	0
High Starting Dose (%) †	**0 (0.0)**	**0 (0.0)**
Low Starting Dose (%) ‡	**0 (0.0)**	**0 (0.0)**
Not Treated with Systemic Corticosteroid (%)	**1 (100.0)**	**0 (0.0)**

† High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
§ Ongoing corticosteroid treatment is censored at the cutoff date or date of death, whichever occurs first.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

Summary of Concomitant Corticosteroid Use for AEOSI Episodes - Thyroiditis
(ASaT Japan Population)

	Pembrolizumab	SOC
Total Episodes	1	0
High Starting Dose (%) †	**0 (0.0)**	**0 (0.0)**
Low Starting Dose (%) ‡	**0 (0.0)**	**0 (0.0)**
Not Treated with Systemic Corticosteroid (%)	**1 (100.0)**	**0 (0.0)**

† High starting dose corticosteroid treatment is defined as ≥ 40 mg/day prednisone or equivalent.
‡ Low starting dose corticosteroid treatment is defined as < 40 mg/day prednisone or equivalent.
§ Ongoing corticosteroid treatment is censored at the cutoff date or date of death, whichever occurs first.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 09MAY2016).

Confidential

付録 2.7.4- 160 各 AEOSI の Grade 別有害事象

024 試験（日本人安全性解析対象集団）

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Adrenal Insufficiency
(ASaT Japan Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	21		19	
with one or more adverse events	0	(0.0)	0	(0.0)
with no adverse events	21	(100.0)	19	(100.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.

Only the highest reported grade of a given adverse event is counted for the individual subject.

Grades are based on NCI CTCAE version 4.03.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Colitis
(ASaT Japan Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	21		19	
with one or more adverse events	1	(4.8)	0	(0.0)
Grade 2	1	(4.8)	0	(0.0)
with no adverse events	20	(95.2)	19	(100.0)
Gastrointestinal disorders	**1**	**(4.8)**	**0**	**(0.0)**
Enterocolitis	1	(4.8)	0	(0.0)
Grade 2	1	(4.8)	0	(0.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.

Only the highest reported grade of a given adverse event is counted for the individual subject.

Grades are based on NCI CTCAE version 4.03.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

Confidential

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Guillain-Barre Syndrome
(ASaT Japan Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	21		19	
with one or more adverse events	0	(0.0)	0	(0.0)
with no adverse events	21	(100.0)	19	(100.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.

Only the highest reported grade of a given adverse event is counted for the individual subject.

Grades are based on NCI CTCAE version 4.03.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Hepatitis
(ASaT Japan Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	21		19	
with one or more adverse events	0	(0.0)	0	(0.0)
with no adverse events	21	(100.0)	19	(100.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.

Only the highest reported grade of a given adverse event is counted for the individual subject.

Grades are based on NCI CTCAE version 4.03.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

C Confidential

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Hyperthyroidism
(ASaT Japan Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	21		19	
with one or more adverse events	1	(4.8)	0	(0.0)
Grade 2	1	(4.8)	0	(0.0)
with no adverse events	20	(95.2)	19	(100.0)
Endocrine disorders	**1**	**(4.8)**	**0**	**(0.0)**
Hyperthyroidism	1	(4.8)	0	(0.0)
Grade 2	1	(4.8)	0	(0.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.

Only the highest reported grade of a given adverse event is counted for the individual subject.

Grades are based on NCI CTCAE version 4.03.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Hypophysitis
(ASaT Japan Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	21		19	
with one or more adverse events	0	(0.0)	0	(0.0)
with no adverse events	21	(100.0)	19	(100.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.

Only the highest reported grade of a given adverse event is counted for the individual subject.

Grades are based on NCI CTCAE version 4.03.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

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Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Hypothyroidism
(ASaT Japan Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	21		19	
with one or more adverse events	3	(14.3)	0	(0.0)
Grade 1	2	(9.5)	0	(0.0)
Grade 2	1	(4.8)	0	(0.0)
with no adverse events	18	(85.7)	19	(100.0)
Endocrine disorders	**3**	**(14.3)**	**0**	**(0.0)**
Hypothyroidism	3	(14.3)	0	(0.0)
Grade 1	2	(9.5)	0	(0.0)
Grade 2	1	(4.8)	0	(0.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.

Only the highest reported grade of a given adverse event is counted for the individual subject.

Grades are based on NCI CTCAE version 4.03.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

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Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Infusion Reactions
(ASaT Japan Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	21		19	
with one or more adverse events	4	(19.0)	0	(0.0)
Grade 1	1	(4.8)	0	(0.0)
Grade 2	3	(14.3)	0	(0.0)
with no adverse events	17	(81.0)	19	(100.0)
Immune system disorders	**1**	**(4.8)**	**0**	**(0.0)**
Hypersensitivity	1	(4.8)	0	(0.0)
Grade 1	1	(4.8)	0	(0.0)
Injury, poisoning and procedural complications	**3**	**(14.3)**	**0**	**(0.0)**
Infusion related reaction	3	(14.3)	0	(0.0)
Grade 2	3	(14.3)	0	(0.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.

Only the highest reported grade of a given adverse event is counted for the individual subject.

Grades are based on NCI CTCAE version 4.03.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Myasthenic Syndrome
(ASaT Japan Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	21		19	
with one or more adverse events	0	(0.0)	0	(0.0)
with no adverse events	21	(100.0)	19	(100.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.

Only the highest reported grade of a given adverse event is counted for the individual subject.

Grades are based on NCI CTCAE version 4.03.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

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Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Myositis
(ASaT Japan Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	21		19	
with one or more adverse events	0	(0.0)	0	(0.0)
with no adverse events	21	(100.0)	19	(100.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.

Only the highest reported grade of a given adverse event is counted for the individual subject.

Grades are based on NCI CTCAE version 4.03.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Nephritis
(ASaT Japan Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	21		19	
with one or more adverse events	0	(0.0)	0	(0.0)
with no adverse events	21	(100.0)	19	(100.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.

Only the highest reported grade of a given adverse event is counted for the individual subject.

Grades are based on NCI CTCAE version 4.03.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

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Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Pancreatitis
(ASaT Japan Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	21		19	
with one or more adverse events	0	(0.0)	0	(0.0)
with no adverse events	21	(100.0)	19	(100.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.

Only the highest reported grade of a given adverse event is counted for the individual subject.

Grades are based on NCI CTCAE version 4.03.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Pneumonitis
(ASaT Japan Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	21		19	
with one or more adverse events	2	(9.5)	1	(5.3)
Grade 2	1	(4.8)	0	(0.0)
Grade 3	0	(0.0)	1	(5.3)
Grade 4	1	(4.8)	0	(0.0)
with no adverse events	19	(90.5)	18	(94.7)
Respiratory, thoracic and mediastinal disorders	**2**	**(9.5)**	**1**	**(5.3)**
Interstitial lung disease	1	(4.8)	0	(0.0)
Grade 2	1	(4.8)	0	(0.0)
Pneumonitis	1	(4.8)	1	(5.3)
Grade 3	0	(0.0)	1	(5.3)
Grade 4	1	(4.8)	0	(0.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.

Only the highest reported grade of a given adverse event is counted for the individual subject.

Grades are based on NCI CTCAE version 4.03.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

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Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Skin
(ASaT Japan Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	21		19	
with one or more adverse events	1	(4.8)	0	(0.0)
Grade 3	1	(4.8)	0	(0.0)
with no adverse events	20	(95.2)	19	(100.0)
Skin and subcutaneous tissue disorders	**1**	**(4.8)**	**0**	**(0.0)**
Rash maculo-papular	1	(4.8)	0	(0.0)
Grade 3	1	(4.8)	0	(0.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.

Only the highest reported grade of a given adverse event is counted for the individual subject.

Grades are based on NCI CTCAE version 4.03.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Thyroiditis
(ASaT Japan Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	21		19	
with one or more adverse events	1	(4.8)	0	(0.0)
Grade 2	1	(4.8)	0	(0.0)
with no adverse events	20	(95.2)	19	(100.0)
Endocrine disorders	**1**	**(4.8)**	**0**	**(0.0)**
Autoimmune thyroiditis	1	(4.8)	0	(0.0)
Grade 2	1	(4.8)	0	(0.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.

Only the highest reported grade of a given adverse event is counted for the individual subject.

Grades are based on NCI CTCAE version 4.03.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

C Confidential

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Type 1 Diabetes Mellitus
(ASaT Japan Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	21		19	
with one or more adverse events	0	(0.0)	0	(0.0)
with no adverse events	21	(100.0)	19	(100.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.

Only the highest reported grade of a given adverse event is counted for the individual subject.

Grades are based on NCI CTCAE version 4.03.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

Subjects With Adverse Events by Maximum Toxicity Grade
(Incidence >0% in One or More Treatment Groups)
AEOSI - Uveitis
(ASaT Japan Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	21		19	
with one or more adverse events	0	(0.0)	0	(0.0)
with no adverse events	21	(100.0)	19	(100.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.

Only the highest reported grade of a given adverse event is counted for the individual subject.

Grades are based on NCI CTCAE version 4.03.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

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付録 2.7.4- 161 臨床検査値の Grade がベースラインより悪化した患者での臨床検査値異常の最大 Grade の要約
（ベースライン及びベースライン後の測定がある患者）
024 試験（日本人安全性解析対象集団）

Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline
(Subjects with Both Baseline and Post-baseline Measurements)
(ASaT Japan Population)

Laboratory Abnormality	Pembrolizumab (N=21)	SOC (N=19)
Alanine Aminotransferase Increased		
Subjects with Baseline and Post-Baseline Value	20	19
Toxicity Grade 1	10 (50.0)	4 (21.1)
Toxicity Grade 2	0 (0.0)	0 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	0 (0.0)	0 (0.0)
All Grades	10 (50.0)	4 (21.1)
Albumin Decreased		
Subjects with Baseline and Post-Baseline Value	20	19
Toxicity Grade 1	3 (15.0)	5 (26.3)
Toxicity Grade 2	1 (5.0)	3 (15.8)
Toxicity Grade 3	2 (10.0)	2 (10.5)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	2 (10.0)	2 (10.5)
All Grades	6 (30.0)	10 (52.6)
Alkaline Phosphatase Increased		
Subjects with Baseline and Post-Baseline Value	20	19
Toxicity Grade 1	4 (20.0)	5 (26.3)
Toxicity Grade 2	0 (0.0)	0 (0.0)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline
(Subjects with Both Baseline and Post-baseline Measurements)
(ASaT Japan Population)

Laboratory Abnormality	Pembrolizumab (N=21)	SOC (N=19)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	0 (0.0)	0 (0.0)
All Grades	4 (20.0)	5 (26.3)
Aspartate Aminotransferase Increased		
Subjects with Baseline and Post-Baseline Value	20	19
Toxicity Grade 1	5 (25.0)	5 (26.3)
Toxicity Grade 2	0 (0.0)	0 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	0 (0.0)	0 (0.0)
All Grades	5 (25.0)	5 (26.3)
Bilirubin Increased		
Subjects with Baseline and Post-Baseline Value	20	19
Toxicity Grade 1	3 (15.0)	0 (0.0)
Toxicity Grade 2	1 (5.0)	0 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	0 (0.0)	0 (0.0)
All Grades	4 (20.0)	0 (0.0)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline
(Subjects with Both Baseline and Post-baseline Measurements)
(ASaT Japan Population)

Laboratory Abnormality	Pembrolizumab (N=21)	SOC (N=19)
Calcium Decreased		
Subjects with Baseline and Post-Baseline Value	20	19
Toxicity Grade 1	3 (15.0)	5 (26.3)
Toxicity Grade 2	3 (15.0)	1 (5.3)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	0 (0.0)	0 (0.0)
All Grades	6 (30.0)	6 (31.6)
Calcium Increased		
Subjects with Baseline and Post-Baseline Value	20	19
Toxicity Grade 1	0 (0.0)	2 (10.5)
Toxicity Grade 2	0 (0.0)	1 (5.3)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	0 (0.0)	0 (0.0)
All Grades	0 (0.0)	3 (15.8)
Creatinine Increased		
Subjects with Baseline and Post-Baseline Value	20	19
Toxicity Grade 1	3 (15.0)	4 (21.1)
Toxicity Grade 2	1 (5.0)	2 (10.5)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline
(Subjects with Both Baseline and Post-baseline Measurements)
(ASaT Japan Population)

Laboratory Abnormality	Pembrolizumab (N=21)	SOC (N=19)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	0 (0.0)	0 (0.0)
All Grades	4 (20.0)	6 (31.6)
Glucose Decreased		
Subjects with Baseline and Post-Baseline Value	19	19
Toxicity Grade 1	0 (0.0)	3 (15.8)
Toxicity Grade 2	0 (0.0)	0 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	0 (0.0)	0 (0.0)
All Grades	0 (0.0)	3 (15.8)
Glucose Increased		
Subjects with Baseline and Post-Baseline Value	19	19
Toxicity Grade 1	7 (36.8)	2 (10.5)
Toxicity Grade 2	2 (10.5)	3 (15.8)
Toxicity Grade 3	0 (0.0)	1 (5.3)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	0 (0.0)	1 (5.3)
All Grades	9 (47.4)	6 (31.6)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline
(Subjects with Both Baseline and Post-baseline Measurements)
(ASaT Japan Population)

Laboratory Abnormality	Pembrolizumab (N=21)	SOC (N=19)
Hemoglobin Decreased		
Subjects with Baseline and Post-Baseline Value	20	19
Toxicity Grade 1	4 (20.0)	5 (26.3)
Toxicity Grade 2	3 (15.0)	5 (26.3)
Toxicity Grade 3	1 (5.0)	5 (26.3)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	1 (5.0)	5 (26.3)
All Grades	8 (40.0)	15 (78.9)
Leukocytes Decreased		
Subjects with Baseline and Post-Baseline Value	20	19
Toxicity Grade 1	0 (0.0)	5 (26.3)
Toxicity Grade 2	0 (0.0)	5 (26.3)
Toxicity Grade 3	0 (0.0)	1 (5.3)
Toxicity Grade 4	0 (0.0)	1 (5.3)
Grade 3-4	0 (0.0)	2 (10.5)
All Grades	0 (0.0)	12 (63.2)
Lymphocytes Decreased		
Subjects with Baseline and Post-Baseline Value	20	19
Toxicity Grade 1	0 (0.0)	2 (10.5)
Toxicity Grade 2	1 (5.0)	0 (0.0)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline
(Subjects with Both Baseline and Post-baseline Measurements)
(ASaT Japan Population)

Laboratory Abnormality	Pembrolizumab (N=21)	SOC (N=19)
Toxicity Grade 3	1 (5.0)	2 (10.5)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	1 (5.0)	2 (10.5)
All Grades	2 (10.0)	4 (21.1)
Magnesium Decreased		
Subjects with Baseline and Post-Baseline Value	19	19
Toxicity Grade 1	4 (21.1)	1 (5.3)
Toxicity Grade 2	0 (0.0)	0 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	0 (0.0)	0 (0.0)
All Grades	4 (21.1)	1 (5.3)
Magnesium Increased		
Subjects with Baseline and Post-Baseline Value	19	19
Toxicity Grade 1	2 (10.5)	2 (10.5)
Toxicity Grade 2	0 (0.0)	0 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	0 (0.0)	0 (0.0)
All Grades	2 (10.5)	2 (10.5)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline
(Subjects with Both Baseline and Post-baseline Measurements)
(ASaT Japan Population)

Laboratory Abnormality	Pembrolizumab (N=21)	SOC (N=19)
Neutrophils Decreased		
Subjects with Baseline and Post-Baseline Value	20	19
Toxicity Grade 1	0 (0.0)	2 (10.5)
Toxicity Grade 2	0 (0.0)	4 (21.1)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	1 (5.3)
Grade 3-4	0 (0.0)	1 (5.3)
All Grades	0 (0.0)	7 (36.8)
Phosphate Decreased		
Subjects with Baseline and Post-Baseline Value	19	18
Toxicity Grade 1	0 (0.0)	1 (5.6)
Toxicity Grade 2	2 (10.5)	2 (11.1)
Toxicity Grade 3	1 (5.3)	1 (5.6)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	1 (5.3)	1 (5.6)
All Grades	3 (15.8)	4 (22.2)
Platelet Decreased		
Subjects with Baseline and Post-Baseline Value	20	19
Toxicity Grade 1	0 (0.0)	5 (26.3)
Toxicity Grade 2	1 (5.0)	0 (0.0)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline
(Subjects with Both Baseline and Post-baseline Measurements)
(ASaT Japan Population)

Laboratory Abnormality	Pembrolizumab (N=21)	SOC (N=19)
Toxicity Grade 3	0 (0.0)	2 (10.5)
Toxicity Grade 4	0 (0.0)	1 (5.3)
Grade 3-4	0 (0.0)	3 (15.8)
All Grades	1 (5.0)	8 (42.1)
Potassium Decreased		
Subjects with Baseline and Post-Baseline Value	20	19
Toxicity Grade 1	3 (15.0)	0 (0.0)
Toxicity Grade 2	0 (0.0)	0 (0.0)
Toxicity Grade 3	1 (5.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	1 (5.0)	0 (0.0)
All Grades	4 (20.0)	0 (0.0)
Potassium Increased		
Subjects with Baseline and Post-Baseline Value	20	19
Toxicity Grade 1	6 (30.0)	9 (47.4)
Toxicity Grade 2	1 (5.0)	3 (15.8)
Toxicity Grade 3	0 (0.0)	1 (5.3)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	0 (0.0)	1 (5.3)
All Grades	7 (35.0)	13 (68.4)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline
(Subjects with Both Baseline and Post-baseline Measurements)
(ASaT Japan Population)

Laboratory Abnormality	Pembrolizumab (N=21)	SOC (N=19)
Prothrombin Intl. Normalized Ratio Increased		
Subjects with Baseline and Post-Baseline Value	10	9
Toxicity Grade 1	1 (10.0)	0 (0.0)
Toxicity Grade 2	0 (0.0)	0 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	0 (0.0)	0 (0.0)
All Grades	1 (10.0)	0 (0.0)
Sodium Decreased		
Subjects with Baseline and Post-Baseline Value	20	19
Toxicity Grade 1	5 (25.0)	7 (36.8)
Toxicity Grade 2	0 (0.0)	0 (0.0)
Toxicity Grade 3	1 (5.0)	3 (15.8)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	1 (5.0)	3 (15.8)
All Grades	6 (30.0)	10 (52.6)
Sodium Increased		
Subjects with Baseline and Post-Baseline Value	20	19
Toxicity Grade 1	1 (5.0)	0 (0.0)
Toxicity Grade 2	0 (0.0)	0 (0.0)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline (Subjects with Both Baseline and Post-baseline Measurements) (ASaT Japan Population)

Laboratory Abnormality	Pembrolizumab (N=21)	SOC (N=19)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Grade 3-4	0 (0.0)	0 (0.0)
All Grades	1 (5.0)	0 (0.0)

If a subject had more than one graded abnormalities for a lab test, only the highest grade is counted.
Grades are based on NCI CTCAE version 4.03.
Note: For each laboratory abnormality, the denominator is the number of subjects who had a baseline and post-baseline value for that laboratory test.
Reporting for the lab tests goes through 30 days after the end of treatment for each subject.
(Database Cutoff Date: 09MAY2016)

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付録 2.7.4- 162 臨床検査値の Grade がベースラインより悪化した患者での臨床検査値異常の最大 Grade の要約 024 試験（日本人安全性解析対象集団）

Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline
(ASaT Japan Population)

Laboratory Test	Pembrolizumab (N=21)	SOC (N=19)
APTT Increased		
All Grades	1 (4.8)	0 (0.0)
Toxicity Grade 1	1 (4.8)	0 (0.0)
Toxicity Grade 2	0 (0.0)	0 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Alanine Aminotransferase Increased		
All Grades	11 (52.4)	4 (21.1)
Toxicity Grade 1	11 (52.4)	4 (21.1)
Toxicity Grade 2	0 (0.0)	0 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Albumin Decreased		
All Grades	7 (33.3)	10 (52.6)
Toxicity Grade 1	3 (14.3)	5 (26.3)
Toxicity Grade 2	2 (9.5)	3 (15.8)
Toxicity Grade 3	2 (9.5)	2 (10.5)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Alkaline Phosphatase Increased		
All Grades	4 (19.0)	5 (26.3)
Toxicity Grade 1	4 (19.0)	5 (26.3)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline (ASaT Japan Population)

Laboratory Test	Pembrolizumab (N=21)	SOC (N=19)
Toxicity Grade 2	0 (0.0)	0 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Aspartate Aminotransferase Increased		
All Grades	6 (28.6)	5 (26.3)
Toxicity Grade 1	6 (28.6)	5 (26.3)
Toxicity Grade 2	0 (0.0)	0 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Bilirubin Increased		
All Grades	4 (19.0)	0 (0.0)
Toxicity Grade 1	3 (14.3)	0 (0.0)
Toxicity Grade 2	1 (4.8)	0 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Calcium Decreased		
All Grades	6 (28.6)	6 (31.6)
Toxicity Grade 1	3 (14.3)	5 (26.3)
Toxicity Grade 2	3 (14.3)	1 (5.3)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline
(ASaT Japan Population)

Laboratory Test	Pembrolizumab (N=21)	SOC (N=19)
Calcium Increased		
All Grades	0 (0.0)	3 (15.8)
Toxicity Grade 1	0 (0.0)	2 (10.5)
Toxicity Grade 2	0 (0.0)	1 (5.3)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Creatinine Increased		
All Grades	4 (19.0)	6 (31.6)
Toxicity Grade 1	3 (14.3)	4 (21.1)
Toxicity Grade 2	1 (4.8)	2 (10.5)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Gamma Glutamyl Transferase Increased		
All Grades	1 (4.8)	1 (5.3)
Toxicity Grade 1	0 (0.0)	1 (5.3)
Toxicity Grade 2	1 (4.8)	0 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Glucose Decreased		
All Grades	1 (4.8)	3 (15.8)
Toxicity Grade 1	1 (4.8)	3 (15.8)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline
(ASaT Japan Population)

Laboratory Test	Pembrolizumab (N=21)	SOC (N=19)
Toxicity Grade 2	0 (0.0)	0 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Glucose Increased		
All Grades	11 (52.4)	6 (31.6)
Toxicity Grade 1	8 (38.1)	2 (10.5)
Toxicity Grade 2	3 (14.3)	3 (15.8)
Toxicity Grade 3	0 (0.0)	1 (5.3)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Hemoglobin Decreased		
All Grades	9 (42.9)	15 (78.9)
Toxicity Grade 1	4 (19.0)	5 (26.3)
Toxicity Grade 2	4 (19.0)	5 (26.3)
Toxicity Grade 3	1 (4.8)	5 (26.3)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Leukocytes Decreased		
All Grades	0 (0.0)	12 (63.2)
Toxicity Grade 1	0 (0.0)	5 (26.3)
Toxicity Grade 2	0 (0.0)	5 (26.3)
Toxicity Grade 3	0 (0.0)	1 (5.3)
Toxicity Grade 4	0 (0.0)	1 (5.3)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline (ASaT Japan Population)

Laboratory Test	Pembrolizumab (N=21)	SOC (N=19)
Lymphocytes Decreased		
All Grades	2 (9.5)	4 (21.1)
Toxicity Grade 1	0 (0.0)	2 (10.5)
Toxicity Grade 2	1 (4.8)	0 (0.0)
Toxicity Grade 3	1 (4.8)	2 (10.5)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Magnesium Decreased		
All Grades	4 (19.0)	1 (5.3)
Toxicity Grade 1	4 (19.0)	1 (5.3)
Toxicity Grade 2	0 (0.0)	0 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Magnesium Increased		
All Grades	2 (9.5)	2 (10.5)
Toxicity Grade 1	2 (9.5)	2 (10.5)
Toxicity Grade 2	0 (0.0)	0 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Neutrophils Decreased		
All Grades	0 (0.0)	7 (36.8)
Toxicity Grade 1	0 (0.0)	2 (10.5)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline
(ASaT Japan Population)

Laboratory Test	Pembrolizumab (N=21)	SOC (N=19)
Toxicity Grade 2	0 (0.0)	4 (21.1)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	1 (5.3)
Phosphate Decreased		
All Grades	3 (14.3)	4 (21.1)
Toxicity Grade 1	0 (0.0)	1 (5.3)
Toxicity Grade 2	2 (9.5)	2 (10.5)
Toxicity Grade 3	1 (4.8)	1 (5.3)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Platelet Decreased		
All Grades	1 (4.8)	8 (42.1)
Toxicity Grade 1	0 (0.0)	5 (26.3)
Toxicity Grade 2	1 (4.8)	0 (0.0)
Toxicity Grade 3	0 (0.0)	2 (10.5)
Toxicity Grade 4	0 (0.0)	1 (5.3)
Potassium Decreased		
All Grades	4 (19.0)	0 (0.0)
Toxicity Grade 1	3 (14.3)	0 (0.0)
Toxicity Grade 2	0 (0.0)	0 (0.0)
Toxicity Grade 3	1 (4.8)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline
(ASaT Japan Population)

Laboratory Test	Pembrolizumab (N=21)	SOC (N=19)
Potassium Increased		
All Grades	8 (38.1)	13 (68.4)
Toxicity Grade 1	7 (33.3)	9 (47.4)
Toxicity Grade 2	1 (4.8)	3 (15.8)
Toxicity Grade 3	0 (0.0)	1 (5.3)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Prothrombin Intl. Normalized Ratio Increased		
All Grades	1 (4.8)	0 (0.0)
Toxicity Grade 1	1 (4.8)	0 (0.0)
Toxicity Grade 2	0 (0.0)	0 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Sodium Decreased		
All Grades	7 (33.3)	10 (52.6)
Toxicity Grade 1	6 (28.6)	7 (36.8)
Toxicity Grade 2	0 (0.0)	0 (0.0)
Toxicity Grade 3	1 (4.8)	3 (15.8)
Toxicity Grade 4	0 (0.0)	0 (0.0)
Sodium Increased		
All Grades	1 (4.8)	0 (0.0)
Toxicity Grade 1	1 (4.8)	0 (0.0)

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Summary of Laboratory Abnormality for Highest Toxicity Grade In Subjects that Worsened from Baseline (ASaT Japan Population)

Laboratory Test	Pembrolizumab (N=21)	SOC (N=19)
Toxicity Grade 2	0 (0.0)	0 (0.0)
Toxicity Grade 3	0 (0.0)	0 (0.0)
Toxicity Grade 4	0 (0.0)	0 (0.0)

If a subject had more than one graded abnormalities for a lab test, only the highest grade is counted.
Grades are based on NCI CTCAE version 4.03.
(Database Cutoff Date: 09MAY2016)

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CTD 第 2 部

2.7　臨床概要

2.7.5　参考文献

MSD 株式会社

2.7.5 参考文献

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添付資料番号	タイトル	著者	掲載紙
[資料5.4: 81]	DETERMINATION OF MK-3475 CONCENTRATIONS IN HUMAN SERUM SAMPLES FROM STUDY NO. MK-3475 PN002 USING A VALIDATED ELECTROCHEMILUMINESCENT (ECL) ASSAY WITH LOWCROSS-BUFFER®	[redacted]	社内資料
[資料5.4: 82]	DETERMINATION OF MK-3475 CONCENTRATIONS IN HUMAN SERUM SAMPLES FROM STUDY NO. MK-3475 PN006 USING A VALIDATED ELECTROCHEMILUMINESCENT (ECL) ASSAY WITH LOWCROSS-BUFFER®	[redacted]	社内資料
[資料5.4: 83]	Interim Analytical Report : Project RDOM : Analysis of Samples Using an ECL Method for the Quantitation of MK-3475 in Human Serum	[redacted]	社内資料
[資料5.4: 87]	The interpretation of scores from the EORTC quality of life questionnaire QLQ-C30.	King MT.	Quality of Life Research 1996;5:555-67.
[資料5.4: 88]	Interpreting the significance of changes in health-related quality-of-life scores.	Osoba D, Rodrigues G, Myles J, et al.	J Clin Oncol 1998;16:139-44.
[資料5.4: 89]	Minimal important differences for interpreting health-related quality of life scores from the EORTC QLQ-C30 in lung cancer patients participating in randomized controlled trials.	Maringwa JT, Quinten C, King M, et al.	Support Care Cancer. 2011;19:1753-60.

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CTD 第 2 部

2.7　臨床概要

2.7.6　個々の試験のまとめ

MSD 株式会社

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略号及び用語の定義

略号	定義	
ADA	anti-drug antibodies	抗薬物（MK-3475）抗体
AEOSI	adverse event of special interest	特に注目すべき有害事象
ALK	anaplastic lymphoma kinase	未分化リンパ腫リン酸化酵素
ALP	alkaline phosphatase	アルカリホスファターゼ
ALT	alanine aminotransferase	アラニンアミノトランスフェラーゼ
APaT	all patients as treated	治験薬を投与されたすべての患者
AST	aspartate aminotransferase	アスパラギン酸アミノトランスフェラーゼ
ATS	all treated set	治験薬を割り付けられ、少なくとも1回投与されたすべての患者
$AUC_{0\text{-}28\ day}$	area under the concentration-time curve (0 to 28 days)	投与開始後28日までの濃度-時間曲線下面積
$AUC_{0\text{-}\infty}$	area under the concentration-time curve (0 to infinity)	投与開始後無限大時間までの濃度-時間曲線下面積
BICR	Blinded Independent Central Radiologist	盲検下独立判定委員会
BOR	best overall response	最良総合効果
CI	confidence interval	信頼区間
CL	Clearance	クリアランス
CLIA	Clinical Laboratory Improvement Amendments	-
C_{max}	maximum serum concentration	最高血清中 MK-3475濃度
CR	complete response	完全奏効
CRA	commercial ready assay	-
CT	computed tomography	コンピュータ断層撮影法
CTA	clinical trial assay	-
CTCAE	Common Terminology Criteria for Adverse Events	有害事象共通用語規準
C_{trough}	concentration at the end of the dosing interval	投与間隔終了時濃度
CV	coefficient of variation	変動係数
DCR	disease control rate	病勢コントロール率
DLT	dose limiting toxicity	用量制限毒性
DOR	duration of response	奏効期間
ECOG	Eastern Cooperative Oncology Group	米国東海岸がん臨床試験グループ
EGFR	epidermal growth factor receptor	上皮成長因子受容体
EORTC	European Organisation for Research and Treatment of Cancer	欧州がん研究・治療機構
FAS	full analysis set	最大解析対象集団
GCP	Good Clinical Practice	医薬品の臨床試験の実施の基準
GM	geometric mean	幾何平均
IHC	Immunohistochemistry	免疫組織化学染色法
irAE	Immune related adverse event	免疫関連の有害事象
IRC	Independent Review Committee	独立判定委員会

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略号及び用語の定義（続き）

略号	定義	
irRC	Immune related response criteria	免疫療法のための治療効果判定基準
ITT	intention-to-treat	intention-to-treat
KRAS	kirsten rat sarcoma viral oncogene homolog	-
MedDRA	Medical Dictionary for Regulatory Activities	ICH 国際医薬用語集
MPS	modified proportion score	ストローマを含まない腫瘍巣のみ及び細胞膜が染色された単核性炎症細胞での染色強度に基づくスコア
NCI	National Cancer Institute	米国国立がん研究所
NPV	negative predictive value	陰性的中率
NR	not reached	未到達
ORR	overall response rate	奏効率
OS	overall survival	全生存期間
PA	prototype assay	-
PD	progressive disease	疾患進行
PD-L1	programmed cell death-ligand 1	プログラム細胞死リガンド1
PFS	progression-free survival	無増悪生存期間
PK	Pharmacokinetic	薬物動態
PPV	positive predictive value	陽性的中率
PR	partial response	部分奏効
PRO	Patient Reported Outcome	-
PS	performance status	全身状態の指標
PS	proportion score	-
Q2W	every 2 weeks	2週間間隔投与
Q3W	every 3 weeks	3週間間隔投与
RECIST 1.1	Response Evaluation Criteria in Solid Tumours, version 1.1	固形がんの治療効果判定のための新ガイドライン 改訂版 version 1.1
ROC	receiver operating characteristic	-
SD	stable disease	安定
SD	standard deviation	標準偏差
$t_{1/2}$	elimination half-life	消失半減期
T_{max}	time to maximum serum concentration	最高血清中 MK-3475濃度到達時間
TPS	tumor proportion score	腫瘍細胞のうち PD-L1発現陽性細胞の割合
TSH	thyroid stimulating hormone	甲状腺刺激ホルモン
V_z	volume of the terminal phase	最終消失相の分布容積

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2.7.6　個々の試験のまとめ

2.7.6.1　臨床試験一覧表

表 2.7.6.1-1　臨床試験一覧

資料区分	実施地域	試験名	相	試験デザイン	対象患者	安全性解析対象症例数	投与群	主な評価項目	試験状況
評価	海外	KEYNOTE-001（001試験）	I	パートC：非盲検、非無作為化 パートF1：非盲検、無作為化 パートF2：非盲検、無作為化/非無作為化 パートF3：非盲検、非無作為化	パートC： 既治療：非小細胞肺癌患者 パートF1： 未治療：PD-L1発現陽性、非小細胞肺癌患者 パートF2： 既治療：PD-L1発現陽性又はPD-L1発現陰性、非小細胞肺癌患者 パートF3： 既治療：PD-L1発現陽性、非小細胞肺癌患者	パートC：　38例 10 mg/kg Q3W：38例 パートF1：合計101例 2 mg/kg Q3W：6例 10 mg/kg Q2W：46例 10 mg/kg Q3W：49例 パートF2：合計356例 10 mg/kg Q2W：156例 10 mg/kg Q3W：200例 パートF3：合計55例 2 mg/kg Q3W：55例	パートC： 10 mg/kg Q3W パートF1： 2 mg/kg Q3W 10 mg/kg Q2W 10 mg/kg Q3W パートF2： 10 mg/kg Q2W 10 mg/kg Q3W パートF3： 2 mg/kg Q3W	安全性 有効性 PK	実施中
評価	国内	KEYNOTE-011（011試験）	I	パートA：非盲検、非無作為化	パートA:進行性固形がん患者	パートA：10例	パートA： 2 mg/kg Q2W 10 mg/kg Q2W	安全性 PK	パートA： 実施中
評価	国内	KEYNOTE-025（025試験）	Ib	非盲検 非無作為化	既治療：非小細胞肺癌患者	38例	10 mg/kg Q3W	安全性 有効性 PK	実施中
評価	国内及び海外	KEYNOTE-010（010試験）	II/III	一部盲検 無作為化 実薬対照3群比較	既治療：非小細胞肺癌患者	合計991例（89例*） ドセタキセル：309例（27例*） MK-3475 2 mg/kg Q3W：339例（28例*） MK-3475 10 mg/kg Q3W：343例（34例*） *：日本人症例数	ドセタキセル75 mg/m^2 Q3W MK-3475 2 mg/kg Q3W MK-3475 10 mg/kg Q3W	安全性 有効性	実施中

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表 2.7.6.1-1　臨床試験一覧（続き）

資料区分	実施地域	試験名	相	試験デザイン	対象患者	安全性解析対症例数	投与群	主な評価項目	試験状況
評価	国内及び海外	KEYNOTE-024（024試験）	III	非盲検 無作為化 実薬対照2群比較	未治療：非小細胞肺癌患者	合計304例（40例*） 標準化学療法群：150例（19例*） MK-3475 200 mg Q3W：154例（21例*） *：日本人症例数	MK-3475 200 mg Q3W 標準化学療法群 Q3W （以下より選択） ペメトレキセド500 mg/m^2+カルボプラチン AUC5又は6 ペメトレキセド500 mg/m^2+シスプラチン75 mg/m^2 ゲムシタビン1250 mg/m^2+シスプラチン75 mg/m^2 ゲムシタビン1250 mg/m^2+カルボプラチン AUC5又は6 パクリタキセル200 mg/m^2+カルボプラチン AUC5又は6	安全性 有効性	実施中

注：実施中の試験とは、データベースのカットオフ日までに最終来院日を迎えていない臨床試験である。
データベースカットオフ日：001試験：[redacted]年[redacted]月[redacted]日及び[redacted]年[redacted]月[redacted]日、011試験：2014年5月7日、025試験：2015年7月9日、
010試験：2015年9月30日、024試験：2016年5月9日

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表 2.7.6.1-2　臨床試験一覧（臨床薬理検討部分）

資料区分	実施地域	試験名	相	試験デザイン	対象患者	臨床薬理評価対象例数	投与群	主な評価項目	試験状況
評価	海外	KEYNOTE-001（001試験）－臨床薬理検討部分－	I	パートA+A1：非盲検、非無作為化 パートA2：非盲検、無作為化 パートB1：非盲検、非無作為化 パートB2：非盲検、無作為化 パートD：非盲検、無作為化	パートA共通： 進行性固形がん患者 パートB及びD共通： 進行性悪性黒色腫患者 パートB1：IPI未治療患者及びIPI既治療患者 パートB2：IPI抵抗性患者 パートD：IPI未治療患者	パートA+A1：合計17例 パートA2：合計13例 パートB1：合計135例 2 mg/kg Q3W：22例 10 mg/kg Q2W：57例 10 mg/kg Q3W：56例 パートB2：合計173例 2 mg/kg Q3W：89例 10 mg/kg Q3W：84例 パートD：合計103例 2 mg/kg Q3W：51例 10 mg/kg Q3W：52例	パートA+A1：1 mg/kg Q2W 10 mg/kg Q2W 3 mg/kg Q2W パートA2：2 mg/kg Q3W 10 mg/kg Q3W† パートB1：2 mg/kg Q3W 10 mg/kg Q2W 10 mg/kg Q3W パートB2：2 mg/kg Q3W 10 mg/kg Q3W パートD：2 mg/kg Q3W 10 mg/kg Q3W	臨床薬理	実施中

注：実施中の試験とは、データベースのカットオフ日までに最終来院日を迎えていない臨床試験である。
データベースカットオフ日：001試験：[redacted]年[redacted]月[redacted]日
PK：薬物動態、IPI：イピリムマブ
† サイクル1に3コホートで患者内用量漸増を行い、サイクル2から2又は10 mg/kg Q3Wのいずれかで投与した。詳細は[2.7.2.2.1.1 項]の表2.7.2-4参照。

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2.7.6.2 個々の臨床試験のまとめ

2.7.6.2.1 固形がん、悪性黒色腫、及び非小細胞肺癌患者を対象とした第 I 相試験［海外試験］［評価資料］（KEYNOTE-001試験、以下001試験）

2.7.6.2.1.1 試験方法の概要

治験実施医療機関

多施設共同、47施設（米国、フランス、イタリア、韓国、スペイン、英国、カナダ、ノルウェー、台湾、オーストラリア）

公表文献

- Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 2015;372:2018-28

治験実施期間

[redacted]年[redacted]月[redacted]日～実施中

開発の相

第 I 相

治験デザイン

本試験は、局所進行性又は転移性固形がん、悪性黒色腫又は非小細胞肺癌患者を対象とした MK-3475静脈内投与の非盲検、第 I 相試験である。本試験のパート A では、従来の3+3デザインを用いた用量漸増を行った。パート B 及び D では悪性黒色腫の患者を組み入れた。パート C では非小細胞肺癌の既治療患者を組み入れ、MK-3475 10 mg/kg を3週間間隔（Q3W）で投与し、安全性、忍容性及び抗腫瘍効果を評価した。非小細胞肺癌の未治療患者を対象としたパート F1 及び非小細胞肺癌で2レジメン以上の前治療歴がある患者を対象としたパート F2では、PD-L1 発現陽性の患者に MK-3475 10 mg/kg 2週間間隔（Q2W）又は Q3W で投与し、安全性、忍容性及び抗腫瘍効果を検討した。さらにパート F2では非小細胞肺癌で2レジメン以上の前治療歴があり、かつ PD-L1発現陰性の患者に10 mg/kg Q2W を投与した。パート F3では非小細胞肺癌の既治療がありかつ PD-L1発現陽性の患者に2 mg/kg Q3W を投与し、安全性、忍容性及び抗腫瘍効果を検討した。

本項では、治験総括報告書第4版（データベースカットオフ日：[redacted]年[redacted]月[redacted]日）の安全性及び有効性データの要約を示す。本試験の治験総括報告書第4版はパート C、F1、F2及び F3（患者数550例）に基づいたものであり、未治療又は既治療の非小細胞肺癌の PD-L1発現陽性又は陰性患者に MK-3475を3つの用法・用量（2 mg/kg Q3W、10 mg/kg Q2W、及び10 mg/kg Q3W）で投与した際のデータで構成した。パート A、B 及び D のデータは、治験総括報告書第1版及び

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第2版に記載した。

主要目的

1) 切除不能の進行性固形がん（非小細胞肺癌又は悪性黒色腫を含む）を有する成人患者を対象に、MK-3475単独療法の忍容性及び安全性プロファイルを評価する。
2) 固形がんの治療効果判定のための新ガイドライン改訂版 version 1.1（RECIST 1.1）を用い、過去に全身療法を1レジメン以上受けたことがある PD-L1高発現の非小細胞肺癌患者に対する MK-3475の抗腫瘍効果を評価する。

副次的目的

1) 免疫療法のための治療効果判定基準（irRC）を用いて、イピリムマブ抵抗性の悪性黒色腫患者及びイピリムマブ未治療の悪性黒色腫患者、PD-L1発現陽性の腫瘍を有するイピリムマブ抵抗性の悪性黒色腫患者及びイピリムマブ未治療の悪性黒色腫患者、並びに過去に全身療法を1レジメン以上受けたことがある PD-L1高発現の非小細胞肺癌患者の奏効率（ORR）を評価する。
2) MK-3475の単剤療法の薬物動態（PK）プロファイルを検討する。
3) 有効性バイオマーカー候補と MK-3475の抗腫瘍効果との関係を検討する。
4) MK-3475を投与された非小細胞肺癌患者の奏効期間（DOR）、無増悪生存期間（PFS）、及び全生存期間（OS）を評価する。

各パートの投与患者数

表 2.7.6.2.1-1 各パートの患者数（001 試験）

パート	MK-3475群	患者数
パート C 進行性非小細胞肺癌（既治療）	10 mg/kg Q3W	38例
パート F1 非小細胞肺癌（PD-L1発現陽性、未治療、無作為割付け）*	2 mg/kg Q3W	6例
	10 mg/kg Q2W	46例
	10 mg/kg Q3W	49例
パート F2 非小細胞肺癌（PD-L1発現陽性、既治療、無作為割付け）	10 mg/kg Q2W	113例
	10 mg/kg Q3W	167例
パート F2 非小細胞肺癌（PD-L1発現陰性、既治療）	10 mg/kg Q2W	43例
パート F2 非小細胞肺癌（PD-L1発現陽性、既治療）	10 mg/kg Q3W	33例
パート F3 非小細胞肺癌（PD-L1発現陽性、既治療）	2 mg/kg Q3W	55例
* 最初の11例は治験実施計画書第6版に基づき、MK-3475 2 mg/kg Q3W 又は10 mg/kg Q3W のいずれかに1:1で無作為割付けをした。その後は治験実施計画書第7版に基づき、90例を MK-3475 10 mg/kg Q3W 又は10 mg/kg Q2W のいずれかに1:1で無作為割付けをした。		

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試験の状況（データベースカットオフ日）

パート C、F1、F2及び F3：[redacted]（治験総括報告書第4版）

最初の患者の初回来院日～最後の患者の最終来院日

C：[redacted]～進行中

F1：[redacted]～進行中

F2：[redacted]～進行中

F3：[redacted]～進行中

ロット番号

表 2.7.6.2.1-2 パート C、F1、F2 及び F3 の治験薬の内容（001 試験）

Bulk Product Description	Manufacturing Lot Number
HLSV MK-3475、50 mg/vial（Brinny, SCH-900475）	DL00018212, DL00018225, DL00018226, DL00018244, DL00018249, DL00018250, DL00018362, DL00018363, DL00018390, DL00018600, DL00018650, DL00018652, DL00018665, DL00018671, DL00018824, GL00001230, GL00001231, GL00001633, GL00001773, GL00001774
HLSV MK-3475、50 mg/ vial（SCH-900475, FM005386-1-1）	GL00000057, GL00000064, GL00000065, GL00000111, GL00000173, GL00000311, GL00000690, GL00000715, GL00000746, GL00000820, GL00000943, GL00000959, GL00001014, GL00001155, GL00001179, GL00001435, GL00001539, GL00002307
SCH 900475 ANTI-PD-1 ANTIBODY POWDER FOR INJ. 50 MG/VIAL	W-H03526, W-H03619, W-H03857, W-H04028, W-H04368, W-H04369
(Database Cutoff Date: [redacted])	

評価基準

有効性

1) ORR：ORR を、解析対象集団で完全奏効（CR）又は部分奏効（PR）が認められた患者の割合と定義した。ORR は、RECIST 1.1を用いた盲検化された独立判定委員会（IRC）評価及び irRC を用いた治験担当医師評価に基づき検討した。
2) 病勢コントロール率（DCR）：DCR を、解析対象集団で CR、PR 又は安定（SD）が認められた患者の割合と定義した。DCR は、RECIST 1.1を用いた IRC 評価及び irRC を用いた治験担当医師評価に基づき検討した。
3) DOR：CR 又は PR が認められた患者に関して、DOR を CR 又は PR のエビデンスが初めて記録されてから疾患進行（PD）までの期間と定義した。
4) PFS：PFS を、無作為割付から PD の確定又は原因を問わない死亡のいずれか先に生じた時点までの期間と定義した。PFS は、RECIST 1.1を用いた IRC 評価又は irRC を用いた治験担当医師評価に基づき検討した。
5) OS：OS を、治験薬投与開始から原因を問わない死亡までの期間と定義した。

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統計計画及び解析

主要解析

本試験の有効性の主要評価項目はORRである。非小細胞肺癌患者の抗腫瘍効果はRECIST 1.1を用いたIRCによる評価とした。各患者集団、場合によっては各用法・用量でORRの95%信頼区間（CI）を算出した。最長の追跡時点でKaplan-Meier法の累積奏効率をORRの推定値として計算した。投与群間の比較については、用法・用量の違いを評価した。

主要解析集団

主要評価項目のORRは既治療の患者集団を対象とした。この集団はBiomarker Validation Setを構成するパートF2の患者のうち、ベースライン時に免疫組織化学染色法（IHC）にて、tumor proportion score（TPS）≧50%（PD-L1高発現）であった患者で構成した。PD-L1高発現のカットオフ値を決定するため、別途22C3抗ヒトPD-L1抗体を用いて実施したIHC（clinical trial assay : CTA)を実施した。すべての患者はプラチナ製剤併用化学療法の治療歴があり、非小細胞肺癌に対するプラチナ製剤併用化学療法開始後にPDが認められていた。EGFR遺伝子変異陽性又はALK融合遺伝子陽性の患者は非小細胞肺癌に対する適切なチロシンキナーゼ阻害剤による治療開始後、PDが認められていた。

また、既治療の患者集団と同様に未治療の患者集団で解析を行った。この集団はBiomarker Validation Setを構成するパートF1の患者のうち、ベースライン時にIHCにて、CRA（commercial ready assay）で決定したPD-L1高発現であった患者から構成された。パートF1では全身性の化学療法を受けた患者は原則対象としないが、術後補助化学療法完了から1年以上経過後に再発した患者は適格とした。EGFR感受性遺伝子変異型又はALK融合遺伝子陽性患者はパートF1から除外した。

副次解析

副次評価項目は、irRCに基づき治験担当医師が評価したORRである。RECIST 1.1及びirRCに基づき評価したDCR、DOR及びPFS並びにOSについても評価した。各患者集団、場合によっては各用法・用量でORRの95%CIを算出した。DCRは主要評価項目ではないが、同様の解析を実施した。PFS及びOSにはKaplan-Meier法及び記述統計量を用いた。追跡期間終了時点のORRはKaplan-Meier法により推定するが、パートF3での短い追跡期間を調整するため［追跡期間の中央値は、パートF3で7.7ヵ月、その他の患者は15.7ヵ月］、Kaplan-Meier曲線及び奏効までの期間の記述統計量を提示し、最長の追跡時点でKaplan-Meier法の累積奏効率をORRの推定値として計算した。DOR及び腫瘍量の変化の記述統計量も計算した。用法／用量ごとの違いを検討するため、すべての有効性評価項目で必要に応じて群間比較を実施した。

副次解析集団

ORR、DCR、PFS及びOSを治験薬を投与されたすべての患者（APaT）集団で実施した。APaT集団は、治験薬を投与されたすべての患者とした。

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安全性解析集団

本試験では、安全性データ解析は非小細胞肺癌の全患者（APaT 集団）で実施した。

2.7.6.2.1.2 患者の内訳

パート C、F1、F2及び F3の非小細胞肺癌に関する患者の特性及び内訳を[表 2.7.6.2.1-3]及び[表 2.7.6.2.1-4]に示す。

1,241例の非小細胞肺癌の患者が本試験のパート C 及び F に文書同意した。予備的な治験総括報告書の時点では、560例の患者がパート C 及びパート F に割り付けられた。550例の患者が少なくとも1回の治験薬の投与を受けた[表 2.7.6.2.1-4]。[表 2.7.6.2.1-4]に記載した”Unknown”は治験実施計画書に従い MK-3475の投与が継続していることを示している。パート F3で MK-3475 2 mg/kg Q3W の投与を受けた55例は、他の患者より投与開始が遅いことからパート F3の大部分の患者は MK-3475の投与を継続していた。

ベースラインの特性は各投与群間（MK-3475 2 mg/kg Q3W、10 mg/kg Q3W、及び10 mg/kg Q2W）でばらつきはなかった。年齢の中央値は64.0歳であった[表 2.7.6.2.1-3]。患者の75.4%に喫煙歴があり、転移病変を有していた。非扁平上皮癌の割合が最も高かった。脳転移を有している患者は少数であった。患者の多くが2レジメン以上の投与を受けていた。EGFR 遺伝子変異、ALK 融合遺伝子及び KRAS 遺伝子変異陽性の患者の割合はそれぞれ14.0%、1.6%及び15.8%であった。

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表 2.7.6.2.1-3　患者の特性（パート C+F1+F2+F3）（APaT 集団）（001 試験）

	MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		MK-3475 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	61		287		202		550	
Gender								
Male	32	(52.5)	146	(50.9)	111	(55.0)	289	(52.5)
Female	29	(47.5)	141	(49.1)	91	(45.0)	261	(47.5)
Age (Years)								
< 65	32	(52.5)	148	(51.6)	111	(55.0)	291	(52.9)
>=65	29	(47.5)	139	(48.4)	91	(45.0)	259	(47.1)
Mean	61.9		62.0		63.0		62.3	
SD	11.0		11.2		10.2		10.8	
Median	64.0		64.0		64.0		64.0	
Range	39 to 82		28 to 85		32 to 93		28 to 93	
Race								
American Indian Or Alaska Native	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.2)
Asian	6	(9.8)	45	(15.7)	19	(9.4)	70	(12.7)
Black Or African American	0	(0.0)	12	(4.2)	8	(4.0)	20	(3.6)
Multiracial	1	(1.6)	1	(0.3)	0	(0.0)	2	(0.4)
Native Hawaiian Or Other Pacific Islander	1	(1.6)	0	(0.0)	0	(0.0)	1	(0.2)
White	53	(86.9)	229	(79.8)	173	(85.6)	455	(82.7)
Missing	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.2)
Ethnicity								
Hispanic Or Latino	1	(1.6)	20	(7.0)	8	(4.0)	29	(5.3)
Not Hispanic Or Latino	60	(98.4)	265	(92.3)	194	(96.0)	519	(94.4)
Missing	0	(0.0)	2	(0.7)	0	(0.0)	2	(0.4)
Region								
Australia	5	(8.2)	18	(6.3)	7	(3.5)	30	(5.5)
Canada	3	(4.9)	14	(4.9)	17	(8.4)	34	(6.2)

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表 2.7.6.2.1-3 患者の特性（パート C+F1+F2+F3）（APaT 集団）（001 試験）（続き）

	MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		MK-3475 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Region								
EU	23	(37.7)	49	(17.1)	35	(17.3)	107	(19.5)
East Asia	2	(3.3)	16	(5.6)	13	(6.4)	31	(5.6)
US	28	(45.9)	190	(66.2)	130	(64.4)	348	(63.3)
ECOG								
[0] Normal Activity	20	(32.8)	107	(37.3)	64	(31.7)	191	(34.7)
[1] Symptoms, but ambulatory	41	(67.2)	180	(62.7)	136	(67.3)	357	(64.9)
Unknown	0	(0.0)	0	(0.0)	2	(1.0)	2	(0.4)
Cancer Staging								
III	3	(4.9)	7	(2.4)	11	(5.4)	21	(3.8)
IV	58	(95.1)	280	(97.6)	191	(94.6)	529	(96.2)
Metastatic Staging								
M0	2	(3.3)	7	(2.4)	10	(5.0)	19	(3.5)
M1a	12	(19.7)	83	(28.9)	52	(25.7)	147	(26.7)
M1b	47	(77.0)	197	(68.6)	140	(69.3)	384	(69.8)
Brain Metastasis								
Yes	7	(11.5)	30	(10.5)	21	(10.4)	58	(10.5)
No	54	(88.5)	257	(89.5)	181	(89.6)	492	(89.5)
Number of Unique Prior Systemic Therapies								
0	4	(6.6)	45	(15.7)	45	(22.3)	94	(17.1)
1	16	(26.2)	46	(16.0)	25	(12.4)	87	(15.8)
2	21	(34.4)	76	(26.5)	43	(21.3)	140	(25.5)
3	10	(16.4)	62	(21.6)	45	(22.3)	117	(21.3)
4 or more	10	(16.4)	58	(20.2)	44	(21.8)	112	(20.4)
Baseline Tumor Size (mm)								
Subjects with data	58		261		183		502	
Mean	110		108		118		112	
SD	91		87		82		85	

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表 2.7.6.2.1-3 患者の特性（パート C+F1+F2+F3）（APaT 集団）（001 試験）（続き）

	MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		MK-3475 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Baseline Tumor Size (mm)								
Median	94		87		99		93	
Range	14 to 428		11 to 548		10 to 419		10 to 548	
Histology								
Squamous	10	(16.4)	38	(13.2)	47	(23.3)	95	(17.3)
Non-Squamous	51	(83.6)	243	(84.7)	152	(75.2)	446	(81.1)
Adenosquamous	0	(0.0)	4	(1.4)	3	(1.5)	7	(1.3)
Unknown	0	(0.0)	2	(0.7)	0	(0.0)	2	(0.4)
Smoking Status								
Never	10	(16.4)	85	(29.6)	40	(19.8)	135	(24.5)
Former	45	(73.8)	182	(63.4)	141	(69.8)	368	(66.9)
Current	6	(9.8)	20	(7.0)	21	(10.4)	47	(8.5)
EGFR Mutation								
Yes	4	(6.6)	48	(16.7)	25	(12.4)	77	(14.0)
No	50	(82.0)	225	(78.4)	175	(86.6)	450	(81.8)
Unknown	7	(11.5)	14	(4.9)	2	(1.0)	23	(4.2)
KRAS Mutation								
Yes	10	(16.4)	43	(15.0)	34	(16.8)	87	(15.8)
No	22	(36.1)	133	(46.3)	83	(41.1)	238	(43.3)
Unknown	29	(47.5)	111	(38.7)	85	(42.1)	225	(40.9)
ALK Gene Rearrangement								
Mutation/ Translocation	1	(1.6)	8	(2.8)	0	(0.0)	9	(1.6)
Wild Type	47	(77.0)	232	(80.8)	195	(96.5)	474	(86.2)
Unknown	13	(21.3)	47	(16.4)	7	(3.5)	67	(12.2)
(Database Cutoff Date: [redacted])								

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表 2.7.6.2.1-4 患者の内訳（パート C+F1+F2+F3）（APaT 集団）（001 試験）

	MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		MK-3475 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	61		287		202		550	
Subject Study Medication Disposition								
Discontinued	46	(75.4)	234	(81.5)	165	(81.7)	445	(80.9)
Adverse Event	14	(23.0)	66	(23.0)	44	(21.8)	124	(22.5)
Physician Decision	3	(4.9)	17	(5.9)	14	(6.9)	34	(6.2)
Progressive Disease	21	(34.4)	130	(45.3)	97	(48.0)	248	(45.1)
Protocol Violation	4	(6.6)	14	(4.9)	6	(3.0)	24	(4.4)
Withdrawal By Subject	4	(6.6)	7	(2.4)	4	(2.0)	15	(2.7)
Unknown	15	(24.6)	53	(18.5)	37	(18.3)	105	(19.1)

Each subject is counted once for Subject Study Medication Disposition based on the latest corresponding disposition record.

Unknown: A disposition record did not exist at the time of reporting.

Unknown: For this study, all subjects with Unknown disposition status are still on study at the time of database cutoff.

(Database Cutoff Date: [redacted])

2.7.6.2.1.3 バイオマーカー及びコンパニオン診断薬の開発

2.7.6.2.1.3.1 PD-L1発現解析

PD-L1の発現レベルを測定するために3つの解析［prototype assay (PA)、CTA 及び CRA］を実施した。いずれも非小細胞肺癌患者の腫瘍組織検体にて22C3抗ヒト PD-L1抗体を用いて PD-L1の発現を測定した。001試験では PA、CTA 及び CRA を実施し、010試験では CTA のみを実施した。

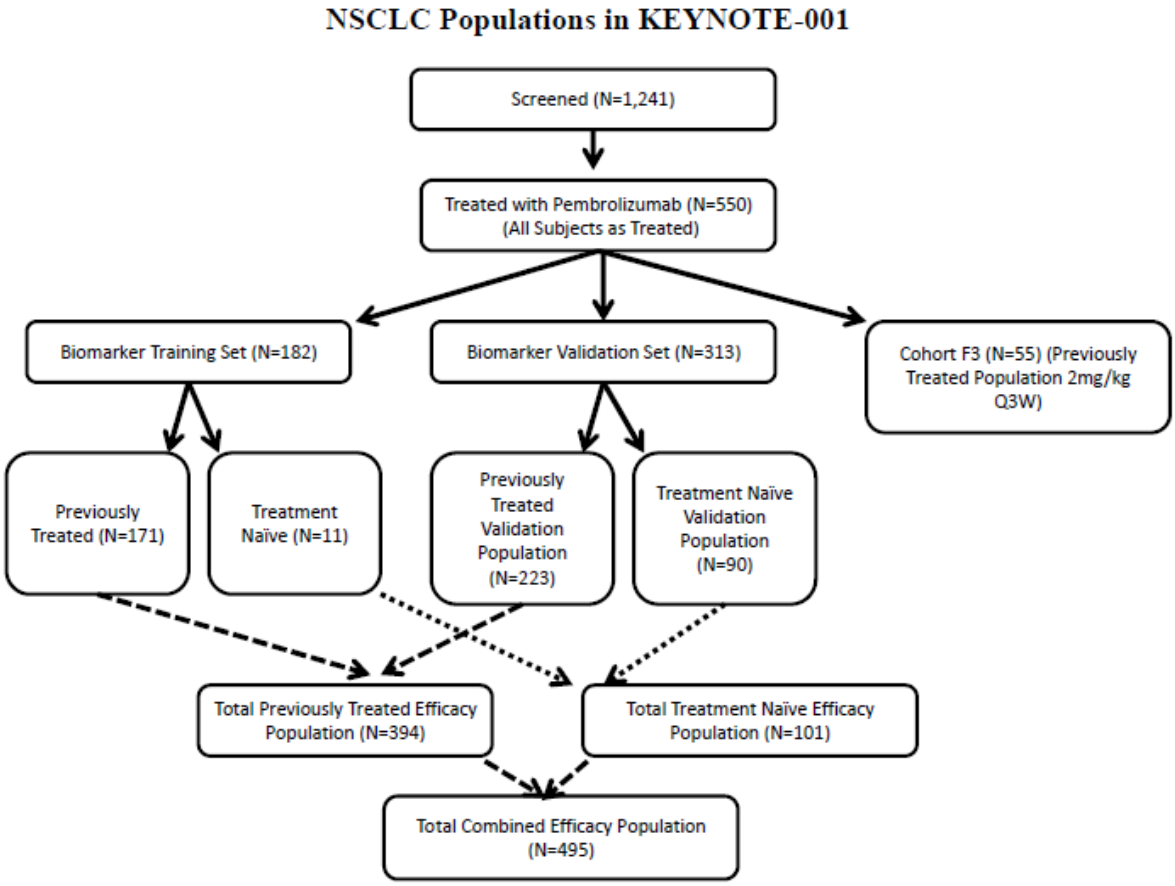
PA は臨床試験のための解析であり、CLIA 認定を受けた臨床検査機関で実施した。CTA は、MK-3475の治療効果がより得られる集団を特定するために、Biomarker Training Set の集団を用いて Dako 社が実施した。CRA は、Biomarker Training Set で設定した PD-L1発現のカットオフ値の臨床的な実用性を確認するために、Biomarker Validation Set 及びパート F3の集団を用いて独立した検査機関が実施した。解析の結果、CTA と CRA は一致していた。Biomarker Training Set 及び Biomarker Validation Set については[2.7.6.2.1.3.2 項]に記載した。PD-L1発現解析の詳細は、[2.7.3.2.1 項]に記載した。

2.7.6.2.1.3.2 非小細胞肺癌でバイオマーカー検討に用いた患者集団

非小細胞肺癌でバイオマーカー検討に用いた患者集団を[図 2.7.6.2.1-1]に示す。

001試験では、1,241例の非小細胞肺癌の患者より文書同意を取得し、560例がパート C、F1、F2又は F3に割り付けられ、550例に治験薬が投与された。一方で、バイオマーカー解析を目的として、別途各パートの患者を併合し、Biomarker Training Set 又は Biomarker Validation Set を構成した。非小細胞肺癌の患者集団の詳細は、[2.7.3.2.1.2 項]に記載した。

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N = number of subjects; Q3W = every 3 weeks.
Data cut-off date: 23-Jan-2015

[資料 5.3.5.2.1.2: P001V04]の 16.4 項

図 2.7.6.2.1-1 非小細胞肺癌でバイオマーカー検討に用いた患者集団（001 試験）

2.7.6.2.1.3.3 PD-L1高発現に対するカットオフ値の決定

Biomarker Training Set を構成する非小細胞肺癌患者182例のうち、少なくとも1回の MK-3475 の投与を受け、irRC を用いた治験担当医師の評価でベースライン時に測定可能病変を有しており、CTA で測定可能な検体を有していた146例より得られた PD-L1の発現解析結果及び治験担当医師による irRC に基づく ORR の評価を用いて、PD-L1高発現に対するカットオフ値を決定した。PD-L1の発現は IHC にて Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, N.J., U.S.A.が Dako 社と共同開発中の22C3抗ヒト PD-L1抗体を用いて測定した。解析には腫瘍細胞のうち PD-L1発現陽性細胞の割合を反映する TPS をスコア化の方法として選択した。なお、PD-L1高発現のカットオフ値の決定の詳細は（[資料5.3.5.2.1.2: P001V04]の付録16.1.9.4）に記載した。

irRC を用いた治験担当医師評価（確定又は未確定）に基づき ROC 曲線を解析した。Youden index により染色強度にかかわらず45～50の TPS が適切なカットオフ値であることが示されたためコンパニオン診断薬としてスコアを簡素化し、PD-L1高発現のカットオフ値を TPS=50%と

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した[図 2.7.6.2.1-2]。

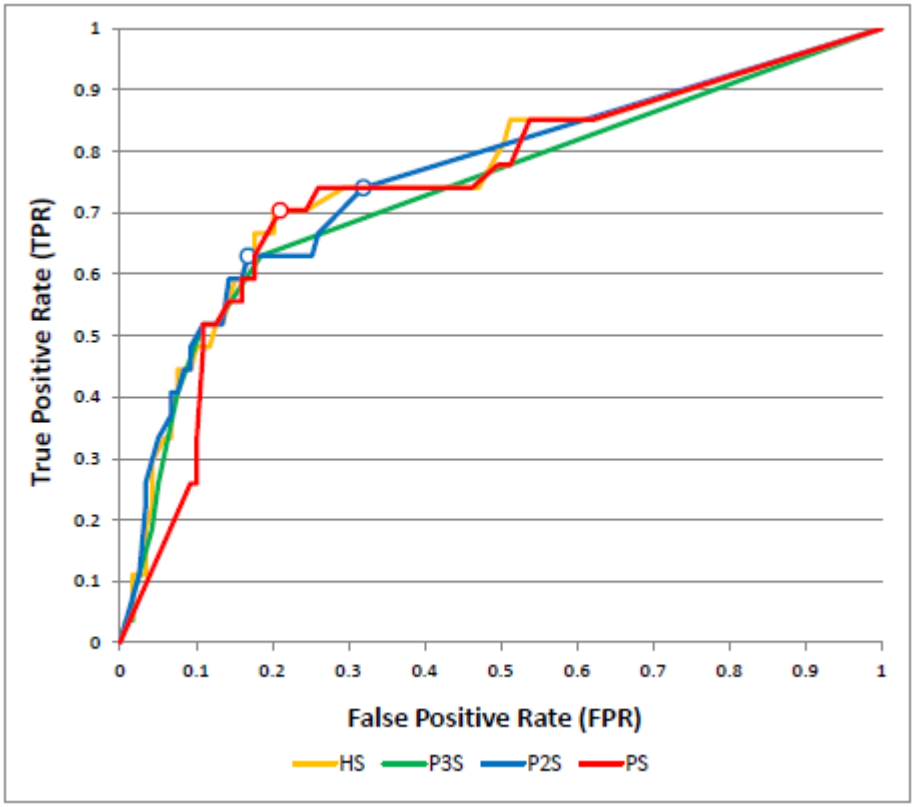


図 2.7.6.2.1-2 Biomarker training Set における ORR と PD-L1 発現量の解析（ROC 解析）（001 試験）

[図 2.7.6.2.1-2]に示す各結果は以下のとおりである。

- Proportion score（PS）：染色強度にかかわらず、染色されたすべての腫瘍細胞の割合。
- Proportion Score 2+ or 3+（P2S）：染色強度が2+又は3+に染色された腫瘍細胞の割合。
- Proportion Score 3+（P3S）：染色強度が3+に染色された腫瘍細胞の割合。
- A modified H-score（HS）：染色強度ごとに重み付けをし、PD-L1発現細胞の割合を数値化した指標。

PD-L1高発現のカットオフ値を TPS=50とし、Biomarker Training Set の146例を対象に、TPS≥50を高発現、TPS<50を低発現又は陰性として ORR との関連をみた場合、irRC に基づく奏効判定における陽性的中率（PPV）は43%、陰性的中率（NPV）は92%であった。RECIST 1.1を用いた IRC に基づく評価では、146例のうち129例に測定可能病変が認められ、PD-L1高発現に関するカットオフ値を TPS=50とした場合の PPV は37%、NPV は89%であった[図 2.7.6.2.1-3]。

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Cut point	Best Overall Response Rate (95% Confidence Interval) by RECIST		
	PD-L1 Positive	PD-L1 Negative	Total
≥50% staining	N=41 37% (22%, 53%) PPV : 37%	N=88 11% (6%, 20%) NPV : 89%	N=129 19% (13%, 27%)
≥1% staining	N=87 25% (17%,36%) PPV : 25%	N=42 7% (2%,20%) NPV: 93%	N=129 19% (13%, 27%)

図 2.7.6.2.1-3 RECIST 1.1 を用いた IRC 評価に基づく PD-L1 高発現に対するカットオフ値を TPS=50 とした場合の ORR（001 試験）

さらに Biomarker Training Set の146例を対象として、irRC を用いた IRC 評価に基づく PFS の解析結果を[表 2.7.6.2.1-5]に示す。PFS の中央値は、PD-L1高発現（TPS≥50）で6.3ヵ月（95%CI：2.3～12.5）、PD-L1低発現（1%≤TPS<50%）で2.9ヵ月（95%CI：2.1～4.4）、PD-L1陰性（1%>TPS）で4.0ヵ月（95%CI：2.1～4.7）であり、PD-L1低発現及び陰性と比較し、PD-L1高発現の集団において PFS の延長傾向が示唆された。

表 2.7.6.2.1-5 Biomarker Training Set の患者における irRC を用いた IRC 評価に基づく PD-L1 発現量ごとの PFS（検体作製時期によらない）（APaT 集団）（001 試験）

	TPS>=50% (N=44)	TPS=1-49% (N=53)	TPS<1% (N=49)	Total (N=146)
Number (%) of PFS Events	32 (72.7)	49 (92.5)	44 (89.8)	125 (85.6)
Person-Months	361	221	197	779
Event Rate/100 Person-Months (%)	8.9	22.2	22.3	16.0
Median PFS (Months)[§]	6.3	2.9	4.0	4.0
95% CI for Median PFS[§]	(2.3,12.5)	(2.1,4.4)	(2.1,4.7)	(2.4,4.7)
PFS rate at 3 Months in % [§]	60.6	48.1	53.5	53.7
PFS rate at 6 Months in % [§]	53.2	25.4	26.8	34.1

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.

[§] From product-limit (Kaplan-Meier) method for censored data.

(Database Cutoff Date: [redacted])

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以上の結果を踏まえ、PD-L1高発現の患者集団において MK-3475による臨床効果が高いと期待されたため、パート F2において MK-3475 10 mg/kg Q3W 又は Q2W のいずれかを投与された PD-L1高発現の既治療患者61例を対象に主要な有効性解析を実施した。

2.7.6.2.1.4　　抗原安定性

[redacted]年[redacted]月に Dako 社で継続していた抗原安定性試験の結果が得られ、スライドガラス上の腫瘍組織検体の PD-L1抗原の最大6ヵ月間の安定性が確認された。抗原安定性の詳細は[2.7.3.2.1.3 項]に記載した。

PD-L1発現に基づいた有効性データを示す際、CRA による評価の6ヵ月以内に作製したスライド検体を入手した患者について評価したデータは「抗原安定期間内」と表記した。染色可能であったが、6ヵ月を超過したスライド検体で評価した患者は、「抗原安定期間内」の表中では PD-L1発現不明（Unknown）に分類した。6ヵ月以上経過したスライド検体を含め、PD-L1検査が可能であった全患者について評価した表や図は、「検体作製時期によらない」と表記した。

2.7.6.2.1.5　　結果

2.7.6.2.1.5.1　　有効性

主要な評価項目の要約を以下に示す。本項では、抗原安定期間内のスライド検体にて評価した Biomarker Validation Set を構成するパート F2の患者のうち、PD-L1高発現（TPS≥50%）の非小細胞肺癌既治療患者61例及び PD-L1発現陽性（TPS≥1%）の非小細胞肺癌の既治療患者142例の有効性の結果を示す。なお、非小細胞肺癌の未治療の患者集団の有効性の結果は[資料5.3.5.2.1.2: P001V04]に記載した。また、非小細胞肺癌の既治療の全集団、PD-L1発現陰性の患者集団及び MK-3475 2 mg/kg を投与されたパート F3の患者集団の有効性の結果は[2.7.3 項]に記載した。

2.7.6.2.1.5.1.1　　ORR

2.7.6.2.1.5.1.1.1　　PD-L1高発現

PD-L1高発現の既治療患者61例について、RECIST 1.1を用いた IRC 評価に基づく ORR は42.6%（95%CI : 30.0～55.9）であった。この患者集団では、MK-3475 10 mg/kg Q2W と MK-3475 10 mg/kg Q3W の ORR に差はみられなかった[表 2.7.6.2.1-6]。

2.7.6.2.1.5.1.1.2　　PD-L1発現陽性

PD-L1発現陽性の既治療患者142例について、RECIST 1.1を用いた IRC 評価に基づく ORR は26.8%（95%CI : 19.7～34.8）であった。この患者集団では、MK-3475 10 mg/kg Q2W と MK-3475 10 mg/kg Q3W の ORR に差はみられなかった[表 2.7.6.2.1-7]。

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表 2.7.6.2.1-6 非小細胞肺癌の既治療患者での RECIST 1.1 を用いた IRC 評価に基づく BOR（確定）の要約（PD-L1 高発現、APaT 集団）（抗原安定期間内）（001 試験）

Response Evaluation	MK-3475 10 mg/kg Q3W (N=34)			MK-3475 10 mg/kg Q2W (N=27)			Total (N=61)		
	n	%	95%CI†	n	%	95%CI†	n	%	95%CI†
Complete Response (CR)	1	2.9	(0.1, 15.3)	0	0.0	(0.0, 12.8)	1	1.6	(0.0, 8.8)
Partial Response (PR)	14	41.2	(24.6, 59.3)	11	40.7	(22.4, 61.2)	25	41.0	(28.6, 54.3)
Overall Response (CR+PR)	**15**	**44.1**	**(27.2, 62.1)**	**11**	**40.7**	**(22.4, 61.2)**	**26**	**42.6**	**(30.0, 55.9)**
Stable Disease (SD)	4	11.8	(3.3, 27.5)	4	14.8	(4.2, 33.7)	8	13.1	(5.8, 24.2)
NonCR/NonPD (NN)	1	2.9	(0.1, 15.3)	0	0.0	(0.0, 12.8)	1	1.6	(0.0, 8.8)
Disease Control (CR+PR+SD+NN)	**20**	**58.8**	**(40.7, 75.4)**	**15**	**55.6**	**(35.3, 74.5)**	**35**	**57.4**	**(44.1, 70.0)**
Progressive Disease (PD)	7	20.6	(8.7, 37.9)	8	29.6	(13.8, 50.2)	15	24.6	(14.5, 37.3)
Non-evaluable (NE)	2	5.9	(0.7, 19.7)	0	0.0	(0.0, 12.8)	2	3.3	(0.4, 11.3)
No Assessment	5	14.7	(5.0, 31.1)	4	14.8	(4.2, 33.7)	9	14.8	(7.0, 26.2)

Only confirmed responses are included in this table.
† Based on binomial exact confidence interval method.
(Database Cutoff Date: [redacted])

表 2.7.6.2.1-7 非小細胞肺癌の既治療患者での RECIST 1.1 を用いた IRC 評価に基づく BOR（確定）の要約（PD-L1 発現陽性）（APaT 集団）（抗原安定期間内）（001 試験）

Response Evaluation	MK-3475 10 mg/kg Q3W (N=76)			MK-3475 10 mg/kg Q2W (N=66)			Total (N=142)		
	n	%	95%CI†	n	%	95%CI†	n	%	95%CI†
Complete Response (CR)	1	1.3	(0.0, 7.1)	0	0.0	(0.0, 5.4)	1	0.7	(0.0, 3.9)
Partial Response (PR)	20	26.3	(16.9, 37.7)	17	25.8	(15.8, 38.0)	37	26.1	(19.1, 34.1)
Overall Response (CR+PR)	**21**	**27.6**	**(18.0, 39.1)**	**17**	**25.8**	**(15.8, 38.0)**	**38**	**26.8**	**(19.7, 34.8)**
Stable Disease (SD)	14	18.4	(10.5, 29.0)	18	27.3	(17.0, 39.6)	32	22.5	(16.0, 30.3)
NonCR/NonPD (NN)	3	3.9	(0.8, 11.1)	0	0.0	(0.0, 5.4)	3	2.1	(0.4, 6.0)
Disease Control (CR+PR+SD+NN)	**38**	**50.0**	**(38.3, 61.7)**	**35**	**53.0**	**(40.3, 65.4)**	**73**	**51.4**	**(42.9, 59.9)**
Progressive Disease (PD)	27	35.5	(24.9, 47.3)	20	30.3	(19.6, 42.9)	47	33.1	(25.4, 41.5)
Non-evaluable (NE)	3	3.9	(0.8, 11.1)	1	1.5	(0.0, 8.2)	4	2.8	(0.8, 7.1)
No Assessment	8	10.5	(4.7, 19.7)	10	15.2	(7.5, 26.1)	18	12.7	(7.7, 19.3)

Only confirmed responses are included in this table.
† Based on binomial exact confidence interval method.
(Database Cutoff Date: [redacted])

2.7.6.2.1.5.1.2　副次評価項目の要約

2.7.6.2.1.5.1.2.1　PD-L1高発現

PD-L1高発現の既治療患者61例において、DOR の中央値は未到達（NR）（範囲：2.1+～13.4+ヵ月）であった。奏効がみられた患者のうちデータベースカットオフ日時点で奏効が持続している患者の割合は81%であった（[資料5.3.5.2.1.2: P001V04]の表11.1-4）。PD-L1高発現の既治療患者61例における PFS の中央値は6.3ヵ月（95%CI : 2.1～10.7）であり[表 2.7.6.2.1-8]、OS の中央値は15.5ヵ月（95%CI：11.1～NR）であった[表 2.7.6.2.1-9]。

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表 2.7.6.2.1-8 非小細胞肺癌の既治療患者の RECIST 1.1 を用いた IRC 評価に基づく PFS
（PD-L1 高発現、APaT 集団）（抗原安定期間内）（001 試験）

	MK-3475 10 mg/kg Q3W (N=34)	MK-3475 10 mg/kg Q2W (N=27)	Total (N=61)
Number (%) of PFS Events	24 (70.6)	15 (55.6)	39 (63.9)
Person-Months	214	193	407
Event Rate/100 Person-Months (%)	11.2	7.8	9.6
Median PFS (Months)[§]	4.3	8.2	6.3
95%CI for Median PFS[§]	(1.8,10.7)	(2.1,.)	(2.1,10.7)
PFS rate at 3 Months in % [§]	58.8	57.7	58.3
PFS rate at 6 Months in % [§]	49.5	57.7	53.2
Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first. [§] From product-limit (Kaplan-Meier) method for censored data. (Database Cutoff Date: [redacted])			

表 2.7.6.2.1-9 非小細胞肺癌の既治療患者の OS
（PD-L1 高発現、APaT 集団）（抗原安定期間内）（001 試験）

	MK-3475 10 mg/kg Q3W (N=34)	MK-3475 10 mg/kg Q2W (N=27)	Total (N=61)
Death (%)	18 (52.9)	9 (33.3)	27 (44.3)
Median Survival (Months)[§]	12.2	15.5	15.5
95%CI for Median Survival[§]	(4.3,.)	(11.1,.)	(11.1,.)
OS rate at 6 Months in % [§]	67.6	81.3	73.6
OS rate at 12 Months in % [§]	52.1	69.3	59.7
OS: Overall survival. [§] From product-limit (Kaplan-Meier) method for censored data. (Database Cutoff Date: [redacted])			

2.7.6.2.1.5.1.2.2　　PD-L1発現陽性

PD-L1発現陽性の既治療患者142例において、DOR の中央値は NR（範囲：1.9+～13.4+ヵ月）であった。奏効がみられた患者のうちデータベースカットオフ日時点で奏効が持続している患者の割合は84%であった（[資料5.3.5.2.1.2: P001V04]の表14.5.2-68）。PD-L1発現陽性の既治療患者142例における PFS の中央値は4.1ヵ月（95%CI : 2.2～4.6）であり[表 2.7.6.2.1-10]、OS の中央値は14.0ヵ月（10.5～NR）であった[表 2.7.6.2.1-11]。

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表 2.7.6.2.1-10　　非小細胞肺癌の既治療患者の RECIST 1.1 を用いた IRC 評価に基づく PFS（PD-L1 発現陽性、APaT 集団）（抗原安定期間内）（001 試験）

	MK-3475 10 mg/kg Q3W (N=76)	MK-3475 10 mg/kg Q2W (N=66)	Total (N=142)
Number (%) of PFS Events	56 (73.7)	47 (71.2)	103 (72.5)
Person-Months	407	372	779
Event Rate/100 Person-Months (%)	13.8	12.6	13.2
Median PFS (Months)[§]	3.3	4.2	4.1
95%CI for Median PFS[§]	(2.1,5.4)	(2.2,6.5)	(2.2,4.6)
PFS rate at 3 Months in % [§]	51.3	56.7	53.8
PFS rate at 6 Months in % [§]	38.0	43.9	40.7
Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first. [§] From product-limit (Kaplan-Meier) method for censored data. (Database Cutoff Date: [redacted])			

表 2.7.6.2.1-11　　非小細胞肺癌の既治療患者の OS（PD-L1 発現陽性、APaT 集団）（抗原安定期間内）（001 試験）

	MK-3475 10 mg/kg Q3W (N=76)	MK-3475 10 mg/kg Q2W (N=66)	Total (N=142)
Death (%)	37 (48.7)	30 (45.5)	67 (47.2)
Median Survival (Months)[§]	14.0	15.5	14.0
95%CI for Median Survival[§]	(8.3,.)	(6.9,.)	(10.5,.)
OS rate at 6 Months in % [§]	67.1	66.3	66.8
OS rate at 12 Months in % [§]	52.3	55.3	53.9
OS: Overall survival. [§] From product-limit (Kaplan-Meier) method for censored data. (Database Cutoff Date: [redacted])			

2.7.6.2.1.5.2　　薬物動態及び免疫原性

非小細胞肺癌患者に10 mg/kg Q3W 投与時の血清中 MK-3475濃度［最高血清中 MK-3475濃度（Cmax）及び投与間隔終了時濃度（Ctrough）］は2 mg/kg Q3W 投与時の約5倍であり、この用量範囲では MK-3475の曝露量が用量比例性を示すことが確認された。MK-3475の PK の個体間変動は小さいか若しくは中程度である［変動係数（CV）：25%～63%］。

免疫原性の評価には抗薬物（MK-3475）抗体（ADA）測定用検体が得られ、MK-3475の投与を受けた419例のうち、MK3475の初回投与開始後に検体が得られた290例の非小細胞肺癌患者を含めた。評価の結果、不確定が274例、陰性が16例で、陽性患者は認められなかった。

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2.7.6.2.1.5.3　　安全性

安全性解析の要約

MK-3475の安全性及び忍容性は、有害事象、臨床検査値、心電図及びバイタルサインを含むあらゆるパラメータを使用し、臨床的に評価した。有害事象は各用法・用量での発現回数及び発現頻度を用いて要約した。臨床検査値、バイタルサイン及び他の安全性の評価項目は適宜要約した。

有害事象の要約を[表 2.7.6.2.1-12]に示す。安全性解析は治験薬の投与を受けた全550例を対象とした。3群間（MK-3475 2 mg/kg Q3W、10 mg/kg Q3W 及び10 mg/kg Q2W）での有害事象の発現割合は類似していた。全患者で高頻度に発現した有害事象は、疲労（36.7%）、食欲減退（25.8%）、呼吸困難（23.5%）及び咳嗽（22.9%）であった。副作用、重篤な有害事象及び有害事象による中止の発現割合は3群間で概して同程度であった。新生物進行、悪性新生物進行及び PD 以外の事象による死亡は低頻度（2.7%）であり、3群間で類似していた。また、死亡例のうち3例（0.6%）の事象が治験薬との因果関係がありと判断された。PD-L1高発現（ベースライン時）の患者に発現した有害事象は全体集団と類似していた。

免疫関連の特に注目すべき有害事象（AEOSI）は非小細胞肺癌の全患者集団のうち14.5%にみられ、10 mg/kg の2つの用法（Q3W 及び Q2W）間で発現割合は類似していた。全患者集団で最も高頻度に発現した免疫関連の AEOSI は、甲状腺機能低下症（7.6%）であった。PD-L1高発現（ベースライン時）の患者に発現した免疫関連の AEOSI は全体集団と類似していた。

MK-3475 10 mg/kg Q3W の患者1例が事前に規定した薬剤性肝障害の基準に合致した。この患者にはベースライン時に肝転移が確認されており、MK-3475投与開始から1.5ヵ月以内に PD により死亡していることから MK-3475との因果関係判定は困難であった。 MK-3475の投与によるバイタルサインの変動はなかった。現時点では MK-3475により QTc 間隔の延長は認められていない。001試験の結果に基づき、MK-3475の忍容性が確認され、管理可能な安全性プロファイルが示された。

すべての有害事象、副作用及び重篤な有害事象を[付録 2.7.4-8]、[付録 2.7.4-9]、[付録 2.7.4-37]に示す。

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表 2.7.6.2.1-12　有害事象の要約

（パート C+F1+F2+F3）（APaT 集団）（001 試験）

	MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		MK-3475 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	61		287		202		550	
with one or more adverse events	58	(95.1)	276	(96.2)	197	(97.5)	531	(96.5)
with no adverse event	3	(4.9)	11	(3.8)	5	(2.5)	19	(3.5)
with drug-related† adverse events	31	(50.8)	201	(70.0)	148	(73.3)	380	(69.1)
with toxicity grade 3-5 adverse events	26	(42.6)	130	(45.3)	94	(46.5)	250	(45.5)
with toxicity grade 3-5 drug-related adverse events	5	(8.2)	34	(11.8)	19	(9.4)	58	(10.5)
with serious adverse events	27	(44.3)	108	(37.6)	82	(40.6)	217	(39.5)
with serious drug-related adverse events	6	(9.8)	23	(8.0)	13	(6.4)	42	(7.6)
who died	2	(3.3)	7	(2.4)	6	(3.0)	15	(2.7)
who died due to a drug-related adverse event	1	(1.6)	1	(0.3)	0	(0.0)	2	(0.4)
discontinued‡ due to an adverse event	9	(14.8)	40	(13.9)	30	(14.9)	79	(14.4)
discontinued due to a drug-related adverse event	4	(6.6)	11	(3.8)	8	(4.0)	23	(4.2)
discontinued due to a serious adverse event	9	(14.8)	30	(10.5)	22	(10.9)	61	(11.1)
discontinued due to a serious drug-related adverse event	4	(6.6)	8	(2.8)	6	(3.0)	18	(3.3)

† Determined by the investigator to be related to the drug.

‡ Study medication withdrawn.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

(Database Cutoff Date: [redacted])

2.7.6.2.1.6　　結論

本治験のパート C 及びパート F に組み入れられた非小細胞肺癌患者550例のデータより、MK-3475の有効性、PK 及び安全性に関して以下の結論が得られた。

2.7.6.2.1.6.1　　有効性

1) PD-L1高発現の非小細胞肺癌既治療の患者（N=61）では、RECIST 1.1を用いた IRC 評価に基づく ORR は42.6%であり、MK-3475の明らかな治療効果が示された。
2) PD-L1高発現の非小細胞肺癌既治療の患者では、奏効がみられた患者のうちデータベースカットオフ日時点で奏効が持続している患者は81%であった。
3) PD-L1発現陽性の非小細胞肺癌既治療の患者（N=142）では、RECIST 1.1を用いた IRC 評価に基づく ORR は26.8%であり、MK-3475の治療効果が示された。
4) PD-L1発現陽性の非小細胞肺癌既治療の患者では、奏効がみられた患者のうちデータベースカットオフ日時点で奏効が持続している患者は84%であった。

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5)　MK-3475 2 mg/kg Q3W と MK-3475 10 mg/kg Q3W の両群間の ORR に差はみられなかった。

2.7.6.2.1.6.2　　薬物動態及び免疫原性

1)　MK-3475 2～10 mg/kg Q3W の用量範囲において、MK-3475の曝露量は用量比例性を示すことが確認された。
2)　MK-3475が ADA 産生を惹起する可能性は低いと考えられた。

2.7.6.2.1.6.3　　安全性

非小細胞肺癌患者では、MK-3475は良好な忍容性を示し、AEOSI の発現割合も低かった。

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2.7.6.2.2　進行性固形がん患者を対象とした第Ⅰ相試験［国内試験］［評価資料］（KEYNOTE-011試験、以下011試験）

2.7.6.2.2.1　試験方法の概要

治験責任医師／治験実施医療機関

中川　和彦　他／多施設共同（2施設）

公表文献

1) Seto T, Shimizu T, Hirai F, et al. Phase 1 study of Pembrolizumab (anti-PD-1 monoclonal antibody; MK-3475) in Japanese patients with advanced solid tumors. APLCC 2014: IASLC Asia Pacific Lung Cancer Conference; 2014 Nov 6-8, Kuala Lumpur, Malaysia.
2) Shimizu T, Seto T, Hirai F, et al. Phase 1 study of Pembrolizumab (anti-PD-1 monoclonal antibody; MK-3475) in Japanese patients with advanced solid tumors. The 55th Annual Meeting of the Japan Lung Cancer Society 2014 Nov 14-16. Kyoto, Japan.

治験実施期間

[redacted]年[redacted]月[redacted]日～実施中（データベースカットオフ日：2014年5月7日）

開発の相

第Ⅰ相

治験デザイン

本試験は、進行性固形がん患者及び進行性非小細胞肺癌患者を対象とした非盲検、非無作為化、多施設共同第Ⅰ相試験である。本試験は2つのコホート；パートA［標準的治療が無効となった進行性固形がん患者（3～12例）に対するMK-3475単独療法］及びパートB［未治療の進行性非小細胞肺癌患者（6～18例）に対するMK-3475とシスプラチン／ペメトレキセド又はカルボプラチン／パクリタキセルの併用療法］からなる。安全性及び忍容性の評価のため、1コース目を用量制限毒性（DLT）評価期間とし、3+3デザインによりDLTを評価した。2コース目以降は、原疾患の進行又は許容できない毒性の発現等の中止規準に該当しない限り治療を継続した。

主要目的

1) 進行性固形がん患者に対するMK-3475の単独療法、及び進行性非小細胞肺癌患者に対するMK-3475とシスプラチン／ペメトレキセド又はカルボプラチン／パクリタキセルの併用療法の安全性及び忍容性を評価する。

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副次目的

1) MK-3475の単独療法、及びMK-3475とシスプラチン／ペメトレキセド又はカルボプラチン／パクリタキセルの併用療法における MK-3475の PK を評価する。

探索的目的

1) ADA の発現を評価する。
2) 進行性固形がん患者に対する MK-3475の単独療法、及び進行性非小細胞肺癌患者に対するMK-3475とシスプラチン／ペメトレキセド又はカルボプラチン／パクリタキセルの併用療法の抗腫瘍効果を評価する。
3) PD-L1の発現量と MK-3475の腫瘍縮小効果との相関を評価する。
4) MK-3475に起因する間質性肺疾患を診断するために、胸部画像の変化及びその特徴を評価する。

ロット番号

表 2.7.6.2.2-1 治験薬の内容（011 試験）

治験薬	剤型	力価	ロット番号	包装番号	有効期限
MK-3475	静注用凍結乾燥粉末	50 mg	GL00001068	DL00018122	2015年01月31日
MK-3475	静注用凍結乾燥粉末	50 mg	DL00018225	DL00018426	2015年02月28日

診断／組入れ基準

選択基準：

以下の基準をすべて満たした患者を対象とした。

1) 各パートについて以下の基準を満たす患者；

パート A（単独療法）

組織学的又は細胞学的に固形がんと診断され、転移性又は局所進行性（局所療法の適応とならない）の病変を有する患者

- 患者が有する悪性腫瘍に対して確立した抗がん剤標準治療が無効又は不耐容である、又は治験担当医師から医学的理由により特定の標準的治療に不適格であると判断されていること

パート B（併用療法）

組織学的又は細胞学的に非小細胞肺癌と診断され、病期がⅢB／Ⅳである患者

- 化学療法が未実施であること

2) 同意取得時に20歳以上の男性又は女性の患者
3) ECOG PS が0又は1の患者
4) 適切な臓器機能を有する患者
5) 妊娠の可能性のある女性患者については、スクリーニング時の尿又は血清妊娠検査が陰性であること。尿検査が陽性又は陰性であることが確認できない場合は、血清による妊娠検査を実施し、陰性である患者が本試験に組み入れられる。

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6)　女性患者の場合：
- 妊娠の可能性がない女性（ただし、薬剤投与などの医学的理由による場合を除く）
- 妊娠の可能性のある女性については、スクリーニングから治験薬最終投与後120日まで、適切な二重避妊法を実施することに同意する患者

7)　男性患者の場合：
パートナーが妊娠する可能性がある場合は、スクリーニングから治験薬最終投与後120日まで、適切な二重避妊法を実施することに同意する患者。パートナーが妊娠している場合は、男性患者はコンドームの使用に同意すること。妊娠しているパートナーに対して更に避妊法を実施する必要はない。

8)　自由意思により、治験の参加について文書による同意を得ている患者。将来の生物医学研究の参加に関しても患者から同意を得ること。ただし、将来の生物医学研究へ参加せず本試験のみに参加することは可能である。

評価基準

安全性

NCI CTCAE version 4.0に基づき Grade 分類したすべての有害事象、血液一般検査、血液生化学検査、尿検査、身体所見、バイタルサイン、12誘導心電図、ECOG PS、胸部画像所見等の結果を用いて評価した。また、効果安全性評価委員は、専門的、客観的な観点から DLT 評価期間における DLT 及び安全性情報を評価した。MK-3475に起因する間質性肺疾患を評価するため、すべての CT 画像を独立した放射線医師が評価し、その後効果安全性評価委員が臨床データを踏まえて胸部 CT 画像の異常所見を総合的に評価した。

薬物動態及び免疫原性

PK：血清中 MK-3475濃度及び PK パラメータ［投与開始後28日までの濃度-時間曲線下面積（$AUC_{0\text{-}28\ day}$）、投与開始後無限大時間までの濃度-時間曲線下面積（$AUC_{0\text{-}\infty}$）、C_{max}、最高血清中 MK-3475濃度到達時間（T_{max}）、最終消失相の分布容積（V_z）、クリアランス（CL）、消失半減期（$t_{1/2}$）（ノンコンパートメント解析）］を評価した。

免疫原性：ブリッジング電気化学発光法を用いて測定した。スクリーニング試験、確認試験及び抗体価試験の標準的な3段階法にて ADA の評価を行った。確認試験にて、少なくとも1つの投与前若しくは投与後検体が陽性である場合を陽性とした。

PD-L1発現解析

提出されたホルマリン固定パラフィン包埋腫瘍組織検体を用いて、IHC により PD-L1発現を確認した。単核炎症性細胞を含むマクロファージ又はストローマを含まない腫瘍巣のみ及び細胞膜が染色された単核性炎症細胞での染色強度に基づくスコア（MPS）が0よりも大きい場合に PD-L1発現陽性と判定した。

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有効性

irRC 及び RECIST 1.1に基づく治験担当医師の評価、中央画像判定機関が評価した全腫瘍量の解析

統計計画及び解析

安全性

DLT 評価期間（治験薬の初回投与後4週間）に発現した DLT の発現頻度をパート A の投与レベル及びパート B のコホートごとに表に要約した。DLT が発現した場合は、DLT 発現率の点推定値及びその90%ベイズ流予測区間を計算し、最初に DLT が発現するまでの時間及び持続時間に関する要約統計量［平均値、標準偏差（SD）、中央値、範囲］を示した。すべての有害事象は、器官別大分類及び基本語ごとに、1件以上発現した症例数（%）を表に要約した。血液一般検査、血液生化学検査、尿検査、胸部画像所見、有害事象、12誘導心電図、バイタルサイン、臨床所見、ECOG PS 等も投与レベル／コホートごとに要約した。

薬物動態

MK-3475の PK パラメータ $AUC_{0\text{-}28\ days}$、$AUC_{0\text{-}\infty}$、C_{max}、V_z、CL、$t_{1/2}$については幾何平均値、CV を、T_{max} については最小値、中央値及び最大値をそれぞれ算出し、要約した。

有効性

ORR 及びその正確な95%CI を算出した。また、腫瘍縮小効果（CR、PR、SD、PD）を投与レベル／コホートごとに要約した。

探索的な解析として、PD-L1の発現量と腫瘍縮小効果との相関を検討した。

データベースカットオフ日（[redacted]年[redacted]月[redacted]日）時点で、パート A のみ実施中、パート B は開始前であるため、本章にはパート A の結果のみ記載する。

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2.7.6.2.2.2　　患者の内訳

患者の特性を[表 2.7.6.2.2-2]に、患者の内訳を[表 2.7.6.2.2-3]に示す。

表 2.7.6.2.2-2 患者の特性（ATS 集団）（011 試験　パート A）

	MK-3475 2 mg/kg Q2W		MK-3475 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	3		7		10	
Gender						
Male	2	(66.7)	3	(42.9)	5	(50.0)
Female	1	(33.3)	4	(57.1)	5	(50.0)
Age (Years)						
<65	1	(33.3)	5	(71.4)	6	(60.0)
>=65	2	(66.7)	2	(28.6)	4	(40.0)
Mean	61.3		64.3		63.4	
SD	6.4		13.6		11.6	
Median	65.0		61.0		62.0	
Range	54 to 65		52 to 91		52 to 91	
Race						
Asian	3	(100.0)	7	(100.0)	10	(100.0)
Ethnicity						
Not Hispanic Or Latino	3	(100.0)	7	(100.0)	10	(100.0)
Weight (kg)						
Subjects with data	3		7		10	
Mean	74.9		53.8		60.2	
SD	4.7		12.1		14.4	
Median	74.4		53.9		61.7	
Range	70.5 to 79.9		39.4 to 71.7		39.4 to 79.9	
Height (cm)						
Subjects with data	3		7		10	
Mean	173.0		160.8		164.4	
SD	8.8		8.7		10.1	
Median	176.1		159.9		162.8	
Range	163.1 to 179.8		152.1 to 176.8		152.1 to 179.8	
ECOG						
0	2	(66.7)	2	(28.6)	4	(40.0)
1	1	(33.3)	5	(71.4)	6	(60.0)
Stage at Study Entry						
IV	3	(100.0)	7	(100.0)	10	(100.0)
Oncologic Diagnosis						
NSCLC	1	(33.3)	4	(57.1)	5	(50.0)
Breast cancer	0	(0.0)	1	(14.3)	1	(10.0)
Malignant melanoma	1	(33.3)	2	(28.6)	3	(30.0)
Extramammary Paget's disease	1	(33.3)	0	(0.0)	1	(10.0)
Number of Prior Regimen						
0	1	(33.3)	1	(14.3)	2	(20.0)
2	0	(0.0)	2	(28.6)	2	(20.0)
5	1	(33.3)	2	(28.6)	3	(30.0)
9	1	(33.3)	0	(0.0)	1	(10.0)
10	0	(0.0)	1	(14.3)	1	(10.0)
13	0	(0.0)	1	(14.3)	1	(10.0)
Number of Prior Regimen						
Subjects with data	3		7		10	
Mean	4.7		5.3		5.1	
SD	4.5		4.7		4.4	
Median	5.0		5.0		5.0	
Range	0.0 to 9.0		0.0 to 13.0		0.0 to 13.0	

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表 2.7.6.2.2-3 患者の内訳（011 試験　パート A）

	MK-3475 2 mg/kg Q2W n	(%)	MK-3475 10 mg/kg Q2W n	(%)	Total n	(%)
SCREENING FAILURES	-		-		1	
RANDOMIZED	3		7		10	
DISCONTINUED	3	(100.0)	6	(85.7)	9	(90.0)
Adverse Event	0	(0.0)	1	(14.3)	1	(10.0)
Progressive Disease	3	(100.0)	5	(71.4)	8	(80.0)
ON-GOING	0	(0.0)	1	(14.3)	1	(10.0)
Each patient is counted once for Study Disposition based on the latest corresponding disposition record.						

2.7.6.2.2.3　結果

2.7.6.2.2.3.1　安全性

有害事象の要約を[表 2.7.6.2.2-4]に示す。安全性は治験薬を割り付けられ、少なくとも1回投与されたすべての患者（ATS）を解析集団とした。データベースカットオフ時点で、パート A の投与レベル1（2 mg/kg Q2W）で3例、投与レベル2（10 mg/kg Q2W）で7例に MK-3475を投与した。DLT は、投与レベル2の DLT 評価対象外の1例（DLT 評価期間中に原疾患の悪化により投与を中止）を除く9例（投与レベル1：3例、投与レベル2：6例）で評価し、いずれの症例でも認められなかった。

MK-3475が投与された10例のうち全例に有害事象が認められた。3例以上に認められた有害事象は疲労（4例）、末梢性浮腫、発熱、食欲減退、低ナトリウム血症及び呼吸困難（各3例）であった。副作用は8例に認められ、2例以上に認められた副作用は悪心、倦怠感、発熱、アスパラギン酸アミノトランスフェラーゼ（AST）増加及びアラニンアミノトランスフェラーゼ（ALT）増加（各2例）であった。ほとんどの副作用が Grade 1又は2であった。重篤な有害事象は、1例に3件認められ、Grade 3 AST 増加、Grade 3 ALT 増加及び Grade 4脳梗塞であった。このうち重篤な副作用は Grade 3 AST 増加及び Grade 3 ALT 増加であった。本試験において死亡は認められなかった。有害事象により治験を中止した患者は1例であった。本事象は Grade 4の脳梗塞であり、治験薬との因果関係は治験担当医師により否定された。

Grade 3又は4の有害事象は4例に認められ、そのうち3例で認められた有害事象は Grade 3低ナトリウム血症であった。Grade 3の副作用は1例に認められ、Grade 3 AST 増加、Grade 3 ALT 増加及び Grade 3 低ナトリウム血症であった。

報告された免疫関連の有害事象（irAE）は、Grade 3 AST 増加及び Grade 3 ALT 増加、Grade 1 血中甲状腺刺激ホルモン（TSH）増加及び Grade 1 肺臓炎であった。

間質性肺疾患の評価は、治験担当医師の評価に加え、独立した放射線医師及び効果安全性評価委員が評価した。[redacted]年[redacted]月[redacted]日までに撮影されたすべての患者の胸部 CT 画像を、独立した放射線医師が評価した結果、治験担当医師より報告があった1例（Grade 1の肺臓炎）を含めて3例で異常所見が認められた。これらの症例について効果安全性評価委員が臨床データも踏まえて総合的に間質性肺疾患の評価を行った。その結果、いずれの画像所見も治験薬との因果関係を否定できない無症候性の間質性肺疾患（Grade 1）と判定された。

すべての有害事象、副作用及び重篤な有害事象を[付録 2.7.4-89]、[付録 2.7.4-90]、[表 2.7.4-47]

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に示す。

表 2.7.6.2.2-4 有害事象の要約（ATS 集団）（011 試験　パート A）

	MK-3475 2 mg/kg Q2W (N=3)		MK-3475 10 mg/kg Q2W (N=7)		Total (N=10)	
	n	(%)	n	(%)	n	(%)
With one or more adverse events	3	(100.0)	7	(100.0)	10	(100.0)
With no adverse event	0	(0.0)	0	(0.0)	0	(0.0)
With drug-related adverse events	2	(66.7)	6	(85.7)	8	(80.0)
With serious adverse events	0	(0.0)	1	(14.3)	1	(10.0)
With serious drug-related adverse events	0	(0.0)	1	(14.3)	1	(10.0)
Who died	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to adverse event	0	(0.0)	1	(14.3)	1	(10.0)
Discontinued due to drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to serious adverse event	0	(0.0)	1	(14.3)	1	(10.0)
Discontinued due to serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
Drug-related adverse events are adverse events determined by the investigator to be possibly, probably, or definitely drug related. MedDRA preferred terms ‘Malignant neoplasm progression’ not related to the drug are excluded.						

2.7.6.2.2.3.2　　薬物動態及び免疫原性

[表 2.7.6.2.2-5]に示すように、MK-3475の PK において、CL は低く、V_z は小さく、$t_{1/2}$は長く、一般的に抗体薬にて認められている特徴を示した。MK-3475の2又は10 mg/kg を初回静脈内投与した際の MK-3475の血清中濃度は緩やかに消失し、$t_{1/2}$の幾何平均値は18日であった。MK-3475を2又は10 mg/kg で初回静脈内投与した際の MK-3475の曝露量（$AUC_{0-\infty}$及び C_{max}）は概して用量に比例して増加し、これと一致して CL 及び V_z の幾何平均値は2及び10 mg/kg で概して類似していた。

日本人固形がん患者にて ADA の産生は認められなかった（カットオフ：[redacted]年[redacted]月[redacted]日）。

表 2.7.6.2.2-5 MK-3475 を 2 又は 10 mg/kg で初回静脈内投与した際の MK-3475 の PK パラメータ（011 試験　パート A）

PK パラメータ		2 mg/kg (N=3)		10 mg/kg (N=7)	
		GM	(%CV)	GM	(%CV)
C_{max}	(μg/mL)	47.4	(19)	250	(23)
T_{max} †	(day)	0.223	(0.00208-0.233)	0.00903	(0.000694-0.232)
$AUC_{0-28\ day}$	(μg･day/mL)	507	(20)	2219	(32)
$AUC_{0-\infty}$	(μg･day/mL)	812	(45)	3410	(56)
$t_{1/2}$	(day)	18.4	(56)	18.1	(68)
V_z	(mL/kg)	65.3	(21)	76.5	(34)
CL	(mL/day/kg)	2.46	(45)	2.93	(56)
GM = 幾何平均値、CV = 変動係数 † T_{max} =中央値（範囲）					

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2.7.6.2.2.3.3　　有効性

有効性解析は、MK-3475を投与された10例のうち、測定可能病変を持たない患者1例を除いた、9例を対象とした。9例の内訳は、非小細胞肺癌5例、悪性黒色腫3例及び乳癌1例であった。

RECIST 1.1に基づく奏効例（CR 又は PR）は9例中2例（22.2%、95%CI：2.8～60.0）であった。PR を認めた2例は、10 mg/kg Q2W（投与レベル2）を投与された悪性黒色腫患者及び非小細胞肺癌患者の各1例であった。いずれの患者においても irRC に基づく PR が認められた。RECIST 1.1 に基づく PFS の中央値は60.0日であり、irRC に基づく PFS の中央値は42.5日であった。また、奏効例2例の奏効までの期間は46日（悪性黒色腫患者）及び41日（非小細胞肺癌患者）であった。

提出された腫瘍検体を用いて IHC にて PD-L1発現を解析した。PD-L1発現解析が可能な検体を提出し、かつ有効性解析対象であったのは5例であった。このうち PD-L1発現陽性が2例、PD-L1発現陰性が3例であった。RECIST 1.1及び irRC に基づく奏効は、PD-L1発現陽性の2例で認められなかったが、PD-L1発現陰性の3例中1例で PR が認められた。

2.7.6.2.2.4　　結論

- 日本人の進行性固形がん患者に対する2 mg/kg 又は10 mg/kg の静脈内投与では、いずれの用量においても DLT の発現は認められず全般に良好な忍容性を示した。日本人患者の安全性プロファイルは、非日本人患者と類似していた。
- MK-3475の PK は、CL は低く、V_z は小さく、$t_{1/2}$は長かった。日本人固形がん患者における MK-3475の曝露量は2及び10 mg/kg の用量範囲で概して用量に比例して増加した。また、MK-3475の投与による ADA の産生は認められなかった。
- 探索的な抗腫瘍効果の評価では、RECIST 1.1及び irRC に基づく奏効が9例中2例（22.2%）に認められた（悪性黒色腫患者1例、非小細胞肺癌患者1例、いずれも10 mg/kg Q2W）。PD-L1発現解析では、評価例数が限られていたため、PD-L1発現と MK-3475による奏効との間に相関があるかは明らかでなかった。

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2.7.6.2.3　PD-L1発現陽性の進行性非小細胞肺癌患者を対象とした後期第Ⅰ相試験［国内試験］［評価資料］（KEYNOTE-025試験、以下025試験）

2.7.6.2.3.1　試験方法の概要

治験責任医師／治験実施医療機関

西尾誠人　他／多施設共同（13施設）

公表文献

なし

治験実施期間

[redacted]年[redacted]月[redacted]日～実施中（データベースカットオフ日：2015年7月9日）

開発の相

後期第Ⅰ相

治験デザイン

本試験はPD-L1発現陽性の進行性非小細胞肺癌患者を対象としたMK-3475単独療法の、非盲検、非無作為化、多施設共同後期第Ⅰ相試験である。本試験には必須の検査として新たに生検にて採取された腫瘍組織で PD-L1発現陽性が確認された非小細胞肺癌患者が組み入れられ、MK-3475 10 mg/kg を Q3W で静脈内投与した。PD-L1高発現の患者12例を組み入れるため、目標症例数をPD-L1発現陽性の患者24例とした。患者は、MK-3475 10 mg/kg を Q3W で投与され、PD や許容できない毒性の発現及び MK-3475の2年間の投与完了などの、患者ごとの治験の中止基準に合致するまで継続した。

主要目的

1) PD-L1高発現の進行性非小細胞肺癌患者に MK-3475を投与した際の、RECIST 1.1に基づくORR を評価する。
1) PD-L1発現陽性の進行性非小細胞肺癌患者に MK-3475を投与した際の、安全性及び忍容性を評価する。

副次的目的

1) PD-L1高発現の進行性非小細胞肺癌患者に MK-3475を投与した際の、RECIST 1.1に基づくDOR、PFS、及び OS を評価する。
2) PD-L1高発現の進行性非小細胞肺癌患者に MK-3475を投与した際の、irRC に基づく ORR、DOR、及び PFS を評価する。
3) PD-L1発現陽性の進行性非小細胞肺癌患者に MK-3475を投与した際の、RECIST 1.1又は

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irRC に基づく ORR、DOR、PFS、及び OS を評価する。

探索的目的

1) PD-L1発現陽性の進行性非小細胞肺癌患者における腫瘍体積量の変化を評価する。
2) MK-3475の PK を評価する。
3) ADA の発現を評価する。
4) MK-3475に起因する間質性肺疾患を診断するために、胸部画像の変化及びその特徴を評価する。

ロット番号

表 2.7.6.2.3-1 治験薬の内容（025 試験）

治験薬	剤型	力価	ロット番号	包装番号	有効期限
MK-3475	静注用凍結乾燥粉末	50 mg	DL00018501	DL00018250	2016年2月29日
MK-3475	静注用凍結乾燥粉末	50 mg	DL00019282	DL00019243	2016年11月30日

診断／組入れ基準

1) 組織学的又は細胞学的に非小細胞肺癌と診断され、RECIST 1.1により定義される測定可能病変を1つ以上有する患者
2) 病期ⅢB／Ⅳ又は再発例で、プラチナ製剤併用化学療法後に、治験担当医師の画像判定により RECIST 1.1に基づき PD が確認された患者
   a EGFR 感受性変異を有する患者は、プラチナ製剤併用化学療法と同様に EGFR チロシンキナーゼ阻害剤による治療後に、RECIST 1.1に基づく画像判定により PD が確認されていなければならない。
   b ALK 融合遺伝子陽性の患者は、上述したプラチナ製剤併用化学療法と同様にクリゾチニブによる治療後に PD が確認されていなければならない。
3) 非小細胞肺癌に対する全身療法による前治療が2レジメンまでの患者。ただし EGFR 感受性変異又は ALK 融合遺伝子陽性の患者は3レジメンまで可能とした。
4) 同意取得時に20歳以上の男性又は女性の患者
5) ECOG PS が0又は1の患者
6) 適切な臓器機能を有する患者
7) 3ヵ月以上の生存が見込まれた患者
8) 生検前に放射線照射を受けていない病変から、新たに採取されたホルマリン固定腫瘍組織検体が PD-L1解析のために提出可能な患者。
9) 中央測定機関で実施する IHC により、PD-L1の発現（高発現又は低発現）が確認された腫瘍を有する患者。
10) 直近に受けた化学療法の毒性が Grade 1以下に回復した患者。
11) 妊娠の可能性のある女性患者については、スクリーニング時の尿又は血清妊娠検査が陰性であること。

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12) 女性患者の場合：
   - 妊娠の可能性がない患者
   - 妊娠の可能性のある患者については、スクリーニングから治験薬最終投与後120日まで、適切な二重避妊法を実施することに同意した患者。

13) 男性患者の場合：
   - パートナーが妊娠する可能性がある場合は、スクリーニングから治験薬最終投与後120日まで、適切な二重避妊法を実施することに同意した患者。

14) 自由意思により、治験の参加について文書による同意を得た患者。

評価基準

安全性

NCI CTCAE version 4.0に基づき Grade 分類したすべての有害事象、血液一般検査、血液生化学検査、尿検査、身体所見、バイタルサイン、12誘導心電図、ECOG PS、胸部画像所見等の結果を用いて評価した。また、効果安全性評価委員は、専門的、客観的な観点から安全性情報を評価した。MK-3475に起因する間質性肺疾患を評価するため、すべての胸部 CT 画像を独立した放射線医師が評価し、その後効果安全性評価委員が臨床データを踏まえて胸部 CT 画像の異常所見を総合的に評価した。

有効性

治験担当医師が irRC を用いて、中央判定機関が RECIST ver. 1.1及び腫瘍体積量の解析にて腫瘍縮小効果を判定した。

薬物動態及び免疫原性

PK：MK-3475の C_{trough}、1及び6コースにおける C_{max} 及び1コースの投与後72～120時間の血清中MK-3475濃度を評価した。また C_{trough} の経時的時推移から定常状態の到達時間を検討した。
免疫原性：スクリーニング試験、確認試験及び抗体価試験の標準的な3段階法にて ADA の評価を行った。確認試験にて、ADA の測定結果が MK-3475投与の有無にかかわらず1時点以上陽性を示した場合を陽性とした（なお、ADA 陽性は MK-3475投与による陽性と投与によらない陽性にそれぞれ分類した）。

PD-L1発現解析

新たに生検にて採取した腫瘍組織検体を用いて、IHC により PD-L1発現を確認した。PD-L1染色強度にかかわらず1%以上の腫瘍細胞で PD-L1発現が認められた場合を PD-L1発現陽性と定義し、これらの患者が本試験に組み入れられた。また、50%以上の腫瘍細胞で PD-L1発現が認められた場合を PD-L1高発現と定義し、レトロスペクティブに有効性との関連を解析した。

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統計計画及び解析

有効性

本試験における主要な有効性解析対象集団は、最大解析対象集団（FAS）とした。FAS は割り付けられたすべての患者のうち、治験薬を1回も投与されていない、ベースラインのデータを必要とする解析のベースラインのデータがない患者を除いた部分集団とした。

ORR 及びその正確な95% CI を算出し、また想定した ORR の閾値である15%との比較も行った。進行性非小細胞肺癌患者の標的病変及び非標的病変の腫瘍縮小効果（CR、PR、PD、SD）を要約した。DOR に関する要約統計量（平均値、SD、中央値、範囲）を示した。PD-L1高発現の進行性非小細胞肺癌患者に MK-3475を投与したときの PFS、並びに OS を Kaplan-Meier 法を用いて解析した。

安全性

本試験における安全性解析対象集団は、ATS とした。ATS は治験薬を割り付けられ、少なくとも1回投与されたすべての患者からなる。すべての有害事象は、器官分類及び基本語ごとに、1件以上発現した症例数（%）を表に要約した。血液一般検査、血液生化学検査、尿検査、胸部画像所見、有害事象、12誘導心電図、バイタルサイン、臨床所見、ECOG PS 等も要約した。

薬物動態

MK-3475の C_{trough}、C_{max}（1及び6コース）及び1コースの投与後72～120時間の血清中 MK-3475 濃度について幾何平均値及び CV を算出し、要約した。

免疫原性

ADA の結果を要約した。

2.7.6.2.3.2　　患者の内訳

患者の特性及び内訳を[表 2.7.6.2.3-2]及び[表 2.7.6.2.3-3]に要約する。

38例に治験薬が投与され、データベースカットオフ時点で、29例（76.3%）が治験薬投与を中止していた。

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表 2.7.6.2.3-2 患者の特性（ATS 集団）（025 試験）

	MK-3475 10 mg/kg Q3W	
	n	(%)
Subjects in population	38	
Gender		
Male	26	(68.4)
Female	12	(31.6)
Age (Years)		
< 65	15	(39.5)
>= 65	23	(60.5)
Mean	63.6	
SD	8.5	
Median	66.0	
Range	41 to 78	
Race		
Asian	38	(100.0)
Ethnicity		
Not Hispanic Or Latino	38	(100.0)
ECOG		
[0] Normal Activity	12	(31.6)
[1] Symptoms, but ambulatory	26	(68.4)
Metastatic Staging		
M0	3	(7.9)
M1	1	(2.6)
M1A	11	(28.9)
M1B	23	(60.5)
Histology		
ADENOCARCINOMA	29	(76.3)
ADENOSQUAMOUS	2	(5.3)
NON SMALL CELL	1	(2.6)
SQUAMOUS CELL CARCINOMA	6	(15.8)
Brain Metastasis		
Yes	6	(15.8)
No	32	(84.2)
Number of Prior Systemic Therapies		
1	15	(39.5)
2	18	(47.4)
3	5	(13.2)
Baseline Tumor Size (mm) RECIST 1.1 for Central Assessment		
Subjects with data	37	
Mean	68.1	
SD	66.0	
Median	46.0	
Range	15 to 272	

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表 2.7.6.2.3-2 患者の特性（ATS 集団）（025 試験）（続き）

	MK-3475 10 mg/kg Q3W	
	n	(%)
Baseline Tumor Size (mm) RECIST 1.1 Group		
< Median	18	(47.4)
>= Median	19	(50.0)
Missing	1	(2.6)
Baseline Tumor Size (mm2) irRC for Site Assessment		
Subjects with data	38	
Mean	2947.9	
SD	3203.6	
Median	1978.2	
Range	154 to 15635	
Baseline Tumor Size (mm2) irRC Group		
< Median	19	(50.0)
>= Median	19	(50.0)
Smoking Status		
Never	13	(34.2)
Former	25	(65.8)
PD-L1 Expression		
Strongly Positive	12	(31.6)
Weakly Positive	26	(68.4)
EGFR Mutation		
MUTANT	10	(26.3)
WILD TYPE	28	(73.7)
ALK Gene Rearrangement		
MUTANT	2	(5.3)
WILD TYPE	36	(94.7)

表 2.7.6.2.3-3 患者の内訳（ATS 集団（025 試験）

	MK-3475 10 mg/kg Q3W	
	n	(%)
Screened	84	
Screen Failure	46	
Subjects in population	38	
Subject Study Medication Disposition		
Discontinued	29	(76.3)
Adverse Event	3	(7.9)
Clinical Progression	4	(10.5)
Death	1	(2.6)
Excluded Medication	2	(5.3)
Physician Decision	1	(2.6)
Progressive Disease	18	(47.4)
Status Not Recorded	9	(23.7)

Each subject is counted once for Subject Study Medication Disposition based on the latest corresponding disposition record.

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2.7.6.2.3.3　　結果

2.7.6.2.3.3.1　　有効性

本試験では、PD-L1発現陽性患者38例（このうち、PD-L1高発現患者は12例）に MK-3475が投与された。PD-L1高発現の患者のうち1例は、中央判定機関で、ベースラインの画像で RECIST 1.1により定義される測定可能病変がないと判定された。したがって中央判定機関が評価した RECIST 1.1及び enhanced RECIST に基づく ORR 及び DOR は、上記症例を除外し、PD-L1高発現患者11例、PD-L1発現陽性患者37例（FAS）を対象に解析を行った。治験担当医師が評価した irRC に基づく ORR、中央判定機関が評価した RECIST 1.1及び治験担当医師が評価した irRC に基づく PFS、及び OS は、PD-L1高発現患者12例、PD-L1発現陽性患者38例（ATS）を対象に行った。

本試験の主要目的である PD-L1高発現の非小細胞肺癌患者の RECIST 1.1に基づく ORR 及び本試験におけるその他の有効性評価項目の要約を、[表 2.7.6.2.3-4]及び[表 2.7.6.2.3-5]に示す。また、PD-L1高発現及び PD-L1発現陽性の非小細胞肺癌患者の RECIST 1.1に基づく waterfall プロット、swimmer プロット及び spider プロットを[図 2.7.6.2.3-1]～[図 2.7.6.2.3-5]に示す。

本試験の主要目的である PD-L1高発現の非小細胞肺癌患者11例の RECIST 1.1に基づく ORR（中央判定）は27.3%（11例中3例、95%CI：6.0～61.0）であった。データベースカットオフ時点で、RECIST 1.1に基づく DOR の中央値には達しておらず、DOR の範囲は、17.1+週～46.1+週であった。また、RECIST 1.1に基づく奏効例3例のうち全例（100%）が奏効を持続していた。

PD-L1発現陽性の非小細胞肺癌患者37例の RECIST 1.1に基づく ORR（中央判定）は18.9%（37例中7例、95%CI：8.0～35.2）であった。PD-L1高発現の非小細胞肺癌患者12例及び PD-L1発現陽性の非小細胞肺癌患者38例の irRC に基づく ORR（治験担当医師の評価）はそれぞれ25.0%（3例、95%CI：5.5～57.2）、18.4%（7例、95%CI：7.7～34.3）であった。データベースカットオフ時点で、PD-L1発現陽性患者の RECIST 1.1評価（中央判定）、PD-L1高発現の患者及び PD-L1発現陽性患者の irRC 評価（治験担当医師の評価）のいずれにおいても、DOR は中央値には達しておらず、DOR の範囲は、PD-L1発現陽性患者の RECIST 1.1評価が9.1+週～46.1+週、PD-L1高発現患者の irRC 評価が18.1週～36.3+週、PD-L1発現陽性患者の irRC 評価が17.1週～37.1+週であった。また、PD-L1発現陽性患者の RECIST 1.1に基づく奏効例7例のうち6例（85.7%）、PD-L1高発現患者の irRC に基づく奏効例3例のうち2例（66.7%）、PD-L1発現陽性患者の irRC に基づく奏効例7例のうち5例（71.4%）が奏効を継続していた。

PD-L1高発現の非小細胞肺癌患者12例及び PD-L1発現陽性の非小細胞肺癌患者38例の、RECIST 1.1に基づく PFS（中央判定）の中央値はそれぞれ4.1ヵ月［95%CI：1.6～NR］及び3.8ヵ月（95%CI：2.0～6.2）であり、6ヵ月 PFS 率はそれぞれ41.7%及び38.8%であった。PD-L1高発現の非小細胞肺癌患者12例及び PD-L1発現陽性の非小細胞肺癌患者38例の、irRC に基づく PFS（治験担当医師の評価）の中央値は、それぞれ4.1ヵ月（95%CI：2.8～12.5）及び4.2ヵ月（95%CI：3.4～6.3）であり、6ヵ月 PFS 率はそれぞれ45.5%及び45.3%であった。

PD-L1高発現の非小細胞肺癌患者12例及び PD-L1発現陽性の非小細胞肺癌患者38例はデータベースカットオフ時点で OS の中央値には達しておらず、6ヵ月生存率はそれぞれ83.3%及び76.3%、

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1年生存率はそれぞれ56.3%及び51.0%であった。

表 2.7.6.2.3-4 RECIST 1.1 に基づく PD-L1 高発現の患者の ORR
（中央判定、Confirmed、FAS）（025 試験）

Response Evaluation	PD-L1 Strong		
	n	%	95% CI†
Subjects in population	**11**		
Complete Response (CR)	0	0.0	(0.0, 28.5)
Partial Response (PR)	3	27.3	(6.0, 61.0)
Overall Response (CR+PR)	**3**	**27.3**	**(6.0, 61.0)**
Stable Disease (SD)	4	36.4	(10.9, 69.2)
Progressive Disease (PD)	4	36.4	(10.9, 69.2)

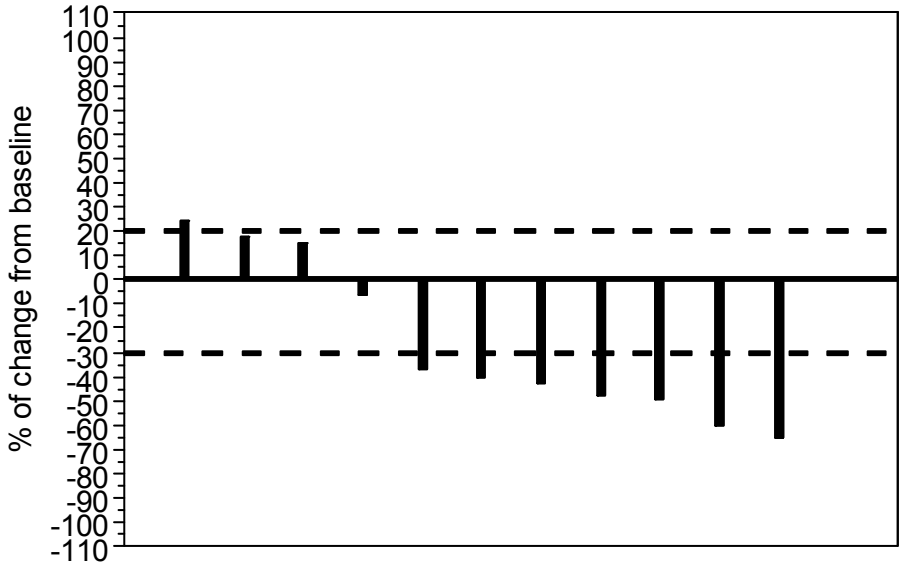
Only confirmed responses are included.
† Based on binomial exact confidence interval method.

表 2.7.6.2.3-5 有効性評価項目の要約（025 試験）

	PD-L1 Strong	PD-L1 Weak	Total
Number of Patients (FAS/ATS)	11/12	26/26	37/38
ORR (Central Assessment per RECIST 1.1, FAS population)			
Confirmed ORR –% (95%CI*)	27.3% (6.0, 61.0)	15.4% (4.4, 34.9)	18.9% (8.0, 35.2)
ORR (Investigator Assessment per irRC, ATS population)			
Confirmed ORR –% (95%CI*)	25.0% (5.5, 57.2)	15.4% (4.4, 34.9)	18.4% (7.7, 34.3)
Response Duration† (Central Assessment per RECIST 1.1, FAS population with Confirmed Responders)			
Median in weeks (range)‡	Not reached (17.1+, 46.1+)	Not reached (9.1+, 37.1+)	Not reached (9.1+, 46.1+)
On-going Response Subjects (%)	100.0%	75.0%	85.7%
Median Time to Response in Weeks (range)	8.3 (8.1,18.4)	13.6 (9.1,54.0)	9.1 (8.1,54.0)
Response Duration† (Investigator Assessment per irRC, ATS population with Confirmed Responders)			
Median in weeks (range)‡	Not reached (18.1 , 36.3+)	Not reached (17.1 , 37.1+)	Not reached (17.1 , 37.1+)
On-going Response Subjects (%)	66.7%	75.0%	71.4%
Median Time to Response in Weeks (range)	9.1 (8.4,18.1)	9.1 (8.1,45.0)	9.1 (8.1,45.0)
PFS† (Central Assessment per RECIST 1.1, ATS population)			
Median in Months (95%CI)	4.1 (1.6,.)	2.1 (1.9,6.2)	3.8 (2.0,6.2)
PFS rate at 6 Months in %	41.7%	37.8%	38.8%
PFS† (Investigator Assessment per irRC, ATS population)			
Median in Months (95%CI)	4.1 (2.8,12.5)	4.2 (2.9,7.6)	4.2 (3.4,6.3)
PFS rate at 6 Months in %	45.5%	45.3%	45.3%
OS† (ATS Population)			
Median in months (95%CI)	Not reached (5.9,.)	Not reached (5.9,.)	Not reached (5.9,.)
OS Rate at 6 Months in %	83.3%	73.1%	76.3%
OS Rate at 12 Months in %	56.3%	52.0%	51.0%

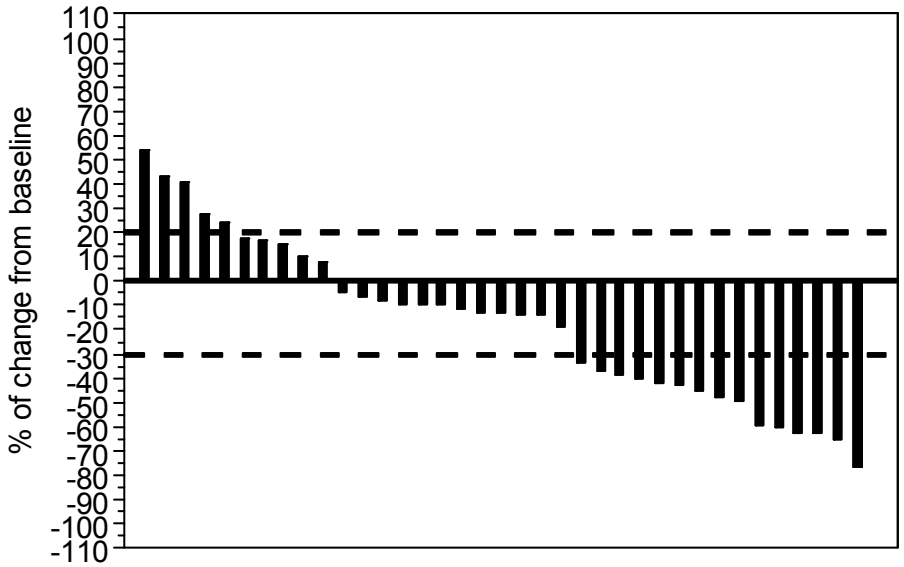
* Based on binomial exact confidence interval method.
† From product-limit (Kaplan-Meier) method for censored data.
‡ "+" indicates there is no progressive disease by the time of last disease assessment.

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Percentage changes >100% were truncated at 100%.

図 2.7.6.2.3-1 PD-L1 高発現の患者の RECIST 1.1 に基づく Waterfall プロット
（中央判定、FAS）（025 試験）



Percentage changes >100% were truncated at 100%.

図 2.7.6.2.3-2 PD-L1 発現陽性の患者の RECIST 1.1 に基づく Waterfall プロット
（中央判定、FAS）（025 試験）

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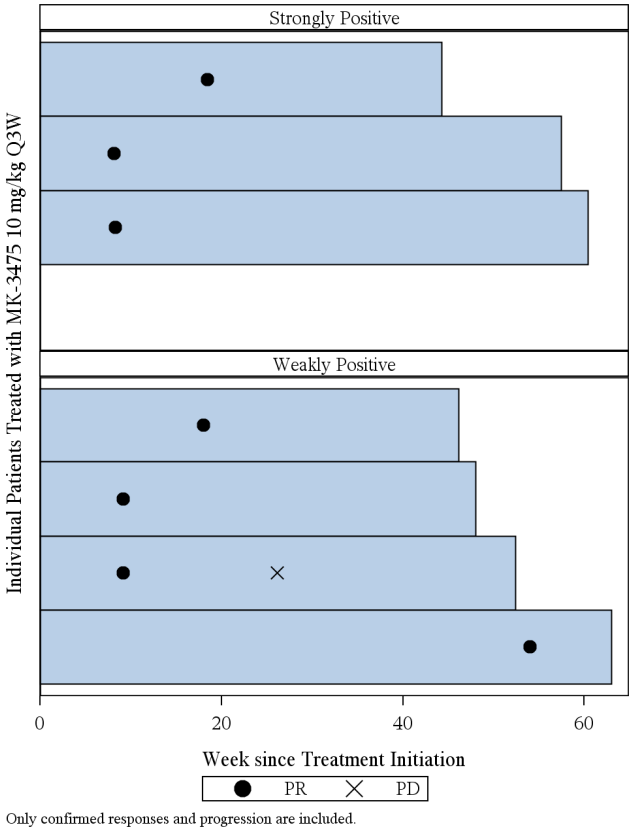
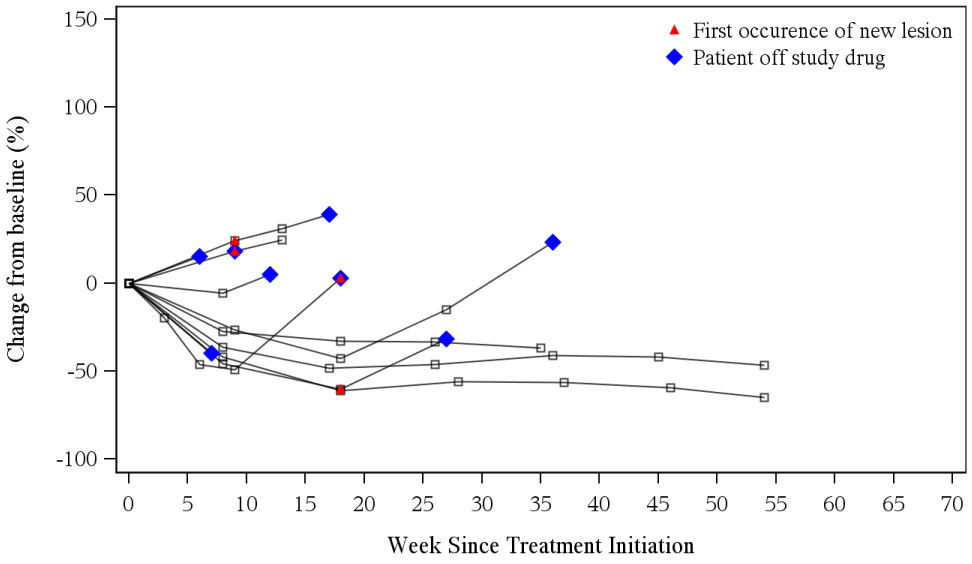


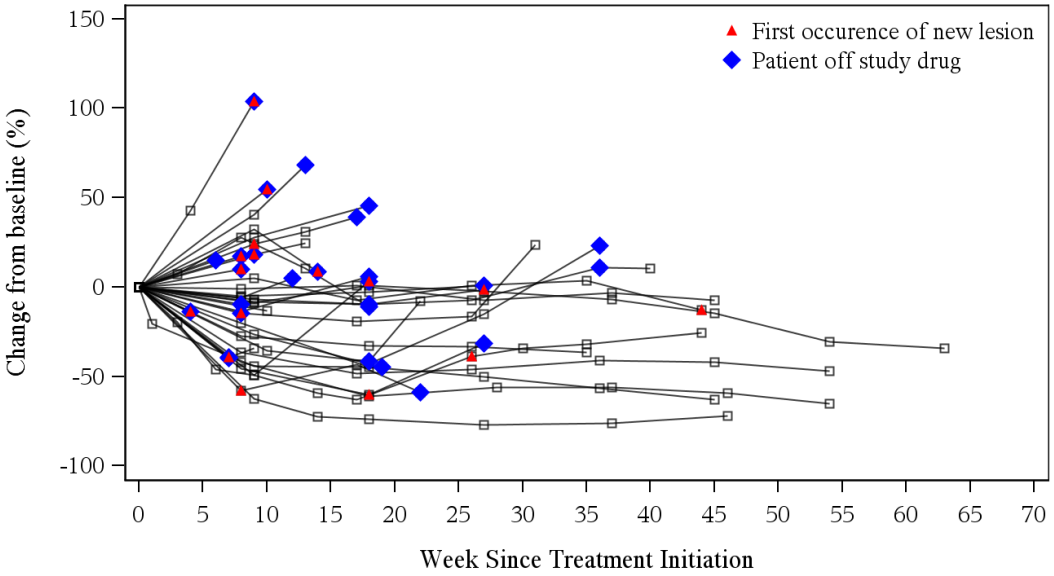
図 2.7.6.2.3-3 PD-L1 発現陽性の患者の RECIST 1.1 に基づく Swimmer プロット
（中央判定、FAS）（025 試験）



025093: First new lesion occurred on Week 16.

図 2.7.6.2.3-4 PD-L1 高発現の患者の RECIST 1.1 に基づく Spider プロット
（中央判定、FAS）（025 試験）

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025017: First new lesion occurred on Week 9.
025093: First new lesion occurred on Week 16.

図 2.7.6.2.3-5 PD-L1 発現陽性の患者の RECIST 1.1 に基づく Spider プロット（中央判定、FAS）（025 試験）

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2.7.6.2.3.3.2　　薬物動態及び免疫原性

日本人非小細胞肺癌患者（38例）に MK-3475を10 mg/kg、Q3W で反復静脈内投与した際の C_{max} の幾何平均値（%CV）は、1コース及び6コースで、それぞれ210 (20.3)及び310 (21.8) µg/mL であり、6コースの C_{max} は1コースに比べて約1.5倍上昇した。MK-3475の C_{trough} は、投与回数に伴って増加し、8コース（約147日）までに定常状態に到達し、その C_{trough} の幾何平均値（%CV）は、108 (41.0) µg/mL であった。

ADA について、日本人非小細胞肺癌患者全例（38例）が評価可能であり、このうち2例が陽性であり、いずれも MK-3475投与による陽性と判定した。

このように、MK-3475の投与によって ADA 陽性となった患者は2例と限られているものの、免疫原性と MK-3475の曝露量、有効性及び安全性に対して関連は認められないことが示唆された。

2.7.6.2.3.3.3　　安全性

本試験の治験薬の曝露を[表 2.7.6.2.3-6]に示す。38例に MK-3475が投与され、投与期間の中央値は106.0日（範囲：1-435日）、投与回数の中央値は6回（範囲：1-19回）であった。

本試験の有害事象の要約を[表 2.7.6.2.3-7]に示す。有害事象は、安全性解析対象例38例のうち、全例（100.0%）に認められ、副作用は33例（86.8%）に認められた。Grade 3以上の有害事象を発現した患者は19例（50.0%）、Grade 3以上の副作用を発現した患者は8例（21.1%）であった。

38例中4例以上（10%以上）に認められた有害事象は、発熱（10例、26.3%）、倦怠感（9例、23.7%）、下痢、AST 増加、食欲減退（各8例、21.1%）、ALT 増加、血中アルカリホスファターゼ（ALP）増加、発疹（各6例、15.8%）、悪心、疲労、体重減少、リンパ球数減少、頭痛、そう痒症、斑状丘疹状皮疹（各5例、13.2%）、γ-グルタミルトランスフェラーゼ（γ-GTP）増加、低アルブミン血症、関節痛、背部痛、咳嗽、呼吸困難（各4例、10.5%）であった。Grade 3以上の有害事象は19例（50.0%）で認められ、2例以上で報告された事象は AST 増加、リンパ球数減少（各3例、7.9%）、ALT 増加、γ-GTP 増加、血小板数減少、低ナトリウム血症（各2例、5.3%）であった。

副作用は38例中33例（86.8%）に認められ、そのほとんどが Grade 1又は2であった。38例中4例以上（10%以上）で認められた副作用は倦怠感（8例、21.1%）、下痢（6例、15.8%）、AST 増加、食欲減退、そう痒症、発疹、斑状丘疹状皮疹（各5例、13.2%）、悪心、疲労、ALT 増加、関節痛（各4例、10.5%）であった。Grade 3以上の副作用は8例（21.1%）であり、リンパ球数減少（2例、5.3%）、下痢、AST 増加、ALT 増加、血中リン減少、血小板数減少、食欲減退、低カルシウム血症、食道癌、視神経炎、間質性肺炎、誤嚥性肺炎（各1例、2.6%）であった。

重篤な有害事象は38例中11例（28.9%）に発現し、重篤な副作用は38例中8例（21.1%）に発現した。報告された重篤な副作用は Grade 5 間質性肺疾患及び Grade 4 誤嚥性肺炎を発現した患者が1例（2.6%）、Grade 2 間質性肺疾患、Grade 4 視神経炎、Grade 3 食欲減退、Grade 3 食道癌、Grade 2 憩室炎、Grade 2 脳血管発作、Grade 2 器質化肺炎を発現した患者が各1例（2.6%）であり、このうち Grade 2の重篤な副作用が回復又は軽快した。

死亡に至った有害事象を発現した患者は38例中1例（2.6%）であり、間質性肺疾患（治験薬と

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因果関係あり）であった。当該死亡例以外で治験薬の投与中止に至った有害事象は　間質性肺疾患（Grade 2）が1例（2.6%）、視神経炎（Grade 4）が1例（2.6%）であり、いずれも副作用と判定された。

AEOSI として、38例中、肺臓炎が4例（10.5% ; Grade 5 間質性肺疾患 1例、Grade 2 間質性肺疾患 1例、Grade 2 器質化肺炎 1例、Grade 2 肺臓炎 1例）、大腸炎が2例（5.3% ; Grade 2 大腸炎 1例、Grade 1 腸炎 1例）、甲状腺機能低下症が2例（5.3% ; Grade 1 甲状腺機能低下症 2例）、甲状腺機能亢進症が1例（2.6% ; Grade 2 甲状腺機能亢進症）、Infusion reaction が1例（2.6% ; Grade 1 過敏症）及びぶどう膜炎が1例（2.6% ; Grade 2 ぶどう膜炎）に報告された。Infusion reaction を除くすべての事象が副作用と判定された。治験担当医師から報告された肺臓炎（Grade 2 間質性肺疾患、Grade 5 間質性肺疾患、Grade 2 器質化肺炎、Grade 2 肺臓炎）について効果安全性評価委員会で評価を行った。その結果、Grade 5 間質性肺疾患が MK-3475との因果関係があると判定された。他の肺臓炎については、判定不能又は MK-3475と因果関係がないと判定された。

すべての有害事象、副作用及び重篤な有害事象を[表 2.7.4-37]、[表 2.7.4-38]、[付録2.7.4-113]に示す。

表 2.7.6.2.3-6 治験薬の曝露（ATS 集団）（025 試験）

	MK-3475 10 mg/kg Q3W
Subjects in population	38
Study Days On-Therapy (days)	
Mean	159.92
Median	106.00
SD	126.39
Range	1.00 to 435.00
Number of Administrations	
Mean	8.08
Median	6.00
SD	5.56
Range	1.00 to 19.00

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表 2.7.6.2.3-7 有害事象の要約（ATS 集団）（025 試験）

	MK-3475 10 mg/kg Q3W	
	n	(%)
Subjects in population	38	
with one or more adverse events	38	(100.0)
with no adverse event	0	(0.0)
with drug-related† adverse events	33	(86.8)
with Grade 3- 5 adverse events	19	(50.0)
with Grade 3- 5 drug-related adverse events	8	(21.1)
with serious adverse events	11	(28.9)
with serious drug-related adverse events	8	(21.1)
who died	1	(2.6)
with drug-related death	1	(2.6)
discontinued‡ due to an adverse event	3	(7.9)
discontinued due to a drug-related adverse event	3	(7.9)
discontinued due to a serious adverse event	3	(7.9)
discontinued due to a serious drug-related adverse event	3	(7.9)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
Grades are based on NCI CTCAE version 4.0.
MedDRA preferred terms 'Neoplasm Progression', 'Malignant Neoplasm Progression' and 'Disease Progression' not related to the drug is excluded.

2.7.6.2.3.4　　結論

既治療の PD-L1発現陽性の進行性非小細胞肺癌患者に MK-3475を Q3W で投与する本試験において、以下の結論を得た。

1) 有効性主要評価項目の、PD-L1高発現の非小細胞肺癌患者における RECIST 1.1に基づく ORR（中央判定）は27.3%（95%CI：6.0～61.0）であった。データベースカットオフ時点で DOR の中央値には達しておらず、DOR の範囲は17.1+週～46.1+週であった。また、RECIST 1.1に基づく奏効例3例のうち全例（100%）が奏効を持続していた。
2) 非小細胞肺癌患者に MK-3475 10mg/kg を Q3W で投与した際の忍容性は概して良好であり、安全性プロファイルはこれまでの MK-3475の臨床試験と比べて大きな差異はなかった。
3) PD-L1発現陽性の非小細胞肺癌患者の RECIST 1.1に基づく ORR（中央判定）は18.9%（95%CI：8.0～35.2）であった。PD-L1高発現の非小細胞肺癌患者及び PD-L1発現陽性の非小細胞肺癌患者の irRC に基づく ORR（治験担当医師の評価）はそれぞれ25.0%（95%CI：5.5～57.2）、18.4%（95%CI：7.7～34.3）であった。データベースカットオフ時点で、PD-L1発現陽性患者の RECIST 1.1評価（中央判定）、PD-L1高発現の患者及び PD-L1発現陽性患者の irRC 評価（治験担当医師の評価）のいずれにおいても DOR は中央値には達しておらず、DOR の範囲は、PD-L1発現陽性患者の RECIST 1.1評価が9.1+週～46.1+週、PD-L1高発現患者の irRC 評価が18.1週～36.3+週、PD-L1発現陽性患者の irRC 評価が17.1週～37.1+週であった。また、PD-L1発現陽性患者の RECIST 1.1に基づく奏効例7例のうち6例（85.7%）、PD-L1高発現患者の irRC に基づく奏効例3例のうち2例（66.7%）PD-L1発現陽性患者の irRC に基づく奏効例7例のうち5例（71.4%）が奏効を継続していた。

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4) PD-L1高発現の非小細胞肺癌患者及びPD-L1発現陽性の非小細胞肺癌患者のRECIST1.1に基づくPFS（中央判定）の中央値は、それぞれ4.1ヵ月（95%CI：1.6～NR）及び3.8ヵ月（95%CI：2.0～6.2）であり、6ヵ月PFS率はそれぞれ41.7%及び38.8%であった。irRCに基づくPFS（治験担当医師の評価）の中央値は、それぞれ4.1ヵ月（95%CI：2.8～12.5）及び4.2ヵ月　（95%CI：3.4～6.3）であり、6ヵ月PFS率はそれぞれ45.5%及び45.3%であった。
5) PD-L1高発現の非小細胞肺癌患者12例及びPD-L1発現陽性の非小細胞肺癌患者38例は、データベースカットオフ時点でOSの中央値に達しておらず、6ヵ月生存率はそれぞれ83.3%及び76.3%、1年生存率はそれぞれ56.3%及び51.0%であった。
6) 日本人非小細胞肺癌患者（38例）にMK-3475を10 mg/kg、Q3Wで反復静脈内投与した際のC_{max}の幾何平均値（%CV）は、6コースで310 (21.8) µg/mLであり 1コースと比べて約1.5倍上昇した。MK-3475のC_{trough}は、8コース（約147日）までに定常状態に到達し、その幾何平均値（%CV）は、108 (41.0) µg/mLであった。
7) ADAは、日本人非小細胞肺癌患者38例のうち2例がMK-3475投与による陽性であり、いずれもMK-3475投与による陽性と判定した。

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2.7.6.2.4　PD-L1発現陽性の進行非小細胞肺癌患者を対象とした第Ⅱ／Ⅲ相試験［国際共同試験］［評価資料］（KEYNOTE-010試験、以下010試験）

2.7.6.2.4.1　試験方法の概要

治験実施医療機関

多施設共同、24ヵ国198施設（国内34施設）

公表文献

Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2015; Published online 2015 Dec 19.

治験実施期間

2013年8月28日～実施中（データベースカットオフ日：2015年9月30日）

開発の相

第Ⅱ／Ⅲ相

治験デザイン

本試験は、プラチナ製剤併用化学療法の施行後に疾患進行が認められた PD-L1発現陽性の非小細胞肺癌患者を対象に、MK-3475を二通りの用量で静脈内投与し、ドセタキセルとの比較を行った、非盲検の国際共同無作為化第Ⅱ／Ⅲ相試験である。PD-L1高発現の患者で MK-3475とドセタキセルの有効性を比較するため、約920例（うち日本人患者66例）の登録が予定された。

患者は MK-3475 2 mg/kg Q3W、MK-3475 10 mg/kg Q3W 又はドセタキセル 75 mg/m^2 Q3W のいずれかの治療を受ける群に1:1:1で無作為割付けされた。層別因子は、腫瘍の PD-L1発現割合（高発現：TPS≥50%、低発現：1%≤TPS<50%）、ECOG PS（0、1）、及び治験実施医療機関の地域（東アジア、東アジア以外）とした。

患者は9週（63±7日）ごとに放射線画像診断による評価を受けた。すべての画像は独立した放射線科医による評価に提出され、RECIST 1.1に基づいて ORR 及び PFS の判定が行われた。治験担当医師は、irRC を用いて治療方針を決定した。有害事象は治験期間を通して評価され、NCI CTCAE Version 4.0に沿って程度の Grade 分類が行われた。

2回目の中間解析において独立データモニタリング委員会は試験の継続を勧告したため、以下に示すのは最終解析の結果である。最終解析は、PD-L1高発現の患者において死亡イベント数が約200となった時点で行われた。

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主要目的

8) PD-L1高発現の非小細胞肺癌の既治療患者に MK-3475又はドセタキセルを投与した際の OS を比較する。
2) PD-L1高発現の非小細胞肺癌の既治療患者に MK-3475又はドセタキセルを投与した際の、RECIST 1.1に基づき中央判定機関が評価した PFS を比較する。
3) PD-L1発現陽性の非小細胞肺癌の既治療患者に MK-3475又はドセタキセルを投与した際の OS を比較する。
4) PD-L1発現陽性の非小細胞肺癌の既治療患者に MK-3475又はドセタキセルを投与した際の、中央判定機関が RECIST 1.1に基づき評価した PFS を比較する。
5) PD-L1高発現及び PD-L1発現陽性の非小細胞肺癌の既治療患者に MK-3475を投与した際の安全性及び忍容性を評価する。

副次的目的

1) PD-L1高発現及び PD-L1発現陽性の非小細胞肺癌の既治療患者に MK-3475又はドセタキセルを投与した際の、中央判定機関が RECIST 1.1に基づき評価した ORR を比較する。
2) PD-L1高発現及び PD-L1発現陽性の非小細胞肺癌の既治療患者に MK-3475又はドセタキセルを投与した際の、中央判定機関が RECIST 1.1に基づき評価した DOR を比較する。

重要な探索的目的の一つとして、全般的な健康状態や生活の質の指標である EORTC QLQ-C30 を用いて患者が報告する9週時点での治療効果について、治療前からの変化及び改善／悪化の割合を評価した。

ロット番号

表 2.7.6.2.4-1 治験薬の内容（010 試験）

Bulk Product Description	Manufacturing Lot Number
HLSV MK-3475, 50mg/vial (Brinny, SCH-900475)	DL00018212, DL00018226, DL00018243, DL00018362, DL00018650, DL00019202, DL00019243, GL00001067, GL00001633, GL00001635
HSS MK-3475, 100 mg/vial	DL00018283, DL00018391, DL00018801, DL00018950, DL00019172, DL00019474
HSSV Docetaxel 80mg / 4mL Vial (ex-Germany)	DL00017998, DL00018285, DL00018601, DL00018719, DL00019189, DL00019776

診断／組入れ基準

選択基準（抜粋）：

1) 治験の参加について文書による同意を得ている患者
2) 同意取得時の年齢が18歳以上の患者
3) 3ヵ月以上の生存が見込まれる患者

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4) 組織学的又は細胞学的に非小細胞肺癌と診断され、RECIST 1.1により定義される測定可能病変を1つ以上有する患者
5) 病期ⅢB／Ⅳ又は再発例で、少なくとも2コースのプラチナ製剤併用化学療法後に、RECIST 1.1に基づく PD が確認された患者
6) ECOG PS が0又は1の患者
7) 適切な臓器機能を有する患者
8) 中央測定機関で実施する IHC により、PD-L1の発現（高発現又は低発現）が確認された腫瘍を有する患者

評価基準

有効性

1) OS：OS を、無作為割付けの時点から原因を問わない死亡までの期間と定義した。最終解析時に死亡が報告されていない患者は最終のフォローアップ日で打切りとした。
2) RECIST 1.1に基づく PFS：PFS を、無作為割付けの時点から中央判定機関の盲検下での RECIST　1.1に基づく PD の確定又は原因を問わない死亡のいずれか先に生じた方までの期間と定義した。
3) ORR：ORR を、解析対象集団で CR 又は PR が認められた患者の割合と定義した。奏効（CR、PR）は、中央判定機関の盲検下での RECIST 1.1を用いた評価に基づいた。irRC に基づき治験責任医師又は分担医師が評価する ORR も検討した。
4) irRC に基づく PFS：PFS を、無作為割付けの時点から中央判定機関の盲検下での irRC に基づく PD の確定又は原因を問わない死亡のいずれか先に生じた方までの期間と定義した。
5) DOR：CR 又は PR が認められた患者に関して、DOR を CR 又は PR のエビデンスが初めて記録された時点から PD 又は死亡までの期間と定義した。解析時点で PD が認められなかった患者又は死亡していなかった患者の DOR は、最終腫瘍評価日で打切りとした。DOR は、盲検下の中央判定機関による RECIST 1.1に基づく評価、及び治験責任医師又は分担医師による irRC に基づく評価により計算した。

安全性

治験責任医師、治験分担医師又は指名された者は、各患者について、新たな有害事象の発現又は有害事象の悪化を評価した。NCI CTCAE Version 4.0に従い有害事象を Grade 分類し、これを記録した。毒性は、重篤度、因果関係、Grade 分類及び治験薬に対する処置などの点から評価した。

irAE は、他の原因が同定されない、治験薬の投与に関連する有害事象として定義され、免疫による現象として矛盾がないものとした。irAE として分類する前に、腫瘍、感染、代謝、中毒性又はそのほかの原因を除外した。irAE の診断時に、免疫学的、血清学的又は組織学的（生体組織検査）なデータを使用した。

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統計計画及び解析

有効性

本試験では、PD-L1高発現患者及びPD-L1発現陽性患者のintention-to-treat（ITT）集団を有効性データ解析の主要な解析対象集団とした。

各患者集団のOS及びPFSの推定にはKaplan-Meier法を用い、群間比較には層別ログランク検定を用いた。OS及びPFSの投与群による差異の程度（ハザード比など）を評価するために層別Cox比例ハザードモデルを用い、タイデータにはEfron法で対応した。ハザード比と、投与群を唯一の共変量とする層別Cox比例ハザードモデルに基づく95%CIを報告した。

投与群間のORRの比較には、層別Miettinen and Nurminen法を使用した。MK-3475各群と対照群とのORRの差について、95%CIを計算した。1回目の中間解析では用量選択のため、MK-3475の二群間でみられたORRの差についてP値を計算した。早期脱落を含む、フォローアップ期間が27週以上の患者に対して、ORRの部分集団解析を実施した。

Kaplan-Meier法による中央値と四分位点を用いて記述的にDORを要約した。CR又はPRが認められた患者で構成される部分集団のみをDORの解析に含めた。

安全性

本試験の安全性データの解析では、無作為割付けを受けた患者のうち、治験薬の投与を1回以上受けたすべての患者であるAPaT集団を用いた。

安全性及び忍容性は、2015年9月30日のデータベースカットオフ日までに報告された有害事象、臨床検査値、バイタルサイン及び心電図を含むすべての安全性評価項目を用いて、臨床的及び統計的な観点から評価した。

安全性データの解析は段階的な方法（tiered approach）を用いた。段階（tier）によって実施する解析が異なる。事前に規定した特に関心のある安全性評価項目又は有害事象を「Tier 1」の安全性評価項目とし、群間比較のためP値及び95%CIを用いて統計学的有意性を評価した。その他の安全性評価項目は「Tier 2」又は「Tier 3」とした。いずれかの投与群で4例以上発現した事象はTier 2とし、それ以外のすべての有害事象及び事前に規定した範囲を超える検査値の変動はTier 3とした。Tier 2の評価項目については群間比較のための差の点推定値とその95%CIを用いて評価し、Tier 3の評価項目については投与群ごとの点推定値のみを算出した。

MK-3475群でより長くなると予想された追跡期間の影響を適切に考慮するため、「Tier 1」の有害事象及びGrade 3～5の有害事象について、最初の有害事象発現までの期間に関するtime-to-event解析をOSと同様の方法で行った。すなわち、最初の有害事象発現までの期間における投与群間差は層別ログランク検定を用いて評価し、タイデータにはEfron法で対応する層別Cox比例ハザードモデル用いて投与群間差のハザード比及びその95%CIを評価した。

また、Grade 3～5の有害事象の発現割合、及び最初の4コースにおけるコースごとのGrade 3～5の有害事象の発現割合について、曝露期間を調整した群間差に関するP値及び95%CIを層別Miettinen and Nurminen法を用いて評価した。有害事象の期間の定義は、治験薬投与開始から最終投与後30日までとした。ただし重篤な有害事象に関しては、追跡期間を延長し治験薬投与開始か

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ら最終投与後90日までとした。

2.7.6.2.4.2　　患者の内訳

試験全体の患者集団及び日本人患者の特性及び内訳を[表 2.7.6.2.4-2]及び[表 2.7.6.2.4-3]に要約する。日本から登録された91例については、非喫煙者及びEGFR遺伝子変異陽性患者の割合が比較的高い傾向がみられた他は、試験全体の患者集団と特性が大きく異なることはなかった。[表2.7.6.2.4-3]中に“Unknown”と記載されている患者は、データベースカットオフ時点で治験薬による治療が継続されていることを示す。各背景因子は、MK-3475 2 mg/kg群、10 mg/kg群及びドセタキセル群で大きな偏りはみられなかった。

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表 2.7.6.2.4-2 患者の特性（ITT 集団）（010 試験）

	Overall Population								Japan Subgroup							
	Docetaxel 75 mg/m^2 Q3W		MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		Total		Docetaxel 75 mg/m^2 Q3W		MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	343		344		346		1,033		29		28		34		91	
Gender																
Male	209	(60.9)	212	(61.6)	213	(61.6)	634	(61.4)	23	(79.3)	17	(60.7)	20	(58.8)	60	(65.9)
Female	134	(39.1)	132	(38.4)	133	(38.4)	399	(38.6)	6	(20.7)	11	(39.3)	14	(41.2)	31	(34.1)
Age (Years)																
<65	209	(60.9)	201	(58.4)	194	(56.1)	604	(58.5)	15	(51.7)	11	(39.3)	15	(44.1)	41	(45.1)
>=65	134	(39.1)	143	(41.6)	152	(43.9)	429	(41.5)	14	(48.3)	17	(60.7)	19	(55.9)	50	(54.9)
Mean	61.6		62.1		62.3		62.0		60.8		63.9		63.9		62.9	
SD	9.8		9.6		9.7		9.7		13.5		10.7		10.7		11.6	
Median	62.0		63.0		63.0		63.0		64.0		65.5		66.0		65.0	
Range	33 to 82		29 to 82		20 to 88		20 to 88		34 to 77		30 to 79		38 to 78		30 to 79	
Race																
American Indian Or Alaska Native	0	(0.0)	2	(0.6)	3	(0.9)	5	(0.5)								
Asian	72	(21.0)	73	(21.2)	72	(20.8)	217	(21.0)	29	(100.0)	28	(100.0)	34	(100.0)	91	(100.0)
Black Or African American	7	(2.0)	13	(3.8)	8	(2.3)	28	(2.7)								
Multiple	1	(0.3)	1	(0.3)	2	(0.6)	4	(0.4)								
Native Hawaiian Or Other Pacific Islander	1	(0.3)	2	(0.6)	0	(0.0)	3	(0.3)								
White	251	(73.2)	246	(71.5)	250	(72.3)	747	(72.3)								
Missing	11	(3.2)	7	(2.0)	11	(3.2)	29	(2.8)								
Region																
Non-East Asian	281	(81.9)	280	(81.4)	282	(81.5)	843	(81.6)								
East Asian	62	(18.1)	64	(18.6)	64	(18.5)	190	(18.4)	29	(100.0)	28	(100.0)	34	(100.0)	91	(100.0)
Smoker																
Never Smoker	67	(19.5)	63	(18.3)	60	(17.3)	190	(18.4)	5	(17.2)	9	(32.1)	13	(38.2)	27	(29.7)
Current/Ex Smoker	269	(78.4)	279	(81.1)	285	(82.4)	833	(80.6)	24	(82.8)	19	(67.9)	21	(61.8)	64	(70.3)
Missing	7	(2.0)	2	(0.6)	1	(0.3)	10	(1.0)								

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表 2.7.6.2.4-2 患者の特性（ITT 集団）（010 試験）（続き）

	Overall Population								Japan Subgroup							
	Docetaxel 75 mg/m^2 Q3W		MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		Total		Docetaxel 75 mg/m^2 Q3W		MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
ECOG																
0	116	(33.8)	112	(32.6)	120	(34.7)	348	(33.7)	13	(44.8)	14	(50.0)	15	(44.1)	42	(46.2)
1	224	(65.3)	229	(66.6)	225	(65.0)	678	(65.6)	16	(55.2)	14	(50.0)	19	(55.9)	49	(53.8)
2	1	(0.3)	3	(0.9)	1	(0.3)	5	(0.5)								
3	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)								
MISSING	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)								
Cancer Stage																
IA	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.1)								
IB	1	(0.3)	1	(0.3)	0	(0.0)	2	(0.2)								
IIB	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.1)								
IIIA	8	(2.3)	5	(1.5)	4	(1.2)	17	(1.6)								
IIIB	22	(6.4)	21	(6.1)	26	(7.5)	69	(6.7)	5	(17.2)	3	(10.7)	7	(20.6)	15	(16.5)
IV	312	(91.0)	315	(91.6)	316	(91.3)	943	(91.3)	24	(82.8)	25	(89.3)	27	(79.4)	76	(83.5)
Non-small Cell Histology																
SQUAMOUS	66	(19.2)	76	(22.1)	80	(23.1)	222	(21.5)	9	(31.0)	6	(21.4)	3	(8.8)	18	(19.8)
NON-SQUAMOUS	240	(70.0)	240	(69.8)	244	(70.5)	724	(70.1)	18	(62.1)	21	(75.0)	29	(85.3)	68	(74.7)
MIXED	4	(1.2)	3	(0.9)	3	(0.9)	10	(1.0)								
OTHER	6	(1.7)	6	(1.7)	3	(0.9)	15	(1.5)								
UNKNOWN	27	(7.9)	19	(5.5)	16	(4.6)	62	(6.0)	2	(6.9)	1	(3.6)	2	(5.9)	5	(5.5)
PD-L1 Status																
WEAKLY POSITIVE	191	(55.7)	205	(59.6)	195	(56.4)	591	(57.2)	18	(62.1)	18	(64.3)	21	(61.8)	57	(62.6)
STRONGLY POSITIVE	152	(44.3)	139	(40.4)	151	(43.6)	442	(42.8)	11	(37.9)	10	(35.7)	13	(38.2)	34	(37.4)
EGFR Mutation																
MUTANT	26	(7.6)	28	(8.1)	32	(9.2)	86	(8.3)	3	(10.3)	7	(25.0)	11	(32.4)	21	(23.1)
WILD TYPE	294	(85.7)	293	(85.2)	288	(83.2)	875	(84.7)	25	(86.2)	18	(64.3)	22	(64.7)	65	(71.4)
UNDETERMINED	13	(3.8)	15	(4.4)	17	(4.9)	45	(4.4)	0	(0.0)	2	(7.1)	0	(0.0)	2	(2.2)
Missing	10	(2.9)	8	(2.3)	9	(2.6)	27	(2.6)	1	(3.4)	1	(3.6)	1	(2.9)	3	(3.3)

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表 2.7.6.2.4-2 患者の特性（ITT 集団）（010 試験）（続き）

	Overall Population								Japan Subgroup							
	Docetaxel 75 mg/m^2 Q3W		MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		Total		Docetaxel 75 mg/m^2 Q3W		MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
ALK Translocation Status																
MUTANT	2	(0.6)	2	(0.6)	4	(1.2)	8	(0.8)	0	(0.0)	1	(3.6)	1	(2.9)	2	(2.2)
WILD TYPE	310	(90.4)	307	(89.2)	305	(88.2)	922	(89.3)	24	(82.8)	23	(82.1)	25	(73.5)	72	(79.1)
UNDETERMINED	20	(5.8)	22	(6.4)	26	(7.5)	68	(6.6)	2	(6.9)	3	(10.7)	5	(14.7)	10	(11.0)
Missing	11	(3.2)	13	(3.8)	11	(3.2)	35	(3.4)	3	(10.3)	1	(3.6)	3	(8.8)	7	(7.7)
Prior Lines of Systemic Therapy																
ADJUVANT	3	(0.9)	6	(1.7)	7	(2.0)	16	(1.5)								
NEO ADJUVANT	0	(0.0)	1	(0.3)	1	(0.3)	2	(0.2)								
FIRST LINE	235	(68.5)	243	(70.6)	235	(67.9)	713	(69.0)	17	(58.6)	16	(57.1)	17	(50.0)	50	(54.9)
SECOND LINE	75	(21.9)	66	(19.2)	69	(19.9)	210	(20.3)	6	(20.7)	8	(28.6)	10	(29.4)	24	(26.4)
THIRD LINE	20	(5.8)	18	(5.2)	27	(7.8)	65	(6.3)	4	(13.8)	3	(10.7)	5	(14.7)	12	(13.2)
FOURTH LINE	6	(1.7)	6	(1.7)	3	(0.9)	15	(1.5)	2	(6.9)	0	(0.0)	0	(0.0)	2	(2.2)
FIFTH LINE OR GREATER	3	(0.9)	3	(0.9)	4	(1.2)	10	(1.0)	0	(0.0)	1	(3.6)	2	(5.9)	3	(3.3)
Missing	1	(0.3)	1	(0.3)	0	(0.0)	2	(0.2)								

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表 2.7.6.2.4-3 患者の内訳（ITT 集団）（010 試験）

	Overall Population								Japan Subgroup							
	Docetaxel 75 mg/m^2 Q3W		MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		Total		Docetaxel 75 mg/m^2 Q3W		MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	343		344		346		1,033		29		28		34		91	
Study Medication Disposition																
Completed	15	(4.4)	0	(0.0)	0	(0.0)	15	(1.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued	317	(92.4)	270	(78.5)	271	(78.3)	858	(83.1)	26	(89.7)	19	(67.9)	28	(82.4)	73	(80.2)
Adverse Event	47	(13.7)	33	(9.6)	32	(9.2)	112	(10.8)	7	(24.1)	2	(7.1)	4	(11.8)	13	(14.3)
Death	21	(6.1)	21	(6.1)	21	(6.1)	63	(6.1)	1	(3.4)	0	(0.0)	1	(2.9)	2	(2.2)
Other	1	(0.3)	3	(0.9)	7	(2.0)	11	(1.1)	0	(0.0)	1	(3.6)	0	(0.0)	1	(1.1)
Physician Decision	113	(32.9)	82	(23.8)	74	(21.4)	269	(26.0)	7	(24.1)	4	(14.3)	10	(29.4)	21	(23.1)
Progressive Disease	89	(25.9)	124	(36.0)	126	(36.4)	339	(32.8)	9	(31.0)	12	(42.9)	13	(38.2)	34	(37.4)
Protocol Violation	1	(0.3)	2	(0.6)	1	(0.3)	4	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Withdrawal By Subject	45	(13.1)	5	(1.5)	10	(2.9)	60	(5.8)	2	(6.9)	0	(0.0)	0	(0.0)	2	(2.2)
Unknown	11	(3.2)	74	(21.5)	75	(21.7)	160	(15.5)	3	(10.3)	9	(32.1)	6	(17.6)	18	(19.8)

Each subject is counted once for Study Medication Disposition based on the latest corresponding disposition record.
Unknown: A disposition record did not exist at the time of reporting.
Database Cutoff Date: 30SEP2015

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2.7.6.2.4.3　　結果

2.7.6.2.4.3.1　　有効性

本試験に登録され無作為割付けをされた患者1,034例のうち、339例に MK-3475 2 mg/kg、343例に MK-3475 10 mg/kg、及び309例にドセタキセルが投与され、43例は治験薬の投与を受けなかった。本試験の有効性解析は、医薬品の臨床試験の実施の基準（GCP）不遵守があり組入れ中止となったロシアの医療機関で登録された1例を除いた1,033例（ITT 集団）を対象とした。ITT 集団のうち、PD-L1高発現患者は442例であった。

PD-L1高発現患者における有効性の主要評価項目及び副次的評価項目の要約を[表 2.7.6.2.4-4]に、PD-L1 発現陽性患者における有効性の主要評価項目及び副次的評価項目の要約を[表 2.7.6.2.4-5]に示す。

表 2.7.6.2.4-4 PD-L1 高発現患者における有効性評価項目の要約（ITT 集団）（010 試験）

Treatment	Overall Population				Japan Subgroup			
	N	Median (Months) (95%CI)†	Treatment vs. Docetaxel Hazard Ratio (95%CI)‡	p-Value§	N	Median (Months) (95%CI)†	Treatment vs. Docetaxel Hazard Ratio (95%CI)‡	p-Value§
OS								
Docetaxel 75 mg/m^2 Q3W	152	8.2 (6.4, 10.7)	---	---	11	Not Reached (3.9, .)	---	---
MK-3475 2 mg/kg Q3W	139	14.9 (10.4, .)	0.54 (0.38, 0.77)	0.00024	10	Not Reached (6.9, .)	0.49 (0.08, 3.08)	0.22074
MK-3475 10 mg/kg Q3W	151	17.3 (11.8, .)	0.50 (0.36, 0.70)	0.00002	13	Not Reached (4.8, .)	1.18 (0.28, 5.08)	0.58963
PFS								
Docetaxel 75 mg/m^2 Q3W	152	4.1 (3.6, 4.3)	---	---	11	4.7 (1.8, .)	---	---
MK-3475 2 mg/kg Q3W	139	5.2 (4.0, 6.5)	0.58 (0.43, 0.77)	0.00009	10	6.2 (2.0, 6.9)	1.12 (0.35, 3.56)	0.57329
MK-3475 10 mg/kg Q3W	151	5.2 (4.1, 8.1)	0.59 (0.45, 0.78)	0.00007	13	4.3 (1.9, .)	1.44 (0.48, 4.30)	0.74233
	N	ORR (%) (95%CI)	Difference in % vs. Docetaxel Estimate (95%CI)‖	p-Value¶	N	ORR (%) (95%CI)	Difference in % vs. Docetaxel Estimate (95%CI)‖	p-Value¶
ORR								
Docetaxel 75 mg/m^2 Q3W	152	7.9 (4.1,13.4)	---	---	11	27.3 (6.0,61.0)	---	---
MK-3475 2 mg/kg Q3W	139	30.2 (22.7,38.6)	23.3 (14.8,32.1)	<0.00001	10	20.0 (2.5,55.6)	-7.3 (-43.0,31.1)	0.64854
MK-3475 10 mg/kg Q3W	151	29.1 (22.0,37.1)	22.2 (14.0,30.7)	<0.00001	13	30.8 (9.1,61.4)	3.5 (-33.5,38.4)	0.42708

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate. Stratified by ECOG (0 vs. 1), Geographic region (East Asian vs. non-East Asian) and PD-L1 status (Strongly Positive , Weakly Positive, and Unknown Positive) for overall population.
§ One-sided p-value based on log-rank test.
Responses are based on IRC assessments per RECIST 1.1 with confirmation.
‖ Based on Miettinen & Nurminen method. Stratified by ECOG (0 vs. 1), Geographic region (East Asian vs. non-East Asian) and PD-L1 status (Strongly Positive , Weakly Positive and Unknown Positive) for overall population; if no patients are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.
¶ One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
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表 2.7.6.2.4-5 PD-L1 発現陽性患者における有効性評価項目の要約（ITT 集団）（010 試験）

Treatment	Overall Population				Japan Subgroup			
	N	Median (Months) (95%CI)[†]	Treatment vs. Docetaxel Hazard Ratio (95%CI)[‡]	Treatment vs. Docetaxel p-Value[§]	N	Median (Months) (95%CI)[†]	Treatment vs. Docetaxel Hazard Ratio (95%CI)[‡]	Treatment vs. Docetaxel p-Value[§]
OS								
Docetaxel 75 mg/m^2 Q3W	343	8.5 (7.5, 9.8)	---	---	29	14.5 (7.5, .)	---	---
MK-3475 2 mg/kg Q3W	344	10.4 (9.4, 11.9)	0.71 (0.58, 0.88)	0.00076	28	9.8 (8.2, .)	1.03 (0.45, 2.35)	0.53216
MK-3475 10 mg/kg Q3W	346	12.7 (10.0, 17.3)	0.61 (0.49, 0.75)	<0.00001	34	Not Reached (8.5, .)	0.79 (0.34, 1.83)	0.29261
PFS								
Docetaxel 75 mg/m^2 Q3W	343	4.0 (3.1, 4.2)	---	---	29	5.6 (2.1, 7.5)	---	---
MK-3475 2 mg/kg Q3W	344	3.9 (3.1, 4.1)	0.88 (0.73, 1.04)	0.06758	28	4.0 (2.1, 6.2)	1.44 (0.75, 2.73)	0.86250
MK-3475 10 mg/kg Q3W	346	4.0 (2.6, 4.3)	0.79 (0.66, 0.94)	0.00462	34	4.2 (2.1, 6.0)	1.16 (0.64, 2.11)	0.68892
	N	ORR (%) (95%CI)	Difference in % vs. Docetaxel Estimate (95%CI)[‖]	Difference in % vs. Docetaxel p-Value[¶]	N	ORR (%) (95%CI)	Difference in % vs. Docetaxel Estimate (95%CI)[‖]	Difference in % vs. Docetaxel p-Value[¶]
ORR								
Docetaxel 75 mg/m^2 Q3W	343	9.3 (6.5,12.9)	---	---	29	20.7 (8.0,39.7)	---	---
MK-3475 2 mg/kg Q3W	344	18.0 (14.1,22.5)	8.7 (3.6,13.9)	0.00045	28	14.3 (4.0,32.7)	-6.4 (-26.9,14.4)	0.73562
MK-3475 10 mg/kg Q3W	346	18.5 (14.5,23.0)	9.1 (4.1,14.3)	0.00024	34	17.6 (6.8,34.5)	-3.0 (-23.7,16.8)	0.61947

[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with treatment as a covariate. Stratified by ECOG (0 vs. 1), Geographic region (East Asian vs. non-East Asian) and PD-L1 status (Strongly Positive , Weakly Positive, and Unknown Positive) for overall population.
[§] One-sided p-value based on log-rank test.
Responses are based on IRC assessments per RECIST 1.1 with confirmation.
[‖] Based on Miettinen & Nurminen method. Stratified by ECOG (0 vs. 1), Geographic region (East Asian vs. non-East Asian) and PD-L1 status (Strongly Positive , Weakly Positive and Unknown Positive) for overall population; if no patients are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.
[¶] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
Database Cutoff Date: 30SEP2015

PD-L1高発現患者における OS の Kaplan-Meier 曲線を[図 2.7.6.2.4-1]に示す。ドセタキセル群に対する MK-3475 2 mg/kg Q3W 群のハザード比は0.54（95%CI：0.38～0.77、片側 P 値：0.00024）、MK-3475 10 mg/kg Q3W 群のハザード比は0.50（95%CI : 0.36～0.70、片側 P 値 : 0.00002）であり、MK-3475の両群ともドセタキセル群と比較して有意に OS が延長していた。MK-3475の二群間における差はみられず、ハザード比は1.12（95%CI：0.77～1.62、両側 P 値：0.53513）であった。

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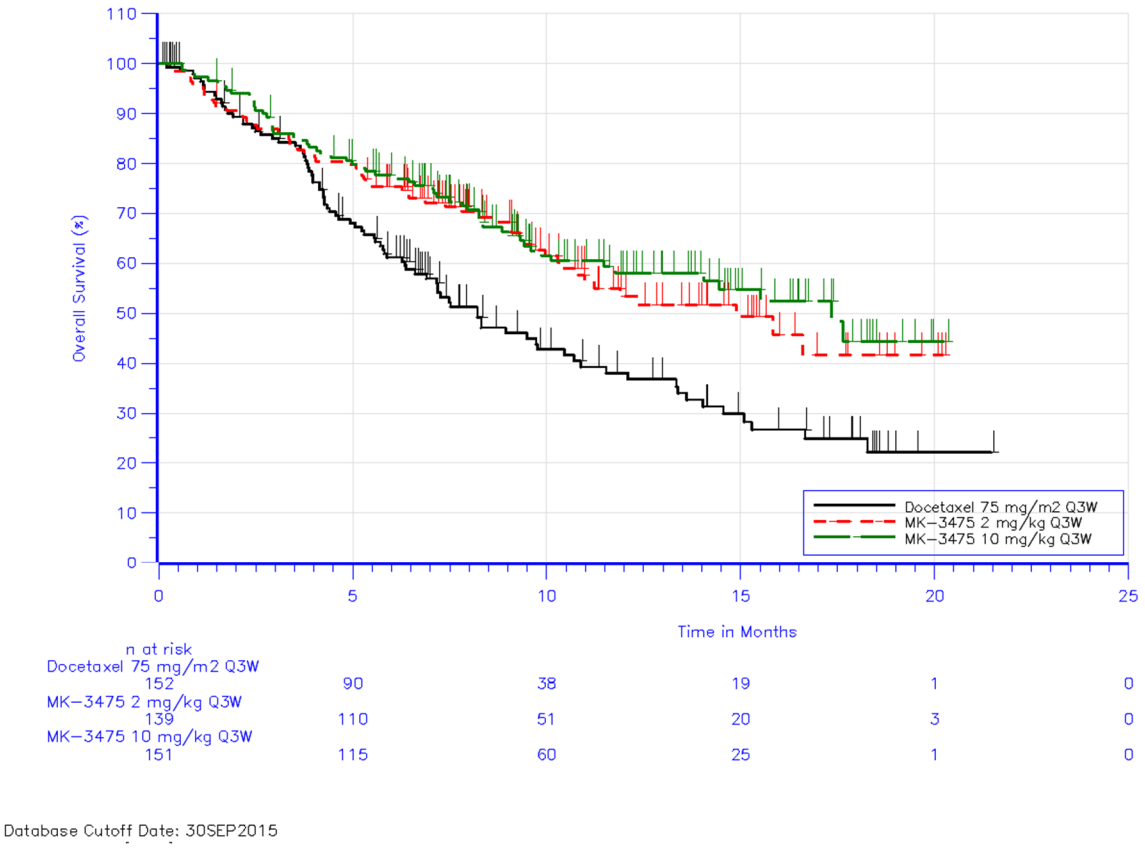


図 2.7.6.2.4-1 PD-L1 高発現患者における OS（ITT 集団）（010 試験）

PD-L1発現陽性患者における OS の Kaplan-Meier 曲線を[図 2.7.6.2.4-2]に示す。ドセタキセル群に対する MK-3475 2 mg/kg Q3W 群のハザード比は0.71（95%CI：0.58～0.88、片側 P 値：0.00076）、MK-3475 10 mg/kg Q3W 群のハザード比は0.61（95%CI：0.49～0.75、片側 P 値：0.00001未満）であり、MK-3475の両群ともドセタキセル群と比較して有意に OS が延長していた。MK-3475の二群間における差はみられず、ハザード比は1.17（95%CI：0.94～1.45、両側 P 値：0.15511）であった。

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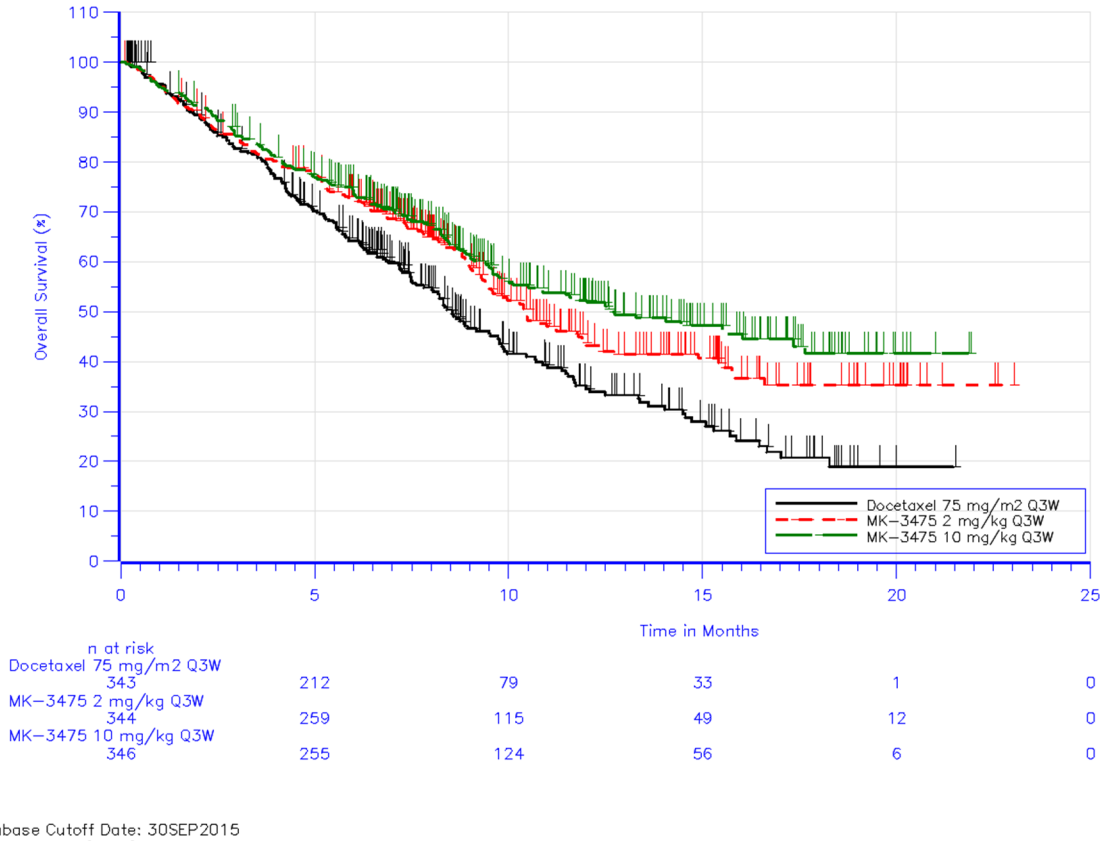


図 2.7.6.2.4-2 PD-L1 発現陽性患者における OS（ITT 集団）（010 試験）

PD-L1高発現患者における RECIST 1.1に基づく中央判定による PFS について、ドセタキセル群に対する MK-3475 2 mg/kg Q3W 群のハザード比は0.58（95%CI：0.43～0.77、片側 P 値：0.00009）、MK-3475 10 mg/kg Q3W 群のハザード比は0.59（95%CI：0.45～0.78、片側 P 値：0.00007）であり、MK-3475の両群ともドセタキセル群と比較して有意に PFS が延長していた。MK-3475の二群間における差はみられず、ハザード比は1.00（95%CI：0.74～1.35、両側 P 値：0.99358）であった。

PD-L1発現陽性患者における RECIST 1.1に基づく中央判定による PFS について、ドセタキセル群に対する MK-3475 2 mg/kg Q3W 群のハザード比は0.88（95%CI：0.73～1.04、片側 P 値：0.06758）、MK-3475 10 mg/kg Q3W 群のハザード比は0.79（95%CI：0.66～0.94、片側 P 値：0.00462）であり、治験実施計画書で規定した有意水準（0.001）を下回らなかったため統計的有意差は検出できなかったものの、MK-3475の両群ともドセタキセル群と比較して PFS が延長する傾向が認められた。MK-3475の二群間における差はみられず、ハザード比は1.09（95%CI：0.91～1.30、両側 P 値：0.34431）であった。

PD-L1高発現患者における ORR は、MK-3475 2 mg/kg Q3W 群で30.2%、MK-3475 10 mg/kg Q3W 群で29.1%、及びドセタキセル群で7.9%であった。層別 Miettinen and Nurminen 法により算出されたドセタキセル群に対する MK-3475 2 mg/kg Q3W 群の ORR の増分は23.3%（片側 P 値：0.00001未満）、MK-3475 10 mg/kg Q3W 群の ORR の増分は22.2%（片側 P 値：0.00001未満）であり、MK-3475の両群ともドセタキセル群と比較して有意に高い ORR を示した。

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PD-L1発現陽性患者における ORR は、MK-3475 2 mg/kg Q3W 群で18.0%、MK-3475 10 mg/kg Q3W 群で18.5%、及びドセタキセル群で9.3%であった。ドセタキセル群に対する MK-3475 2 mg/kg Q3W 群の ORR の増分は8.7%（片側 P 値：0.00045）、MK-3475 10 mg/kg Q3W 群の ORR の増分は9.1%（片側 P 値：0.00024）であり、MK-3475の両群ともドセタキセル群と比較して有意に高い ORR を示した。

PD-L1高発現患者における DOR の中央値は、MK-3475 2 mg/kg Q3W 群で NR（範囲：20+～512+日）、MK-3475 10 mg/kg Q3W 群で NR（範囲：64+～542+日）、及びドセタキセル群で246日（範囲：63+～268+）であった。PD-L1発現陽性患者における DOR の中央値は、MK-3475 2 mg/kg Q3W 群で NR（範囲：20+～610+日）、MK-3475 10 mg/kg Q3W 群で NR（範囲：64+～542+日）、及びドセタキセル群で189日（範囲：43+～268+）であった。

日本人集団における MK-3475の有効性について、PD-L1高発現患者での要約を[表 2.7.6.2.4-4]の右列に、PD-L1発現陽性患者での要約を[表 2.7.6.2.4-5]の右列に示した。日本人集団における MK-3475併合群のドセタキセル群に対する OS のハザード比は、PD-L1高発現患者で0.83（95%CI：0.21～3.27）、PD-L1発現陽性患者で0.88（95%CI：0.43～1.81）であった[資料5.3.5.4.5: P010_J_list]。日本人集団での結果は、患者数が比較的少ないことに起因するばらつきがみられたものの、概して試験全体の患者集団で観察された結果と同様の傾向を示した。

2.7.6.2.4.3.2　　安全性

本試験の安全性解析は、本試験に登録され無作為割付けを受けた PD-L1発現陽性患者1,034例のうち、治験薬の投与を受けなかった43例を除く991例（APaT 集団）を対象とした。試験全体の患者集団及び日本人集団における治験薬の曝露を[表 2.7.6.2.4-6]に、本試験で認められた安全性解析の結果を[表 2.7.6.2.4-7]にそれぞれ要約する。投与コース数の中央値は MK-3475の両群でそれぞれ6、ドセタキセル群で3であり、治験薬の曝露は MK-3475群がドセタキセル群より大きかった。

平均投与期間は MK-3475群の方が約2倍長かったにもかかわらず、有害事象の発現頻度は MK-3475群とドセタキセル群とで類似していた。副作用による治験薬の投与中止は MK-3475併合群の方がドセタキセル群より少なく（4.7%対10.0%）、Grade 3～5の副作用も MK-3475併合群の方がドセタキセル群より頻度が低かった（14.4%対35.3%）。副作用による死亡についても頻度は低く、MK-3475併合群で0.9%に対しドセタキセル群では1.6%であった。

MK-3475群で高頻度にみられた有害事象は、2 mg/kg Q3W 群では食欲減退（28.3%）、疲労（26.8%）、及び呼吸困難（24.8%）、10 mg/kg Q3W 群では疲労（23.3%）、食欲減退（21.0%）、及び呼吸困難（21.0%）であった。これらの有害事象により治験薬の投与中止に至った患者は少数で、これらの有害事象は概して軽度で忍容可能であった。貧血、発熱性好中球減少症、及び好中球数減少といった血液毒性は、MK-3475群と比較してドセタキセル群でより高頻度に認められ、これは流涙増加、下痢、口内炎、末梢性ニューロパチー、及び脱毛症についても同様であった。反対に、甲状腺機能亢進症及び甲状腺機能低下症は MK-3475群においてドセタキセル群よりも高頻度にみられた。

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特に注目すべき有害事象（AEOSI）

MK-3475の免疫学的な活性と関連した有害事象についてより特異的に評価するため、治験担当医師による免疫関連か否かの判定によらない AEOSI について評価を行った。AEOSI の主なものは、免疫に関連した可能性があり既承認の米国添付文書に記載されている有害事象とした。PD-L1発現陽性患者において、MK-3475併合群の133例（19.5%）及びドセタキセル群の13例（4.2%）に免疫関連の AEOSI がみられた。事前に予想されたとおり、ドセタキセル群で発現した免疫関連の AEOSI は MK-3475群よりも低頻度であったが、これはドセタキセルの作用機序が微小管阻害によるものであり免疫機構の賦活に直接関与しないことによる。ここで示された頻度は、治験担当医師による評価を考慮していないため、真に免疫に関連した有害事象よりも過大に評価されている可能性が高い。MK-3475併合群でみられた免疫関連の AEOSI の多くは Grade 1又は2であり、Grade 3～5の AEOSI は36例（5.3%）であった（ドセタキセル群では4例、1.3%）。またほとんどの免疫関連の AEOSI は、副腎皮質ホルモン剤による治療、MK-3475の休薬、又はその両者により管理可能であった。免疫関連の AEOSI により治験薬の投与中止に至った症例は、中止の原因によらず少数（15例、2.2%）であった（ドセタキセル群では5例、1.6%）。

MK-3475併合群で比較的高頻度にみられた免疫関連の AEOSI は、甲状腺機能低下症（8.2%）、甲状腺機能亢進症（4.7%）、及び肺臓炎（4.5%）であった。甲状腺機能低下症及び甲状腺機能亢進症の多くは Grade 1又は2であった。これらの事象は概して、甲状腺ホルモン補充療法、MK-3475の休薬、又はその両者により速やかに管理可能であった。甲状腺機能低下症による治験薬の投与中止は1例のみであり（10 mg/kg Q3W 群）、甲状腺機能亢進症による治験薬の投与中止はみられなかった。AEOSI としての肺臓炎には、基本語として肺臓炎及び間質性肺疾患を含めた。本試験において、MK-3475群の31例（2 mg/kg Q3W 群の16例、4.7%、及び10 mg/kg Q3W 群の15例、4.4%）及びドセタキセル群の6例（1.9%）に肺臓炎が認められた。MK-3475併合群で肺臓炎を発現した31例のうち、データベースカットオフ時点で18例は副腎皮質ホルモン剤の治療と MK-3475の休薬により完全に回復していた。多くは Grade 1又は2であり、MK-3475併合群の14例（2.1%）に Grade 3～5の肺臓炎がみられた。ドセタキセル群では Grade 3～5の肺臓炎が2例（0.6%）発現した。MK-3475群の3例が治験薬との因果関係が否定できない肺臓炎により死亡したが、そのうち2例は肺炎の病歴を有していた。MK-3475併合群で肺臓炎により治験薬の投与中止に至った症例は少数（12例、1.8%）にとどまった（ドセタキセル群では5例、1.6%）。試験全体における肺臓炎の発現割合（4.5%）、及び死亡例3例（2例は肺炎の病歴を有していた）を含む Grade 3～5の肺臓炎の発現割合（2.1%）は、001試験の非小細胞肺癌患者で観察された割合と類似していた（全事象：3.6%、Grade 3～5：1.8%）。

日本人集団における有害事象の要約を[表 2.7.6.2.4-7]の右列に示した。日本人集団で観察された MK-3475の安全性プロファイルは、概して試験全体の患者集団で観察されたものと同様の傾向を示した。

全集団のすべての有害事象、副作用及び重篤な有害事象を[付録 2.7.4-13]、[付録 2.7.4-21]及び[付録 2.7.4-40]に示す。日本人集団のすべての有害事象、副作用及び重篤な有害事象を[付録

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2.7.4-97]、[付録 2.7.4-105]及び[付録 2.7.4-115]に示す。

2.7.6.2.4.4　　結論

本試験では、OS を始めとした有効性評価項目について、MK-3475はドセタキセルと比較して臨床的に意味のある改善を示した。また安全性についても、MK-3475の平均治療期間はドセタキセルの2倍程度長かったにもかかわらず、Grade 3～5の副作用は MK-3475併合群でドセタキセル群より頻度が低く、AEOSI の多くは軽度かつ管理可能であった。MK-3475は、PD-L1を発現する進行非小細胞肺癌の患者において、良好なベネフィットリスクバランスを示した。

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表 2.7.6.2.4-6 治験薬の曝露（APaT 集団）（010 試験）

	Overall Population			Japan Subgroup		
	Docetaxel 75 mg/m^2 Q3W	MK-3475 2 mg/kg Q3W	MK-3475 10 mg/kg Q3W	Docetaxel 75 mg/m^2 Q3W	MK-3475 2 mg/kg Q3W	MK-3475 10 mg/kg Q3W
	N=309	N=339	N=343	N=27	N=28	N=34
Study Days On-Therapy (days)						
Mean	81.55	151.13	155.39	99.56	133.39	132.35
Median	62.00	106.00	106.00	81.00	117.50	105.50
SD	72.34	143.87	148.00	93.10	83.67	128.40
Range	1.00 to 416.00	1.00 to 681.00	1.00 to 632.00	1.00 to 349.00	1.00 to 316.00	1.00 to 485.00
Number of Administrations						
Mean	4.65	7.77	7.94	5.33	6.96	6.71
Median	3.00	6.00	6.00	4.00	6.50	6.00
SD	3.25	6.39	6.55	4.07	3.82	5.60
Range	1.00 to 18.00	1.00 to 26.00	1.00 to 26.00	1.00 to 17.00	1.00 to 16.00	1.00 to 23.00
Database Cutoff Date: 30SEP2015						

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表 2.7.6.2.4-7 有害事象の要約（APaT 集団）（010 試験）

	Overall Population						Japan Subgroup					
	Docetaxel 75 mg/m^2 Q3W		MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		Docetaxel 75 mg/m^2 Q3W		MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	309		339		343		27		28		34	
with one or more adverse events	297	(96.1)	331	(97.6)	330	(96.2)	26	(96.3)	28	(100.0)	34	(100.0)
with no adverse event	12	(3.9)	8	(2.4)	13	(3.8)	1	(3.7)	0	(0.0)	0	(0.0)
with drug-related† adverse events	251	(81.2)	215	(63.4)	226	(65.9)	26	(96.3)	22	(78.6)	30	(88.2)
with toxicity grade 3-5 adverse events	173	(56.0)	158	(46.6)	156	(45.5)	23	(85.2)	12	(42.9)	16	(47.1)
with toxicity grade 3-5 drug-related adverse events	109	(35.3)	43	(12.7)	55	(16.0)	23	(85.2)	4	(14.3)	10	(29.4)
with serious adverse events	107	(34.6)	115	(33.9)	131	(38.2)	7	(25.9)	7	(25.0)	15	(44.1)
with serious drug-related adverse events	42	(13.6)	32	(9.4)	39	(11.4)	4	(14.8)	5	(17.9)	9	(26.5)
who died	15	(4.9)	17	(5.0)	26	(7.6)	3	(11.1)	0	(0.0)	2	(5.9)
who died due to a drug-related adverse event	5	(1.6)	3	(0.9)	3	(0.9)	2	(7.4)	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	42	(13.6)	28	(8.3)	26	(7.6)	6	(22.2)	1	(3.6)	3	(8.8)
discontinued due to a drug-related adverse event	31	(10.0)	15	(4.4)	17	(5.0)	6	(22.2)	0	(0.0)	2	(5.9)
discontinued due to a serious adverse event	19	(6.1)	24	(7.1)	20	(5.8)	2	(7.4)	1	(3.6)	2	(5.9)
discontinued due to a serious drug-related adverse event	11	(3.6)	11	(3.2)	13	(3.8)	2	(7.4)	0	(0.0)	2	(5.9)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
MedDRA preferred terms 'Neoplasm Progression' ,'Malignant Neoplasm Progression'　and 'Disease Progression' not related to the drug are excluded.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 30SEP2015)

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2.7.6.2.5　PD-L1高発現の転移性非小細胞肺癌の未治療患者を対象としたMK-3475とプラチナ製剤併用化学療法を比較する無作為化非盲検第Ⅲ相試験［国際共同試験］［評価資料］（KEYNOTE-024試験、以下024試験）

2.7.6.2.5.1　試験方法の概要

治験実施医療機関

多施設共同、16ヵ国146施設（国内23施設）

公表文献

該当なし

治験実施期間

2014年10月～実施中（データベースカットオフ日：2016年5月9日）

開発の相

Ⅲ相

治験デザイン

本試験では、PD-L1高発現（TPS≥50%）かつEGFR遺伝子変異／ALK融合遺伝子陰性で未治療の進行非小細胞肺癌患者を対象に、MK-3475 200 mg Q3Wを標準化学療法（プラチナ製剤併用化学療法）と比較した、非盲検の第Ⅲ相試験である。305例の患者が、MK-3475 200 mg Q3W、又は標準化学療法のいずれかに1：1の割合で無作為割付けされた。標準化学療法群に割り付けられた患者は、以下に示す投与群のうち、治験担当医師が無作為割付け前に選択した薬剤の組み合わせを投与された。

- カルボプラチン・ペメトレキセド併用療法及びペメトレキセド維持療法（非扁平上皮癌患者のみ）
- シスプラチン・ペメトレキセド併用療法及びペメトレキセド維持療法（非扁平上皮癌患者のみ）
- シスプラチン・ゲムシタビン併用療法
- カルボプラチン・ゲムシタビン併用療法
- カルボプラチン・パクリタキセル併用療法及びペメトレキセド維持療法（維持療法は非扁平上皮癌患者のみ）

無作為割付けでは、ECOG PS（0、1）、非小細胞肺癌の組織型（扁平上皮癌、非扁平上皮癌）及び登録施設の地域（東アジア、東アジア以外）を層別因子とした。

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患者は9週（63±7日）ごとに放射線画像診断による評価を受けた。すべての画像は、盲検下独立判定委員会（BICR）により評価され、RESCIST 1.1に基づいて ORR 及び PFS の判定が行われた。MK-3475及び標準化学療法の投与は、疾患進行、許容できない有害事象、治療継続を困難とする併存疾患、治験担当医師の判断、患者の同意撤回、患者の妊娠、治験手順の不遵守、管理上の理由による投与中止、又は35回の MK-3475投与完了まで継続することとした。ただし BICR により RECIST 1.1に基づく疾患進行と判定された後も、患者が臨床的に安定しており、治験薬投与によるベネフィットが得られていると治験担当医師が判断した場合、治験薬の投与継続を可能とした。有害事象は治験期間を通して評価され、NCI-CTCAE Version 4.0に沿って程度の Grade 分類が行われた。

標準化学療法群に割り付けられた患者が、BICR により RECIST 1.1に基づく疾患進行と判定され、クロスオーバーに関する基準をすべて満たした場合は、MK-3475の投与を受けられることとした。

治験薬の投与中止後、すべての患者について有害事象を少なくとも30日間追跡した。また、患者が死亡、同意撤回、又は追跡不能となるまで、本試験以外の抗がん治療の開始や病勢の悪化を含めた疾患の状態を追跡調査した。

主要目的

1) PD-L1高発現の転移性非小細胞肺癌の未治療患者に MK-3475又は標準化学療法を投与した際の、RECIST 1.1に基づき BICR が評価した PFS を比較する。

副次的目的

1) PD-L1高発現の転移性非小細胞肺癌の未治療患者における MK-3475の安全性及び忍容性を評価する。
2) PD-L1高発現の転移性非小細胞肺癌の未治療患者に MK-3475又は標準化学療法を投与した際の、OS を比較する。
3) PD-L1高発現の転移性非小細胞肺癌の未治療患者に MK-3475又は標準化学療法を投与した際の、RECIST 1.1に基づき BICR が評価した ORR を比較する。

探索的目的

PD-L1高発現の転移性非小細胞肺癌の未治療患者に MK-3475又は標準化学療法を投与した際の、irRC に基づく PFS 及び ORR、RECIST 1.1に基づき BICR 及び治験担当医師が評価した奏効期間、RECIST 1.1に基づき治験担当医師が評価した PFS2（2次治療における PFS）、生活の質（QoL）に関する Patient Reported Outcome（PRO）を比較する。また、MK-3475の投与を受けた患者における、奏効を予測するための遺伝子シグネチャーを評価する。

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ロット番号

表 2.7.6.2.5-1 治験薬の内容（024 試験）

Bulk Product Description	Manufacturing Lot Number
HLSV Gemcitabine 1000 mg, 50 mL Vial (ex-UK)	DL00018935, DL00019179
HLSV Gemcitabine 1000 mg/vial (ex-DE)	DL00019430
HLSV Pemetrexed (ALIMTA) 500 mg Vial (ex-Germany)	DL00018941, DL00019180, DL00019229, DL00019472
HSS MK-3475, 100 mg/vial	DL00018609, DL00018801, DL00019172
HSSV Carboplatin 10 mg/mL, 600 mg Vial (ex-Germany)	DL00019431, DL00019477
HSSV Carboplatin 10 mg/mL, 600 mg Vial (ex-UK)	DL00018936, DL00019128, DL00019276
HSSV Cisplatin 1 mg/mL, 50 mL Vial (ex-Germany)	DL00018939, DL00019132, DL00019382
HSSV Paclitaxel 6 mg/mL, 100 mg Vial (ex-UK)	DL00018959, DL00019111, DL00019294, DL00019295

診断／組入れ基準

選択基準（抜粋）：

1) 組織学的又は細胞学的に非小細胞肺癌と診断され、EGFR 感受性遺伝子変異陰性及び ALK 遺伝子転座陰性で転移性非小細胞肺癌に対する全身化学療法の治療歴がないⅣ期の患者
2) 実施医療機関による RECIST 1.1の評価に基づき、測定可能病変を有する患者
3) 同意取得時の年齢が18歳以上の患者
4) 3ヵ月以上の生存が見込まれる患者
5) ECOG PS が0又は1の患者
6) 適切な臓器機能が保持された患者
7) 悪性腫瘍の既往歴がない患者
8) PD-L1の発現を評価するために、Ⅳ期の診断時以降に、放射線照射を受けていない腫瘍病変から採取したホルマリン固定腫瘍組織検体を提出できる患者
9) EGFR 感受性遺伝子変異陰性及び ALK 遺伝子転座陰性の患者
10) 中央判定機関で IHC 法によって PD-L1高発現が確認された患者
11) 妊娠の可能性がない女性患者
12) 妊娠の可能性がある女性患者：スクリーニング時から MK-3475の最終投与後120日まで、及び治験実施計画書に規定された化学療法の最終投与後180日まで、適切な二重避妊法を使用することに同意した患者
13) 妊娠の可能性があるパートナーがいる男性患者：スクリーニング時から MK-3475の最終投与後120日まで適切な二重避妊法を使用することに同意した患者
14) 自由意思により、治験の参加について文書による同意を得ている患者

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評価基準

有効性

1) RECIST 1.1に基づく PFS：PFS を、無作為割付けの時点から BICR の RECIST 1.1に基づく PD 又は死亡（原因を問わない）のいずれか先に生じた時点までの期間と定義した。
2) OS：OS を、無作為割付けの時点から死亡（原因を問わない）までの期間と定義した。最終解析時に死亡が報告されていない患者は最終のフォローアップ日で打切りとした。
3) ORR：ORR を、解析対象集団で CR 又は PR が認められた患者の割合と定義した。奏効（CR、PR）は、BICR の RECIST 1.1を用いた評価に基づいた。

安全性

安全性評価項目は、NCI CTCAE version 4.0に基づき Grade 分類したすべての有害事象、臨床検査値、バイタルサイン及び心電図とした。

統計計画及び解析

有効性

本項では、主要評価項目である PFS の最終解析計画を示す。ORR 及び OS は副次評価項目とし、奏効期間は探索的評価項目とした intention-to-treat（ITT）の患者集団を解析対象集団とした。さらに、異なる打ち切り規則を用いた感度解析も行った。

ノンパラメトリック法である Kaplan-Meier 法を用いて、各投与群の PFS 及び OS の生存曲線を推定した。PFS 及び OS の投与群間差は層別ログランク検定を用いて評価した。投与群をモデルに含めた層別 Cox 比例ハザードモデル（タイデータには Efron 法で対応）に基づき、ハザード比及びその95%信頼区間（CI）を計算した。層別ログランク検定と層別 Cox 比例ハザードモデルの双方とも、無作為化に用いた層別因子を考慮した。

投与群間の ORR の比較には、層別 Miettinen and Nurminen 法を用いた。MK-3475群と標準化学療法群の ORR の差の95%CI 及び P 値を計算した。解析には、無作為化に用いた層別因子を用いた。

Kaplan-Meier 法による中央値と四分位数を用いて、奏効期間を記述的に要約した。CR 又は PR となった患者で構成される部分集団のみ本解析に含めた。

解析対象集団及び解析時点

本治験では、intention-to-treat（ITT）の患者集団を有効性データ解析の主要な解析対象集団とした。

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安全性

本治験における安全性の主要な解析対象集団は All Subjects as Treated（ASaT）とした。ASaT は無作為化され、治験薬が1回以上投与されたすべての患者から構成される。

安全性及び忍容性は、有害事象、臨床検査値、バイタルサイン及び心電図を含むすべての安全性評価項目を用いて、臨床的な観点から評価した。

安全性データの解析は段階的な方法（tiered approach）を用いた。段階（tier）によって実施する解析が異なる。安全性パラメーターや特に関心のある有害事象を「Tier 1」の事前に規定した安全性評価項目とし、群間比較に関する統計的検定の P 値及び95%信頼区間を算出した。その他の安全性評価項目は「Tier 2」又は「Tier 3」とした。Tier 2の評価項目については群間比較のための差の点推定値とその95%信頼区間を用いて評価し、Tier 3の評価項目については投与群ごとの点推定値のみを算出した。本治験実施計画書で Tier 1の事象は設定しなかった。安全性の群間比較に関する統計的検定の P 値は計算しなかった。

Tier 1の事象として事前に規定しない有害事象（基本語及び器官別大分類）並びに臨床検査値、バイタルサイン及び心電図の事前に規定した範囲を超える変動は、発現した例数に基づき Tier 2 又は Tier 3に分類した。いずれかの投与群で4例以上発現した事象は Tier 2とし、それ以外のすべての有害事象及び事前に規定した範囲を超える変動は Tier 3とした。

各群の例数が等しく、発現数が4例未満のときには、発現率の群間差の95%信頼区間は常に0を含み、意味のある差の解釈を与えないことから、4例以上を基準とした。多く95%信頼区間は多重性を調整せずに算出されるため、結果の評価の際に有用な記述的な指標であるが、有害事象及び事前に規定した範囲を超える変動の群間差が統計的に有意であるかを評価する正式な方法ではない。

Tier 1の事象として事前に規定しない臨床検査値、バイタルサイン及び心電図のベースラインからの変化量のような連続量の測定値は Tier 3とした。ベースライン、投与期間中、及びベースラインからの変化量の要約統計量を投与群ごとに表形式にて報告した。また、投与群間の差の要約統計量についても、群間差に関する名目上の P 値とともに提示した。ベースラインからの変化量の平均値と標準誤差の経時変化のグラフを作成した。

解析対象集団及び解析時点

本治験における安全性解析対象集団は All Subjects as Treated（ASaT）とした。ASaT は無作為化され、治験薬が1回以上投与されたすべての患者から構成される。ASaT を用いた安全性解析では、患者は実際に投与された治験薬に対応する群に含めた。臨床検査値又はバイタルサインの解析には、1回以上投与された後、1つ以上の各評価項目の測定値を必要とした。ベースラインからの変化量の評価には、ベースラインの測定値も必要とした。

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2.7.6.2.5.2　　患者の内訳

全集団及び日本人集団の特性及び内訳を[表 2.7.6.2.5-2]及び[表 2.7.6.2.5-3]に要約する。

男性（61.3%）、白人（82.3%）、東アジア人以外（86.9%）、Ⅳ期の腺癌（69.5%）、術前補助化学療法なし（98.7%）、及び術後補助化学療法なし（97%）の患者が多数を占め、ECOG PS は1である患者が多かった（64.6%）。投与開始前の特性は概して両投与群で類似していたが、喫煙歴については投与群間での偏りが認められた。すなわち非喫煙者の割合は、標準化学療法群（12.6%）がMK-3475群（3.2%）より高かった。また、脳転移を有する患者の割合に関しては、MK-3475群（11.7%）が標準化学療法群（6.6%）より高かった。全集団と比較して、日本人集団では MK-3475群及び標準化学療法群ともに男性の割合が高く、喫煙者の割合が低かったことを除き、全集団と日本人集団の患者の特性に関して、臨床的に意味のある差は認められなかった。

データベースカットオフ時点で当初割り付けられた治験薬を継続していた患者の割合は、MK-3475群（48.1%）が標準化学療法群（10.0%）と比べて高かった。疾患進行のため投与を中止した患者は、標準化学療法群（42.0%）が MK-3475群（29.9%）と比べて多かった。有害事象による投与中止、臨床的に判断された疾患進行による投与中止、患者の同意撤回による投与中止の割合は、両群で類似していた。死亡による投与中止（標準化学療法群：6.0%、MK-3475群：3.9%）及び治験担当医師の判断による投与中止（標準化学療法群：4.7%、MK-3475群：0.6%）は、標準化学療法群でより多くみられた。標準化学療法群において、治験実施計画書に規定された4～6サイクルのプラチナ製剤併用化学療法を完了し、かつその時点で疾患進行が認められなかった患者のみが「Completed」に分類されている。MK-3475群では、データカットオフ時点の投与期間が最長でも2年未満であったため、投与完了（2年間）に至った患者はなかった。日本人集団における患者の内訳についても、全集団と同様の傾向を示した。

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表 2.7.6.2.5-2 患者の特性（ITT 集団）（024 試験）

	Overall Population						Japan Subgroup					
	MK-3475 200 mg Q3W		標準化学療法		Total		MK-3475 200 mg Q3W		標準化学療法		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	154		151		305		21		19		40	
Gender												
Male	92	(59.7)	95	(62.9)	187	(61.3)	16	(76.2)	18	(94.7)	34	(85.0)
Female	62	(40.3)	56	(37.1)	118	(38.7)	5	(23.8)	1	(5.3)	6	(15.0)
Age (Years)												
< 65	77	(50.0)	64	(42.4)	141	(46.2)	9	(42.9)	6	(31.6)	15	(37.5)
>= 65	77	(50.0)	87	(57.6)	164	(53.8)	12	(57.1)	13	(68.4)	25	(62.5)
Mean	63.9	-	64.6	-	64.2	-	63.9	-	65.9	-	64.9	-
SD	10.1	-	9.5	-	9.8	-	9.8	-	6.8	-	8.5	-
Median	64.5	-	66.0	-	65.0	-	66.0	-	67.0	-	66.5	-
Range	33 to 90	-	38 to 85	-	33 to 90	-	40 to 80	-	53 to 77	-	40 to 80	-
Race												
American Indian Or Alaska Native	0	(0.0)	1	(0.7)	1	(0.3)	-	-	-	-	-	-
Asian	25	(16.2)	21	(13.9)	46	(15.1)	21	(100.0)	19	(100.0)	40	(100.0)
Black Or African American	2	(1.3)	2	(1.3)	4	(1.3)	-	-	-	-	-	-
Native Hawaiian Or Other Pacific Islander	0	(0.0)	1	(0.7)	1	(0.3)	-	-	-	-	-	-
White	125	(81.2)	126	(83.4)	251	(82.3)	-	-	-	-	-	-
Missing	2	(1.3)	0	(0.0)	2	(0.7)	-	-	-	-	-	-
Ethnicity												
Hispanic Or Latino	1	(0.6)	5	(3.3)	6	(2.0)	-	-	-	-	-	-
Not Hispanic Or Latino	147	(95.5)	135	(89.4)	282	(92.5)	21	(100.0)	18	(94.7)	39	(97.5)
Not Reported	4	(2.6)	6	(4.0)	10	(3.3)	0	(0.0)	1	(5.3)	1	(2.5)
Unknown	2	(1.3)	5	(3.3)	7	(2.3)	-	-	-	-	-	-
ECOG												
0	54	(35.1)	53	(35.1)	107	(35.1)	7	(33.3)	8	(42.1)	15	(37.5)
1	99	(64.3)	98	(64.9)	197	(64.6)	14	(66.7)	11	(57.9)	25	(62.5)
2	1	(0.6)	0	(0.0)	1	(0.3)	-	-	-	-	-	-

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表 2.7.6.2.5-2 患者の特性（ITT 集団）（024 試験）（続き）

	Overall Population						Japan Subgroup					
	MK-3475 200 mg Q3W		標準化学療法		Total		MK-3475 200 mg Q3W		標準化学療法		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Cancer Stage at Screening												
IIIB	1	(0.6)	1	(0.7)	2	(0.7)	-	-	-	-	-	-
IV	153	(99.4)	150	(99.3)	303	(99.3)	21	(100.0)	19	(100.0)	40	(100.0)
Geographic Region of Enrolling Site												
Non(East Asia	133	(86.4)	132	(87.4)	265	(86.9)	-	-	-	-	-	-
East Asia	21	(13.6)	19	(12.6)	40	(13.1)	21	(100.0)	19	(100.0)	40	(100.0)
Histology												
ADENOCARCINOMA	104	(67.5)	108	(71.5)	212	(69.5)	14	(66.7)	16	(84.2)	30	(75.0)
ADENOSQUAMOUS	2	(1.3)	2	(1.3)	4	(1.3)	-	-	-	-	-	-
LARGE CELL CARCINOMA	2	(1.3)	2	(1.3)	4	(1.3)	-	-	-	-	-	-
NON(SQUAMOUS CELL CARCINOMA	5	(3.2)	7	(4.6)	12	(3.9)	3	(14.3)	1	(5.3)	4	(10.0)
POORLY DIFFERENTIATED	9	(5.8)	3	(2.0)	12	(3.9)	1	(4.8)	1	(5.3)	2	(5.0)
SARCOMATOID	3	(1.9)	2	(1.3)	5	(1.6)	-	-	-	-	-	-
SQUAMOUS CELL CARCINOMA	29	(18.8)	26	(17.2)	55	(18.0)	3	(14.3)	1	(5.3)	4	(10.0)
POORLY DIFFERENTIATED SQUAMOUS CELL CARCINOMA	0	(0.0)	1	(0.7)	1	(0.3)	-	-	-	-	-	-
Smoking Status												
Current	34	(22.1)	31	(20.5)	65	(21.3)	0	(0.0)	1	(5.3)	1	(2.5)
Former	115	(74.7)	101	(66.9)	216	(70.8)	20	(95.2)	18	(94.7)	38	(95.0)
Never	5	(3.2)	19	(12.6)	24	(7.9)	1	(4.8)	0	(0.0)	1	(2.5)

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表 2.7.6.2.5-2 患者の特性（ITT 集団）（024 試験）（続き）

	Overall Population						Japan Subgroup					
	MK-3475 200 mg Q3W		標準化学療法		Total		MK-3475 200 mg Q3W		標準化学療法		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Brain Metastasis Status at Baseline												
Y	18	(11.7)	10	(6.6)	28	(9.2)	1	(4.8)	1	(5.3)	2	(5.0)
N	136	(88.3)	141	(93.4)	277	(90.8)	20	(95.2)	18	(94.7)	38	(95.0)
Baseline Tumor Size (mm)												
Subjects with data	151	-	150	-	301	-	20	-	19	-	39	-
Mean	90.9	-	99.8	-	95.3	-	81.7	-	88.6	-	85.1	-
SD	53.4	-	63.4	-	58.6	-	55.5	-	72.4	-	63.5	-
Median	82	-	84	-	83	-	68	-	77	-	72	-
Range	14 to 322	-	14 to 369	-	14 to 369	-	20 to 245	-	15 to 251	-	15 to 251	-
Baseline Weight (kg)												
Subjects with data	154	-	151	-	305	-	21	-	19	-	40	-
Mean	68.8	-	72.7	-	70.7	-	58.4	-	63.6	-	60.9	-
SD	13.7	-	17.2	-	15.6	-	8.4	-	11.1	-	10	-
Median	69	-	70	-	69	-	58	-	64	-	61	-
Range	38 to 110	-	39 to 132	-	38 to 132	-	38 to 69	-	47 to 86	-	38 to 86	-
Prior Adjuvant Therapy												
Yes	6	(3.9)	3	(2.0)	9	(3.0)	-	-	-	-	-	-
No	148	(96.1)	148	(98.0)	296	(97.0)	21	(100.0)	19	(100.0)	40	(100.0)
Prior Neo(adjuvant Therapy												
Yes	3	(1.9)	1	(0.7)	4	(1.3)	-	-	-	-	-	-
No	151	(98.1)	150	(99.3)	301	(98.7)	21	(100.0)	19	(100.0)	40	(100.0)
(Database Cutoff Date: 09MAY2016).												

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表 2.7.6.2.5-3 患者の内訳（ITT 集団）（024 試験）

	Overall Population		Japan Subgroup	
	MK-3475 200 mg Q3W n (%)	標準化学療法 n (%)	MK-3475 200 mg Q3W n (%)	標準化学療法 n (%)
Subjects in population	154	151	21	19
Status for Trial				
Discontinued	47 (30.5)	69 (45.7)	3 (14.3)	6 (31.6)
Adverse Event	9 (5.8)	8 (5.3)	0 (0.0)	2 (10.5)
Death	33 (21.4)	55 (36.4)	3 (14.3)	4 (21.1)
Progressive Disease	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Withdrawal By Subject	5 (3.2)	5 (3.3)	0 (0.0)	0 (0.0)
Status Not Recorded	107 (69.5)	82 (54.3)	18 (85.7)	13 (68.4)
Status for Study Medication in Trial Segment Treatment				
Started	154	150	21	19
Completed	0 (0.0)	29 (19.3)	0 (0.0)	2 (10.5)
Discontinued	80 (51.9)	106 (70.7)	8 (38.1)	16 (84.2)
Adverse Event	17 (11.0)	16 (10.7)	2 (9.5)	2 (10.5)
Clinical Progression	5 (3.2)	6 (4.0)	1 (4.8)	0 (0.0)
Complete Response	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Death	6 (3.9)	9 (6.0)	0 (0.0)	0 (0.0)
Physician Decision	1 (0.6)	7 (4.7)	0 (0.0)	0 (0.0)
Progressive Disease	46 (29.9)	63 (42.0)	5 (23.8)	14 (73.7)
Withdrawal By Subject	4 (2.6)	5 (3.3)	0 (0.0)	0 (0.0)
Status Not Recorded	74 (48.1)	15 (10.0)	13 (61.9)	1 (5.3)
Status for Study Medication in Trial Segment Cross Over Treatment				
Started	0	66	0	7
Discontinued	0 (0.0)	28 (42.4)	0 (0.0)	1 (14.3)
Adverse Event	0 (0.0)	2 (3.0)	0 (0.0)	0 (0.0)
Clinical Progression	0 (0.0)	1 (1.5)	0 (0.0)	1 (14.3)
Death	0 (0.0)	5 (7.6)	0 (0.0)	0 (0.0)
Physician Decision	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)
Progressive Disease	0 (0.0)	19 (28.8)	0 (0.0)	0 (0.0)
Status Not Recorded	0 (0.0)	38 (57.6)	0 (0.0)	6 (85.7)

Each subject is counted once for Study Medication Disposition.
Status not Recorded for subjects that are continuing in trial or trial segment.
(Database Cutoff Date: 09MAY2016).

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2.7.6.2.5.3　結果

2.7.6.2.5.3.1　有効性

本治験は、PD-L1高発現の非小細胞肺癌の未治療患者305例を MK-3475群又は標準化学療法群に1：1で無作為に割り付けた。2回目の中間解析時点で得られた PFS、OS 及び ORR の解析結果の要約を[表 2.7.6.2.5-4]及び[表 2.7.6.2.5-5]に示す。

主要評価項目である PFS は、BICR が RECIST 1.1に基づき評価した。2回目の中間解析のデータカットオフ時点で、計189件の PFS のイベントが観察された。MK-3475群の標準化学療法群に対する PFS のハザード比は0.50（95%CI：0.37～0.68）であり、MK-3475は標準化学療法と比較して、PFS を有意に延長した。PFS の中央値は標準化学療法群で6.0ヵ月であったのに対し、MK-3475群で10.3ヵ月であった。なお、標準化学療法群において観察された PFS の中央値6.0ヵ月は、これまでに行われたプラチナ製剤併用化学療法及びペメトレキセドによる維持療法の試験結果と一貫していた。PFS の Kaplan-Meier 曲線は、試験早期の4ヶ月前後から MK-3475群が標準化学療法群を上回り始め、全期間を通じて交差することなく、時間とともにその差が拡大した。[図 2.7.6.2.5-1]。

副次評価項目である OS は、2回目の中間解析のデータカットオフ時点で、計108件（35.4%）のイベントが観察された。MK-3475群の標準化学療法群に対するハザード比は0.60（95%CI：0.41～0.89）であり、MK-3475による OS の改善は統計的に有意であった。OS の中央値はいずれの群でも中央値に達していなかった。OS の Kaplan-Meier 曲線は、1ヵ月前後から MK-3475群が標準化学療法群を上回り始め、全期間を通じて交差することなく、時間とともにその差が拡大した[図 2.7.6.2.5-2]。データベースカットオフ時点で観察されていた OS イベントが比較的少なく（35.4%）、治験実施計画書に規定された標準化学療法群の MK-3475へのクロスオーバーによる検出力低下の可能性にもかかわらず、MK-3475による OS の延長は統計的に有意であった。なお、データカットオフ時点で、標準化学療法群の患者の44%（66例）が治験実施計画書に基づくクロスオーバーを行った。

副次評価項目である ORR は BICR が RECIST 1.1に基づき評価した。MK-3475群で観察された ORR は、標準化学療法群と比較して著しく高く、それぞれ44.8%、27.8%であった。また標準化学療法群において観察された27.8%の ORR は、これまでに行われたプラチナ製剤併用化学療法及びペメトレキセドによる維持療法の試験結果と一貫していた。RECIST 1.1に基づき BICR が評価した奏効期間の中央値は、MK-3475群で未到達（範囲：1.9+～14.5+）、標準化学療法群で6.3ヵ月（範囲：2.1+～12.6+）であった。

日本人集団における MK-3475の有効性の要約を[表 2.7.6.2.5-4]及び[表 2.7.6.2.5-5]の右列に示す。日本人集団における MK-3475群の標準化学療法群に対する PFS のハザード比は0.35（95%CI：0.14～0.91）、OS のハザード比は0.40（95%CI：0.10～1.61）であり、化学療法群と比較して MK-3475群で PFS 及び OS が延長した。また、ORR は MK-3475群で57.1%（95%CI：34.0～78.2）、標準化学療法群で21.1%（95%CI：6.1～45.6）であった。なお、データカットオフ時点で、標準化学療法群の患者の36.8%（7例）が治験実施計画書に基づくクロスオーバーを行った。

以上より、日本人集団での結果は、全集団で観察された結果と同様の傾向を示した。

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表 2.7.6.2.5-4 PFS 及び OS の要約（ITT 集団）（024 試験）

Treatment	Overall Population				Japan Subgroup			
	N	Median (Months) (95%CI)†	MK-3475 vs. SOC Hazard Ratio (95%CI)‡	MK-3475 vs. SOC p-Value‡‡	N	Median (Months) (95%CI)†	MK-3475 vs. SOC Hazard Ratio (95%CI)‡	MK-3475 vs. SOC p-Value‡‡
PFS								
MK-3475 200 mg Q3W	154	10.3 (6.7, .)	---	---	21	Not Reached (4.2, .)	0.35 (0.14, 0.91)	0.013
標準化学療法	151	6.0 (4.2, 6.2)	0.50 (0.37, 0.68)	<0.001	19	4.1 (2.8, 8.3)	---	---
OS								
MK-3475 200 mg Q3W	154	Not Reached (., .)	---	---	21	Not Reached (., .)	0.40 (0.10, 1.61)	0.091
標準化学療法	151	Not Reached (9.4, .)	0.60 (0.41, 0.89)	0.005	19	Not Reached (5.2, .)	---	---

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous).

‡‡ One-sided p-value based on log-rank test.

(Database Cutoff Date: 09MAY2016)

表 2.7.6.2.5-5 ORR の要約（ITT 集団）（024 試験）

Treatment	Overall Population				Japan Subgroup			
	N	Objective Response Rate (%) (95% CI)	Difference in % MK-3475 vs. SOC Estimate (95% CI)†	Difference in % MK-3475 vs. SOC p-Value††	N	Objective Response Rate (%) (95% CI)	Difference in % MK-3475 vs. SOC Estimate (95% CI)†	Difference in % MK-3475 vs. SOC p-Value††
ORR								
MK-3475 200 mg Q3W	154	44.8 (36.8,53.0)	16.6 (6.0,27.0)	0.0011	21	57.1 (34.0,78.2)	33.3 (3.3,59.0)	0.0151
標準化学療法	151	27.8 (20.8,35.7)	---	---	19	21.1 (6.1,45.6)	---	---

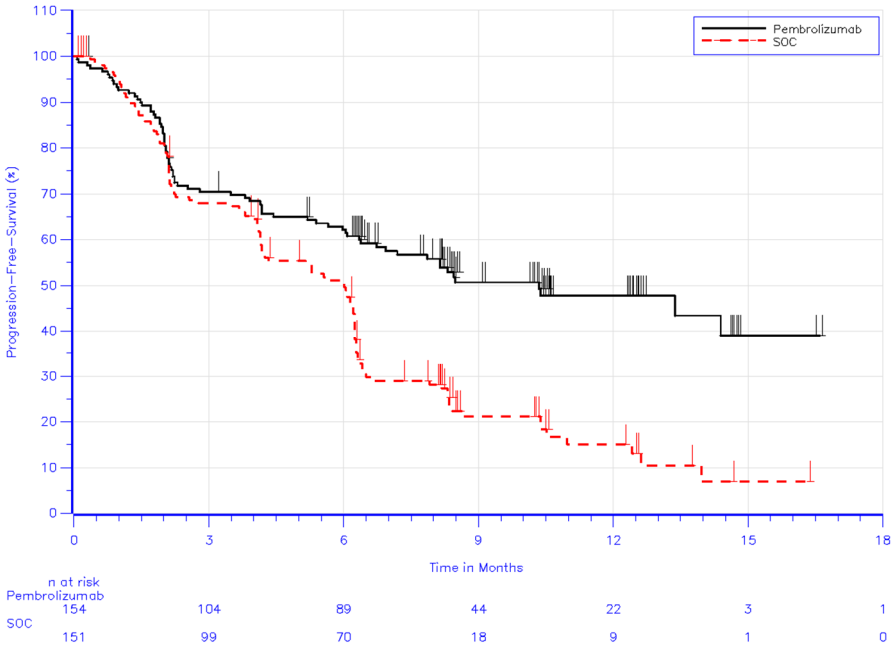
† Based on Miettinen & Nurminen method stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous). If no subjects are in one of the treatment involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.

†† One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.

Responses are based on BICR assessments per RECIST 1.1 with confirmation.

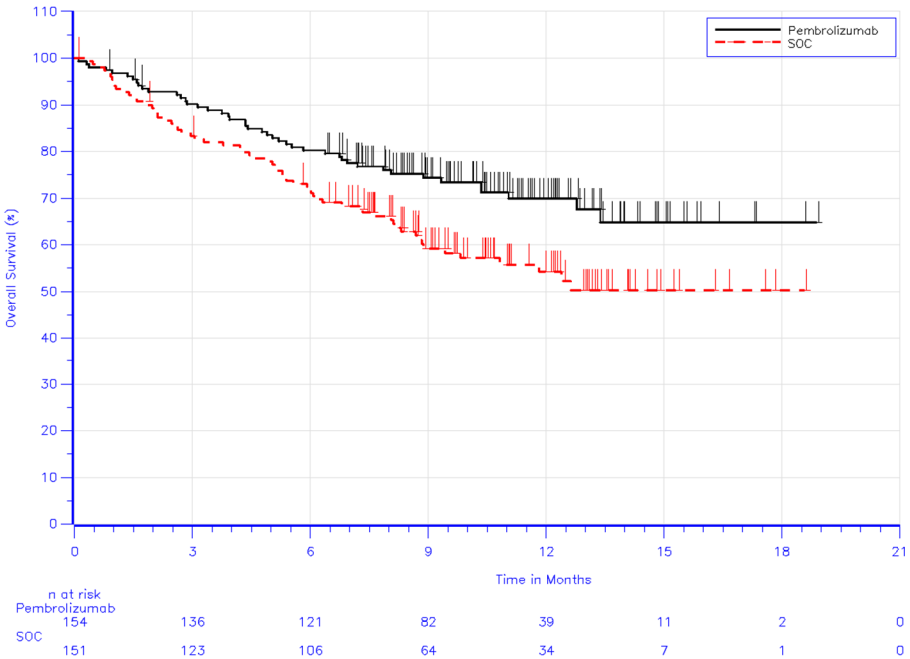
(Database Cutoff Date: 09MAY2016)

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(Database Cutoff Date: 09MAY2016)
Source:　[P024V01MK3475: analysis-adsl; adtte]

図 2.7.6.2.5-1 PFS のカプラン・マイヤー曲線（ITT 集団）（024 試験）



(Database Cutoff Date: 09MAY2016)
Source:　[P024V01MK3475: analysis-adsl; adtte]

図 2.7.6.2.5-2 OS のカプラン・マイヤー曲線（ITT 集団）（024 試験）

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2.7.6.2.5.3.2　　安全性

本試験の安全性解析は、本試験に登録され無作為割付けを受けた PD-L1高発現の非小細胞肺癌の未治療患者305例のうち、治験薬の投与を受けなかった1例を除く304例（ASaT 集団）を対象とした。試験全体の患者集団及び日本人集団における治験薬の曝露を[表 2.7.6.2.5-6]に、本試験で認められた安全性解析の結果を[表 2.7.6.2.5-7]にそれぞれ要約する。投与数の中央値は MK-3475群でそれぞれ10.50、標準化学療法群で6.00であり、MK-3475群の投与数は標準化学療法群と比較して多かった。

本治験でみられた MK-3475の安全性プロファイルは、これまでの進行非小細胞肺癌や他のがん腫を対象とした試験でみられたものと同様であった。また、標準化学療法の安全性プロファイルも予想される範囲内であった。MK-3475による免疫関連の有害事象（肺臓炎等）の発現割合は標準化学療法群より高かったが、大部分が Grade 1又は2であり死亡に至った事象はなかった。Grade 2以上の特に注目すべき有害事象（AEOSI）は、治験薬の休薬及び副腎皮質ホルモン剤投与により管理可能であった。MK-3475群での安全性は標準化学療法群と比較して忍容であり、有害事象は管理可能であった。また、MK-3475群の投与期間の中央値は標準化学療法群の2倍以上であったにもかかわらず、すべての副作用、Grade 3～5の副作用、治験薬投与の中止に至った副作用、及び副作用による死亡の発現割合は、標準化学療法群と比較して MK-3475群の方が低かった[表 2.7.6.2.5-7]。

MK-3475群で高頻度みられた有害事象は呼吸困難（22.1%）、下痢（20.8%）、便秘（20.8%）、疲労（20.8%）、食欲減退（20.1%）であり、標準化学療法群で高頻度にみられた有害事象は貧血（52.7%）、悪心（46.7%）、疲労（35.3%）、食欲減退（32.7%）、好中球減少症（24%）、嘔吐（24%）、便秘（22.7%）、下痢（22%）であった。Grade 3～5の副作用の発現頻度は低く、MK-3475群では下痢（3.9%）、肺臓炎（2.6%）、貧血（1.9%）であり、標準化学療法群では貧血（19.3%）、好中球減少症（13.3%）、血小板数減少（6.0%）、血小板減少症（5.3%）であった。MK-3475群で多くみられた AEOSI は甲状腺機能低下症（9.1%）及び甲状腺機能亢進症（7.8%）であった。

日本人集団における有害事象の要約を[表 2.7.6.2.5-7]の右列に示す。日本人集団で観察された MK-3475の安全性プロファイルは、概して全集団で観察されたものと同様の傾向を示した。

全集団のすべての有害事象、副作用及び重篤な有害事象を[付録 2.7.4-135]、[付録 2.7.4-136]及び[付録 2.7.4-137]に示す。日本人集団のすべての有害事象、副作用及び重篤な有害事象を[付録 2.7.4-153]、[付録 2.7.4-154]及び[付録 2.7.4-155]に示す。

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表 2.7.6.2.5-6 治験薬の曝露（ASaT 集団）（024 試験）

	Overall Population		Japan Subgroup	
	MK-3475 200 mg Q3W	標準化学療法	MK-3475 200 mg Q3W	標準化学療法
	N=154	N=150	N=21	N=19
Study Days On-Therapy (days)				
Mean	205.73	120.83	242.19	117.47
Median	214.00	106.00	232.00	106.00
SD	144.93	105.94	120.75	103.24
Range	1.00 to 568.00	1.00 to 511.00	1.00 to 526.00	1.00 to 358.00
Number of Administrations				
Mean	10.24	6.18	12.00	6.05
Median	10.50	6.00	12.00	5.00
SD	6.71	4.72	5.78	4.43
Range	1.00 to 26.20	1.00 to 25.00	1.00 to 26.00	1.00 to 16.00

Database Cutoff Date: 09MAY2016

表 2.7.6.2.5-7 有害事象の要約（ASaT 集団）（024 試験）

	Overall Population				Japan Subgroup			
	MK-3475 200 mg Q3W		標準化学療法		MK-3475 200 mg Q3W		標準化学療法	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	154		150		21		19	
with one or more adverse events	148	(96.1)	145	(96.7)	21	(100.0)	18	(94.7)
with no adverse event	6	(3.9)	5	(3.3)	0	(0.0)	1	(5.3)
with drug-related[†] adverse events	113	(73.4)	135	(90.0)	20	(95.2)	18	(94.7)
with toxicity grade 3-5 adverse events	82	(53.2)	109	(72.7)	10	(47.6)	12	(63.2)
with toxicity grade 3-5 drug-related adverse events	41	(26.6)	80	(53.3)	7	(33.3)	9	(47.4)
with serious adverse events	68	(44.2)	66	(44.0)	7	(33.3)	7	(36.8)
with serious drug-related adverse events	33	(21.4)	31	(20.7)	4	(19.0)	5	(26.3)
who died	9	(5.8)	7	(4.7)	0	(0.0)	2	(10.5)
who died due to a drug-related adverse event	1	(0.6)	3	(2.0)	0	(0.0)	1	(5.3)
discontinued[‡] due to an adverse event	14	(9.1)	21	(14.0)	2	(9.5)	1	(5.3)
discontinued due to a drug-related adverse event	11	(7.1)	16	(10.7)	2	(9.5)	1	(5.3)
discontinued due to a serious adverse event	13	(8.4)	11	(7.3)	2	(9.5)	1	(5.3)
discontinued due to a serious drug-related adverse event	10	(6.5)	7	(4.7)	2	(9.5)	1	(5.3)

[†] Determined by the investigator to be related to the drug.

[‡] Study medication withdrawn.

MedDRA preferred terms "Neoplasm Progression" and "Malignant Neoplasm Progression" not related to the drug are excluded.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 09MAY2016).

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2.7.6.2.5.4　　結論

PD-L1高発現の非小細胞肺癌の未治療患者に対し、MK-3475はペメトレキセド維持療法を含む標準化学療法と比較し、PFS 及び OS のいずれも有意な延長を示した。本治験でみられた MK-3475 の安全性プロファイルは、これまでに非小細胞肺癌や他のがん種を対象とした臨床試験で報告されたものと同様であり、標準化学療法と比べて良好であった。

以上より、PD-L1高発現の非小細胞肺癌の未治療患者において、MK-3475は良好なベネフィットリスクバランスを示した。

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2.7.6.2.6　固形がん、悪性黒色腫、及び非小細胞肺癌患者を対象とした第Ⅰ相試験、臨床薬理検討部分［海外試験］［評価資料］（KEYNOTE-001試験、以下001試験）

本項では、治験総括報告書第1版（データベースカットオフ日：[redacted]年[redacted]月[redacted]日）の臨床薬理の成績（薬物動態及びT細胞の免疫学的特性）の要約を示す。これらの成績は、本試験のパートA、A1、A2、B及びDより得られた。

2.7.6.2.6.1　試験方法の概要

治験責任医師／治験実施医療機関

多施設共同、23施設（米国、フランス、オーストラリア及びカナダ）

治験実施期間

[redacted]年[redacted]月[redacted]日～実施中（データベースカットオフ日：[redacted]年[redacted]月[redacted]日）

開発の相

第I相

治験デザイン

本試験は、局所進行性又は転移性の固形がん、悪性黒色腫、又は非小細胞肺癌患者を対象としたMK-3475静脈内投与の非盲検、第I相試験である。本試験のパートAでは、従来の3+3デザインを用いた用量漸増を行った。患者3～6例から構成されるコホートを漸増用量1、3又は10 mg/kgを2週間間隔（Q2W）で順次組み入れた。用量漸増パートの終了後、パートA1及びA2に患者を追加して組み入れ、MK-3475のPK及び薬力学の特性を検討した。パートB及びDでは転移性悪性黒色腫患者を組み入れ、MK-3475の安全性と抗腫瘍効果を評価した。また、パートBでは、転移性悪性黒色腫患者を対象に10 mg/kg Q2W、10 mg/kgを3週間間隔（Q3W）、及び2 mg/kg Q3Wの異なる3つの用法・用量を検討した。パートCでは非小細胞肺癌患者にMK-3475 10 mg/kgをQ3Wで投与し、安全性及び抗腫瘍効果を評価した。非小細胞肺癌の未治療患者を対象としたパートF1及び非小細胞肺癌で前治療歴がある患者を対象としたパートF2では、PD-L1発現陽性の患者にMK-3475 10 mg/kgをQ2W又はQ3Wで投与し、安全性及び抗腫瘍効果を検討した。

主要目的

1) 切除不能の進行性固形がん（非小細胞肺癌又は悪性黒色腫を含む）を有する成人患者を対象に、MK-3475単独療法の忍容性及び安全性プロファイルを評価する。
4) RECIST 1.1に基づき、悪性黒色腫及び非小細胞肺癌でのMK-3475の抗腫瘍効果を評価する。
5) イピリムマブ未治療患者にMK-3475を投与したときの腫瘍におけるバイオマーカー陽性度と腫瘍縮小効果との相関を評価し、イピリムマブ未治療の悪性黒色腫患者から得られた腫瘍検体を用いてPD-L1発現のカットポイントを検討する。

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6) RECIST 1.1を用い、イピリムマブ抵抗性の悪性黒色腫患者及びPD-L1発現腫瘍を有するイピリムマブ抵抗性の悪性黒色腫患者に対するMK-3475の抗腫瘍効果を評価する。

副次的目的

1) irRCを用いて、イピリムマブ抵抗性の悪性黒色腫患者及びイピリムマブ未治療の悪性黒色腫患者、PD-L1発現腫瘍を有するイピリムマブ抵抗性の悪性黒色腫患者及びイピリムマブ未治療の悪性黒色腫患者、並びに過去に全身療法を1レジメン以上受けたことがあるPD-L1高発現の非小細胞肺癌患者のORRを評価する。
7) MK-3475のPKプロファイルを検討する。
8) 末梢血における標的との結合及び標的の調節（PD-1受容体占有率及び受容体活性の調節）を評価する。
9) MK-3475を投与した悪性黒色腫患者の奏効期間、PFS、及びOSを評価する。

薬物動態を評価した患者数（パートA、A1及びA2）

表 2.7.6.2.6-1 薬物動態を評価した患者数（パートA、A1及びA2）

コホート	MK-3475投与群	患者数
パートA 固形がん	1 mg/kg Q2W	4
	3 mg/kg Q2W	3
	10 mg/kg Q2W	3
パートA1 固形がん	10 mg/kg Q2W	7
パートA2 固形がん	サイクル1において0.005 mg/kg、0.3 mg/kg、2.0 mg/kgの順で漸増投与。サイクル2以降2 mg/kg Q3W	4
	サイクル1において0.02 mg/kg、0.3 mg/kg、2.0 mg/kgの順に漸増投与。サイクル2以降2 mg/kg Q3W	3
	サイクル1において0.06 mg/kg、1.0 mg/kg、10 mg/kgの順に漸増投与。サイクル2以降10 mg/kg Q3W	6

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T 細胞の免疫学的特性を評価した患者数（パート B1、B2及び D）

表 2.7.6.2.6-2 T 細胞の免疫学的特性を評価した患者数（パート B1、B2 及び D）

コホート	MK-3475投与群	患者数[1]	患者数[2]
非無作為化			
パート B1 悪性黒色腫 イピリムマブ未治療	2 mg/kg Q3W	22	20
	10 mg/kg Q3W	24	19
	10 mg/kg Q2W	41	37
パート B1 悪性黒色腫 イピリムマブ既治療	10 mg/kg Q3W	32	29
	10 mg/kg Q2W	16	15
無作為化			
パート B2 悪性黒色腫 イピリムマブ抵抗性	2 mg/kg Q3W	89	84
	10 mg/kg Q3W	84	71
パート D 悪性黒色腫 イピリムマブ未治療	10 mg/kg Q3W	52	48
	2 mg/kg Q3W	51	44

[1]：MK-3475を投与した患者数
[2]：MK-3475を投与した患者のうち、T 細胞の免疫学的特性のデータが、ベースライン時に加え、投与後の少なくとも1時点で得られた患者数

試験の状況（データベースカットオフ日：[redacted]年[redacted]月[redacted]日）

最初の患者の初回来院日～最後の患者の最終来院日

パート A：[redacted]年[redacted]月[redacted]日～[redacted]年[redacted]月[redacted]日

A1：[redacted]年[redacted]月[redacted]日～[redacted]年[redacted]月[redacted]日

A2：[redacted]年[redacted]月[redacted]日～進行中

B1：[redacted]年[redacted]月[redacted]日～進行中

B2：[redacted]年[redacted]月[redacted]日～進行中

B3：[redacted]年[redacted]月[redacted]日～進行中

D：[redacted]年[redacted]月[redacted]日～進行中

2.7.6.2.6.2　　結果

薬物動態の要約

MK-3475の薬物動態プロファイルは、他のモノクローナル抗体薬と同様に、クリアランスは低く、分布容積は小さかった。MK-3475の曝露量は、1～10 mg/kg の用量範囲でおおむね用量比例的に増加した。

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T 細胞の免疫学的特性の要約

ヒト末梢血中の T 細胞数と、そのうちの活性化 T 細胞の割合を算出し、MK-3475の薬力学的作用を評価した。その結果、MK-3475は PD-1を阻害することにより、末梢血中において T 細胞の総数を変化させることなく T 細胞の活性化を誘導することが示された。

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