表 2.7.3.3.2.1-1　人口統計学的特性（FeDeriCa 試験，ITT 集団）

	Pertuzumab IV + Trastuzumab IV Arm (N=252)	Pertuzumab + Trastuzumab FDC SC Arm (N=248)	Total (N=500)
Age (yr.)			
n	252	248	500
Mean (SD)	50.34 (10.79)	51.66 (10.72)	50.99 (10.76)
Median	49.00	52.00	51.00
Range	27.0 - 76.0	25.0 - 81.0	25.0 - 81.0
Age (yr.)			
n	252	248	500
<35	14 (5.6%)	16 (6.5%)	30 (6.0%)
35-39	24 (9.5%)	17 (6.9%)	41 (8.2%)
40-49	93 (36.9%)	70 (28.2%)	163 (32.6%)
50-64	88 (34.9%)	119 (48.0%)	207 (41.4%)
65-74	30 (11.9%)	22 (8.9%)	52 (10.4%)
>=75	3 (1.2%)	4 (1.6%)	7 (1.4%)
Sex			
n	252	248	500
Female	250 (99.2%)	248 (100%)	498 (99.6%)
Male	2 (0.8%)	0	2 (0.4%)
Ethnicity			
n	252	248	500
Hispanic or Latino	32 (12.7%)	42 (16.9%)	74 (14.8%)
Not Hispanic or Latino	200 (79.4%)	189 (76.2%)	389 (77.8%)
Not Reported	16 (6.3%)	13 (5.2%)	29 (5.8%)
Unknown	4 (1.6%)	4 (1.6%)	8 (1.6%)
Race			
n	252	248	500
American Indian or Alaska native	10 (4.0%)	10 (4.0%)	20 (4.0%)
Asian	54 (21.4%)	51 (20.6%)	105 (21.0%)
Black or African American	3 (1.2%)	3 (1.2%)	6 (1.2%)
Native Hawaiian or Other Pacific Islander	0	0	0
White	164 (65.1%)	165 (66.5%)	329 (65.8%)
Multiple	2 (0.8%)	3 (1.2%)	5 (1.0%)
Unknown	19 (7.5%)	16 (6.5%)	35 (7.0%)
Weight (kg) at baseline			
n	252	248	500
Mean (SD)	67.92 (14.39)	68.89 (15.98)	68.41 (15.19)
Median	66.00	65.00	65.01
Range	40.0 - 126.0	40.5 - 136.0	40.0 - 136.0

	Pertuzumab IV + Trastuzumab IV Arm (N=252)	Pertuzumab + Trastuzumab FDC SC Arm (N=248)	Total (N=500)
Height (cm) at baseline			
n	252	248	500
Mean (SD)	161.89 (7.32)	161.51 (6.41)	161.70 (6.88)
Median	162.00	161.00	162.00
Range	145.0 - 185.0	146.0 - 179.0	145.0 - 185.0
BMI (WHO Classification) [1]			
n	252	248	500
Underweight	3 (1.2%)	7 (2.8%)	10 (2.0%)
Normal	120 (47.6%)	112 (45.2%)	232 (46.4%)
Overweight	80 (31.7%)	75 (30.2%)	155 (31.0%)
Obese	49 (19.4%)	54 (21.8%)	103 (20.6%)
Smoking Status			
n	252	248	500
Ever smoked	64 (25.4%)	68 (27.4%)	132 (26.4%)
Never smoked	188 (74.6%)	180 (72.6%)	368 (73.6%)
Menopausal Status at Screening			
n	252	248	500
Pre-menopausal	144 (57.1%)	118 (47.6%)	262 (52.4%)
Post-menopausal	106 (42.1%)	130 (52.4%)	236 (47.2%)
Unknown	2 (0.8%)	0	2 (0.4%)
Baseline ECOG Performance Status			
n	252	248	500
0	235 (93.3%)	227 (91.5%)	462 (92.4%)
1	16 (6.3%)	19 (7.7%)	35 (7.0%)
Unknown	1 (0.4%)	2 (0.8%)	3 (0.6%)

Denominator for percentages is the number of patients in the ITT population.
[1] BMI (kg/m2): Underweight <18.5; Normal 18.5-<25.0; Overweight 25.0-<30.0; Obese >=30.0

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Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CSR/prod/output/ah_sa7796_t_dm_IT_04JUL2019_40324.out
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［5.3.5.1-1-1 Table 6 を再掲］

表 2.7.3.3.2.1-2 ベースラインの疾患特性（FeDeriCa 試験，ITT 集団）

	Pertuzumab IV + Trastuzumab IV Arm (N=252)	Pertuzumab + Trastuzumab FDC SC Arm (N=248)
Time since initial diagnosis [Weeks]		
n	250	247
Mean (SD)	6.25 (2.82)	6.50 (3.12)
Median	5.71	5.71
Min - Max	1.9 - 24.4	2.3 - 28.1
Site of primary tumor		
n	252	248
Right	124 (49.2%)	114 (46.0%)
Left	128 (50.8%)	134 (54.0%)
Histologic subtype		
n	252	248
Invasive carcinoma of no special type (NST)	194 (77.0%)	197 (79.4%)
Invasive lobular carcinoma	16 (6.3%)	13 (5.2%)
Invasive micropapillary carcinoma	2 (0.8%)	1 (0.4%)
Mucinous carcinoma	3 (1.2%)	2 (0.8%)
Apocrine carcinoma	3 (1.2%)	2 (0.8%)
Other	34 (13.5%)	33 (13.3%)
Histological grade		
n	252	248
GX	2 (0.8%)	4 (1.6%)
G1	9 (3.6%)	3 (1.2%)
G2	119 (47.2%)	116 (46.8%)
G3	80 (31.7%)	90 (36.3%)
No residual tumor	0	0
Unknown	42 (16.7%)	35 (14.1%)
Primary tumor estrogen receptor status (Central Lab)		
n	252	248
Estrogen receptor positive	152 (60.3%)	150 (60.5%)
Estrogen receptor negative	100 (39.7%)	97 (39.1%)
Estrogen receptor unknown	0	1 (0.4%)
Primary tumor progesterone receptor status (Central Lab)		
n	252	248
Progesterone receptor positive	116 (46.0%)	98 (39.5%)
Progesterone receptor negative	135 (53.6%)	149 (60.1%)
Progesterone receptor unknown	1 (0.4%)	1 (0.4%)
HER2 Immunohistochemistry (Central Lab)		
n	252	248
0	3 (1.2%)	0
1+	6 (2.4%)	2 (0.8%)
2+	68 (27.0%)	74 (29.8%)
3+	175 (69.4%)	170 (68.5%)
Unknown	0	2 (0.8%)

	Pertuzumab IV + Trastuzumab IV Arm (N=252)	Pertuzumab + Trastuzumab FDC SC Arm (N=248)
HER2 ISH (Central Lab)		
n	252	248
ISH+	252 (100%)	247 (99.6%)
ISH-	0	1 (0.4%)
Unknown	0	0
Clinical staging - Primary tumor		
n	252	248
TX	0	0
Tis	0	0
T1a	1 (0.4%)	0
T1b	2 (0.8%)	1 (0.4%)
T1c	11 (4.4%)	10 (4.0%)
T2	166 (65.9%)	154 (62.1%)
T3	37 (14.7%)	42 (16.9%)
T4a	9 (3.6%)	3 (1.2%)
T4b	17 (6.7%)	31 (12.5%)
T4c	2 (0.8%)	1 (0.4%)
T4d	7 (2.8%)	6 (2.4%)
Clinical staging - Regional lymph nodes		
n	252	248
NX	2 (0.8%)	0
N0	109 (43.3%)	101 (40.7%)
N1	107 (42.5%)	102 (41.1%)
N2a	13 (5.2%)	25 (10.1%)
N2b	2 (0.8%)	3 (1.2%)
N3a	8 (3.2%)	5 (2.0%)
N3b	6 (2.4%)	5 (2.0%)
N3c	5 (2.0%)	7 (2.8%)
Clinical stage at presentation		
n	252	248
II-IIIA	202 (80.2%)	196 (79.0%)
IIIB-IIIC	50 (19.8%)	52 (21.0%)

Denominator for percentages is the number of patients in the ITT population. Unknown includes not applicable.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CSR/prod/program/t_dm_strata_base.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CSR/prod/output/t_dm_strata_base_IT_04JUL2019_40324.out
09SEP2019 17:16

［5.3.5.1-1-1 Table 8 を再掲］

表 2.7.3.3.2.1-3 ランダム化層別因子（FeDeriCa 試験，ITT 集団）

	Pertuzumab IV + Trastuzumab IV Arm (N=252)	Pertuzumab + Trastuzumab FDC SC Arm (N=248)
Hormonal receptor status (based on central assessment):		
ER negative and PgR negative	97 (38.5%)	96 (38.7%)
ER positive or PgR positive	155 (61.5%)	151 (60.9%)
Unknown	0	1 (0.4%)
Type of chemotherapy		
ddAC followed by paclitaxel	120 (47.6%)	120 (48.4%)
AC followed by docetaxel	132 (52.4%)	128 (51.6%)
Clinical stage at presentation		
Stage II-IIIA	201 (79.8%)	198 (79.8%)
Stage IIIB-IIIC	51 (20.2%)	50 (20.2%)

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Output:
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19NOV2019 9:45

［5.3.5.1-1-1 Table 7 を再掲］

2.7.3.3.2.2 PHranceSCa 試験

両群の ITT 集団における人口統計学的特性（表 2.7.3.3.2.2-1）及びベースラインの疾患特性（表 2.7.3.3.2.2-2）は，全体的に均衡がとれていた。

全例が女性，被験者の大半が白人であり（A 群77.5%，B 群83.8%），年齢中央値は47.0歳（A 群48.0歳，B 群47.0歳）であった。

大多数の被験者は4サイクル以上の術前補助療法を受けており（A 群93.8%，B 群87.5%），ベースライン時の ECOG PS が0（A 群87.5%，B 群87.5%）であった。

被験者の多くは非特殊型浸潤性乳癌（A 群55.0%，B 群62.5%）であった。組織学的グレード分類では Grade 2（A 群47.5%，B 群42.5%）又は Grade 3（A 群37.5%，B 群46.3%）の被験者が多かった。

ランダム化層別因子に関しては表 2.7.3.3.2.2-3に示した。アントラサイクリン系 + タキサン系の術前補助療法を受けた被験者が多く（A 群68.8%，B 群66.3%），術前補助療法の効果は pCR の被験者が多かった（A 群65.0%，B 群62.5%）。ホルモン受容体陽性の疾患が多かった（A 群66.3%，B 群63.8%）。

表 2.7.3.3.2.2-1 人口統計学的特性（PHranceSCa 試験，ITT 集団）

	Arm A P+H IV/PH FDC SC (N=80)	Arm B PH FDC SC/P+H IV (N=80)	All Patients (N=160)
Age (yr)			
n	80	80	160
Mean (SD)	49.4 (11.6)	48.2 (12.1)	48.8 (11.8)
Median	48.0	47.0	47.0
25% and 75%-ile	40.0 - 58.0	39.5 - 55.0	40.0 - 56.0
Min - Max	26 - 74	22 - 80	22 - 80
Age Group (yr), n(%)			
< 35	5 (6.3%)	8 (10.0%)	13 (8.1%)
35-39	14 (17.5%)	12 (15.0%)	26 (16.3%)
40-49	27 (33.8%)	25 (31.3%)	52 (32.5%)
50-64	22 (27.5%)	27 (33.8%)	49 (30.6%)
65-74	12 (15.0%)	6 (7.5%)	18 (11.3%)
≥ 75	0	2 (2.5%)	2 (1.3%)
Sex, n(%)			
Male	0	0	0
Female	80 (100%)	80 (100%)	160 (100%)
Ethnicity, n(%)			
Hispanic or Latino	17 (21.3%)	21 (26.3%)	38 (23.8%)
Not Hispanic or Latino	59 (73.8%)	54 (67.5%)	113 (70.6%)
Not Reported	2 (2.5%)	2 (2.5%)	4 (2.5%)
Unknown	2 (2.5%)	3 (3.8%)	5 (3.1%)
Race, n(%)			
American Indian or Alaska Native	5 (6.3%)	3 (3.8%)	8 (5.0%)
Asian	8 (10.0%)	4 (5.0%)	12 (7.5%)
Black or African American	2 (2.5%)	2 (2.5%)	4 (2.5%)
Native Hawaiian or Other Pacific Islander	0	0	0
White	62 (77.5%)	67 (83.8%)	129 (80.6%)
Unknown	3 (3.8%)	4 (5.0%)	7 (4.4%)
Baseline weight (kg)			
n	80	80	160
Mean (SD)	67.36 (12.08)	70.21 (14.15)	68.78 (13.20)
Median	67.45	69.60	68.00
25% and 75%-ile	57.40 - 76.00	58.20 - 78.25	58.00 - 76.00
Min - Max	46.4 - 99.0	47.5 - 119.0	46.4 - 119.0
ECOG performance status, n(%)			
n	80	80	160
0	70 (87.5%)	70 (87.5%)	140 (87.5%)
1	10 (12.5%)	10 (12.5%)	20 (12.5%)
Number of cycles of prior neoadjuvant pertuzumab IV and Trastuzumab IV, n(%)			
< 4	5 (6.3%)	10 (12.5%)	15 (9.4%)
≥ 4	75 (93.8%)	70 (87.5%)	145 (90.6%)

Extract Date:09APR2020 Cutoff Date:24FEB2020
Source: t_dm_IT

［5.3.5.1-3 Table 5 を再掲］

表 2.7.3.3.2.2-2 ベースラインの疾患特性（PHranceSCa 試験，ITT 集団）

	Arm A P+H IV/ PH FDC SC (N=80)	Arm B PH FDC SC / P+H IV (N=80)	All Patients (N=160)
Time since initial diagnosis to randomization (weeks)			
n	78	78	156
Mean (SD)	33.874 (7.022)	34.441 (8.111)	34.158 (7.567)
Median	32.214	32.429	32.357
25% and 75%-ile	29.000 – 37.857	30.143 – 37.286	29.500 – 37.429
Min - Max	20.71 – 58.29	19.29 – 71.14	19.29 – 71.14
Time since last surgery to randomization (weeks)			
n	80	80	160
Mean (SD)	4.20 (1.38)	4.34 (2.10)	4.27 (1.77)
Median	4.14	4.00	4.14
25% and 75%-ile	3.14 - 5.00	3.14 - 5.00	3.14 - 5.00
Min - Max	2.0 - 8.6	1.9 - 18.0	1.9 - 18.0
Site of primary tumor, n(%)			
n	80	80	160
Right	38 (47.5%)	47 (58.8%)	85 (53.1%)
Left	42 (52.5%)	33 (41.3%)	75 (46.9%)
Bilateral	0	0	0
Primary tumor focality, n(%)			
n	80	80	160
Unifocal	57 (71.3%)	55 (68.8%)	112 (70.0%)
Multifocal	23 (28.8%)	25 (31.3%)	48 (30.0%)
Histologic subtype, n(%)*			
Invasive carcinoma of no special type (NST)	44 (55.0%)	50 (62.5%)	94 (58.8%)
Invasive lobular carcinoma	8 (10.0%)	4 (5.0%)	12 (7.5%)
Invasive micropapillary carcinoma	1 (1.3%)	1 (1.3%)	2 (1.3%)
Mucinous carcinoma	0	1 (1.3%)	1 (0.6%)
Apocrine carcinoma	0	1 (1.3%)	1 (0.6%)
Other	29 (36.3%)	26 (32.5%)	55 (34.4%)
Histological grade, n(%)			
n	80	80	160
G1	1 (1.3%)	2 (2.5%)	3 (1.9%)
G2	38 (47.5%)	34 (42.5%)	72 (45.0%)
G3	30 (37.5%)	37 (46.3%)	67 (41.9%)
No residual tumor	1 (1.3%)	2 (2.5%)	3 (1.9%)
GX/Unknown	10 (12.5%)	5 (6.3%)	15 (9.4%)
Clinical stage at presentation, n(%)			
n	80	80	160
Stage II-IIIA	68 (85.0%)	68 (85.0%)	136 (85.0%)
Stage IIIB-IIIC	12 (15.0%)	12 (15.0%)	24 (15.0%)

* Patients may have had more than 1 histological subtype, therefore the same patient may have been counted in different categories.
Extract Date:09APR2020 Cutoff Date:24FEB2020
Source: t_dm_bchist_IT

［5.3.5.1-3 Table 7 を再掲］

表 2.7.3.3.2.2-3 ランダム化層別因子（PHranceSCa 試験，ITT 集団）

	Arm A P+H IV/ PH FDC SC (N=80)	Arm B PH FDC SC/ P+H IV (N=80)	All Patients (N=160)
Prior Neoadjuvant chemotherapy regimen (IxRS)			
n	80	80	160
Anthracyclines + taxanes	55 (68.8%)	53 (66.3%)	108 (67.5%)
Carboplatin + taxanes	22 (27.5%)	23 (28.8%)	45 (28.1%)
Taxanes only	3 (3.8%)	4 (5.0%)	7 (4.4%)
Pathological complete response to prior neoadjuvant treatment (IxRS)			
n	80	80	160
pCR	52 (65.0%)	50 (62.5%)	102 (63.8%)
Non-pCR	28 (35.0%)	30 (37.5%)	58 (36.3%)
Hormone receptor status (IxRS)			
n	80	80	160
Estrogen receptor ER-positive and/or progesterone receptor PgR positive	53 (66.3%)	51 (63.8%)	104 (65.0%)
ER-negative and PgR-negative	27 (33.8%)	29 (36.3%)	56 (35.0%)
Hormone receptor status (eCRF)			
n	80	80	160
Estrogen receptor ER-positive and/or progesterone receptor PgR positive	54 (67.5%)	52 (65.0%)	106 (66.3%)
ER-negative and PgR-negative	26 (32.5%)	28 (35.0%)	54 (33.8%)

Extract Date:09APR2020 Cutoff Date:24FEB2020
Source: t_dm_IT

［5.3.5.1-3 Table 6 を再掲］

2.7.3.3.3 有効性の結果（FeDeriCa 試験）

2.7.3.3.3.1 主な有効性評価項目

1) tpCR 率

主な有効性の評価項目は，8サイクルの術前補助療法後の tpCR 率（乳房及び腋窩における浸潤性病変の消失，すなわち ypT0/is，ypN0と定義）であった。ITT 集団における tpCR 率は，両群間で同等（P + H IV 群で59.5%，本剤群で59.7%）であり，tpCR 率の差は0.15%（95%CI：−8.67～8.97）であった（表 2.7.3.2.1-1）。

主要評価項目であるペルツズマブの C_{trough} 及びトラスツズマブの C_{trough} に関する本剤群の P + H IV 群に対する非劣性が検証されたため，国内追加事項に従って，本邦では tpCR 率に関する非劣性仮説を検証した（表 2.7.3.3.3.1-1）。tpCR 率の差の90%CI は−7.28%～7.59%であり，CI の下限が非劣性マージンである−12.5%を上回ったため，本剤群の P + H IV 群に対する tpCR 率の非劣性が検証された。すなわち，本剤群が P + H IV 群に対して少なくとも tpCR 率で12.5%以上劣らないことが検証された。

表 2.7.3.3.3.1-1　tpCR 率の非劣性仮説の検証（FeDeriCa 試験，ITT 集団）

Summary of Total Pathological Complete Response (tpCR): ITT Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

Total Pathological Complete Response

	Pertuzumab IV + Trastuzumab IV Arm (N=252)		Pertuzumab + Trastuzumab FDC SC Arm (N=248)
tpCR(absence of invasive neoplastic cells in breast and in the axillary lymph nodes)	150 (59.5%)		148 (59.7%)
Exact 90% CI for tpCR Rate [1]	(54.18, 64.70)		(54.29, 64.90)
Difference in tpCR Rate (SC minus IV arm)		0.15	
90% CI for the difference in tpCR [2]		(-7.28, 7.59)	

[1] Confidence Interval for one sample binomial proportion using Pearson-Clopper method.
[2] Continuity correction of Anderson and Hauck (1986) has been used in this calculation.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/program/t_ef2.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/output/t_ef2_TPCR_IT.out
26MAR2020 22:12 Page 1 of 1

［5.3.5.3-1 t_ef2_TPCR_IT を再掲］

2) 手術時の腫瘍の特徴

手術時の腫瘍の病理学的特徴を表 2.7.3.3.3.1-2に，疾患特性の要約を表 2.7.3.3.3.1-3に示した。

P + H IV 群の239/252例，本剤群の234/248例が手術を施行した。手術時に，P + H IV 群の51.6%（130/252例），本剤群の52.4%（130/248例）は，乳房に残存腫瘍を認めなかった。手術時，最も一般的な組織型は非特殊型浸潤癌（P + H IV 群27.8%，本剤群26.6%，以降同順）であり，組織学的グレード分類は Grade 2（14.7%，16.1%）であった。