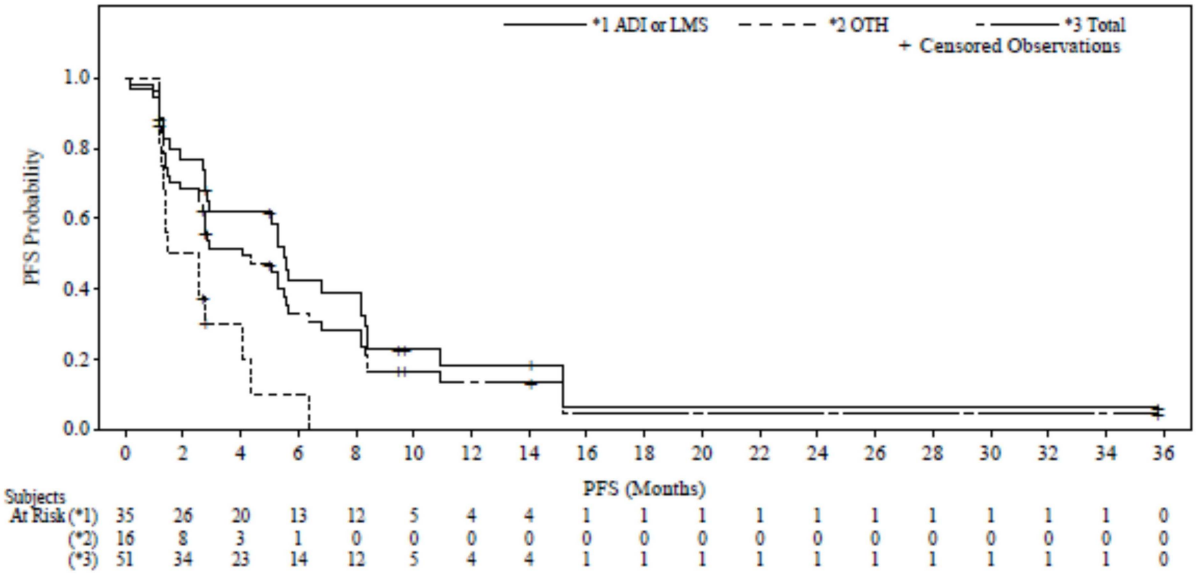


図 2.7.6.3-1　無増悪生存期間（PFS）の Kaplan-Meier プロット（FAS）（国内 217 試験）

ADI = adipocytic sarcoma, LMS = leiomyosarcoma, OTH = other types of eligible soft tissue sarcoma, PFS = progression-free survival.

（添付資料 5.3.5.2.2 の Figure 3 を引用）

2.7.6.3.6.3　全生存期間（OS）（副次評価項目）

OS の結果を表 2.7.6.3-10 に，OS の Kaplan-Meier プロットを図 2.7.6.3-2 に示した。

データカットオフ時の死亡例は 38 例（74.5%）であった。脂肪肉腫及び平滑筋肉腫，その他の悪性軟部腫瘍，合計における OS の中央値（95%信頼区間）はそれぞれ 16.95 ヵ月（11.01，20.47），7.64 ヵ月（3.84，16.13），13.17 ヵ月（9.49，18.33）であった。また，合計における 6，12，18，24 ヵ月の生存率はそれぞれ 78.4%，52.9%，37.3%，27.5%であった。

表 2.7.6.3-10　全生存期間（OS）の結果（FAS）（国内 217 試験）

	脂肪肉腫/ 平滑筋肉腫 35 例	その他の 悪性軟部腫瘍 16 例	合計 51 例
イベント（死亡）を発生した 被験者数，例数（%）	25 (71.4)	13 (81.3)	38 (74.5)
死亡，例数（%）	25 (71.4)	13 (81.3)	38 (74.5)
打ち切り例，例数（%）	10 (28.6)	3 (18.8)	13 (25.5)
データカットオフ前の打ち切り例 [a]， 例数（%）	1 (2.9)	0	1 (2.0)
データカットオフ時の打ち切り例， 例数（%）	9 (25.7)	3 (18.8)	12 (23.5)
OS（月）			
中央値（95%信頼区間）[b]	16.95 (11.01, 20.47)	7.64 (3.84, 16.13)	13.17 (9.49, 18.33)
第 1 四分位値（95%信頼区間）[b]	9.49 (3.38, 11.53)	3.88 (1.74, 7.29)	6.83 (3.38, 9.59)
第 3 四分位値（95%信頼区間）[b]	31.15 (19.38, NE)	16.76 (7.29, NE)	31.15 (17.38, NE)
イベント（死亡）／ 打ち切り時間の範囲	2.0, 35.8+	1.7, 33.5+	1.7, 35.8+
生存率			
6 ヵ月生存率（95%信頼区間）[b]	82.9 (65.8, 91.9)	68.8 (40.5, 85.6)	78.4 (64.4, 87.4)
12 ヵ月生存率（95%信頼区間）[b]	57.1 (39.3, 71.5)	43.8 (19.8, 65.6)	52.9 (38.5, 65.5)
18 ヵ月生存率（95%信頼区間）[b]	45.7 (28.9, 61.0)	18.8 (4.6, 40.2)	37.3 (24.3, 50.2)
24 ヵ月生存率（95%信頼区間）[b]	31.4 (17.1, 46.8)	18.8 (4.6, 40.2)	27.5 (16.1, 40.0)

NE ＝not estimable，OS＝overall survival.
a: データカットオフ前に打ち切りとなった被験者には追跡不能例又は同意撤回例を含む。
b: OS（95%信頼区間）は Kaplan-Meier 推定値及び Greenwood 式に基づき算出した。95%信頼区間の算出には log-log 変換による generalized Brookmeyer and Crowley 法を用いた。
+: 打ち切り例

（添付資料 5.3.5.2.2 の Table 26 を引用）

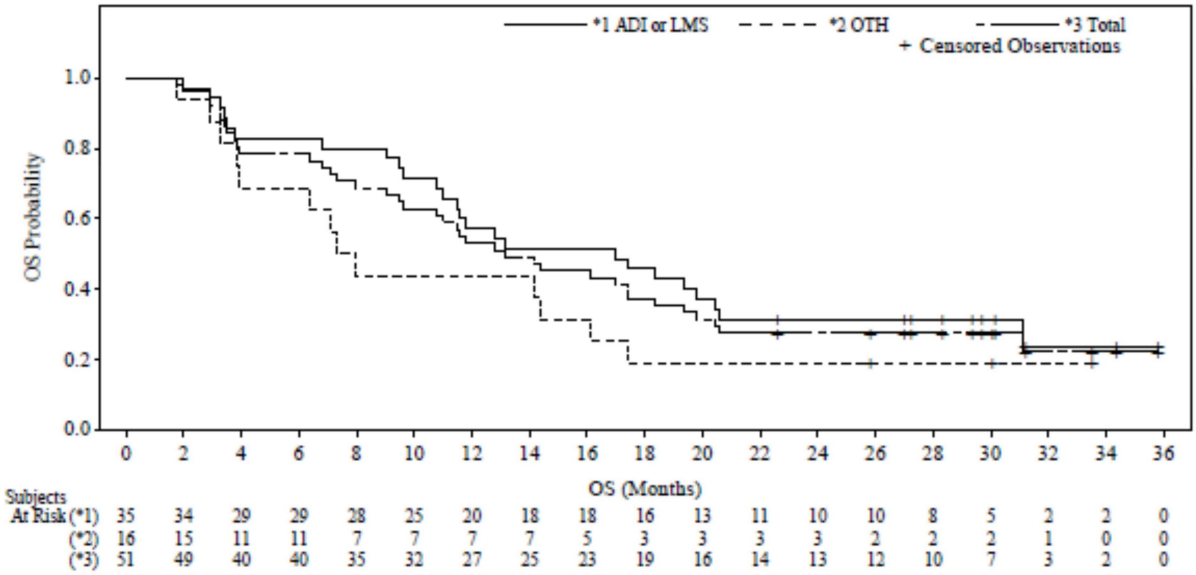


図 2.7.6.3-2　全生存期間（OS）の Kaplan-Meier プロット（FAS）（国内 217 試験）

ADI = adipocytic sarcoma, LMS = leiomyosarcoma, OS = overall survival, OTH = other types of eligible soft tissue sarcoma.

（添付資料 5.3.5.2.2 の Figure 4 を引用）

2.7.6.3.6.4　抗腫瘍効果（副次評価項目）

抗腫瘍効果の結果を表 2.7.6.3-11 に示した。また，標的病変の総計和のベースラインから最小値への変化率を図 2.7.6.3-3 に示した。

本治験では奏効例はみられなかったが，脂肪肉腫及び平滑筋肉腫，その他の悪性軟部腫瘍，合計における DCR はそれぞれ 80.0%（28/35 例），50.0%（8/16 例），70.6%（36/51 例）であった。また，脂肪肉腫及び平滑筋肉腫，その他の悪性軟部腫瘍，合計における CBR はそれぞれ 74.3%（26/35 例），50.0%（8/16 例），66.7%（34/51 例），dSDR はそれぞれ 74.3%（26/35 例），50.0%（8/16 例），66.7%（34/51 例）であった。

表 2.7.6.3-11　抗腫瘍効果（FAS）（国内 217 試験）

	脂肪肉腫/ 平滑筋肉腫 35 例	その他の 悪性軟部腫瘍 16 例	合計 51 例
最良総合効果，例数（%）			
CR	0	0	0
PR	0	0	0
SD	28 (80.0)	8 (50.0)	36 (70.6)
PD	7 (20.0)	8 (50.0)	15 (29.4)
NE	0	0	0
不明	0	0	0
ORR，例数（%）	0	0	0
95%信頼区間 [a]	0.0, 10.0	0.0, 20.6	0.0, 7.0
DCR，例数（%）	28 (80.0)	8 (50.0)	36 (70.6)
95%信頼区間 [a]	63.1, 91.6	24.7, 75.3	56.2, 82.5
CBR，例数（%）	26 (74.3)	8 (50.0)	34 (66.7)
95%信頼区間 [a]	56.7, 87.5	24.7, 75.3	52.1, 79.2
dSDR，例数（%）	26 (74.3)	8 (50.0)	34 (66.7)
95%信頼区間 [a]	56.7, 87.5	24.7, 75.3	52.1, 79.2

CBR = clinical benefit rate，CR = complete response，DCR = disease control rate，dSDR = durable stable disease rate，NE ＝not evaluable，ORR = objective response rate，PD = progressive disease，PR = partial response，SD = stable disease.
a: 2 項分布を用いた正確な 95%信頼区間

（添付資料 5.3.5.2.2 の Table 27 を引用）

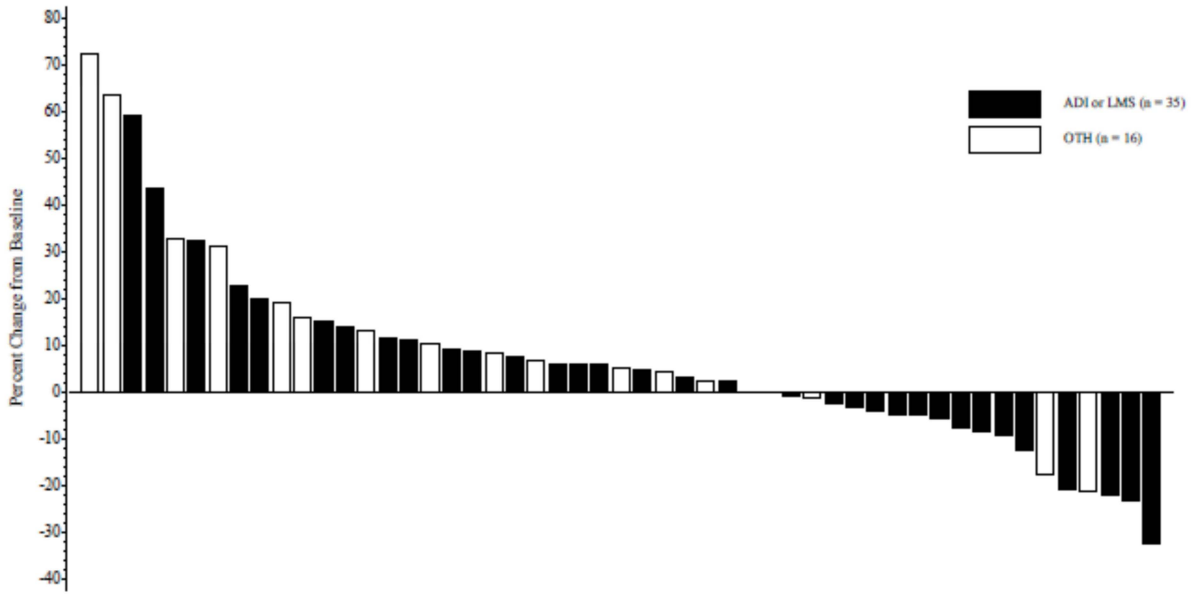


図 2.7.6.3-3　標的病変の総計和のベースラインから最小値への変化率（FAS）（国内 217 試験）

ADI = adipocytic sarcoma, LMS = leiomyosarcoma, OTH = other types of eligible soft tissue sarcoma.

（添付資料 5.3.5.2.2 の Figure 5 を引用）

2.7.6.3.7　安全性の結果

本治験における有害事象の概要を表 2.7.6.3-12 に示した。

有害事象は 100.0%（51/51 例）に認められ，治験薬との因果関係が否定できない有害事象（副作用）は 100.0%（51/51 例）に認められた。発現率が 10%以上（合計の全 Grade の発現率が 10%以上）の有害事象を表 2.7.6.3-13 に示した。

投与期間中又は追跡期間中（治験薬最終投与後 30 日まで）の死亡は 2.0%（1/51 例）に認められ，死亡に至った有害事象は心不全であった。当該有害事象は，治験薬との因果関係が否定された。

重篤な有害事象は，29.4%（15/51 例）に認められた。主な重篤な有害事象（合計で 2 例以上）は，癌疼痛（3 例［5.9%］），イレウス（2 例［3.9%］）であった。これらの有害事象は，治験薬との因果関係が否定された。

治験薬の投与中止に至った有害事象は，7.8%（4/51 例）に認められた。治験薬の投与中止に至った有害事象は，心不全，感染性胸水，肺炎，間質性肺疾患（各 1 例［2.0%］）であった。このうち，感染性胸水，間質性肺疾患は，治験薬との因果関係が否定されなかった。

表 2.7.6.3-12　有害事象の概要（安全性解析対象集団）（国内 217 試験）

	脂肪肉腫/ 平滑筋肉腫 35 例	その他の 悪性軟部腫瘍 16 例	合計 51 例
有害事象	35 (100.0)	16 (100.0)	51 (100.0)
副作用	35 (100.0)	16 (100.0)	51 (100.0)
CTCAE Grade 3 以上の有害事象	33 (94.3)	16 (100.0)	49 (96.1)
CTCAE Grade 3 以上の副作用	33 (94.3)	15 (93.8)	48 (94.1)
重篤な有害事象	10 (28.6)	5 (31.3)	15 (29.4)
死亡	1 (2.9)	0	1 (2.0)
重篤な副作用	5 (14.3)	0	5 (9.8)
死亡	0	0	0
治験薬の用量調整に至った有害事象			
治験薬の投与中止に至った有害事象	2 (5.7)	2 (12.5)	4 (7.8)
治験薬の投与減量に至った有害事象	12 (34.3)	4 (25.0)	16 (31.4)
治験薬の投与休薬に至った有害事象	0	0	0
治験薬の用量調整に至った副作用			
治験薬の投与中止に至った副作用	1 (2.9)	1 (6.3)	2 (3.9)
治験薬の投与減量に至った副作用	12 (34.3)	4 (25.0)	16 (31.4)
治験薬の投与休薬に至った副作用	0	0	0

数字は発現例数，（　）内は発現率（%）
副作用：治験薬との因果関係が否定できない有害事象

（添付資料 5.3.5.2.2 の Table 33 を引用）

2.7.6.3.7.1　主な有害事象及び副作用

主な有害事象（合計の全 Grade の発現率が 10%以上）の発現例数（発現率）を表 2.7.6.3-13 に示した。また，主な副作用（合計の全 Grade の発現率が 10%以上）の発現例数（発現率）を表 2.7.6.3-14 に示した。全ての有害事象及び副作用（全 Grade，Grade 3 以上）を付録 2.7.6-7 及び付録 2.7.6-8 に示した。

発現率が 30%以上の有害事象は，白血球減少症（100.0%，51/51 例），好中球減少症（98.0%，50/51 例），リンパ球減少症（78.4%，40/51 例），貧血（47.1%，24/51 例），癌疼痛（45.1%，23/51 例），悪心，発熱（各 41.2%，21/51 例），倦怠感（39.2%，20/51 例），便秘，末梢性ニューロパチー（各 31.4%，16/51 例）であった。

発現率が 30%以上の副作用は，白血球減少症（100.0%，51/51 例），好中球減少症（98.0%，50/51 例），リンパ球減少症（78.4%，40/51 例），貧血（47.1%，24/51 例），発熱（41.2%，21/51 例），倦怠感（39.2%，20/51 例），悪心（37.3%，19/51 例）であった。

Grade 3 以上の有害事象は 96.1%（49/51 例）に発現し，主な Grade 3 以上の有害事象は，好中球減少症（86.3%，44/51 例），白血球減少症（74.5%，38/51 例），リンパ球減少症（33.3%，17/51 例），貧血（13.7%，7/51 例），低リン酸血症（9.8%，5/51 例），発熱性好中球減少症（7.8%，4/51 例）であった。

Grade 3 以上の副作用は 94.1%（48/51 例）に発現し，主な Grade 3 以上の副作用は，好中球減少症（86.3%，44/51 例），白血球減少症（74.5%，38/51 例），リンパ球減少症（31.4%，16/51 例），貧血（11.8%，6/51 例），発熱性好中球減少症（7.8%，4/51 例）であった。

表 2.7.6.3-13　主な有害事象（安全性解析対象集団）（国内 217 試験）

有害事象名 ［MedDRA Version 17.1］ ＜SOC＞ PT	脂肪肉腫/平滑筋肉腫 35 例		その他の悪性軟部腫瘍 16 例		合計 51 例	
	全 Grade	Grade 3 以上	全 Grade	Grade 3 以上	全 Grade	Grade 3 以上
発現例数（発現率）	35 (100.0)	33 (94.3)	16 (100.0)	16 (100.0)	51 (100.0)	49 (96.1)
＜血液およびリンパ系障害＞	35 (100.0)	33 (94.3)	16 (100.0)	15 (93.8)	51 (100.0)	48 (94.1)
貧血	17 (48.6)	4 (11.4)	7 (43.8)	3 (18.8)	24 (47.1)	7 (13.7)
白血球減少症	35 (100.0)	25 (71.4)	16 (100.0)	13 (81.3)	51 (100.0)	38 (74.5)
リンパ球減少症	29 (82.9)	13 (37.1)	11 (68.8)	4 (25.0)	40 (78.4)	17 (33.3)
好中球減少症	35 (100.0)	30 (85.7)	15 (93.8)	14 (87.5)	50 (98.0)	44 (86.3)
＜胃腸障害＞	22 (62.9)	1 (2.9)	11 (68.8)	1 (6.3)	33 (64.7)	2 (3.9)
便秘	11 (31.4)	0	5 (31.3)	0	16 (31.4)	0
下痢	7 (20.0)	0	0	0	7 (13.7)	0
悪心	14 (40.0)	0	7 (43.8)	0	21 (41.2)	0
口内炎	9 (25.7)	0	4 (25.0)	0	13 (25.5)	0
＜一般・全身障害および投与部位の状態＞	25 (71.4)	2 (5.7)	16 (100.0)	0	41 (80.4)	2 (3.9)
疲労	5 (14.3)	0	4 (25.0)	0	9 (17.6)	0
倦怠感	12 (34.3)	0	8 (50.0)	0	20 (39.2)	0
発熱	15 (42.9)	1 (2.9)	6 (37.5)	0	21 (41.2)	1 (2.0)
＜感染症および寄生虫症＞	23 (65.7)	2 (5.7)	4 (25.0)	1 (6.3)	27 (52.9)	3 (5.9)
鼻咽頭炎	10 (28.6)	0	1 (6.3)	0	11 (21.6)	0
上気道感染	10 (28.6)	0	1 (6.3)	0	11 (21.6)	0

数字は発現例数，（ ）内は発現率（%）
本表では，合計の全 Grade の発現率が 10%以上の有害事象を示した。

（添付資料 5.3.5.2.2 の Table 35，Table 14.3.1.2.3.1 を引用）

表 2.7.6.3-13　主な有害事象（安全性解析対象集団）（国内 217 試験）（続き）

有害事象名 ［MedDRA Version 17.1］ ＜SOC＞ PT	脂肪肉腫/平滑筋肉腫 35 例		その他の悪性軟部腫瘍 16 例		合計 51 例	
	全 Grade	Grade 3 以上	全 Grade	Grade 3 以上	全 Grade	Grade 3 以上
発現例数（発現率）	35 (100.0)	33 (94.3)	16 (100.0)	16 (100.0)	51 (100.0)	49 (96.1)
＜臨床検査＞	23 (65.7)	3 (8.6)	10 (62.5)	2 (12.5)	33 (64.7)	5 (9.8)
アラニンアミノトランスフェラーゼ増加	10 (28.6)	2 (5.7)	4 (25.0)	1 (6.3)	14 (27.5)	3 (5.9)
アスパラギン酸アミノトランスフェラーゼ増加	10 (28.6)	2 (5.7)	3 (18.8)	0	13 (25.5)	2 (3.9)
血中クレアチンホスホキナーゼ増加	6 (17.1)	0	2 (12.5)	0	8 (15.7)	0
血中乳酸脱水素酵素増加	6 (17.1)	0	5 (31.3)	0	11 (21.6)	0
C-反応性蛋白増加	4 (11.4)	0	2 (12.5)	0	6 (11.8)	0
＜代謝および栄養障害＞	19 (54.3)	5 (14.3)	11 (68.8)	5 (31.3)	30 (58.8)	10 (19.6)
食欲減退	7 (20.0)	0	5 (31.3)	0	12 (23.5)	0
低アルブミン血症	6 (17.1)	1 (2.9)	4 (25.0)	1 (6.3)	10 (19.6)	2 (3.9)
低カリウム血症	3 (8.6)	1 (2.9)	3 (18.8)	2 (12.5)	6 (11.8)	3 (5.9)
低リン酸血症	3 (8.6)	2 (5.7)	5 (31.3)	3 (18.8)	8 (15.7)	5 (9.8)
＜筋骨格系および結合組織障害＞	12 (34.3)	1 (2.9)	4 (25.0)	0	16 (31.4)	1 (2.0)
背部痛	5 (14.3)	0	2 (12.5)	0	7 (13.7)	0
＜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）＞	14 (40.0)	1 (2.9)	11 (68.8)	4 (25.0)	25 (49.0)	5 (9.8)
癌疼痛	13 (37.1)	0	10 (62.5)	3 (18.8)	23 (45.1)	3 (5.9)
＜神経系障害＞	21 (60.0)	0	8 (50.0)	0	29 (56.9)	0
味覚異常	10 (28.6)	0	2 (12.5)	0	12 (23.5)	0
頭痛	4 (11.4)	0	2 (12.5)	0	6 (11.8)	0
末梢性ニューロパチー	14 (40.0)	0	2 (12.5)	0	16 (31.4)	0

数字は発現例数，（　）内は発現率（%）
本表では，合計の全 Grade の発現率が 10%以上の有害事象を示した。

（添付資料 5.3.5.2.2 の Table 35，Table 14.3.1.2.3.1 を引用）

表 2.7.6.3-13　主な有害事象（安全性解析対象集団）（国内 217 試験）（続き）

有害事象名 ［MedDRA Version 17.1］ ＜SOC＞ PT	脂肪肉腫/平滑筋肉腫 35 例		その他の悪性軟部腫瘍 16 例		合計 51 例	
	全 Grade	Grade 3 以上	全 Grade	Grade 3 以上	全 Grade	Grade 3 以上
発現例数（発現率）	35 (100.0)	33 (94.3)	16 (100.0)	16 (100.0)	51 (100.0)	49 (96.1)
＜呼吸器，胸郭および縦隔障害＞	14 (40.0)	2 (5.7)	8 (50.0)	0	22 (43.1)	2 (3.9)
咳嗽	4 (11.4)	0	2 (12.5)	0	6 (11.8)	0
＜皮膚および皮下組織障害＞	19 (54.3)	0	5 (31.3)	0	24 (47.1)	0
脱毛症	11 (31.4)	0	3 (18.8)	0	14 (27.5)	0
発疹	4 (11.4)	0	2 (12.5)	0	6 (11.8)	0

数字は発現例数，（　）内は発現率（%）
本表では，合計の全 Grade の発現率が 10%以上の有害事象を示した。

（添付資料 5.3.5.2.2 の Table 35，Table 14.3.1.2.3.1 を引用）

表 2.7.6.3-14　主な副作用（安全性解析対象集団）（国内 217 試験）

有害事象名 ［MedDRA Version 17.1］ ＜SOC＞ PT	脂肪肉腫/平滑筋肉腫 35 例		その他の悪性軟部腫瘍 16 例		合計 51 例	
	全 Grade	Grade 3 以上	全 Grade	Grade 3 以上	全 Grade	Grade 3 以上
発現例数（発現率）	35 (100.0)	33 (94.3)	16 (100.0)	15 (93.8)	51 (100.0)	48 (94.1)
＜血液およびリンパ系障害＞	35 (100.0)	33 (94.3)	16 (100.0)	15 (93.8)	51 (100.0)	48 (94.1)
貧血	17 (48.6)	3 (8.6)	7 (43.8)	3 (18.8)	24 (47.1)	6 (11.8)
白血球減少症	35 (100.0)	25 (71.4)	16 (100.0)	13 (81.3)	51 (100.0)	38 (74.5)
リンパ球減少症	29 (82.9)	12 (34.3)	11 (68.8)	4 (25.0)	40 (78.4)	16 (31.4)
好中球減少症	35 (100.0)	30 (85.7)	15 (93.8)	14 (87.5)	50 (98.0)	44 (86.3)
＜胃腸障害＞	19 (54.3)	0	10 (62.5)	0	29 (56.9)	0
便秘	6 (17.1)	0	2 (12.5)	0	8 (15.7)	0
悪心	13 (37.1)	0	6 (37.5)	0	19 (37.3)	0
口内炎	9 (25.7)	0	4 (25.0)	0	13 (25.5)	0
＜一般・全身障害および投与部位の状態＞	24 (68.6)	2 (5.7)	16 (100.0)	0	40 (78.4)	2 (3.9)
疲労	5 (14.3)	0	4 (25.0)	0	9 (17.6)	0
倦怠感	12 (34.3)	0	8 (50.0)	0	20 (39.2)	0
発熱	15 (42.9)	1 (2.9)	6 (37.5)	0	21 (41.2)	1 (2.0)
＜感染症および寄生虫症＞	14 (40.0)	2 (5.7)	3 (18.8)	0	17 (33.3)	2 (3.9)
鼻咽頭炎	6 (17.1)	0	0	0	6 (11.8)	0
上気道感染	6 (17.1)	0	0	0	6 (11.8)	0

数字は発現例数，（　）内は発現率（%）
副作用：治験薬との因果関係が否定できない有害事象
本表では，合計の全 Grade の発現率が 10%以上の副作用を示した。

（添付資料 5.3.5.2.2 の Table 14.3.1.2.3.2，Table 14.3.1.2.7.2 を引用）

表 2.7.6.3-14　主な副作用（安全性解析対象集団）（国内 217 試験）（続き）

有害事象名 ［MedDRA Version 17.1］ ＜SOC＞ PT	脂肪肉腫/平滑筋肉腫 35 例		その他の悪性軟部腫瘍 16 例		合計 51 例	
	全 Grade	Grade 3 以上	全 Grade	Grade 3 以上	全 Grade	Grade 3 以上
発現例数（発現率）	35 (100.0)	33 (94.3)	16 (100.0)	15 (93.8)	51 (100.0)	48 (94.1)
＜臨床検査＞	20 (57.1)	3 (8.6)	7 (43.8)	1 (6.3)	27 (52.9)	4 (7.8)
アラニンアミノトランスフェラーゼ増加	8 (22.9)	2 (5.7)	4 (25.0)	1 (6.3)	12 (23.5)	3 (5.9)
アスパラギン酸アミノトランスフェラーゼ増加	9 (25.7)	2 (5.7)	3 (18.8)	0	12 (23.5)	2 (3.9)
血中クレアチンホスホキナーゼ増加	5 (14.3)	0	2 (12.5)	0	7 (13.7)	0
血中乳酸脱水素酵素増加	4 (11.4)	0	4 (25.0)	0	8 (15.7)	0
＜代謝および栄養障害＞	13 (37.1)	2 (5.7)	10 (62.5)	4 (25.0)	23 (45.1)	6 (11.8)
食欲減退	6 (17.1)	0	5 (31.3)	0	11 (21.6)	0
低アルブミン血症	3 (8.6)	1 (2.9)	3 (18.8)	1 (6.3)	6 (11.8)	2 (3.9)
低リン酸血症	2 (5.7)	1 (2.9)	4 (25.0)	2 (12.5)	6 (11.8)	3 (5.9)
＜神経系障害＞	21 (60.0)	0	6 (37.5)	0	27 (52.9)	0
味覚異常	10 (28.6)	0	2 (12.5)	0	12 (23.5)	0
頭痛	4 (11.4)	0	2 (12.5)	0	6 (11.8)	0
末梢性ニューロパチー	13 (37.1)	0	2 (12.5)	0	15 (29.4)	0
＜皮膚および皮下組織障害＞	18 (51.4)	0	5 (31.3)	0	23 (45.1)	0
脱毛症	11 (31.4)	0	3 (18.8)	0	14 (27.5)	0

数字は発現例数，（　）内は発現率（%）
副作用：治験薬との因果関係が否定できない有害事象
本表では，合計の全 Grade の発現率が 10%以上の副作用を示した。

（添付資料 5.3.5.2.2 の Table 14.3.1.2.3.2，Table 14.3.1.2.7.2 を引用）

2.7.6.3.7.2 死亡及び重篤な有害事象

投与期間中又は治験薬最終投与後 30 日までの有害事象による死亡例は 1 例であり，Grade 2 の心不全が第 67 日目（63 日間の投与後）にみられ，第 71 日目に Grade 3 に悪化した後，第 106 日目に死亡した。当該被験者（42 歳，女性）は，前治療においてアドリアマイシンを使用しており，治験担当医師はアドリアマイシンが原因による心不全と判断し，治験薬との因果関係は否定された。

死亡を含む全ての重篤な有害事象及び副作用の発現例数（発現率）を表 2.7.6.3-15 に示した。死亡を含む全ての重篤な有害事象一覧を表 2.7.6.3-16 に示した。また，これらの重篤な有害事象の詳細な経過を付録 2.7.6-9 に示した。

重篤な有害事象は 29.4%（15/51 例）に，重篤な副作用は 9.8%（5/51 例）に発現した。主な重篤な有害事象（合計で 2 例以上）は，癌疼痛（5.9%，3/51 例），イレウス（3.9%，2/51 例）であった。

表 2.7.6.3-15　重篤な有害事象（安全性解析対象集団）（国内 217 試験）

有害事象名 ［MedDRA Version 17.1］ ＜SOC＞ PT	脂肪肉腫/平滑筋肉腫 35 例		その他の悪性軟部腫瘍 16 例		合計 51 例	
	有害事象	副作用	有害事象	副作用	有害事象	副作用
発現例数（発現率）	10 (28.6)	5 (14.3)	5 (31.3)	0	15 (29.4)	5 (9.8)
＜血液およびリンパ系障害＞	1 (2.9)	1 (2.9)	0	0	1 (2.0)	1 (2.0)
発熱性好中球減少症	1 (2.9)	1 (2.9)	0	0	1 (2.0)	1 (2.0)
＜心臓障害＞	1 (2.9)	0	0	0	1 (2.0)	0
心不全	1 (2.9)	0	0	0	1 (2.0)	0
＜眼障害＞	1 (2.9)	0	0	0	1 (2.0)	0
白内障	1 (2.9)	0	0	0	1 (2.0)	0
＜胃腸障害＞	1 (2.9)	0	1 (6.3)	0	2 (3.9)	0
イレウス	1 (2.9)	0	1 (6.3)	0	2 (3.9)	0
＜肝胆道系障害＞	1 (2.9)	1 (2.9)	0	0	1 (2.0)	1 (2.0)
肝出血	1 (2.9)	1 (2.9)	0	0	1 (2.0)	1 (2.0)
＜感染症および寄生虫症＞	2 (5.7)	2 (5.7)	1 (6.3)	0	3 (5.9)	2 (3.9)
感染性胸水	1 (2.9)	1 (2.9)	0	0	1 (2.0)	1 (2.0)
肺炎	0	0	1 (6.3)	0	1 (2.0)	0
レンサ球菌感染	1 (2.9)	1 (2.9)	0	0	1 (2.0)	1 (2.0)
＜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）＞	2 (5.7)	1 (2.9)	3 (18.8)	0	5 (9.8)	1 (2.0)
癌疼痛	1 (2.9)	0	2 (12.5)	0	3 (5.9)	0
腫瘍性塞栓症	0	0	1 (6.3)	0	1 (2.0)	0
腫瘍出血	1 (2.9)	1 (2.9)	0	0	1 (2.0)	1 (2.0)

数字は発現例数，（　）内は発現率（%）
副作用：治験薬との因果関係が否定できない有害事象

（添付資料 5.3.5.2.2 の Table 40，Table 14.3.1.2.5.2 を引用）

表 2.7.6.3-15　重篤な有害事象（安全性解析対象集団）（国内 217 試験）（続き）

有害事象名 ［MedDRA Version 17.1］ ＜SOC＞ PT	脂肪肉腫/平滑筋肉腫 35 例		その他の悪性軟部腫瘍 16 例		合計 51 例	
	有害事象	副作用	有害事象	副作用	有害事象	副作用
発現例数（発現率）	10 (28.6)	5 (14.3)	5 (31.3)	0	15 (29.4)	5 (9.8)
＜腎および尿路障害＞	1 (2.9)	0	0	0	1 (2.0)	0
水腎症	1 (2.9)	0	0	0	1 (2.0)	0
＜呼吸器，胸郭および縦隔障害＞	2 (5.7)	1 (2.9)	0	0	2 (3.9)	1 (2.0)
呼吸困難	1 (2.9)	0	0	0	1 (2.0)	0
肺塞栓症	1 (2.9)	1 (2.9)	0	0	1 (2.0)	1 (2.0)

数字は発現例数，（　）内は発現率（%）
副作用：治験薬との因果関係が否定できない有害事象

（添付資料 5.3.5.2.2 の Table 40，Table 14.3.1.2.5.2 を引用）

表 2.7.6.3-16　重篤な有害事象一覧（安全性解析対象集団）（国内 217 試験）

被験者識別コード	年齢[a] 性別 人種	発現日[b]（発現時用量）	有害事象 MedDRA (PT) Version 17.1	CTCAE Grade	転帰 持続期間	治験薬の処置	治験薬との因果関係
脂肪肉腫							
20022009	3[redacted]歳 女性 Japanese	50 日目 (1.4 mg/m^2)	レンサ球菌感染	1	–	投与減量	おそらく関連あり
		84 日目		2	–	投与減量	おそらく関連あり
		88 日目		3	回復 32 日間	投与減量	おそらく関連あり
20032001	6[redacted]歳 男性 Japanese	85 日目 (1.1 mg/m^2)	イレウス	3	回復 23 日間	用量変更なし	関連なし
		114 日目 (0.7 mg/m^2)	イレウス	2	回復 18 日間	用量変更なし	関連なし
		143 日目 (0.7 mg/m^2)	発熱性好中球減少症	3	回復 11 日間	用量変更なし	おそらく関連あり
20082005	6[redacted]歳 男性 Japanese	44 日目 (1.4 mg/m^2)	感染性胸水	3	回復 29 日間	投与中止	おそらく関連あり
20122002	4[redacted]歳 男性 Japanese	293 日目 (1.4 mg/m^2)	水腎症	3	未回復 該当せず	該当せず	関連なし
20122004	6[redacted]歳 女性 Japanese	116 日目 (1.1 mg/m^2)	白内障	1	–	用量変更なし	関連なし
		176 日目		2	–	用量変更なし	関連なし
		206 日目		3	軽快 該当せず	用量変更なし	関連なし
平滑筋肉腫							
20032002	4[redacted]歳 女性 Japanese	67 日目 (1.4 mg/m^2)	心不全	2	–	投与中止	関連なし
		71 日目		3	死亡 36 日間	投与中止	関連なし
20042001	3[redacted]歳 男性 Japanese	46 日目 (1.4 mg/m^2)	肺塞栓症	4	軽快 該当せず	用量変更なし	おそらく関連あり
20082001	5[redacted]歳 女性 Japanese	111 日目 (1.4 mg/m^2)	肝出血	3	回復 24 日間	投与減量	おそらく関連あり
		269 日目 (1.1 mg/m^2)	腫瘍出血	3	回復 20 日間	用量変更なし	おそらく関連あり

a: 同意取得時の年齢
b: 発現日は投与開始日を 1 日目として起算

（添付資料 5.3.5.2.2 の Table 39 を引用）

表 2.7.6.3-16　重篤な有害事象一覧（安全性解析対象集団）（国内 217 試験）（続き）

被験者識別コード	年齢[a] 性別 人種	発現日[b]（発現時用量）	有害事象 MedDRA (PT) Version 17.1	CTCAE Grade	転帰 持続期間	治験薬の処置	治験薬との因果関係
平滑筋肉腫（続き）							
20092003	3[redacted]歳 男性 Japanese	7 日目 (1.4 mg/m^2)	癌疼痛	2	軽快 該当せず	用量変更なし	関連なし
20132005	4[redacted]歳 男性 Japanese	16 日目 (1.4 mg/m^2)	呼吸困難	2	–	用量変更なし	関連なし
		30 日目		3	未回復 該当せず	用量変更なし	関連なし
その他の悪性軟部腫瘍							
20012001	5[redacted]歳 女性 Japanese	106 日目 (0.7 mg/m^2)	肺炎	2	–	投与中止	関連なし
		111 日目		3	軽快 該当せず	投与中止	関連なし
20042004	7[redacted]歳 男性 Japanese	22 日目 (1.4 mg/m^2)	癌疼痛	1	–	用量変更なし	関連なし
		29 日目		2	–	用量変更なし	関連なし
		37 日目		3	軽快 該当せず	用量変更なし	関連なし
20062005	4[redacted]歳 女性 Japanese	124 日目 (1.4 mg/m^2)	腫瘍性塞栓症	3	未回復 該当せず	用量変更なし	関連なし
20082002	3[redacted]歳 男性 Japanese	40 日目 (1.4 mg/m^2)	イレウス	3	未回復 該当せず	用量変更なし	関連なし
20082003	3[redacted]歳 男性 Japanese	84 日目 (1.4 mg/m^2)	癌疼痛	1	–	用量変更なし	関連なし
		95 日目		2	軽快 該当せず	用量変更なし	関連なし

a: 同意取得時の年齢
b: 発現日は投与開始日を 1 日目として起算

（添付資料 5.3.5.2.2 の Table 39 を引用）

2.7.6.3.7.3　治験薬の投与中止に至った有害事象

治験薬の投与中止に至った有害事象一覧を表 2.7.6.3-17 に示した。

治験薬の投与中止に至った有害事象は 7.8%（4/51 例）に発現し，その内訳は，心不全，感染性胸水，肺炎，間質性肺疾患（各 2.0%，1/51 例）であった。

表 2.7.6.3-17　治験薬の投与中止に至った有害事象一覧（安全性解析対象集団）（国内 217 試験）

被験者識別コード	年齢[a] 性別 人種	発現日[b]（発現時用量）	有害事象 MedDRA (PT) Version 17.1	CTCAE Grade	重篤性	転帰 持続期間	治験薬との因果関係
脂肪肉腫							
20082005	6[redacted]歳 男性 Japanese	44 日目 (1.4 mg/m^2)	感染性胸水	3	重篤	回復 29 日間	おそらく関連あり
平滑筋肉腫							
20032002	4[redacted]歳 女性 Japanese	67 日目 (1.4 mg/m^2)	心不全	2	重篤	–	関連なし
		71 日目		3		死亡 36 日間	関連なし
その他の悪性軟部腫瘍							
20012001	5[redacted]歳 女性 Japanese	106 日目 (0.7 mg/m^2)	肺炎	2	重篤	–	関連なし
		111 日目		3		軽快 該当せず	関連なし
20062004	5[redacted]歳 女性 Japanese	48 日目 (1.1 mg/m^2)	間質性肺疾患	1	非重篤	未回復 該当せず	おそらく関連あり

a: 同意取得時の年齢
b: 発現日は投与開始日を 1 日目として起算

（添付資料 5.3.5.2.2 の Table 41 を引用）

2.7.6.3.7.4 臨床検査値

治験薬投与開始後の全ての臨床検査において，各臨床検査別に臨床上問題となる顕著な臨床検査値異常（TEMAV）を示した被験者数及び発現率を算出した。血液学的検査項目では，好中球（低値；86.3%［44/51 例］），白血球数（低値；74.5%［38/51 例］），リンパ球数（低値；33.3%［17/51 例］）及びヘモグロビン（低値；15.7%［8/51 例］）に TEMAV が認められた。血液生化学検査では，アラニンアミノトランスフェラーゼ（高値；7.8%［4/51 例］），リン酸塩（低値；7.8%［4/51 例］），カリウム（低値；5.9%［3/51 例］）及びグルコース（高値；5.9%［3/51 例］）に TEMAV が認められた。

治験期間を通して，好中球数が Grade 3 及び Grade 4（最低値）となった被験者は 5 例（9.8%）及び 39 例（76.5%）であった。

第 1 サイクルで好中球数が Grade 3 又は Grade 4 の最低値となるまでの期間及び回復するまでの期間を Kaplan-Meier により推定した。ただし，最低値となるまでの期間は好中球数の最低値に到達する最も短い期間とし，Grade 3 又は Grade 4 の発現がない被験者は打ち切りとした。全体で 41 例（80.4%）が Grade 3 又は Grade 4 の最低値に到達し，最低値を発現するまでの期間の中央値は 15.0 日であった。全例の 41 例が最低値から Grade 2 以下の値に回復し，回復するまでの期間の中央値は 8.0 日（最大値 15 日）であった。

2.7.6.3.7.5 バイタルサイン，心電図

全体で 2 例にバイタルサインの臨床的に重要な異常が認められた。バイタルサインに関連する有害事象のうち，1 例は Grade 2 の心不全が第 67 日目（63 日間の投与後）にみられ，第 71 日目に Grade 3 に悪化した後，第 106 日目に死亡した。その他，Grade 3 の発熱，体重増加，呼吸困難が各 1 例にみられ，Grade 4 となった被験者はみられなかった。

本薬群では，血圧の臨床的に重要な異常は認められなかった。投与前からの QTcF の変化量が 60 msec を超えた被験者が 3 例（5.9%），投与後の QTcF が 500 msec を超えた被験者が 2 例（3.9%）であった。

2.7.6.3.8 結論

主要評価項目である PFR_{12wks} において，脂肪肉腫及び平滑筋肉腫，その他の悪性軟部腫瘍，合計における PFR_{12wks} はそれぞれ 60.0%，31.3%，51.0%であった。脂肪肉腫及び平滑筋肉腫，その他の悪性軟部腫瘍，合計における PFS の中央値はそれぞれ 5.52 ヵ月，2.01 ヵ月，4.07 ヵ月であった。また，脂肪肉腫及び平滑筋肉腫，その他の悪性軟部腫瘍，合計における OS の中央値はそれぞれ 16.95 ヵ月，7.64 ヵ月，13.17 ヵ月であった。以上の結果から，進行又は再発悪性軟部腫瘍の患者におけるエリブリンの有効性が示された。

主な有害事象は血液学的事象であった。主な Grade 3 以上の有害事象は，好中球減少症（86.3%），白血球減少症（74.5%），リンパ球減少症（33.3%），貧血（13.7%），低リン酸血症（9.8%）及び発熱性好中球減少症（7.8%）であった。これらの事象はこれまでに報告されている本薬の安全性プロファイルと一致していた。エリブリンは進行又は再発悪性軟部腫瘍の患者に対しても，忍容性のプロファイルは許容される範囲であり，臨床管理可能であった。

2.7.6.4 付録

付録 2.7.6-1　SOC/PT/Grade（全 Grade，Grade 3 以上）別の有害事象発現率（外国 309 試験）
付録 2.7.6-2　SOC/PT/Grade（全 Grade，Grade 3 以上）別の副作用発現率（外国 309 試験）
付録 2.7.6-3　死亡又は重篤な有害事象の被験者ごとの叙述（外国 309 試験）
付録 2.7.6-4　SOC/PT/Grade（全 Grade，Grade 3 以上）別の有害事象発現率（外国 207 試験）
付録 2.7.6-5　SOC/PT/Grade（全 Grade，Grade 3 以上）別の副作用発現率（外国 207 試験）
付録 2.7.6-6　死亡又は重篤な有害事象の被験者ごとの叙述（外国 207 試験）
付録 2.7.6-7　SOC/PT/Grade（全 Grade，Grade 3 以上）別の有害事象発現率（国内 217 試験）
付録 2.7.6-8　SOC/PT/Grade（全 Grade，Grade 3 以上）別の副作用発現率（国内 217 試験）
付録 2.7.6-9　死亡又は重篤な有害事象の被験者ごとの叙述（国内 217 試験）

付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
Any TEAEs	224 (99.1)	152 (67.3)	218 (97.3)	126 (56.3)	442 (98.2)	278 (61.8)
血液およびリンパ系障害	137 (60.6)	97 (42.9)	124 (55.4)	72 (32.1)	261 (58.0)	169 (37.6)
貧血	67 (29.6)	16 (7.1)	69 (30.8)	27 (12.1)	136 (30.2)	43 (9.6)
発熱性好中球減少症	2 (0.9)	2 (0.9)	3 (1.3)	2 (0.9)	5 (1.1)	4 (0.9)
ヘモグロビン血症	3 (1.3)	2 (0.9)	1 (0.4)	0	4 (0.9)	2 (0.4)
内出血発生の増加傾向	0	0	1 (0.4)	0	1 (0.2)	0
白血球増加症	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
白血球減少症	36 (15.9)	23 (10.2)	23 (10.3)	10 (4.5)	59 (13.1)	33 (7.3)
リンパ節痛	1 (0.4)	0	0	0	1 (0.2)	0
リンパ節症	1 (0.4)	0	0	0	1 (0.2)	0
リンパ球減少症	3 (1.3)	3 (1.3)	6 (2.7)	3 (1.3)	9 (2.0)	6 (1.3)
好中球減少症	99 (43.8)	80 (35.4)	53 (23.7)	35 (15.6)	152 (33.8)	115 (25.6)
汎血球減少症	0	0	4 (1.8)	3 (1.3)	4 (0.9)	3 (0.7)
血小板減少症	13 (5.8)	1 (0.4)	62 (27.7)	34 (15.2)	75 (16.7)	35 (7.8)
血小板増加症	1 (0.4)	0	0	0	1 (0.2)	0

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付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226)		Dacarbazine (N=224)		Total (N=450)	
	All Grades n(%)	Grade >= 3 n(%)	All Grades n(%)	Grade >= 3 n(%)	All Grades n(%)	Grade >= 3 n(%)
心臓障害	14 (6.2)	1 (0.4)	20 (8.9)	3 (1.3)	34 (7.6)	4 (0.9)
心房細動	2 (0.9)	0	2 (0.9)	1 (0.4)	4 (0.9)	1 (0.2)
心房粗動	1 (0.4)	0	0	0	1 (0.2)	0
徐脈	1 (0.4)	0	0	0	1 (0.2)	0
右脚ブロック	1 (0.4)	0	0	0	1 (0.2)	0
心停止	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
うっ血性心不全	0	0	1 (0.4)	0	1 (0.2)	0
期外収縮	0	0	1 (0.4)	0	1 (0.2)	0
動悸	2 (0.9)	0	0	0	2 (0.4)	0
心嚢液貯留	1 (0.4)	1 (0.4)	1 (0.4)	0	2 (0.4)	1 (0.2)
洞性頻脈	3 (1.3)	0	7 (3.1)	0	10 (2.2)	0
上室性頻脈	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
頻脈	5 (2.2)	0	7 (3.1)	1 (0.4)	12 (2.7)	1 (0.2)
耳および迷路障害	9 (4.0)	0	5 (2.2)	0	14 (3.1)	0
難聴	1 (0.4)	0	0	0	1 (0.2)	0
耳閉	0	0	1 (0.4)	0	1 (0.2)	0

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付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
耳および迷路障害 (contd)						
耳痛	3 (1.3)	0	1 (0.4)	0	4 (0.9)	0
耳鳴	4 (1.8)	0	0	0	4 (0.9)	0
回転性めまい	1 (0.4)	0	2 (0.9)	0	3 (0.7)	0
前庭障害	0	0	1 (0.4)	0	1 (0.2)	0
内分泌障害	1 (0.4)	0	0	0	1 (0.2)	0
甲状腺機能低下症	1 (0.4)	0	0	0	1 (0.2)	0
眼障害	28 (12.4)	0	13 (5.8)	0	41 (9.1)	0
眼精疲労	0	0	1 (0.4)	0	1 (0.2)	0
眼瞼炎	2 (0.9)	0	0	0	2 (0.4)	0
失明	2 (0.9)	0	0	0	2 (0.4)	0
白内障	2 (0.9)	0	0	0	2 (0.4)	0
眼乾燥	3 (1.3)	0	0	0	3 (0.7)	0
眼刺激	3 (1.3)	0	0	0	3 (0.7)	0
眼痛	1 (0.4)	0	0	0	1 (0.2)	0

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付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
眼障害 (contd)						
眼そう痒症	1 (0.4)	0	0	0	1 (0.2)	0
緑内障	0	0	1 (0.4)	0	1 (0.2)	0
流涙増加	18 (8.0)	0	1 (0.4)	0	19 (4.2)	0
黄斑線維症	0	0	1 (0.4)	0	1 (0.2)	0
眼充血	3 (1.3)	0	0	0	3 (0.7)	0
黄疸眼	1 (0.4)	0	0	0	1 (0.2)	0
霧視	4 (1.8)	0	8 (3.6)	0	12 (2.7)	0
視力障害	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
硝子体浮遊物	1 (0.4)	0	0	0	1 (0.2)	0
胃腸障害	178 (78.8)	18 (8.0)	162 (72.3)	21 (9.4)	340 (75.6)	39 (8.7)
腹部不快感	5 (2.2)	0	4 (1.8)	0	9 (2.0)	0
腹部膨満	16 (7.1)	0	12 (5.4)	0	28 (6.2)	0
腹痛	45 (19.9)	4 (1.8)	33 (14.7)	8 (3.6)	78 (17.3)	12 (2.7)
下腹部痛	0	0	3 (1.3)	0	3 (0.7)	0
上腹部痛	19 (8.4)	0	13 (5.8)	1 (0.4)	32 (7.1)	1 (0.2)

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付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

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胃腸障害 (contd)						
異常便	1 (0.4)	0	0	0	1 (0.2)	0
後天性巨舌症	1 (0.4)	0	0	0	1 (0.2)	0
肛門出血	1 (0.4)	0	0	0	1 (0.2)	0
肛門の炎症	0	0	1 (0.4)	0	1 (0.2)	0
アフタ性口内炎	3 (1.3)	0	0	0	3 (0.7)	0
便秘	71 (31.4)	2 (0.9)	58 (25.9)	1 (0.4)	129 (28.7)	3 (0.7)
下痢	38 (16.8)	1 (0.4)	36 (16.1)	2 (0.9)	74 (16.4)	3 (0.7)
憩室	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
口内乾燥	12 (5.3)	0	4 (1.8)	0	16 (3.6)	0
十二指腸瘻	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
消化不良	18 (8.0)	1 (0.4)	7 (3.1)	1 (0.4)	25 (5.6)	2 (0.4)
嚥下障害	3 (1.3)	0	0	0	3 (0.7)	0
心窩部不快感	1 (0.4)	0	0	0	1 (0.2)	0
便失禁	1 (0.4)	0	0	0	1 (0.2)	0
軟便	1 (0.4)	0	0	0	1 (0.2)	0
放屁	1 (0.4)	0	2 (0.9)	0	3 (0.7)	0

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付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
胃腸障害 (contd)						
食中毒	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
排便回数増加	0	0	1 (0.4)	0	1 (0.2)	0
機能性胃腸障害	1 (0.4)	0	0	0	1 (0.2)	0
胃腸管瘻	1 (0.4)	0	0	0	1 (0.2)	0
胃腸出血	1 (0.4)	0	1 (0.4)	1 (0.4)	2 (0.4)	1 (0.2)
消化器痛	1 (0.4)	0	0	0	1 (0.2)	0
胃腸音異常	0	0	1 (0.4)	0	1 (0.2)	0
出血性胃腸潰瘍	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
胃食道逆流性疾患	9 (4.0)	0	4 (1.8)	0	13 (2.9)	0
歯肉出血	1 (0.4)	0	3 (1.3)	0	4 (0.9)	0
歯肉紅斑	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
歯肉痛	2 (0.9)	0	1 (0.4)	0	3 (0.7)	0
歯肉腫脹	1 (0.4)	0	0	0	1 (0.2)	0
舌炎	1 (0.4)	0	0	0	1 (0.2)	0
吐血	1 (0.4)	0	0	0	1 (0.2)	0
血便排泄	0	0	3 (1.3)	0	3 (0.7)	0

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付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
胃腸障害 (contd)						
血性腹水	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
痔核	2 (0.9)	0	2 (0.9)	0	4 (0.9)	0
口の感覚鈍麻	3 (1.3)	0	0	0	3 (0.7)	0
イレウス	1 (0.4)	0	0	0	1 (0.2)	0
胃排出不全	1 (0.4)	0	0	0	1 (0.2)	0
単径ヘルニア	1 (0.4)	0	0	0	1 (0.2)	0
腸出血	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
腸管虚血	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
腸閉塞	5 (2.2)	4 (1.8)	5 (2.2)	4 (1.8)	10 (2.2)	8 (1.8)
大腸閉塞	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
大腸穿孔	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
口唇痛	1 (0.4)	0	0	0	1 (0.2)	0
弛緩歯	1 (0.4)	0	0	0	1 (0.2)	0
メレナ	0	0	1 (0.4)	0	1 (0.2)	0
口腔内潰瘍形成	3 (1.3)	0	1 (0.4)	0	4 (0.9)	0
悪心	91 (40.3)	2 (0.9)	106 (47.3)	1 (0.4)	197 (43.8)	3 (0.7)

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胃腸障害 (contd)						
嚥下痛	1 (0.4)	0	0	0	1 (0.2)	0
食道閉塞症	0	0	1 (0.4)	0	1 (0.2)	0
食道炎	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
口腔内分泌物	0	0	1 (0.4)	0	1 (0.2)	0
口腔障害	1 (0.4)	0	0	0	1 (0.2)	0
口腔知覚不全	1 (0.4)	0	0	0	1 (0.2)	0
口腔内痛	2 (0.9)	0	2 (0.9)	0	4 (0.9)	0
口の錯感覚	0	0	2 (0.9)	0	2 (0.4)	0
直腸出血	3 (1.3)	0	0	0	3 (0.7)	0
直腸しぶり	1 (0.4)	0	0	0	1 (0.2)	0
レッチング	1 (0.4)	0	0	0	1 (0.2)	0
後腹膜出血	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
流涎過多	0	0	1 (0.4)	0	1 (0.2)	0
小腸閉塞	3 (1.3)	2 (0.9)	3 (1.3)	2 (0.9)	6 (1.3)	4 (0.9)
口内炎	31 (13.7)	2 (0.9)	11 (4.9)	1 (0.4)	42 (9.3)	3 (0.7)
亜イレウス	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)

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Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226)		Dacarbazine (N=224)		Total (N=450)	
	All Grades n(%)	Grade >= 3 n(%)	All Grades n(%)	Grade >= 3 n(%)	All Grades n(%)	Grade >= 3 n(%)
胃腸障害 (contd)						
舌腫脹	1 (0.4)	0	0	0	1 (0.2)	0
舌の運動障害	1 (0.4)	0	0	0	1 (0.2)	0
舌潰瘍	1 (0.4)	0	0	0	1 (0.2)	0
歯の脱落	1 (0.4)	0	0	0	1 (0.2)	0
歯痛	2 (0.9)	0	0	0	2 (0.4)	0
嘔吐	43 (19.0)	2 (0.9)	50 (22.3)	1 (0.4)	93 (20.7)	3 (0.7)
一般・全身障害および投与部位の状態	172 (76.1)	15 (6.6)	153 (68.3)	16 (7.1)	325 (72.2)	31 (6.9)
適用部位発疹	0	0	1 (0.4)	0	1 (0.2)	0
無力症	47 (20.8)	4 (1.8)	51 (22.8)	7 (3.1)	98 (21.8)	11 (2.4)
突出痛	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
カテーテル留置部位浮腫	1 (0.4)	0	0	0	1 (0.2)	0
カテーテル留置部位疼痛	3 (1.3)	0	1 (0.4)	0	4 (0.9)	0
カテーテル留置部位関連反応	0	0	1 (0.4)	0	1 (0.2)	0
胸部不快感	2 (0.9)	0	3 (1.3)	0	5 (1.1)	0
悪寒	11 (4.9)	0	2 (0.9)	0	13 (2.9)	0

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付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
一般・全身障害および投与部位の状態 (contd)						
活動性低下	1 (0.4)	0	0	0	1 (0.2)	0
医療機器不具合	1 (0.4)	0	0	0	1 (0.2)	0
医療機器閉塞	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
早期満腹	0	0	1 (0.4)	0	1 (0.2)	0
顔面浮腫	3 (1.3)	0	0	0	3 (0.7)	0
疲労	99 (43.8)	7 (3.1)	86 (38.4)	3 (1.3)	185 (41.1)	10 (2.2)
歩行障害	4 (1.8)	0	1 (0.4)	1 (0.4)	5 (1.1)	1 (0.2)
全身健康状態低下	3 (1.3)	2 (0.9)	1 (0.4)	1 (0.4)	4 (0.9)	3 (0.7)
全身性浮腫	2 (0.9)	0	1 (0.4)	0	3 (0.7)	0
異常高熱	1 (0.4)	0	0	0	1 (0.2)	0
高熱	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
低体温	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
炎症	0	0	1 (0.4)	0	1 (0.2)	0
インフルエンザ様疾患	5 (2.2)	0	4 (1.8)	0	9 (2.0)	0
注入部位炎症	1 (0.4)	0	0	0	1 (0.2)	0
注入部位疼痛	0	0	2 (0.9)	0	2 (0.4)	0

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付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

	Eribulin (N=226)		Dacarbazine (N=224)		Total (N=450)	
MedDRA System Organ Class Preferred Term	All Grades n(%)	Grade >= 3 n(%)	All Grades n(%)	Grade >= 3 n(%)	All Grades n(%)	Grade >= 3 n(%)
一般・全身障害および投与部位の状態 (contd)						
注射部位疼痛	1 (0.4)	0	0	0	1 (0.2)	0
注射部位反応	1 (0.4)	0	0	0	1 (0.2)	0
局所腫脹	0	0	1 (0.4)	0	1 (0.2)	0
倦怠感	2 (0.9)	0	2 (0.9)	0	4 (0.9)	0
非心臓性胸痛	5 (2.2)	0	3 (1.3)	1 (0.4)	8 (1.8)	1 (0.2)
末梢性浮腫	27 (11.9)	0	17 (7.6)	1 (0.4)	44 (9.8)	1 (0.2)
疼痛	0	0	1 (0.4)	0	1 (0.2)	0
末梢腫脹	4 (1.8)	0	4 (1.8)	1 (0.4)	8 (1.8)	1 (0.2)
発熱	63 (27.9)	2 (0.9)	31 (13.8)	1 (0.4)	94 (20.9)	3 (0.7)
肝胆道系障害	10 (4.4)	4 (1.8)	7 (3.1)	2 (0.9)	17 (3.8)	6 (1.3)
胆管拡張	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
胆管炎	1 (0.4)	0	1 (0.4)	1 (0.4)	2 (0.4)	1 (0.2)
胆嚢炎	1 (0.4)	0	1 (0.4)	1 (0.4)	2 (0.4)	1 (0.2)
胆汁うっ滞	0	0	2 (0.9)	0	2 (0.4)	0
肝不全	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)

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付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
肝胆道系障害 (contd)						
肝機能異常	0	0	1 (0.4)	0	1 (0.2)	0
肝臓痛	1 (0.4)	0	0	0	1 (0.2)	0
肝細胞損傷	1 (0.4)	0	0	0	1 (0.2)	0
肝腫大	1 (0.4)	0	0	0	1 (0.2)	0
肝毒性	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
高ビリルビン血症	5 (2.2)	3 (1.3)	2 (0.9)	0	7 (1.6)	3 (0.7)
黄疸	1 (0.4)	0	1 (0.4)	1 (0.4)	2 (0.4)	1 (0.2)
免疫系障害	3 (1.3)	0	2 (0.9)	1 (0.4)	5 (1.1)	1 (0.2)
化学物質アレルギー	0	0	1 (0.4)	0	1 (0.2)	0
造影剤アレルギー	0	0	1 (0.4)	0	1 (0.2)	0
薬物過敏症	2 (0.9)	0	1 (0.4)	1 (0.4)	3 (0.7)	1 (0.2)
過敏症	1 (0.4)	0	0	0	1 (0.2)	0
感染症および寄生虫症	98 (43.4)	23 (10.2)	62 (27.7)	11 (4.9)	160 (35.6)	34 (7.6)
腹部感染	1 (0.4)	0	0	0	1 (0.2)	0

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付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
感染症および寄生虫症 (contd)						
腹部敗血症	1 (0.4)	0	0	0	1 (0.2)	0
細菌性関節炎	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
気管支炎	4 (1.8)	0	5 (2.2)	0	9 (2.0)	0
気管支肺炎	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
カンジダ尿	0	0	1 (0.4)	0	1 (0.2)	0
カテーテル留置部位蜂巣炎	1 (0.4)	0	0	0	1 (0.2)	0
カテーテル留置部位感染	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
蜂巣炎	2 (0.9)	0	2 (0.9)	1 (0.4)	4 (0.9)	1 (0.2)
クロストリジウム・ディフィシレ大腸炎	0	0	1 (0.4)	0	1 (0.2)	0
結膜炎	2 (0.9)	0	1 (0.4)	0	3 (0.7)	0
膀胱炎	1 (0.4)	1 (0.4)	2 (0.9)	0	3 (0.7)	1 (0.2)
医療機器関連感染	4 (1.8)	2 (0.9)	2 (0.9)	1 (0.4)	6 (1.3)	3 (0.7)
耳感染	3 (1.3)	0	2 (0.9)	0	5 (1.1)	0
丹毒	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
毛包炎	2 (0.9)	0	0	0	2 (0.4)	0
せつ	1 (0.4)	0	0	0	1 (0.2)	0

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付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
感染症および寄生虫症 (contd)						
胃腸炎	1 (0.4)	0	0	0	1 (0.2)	0
ウイルス性胃腸炎	0	0	1 (0.4)	0	1 (0.2)	0
鼻径部感染	1 (0.4)	0	0	0	1 (0.2)	0
単純ヘルペス	0	0	1 (0.4)	0	1 (0.2)	0
帯状疱疹	3 (1.3)	0	2 (0.9)	0	5 (1.1)	0
感染性皮膚嚢腫	1 (0.4)	0	0	0	1 (0.2)	0
感染	2 (0.9)	0	2 (0.9)	1 (0.4)	4 (0.9)	1 (0.2)
インフルエンザ	6 (2.7)	0	2 (0.9)	0	8 (1.8)	0
迷路炎	0	0	1 (0.4)	0	1 (0.2)	0
肝膿瘍	1 (0.4)	0	0	0	1 (0.2)	0
限局性感染	1 (0.4)	0	0	0	1 (0.2)	0
下気道感染	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
真菌性下気道感染	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
肺感染	2 (0.9)	1 (0.4)	0	0	2 (0.4)	1 (0.2)
鼻咽頭炎	8 (3.5)	0	6 (2.7)	0	14 (3.1)	0
好中球減少性敗血症	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)

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付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
感染症および寄生虫症 (contd)						
口腔細菌感染	1 (0.4)	0	0	0	1 (0.2)	0
口腔カンジダ症	5 (2.2)	0	2 (0.9)	0	7 (1.6)	0
口腔真菌感染	0	0	2 (0.9)	1 (0.4)	2 (0.4)	1 (0.2)
口腔ヘルペス	0	0	2 (0.9)	0	2 (0.4)	0
眼窩感染	1 (0.4)	0	0	0	1 (0.2)	0
外耳炎	0	0	1 (0.4)	0	1 (0.2)	0
腹膜炎	2 (0.9)	1 (0.4)	0	0	2 (0.4)	1 (0.2)
細菌性腹膜炎	2 (0.9)	2 (0.9)	0	0	2 (0.4)	2 (0.4)
咽頭炎	4 (1.8)	1 (0.4)	3 (1.3)	0	7 (1.6)	1 (0.2)
肺炎	8 (3.5)	4 (1.8)	3 (1.3)	3 (1.3)	11 (2.4)	7 (1.6)
術後創感染	0	0	1 (0.4)	0	1 (0.2)	0
シュードモナス性菌血症	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
腎盂腎炎	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
気道感染	1 (0.4)	0	2 (0.9)	1 (0.4)	3 (0.7)	1 (0.2)
鼻炎	4 (1.8)	0	2 (0.9)	0	6 (1.3)	0
敗血症	1 (0.4)	0	0	0	1 (0.2)	0

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付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
感染症および寄生虫症 (contd)						
敗血症性ショック	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
セラチア性菌血症	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
副鼻腔炎	3 (1.3)	0	0	0	3 (0.7)	0
軟部組織感染	1 (0.4)	0	0	0	1 (0.2)	0
ブドウ球菌性菌血症	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
ブドウ球菌感染	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
白癬感染	1 (0.4)	0	0	0	1 (0.2)	0
歯膿瘍	0	0	1 (0.4)	0	1 (0.2)	0
気管炎	0	0	1 (0.4)	0	1 (0.2)	0
上気道感染	20 (8.8)	1 (0.4)	9 (4.0)	0	29 (6.4)	1 (0.2)
尿路感染	25 (11.1)	5 (2.2)	12 (5.4)	1 (0.4)	37 (8.2)	6 (1.3)
尿路性敗血症	1 (0.4)	0	0	0	1 (0.2)	0
前庭神経炎	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
ウイルス性上気道感染	1 (0.4)	0	0	0	1 (0.2)	0
外陰膣真菌感染	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
創傷感染	0	0	1 (0.4)	0	1 (0.2)	0

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付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
傷害、中毒および処置合併症	19 (8.4)	4 (1.8)	12 (5.4)	1 (0.4)	31 (6.9)	5 (1.1)
投与に伴う反応	0	0	2 (0.9)	0	2 (0.4)	0
足関節部骨折	0	0	1 (0.4)	0	1 (0.2)	0
挫傷	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
焼痂	1 (0.4)	0	0	0	1 (0.2)	0
転倒	4 (1.8)	0	2 (0.9)	0	6 (1.3)	0
上腕骨骨折	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
切開部位紅斑	1 (0.4)	0	0	0	1 (0.2)	0
切開部位痛	1 (0.4)	0	0	0	1 (0.2)	0
注入に伴う反応	2 (0.9)	0	0	0	2 (0.4)	0
関節損傷	1 (0.4)	0	0	0	1 (0.2)	0
裂傷	1 (0.4)	0	0	0	1 (0.2)	0
靭帯捻挫	2 (0.9)	0	0	0	2 (0.4)	0
眼窩周囲出血	1 (0.4)	0	0	0	1 (0.2)	0
処置後出血	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
処置による出血	1 (0.4)	0	0	0	1 (0.2)	0
処置による疼痛	3 (1.3)	1 (0.4)	0	0	3 (0.7)	1 (0.2)

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Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
傷害、中毒および処置合併症 (contd)						
放射線性肺臓炎	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
脊椎圧迫骨折	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
ストーマ部疼痛	0	0	1 (0.4)	0	1 (0.2)	0
サンバーン	0	0	1 (0.4)	0	1 (0.2)	0
舌損傷	1 (0.4)	0	0	0	1 (0.2)	0
各種物質毒性	0	0	1 (0.4)	0	1 (0.2)	0
輸血反応	0	0	1 (0.4)	0	1 (0.2)	0
創傷	2 (0.9)	0	0	0	2 (0.4)	0
創離開	1 (0.4)	1 (0.4)	1 (0.4)	0	2 (0.4)	1 (0.2)
創部内臓脱出	1 (0.4)	0	0	0	1 (0.2)	0
誤薬投与	0	0	1 (0.4)	0	1 (0.2)	0
臨床検査	80 (35.4)	35 (15.5)	64 (28.6)	31 (13.8)	144 (32.0)	66 (14.7)
アラニンアミノトランスフェラーゼ増加	18 (8.0)	3 (1.3)	9 (4.0)	4 (1.8)	27 (6.0)	7 (1.6)
アスパラギン酸アミノトランスフェラーゼ増加	21 (9.3)	1 (0.4)	6 (2.7)	2 (0.9)	27 (6.0)	3 (0.7)
血中アルブミン減少	1 (0.4)	0	0	0	1 (0.2)	0

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A subject with two or more adverse events in the same system organ class (or with the same preferred term) is counted once for that system organ class (or preferred term).
Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_6_1.sas 18JUN201513:40

付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
臨床検査 (contd)						
血中アルカリホスファターゼ増加	10 (4.4)	1 (0.4)	11 (4.9)	2 (0.9)	21 (4.7)	3 (0.7)
血中ビリルビン増加	1 (0.4)	1 (0.4)	2 (0.9)	0	3 (0.7)	1 (0.2)
血中カルシウム減少	1 (0.4)	0	0	0	1 (0.2)	0
血中クレアチニン増加	5 (2.2)	0	3 (1.3)	0	8 (1.8)	0
血中ブドウ糖増加	0	0	1 (0.4)	0	1 (0.2)	0
血中乳酸脱水素酵素増加	12 (5.3)	0	7 (3.1)	0	19 (4.2)	0
血中マグネシウム減少	1 (0.4)	0	0	0	1 (0.2)	0
血中リン減少	0	0	1 (0.4)	0	1 (0.2)	0
血中カリウム減少	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
血圧上昇	0	0	1 (0.4)	0	1 (0.2)	0
血中尿素増加	1 (0.4)	0	0	0	1 (0.2)	0
心雑音	1 (0.4)	0	0	0	1 (0.2)	0
腎クレアチニン・クリアランス減少	1 (0.4)	0	0	0	1 (0.2)	0
心電図ＱＴ延長	15 (6.6)	5 (2.2)	11 (4.9)	3 (1.3)	26 (5.8)	8 (1.8)
心電図Ｔ波逆転	1 (0.4)	0	0	0	1 (0.2)	0
γ－グルタミルトランスフェラーゼ増加	5 (2.2)	3 (1.3)	2 (0.9)	2 (0.9)	7 (1.6)	5 (1.1)

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Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_6_1.sas 18JUN201513:40

付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
臨床検査 (contd)						
グリコヘモグロビン増加	1 (0.4)	0	0	0	1 (0.2)	0
ヘマトクリット減少	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
ヘモグロビン減少	7 (3.1)	0	3 (1.3)	3 (1.3)	10 (2.2)	3 (0.7)
心拍数増加	0	0	1 (0.4)	0	1 (0.2)	0
国際標準比増加	3 (1.3)	1 (0.4)	0	0	3 (0.7)	1 (0.2)
リパーゼ増加	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
リンパ球数減少	3 (1.3)	0	10 (4.5)	4 (1.8)	13 (2.9)	4 (0.9)
好中球数減少	19 (8.4)	16 (7.1)	12 (5.4)	6 (2.7)	31 (6.9)	22 (4.9)
便潜血陽性	0	0	1 (0.4)	0	1 (0.2)	0
血小板数減少	2 (0.9)	2 (0.9)	17 (7.6)	7 (3.1)	19 (4.2)	9 (2.0)
総蛋白減少	2 (0.9)	0	0	0	2 (0.4)	0
赤血球数減少	2 (0.9)	0	1 (0.4)	0	3 (0.7)	0
トランスアミナーゼ上昇	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
尿中ケトン体陽性	1 (0.4)	0	0	0	1 (0.2)	0
体重減少	7 (3.1)	0	8 (3.6)	0	15 (3.3)	0
体重増加	2 (0.9)	0	0	0	2 (0.4)	0

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Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_6_1.sas 18JUN201513:40

付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
臨床検査 (contd)						
白血球数減少	16 (7.1)	8 (3.5)	15 (6.7)	8 (3.6)	31 (6.9)	16 (3.6)
白血球数増加	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
尿中白血球陽性	1 (0.4)	0	0	0	1 (0.2)	0
代謝および栄養障害	83 (36.7)	23 (10.2)	71 (31.7)	16 (7.1)	154 (34.2)	39 (8.7)
悪液質	1 (0.4)	0	0	0	1 (0.2)	0
食欲減退	43 (19.0)	1 (0.4)	43 (19.2)	2 (0.9)	86 (19.1)	3 (0.7)
脱水	6 (2.7)	0	8 (3.6)	2 (0.9)	14 (3.1)	2 (0.4)
糖尿病	1 (0.4)	0	0	0	1 (0.2)	0
食物不耐性	1 (0.4)	0	0	0	1 (0.2)	0
高カルシウム血症	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
高コレステロール血症	0	0	1 (0.4)	0	1 (0.2)	0
高クレアチニン血症	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
高血糖	17 (7.5)	7 (3.1)	6 (2.7)	3 (1.3)	23 (5.1)	10 (2.2)
高カリウム血症	1 (0.4)	0	3 (1.3)	1 (0.4)	4 (0.9)	1 (0.2)
高脂血症	1 (0.4)	0	0	0	1 (0.2)	0

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付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
代謝および栄養障害 (contd)						
高マグネシウム血症	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
高ナトリウム血症	0	0	1 (0.4)	0	1 (0.2)	0
高尿酸血症	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
低アルブミン血症	11 (4.9)	2 (0.9)	7 (3.1)	1 (0.4)	18 (4.0)	3 (0.7)
低カルシウム血症	10 (4.4)	3 (1.3)	10 (4.5)	0	20 (4.4)	3 (0.7)
低血糖症	2 (0.9)	0	2 (0.9)	0	4 (0.9)	0
低カリウム血症	23 (10.2)	6 (2.7)	9 (4.0)	4 (1.8)	32 (7.1)	10 (2.2)
低マグネシウム血症	7 (3.1)	1 (0.4)	3 (1.3)	0	10 (2.2)	1 (0.2)
低ナトリウム血症	6 (2.7)	4 (1.8)	8 (3.6)	4 (1.8)	14 (3.1)	8 (1.8)
低リン酸血症	6 (2.7)	2 (0.9)	4 (1.8)	1 (0.4)	10 (2.2)	3 (0.7)
鉄欠乏	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
乳酸アシドーシス	1 (0.4)	0	0	0	1 (0.2)	0
栄養障害	1 (0.4)	0	0	0	1 (0.2)	0
代謝性アシドーシス	1 (0.4)	0	0	0	1 (0.2)	0
筋骨格系および結合組織障害	104 (46.0)	7 (3.1)	90 (40.2)	10 (4.5)	194 (43.1)	17 (3.8)

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付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
筋骨格系および結合組織障害 (contd)						
関節痛	19 (8.4)	0	13 (5.8)	0	32 (7.1)	0
関節炎	1 (0.4)	0	0	0	1 (0.2)	0
背部痛	35 (15.5)	4 (1.8)	31 (13.8)	3 (1.3)	66 (14.7)	7 (1.6)
骨痛	3 (1.3)	0	11 (4.9)	1 (0.4)	14 (3.1)	1 (0.2)
側腹部痛	4 (1.8)	0	4 (1.8)	0	8 (1.8)	0
鼡径部痛	3 (1.3)	0	1 (0.4)	0	4 (0.9)	0
顎障害	1 (0.4)	0	0	0	1 (0.2)	0
関節腫脹	2 (0.9)	0	1 (0.4)	0	3 (0.7)	0
四肢不快感	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
咀嚼障害	1 (0.4)	0	0	0	1 (0.2)	0
筋肉疲労	1 (0.4)	0	0	0	1 (0.2)	0
筋痙縮	13 (5.8)	0	7 (3.1)	0	20 (4.4)	0
筋力低下	7 (3.1)	0	3 (1.3)	1 (0.4)	10 (2.2)	1 (0.2)
筋骨格系胸痛	11 (4.9)	0	6 (2.7)	1 (0.4)	17 (3.8)	1 (0.2)
筋骨格不快感	2 (0.9)	0	1 (0.4)	0	3 (0.7)	0
筋骨格痛	12 (5.3)	0	11 (4.9)	3 (1.3)	23 (5.1)	3 (0.7)

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付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

	Eribulin (N=226)		Dacarbazine (N=224)		Total (N=450)	
MedDRA System Organ Class Preferred Term	All Grades n(%)	Grade >= 3 n(%)	All Grades n(%)	Grade >= 3 n(%)	All Grades n(%)	Grade >= 3 n(%)
筋骨格系および結合組織障害 (contd)						
筋骨格硬直	2 (0.9)	0	0	0	2 (0.4)	0
筋肉痛	23 (10.2)	0	17 (7.6)	0	40 (8.9)	0
ミオパチー	1 (0.4)	0	0	0	1 (0.2)	0
頚部痛	4 (1.8)	0	1 (0.4)	0	5 (1.1)	0
四肢痛	20 (8.8)	0	18 (8.0)	2 (0.9)	38 (8.4)	2 (0.4)
顎痛	2 (0.9)	0	0	0	2 (0.4)	0
病的骨折	2 (0.9)	2 (0.9)	1 (0.4)	1 (0.4)	3 (0.7)	3 (0.7)
肩回旋筋腱板症候群	2 (0.9)	0	0	0	2 (0.4)	0
軟部組織腫瘤	0	0	1 (0.4)	0	1 (0.2)	0
脊椎痛	1 (0.4)	1 (0.4)	2 (0.9)	1 (0.4)	3 (0.7)	2 (0.4)
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）	19 (8.4)	10 (4.4)	18 (8.0)	6 (2.7)	37 (8.2)	16 (3.6)
基底細胞癌	1 (0.4)	0	0	0	1 (0.2)	0
癌疼痛	4 (1.8)	2 (0.9)	1 (0.4)	0	5 (1.1)	2 (0.4)
頭蓋内腫瘍出血	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
平滑筋肉腫	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)

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付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
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） (contd)						
悪性腹水	0	0	3 (1.3)	1 (0.4)	3 (0.7)	1 (0.2)
悪性新生物進行	2 (0.9)	1 (0.4)	0	0	2 (0.4)	1 (0.2)
悪性胸水	2 (0.9)	0	4 (1.8)	1 (0.4)	6 (1.3)	1 (0.2)
腹腔内転移	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
骨転移	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
肺転移	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	2 (0.4)	2 (0.4)
頸部転移	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
転移	0	0	1 (0.4)	0	1 (0.2)	0
転移部痛	2 (0.9)	1 (0.4)	2 (0.9)	0	4 (0.9)	1 (0.2)
骨髄異形成症候群	0	0	1 (0.4)	0	1 (0.2)	0
粘液型脂肪肉腫	1 (0.4)	0	0	0	1 (0.2)	0
腫瘍熱	1 (0.4)	0	0	0	1 (0.2)	0
腫瘍出血	1 (0.4)	1 (0.4)	1 (0.4)	0	2 (0.4)	1 (0.2)
腫瘍疼痛	1 (0.4)	1 (0.4)	5 (2.2)	1 (0.4)	6 (1.3)	2 (0.4)
腫瘍の潰瘍形成	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)

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付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
神経系障害	112 (49.6)	13 (5.8)	75 (33.5)	5 (2.2)	187 (41.6)	18 (4.0)
味覚消失	1 (0.4)	0	0	0	1 (0.2)	0
意識変容状態	0	0	1 (0.4)	0	1 (0.2)	0
断端痛	0	0	1 (0.4)	0	1 (0.2)	0
失声症	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
平衡障害	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
灼熱感	1 (0.4)	0	6 (2.7)	0	7 (1.6)	0
頚腕症候群	1 (0.4)	0	0	0	1 (0.2)	0
痙攣	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
意識レベルの低下	0	0	1 (0.4)	0	1 (0.2)	0
注意力障害	4 (1.8)	0	0	0	4 (0.9)	0
浮動性めまい	21 (9.3)	0	16 (7.1)	0	37 (8.2)	0
異常感覚	1 (0.4)	0	2 (0.9)	0	3 (0.7)	0
味覚異常	18 (8.0)	0	5 (2.2)	0	23 (5.1)	0
頭痛	41 (18.1)	0	21 (9.4)	0	62 (13.8)	0
感覚鈍麻	5 (2.2)	1 (0.4)	3 (1.3)	0	8 (1.8)	1 (0.2)
嗅覚減退	1 (0.4)	0	0	0	1 (0.2)	0

TEAE = treatment-emergent adverse event, Graded using Common Terminology Criteria for Adverse Events (CTCAE)
A subject with two or more adverse events in the same system organ class (or with the same preferred term) is counted once for that system organ class (or preferred term).
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Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_6_1.sas 18JUN201513:40

付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
神経系障害 (contd)						
嗜眠	6 (2.7)	1 (0.4)	0	0	6 (1.3)	1 (0.2)
固有感覚の欠如	1 (0.4)	0	0	0	1 (0.2)	0
記憶障害	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
精神的機能障害	0	0	1 (0.4)	0	1 (0.2)	0
片頭痛	2 (0.9)	0	0	0	2 (0.4)	0
前兆を伴う片頭痛	0	0	1 (0.4)	0	1 (0.2)	0
単麻痺	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
神経痛	1 (0.4)	0	2 (0.9)	1 (0.4)	3 (0.7)	1 (0.2)
末梢性ニューロパチー	1 (0.4)	0	0	0	1 (0.2)	0
神経毒性	0	0	1 (0.4)	0	1 (0.2)	0
錯感覚	20 (8.8)	1 (0.4)	7 (3.1)	0	27 (6.0)	1 (0.2)
嗅覚錯誤	0	0	1 (0.4)	0	1 (0.2)	0
末梢性運動ニューロパチー	5 (2.2)	2 (0.9)	1 (0.4)	1 (0.4)	6 (1.3)	3 (0.7)
末梢性感覚運動ニューロパチー	2 (0.9)	0	0	0	2 (0.4)	0
末梢性感覚ニューロパチー	46 (20.4)	4 (1.8)	8 (3.6)	0	54 (12.0)	4 (0.9)
幻痛	0	0	1 (0.4)	0	1 (0.2)	0

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Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_6_1.sas 18JUN201513:40

付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
神経系障害 (contd)						
多発ニューロパチー	1 (0.4)	1 (0.4)	1 (0.4)	0	2 (0.4)	1 (0.2)
失神寸前の状態	1 (0.4)	1 (0.4)	1 (0.4)	0	2 (0.4)	1 (0.2)
神経根痛	0	0	1 (0.4)	0	1 (0.2)	0
下肢静止不能症候群	1 (0.4)	0	0	0	1 (0.2)	0
坐骨神経痛	2 (0.9)	0	0	0	2 (0.4)	0
感覚障害	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
副鼻腔炎に伴う頭痛	1 (0.4)	0	0	0	1 (0.2)	0
傾眠	7 (3.1)	0	5 (2.2)	0	12 (2.7)	0
脊髄圧迫	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
失神	0	0	3 (1.3)	3 (1.3)	3 (0.7)	3 (0.7)
緊張性頭痛	0	0	2 (0.9)	0	2 (0.4)	0
振戦	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
精神障害	48 (21.2)	1 (0.4)	35 (15.6)	0	83 (18.4)	1 (0.2)
感情障害	3 (1.3)	0	0	0	3 (0.7)	0
激越	3 (1.3)	1 (0.4)	1 (0.4)	0	4 (0.9)	1 (0.2)

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Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_6_1.sas 18JUN201513:40

付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
精神障害 (contd)						
不安	12 (5.3)	0	14 (6.3)	0	26 (5.8)	0
精神緩慢	0	0	1 (0.4)	0	1 (0.2)	0
カタトニー	1 (0.4)	0	0	0	1 (0.2)	0
錯乱状態	3 (1.3)	0	0	0	3 (0.7)	0
譫妄	1 (0.4)	0	0	0	1 (0.2)	0
抑うつ気分	1 (0.4)	0	0	0	1 (0.2)	0
うつ病	4 (1.8)	0	6 (2.7)	0	10 (2.2)	0
多幸気分	0	0	2 (0.9)	0	2 (0.4)	0
幻覚	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
不眠症	22 (9.7)	0	10 (4.5)	0	32 (7.1)	0
易刺激性	2 (0.9)	0	0	0	2 (0.4)	0
気分変化	1 (0.4)	0	0	0	1 (0.2)	0
精神病性障害	0	0	1 (0.4)	0	1 (0.2)	0
落ち着きのなさ	0	0	1 (0.4)	0	1 (0.2)	0
睡眠障害	2 (0.9)	0	2 (0.9)	0	4 (0.9)	0

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Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_6_1.sas 18JUN201513:40

付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
腎および尿路障害	20 (8.8)	1 (0.4)	17 (7.6)	1 (0.4)	37 (8.2)	2 (0.4)
膀胱痛	1 (0.4)	0	0	0	1 (0.2)	0
黄疸尿	0	0	1 (0.4)	0	1 (0.2)	0
排尿困難	7 (3.1)	0	4 (1.8)	0	11 (2.4)	0
遺尿	0	0	1 (0.4)	0	1 (0.2)	0
糖尿	2 (0.9)	0	2 (0.9)	0	4 (0.9)	0
血尿	2 (0.9)	1 (0.4)	1 (0.4)	0	3 (0.7)	1 (0.2)
水腎症	2 (0.9)	0	1 (0.4)	0	3 (0.7)	0
尿意切迫	2 (0.9)	0	0	0	2 (0.4)	0
夜間頻尿	0	0	1 (0.4)	0	1 (0.2)	0
頻尿	3 (1.3)	0	4 (1.8)	0	7 (1.6)	0
多尿	1 (0.4)	0	0	0	1 (0.2)	0
蛋白尿	1 (0.4)	0	2 (0.9)	0	3 (0.7)	0
急性腎不全	2 (0.9)	0	2 (0.9)	0	4 (0.9)	0
排尿躊躇	0	0	1 (0.4)	0	1 (0.2)	0
尿失禁	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
尿閉	1 (0.4)	0	0	0	1 (0.2)	0

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Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_6_1.sas 18JUN201513:40

付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
腎および尿路障害 (contd)						
尿路障害	0	0	1 (0.4)	0	1 (0.2)	0
尿路痛	1 (0.4)	0	0	0	1 (0.2)	0
生殖系および乳房障害	10 (4.4)	0	5 (2.2)	0	15 (3.3)	0
後天性包茎	1 (0.4)	0	0	0	1 (0.2)	0
勃起不全	2 (0.9)	0	0	0	2 (0.4)	0
卵管障害	1 (0.4)	0	0	0	1 (0.2)	0
不正子宮出血	0	0	1 (0.4)	0	1 (0.2)	0
乳頭痛	1 (0.4)	0	0	0	1 (0.2)	0
性器浮腫	1 (0.4)	0	0	0	1 (0.2)	0
骨盤不快感	0	0	1 (0.4)	0	1 (0.2)	0
骨盤痛	0	0	2 (0.9)	0	2 (0.4)	0
会陰痛	1 (0.4)	0	0	0	1 (0.2)	0
陰嚢浮腫	0	0	1 (0.4)	0	1 (0.2)	0
精巣浮腫	0	0	1 (0.4)	0	1 (0.2)	0
腟出血	1 (0.4)	0	0	0	1 (0.2)	0

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付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
生殖系および乳房障害 (contd)						
膣の炎症	1 (0.4)	0	0	0	1 (0.2)	0
外陰膣乾燥	2 (0.9)	0	0	0	2 (0.4)	0
外陰膣そう痒症	1 (0.4)	0	0	0	1 (0.2)	0
呼吸器、胸郭および縦隔障害	92 (40.7)	16 (7.1)	75 (33.5)	12 (5.4)	167 (37.1)	28 (6.2)
急性呼吸不全	2 (0.9)	1 (0.4)	0	0	2 (0.4)	1 (0.2)
無気肺	1 (0.4)	0	1 (0.4)	1 (0.4)	2 (0.4)	1 (0.2)
気管支痙攣	0	0	1 (0.4)	0	1 (0.2)	0
咳嗽	39 (17.3)	0	28 (12.5)	0	67 (14.9)	0
発声障害	8 (3.5)	0	3 (1.3)	0	11 (2.4)	0
呼吸困難	36 (15.9)	5 (2.2)	36 (16.1)	5 (2.2)	72 (16.0)	10 (2.2)
労作性呼吸困難	2 (0.9)	0	5 (2.2)	1 (0.4)	7 (1.6)	1 (0.2)
鼻出血	4 (1.8)	0	3 (1.3)	1 (0.4)	7 (1.6)	1 (0.2)
喀血	0	0	3 (1.3)	0	3 (0.7)	0
しゃっくり	1 (0.4)	0	3 (1.3)	1 (0.4)	4 (0.9)	1 (0.2)
高炭酸ガス血症	1 (0.4)	0	0	0	1 (0.2)	0

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Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_6_1.sas 18JUN201513:40

付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
呼吸器、胸郭および縦隔障害 (contd)						
鼻閉	5 (2.2)	0	4 (1.8)	0	9 (2.0)	0
鼻部不快感	0	0	1 (0.4)	0	1 (0.2)	0
鼻潰瘍	1 (0.4)	0	0	0	1 (0.2)	0
口腔咽頭痛	12 (5.3)	0	5 (2.2)	0	17 (3.8)	0
呼吸時疼痛	1 (0.4)	1 (0.4)	1 (0.4)	0	2 (0.4)	1 (0.2)
副鼻腔分泌過多	0	0	1 (0.4)	0	1 (0.2)	0
咽頭紅斑	2 (0.9)	0	0	0	2 (0.4)	0
胸水	4 (1.8)	1 (0.4)	5 (2.2)	1 (0.4)	9 (2.0)	2 (0.4)
誤嚥性肺炎	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
気胸	1 (0.4)	0	1 (0.4)	1 (0.4)	2 (0.4)	1 (0.2)
湿性咳嗽	3 (1.3)	0	2 (0.9)	0	5 (1.1)	0
肺塞栓症	4 (1.8)	4 (1.8)	3 (1.3)	1 (0.4)	7 (1.6)	5 (1.1)
肺水腫	1 (0.4)	0	0	0	1 (0.2)	0
肺血栓症	1 (0.4)	0	0	0	1 (0.2)	0
呼吸不全	4 (1.8)	4 (1.8)	2 (0.9)	2 (0.9)	6 (1.3)	6 (1.3)
鼻痛	1 (0.4)	0	0	0	1 (0.2)	0

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付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
呼吸器、胸郭および縦隔障害 (contd)						
アレルギー性鼻炎	1 (0.4)	0	0	0	1 (0.2)	0
鼻漏	10 (4.4)	0	3 (1.3)	0	13 (2.9)	0
副鼻腔うっ血	2 (0.9)	0	0	0	2 (0.4)	0
くしゃみ	0	0	1 (0.4)	0	1 (0.2)	0
咽喉刺激感	0	0	1 (0.4)	0	1 (0.2)	0
上気道咳症候群	2 (0.9)	0	1 (0.4)	0	3 (0.7)	0
喘鳴	0	0	2 (0.9)	0	2 (0.4)	0
皮膚および皮下組織障害	109 (48.2)	1 (0.4)	45 (20.1)	1 (0.4)	154 (34.2)	2 (0.4)
日光角化症	1 (0.4)	0	0	0	1 (0.2)	0
脱毛症	79 (35.0)	1 (0.4)	6 (2.7)	0	85 (18.9)	1 (0.2)
血性水疱	0	0	1 (0.4)	0	1 (0.2)	0
皮膚嚢腫	1 (0.4)	0	0	0	1 (0.2)	0
皮膚炎	1 (0.4)	0	0	0	1 (0.2)	0
ざ瘡様皮膚炎	1 (0.4)	0	0	0	1 (0.2)	0
アレルギー性皮膚炎	0	0	1 (0.4)	0	1 (0.2)	0

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付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
皮膚および皮下組織障害 (contd)						
おむつ皮膚炎	1 (0.4)	0	0	0	1 (0.2)	0
皮膚乾燥	5 (2.2)	0	5 (2.2)	0	10 (2.2)	0
湿疹	1 (0.4)	0	0	0	1 (0.2)	0
紅斑	4 (1.8)	0	4 (1.8)	0	8 (1.8)	0
毛髪変色	1 (0.4)	0	0	0	1 (0.2)	0
多汗症	4 (1.8)	0	3 (1.3)	0	7 (1.6)	0
睫毛眉毛脱落症	1 (0.4)	0	0	0	1 (0.2)	0
爪床圧痛	0	0	1 (0.4)	0	1 (0.2)	0
爪の障害	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
爪線状隆起	0	0	1 (0.4)	0	1 (0.2)	0
爪毒性	1 (0.4)	0	0	0	1 (0.2)	0
寝汗	3 (1.3)	0	0	0	3 (0.7)	0
爪甲離床症	1 (0.4)	0	0	0	1 (0.2)	0
爪甲脱落症	1 (0.4)	0	0	0	1 (0.2)	0
皮膚疼痛	1 (0.4)	0	2 (0.9)	0	3 (0.7)	0
手掌・足底発赤知覚不全症候群	2 (0.9)	0	0	0	2 (0.4)	0

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付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
皮膚および皮下組織障害 (contd)						
点状出血	0	0	3 (1.3)	1 (0.4)	3 (0.7)	1 (0.2)
光線過敏性反応	1 (0.4)	0	8 (3.6)	0	9 (2.0)	0
そう痒症	9 (4.0)	0	5 (2.2)	0	14 (3.1)	0
全身性そう痒症	1 (0.4)	0	0	0	1 (0.2)	0
発疹	9 (4.0)	0	7 (3.1)	0	16 (3.6)	0
斑状丘疹状皮疹	1 (0.4)	0	0	0	1 (0.2)	0
そう痒性皮疹	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
瘢痕痛	1 (0.4)	0	0	0	1 (0.2)	0
皮膚亀裂	2 (0.9)	0	1 (0.4)	0	3 (0.7)	0
皮膚色素過剰	1 (0.4)	0	0	0	1 (0.2)	0
皮膚病変	2 (0.9)	0	1 (0.4)	0	3 (0.7)	0
皮膚潰瘍	1 (0.4)	0	0	0	1 (0.2)	0
日光皮膚炎	0	0	1 (0.4)	0	1 (0.2)	0
皮膚のべとつき感	1 (0.4)	0	0	0	1 (0.2)	0
顔面腫脹	1 (0.4)	0	2 (0.9)	0	3 (0.7)	0
毛細血管拡張症	0	0	1 (0.4)	0	1 (0.2)	0

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Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_6_1.sas 18JUN201513:40

付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
皮膚および皮下組織障害 (contd)						
蕁麻疹	1 (0.4)	0	0	0	1 (0.2)	0
血管障害	35 (15.5)	3 (1.3)	30 (13.4)	8 (3.6)	65 (14.4)	11 (2.4)
深部静脈血栓症	1 (0.4)	0	4 (1.8)	3 (1.3)	5 (1.1)	3 (0.7)
潮紅	6 (2.7)	0	3 (1.3)	0	9 (2.0)	0
血腫	0	0	1 (0.4)	0	1 (0.2)	0
ほてり	5 (2.2)	0	3 (1.3)	0	8 (1.8)	0
高血圧	7 (3.1)	1 (0.4)	7 (3.1)	2 (0.9)	14 (3.1)	3 (0.7)
低血圧	13 (5.8)	1 (0.4)	6 (2.7)	2 (0.9)	19 (4.2)	3 (0.7)
頸静脈血栓症	0	0	1 (0.4)	0	1 (0.2)	0
リンパ浮腫	1 (0.4)	0	2 (0.9)	0	3 (0.7)	0
起立性低血圧	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
末梢静脈疾患	1 (0.4)	0	0	0	1 (0.2)	0
静脈炎	1 (0.4)	0	0	0	1 (0.2)	0
高血圧前症	1 (0.4)	0	0	0	1 (0.2)	0
ショック	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)

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Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_6_1.sas 18JUN201513:40

付録 2.7.6-1
Study 309
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
血管障害 (contd)						
上大静脈症候群	1 (0.4)	0	0	0	1 (0.2)	0
血管痛	0	0	1 (0.4)	0	1 (0.2)	0
大静脈血栓症	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	2 (0.4)	2 (0.4)
静脈血栓症	0	0	2 (0.9)	0	2 (0.4)	0

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Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_6_1.sas 18JUN201513:40

付録 2.7.6-2
Study 309
Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
Any treatment-related TEAEs	210 (92.9)	123 (54.4)	203 (90.6)	90 (40.2)	413 (91.8)	213 (47.3)
血液およびリンパ系障害	127 (56.2)	90 (39.8)	116 (51.8)	67 (29.9)	243 (54.0)	157 (34.9)
貧血	55 (24.3)	10 (4.4)	59 (26.3)	21 (9.4)	114 (25.3)	31 (6.9)
発熱性好中球減少症	2 (0.9)	2 (0.9)	2 (0.9)	2 (0.9)	4 (0.9)	4 (0.9)
ヘモグロビン血症	3 (1.3)	2 (0.9)	1 (0.4)	0	4 (0.9)	2 (0.4)
内出血発生の増加傾向	0	0	1 (0.4)	0	1 (0.2)	0
白血球増加症	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
白血球減少症	35 (15.5)	22 (9.7)	21 (9.4)	8 (3.6)	56 (12.4)	30 (6.7)
リンパ節症	1 (0.4)	0	0	0	1 (0.2)	0
リンパ球減少症	1 (0.4)	1 (0.4)	6 (2.7)	3 (1.3)	7 (1.6)	4 (0.9)
好中球減少症	96 (42.5)	76 (33.6)	53 (23.7)	35 (15.6)	149 (33.1)	111 (24.7)
汎血球減少症	0	0	3 (1.3)	2 (0.9)	3 (0.7)	2 (0.4)
血小板減少症	13 (5.8)	1 (0.4)	59 (26.3)	34 (15.2)	72 (16.0)	35 (7.8)
心臓障害	2 (0.9)	1 (0.4)	6 (2.7)	0	8 (1.8)	1 (0.2)
心嚢液貯留	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)

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Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_6_2.sas 18JUN201520:59

付録 2.7.6-2
Study 309
Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
心臓障害 (contd)						
洞性頻脈	0	0	3 (1.3)	0	3 (0.7)	0
頻脈	1 (0.4)	0	3 (1.3)	0	4 (0.9)	0
耳および迷路障害	5 (2.2)	0	2 (0.9)	0	7 (1.6)	0
難聴	1 (0.4)	0	0	0	1 (0.2)	0
耳鳴	3 (1.3)	0	0	0	3 (0.7)	0
回転性めまい	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
前庭障害	0	0	1 (0.4)	0	1 (0.2)	0
眼障害	22 (9.7)	0	6 (2.7)	0	28 (6.2)	0
眼精疲労	0	0	1 (0.4)	0	1 (0.2)	0
眼瞼炎	2 (0.9)	0	0	0	2 (0.4)	0
失明	1 (0.4)	0	0	0	1 (0.2)	0
眼乾燥	2 (0.9)	0	0	0	2 (0.4)	0
眼刺激	3 (1.3)	0	0	0	3 (0.7)	0
眼痛	1 (0.4)	0	0	0	1 (0.2)	0

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付録 2.7.6-2
Study 309
Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
眼障害 (contd)						
流涙増加	15 (6.6)	0	0	0	15 (3.3)	0
眼充血	3 (1.3)	0	0	0	3 (0.7)	0
霧視	3 (1.3)	0	4 (1.8)	0	7 (1.6)	0
視力障害	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
硝子体浮遊物	1 (0.4)	0	0	0	1 (0.2)	0
胃腸障害	132 (58.4)	9 (4.0)	133 (59.4)	5 (2.2)	265 (58.9)	14 (3.1)
腹部膨満	5 (2.2)	0	4 (1.8)	0	9 (2.0)	0
腹痛	9 (4.0)	0	1 (0.4)	0	10 (2.2)	0
下腹部痛	0	0	1 (0.4)	0	1 (0.2)	0
上腹部痛	5 (2.2)	0	5 (2.2)	0	10 (2.2)	0
後天性巨舌症	1 (0.4)	0	0	0	1 (0.2)	0
肛門の炎症	0	0	1 (0.4)	0	1 (0.2)	0
アフタ性口内炎	3 (1.3)	0	0	0	3 (0.7)	0
便秘	38 (16.8)	0	28 (12.5)	1 (0.4)	66 (14.7)	1 (0.2)
下痢	30 (13.3)	1 (0.4)	22 (9.8)	0	52 (11.6)	1 (0.2)

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付録 2.7.6-2
Study 309
Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
胃腸障害 (contd)						
口内乾燥	9 (4.0)	0	3 (1.3)	0	12 (2.7)	0
消化不良	9 (4.0)	1 (0.4)	5 (2.2)	1 (0.4)	14 (3.1)	2 (0.4)
嚥下障害	1 (0.4)	0	0	0	1 (0.2)	0
放屁	1 (0.4)	0	0	0	1 (0.2)	0
食中毒	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
胃腸管瘻	1 (0.4)	0	0	0	1 (0.2)	0
胃腸出血	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
胃食道逆流性疾患	6 (2.7)	0	1 (0.4)	0	7 (1.6)	0
歯肉出血	0	0	2 (0.9)	0	2 (0.4)	0
歯肉紅斑	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
歯肉痛	1 (0.4)	0	0	0	1 (0.2)	0
歯肉腫脹	1 (0.4)	0	0	0	1 (0.2)	0
舌炎	1 (0.4)	0	0	0	1 (0.2)	0
口の感覚鈍麻	3 (1.3)	0	0	0	3 (0.7)	0
腸閉塞	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
口腔内潰瘍形成	3 (1.3)	0	1 (0.4)	0	4 (0.9)	0

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付録 2.7.6-2
Study 309
Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
胃腸障害 (contd)						
悪心	75 (33.2)	2 (0.9)	101 (45.1)	0	176 (39.1)	2 (0.4)
嚥下痛	1 (0.4)	0	0	0	1 (0.2)	0
口腔知覚不全	1 (0.4)	0	0	0	1 (0.2)	0
口腔内痛	2 (0.9)	0	1 (0.4)	0	3 (0.7)	0
口の錯感覚	0	0	1 (0.4)	0	1 (0.2)	0
直腸出血	1 (0.4)	0	0	0	1 (0.2)	0
後腹膜出血	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
流涎過多	0	0	1 (0.4)	0	1 (0.2)	0
口内炎	26 (11.5)	2 (0.9)	9 (4.0)	1 (0.4)	35 (7.8)	3 (0.7)
舌の運動障害	1 (0.4)	0	0	0	1 (0.2)	0
舌潰瘍	1 (0.4)	0	0	0	1 (0.2)	0
嘔吐	27 (11.9)	1 (0.4)	38 (17.0)	0	65 (14.4)	1 (0.2)
一般・全身障害および投与部位の状態	136 (60.2)	9 (4.0)	121 (54.0)	7 (3.1)	257 (57.1)	16 (3.6)
無力症	36 (15.9)	2 (0.9)	41 (18.3)	4 (1.8)	77 (17.1)	6 (1.3)
胸部不快感	0	0	1 (0.4)	0	1 (0.2)	0

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付録 2.7.6-2
Study 309
Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

	Eribulin (N=226)		Dacarbazine (N=224)		Total (N=450)	
MedDRA System Organ Class Preferred Term	All Grades n(%)	Grade >= 3 n(%)	All Grades n(%)	Grade >= 3 n(%)	All Grades n(%)	Grade >= 3 n(%)
一般・全身障害および投与部位の状態 (contd)						
悪寒	8 (3.5)	0	1 (0.4)	0	9 (2.0)	0
活動性低下	1 (0.4)	0	0	0	1 (0.2)	0
顔面浮腫	2 (0.9)	0	0	0	2 (0.4)	0
疲労	83 (36.7)	6 (2.7)	76 (33.9)	1 (0.4)	159 (35.3)	7 (1.6)
歩行障害	3 (1.3)	0	0	0	3 (0.7)	0
全身性浮腫	1 (0.4)	0	0	0	1 (0.2)	0
低体温	1 (0.4)	0	0	0	1 (0.2)	0
インフルエンザ様疾患	3 (1.3)	0	3 (1.3)	0	6 (1.3)	0
注入部位疼痛	0	0	2 (0.9)	0	2 (0.4)	0
注射部位反応	1 (0.4)	0	0	0	1 (0.2)	0
倦怠感	2 (0.9)	0	2 (0.9)	0	4 (0.9)	0
末梢性浮腫	9 (4.0)	0	5 (2.2)	1 (0.4)	14 (3.1)	1 (0.2)
末梢腫脹	0	0	1 (0.4)	0	1 (0.2)	0
発熱	33 (14.6)	1 (0.4)	10 (4.5)	1 (0.4)	43 (9.6)	2 (0.4)
肝胆道系障害	3 (1.3)	2 (0.9)	1 (0.4)	1 (0.4)	4 (0.9)	3 (0.7)

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付録 2.7.6-2
Study 309
Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
肝胆道系障害 (contd)						
肝不全	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
肝細胞損傷	1 (0.4)	0	0	0	1 (0.2)	0
肝毒性	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
高ビリルビン血症	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
黄疸	1 (0.4)	0	0	0	1 (0.2)	0
免疫系障害	1 (0.4)	0	1 (0.4)	1 (0.4)	2 (0.4)	1 (0.2)
薬物過敏症	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
過敏症	1 (0.4)	0	0	0	1 (0.2)	0
感染症および寄生虫症	24 (10.6)	7 (3.1)	16 (7.1)	4 (1.8)	40 (8.9)	11 (2.4)
気管支炎	1 (0.4)	0	0	0	1 (0.2)	0
気管支肺炎	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
カテーテル留置部位蜂巣炎	1 (0.4)	0	0	0	1 (0.2)	0
蜂巣炎	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
クロストリジウム・ディフィシレ大腸炎	0	0	1 (0.4)	0	1 (0.2)	0

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Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_6_2.sas 18JUN201520:59

付録 2.7.6-2
Study 309
Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226)		Dacarbazine (N=224)		Total (N=450)	
	All Grades n(%)	Grade >= 3 n(%)	All Grades n(%)	Grade >= 3 n(%)	All Grades n(%)	Grade >= 3 n(%)
感染症および寄生虫症 (contd)						
耳感染	2 (0.9)	0	0	0	2 (0.4)	0
毛包炎	2 (0.9)	0	0	0	2 (0.4)	0
帯状疱疹	0	0	2 (0.9)	0	2 (0.4)	0
感染	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
真菌性下気道感染	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
鼻咽頭炎	0	0	1 (0.4)	0	1 (0.2)	0
好中球減少性敗血症	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
口腔カンジダ症	3 (1.3)	0	2 (0.9)	0	5 (1.1)	0
口腔真菌感染	0	0	1 (0.4)	0	1 (0.2)	0
外耳炎	0	0	1 (0.4)	0	1 (0.2)	0
咽頭炎	2 (0.9)	1 (0.4)	0	0	2 (0.4)	1 (0.2)
肺炎	3 (1.3)	3 (1.3)	2 (0.9)	2 (0.9)	5 (1.1)	5 (1.1)
気道感染	1 (0.4)	0	0	0	1 (0.2)	0
鼻炎	1 (0.4)	0	0	0	1 (0.2)	0
軟部組織感染	1 (0.4)	0	0	0	1 (0.2)	0
白癬感染	1 (0.4)	0	0	0	1 (0.2)	0

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付録 2.7.6-2
Study 309
Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
感染症および寄生虫症 (contd)						
上気道感染	4 (1.8)	1 (0.4)	0	0	4 (0.9)	1 (0.2)
尿路感染	1 (0.4)	0	5 (2.2)	0	6 (1.3)	0
傷害、中毒および処置合併症	2 (0.9)	0	4 (1.8)	0	6 (1.3)	0
投与に伴う反応	0	0	2 (0.9)	0	2 (0.4)	0
挫傷	0	0	1 (0.4)	0	1 (0.2)	0
転倒	1 (0.4)	0	0	0	1 (0.2)	0
注入に伴う反応	1 (0.4)	0	0	0	1 (0.2)	0
サンバーン	0	0	1 (0.4)	0	1 (0.2)	0
臨床検査	67 (29.6)	29 (12.8)	47 (21.0)	27 (12.1)	114 (25.3)	56 (12.4)
アラニンアミノトランスフェラーゼ増加	15 (6.6)	3 (1.3)	6 (2.7)	3 (1.3)	21 (4.7)	6 (1.3)
アスパラギン酸アミノトランスフェラーゼ増加	16 (7.1)	1 (0.4)	4 (1.8)	1 (0.4)	20 (4.4)	2 (0.4)
血中アルブミン減少	1 (0.4)	0	0	0	1 (0.2)	0
血中アルカリホスファターゼ増加	6 (2.7)	0	7 (3.1)	1 (0.4)	13 (2.9)	1 (0.2)
血中ビリルビン増加	0	0	2 (0.9)	0	2 (0.4)	0

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付録 2.7.6-2
Study 309
Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
臨床検査 (contd)						
血中カルシウム減少	1 (0.4)	0	0	0	1 (0.2)	0
血中クレアチニン増加	3 (1.3)	0	1 (0.4)	0	4 (0.9)	0
血中乳酸脱水素酵素増加	6 (2.7)	0	4 (1.8)	0	10 (2.2)	0
血中リン減少	0	0	1 (0.4)	0	1 (0.2)	0
血中カリウム減少	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
血中尿素増加	1 (0.4)	0	0	0	1 (0.2)	0
腎クレアチニン・クリアランス減少	1 (0.4)	0	0	0	1 (0.2)	0
心電図ＱＴ延長	14 (6.2)	5 (2.2)	7 (3.1)	1 (0.4)	21 (4.7)	6 (1.3)
γ－グルタミルトランスフェラーゼ増加	2 (0.9)	1 (0.4)	2 (0.9)	1 (0.4)	4 (0.9)	2 (0.4)
ヘマトクリット減少	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
ヘモグロビン減少	6 (2.7)	0	2 (0.9)	2 (0.9)	8 (1.8)	2 (0.4)
リンパ球数減少	2 (0.9)	0	10 (4.5)	4 (1.8)	12 (2.7)	4 (0.9)
好中球数減少	18 (8.0)	15 (6.6)	12 (5.4)	6 (2.7)	30 (6.7)	21 (4.7)
血小板数減少	1 (0.4)	1 (0.4)	16 (7.1)	7 (3.1)	17 (3.8)	8 (1.8)
総蛋白減少	2 (0.9)	0	0	0	2 (0.4)	0
赤血球数減少	2 (0.9)	0	1 (0.4)	0	3 (0.7)	0

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付録 2.7.6-2
Study 309
Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
臨床検査 (contd)						
トランスアミナーゼ上昇	1 (0.4)	0	0	0	1 (0.2)	0
尿中ケトン体陽性	1 (0.4)	0	0	0	1 (0.2)	0
体重減少	5 (2.2)	0	3 (1.3)	0	8 (1.8)	0
白血球数減少	16 (7.1)	7 (3.1)	15 (6.7)	8 (3.6)	31 (6.9)	15 (3.3)
白血球数増加	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
代謝および栄養障害	45 (19.9)	9 (4.0)	37 (16.5)	6 (2.7)	82 (18.2)	15 (3.3)
食欲減退	32 (14.2)	1 (0.4)	25 (11.2)	1 (0.4)	57 (12.7)	2 (0.4)
脱水	2 (0.9)	0	5 (2.2)	1 (0.4)	7 (1.6)	1 (0.2)
高コレステロール血症	0	0	1 (0.4)	0	1 (0.2)	0
高クレアチニン血症	0	0	1 (0.4)	0	1 (0.2)	0
高血糖	3 (1.3)	2 (0.9)	1 (0.4)	1 (0.4)	4 (0.9)	3 (0.7)
低アルブミン血症	3 (1.3)	0	0	0	3 (0.7)	0
低カルシウム血症	1 (0.4)	0	3 (1.3)	0	4 (0.9)	0
低カリウム血症	8 (3.5)	3 (1.3)	2 (0.9)	1 (0.4)	10 (2.2)	4 (0.9)
低マグネシウム血症	4 (1.8)	1 (0.4)	1 (0.4)	0	5 (1.1)	1 (0.2)

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付録 2.7.6-2
Study 309
Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

	Eribulin (N=226)		Dacarbazine (N=224)		Total (N=450)	
MedDRA System Organ Class Preferred Term	All Grades n(%)	Grade >= 3 n(%)	All Grades n(%)	Grade >= 3 n(%)	All Grades n(%)	Grade >= 3 n(%)
代謝および栄養障害 (contd)						
低ナトリウム血症	3 (1.3)	2 (0.9)	2 (0.9)	1 (0.4)	5 (1.1)	3 (0.7)
低リン酸血症	2 (0.9)	1 (0.4)	3 (1.3)	1 (0.4)	5 (1.1)	2 (0.4)
筋骨格系および結合組織障害	41 (18.1)	0	24 (10.7)	0	65 (14.4)	0
関節痛	10 (4.4)	0	4 (1.8)	0	14 (3.1)	0
関節炎	1 (0.4)	0	0	0	1 (0.2)	0
背部痛	5 (2.2)	0	2 (0.9)	0	7 (1.6)	0
骨痛	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
顎障害	1 (0.4)	0	0	0	1 (0.2)	0
咀嚼障害	1 (0.4)	0	0	0	1 (0.2)	0
筋肉疲労	1 (0.4)	0	0	0	1 (0.2)	0
筋痙縮	7 (3.1)	0	3 (1.3)	0	10 (2.2)	0
筋力低下	4 (1.8)	0	0	0	4 (0.9)	0
筋骨格系胸痛	2 (0.9)	0	1 (0.4)	0	3 (0.7)	0
筋骨格痛	2 (0.9)	0	3 (1.3)	0	5 (1.1)	0
筋骨格硬直	2 (0.9)	0	0	0	2 (0.4)	0

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付録 2.7.6-2
Study 309
Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

	Eribulin (N=226)		Dacarbazine (N=224)		Total (N=450)	
MedDRA System Organ Class Preferred Term	All Grades n(%)	Grade >= 3 n(%)	All Grades n(%)	Grade >= 3 n(%)	All Grades n(%)	Grade >= 3 n(%)
筋骨格系および結合組織障害 (contd)						
筋肉痛	15 (6.6)	0	13 (5.8)	0	28 (6.2)	0
四肢痛	5 (2.2)	0	3 (1.3)	0	8 (1.8)	0
顎痛	1 (0.4)	0	0	0	1 (0.2)	0
軟部組織腫瘤	0	0	1 (0.4)	0	1 (0.2)	0
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）	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
腫瘍疼痛	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
神経系障害	86 (38.1)	10 (4.4)	42 (18.8)	2 (0.9)	128 (28.4)	12 (2.7)
味覚消失	1 (0.4)	0	0	0	1 (0.2)	0
平衡障害	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
灼熱感	1 (0.4)	0	6 (2.7)	0	7 (1.6)	0
痙攣	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
意識レベルの低下	0	0	1 (0.4)	0	1 (0.2)	0
注意力障害	3 (1.3)	0	0	0	3 (0.7)	0
浮動性めまい	11 (4.9)	0	7 (3.1)	0	18 (4.0)	0

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付録 2.7.6-2
Study 309
Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226)		Dacarbazine (N=224)		Total (N=450)	
	All Grades n(%)	Grade >= 3 n(%)	All Grades n(%)	Grade >= 3 n(%)	All Grades n(%)	Grade >= 3 n(%)
神経系障害 (contd)						
異常感覚	1 (0.4)	0	0	0	1 (0.2)	0
味覚異常	18 (8.0)	0	3 (1.3)	0	21 (4.7)	0
頭痛	23 (10.2)	0	15 (6.7)	0	38 (8.4)	0
感覚鈍麻	5 (2.2)	1 (0.4)	0	0	5 (1.1)	1 (0.2)
嗜眠	3 (1.3)	1 (0.4)	0	0	3 (0.7)	1 (0.2)
固有感覚の欠如	1 (0.4)	0	0	0	1 (0.2)	0
記憶障害	0	0	1 (0.4)	0	1 (0.2)	0
神経痛	0	0	1 (0.4)	0	1 (0.2)	0
末梢性ニューロパチー	1 (0.4)	0	0	0	1 (0.2)	0
錯感覚	17 (7.5)	1 (0.4)	4 (1.8)	0	21 (4.7)	1 (0.2)
嗅覚錯誤	0	0	1 (0.4)	0	1 (0.2)	0
末梢性運動ニューロパチー	5 (2.2)	2 (0.9)	0	0	5 (1.1)	2 (0.4)
末梢性感覚運動ニューロパチー	2 (0.9)	0	0	0	2 (0.4)	0
末梢性感覚ニューロパチー	43 (19.0)	4 (1.8)	5 (2.2)	0	48 (10.7)	4 (0.9)
多発ニューロパチー	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
失神寸前の状態	1 (0.4)	1 (0.4)	1 (0.4)	0	2 (0.4)	1 (0.2)

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付録 2.7.6-2
Study 309
Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
神経系障害 (contd)						
下肢静止不能症候群	1 (0.4)	0	0	0	1 (0.2)	0
感覚障害	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
傾眠	2 (0.9)	0	1 (0.4)	0	3 (0.7)	0
失神	0	0	2 (0.9)	2 (0.9)	2 (0.4)	2 (0.4)
緊張性頭痛	0	0	1 (0.4)	0	1 (0.2)	0
振戦	1 (0.4)	0	0	0	1 (0.2)	0
精神障害	11 (4.9)	1 (0.4)	6 (2.7)	0	17 (3.8)	1 (0.2)
感情障害	1 (0.4)	0	0	0	1 (0.2)	0
激越	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
不安	0	0	2 (0.9)	0	2 (0.4)	0
錯乱状態	1 (0.4)	0	0	0	1 (0.2)	0
うつ病	0	0	1 (0.4)	0	1 (0.2)	0
不眠症	7 (3.1)	0	2 (0.9)	0	9 (2.0)	0
易刺激性	1 (0.4)	0	0	0	1 (0.2)	0
落ち着きのなさ	0	0	1 (0.4)	0	1 (0.2)	0

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付録 2.7.6-2
Study 309
Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
精神障害 (contd)						
睡眠障害	0	0	1 (0.4)	0	1 (0.2)	0
腎および尿路障害	5 (2.2)	0	3 (1.3)	0	8 (1.8)	0
排尿困難	1 (0.4)	0	0	0	1 (0.2)	0
血尿	0	0	1 (0.4)	0	1 (0.2)	0
頻尿	1 (0.4)	0	2 (0.9)	0	3 (0.7)	0
多尿	1 (0.4)	0	0	0	1 (0.2)	0
蛋白尿	1 (0.4)	0	0	0	1 (0.2)	0
尿路痛	1 (0.4)	0	0	0	1 (0.2)	0
生殖系および乳房障害	6 (2.7)	0	0	0	6 (1.3)	0
勃起不全	2 (0.9)	0	0	0	2 (0.4)	0
乳頭痛	1 (0.4)	0	0	0	1 (0.2)	0
腟出血	1 (0.4)	0	0	0	1 (0.2)	0
腟の炎症	1 (0.4)	0	0	0	1 (0.2)	0
外陰腟乾燥	2 (0.9)	0	0	0	2 (0.4)	0

TEAE = treatment-emergent adverse event, Graded using Common Terminology Criteria for Adverse Events (CTCAE)
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
A subject with two or more adverse events in the same system organ class (or with the same preferred term) is counted once for that system organ class (or preferred term).
Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_6_2.sas 18JUN201520:59

付録 2.7.6-2
Study 309
Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
生殖系および乳房障害 (contd)						
外陰膣そう痒症	1 (0.4)	0	0	0	1 (0.2)	0
呼吸器、胸郭および縦隔障害	37 (16.4)	0	14 (6.3)	2 (0.9)	51 (11.3)	2 (0.4)
咳嗽	15 (6.6)	0	1 (0.4)	0	16 (3.6)	0
発声障害	5 (2.2)	0	1 (0.4)	0	6 (1.3)	0
呼吸困難	10 (4.4)	0	6 (2.7)	0	16 (3.6)	0
労作性呼吸困難	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
鼻出血	3 (1.3)	0	1 (0.4)	1 (0.4)	4 (0.9)	1 (0.2)
しゃっくり	0	0	1 (0.4)	0	1 (0.2)	0
鼻閉	3 (1.3)	0	0	0	3 (0.7)	0
口腔咽頭痛	6 (2.7)	0	0	0	6 (1.3)	0
副鼻腔分泌過多	0	0	1 (0.4)	0	1 (0.2)	0
咽頭紅斑	1 (0.4)	0	0	0	1 (0.2)	0
気胸	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
湿性咳嗽	1 (0.4)	0	0	0	1 (0.2)	0
肺塞栓症	0	0	1 (0.4)	0	1 (0.2)	0

TEAE = treatment-emergent adverse event, Graded using Common Terminology Criteria for Adverse Events (CTCAE)
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
A subject with two or more adverse events in the same system organ class (or with the same preferred term) is counted once for that system organ class (or preferred term).
Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_6_2.sas 18JUN201520:59

付録 2.7.6-2
Study 309
Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
呼吸器、胸郭および縦隔障害 (contd)						
鼻痛	1 (0.4)	0	0	0	1 (0.2)	0
鼻漏	4 (1.8)	0	1 (0.4)	0	5 (1.1)	0
副鼻腔うっ血	1 (0.4)	0	0	0	1 (0.2)	0
上気道咳症候群	1 (0.4)	0	0	0	1 (0.2)	0
皮膚および皮下組織障害	93 (41.2)	1 (0.4)	31 (13.8)	1 (0.4)	124 (27.6)	2 (0.4)
脱毛症	78 (34.5)	1 (0.4)	6 (2.7)	0	84 (18.7)	1 (0.2)
ざ瘡様皮膚炎	1 (0.4)	0	0	0	1 (0.2)	0
アレルギー性皮膚炎	0	0	1 (0.4)	0	1 (0.2)	0
皮膚乾燥	5 (2.2)	0	2 (0.9)	0	7 (1.6)	0
紅斑	2 (0.9)	0	3 (1.3)	0	5 (1.1)	0
毛髪変色	1 (0.4)	0	0	0	1 (0.2)	0
多汗症	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
睫毛眉毛脱落症	1 (0.4)	0	0	0	1 (0.2)	0
爪の障害	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
爪線状隆起	0	0	1 (0.4)	0	1 (0.2)	0

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Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
A subject with two or more adverse events in the same system organ class (or with the same preferred term) is counted once for that system organ class (or preferred term).
Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_6_2.sas 18JUN201520:59

付録 2.7.6-2
Study 309
Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
皮膚および皮下組織障害 (contd)						
爪毒性	1 (0.4)	0	0	0	1 (0.2)	0
爪甲離床症	1 (0.4)	0	0	0	1 (0.2)	0
爪甲脱落症	1 (0.4)	0	0	0	1 (0.2)	0
皮膚疼痛	0	0	1 (0.4)	0	1 (0.2)	0
手掌・足底発赤知覚不全症候群	2 (0.9)	0	0	0	2 (0.4)	0
点状出血	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
光線過敏性反応	1 (0.4)	0	8 (3.6)	0	9 (2.0)	0
そう痒症	4 (1.8)	0	3 (1.3)	0	7 (1.6)	0
全身性そう痒症	1 (0.4)	0	0	0	1 (0.2)	0
発疹	5 (2.2)	0	4 (1.8)	0	9 (2.0)	0
瘢痕痛	1 (0.4)	0	0	0	1 (0.2)	0
皮膚亀裂	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
皮膚色素過剰	1 (0.4)	0	0	0	1 (0.2)	0
皮膚潰瘍	1 (0.4)	0	0	0	1 (0.2)	0
日光皮膚炎	0	0	1 (0.4)	0	1 (0.2)	0
皮膚のべとつき感	1 (0.4)	0	0	0	1 (0.2)	0

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Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
A subject with two or more adverse events in the same system organ class (or with the same preferred term) is counted once for that system organ class (or preferred term).
Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_6_2.sas 18JUN201520:59

付録 2.7.6-2
Study 309
Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Eribulin (N=226) All Grades n(%)	Eribulin (N=226) Grade >= 3 n(%)	Dacarbazine (N=224) All Grades n(%)	Dacarbazine (N=224) Grade >= 3 n(%)	Total (N=450) All Grades n(%)	Total (N=450) Grade >= 3 n(%)
皮膚および皮下組織障害 (contd)						
顔面腫脹	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
毛細血管拡張症	0	0	1 (0.4)	0	1 (0.2)	0
蕁麻疹	1 (0.4)	0	0	0	1 (0.2)	0
血管障害	15 (6.6)	0	11 (4.9)	1 (0.4)	26 (5.8)	1 (0.2)
深部静脈血栓症	0	0	1 (0.4)	0	1 (0.2)	0
潮紅	4 (1.8)	0	0	0	4 (0.9)	0
血腫	0	0	1 (0.4)	0	1 (0.2)	0
ほてり	3 (1.3)	0	2 (0.9)	0	5 (1.1)	0
高血圧	3 (1.3)	0	3 (1.3)	0	6 (1.3)	0
低血圧	4 (1.8)	0	2 (0.9)	1 (0.4)	6 (1.3)	1 (0.2)
起立性低血圧	1 (0.4)	0	0	0	1 (0.2)	0
血管痛	0	0	1 (0.4)	0	1 (0.2)	0
静脈血栓症	0	0	1 (0.4)	0	1 (0.2)	0

TEAE = treatment-emergent adverse event, Graded using Common Terminology Criteria for Adverse Events (CTCAE)
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
A subject with two or more adverse events in the same system organ class (or with the same preferred term) is counted once for that system organ class (or preferred term).
Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

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付録2.7.6-3　死亡又は重篤な有害事象の被験者ごとの叙述（外国309試験）

死亡又は死亡以外の重篤な有害事象が認められた被験者に関する叙述を以下に示した。

被験者番号	投与群	転帰が死亡の重篤な有害事象	死亡以外の重篤な有害事象
11011002	ダカルバジン群		X
11031005	本薬群		X
11031006	ダカルバジン群		X
11031008	ダカルバジン群		X
11041003	本薬群		X
11041005	ダカルバジン群		X
11051003	本薬群		X
11061002	ダカルバジン群		X
11071007	本薬群		X
11091001	ダカルバジン群		X
11091005	本薬群		X
11101001	ダカルバジン群		X
11101006	本薬群		X
11101009	本薬群		X
11121002	本薬群	X	X
11131014	本薬群		X
11141002	本薬群		X
11141004	本薬群		X
11141007	ダカルバジン群		X
11141009	本薬群		X
11141010	ダカルバジン群		X
11151001	ダカルバジン群		X
11151002	本薬群		X
11191003	本薬群		X
11191004	本薬群		X
11191005	ダカルバジン群		X
11191006	ダカルバジン群		X
11191012	本薬群		X
11191013	本薬群		X
11211003	本薬群		X
11211004	本薬群	X	X
11211005	ダカルバジン群		X
11211014	本薬群		X
11211021	本薬群		X
11211025	本薬群		X
11211026	ダカルバジン群	X	X
11211028	ダカルバジン群		X

被験者番号	投与群	転帰が死亡の重篤な有害事象	死亡以外の重篤な有害事象
11211030	ダカルバジン群		X
11221001	本薬群		X
11221004	ダカルバジン群		X
11221006	本薬群		X
11221007	ダカルバジン群		X
11231001	ダカルバジン群		X
11231004	ダカルバジン群		X
11251002	本薬群		X
11271001	本薬群		X
11271003	本薬群		X
11271004	本薬群		X
11271006	ダカルバジン群		X
11291001	本薬群	X	X
11291005	ダカルバジン群		X
11361001	ダカルバジン群		X
11381002	ダカルバジン群		X
11391004	ダカルバジン群		X
11991002	本薬群		X
11991004	本薬群		X
11991005	ダカルバジン群		X
12011003	ダカルバジン群		X
12021002	ダカルバジン群		X
12021005	ダカルバジン群		X
14031001	ダカルバジン群		X
14051001	本薬群	X	X
17011001	ダカルバジン群		X
17021002	ダカルバジン群		X
17021004	本薬群	X	X
17021006	本薬群		X
17021007	本薬群	X	X
17021008	ダカルバジン群		X
17021013	本薬群		X
17021016	ダカルバジン群		X
18011001	本薬群		X
18011003	ダカルバジン群		X
18011005	本薬群		X
18011006	本薬群		X
18011007	本薬群		X
18011008	本薬群		X
19011003	ダカルバジン群		X

被験者番号	投与群	転帰が死亡の重篤な有害事象	死亡以外の重篤な有害事象
19021002	本薬群		X
19021011	本薬群		X
19021012	本薬群		X
19031001	本薬群		X
19041011	ダカルバジン群		X
19041013	本薬群		X
19041014	ダカルバジン群		X
19041018	ダカルバジン群		X
19081006	ダカルバジン群		X
19081007	ダカルバジン群	X	X
19081011	本薬群		X
19081014	ダカルバジン群		X
19081016	本薬群		X
19081017	ダカルバジン群		X
21011001	本薬群		X
21011002	ダカルバジン群		X
21031002	ダカルバジン群		X
21031004	ダカルバジン群		X
21041005	ダカルバジン群		X
22011005	ダカルバジン群		X
22021003	本薬群		X
22031003	ダカルバジン群		X
22041011	本薬群	X	
22051003	本薬群		X
22061001	本薬群	X	
22061002	ダカルバジン群	X	
22081002	ダカルバジン群		X
23011003	本薬群		X
23011007	本薬群		X
23021001	ダカルバジン群		X
23021002	ダカルバジン群		X
24011002	ダカルバジン群		X
24011004	本薬群	X	X
24031004	ダカルバジン群		X
24031006	本薬群		X
24051005	ダカルバジン群		X
24071001	ダカルバジン群		X
26011006	ダカルバジン群		X
26011007	ダカルバジン群		X
26011009	本薬群		X

被験者番号	投与群	転帰が死亡の重篤な有害事象	死亡以外の重篤な有害事象
26021005	ダカルバジン群		X
26031003	本薬群		X
32011001	ダカルバジン群		X
32041002	本薬群		X
33011004	ダカルバジン群		X
35011002	本薬群		X
35011005	ダカルバジン群		X
35031001	ダカルバジン群		X
35061012	本薬群		X
41011001	本薬群		X
41011004	本薬群		X
41011005	ダカルバジン群		X
41021002	ダカルバジン群		X
41031002	ダカルバジン群		X
41031003	本薬群		X
41031005	本薬群		X
44041001	本薬群	X	X
44041005	本薬群		X
46031002	本薬群		X
46041008	本薬群		X
46041009	ダカルバジン群		X
47031003	本薬群		X
48021001	本薬群		X
48081001	ダカルバジン群		X
48091003	本薬群		X
48091008	ダカルバジン群		X
48111002	ダカルバジン群		X
48111004	本薬群		X
48121004	本薬群		X
48121005	本薬群		X

転帰が死亡の重篤な有害事象（本薬群；10例）

被験者番号	11121002
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
転帰が死亡の重篤な有害事象	好中球減少性敗血症/Neutropenic sepsis
死亡以外の重篤な有害事象	好中球減少性敗血症/Neutropenic sepsis
治験薬の投与中止に至った有害事象	好中球減少性敗血症/Neutropenic sepsis

A 68-year-old white female was diagnosed with high grade leiomyosarcoma in uterus on 07 Dec 1999. The last date of disease progression was 07 Dec 2012. Significant medical history included alopecia, cough, constipation, deep vein thrombosis, hypertension, hyperthyroidism, myalgia, dyspnoea, and sinus tachycardia. At Screening, tumor assessments of target/non-target lesions via CT scan showed left upper lobe and right lower lobe lung masses. The subject received previous radiotherapy to chest wall in association with axillary node. Previous anticancer therapy included carboplatin, doxorubicin, gemcitabine, paclitaxel and docetaxel. Prior and concomitant medications included azithromycin, codeine, diphenhydramine, enoxaparin, fish oil, fluconazole, gabapentin, granisetron, levothyroxine, metoprolol, ondansetron, prednisone, and ranitidine. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 54), the subject was hospitalized for neutropenic sepsis (Grade 4) with symptoms of shortness of breath, throat pain, severe body pains, dehydration, hypotension, tachycardia and hypoxia. Laboratory results showed absolute neutrophil count of 0.1 x10^9/L (NR: 1.7-7.9). She was treated with vasopressors, levofloxacin and cefepime. The study drug was withdrawn due to neutropenic sepsis and the subject received the last dose of the study drug on [redacted] (Day 49).

On [redacted] (Day 56, 7 days after last dose), the subject died due to neutropenic sepsis. The Investigator considered neutropenic sepsis serious and possibly related to the study drug.

被験者番号	11211004
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
転帰が死亡の重篤な有害事象	急性呼吸不全/Acute respiratory failure
死亡以外の重篤な有害事象	急性呼吸不全/Acute respiratory failure
治験薬の投与中止に至った有害事象	急性呼吸不全/Acute respiratory failure
病勢進行による死亡	Yes

A 50-year-old white female was diagnosed with high grade leiomyosarcoma in left thigh on 26 Oct 2009. The last date of disease progression was 16 Mar 2011. Significant medical history included cough, fatigue, paraesthesia, gastrooesophageal reflux disease, hysterosalpingo-oophorectomy, non-cardiac chest pain, asthenia, arthralgia, hepatic cyst, kidney malrotation, mitral valve incompetence, urinary tract infection, exertional dyspnea, sinus tachycardia, endometrial ablation, and tricuspid valve incompetence. At Screening, tumor assessments of target/non-target lesions via CT scan showed left upper lobe, left lower lobe, right upper lobe and right middle lobe lung masses, multiple intramuscular masses, and lesions in right posterior thigh, right hip, right intercostal muscle, left deltoid, pleural effusion, right posterior inferior paraspinal, left medial thigh, right iliopsoas muscle and right posterior thigh. The subject received previous radiotherapy to right posterior thigh. Previous anticancer therapy included doxorubicin, th-cr-302 (investigational drug) and trabectedin. Prior and concomitant medications included alprazolam, benzonatate, dextrose and sodium chloride injection, digoxin, diltiazem, enoxaparin, estradiol, eszopiclone, fexofenadine, filgrastim, fluconazole, furosemide, granisetron, iron, megestrol, nebivolol, ondansetron, pantoprazole, paracetamol, pegfilgrastim, prochlorperazine, salbutamol, tussionex pennkinetic, and vancomycin. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 61), the subject was hospitalized for acute respiratory failure (Grade 4). She also experienced asthenia (Grade 2), decreased appetite (Grade 2), dyspnea (Grade 2), hypotension (Grade 1), lactic acidosis (Grade 1), supraventricular tachycardia (Grade 1), hypercapnia (Grade 1), lethargy (Grade 1), hyperbilirubinaemia (Grade 1), thrombocytopenia (Grade 1), somnolence (Grade 1), hematuria (Grade 1), pneumonia (Grade 2) and sepsis (Grade 2). Chest x-ray and CT scan showed extensive pulmonary mass. The subject was treated with oxygen, furosemide, albumin human, calcium carbonate, doripenem, cefepime, dexamethasone, hydromorphone, levofloxacin, and methylprednisolone. The subject was withdrawn from the study due to acute respiratory failure and clinical disease progression. The last dose of the study drug was received on [redacted] (Day 57). The Investigator considered acute respiratory failure serious and not related to the study drug but related to the disease progression and pneumonia and all other events non-serious and not related to the study drug.

On [redacted] (Day 66, 9 days after last dose), the subject died due to worsening of acute respiratory failure secondary to disease progression.

被験者番号	11291001
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
転帰が死亡の重篤な有害事象	腸閉塞/Intestinal obstruction
死亡以外の重篤な有害事象	腸管虚血/Intestinal ischaemia, 腎盂腎炎/Pyelonephritis, 小腸閉塞/Small intestinal obstruction, 尿路感染/Urinary tract infection
治験薬の投与中止に至った有害事象	腸管虚血/Intestinal ischaemia

A 44-year-old white female was diagnosed with high grade dedifferentiated adipocytic sarcoma in pancreas on 12 Oct 2009. The last date of disease progression was 29 Dec 2011. Significant medical history included sarcoma excision, tumor excision, abdominal pain, adrenal insufficiency, chemo-induced menopause, constipation, depression, dysuria, anaemia, urinary tract infection, nausea, vomiting, pancreatectomy, rib excision, and splenectomy. At Screening, tumor assessments of target/non-target lesions via CT scan showed retroperitoneal mass filling whole abdomen, subumbilical retroperitoneal mass, shoulder girdle mass, left costophrenic mass, lesions in left lateral rib space between 9 and 10, multiple sacral and lumbar masses. The subject received previous radiotherapy to soft tissue mass of the pelvis, to left lower lung mass and to the left rib at L1. Previous anticancer therapy included doxorubicin and ifosfamide. Prior and concomitant medications included bisacodyl, blood and related products, cyclobenzaprine, dexamethasone, docusate w/senna, gabapentin, hydromorphone, lactulose, lorazepam, macrogol, metoclopramide, morphine, ondansetron, oxycodone, and prochlorperazine. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 10), the subject was hospitalized for urinary tract infection (Grade 3) associated with fever of 39 degree celsius (NR: 36.5-37.2). She was treated with bactrim, potassium, ciprofloxacin, and piperacillin/tazobactam. On [redacted] (Day 12), the subject recovered from this event. The Investigator considered urinary tract infection serious and not related to the study drug, but related to the urinary stent and history of chronic urinary tract infections. The study drug dose was not changed.

On [redacted] (Day 58), the subject was hospitalized for small intestinal obstruction (Grade 3) associated with abdominal bloating, nausea and vomiting with meals. On physical examination, abdomen was distended and tympanitic in upper quadrants with large firm mass in lower quadrants extending almost to umbilicus. Abdominal CT showed high grade or complete small bowel obstruction. She was treated with potassium, IV fluid, and ondansetron. She underwent ascending loop colostomy and was kept on total parenteral nutrition. On [redacted] (Day 68), she recovered from this event. The Investigator considered intestinal obstruction serious and not related to the study drug, but related to the tumor burden. The study drug dose was not changed.

On [redacted] (Day 95), the subject was hospitalized for pyelonephritis (Grade 3) with low grade fever, WBC count of 27 x 10^9/L (NR: 4.4-11), creatinine of 2.43 mg/dl (NR: 0.6-1.1) and positive urinary culture with enterococcus bacteria. She underwent urinary stent exchange and was treated with ceftriaxone, fluvoxamine, amoxicillin, hydromorphone, potassium and oxybutynin. On [redacted] (Day 99), she recovered from this event. The Investigator considered pyelonephritis serious and not related to the study drug. The study drug dose was not changed.

On [redacted] (Day 127), the subject was again hospitalized for intestinal ischemia (Grade 3). Laboratory test showed potassium of 3.3mmol/L (NR: 3.5-5.5). She was treated with potassium. The study drug was withdrawn due to this event and the last dose of study drug was received on [redacted] (Day 125). On [redacted] (Day 131), she recovered from this event. The Investigator considered intestinal ischemia serious and not related to the study drug.

On [redacted] (Day 153, 28 days after last dose), the subject died due to intestinal obstruction secondary to clinical progression. No other information was provided. The Investigator considered intestinal obstruction serious and not related to the study drug.

被験者番号	14051001
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
転帰が死亡の重篤な有害事象	誤嚥性肺炎/Pneumonia aspiration
死亡以外の重篤な有害事象	誤嚥性肺炎/Pneumonia aspiration，骨転移/Metastases to bone，頚部転移/Metastases to neck
治験薬の投与中止に至った有害事象	誤嚥性肺炎/Pneumonia aspiration

A 72-year-old white female was diagnosed with intermediate grade leiomyosarcoma in medial calf of the left leg on 18 Mar 2010. The last date of disease progression was 20 Feb 2013. Significant medical history included asthma, wrist fracture, hypertension, metastases to neck, radical neck dissection and arthralgia. At Screening, tumor assessments of target/non-target lesions via CT scan showed left lower lobe lung mass, left and right adrenal mass, right iliacus mass, lesions in left sartorius muscle, right abductor muscle and left upper chest wall. The subject received previous radiotherapy to the left leg and previous anticancer therapy included doxorubicin, carboplatin and ifosfamide. Prior and concomitant medications included ascorbic acid, fish oil, iron, lidocaine, metoclopramide, morphine, ondansetron, paracetamol, sodium bicarbonate, temazepam, tibolone and verapamil. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 88), the subject was hospitalized for elective surgery of excision of the metastatic lesion to the right neck and sacrum (Grade 3). The subject was noted to have metastatic to sacrum (Grade 2) on [redacted] (Day 43). The study drug was interrupted due to these events. She received treatment with temazepam and paracetamol. On [redacted] (Day 91), the subject experienced increased shortness of breath secondary to aspiration pneumonia (Grade 4) from the neck incision. She was treated with hyoscine, midazolam and morphine. The study drug was withdrawn due to aspiration pneumonia. The last dose of the study drug was received on [redacted] (Day 71). She did not recover from these events. On [redacted] (Day 92, 21 days after last dose), the subject died due to worsening of aspiration pneumonia. The Investigator considered metastases to neck, metastases to bone and aspiration pneumonia serious and not related to the study drug.

被験者番号	17021004
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
転帰が死亡の重篤な有害事象	全身健康状態低下/General physical health deterioration
死亡以外の重篤な有害事象	発熱性好中球減少症/Febrile neutropenia
病勢進行による死亡	Yes

A 67-year-old white male was diagnosed with high grade dedifferentiated adipocytic sarcoma of skin on 10 Nov 2003. The last date of disease progression was 17 Oct 2011. Significant medical history included anemia, anxiety, insomnia, mood alteration, articular calcification, dyspnea, fatigue, inguinal hernia repair, hepatic cyst, hepatic steatosis, pancreatic steatosis, lipoma excision, non-cardiac chest pain, trigeminal neuralgia, tumor pain, pleural effusion and uvuloplasty. At screening, tumor assessments of target/non-target lesions via CT scan showed left axilla musculoskeletal mass, right middle lobe and left lower lobe lung masses, and lesions in right gluteus soft tissue. The subject received previous radiotherapy to left scapula and previous anticancer therapy included doxorubicin, and ifosfamide. Prior and concomitant medications included alprazolam, duovent, fusidic acid, haloperidol, lormetazepam, miconazole, morphine, movicol, paracetamol, potassium, tramadol, and ultracet. ECOG performance status at screening was 2.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 10), the subject was hospitalized for febrile neutropenia (Grade 3) with neutrophil count of 0.3 x 10^9/L (NR: 2.5-7.8), also associated with fever, dyspnea, and general physical deterioration. The subject was treated with piperacillin/tazobactam, morphine and duovent. The study drug dose was not changed. On [redacted] (Day 18), the subject recovered with sequelae from this event. The Investigator considered febrile neutropenia serious and probably related to the study drug.

On [redacted] (Day 18), the subject was withdrawn from the study due to clinical disease progression and the last dose of the study drug was received on [redacted] (Day 8). On [redacted] (Day 22, 14 days after last dose), the subject died due to general physical health deterioration secondary to disease progression.

被験者番号	17021007
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
転帰が死亡の重篤な有害事象	大腸穿孔/Large intestine perforation
死亡以外の重篤な有害事象	大腸穿孔/Large intestine perforation, 腹膜炎/Peritonitis
病勢進行による死亡	Yes

A 52 year-old white female was diagnosed with high grade leiomyosarcoma in musculus adductor brevis on 20 Aug 2007. The last date of disease progression was 19 Mar 2012. Significant medical history included alopecia, anemia, muscle biopsy, oesophageal candidiasis, right hemipelvectomy, and tumor pain. At Screening, tumor assessments of target/non-target lesions via CT scan showed right adrenal mass, multiple lung masses, lesions in right and left flank soft tissue, and multiple soft tissue trunk lesions. The subject received previous radiotherapy to right leg/foot and previous anticancer therapy included doxorubicin and ifosfamide. Prior and concomitant medications included alizapride, alprazolam, amikacin, packed blood cells transfusion, chlorpromazine, ciprofloxacin, fluconazole, furosemide, haloperidol, lorazepam, magnesium sulfate, methylprednisolone, miconazole, naproxen, pantoprazole, paracetamol, pipracillin/tazobactam, potassium, sterimar and vitapantol. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 22), the subject experienced fatigue (Grade 3) and recovered from this event on [redacted] (Day 28). On [redacted] (Day 29), the study drug dose was reduced to 1.1 mg/m^2 due to this event. The Investigator considered fatigue non-serious and probably related to the study drug.

On [redacted] (Day 75), the subject was hospitalized for abdominal pain, nausea, vomiting and anorexia. She was diagnosed with peritonitis (Grade 3) secondary to a sigmoid colon perforation (Grade 3) (large intestine perforation) and was treated with morphine. CT scan confirmed sigmoid perforation and peritonitis. On [redacted] (Day 76), tumor response assessment showed disease progression and the subject was withdrawn from the study. The last dose of the study drug was received on [redacted] (Day 64). She did not recover from these events. On [redacted] (Day 94, 30 days after last dose), the subject died due to worsening of large intestine perforation secondary to disease progression. The Investigator considered peritonitis and large intestine perforation serious and not related to the study drug but related to disease progression.

被験者番号	22041011
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
転帰が死亡の重篤な有害事象	呼吸不全/Respiratory failure
病勢進行による死亡	Yes

A 47-year-old white female was diagnosed with high grade leiomyosarcoma in the uterus on 06 Dec 2010. The last date of disease progression was 27 Apr 2012. Significant medical history included chronic venous insufficiency, depression and factor V deficiency. At Screening, tumor assessments of target/non-target lesions via CT scan showed right pleural mass, left lower and left upper lobe lung masses. Previous anticancer therapy included doxorubicin and ifosfamide. Prior and concomitant medications included furosemide, gabapentin, levosulpiride, nadroparin, nystatin, oxygen therapy, paracetamol, prednisone, rabeprazole, sennoside a+b, tramadol and venlafaxine. At Baseline, peripheral neuropathy was 0 and ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 15), the subject experienced peripheral sensory neuropathy in limbs (Grade 1) and worsened to Grade 2 on [redacted] (Day 22). On [redacted] (Day 29), the study drug dose was reduced to 1.1 mg/m^2. She did not recover from this event. The Investigator considered peripheral sensory neuropathy non-serious and probably related to the study drug.

On [redacted] (Day 38), tumor response assessment showed unequivocal progression of an individual lesion in left upper lobe of the lung. On [redacted] (Day 43), the subject was withdrawn from the study due to disease progression and received the last dose of the study drug on [redacted] (Day 36). On [redacted] (Day 43), the subject experienced respiratory insufficiency (Grade 3) secondary to disease progression and was treated with oxygen and dexamethasone. On [redacted] (Day 50, 14 days after last dose), the subject died due to respiratory failure. The Investigator considered respiratory insufficiency serious and not related to the study drug, but related to disease progression.

被験者番号	22061001
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
転帰が死亡の重篤な有害事象	肺転移/Metastases to lung
病勢進行による死亡	不明

A 61-year-old white female was diagnosed with high grade leiomyosarcoma in ischial pubic on 27 Nov 2010. The last date of disease progression was 03 Aug 2012. Significant medical history included lung biopsy, cholecystectomy, excision of neurofibroma in left thigh and hysterosalpingo-oophorectomy. At Screening, tumor assessments of target/non-target lesions via CT scan showed left upper lobe and left lower lobe lung masses and lesions in soft tissue trunk. The subject received previous radiotherapy to left ischio-pubic branch and previous anticancer therapy included cyclophosphamide, epirubicin, gemcitabine and ifosfamide. Prior and concomitant medications included dexamethasone, glibenclamide and insulin. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

As reported by family member, on [redacted] (Day 34, 5 days after the last dose), the subject died suddenly due to lung metastasis secondary to clinical disease progression. The subject received the last dose of the study drug on [redacted] (Day 29). The Investigator considered this event serious and not related to the study drug.

被験者番号	24011004
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
転帰が死亡の重篤な有害事象	敗血症性ショック/Septic shock
死亡以外の重篤な有害事象	敗血症性ショック/Septic shock
治験薬の投与中止に至った有害事象	敗血症性ショック/Septic shock

A 69-year-old white female was diagnosed with high grade dedifferentiated adipocytic sarcoma in retroperitoneum on Oct 2009. The last date of disease progression was 02 Jan 2012. Significant medical history included anxiety, hypercholesterolaemia, hypertension, obesity, tumor excision, diabetes mellitus, malignant pituitary tumour, and pheochromocytoma excision. At Screening, tumor assessments of target/non-target lesions via CT scan showed left kidney mass, retroperitoneal mass with in contact of renal vein, and right lower lobe liver mass. Previous anticancer therapy included doxorubicin, gemcitabine, docetaxel and trabectedin. Prior and concomitant medications included augmentin, dexamethasone, fentanyl, furosemide, irbesartan, levofloxacin, lormetazepam, magnesium, megestrol, metformin, omeprazole, ondansetron, and venlafaxine. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 59), the subject complained of dyspnea. She was found to have poor performance status, low oxygen saturation and tachypnea. Her ECOG performance status on Day 43 * was 2. The subject was diagnosed with septic shock cause unknown (Grade 4). During hospitalization, the subject was found to have worsening asthenia (Grade 4), muscular weakness (Grade 1), neutropenia (Grade 4), lymphopenia (Grade 3), anemia (Grade 2) and pleural effusion (Grade 2). Laboratory tests showed absolute neutrophil count of 0.34 x 10^9/L (NR: 1.7 – 7.9), WBC count of 0.63 x 10^9/L (NR: 3.7 – 11), and hemoglobin of 96 g/L (NR: 110-155). The subject was treated with dexketoprofen, filgrastim, bemiparin, pipracillin/tazpbactam, lorazepam, heparin, tramadol, insulin, gelatin (substitute and perfusion solution) and morphine. The study drug was withdrawn due to septic shock and the subject received the last dose of the study drug on [redacted] (Day 57). On [redacted] (Day 60, 3 days after the last dose), the subject died due to septic shock. The Investigator considered septic shock serious and not related to the study drug; urinary tract infection, asthenia, muscular weakness, neutropenia, lymphopenia, anemia, and pleural effusion non-serious and not related to the study drug.

* 新薬承認情報提供時に置き換え

被験者番号	44041001
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
転帰が死亡の重篤な有害事象	呼吸不全/Respiratory failure
死亡以外の重篤な有害事象	好中球減少症/Neutropenia，呼吸不全/Respiratory failure
病勢進行による死亡	不明

A 56-year-old white female was diagnosed with high grade leiomyosarcoma in corpus uteri on 19 Aug 2009. The last date of disease progression was 08 Nov 2011. Significant medical history included chronic bronchitis, chronic laryngitis, alopecia, liver metastasectomy, lung metastasectomy, osteoporosis and peripheral sensory neuropathy. At Screening, tumor assessments of target/non-target lesions via CT scan showed right middle lobe, right lower lobe and left lower lobe lung masses, left medial/quadrate lobe, right lower lobe liver masses and uterine mass. Previous anticancer therapy included carboplatin, docetaxel, epirubicin, gemcitabine and paclitaxel. Prior and concomitant medications included filgrastim. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 8), the subject experienced neutropenia (Grade 3) with absolute neutrophil count (ANC) of 0.9 x 10^9/L (NR: 1.7-7.9) and was treated with filgrastim. On [redacted] (Day 22), the subject recovered from this event with ANC of 7.1 x10^9/L. The Investigator considered neutropenia serious and probably related to the study drug. The study drug dose was reduced to 1.1 mg/m^2 on [redacted] (Day 22) due to this event.

On [redacted] (Day 50), the subject experienced recurrent neutropenia (Grade 3) with ANC of 1.0 x 10^9/L and recovered from this event with ANC of 10.1 x10^9/L on [redacted] (Day 63). The Investigator considered recurrent neutropenia non-serious and probably related to the study drug. The study drug dose was interrupted due to this event on [redacted] (Day 50) and resumed at a reduced dose of 0.7 mg/m^2 on [redacted] (Day 64).

On [redacted] (Day 85), the subject was hospitalized for respiratory insufficiency (Grade 3) with symptoms of severe dyspnea, massive edema, oliguria and altered general status. She was treated with metoclopramide, hydrocortisone, phenobarbital enoxaparin, morphine and furosemide and recovered with sequelae on [redacted] (Day 90). The Investigator considered respiratory insufficiency serious and not related to the study drug. On [redacted] (Day 97, 26 days after last dose), the subject died due to worsening of respiratory insufficiency secondary to clinical disease progression. The last dose of the study drug was received on [redacted] (Day 71).

死亡以外のその他の重篤な有害事象（本薬群；66例）

被験者番号	11031005
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	白血球減少症/Leukopenia，好中球減少症/Neutropenia

A 51-year-old white female was diagnosed with high grade leiomyosarcoma in pelvis on 26 May 2011. The last date of disease progression was 18 Jul 2012. Significant medical history included allergies to contrast media, adhesive tape, dilaudid, lisinopril, alpha I proteinase inhibitor and sulfa drugs, vitamin b12 deficiency, benign essential hypertension, cervical polyp, tuberculin test positive, uterine fibroids, uterine leiomyoma, decreased lymphocyte count, tongue disorder, pelvic pain and drug eruption. At screening, tumor assessments of target/non-target lesions via CT scan showed right and left obturator internus mass, liver mass, right and left lower lobe pulmonary nodule and hypodense lesion in segment 6 of the liver. The subject received previous radiotherapy to the pelvic tumor. Previous anticancer therapy included gemcitabine, docetaxel, doxorubicin and ifosfamide. Prior and concomitant medications included acetylsalicylic acid, famotidine, lidocaine, lorazepam, naproxen, ondansetron, oxycocet, prochlorperazine, senna alexandrina, sumatriptan and telmisartan. ECOG performance status at screening was 0.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 14), the subject experienced neutropenia (Grade 4) and leukopenia (Grade 4). Laboratory results showed WBC count 0.7 x10^9/L (NR: 3.7-11), neutrophil count 0.1 x 10^9/L (NR: 1.7 – 7.9). On [redacted] (Day 22), the events of leukopenia improved to grade 2 and neutropenia improved to grade 1. The Investigator considered neutropenia and leukopenia serious and probably related to the study drug.

On [redacted] (Day 35), the subject experienced neutropenia (Grade 4) and leukopenia (Grade 4). Laboratory results showed WBC count 0.7 x10^9/L, and neutrophil count 0.2 x 10^9/L. The subject recovered from leukopenia on [redacted] (Day 42) with repeat WBC count of 4.3x10^9/L and did not recover from neutropenia. On [redacted] (Day 42), the events of neutropenia and leukopenia improved to Grade 3. The Investigator considered leukopenia and neutropenia serious and probably related to the study drug.

On [redacted] (Day 178), the tumor response assessment showed disease progression and the subject was withdrawn from the study. The subject received the last dose of the study drug on [redacted] (Day 164).

被験者番号	11041003
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	食道炎/Esophagitis

A 76-year-old hispanic female was diagnosed with high grade leiomyosarcoma in uterus on 15 Jan 2007. The last date of disease progression was 21 Jun 2011. Significant medical history included abdominal pain, bronchitis, decreased lymphocytes, hypercholesterolemia, intermittent anorexia, total abdominal hysterectomy and bilateral salpingo-oophorectomy, breast biopsy, cholecystectomy, hypertension, stomatitis, rapid heart rate and upper respiratory tract infection. At Screening, tumor assessments of target/non-target lesions via CT scan showed anterior mediastinal lung mass, mid abdomen subcutaneous lesion, pancreatic mass, right hepatic lobe mass, left lower lobe lung mass and bilateral pulmonary nodules. The subject received previous radiotherapy to the whole pelvis. Previous anticancer therapy included gemcitabine, docetaxel, carboplatin, letrozole, doxorubicin, ifosamide, temozolomide, trabectedin, doxorubicin, cyclophosphamide, and thalidomide. Prior and concomitant medications included alprazolam, alteplase, amifostine, duloxetine, dyazide, gabapentin, granisetron, heparin, hydroxyzine, magnesium sulfate, megestrol, metoclopramide, morphine, omeprazole, ondansetron, pantoprazole, paroxetine, pneumococcal vaccine, red blood cells, saliva substitute, sodium chloride, stomatologicals mouth preparations, triamcinolone, trolamine, vicodin and zolpidem. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 22), the subject was hospitalized for esophagitis (Grade 3) and distended abdomen (Grade 2). She underwent abdominal X-ray and upper gastrointestinal endoscopy which revealed plaques in the upper esophagus and normal small bowel. She was treated with sodium chloride, prochlorperazine and fluconazole and recovered from esophagitis on [redacted] (Day 24). The Investigator considered esophagitis serious and not related to the study drug and distended abdomen non-serious and not related to the study drug.

On [redacted] (Day 29), the subject withdrew from the study and received the last dose of the study drug on [redacted] (Day 1).

被験者番号	11051003
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	貧血/Anemia, Asthenia/無力症, 心房細動/Atrial fibrillation, 発熱性好中球減少症/Febrile neutropenia, 転移部痛/Metastatic pain, 急性腎不全/Renal failure acute, 気胸/Pneumothorax, 呼吸不全/Respiratory failure

A 47-year-old white male was diagnosed with high grade leiomyosarcoma in the right thigh on 06 May 2011. The last date of disease progression was 17 Jul 2012. Significant medical history included anemia, atrial fibrillation, bilateral lung nodules, pneumothorax, chest discomfort, chills, dry cough, increased blood creatinine, fatigue, asthenia, hemoptysis, hypertension, hypokalemia, pollakiuria, sarcoma, pleural effusion, flank pain, musculoskeletal pain, shortness of breath and sarcoma excision. At Screening, tumor assessments of target/non-target lesions via CT scan showed right upper lobe lung mass, left lower lobe lung mass, multiple bilateral pulmonary nodules, right and left pleural effusion. The subject received previous radiotherapy to the soft tissue sarcoma in right thigh. Previous anticancer therapy included doxorubicin, ifosfamide, gemcitabine, docetaxel, vinorelbine, and pazopanib. Prior and concomitant medications included acetylcysteine, amlodipine, benzonatate, cefazolin, cyclobenzaprine, dexamethasone, diltiazem, diovan triple, docusate with senna, fentanyl, glycopyrronium, haloperidol, heparin, hydralazine, hydrochlorothiazide, hydromorphone, influenza vaccine, lidocaine, lorazepam, macrogol, morphine, ondansetron, pantoprazole, piperacillin/tazobactam, potassium, prednisone, red blood cells, rivaroxaban, salbutamol, valsartan and vicodin. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 5), the subject was hospitalized for dyspnea on exertion (Grade 2) and atrial fibrillation (Grade 2). Chest X-ray and CT scan showed large loculated right hydropneumothorax. A right sided thoracocentesis drained over 500ml of sero-sanguinous fluid. On [redacted] (Day 8), the study drug was delayed and the subject underwent right sided video assisted thoracoscopic surgery with talc pleurodesis. He recovered from these events on [redacted] (Day 13). The Investigator considered pneumothorax and atrial fibrillation serious and not related to the study drug. The study drug was resumed on [redacted] (Day 12).

On [redacted] (Day 20), the subject was hospitalized for anemia (Grade 3), febrile neutropenia (Grade 2), acute renal failure (Grade 2) and asthenia (Grade 2). Laboratory tests showed that his temperature was 37.8 degree celsius (NR: 36.5-37.2), hemoglobin 82 g/L (NR: 110-155), creatinine 301 umol/L (NR: 62-124), BUN 7.85 mmol/L (NR: 1.78 -7.1), potassium 3.3 mmol/L (NR: 3.5 – 5) and neutrophil count was 1.1 x10^9/L (NR: 1.7 – 7.9). He was treated with vancomycin, piperaciliin/tazobactam, tobramycin, paracetomol, and transfused with red blood cells. He recovered from febrile neutropenia on [redacted] (Day 23) and did not recover from anemia and acute renal failure. The Investigator considered anemia, febrile neutropenia, asthenia serious and possibly related to the study drug and acute renal failure serious and not related to the study drug.

On [redacted] (Day 22), the tumor response assessment showed disease progression and the subject was withdrawn from the study. The subject received the last dose of the study drug on [redacted] (Day 12).

On [redacted] (Day 39), the subject was hospitalized for metastatic chest pain (Grade 3) and respiratory failure (Grade 4). His vitals were blood pressure 138/72 mmHg, pulse 112 beats/minute, respiratory rate16 beats/minute and temperature of 35.8 C. He was treated with hydromorphone. The subject did not recover from these events. The Investigator considered chest pain and respiratory failure serious and not related to the study drug.

The subject died on [redacted] (Day 46, 34 days after the last dose) due to disease progression.

被験者番号	11071007
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	粘液型脂肪肉腫/Myxoid liposarcoma

A 52-year old white female was diagnosed histologically with intermediate grade myxoid liposarcoma in left thigh on 09 Aug 2005. The last date of disease progression was 14 Dec 2012. Significant medical history included bile duct stent insertion, myalgia, muscle spasms, bile duct perforation arthralgiaand peripheral sensory neuropathy. At screening, tumor assessments of target/non-target lesions via CT scan showed retropleural and peritoneal/omental masses. The subject received previous radiotherapy to L2-L3 paravertebral area. Previous anticancer therapy included cixutumumab, doxorubicin, ifosfamide and trabectedin. Prior and concomitant medications included amitriptyline, desflurane, docusate, ephedrine, flebobag ringlact, gabapentin, granisetron, ibuprofen, levofloxacin, lidocaine, lorazepam, magnesium hydroxide, mirtazapine, naproxen, nystatin, paracetamol, pegfilgrastim, penciclovir, hydrocodone-acetaminophen, prochlorperazine, suxamethonium, ampicillin/sulbactam and zolpidem. At Screening, peripheral sensory neuropathy was 0 and ECOG performance status was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 8), the subject experienced neutropenia (Grade 4) with white blood cell (WBC) count of 1.5 x10^9/L (NR: 3.7-11) and neutrophil count 0.3 x 10^9/L (NR: 1.7 – 7.9). She was treated with pegfilgrastim and recovered from neutropenia on [redacted] (Day 15). On the same day, study drug dose was reduced to 1.1 mg/m^2 due to neutropenia. The Investigator considered neutropenia non-serious and probably related to the study drug.

On [redacted] (Day 162), the subject experienced peripheral sensory neuropathy (Grade 2). On the same day, the study drug dose was reduced to 0.7 mg/m^2 due to neuropathy. She was treated with gabapentin and recovered from the event of neuropathy on [redacted] (Day 176). The Investigator considered this event non-serious and probably related to the study drug.

On [redacted] (Day 297), the subject was withdrawn from the study due to clinical disease progression. The subject received the last dose of the study drug on the same day.

On [redacted] (Day 317), the subject was hospitalized for surgical resection of cystic myxoid liposarcoma (Grade 1). She was treated with sevoflurane, midazolam, phenylephrine, fentanyl, ondansetron, dexamethasone, propofol, lidocaine, rocuronium, cefoxitin, ketamine, hydromorphone, glycopyronium, neostigmine and heparin. On [redacted] (Day 319), myxoid liposarcoma lesion was considered as recovered. The Investigator considered this event serious and not related to the study drug.

被験者番号	11091005
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	呼吸困難/Dyspnea，白血球減少症/Leukopenia，好中球減少症/Neutropenia，非心臓性胸痛/Non-cardiac chest pain[注)]，上大静脈症候群/Superior vena cava syndrome

注）非心臓性胸痛は投与前に発現しており，重篤な有害事象として集計されていない。

A 34-year old african-american female was diagnosed with high grade pleomorphic liposarcoma in right thigh on 10 Dec 2009. The last date of disease progression was 13 Apr 2012. Significant medical history included hypersensitivity to bactrim, brachytherapy, cancer pain, pulmonary embolism, wide local excision right thigh mass, cervical dysplasia, dysphagia and pneumonia. At Screening, tumor assessments of target/non-target lesions via CT scan showed mediastinal and pleural based lesions. The subject received previous radiotherapy to the right medial thigh, proximal femur, right neck, nodes and soft tissue. Previous anticancer therapy included docetaxel, gemcitabine, doxorubicin, ifosfamide, and temozolomide. Prior and concomitant medications included alteplase, bisacodyl, diphenhydramine, enoxaparin, famotidine, fentanyl, hydromorphone, ibuprofen, loperamide, midazolam, morphine, ondansetron, oxycodone, paracetamol, potassium, promethazine, red blood cells, stomatologicals and hydrocodone/acetaminophen. ECOG performance status at screening was 0.

On [redacted] (Day -10), the subject was hospitalized for non-cardiac chest pain (Grade 4). He was treated with morphine and hydromorphone and recovered on [redacted] (Day -6). The Investigator considered non-cardiac chest pain serious and not related to the study drug.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 8), the subject experienced neutropenia (Grade 3) with neutrophil count of 1.4 x 10^9/L (NR: 1.7 – 7.9) and leukopenia (Grade 2) with WBC count of 2.5 x 10^9/L (NR: 3.7 – 11). On [redacted] (Day 15), the subject was hospitalized for worsening shortness of breath (Grade 2). The neutropenia worsened to Grade 4 with neutrophil count of 0.2 x 10^9/L and leukopenia worsened to Grade 3 with WBC count of 1.2 x 10^9/L. Chest X-ray showed complete opacification of the right lung with increased pleural effusion and bronchoscopy showed compression of the right main bronchus. On [redacted] (Day 19), the subject experienced worsening pleural effusion of unknown etiology (Grade 3) which started on [redacted] (Day -6). On [redacted] (Day 21), a diagnosis of possible superior vena cava syndrome (Grade 2) was also made. The subject was treated with ipratropium with salbutamol. A pleural catheter was placed on the right side on [redacted] (Day 25). The subject recovered from neutropenia on [redacted] (Day 19) and from leukopenia on [redacted] (Day 20). She did not recover from pleural effusion, worsening shortness of breath and possible superior vena cava syndrome. The Investigator considered neutropenia serious (important medical event) and probably related to the study drug; dyspnea and possible superior vena cava syndrome serious and not related to the study drug but related to disease progression; leukopenia serious and possibly related to the study drug; and pleural effusion non-serious and not related to the study drug.

On [redacted] (Day19), the tumor response assessment showed disease progression and the subject was withdrawn from the study. The subject received the last dose of the study drug on [redacted] (Day 8).

被験者番号	11101006
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	細菌性腹膜炎/Bacterial peritonitis

A 32-year-old white female was diagnosed with high grade leiomyosarcoma in retroperitoneum on 16 Feb 2007. The last date of disease progression was 01 Dec 2011. Significant medical history included abdominal pain, asthma, cholecystectomy, exploratory laparotomy with sigmoid colectomy, gastrointestinal viral infection, left and right partial hepatectomy, mycoplasma pneumonia, omentectomy, partial gastrectomy, small intestinal resection and vulvovaginal mycotic infection. At Screening, tumor assessments of target/non-target lesions via CT scan showed right middle lobe lung mass, right upper quadrant mass, pelvis mass, multiple bilateral pulmonary nodules, multiple abdominal masses and multiple pelvic masses. Previous anticancer therapy included doxorubicin, ifosfamide, ridaforolimus, gemcitabine, docetaxel, vinorelbine, tamoxifen, temozolomide and trabectedin. Prior and concomitant medications included calcium with vitamin D, cyclobenzaprine, dexamethasone, docusate, fentanyl, fluconazole, fluoxetine, furosemide, hydromorphone, ibuprofen, lactulose, lidocaine, lorazepam, macrogol, mesna, mirtazapine, modafinil, morphine, nystatin, obetrol , ondansetron, oxycocet, oxycodone, paracetamol, prochlorperazine, red blood cells, sodium chloride, stomatologicals mouth preparations, vicodin and vitamins. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 6), the subject complained of persistent abdominal pain which started as Grade 2 on [redacted] (Day -12). A therapeutic paracentesis was performed which removed 1.5 liters of purulent fluid. Microbiological tests showed multiple species of bacteria. The subject was diagnosed and hospitalized for bacterial peritonitis (Grade 3) and abdominal sepsis (Grade 1). The subject was treated with ceftazidime, vancomycin, metronidazole, aztreonam and ciprofloxacin. On [redacted] (Day 8), KUB radiography showed possible foreign body or intra-abdominal abscess. On the same day, subject was found to have erythema at surgical scar (Grade 1). The study drug was interrupted due to erythema and intra-abdominal sepsis. The subject underwent exploratory laparotomy with drainage of the intraperitoneal abscess, lysis of the adhesions and loop ileostomy. On [redacted] (Day 16), the subject recovered from bacterial peritonitis and abdominal sepsis and did not recover from erythema at surgical scar. The Investigator considered bacterial peritonitis serious and not related to the study drug; abdominal sepsis and erythema at surgical scar non-serious and not related to the study drug. On [redacted] (Day 21), the study drug was resumed at a reduced dose of 1.1 mg/ m^2 due to peritonitis.

On [redacted] (Day 36), the tumor response assessment showed disease progression and the subject was withdrawn from the study. The subject received the last dose of the study drug on [redacted] (Day 28).

被験者番号	11101009
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	低リン酸血症/Hypophosphataemia,リンパ球減少症/Lymphopenia, シュードモナス性菌血症/Pseudomonal bacteraemia

A 33-year-old white male was diagnosed with intermediate grade myxoid liposarcoma in left thigh in 2003. The last date of disease progression was 04 Mar 2013. Significant medical history included lung biopsy, myxoid liposarcoma and sarcoma excision. At Screening, tumor assessments of target/non-target lesions via CT scan showed left pleural nodule, left pulmonary nodule and lesions in right femur bone. The subject received previous radiotherapy to left posterior thigh and pelvis. Previous anticancer therapy included doxorubicin, ifosfamide and trabectedin. Prior and concomitant medications included ascorbic acid, azithromycin, calcium carbonate, cetirizine, ciprofloxacin, dexamethasone, diphenhydramine, docusate, erythromycin, hydrocortisone, lidocaine, lorazepam, macrogol, omeprazole, ondansetron, pegfilgrastim, prochlorperazine, senna alexandrina and sodium chloride. ECOG performance status at screening was 0.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 97), the subject was hospitalized for pseudomonal bacteremia (Grade 3), hypophosphatemia (Grade 3) and lymphopenia (Grade 3) with lymphocyte count of 0.25 th/cmm (NR: 1- 4.88); phosphorus of 1.0 mg/dL (NR: 2.6-4.5), white blood cell count of 2.5 th/cmm (NR: 4.5-11.0); and red blood cell count of 4.3 mil/cmm (NR: 4.50-5.90). The study drug was interrupted due to bacteremia and was treated with cefepime. He recovered from pseudomonal bacteremia and hypophosphatemia on [redacted] (Day 100) and from lymphopenia on [redacted] (Day 101). The Investigator considered pseudomonal bacteremia serious and not related to the study drug; hypophosphatemia and lymphopenia serious and possibly related to the study drug. The study drug was resumed on [redacted] (Day 113).

On [redacted] (Day 446), the tumor response assessment showed disease progression and the subject was withdrawn from the study. The subject received the last dose of the study drug on [redacted] (Day 442).

被験者番号	11131014
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	痙攣/Convulsion, 好中球減少症/Neutropenia, 肺塞栓症/Pulmonary embolism

A 49-year-old white male was diagnosed with high grade adipocytic myxoid liposarcoma in right posterior thigh on 24 Mar 2011. The last date of disease progression was 24 Apr 2013. Significant medical history included nephrectomy, retroperitoneal mass excision, tumor excision (right posterior thigh), Parkinson's disease, and spinal cord compression. At Screening, tumor assessments of target/non-target lesions via CT scan showed peritoneal/omental mass, retroperitoneal mass, liver mass, gluteal mass, perisplenic mass, colorectal mass, rectal bone lesions and lung nodules. The subject received previous radiotherapy to posterior thigh, cervical and thoracic regio T4-T6, T9-T-11, L3-L5, T5 and T10. Previous anticancer therapy included blinded-palifosfamide (investigational trial), trabectedin, doxorubicin and ifosfamide. Prior and concomitant medications included amantadine, baclofen, furosemide, gabapentin, lorazepam, omeprazole, oxycodone, pramipexole, prednisone, prochlorperazine, senna alexandrina and sinemet. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 8), the subject experienced decreased neutrophil count (Grade 4) and anemia (Grade 2) with neutrophil count of 0.4 K/cumm (NR: 1.8 - 6.6) and hemoglobin of 82 g/L (NR: 125-170). On [redacted] (Day 15), the study drug dose was reduced to 1.1 mg/m^2 due to decreased neutrophil count. The subject was treated with blood transfusion and recovered on the same day from decreased neutrophil count. He recovered from anemia on [redacted] (Day 29). The Investigator considered decreased neutrophil count non-serious and probably related to the study drug and anemia is non-serious and possibly related to the study drug.

On [redacted] (Day 37), the subject was hospitalized for convulsion (Grade 3) and neutropenia (Grade 3) with neutrophil count of 0.8 x 10^9/L (NR: 1.7 – 7.9). CT scan and MRI of brain were normal and he was treated with levetiracetam. The subject recovered from neutropenia on [redacted] (Day 43). On [redacted] (Day 48), the subject recovered with sequelae from convulsion. The Investigator considered convulsion serious and possibly related to the study drug and neutropenia serious and probably related to the study drug.

On [redacted] (Day 36), the tumor response assessment showed disease progression and the subject was withdrawn from the study. The subject received the last dose of the study drug on [redacted] (Day 29).

On [redacted] (Day 59), the subject developed acute dyspnea and was hospitalized for pulmonary embolism due to cancer (Grade 4) with blood pressure of 70/40 mm Hg. CT scan of the chest showed no acute pathology or structural abnormalities. The subject was treated with IVC filter placement and did not recover from this event. On [redacted] (Day 62), the subject experienced respiratory distress and he was emergently intubated. On the same day (Day 62, 33 days after the last dose), the subject died due to respiratory failure secondary to progressive disease. The Investigator considered pulmonary embolism and respiratory failure serious and not related to the study drug.

被験者番号	11141002
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	上腕骨骨折/Humerus fracture
治験薬の投与中止に至った有害事象	末梢性感覚ニューロパチー/Peripheral sensory neuropathy

A 73-year-old white female was diagnosed with high grade leiomyosarcoma in uterus on 09 Jan 2006. The last date of disease progression was 22 Feb 2012. Significant medical history included resection of uterine leiomyosarcoma, resection of left-sided subcutaneous mass with complete abdominal hysterectomy. At Screening, tumor assessments of target/non-target lesions via CT scan showed left lateral lobe liver mass and right lower lobe liver mass. Previous anticancer therapy included doxorucicin, gemcitabine and docetaxel. Prior and concomitant medications included antacids, bactrim, calcium citrate with vitamin D, clotrimazole, colecalciferol, hydrocodone, levothyroxine, loratadine, minerals with vitamins, pegfilgrastim, sucralfate, vitamins and warfarin. At Screening, peripheral neuropathy was Grade 0 and ECOG performance status was 0.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 148), the subject was hospitalized for fracture of the humerus (Grade 3) secondary to fall (Grade 2). She also experienced ankle/pedal edema (Grade 1), and sensory touch disturbance of the hands (Grade 1) which was ongoing since [redacted] (Day 39) as Grade 1. The subject underwent proximal humerus resection with endoscopic reconstruction and removal of post-operative drain. The subject recovered on [redacted] (Day 180) from fracture of the humerus and did not recover from sensory disturbance and ankle/pedal edema. The Investigator considered fracture of the humerus serious and not related to the study drug; and ankle/pedal edema and sensory touch disturbance of the hands non-serious and possibly related to the study drug.

On [redacted] (Day 162), the subject experienced peripheral sensory neuropathy (Grade 3). The subject did not recover from peripheral sensory neuropathy. The study drug was withdrawn due to this event. The subject received the last dose of the study drug on [redacted] (Day 148). The Investigator considered peripheral sensory neuropathy non-serious and possibly related to the study drug.

被験者番号	11141004
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	貧血/Anemia

A 65-year-old white female was diagnosed with high grade leiomyosarcoma in uterus on 15 Dec 2009. The last date of disease progression was 17 Apr 2012. Significant medical history included malignant melanoma, and hysterosalpingo-oophorectomy. At Screening, tumor assessments of target/non-target lesions via CT scan showed left lower lobe lung mass and right and left pelvic lesions. Previous anticancer therapy included doxorubicn, gemcitabine, ifosfamide, docetaxel and trabectedin. Prior and concomitant medications included ondansetron, potassium, prochlorperazine and tramadol. ECOG performance status at screening was 0.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 8), the subject experienced neutropenia (Grade 3) with absolute neutrophil count of 1.2 x 10^9/L (NR: 1.7-7.9). The subject was treated with pegfilgrastim and recovered from neutropenia on [redacted] (Day 22). The Investigator considered neutropenia non-serious and probably related to the study drug. The study drug dose was reduced to 1.1mg/ m^2 due to this event.

On [redacted] (Day 42), the subject experienced anemia (Grade 3) with hemoglobin of 70 g/L (NR: 110-155) and hematocrit of 21.7% (NR: 33-47). She was transfused with packed human blood cells and recovered from anemia on [redacted] (Day 47). The Investigator considered anemia serious (important medical event) and possibly related to the study drug.

On [redacted] (Day 30), the tumor response assessment showed disease progression and the subject was withdrawn from the study. The subject received the last dose of study drug on [redacted] (Day 29).

被験者番号	11141009
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	好中球減少症/Neutropenia

A 71-year-old white female was diagnosed with intermediate grade leiomyosarcoma in uterus on 22 Feb 2002. The last date of disease progression was 06 Mar 2013. Significant medical history included dyspnoea, excision of left buttock metastasis, excision left buttock metastasis, right lateral chest wall mass excision, excision right distal vastus medialis muscle, resection of right knee and right hip masses, haemoglobinaemia, hypertension, left thoracotomy, osteopenia, retroperitoneal resection of leiomyosarcoma with right nephrectomy, right hepatectomy and right thoracotomy with wedge resections. At Screening, tumor assessments of target/non-target lesions via CT scan showed left posterior lung mass and left medial lung mass. The subject received previous radiotherapy to right kidney mass, right buttock combined with right periacetabular soft tissue and right knee. Previous anticancer therapy included doxorubicin, gemcitabine, ifosfamide, sorafenib, pazopanib, docetaxel, trabectedin and letrozole. Prior and concomitant medications included packed human blood cells, carvedilol, celecoxib, chlortalidone, colecalciferol, coroval b, cyanocobalamin, fentanyl, hydromorphone, letrozole, lorazepam, magnesium, ondansetron, senokot-s and vitamins. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 8), the subject experienced neutropenia (Grade 3) with neutrophil count of 0.61 x 10^9/L (NR: 1.7 – 7.9). The study drug dose was interrupted due to this event. On [redacted] (Day 9), the subject experienced neutropenia (Grade 4) with neutrophil count of 0.34 x 10^9/L and hemoglobinemia (Grade 4) with hemoglobin 10.1g/dL (NR: 11.0 – 15.5). The subject was treated with filgramstim and recovered on [redacted] (Day 22) from these events. On the same day, the study drug was resumed at reduced dose of 1.1 mg/m^2 due to these events. The Investigator considered neutropenia serious (important medical event) and probably related to the study drug; hemoglobinemia non-serious and probably related to the study drug.

On [redacted] (Day 29), the subject experienced neutropenia (Grade 3) with neutrophil count of 0.76 x 10^9/L. She was treated with filgramstim and recovered on [redacted] (Day 32). The study drug dose was reduced to 0.7 mg/m^2 due to this event. The Investigator considered neutropenia serious (important medical event) and probably related to the study drug.

On [redacted](Day 86), tumor response assessment showed disease progression and the subject was withdrawn from the study. The subject received the last dose of the study drug on [redacted] (Day 74).

被験者番号	11151002
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	白血球減少症/Leukopenia，好中球減少症/Neutropenia

A 57-year-old white male was diagnosed with high grade adipocytc dedifferentiated in pancreas on 25 Feb 2008. The last date of disease progression was in Jan 2012. Significant medical history included mesenteric mass resection, abdominal hernia, drug hypersensitivity to prochloperazine and hypertension. At Screening, tumor assessments of target/non-target lesions via CT scan showed right upper abdominal quadrant lesion, right lateral abdominal mass and right lower lung lobe lung mass. Previous anticancer therapy included doxorubicin, trabectedin and ifosfamide. Prior and concomitant medications included cibadrex, omeprazole, and triamcinolone. ECOG performance status at screening was 0.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 15), the subject experienced neutropenia (Grade 4) and leukopenia (Grade 3) with absolute neutrophil count of 0.4 x10^9/L (NR: 1.7-7.9) and WBC count of 1.4 x10^9/L (NR: 3.7-11). The subject recovered from neutropenia and leukopenia on [redacted] (Day 21). The Investigator considered these events serious (important medical events) and probably related to the study drug.

On [redacted] (Day 43), the subject withdrew his consent from the study. The subject received the last dose of study drug on [redacted] (Day 29).

被験者番号	11191003
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	病的骨折/Pathological fracture，創離開/Wound dehiscence

A 69-year-old white male was diagnosed with high grade adipocytic pleomorphic in right thigh on 07 Sep 2005. The last date of disease progression was 14 Sep 2011. Significant medical history included deep vein thrombosis, pathological right femur fracture, impaired glucose intolerance, hypercholesterolemia, hyperlipidemia, hypertension, peripheral edema, left femur sarcoma removal and resection of pleomorphic liposarcoma, obstructive sleep apnea, gastrectomy, splenectomy and pancreatectomy. At Screening, tumor assessments of target/non-target lesions via CT scan showed right anterior and posterior liver mass and multiple liver lesions. The subject received previous radiotherapy to left hip and right thigh. Previous anticancer therapy included ifosfamide, doxorubicin, gemcitabine and docetaxel. Prior and concomitant medications included ascorbic acid, cefalexin, filgrastim, iron, natural alterna, flaxseed oil plus lecithin, nicotinic acid, oxycocet, pantoprazole, pegfilgrastim, polysaccharide-iron complex, simvastatin, vicodin and warfarin. ECOG performance status at screening was 0.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 28), the subject experienced decreased white blood cells (WBC) (Grade 3) with WBC count of 1 x 10^9/L (NR: 3.7 – 11). On [redacted] (Day 29), the subject was found to have decreased neutrophils (Grade 4) with neutrophil count of 0.2x 10^9/L (NR: 1.7-7.9). The subject was treated with filgrastim. The study drug was interrupted due to both these events. On [redacted] (Day 36), the subject recovered from the events of decreased WBC and decreased neutrophils. The study drug was resumed at reduced dose of 1.1 mg/ m^2 due to decreased WBC. The Investigator considered these events non-serious and probably related to the study drug.

On [redacted] (Day 43), the subject experienced decreased neutrophils (Grade 3) with neutrophil count of 1 x 10^9/L and decreased WBC (Grade 3) with WBC count of 1.5 x 10^9/L. On [redacted] (Day 50), decreased white blood cell count improved to Grade 2 and decreased neutrophil worsened to Grade 3. Laboratory tests showed WBC count of 2.78 x10 ^9/L and absolute neutrophil count of 0.5 x10 ^9/L. The subject was treated with filgrastim. On [redacted] (Day 57), the subject recovered from decreased neutrophils and decreased WBC. On the same day, the study drug dose was reduced to 0.7 mg/ m^2 due to decreased neutrophils and decreased WBC. The Investigator considered these events non-serious and probably related to the study drug.

O [redacted] (Day 70), the subject was hospitalized with right hip pain. X-ray confirmed pathological right femur fracture (Grade 3). On [redacted] (Day 72), right proximal femoral replacement was performed. The subject was treated with procet and atorvastatin. On [redacted] (Day 89), the subject was re-hospitalized for wound dehiscence (Grade 3) after the removal of staples following the procedure. The subject underwent right thigh incision and drainage surgery and was treated with hydromorphone, vancomycin, cefepime and ceftriaxone. He recovered from wound dehiscence on [redacted] (Day 96) and from pathological fracture of femur on [redacted] (Day 181). The Investigator considered pathological fracture and wound dehiscence serious and not related to the study drug.

On [redacted] (Day 398), the tumor response assessment showed disease progression and the subject was withdrawn from the study. The subject received the last dose of the study drug on [redacted] (Day 384).

被験者番号	11191004
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	肺炎/Pneumonia

A 56-year-old white male was diagnosed with high grade adipocytic dedifferentiated in stomach in Aug 2007. The last date of disease progression was 04 Nov 2011. Significant medical history included dyspnea, sarcoma excision, hypertension, left iliopsoas mass excision, hypoaesthesia, abdominal pain, palmar-plantar erythrodysaesthesia syndrome, paresthesias of fingertips and muscular weakness. At Screening, tumor assessments of target/non-target lesions via CT scan showed left upper quadrant soft tissue mass, left psoas muscle mass, left retroperitoneum thickening, left upper lobe lung mass and subcentimeter liver lesion. The subject received previous radiotherapy to retroperitoneum adenopathy. Previous anticancer therapy included luminespib, docetaxel, gemcitabine, trabectedin, doxorubicin, ifosfamide and sorafenib. Prior and concomitant medications included amlodipine, augmentin, citalopram, dronabinol, fentanyl, filgrastim, gabapentin, lactulose, lisinopril, lorazepam, morphine, paracetamol, pegfilgrastim, sennoside a+b, zolpidem. At Screening, peripheral neuropathy was Grade 0 and ECOG performance status was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 2), the subject was hospitalized for pneumonia (Grade 2). The subject underwent a chest X-ray and was treated with levofloxacin, vancomycin and piperacillin/tazobactam. He recovered from pneumonia on [redacted] (Day 5). The Investigator considered pneumonia serious and not related to the study drug.

On [redacted] (Day 155), the subject experienced decreased neutrophil count (Grade 3) with neutrophil count of 0.9 x 10^9/L (NR: 1.7 -7.9). The subject recovered from this event on [redacted] (Day 161). On [redacted] (Day 176), the study drug dose was reduced to 1.1 mg/m^2. The Investigator considered decreased neutrophil count non-serious and probably related to the study drug.

On [redacted] (Day 225), the subject experienced hypoaesthesia of bilateral hands (Grade 3) and paraesthesia of left first toe (Grade 3). The subject had hypoaesthesia of the bilateral hand (Grade 1) since [redacted] (Day 58). The subject did not recover from hypoaesthesia of the bilateral hands and recovered from paraesthesia of left first toe on [redacted] (Day 300). The study drug dose was reduced to 0.7 mg/m^2 due to hypoaesthesia of the bilateral hands. The Investigator considered these events non-serious and probably related to the study drug

On [redacted] (Day 464), tumor response assessment showed disease progression and the subject was withdrawn from the study. The subject received the last dose of the study drug on [redacted] (Day 454).

被験者番号	11191012
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	真菌性下気道感染/Lower respiratory tract infection fungal

A 56-year-old white female was diagnosed with high grade adipocytic pleomorphic in kidney on 23 Jan 2009. The last date of disease progression was 22 Oct 2012. Significant medical history included anemia, osteoarthritis, hyperlipidemia, spinal laminectomy, and right nephrectomy. At Screening, tumor assessments of target/non-target lesions via MRI showed right side retroperitoneal mass. The subject received previous radiotherapy to left upper lobe lung mass. Previous anticancer therapy included doxorubicin, gemcitabine and docetaxel. Prior and concomitant medications included diphenhydramine, ezetimibe, hydrocodone, iron, ondansetron, red blood cell transfusion, sodium chloride and ultra b 100 complexes. ECOG performance status at screening was 0.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 43), the subject experienced fungal lower respiratory tract infection (Grade 3) confirmed by CT scan of the chest. The study drug was interrupted and the subject was treated with flucanozole. She underwent a repeat CT scan which showed improvement and recovered from this event on [redacted] (Day 56). The Investigator considered lower respiratory tract infection serious (important medical event) and possibly related to the study drug. The study drug was resumed on [redacted] (Day 55).

On [redacted] (Day 85), the subject withdrew from the study by choice and received the last dose of the study drug on [redacted] (Day 71).

被験者番号	11191013
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	癌疼痛/Cancer pain, 大静脈血栓症/Vena cava thrombosis

A 54-year-old white female was diagnosed with high grade leiomyosarcoma in uterus on 12 Aug 2011. The last date of disease progression was 29 Jan 2013. Significant medical history included chronic abdominal pain, diabetes, gastrooesophageal reflux disease, hypercholesterolemia, hypertension, lower extremity edema, musculoskeletal pain, herpes zoster, urinary incontinence and vaginal haemorrhage. At Screening, tumor assessments of target/non-target lesions via CT scan showed the right hepatic lobe mass, lesions in soft tissue trunk, right lower lobe lung mass and peritoneal mass. The subject received previous radiotherapy to right pelvic bone lesion and single uterine tumor. Previous anticancer therapy included an investigational drug, doxorubicin, gemcitabine, docetaxel, bevacizumab/placebo, ifosfamide, and pazopanib. Prior and concomitant medications included diphenhydramine, docusate, fentanyl, gabapentin, heparin, hydrocodone, hydromorphone, lactulose, lansoprazole, levofloxacin, metoprolol, ondansetron, sodium chloride and zolpidem. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 10), the subject experienced headache (Grade 1). On [redacted] (Day 15), the subject started experiencing abdominal pain (Grade 2), constipation (Grade 1) and dysgeusia (Grade 1). Treatment with hydrocodone, lactulose and docusate was given. On [redacted] (Day 21), the subject experienced worsening of abdominal pain (Grade 3). On the same day, CT scan showed disease progression and thrombus in inferior vena cava (Grade 3) and the subject was withdrawn from the study. The subject received the last dose of the study drug on [redacted] (Day 8). She was treated with enoxaparin, geparin, hydromorphone and sodium chloride was given. The subject did not recover from constipation, dysgeusia, abdominal pain, headache and inferior vena cava thrombosis. The Investigator considered abdominal cancer pain and vena cava thrombosis serious and not related to the study drug; dysgeusia non-serious and probably related to the study drug; headache non-serious and possibly related to the study drug; and constipation non-serious and not related to study drug.

被験者番号	11211003
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	好中球減少症/Neutropenia

A 30-year-old white female was diagnosed with high grade leiomyosarcoma in uterus on 26 Mar 2010. The last date of disease progression was 18 Feb 2011. Significant medical history included anemia, ascites, back pain, cardiomyopathy, constipation, cough, decreased blood iron, hepatic lesion, decreased ejection fraction, lower abdominal pain, metastases to lung,nausea, vomiting, malignant pleural effusion, skin neoplasm excision, exertional dyspnoea, peripheral swelling, and tricuspid valve incompetence. At Screening, tumor assessments of target/non-target lesions via CT scan showed right upper lobe lung mass, pelvic masses, lesions in right and left pelvic cul-de-sac, right breast, heart, bilateral pleural effusion and bilateral lung nodules. The subject received previous radiotherapy to the right and left upper lobe lung masses. Previous anticancer therapy included docetaxel, gemcitabine, and trabectedin. Prior and concomitant medications included azithromycin, cefdinir, codeine with guaifenesin, dexamethasone, docusate, fluticasone, granisetron, lansoprazole, montelukast, pegfilgrastim, filgrastim, promethazine with dextromethorphan, prochlorperazine, and promethazine. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 15) the subject experienced neutropenia (Grade 4), with neutrophil count 0.4 K/mm^3 (NR: 2-7.8). She was treated with filgrastim and recovered from neutropenia on [redacted] (Day 19). The Investigator considered neutropenia serious and probably related to the study drug.

On [redacted] (Day 142), tumor response assessment showed disease progression and the subject was withdrawn from the study. The last dose of the study drug was received on [redacted] (Day 134).

被験者番号	11211014
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	発熱/Pyrexia

A 43-year-old native hawaiian or other pacific islander female was diagnosed with high grade leiomyosarcoma in uterus on 09 Mar 2010. The last date of disease progression was 24 Jul 2011. Significant medical history included adenomyosis, anaemia, partial lung resection, cervicitis, colitis, dysfunctional uterine bleeding, endocervical curettage, uterine dilation and curettage, endometriosis, hepatic steatosis, hyperglycemia, hypoalbuminemia, increased alkaline phosphatase, increased blood lactate dehydrogenase, left pneumothorax, pleural effusion, two partial lung resections, multiple lung metastases,pulmonary embolism, retroperitoneal lymph node metastasis, sepsis, renal mass, type 2 diabetes mellitus, urinary tract yeast infection and abdominal hernia. At Screening, tumor assessments of target/non-target lesions via CT scan showed pelvic lesion, bilateral lung nodules, and ascites. Previous anticancer therapy included docetaxel, gemcitabine, doxorubicin, and ifosfamide. Prior and concomitant medications included albumin human, alprazolam, bupivacaine, dexamethasone, dextrose and sodium chloride injection, diphenhydramine, docusate, dronabinol, electrolytes w/ polyethylene glycol 3350, erythropoietin human, fentanyl, filgrastim, flebobag ring lactate, fluconazole, glipizide, glucose, granisetron, heparin, hydrocodone, hydromorphone, influenza vaccine, insulin, human insulin, insulin lispro, iron, levofloxacin, lidocaine, lorazepam, magnesium sulfate, metformin, methadone, metoclopramide, ondansetron, pantoprazole, paracetamol, pegfilgrastim, plasma, platelets, pneumococcal vaccine, potassium, red blood cells, sodium chloride, hydrocodone/acetaminophen, vitamins and zolpidem. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 25), the subject experienced chills (Grade 1), night sweats (Grade 2), and hot flashes (Grade 2). On [redacted] (Day 27), the subject was hospitalized for pyrexia (Grade 1). During hospitalization, the subject also experienced neutropenia (Grade1), anxiety (Grade 1) and dizziness (Grade1). The study drug was interrupted due to fever. She was treated with vancomycin, primaxin and alprazolam. She recovered from night sweats, hot flashes, dizziness and chills on [redacted] (Day 28) and from fever, anxiety and neutropenia on [redacted] (Day 29). The Investigator considered pyrexia serious and not related to the study drug; neutropenia non-serious and possibly related to the study drug; and chills, night sweats, hot flashes anxiety and dizziness non-serious and not related to the study drug. The study drug was resumed on [redacted] (Day 43).

On [redacted] (Day 92), the subject experienced worsening hyperglycemia (Grade 3). She was treated with glipizide, metformin and insulin. She recovered from this event on [redacted] (Day 105). The Investigator considered this event non-serious and not related to the study drug. On [redacted] (Day 106), the study drug dose was reduced to 1.1 mg/m^2 due to this event.

On [redacted] (Day 133), the subject was withdrawn from the study to undergo tumor resection. The subject received the last dose of the study drug on [redacted] (Day 113).

被験者番号	11211021
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	腹痛/Abdominal pain

A 66-year-old Chinese female was diagnosed with high grade leiomyosarcoma in uterus on 21 Aug 2009. The last date of disease progression was 18 Nov 2011. Significant medical history included abdominal discomfort, lower abdominal pain, polyarthritis, atopic dermatitis, bilateral hydronephrosis, bilateral pelvic calciectasis, bilateral ureteral dissection, lymph node calcification, musculoskeletal pain, colon repair, spinal osteoarthritis, duodenal diverticulosis, omentectomy, adhesiolysis, cholelithiasis, hypogastric arterial ligation, abdominal distension, haemangioma of L1 vertebral body, hepatic cyst, renal cyst, aortic arteriosclerosis, mitral valve incompetence, small intestinal obstruction, ovarian adenoma, osteopenia, pelvic lymph node dissection, pleural calcifications, radical total abdominal hysterectomy with bilateral salphingo-oophorectomy, sarcoma excisions for recurrent abdominal, small bowel, and mesenteric sarcoma, and pulmonary granuloma. At Screening, tumor assessments of target/non-target lesions via CT scan showed peritoneal/omental mass. Previous anticancer therapy included gemcitabine, docetaxel, doxorubicin, and TH-302. Prior and concomitant medications included bisacodyl, calcium, darbepoetin alfa, dexamethasone, dextrose and sodium chloride injection, diphenhydramine, docusate, enemas, ertapenem, filgrastim, fish oil, furosemide, granisetron, imipenem, interferon, lactulose, levosalbutamol, lorazepam, polyethylene glycol, magnesium sulfate, metoclopramide, ondansetron, paracetamol, potassium, red blood cells, simeticone, sodium bicarbonate, vancomycin, and vitamin D. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 15), the subject experienced increase in abdominal distension (Grade 2). She did not recover from this event. On [redacted] (Day 36), the subject was hospitalized for worsening of abdominal pain related to disease progression (Grade 2). She also experienced urosepsis (Grade 2), urinary retention (Grade 2), constipation (Grade2), abdominal distension (Grade 2) and food intolerance (Grade 2). On the same day, tumor response assessment showed disease progression and the subject was withdrawn from the study. She received the last dose of the study drug on [redacted] (Day 29). The subject was treated with docusate, hydrocodone/acetaminophen, morphine, enema, ertepenam, vancomycin, imepenem, lactulose, dextrose and sodium chloride injection, lidocaine, biscodyl, polyethylene glycol 3350 and hydromorphone and a foley catheter was inserted. She recovered from urosepsis and abdominal pain on [redacted] (Day 60) and from food intolerance on [redacted] (Day 62). She did not recover from abdominal distension, urinary retention and constipation. The Investigator considered abdominal pain serious and not related to the study drug; urosepsis, urinary retention, constipation, abdominal distension, and food intolerance non-serious and not related to the study drug but related to the disease under study.

On [redacted] (Day 129, 100 days after the last dose), the subject died due to disease progression.

被験者番号	11211025
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	無力症/Asthenia，国際標準比増加/International normalized ratio increased

A 57-year-old white female was diagnosed with high grade leiomyosarcoma in uterus on 21 Jan 2011. The last date of disease progression was 27 Jan 2012. Significant medical history included anemia, bilateral salphingo-oophorectomy, deep vein thrombosis, hypertension, hypoalbuminaemia, increased creatinine, increased lactate dehydrogenase, fatigue, gastro-esophageal reflux disease, hematuria, IVC filter placement, leucopenia, spleen disorder, superficial thrombophlebitis, deep vein thrombosis, right hydronephrosis, splenic hemangiomas, thrombophlebitis, total abdominal hysterectomy and ureteral stent placement. At Screening, tumor assessments of target/non-target lesions via CT scan showed anterior pelvis mass, posterior margin of bladder mass, left rectus muscle mass and multiple retroperitoneal masses. Previous anticancer therapy included docetaxel, gemcitabine, doxorubicin, epirubicin, ifosfamide and temozolomide. Prior and concomitant medications included bisacodyl, cefotetan, ciprofloxacin, colecalciferol, dexamethasone, diphenhydramine, docusate, dronabinol, enemas, erythropoietin human, escitalopram, esomeprazole, famotidine, fat emulsion, fentanyl, filgrastim, folic acid, furosemide, granisetron, hydrocodone, hydromorphone, hyoscine, ipratropium, iron, loratadine, magnesium hydroxide, magnesium sulfate, mesna, methylnaltrexone, metoprolol, morphine, neutra-phos-k, ondansetron, oxygen, palonosetron, pantoprazole, paracetamol, potassium, prednisone, probiotics, promethazine, ranitidine, red blood cells, salbutamol, senna alexandrina, sodium bicarbonate, sodium chloride, sodium phosphate, sodium polystyrene sulfonate, solutions for parenteral nutrition, unspecified herbal and traditional medicine, vitamin B complex, vitamins and warfarin. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 35), the subject experienced neutropenia (Grade 4) with absolute neutrophil count of 0.6 x10^9/L (NR: 1.7-7.9). The subject was treated with filgrastim and recovered on [redacted] (Day 42). On the same day, the tumor response assessment showed disease progression and the subject was withdrawn from the study. The subject received the last dose of the study drug on [redacted] (Day 36). The Investigator considered neutropenia non-serious and possibly related to the study drug.

On [redacted] (Day 42), the subject started experiencing hematuria (Grade 3). On [redacted] (Day 49), the subject experienced worsening of hypoalbuminemia (Grade 2), intermittent nausea (Grade 1), intermittent vomiting (Grade 1) and worsening of anemia (Grade 2). On [redacted] (Day 52), the subject was hospitalized with increased international normalised ratio (INR) (Grade 3) due to warfarin, asthenia (Grade 3), acute renal failure (Grade 3), hypotension (Grade 1), hydronephrosis (Grade 2), increased abdominal distension (Grade 2) and bilateral malignant pleural effusion (Grade 2). On [redacted] (Day 53), the subject experienced hemorrhagic ascites (Grade 3), metabolic acidosis (Grade 2), worsening of ongoing anemia (Grade 4) and intermittent hyperkalemia (Grade 1). On [redacted] (Day 57), the subject experienced acute respiratory failure (Grade 2). Laboratory tests showed INR of 15.7, prothrombin time of 120 seconds, partial thrombin time of 135 seconds, hemoglobin of 89 g/L (NR: 110-155), BUN of 33 mg/dL (NR: 5-25), creatinine of 1.8 mg/dL (NR: 0.6-1.2), potassium of 4.5 mmol/L (NR: 3.5-5), chloride of 106 mmol/L (NR: 95-110) and sodium 140 mmol/L (NR: 133-145). She underwent paracentesis for ascites; bilateral ureteroscopy stent dilation and change for hydronephrosis. The subject was treated with sodium chloride, ondansetron, sodium bicarbonate, hydrocodone, phytomenadione, human erythropoietin, red blood cells, paracetomol, diphenhydramine, dexamethasone, total parenteral nutrition, dronabinol, hyoscine, and plasma. She did not recover from hematuria, hypoalbuminemia, anemia, nausea, vomiting, hydronephrosis, abdominal distension, bilateral pleural effusion, hemorrhagic ascites, acute renal failure and acute respiratory failure. She recovered from metabolic acidosis on [redacted] (Day 56), from hypotension on [redacted] (Day 58), from increased and asthenia on [redacted] (Day 104). The Investigator considered increased INR serious and not related to the study drug; asthenia serious and not related to the study drug but related to the disease; hematuria, worsening of hypoalbuminemia, worsening of anemia, intermittent nausea, intermittent vomiting, intermittent hyperkalemia, hydronephrosis, increased abdominal distension, metabolic acidosis, bilateral pleural effusion, acute renal failure, hemorrhagic ascites ,acute respiratory failure non-serious and not related to the study drug.

On [redacted] (Day 119, 84 days after last study drug dose), the subject died due to disease progression.

被験者番号	11221001
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	癌疼痛/Cancer pain, 低カリウム血症/Hypokalaemia

A 51-year-old white female was diagnosed with high grade leiomyosarcoma in uterus on 29 Jul 2004. The last date of disease progression was 17 Jan 2012. Significant medical history included benign breast neoplasm, chemotherapy related anemia, peripheral edema, hepatitis C, left parietotemporal brain metastases resection, hysterosalpingo-oophorectomy, carcinoid tumor of small bowel, muscular weakness, pulmonary metastasectomy, and chest pain. At Screening, tumor assessments of target/non-target lesions via CT scan showed colorectal mass, right lower lung anterior and posterior masses, right upper chest lesion, right psoas mass, left gluteal mass, left adrenal mass and right subscapularis mass. The subject received previous radiotherapy to the left chest, pelvis, left shoulder and thoracic spine. Previous anticancer therapy included doxorubicin, gemcitabine, protein kinase inhibitors, docetaxel, trabectedin, pazopanib, and protein kinase inhibitors. Prior and concomitant medications included colecalciferol, cyclobenzaprine, dexamethasone, docusate, enoxaparin, furosemide, lorazepam, magnesium sulfate, metoclopramide, morphine, omeprazole, ondansetron, acetaminophen/oxycodone, oxycodone, senna alexandrina. At Screening, peripheral neuropathy was Grade 0 and ECOG performance status was 2.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 50), the subject experienced decreased neutrophil count (Grade 3) with neutrophil count of 0.7 x 10^9/L (NR: 1.7 – 7.9). She recovered from neutrophil count decreased on [redacted] (Day 57). The study drug dose was reduced to 1.1mg/m^2. The Investigator considered this event non-serious and probably related to the study drug,

On [redacted] (Day 71), the subject experienced decreased neutrophil count (Grade 3) with neutrophil count of 0.6 x 10^9/L and peripheral sensorimotor neuropathy (Grade 1). She recovered from decreased neutrophil count on [redacted] (Day 79) and from peripheral sensorimotor neuropathy on [redacted] (Day 92). On [redacted] (Day 85), the study drug dose was reduced to 0.7 mg/m^2 due to peripheral sensorimotor neuropathy. The Investigator considered decreased neutrophil count and peripheral sensorimotor neuropathy non-serious and probably related to the study drug.

On [redacted] (Day 11), the subject was hospitalized for cancer pain (Grade 3). On [redacted] (Day 13), she experienced hypokalemia (Grade 2) with potassium level of 3.2 mmol/L (NR: 3.5-5.0). The event of hypokalemia worsened to Grade 3 on [redacted] (Day 23) with a potassium level of 2.5 mmol/L (NR: 3.5-5.0). She was treated with morphine, potassium and ketorolac. She recovered on [redacted] (Day 17) from cancer pain and from hypokalemia on [redacted] (Day 29). The Investigator considered cancer pain serious and not related to the study drug; hypokalemia serious (important medical event) and probably related to the study drug.

On [redacted] (Day 147), tumor response assessment showed disease progression and the subject was withdrawn from the study. The subject received the last dose of the study drug on [redacted] (Day 134).

被験者番号	11221006
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	カテーテル留置部位感染/Catheter site infection, ブドウ球菌感染/Staphylococcal infection

A 75-year-old white male was diagnosed with intermediate grade leiomyosarcoma in right knee on 13 Oct 1987. The last date of disease progression was 08 Apr 2013. Significant medical history included asthma, atrial fibrillation, bilateral lower edema, cystitis, urinary retention, bladder catheterisation, coronary artery disease, coronary arterial stent insertion, dysuria, goitre, gout, hyperlipidaemia, hypertension, hypokalaemia, insomnia, stomatitis, myocardial infarction, polyneuropathy, proteinuria, resection of mass in popliteal fossa, thrombocytopenia, enthesopathy, urinary tract infection, unspecified hereditary and congenital neuropathy. At Screening, tumor assessments of target/non-target lesions via CT scan showed left lung mass, liver metastasis, right adrenal metastasis, right subhepatic metastasis, right paraspinal mass, colorectal mass, left renal capsular mass, left peritoneal mass and left subcutaneous mass. The subject received previous radiotherapy to the lateral aspect of the right knee (popliteal fossa) and to a low neck mass. Previous anticancer therapy included doxorubicin, gemcitabine, olaratumab and trabectedin. Prior and concomitant medications included acetylsalicylic acid, allopurinol, antifungals for topical use, cefalexin, dexamethasone, docusate, doxazosin, dutasteride, fluconazole, furosemide, gabapentin, hydrochlorothiazide, lorazepam, lovastatin, meclozine, methylphenidate, metoprolol, naproxen, ondansetron, oxybutynin, oxycodone/acetaminophen, oxycodone, potassium, prednisone, prochlorperazine, senna alexandrina, stomatologicals, mouth preparations, sulfasalazine and zolpidem. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 100), the subject was hospitalized for catheter site infection (Grade 3) and the study drug was interrupted. The subject was treated with vancomycin and benzocaine and underwent removal of the porta catheter. On [redacted] (Day 101), the subject experienced pain due to port-a-cath removal (Grade 1) and two days later developed wound due to port-a-cath removal (Grade 1). A wound culture showed epithelial cells, gram positive cocci, red blood cells, and staphylococcus aureus. Treatment included oxycodone, vancomycin and benzocaine. On [redacted] (Day 103), the subject recovered from catheter site infection. The study drug was remained interrupted due to this event and cephalexin was added for treatment. On [redacted] (Day 112), the subject recovered from pain due to port-a-cath removal. On [redacted] (Day 144), the subject recovered from wound due to port-a-cath removal and the study drug was resumed. The Investigator considered catheter site infection serious and not related to the study drug; pain due to port-a-cath removal and wound due to port-a cath removal non serious and not related to study drug.

On [redacted] (Day 136), the subject was hospitalized for staphylococcal infection of left elbow (Grade 3) and cellulitis (Grade 1). X-ray of the left elbow and culture of the wound confirmed the condition. The subject was treated with vancomycin, and cefazolin and recovered from staphylococcal infection and cellulitis on [redacted] (Day 143). The Investigator considered staphylococcal infection serious and not related to the study drug; cellulitis non-serious and not related to the study drug.

On [redacted] (Day 349), tumor response assessment showed disease progression and the subject was withdrawn from the study. The subject received the last dose of the study drug on [redacted] (Day 347).

被験者番号	11251002
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	処置後出血/Post procedural haemorrhage

A 67-year-old white male was diagnosed with high grade leiomyosarcoma in retroperitoneum on 07 Dec 2011. The last date of disease progression was 07 Mar 2012. Significant medical history included abdominal distension, arthralgia, hypercholesterolaemia, hypertension, neutropenia, pruritus, prolonged QT interval, lower pain, dysphonia, hypoalbuminaemia, hypothyroidism, low back pain, and dyspnea. At Screening, tumor assessments of target/non-target lesions via CT scan showed soft tissue mass centered in right peritoneum. Previous anticancer therapy included doxorubicin, etoposide and ifosfamide. Prior and concomitant medications included albumin, bupivacaine, calcium chloride, calcium gluconate, cefoxitin, ciprofloxacin, cisatracurium, dexamethasone, diphenhydramine, docusate, ephedrine, epinephrine, famotidine, fentanyl, flebobag ring lact, heparin, hydrocortisone, hydromorphone, hyoscine, ibuprofen, insulin, levothyroxine, lidocaine, lisinopril, loperamide, loratadine, lorazepam, magnesium hydroxide, magnesium sulfate, midazolam, naproxen, norepinephrine, ondansetron, osmotan, oxycodone/acetaminophen, oxycodone, paracetamol, phenylephrine, electrolytes, prochlorperazine, propofol, red blood cells, senna alexandrina, simvastatin, sodium chloride, stomatologicals, mouth preparations, triamcinolone, vasopressin, vecuronium, warfarin and lidocaine-epinephrine. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 83), the subject withdrew from the study by choice and received the last dose of the study drug on [redacted] (Day 71).

On [redacted] (Day 94), the subject was hospitalized for exploratory laparotomy with removal of large retroperitoneal mass and experienced post procedural intrabdominal hemorrhage (Grade 4), anemia (Grade 3), hypotension (Grade 4), hyperglycemia (Grade 2) and hypocalcemia (Grade 2). Per the hospital report, a 30 x 25 cm retroperitoneal sarcoma mass was removed along with right nephrectomy, right adrenalectomy, segmental resection of inferior vena cava, primary resection, reconstruction, and repair of liver deserosalization. On [redacted] (Day 95), the subject experienced decreased platelet count (Grade 3). Laboratory results showed calcium of 1.85 mmol/L (NR: 2.15 – 2.65), hemoglobin of 72 g/L (NR: 125-170), and platelet count of 45 x 10^9/L (NR: 125-375). The subject was treated with albumin, red blood cells, plasma, platelets, calcium chloride, calcium gluconate, hydrocortisone, norepinephrine, flebobag-ring-lact, sodium chloride, ephedrine, epinephrine, phenylephrine, insulin, vasopressin and phytomenadione. On the same day, venous cauterization and lumbar vein cauterization were performed. The subject recovered from intra-abdominal bleeding, hyperglycemia and hypocalcemia on [redacted] (Day 95) and the event of anemia improved to Grade 2. He recovered from low platelets on [redacted] (Day 96), from hypotension on [redacted] (Day 97), and from anemia on [redacted] (Day 104). The Investigator considered post-procedural hemorrhage serious and not related to the study drug; anemia, hypocalcemia, decreased platelets, hypotension non-serious and not related to the study drug.

被験者番号	11271001
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	腹痛/Abdominal pain, 便秘/Constipation, 肝毒性/Hepatotoxicity, 高ビリルビン血症/Hyperbilirubinaemia, 好中球減少症/Neutropenia

A 41-year-old african-american male was diagnosed with intermediate grade leiomyosarcoma in the kidney on 05 Nov 2007. The last date of disease progression was 31 May 2012. Significant medical history included abdominal pain, biopsy of mesenteric mass, biopsy of omentum, chronic renal insufficiency, liver biopsy, elevated blood urea, elevated bilirubin, elevated creatinine, erectile dysfunction, ischemic necrosis of the liver, ischemic necrosis of the liver, right nephrectomy, herpes zoster, bilateral lower extremity swelling, elevated alkaline phosphatase, elevated lactate dehydrogenase and hypertension. At Screening, tumor assessments of target/non-target lesions via CT scan showed right paratracheal lymphadenopathy, left lateral lobe liver lesion, mesenteric lesion, left lower lobe lung lesion and subcentimeter pulmonary nodules. The subject received previous radiotherapy to right retroperitoneum, entire lumbar spine and slightly less than half of his thoracic spine. Previous anticancer therapy included docetaxel, doxorubicin, gemcitabine, ifosfamide and pazopanib. Prior and concomitant medications included hydromorphone, hydroxyzine, macrogol, ondansetron, oxycodone, pantoprazole, piperacillin/tazobactam, prochlorperazine, promethazine, red blood cells, temazepam and vitamins. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 8), the subject experienced hepatotoxicity (Grade 3). Laboratory results showed AST of 289 U/L (NR: 10-43); ALT of 125 U/L (NR: 10-40) and the study drug was interrupted due to this event. On [redacted] (Day 13), the subject was hospitalized with hyperbilirubinemia (Grade 3), vomiting (Grade 3), decreased appetite (Grade 2), jaundice (Grade 2), worsening hepatotoxicity (Grade 4) and neutropenia (Grade 4). Laboratory results showed total bilirubin110.8 umol/L (NR: 1.7-18.8); direct bilirubin 57.8 umol/L (NR: 0-6.8), white blood cell count 3.6 x10^9/L (NR: 3.7-11); AST 120 U/L; ALT 125 U/L; alkaline phosphatase 613 U/L (NR: 43-115) and neutrophil count of 0.2 x 10^9/L (NR: 1.7 – 7.9). The study drug was interrupted due to these events. During hospitalization, ultrasound of the bile duct showed intrahepatic biliary ductal dilation. On [redacted] (Day13), tumor response assessment showed disease progression and the subject was withdrawn from the study. The subject received the last dose of the study drug on [redacted] (Day 1). On [redacted] (Day 16), biliary obstruction was confirmed by magnetic resonance cholangiopancreatography **and** a percutaneous biliary drain was inserted. He was treated with promethazine and filgrastim. He recovered from neutropenia on [redacted] (Day 16) and did not recover from hyperbilirubinemia, vomiting, jaundice, decreased appetite and hepatotoxicity. The Investigator considered worsening hepatotoxicity serious and not related to the study drug but related to the disease; hyperbilirubinemia serious and not related to study drug but related to the biliary obstruction; neutropenia serious and probably related to the study drug; vomiting, jaundice, decreased appetite non-serious and possibly related to the study drug.

On [redacted] (Day 26), the subject was hospitalized for abdominal pain (Grade 3) and constipation (Grade 2). He was treated with hydromorphone, oxycodone, docusate/senna, lactulose and promethazine. He recovered from both events on [redacted] (Day 27). The Investigator considered abdominal pain and constipation serious and not related to the study drug.

The subject died on [redacted] (Day 62, 61 days after the last dose) due to disease progression.

被験者番号	11271003
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	発熱/Pyrexia
治験薬の投与中止に至った有害事象	発熱/Pyrexia

A 44-year-old white female was diagnosed with intermediate grade leiomyosarcoma in uterus on 28 Oct 2009. The last date of disease progression was 19 Jul 2012. Significant medical history included allergy to penicillin, codeine and compazine, salpingo-oophorectomy bilateral, biopsy chest wall; fungating wound, drainage from left posterior chest wall, dyspepsia, left pleural decortication, pleurex catheter infection, pleurex catheter placement, hysterectomy, talc pleurodesis and tumour pain. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions in left hemithorax, right lower and left lower lobe lung, and left pleural effusion. Previous anticancer therapy included gemcitabine, docetaxel, doxorubicin, and investigational drug. Prior and concomitant medications included docusate, dronabinol, fentanyl, furosemide, ibuprofen, lorazepam, macrogol, magnesium hydroxide, omeprazole, ondansetron, sennoside, hydrocodone/acetaminophen and vitamins. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 14), the subject experienced anemia (Grade 3) with hemoglobin 91 g/L (NR: 110-155) and hematocrit 29.2% (NR: 33-47). On [redacted] (Day 23), the subject was hospitalized for pyrexia (Grade 1) related to the pre-existing fungating lesion on the left posterior chest wall. Her temperature was 38 degree Celsius (NR: 36 –37.2); hemoglobin 95 g/L, and hematocrit 29.2 %. The study drug was withdrawn due to this event. The subject was treated with metronidazole, vancomycin and sulfamethoxazole/trimethoprim. On [redacted] (Day 26), the event of anemia worsened to Grade 4 with hemoglobin 77 g/L and hematocrit 24 L/L and two units of RBC were transfused. On [redacted] (Day 30), the subject was withdrawn from study due to risk of fungating lesion and for the preparation of surgery. The subject received the last dose of the study drug on [redacted] (Day 22). The subject recovered from pyrexia and anemia on [redacted] (Day 149). The Investigator considered pyrexia serious and not related to the study drug; and anemia non-serious and probably related to the study drug.

被験者番号	11271004
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	好中球減少症/Neutropenia

A 63-year-old african-american female was diagnosed with high grade leiomyosarcoma in left kidney on 23 Jun 2008. The last date of disease progression was 04 Sep 2012. Significant medical history included coronary artery disease, decreased appetite, hyperlipidemia, hysterectomy, pharyngeal operation, febrile neutropenia, hypertension, left radical nephrectomy, exploratory laparotomy and throat cancer. At Screening, tumor assessments of target/non-target lesions via CT scan showed right lower lobe liver masses, right and left lower lobe lung masses, left nephrectomy bed nodule and right adnexal lesion. Previous anticancer therapy included gemcitabine, docetaxel, and doxorubicin. Prior and concomitant medications included amlodipine, dronabinol, lisinopril, naproxen, paracetamol, prochlorperazine, and senokot-s. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 15), the subject experienced neutropenia (Grade 4) with absolute neutrophil count of 0.4 x10^9/L (NR: 1.7-7.9). She was treated with pegfilgrastim and recovered on [redacted] (Day 22). The study drug dose was reduced to 1.1 mg/m^2 due to neutropenia. The Investigator considered this event serious (important medical event) and probably related to the study drug.

On [redacted] (Day 50), the subject experienced neutropenia (Grade 3) with neutrophil count of 0.9 x10^9/L. The subject recovered from this event on [redacted] (Day 62). The study drug dose was reduced to 0.7 mg/m^2 due to this event. The Investigator considered neutropenia non-serious and probably related to the study drug.

On [redacted] (Day 141), the tumor response assessment showed disease progression and the subject was withdrawn from the study. The subject received the last dose of the study drug on [redacted] (Day 132).

被験者番号	11991002
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	肺塞栓症/Pulmonary embolism, 放射線性肺臓炎/Radiation pneumonitis

A 66-year-old white female was diagnosed with high grade leiomyosarcoma in cervix on 27 Feb 1997. The last date of disease progression was 12 Dec 2011. Significant medical history included kidney ablation, cervical fibroid removal, left adrenalectomy, vena cava thrombosis, cough, urticaria, bilateral cataracts, bilateral salpingo-oophorectomy, exertional dyspnea, fibromyalgia, hypertension, pelvic lymph node dissection, bronchial hyperreactivity, lung lobectomy, resection of subcutaneous left groin mass , left groin mass , abdominal wall mass , right arm subcutaneous mass, vulvar mass, paravertebral mass, several scalp lesions, left buttock intramuscular mass, allergy to sulfa and lisinopril/hydrochlorthiazide and total abdominal hysterectomy. At Screening, tumor assessments of target/non-target lesions via CT scan showed left erector spinae muscular lesion, right anterior abdominal wall subcutaneous lesion and multiple pulmonary nodules. The subject received previous radiotherapy to left upper and lower lobe lung masses and right paravertebral region. Previous anticancer therapy included trabectedin, gemcitabine, docetaxel, doxorubicin, sorafenib, and vinorelbine. Prior and concomitant medications included benzonatate, filgrastim, fondaparinux, hydrochlorothiazide, loratadine, lorazepam, macrogol, magnesium hydroxide, ondansetron, paracetamol, prochlorperazine, red blood cells, senna alexandrina, trazodone, valaciclovir and vitamins. ECOG performance status at screening was 0.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 18), the subject was hospitalized for left lower lobe pulmonary embolism (Grade 3) and radiation pneumonitis (Grade 3). The study drug was interrupted due to pulmonary embolism. Chest CT scan confirmed bilateral pneumonitis and pulmonary embolus. The subject was treated with oxygen, dalteparin, and guaifenesin/codeine. The subject recovered from pulmonary embolism on [redacted] (Day 23) and from radiation pneumonitis on [redacted] (Day 120). The Investigator considered pulmonary embolism serious and not related to the study drug and radiation pneumonitis serious and not related to the study drug but related to previous lung radiation. The study drug was resumed at a reduced dose of 1.1 mg/m^2 on [redacted] (Day 29) due to radiation pneumonitis.

On [redacted] (Day 519), the tumor response assessment showed disease progression and the subject was withdrawn from the study. The last dose of the study drug was received on [redacted] (Day 512).

被験者番号	11991004
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	背部痛/Back pain

A 60-year-old white male was diagnosed with high grade leiomyosarcoma in inferior vena cava on 06 Aug 2009. The last date of disease progression was 31 May 2012. Significant medical history included spinal fusion surgery, crohn's disease, dupuyten's contracture, vertebroplasty, road traffic accident, osteopenia, peripheral nerve transposition, drug hypersensitivity to percocet, carpal tunnel syndrome, carpal tunnel decompression, cervical radiculopathy, cholecystectomy, cholecystitis, degenerative disk disease, excision right adrenal mass, extensive arthroscopic debridement of right shoulder, hyperlipidaemia, hypertension, central venous catheterisation, left video-assisted thoracoscopic wedge resection of metastatic leiomyosarcoma, lumbar vertebral fracture, osteoarthritis, sleep apnea syndrome, pharyngeal reconstruction, venous operation, restless leg syndrome, tenotomy, nephrectomy, joint instability, skin cancer excision, skin neoplasm excision and rotator cuff repair. At Screening, tumor assessments of target/non-target lesions via CT scan showed right and left lower lobe lung masses, left quadrate lobe liver mass, right lower lobe liver mass, multiple liver lesions not localized to any one quadrant and multiple bilateral pulmonary nodules not localized to any one quadrant. Previous anticancer therapy included doxorubicin and trabectedin. Prior and concomitant medications included acetylsalicylic acid, alprazolam, bupropion, calcium w/vitamin d, diltiazem, gabapentin, ibuprofen, lorazepam, metoprolol, omeprazole, oxycodone, prochlorperazine, sertraline, sinemet, sodium chloride, stomatologicals, mouth preparations, tamsulosin and zolpidem. ECOG performance status at screening was 0.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 134), the subject was hospitalized for left lower back pain (Grade 3). He was treated with morphine and recovered from back pain on [redacted] (Day 136). The Investigator considered this event serious and not related to the study drug.

On [redacted] (Day 141), the tumor response assessment showed disease progression and the subject was withdrawn from the study. The subject received the last dose of the study drug on [redacted] (Day 134).

被験者番号	17021006
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	好中球数減少/Neutrophil count decreased，過敏症/Hypersensitivity，白血球数減少/White blood cell decreased

A 67-year-old white male was diagnosed with intermediate grade mediastinal leiomyosarcoma on 03 Dec 2008. The last date of disease progression was 27 Dec 2011. Significant medical history included colon diverticulum, gastric ulcer, hepatitis, increase alanine aminotransferase, intervertebral disc protrusion, large intestine polyp, myositis ossificans, decreased neutrophil count, esophagitis, pancreatitis, excision of ampulla of vater, tumor pain and decreased white blood cell count. At Screening, tumor assessments of target/non-target lesions via CT scan showed right middle lobe (lateral & medial) lung mass, left medial lobe liver mass, lesions in paragastric soft tissue, abdominal wall soft tissue, soft tissue next to left renal fascia, lesion in chest wall, intramuscular lesion in left gluteus and intramuscular paravertebral spine lesion. The subject received previous radiotherapy to D10-D12 dorsal vertebral lesions and boost vertebral lesions. Previous anticancer therapy included doxorubicin and ifosfamide. Prior and concomitant medications included acetylcysteine, acuafil, alizapride, cetirizine, chlorphenamine, colludol, dexamethasone, diclofenac, methylprednisolone, movicol, omeprazole, paracetamol/caffeine, paracetamol, ranitidine, stomatologicals, mouth preparations and tramadol. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 8), the subject experienced decreased neutrophil count (Grade 3) with neutrophil count of 0.4 x10^9/L (NR: 1.7 – 7.9) and decreased white blood cell (WBC) count (Grade 3) with WBC count of 3.4 x10^9/L (NR: 3.7-11). The study drug was interrupted due to decreased white blood cell. The subject recovered from decreased neutrophil count on [redacted] (Day 22) and from decreased WBC on [redacted] (Day 21). On [redacted] (Day 22), the study drug dose was resumed at reduced dose of 1.1 mg/m^2. The Investigator considered both these events serious (important medical events) and probably related to the study drug.

On [redacted] (Day 29), the subject experienced decreased neutrophil count (Grade 1) with neutrophil count of 1.8 x 10^9/L and decreased WBC count (Grade 2) with WBC count of 2.7 x 10^9/L. On [redacted] (Day 36), the decreased neutrophil count worsened to Grade 4 with neutrophil count of 0.4 x 10^9/L. The study drug dose was interrupted due to both these events. The subject recovered from both these events on [redacted] (Day 42). The Investigator considered both events serious (important medical events) and probably related to the study drug. The study drug was resumed on [redacted] (Day 43).

On [redacted] (Day 57), the subject experienced decreased neutrophil count (Grade 4) with neutrophil count of 0.4 x 10^9/L and decreased WBC count (Grade 3) with WBC count of 1.5 x 10^9/L. The study drug was interrupted due to decreased WBC count. On [redacted] (Day 64), decreased neutrophil count improved to Grade 2 and the study drug remained interrupted due to this event. He recovered from decreased neutrophil count on 02 May 2012 (Day 98) and from decreased WBC count on [redacted] (Day 70). The study drug was resumed on [redacted] (Day 71). The Investigator considered both events serious (important medical events) and probably related to the study drug.

On [redacted] (Day 141) the subject experienced decreased neutrophil count (Grade 3) with neutrophil count of 1.7 x 10^9/L. The study drug was interrupted due to this event. He recovered on [redacted] (Day 144). On [redacted] (Day 148), the study drug was resumed at the same dose. The Investigator considered this event serious (important medical event) and probably related to the study drug.

On [redacted] (Day 148), the subject experienced hypersensitivity reaction (Grade 1) to the study drug with symptoms of cough, sweating and hot flashes. On the same day, the symptoms resolved and he recovered without treatment. The Investigator considered this event serious (important medical event) and probably related to the study drug. The study drug dose was not changed.

On [redacted] (Day 253) the subject experienced decreased neutrophil count (Grade 3). The study drug was interrupted due to this event. He recovered from this event on [redacted] (Day 259). The study drug dose was resumed on [redacted] (Day 260). The Investigator considered this event serious (important medical event) and probably related to the study drug.

On [redacted] (Day 316), the subject experienced decreased neutrophil count (Grade 4). He recovered from this event on [redacted] (Day 323). On the same day, the study drug dose was reduced to 0.7 mg/m^2 due to this event. The Investigator considered this event serious (important medical event) and probably related to the study drug.

On [redacted] (Day 771), the tumor response assessment showed disease progression and the subject was withdrawn from the study. The subject received the last dose of the study drug on [redacted] (Day 764).

被験者番号	17021013
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	心電図QT延長/Electrocardiogram QT prolonged

A 63-year-old white female was diagnosed with high grade leiomyosarcoma in uterus on 04 Aug 2009. The last date of disease progression was 16 Oct 2012. Significant medical history included transient ischaemic attack, tumour ulceration, anxiety, depression, hypercholesterolemia, post herpetic neuralgia, resection of metastasis, ileectomy and herpes zoster. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions in abdominal wall and mesentery. Previous anticancer therapy included doxorubicin, palifosfamide/placebo (investigational drug) and trabectedin. Prior and concomitant medications included alginic acid, alprazolam, aspirin/dipyridamole, atorvastatin, citalopram, cloxazolam, fentanyl, fusidic acid, polyethylene glycol 4000, medroxyprogesterone, morphine, movicol, oxycodone, paracetamol, povidone-iodine, tramadol and trazodone. ECOG performance status at screening was 0.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 78), the subject was found to have prolonged electrocardiogram QT interval (Grade 3) with QTcB interval of 510 msec (see table below). ECG suggested abnormal, non-clinically significant left axis deviation and right bundle branch block with calcium of 2.05 mmol/L (NR: 2.12-2.62) and potassium of 3.4 mmol/L (NR: 3.5-5). The subject did not recover from abnormal cardiac findings. On the same day, tumor response assessment showed disease progression and the subject was withdrawn from the study. The last dose of the study drug was received on [redacted] (Day 71). The Investigator considered prolonged electrocardiogram QT interval serious (important medical event) and possibly related to the study drug.

Date of Visit	QTcB Interval (msec) (NR: <450)
Day −2 *	500
Day 1 *	462
Day 8 *	443
Day 13 *	450
Day 29 *	468
Day 50 *	498
Day 64 *	504
Day 71 *	495
Day 78 *	510

* 新薬承認情報提供時に置き換え

被験者番号	18011001
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	肺感染/Lung infection

A 58-year-old white female was diagnosed with intermediate grade leiomyosarcoma in uterus on 06 Dec 2005. The last date of disease progression was Oct 2011. Significant medical history included neuralgia and peripheral sensory neuropathy. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions in left upper and right middle lobes of the lung, diaphragm, and several non-target lesions in right and left lung. The subject received previous radiotherapy to uterine mass and bone and previous anticancer therapy included cryoablation with argon and helium iodine seeds implantation, doxorubicin, letrozole, docetaxel, gemcitabine, ifosfamide and trabectedin. Prior and concomitant medications included amitriptyline, dalteparin, estradiol, morphine, nortriptyline, pantoprazole, paracetamol and prednisolone. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 35), the subject was hospitalized for lung infection (Grade 3) associated with dyspnea (Grade 3) and fever of 38.8 degrees Celsius (NR: 36.5-37.2). The subject was treated with oxygen, pipracillin/tazobactam, ciprofloxacin, amoxicillin/potassium clavulanate, fenoterol/ipratropium, methylprednisolone and morphine. The study drug was interrupted due to this event on [redacted] (Day 59). On [redacted] (Day 65), tumor response assessment showed disease progression and the subject was withdrawn from study. The last dose of the study drug was received on [redacted] (Day 50). On [redacted] (Day 72), the subject recovered from this event. The Investigator considered lung infection serious and not related to study drug; dyspnea non-serious and not related to the study drug, but related to disease progression.

被験者番号	18011005
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	肺塞栓症/Pulmonary embolism, 発熱/Pyrexia

A 57-year-old white male was diagnosed with intermediate grade round cell adipocytic sarcoma in the right femur on 28 Jun 2010. The last date of disease progression was 23 Aug 2012. Medical history included depression, diarrhea, nausea, neuralgia, pulmonary embolism, vomiting, drug hypersensitivity to penicillin and peripheral sensory neuropathy. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions next to the heart and in the left thigh. The subject received previous radiotherapy to left crus and previous anticancer therapy included doxorubicin, ifosfamide and belinostat. Prior and concomitant medications included citalopram, domperidone, fluconazole, metoprolol, ondansetron, oxygen, potassium, prednisolone, sulfamethizole and tinzaparin. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 28), the subject experienced pyrexia (Grade 2) and was admitted to the hospital the following day for further evaluation. The pyrexia was attributed to the pulmonary embolism (Grade 3) which was a radiologic finding on [redacted] (Day -3) and the subject was asymptomatic at that time. The subject was treated with tinzaparin and the study drug was interrupted due to pyrexia. On [redacted] (Day 31), the subject recovered from pyrexia. The Investigator considered pyrexia serious and not related to the study drug and pulmonary embolism non-serious and not related to the study drug. On [redacted] (Day 46), the study drug was resumed at the same dose.

On [redacted] (Day 69), the subject was again hospitalized for pulmonary embolism (Grade 3) and also experienced atrial flutter (Grade 1) sinus tachycardia (Grade 1), dyspnea (Grade 3), and hypotension (grade 1). CT scan of the chest showed large saddle emboli. The subject was treated with dalteparin and citalopram. On [redacted] (Day 71), the subject recovered from this event. The Investigator considered pulmonary embolism, serious and not related to the study drug but related to the previous thromboembolic event, hypotension non-serious and not related to the study drug but related to underlying cancer; dyspnea is non-serious and not related to the study drug but related to the pulmonary embolism; sinus tachycardia and atrial flutter non-serious and not related to the study drug.

On [redacted] (Day 90), the subject was withdrawn from the study by Investigator since the subject's condition was not suitable for any more cancer treatments. The last dose of the study drug was received on [redacted] (Day 55).

被験者番号	18011006
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	腹痛/Abdominal pain、発熱/Pyrexia

A 58-year-old half african half white male was diagnosed with intermediate grade dedifferentiated adipocytic sarcoma in the right foot in 2007 and myxoid liposarcoma on 14 Mar 1997. The last date of disease progression was 01 Nov 2012. Medical history included tumor pain and tachycardia. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions in right middle lobe of lung, right retrocrural space, right lower lobe and other areas of liver. The subject received previous radiotherapy to dorsal side of right foot and previous anticancer therapy included doxorubicin, ifosfamide and trabectedin. Prior and concomitant medications included acetylcysteine, cetirizine, ciprofloxacin, fluconazole, metronidazole, movicol, pantoprazole, paracetamol, piperacillin, platelets, potassium and propofol. ECOG performance status at screening was 0.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 4), the subject was hospitalized for pyrexia (Grade 2) and was treated with piperacillin/tazobactam, metronidazole, gentamicin and amoxicillin/clavulanic acid. On [redacted] (Day 8), the subject recovered from this event. The Investigator considered pyrexia serious and not related to the study drug. The study drug was interrupted on [redacted] (Day 8) due to this event.

On [redacted] (Day 15), the subject was again hospitalized for pyrexia (Grade 2) with temperature of 38.6 degree Celsius (NR: 36.1 – 37.2) and treated with amoxicillin/clavulanic acid and metronidazole. The subject recovered on [redacted] (Day 16). The Investigator considered pyrexia serious and not related to the study drug. The study drug dose was not changed.

On [redacted] (Day 21), the subject was hospitalized for abdominal pain (Grade 2). On [redacted] (Day 23), the subject experienced cholangitis (Grade 2) and underwent endoscopic retrograde cholangiopancreatography which showed an infectious and clotted stent. On [redacted] (Day 24), the subject experienced decreased platelet count (Grade 1) which worsened to Grade 4 with platelet count of 29 x 10^9/L (NR: 125 – 375) on [redacted] (Day 26). On [redacted] (Day 31), the subject experienced sub capsular liver abscess (Grade 2) and a drain was placed. Treatment included morphine, ibuprofen, piperacillin, gentamycin, metronidazole and platelets. He recovered from cholangitis on [redacted] (Day 30), from liver abscess on [redacted] (Day 46), from abdominal pain on [redacted] (Day 47), and from decreased platelet count on [redacted] (Day 158). The Investigator considered abdominal pain serious and not related to the study drug but related to the liver abscess secondary to the liver metastasis; decreased platelet count non-serious and probably related to the study drug; cholangitis and liver abscess non-serious and not related to the study drug. On [redacted] (Day 75), the study drug was reduced to 0.7 mg/m^2 due to abdominal pain and decreased platelet count.

On [redacted] (Day 236), tumor response assessment showed disease progression and the subject was withdrawn from study. The last dose of the study drug was received on [redacted] (Day 230).

被験者番号	18011007
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	肺感染/Lung infection

A 59-year-old white female was diagnosed with high grade leiomyosarcoma in uterus on 21 Jun 2011. The last date of disease progression was 14 Nov 2012. Significant medical history included fatigue and tumor pain. At Screening, tumor assessments of target/non-target lesions via CT scan showed left lingular lobe lung mass, right middle lobe lung mass, right lower lobe liver mass, right lung mass with impact in costae with destruction, and left medial/quadrate lobe liver mass. The subject received previous radiotherapy to TH 4 and TH6 vertebral lesion and left leg crus. Previous anticancer therapy included doxorubicin, ifosfamide, pazopanib and trabectedin. Prior and concomitant medications included gabapentin, morphine and zoledronic acid. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 19), the subject was hospitalized for fever and cough; an x-ray of thorax confirmed lung infection (Grade 2). She was treated with cefuroxime and roxithromycin. On [redacted] (Day 21), she recovered from this event. On [redacted] (Day 25), the subject was re-admitted to the hospital for lung infection (Grade 2). The study drug was interrupted due to this event. She was treated with cefuroxime. On [redacted] (Day 33), the subject experienced neutropenia (Grade 2) with neutrophil count of 1.2 x 10^9/L (NR: 1.7 – 7.9). On [redacted] (Day 35), she recovered from lung infection. On [redacted] (Day 37), the study drug was restarted at a reduced dose of 1.1 mg/m^2 due to neutropenia. She recovered from neutropenia on [redacted] (Day 43). The Investigator considered lung infection serious and not related to the study drug, but related to the general condition; and neutropenia non-serious and probably related to the study drug.

On [redacted] (Day 46), tumor response assessment showed disease progression and the subject was withdrawn from the study. The last dose of the study drug was received on [redacted] (Day 45).

被験者番号	18011008
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	発熱/Pyrexia，脊髄圧迫/Spinal cord compression
治験薬の投与中止に至った有害事象	脊髄圧迫/Spinal cord compression

A 66-year-old white male was diagnosed with high grade leiomyosarcoma in right crus on 19 Feb 2002. The last date of disease progression was 01 Feb 2013. Significant medical history included arteriosclerosis in coronary arteries and cholelithiasis. At Screening, tumor assessments of target/non-target lesions via CT scan showed left lower lobe lung mass and lesions in right thorax wall, left side abdominal wall, right gluteal region, and multiple metastases in skull, spine, thorax, pelvis, and limbs. The subject had previous radiotherapy to right arm humerus, leftarm proximal humerus and left arm humerus. Previous anticancer therapy included doxorubicin and ifosfamide. Prior and concomitant medications included domperidone, ibuprofen, morphine, pantoprazole, paracetamol, pegfilgrastim and prednisolone. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated

On [redacted] (Day 10), the subject was hospitalized for pyrexia (Grade 2). He was treated with piperacillin/tazobactam and amoxicillin/clavulanic acid. On [redacted] (Day 11), the subject recovered from fever. The Investigator considered fever serious and possibly related to the study drug.

On [redacted] (Day 223), CT scan showed progression of multiple bone lesions. On [redacted] (Day 226), the subject was hospitalized for control problems with difficulties in right and left extremities and was diagnosed with spinal cord compression (Grade 3). MRI showed malignant transverse lesion of spinal cord in L2-L3 with progressive disease and bone metastases were visible in the right femoral neck. He was treated with prednisolone, pantoprazole and morphine. The study drug was withdrawn due to this event. He received the last dose of the study drug on [redacted] (Day 220). On [redacted] (Day 239), he underwent surgery for spinal cord compression and he recovered on [redacted] (Day 246). The Investigator considered spinal cord compression serious and not related to the study drug.

被験者番号	19021002
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	尿路感染/Urinary tract infection

A 52-year-old male was diagnosed with intermediate grade dedifferentiated adipocytic sarcoma in retroperitoneum on 06 Jan 2011. The last date of disease progression was 04 Apr 2012. Significant medical history included dilatation of the left cavitie uretero- pyelocaliectasis, on ureteral catheter, peripheral edema, thrombophlebitis and tumor excision. At Screening, tumor assessments of target/non-target lesions via CT scan showed peritoneal/omental mass. The subject received previous radiotherapy to retroperitoneal gastric mass and previous anticancer therapy included doxorubicin and trabectedin. Prior and concomitant medications included augmentin, bactrim, ciprofloxacin, dexamethasone, lactulose, metoclopramide, metopimazine, modane, ondansetron, oxycodone, pantoprazole, paracetamol, prednisolone, red blood cells, spasfon and tinzaparin. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 14), the subject experienced urinary tract infection (Grade 2) associated with pyrexia (Grade 1). The subject was treated with amoxicillin/clavulunate and ciprofloxacin and underwent replacement of ureteral catheter. On [redacted] (Day 36), the subject was hospitalized for persistent urinary tract infection (Grade 3) associated with fever and chills. On physical examination, there was an inflammation and pain around the edge of the catheter combined with purulent discharge and urine culture showed multidrug resistant Escherichia coli. The subject was treated with amikacin and piperacillin/tazobactam. On [redacted] (Day 37), the subject recovered from this event. The Investigator considered urinary tract infection serious and not related to the study drug, but related to bacterial infection in ureteral catheter. The study drug dose was not changed.

On [redacted] (Day 40), tumor response assessment showed disease progression and the subject was withdrawn from study. The last dose of the study drug was received on [redacted] (Day 29).

被験者番号	19021011
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	病的骨折/Pathological fracture

A 65-year-old female was diagnosed with high grade pleomorphic adipocytic sarcoma in the connective tissue of left superior member (elbow) on 10 Apr 2009. The last date of disease progression was 25 Jun 2012. Significant medical history included hypertension, colostomy, phlebitis, and tumor pain. At Screening, tumor assessments of target/non-target lesions via CT scan showed left lower lobe lung mass, mediastinal thymic thoracic adenopathy, peritoneal/omental mass and lesions in anterior upper right of skin. The subject received previous radiotherapy to left shoulder girdle lesion and left lower lobe lung mass. Previous anticancer therapy included doxorubicin and ifosfamide. Prior and concomitant medications included augmentin, ciprofloxacin, dexamethasone, domperidone, ketoprofen, lactulose, lercanidipine, loperamide, lorazepam, metoclopramide, movicol, ondansetron, oxycodone, pantoprazole, paracetamol, prednisolone, pregabalin, red blood cells and tinzaparin. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 42), tumor response assessment showed disease progression. On the same day, the subject received the last dose of study drug and was withdrawn from the study.

On [redacted] (Day 49), the subject was hospitalized for pathological fracture of left femur (Grade 3) and she underwent percutaneous plate osteosynthesis of left femur. On [redacted] (Day 66), the subject recovered from this event. The Investigator considered pathological fracture serious and not related to the study drug, but related to tumor.

被験者番号	19021012
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	腸閉塞/Intestinal obstruction

A 62-year-old female was diagnosed with intermediate grade leiomyosarcoma in large intestine on 25 May 1999. The last date of disease progression was 13 Jul 2012. Significant medical history included osteoporosis, tumour pain and tumour excision. At Screening, tumor assessments of target/non-target lesions via CT scan showed right lower lobe liver mass, left lateral lobe liver mass, lesions in trunk and peritoneal/omental mass. Previous anticancer therapy included doxorubicin, gemcitabine and ifosfamide. Prior and concomitant medications included augmentin, dexamethasone, domperidone, enoxaparin, esomeprazole, fentanyl, lekovit ca, metoclopramide, ondansetron, paracetamol, prednisolone, prednisone, spasfon and tramadol. ECOG performance status at screening was 0.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 258), the subject was hospitalized for intestinal obstruction (Grade 3) with fecaloid vomiting. Gastrointestinal examination showed abdominal distension, painful palpation of right hydrochondrium and flank and significant irregular hepatomegaly. The study drug was interrupted due to intestinal obstruction. On [redacted] (Day 259), the subject was found to have anemia (Grade 3) with RBC count 3.29 x 10^12/L (NR: 3.7 – 5.2) and hemoglobin at 103 g/L (NR: 110 -155). The subject was transfused with 2 units of red blood cells, and treated with methylprednisolone, trimebutine, morphine, lactulose, rabeprazole, antacids and sterculia urens. On [redacted] (Day 259), tumor response assessment showed disease progression. On [redacted] (Day 268), the subject was withdrawn from the study due to disease progression. The last dose of study drug was received on [redacted] (Day 248). On [redacted] (Day 265), the subject recovered from anemia and intestinal obstruction. The Investigator considered intestinal obstruction serious and possibly related to the study drug and anemia non serious and not related to study drug.

被験者番号	19031001
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	無力症/Asthenia，下痢/Diarrhea

A 75-year-old female was diagnosed with intermediate grade dedifferentiated adipocytic sarcoma in retroperitoneum in 2003. The last date of disease progression was 13 Mar 2012. Significant medical history included eventration repair, anemia, asthma, constipation, sarcoma excision, right nephrectomy and right iliac tumor pain. At Screening, tumor assessments of target/non-target lesions via CT scan showed retroperitoneal mass. Previous anticancer therapy included doxorubicin and etoposide. Prior and concomitant medications included allopurinol, bisacodyl, budesonide, cefixime, filgrastim, formoterol, frubienzym, givalex, glycerol, granulocyte colony stimulating factor, heptaminol, lenograstim, metoclopramide, paracetamol, pegfilgrastim, proteins, red blood cells, tiotropium and zolpidem. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 147)), the subject was hospitalized for worsening of diarrhea (Grade 3) and asthenia to (Grade 3). The subject had an intermittent asthenia (Grade 2) since [redacted] (Day 29) and intermittent diarrhea (Grade 2) since [redacted] (Day 60). The study drug was interrupted due to these events. On [redacted] (Day 152), the subject requested to be discharged to home. On [redacted] (Day 153) her condition worsened and she was re-hospitalized for management of diarrhea and was found to have hypokalemia (Grade 3) with potassium of 2.6 mmol/L (NR: 3.5-5). The subject was treated with IV fluids, racecadotril, diosmectite and loperamide. On [redacted] (Day 156), tumor response assessment showed disease progression and the subject was withdrawn from the study. The last dose of the study drug was received on [redacted] (Day 134). On [redacted] (Day159), the subject recovered from hypokalemia and on [redacted] (Day 166), the subject recovered from diarrhea and asthenia. The Investigator considered diarrhea, and asthenia serious and possibly related to the study drug; and hypokalemia non-serious and not related to the study drug.

被験者番号	19041013
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	後腹膜出血/Retroperitoneal haemorrhage

A 52-year-old female was diagnosed with high grade leiomyosarcoma in uterus on 05 May 2000. The last date of disease progression was 21 Nov 2012. Significant medical history included hysterectomy, brachial thrombosis and cough. At Screening, tumor assessments of target/non-target lesions via CT scan showed right upper lobe and lower lobe lung mass, left pre-renal mass, right pleural effusion, and right pleural mass. The subject received previous radiotherapy to uterine mass and previous anticancer therapy included an unknown anthracycline, sorafenib and trabectedin. Prior and concomitant medications included estradiol, macrogol, paracetamol and tinzaparin. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 41), the subject was hospitalized for retroperitoneal hemorrhage (Grade 4) associated with intense abdominal pain, tachycardia and hypotension. Abdominal ultrasound showed left adrenal hematoma with moderate intraperitoneal effusion and CT scan showed hemoretroperitoneum and hemoperitoneum secondary to the rupture of the left metastatic adrenal gland. The subject was transfused with packed red blood cells and treated with morphine, hetastarch, sodium chloride, magnesium sulfate, tranexamic acid, methylprednisolone and paracetamol. On [redacted] (Day 52), the study drug dose was reduced to 1.1 mg/m^{2}due to this event. On [redacted] (Day 55), the subject recovered from this event. The Investigator considered retroperitoneal hemorrhage serious and possibly related to the study drug.

On [redacted] (Day 87), tumor response assessment showed disease progression and the subject was withdrawn from study. The last dose of study drug was received on [redacted] (Day 79).

被験者番号	19081011
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	発熱/Pyrexia

A 65-year-old female was diagnosed with high grade leiomyosarcoma in liver on 06 Jul 2009. The last date of disease progression was 24 Oct 2012. Medical history included adrenalectomy, diarrhea, oral herpes, re-operation of a nodule in the left parietal scalp and resection of a leiomyosarcoma of the vena cava. At Screening, tumor assessments of target/non-target lesions via CT scan showed left lung lesion, right lung lesions, hepatic lesions, pulmonary lesions, inferior vena cava and peritoneal/omental mass. The subject received previous radiotherapy to the vena cava liver mass and right leg soft tissue. Previous anticancer therapy included doxorubicin, cyclophosphamide and ifosfamide. Prior and concomitant medications included aciclovir, amphotericin b, aprepitant, colecalciferol, colestyramine, donormyl, lonarid n, metopimazine, mirtazapine, ondansetron, paracetamol, prednisolone, saccharomyces boulardii, stomatological mouth preparations, ultracet, unspecified herbal and traditional medicine. ECOG performance status at screening was 0.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 3), the subject was hospitalized for pyrexia (Grade 1) with temperature of 39 degree celsius (NR: 36.5-37.2) and treated with amoxicillin/clavulanic acid, suprofen and paracetamol. On [redacted] (Day 3), the subject recovered from pyrexia. The Investigator considered pyrexia serious and not related to the study drug.

On [redacted] (Day 141), tumor response assessment showed disease progression and the subject was withdrawn from the study. The last dose of the study drug was received on [redacted] (Day 127).

被験者番号	19081016
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	肺塞栓症/Pulmonary embolism

A 58-year-old female was diagnosed with high grade leiomyosarcoma in uterus on 21 Dec 2011. The last date of disease progression was 22 Jan 2013. Significant medical history included bilateral salpingo-oophorectomy, hysterectomy, type 2 diabetes mellitus and cerebrovascular accident. At Screening, tumor assessments of target/non-target lesions via CT scan showed lung mass, right adrenal mass, pancreatic mass, corporeo-caudal pancreatic mass, pulmonary nodules and splenic nodules. The subject received previous radiotherapy to the pelvis. Previous anticancer therapy included doxorubicin, ifosfamide, gemcitabine and pazopanib. Prior and concomitant medications included acetylsalicylic acid, insulin, metformin, ondansetron, paracetamol, red blood cells and stomatological mouth preparations. ECOG performance status at screening was 0.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 43), tumor response assessment showed disease progression and asymptomatic pulmonary embolism. The subject was subsequently hospitalized for pulmonary embolism (Grade 3) and she was treated with tinzaparin. The subject was withdrawn from study due to disease progression and the last dose of the study drug was received on [redacted] (Day 35). On [redacted] (Day 45), the subject recovered from pulmonary embolism. The Investigator considered pulmonary embolism serious and not related to the study drug.

被験者番号	21011001
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	細菌性腹膜炎/Bacterial peritonitis

A 49-year-old white male was diagnosed with high grade dedifferentiated liposarcoma in small intestine on 11 Feb 2011. The last date of disease progression was 26 Jul 2012. Significant medical history included asthma, peripheral edema, hypotension and tumour pain. At Screening, tumor assessments of target/non-target lesions via CT scan showed mediastinum, retro and right parasternal lymph node, mesenteric adenopathy, retroperitoneal mass and multiple tumor lesions. Previous anticancer therapy included doxorubicin, ifosfamide and trabectedin. Prior and concomitant medications included dexamethasone, fentanyl, metamizole, pantoprazole, and torasemide. ECOG performance status at screening was 1.

On [redacted] (Day 1) treatment with the study drug was initiated.

On [redacted] (Day 6), the subject was hospitalized with dyspnea and diagnosed with bacterial peritonitis (Grade 3). He was treated with piperacillin, tazobactam, metronidazole, ertapenem, spironolactone and furosemide. On [redacted] (Day 14), ascites puncture was performed. The study drug was interrupted due to bacterial peritonitis. The study drug was never resumed because per Investigator the subject was physically unable to attend the treatment due to the bacterial peritonitis and there was very large interval since last dose to continue next dose. The subject received the last dose of the study drug on [redacted] (Day 1). The subject was considered recovering from this event. The Investigator considered bacterial peritonitis serious and not related to the study drug.

被験者番号	22021003
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	貧血/Anaemia
病勢進行による死亡	Yes

A 53-year-old white female was diagnosed with intermediate grade leiomyosarcoma in retroperitoneum on 11 Sep 2007. The last date of disease progression was 24 Jan 2012. Significant medical history included increased platelet count, insomnia, hypertension, jugular vein thrombosis, mass excision, nephrectomy and surgery at peritoneal lesion. At Screening, tumor assessments of target/non-target lesions via CT scan showed right middle lobe lung mass, lesions in anterior right torax, right kidney lesion, superior left abdomen lesion and multiple lung lesions. Previous anticancer therapy included epirubicin, gemcitabine, ifosfamide, docetaxel and trabectedin. Prior and concomitant medications included acetylsalicylic acid, alprazolam, biselect, ceftriaxone, dexamethasone, midodrine, ondansetron, paracetamol, prednisone and warfarin. ECOG performance status at screening was 1.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 38), the subject was hospitalized for anemia (Grade 3) with hemoglobin of 73 g/L (NR: 110 – 155) and was transfused with red blood cells. On [redacted] (Day 41), she recovered from this event. The Investigator considered anemia serious and probably related to the study drug. On [redacted] (Day 50), the study drug dose was reduced to 1.1 mg/m^2 due to this event.

On [redacted] (Day 57), tumor response assessment showed disease progression and the subject was withdrawn from study. The subject received the last dose of the study drug on the same day (Day 57).

On [redacted] (Day 74, 17 days after last dose), the subject died due to disease progression.

被験者番号	22051003
投与群	本薬群：1.4 mg/m^2 IV on Days 1 and 8, every 21 days
死亡以外の重篤な有害事象	疲労/Fatigue，腫瘍出血/Tumor hemorrhage

A 41-year-old white female was diagnosed with intermediate grade leiomyosarcoma in connective and soft tissue left femur in Nov 2009. The last date of disease progression was 18 Mar 2013. Significant medical history included inferior right and left lung lobectomy, sarcoma excision and tumor excision in right leg. At Screening, tumor assessments of target/non-target lesions via CT scan showed left upper lung mass, right middle and lower lobe lung masses. The subject received previous radiotherapy to right upper lobe of lung and right leg. Previous anticancer therapy included doxorubicin, ifosfamide, gemcitabine, and trabectedin. Prior and concomitant medications included omeprazole and tranexamic acid. ECOG performance status at screening was 0.

On [redacted] (Day 1), treatment with study drug was initiated.

On [redacted] (Day 5), the subject was hospitalized for fatigue (Grade 2) and dyspnea. On [redacted] (Day 6), chest X-ray and CT scan revealed increased lesions in the lungs, bronchial bleeding and no evidence of thromboembolism. The subject was diagnosed with bronchial tumor bleeding (Grade 3) due to metastasis and treated with methylprednisolone, oxygen and electrolytes. On the same day, tumor response assessment showed disease progression and the subject was withdrawn from the study. The last dose of the study drug was received on [redacted] (Day 1). On [redacted] (Day 13), the subject recovered from fatigue and tumor hemorrhage. The Investigator considered tumor hemorrhage serious and not related to the study drug and fatigue serious and possibly related to the study drug.