## 表 2.7.4.7.1-3　抗 HER2療法の曝露状況の要約（FeDeriCa 試験，試験全体，術前補助療法期間）

| | Pertuzumab IV + Trastuzumab IV Arm | | Pertuzumab + Trastuzumab FDC SC Arm |
|---|---|---|---|
| | Pertuzumab IV (N=247) | Trastuzumab IV (N=246) | Pertuzumab and Trastuzumab FDC SC (N=243) |
| Completed assigned therapy | | | |
| Yes | 241 (97.6%) | 241 (98.0%) | 234 (96.3%) |
| No | 6 ( 2.4%) | 5 ( 2.0%) | 9 ( 3.7%) |
| Number of cycles | | | |
| n | 247 | 246 | 243 |
| Mean | 4.0 | 4.0 | 3.9 |
| SD | 0.4 | 0.3 | 0.5 |
| Median | 4.0 | 4.0 | 4.0 |
| Min - Max | 1 - 5 | 1 - 5 | 1 - 5 |
| Treatment duration [Weeks] | | | |
| n | 247 | 246 | 243 |
| Mean | 9.4 | 9.4 | 9.1 |
| SD | 1.6 | 1.4 | 1.7 |
| Median | 9.1 | 9.1 | 9.1 |
| Min - Max | 0 - 18 | 0 - 18 | 0 - 13 |
| Dose intensity [%] [1] | | | |
| n | 978 | 976 | 951 |
| Mean | 99.89 | 99.35 | 100.00 |
| SD | 2.63 | 3.06 | 0.00 |
| Median | 100.00 | 100.00 | 100.00 |
| Min - Max | 21.7 - 100.0 | 82.8 - 115.9 | 100.0 - 100.0 |
| Total cumulative dose [mg] | | | |
| n | 247 | 246 | 243 |
| Mean | 2093.09 | 1752.96 | 5293.83 |
| SD | 210.92 | 402.64 | 613.96 |
| Median | 2100.00 | 1690.00 | 5400.00 |
| Min - Max | 182.0 - 2940.0 | 466.0 - 3250.0 | 1800.0 - 6600.0 |
| Number of patients with at least one dose delay [3] | | | |
| n | 247 | 246 | 243 |
| Yes | 79 (32.0%) | 83 (33.7%) | 72 (29.6%) |
| No | 168 (68.0%) | 163 (66.3%) | 171 (70.4%) |
| Number of patients with at least one dose delay Due to AE | | | |
| n | 247 | 246 | 243 |
| Yes | 54 (21.9%) | 57 (23.2%) | 54 (22.2%) |
| No | 193 (78.1%) | 189 (76.8%) | 189 (77.8%) |
| Number of cycles of study drug received | 247 ( 100%) | 246 ( 100%) | 243 ( 100%) |
| Cycle number [2] | | | |
| 1- | 3 ( 1.2%) | 2 ( 0.8%) | 6 ( 2.5%) |
| 2- | 1 ( 0.4%) | 1 ( 0.4%) | 2 ( 0.8%) |
| 3- | 2 ( 0.8%) | 2 ( 0.8%) | 1 ( 0.4%) |
| 4- | 238 (96.4%) | 239 (97.2%) | 232 (95.5%) |
| 5- | 3 ( 1.2%) | 2 ( 0.8%) | 2 ( 0.8%) |

[1] Dose intensity = 100% * actual amount of drug received per cycle / planned dose per cycle.
[2] Pertuzumab IV + Trastuzumab IV or Pertuzumab and Trastuzumab FDC SC will be given for 4 cycles (Q3W) concurrently with the taxane component of chemotherapy.
[3] For HER2 treatment dose modification was not allowed however a dose delay of up to 6 weeks due to adverse event was permitted.
Note that a small number of patients received Cycle 9 HER2 therapy before surgery, and therefore have a count of 5 neoadjuvant cycles.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CSR/prod/program/t_ex.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CSR/prod/output/t_ex_NEOS_HER2_SE_04JUL2019_40324.out
20SEP2019 13:25

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［5.3.5.1-1-1 t_ex_NEOS_HER2_SE_04JUL2019_40324 を再掲］

## 表 2.7.4.7.1-4　抗 HER2療法の曝露状況の要約（FeDeriCa 試験，試験全体，術前 + 術後補助療法期間）

| | Pertuzumab IV + Trastuzumab IV Arm | | | Pertuzumab + Trastuzumab FDC SC Arm |
|---|---|---|---|---|
| | Pertuzumab IV (N=247) | Trastuzumab IV (N=246) | Trastuzumab SC [1] (N=61) | Pertuzumab and Trastuzumab FDC SC (N=243) |
| Completed assigned therapy | | | | |
| Yes | 0 | 0 | 0 | 0 |
| No | 247 ( 100%) | 246 ( 100%) | 61 ( 100%) | 243 ( 100%) |
| Number of cycles | | | | |
| n | 247 | 246 | 61 | 243 |
| Mean | 7.3 | 6.4 | 3.6 | 7.5 |
| SD | 2.3 | 2.4 | 1.9 | 2.3 |
| Median | 7.0 | 6.0 | 3.0 | 7.0 |
| Min - Max | 1 - 14 | 1 - 14 | 1 - 9 | 1 - 13 |
| Treatment duration [Weeks] | | | | |
| n | 247 | 246 | 61 | 243 |
| Mean | 23.7 | 20.0 | 8.2 | 24.3 |
| SD | 7.9 | 9.2 | 5.6 | 7.9 |
| Median | 24.0 | 21.1 | 6.6 | 24.1 |
| Min - Max | 0 - 45 | 0 - 45 | 0 - 24 | 0 - 42 |
| Dose intensity [%] [2] | | | | |
| n | 1809 | 1584 | 222 | 1820 |
| Mean | 100.00 | 99.38 | 100.00 | 99.98 |
| SD | 3.04 | 3.31 | 0.00 | 0.78 |
| Median | 100.00 | 100.00 | 100.00 | 100.00 |
| Min - Max | 21.7 - 200.0 | 73.5 - 115.9 | 100.0 - 100.0 | 66.7 - 100.0 |
| Total cumulative dose [mg] | | | | |
| n | 247 | 246 | 61 | 243 |
| Mean | 3829.20 | 2839.75 | 2183.61 | 10079.01 |
| SD | 1047.18 | 1241.54 | 1133.31 | 2857.56 |
| Median | 3780.00 | 2736.00 | 1800.00 | 9600.00 |
| Min - Max | 182.0 - 6720.0 | 466.0 - 7204.0 | 600.0 - 5400.0 | 1800.0 - 16800.0 |
| Number of patients with at least one dose delay [3] | | | | |
| n | 247 | 246 | 61 | 243 |
| Yes | 90 (36.4%) | 89 (36.2%) | 8 (13.1%) | 82 (33.7%) |
| No | 157 (63.6%) | 157 (63.8%) | 53 (86.9%) | 161 (66.3%) |
| Number of patients with at least one dose delay Due to AE | | | | |
| n | 247 | 246 | 61 | 243 |
| Yes | 61 (24.7%) | 63 (25.6%) | 1 ( 1.6%) | 57 (23.5%) |
| No | 186 (75.3%) | 183 (74.4%) | 60 (98.4%) | 186 (76.5%) |
| Number of cycles of study drug received | 247 ( 100%) | 246 ( 100%) | 61 ( 100%) | 243 ( 100%) |

[1] Subset of patients who switched from Trastuzumab IV to Trastuzumab SC in the Adjuvant Phase (i.e. from Cycle 5) and continued with Pertuzumab IV.
[2] Dose intensity = 100% * actual amount of drug received per cycle / planned dose per cycle.
[3] For HER2 treatment dose modification was not allowed however a dose delay of up to 6 weeks due to adverse event was permitted.
[4] Pertuzumab IV + Trastuzumab IV or Pertuzumab and Trastuzumab FDC SC will be given for 4 cycles in Neoadjuvant phase and another 14 cycles in the Adjuvant phase.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CSR/prod/program/t_ex.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CSR/prod/output/t_ex_HER2_SE_04JUL2019_40324.out
13SEP2019 13:20

Summary of Exposure to Overall Planned HER2 Targeted Therapy (Neoadjuvant + Adjuvant Phase): Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| | Pertuzumab IV + Trastuzumab IV Arm | | | Pertuzumab + Trastuzumab FDC SC Arm |
|---|---|---|---|---|
| | Pertuzumab IV (N=247) | Trastuzumab IV (N=246) | Trastuzumab SC [1] (N=61) | Pertuzumab and Trastuzumab FDC SC (N=243) |
| Cycle number [4] | | | | |
| 1- | 3 ( 1.2%) | 2 ( 0.8%) | 7 (11.5%) | 6 ( 2.5%) |
| 2- | 1 ( 0.4%) | 1 ( 0.4%) | 12 (19.7%) | 2 ( 0.8%) |
| 3- | 1 ( 0.4%) | 1 ( 0.4%) | 13 (21.3%) | 1 ( 0.4%) |
| 4- | 23 ( 9.3%) | 80 (32.5%) | 10 (16.4%) | 9 ( 3.7%) |
| 5- | 21 ( 8.5%) | 19 ( 7.7%) | 11 (18.0%) | 24 ( 9.9%) |
| 6- | 40 (16.2%) | 27 (11.0%) | 3 ( 4.9%) | 31 (12.8%) |
| 7- | 47 (19.0%) | 34 (13.8%) | 2 ( 3.3%) | 51 (21.0%) |
| 8- | 38 (15.4%) | 30 (12.2%) | 2 ( 3.3%) | 46 (18.9%) |
| 9- | 33 (13.4%) | 23 ( 9.3%) | 1 ( 1.6%) | 31 (12.8%) |
| 10- | 22 ( 8.9%) | 16 ( 6.5%) | 0 | 15 ( 6.2%) |
| 11- | 8 ( 3.2%) | 6 ( 2.4%) | 0 | 15 ( 6.2%) |
| 12- | 5 ( 2.0%) | 3 ( 1.2%) | 0 | 10 ( 4.1%) |
| 13- | 4 ( 1.6%) | 3 ( 1.2%) | 0 | 2 ( 0.8%) |
| 14- | 1 ( 0.4%) | 1 ( 0.4%) | 0 | 0 |
| 15- | 0 | 0 | 0 | 0 |
| 16- | 0 | 0 | 0 | 0 |
| 17- | 0 | 0 | 0 | 0 |
| 18- | 0 | 0 | 0 | 0 |

[1] Subset of patients who switched from Trastuzumab IV to Trastuzumab SC in the Adjuvant Phase (i.e. from Cycle 5) and continued with Pertuzumab IV.
[2] Dose intensity = 100% * actual amount of drug received per cycle / planned dose per cycle.
[3] For HER2 treatment dose modification was not allowed however a dose delay of up to 6 weeks due to adverse event was permitted.
[4] Pertuzumab IV + Trastuzumab IV or Pertuzumab and Trastuzumab FDC SC will be given for 4 cycles in Neoadjuvant phase and another 14 cycles in the Adjuvant phase.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CSR/prod/program/t_ex.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CSR/prod/output/t_ex_HER2_SE_04JUL2019_40324.out
13SEP2019 13:20



［5.3.5.1-1-1 t_ex_HER2_SE_04JUL2019_40324 を再掲］

## 表 2.7.4.7.1-5　抗 HER2療法の曝露状況の要約（PHranceSCa 試験，治療クロスオーバー期間）

Study Treatment Exposure during the Cross-Over Period by Treatment Sequence, Safety-Evaluable Population
Protocol: MO40628
Primary Analysis

| | PH IV / PH FDC SC (N=80) | | PH FDC SC / PH IV (N=80) | |
|---|---|---|---|---|
| | Pertuzumab IV + Trastuzumab IV | Pertuzumab and Trastuzumab FDC SC | Pertuzumab and Trastuzumab FDC SC | Pertuzumab IV + Trastuzumab IV |
| Number of cycles initiated | | | | |
| n | 80 | 80 | 80 | 80 |
| Mean (SD) | 3.0 (0.0) | 3.0 (0.0) | 3.0 (0.0) | 3.0 (0.0) |
| Median | 3.0 | 3.0 | 3.0 | 3.0 |
| 25% and 75%-ile | 3.0 - 3.0 | 3.0 - 3.0 | 3.0 - 3.0 | 3.0 - 3.0 |
| Min - Max | 3 - 3 | 3 - 3 | 3 - 3 | 3 - 3 |
| 1 | 0 | 0 | 0 | 0 |
| 2 | 0 | 0 | 0 | 0 |
| 3 | 80 ( 100%) | 80 ( 100%) | 80 ( 100%) | 80 ( 100%) |
| Treatment duration (weeks) | | | | |
| n | 80 | 80 | 80 | 80 |
| Mean (SD) | 6.17 (0.15) | 6.23 (0.39) | 6.16 (0.19) | 6.23 (0.37) |
| Median | 6.14 | 6.14 | 6.14 | 6.14 |
| 25% and 75%-ile | 6.14 - 6.14 | 6.14 - 6.21 | 6.14 - 6.14 | 6.14 - 6.29 |
| Min - Max | 5.9 - 6.9 | 5.7 - 8.3 | 5.7 - 7.3 | 5.7 - 8.7 |
| Number of patients with at least one dose delay | | | | |
| n | 80 | 80 | 80 | 80 |
| Yes | 1 ( 1.3%) | 9 (11.3%) | 1 ( 1.3%) | 8 (10.0%) |
| No | 79 (98.8%) | 71 (88.8%) | 79 (98.8%) | 72 (90.0%) |

A cycle is considered as initiated if any component of study treatment has been administered.
Treatment duration is defined as (last dosing date  first dosing date + 1)/7.
Extract Date:09APR2020  Cutoff Date:24FEB2020

Program: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/PDMA_CSRPrimaryAnalysis/prod/program/t_ex_co_seq.sas
Output: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/PDMA_CSRPrimaryAnalysis/prod/output/t_ex_co_seq_SE.out
05MAY2020 23:38

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［5.3.5.1-3 t_ex_co_seq_SE を再掲］

## 表 2.7.4.7.1-6　抗 HER2療法の曝露状況の要約（PHranceSCa 試験，治療継続期間）

Study Treatment Exposure during the Continuation Period, Safety-Evaluable Population
Protocol: MO40628
Primary Analysis

| | Pertuzumab IV + Trastuzumab IV (N=21) | | Pertuzumab and Trastuzumab FDC SC (N=137) | |
|---|---|---|---|---|
| | PH IV | PH FDC SC | PH IV | PH FDC SC |
| Number of cycles initiated | | | | |
| n | 21 | 0 | 1 | 137 |
| Mean (SD) | 5.4 (1.9) | NE (NE) | 1.0 (NE) | 5.0 (2.3) |
| Median | 5.0 | NE | 1.0 | 5.0 |
| 25% and 75%-ile | 4.0 - 7.0 | NE | 1.0 - 1.0 | 3.0 - 7.0 |
| Min - Max | 2 - 8 | NE - NE | 1 - 1 | 1 - 9 |
| 1 | 0 | 0 | 1 (0.7%) | 6 ( 4.4%) |
| 2 | 1 ( 4.8%) | 0 | 0 | 21 (15.3%) |
| 3 | 3 (14.3%) | 0 | 0 | 16 (11.7%) |
| 4 | 4 (19.0%) | 0 | 0 | 16 (11.7%) |
| 5 | 3 (14.3%) | 0 | 0 | 14 (10.2%) |
| 6 | 4 (19.0%) | 0 | 0 | 24 (17.5%) |
| 7 | 1 ( 4.8%) | 0 | 0 | 11 ( 8.0%) |
| 8 | 5 (23.8%) | 0 | 0 | 27 (19.7%) |
| 9 | 0 | 0 | 0 | 2 ( 1.5%) |
| Treatment duration (weeks) | | | | |
| n | 21 | 0 | 1 | 137 |
| Mean (SD) | 13.55 (5.86) | NE (NE) | 0.14 (NE) | 12.26 (6.82) |
| Median | 13.14 | NE | 0.14 | 12.14 |
| 25% and 75%-ile | 9.14 - 18.14 | NE | 0.14 - 0.14 | 6.29 - 18.14 |
| Min - Max | 3.1 - 22.7 | NE - NE | 0.1 - 0.1 | 0.1 - 24.3 |
| Number of patients with at least one dose delay | | | | |
| n | 21 | 0 | 1 | 137 |
| Yes | 2 ( 9.5%) | 0 | 0 | 17 (12.4%) |
| No | 19 (90.5%) | 0 | 1 (100%) | 120 (87.6%) |

A cycle is considered as initiated if any component of study treatment has been administered.
Treatment duration is defined as (last dosing date  first dosing date + 1)/7.
Extract Date:09APR2020  Cutoff Date:24FEB2020

Program: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/PDMA_CSRPrimaryAnalysis/prod/program/t_ex_cont.sas
Output: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/PDMA_CSRPrimaryAnalysis/prod/output/t_ex_cont_SE.out
05MAY2020 21:24

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［5.3.5.1-3 t_ex_cont_SE を再掲］

## 2.7.4.7.2 注目すべき有害事象

### 表 2.7.4.7.2-1 注目すべき有害事象の要約（FeDeriCa 試験，試験全体）

Adverse Events to Monitor by Relation: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| Adverse Events to Monitor<br>MedDRA Preferred Term | Adverse Events | | Related Adverse Events | |
|---|---|---|---|---|
| | Pertuzumab + Trastuzumab FDC SC Arm (N=248) | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) | Pertuzumab IV + Trastuzumab IV Arm (N=252) |
| Administration-Related Reactions (ARRs) Adverse Events Which Occurred within 24h of HER2 Treatment | | | | |
| Total number of patients with at least one adverse event | 43 ( 17.3%) | 34 ( 13.5%) | 41 ( 16.5%) | 31 ( 12.3%) |
| 注射部位反応 | 32 ( 12.9%) | 1 ( 0.4%) | 32 ( 12.9%) | 1 ( 0.4%) |
| 注射に伴う反応 | 2 ( 0.8%) | 1 ( 0.4%) | 2 ( 0.8%) | 1 ( 0.4%) |
| 発疹 | 2 ( 0.8%) | 1 ( 0.4%) | 2 ( 0.8%) | 1 ( 0.4%) |
| そう痒症 | 1 ( 0.4%) | 0 | 0 | 0 |
| ほてり | 1 ( 0.4%) | 0 | 1 ( 0.4%) | 0 |
| 低血圧 | 1 ( 0.4%) | 0 | 0 | 0 |
| 適用部位疼痛 | 1 ( 0.4%) | 0 | 1 ( 0.4%) | 0 |
| 頭痛 | 1 ( 0.4%) | 1 ( 0.4%) | 1 ( 0.4%) | 0 |
| 動悸 | 1 ( 0.4%) | 0 | 1 ( 0.4%) | 0 |
| 発熱 | 1 ( 0.4%) | 0 | 1 ( 0.4%) | 0 |
| 不眠症 | 1 ( 0.4%) | 0 | 1 ( 0.4%) | 0 |
| 末梢性浮腫 | 1 ( 0.4%) | 0 | 0 | 0 |
| 無力症 | 1 ( 0.4%) | 2 ( 0.8%) | 1 ( 0.4%) | 1 ( 0.4%) |
| 嘔吐 | 1 ( 0.4%) | 0 | 1 ( 0.4%) | 0 |
| 咳嗽 | 0 | 1 ( 0.4%) | 0 | 0 |
| 筋肉痛 | 0 | 3 ( 1.2%) | 0 | 2 ( 0.8%) |
| 注入に伴う反応 | 0 | 25 ( 9.9%) | 0 | 25 ( 9.9%) |
| 鼻漏 | 0 | 1 ( 0.4%) | 0 | 1 ( 0.4%) |
| 浮動性めまい | 0 | 1 ( 0.4%) | 0 | 0 |
| 味覚異常 | 0 | 1 ( 0.4%) | 0 | 0 |
| 薬物過敏症 | 0 | 1 ( 0.4%) | 0 | 1 ( 0.4%) |
| Anaphylaxis and Hypersensitivity Adverse Events Occurring During HER2 Targeted Treatment Period | | | | |
| Total number of patients with at least one adverse event | 4 ( 1.6%) | 4 ( 1.6%) | 2 ( 0.8%) | 2 ( 0.8%) |

Investigator text for AEs encoded using MedDRA version 22.0.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the closest relationship for this preferred term.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/program/aerel_aesi.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/output/aerel_aesi_SE_wo40324.out
27AUG2020 22:48

Adverse Events to Monitor by Relation: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| Adverse Events to Monitor<br>MedDRA Preferred Term | Adverse Events<br>Pertuzumab + Trastuzumab FDC SC Arm (N=248) | Adverse Events<br>Pertuzumab IV + Trastuzumab IV Arm (N=252) | Related Adverse Events<br>Pertuzumab + Trastuzumab FDC SC Arm (N=248) | Related Adverse Events<br>Pertuzumab IV + Trastuzumab IV Arm (N=252) |
|---|---|---|---|---|
| 注射に伴う反応 | 3 ( 1.2%) | 1 ( 0.4%) | 2 ( 0.8%) | 1 ( 0.4%) |
| 過敏症 | 1 ( 0.4%) | 1 ( 0.4%) | 0 | 0 |
| 薬物過敏症 | 1 ( 0.4%) | 2 ( 0.8%) | 0 | 1 ( 0.4%) |
| Cardiac Dysfunction Adverse Events | | | | |
| Total number of patients with at least one adverse event | 41 ( 16.5%) | 41 ( 16.3%) | 14 ( 5.6%) | 18 ( 7.1%) |
| 末梢性浮腫 | 17 ( 6.9%) | 20 ( 7.9%) | 4 ( 1.6%) | 2 ( 0.8%) |
| 駆出率減少 | 9 ( 3.6%) | 14 ( 5.6%) | 5 ( 2.0%) | 14 ( 5.6%) |
| 浮腫 | 7 ( 2.8%) | 7 ( 2.8%) | 1 ( 0.4%) | 0 |
| 左室機能不全 | 3 ( 1.2%) | 3 ( 1.2%) | 2 ( 0.8%) | 2 ( 0.8%) |
| 心不全 | 2 ( 0.8%) | 2 ( 0.8%) | 2 ( 0.8%) | 2 ( 0.8%) |
| 末梢腫脹 | 2 ( 0.8%) | 0 | 0 | 0 |
| 肺水腫 | 1 ( 0.4%) | 0 | 0 | 0 |
| 夜間呼吸困難 | 1 ( 0.4%) | 0 | 1 ( 0.4%) | 0 |
| Diarrhoea Adverse Events | | | | |
| Total number of patients with at least one adverse event | 145 ( 58.5%) | 139 ( 55.2%) | 76 ( 30.6%) | 82 ( 32.5%) |
| 下痢 | 145 ( 58.5%) | 139 ( 55.2%) | 76 ( 30.6%) | 82 ( 32.5%) |
| Exposure During Pregnancy / Exposure during Breast Feeding / Pregnancy Complications / Oligohydramnios / Congenital Abnormalities Adverse Events | | | | |
| Total number of patients with at least one adverse event | 1 ( 0.4%) | 1 ( 0.4%) | 0 | 1 ( 0.4%) |
| 表皮融解 | 1 ( 0.4%) | 1 ( 0.4%) | 0 | 1 ( 0.4%) |
| Interstitial Lung Disease (ILD) Adverse Events | | | | |
| Total number of patients with at least one adverse event | 3 ( 1.2%) | 2 ( 0.8%) | 2 ( 0.8%) | 0 |
| 肺臓炎 | 2 ( 0.8%) | 2 ( 0.8%) | 1 ( 0.4%) | 0 |
| 肺線維症 | 1 ( 0.4%) | 0 | 1 ( 0.4%) | 0 |
| Investigator Reported Local Injection/Infusion site reaction (ISR) Related to HER2 targeted therapy which occurred during or immediately after a HER2 Targeted Therapy | | | | |

Investigator text for AEs encoded using MedDRA version 22.0.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the closest relationship for this preferred term.

Adverse Events to Monitor by Relation: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| Adverse Events to Monitor<br>MedDRA Preferred Term | Adverse Events<br>Pertuzumab + Trastuzumab FDC SC Arm (N=248) | Adverse Events<br>Pertuzumab IV + Trastuzumab IV Arm (N=252) | Related Adverse Events<br>Pertuzumab + Trastuzumab FDC SC Arm (N=248) | Related Adverse Events<br>Pertuzumab IV + Trastuzumab IV Arm (N=252) |
|---|---|---|---|---|
| Total number of patients with at least one adverse event | 21 ( 8.5%) | 0 | 21 ( 8.5%) | 0 |
| 注射部位反応 | 21 ( 8.5%) | 0 | 21 ( 8.5%) | 0 |
| Investigator Reported Systemic Injection/Infusion Related reaction (IRR) Related to HER2 targeted therapy which occurred during or immediately after a HER2 Targeted Therapy | | | | |
| Total number of patients with at least one adverse event | 1 ( 0.4%) | 23 ( 9.1%) | 1 ( 0.4%) | 23 ( 9.1%) |
| 注射に伴う反応 | 1 ( 0.4%) | 0 | 1 ( 0.4%) | 0 |
| 注入に伴う反応 | 0 | 23 ( 9.1%) | 0 | 23 ( 9.1%) |
| Neutropenia / Febrile Neutropenia Adverse Events | | | | |
| Total number of patients with at least one adverse event | 119 ( 48.0%) | 133 ( 52.8%) | 21 ( 8.5%) | 21 ( 8.3%) |
| 好中球減少症 | 52 ( 21.0%) | 64 ( 25.4%) | 8 ( 3.2%) | 6 ( 2.4%) |
| 好中球数減少 | 42 ( 16.9%) | 50 ( 19.8%) | 7 ( 2.8%) | 9 ( 3.6%) |
| 白血球減少症 | 18 ( 7.3%) | 34 ( 13.5%) | 2 ( 0.8%) | 5 ( 2.0%) |
| 白血球数減少 | 17 ( 6.9%) | 31 ( 12.3%) | 6 ( 2.4%) | 9 ( 3.6%) |
| 発熱性好中球減少症 | 16 ( 6.5%) | 14 ( 5.6%) | 1 ( 0.4%) | 0 |
| リンパ球数減少 | 7 ( 2.8%) | 6 ( 2.4%) | 1 ( 0.4%) | 0 |
| リンパ球減少症 | 3 ( 1.2%) | 7 ( 2.8%) | 1 ( 0.4%) | 2 ( 0.8%) |
| 好中球減少性敗血症 | 3 ( 1.2%) | 1 ( 0.4%) | 0 | 0 |
| Serious Mucositis Adverse Events | | | | |
| Total number of patients with at least one adverse event | 3 ( 1.2%) | 4 ( 1.6%) | 1 ( 0.4%) | 0 |
| 胃腸炎 | 1 ( 0.4%) | 1 ( 0.4%) | 0 | 0 |
| 出血性胃炎 | 1 ( 0.4%) | 0 | 0 | 0 |
| 大腸炎 | 1 ( 0.4%) | 1 ( 0.4%) | 1 ( 0.4%) | 0 |
| 咽頭炎 | 0 | 1 ( 0.4%) | 0 | 0 |
| 粘膜の炎症 | 0 | 1 ( 0.4%) | 0 | 0 |
| Serious Rash / Skin Reactions Adverse Events | | | | |
| Total number of patients with at least one adverse event | 1 ( 0.4%) | 0 | 0 | 0 |

Investigator text for AEs encoded using MedDRA version 22.0.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the closest relationship for this preferred term.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/program/aerel_aesi.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/output/aerel_aesi_SE_wo40324.out
27AUG2020 22:48

Adverse Events to Monitor by Relation: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| Adverse Events to Monitor MedDRA Preferred Term | Adverse Events | | Related Adverse Events | |
|---|---|---|---|---|
| | Pertuzumab + Trastuzumab FDC SC Arm (N=248) | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) | Pertuzumab IV + Trastuzumab IV Arm (N=252) |
| 紅斑 | 1 ( 0.4%) | 0 | 0 | 0 |

Investigator text for AEs encoded using MedDRA version 22.0.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the closest relationship for this preferred term.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/program/aerel_aesi.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/output/aerel_aesi_SE_wo40324.out
27AUG2020 22:48 Page 4 of 4

［5.3.5.3-1 aerel_aesi_SE_wo40324を再掲］

# 表 2.7.4.7.2-2 注目すべき有害事象の重症度別の要約（FeDeriCa 試験，試験全体）

Adverse Events to Monitor by Grade: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| Adverse Events to Monitor<br>MedDRA Preferred Term | Pertuzumab + Trastuzumab FDC SC Arm (N=248) | | Pertuzumab IV + Trastuzumab IV Arm (N=252) | |
|---|---|---|---|---|
| | All Grade | Grade 3-5 | All Grade | Grade 3-5 |
| Administration-Related Reactions (ARRs) Adverse Events Which Occurred within 24h of HER2 Treatment | | | | |
| Total number of patients with at least one adverse event | 43 ( 17.3%) | 0 | 34 ( 13.5%) | 3 ( 1.2%) |
| 注射部位反応 | 32 ( 12.9%) | 0 | 1 ( 0.4%) | 0 |
| 注射に伴う反応 | 2 ( 0.8%) | 0 | 1 ( 0.4%) | 0 |
| 発疹 | 2 ( 0.8%) | 0 | 1 ( 0.4%) | 0 |
| そう痒症 | 1 ( 0.4%) | 0 | 0 | 0 |
| ほてり | 1 ( 0.4%) | 0 | 0 | 0 |
| 低血圧 | 1 ( 0.4%) | 0 | 0 | 0 |
| 適用部位疼痛 | 1 ( 0.4%) | 0 | 0 | 0 |
| 頭痛 | 1 ( 0.4%) | 0 | 1 ( 0.4%) | 1 ( 0.4%) |
| 動悸 | 1 ( 0.4%) | 0 | 0 | 0 |
| 発熱 | 1 ( 0.4%) | 0 | 0 | 0 |
| 不眠症 | 1 ( 0.4%) | 0 | 0 | 0 |
| 末梢性浮腫 | 1 ( 0.4%) | 0 | 0 | 0 |
| 無力症 | 1 ( 0.4%) | 0 | 2 ( 0.8%) | 0 |
| 嘔吐 | 1 ( 0.4%) | 0 | 0 | 0 |
| 咳嗽 | 0 | 0 | 1 ( 0.4%) | 0 |
| 筋肉痛 | 0 | 0 | 3 ( 1.2%) | 0 |
| 注入に伴う反応 | 0 | 0 | 25 ( 9.9%) | 2 ( 0.8%) |
| 鼻漏 | 0 | 0 | 1 ( 0.4%) | 0 |
| 浮動性めまい | 0 | 0 | 1 ( 0.4%) | 0 |
| 味覚異常 | 0 | 0 | 1 ( 0.4%) | 0 |
| 薬物過敏症 | 0 | 0 | 1 ( 0.4%) | 0 |
| Anaphylaxis and Hypersensitivity Adverse Events Occurring During HER2 Targeted Treatment Period | | | | |
| Total number of patients with at least one adverse event | 4 ( 1.6%) | 0 | 4 ( 1.6%) | 0 |
| 注射に伴う反応 | 3 ( 1.2%) | 0 | 1 ( 0.4%) | 0 |
| 過敏症 | 1 ( 0.4%) | 0 | 1 ( 0.4%) | 0 |

Investigator text for AEs encoded using MedDRA version 22.0.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the greatest intensity for this preferred term.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/program/aegrd_aesi.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/output/aegrd_aesi_SE_wo40324.out
27AUG2020 23:01

Adverse Events to Monitor by Grade: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| Adverse Events to Monitor<br>MedDRA Preferred Term | Pertuzumab + Trastuzumab FDC SC Arm (N=248) | | Pertuzumab IV + Trastuzumab IV Arm (N=252) | |
|---|---|---|---|---|
| | All Grade | Grade 3-5 | All Grade | Grade 3-5 |
| 薬物過敏症 | 1 ( 0.4%) | 0 | 2 ( 0.8%) | 0 |
| Cardiac Dysfunction Adverse Events | | | | |
| Total number of patients with at least one adverse event | 41 ( 16.5%) | 1 ( 0.4%) | 41 ( 16.3%) | 4 ( 1.6%) |
| 末梢性浮腫 | 17 ( 6.9%) | 0 | 20 ( 7.9%) | 0 |
| 駆出率減少 | 9 ( 3.6%) | 0 | 14 ( 5.6%) | 2 ( 0.8%) |
| 浮腫 | 7 ( 2.8%) | 0 | 7 ( 2.8%) | 1 ( 0.4%) |
| 左室機能不全 | 3 ( 1.2%) | 0 | 3 ( 1.2%) | 0 |
| 心不全 | 2 ( 0.8%) | 1 ( 0.4%) | 2 ( 0.8%) | 1 ( 0.4%) |
| 末梢腫脹 | 2 ( 0.8%) | 0 | 0 | 0 |
| 肺水腫 | 1 ( 0.4%) | 0 | 0 | 0 |
| 夜間呼吸困難 | 1 ( 0.4%) | 0 | 0 | 0 |
| Diarrhoea Adverse Events | | | | |
| Total number of patients with at least one adverse event | 145 ( 58.5%) | 17 ( 6.9%) | 139 ( 55.2%) | 12 ( 4.8%) |
| 下痢 | 145 ( 58.5%) | 17 ( 6.9%) | 139 ( 55.2%) | 12 ( 4.8%) |
| Exposure During Pregnancy / Exposure during Breast Feeding / Pregnancy Complications / Oligohydramnios / Congenital Abnormalities Adverse Events | | | | |
| Total number of patients with at least one adverse event | 1 ( 0.4%) | 0 | 1 ( 0.4%) | 0 |
| 表皮融解 | 1 ( 0.4%) | 0 | 1 ( 0.4%) | 0 |
| Interstitial Lung Disease (ILD) Adverse Events | | | | |
| Total number of patients with at least one adverse event | 3 ( 1.2%) | 0 | 2 ( 0.8%) | 0 |
| 肺臓炎 | 2 ( 0.8%) | 0 | 2 ( 0.8%) | 0 |
| 肺線維症 | 1 ( 0.4%) | 0 | 0 | 0 |
| Investigator Reported Local Injection/Infusion site reaction (ISR) Related to HER2 targeted therapy which occurred during or immediately after a HER2 Targeted Therapy | | | | |
| Total number of patients with at least one adverse event | 21 ( 8.5%) | 0 | 0 | 0 |
| 注射部位反応 | 21 ( 8.5%) | 0 | 0 | 0 |
| Investigator Reported Systemic Injection/Infusion Related reaction (IRR) Related to HER2 targeted therapy which occurred during or immediately after a HER2 Targeted Therapy | | | | |

Investigator text for AEs encoded using MedDRA version 22.0.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the greatest intensity for this preferred term.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/program/aegrd_aesi.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/output/aegrd_aesi_SE_wo40324.out
27AUG2020 23:01

Adverse Events to Monitor by Grade: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| Adverse Events to Monitor<br>MedDRA Preferred Term | Pertuzumab + Trastuzumab FDC SC Arm (N=248) | | Pertuzumab IV + Trastuzumab IV Arm (N=252) | |
|---|---|---|---|---|
| | All Grade | Grade 3-5 | All Grade | Grade 3-5 |
| Total number of patients with at least one adverse event | 1 ( 0.4%) | 0 | 23 ( 9.1%) | 2 ( 0.8%) |
| 注射に伴う反応 | 1 ( 0.4%) | 0 | 0 | 0 |
| 注入に伴う反応 | 0 | 0 | 23 ( 9.1%) | 2 ( 0.8%) |
| Neutropenia / Febrile Neutropenia Adverse Events | | | | |
| Total number of patients with at least one adverse event | 119 ( 48.0%) | 81 ( 32.7%) | 133 ( 52.8%) | 85 ( 33.7%) |
| 好中球減少症 | 52 ( 21.0%) | 35 ( 14.1%) | 64 ( 25.4%) | 34 ( 13.5%) |
| 好中球数減少 | 42 ( 16.9%) | 27 ( 10.9%) | 50 ( 19.8%) | 31 ( 12.3%) |
| 白血球減少症 | 18 ( 7.3%) | 6 ( 2.4%) | 34 ( 13.5%) | 5 ( 2.0%) |
| 白血球数減少 | 17 ( 6.9%) | 9 ( 3.6%) | 31 ( 12.3%) | 18 ( 7.1%) |
| 発熱性好中球減少症 | 16 ( 6.5%) | 16 ( 6.5%) | 14 ( 5.6%) | 14 ( 5.6%) |
| リンパ球数減少 | 7 ( 2.8%) | 3 ( 1.2%) | 6 ( 2.4%) | 3 ( 1.2%) |
| リンパ球減少症 | 3 ( 1.2%) | 1 ( 0.4%) | 7 ( 2.8%) | 3 ( 1.2%) |
| 好中球減少性敗血症 | 3 ( 1.2%) | 3 ( 1.2%) | 1 ( 0.4%) | 1 ( 0.4%) |
| Serious Mucositis Adverse Events | | | | |
| Total number of patients with at least one adverse event | 3 ( 1.2%) | 2 ( 0.8%) | 4 ( 1.6%) | 4 ( 1.6%) |
| 胃腸炎 | 1 ( 0.4%) | 1 ( 0.4%) | 1 ( 0.4%) | 1 ( 0.4%) |
| 出血性胃炎 | 1 ( 0.4%) | 0 | 0 | 0 |
| 大腸炎 | 1 ( 0.4%) | 1 ( 0.4%) | 1 ( 0.4%) | 1 ( 0.4%) |
| 咽頭炎 | 0 | 0 | 1 ( 0.4%) | 1 ( 0.4%) |
| 粘膜の炎症 | 0 | 0 | 1 ( 0.4%) | 1 ( 0.4%) |
| Serious Rash / Skin Reactions Adverse Events | | | | |
| Total number of patients with at least one adverse event | 1 ( 0.4%) | 0 | 0 | 0 |
| 紅斑 | 1 ( 0.4%) | 0 | 0 | 0 |

Investigator text for AEs encoded using MedDRA version 22.0.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the greatest intensity for this preferred term.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/program/aegrd_aesi.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/output/aegrd_aesi_SE_wo40324.out
27AUG2020 23:01



［5.3.5.3-1 aegrd_aesi_SE_wo40324 を再掲］

# 表 2.7.4.7.2-3 重篤な有害事象として報告された注目すべき有害事象の要約（FeDeriCa 試験，試験全体）

Serious Adverse Events to Monitor by Relation: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| Adverse Events to Monitor<br>MedDRA Preferred Term | Adverse Events | | Related Adverse Events | |
|---|---|---|---|---|
| | Pertuzumab + Trastuzumab FDC SC Arm (N=248) | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) | Pertuzumab IV + Trastuzumab IV Arm (N=252) |
| Administration-Related Reactions (ARRs) Adverse Events Which Occurred within 24h of HER2 Treatment | | | | |
| Total number of patients with at least one adverse event | 0 | 2 ( 0.8%) | 0 | 2 ( 0.8%) |
| 注入に伴う反応 | 0 | 2 ( 0.8%) | 0 | 2 ( 0.8%) |
| Cardiac Dysfunction Adverse Events | | | | |
| Total number of patients with at least one adverse event | 3 ( 1.2%) | 2 ( 0.8%) | 2 ( 0.8%) | 2 ( 0.8%) |
| 心不全 | 2 ( 0.8%) | 2 ( 0.8%) | 2 ( 0.8%) | 2 ( 0.8%) |
| 肺水腫 | 1 ( 0.4%) | 0 | 0 | 0 |
| Diarrhoea Adverse Events | | | | |
| Total number of patients with at least one adverse event | 1 ( 0.4%) | 2 ( 0.8%) | 1 ( 0.4%) | 0 |
| 下痢 | 1 ( 0.4%) | 2 ( 0.8%) | 1 ( 0.4%) | 0 |
| Interstitial Lung Disease (ILD) Adverse Events | | | | |
| Total number of patients with at least one adverse event | 2 ( 0.8%) | 1 ( 0.4%) | 1 ( 0.4%) | 0 |
| 肺臓炎 | 2 ( 0.8%) | 1 ( 0.4%) | 1 ( 0.4%) | 0 |
| Investigator Reported Systemic Injection/Infusion Related reaction (IRR) Related to HER2 targeted therapy which occurred during or immediately after a HER2 Targeted Therapy | | | | |
| Total number of patients with at least one adverse event | 0 | 2 ( 0.8%) | 0 | 2 ( 0.8%) |
| 注入に伴う反応 | 0 | 2 ( 0.8%) | 0 | 2 ( 0.8%) |
| Neutropenia / Febrile Neutropenia Adverse Events | | | | |
| Total number of patients with at least one adverse event | 16 ( 6.5%) | 15 ( 6.0%) | 1 ( 0.4%) | 0 |
| 発熱性好中球減少症 | 9 ( 3.6%) | 10 ( 4.0%) | 1 ( 0.4%) | 0 |
| 好中球減少性敗血症 | 3 ( 1.2%) | 1 ( 0.4%) | 0 | 0 |
| 好中球数減少 | 3 ( 1.2%) | 1 ( 0.4%) | 0 | 0 |
| 好中球減少症 | 1 ( 0.4%) | 3 ( 1.2%) | 0 | 0 |
| 白血球数減少 | 1 ( 0.4%) | 0 | 0 | 0 |
| Serious Mucositis Adverse Events | | | | |

Investigator text for AEs encoded using MedDRA version 22.0.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the closest relationship for this preferred term.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/program/aerel_aesi.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/output/aerel_aesi_SER_SE_wo40324.out
27AUG2020 22:50

Serious Adverse Events to Monitor by Relation: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| Adverse Events to Monitor<br>MedDRA Preferred Term | Adverse Events | | Related Adverse Events | |
|---|---|---|---|---|
| | Pertuzumab + Trastuzumab FDC SC Arm (N=248) | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) | Pertuzumab IV + Trastuzumab IV Arm (N=252) |
| Total number of patients with at least one adverse event | 3 ( 1.2%) | 4 ( 1.6%) | 1 ( 0.4%) | 0 |
| 胃腸炎 | 1 ( 0.4%) | 1 ( 0.4%) | 0 | 0 |
| 出血性胃炎 | 1 ( 0.4%) | 0 | 0 | 0 |
| 大腸炎 | 1 ( 0.4%) | 1 ( 0.4%) | 1 ( 0.4%) | 0 |
| 咽頭炎 | 0 | 1 ( 0.4%) | 0 | 0 |
| 粘膜の炎症 | 0 | 1 ( 0.4%) | 0 | 0 |
| Serious Rash / Skin Reactions Adverse Events | | | | |
| Total number of patients with at least one adverse event | 1 ( 0.4%) | 0 | 0 | 0 |
| 紅斑 | 1 ( 0.4%) | 0 | 0 | 0 |

Investigator text for AEs encoded using MedDRA version 22.0.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the closest relationship for this preferred term.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/program/aerel_aesi.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/output/aerel_aesi_SER_SE_wo40324.out
27AUG2020 22:50 Page 2 of 2

［5.3.5.3-1 aerel_aesi_SER_SE_wo40324 を再掲］

## 表 2.7.4.7.2-4 治験薬の投与中止に至った注目すべき有害事象の要約（FeDeriCa 試験，試験全体）

Adverse Events to Monitor Leading to Withdrawal of HER2 Targeted Therapy by Relation: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| Adverse Events to Monitor<br>MedDRA Preferred Term | Adverse Events | | Related Adverse Events | |
|---|---|---|---|---|
| | Pertuzumab + Trastuzumab FDC SC Arm (N=248) | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) | Pertuzumab IV + Trastuzumab IV Arm (N=252) |
| Administration-Related Reactions (ARRs) Adverse Events Which Occurred within 24h of HER2 Treatment | | | | |
| Total number of patients with at least one adverse event | 0 | 1 ( 0.4%) | 0 | 1 ( 0.4%) |
| 薬物過敏症 | 0 | 1 ( 0.4%) | 0 | 1 ( 0.4%) |
| Anaphylaxis and Hypersensitivity Adverse Events Occurring During HER2 Targeted Treatment Period | | | | |
| Total number of patients with at least one adverse event | 0 | 1 ( 0.4%) | 0 | 1 ( 0.4%) |
| 薬物過敏症 | 0 | 1 ( 0.4%) | 0 | 1 ( 0.4%) |
| Cardiac Dysfunction Adverse Events | | | | |
| Total number of patients with at least one adverse event | 2 ( 0.8%) | 5 ( 2.0%) | 2 ( 0.8%) | 5 ( 2.0%) |
| 駆出率減少 | 1 ( 0.4%) | 3 ( 1.2%) | 1 ( 0.4%) | 3 ( 1.2%) |
| 心不全 | 1 ( 0.4%) | 2 ( 0.8%) | 1 ( 0.4%) | 2 ( 0.8%) |
| Interstitial Lung Disease (ILD) Adverse Events | | | | |
| Total number of patients with at least one adverse event | 2 ( 0.8%) | 0 | 2 ( 0.8%) | 0 |
| 肺線維症 | 1 ( 0.4%) | 0 | 1 ( 0.4%) | 0 |
| 肺臓炎 | 1 ( 0.4%) | 0 | 1 ( 0.4%) | 0 |

Investigator text for AEs encoded using MedDRA version 22.0.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the closest relationship for this preferred term.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/program/aerel_aesi.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/output/aerel_aesi_DSCH2_SE_wo40324.out
27AUG2020 22:54 Page 1 of 1

［5.3.5.3-1 aerel_aesi_DSCH2_SE_wo40324 を再掲］

## 表 2.7.4.7.2-5 いずれかの治験治療の投与中止に至った注目すべき有害事象の要約（FeDeriCa 試験，試験全体）

Adverse Events to Monitor Leading to Withdrawal of Any Study Treatment by Relation: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| Adverse Events to Monitor<br>MedDRA Preferred Term | Adverse Events | | Related Adverse Events | |
|---|---|---|---|---|
| | Pertuzumab + Trastuzumab FDC SC Arm (N=248) | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) | Pertuzumab IV + Trastuzumab IV Arm (N=252) |
| Administration-Related Reactions (ARRs) Adverse Events Which Occurred within 24h of HER2 Treatment | | | | |
| Total number of patients with at least one adverse event | 0 | 1 ( 0.4%) | 0 | 1 ( 0.4%) |
| 薬物過敏症 | 0 | 1 ( 0.4%) | 0 | 1 ( 0.4%) |
| Anaphylaxis and Hypersensitivity Adverse Events Occurring During HER2 Targeted Treatment Period | | | | |
| Total number of patients with at least one adverse event | 0 | 1 ( 0.4%) | 0 | 1 ( 0.4%) |
| 薬物過敏症 | 0 | 1 ( 0.4%) | 0 | 1 ( 0.4%) |
| Cardiac Dysfunction Adverse Events | | | | |
| Total number of patients with at least one adverse event | 2 ( 0.8%) | 5 ( 2.0%) | 2 ( 0.8%) | 5 ( 2.0%) |
| 駆出率減少 | 1 ( 0.4%) | 3 ( 1.2%) | 1 ( 0.4%) | 3 ( 1.2%) |
| 心不全 | 1 ( 0.4%) | 2 ( 0.8%) | 1 ( 0.4%) | 2 ( 0.8%) |
| Diarrhoea Adverse Events | | | | |
| Total number of patients with at least one adverse event | 2 ( 0.8%) | 2 ( 0.8%) | 1 ( 0.4%) | 0 |
| 下痢 | 2 ( 0.8%) | 2 ( 0.8%) | 1 ( 0.4%) | 0 |
| Interstitial Lung Disease (ILD) Adverse Events | | | | |
| Total number of patients with at least one adverse event | 3 ( 1.2%) | 0 | 2 ( 0.8%) | 0 |
| 肺臓炎 | 2 ( 0.8%) | 0 | 1 ( 0.4%) | 0 |
| 肺線維症 | 1 ( 0.4%) | 0 | 1 ( 0.4%) | 0 |
| Neutropenia / Febrile Neutropenia Adverse Events | | | | |
| Total number of patients with at least one adverse event | 3 ( 1.2%) | 2 ( 0.8%) | 0 | 0 |
| 好中球数減少 | 2 ( 0.8%) | 1 ( 0.4%) | 0 | 0 |
| 好中球減少症 | 1 ( 0.4%) | 0 | 0 | 0 |
| 白血球減少症 | 0 | 1 ( 0.4%) | 0 | 0 |
| 白血球数減少 | 0 | 1 ( 0.4%) | 0 | 0 |
| Serious Mucositis Adverse Events | | | | |
| Total number of patients with at least one adverse event | 0 | 2 ( 0.8%) | 0 | 0 |

Investigator text for AEs encoded using MedDRA version 22.0.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the closest relationship for this preferred term.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/program/aerel_aesi.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/output/aerel_aesi_DSC_SE_wo40324.out
27AUG2020 22:52

Adverse Events to Monitor Leading to Withdrawal of Any Study Treatment by Relation: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| Adverse Events to Monitor MedDRA Preferred Term | Adverse Events | | Related Adverse Events | |
|---|---|---|---|---|
| | Pertuzumab + Trastuzumab FDC SC Arm (N=248) | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) | Pertuzumab IV + Trastuzumab IV Arm (N=252) |
| 大腸炎 | 0 | 1 ( 0.4%) | 0 | 0 |
| 粘膜の炎症 | 0 | 1 ( 0.4%) | 0 | 0 |

Investigator text for AEs encoded using MedDRA version 22.0.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the closest relationship for this preferred term.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/program/aerel_aesi.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/output/aerel_aesi_DSC_SE_wo40324.out
27AUG2020 22:52



［5.3.5.3-1 aerel_aesi_DSC_SE_wo40324 を再掲］

# 表 2.7.4.7.2-6 治験薬の用量変更に至った注目すべき有害事象の要約（FeDeriCa 試験，試験全体）

Adverse Events to Monitor Leading to Dose Delay of HER2 Targeted Therapy by Relation: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| Adverse Events to Monitor<br>MedDRA Preferred Term | Adverse Events | | Related Adverse Events | |
|---|---|---|---|---|
| | Pertuzumab + Trastuzumab FDC SC Arm (N=248) | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) | Pertuzumab IV + Trastuzumab IV Arm (N=252) |
| Administration-Related Reactions (ARRs) Adverse Events Which Occurred within 24h of HER2 Treatment | | | | |
| Total number of patients with at least one adverse event | 0 | 6 ( 2.4%) | 0 | 6 ( 2.4%) |
| 注入に伴う反応 | 0 | 6 ( 2.4%) | 0 | 6 ( 2.4%) |
| Anaphylaxis and Hypersensitivity Adverse Events Occurring During HER2 Targeted Treatment Period | | | | |
| Total number of patients with at least one adverse event | 1 ( 0.4%) | 0 | 0 | 0 |
| 薬物過敏症 | 1 ( 0.4%) | 0 | 0 | 0 |
| Cardiac Dysfunction Adverse Events | | | | |
| Total number of patients with at least one adverse event | 3 ( 1.2%) | 4 ( 1.6%) | 3 ( 1.2%) | 4 ( 1.6%) |
| 駆出率減少 | 2 ( 0.8%) | 3 ( 1.2%) | 2 ( 0.8%) | 3 ( 1.2%) |
| 心不全 | 1 ( 0.4%) | 0 | 1 ( 0.4%) | 0 |
| 左室機能不全 | 0 | 1 ( 0.4%) | 0 | 1 ( 0.4%) |
| Diarrhoea Adverse Events | | | | |
| Total number of patients with at least one adverse event | 3 ( 1.2%) | 3 ( 1.2%) | 2 ( 0.8%) | 2 ( 0.8%) |
| 下痢 | 3 ( 1.2%) | 3 ( 1.2%) | 2 ( 0.8%) | 2 ( 0.8%) |
| Investigator Reported Systemic Injection/Infusion Related reaction (IRR) Related to HER2 targeted therapy which occurred during or immediately after a HER2 Targeted Therapy | | | | |
| Total number of patients with at least one adverse event | 0 | 6 ( 2.4%) | 0 | 6 ( 2.4%) |
| 注入に伴う反応 | 0 | 6 ( 2.4%) | 0 | 6 ( 2.4%) |
| Neutropenia / Febrile Neutropenia Adverse Events | | | | |
| Total number of patients with at least one adverse event | 19 ( 7.7%) | 18 ( 7.1%) | 1 ( 0.4%) | 1 ( 0.4%) |
| 好中球減少症 | 8 ( 3.2%) | 8 ( 3.2%) | 0 | 0 |
| 好中球数減少 | 8 ( 3.2%) | 6 ( 2.4%) | 1 ( 0.4%) | 1 ( 0.4%) |
| 白血球数減少 | 4 ( 1.6%) | 2 ( 0.8%) | 1 ( 0.4%) | 0 |
| 白血球減少症 | 2 ( 0.8%) | 3 ( 1.2%) | 0 | 0 |

Investigator text for AEs encoded using MedDRA version 22.0.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the closest relationship for this preferred term.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/program/aerel_aesi.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/output/aerel_aesi_DSMH2_SE_wo40324.out
27AUG2020 22:57

Adverse Events to Monitor Leading to Dose Delay of HER2 Targeted Therapy by Relation: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| Adverse Events to Monitor<br>MedDRA Preferred Term | Adverse Events | | Related Adverse Events | |
|---|---|---|---|---|
| | Pertuzumab + Trastuzumab FDC SC Arm (N=248) | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) | Pertuzumab IV + Trastuzumab IV Arm (N=252) |
| 好中球減少性敗血症 | 1 ( 0.4%) | 0 | 0 | 0 |
| 発熱性好中球減少症 | 1 ( 0.4%) | 2 ( 0.8%) | 0 | 0 |
| リンパ球数減少 | 0 | 1 ( 0.4%) | 0 | 0 |
| Serious Rash / Skin Reactions Adverse Events | | | | |
| Total number of patients with at least one adverse event | 1 ( 0.4%) | 0 | 0 | 0 |
| 紅斑 | 1 ( 0.4%) | 0 | 0 | 0 |

Investigator text for AEs encoded using MedDRA version 22.0.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the closest relationship for this preferred term.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/program/aerel_aesi.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/output/aerel_aesi_DSMH2_SE_wo40324.out
27AUG2020 22:57 Page 2 of 2

［5.3.5.3-1 aerel_aesi_DSMH2_SE_wo40324 を再掲］

# 表 2.7.4.7.2-7 いずれかの治験治療の用量変更に至った注目すべき有害事象の要約（FeDeriCa 試験，試験全体）

Adverse Events to Monitor Leading to Dose Modification of Any Study Treatment by Relation: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| Adverse Events to Monitor<br>MedDRA Preferred Term | Adverse Events<br>Pertuzumab + Trastuzumab FDC SC Arm (N=248) | Adverse Events<br>Pertuzumab IV + Trastuzumab IV Arm (N=252) | Related Adverse Events<br>Pertuzumab + Trastuzumab FDC SC Arm (N=248) | Related Adverse Events<br>Pertuzumab IV + Trastuzumab IV Arm (N=252) |
|---|---|---|---|---|
| Administration-Related Reactions (ARRs) Adverse Events Which Occurred within 24h of HER2 Treatment | | | | |
| Total number of patients with at least one adverse event | 0 | 8 ( 3.2%) | 0 | 7 ( 2.8%) |
| 注入に伴う反応 | 0 | 7 ( 2.8%) | 0 | 7 ( 2.8%) |
| 頭痛 | 0 | 1 ( 0.4%) | 0 | 0 |
| 浮動性めまい | 0 | 1 ( 0.4%) | 0 | 0 |
| Anaphylaxis and Hypersensitivity Adverse Events Occurring During HER2 Targeted Treatment Period | | | | |
| Total number of patients with at least one adverse event | 2 ( 0.8%) | 0 | 0 | 0 |
| 過敏症 | 1 ( 0.4%) | 0 | 0 | 0 |
| 薬物過敏症 | 1 ( 0.4%) | 0 | 0 | 0 |
| Cardiac Dysfunction Adverse Events | | | | |
| Total number of patients with at least one adverse event | 3 ( 1.2%) | 7 ( 2.8%) | 3 ( 1.2%) | 4 ( 1.6%) |
| 駆出率減少 | 2 ( 0.8%) | 3 ( 1.2%) | 2 ( 0.8%) | 3 ( 1.2%) |
| 心不全 | 1 ( 0.4%) | 0 | 1 ( 0.4%) | 0 |
| 左室機能不全 | 0 | 1 ( 0.4%) | 0 | 1 ( 0.4%) |
| 浮腫 | 0 | 1 ( 0.4%) | 0 | 0 |
| 末梢性浮腫 | 0 | 2 ( 0.8%) | 0 | 0 |
| Diarrhoea Adverse Events | | | | |
| Total number of patients with at least one adverse event | 17 ( 6.9%) | 15 ( 6.0%) | 5 ( 2.0%) | 6 ( 2.4%) |
| 下痢 | 17 ( 6.9%) | 15 ( 6.0%) | 5 ( 2.0%) | 6 ( 2.4%) |
| Investigator Reported Systemic Injection/Infusion Related reaction (IRR) Related to HER2 targeted therapy which occurred during or immediately after a HER2 Targeted Therapy | | | | |
| Total number of patients with at least one adverse event | 0 | 6 ( 2.4%) | 0 | 6 ( 2.4%) |
| 注入に伴う反応 | 0 | 6 ( 2.4%) | 0 | 6 ( 2.4%) |
| Neutropenia / Febrile Neutropenia Adverse Events | | | | |

Investigator text for AEs encoded using MedDRA version 22.0.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the closest relationship for this preferred term.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/program/aerel_aesi.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/output/aerel_aesi_DSM_SE_wo40324.out
27AUG2020 22:56

Adverse Events to Monitor Leading to Dose Modification of Any Study Treatment by Relation: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| Adverse Events to Monitor<br>MedDRA Preferred Term | Adverse Events<br>Pertuzumab + Trastuzumab FDC SC Arm (N=248) | Adverse Events<br>Pertuzumab IV + Trastuzumab IV Arm (N=252) | Related Adverse Events<br>Pertuzumab + Trastuzumab FDC SC Arm (N=248) | Related Adverse Events<br>Pertuzumab IV + Trastuzumab IV Arm (N=252) |
|---|---|---|---|---|
| Total number of patients with at least one adverse event | 39 ( 15.7%) | 41 ( 16.3%) | 3 ( 1.2%) | 3 ( 1.2%) |
| 好中球減少症 | 20 ( 8.1%) | 25 ( 9.9%) | 1 ( 0.4%) | 2 ( 0.8%) |
| 好中球数減少 | 11 ( 4.4%) | 8 ( 3.2%) | 1 ( 0.4%) | 1 ( 0.4%) |
| 発熱性好中球減少症 | 5 ( 2.0%) | 5 ( 2.0%) | 1 ( 0.4%) | 0 |
| 白血球減少症 | 4 ( 1.6%) | 10 ( 4.0%) | 0 | 0 |
| 白血球数減少 | 4 ( 1.6%) | 4 ( 1.6%) | 1 ( 0.4%) | 0 |
| 好中球減少性敗血症 | 2 ( 0.8%) | 1 ( 0.4%) | 0 | 0 |
| リンパ球数減少 | 0 | 1 ( 0.4%) | 0 | 0 |
| Serious Mucositis Adverse Events | | | | |
| Total number of patients with at least one adverse event | 1 ( 0.4%) | 1 ( 0.4%) | 0 | 0 |
| 胃腸炎 | 1 ( 0.4%) | 1 ( 0.4%) | 0 | 0 |
| Serious Rash / Skin Reactions Adverse Events | | | | |
| Total number of patients with at least one adverse event | 1 ( 0.4%) | 0 | 0 | 0 |
| 紅斑 | 1 ( 0.4%) | 0 | 0 | 0 |

Investigator text for AEs encoded using MedDRA version 22.0.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the closest relationship for this preferred term.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/program/aerel_aesi.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/output/aerel_aesi_DSM_SE_wo40324.out
27AUG2020 22:56 Page 2 of 2

［5.3.5.3-1 aerel_aesi_DSM_SE_wo40324 を再掲］

# 表 2.7.4.7.2-8 注目すべき有害事象の要約（PHranceSCa 試験）

Adverse Events to Monitor by Relation, Safety-Evaluable Population
Protocol: MO40628
Primary Analysis

| Adverse Events to Monitor MedDRA Preferred Term | Adverse Events | | | | | Related Adverse Events | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | PH FDC SC Cross-Over (N=160) | PH IV Cross-Over (N=160) | PH FDC SC Continuation (N=137) | PH IV Continuation (N=21) | All Patients (N=160) | PH FDC SC Cross-Over (N=160) | PH IV Cross-Over (N=160) | PH FDC SC Continuation (N=137) | PH IV Continuation (N=21) | All Patients (N=160) |
| Administration Related Reactions | | | | | | | | | | |
| Total number of patients with at least one adverse event | 38 ( 23.8%) | 9 ( 5.6%) | 13 ( 9.5%) | 0 | 52 ( 32.5%) | 38 ( 23.8%) | 8 ( 5.0%) | 11 ( 8.0%) | 0 | 50 ( 31.3%) |
| 注射部位反応 | 36 ( 22.5%) | 0 | 10 ( 7.3%) | 0 | 42 ( 26.3%) | 36 ( 22.5%) | 0 | 10 ( 7.3%) | 0 | 42 ( 26.3%) |
| 注射に伴う反応 | 3 ( 1.9%) | 0 | 2 ( 1.5%) | 0 | 4 ( 2.5%) | 3 ( 1.9%) | 0 | 2 ( 1.5%) | 0 | 4 ( 2.5%) |
| 頭痛 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 筋痙縮 | 0 | 1 ( 0.6%) | 1 ( 0.7%) | 0 | 2 ( 1.3%) | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 高血圧 | 0 | 0 | 1 ( 0.7%) | 0 | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 0 |
| 注入に伴う反応 | 0 | 6 ( 3.8%) | 0 | 0 | 6 ( 3.8%) | 0 | 6 ( 3.8%) | 0 | 0 | 6 ( 3.8%) |
| 注入部位反応 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 頭部不快感 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 0 |
| 嘔吐 | 0 | 0 | 1 ( 0.7%) | 0 | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 0 |
| Anaphylaxis and Hypersensitivity | | | | | | | | | | |
| Total number of patients with at least one adverse event | 3 ( 1.9%) | 0 | 2 ( 1.5%) | 0 | 4 ( 2.5%) | 3 ( 1.9%) | 0 | 2 ( 1.5%) | 0 | 4 ( 2.5%) |
| 注射に伴う反応 | 3 ( 1.9%) | 0 | 2 ( 1.5%) | 0 | 4 ( 2.5%) | 3 ( 1.9%) | 0 | 2 ( 1.5%) | 0 | 4 ( 2.5%) |
| Asymptomatic Decline in LVEF | | | | | | | | | | |
| Total number of patients with at least one adverse event | 1 ( 0.6%) | 2 ( 1.3%) | 0 | 0 | 3 ( 1.9%) | 1 ( 0.6%) | 2 ( 1.3%) | 0 | 0 | 3 ( 1.9%) |
| 駆出率減少 | 1 ( 0.6%) | 2 ( 1.3%) | 0 | 0 | 3 ( 1.9%) | 1 ( 0.6%) | 2 ( 1.3%) | 0 | 0 | 3 ( 1.9%) |

Investigator text for AEs encoded using MedDRA version 22.1.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the closest relationship for this preferred term.
Extract Date:09APR2020 Cutoff Date:24FEB2020

Program: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD2/prod/program/aerel_aesi.sas
Output: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD2/prod/output/aerel_aesi_SE_mo40628.out
24AUG2020 8:42

Adverse Events to Monitor by Relation, Safety-Evaluable Population
Protocol: MO40628
Primary Analysis

| Adverse Events to Monitor MedDRA Preferred Term | Adverse Events | | | | | Related Adverse Events | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | PH FDC SC Cross-Over (N=160) | PH IV Cross-Over (N=160) | PH FDC SC Continuation (N=137) | PH IV Continuation (N=21) | All Patients (N=160) | PH FDC SC Cross-Over (N=160) | PH IV Cross-Over (N=160) | PH FDC SC Continuation (N=137) | PH IV Continuation (N=21) | All Patients (N=160) |
| Cardiac Dysfunction | | | | | | | | | | |
| Total number of patients with at least one adverse event | 4 ( 2.5%) | 5 ( 3.1%) | 3 ( 2.2%) | 0 | 11 ( 6.9%) | 4 ( 2.5%) | 3 ( 1.9%) | 2 ( 1.5%) | 0 | 8 ( 5.0%) |
| 駆出率減少 | 4 ( 2.5%) | 3 ( 1.9%) | 1 ( 0.7%) | 0 | 7 ( 4.4%) | 4 ( 2.5%) | 3 ( 1.9%) | 1 ( 0.7%) | 0 | 7 ( 4.4%) |
| 急性肺水腫 | 0 | 0 | 1 ( 0.7%) | 0 | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 0 |
| 末梢性浮腫 | 0 | 2 ( 1.3%) | 1 ( 0.7%) | 0 | 3 ( 1.9%) | 0 | 0 | 1 ( 0.7%) | 0 | 1 ( 0.6%) |
| Diarrhoea Grade >= 3 | | | | | | | | | | |
| Total number of patients with at least one adverse event | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 下痢 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| Interstitial Lung Disease (ILD) | | | | | | | | | | |
| Total number of patients with at least one adverse event | 0 | 0 | 1 ( 0.7%) | 0 | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 0 |
| 放射線肺臓炎 | 0 | 0 | 1 ( 0.7%) | 0 | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 0 |
| Neutropenia / Febrile Neutropenia | | | | | | | | | | |
| Total number of patients with at least one adverse event | 3 ( 1.9%) | 8 ( 5.0%) | 3 ( 2.2%) | 0 | 12 ( 7.5%) | 0 | 5 ( 3.1%) | 2 ( 1.5%) | 0 | 7 ( 4.4%) |
| 白血球数減少 | 3 ( 1.9%) | 2 ( 1.3%) | 0 | 0 | 4 ( 2.5%) | 0 | 2 ( 1.3%) | 0 | 0 | 2 ( 1.3%) |
| リンパ球減少症 | 0 | 4 ( 2.5%) | 0 | 0 | 4 ( 2.5%) | 0 | 2 ( 1.3%) | 0 | 0 | 2 ( 1.3%) |

Investigator text for AEs encoded using MedDRA version 22.1.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the closest relationship for this preferred term.
Extract Date:09APR2020 Cutoff Date:24FEB2020

Program: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD2/prod/program/aerel_aesi.sas
Output: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD2/prod/output/aerel_aesi_SE_mo40628.out
24AUG2020 8:42

Adverse Events to Monitor by Relation, Safety-Evaluable Population
Protocol: MO40628
Primary Analysis

| | Adverse Events | | | | | Related Adverse Events | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Adverse Events to Monitor MedDRA Preferred Term | PH FDC SC Cross-Over (N=160) | PH IV Cross-Over (N=160) | PH FDC SC Continuation (N=137) | PH IV Continuation (N=21) | All Patients (N=160) | PH FDC SC Cross-Over (N=160) | PH IV Cross-Over (N=160) | PH FDC SC Continuation (N=137) | PH IV Continuation (N=21) | All Patients (N=160) |
| リンパ球数減少 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 好中球減少症 | 0 | 1 ( 0.6%) | 2 ( 1.5%) | 0 | 3 ( 1.9%) | 0 | 1 ( 0.6%) | 1 ( 0.7%) | 0 | 2 ( 1.3%) |
| 好中球数減少 | 0 | 1 ( 0.6%) | 1 ( 0.7%) | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.7%) | 0 | 1 ( 0.6%) |
| 白血球減少症 | 0 | 2 ( 1.3%) | 0 | 0 | 2 ( 1.3%) | 0 | 2 ( 1.3%) | 0 | 0 | 2 ( 1.3%) |
| Pregnancy and Neonatal Related | | | | | | | | | | |
| Total number of patients with at least one adverse event | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 0 |
| 乳腺炎 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 0 |
| Pulmonary Events (ARR) | | | | | | | | | | |
| Total number of patients with at least one adverse event | 11 ( 6.9%) | 25 ( 15.6%) | 11 ( 8.0%) | 3 ( 14.3%) | 45 ( 28.1%) | 4 ( 2.5%) | 8 ( 5.0%) | 2 ( 1.5%) | 0 | 13 ( 8.1%) |
| そう痒症 | 3 ( 1.9%) | 7 ( 4.4%) | 5 ( 3.6%) | 0 | 13 ( 8.1%) | 3 ( 1.9%) | 1 ( 0.6%) | 1 ( 0.7%) | 0 | 4 ( 2.5%) |
| 紅斑 | 2 ( 1.3%) | 7 ( 4.4%) | 0 | 0 | 9 ( 5.6%) | 0 | 0 | 0 | 0 | 0 |
| 発疹 | 2 ( 1.3%) | 2 ( 1.3%) | 2 ( 1.5%) | 2 ( 9.5%) | 8 ( 5.0%) | 0 | 1 ( 0.6%) | 1 ( 0.7%) | 0 | 2 ( 1.3%) |
| 咳嗽 | 1 ( 0.6%) | 5 ( 3.1%) | 3 ( 2.2%) | 0 | 9 ( 5.6%) | 0 | 0 | 0 | 0 | 0 |
| 呼吸困難 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) | 0 | 0 | 0 | 0 | 0 |
| 潮紅 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 喘息 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 0 |
| そう痒性皮疹 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 0 |
| 顔面腫脹 | 0 | 0 | 1 ( 0.7%) | 0 | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 0 |
| 顔面浮腫 | 0 | 0 | 0 | 1 ( 4.8%) | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 0 |
| 注入に伴う反応 | 0 | 6 ( 3.8%) | 0 | 0 | 6 ( 3.8%) | 0 | 6 ( 3.8%) | 0 | 0 | 6 ( 3.8%) |

Investigator text for AEs encoded using MedDRA version 22.1.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the closest relationship for this preferred term.
Extract Date:09APR2020 Cutoff Date:24FEB2020

Program: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD2/prod/program/aerel_aesi.sas
Output: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD2/prod/output/aerel_aesi_SE_mo40628.out
24AUG2020 8:42

Adverse Events to Monitor by Relation, Safety-Evaluable Population
Protocol: MO40628
Primary Analysis

| Adverse Events to Monitor MedDRA Preferred Term | Adverse Events | | | | | Related Adverse Events | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | PH FDC SC Cross-Over (N=160) | PH IV Cross-Over (N=160) | PH FDC SC Continuation (N=137) | PH IV Continuation (N=21) | All Patients (N=160) | PH FDC SC Cross-Over (N=160) | PH IV Cross-Over (N=160) | PH FDC SC Continuation (N=137) | PH IV Continuation (N=21) | All Patients (N=160) |
| 低血圧 | 0 | 0 | 1 ( 0.7%) | 0 | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 0 |
| 鼻閉塞 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 0 |

Investigator text for AEs encoded using MedDRA version 22.1.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the closest relationship for this preferred term.
Extract Date:09APR2020 Cutoff Date:24FEB2020

Program: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD2/prod/program/aerel_aesi.sas
Output: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD2/prod/output/aerel_aesi_SE_mo40628.out
24AUG2020 8:42



［5.3.5.3-1 aerel_aesi_SE_mo40628 を再掲］

# 表 2.7.4.7.2-9 注目すべき有害事象の重症度別の要約（PHranceSCa 試験）

Adverse Events to Monitor by Grade, Safety-Evaluable Population
Protocol: MO40628
Primary Analysis

| Adverse Events to Monitor MedDRA Preferred Term | PH FDC SC Cross-Over (N=160) | | PH IV Cross-Over (N=160) | | PH FDC SC Continuation (N=137) | | PH IV Continuation (N=21) | | All Patients (N=160) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | All Grade | Grade 3-5 | All Grade | Grade 3-5 | All Grade | Grade 3-5 | All Grade | Grade 3-5 | All Grade | Grade 3-5 |
| Administration Related Reactions | | | | | | | | | | |
| Total number of patients with at least one adverse event | 38 ( 23.8%) | 0 | 9 ( 5.6%) | 0 | 13 ( 9.5%) | 0 | 0 | 0 | 52 ( 32.5%) | 0 |
| 注射部位反応 | 36 ( 22.5%) | 0 | 0 | 0 | 10 ( 7.3%) | 0 | 0 | 0 | 42 ( 26.3%) | 0 |
| 注射に伴う反応 | 3 ( 1.9%) | 0 | 0 | 0 | 2 ( 1.5%) | 0 | 0 | 0 | 4 ( 2.5%) | 0 |
| 頭痛 | 1 ( 0.6%) | 0 | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 0 | 2 ( 1.3%) | 0 |
| 筋痙縮 | 0 | 0 | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 0 | 0 | 0 | 2 ( 1.3%) | 0 |
| 高血圧 | 0 | 0 | 0 | 0 | 1 ( 0.7%) | 0 | 0 | 0 | 1 ( 0.6%) | 0 |
| 注入に伴う反応 | 0 | 0 | 6 ( 3.8%) | 0 | 0 | 0 | 0 | 0 | 6 ( 3.8%) | 0 |
| 注入部位反応 | 0 | 0 | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 0 | 1 ( 0.6%) | 0 |
| 頭部不快感 | 0 | 0 | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 0 | 1 ( 0.6%) | 0 |
| 嘔吐 | 0 | 0 | 0 | 0 | 1 ( 0.7%) | 0 | 0 | 0 | 1 ( 0.6%) | 0 |
| Anaphylaxis and Hypersensitivity | | | | | | | | | | |
| Total number of patients with at least one adverse event | 3 ( 1.9%) | 0 | 0 | 0 | 2 ( 1.5%) | 0 | 0 | 0 | 4 ( 2.5%) | 0 |
| 注射に伴う反応 | 3 ( 1.9%) | 0 | 0 | 0 | 2 ( 1.5%) | 0 | 0 | 0 | 4 ( 2.5%) | 0 |
| Asymptomatic Decline in LVEF | | | | | | | | | | |
| Total number of patients with at least one adverse event | 1 ( 0.6%) | 0 | 2 ( 1.3%) | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 3 ( 1.9%) | 1 ( 0.6%) |
| 駆出率減少 | 1 ( 0.6%) | 0 | 2 ( 1.3%) | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 3 ( 1.9%) | 1 ( 0.6%) |
| Cardiac Dysfunction | | | | | | | | | | |
| Total number of patients with at least one adverse event | 4 ( 2.5%) | 0 | 5 ( 3.1%) | 1 ( 0.6%) | 3 ( 2.2%) | 0 | 0 | 0 | 11 ( 6.9%) | 1 ( 0.6%) |
| 駆出率減少 | 4 ( 2.5%) | 0 | 3 ( 1.9%) | 1 ( 0.6%) | 1 ( 0.7%) | 0 | 0 | 0 | 7 ( 4.4%) | 1 ( 0.6%) |
| 急性肺水腫 | 0 | 0 | 0 | 0 | 1 ( 0.7%) | 0 | 0 | 0 | 1 ( 0.6%) | 0 |

Investigator text for AEs encoded using MedDRA version 22.1.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the greatest intensity for this preferred term.
Extract Date:09APR2020 Cutoff Date:24FEB2020

Program: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD2/prod/program/aegrd_aesi.sas
Output: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD2/prod/output/aegrd_aesi_SE_mo40628.out
24AUG2020 8:43

Adverse Events to Monitor by Grade, Safety-Evaluable Population
Protocol: MO40628
Primary Analysis

| Adverse Events to Monitor MedDRA Preferred Term | PH FDC SC Cross-Over (N=160) | | PH IV Cross-Over (N=160) | | PH FDC SC Continuation (N=137) | | PH IV Continuation (N=21) | | All Patients (N=160) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | All Grade | Grade 3-5 | All Grade | Grade 3-5 | All Grade | Grade 3-5 | All Grade | Grade 3-5 | All Grade | Grade 3-5 |
| 末梢性浮腫 | 0 | 0 | 2 ( 1.3%) | 0 | 1 ( 0.7%) | 0 | 0 | 0 | 3 ( 1.9%) | 0 |
| Diarrhoea Grade >= 3 | | | | | | | | | | |
| Total number of patients with at least one adverse event | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 0 | 0 | 1 ( 0.6%) | 1 ( 0.6%) |
| 下痢 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 0 | 0 | 1 ( 0.6%) | 1 ( 0.6%) |
| Interstitial Lung Disease (ILD) | | | | | | | | | | |
| Total number of patients with at least one adverse event | 0 | 0 | 0 | 0 | 1 ( 0.7%) | 0 | 0 | 0 | 1 ( 0.6%) | 0 |
| 放射線肺臓炎 | 0 | 0 | 0 | 0 | 1 ( 0.7%) | 0 | 0 | 0 | 1 ( 0.6%) | 0 |
| Neutropenia / Febrile Neutropenia | | | | | | | | | | |
| Total number of patients with at least one adverse event | 3 ( 1.9%) | 0 | 8 ( 5.0%) | 1 ( 0.6%) | 3 ( 2.2%) | 1 ( 0.7%) | 0 | 0 | 12 ( 7.5%) | 2 ( 1.3%) |
| 白血球数減少 | 3 ( 1.9%) | 0 | 2 ( 1.3%) | 0 | 0 | 0 | 0 | 0 | 4 ( 2.5%) | 0 |
| リンパ球減少症 | 0 | 0 | 4 ( 2.5%) | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 4 ( 2.5%) | 1 ( 0.6%) |
| リンパ球数減少 | 0 | 0 | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 0 | 1 ( 0.6%) | 0 |
| 好中球減少症 | 0 | 0 | 1 ( 0.6%) | 0 | 2 ( 1.5%) | 1 ( 0.7%) | 0 | 0 | 3 ( 1.9%) | 1 ( 0.6%) |
| 好中球数減少 | 0 | 0 | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 0 | 0 | 0 | 1 ( 0.6%) | 0 |
| 白血球減少症 | 0 | 0 | 2 ( 1.3%) | 0 | 0 | 0 | 0 | 0 | 2 ( 1.3%) | 0 |
| Pregnancy and Neonatal Related | | | | | | | | | | |
| Total number of patients with at least one adverse event | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 ( 0.6%) | 0 |
| 乳腺炎 | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 ( 0.6%) | 0 |
| Pulmonary Events (ARR) | | | | | | | | | | |
| Total number of patients with at least one adverse event | 11 ( 6.9%) | 1 ( 0.6%) | 25 ( 15.6%) | 0 | 11 ( 8.0%) | 0 | 3 ( 14.3%) | 0 | 45 ( 28.1%) | 1 ( 0.6%) |

Investigator text for AEs encoded using MedDRA version 22.1.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the greatest intensity for this preferred term.
Extract Date:09APR2020 Cutoff Date:24FEB2020

Program: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD2/prod/program/aegrd_aesi.sas
Output: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD2/prod/output/aegrd_aesi_SE_mo40628.out
24AUG2020 8:43

Adverse Events to Monitor by Grade, Safety-Evaluable Population
Protocol: MO40628
Primary Analysis

| Adverse Events to Monitor MedDRA Preferred Term | PH FDC SC Cross-Over (N=160) | | PH IV Cross-Over (N=160) | | PH FDC SC Continuation (N=137) | | PH IV Continuation (N=21) | | All Patients (N=160) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | All Grade | Grade 3-5 | All Grade | Grade 3-5 | All Grade | Grade 3-5 | All Grade | Grade 3-5 | All Grade | Grade 3-5 |
| そう痒症 | 3 ( 1.9%) | 0 | 7 ( 4.4%) | 0 | 5 ( 3.6%) | 0 | 0 | 0 | 13 ( 8.1%) | 0 |
| 紅斑 | 2 ( 1.3%) | 0 | 7 ( 4.4%) | 0 | 0 | 0 | 0 | 0 | 9 ( 5.6%) | 0 |
| 発疹 | 2 ( 1.3%) | 0 | 2 ( 1.3%) | 0 | 2 ( 1.5%) | 0 | 2 ( 9.5%) | 0 | 8 ( 5.0%) | 0 |
| 咳嗽 | 1 ( 0.6%) | 0 | 5 ( 3.1%) | 0 | 3 ( 2.2%) | 0 | 0 | 0 | 9 ( 5.6%) | 0 |
| 呼吸困難 | 1 ( 0.6%) | 0 | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 0 | 2 ( 1.3%) | 0 |
| 潮紅 | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 ( 0.6%) | 0 |
| 喘息 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 0 | 0 | 1 ( 0.6%) | 1 ( 0.6%) |
| そう痒性皮疹 | 0 | 0 | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 0 | 1 ( 0.6%) | 0 |
| 顔面腫脹 | 0 | 0 | 0 | 0 | 1 ( 0.7%) | 0 | 0 | 0 | 1 ( 0.6%) | 0 |
| 顔面浮腫 | 0 | 0 | 0 | 0 | 0 | 0 | 1 ( 4.8%) | 0 | 1 ( 0.6%) | 0 |
| 注入に伴う反応 | 0 | 0 | 6 ( 3.8%) | 0 | 0 | 0 | 0 | 0 | 6 ( 3.8%) | 0 |
| 低血圧 | 0 | 0 | 0 | 0 | 1 ( 0.7%) | 0 | 0 | 0 | 1 ( 0.6%) | 0 |
| 鼻閉塞 | 0 | 0 | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 0 | 1 ( 0.6%) | 0 |

Investigator text for AEs encoded using MedDRA version 22.1.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the greatest intensity for this preferred term.
Extract Date:09APR2020 Cutoff Date:24FEB2020

Program: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD2/prod/program/aegrd_aesi.sas
Output: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD2/prod/output/aegrd_aesi_SE_mo40628.out
24AUG2020 8:43



［5.3.5.3-1 aegrd_aesi_SE_mo40628 を再掲］

## 表 2.7.4.7.2-10 重篤な有害事象として報告された注目すべき有害事象の要約（PHranceSCa 試験）

Serious Adverse Events to Monitor by Relation, Safety-Evaluable Population
Protocol: MO40628
Primary Analysis

| | Adverse Events | | | | | Related Adverse Events | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Adverse Events to Monitor MedDRA Preferred Term | PH FDC SC Cross-Over (N=160) | PH IV Cross-Over (N=160) | PH FDC SC Continuation (N=137) | PH IV Continuation (N=21) | All Patients (N=160) | PH FDC SC Cross-Over (N=160) | PH IV Cross-Over (N=160) | PH FDC SC Continuation (N=137) | PH IV Continuation (N=21) | All Patients (N=160) |
| Asymptomatic Decline in LVEF | | | | | | | | | | |
| Total number of patients with at least one adverse event | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) |
| 駆出率減少 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) |
| Cardiac Dysfunction | | | | | | | | | | |
| Total number of patients with at least one adverse event | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) |
| 駆出率減少 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) |
| Pulmonary Events (ARR) | | | | | | | | | | |
| Total number of patients with at least one adverse event | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 0 |
| 喘息 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) | 0 | 0 | 0 | 0 | 0 |

Investigator text for AEs encoded using MedDRA version 22.1.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the closest relationship for this preferred term.
Extract Date:09APR2020 Cutoff Date:24FEB2020

Program: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD2/prod/program/aerel_aesi.sas
Output: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD2/prod/output/aerel_aesi_SER_SE_mo40628.out
24AUG2020 8:44 Page 1 of 1

［5.3.5.3-1 aerel_aesi_SER_SE_mo40628 を再掲］

## 表 2.7.4.7.2-11 治験薬の用量変更に至った注目すべき有害事象の要約（PHranceSCa 試験）

Adverse Events to Monitor Leading to Any Study Drug Interruption by Treatment Period, Safety-Evaluable Population
Protocol: MO40628
Primary Analysis

| | Adverse Events | | | | | Related Adverse Events | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Adverse Events to Monitor MedDRA Preferred Term | PH FDC SC Cross-Over (N=160) | PH IV Cross-Over (N=160) | PH FDC SC Continuation (N=137) | PH IV Continuation (N=21) | All Patients (N=160) | PH FDC SC Cross-Over (N=160) | PH IV Cross-Over (N=160) | PH FDC SC Continuation (N=137) | PH IV Continuation (N=21) | All Patients (N=160) |
| Asymptomatic Decline in LVEF | | | | | | | | | | |
| Total number of patients with at least one adverse event | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 駆出率減少 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| Cardiac Dysfunction | | | | | | | | | | |
| Total number of patients with at least one adverse event | 2 ( 1.3%) | 2 ( 1.3%) | 0 | 0 | 4 ( 2.5%) | 2 ( 1.3%) | 2 ( 1.3%) | 0 | 0 | 4 ( 2.5%) |
| 駆出率減少 | 2 ( 1.3%) | 2 ( 1.3%) | 0 | 0 | 4 ( 2.5%) | 2 ( 1.3%) | 2 ( 1.3%) | 0 | 0 | 4 ( 2.5%) |

Investigator text for AEs encoded using MedDRA version 22.1.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the closest relationship for this preferred term.
Extract Date:09APR2020 Cutoff Date:24FEB2020

Program: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD2/prod/program/aerel_aesi.sas
Output: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD2/prod/output/aerel_aesi_DSMALL_SE_mo40628.out
24AUG2020 8:44 Page 1 of 1

［5.3.5.3-1 aerel_aesi_DSMALL_SE_mo40628 を再掲］

## 表 2.7.4.7.2-12 注目すべき有害事象の要約（BO30185試験, Part 2コホート C）

Adverse Events to Monitor by Relation: Part 2, Safety Evaluated Population
Protocol: BO30185
Clinical cut-off date: 31MAY2018
Database lock date: 26JUL2018

| Adverse Events to Monitor<br>MedDRA Preferred Term | Adverse Events<br>Perjeta 600 mg SC + Herceptin 600 mg SC (coformulated)<br>Cohort C<br>(N=20) | Related Adverse Events<br>Perjeta 600 mg SC + Herceptin 600 mg SC (coformulated)<br>Cohort C<br>(N=20) |
|---|---|---|
| Diarrhoea | | |
| Total number of patients with at least one adverse event | 17 ( 85.0%) | 16 ( 80.0%) |
| 下痢 | 17 ( 85.0%) | 16 ( 80.0%) |
| Mucositis GI Tract | | |
| Total number of patients with at least one adverse event | 2 ( 10.0%) | 2 ( 10.0%) |
| 口腔内潰瘍形成 | 1 ( 5.0%) | 1 ( 5.0%) |
| 舌炎 | 1 ( 5.0%) | 1 ( 5.0%) |
| Possible Administration Related Reactions | | |
| Total number of patients with at least one adverse event | 11 ( 55.0%) | 10 ( 50.0%) |
| 頭痛 | 9 ( 45.0%) | 8 ( 40.0%) |
| 注射部位反応 | 5 ( 25.0%) | 5 ( 25.0%) |
| 嘔吐 | 3 ( 15.0%) | 3 ( 15.0%) |
| ほてり | 1 ( 5.0%) | 1 ( 5.0%) |
| 関節痛 | 1 ( 5.0%) | 1 ( 5.0%) |
| 動悸 | 1 ( 5.0%) | 1 ( 5.0%) |
| Rash | | |
| Total number of patients with at least one adverse event | 8 ( 40.0%) | 6 ( 30.0%) |
| 発疹 | 4 ( 20.0%) | 3 ( 15.0%) |
| ざ瘡 | 1 ( 5.0%) | 1 ( 5.0%) |
| ざ瘡様皮膚炎 | 1 ( 5.0%) | 1 ( 5.0%) |
| 丘疹性皮疹 | 1 ( 5.0%) | 1 ( 5.0%) |
| 皮膚剥脱 | 1 ( 5.0%) | 1 ( 5.0%) |
| 毛包炎 | 1 ( 5.0%) | 0 |

Investigator text for AEs encoded using MedDRA version 21.0.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the closest relationship for this preferred term.

Program: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/program/aerel_aesi.sas
Output: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/output/aerel_aesi_SE_P2_c_bo30185.out
24AUG2020 12:03 Page 1 of 1

［5.3.5.3-1 aerel_aesi_SE_P2_c_bo30185 を再掲］

## 表 2.7.4.7.2-13 注目すべき有害事象の重症度別の要約（BO30185試験，Part 2コホート C）

Adverse Events to Monitor by Grade: Part 2, Safety Evaluated Population
Protocol: BO30185
Clinical cut-off date: 31MAY2018
Database lock date: 26JUL2018

| Adverse Events to Monitor<br>MedDRA Preferred Term | Perjeta 600 mg SC + Herceptin 600 mg SC (coformulated) Cohort C (N=20)<br>All Grade | <br>Grade 3-5 |
|---|---|---|
| Diarrhoea | | |
| Total number of patients with at least one adverse event | 17 ( 85.0%) | 0 |
| 下痢 | 17 ( 85.0%) | 0 |
| Mucositis GI Tract | | |
| Total number of patients with at least one adverse event | 2 ( 10.0%) | 0 |
| 口腔内潰瘍形成 | 1 ( 5.0%) | 0 |
| 舌炎 | 1 ( 5.0%) | 0 |
| Possible Administration Related Reactions | | |
| Total number of patients with at least one adverse event | 11 ( 55.0%) | 0 |
| 頭痛 | 9 ( 45.0%) | 0 |
| 注射部位反応 | 5 ( 25.0%) | 0 |
| 嘔吐 | 3 ( 15.0%) | 0 |
| ほてり | 1 ( 5.0%) | 0 |
| 関節痛 | 1 ( 5.0%) | 0 |
| 動悸 | 1 ( 5.0%) | 0 |
| Rash | | |
| Total number of patients with at least one adverse event | 8 ( 40.0%) | 0 |
| 発疹 | 4 ( 20.0%) | 0 |
| ざ瘡 | 1 ( 5.0%) | 0 |
| ざ瘡様皮膚炎 | 1 ( 5.0%) | 0 |
| 丘疹性皮疹 | 1 ( 5.0%) | 0 |
| 皮膚剥脱 | 1 ( 5.0%) | 0 |
| 毛包炎 | 1 ( 5.0%) | 0 |

Investigator text for AEs encoded using MedDRA version 21.0.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the greatest intensity for this preferred term.

Program: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/program/aegrd_aesi.sas
Output: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/output/aegrd_aesi_SE_P2_c_bo30185.out
24AUG2020 12:03 Page 1 of 1

［5.3.5.3-1 aegrd_aesi_SE_P2_c_bo30185 再掲］

## 2.7.4.7.3 日本部分集団の結果

### 表 2.7.4.7.3-1 化学療法の曝露状況の要約（FeDeriCa 試験，日本部分集団，P + H IV 群）

Summary of Exposure to Chemotherapy in Pertuzumab IV + Trastuzumab IV arm by Treatment Regimen: Safety Population, Japan Subgroup
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| | Pertuzumab IV + Trastuzumab IV Arm | | |
|---|---|---|---|
| | AC ---> Docetaxel | | |
| | Doxorubicin (N=21) | Cyclophos[1] (N=21) | Docetaxel (N=18) |
| Completed assigned therapy | | | |
| Yes | 20 (95.2%) | 20 (95.2%) | 16 (88.9%) |
| No | 1 ( 4.8%) | 1 ( 4.8%) | 2 (11.1%) |
| Number of cycles of study drug received | | | |
| n | 21 | 21 | 18 |
| Mean | 3.9 | 3.9 | 3.9 |
| SD | 0.4 | 0.4 | 0.3 |
| Median | 4.0 | 4.0 | 4.0 |
| Min - Max | 2 - 4 | 2 - 4 | 3 - 4 |
| Treatment duration [Weeks] | | | |
| n | 21 | 21 | 18 |
| Mean | 9.3 | 9.3 | 8.9 |
| SD | 1.2 | 1.2 | 1.0 |
| Median | 9.1 | 9.1 | 9.1 |
| Min - Max | 5 - 12 | 5 - 12 | 6 - 10 |

[1] Cyclophosphamide
[2] Dose intensity = 100% * actual amount of drug received per cycle / planned dose per cycle
[3] Patients will receive in total 8 cycles of neoadjuvant chemotherapy. This will include 4 cycles of ddAC every 2 weeks (Q2W) followed by paclitaxel Q1W for 12 weeks or 4 cycles of doxorubicin plus cyclophosphamide (AC) Q3W followed by docetaxel Q3W for 4 cycles.
4 Cycles = 12 dose of Paclitaxel.
Dose Modification includes Dose Increase, Dose Decrease, Dose Interuption.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/program/t_ex_sum.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/output/t_ex_sum_ARMA_SE_jp.out
26MAR2020 22:05

Summary of Exposure to Chemotherapy in Pertuzumab IV + Trastuzumab IV arm by Treatment Regimen: Safety Population, Japan Subgroup
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| | Pertuzumab IV + Trastuzumab IV Arm | | |
|---|---|---|---|
| | AC ---> Docetaxel | | |
| | Doxorubicin (N=21) | Cyclophos[1] (N=21) | Docetaxel (N=18) |
| Dose intensity [%] [2] | | | |
| n | 82 | 82 | 70 |
| Mean | 98.25 | 98.58 | 98.26 |
| SD | 1.71 | 1.58 | 1.46 |
| Median | 98.07 | 98.90 | 97.63 |
| Min - Max | 94.9 - 101.3 | 95.7 - 101.3 | 96.3 - 101.3 |
| Total cumulative dose [mg] | | | |
| n | 21 | 21 | 18 |
| Mean | 361.86 | 3630.74 | 445.13 |
| SD | 49.79 | 499.26 | 54.28 |
| Median | 360.00 | 3609.60 | 440.00 |
| Min - Max | 181.2 - 441.1 | 1812.0 - 4411.2 | 364.0 - 579.0 |
| Number of patients with at least one dose delay | | | |
| n | 21 | 21 | 18 |
| Yes | 4 (19.0%) | 4 (19.0%) | 3 (16.7%) |
| No | 17 (81.0%) | 17 (81.0%) | 15 (83.3%) |

[1] Cyclophosphamide
[2] Dose intensity = 100% * actual amount of drug received per cycle / planned dose per cycle
[3] Patients will receive in total 8 cycles of neoadjuvant chemotherapy. This will include 4 cycles of ddAC every 2 weeks (Q2W) followed by paclitaxel Q1W for 12 weeks or 4 cycles of doxorubicin plus cyclophosphamide (AC) Q3W followed by docetaxel Q3W for 4 cycles.
4 Cycles = 12 dose of Paclitaxel.
Dose Modification includes Dose Increase, Dose Decrease, Dose Interuption.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/program/t_ex_sum.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/output/t_ex_sum_ARMA_SE_jp.out
26MAR2020 22:05

Summary of Exposure to Chemotherapy in Pertuzumab IV + Trastuzumab IV arm by Treatment Regimen: Safety Population, Japan Subgroup
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| | Pertuzumab IV + Trastuzumab IV Arm | | |
|---|---|---|---|
| | AC ---> Docetaxel | | |
| | Doxorubicin (N=21) | Cyclophos[1] (N=21) | Docetaxel (N=18) |
| Number of patients with at least one dose delay - Due to AE | | | |
| n | 21 | 21 | 18 |
| Yes | 4 (19.0%) | 4 (19.0%) | 2 (11.1%) |
| No | 17 (81.0%) | 17 (81.0%) | 16 (88.9%) |
| Number of patients with at least one dose modification | | | |
| n | 21 | 21 | 18 |
| Yes | 0 | 0 | 5 (27.8%) |
| No | 21 ( 100%) | 21 ( 100%) | 13 (72.2%) |
| Number of cycles of study drug received | 21 ( 100%) | 21 ( 100%) | 18 ( 100%) |
| Cycle number [3] | | | |
| 2 | 1 ( 4.8%) | 1 ( 4.8%) | 0 |
| 3 | 0 | 0 | 2 (11.1%) |
| 4 | 20 (95.2%) | 20 (95.2%) | 16 (88.9%) |

[1] Cyclophosphamide
[2] Dose intensity = 100% * actual amount of drug received per cycle / planned dose per cycle
[3] Patients will receive in total 8 cycles of neoadjuvant chemotherapy. This will include 4 cycles of ddAC every 2 weeks (Q2W) followed by paclitaxel Q1W for 12 weeks or 4 cycles of doxorubicin plus cyclophosphamide (AC) Q3W followed by docetaxel Q3W for 4 cycles.
4 Cycles = 12 dose of Paclitaxel.
Dose Modification includes Dose Increase, Dose Decrease, Dose Interuption.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/program/t_ex_sum.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/output/t_ex_sum_ARMA_SE_jp.out
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［5.3.5.3-1 t_ex_sum_ARMA_SE_jp を再掲］

# 表 2.7.4.7.3-2 化学療法の曝露状況の要約（FeDeriCa 試験，日本部分集団，本剤群）

Summary of Exposure to Chemotherapy in Pertuzumab and Trastuzumab FDC SC arm by Treatment Regimen: Safety Population, Japan Subgroup
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| | Pertuzumab + Trastuzumab FDC SC Arm | | |
|---|---|---|---|
| | AC ---> Docetaxel | | |
| | Doxorubicin (N=20) | Cyclophos[1] (N=20) | Docetaxel (N=19) |
| Completed assigned therapy | | | |
| Yes | 19 (95.0%) | 19 (95.0%) | 16 (84.2%) |
| No | 1 ( 5.0%) | 1 ( 5.0%) | 3 (15.8%) |
| Number of cycles of study drug received | | | |
| n | 20 | 20 | 19 |
| Mean | 4.0 | 4.0 | 3.7 |
| SD | 0.2 | 0.2 | 0.7 |
| Median | 4.0 | 4.0 | 4.0 |
| Min - Max | 3 - 4 | 3 - 4 | 1 - 4 |
| Treatment duration [Weeks] | | | |
| n | 20 | 20 | 19 |
| Mean | 9.3 | 9.3 | 8.6 |
| SD | 0.7 | 0.7 | 2.3 |
| Median | 9.1 | 9.1 | 9.1 |
| Min - Max | 7 - 10 | 7 - 10 | 0 - 10 |

[1] Cyclophosphamide
[2] Dose intensity = 100% * actual amount of drug received per cycle / planned dose per cycle
[3] Patients will receive in total 8 cycles of neoadjuvant chemotherapy. This will include 4 cycles of ddAC every 2 weeks (Q2W) followed by paclitaxel Q1W for 12 weeks or 4 cycles of doxorubicin plus cyclophosphamide (AC) Q3W followed by docetaxel Q3W for 4 cycles.
4 Cycles = 12 dose of Paclitaxel.
Dose Modification includes Dose Increase, Dose Decrease, Dose Interuption.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/program/t_ex_sum.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/output/t_ex_sum_ARMB_SE_jp.out
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Summary of Exposure to Chemotherapy in Pertuzumab and Trastuzumab FDC SC arm by Treatment Regimen: Safety Population, Japan Subgroup
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| | Pertuzumab + Trastuzumab FDC SC Arm | | |
|---|---|---|---|
| | AC ---> Docetaxel | | |
| | Doxorubicin (N=20) | Cyclophos[1] (N=20) | Docetaxel (N=19) |
| Dose intensity [%] [2] | | | |
| n | 79 | 79 | 71 |
| Mean | 98.22 | 98.46 | 98.23 |
| SD | 1.74 | 1.61 | 1.87 |
| Median | 98.42 | 98.42 | 98.20 |
| Min - Max | 94.3 - 101.5 | 95.5 - 101.5 | 92.5 - 101.3 |
| Total cumulative dose [mg] | | | |
| n | 20 | 20 | 19 |
| Mean | 366.70 | 3675.80 | 436.68 |
| SD | 37.30 | 374.60 | 99.82 |
| Median | 372.60 | 3726.00 | 464.00 |
| Min - Max | 257.6 - 425.8 | 2576.0 - 4257.6 | 109.0 - 550.0 |
| Number of patients with at least one dose delay | | | |
| n | 20 | 20 | 19 |
| Yes | 5 (25.0%) | 5 (25.0%) | 5 (26.3%) |
| No | 15 (75.0%) | 15 (75.0%) | 14 (73.7%) |

[1] Cyclophosphamide
[2] Dose intensity = 100% * actual amount of drug received per cycle / planned dose per cycle
[3] Patients will receive in total 8 cycles of neoadjuvant chemotherapy. This will include 4 cycles of ddAC every 2 weeks (Q2W) followed by paclitaxel Q1W for 12 weeks or 4 cycles of doxorubicin plus cyclophosphamide (AC) Q3W followed by docetaxel Q3W for 4 cycles.
4 Cycles = 12 dose of Paclitaxel.
Dose Modification includes Dose Increase, Dose Decrease, Dose Interuption.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/program/t_ex_sum.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/output/t_ex_sum_ARMB_SE_jp.out
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Summary of Exposure to Chemotherapy in Pertuzumab and Trastuzumab FDC SC arm by Treatment Regimen: Safety Population, Japan Subgroup
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| | Pertuzumab + Trastuzumab FDC SC Arm | | |
|---|---|---|---|
| | AC ---> Docetaxel | | |
| | Doxorubicin (N=20) | Cyclophos[1] (N=20) | Docetaxel (N=19) |
| Number of patients with at least one dose delay - Due to AE | | | |
| n | 20 | 20 | 19 |
| Yes | 5 (25.0%) | 5 (25.0%) | 5 (26.3%) |
| No | 15 (75.0%) | 15 (75.0%) | 14 (73.7%) |
| Number of patients with at least one dose modification | | | |
| n | 20 | 20 | 19 |
| Yes | 0 | 0 | 1 ( 5.3%) |
| No | 20 ( 100%) | 20 ( 100%) | 18 (94.7%) |
| Number of cycles of study drug received | 20 ( 100%) | 20 ( 100%) | 19 ( 100%) |
| Cycle number [3] | | | |
| 1 | 0 | 0 | 1 ( 5.3%) |
| 3 | 1 ( 5.0%) | 1 ( 5.0%) | 2 (10.5%) |
| 4 | 19 (95.0%) | 19 (95.0%) | 16 (84.2%) |

[1] Cyclophosphamide
[2] Dose intensity = 100% * actual amount of drug received per cycle / planned dose per cycle
[3] Patients will receive in total 8 cycles of neoadjuvant chemotherapy. This will include 4 cycles of ddAC every 2 weeks (Q2W) followed by paclitaxel Q1W for 12 weeks or 4 cycles of doxorubicin plus cyclophosphamide (AC) Q3W followed by docetaxel Q3W for 4 cycles.
4 Cycles = 12 dose of Paclitaxel.
Dose Modification includes Dose Increase, Dose Decrease, Dose Interuption.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/program/t_ex_sum.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/output/t_ex_sum_ARMB_SE_jp.out
26MAR2020 22:08 Page 3 of 3

［5.3.5.3-1 t_ex_sum_ARMB_SE_jp を再掲］

# 表 2.7.4.7.3-3 抗 HER2療法の曝露状況の要約（FeDeriCa 試験，日本部分集団，術前補助療法期間）

Summary of Exposure to HER2 Targeted Therapy at Neoadjuvant Phase: Safety Population, Japan Subgroup
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| | Pertuzumab IV + Trastuzumab IV Arm | | Pertuzumab + Trastuzumab FDC SC Arm |
|---|---|---|---|
| | Pertuzumab IV (N=19) | Trastuzumab IV (N=18) | Pertuzumab and Trastuzumab FDC SC (N=19) |
| Completed assigned therapy | | | |
| Yes | 18 (94.7%) | 18 ( 100%) | 19 ( 100%) |
| No | 1 ( 5.3%) | 0 | 0 |
| Number of cycles | | | |
| n | 19 | 18 | 19 |
| Mean | 3.8 | 4.0 | 4.1 |
| SD | 0.7 | 0.0 | 0.2 |
| Median | 4.0 | 4.0 | 4.0 |
| Min - Max | 1 - 4 | 4 - 4 | 4 - 5 |
| Treatment duration [Weeks] | | | |
| n | 19 | 18 | 19 |
| Mean | 8.7 | 9.2 | 9.6 |
| SD | 2.1 | 0.3 | 0.9 |
| Median | 9.1 | 9.1 | 9.1 |
| Min - Max | 0 - 10 | 9 - 10 | 9 - 13 |
| Dose intensity [%] [1] | | | |
| n | 73 | 72 | 77 |
| Mean | 98.93 | 99.59 | 100.00 |
| SD | 9.17 | 1.69 | 0.00 |
| Median | 100.00 | 100.00 | 100.00 |
| Min - Max | 21.7 - 100.0 | 89.8 - 100.0 | 100.0 - 100.0 |

[1] Dose intensity = 100% * actual amount of drug received per cycle / planned dose per cycle.
[2] Pertuzumab IV + Trastuzumab IV or Pertuzumab and Trastuzumab FDC SC will be given for 4 cycles (Q3W) concurrently with the taxane component of chemotherapy.
[3] For HER2 treatment dose modification was not allowed however a dose delay of up to 6 weeks due to adverse event was permitted.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/program/t_ex.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/output/t_ex_NEOS_HER2_SE_jp.out
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Summary of Exposure to HER2 Targeted Therapy at Neoadjuvant Phase: Safety Population, Japan Subgroup
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| | Pertuzumab IV + Trastuzumab IV Arm | | Pertuzumab + Trastuzumab FDC SC Arm |
|---|---|---|---|
| | Pertuzumab IV (N=19) | Trastuzumab IV (N=18) | Pertuzumab and Trastuzumab FDC SC (N=19) |
| Total cumulative dose [mg] | | | |
| n | 19 | 18 | 19 |
| Mean | 2021.16 | 1577.13 | 5463.16 |
| SD | 455.64 | 348.24 | 275.30 |
| Median | 2100.00 | 1405.30 | 5400.00 |
| Min - Max | 182.0 - 2520.0 | 1253.0 - 2625.4 | 5400.0 - 6600.0 |
| Number of patients with at least one dose delay [3] | | | |
| n | 19 | 18 | 19 |
| Yes | 5 (26.3%) | 4 (22.2%) | 4 (21.1%) |
| No | 14 (73.7%) | 14 (77.8%) | 15 (78.9%) |
| Number of patients with at least one dose delay - Due to AE | | | |
| n | 19 | 18 | 19 |
| Yes | 5 (26.3%) | 4 (22.2%) | 4 (21.1%) |
| No | 14 (73.7%) | 14 (77.8%) | 15 (78.9%) |
| Number of cycles of study drug received | 19 ( 100%) | 18 ( 100%) | 19 ( 100%) |
| Cycle number [2] | | | |
| 1- | 1 ( 5.3%) | 0 | 0 |
| 4- | 18 (94.7%) | 18 ( 100%) | 18 (94.7%) |
| 5- | 0 | 0 | 1 ( 5.3%) |

[1] Dose intensity = 100% * actual amount of drug received per cycle / planned dose per cycle.
[2] Pertuzumab IV + Trastuzumab IV or Pertuzumab and Trastuzumab FDC SC will be given for 4 cycles (Q3W) concurrently with the taxane component of chemotherapy.
[3] For HER2 treatment dose modification was not allowed however a dose delay of up to 6 weeks due to adverse event was permitted.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/program/t_ex.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/output/t_ex_NEOS_HER2_SE_jp.out
30MAR2020 10:40



［5.3.5.3-1 t_ex_NEOS_HER2_SE_jp を再掲］

# 表 2.7.4.7.3-4 抗 HER2療法の曝露状況の要約（FeDeriCa 試験，日本部分集団，術前 + 術後補助療法期間）

Summary of Exposure to Overall Planned HER2 Targeted Therapy (Neoadjuvant + Adjuvant Phase): Safety Population, Japan Subgroup
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| | Pertuzumab IV + Trastuzumab IV Arm | | Pertuzumab + Trastuzumab FDC SC Arm |
|---|---|---|---|
| | Pertuzumab IV (N=19) | Trastuzumab IV (N=18) | Pertuzumab and Trastuzumab FDC SC (N=19) |
| Completed assigned therapy | | | |
| Yes | 0 | 0 | 0 |
| No | 19 ( 100%) | 18 ( 100%) | 19 ( 100%) |
| Number of cycles | | | |
| n | 19 | 18 | 19 |
| Mean | 5.0 | 5.2 | 5.6 |
| SD | 1.6 | 1.3 | 1.3 |
| Median | 5.0 | 5.0 | 5.0 |
| Min - Max | 1 - 8 | 4 - 8 | 4 - 9 |
| Treatment duration [Weeks] | | | |
| n | 19 | 18 | 19 |
| Mean | 15.2 | 16.0 | 17.8 |
| SD | 6.8 | 6.0 | 5.3 |
| Median | 17.1 | 17.5 | 18.1 |
| Min - Max | 0 - 26 | 9 - 26 | 9 - 27 |
| Dose intensity [%] [2] | | | |
| n | 95 | 94 | 106 |
| Mean | 99.18 | 99.53 | 100.00 |
| SD | 8.04 | 2.27 | 0.00 |
| Median | 100.00 | 100.00 | 100.00 |
| Min - Max | 21.7 - 100.0 | 89.8 - 108.7 | 100.0 - 100.0 |

[1] Subset of patients who switched from Trastuzumab IV to Trastuzumab SC in the Adjuvant Phase (i.e. from Cycle 5) and continued with Pertuzumab IV.
[2] Dose intensity = 100% * actual amount of drug received per cycle / planned dose per cycle.
[3] For HER2 treatment dose modification was not allowed however a dose delay of up to 6 weeks due to adverse event was permitted.
[4] Pertuzumab IV + Trastuzumab IV or Pertuzumab and Trastuzumab FDC SC will be given for 4 cycles in Neoadjuvant phase and another 14 cycles in the Adjuvant phase.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/program/t_ex.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/output/t_ex_HER2_SE_jp.out
30MAR2020 10:38

Summary of Exposure to Overall Planned HER2 Targeted Therapy (Neoadjuvant + Adjuvant Phase): Safety Population, Japan Subgroup
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| | Pertuzumab IV + Trastuzumab IV Arm | | Pertuzumab + Trastuzumab FDC SC Arm |
|---|---|---|---|
| | Pertuzumab IV (N=19) | Trastuzumab IV (N=18) | Pertuzumab and Trastuzumab FDC SC (N=19) |
| Total cumulative dose [mg] | | | |
| n | 19 | 18 | 19 |
| Mean | 2772.74 | 2090.02 | 7736.84 |
| SD | 1005.21 | 591.34 | 1753.79 |
| Median | 2940.00 | 2100.00 | 7200.00 |
| Min - Max | 182.0 - 4620.0 | 1326.0 - 3221.0 | 5400.0 - 12000.0 |
| Number of patients with at least one dose delay [3] | | | |
| n | 19 | 18 | 19 |
| Yes | 5 (26.3%) | 5 (27.8%) | 4 (21.1%) |
| No | 14 (73.7%) | 13 (72.2%) | 15 (78.9%) |
| Number of patients with at least one dose delay - Due to AE | | | |
| n | 19 | 18 | 19 |
| Yes | 5 (26.3%) | 5 (27.8%) | 4 (21.1%) |
| No | 14 (73.7%) | 13 (72.2%) | 15 (78.9%) |
| Number of cycles of study drug received | 19 ( 100%) | 18 ( 100%) | 19 ( 100%) |

[1] Subset of patients who switched from Trastuzumab IV to Trastuzumab SC in the Adjuvant Phase (i.e. from Cycle 5) and continued with Pertuzumab IV.
[2] Dose intensity = 100% * actual amount of drug received per cycle / planned dose per cycle.
[3] For HER2 treatment dose modification was not allowed however a dose delay of up to 6 weeks due to adverse event was permitted.
[4] Pertuzumab IV + Trastuzumab IV or Pertuzumab and Trastuzumab FDC SC will be given for 4 cycles in Neoadjuvant phase and another 14 cycles in the Adjuvant phase.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/program/t_ex.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/output/t_ex_HER2_SE_jp.out
30MAR2020 10:38

Summary of Exposure to Overall Planned HER2 Targeted Therapy (Neoadjuvant + Adjuvant Phase): Safety Population, Japan Subgroup
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| | Pertuzumab IV + Trastuzumab IV Arm | | Pertuzumab + Trastuzumab FDC SC Arm |
|---|---|---|---|
| | Pertuzumab IV (N=19) | Trastuzumab IV (N=18) | Pertuzumab and Trastuzumab FDC SC (N=19) |
| Cycle number [4] | | | |
| 1- | 1 ( 5.3%) | 0 | 0 |
| 2- | 0 | 0 | 0 |
| 3- | 0 | 0 | 0 |
| 4- | 7 (36.8%) | 7 (38.9%) | 4 (21.1%) |
| 5- | 5 (26.3%) | 5 (27.8%) | 6 (31.6%) |
| 6- | 2 (10.5%) | 2 (11.1%) | 5 (26.3%) |
| 7- | 3 (15.8%) | 3 (16.7%) | 3 (15.8%) |
| 8- | 1 ( 5.3%) | 1 ( 5.6%) | 0 |
| 9- | 0 | 0 | 1 ( 5.3%) |
| 10- | 0 | 0 | 0 |
| 11- | 0 | 0 | 0 |
| 12- | 0 | 0 | 0 |
| 13- | 0 | 0 | 0 |
| 14- | 0 | 0 | 0 |
| 15- | 0 | 0 | 0 |
| 16- | 0 | 0 | 0 |
| 17- | 0 | 0 | 0 |
| 18- | 0 | 0 | 0 |

[1] Subset of patients who switched from Trastuzumab IV to Trastuzumab SC in the Adjuvant Phase (i.e. from Cycle 5) and continued with Pertuzumab IV.
[2] Dose intensity = 100% * actual amount of drug received per cycle / planned dose per cycle.
[3] For HER2 treatment dose modification was not allowed however a dose delay of up to 6 weeks due to adverse event was permitted.
[4] Pertuzumab IV + Trastuzumab IV or Pertuzumab and Trastuzumab FDC SC will be given for 4 cycles in Neoadjuvant phase and another 14 cycles in the Adjuvant phase.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/program/t_ex.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/output/t_ex_HER2_SE_jp.out
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［5.3.5.3-1 t_ex_HER2_SE_jp を再掲］

## 表 2.7.4.7.3-5 いずれかの群で発現率が10%以上の有害事象の要約（FeDeriCa 試験，日本部分集団）

Adverse Events with an Incidence Rate at Least 10% by Relation: Safety Population, Japan Subgroup
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| | Adverse Events | | Related Adverse Events | |
|---|---|---|---|---|
| MedDRA Preferred Term | Pertuzumab + Trastuzumab FDC SC Arm (N=20) | Pertuzumab IV + Trastuzumab IV Arm (N=21) | Pertuzumab + Trastuzumab FDC SC Arm (N=20) | Pertuzumab IV + Trastuzumab IV Arm (N=21) |
| Total number of patients with at least one adverse event | 20 (100.0%) | 21 (100.0%) | 15 ( 75.0%) | 14 ( 66.7%) |
| 脱毛症 | 17 ( 85.0%) | 20 ( 95.2%) | 1 ( 5.0%) | 0 |
| 悪心 | 15 ( 75.0%) | 16 ( 76.2%) | 2 ( 10.0%) | 3 ( 14.3%) |
| 便秘 | 15 ( 75.0%) | 14 ( 66.7%) | 1 ( 5.0%) | 0 |
| 下痢 | 14 ( 70.0%) | 12 ( 57.1%) | 9 ( 45.0%) | 8 ( 38.1%) |
| 口内炎 | 11 ( 55.0%) | 12 ( 57.1%) | 2 ( 10.0%) | 4 ( 19.0%) |
| 好中球数減少 | 9 ( 45.0%) | 5 ( 23.8%) | 0 | 1 ( 4.8%) |
| 倦怠感 | 8 ( 40.0%) | 5 ( 23.8%) | 2 ( 10.0%) | 0 |
| 貧血 | 8 ( 40.0%) | 8 ( 38.1%) | 0 | 1 ( 4.8%) |
| 末梢性浮腫 | 8 ( 40.0%) | 6 ( 28.6%) | 2 ( 10.0%) | 1 ( 4.8%) |
| 味覚異常 | 8 ( 40.0%) | 10 ( 47.6%) | 2 ( 10.0%) | 2 ( 9.5%) |
| 処置による疼痛 | 7 ( 35.0%) | 4 ( 19.0%) | 0 | 0 |
| 末梢性感覚ニューロパチー | 7 ( 35.0%) | 10 ( 47.6%) | 2 ( 10.0%) | 2 ( 9.5%) |
| 筋肉痛 | 6 ( 30.0%) | 6 ( 28.6%) | 1 ( 5.0%) | 2 ( 9.5%) |
| 発疹 | 6 ( 30.0%) | 4 ( 19.0%) | 3 ( 15.0%) | 1 ( 4.8%) |
| 皮膚乾燥 | 6 ( 30.0%) | 4 ( 19.0%) | 2 ( 10.0%) | 0 |
| アラニンアミノトランスフェラーゼ増加 | 5 ( 25.0%) | 3 ( 14.3%) | 0 | 2 ( 9.5%) |
| 爪変色 | 5 ( 25.0%) | 5 ( 23.8%) | 1 ( 5.0%) | 0 |
| 疲労 | 5 ( 25.0%) | 5 ( 23.8%) | 1 ( 5.0%) | 2 ( 9.5%) |
| 疼痛 | 5 ( 25.0%) | 3 ( 14.3%) | 0 | 0 |
| アスパラギン酸アミノトランスフェラーゼ増加 | 4 ( 20.0%) | 2 ( 9.5%) | 1 ( 5.0%) | 0 |
| 関節痛 | 4 ( 20.0%) | 6 ( 28.6%) | 2 ( 10.0%) | 3 ( 14.3%) |
| 手掌・足底発赤知覚不全症候群 | 4 ( 20.0%) | 6 ( 28.6%) | 2 ( 10.0%) | 1 ( 4.8%) |
| 上咽頭炎 | 4 ( 20.0%) | 4 ( 19.0%) | 1 ( 5.0%) | 0 |
| 食欲減退 | 4 ( 20.0%) | 8 ( 38.1%) | 0 | 2 ( 9.5%) |
| 白血球数減少 | 4 ( 20.0%) | 6 ( 28.6%) | 2 ( 10.0%) | 1 ( 4.8%) |
| 発熱 | 4 ( 20.0%) | 7 ( 33.3%) | 0 | 2 ( 9.5%) |
| 発熱性好中球減少症 | 4 ( 20.0%) | 4 ( 19.0%) | 0 | 0 |
| 不眠症 | 4 ( 20.0%) | 5 ( 23.8%) | 0 | 1 ( 4.8%) |
| ドライアイ | 3 ( 15.0%) | 0 | 1 ( 5.0%) | 0 |
| 胃炎 | 3 ( 15.0%) | 1 ( 4.8%) | 0 | 0 |
| 歯周病 | 3 ( 15.0%) | 1 ( 4.8%) | 0 | 0 |
| 注射部位反応 | 3 ( 15.0%) | 0 | 3 ( 15.0%) | 0 |
| 背部痛 | 3 ( 15.0%) | 1 ( 4.8%) | 1 ( 5.0%) | 1 ( 4.8%) |
| 浮腫 | 3 ( 15.0%) | 4 ( 19.0%) | 1 ( 5.0%) | 0 |
| 末梢性ニューロパチー | 3 ( 15.0%) | 2 ( 9.5%) | 0 | 1 ( 4.8%) |
| 嘔吐 | 3 ( 15.0%) | 4 ( 19.0%) | 0 | 2 ( 9.5%) |
| リンパ球数減少 | 2 ( 10.0%) | 2 ( 9.5%) | 0 | 0 |
| 咽頭炎 | 2 ( 10.0%) | 2 ( 9.5%) | 0 | 0 |
| 顔面浮腫 | 2 ( 10.0%) | 0 | 0 | 0 |
| 結膜炎 | 2 ( 10.0%) | 1 ( 4.8%) | 0 | 1 ( 4.8%) |
| 口角口唇炎 | 2 ( 10.0%) | 0 | 0 | 0 |
| 紅斑 | 2 ( 10.0%) | 1 ( 4.8%) | 0 | 0 |
| 上気道感染 | 2 ( 10.0%) | 4 ( 19.0%) | 0 | 0 |
| 創合併症 | 2 ( 10.0%) | 6 ( 28.6%) | 0 | 0 |
| 爪囲炎 | 2 ( 10.0%) | 1 ( 4.8%) | 1 ( 5.0%) | 1 ( 4.8%) |
| 斑状丘疹状皮疹 | 2 ( 10.0%) | 2 ( 9.5%) | 1 ( 5.0%) | 1 ( 4.8%) |
| 薬物性肝障害 | 2 ( 10.0%) | 0 | 1 ( 5.0%) | 0 |
| 漿液腫 | 2 ( 10.0%) | 1 ( 4.8%) | 0 | 0 |

Investigator text for AEs encoded using MedDRA version 22.0.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the closest relationship for this preferred term.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/program/aerel.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/output/aerel_p10_SE_jp_wo40324.out
27AUG2020 22:26

Adverse Events with an Incidence Rate at Least 10% by Relation: Safety Population, Japan Subgroup
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA Preferred Term | Adverse Events | | Related Adverse Events | |
|---|---|---|---|---|
| | Pertuzumab + Trastuzumab FDC SC Arm (N=20) | Pertuzumab IV + Trastuzumab IV Arm (N=21) | Pertuzumab + Trastuzumab FDC SC Arm (N=20) | Pertuzumab IV + Trastuzumab IV Arm (N=21) |
| 膀胱炎 | 2 ( 10.0%) | 1 ( 4.8%) | 0 | 1 ( 4.8%) |
| そう痒症 | 1 ( 5.0%) | 5 ( 23.8%) | 1 ( 5.0%) | 4 ( 19.0%) |
| 咳嗽 | 1 ( 5.0%) | 5 ( 23.8%) | 0 | 1 ( 4.8%) |
| 血管炎 | 1 ( 5.0%) | 3 ( 14.3%) | 0 | 0 |
| 頭痛 | 1 ( 5.0%) | 4 ( 19.0%) | 0 | 0 |
| 注入に伴う反応 | 0 | 5 ( 23.8%) | 0 | 5 ( 23.8%) |
| 爪線状隆起 | 0 | 3 ( 14.3%) | 0 | 1 ( 4.8%) |
| 浮動性めまい | 0 | 3 ( 14.3%) | 0 | 0 |

Investigator text for AEs encoded using MedDRA version 22.0.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the closest relationship for this preferred term.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/program/aerel.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/output/aerel_p10_SE_jp_wo40324.out
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［5.3.5.3-1 aerel_p10_SE_jp_wo40324 を再掲］

## 表 2.7.4.7.3-6 いずれかの群で発現率が10%以上の有害事象の重症度別の要約（FeDeriCa 試験, 日本部分集団）

Adverse Events with an Incidence Rate at Least 10% by Grade: Safety Population, Japan Subgroup
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| | Pertuzumab + Trastuzumab FDC SC Arm (N=20) | | Pertuzumab IV + Trastuzumab IV Arm (N=21) | |
|---|---|---|---|---|
| MedDRA Preferred Term | All Grade | Grade 3-5 | All Grade | Grade 3-5 |
| Total number of patients with at least one adverse event | 20 (100.0%) | 13 ( 65.0%) | 21 (100.0%) | 12 ( 57.1%) |
| 脱毛症 | 17 ( 85.0%) | 0 | 20 ( 95.2%) | 0 |
| 悪心 | 15 ( 75.0%) | 1 ( 5.0%) | 16 ( 76.2%) | 0 |
| 便秘 | 15 ( 75.0%) | 0 | 14 ( 66.7%) | 0 |
| 下痢 | 14 ( 70.0%) | 2 ( 10.0%) | 12 ( 57.1%) | 0 |
| 口内炎 | 11 ( 55.0%) | 1 ( 5.0%) | 12 ( 57.1%) | 0 |
| 好中球数減少 | 9 ( 45.0%) | 6 ( 30.0%) | 5 ( 23.8%) | 4 ( 19.0%) |
| 倦怠感 | 8 ( 40.0%) | 0 | 5 ( 23.8%) | 0 |
| 貧血 | 8 ( 40.0%) | 1 ( 5.0%) | 8 ( 38.1%) | 1 ( 4.8%) |
| 末梢性浮腫 | 8 ( 40.0%) | 0 | 6 ( 28.6%) | 0 |
| 味覚異常 | 8 ( 40.0%) | 0 | 10 ( 47.6%) | 0 |
| 処置による疼痛 | 7 ( 35.0%) | 0 | 4 ( 19.0%) | 0 |
| 末梢性感覚ニューロパチー | 7 ( 35.0%) | 0 | 10 ( 47.6%) | 0 |
| 筋肉痛 | 6 ( 30.0%) | 0 | 6 ( 28.6%) | 1 ( 4.8%) |
| 発疹 | 6 ( 30.0%) | 1 ( 5.0%) | 4 ( 19.0%) | 0 |
| 皮膚乾燥 | 6 ( 30.0%) | 0 | 4 ( 19.0%) | 0 |
| アラニンアミノトランスフェラーゼ増加 | 5 ( 25.0%) | 2 ( 10.0%) | 3 ( 14.3%) | 0 |
| 爪変色 | 5 ( 25.0%) | 0 | 5 ( 23.8%) | 0 |
| 疲労 | 5 ( 25.0%) | 2 ( 10.0%) | 5 ( 23.8%) | 1 ( 4.8%) |
| 疼痛 | 5 ( 25.0%) | 0 | 3 ( 14.3%) | 0 |
| アスパラギン酸アミノトランスフェラーゼ増加 | 4 ( 20.0%) | 1 ( 5.0%) | 2 ( 9.5%) | 0 |
| 関節痛 | 4 ( 20.0%) | 0 | 6 ( 28.6%) | 1 ( 4.8%) |
| 手掌・足底発赤知覚不全症候群 | 4 ( 20.0%) | 1 ( 5.0%) | 6 ( 28.6%) | 0 |
| 上咽頭炎 | 4 ( 20.0%) | 0 | 4 ( 19.0%) | 0 |
| 食欲減退 | 4 ( 20.0%) | 2 ( 10.0%) | 8 ( 38.1%) | 1 ( 4.8%) |
| 白血球数減少 | 4 ( 20.0%) | 2 ( 10.0%) | 6 ( 28.6%) | 4 ( 19.0%) |
| 発熱 | 4 ( 20.0%) | 0 | 7 ( 33.3%) | 0 |
| 発熱性好中球減少症 | 4 ( 20.0%) | 4 ( 20.0%) | 4 ( 19.0%) | 4 ( 19.0%) |
| 不眠症 | 4 ( 20.0%) | 0 | 5 ( 23.8%) | 0 |
| ドライアイ | 3 ( 15.0%) | 0 | 0 | 0 |
| 胃炎 | 3 ( 15.0%) | 0 | 1 ( 4.8%) | 0 |
| 歯周病 | 3 ( 15.0%) | 0 | 1 ( 4.8%) | 0 |
| 注射部位反応 | 3 ( 15.0%) | 0 | 0 | 0 |
| 背部痛 | 3 ( 15.0%) | 0 | 1 ( 4.8%) | 0 |
| 浮腫 | 3 ( 15.0%) | 0 | 4 ( 19.0%) | 0 |
| 末梢性ニューロパチー | 3 ( 15.0%) | 0 | 2 ( 9.5%) | 0 |
| 嘔吐 | 3 ( 15.0%) | 0 | 4 ( 19.0%) | 0 |
| リンパ球数減少 | 2 ( 10.0%) | 1 ( 5.0%) | 2 ( 9.5%) | 2 ( 9.5%) |
| 咽頭炎 | 2 ( 10.0%) | 0 | 2 ( 9.5%) | 1 ( 4.8%) |
| 顔面浮腫 | 2 ( 10.0%) | 0 | 0 | 0 |
| 結膜炎 | 2 ( 10.0%) | 0 | 1 ( 4.8%) | 0 |
| 口角口唇炎 | 2 ( 10.0%) | 0 | 0 | 0 |
| 紅斑 | 2 ( 10.0%) | 0 | 1 ( 4.8%) | 0 |
| 上気道感染 | 2 ( 10.0%) | 0 | 4 ( 19.0%) | 0 |
| 創合併症 | 2 ( 10.0%) | 0 | 6 ( 28.6%) | 0 |
| 爪囲炎 | 2 ( 10.0%) | 0 | 1 ( 4.8%) | 0 |
| 斑状丘疹状皮疹 | 2 ( 10.0%) | 0 | 2 ( 9.5%) | 0 |
| 薬物性肝障害 | 2 ( 10.0%) | 0 | 0 | 0 |
| 漿液腫 | 2 ( 10.0%) | 0 | 1 ( 4.8%) | 0 |
| 膀胱炎 | 2 ( 10.0%) | 0 | 1 ( 4.8%) | 0 |
| そう痒症 | 1 ( 5.0%) | 0 | 5 ( 23.8%) | 1 ( 4.8%) |
| 咳嗽 | 1 ( 5.0%) | 0 | 5 ( 23.8%) | 0 |
| 血管炎 | 1 ( 5.0%) | 0 | 3 ( 14.3%) | 0 |
| 頭痛 | 1 ( 5.0%) | 0 | 4 ( 19.0%) | 0 |

Investigator text for AEs encoded using MedDRA version 22.0.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the greatest intensity for this preferred term.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/program/aegrd.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/output/aegrd_p10_SE_jp_wo40324.out
27AUG2020 22:44

Adverse Events with an Incidence Rate at Least 10% by Grade: Safety Population, Japan Subgroup
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| | Pertuzumab + Trastuzumab FDC SC Arm (N=20) | | Pertuzumab IV + Trastuzumab IV Arm (N=21) | |
|---|---|---|---|---|
| MedDRA Preferred Term | All Grade | Grade 3-5 | All Grade | Grade 3-5 |
| 注入に伴う反応 | 0 | 0 | 5 ( 23.8%) | 0 |
| 爪線状隆起 | 0 | 0 | 3 ( 14.3%) | 0 |
| 浮動性めまい | 0 | 0 | 3 ( 14.3%) | 0 |

Investigator text for AEs encoded using MedDRA version 22.0.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the greatest intensity for this preferred term.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/program/aegrd.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/output/
aegrd_p10_SE_jp_wo40324.out
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［5.3.5.3-1 aegrd_p10_SE_jp_wo40324 を再掲］

## 表 2.7.4.7.3-7 重篤な有害事象の要約（FeDeriCa 試験，日本部分集団）

Serious Adverse Events by Relation: Safety Population, Japan Subgroup
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA Preferred Term | Adverse Events | | Related Adverse Events | |
|---|---|---|---|---|
| | Pertuzumab + Trastuzumab FDC SC Arm (N=20) | Pertuzumab IV + Trastuzumab IV Arm (N=21) | Pertuzumab + Trastuzumab FDC SC Arm (N=20) | Pertuzumab IV + Trastuzumab IV Arm (N=21) |
| Total number of patients with at least one adverse event | 3 ( 15.0%) | 4 ( 19.0%) | 0 | 0 |
| 好中球数減少 | 1 ( 5.0%) | 0 | 0 | 0 |
| 塞栓症 | 1 ( 5.0%) | 0 | 0 | 0 |
| 出血性胃炎 | 1 ( 5.0%) | 0 | 0 | 0 |
| 肺臓炎 | 1 ( 5.0%) | 1 ( 4.8%) | 0 | 0 |
| 発熱性好中球減少症 | 1 ( 5.0%) | 2 ( 9.5%) | 0 | 0 |
| 咽頭炎 | 0 | 1 ( 4.8%) | 0 | 0 |
| 術後創感染 | 0 | 1 ( 4.8%) | 0 | 0 |
| 粘膜の炎症 | 0 | 1 ( 4.8%) | 0 | 0 |

Investigator text for AEs encoded using MedDRA version 22.0.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the closest relationship for this preferred term.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/program/aerel.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/output/aerel_SER_SE_jp_wo40324.out
27AUG2020 22:29 Page 1 of 1

［5.3.5.3-1 aerel_SER_SE_jp_wo40324 を再掲］

## 表 2.7.4.7.3-8 治験薬の投与中止に至った有害事象の要約（FeDeriCa 試験，日本部分集団）

Adverse Events Leading to Withdrawal of HER2 Targeted Therapy by Relation: Safety Population, Japan Subgroup
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA Preferred Term | Adverse Events | | Related Adverse Events | |
|---|---|---|---|---|
| | Pertuzumab + Trastuzumab FDC SC Arm (N=20) | Pertuzumab IV + Trastuzumab IV Arm (N=21) | Pertuzumab + Trastuzumab FDC SC Arm (N=20) | Pertuzumab IV + Trastuzumab IV Arm (N=21) |
| Total number of patients with at least one adverse event | 0 | 1 ( 4.8%) | 0 | 1 ( 4.8%) |
| 薬物過敏症 | 0 | 1 ( 4.8%) | 0 | 1 ( 4.8%) |

Investigator text for AEs encoded using MedDRA version 22.0.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the closest relationship for this preferred term.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/program/aerel.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/output/aerel_DSCH2_SE_jp_wo40324.out
27AUG2020 22:37 Page 1 of 1

［5.3.5.3-1 aerel_DSCH2_SE_jp_wo40324 を再掲］

## 表 2.7.4.7.3-9 いずれかの治験治療の投与中止に至った有害事象の要約（FeDeriCa 試験，日本部分集団）

Adverse Events Leading to Withdrawal of Any Study Treatment by Relation: Safety Population, Japan Subgroup
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA Preferred Term | Adverse Events | | Related Adverse Events | |
|---|---|---|---|---|
| | Pertuzumab + Trastuzumab FDC SC Arm (N=20) | Pertuzumab IV + Trastuzumab IV Arm (N=21) | Pertuzumab + Trastuzumab FDC SC Arm (N=20) | Pertuzumab IV + Trastuzumab IV Arm (N=21) |
| Total number of patients with at least one adverse event | 3 ( 15.0%) | 2 ( 9.5%) | 0 | 1 ( 4.8%) |
| アスパラギン酸アミノトランスフェラーゼ増加 | 1 ( 5.0%) | 0 | 0 | 0 |
| アラニンアミノトランスフェラーゼ増加 | 1 ( 5.0%) | 0 | 0 | 0 |
| 好中球数減少 | 1 ( 5.0%) | 0 | 0 | 0 |
| 食欲減退 | 1 ( 5.0%) | 0 | 0 | 0 |
| 肺臓炎 | 1 ( 5.0%) | 0 | 0 | 0 |
| 粘膜の炎症 | 0 | 1 ( 4.8%) | 0 | 0 |
| 薬物過敏症 | 0 | 1 ( 4.8%) | 0 | 1 ( 4.8%) |

Investigator text for AEs encoded using MedDRA version 22.0.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the closest relationship for this preferred term.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/program/aerel.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/output/aerel_DSC_SE_jp_wo40324.out
27AUG2020 22:33 Page 1 of 1

［5.3.5.3-1 aerel_DSC_SE_jp_wo40324 を再掲］

# 表 2.7.4.7.3-10 注目すべき有害事象の要約（FeDeriCa 試験，日本部分集団）

Adverse Events to Monitor by Relation: Safety Population, Japan Subgroup
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| Adverse Events to Monitor<br>MedDRA Preferred Term | Adverse Events | | Related Adverse Events | |
|---|---|---|---|---|
| | Pertuzumab + Trastuzumab FDC SC Arm (N=20) | Pertuzumab IV + Trastuzumab IV Arm (N=21) | Pertuzumab + Trastuzumab FDC SC Arm (N=20) | Pertuzumab IV + Trastuzumab IV Arm (N=21) |
| Administration-Related Reactions (ARRs) Adverse Events Which Occurred within 24h of HER2 Treatment | | | | |
| Total number of patients with at least one adverse event | 4 ( 20.0%) | 6 ( 28.6%) | 3 ( 15.0%) | 6 ( 28.6%) |
| 注射部位反応 | 3 ( 15.0%) | 0 | 3 ( 15.0%) | 0 |
| 末梢性浮腫 | 1 ( 5.0%) | 0 | 0 | 0 |
| 注入に伴う反応 | 0 | 5 ( 23.8%) | 0 | 5 ( 23.8%) |
| 薬物過敏症 | 0 | 1 ( 4.8%) | 0 | 1 ( 4.8%) |
| Anaphylaxis and Hypersensitivity Adverse Events Occurring During HER2 Targeted Treatment Period | | | | |
| Total number of patients with at least one adverse event | 0 | 1 ( 4.8%) | 0 | 1 ( 4.8%) |
| 薬物過敏症 | 0 | 1 ( 4.8%) | 0 | 1 ( 4.8%) |
| Cardiac Dysfunction Adverse Events | | | | |
| Total number of patients with at least one adverse event | 11 ( 55.0%) | 10 ( 47.6%) | 3 ( 15.0%) | 1 ( 4.8%) |
| 末梢性浮腫 | 8 ( 40.0%) | 6 ( 28.6%) | 2 ( 10.0%) | 1 ( 4.8%) |
| 浮腫 | 3 ( 15.0%) | 4 ( 19.0%) | 1 ( 5.0%) | 0 |
| Diarrhoea Adverse Events | | | | |
| Total number of patients with at least one adverse event | 14 ( 70.0%) | 12 ( 57.1%) | 9 ( 45.0%) | 8 ( 38.1%) |
| 下痢 | 14 ( 70.0%) | 12 ( 57.1%) | 9 ( 45.0%) | 8 ( 38.1%) |
| Exposure During Pregnancy / Exposure during Breast Feeding / Pregnancy Complications / Oligohydramnios / Congenital Abnormalities Adverse Events | | | | |
| Total number of patients with at least one adverse event | 1 ( 5.0%) | 1 ( 4.8%) | 0 | 1 ( 4.8%) |
| 表皮融解 | 1 ( 5.0%) | 1 ( 4.8%) | 0 | 1 ( 4.8%) |
| Interstitial Lung Disease (ILD) Adverse Events | | | | |
| Total number of patients with at least one adverse event | 1 ( 5.0%) | 2 ( 9.5%) | 0 | 0 |
| 肺臓炎 | 1 ( 5.0%) | 2 ( 9.5%) | 0 | 0 |

Investigator text for AEs encoded using MedDRA version 22.0.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the closest relationship for this preferred term.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/program/aerel_aesi.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/output/aerel_aesi_SE_jp_wo40324.out
27AUG2020 22:59

Adverse Events to Monitor by Relation: Safety Population, Japan Subgroup
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| Adverse Events to Monitor<br>MedDRA Preferred Term | Adverse Events | | Related Adverse Events | |
|---|---|---|---|---|
| | Pertuzumab + Trastuzumab FDC SC Arm (N=20) | Pertuzumab IV + Trastuzumab IV Arm (N=21) | Pertuzumab + Trastuzumab FDC SC Arm (N=20) | Pertuzumab IV + Trastuzumab IV Arm (N=21) |
| Investigator Reported Local Injection/Infusion site reaction (ISR) Related to HER2 targeted therapy which occurred during or immediately after a HER2 Targeted Therapy | | | | |
| Total number of patients with at least one adverse event | 2 ( 10.0%) | 0 | 2 ( 10.0%) | 0 |
| 注射部位反応 | 2 ( 10.0%) | 0 | 2 ( 10.0%) | 0 |
| Investigator Reported Systemic Injection/Infusion Related reaction (IRR) Related to HER2 targeted therapy which occurred during or immediately after a HER2 Targeted Therapy | | | | |
| Total number of patients with at least one adverse event | 0 | 4 ( 19.0%) | 0 | 4 ( 19.0%) |
| 注入に伴う反応 | 0 | 4 ( 19.0%) | 0 | 4 ( 19.0%) |
| Neutropenia / Febrile Neutropenia Adverse Events | | | | |
| Total number of patients with at least one adverse event | 11 ( 55.0%) | 12 ( 57.1%) | 2 ( 10.0%) | 2 ( 9.5%) |
| 好中球数減少 | 9 ( 45.0%) | 5 ( 23.8%) | 0 | 1 ( 4.8%) |
| 白血球数減少 | 4 ( 20.0%) | 6 ( 28.6%) | 2 ( 10.0%) | 1 ( 4.8%) |
| 発熱性好中球減少症 | 4 ( 20.0%) | 4 ( 19.0%) | 0 | 0 |
| リンパ球数減少 | 2 ( 10.0%) | 2 ( 9.5%) | 0 | 0 |
| Serious Mucositis Adverse Events | | | | |
| Total number of patients with at least one adverse event | 1 ( 5.0%) | 2 ( 9.5%) | 0 | 0 |
| 出血性胃炎 | 1 ( 5.0%) | 0 | 0 | 0 |
| 咽頭炎 | 0 | 1 ( 4.8%) | 0 | 0 |
| 粘膜の炎症 | 0 | 1 ( 4.8%) | 0 | 0 |

Investigator text for AEs encoded using MedDRA version 22.0.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the closest relationship for this preferred term.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/program/aerel_aesi.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/output/aerel_aesi_SE_jp_wo40324.out
27AUG2020 22:59



［5.3.5.3-1 aerel_aesi_SE_jp_wo40324 を再掲］

# 表 2.7.4.7.3-11 注目すべき有害事象の重症度別の要約（FeDeriCa 試験，日本部分集団）

Adverse Events to Monitor by Grade: Safety Population, Japan Subgroup
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| Adverse Events to Monitor<br>MedDRA Preferred Term | Pertuzumab + Trastuzumab FDC SC Arm (N=20) | | Pertuzumab IV + Trastuzumab IV Arm (N=21) | |
|---|---|---|---|---|
| | All Grade | Grade 3-5 | All Grade | Grade 3-5 |
| Administration-Related Reactions (ARRs) Adverse Events Which Occurred within 24h of HER2 Treatment | | | | |
| Total number of patients with at least one adverse event | 4 ( 20.0%) | 0 | 6 ( 28.6%) | 0 |
| 注射部位反応 | 3 ( 15.0%) | 0 | 0 | 0 |
| 末梢性浮腫 | 1 ( 5.0%) | 0 | 0 | 0 |
| 注入に伴う反応 | 0 | 0 | 5 ( 23.8%) | 0 |
| 薬物過敏症 | 0 | 0 | 1 ( 4.8%) | 0 |
| Anaphylaxis and Hypersensitivity Adverse Events Occurring During HER2 Targeted Treatment Period | | | | |
| Total number of patients with at least one adverse event | 0 | 0 | 1 ( 4.8%) | 0 |
| 薬物過敏症 | 0 | 0 | 1 ( 4.8%) | 0 |
| Cardiac Dysfunction Adverse Events | | | | |
| Total number of patients with at least one adverse event | 11 ( 55.0%) | 0 | 10 ( 47.6%) | 0 |
| 末梢性浮腫 | 8 ( 40.0%) | 0 | 6 ( 28.6%) | 0 |
| 浮腫 | 3 ( 15.0%) | 0 | 4 ( 19.0%) | 0 |
| Diarrhoea Adverse Events | | | | |
| Total number of patients with at least one adverse event | 14 ( 70.0%) | 2 ( 10.0%) | 12 ( 57.1%) | 0 |
| 下痢 | 14 ( 70.0%) | 2 ( 10.0%) | 12 ( 57.1%) | 0 |
| Exposure During Pregnancy / Exposure during Breast Feeding / Pregnancy Complications / Oligohydramnios / Congenital Abnormalities Adverse Events | | | | |
| Total number of patients with at least one adverse event | 1 ( 5.0%) | 0 | 1 ( 4.8%) | 0 |
| 表皮融解 | 1 ( 5.0%) | 0 | 1 ( 4.8%) | 0 |
| Interstitial Lung Disease (ILD) Adverse Events | | | | |
| Total number of patients with at least one adverse event | 1 ( 5.0%) | 0 | 2 ( 9.5%) | 0 |
| 肺臓炎 | 1 ( 5.0%) | 0 | 2 ( 9.5%) | 0 |
| Investigator Reported Local Injection/Infusion site reaction (ISR) Related to HER2 targeted therapy which occurred during or immediately after a HER2 Targeted Therapy | | | | |
| Total number of patients with at least one adverse event | 2 ( 10.0%) | 0 | 0 | 0 |
| 注射部位反応 | 2 ( 10.0%) | 0 | 0 | 0 |

Investigator text for AEs encoded using MedDRA version 22.0.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the greatest intensity for this preferred term.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/program/aegrd_aesi.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/output/aegrd_aesi_SE_jp_wo40324.out
27AUG2020 23:03

Adverse Events to Monitor by Grade: Safety Population, Japan Subgroup
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| Adverse Events to Monitor<br>MedDRA Preferred Term | Pertuzumab + Trastuzumab FDC SC Arm (N=20) | | Pertuzumab IV + Trastuzumab IV Arm (N=21) | |
|---|---|---|---|---|
| | All Grade | Grade 3-5 | All Grade | Grade 3-5 |
| Investigator Reported Systemic Injection/Infusion Related reaction (IRR) Related to HER2 targeted therapy which occurred during or immediately after a HER2 Targeted Therapy | | | | |
| Total number of patients with at least one adverse event | 0 | 0 | 4 ( 19.0%) | 0 |
| 注入に伴う反応 | 0 | 0 | 4 ( 19.0%) | 0 |
| Neutropenia / Febrile Neutropenia Adverse Events | | | | |
| Total number of patients with at least one adverse event | 11 ( 55.0%) | 9 ( 45.0%) | 12 ( 57.1%) | 10 ( 47.6%) |
| 好中球数減少 | 9 ( 45.0%) | 6 ( 30.0%) | 5 ( 23.8%) | 4 ( 19.0%) |
| 白血球数減少 | 4 ( 20.0%) | 2 ( 10.0%) | 6 ( 28.6%) | 4 ( 19.0%) |
| 発熱性好中球減少症 | 4 ( 20.0%) | 4 ( 20.0%) | 4 ( 19.0%) | 4 ( 19.0%) |
| リンパ球数減少 | 2 ( 10.0%) | 1 ( 5.0%) | 2 ( 9.5%) | 2 ( 9.5%) |
| Serious Mucositis Adverse Events | | | | |
| Total number of patients with at least one adverse event | 1 ( 5.0%) | 0 | 2 ( 9.5%) | 2 ( 9.5%) |
| 出血性胃炎 | 1 ( 5.0%) | 0 | 0 | 0 |
| 咽頭炎 | 0 | 0 | 1 ( 4.8%) | 1 ( 4.8%) |
| 粘膜の炎症 | 0 | 0 | 1 ( 4.8%) | 1 ( 4.8%) |

Investigator text for AEs encoded using MedDRA version 22.0.
All counts represent subjects. Multiple occurrences of the same AE in one individual are counted once at the greatest intensity for this preferred term.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/program/aegrd_aesi.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD2/prod/output/aegrd_aesi_SE_jp_wo40324.out
27AUG2020 23:03



［5.3.5.3-1 aegrd_aesi_SE_jp_wo40324 を再掲］

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## 2.7.5 参考文献

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該当なし。

2) 2.7.2 で引用した文献
2.7.2.5項に記載した。

3) 2.7.3 で引用した文献
2.7.3.6項に記載した。

4) 2.7.4 で引用した文献
該当なし。

5) 2.7.6 で引用した文献
該当なし。

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## 2.7.6 個々の試験のまとめ

**表 2.7.6-1 臨床試験一覧表**

| 試験番号 | 相<br>依頼者 | 試験<br>方法 | 対象 | 症例数 | 治療群 | 主要評価項目 | CTD番号 |
|---|---|---|---|---|---|---|---|
| WO40324<br>FeDeriCa<br>【国際共同】 | III<br>Roche/中外 | 非盲検<br>ランダム化 | HER2陽性早期乳癌患者 | 500<br>A: 252<br>B: 248 | A：Chemo+H(IV)+P(IV)→H(IV)又はH(SC)+P(IV)<br>B：Chemo+本剤→本剤 | PK非劣性<br>($C_{trough}$) | 5.3.5.1-1<br><評価> |
| MO40628<br>PHranceSCa<br>【海外】 | II<br>Roche | 非盲検<br>ランダム化<br>クロスオーバー | HER2陽性早期乳癌患者 | 160<br>A: 80<br>B: 80 | A：H(IV)+P(IV) →本剤<br>B：本剤→ H(IV)+P(IV) | 被験者選好 | 5.3.5.1-2<br>5.3.5.1-3<br><評価> |
| BO30185<br>【海外】 | I<br>Roche | 非盲検 | Part 1：健康成人男性<br>Part 2：早期乳癌患者 | Part 1: 48<br>Part 2: 40 | Part 1<br>P(IV)又はP(SC)，H(SC), H(SC)+P(SC) *1<br><br>Part 2<br>コホートB：H(SC)+P(SC) *1,<br>コホートC：本剤 | PK | 5.3.3.2-1<br><評価> |

H : trastuzumab (Herceptin), P : pertuzumab (Perjeta), chemo : doxorubicin + cyclophosphamide(AC) → docetaxel, 又は dose-dense AC(ddAC) → paclitaxel, IV : intravenous, SC : subcutaneous, PK : 薬物動態, $C_{trough}$ : 血清中トラフ濃度

*1 実施医療機関でペルツズマブ（SC）及びトラスツズマブ（SC）を投与直前に混合した SC 製剤を投与

## 2.7.6.1 概要

### 2.7.6.1.1 WO40324試験（FeDeriCa 試験）

1) 試験の標題

A phase III, randomized, multicenter, open-label, two-arm study to evaluate the pharmacokinetics, efficacy, and safety of subcutaneous administration of the fixed-dose combination of pertuzumab and trastuzumab in combination with chemotherapy in patients with HER2-positive early breast cancer.

2) フェーズ

第 III 相

3) 治験依頼者

F. Hoffmann-La Roche 社

4) 治験実施国（施設数）

アルゼンチン（3），ベルギー（6），ブラジル（3），カナダ（5），チェコ共和国（2），フランス（7），ドイツ（8），イタリア（6），日本(16)，メキシコ（3），ポーランド（6），韓国（4），ロシア連邦（6），スペイン（9），台湾（3），タイ(3)，ウクライナ（5），イギリス（7），米国（4）

5) 治験実施期間

最初の被験者のランダム化日：2018 年 6 月 14 日
最後の被験者のランダム化日：2018 年 12 月 24 日
主要解析のデータカットオフ日：2019 年 7 月 4 日

6) 目的

- 主要目的

ペルツズマブとトラスツズマブの混合皮下投与製剤（本剤）におけるサイクル 7 時点（サイクル 8 投与前）の血清中定常状態ペルツズマブ濃度（$C_{trough}$）の非劣性をペルツズマブ静脈内投与（IV）と比較して実証する。

- 副次的目的
  - 本剤におけるサイクル 7 時点（サイクル 8 投与前）の血清中定常状態トラスツズマブ濃度（$C_{trough}$）の非劣性をトラスツズマブ IV と比較して実証する。
  - 本剤の有効性をペルツズマブ IV + トラスツズマブ IV（P + H IV）と比較評価する。
  - 本剤の安全性を P + H IV と比較評価する。

その他の探索的目的には，PK，有効性，免疫原性及びバイオマーカーの評価が含まれた。

7) 試験デザイン

FeDeriCa 試験は，術前／術後補助療法における HER2 陽性早期乳癌患者を対象とした進行中の第 III 相多施設共同非盲検 2 群ランダム化試験である。

8) 被験者数

500 例を 2 つの治療群（P + H IV 群 252 例，本剤群 248 例）のいずれかに 1：1 でランダム化した。

9) 診断及び主要な組入れ基準

腫瘍サイズが ＞ 2 cm 又はリンパ節転移陽性の手術可能又は局所進行／炎症性の HER2 陽性乳癌患者を登録した。

10) 治験薬，投与方法
初回用量（ペルツズマブ 1200 mg + トラスツズマブ 600 mg の SC），維持用量（ペルツズマブ 600 mg + トラスツズマブ 600 mg の SC）を，3 週間毎に 4 サイクル投与。

11) 対照薬，投与方法
初回用量（ペルツズマブ IV 840 mg + トラスツズマブ IV 8 mg/kg），維持用量（ペルツズマブ IV 420 mg + トラスツズマブ IV 6 mg/kg）を，3 週間毎に 4 サイクル投与。ただし，トラスツズマブ SC が日常的に使用されている国では，治験責任（分担）医師の判断で，術後補助療法期間はトラスツズマブ IV からトラスツズマブ SC への切り替えが許容された。

12) アントラサイクリンをベースとした化学療法
P + H IV 又は本剤の投与前に，すべての被験者は以下のいずれかの化学療法を投与された。
- ドキソルビシン IV 60 mg/m$^2$ 及びシクロホスファミド IV 600 mg/m$^2$ を 2 週間毎（ddAC）に 4 サイクル，その後パクリタキセル 80 mg/m$^2$ を 1 週間毎に 12 サイクル。
- ドキソルビシン IV 60 mg/m$^2$ 及びシクロホスファミド IV 600 mg/m$^2$ を 3 週間毎（AC）に 4 サイクル，その後，ドセタキセル IV 75 mg/m$^2$ を 3 週間毎に 4 サイクル（用量制限毒性が生じない場合は 100 mg/m$^2$ に増量可）。

ddAC／AC 投与後，パクリタキセル又はドセタキセルレジメンを，術前補助療法期間は P + H IV 又は本剤と併用して投与した。

13) 評価基準

a. 薬物動態:
- 主要薬物動態評価項目
  サイクル 7（サイクル 8 投与前）の血清中定常状態ペルツズマブ濃度（$C_{trough}$）
- 副次的薬物動態評価項目
  サイクル 7（サイクル 8 投与前）の血清中定常状態トラスツズマブ濃度（$C_{trough}$）

更に，探索的な薬物動態評価項目も評価した。

b. 有効性
- 副次的有効性評価項目
  本剤群の全病理学的完全奏効（tpCR）率を P + H IV 群と比較する。
- その他の副次的有効性評価項目
  浸潤癌無病生存期間（iDFS），イベントフリー生存期間（EFS），遠隔再発までの期間（DRFI）及び全生存期間（OS）は，最終試験報告書に提示する予定である。

更に，探索的な有効性評価項目も評価した。

c. 薬力学
該当せず

d. 安全性
- 副次的安全性評価項目
  - 有害事象及び重篤な有害事象の発現率及び重症度。重症度は National Cancer Institute 有害事象共通用語規準（NCI CTCAE）v4.0 に従って判定。
  - NCI CTCAE v4.0 による臨床検査値異常

- 主要な心臓関連事象
  - ベースラインから 10%ポイント以上の左室駆出率（LVEF）低下かつ LVEF が 50%未満に低下したニューヨーク心臓協会（NYHA）クラス III 又は IV の心不全
  - 心臓死
- 副次的な心臓関連事象
  - ベースラインから 10%ポイント以上の LVEF 低下かつ LVEF が 50%未満に低下した無症候性又は NYHA クラス II の症候性左室収縮機能不全（「駆出率減少」）。なお，約 3 週間以内の再測定で上記の LVEF 低下が再び確認された場合に確定される。

14) 統計的手法

ペルツズマブ及びトラスツズマブの SC と IV の非劣性検定は，多重検定を調整するために階層的な検定手順を用いて実施し，全体の第 1 種過誤率を片側 5%の有意水準に制御した。以下の仮説を検証した。

- $H_0$：SC は IV に対して劣性である［IV に対する SC の $C_{trough}SC$／$C_{trough}IV$ の幾何平均比（GMR）が 0.8 未満］
- $H_1$：SC は IV に対して非劣性である（IV に対する SC の $C_{trough}SC$／$C_{trough}IV$ の GMR が 0.8 以上）

階層的検定手順は，以下のステップに従った。

a. 片側 5%の有意水準で，主要評価項目（サイクル 7 のペルツズマブ血清中 $C_{trough}SC$／$C_{trough}IV$）を検定する。有意であれば，ステップ b へ進み，そうでなければ中止する。
b. 片側 5%の有意水準で，副次的評価項目（サイクル 7 のトラスツズマブ血清中 $C_{trough}SC$／$C_{trough}IV$）を検定する。

ペルツズマブの SC と IV の非劣性は片側検定により評価した。GMR の 90%信頼区間（CI）の下限値が 0.8 以上であれば，帰無仮説が棄却され，非劣性であると結論付けられる。

15) 方法

治験責任医師は，治験実施計画書に規定された術前補助化学療法のいずれかを選択した。音声／ウェブ自動応答システムを利用し，置換ブロックランダム化手順を用いて，被験者を以下の層別因子に従って，2 つの治療群に 1：1 にランダム化した。

- ホルモン受容体の状態（中央検査機関による評価に基づく）：エストロゲン受容体（ER）陽性又はプロゲステロン受容体（PgR）陽性 vs. ER 陰性及び PgR 陰性
- 初診時の臨床病期：II～IIIA 期 vs. IIIB～IIIC 期
- 化学療法の種類：ddAC 後パクリタキセル vs. AC 後ドセタキセル

被験者の登録には腫瘍の大きさ> 2 cm 又はリンパ節転移陽性で， HER2 陽性乳癌であることが中央検査機関で確認されていることが必要とされた。

いずれの群も 8 サイクルの術前補助療法完了後，手術を受けることとした。手術を受けたすべての被験者は，術前補助療法期間に投与したものと同じ抗 HER2 療法を術後補助療法期間に継続して投与した。

すべての被験者は治験薬の投与初日から投与終了又は中止時来院（治験薬最終投与 28 日後）まで追跡調査した。治験薬投与終了後，最終被験者の最終投与から少なくとも 3 年間，被験者の安全性及び有効性を追跡調査することとした。

16) 結果

a. 薬物動態の結果

主要，副次的及び探索的な PK 解析［曝露量-反応関係及び薬物間相互作用（DDI）解析は除く］は，Per Protocol PK（PPP）集団（すなわち，事前に定義した治験実施計画書の基準を遵守した集団）を対象に実施した。
主要評価項目であるサイクル 7（サイクル 8 投与前）のペルツズマブ $C_{trough}$ について，P + H IV 群に対する本剤群の非劣性が検証された。P + H IV 群に対する本剤群の $C_{trough}$ の GMR は 1.22，両側 90%CI の下限値は 1.14 であり，事前に設定した非劣性マージンの 0.8 を上回った。
副次的評価項目であるサイクル 7（サイクル 8 投与前）のトラスツズマブ $C_{trough}$ についても P + H IV 群に対する本剤群の非劣性が検証された。P + H IV 群に対する本剤群の $C_{trough}$ の GMR は 1.33，両側 90%CI の下限値は 1.24 であり，事前に設定した非劣性マージンの 0.8 を上回った。
探索的 PK 解析の結果，初回投与後のペルツズマブ及びトラスツズマブの曝露量は，P + H IV 投与群における標準的な IV 投与と本剤で同等であり，サイクル 5（サイクル 6 投与前）の $C_{trough}$ 値に基づくと曝露量が損なわれないことが示された。曝露量-反応関係の分析では，ペルツズマブ曝露量の増加が tpCR 率の僅かな上昇と関連することが示された。
評価した安全性評価項目（投与に伴う反応，重篤な有害事象，心毒性，あらゆる Grade の過敏症及びアナフィラキシー事象，Grade 3 以上の有害事象，及び Grade 3 以上の下痢と好中球減少症）のいずれについても，曝露量と安全性との間に明確な関連は認められなかった。本剤として投与した場合，トラスツズマブ PK に対するペルツズマブの影響は認められなかった。

b. 有効性の結果

術前補助療法 8 サイクル後に tpCR を達成した intent-to-treat（ITT）集団の被験者の割合は，両群間で同等（P + H IV 群 59.5%，本剤群 59.7%）であり，差は 0.15%（95%CI：−8.67～8.97）であった。事前に規定した複数の臨床的に重要な部分集団を対象とした部分集団解析では，両群間の tpCR 率に顕著な差は認められず，ITT 集団全体の結果との一貫性が示された。
乳癌病理学的完全奏効（bpCR）及び German Breast Group 基準による病理学的完全奏効（GBG pCR）を含む探索的解析の結果は，主な有効性の結果と一致していた。両群の被験者の大半は，術前補助療法により臨床的奏効［完全奏効（CR）又は部分奏効（PR）］を示した。
データカットオフ時点では，被験者が術後補助療法期間中であったため，事象発現までの時間（time-to-event，以下，TTE）の評価項目，すなわち，iDFS，乳癌以外の二次性原発癌を含む iDFS，EFS，乳癌以外の二次性原発癌を含む EFS，DRFI 及び OS の解析にはデータが不十分であった（解析は実施されなかった）。

c. 安全性の結果

本剤群における全体的な安全性プロファイル及び忍容性は，P + H IV 群と同等であった。主な所見は以下のとおりであった:

- 治療への曝露は両群間で均衡がとれており，ほとんどの被験者（P+ H IV 群 96%，本剤群 94.4%）は計画どおりに術前補助療法を完了した。
- ほぼ全ての被験者が少なくとも 1 件の有害事象を経験した（P + H IV 群 99.6%，本剤群 100.0%）。
- 高頻度に報告された（いずれかの群で 30%以上の発現率）全 Grade の有害事象（P + H IV 群，本剤群の順）は，脱毛症（70.2%，77.0%），悪心（60.3%，58.9%），下痢（55.2%，58.5%），貧血（40.9%，33.9%），無力症（30.2%，28.2%）であった。

- 有害事象，重篤な有害事象，Grade 3 以上の有害事象，抗 HER2 療法の投与中止に至った有害事象を 1 件以上発現した被験者の割合は，両群間で同様であった。
- 主要な心臓関連事象の発現率は低かった［P + H IV 群なし，本剤群 2 例（0.8%）］。
- 副次的な心臓関連事象の発現率（ベースラインから 10%ポイント以上の LVEF 低下かつ LVEF が 50%未満に低下し，約 3 週間以内の再測定で LVEF 低下が確認されたものと定義）は低く，P + H IV 群では 2 例（0.8%），本剤群では 1 例（0.4%）であった。
- 注目すべき有害事象の発現率は，HER2 陽性乳癌試験においてトラスツズマブと化学療法との併用試験で認められた既知のペルツズマブの安全性プロファイルとも一致していた。
  - 下痢の発現率及び重症度は，両群間で同等であり（P+ H IV 群 55.2%，本剤群 58.5%），大部分は軽度であった。
  - 好中球減少症／発熱性好中球減少症／白血球減少症の発現率及び重症度は，両群間で同等であった（P+ H IV 群 52.8%，本剤群 48.0%）。
  - 全体として，アナフィラキシー及び過敏症の発現率及び重症度は，両群とも低く（P + H IV 群 2%，本剤群 1.6%），ほとんどが軽度であった。
  - 抗 HER2 療法から 24 時間以内に発生した投与に伴う反応は，P + H IV 群と比較して本剤群でわずかに高かった（P + H IV 群 13.5%，本剤群 17.3%），大部分は軽度であった。

d. 免疫原性試験の結果

Treatment Emergent 抗薬物抗体（ADA）の発現率は，両群間で同等であった。P + H IV 群では，ペルツズマブ及びトラスツズマブに対する Treatment Emergent ADA の発現率は，それぞれ 3.0%（7/237 例）及び 0.4%（1/237 例）であった。本剤群では，ペルツズマブ，トラスツズマブ及び rHuPH20 に対する Treatment Emergent ADA の発現率は，それぞれ 4.8%（11/231 例），0.9%（2/232 例）及び 0.9%（2/225 例）であった。探索的解析では，ペルツズマブ，トラスツズマブ及び rHuPH20 に対する Treatment Emergent ADA の発現は，PK，有効性又は安全性に関して明らかな臨床的影響を及ぼさないことが示された。

17) 結論

FeDeriCa 試験の主要解析結果から，HER2 陽性早期乳癌患者において，サイクル 7（サイクル 8 投与前）のペルツズマブ及びトラスツズマブ $C_{trough}$ について，既承認の P + H IV に対する本剤の非劣性が示された。

tpCR 率は両群間で同等（P + H IV 群 59.5%，本剤群 59.7%）であり，本剤の有効性は P + H IV と同等であった。これらの結果は，ペルツズマブ，トラスツズマブ及び化学療法を用いた他の術前補助療法の試験で観察された tpCR 率と一致している。

全体として，本剤の投与経路（SC）に関連する投与に伴う反応（ARR）を除いて，本剤群と P + H IV 群の安全性の結果は同等であり，HER2 陽性乳癌を対象としてペルツズマブをトラスツズマブ及び化学療法と併用投与した際の既知の安全性プロファイルと一致していた。ARR はほとんどが軽度であった。新たな又は予想外の毒性は認められなかった。

ADA のベースライン後の発現率は低く，P + H IV 群と本剤群で同等であった。ADA の発現は，PK，有効性又は安全性に関して明らかな臨床的影響を及ぼさないことが示された。

結論として，P + H IV と本剤の PK の非劣性及び有効性と安全性の同等性を考慮すると，本剤は FeDeriCa 試験の主要解析で良好なベネフィットリスクが確立され，HER2 陽性乳癌に対して侵襲性が低く迅速な投与方法を提供すると考えられた。

18) 報告書作成日

20[redacted]年 [redacted]月

## 2.7.6.1.2 MO40628試験（PHranceSCa 試験）

### 2.7.6.1.2.1 Interim CSR

1) 試験の標題

A Randomized, Multicenter, Open-label Cross-over Study to Evaluate Patient Preference and Satisfaction of Subcutaneous Administration of the Fixed-dose Combination of Pertuzumab and Trastuzumab in Patients with HER2-positive Early Breast Cancer.

2) フェーズ

第 II 相

3) 治験依頼者

F. Hoffmann-La Roche 社

4) 治験責任医師／治験実施国（施設数）

治験調整医師：[redacted]

12 カ国 32 施設，多施設国際共同試験

アルゼンチン（2），ブラジル（4），チリ（1），フィンランド（2），香港（2），レバノン（1），パナマ（2），ポルトガル（3），セルビア（2），スペイン（2），スウェーデン（2），米国（9）

5) 治験実施期間

最初の被験者の登録日：2018 年 12 月 18 日

中間解析のデータカットオフ日：2019 年 8 月 20 日

6) 目的

- 主要目的

被験者選好質問票（Patient Preference Questionnaire，PPQ）の質問 1 に対する被験者の回答に基づいて，本剤に対する被験者の選好度を評価する。

- 副次的目的
  - Therapy Administration Satisfaction Questionnaire（TASQ）-SC 及び TASQ-IV の質問 1 に対する被験者の回答に基づく，本剤及び P + H IV に対する満足度。
  - 試験期間中に本剤を選択した被験者の割合に基づく，治療継続期間における被験者の本剤選択率。
  - 治療クロスオーバー期間及び全補助療法投与期間（治療クロスオーバー期間 + 治療継続期間）における本剤及び P + H IV の安全性及び忍容性
  - 本剤から P + H IV 及び P + H IV から本剤への切り替え時の安全性

7) 試験デザイン

本試験は多施設国際共同ランダム化非盲検クロスオーバー試験である。

被験者は以下の治療群に 1：1 でランダム化された。

- A 群：P + H IV を 3 サイクル投与後，本剤を 3 サイクル投与
- B 群：本剤を 3 サイクル投与後，P + H IV を 3 サイクル投与

両群における 3 + 3 サイクルの期間は，治療クロスオーバー期間とし，本剤及び P + H IV が合計 6 サイクル投与された。試験登録前に術前補助療法として投与されたペルツズマブ及びトラスツズマブ治療サイクルは，被験者に対して計画された合計 18 サイクルの抗 HER2 療法サイクルの一部とした。治療クロスオーバー期間終了後，被験者は治療継続期間に移行し，本剤または P + H IV のいずれかを選択して，合計 18 サイクル投与することとした。

8) 被験者数
少なくとも 126 例の評価可能な被験者を得るために，約 140 例の患者をランダム化することが計画された。
データカットオフ日（2019 年 8 月 20 日）時点で，118 例が登録され，A 群に 56 例，B 群に 62 例がランダム化された。

9) 診断及び主要な組入れ基準
組織学的に確認された HER2 陽性の炎症性，局所進行性又は早期乳癌の成人患者で，術前補助療法（ペルツズマブ及びトラスツズマブ）及び術前補助化学療法の完了後に乳癌の手術を受けた患者

10) 治験薬，投与方法
本剤は，体重に基づかない固定用量で，以下の 2 つの用量構成で 3 週間毎に大腿部に投与した。
- 初回用量：ペルツズマブ 1200 mg + トラスツズマブ 600 mg の SC
- 維持用量：ペルツズマブ 600 mg + トラスツズマブ 600 mg の SC

被験者は治療クロスオーバー期間中に 3 サイクルの投与を受けた。治療クロスオーバー期間終了後，被験者は治療継続期間に移行し，本剤又は P + H IV のいずれかを選択して 18 サイクルの予定サイクルを完了した。

11) 対照薬，投与方法
ペルツズマブ IV は体重に基づかない固定用量で，以下の 2 つの用量構成で 3 週間毎に投与された。
- 初回用量：840 mg IV
- 維持用量：420 mg IV

トラスツズマブ IV は体重に基づいて，以下の 2 つの用量構成でペルツズマブの投与及び観察期間終了後に 3 週間毎に投与された。
- 初回用量：8 mg/kg IV
- 維持用量：6 mg/kg IV

被験者は治療クロスオーバー期間中に 3 サイクルの投与を受けた。治療クロスオーバー期間終了後，被験者は治療継続期間に移行し，本剤又は P + H IV のいずれかを選択して 18 サイクルの予定サイクルを完了した。

12) 評価基準
a. 患者報告アウトカム
- 被験者の本剤に対する選好度
- 本剤及び P + H IV に対する被験者の満足度
- 治療継続期間中の本剤の選択率

b. 有効性
本総括報告書では該当しない。

c. 安全性
有害事象，標準的な臨床検査評価，バイタルサイン，Eastern Cooperative Oncology Group の全身状態（ECOG PS），心電図及び製剤の切り替え。

13) 統計的手法

患者報告アウトカム：正式な仮説検定は計画されなかった。すべての変数を記述的に要約した。

安全性：すべての安全性パラメータを記述的に要約した。

14) 結果

a. 患者報告アウトカムの結果

i. 被験者選好：被験者の大多数は P + H IV 投与（17.6%）よりも本剤投与（82.4%，95%CI：69.13%～91.60%）を好んだ。多く報告された選好理由は，「診療所での所要時間が短い」ことと「投与の負担が少ない」ことであった。本剤投与を好んだ被験者の大半（85.7%）は，「非常に強い」又は「かなり強い」選好を示したのに対し，P + H IV 投与を好んだ被験者で「非常に強い」又は「かなり強い」選好を示した被験者は 44.4%であった。

ii. 被験者満足度：被験者選好の結果は，被験者満足度によって支持された。大多数の被験者（90.2%）は本剤投与に「非常に満足」又は「満足」であったのに対し，P + H IV 投与の被験者で「非常に満足」又は「満足」であった被験者は 66.7%であった。本剤と P + H IV の両方での経験について具体的な質問をすると，被験者は本剤投与がより制限の少ない投与経路であり，他の活動のためのより多くの時間を許したと回答することが多かった。

iii. 被験者の薬剤選択：治療継続期間中に本剤投与を選択した被験者の割合と，治療継続期間中の本剤投与による治療継続を好むと回答した被験者の割合は 84.2%で一致していた。

b. 有効性の結果

有効性評価項目の解析については，最終総括報告書に報告する。

c. 安全性の結果

- 中間解析のデータカットオフ時点（投与サイクル数の中央値は 6 サイクル）の安全性プロファイルでは，本剤及び P + H IV は全般的に忍容性が良好であり，本剤投与で新たな安全性のシグナルは認められなかった。P + H IV 製剤と本剤の切り替え（及びその逆）では新たな又は臨床的に重要な安全性上の懸念点は認められなかった。発現した有害事象は P + H IV 及び本剤投与に関する過去の臨床試験と一致していた。
- 多くの被験者で少なくとも 1 件の有害事象が発現した［81/116 例（69.8%）］。
  - 治療クロスオーバー期間中，有害事象の発現率は，P + H IV 投与時（55.7%）と比較して，本剤投与時（61.3%）にわずかに高かった。
- 報告された有害事象の多くは，重症度が Grade 1 又は 2 であった。
  - 試験期間中に Grade 3 の有害事象が 5 例に認められた（本剤投与時 3.2%，P + H IV 投与時 2.3%）。いずれも治療クロスオーバー期間中に発現した。
- 約 1/3 の被験者で治験薬との因果関係が否定できない有害事象が 1 件以上発現した［44/116 例（37.9%）］。
  - 治療クロスオーバー期間中に報告された治験薬との因果関係がある有害事象の発現率は，本剤投与時（37.6%）が P + H IV 投与時（14.8%）に比べて高く，その大部分は ARR であった。
- 試験期間中，約 1/4 の被験者［28/116 例（24.1%）］に 1 件以上の ARR が認められた。発現した ARR はいずれも Grade 1 又は 2 であった。

- 治療クロスオーバー期間中に報告された ARR の発現率は，P + H IV 投与時（3.4%）と比較して，本剤投与時（24.7%）に高かった。
- 本剤投与と関連する局所注射部位反応は 21/116 例（18.1%）に認められた。
- P + H IV 投与と関連する局所注入部位反応はいずれの投与群でも認められなかった。
- 本剤投与と関連する全身性の注射に伴う反応は 2/116 例（1.7%）に認められた。
- P + H IV 投与と関連する全身性の注入に伴う反応は 3/116 例（2.6%）に認められた。
- アナフィラキシー及び過敏症に関連する ARR はいずれも治療クロスオーバー期間の本剤投与時に 2/116 例（1.7%）に認められ，重症度は Grade 1 又は 2 であった。

- 試験期間中，死亡は報告されなかった。
- 重篤な有害事象は，治療クロスオーバー期間中の P + H IV 投与時に 1 例（発熱，Grade 1）認められた。
- 治験薬の投与中止に至った有害事象は認められなかった。
- 治験薬の休薬に至った有害事象は 4 例で少なくとも 1 件以上発現した（本剤投与時 1.1%，P + H IV 投与時 3.4%）。いずれも治療クロスオーバー期間中に発現した。
- 心臓関連の有害事象は治療クロスオーバー期間の本剤投与時に 1 例（不整脈，Grade 1）に発現した。
- 症候性の左心室機能障害（LVD）/うっ血性心不全（CHF）は 4 例（本剤投与時 1.1%，P + H IV 投与時 3.4%）で認められた。いずれも治療クロスオーバー期間中に発現し，2 例は重症度が Grade 3 であった（いずれも B 群）。

15) 結論

- PHranceSCa 試験の中間解析の結果，大多数の被験者が早期乳癌の治療のために P + H IV 投与（17.6%）よりも本剤投与（82.4%）を好むことを示した。多く報告された選好理由は，「診療所での所要時間が短い」ことと「投与の負担が少ない」ことであった。
- 被験者選好の結果は，被験者満足度によって支持された。大多数の被験者（90.2%）は本剤投与に「非常に満足」又は「満足」していた。更に，治療継続期間中に本剤投与による治療継続を選択した被験者は 84.2%であり，被験者選好の結果を支持する結果であった。
- 全体的な安全性プロファイルは，本剤の忍容性が良好であることを示した。新たな安全性シグナルは認められず，認められた有害事象は，P + H IV 投与を用いた過去の臨床試験で得られている結果と一致していた。投与経路に関する有害事象の発現率の違いは Grade 1 又は 2 の局所注射部位反応によるものであり，IV 投与では局所注入部位反応の報告がなく，SC による投与方法が原因であると考えられた。
- P + H IV から本剤への切り替え，又はその逆の切り替えにおいても被験者の忍容性は良好であり，本中間解析のデータカットオフ時点では，新たな又は臨床的に重要な安全性上の懸念は認められなかった。

16) 報告書作成日

20[redacted] 年 [redacted] 月

### 2.7.6.1.2.2 Primary CSR

1) 試験の標題

A Randomized, Multicenter, Open-label Cross-over Study to Evaluate Patient Preference and Satisfaction of Subcutaneous Administration of the Fixed-dose Combination of Pertuzumab and Trastuzumab in Patients with HER2-positive Early Breast Cancer.

2) フェーズ

第 II 相

3) 治験依頼者

F. Hoffmann-La Roche 社

4) 治験責任医師／治験実施国（施設数）

治験調整医師：[redacted]

16 カ国 39 施設，多施設国際共同試験

アルゼンチン（2），ブラジル（4），チリ（1），フィンランド（2），香港（2），ヨルダン（1），レバノン（2），メキシコ（3），パナマ（2），ポルトガル（3），カタール（1），サウジアラビア（1），セルビア（2），スペイン（2），スウェーデン（2），米国（9）

5) 治験実施期間

最初の被験者の登録日：2018 年 12 月 18 日

主要解析のデータカットオフ日：2020 年 2 月 24 日

6) 目的

- 主要目的

PPQ の質問 1 に対する被験者の回答に基づいて，本剤に対する被験者の選好度を評価する。

- 副次的目的
  - TASQ-SC 及び TASQ-IV の質問 1 に対する被験者の回答に基づく，本剤及び P + H IV に対する被験者の満足度。
  - 試験期間中に本剤を選択した被験者の割合に基づく，治療継続期間における被験者の本剤選択率。
  - Healthcare Professional Questionnaires（HCPQ）の個々の質問に対する医療従事者の回答に基づく，本剤による時間／資源利用と利便性に関する医療従事者の認識。
  - European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30（EORTC QLQ-C30 質問票）により評価したベースラインからの症状及び機能の変化に基づく，本剤及び P + H IV の健康関連の質（HRQoL），EORTC QLQ-C30 の全般的健康状態（GHS）/全般的 QOL 尺度（項目 29 及び 30）により評価したサイクル別の HRQoL の平均スコア及びベースラインからの平均変化量。
  - 治療クロスオーバー期間及び全補助療法投与期間（治療クロスオーバー期間 + 治療継続期間）における本剤及び P + H IV の安全性及び忍容性
  - 本剤から P + H IV 及び P + H IV から本剤への切り替え時の安全性

7) 試験デザイン

本試験は多施設国際共同ランダム化非盲検クロスオーバー試験である。

被験者は以下の治療群に 1：1 でランダム化された。

- A 群：P + H IV を 3 サイクル投与後，本剤を 3 サイクル投与
- B 群：本剤を 3 サイクル投与後，P + H IV を 3 サイクル投与

両群における 3 + 3 サイクルの期間は，治療クロスオーバー期間とし，本剤及び P + H IV が合計 6 サイクル投与された。試験登録前に術前補助療法として投与されたペルツズマブ及びトラスツズマブ治療サイクルは，被験者に対して計画された合計 18 サイクルの抗 HER2 療法サイクルの一部とした。治療クロスオーバー期間終了後，被験者は治療継続期間に移行し，本剤又は P + H IV のいずれかを選択して，合計 18 サイクル投与することとした。

8) 被験者数
少なくとも 126 例の評価可能な被験者を得るために約 140 例の被験者をランダム化することが計画された。
データカットオフ（2020 年 2 月 24 日）時点で，160 例が登録され，A 群に 80 例，B 群に 80 例がランダム化された。

9) 診断及び主要な組入れ基準
組織学的に確認された HER2 陽性の炎症性，局所進行性又は早期乳癌の成人患者で，術前補助療法（ペルツズマブ及びトラスツズマブ）及び術前補助化学療法の完了後に乳癌の手術を受けた患者

10) 治験薬，投与方法
本剤は，体重に基づかない固定用量で，以下の 2 つの用量構成で 3 週間毎に大腿部に投与した。
- 初回用量：ペルツズマブ 1200 mg + トラスツズマブ 600 mg の SC
- 維持用量：ペルツズマブ 600 mg + トラスツズマブ 600 mg の SC

被験者は治療クロスオーバー期間中に 3 サイクルの投与を受けた。治療クロスオーバー期間終了後，被験者は治療継続期間に移行し，本剤又は P + H IV のいずれかを選択して 18 サイクルの予定サイクルを完了した。

11) 対照薬，投与方法
a. ペルツズマブ IV は体重に基づかない固定用量で，以下の 2 つの用量構成で 3 週間毎に投与された。
- 初回用量：840 mg IV
- 維持用量：420 mg IV

b. トラスツズマブ IV は体重に基づいて，以下の 2 つの用量構成でペルツズマブの投与及び観察期間終了後に 3 週間毎に投与された。
- 初回用量：8 mg/kg IV
- 維持用量：6 mg/kg IV

被験者は治療クロスオーバー期間中に 3 サイクルの投与を受けた。治療クロスオーバー期間終了後，被験者は治療継続期間に移行し，本剤又は P + H IV のいずれかを選択して 18 サイクルの予定サイクルを完了した。

12) 評価基準
a. 患者報告アウトカム:
- 被験者の本剤に対する選好度
- 本剤及び P + H IV に対する被験者の満足度
- 治療継続期間中の本剤の選択率
- 被験者の GHS/全般的 QOL 尺度，機能及び治療関連症状

b. 医療従事者の認識
本剤による時間／資源利用と利便性に関する医療従事者の認識

c. 有効性
本総括報告書では該当しない。

d. 安全性
有害事象，標準的な臨床検査評価，バイタルサイン，ECOG PS，心電図及び製剤の切り替え。

13) 統計的手法
患者報告アウトカム及び医療従事者の認識：正式な仮説検定は計画されなかった。すべての変数を記述的に要約した。
安全性：すべての安全性パラメータを記述的に要約した。

14) 結果
a. 患者報告アウトカムの結果
i. 被験者選好：被験者の大多数は P + H IV 投与（13.8%）よりも本剤投与（85.0%；95%CI：78.5%～90.2%）を好み，好みがない被験者は 2 例（1.3%）のみだった。多く報告された選好理由は，「診療所での所要時間が短い」ことと「投与の負担が少ない」ことであった。本剤投与を好んだ被験者の大半（92.6%）は，「非常に強い」又は「かなり強い」選好を示したのに対し，P + H IV 投与を好んだ被験者で「非常に強い」又は「かなり強い」選好を示した被験者は 63.6%であった。
ii. 被験者満足度：被験者選好の結果は，被験者満足度によって支持された。大多数の被験者（88.1%）は本剤投与に「非常に満足」又は「満足」であったのに対し，P + H IV 投与の被験者で「非常に満足」又は「満足」であった被験者は 67.5%であった。本剤と P + H IV の両方での経験について具体的な質問をすると，被験者は本剤投与がより制限の少ない投与経路であり，他の活動のためのより多くの時間を許したと回答することが多かった。
iii. 被験者の薬剤選択：治療継続期間中に本剤投与を選択した被験者の割合と，治療継続期間中の本剤投与による治療継続を好むと回答した被験者の割合は 86.9%で一致していた。
iv. HRQoL：治療関連症状，機能及び GHS/HRQoL に関する EORTC QLQ-C30 質問票に対する被験者の回答は，治療クロスオーバー期間中に大きな変化を示さなかった。

b. 医療従事者の認識結果
本剤に対する被験者選好と同様に，医療従事者は被験者にとって P + H IV 投与よりも本剤投与が好ましいことを示した。また，医療従事者は本剤投与による大幅な時間の節約と投与時の資源利用の減少を示した。本剤投与の準備時間中央値は 5 分，投与時間中央値は 7～8 分であったのに対し，P + H IV 投与の準備時間中央値は 15～20 分，投与時間中央値は 60～150 分であった。また，本剤投与のために被験者が治療室で過ごした全体時間の中央値は 33～50 分であったのに対し，P + H IV 治療では 130～300 分であった。

c. 有効性の結果
有効性評価項目の解析については，最終総括報告書に報告する。

d. 安全性の結果

- 本主要解析のデータカットオフ時点（投与サイクル数の中央値は 11 サイクル）の安全性プロファイルでは，本剤及び P + H IV は忍容性が良好であり，本剤投与による新たな安全性のシグナルは認められなかった。発現した有害事象は P + H IV 及び本剤投与に関する過去の臨床試験と一致していた。P + H IV 製剤と本剤の切り替え（及びその逆）では新たな又は臨床的に重要な安全性上の懸念点は認められなかった。
- 多くの被験者で少なくとも 1 件の有害事象が発現した［144/160 例（90.0%）］。
  - 治療クロスオーバー期間中：本剤投与時 75.0%（120/160 例），P + H IV 投与時 70.6%（113/160 例）。
  - 治療継続期間中：本剤投与時 51.1%（70/137 例），P + H IV 投与時 61.9%（13/21 例）。
- 報告された有害事象の多くは，重症度が Grade 1 又は 2 であった。
  - 治療クロスオーバー期間中に報告された Grade 3 の有害事象の発現率は，本剤投与時に 2.5%（4/160 例），P + H IV 投与時に 3.8%（6/160 例）であった。
  - 治療継続期間中に報告された Grade 3 の有害事象の発現率は，本剤投与時に 2.9%（4/137 例），P + H IV 投与時に 9.5%（2/21 例）であった。
- 約半数の被験者で治験薬との因果関係が否定できない有害事象が 1 件以上発現した［79/160 例（49.4%）］。
  - 治療クロスオーバー期間中：本剤投与時 36.3%（58/160 例），P + H IV 投与時 18.8%（30/160 例）。
  - 治療継続期間中：本剤投与時 19.7%（27/137 例），P + H IV 投与時 9.5%（2/21 例）。
- 重篤な有害事象は 10/160 例（6.3%）で報告された。
  - 治療クロスオーバー期間中：本剤投与時 1.3%（2/160 例），P + H IV 投与時 3.8%（6/160 例）。
  - 治療継続期間中：本剤投与時 2.2%（3/137 例），P + H IV 投与時 0%。
- 心臓関連の有害事象は 9/160 例（5.6%）で報告された。
  - 治療クロスオーバー期間中：本剤投与時 3.1%（5/160 例），P + H IV 投与時 1.9%（3/160 例）。
  - 治療継続期間中：本剤投与時 0.7%（1/137 例），P + H IV 投与時 0%。
- 試験期間中，死亡に至った有害事象は報告されなかった。
- 治験薬の投与中止に至った有害事象は，2/160 例（1.3%）で報告された。
  - 治療クロスオーバー期間中：1/160 例（0.6%）が有害事象により本剤の投与中止に至った。
  - 治療継続期間中：1/21 例（4.8%）が有害事象により P + H IV の投与中止に至った。
- 治験薬の休薬に至った有害事象は，9/160 例（5.6%）で報告された。
  - 治療クロスオーバー期間中：本剤投与時 1.3%（2/160 例），P + H IV 投与時 1.9%（3/160 例）。
  - 治療継続期間中：本剤投与時 2.2%（3/137 例），P + H IV 投与時 4.8%（1/21 例）。
- 試験期間中，約半数の被験者に少なくとも 1 件の注目すべき有害事象が発現した［89/160 例（55.6%）］。発現した事象の大半は Grade 1 又は 2 の重症度であった。
  - アナフィラキシー及び過敏症の有害事象は 4/160 例（2.5%）に認められ，いずれも本剤投与時であり，全て Grade 1 又は 2 であった。
  - ARR は 52/160 例（32.5%）に認められ，いずれも Grade 1 又は 2 であった。
    - 治療クロスオーバー期間中：本剤投与時 23.8%（38/160 例），P + H IV 投与時 5.6%（9/160 例）。
    - 治療継続期間中：本剤投与時 9.5%（13/137 例），P + H IV 投与時 0%。
    - 本剤投与と関連する局所注射部位反応は，治療クロスオーバー期間中及び治療継続期間中にそれぞれ 36/160 例（22.5%）及び 10/137 例（7.3%）で認められた。

- P + H IV 投与と関連する局所注入部位反応は，治療クロスオーバー期間中に 1/160 例（0.6%）で認められた。
- 本剤投与と関連する全身性の注射に伴う反応は，治療クロスオーバー期間中及び治療継続期間中にそれぞれ 3/160 例（1.9%）及び 2/137 例（1.5%）で認められた。
- P + H IV 投与と関連する全身性の注入に伴う反応は，治療クロスオーバー期間中に 6/160 例（3.8%）で認められた。

– 心機能障害は 11/160 例（6.9%）に認められた。
- 治療クロスオーバー期間中：本剤投与時 2.5%（4/160 例），P + H IV 投与時 3.1%（5/160 例）。P + H IV 投与では Grade 3 の事象が 1 件認められた。
- 治療継続期間中：本剤投与時 2.2%（3/137 例），P + H IV 投与時 0%。

– Grade 3 以上の下痢は治療クロスオーバー期間の本剤投与時に 1/160 例（0.6%）に認められた。
– 追加のハーセプチン特異的な「アナフィラキシー及び IRR」の基本語（PT）のグループ分けを用いて，潜在的な肺動脈起源の特定の事象，肺動脈事象（ARR）を同定した。これらの事象は 45/160 例（28.1%）で認められた。本剤投与時の 1 件は Grade 3 の事象であった。これらの事象の大半は ARR であり，肺に由来する事象ではなかったことは注目すべきである。
– 妊娠及び新生児関連の事象は，治療クロスオーバー期間中の本剤投与時に 1/160 例（0.6%）で認められ，Grade 2 の事象であった。
– 間質性肺疾患は，治療継続期間中の本剤投与時に 1/137 例（0.7%）に認められ，Grade 1 の事象であった。
– 好中球減少症／発熱性好中球減少症／白血球減少症の有害事象は 12/160 例（7.5%）に認められた。
- 治療クロスオーバー期間中：本剤投与時 1.9%（3/160 例），P + H IV 投与時 5.0%（8/160 例）。P + H IV 投与時に Grade 3 の事象が 1 件認められた。
- 治療継続期間中：本剤投与時 2.2%（3/137 例），P + H IV 投与時 0%。Grade 3 の事象が 1 件認められた。

15) 結論

- PHranceSCa 試験の主要解析の結果，大多数の被験者が P + H IV 投与（13.8%）よりも本剤投与（85.0%）を好み，好みがない被験者は 2 例（1.3%）のみであることを示した。多く報告された選好理由は，「診療所での所要時間が短い」ことと「投与の負担が少ない」ことであった。
- 被験者選好の結果は，被験者満足度によって支持された。大多数の被験者（88.1%）は本剤投与に「非常に満足」又は「満足」していた。更に，治療継続期間中に本剤投与による治療継続を選択した被験者は 86.9%であり，被験者選好の結果を支持する結果であった。
- また，医療従事者の認識でも，調製及び投与のための大幅な時間節約ができること，少ない利用資源ですむこと，並びに被験者が治療室で過ごす全体の時間を短縮できることより，被験者にとって P + H IV 投与より本剤投与が好ましいことが示された。
- 全体的な安全性プロファイルから，本剤の忍容性は良好であることが示された。新たな安全性シグナルは認められず，認められた有害事象は P + H IV 投与を用いた過去の臨床試験で得られている結果と一致していた。投与経路に関する有害事象の違いは Grade 1 又は 2 の局所注射部位反応によるものであり，IV 投与では局所注入部位反応の報告がなく，SC による投与方法が原因であると考えられた。
- P + H IV から本剤への切り替え，又はその逆の切り替えにおいても被験者の忍容性は良好であり，新たな又は臨床的に重要な安全性上の懸念は認められなかった。
- PHranceSCa 試験の安全性結果は，FeDeriCa 試験の本剤の安全性結果を支持している。

16) 報告書作成日
20[redacted] 年 [redacted] 月

### 2.7.6.1.3 BO30185試験

1) 試験の標題
A PHASE I, OPEN-LABEL, TWO-PART, MULTICENTER PERJETA® SUBCUTANEOUS DOSE-FINDING STUDY IN COMBINATION WITH HERCEPTIN® IN HEALTHY MALE VOLUNTEERS AND FEMALE PATIENTS WITH EARLY BREAST CANCER.

2) フェーズ
第 Ib 相

3) 治験依頼者
F. Hoffmann-La Roche 社

4) 治験責任医師／治験実施施設及び国
[redacted]，Christchurch Clinical Studies Trust，ニュージーランド
[redacted]，Auckland Clinical Studies，ニュージーランド

5) 治験実施期間
最初の被験者の登録日：2016 年 6 月 23 日
最終被験者の最終来院日：2018 年 5 月 31 日（データカットオフ日）

6) 目的
- Part 1（用量設定）

本試験の Part 1 の主な目的は，以下のとおりであった。
- ペルツズマブ SC を単剤注射（最終的にはトラスツズマブ SC との同時併用）した場合に，ペルツズマブ IV と同等の曝露をもたらすペルツズマブ SC の初回用量及び維持用量を選択する。
- ペルツズマブ SC をトラスツズマブ SC と混合して 1 回で注射（同時混合）した場合に，ペルツズマブ IV と同等の曝露をもたらすペルツズマブ SC の初回用量及び維持用量を選択する。
- ペルツズマブ SC とトラスツズマブ SC を投与直前に混合した SC 製剤を投与した場合に，rHuPH20 の追加が必要かどうかを評価する。

- Part 2（用量確認）

本試験の Part 2 の主な目的は，以下のとおりであった。
- トラスツズマブ SC との併用投与の一環としてペルツズマブ SC を単剤投与する場合の維持用量を確認する。
- トラスツズマブ SC と投与直前に混合した SC 製剤として投与（混合投与）する場合，又は本剤として投与する場合のペルツズマブ SC の維持用量を確認する。

7) 試験デザイン
本試験はペルツズマブ SC の非盲検，二部構成，多施設共同試験であった。
本試験の Part 1 は健康男性ボランティアを対象とした用量設定試験であり，ペルツズマブ SC の初回用量及び維持用量を決定した。ペルツズマブ SC を 2 つの投与方法で評価する（ペルツズマブ SC を単剤注射，又はペルツズマブ SC をトラスツズマブ SC と混合して 1 回の注射で投与）。
本試験の part 2 は早期乳癌女性患者を対象とした用量確認試験であった。Part 2 コホート B ではペルツズマブ SC をトラスツズマブ SC と混合して投与（両剤を 1 回の注射で投与），

Part 2 コホート C ではペルツズマブ SC をトラスツズマブ SC との配合剤として投与［両剤を配合し 1 つの配合剤（本剤）として投与］した。
Part 2 では，ペルツズマブ SC の用量確認，並びに第 III 相試験前の混合投与コホート及び本剤投与コホートの薬物動態（PK）の検討が行われた。

8) 患者数
Part 1：健康男性ボランティア 48 例が登録された（コホート 1～8 に各 6 例）。
Part 2：早期乳癌女性患者 40 例が登録された（コホート B 及び C に各 20 例）。

9) 診断及び主要な組入れ基準
Part 1：18～45 歳の健康男性ボランティア，body mass index（BMI）は 18～32 kg/$m^2$。
Part 2：以下を満たす 18 歳以上の早期乳癌女性患者：
- 適切な外科的処置で治療された。
- 治験薬投与前 7 カ月より前に標準（術前）術後療法（化学療法／生物学的）を終了した。
- 該当する場合は放射線療法で治療された。

ベースライン時の LVEF ≥ 55%（ECHO 又は MUGA スキャンにより測定）。

10) 治験薬
ペルツズマブ 600 mg，トラスツズマブ 600 mg /10 mL 固定用量混合 注射用液剤
ペルツズマブ 600 mg/5 mL 注射用液剤（rHuPH20 非含有）
ペルツズマブ 600 mg/5 mL 注射用液剤（rHuPH20 含有）
ペルツズマブ 420 mg/14 mL 高濃度注射用液剤
トラスツズマブ 600 mg/5 mL 注射用液剤

11) 投与量/投与経路/用法/期間
全ての健康男性ボランティア及び患者は単回投与を受けた。
Part 1
コホート 1：420 mg ペルツズマブ IV（対照群）
コホート 2：400 mg ペルツズマブ SC
コホート 3：600 mg ペルツズマブ SC
コホート 4：1200 mg ペルツズマブ SC
コホート 5：600 mg トラスツズマブ SC（対照群）
コホート 6：400 mg ペルツズマブ SC + 600 mg トラスツズマブ SC（混合）
コホート 7：1200 mg ペルツズマブ SC + 600 mg トラスツズマブ SC（混合）
コホート 8：1200 mg ペルツズマブ SC（rHuPH20 非含有）+ 600 mg トラスツズマブ SC（混合）

Part 2
コホート B：600 mg ペルツズマブ SC + 600 mg トラスツズマブ SC（混合）。
コホート C：600 mg ペルツズマブ SC + 600 mg トラスツズマブ SC の配合剤［両剤を配合し 1 つの配合剤（本剤）として投与］

12) 併用薬，投与量，投与方法
該当なし

13) 評価基準
a. 有効性

本試験では有効性評価は行われなかった。

b. 薬力学
本試験では薬力学的評価は行われなかった。

c. 薬物動態
Part 1の PK データはノンコンパートメント解析（NCA）を用いて解析し，以下のパラメータを推定した；血清トラフ濃度（$C_{trough}$），0時間から無限大時間まで外挿した血清中薬物濃度-時間曲線下面積（$AUC_{0\text{-}inf}$），最高血清中濃度（$C_{max}$），最高血清中濃度到達時間（$T_{max}$）。更に，ペルツズマブの薬物動態を記述するために母集団薬物動態（popPK）モデルを構築し，popPK モデルに基づく臨床試験シミュレーションを用いて Part 2のペルツズマブ SC の投与量を選択した。
Part 2（コホート B 及び C）の PK データも NCA を用いて解析した。popPK モデル及び popPK モデルに基づく臨床試験シミュレーションをこの追加データで更新した。Part 2 の PK データにより，早期乳癌患者集団におけるペルツズマブ SC の投与量が確認された。第 Ib 相試験のデータに基づき，第 III 相試験のペルツズマブ SC の推奨初回用量及び維持用量が設定された。

d. 免疫原性
ペルツズマブ，トラスツズマブ及び rHuPH20の免疫原性解析：投与期間中及びフォローアップ期間中の ADA の発現例数及び割合（ADA 陽性及び ADA 陰性）。

e. 安全性
本試験の安全性パラメータは，治験実施計画書に規定された安全性に関する臨床検査，バイタルサイン，心電図，左室駆出率（LVEF）からなり，試験スケジュールに従って評価した。重篤な有害事象，注目すべき有害事象，AESI，死亡を含む有害事象は，治験薬との因果関係に関わらず，治験薬最終投与後85日目まで継続的にモニタリングした。
85日後に継続中の事象又は85日以降に発現した治験薬と因果関係のある有害事象は，治験薬投与7カ月後の追跡調査までモニタリングした。

14) 統計的手法
本試験は探索的試験であり，正式な仮説検定は実施されなかった。各コホートの結果を記述的に要約する。
Part 1 及び Part 2 の症例数はシミュレーション法を用いて決定した。サンプル採取スケジュール及び PK パラメータに関する仮定を考慮すると，固定パラメータの推定値の不確実性は，Part 1 のコホートあたり 6 例の健康男性ボランティアでは 30%未満，Part 2 で皮下投与患者 20 例を追加した場合は 20%未満であると予想された。

15) 方法
本試験の Part 1 は用量設定試験であり，健康男性ボランティアを対象にペルツズマブ SC の初回用量及び維持用量を決定した。
Part 1（コホート 2，3，4）のペルツズマブ SC の用量は，トラスツズマブ SC 投与時の PK パラメータを取り入れたペルツズマブ IV の popPK モデルに基づいて選択した。
Part 1 の健康男性ボランティアから収集した PK データを用いた popPK モデル及びモデルに基づくシミュレーションを用いて，Part 2 の早期乳癌患者で確認すべきペルツズマブ SC の用量を選択した。

試験の Part 2 では，標準的な（術前）術後補助療法を完了した早期乳癌患者におけるペルツズマブ SC の用量が確認された。
これにより，Part 1 の用量確認及び同時混合注射と本剤との比較が可能となった。本試験デザインにより，最少人数の被験者の登録でも第 III 相試験のためのペルツズマブ SC の用量及び剤型の選択が可能となった。
5.3.3.2-1 3.1.3 項に記載した popPK モデル及びモデルに基づくシミュレーションを，パート 2 コホート B 及び C で収集した追加の PK データを用いて更新し，ペルツズマブの SC 用量を確認した。

16) 結果

a. 有効性の結果

本試験では有効性データは収集されなかった。

b. 薬力学の結果

本試験では薬力学的データは収集されなかった。

c. 薬物動態の結果

i. ペルツズマブ及びトラスツズマブの PK

Part 1：想定どおり，ペルツズマブ420 mg を静脈内投与した後，血清中ペルツズマブ濃度推移は，明確な分布相と消失相を伴う二相性のパターンを示した。ペルツズマブを皮下投与した場合，最高血清中薬物濃度到達時間（$T_{max}$）は4～7日であり，ペルツズマブの曝露量は概ね用量に比例して増加した。用量比例データを用いて，本剤の初回用量を選択した。2つの抗体製剤を混合して皮下投与しても，トラスツズマブによるペルツズマブ PK への明確な影響は認められなかった。
Part 2：ペルツズマブの曝露量（単剤投与時に観察された PK／NCA による $C_{trough}$ 及び AUC）は，600 mg SC（Part 2コホート B）と420mg IV（Part 1コホート1）で同程度であった。早期乳癌患者（コホート B 及びコホート C）における $C_{max}$ 及び $AUC_{inf}$ を含むペルツズマブ曝露量は，健康男性ボランティアに対してペルツズマブを皮下投与した場合（Part 1コホート3）の曝露量と同等であった。ペルツズマブの PK プロファイルは，コホート C（本剤単回投与時）とコホート B（混合製剤投与時）で同等であった。
コホート B 及び C（ペルツズマブとトラスツズマブを投与時）と Part 1コホート3（ペルツズマブ単剤投与時）を比較した結果，トラスツズマブ SC によるペルツズマブ SC の PK への明確な影響は認められなかった。
rHuPH20濃度を2000 U/mL から1000 U/mL（コホート B）又は667 U/mL（コホート8）に低下させても，ペルツズマブ又はトラスツズマブの PK に明らかな影響は認められなかった。

ii. rHuPH20 の薬物動態

血漿中 rHuPH20濃度は，すべての採血時点で定量限界値未満であり，本試験で用いた用量で浸透吸収促進剤として利用するにあたっては，定量可能な全身曝露はないことが示唆された。

d. 安全性の結果

本試験における安全性の結果は，過去のペルツズマブ IV とトラスツズマブ IV 又は SC の併用療法の使用経験と概ね一致していた。新たな安全性シグナルは確認されなかった。
Part 1

- 健康男性ボランティアの大半［44/48 例（91.7%）］で少なくとも 1 件の有害事象（148 件）が報告された。この内 38 例（79.2%）に治験薬との因果関係が否定できない有害事象が 1 件以上認められた（87 件）。
- 有害事象の大半は Grade 1 又は 2 であった。Grade 3 の有害事象が 2 件（下痢，節足動物咬傷）発現した。いずれの事象も回復した。
- Part 1 では，コホート間で全グレードの有害事象の種類及び発現頻度に顕著な差は認められなかった。
- 死亡，重篤な有害事象，治験薬の投与中止に至った有害事象，AESI の報告はなかった。妊娠の報告はなかった。
- 報告された LVD／CHF の事象はなかった。
- 臨床検査値，バイタルサイン及び心電図パラメータに臨床的に問題となる変動は認められなかった。

Part 2

- 両コホートの全被験者［40/40 例（100%）］に少なくとも 1 件の有害事象が発現し，計 242 件（コホート B で 115 件，コホート C で 127 件）の有害事象が報告された。コホート B では 90%，コホート C では 100%の被験者に治験薬と関連のある有害事象（それぞれ 63 件，89 件）が認められた。
- 有害事象のほとんどが Grade 1 又は 2 であった。Grade 3 の有害事象はコホート B で 1 例（下痢）報告された。本事象は回復した。
- コホート C で重篤な有害事象が 1 例（Grade 3 の蜂巣炎，右腕）報告された。本事象は回復した。
- 死亡，妊娠，治験薬の投与中止に至った有害事象，AESI の報告はなかった。
- コホート B で発現した LVD／CHF の事象は 2 件であった。1 件は Grade 2 の駆出率減少（NYHA クラス I）の無症候性有害事象，もう 1 件は Grade 1 の末梢腫脹（報告名：手の腫脹）であった。コホート C で LVD／CHF の事象は報告されなかった。
- 臨床検査値，バイタルサイン及び心電図パラメータに臨床的に問題となる変動は認められなかった。

17) 結論

BO30185 試験（Part 1 及び 2）の PK 及び安全性結果に基づき，本剤の推奨用量は以下のとおりである。

- 初回用量：ペルツズマブ 1200 mg＋ トラスツズマブ 600 mg（rHuPH20 2000 U/mL）
- 維持用量：ペルツズマブ 600 mg＋ トラスツズマブ 600 mg（rHuPH 20 2000 U/mL）

これらの用量は，それぞれ初回用量 840 mg 及び維持用量 420 mg のペルツズマブ IV 投与と同等の曝露をもたらすことが示されている。

BO30185 試験の安全性の結果は，過去のペルツズマブ IV とトラスツズマブ IV 又は SC の併用療法の使用経験と概ね一致していた。新たな安全性シグナルは確認されなかった。

BO30185 試験の PK，安全性及び忍容性の結果は，本剤の更なる開発を支持するものである。

18) 報告書作成日

20[redacted] 年 [redacted] 月

# 2.7.6.2 付録
## 2.7.6.2.1 有害事象の集計表
### 2.7.6.2.1.1 WO40324試験（FeDeriCa 試験）

表 2.7.6.2.1.1-1 有害事象の要約（FeDeriCa 試験，試験全体）

Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| - Any adverse events - | - Any Grade - | 251 (99.6%) | 248 ( 100%) |
| | 1 | 11 ( 4.4%) | 9 ( 3.6%) |
| | 2 | 107 (42.5%) | 118 (47.6%) |
| | 3 | 87 (34.5%) | 79 (31.9%) |
| | 4 | 45 (17.9%) | 41 (16.5%) |
| | 5 | 1 ( 0.4%) | 1 ( 0.4%) |
| 皮膚および皮下組織障害 | | | |
| - Overall - | - Any Grade - | 219 (86.9%) | 221 (89.1%) |
| | 1 | 43 (17.1%) | 44 (17.7%) |
| | 2 | 170 (67.5%) | 170 (68.5%) |
| | 3 | 6 ( 2.4%) | 7 ( 2.8%) |
| 脱毛症 | - Any Grade - | 177 (70.2%) | 191 (77.0%) |
| | 1 | 25 ( 9.9%) | 27 (10.9%) |
| | 2 | 151 (59.9%) | 163 (65.7%) |
| | 3 | 1 ( 0.4%) | 1 ( 0.4%) |
| 発疹 | - Any Grade - | 44 (17.5%) | 30 (12.1%) |
| | 1 | 32 (12.7%) | 23 ( 9.3%) |
| | 2 | 12 ( 4.8%) | 6 ( 2.4%) |
| | 3 | 0 | 1 ( 0.4%) |
| 皮膚乾燥 | - Any Grade - | 31 (12.3%) | 33 (13.3%) |
| | 1 | 26 (10.3%) | 26 (10.5%) |
| | 2 | 5 ( 2.0%) | 6 ( 2.4%) |
| | 3 | 0 | 1 ( 0.4%) |
| 爪変色 | - Any Grade - | 16 ( 6.3%) | 22 ( 8.9%) |
| | 1 | 16 ( 6.3%) | 19 ( 7.7%) |
| | 2 | 0 | 3 ( 1.2%) |

Investigator text for AEs encoded using MedDRA version 22.0.
All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this patient.
To the SOC Overall row counts, a patient contributes only with the AE occurring with the highest grade within the SOC.
Percentages are based on N in the column headings.
Table includes AEs from Neoadjuvant, Adjuvant and Follow up phase.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/program/t_ae_ctc.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/output/t_ae_ctc_SE_wo40324.out
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Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 爪の障害 | - Any Grade - | 14 ( 5.6%) | 15 ( 6.0%) |
| | 1 | 11 ( 4.4%) | 13 ( 5.2%) |
| | 2 | 2 ( 0.8%) | 2 ( 0.8%) |
| | 3 | 1 ( 0.4%) | 0 |
| 紅斑 | - Any Grade - | 12 ( 4.8%) | 16 ( 6.5%) |
| | 1 | 10 ( 4.0%) | 11 ( 4.4%) |
| | 2 | 2 ( 0.8%) | 5 ( 2.0%) |
| 手掌・足底発赤知覚不全症候群 | - Any Grade - | 12 ( 4.8%) | 15 ( 6.0%) |
| | 1 | 6 ( 2.4%) | 9 ( 3.6%) |
| | 2 | 5 ( 2.0%) | 4 ( 1.6%) |
| | 3 | 1 ( 0.4%) | 2 ( 0.8%) |
| 皮膚炎 | - Any Grade - | 11 ( 4.4%) | 16 ( 6.5%) |
| | 1 | 5 ( 2.0%) | 11 ( 4.4%) |
| | 2 | 6 ( 2.4%) | 5 ( 2.0%) |
| そう痒症 | - Any Grade - | 18 ( 7.1%) | 8 ( 3.2%) |
| | 1 | 13 ( 5.2%) | 6 ( 2.4%) |
| | 2 | 4 ( 1.6%) | 2 ( 0.8%) |
| | 3 | 1 ( 0.4%) | 0 |
| 爪甲剥離症 | - Any Grade - | 11 ( 4.4%) | 10 ( 4.0%) |
| | 1 | 7 ( 2.8%) | 8 ( 3.2%) |
| | 2 | 4 ( 1.6%) | 2 ( 0.8%) |
| 斑状丘疹状皮疹 | - Any Grade - | 5 ( 2.0%) | 6 ( 2.4%) |
| | 1 | 4 ( 1.6%) | 4 ( 1.6%) |
| | 2 | 1 ( 0.4%) | 2 ( 0.8%) |
| 爪毒性 | - Any Grade - | 7 ( 2.8%) | 2 ( 0.8%) |
| | 1 | 4 ( 1.6%) | 1 ( 0.4%) |
| | 2 | 3 ( 1.2%) | 0 |
| | 3 | 0 | 1 ( 0.4%) |

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| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 爪甲脱落症 | - Any Grade - | 3 ( 1.2%) | 5 ( 2.0%) |
| | 1 | 3 ( 1.2%) | 4 ( 1.6%) |
| | 2 | 0 | 1 ( 0.4%) |
| 爪痛 | - Any Grade - | 4 ( 1.6%) | 4 ( 1.6%) |
| | 1 | 4 ( 1.6%) | 4 ( 1.6%) |
| 爪破損 | - Any Grade - | 2 ( 0.8%) | 6 ( 2.4%) |
| | 1 | 1 ( 0.4%) | 4 ( 1.6%) |
| | 2 | 1 ( 0.4%) | 2 ( 0.8%) |
| 皮膚毒性 | - Any Grade - | 4 ( 1.6%) | 3 ( 1.2%) |
| | 1 | 2 ( 0.8%) | 2 ( 0.8%) |
| | 3 | 2 ( 0.8%) | 1 ( 0.4%) |
| 皮膚変色 | - Any Grade - | 2 ( 0.8%) | 5 ( 2.0%) |
| | 1 | 1 ( 0.4%) | 5 ( 2.0%) |
| | 2 | 1 ( 0.4%) | 0 |
| ざ瘡様皮膚炎 | - Any Grade - | 3 ( 1.2%) | 2 ( 0.8%) |
| | 1 | 3 ( 1.2%) | 2 ( 0.8%) |
| 寝汗 | - Any Grade - | 1 ( 0.4%) | 4 ( 1.6%) |
| | 1 | 0 | 4 ( 1.6%) |
| | 2 | 1 ( 0.4%) | 0 |
| 爪ジストロフィー | - Any Grade - | 0 | 5 ( 2.0%) |
| | 1 | 0 | 5 ( 2.0%) |
| 爪色素沈着 | - Any Grade - | 2 ( 0.8%) | 3 ( 1.2%) |
| | 1 | 2 ( 0.8%) | 3 ( 1.2%) |
| 皮膚剥脱 | - Any Grade - | 3 ( 1.2%) | 2 ( 0.8%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 2 | 2 ( 0.8%) | 1 ( 0.4%) |
| | 3 | 1 ( 0.4%) | 0 |

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To the SOC Overall row counts, a patient contributes only with the AE occurring with the highest grade within the SOC.
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Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

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|---|---|---|---|
| そう痒性皮疹 | - Any Grade - | 2 ( 0.8%) | 2 ( 0.8%) |
| | 1 | 2 ( 0.8%) | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 湿疹 | - Any Grade - | 2 ( 0.8%) | 2 ( 0.8%) |
| | 1 | 1 ( 0.4%) | 2 ( 0.8%) |
| | 2 | 1 ( 0.4%) | 0 |
| 水疱性皮膚炎 | - Any Grade - | 3 ( 1.2%) | 1 ( 0.4%) |
| | 1 | 3 ( 1.2%) | 1 ( 0.4%) |
| 爪線状隆起 | - Any Grade - | 3 ( 1.2%) | 1 ( 0.4%) |
| | 1 | 3 ( 1.2%) | 1 ( 0.4%) |
| 皮膚亀裂 | - Any Grade - | 2 ( 0.8%) | 2 ( 0.8%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 0 |
| | 3 | 0 | 1 ( 0.4%) |
| ざ瘡 | - Any Grade - | 1 ( 0.4%) | 2 ( 0.8%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 接触皮膚炎 | - Any Grade - | 1 ( 0.4%) | 2 ( 0.8%) |
| | 1 | 0 | 2 ( 0.8%) |
| | 2 | 1 ( 0.4%) | 0 |
| 皮膚疼痛 | - Any Grade - | 2 ( 0.8%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 0 |
| 瘢痕痛 | - Any Grade - | 0 | 3 ( 1.2%) |
| | 1 | 0 | 2 ( 0.8%) |
| | 2 | 0 | 1 ( 0.4%) |
| アレルギー性皮膚炎 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |

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| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 丘疹 | - Any Grade - | 2 ( 0.8%) | 0 |
| | 1 | 2 ( 0.8%) | 0 |
| 紫斑 | - Any Grade - | 0 | 2 ( 0.8%) |
| | 1 | 0 | 2 ( 0.8%) |
| 足底紅斑 | - Any Grade - | 2 ( 0.8%) | 0 |
| | 1 | 2 ( 0.8%) | 0 |
| 多形紅斑 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| 皮膚色素過剰 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| 皮膚潰瘍 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |
| 蕁麻疹 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 0 |
| | 2 | 0 | 1 ( 0.4%) |
| 光線過敏性反応 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 紅斑性皮疹 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 手皮膚炎 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 色素沈着障害 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 水疱 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 全身性そう痒症 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |

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Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/output/t_ae_ctc_SE_wo40324.out
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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 全身性剥脱性皮膚炎 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 多汗症 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 爪萎縮 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 爪床の炎症 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 爪床圧痛 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 剥脱性発疹 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 皮膚腫脹 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 皮膚色素減少 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 毛細血管拡張症 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 嵌入爪 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 疱疹状皮膚炎 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 胃腸障害 | | | |
| - Overall - | - Any Grade - | 208 (82.5%) | 217 (87.5%) |
| | 1 | 84 (33.3%) | 83 (33.5%) |
| | 2 | 103 (40.9%) | 109 (44.0%) |
| | 3 | 20 ( 7.9%) | 24 ( 9.7%) |
| | 4 | 1 ( 0.4%) | 1 ( 0.4%) |
| 悪心 | - Any Grade - | 152 (60.3%) | 146 (58.9%) |
| | 1 | 96 (38.1%) | 97 (39.1%) |
| | 2 | 52 (20.6%) | 44 (17.7%) |
| | 3 | 4 ( 1.6%) | 5 ( 2.0%) |
| 下痢 | - Any Grade - | 139 (55.2%) | 145 (58.5%) |
| | 1 | 77 (30.6%) | 85 (34.3%) |
| | 2 | 50 (19.8%) | 43 (17.3%) |
| | 3 | 11 ( 4.4%) | 17 ( 6.9%) |
| | 4 | 1 ( 0.4%) | 0 |
| 口内炎 | - Any Grade - | 60 (23.8%) | 62 (25.0%) |
| | 1 | 38 (15.1%) | 41 (16.5%) |
| | 2 | 20 ( 7.9%) | 19 ( 7.7%) |
| | 3 | 2 ( 0.8%) | 2 ( 0.8%) |
| 便秘 | - Any Grade - | 52 (20.6%) | 54 (21.8%) |
| | 1 | 48 (19.0%) | 40 (16.1%) |
| | 2 | 4 ( 1.6%) | 14 ( 5.6%) |
| 嘔吐 | - Any Grade - | 45 (17.9%) | 48 (19.4%) |
| | 1 | 27 (10.7%) | 26 (10.5%) |
| | 2 | 15 ( 6.0%) | 20 ( 8.1%) |
| | 3 | 3 ( 1.2%) | 2 ( 0.8%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 消化不良 | - Any Grade - | 26 (10.3%) | 31 (12.5%) |
| | 1 | 18 ( 7.1%) | 18 ( 7.3%) |
| | 2 | 8 ( 3.2%) | 13 ( 5.2%) |
| 上腹部痛 | - Any Grade - | 14 ( 5.6%) | 18 ( 7.3%) |
| | 1 | 10 ( 4.0%) | 17 ( 6.9%) |
| | 2 | 4 ( 1.6%) | 1 ( 0.4%) |
| 腹痛 | - Any Grade - | 13 ( 5.2%) | 18 ( 7.3%) |
| | 1 | 11 ( 4.4%) | 12 ( 4.8%) |
| | 2 | 2 ( 0.8%) | 5 ( 2.0%) |
| | 3 | 0 | 1 ( 0.4%) |
| 痔核 | - Any Grade - | 9 ( 3.6%) | 21 ( 8.5%) |
| | 1 | 7 ( 2.8%) | 15 ( 6.0%) |
| | 2 | 2 ( 0.8%) | 6 ( 2.4%) |
| 胃食道逆流性疾患 | - Any Grade - | 9 ( 3.6%) | 12 ( 4.8%) |
| | 1 | 4 ( 1.6%) | 6 ( 2.4%) |
| | 2 | 5 ( 2.0%) | 6 ( 2.4%) |
| 口腔内潰瘍形成 | - Any Grade - | 4 ( 1.6%) | 10 ( 4.0%) |
| | 1 | 4 ( 1.6%) | 9 ( 3.6%) |
| | 2 | 0 | 1 ( 0.4%) |
| 胃炎 | - Any Grade - | 5 ( 2.0%) | 7 ( 2.8%) |
| | 1 | 3 ( 1.2%) | 5 ( 2.0%) |
| | 2 | 2 ( 0.8%) | 2 ( 0.8%) |
| アフタ性潰瘍 | - Any Grade - | 6 ( 2.4%) | 5 ( 2.0%) |
| | 1 | 4 ( 1.6%) | 4 ( 1.6%) |
| | 2 | 2 ( 0.8%) | 1 ( 0.4%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 口内乾燥 | - Any Grade - | 7 ( 2.8%) | 4 ( 1.6%) |
| | 1 | 6 ( 2.4%) | 3 ( 1.2%) |
| | 2 | 1 ( 0.4%) | 0 |
| | 3 | 0 | 1 ( 0.4%) |
| 口角口唇炎 | - Any Grade - | 3 ( 1.2%) | 4 ( 1.6%) |
| | 1 | 2 ( 0.8%) | 3 ( 1.2%) |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |
| 腹部膨満 | - Any Grade - | 3 ( 1.2%) | 3 ( 1.2%) |
| | 1 | 3 ( 1.2%) | 3 ( 1.2%) |
| 嚥下痛 | - Any Grade - | 2 ( 0.8%) | 4 ( 1.6%) |
| | 1 | 1 ( 0.4%) | 3 ( 1.2%) |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |
| 鼓腸 | - Any Grade - | 2 ( 0.8%) | 3 ( 1.2%) |
| | 1 | 1 ( 0.4%) | 3 ( 1.2%) |
| | 2 | 1 ( 0.4%) | 0 |
| 歯周病 | - Any Grade - | 2 ( 0.8%) | 3 ( 1.2%) |
| | 1 | 1 ( 0.4%) | 3 ( 1.2%) |
| | 2 | 1 ( 0.4%) | 0 |
| 歯痛 | - Any Grade - | 2 ( 0.8%) | 3 ( 1.2%) |
| | 1 | 1 ( 0.4%) | 2 ( 0.8%) |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |
| 消化器痛 | - Any Grade - | 0 | 5 ( 2.0%) |
| | 1 | 0 | 4 ( 1.6%) |
| | 2 | 0 | 1 ( 0.4%) |
| 嚥下障害 | - Any Grade - | 3 ( 1.2%) | 2 ( 0.8%) |
| | 1 | 2 ( 0.8%) | 2 ( 0.8%) |
| | 2 | 1 ( 0.4%) | 0 |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 肛門の炎症 | - Any Grade - | 4 ( 1.6%) | 1 ( 0.4%) |
| | 1 | 3 ( 1.2%) | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 0 |
| 口腔内痛 | - Any Grade - | 3 ( 1.2%) | 1 ( 0.4%) |
| | 1 | 3 ( 1.2%) | 0 |
| | 2 | 0 | 1 ( 0.4%) |
| 口唇炎 | - Any Grade - | 2 ( 0.8%) | 2 ( 0.8%) |
| | 1 | 2 ( 0.8%) | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 血便排泄 | - Any Grade - | 2 ( 0.8%) | 1 ( 0.4%) |
| | 1 | 2 ( 0.8%) | 1 ( 0.4%) |
| 痔出血 | - Any Grade - | 1 ( 0.4%) | 2 ( 0.8%) |
| | 1 | 1 ( 0.4%) | 2 ( 0.8%) |
| 大腸炎 | - Any Grade - | 1 ( 0.4%) | 2 ( 0.8%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 3 | 1 ( 0.4%) | 1 ( 0.4%) |
| 直腸出血 | - Any Grade - | 3 ( 1.2%) | 0 |
| | 1 | 2 ( 0.8%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 腹部不快感 | - Any Grade - | 3 ( 1.2%) | 0 |
| | 1 | 2 ( 0.8%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 肛門出血 | - Any Grade - | 2 ( 0.8%) | 1 ( 0.4%) |
| | 1 | 2 ( 0.8%) | 1 ( 0.4%) |
| 胃潰瘍 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 下腹部痛 | - Any Grade - | 0 | 2 ( 0.8%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 3 | 0 | 1 ( 0.4%) |
| 歯の知覚過敏 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 0 |
| 歯肉痛 | - Any Grade - | 2 ( 0.8%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 舌痛 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 0 |
| 舌潰瘍 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| 裂肛 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| 肛門周囲痛 | - Any Grade - | 2 ( 0.8%) | 0 |
| | 1 | 2 ( 0.8%) | 0 |
| 胃腸の炎症 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 胃腸毒性 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 4 | 0 | 1 ( 0.4%) |
| 口腔知覚不全 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 口腔内不快感 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 口腔粘膜水疱形成 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 口唇浮腫 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 歯肉出血 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 歯肉潰瘍 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 痔瘻 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 出血性胃炎 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 食道炎 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 舌変色 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 唾液腺痛 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 腹部硬直 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 肛門そう痒症 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 肛門失禁 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 膵炎 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 3 | 0 | 1 ( 0.4%) |
| 齲歯 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |

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| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 一般・全身障害および投与部位の状態 | | | |
| - Overall - | - Any Grade - | 182 (72.2%) | 189 (76.2%) |
| | 1 | 103 (40.9%) | 109 (44.0%) |
| | 2 | 63 (25.0%) | 72 (29.0%) |
| | 3 | 15 ( 6.0%) | 8 ( 3.2%) |
| | 4 | 1 ( 0.4%) | 0 |
| 無力症 | - Any Grade - | 76 (30.2%) | 70 (28.2%) |
| | 1 | 47 (18.7%) | 43 (17.3%) |
| | 2 | 24 ( 9.5%) | 26 (10.5%) |
| | 3 | 5 ( 2.0%) | 1 ( 0.4%) |
| 疲労 | - Any Grade - | 57 (22.6%) | 69 (27.8%) |
| | 1 | 37 (14.7%) | 44 (17.7%) |
| | 2 | 15 ( 6.0%) | 20 ( 8.1%) |
| | 3 | 5 ( 2.0%) | 5 ( 2.0%) |
| 粘膜の炎症 | - Any Grade - | 49 (19.4%) | 36 (14.5%) |
| | 1 | 31 (12.3%) | 20 ( 8.1%) |
| | 2 | 15 ( 6.0%) | 14 ( 5.6%) |
| | 3 | 2 ( 0.8%) | 2 ( 0.8%) |
| | 4 | 1 ( 0.4%) | 0 |
| 発熱 | - Any Grade - | 38 (15.1%) | 30 (12.1%) |
| | 1 | 26 (10.3%) | 24 ( 9.7%) |
| | 2 | 11 ( 4.4%) | 6 ( 2.4%) |
| | 3 | 1 ( 0.4%) | 0 |
| 末梢性浮腫 | - Any Grade - | 20 ( 7.9%) | 17 ( 6.9%) |
| | 1 | 15 ( 6.0%) | 17 ( 6.9%) |
| | 2 | 5 ( 2.0%) | 0 |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 注射部位反応 | - Any Grade - | 2 ( 0.8%) | 32 (12.9%) |
| | 1 | 1 ( 0.4%) | 29 (11.7%) |
| | 2 | 1 ( 0.4%) | 3 ( 1.2%) |
| 倦怠感 | - Any Grade - | 13 ( 5.2%) | 15 ( 6.0%) |
| | 1 | 12 ( 4.8%) | 13 ( 5.2%) |
| | 2 | 0 | 2 ( 0.8%) |
| | 3 | 1 ( 0.4%) | 0 |
| 疼痛 | - Any Grade - | 9 ( 3.6%) | 10 ( 4.0%) |
| | 1 | 3 ( 1.2%) | 7 ( 2.8%) |
| | 2 | 6 ( 2.4%) | 3 ( 1.2%) |
| インフルエンザ様疾患 | - Any Grade - | 8 ( 3.2%) | 9 ( 3.6%) |
| | 1 | 5 ( 2.0%) | 9 ( 3.6%) |
| | 2 | 3 ( 1.2%) | 0 |
| 浮腫 | - Any Grade - | 7 ( 2.8%) | 7 ( 2.8%) |
| | 1 | 5 ( 2.0%) | 6 ( 2.4%) |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |
| | 3 | 1 ( 0.4%) | 0 |
| 胸痛 | - Any Grade - | 5 ( 2.0%) | 6 ( 2.4%) |
| | 1 | 5 ( 2.0%) | 5 ( 2.0%) |
| | 2 | 0 | 1 ( 0.4%) |
| 粘膜乾燥 | - Any Grade - | 5 ( 2.0%) | 2 ( 0.8%) |
| | 1 | 4 ( 1.6%) | 2 ( 0.8%) |
| | 2 | 1 ( 0.4%) | 0 |
| 悪寒 | - Any Grade - | 4 ( 1.6%) | 2 ( 0.8%) |
| | 1 | 3 ( 1.2%) | 2 ( 0.8%) |
| | 2 | 1 ( 0.4%) | 0 |
| 腋窩痛 | - Any Grade - | 2 ( 0.8%) | 3 ( 1.2%) |
| | 1 | 2 ( 0.8%) | 3 ( 1.2%) |

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Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/program/t_ae_ctc.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/output/t_ae_ctc_SE_wo40324.out
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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| カテーテル留置部位疼痛 | - Any Grade - | 2 ( 0.8%) | 2 ( 0.8%) |
| | 1 | 1 ( 0.4%) | 2 ( 0.8%) |
| | 2 | 1 ( 0.4%) | 0 |
| 顔面浮腫 | - Any Grade - | 1 ( 0.4%) | 3 ( 1.2%) |
| | 1 | 1 ( 0.4%) | 3 ( 1.2%) |
| 胸部不快感 | - Any Grade - | 2 ( 0.8%) | 2 ( 0.8%) |
| | 1 | 1 ( 0.4%) | 2 ( 0.8%) |
| | 2 | 1 ( 0.4%) | 0 |
| 限局性浮腫 | - Any Grade - | 2 ( 0.8%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 0 |
| 注射部位疼痛 | - Any Grade - | 0 | 3 ( 1.2%) |
| | 1 | 0 | 2 ( 0.8%) |
| | 2 | 0 | 1 ( 0.4%) |
| 不明確な障害 | - Any Grade - | 2 ( 0.8%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 0 |
| 炎症 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 0 |
| 乾燥症 | - Any Grade - | 2 ( 0.8%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 高熱 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| 腫脹 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 注入部位疼痛 | - Any Grade - | 2 ( 0.8%) | 0 |
| | 1 | 2 ( 0.8%) | 0 |
| 非心臓性胸痛 | - Any Grade - | 0 | 2 ( 0.8%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 不快感 | - Any Grade - | 0 | 2 ( 0.8%) |
| | 1 | 0 | 2 ( 0.8%) |
| 末梢腫脹 | - Any Grade - | 0 | 2 ( 0.8%) |
| | 1 | 0 | 2 ( 0.8%) |
| カテーテル留置部位紅斑 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 異常高熱 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 医療機器関連血栓症 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 医療機器関連合併症 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 空腹 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 結石症 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 3 | 0 | 1 ( 0.4%) |
| 血管穿刺部位出血 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 治癒不良 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 穿刺部位内出血 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 穿刺部位疼痛 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 注射部位紅斑 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 注射部位不快感 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 注射部位変色 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 注入部位出血 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 注入部位反応 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 適用部位そう痒感 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 適用部位疼痛 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 熱感 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 粘膜毒性 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 神経系障害 | | | |
| - Overall - | - Any Grade - | 143 (56.7%) | 148 (59.7%) |
| | 1 | 88 (34.9%) | 101 (40.7%) |
| | 2 | 46 (18.3%) | 38 (15.3%) |
| | 3 | 9 ( 3.6%) | 8 ( 3.2%) |
| | 4 | 0 | 1 ( 0.4%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 頭痛 | - Any Grade - | 50 (19.8%) | 36 (14.5%) |
| | 1 | 34 (13.5%) | 27 (10.9%) |
| | 2 | 14 ( 5.6%) | 9 ( 3.6%) |
| | 3 | 2 ( 0.8%) | 0 |
| 味覚異常 | - Any Grade - | 35 (13.9%) | 41 (16.5%) |
| | 1 | 27 (10.7%) | 34 (13.7%) |
| | 2 | 8 ( 3.2%) | 7 ( 2.8%) |
| 末梢性感覚ニューロパチー | - Any Grade - | 34 (13.5%) | 38 (15.3%) |
| | 1 | 26 (10.3%) | 28 (11.3%) |
| | 2 | 8 ( 3.2%) | 8 ( 3.2%) |
| | 3 | 0 | 2 ( 0.8%) |
| 末梢性ニューロパチー | - Any Grade - | 31 (12.3%) | 28 (11.3%) |
| | 1 | 21 ( 8.3%) | 22 ( 8.9%) |
| | 2 | 5 ( 2.0%) | 5 ( 2.0%) |
| | 3 | 5 ( 2.0%) | 1 ( 0.4%) |
| 浮動性めまい | - Any Grade - | 22 ( 8.7%) | 21 ( 8.5%) |
| | 1 | 18 ( 7.1%) | 21 ( 8.5%) |
| | 2 | 4 ( 1.6%) | 0 |
| 錯感覚 | - Any Grade - | 19 ( 7.5%) | 22 ( 8.9%) |
| | 1 | 15 ( 6.0%) | 18 ( 7.3%) |
| | 2 | 4 ( 1.6%) | 2 ( 0.8%) |
| | 3 | 0 | 2 ( 0.8%) |
| 多発ニューロパチー | - Any Grade - | 8 ( 3.2%) | 9 ( 3.6%) |
| | 1 | 6 ( 2.4%) | 5 ( 2.0%) |
| | 2 | 2 ( 0.8%) | 3 ( 1.2%) |
| | 3 | 0 | 1 ( 0.4%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 神経毒性 | - Any Grade - | 8 ( 3.2%) | 8 ( 3.2%) |
| | 1 | 3 ( 1.2%) | 7 ( 2.8%) |
| | 2 | 5 ( 2.0%) | 1 ( 0.4%) |
| 味覚障害 | - Any Grade - | 6 ( 2.4%) | 7 ( 2.8%) |
| | 1 | 5 ( 2.0%) | 7 ( 2.8%) |
| | 3 | 1 ( 0.4%) | 0 |
| 異常感覚 | - Any Grade - | 5 ( 2.0%) | 2 ( 0.8%) |
| | 1 | 3 ( 1.2%) | 2 ( 0.8%) |
| | 2 | 2 ( 0.8%) | 0 |
| 感覚鈍麻 | - Any Grade - | 3 ( 1.2%) | 4 ( 1.6%) |
| | 1 | 3 ( 1.2%) | 3 ( 1.2%) |
| | 2 | 0 | 1 ( 0.4%) |
| 傾眠 | - Any Grade - | 5 ( 2.0%) | 1 ( 0.4%) |
| | 1 | 3 ( 1.2%) | 1 ( 0.4%) |
| | 2 | 2 ( 0.8%) | 0 |
| 失神 | - Any Grade - | 2 ( 0.8%) | 4 ( 1.6%) |
| | 1 | 1 ( 0.4%) | 0 |
| | 2 | 0 | 1 ( 0.4%) |
| | 3 | 1 ( 0.4%) | 3 ( 1.2%) |
| 神経痛 | - Any Grade - | 1 ( 0.4%) | 3 ( 1.2%) |
| | 1 | 1 ( 0.4%) | 2 ( 0.8%) |
| | 2 | 0 | 1 ( 0.4%) |
| 末梢性運動ニューロパチー | - Any Grade - | 2 ( 0.8%) | 2 ( 0.8%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |
| 振戦 | - Any Grade - | 3 ( 1.2%) | 0 |
| | 1 | 2 ( 0.8%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 知覚過敏 | - Any Grade - | 2 ( 0.8%) | 1 ( 0.4%) |
| | 1 | 2 ( 0.8%) | 1 ( 0.4%) |
| 異痛症 | - Any Grade - | 0 | 2 ( 0.8%) |
| | 1 | 0 | 2 ( 0.8%) |
| 健忘 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| 坐骨神経痛 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |
| 失神寸前の状態 | - Any Grade - | 2 ( 0.8%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| | 3 | 1 ( 0.4%) | 0 |
| 失声症 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| 認知障害 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| 味覚消失 | - Any Grade - | 0 | 2 ( 0.8%) |
| | 1 | 0 | 2 ( 0.8%) |
| 嗜眠 | - Any Grade - | 0 | 2 ( 0.8%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 痙攣発作 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 0 |
| | 4 | 0 | 1 ( 0.4%) |
| てんかん | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| ジスキネジア | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 下肢静止不能症候群 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 感覚異常性大腿神経痛 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 頚腕症候群 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 灼熱感 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 声帯麻痺 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 注意力障害 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 片頭痛 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 味覚減退 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 無嗅覚 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 嗅覚錯誤 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 嗅神経障害 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 血液およびリンパ系障害 | | | |
| - Overall - | - Any Grade - | 143 (56.7%) | 128 (51.6%) |
| | 1 | 29 (11.5%) | 36 (14.5%) |
| | 2 | 59 (23.4%) | 39 (15.7%) |
| | 3 | 29 (11.5%) | 35 (14.1%) |
| | 4 | 26 (10.3%) | 18 ( 7.3%) |
| 貧血 | - Any Grade - | 103 (40.9%) | 84 (33.9%) |
| | 1 | 37 (14.7%) | 37 (14.9%) |
| | 2 | 55 (21.8%) | 44 (17.7%) |
| | 3 | 9 ( 3.6%) | 3 ( 1.2%) |
| | 4 | 2 ( 0.8%) | 0 |
| 好中球減少症 | - Any Grade - | 64 (25.4%) | 52 (21.0%) |
| | 1 | 5 ( 2.0%) | 3 ( 1.2%) |
| | 2 | 25 ( 9.9%) | 14 ( 5.6%) |
| | 3 | 12 ( 4.8%) | 19 ( 7.7%) |
| | 4 | 22 ( 8.7%) | 16 ( 6.5%) |
| 白血球減少症 | - Any Grade - | 34 (13.5%) | 18 ( 7.3%) |
| | 1 | 10 ( 4.0%) | 4 ( 1.6%) |
| | 2 | 19 ( 7.5%) | 8 ( 3.2%) |
| | 3 | 3 ( 1.2%) | 6 ( 2.4%) |
| | 4 | 2 ( 0.8%) | 0 |
| 発熱性好中球減少症 | - Any Grade - | 14 ( 5.6%) | 16 ( 6.5%) |
| | 3 | 11 ( 4.4%) | 14 ( 5.6%) |
| | 4 | 3 ( 1.2%) | 2 ( 0.8%) |
| 血小板減少症 | - Any Grade - | 6 ( 2.4%) | 10 ( 4.0%) |
| | 1 | 5 ( 2.0%) | 9 ( 3.6%) |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 白血球増加症 | - Any Grade - | 4 ( 1.6%) | 7 ( 2.8%) |
| | 1 | 3 ( 1.2%) | 6 ( 2.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| | 3 | 1 ( 0.4%) | 0 |
| リンパ球減少症 | - Any Grade - | 7 ( 2.8%) | 3 ( 1.2%) |
| | 1 | 2 ( 0.8%) | 2 ( 0.8%) |
| | 2 | 2 ( 0.8%) | 0 |
| | 3 | 3 ( 1.2%) | 1 ( 0.4%) |
| 好中球増加症 | - Any Grade - | 2 ( 0.8%) | 2 ( 0.8%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| | 3 | 1 ( 0.4%) | 0 |
| リンパ節炎 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 血小板増加症 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 感染症および寄生虫症 | | | |
| - Overall - | - Any Grade - | 125 (49.6%) | 129 (52.0%) |
| | 1 | 12 ( 4.8%) | 20 ( 8.1%) |
| | 2 | 96 (38.1%) | 98 (39.5%) |
| | 3 | 15 ( 6.0%) | 7 ( 2.8%) |
| | 4 | 1 ( 0.4%) | 4 ( 1.6%) |
| | 5 | 1 ( 0.4%) | 0 |
| 上気道感染 | - Any Grade - | 22 ( 8.7%) | 24 ( 9.7%) |
| | 1 | 2 ( 0.8%) | 0 |
| | 2 | 19 ( 7.5%) | 24 ( 9.7%) |
| | 3 | 1 ( 0.4%) | 0 |

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Percentages are based on N in the column headings.
Table includes AEs from Neoadjuvant, Adjuvant and Follow up phase.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/program/t_ae_ctc.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/output/t_ae_ctc_SE_wo40324.out
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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 上咽頭炎 | - Any Grade - | 21 ( 8.3%) | 19 ( 7.7%) |
| | 1 | 7 ( 2.8%) | 5 ( 2.0%) |
| | 2 | 14 ( 5.6%) | 14 ( 5.6%) |
| 尿路感染 | - Any Grade - | 12 ( 4.8%) | 13 ( 5.2%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 2 | 12 ( 4.8%) | 11 ( 4.4%) |
| | 4 | 0 | 1 ( 0.4%) |
| 爪囲炎 | - Any Grade - | 6 ( 2.4%) | 15 ( 6.0%) |
| | 1 | 3 ( 1.2%) | 9 ( 3.6%) |
| | 2 | 3 ( 1.2%) | 5 ( 2.0%) |
| | 3 | 0 | 1 ( 0.4%) |
| 鼻炎 | - Any Grade - | 8 ( 3.2%) | 9 ( 3.6%) |
| | 1 | 5 ( 2.0%) | 3 ( 1.2%) |
| | 2 | 3 ( 1.2%) | 6 ( 2.4%) |
| 咽頭炎 | - Any Grade - | 6 ( 2.4%) | 10 ( 4.0%) |
| | 1 | 2 ( 0.8%) | 3 ( 1.2%) |
| | 2 | 3 ( 1.2%) | 7 ( 2.8%) |
| | 3 | 1 ( 0.4%) | 0 |
| 結膜炎 | - Any Grade - | 9 ( 3.6%) | 5 ( 2.0%) |
| | 1 | 5 ( 2.0%) | 1 ( 0.4%) |
| | 2 | 4 ( 1.6%) | 4 ( 1.6%) |
| 膀胱炎 | - Any Grade - | 8 ( 3.2%) | 6 ( 2.4%) |
| | 1 | 2 ( 0.8%) | 2 ( 0.8%) |
| | 2 | 6 ( 2.4%) | 4 ( 1.6%) |
| 気道感染 | - Any Grade - | 11 ( 4.4%) | 1 ( 0.4%) |
| | 2 | 11 ( 4.4%) | 1 ( 0.4%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 口腔カンジダ症 | - Any Grade - | 2 ( 0.8%) | 10 ( 4.0%) |
| | 1 | 2 ( 0.8%) | 2 ( 0.8%) |
| | 2 | 0 | 8 ( 3.2%) |
| 口腔ヘルペス | - Any Grade - | 6 ( 2.4%) | 2 ( 0.8%) |
| | 1 | 3 ( 1.2%) | 2 ( 0.8%) |
| | 2 | 3 ( 1.2%) | 0 |
| インフルエンザ | - Any Grade - | 4 ( 1.6%) | 3 ( 1.2%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 2 | 4 ( 1.6%) | 2 ( 0.8%) |
| 肺炎 | - Any Grade - | 2 ( 0.8%) | 5 ( 2.0%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 4 ( 1.6%) |
| | 3 | 1 ( 0.4%) | 0 |
| 気管支炎 | - Any Grade - | 2 ( 0.8%) | 4 ( 1.6%) |
| | 2 | 2 ( 0.8%) | 4 ( 1.6%) |
| 創傷感染 | - Any Grade - | 4 ( 1.6%) | 2 ( 0.8%) |
| | 2 | 4 ( 1.6%) | 2 ( 0.8%) |
| 外陰部腟カンジダ症 | - Any Grade - | 3 ( 1.2%) | 2 ( 0.8%) |
| | 2 | 3 ( 1.2%) | 2 ( 0.8%) |
| 帯状疱疹 | - Any Grade - | 3 ( 1.2%) | 2 ( 0.8%) |
| | 1 | 0 | 2 ( 0.8%) |
| | 2 | 3 ( 1.2%) | 0 |
| 扁桃炎 | - Any Grade - | 1 ( 0.4%) | 4 ( 1.6%) |
| | 1 | 1 ( 0.4%) | 0 |
| | 2 | 0 | 4 ( 1.6%) |
| 腟感染 | - Any Grade - | 1 ( 0.4%) | 4 ( 1.6%) |
| | 2 | 1 ( 0.4%) | 4 ( 1.6%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| ウイルス感染 | - Any Grade - | 2 ( 0.8%) | 2 ( 0.8%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |
| | 3 | 1 ( 0.4%) | 0 |
| ウイルス性気道感染 | - Any Grade - | 2 ( 0.8%) | 2 ( 0.8%) |
| | 2 | 2 ( 0.8%) | 2 ( 0.8%) |
| 外陰腟真菌感染 | - Any Grade - | 2 ( 0.8%) | 2 ( 0.8%) |
| | 2 | 2 ( 0.8%) | 2 ( 0.8%) |
| 限局性感染 | - Any Grade - | 3 ( 1.2%) | 1 ( 0.4%) |
| | 2 | 3 ( 1.2%) | 1 ( 0.4%) |
| 好中球減少性敗血症 | - Any Grade - | 1 ( 0.4%) | 3 ( 1.2%) |
| | 4 | 1 ( 0.4%) | 3 ( 1.2%) |
| 歯膿瘍 | - Any Grade - | 2 ( 0.8%) | 2 ( 0.8%) |
| | 2 | 2 ( 0.8%) | 2 ( 0.8%) |
| 術後創感染 | - Any Grade - | 4 ( 1.6%) | 0 |
| | 2 | 2 ( 0.8%) | 0 |
| | 3 | 2 ( 0.8%) | 0 |
| 真菌性乳腺炎 | - Any Grade - | 2 ( 0.8%) | 2 ( 0.8%) |
| | 2 | 1 ( 0.4%) | 2 ( 0.8%) |
| | 3 | 1 ( 0.4%) | 0 |
| 乳腺炎 | - Any Grade - | 3 ( 1.2%) | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 0 |
| | 3 | 2 ( 0.8%) | 1 ( 0.4%) |
| 皮膚真菌感染 | - Any Grade - | 2 ( 0.8%) | 2 ( 0.8%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |
| | 3 | 1 ( 0.4%) | 0 |

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Percentages are based on N in the column headings.
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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 副鼻腔炎 | - Any Grade - | 1 ( 0.4%) | 3 ( 1.2%) |
| | 2 | 1 ( 0.4%) | 2 ( 0.8%) |
| | 3 | 0 | 1 ( 0.4%) |
| 毛包炎 | - Any Grade - | 2 ( 0.8%) | 2 ( 0.8%) |
| | 1 | 0 | 2 ( 0.8%) |
| | 2 | 2 ( 0.8%) | 0 |
| カンジダ感染 | - Any Grade - | 1 ( 0.4%) | 2 ( 0.8%) |
| | 2 | 1 ( 0.4%) | 2 ( 0.8%) |
| ヘルペスウイルス感染 | - Any Grade - | 2 ( 0.8%) | 1 ( 0.4%) |
| | 2 | 2 ( 0.8%) | 1 ( 0.4%) |
| 胃腸炎 | - Any Grade - | 1 ( 0.4%) | 2 ( 0.8%) |
| | 2 | 0 | 1 ( 0.4%) |
| | 3 | 1 ( 0.4%) | 1 ( 0.4%) |
| 外陰部炎 | - Any Grade - | 2 ( 0.8%) | 1 ( 0.4%) |
| | 2 | 2 ( 0.8%) | 1 ( 0.4%) |
| 喉頭炎 | - Any Grade - | 2 ( 0.8%) | 1 ( 0.4%) |
| | 2 | 2 ( 0.8%) | 1 ( 0.4%) |
| 歯肉炎 | - Any Grade - | 2 ( 0.8%) | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 2 | 2 ( 0.8%) | 0 |
| 足部白癬 | - Any Grade - | 1 ( 0.4%) | 2 ( 0.8%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 爪感染 | - Any Grade - | 1 ( 0.4%) | 2 ( 0.8%) |
| | 2 | 1 ( 0.4%) | 2 ( 0.8%) |
| 敗血症 | - Any Grade - | 2 ( 0.8%) | 1 ( 0.4%) |
| | 3 | 2 ( 0.8%) | 0 |
| | 4 | 0 | 1 ( 0.4%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 蜂巣炎 | - Any Grade - | 2 ( 0.8%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |
| ウイルス性胃腸炎 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |
| クロストリジウム・ディフィシレ大腸炎 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |
| 陰部ヘルペス | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |
| 下気道感染 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 0 |
| | 3 | 0 | 1 ( 0.4%) |
| 外陰腟炎 | - Any Grade - | 0 | 2 ( 0.8%) |
| | 2 | 0 | 2 ( 0.8%) |
| 急性腎盂腎炎 | - Any Grade - | 2 ( 0.8%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| | 3 | 1 ( 0.4%) | 0 |
| 消化管感染 | - Any Grade - | 2 ( 0.8%) | 0 |
| | 2 | 2 ( 0.8%) | 0 |
| 腎盂腎炎 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| 単純ヘルペス | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 0 |
| | 2 | 0 | 1 ( 0.4%) |
| 虫垂炎 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 3 | 1 ( 0.4%) | 1 ( 0.4%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 膿疱性皮疹 | - Any Grade - | 0 | 2 ( 0.8%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 麦粒腫 | - Any Grade - | 0 | 2 ( 0.8%) |
| | 2 | 0 | 2 ( 0.8%) |
| 皮膚感染 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| 鼻ヘルペス | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| 涙嚢炎 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |
| 肛門膿瘍 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| | 3 | 1 ( 0.4%) | 0 |
| カテーテル留置部位感染 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| シュードモナス感染 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 3 | 0 | 1 ( 0.4%) |
| バルトリン腺膿瘍 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| ブドウ球菌感染 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| ライノウイルス感染 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| レンサ球菌感染 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 異型肺炎 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 外陰部膿瘍 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 感染 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 感染性小腸結腸炎 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 気管炎 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 急性副鼻腔炎 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 口腔真菌感染 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 子宮頚管炎 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 歯感染 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 歯周炎 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 歯髄炎 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 手足口病 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 処置後感染 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 真菌感染 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 真菌重複感染 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |

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| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 腎感染 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 性器カンジダ症 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 大腸菌性菌血症 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 3 | 0 | 1 ( 0.4%) |
| 丹毒 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 中耳炎 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 乳房蜂巣炎 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 尿道炎 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 尿路性敗血症 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 5 | 1 ( 0.4%) | 0 |
| 熱性感染症 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 粘膜感染 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 膿痂疹 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 臨床検査 | | | |
| - Overall - | - Any Grade - | 124 (49.2%) | 107 (43.1%) |
| | 1 | 41 (16.3%) | 34 (13.7%) |
| | 2 | 37 (14.7%) | 35 (14.1%) |
| | 3 | 28 (11.1%) | 19 ( 7.7%) |
| | 4 | 18 ( 7.1%) | 19 ( 7.7%) |
| 好中球数減少 | - Any Grade - | 50 (19.8%) | 42 (16.9%) |
| | 1 | 7 ( 2.8%) | 2 ( 0.8%) |
| | 2 | 12 ( 4.8%) | 13 ( 5.2%) |
| | 3 | 15 ( 6.0%) | 10 ( 4.0%) |
| | 4 | 16 ( 6.3%) | 17 ( 6.9%) |
| アラニンアミノトランスフェラーゼ増加 | - Any Grade - | 48 (19.0%) | 35 (14.1%) |
| | 1 | 34 (13.5%) | 27 (10.9%) |
| | 2 | 11 ( 4.4%) | 4 ( 1.6%) |
| | 3 | 3 ( 1.2%) | 4 ( 1.6%) |
| アスパラギン酸アミノトランスフェラーゼ増加 | - Any Grade - | 37 (14.7%) | 26 (10.5%) |
| | 1 | 32 (12.7%) | 22 ( 8.9%) |
| | 2 | 3 ( 1.2%) | 2 ( 0.8%) |
| | 3 | 2 ( 0.8%) | 2 ( 0.8%) |
| 白血球数減少 | - Any Grade - | 31 (12.3%) | 17 ( 6.9%) |
| | 1 | 5 ( 2.0%) | 4 ( 1.6%) |
| | 2 | 8 ( 3.2%) | 4 ( 1.6%) |
| | 3 | 13 ( 5.2%) | 4 ( 1.6%) |
| | 4 | 5 ( 2.0%) | 5 ( 2.0%) |
| 体重減少 | - Any Grade - | 13 ( 5.2%) | 23 ( 9.3%) |
| | 1 | 4 ( 1.6%) | 7 ( 2.8%) |
| | 2 | 7 ( 2.8%) | 15 ( 6.0%) |
| | 3 | 2 ( 0.8%) | 1 ( 0.4%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 駆出率減少 | - Any Grade - | 14 ( 5.6%) | 9 ( 3.6%) |
| | 1 | 5 ( 2.0%) | 4 ( 1.6%) |
| | 2 | 7 ( 2.8%) | 5 ( 2.0%) |
| | 3 | 2 ( 0.8%) | 0 |
| リンパ球数減少 | - Any Grade - | 6 ( 2.4%) | 7 ( 2.8%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| | 2 | 2 ( 0.8%) | 3 ( 1.2%) |
| | 3 | 3 ( 1.2%) | 3 ( 1.2%) |
| γ－グルタミルトランスフェラーゼ増加 | - Any Grade - | 5 ( 2.0%) | 7 ( 2.8%) |
| | 1 | 4 ( 1.6%) | 4 ( 1.6%) |
| | 2 | 1 ( 0.4%) | 3 ( 1.2%) |
| 血中アルカリホスファターゼ増加 | - Any Grade - | 5 ( 2.0%) | 6 ( 2.4%) |
| | 1 | 4 ( 1.6%) | 5 ( 2.0%) |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |
| 血中乳酸脱水素酵素増加 | - Any Grade - | 3 ( 1.2%) | 7 ( 2.8%) |
| | 1 | 3 ( 1.2%) | 7 ( 2.8%) |
| 血小板数減少 | - Any Grade - | 3 ( 1.2%) | 5 ( 2.0%) |
| | 1 | 3 ( 1.2%) | 2 ( 0.8%) |
| | 2 | 0 | 3 ( 1.2%) |
| 体重増加 | - Any Grade - | 4 ( 1.6%) | 3 ( 1.2%) |
| | 1 | 3 ( 1.2%) | 2 ( 0.8%) |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |
| トランスアミナーゼ上昇 | - Any Grade - | 4 ( 1.6%) | 2 ( 0.8%) |
| | 1 | 3 ( 1.2%) | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 0 |
| | 3 | 0 | 1 ( 0.4%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 血中ビリルビン増加 | - Any Grade - | 0 | 3 ( 1.2%) |
| | 1 | 0 | 2 ( 0.8%) |
| | 2 | 0 | 1 ( 0.4%) |
| ビタミンＤ減少 | - Any Grade - | 2 ( 0.8%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| ヘモグロビン減少 | - Any Grade - | 0 | 2 ( 0.8%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 血中クレアチニン増加 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| 体温上昇 | - Any Grade - | 2 ( 0.8%) | 0 |
| | 1 | 2 ( 0.8%) | 0 |
| Ｃ－反応性蛋白増加 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| クロストリジウム検査陽性 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 3 | 1 ( 0.4%) | 0 |
| 肝機能検査値上昇 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 肝酵素上昇 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 3 | 1 ( 0.4%) | 0 |
| 血圧上昇 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 血中カリウム減少 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 血中クレアチンホスホキナーゼ増加 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 血中コレステロール増加 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 血中ブドウ糖増加 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 血中重炭酸塩減少 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 血中尿素増加 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 血中葉酸減少 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 心電図再分極異常 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 心拍数増加 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 皮膚ツルゴール低下 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 毛細血管透過性増加 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 遊離サイロキシン減少 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 筋骨格系および結合組織障害 | | | |
| - Overall - | - Any Grade - | 105 (41.7%) | 124 (50.0%) |
| | 1 | 75 (29.8%) | 88 (35.5%) |
| | 2 | 29 (11.5%) | 34 (13.7%) |
| | 3 | 1 ( 0.4%) | 2 ( 0.8%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 筋肉痛 | - Any Grade - | 43 (17.1%) | 53 (21.4%) |
| | 1 | 30 (11.9%) | 41 (16.5%) |
| | 2 | 12 ( 4.8%) | 11 ( 4.4%) |
| | 3 | 1 ( 0.4%) | 1 ( 0.4%) |
| 関節痛 | - Any Grade - | 45 (17.9%) | 38 (15.3%) |
| | 1 | 33 (13.1%) | 29 (11.7%) |
| | 2 | 11 ( 4.4%) | 9 ( 3.6%) |
| | 3 | 1 ( 0.4%) | 0 |
| 骨痛 | - Any Grade - | 11 ( 4.4%) | 18 ( 7.3%) |
| | 1 | 6 ( 2.4%) | 14 ( 5.6%) |
| | 2 | 5 ( 2.0%) | 4 ( 1.6%) |
| 四肢痛 | - Any Grade - | 16 ( 6.3%) | 13 ( 5.2%) |
| | 1 | 13 ( 5.2%) | 11 ( 4.4%) |
| | 2 | 3 ( 1.2%) | 2 ( 0.8%) |
| 背部痛 | - Any Grade - | 10 ( 4.0%) | 19 ( 7.7%) |
| | 1 | 8 ( 3.2%) | 16 ( 6.5%) |
| | 2 | 2 ( 0.8%) | 3 ( 1.2%) |
| 筋骨格痛 | - Any Grade - | 12 ( 4.8%) | 10 ( 4.0%) |
| | 1 | 10 ( 4.0%) | 6 ( 2.4%) |
| | 2 | 2 ( 0.8%) | 3 ( 1.2%) |
| | 3 | 0 | 1 ( 0.4%) |
| 筋痙縮 | - Any Grade - | 9 ( 3.6%) | 8 ( 3.2%) |
| | 1 | 9 ( 3.6%) | 8 ( 3.2%) |
| 関節腫脹 | - Any Grade - | 0 | 3 ( 1.2%) |
| | 1 | 0 | 2 ( 0.8%) |
| | 2 | 0 | 1 ( 0.4%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 筋骨格系胸痛 | - Any Grade - | 2 ( 0.8%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |
| 頚部痛 | - Any Grade - | 0 | 3 ( 1.2%) |
| | 1 | 0 | 2 ( 0.8%) |
| | 2 | 0 | 1 ( 0.4%) |
| 骨粗鬆症 | - Any Grade - | 2 ( 0.8%) | 1 ( 0.4%) |
| | 2 | 2 ( 0.8%) | 1 ( 0.4%) |
| 脊椎痛 | - Any Grade - | 2 ( 0.8%) | 1 ( 0.4%) |
| | 1 | 2 ( 0.8%) | 0 |
| | 2 | 0 | 1 ( 0.4%) |
| 関節可動域低下 | - Any Grade - | 2 ( 0.8%) | 0 |
| | 1 | 2 ( 0.8%) | 0 |
| 関節硬直 | - Any Grade - | 0 | 2 ( 0.8%) |
| | 1 | 0 | 2 ( 0.8%) |
| 筋骨格硬直 | - Any Grade - | 0 | 2 ( 0.8%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 筋骨格不快感 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| 側腹部痛 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| シェーグレン症候群 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 顎痛 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 関節炎 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 関節周囲炎 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 筋拘縮 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 筋攣縮 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 骨減少症 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 骨膜炎 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 線維筋痛 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 変形性関節症 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 変形性脊椎症 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 翼状肩甲骨 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 腱障害 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 鼡径部痛 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 呼吸器、胸郭および縦隔障害 | | | |
| - Overall - | - Any Grade - | 86 (34.1%) | 98 (39.5%) |
| | 1 | 61 (24.2%) | 66 (26.6%) |
| | 2 | 23 ( 9.1%) | 24 ( 9.7%) |
| | 3 | 2 ( 0.8%) | 7 ( 2.8%) |
| | 4 | 0 | 1 ( 0.4%) |
| 咳嗽 | - Any Grade - | 30 (11.9%) | 33 (13.3%) |
| | 1 | 24 ( 9.5%) | 22 ( 8.9%) |
| | 2 | 6 ( 2.4%) | 10 ( 4.0%) |
| | 3 | 0 | 1 ( 0.4%) |
| 鼻出血 | - Any Grade - | 34 (13.5%) | 27 (10.9%) |
| | 1 | 28 (11.1%) | 26 (10.5%) |
| | 2 | 5 ( 2.0%) | 1 ( 0.4%) |
| | 3 | 1 ( 0.4%) | 0 |
| 呼吸困難 | - Any Grade - | 11 ( 4.4%) | 25 (10.1%) |
| | 1 | 11 ( 4.4%) | 21 ( 8.5%) |
| | 2 | 0 | 2 ( 0.8%) |
| | 3 | 0 | 2 ( 0.8%) |
| 鼻漏 | - Any Grade - | 9 ( 3.6%) | 14 ( 5.6%) |
| | 1 | 8 ( 3.2%) | 12 ( 4.8%) |
| | 2 | 1 ( 0.4%) | 2 ( 0.8%) |
| 口腔咽頭痛 | - Any Grade - | 9 ( 3.6%) | 11 ( 4.4%) |
| | 1 | 8 ( 3.2%) | 9 ( 3.6%) |
| | 2 | 1 ( 0.4%) | 2 ( 0.8%) |
| 鼻乾燥 | - Any Grade - | 6 ( 2.4%) | 7 ( 2.8%) |
| | 1 | 5 ( 2.0%) | 6 ( 2.4%) |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
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| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 労作性呼吸困難 | - Any Grade - | 6 ( 2.4%) | 4 ( 1.6%) |
| | 1 | 6 ( 2.4%) | 2 ( 0.8%) |
| | 2 | 0 | 1 ( 0.4%) |
| | 3 | 0 | 1 ( 0.4%) |
| 湿性咳嗽 | - Any Grade - | 4 ( 1.6%) | 2 ( 0.8%) |
| | 1 | 4 ( 1.6%) | 2 ( 0.8%) |
| アレルギー性鼻炎 | - Any Grade - | 4 ( 1.6%) | 1 ( 0.4%) |
| | 1 | 3 ( 1.2%) | 0 |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |
| 咽頭の炎症 | - Any Grade - | 2 ( 0.8%) | 2 ( 0.8%) |
| | 2 | 2 ( 0.8%) | 2 ( 0.8%) |
| 肺塞栓症 | - Any Grade - | 1 ( 0.4%) | 3 ( 1.2%) |
| | 2 | 1 ( 0.4%) | 0 |
| | 3 | 0 | 2 ( 0.8%) |
| | 4 | 0 | 1 ( 0.4%) |
| 肺臓炎 | - Any Grade - | 2 ( 0.8%) | 2 ( 0.8%) |
| | 2 | 2 ( 0.8%) | 2 ( 0.8%) |
| 鼻閉 | - Any Grade - | 0 | 4 ( 1.6%) |
| | 1 | 0 | 4 ( 1.6%) |
| カタル | - Any Grade - | 1 ( 0.4%) | 2 ( 0.8%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |
| 発声障害 | - Any Grade - | 1 ( 0.4%) | 2 ( 0.8%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 喉頭の炎症 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 0 |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 鼻の炎症 | - Any Grade - | 2 ( 0.8%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 鼻部不快感 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 0 |
| | 2 | 0 | 1 ( 0.4%) |
| 咽喉刺激感 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 気管支痙攣 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 気胸 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 3 | 1 ( 0.4%) | 0 |
| 胸水症 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 上気道性喘鳴 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 3 | 0 | 1 ( 0.4%) |
| 窒息 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 低酸素症 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 乳び胸 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 肺水腫 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 肺線維症 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 鼻粘膜びらん | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |

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Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/output/t_ae_ctc_SE_wo40324.out
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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 夜間呼吸困難 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 傷害、中毒および処置合併症 | | | |
| - Overall - | - Any Grade - | 88 (34.9%) | 77 (31.0%) |
| | 1 | 45 (17.9%) | 36 (14.5%) |
| | 2 | 40 (15.9%) | 36 (14.5%) |
| | 3 | 3 ( 1.2%) | 5 ( 2.0%) |
| 処置による疼痛 | - Any Grade - | 23 ( 9.1%) | 30 (12.1%) |
| | 1 | 13 ( 5.2%) | 13 ( 5.2%) |
| | 2 | 10 ( 4.0%) | 17 ( 6.9%) |
| 注入に伴う反応 | - Any Grade - | 35 (13.9%) | 9 ( 3.6%) |
| | 1 | 16 ( 6.3%) | 3 ( 1.2%) |
| | 2 | 17 ( 6.7%) | 6 ( 2.4%) |
| | 3 | 2 ( 0.8%) | 0 |
| 放射線皮膚損傷 | - Any Grade - | 18 ( 7.1%) | 20 ( 8.1%) |
| | 1 | 13 ( 5.2%) | 17 ( 6.9%) |
| | 2 | 4 ( 1.6%) | 2 ( 0.8%) |
| | 3 | 1 ( 0.4%) | 1 ( 0.4%) |
| 創合併症 | - Any Grade - | 9 ( 3.6%) | 4 ( 1.6%) |
| | 1 | 4 ( 1.6%) | 3 ( 1.2%) |
| | 2 | 5 ( 2.0%) | 1 ( 0.4%) |
| 漿液腫 | - Any Grade - | 3 ( 1.2%) | 9 ( 3.6%) |
| | 1 | 1 ( 0.4%) | 4 ( 1.6%) |
| | 2 | 2 ( 0.8%) | 5 ( 2.0%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 処置後血腫 | - Any Grade - | 0 | 4 ( 1.6%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 2 | 0 | 2 ( 0.8%) |
| | 3 | 0 | 1 ( 0.4%) |
| 注射に伴う反応 | - Any Grade - | 1 ( 0.4%) | 3 ( 1.2%) |
| | 1 | 1 ( 0.4%) | 3 ( 1.2%) |
| 挫傷 | - Any Grade - | 1 ( 0.4%) | 2 ( 0.8%) |
| | 1 | 1 ( 0.4%) | 2 ( 0.8%) |
| 術後創合併症 | - Any Grade - | 1 ( 0.4%) | 2 ( 0.8%) |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |
| | 3 | 0 | 1 ( 0.4%) |
| 処置による悪心 | - Any Grade - | 2 ( 0.8%) | 1 ( 0.4%) |
| | 1 | 2 ( 0.8%) | 1 ( 0.4%) |
| 切開部位浮腫 | - Any Grade - | 3 ( 1.2%) | 0 |
| | 1 | 2 ( 0.8%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 創離開 | - Any Grade - | 2 ( 0.8%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |
| 放射線損傷 | - Any Grade - | 2 ( 0.8%) | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 2 | 2 ( 0.8%) | 0 |
| 腋窩リンパ管線維化症候群 | - Any Grade - | 1 ( 0.4%) | 2 ( 0.8%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |
| 切開部位紅斑 | - Any Grade - | 2 ( 0.8%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 転倒 | - Any Grade - | 0 | 2 ( 0.8%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 靱帯捻挫 | - Any Grade - | 0 | 2 ( 0.8%) |
| | 1 | 0 | 2 ( 0.8%) |
| 血管確保合併症 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 骨挫傷 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 四肢損傷 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 処置による嘔吐 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 処置後炎症 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 処置後出血 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 3 | 0 | 1 ( 0.4%) |
| 処置後不快感 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 処置後便秘 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 上肢骨折 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 静脈損傷 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 切開部位小水疱 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 切開部位知覚低下 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 大腿骨骨折 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 3 | 0 | 1 ( 0.4%) |
| 中毒 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 乳房損傷 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 熱傷 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 弁壊死 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 3 | 0 | 1 ( 0.4%) |
| 瘢痕 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 代謝および栄養障害 | | | |
| - Overall - | - Any Grade - | 79 (31.3%) | 72 (29.0%) |
| | 1 | 62 (24.6%) | 48 (19.4%) |
| | 2 | 15 ( 6.0%) | 18 ( 7.3%) |
| | 3 | 2 ( 0.8%) | 6 ( 2.4%) |
| 食欲減退 | - Any Grade - | 46 (18.3%) | 40 (16.1%) |
| | 1 | 36 (14.3%) | 26 (10.5%) |
| | 2 | 9 ( 3.6%) | 12 ( 4.8%) |
| | 3 | 1 ( 0.4%) | 2 ( 0.8%) |
| 低カリウム血症 | - Any Grade - | 18 ( 7.1%) | 15 ( 6.0%) |
| | 1 | 15 ( 6.0%) | 7 ( 2.8%) |
| | 2 | 3 ( 1.2%) | 4 ( 1.6%) |
| | 3 | 0 | 4 ( 1.6%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 高血糖 | - Any Grade - | 5 ( 2.0%) | 6 ( 2.4%) |
| | 1 | 3 ( 1.2%) | 5 ( 2.0%) |
| | 2 | 2 ( 0.8%) | 1 ( 0.4%) |
| 高コレステロール血症 | - Any Grade - | 4 ( 1.6%) | 5 ( 2.0%) |
| | 1 | 3 ( 1.2%) | 5 ( 2.0%) |
| | 2 | 1 ( 0.4%) | 0 |
| 高クロール血症 | - Any Grade - | 2 ( 0.8%) | 5 ( 2.0%) |
| | 1 | 2 ( 0.8%) | 5 ( 2.0%) |
| 高トリグリセリド血症 | - Any Grade - | 2 ( 0.8%) | 5 ( 2.0%) |
| | 1 | 2 ( 0.8%) | 5 ( 2.0%) |
| 低マグネシウム血症 | - Any Grade - | 3 ( 1.2%) | 4 ( 1.6%) |
| | 1 | 2 ( 0.8%) | 2 ( 0.8%) |
| | 2 | 0 | 2 ( 0.8%) |
| | 3 | 1 ( 0.4%) | 0 |
| 低アルブミン血症 | - Any Grade - | 4 ( 1.6%) | 2 ( 0.8%) |
| | 1 | 4 ( 1.6%) | 2 ( 0.8%) |
| 低鉄血症 | - Any Grade - | 5 ( 2.0%) | 1 ( 0.4%) |
| | 1 | 4 ( 1.6%) | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 0 |
| 高カルシウム血症 | - Any Grade - | 1 ( 0.4%) | 4 ( 1.6%) |
| | 1 | 1 ( 0.4%) | 4 ( 1.6%) |
| 脱水 | - Any Grade - | 4 ( 1.6%) | 0 |
| | 1 | 3 ( 1.2%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 高尿酸血症 | - Any Grade - | 1 ( 0.4%) | 2 ( 0.8%) |
| | 1 | 1 ( 0.4%) | 2 ( 0.8%) |
| 食欲亢進 | - Any Grade - | 0 | 3 ( 1.2%) |
| | 1 | 0 | 3 ( 1.2%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| ビタミンD欠乏 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| 高リン酸塩血症 | - Any Grade - | 0 | 2 ( 0.8%) |
| | 1 | 0 | 2 ( 0.8%) |
| 体液貯留 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| 低カルシウム血症 | - Any Grade - | 0 | 2 ( 0.8%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| ２型糖尿病 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| ビタミンC欠乏 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 栄養障害 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 高カリウム血症 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 高ナトリウム血症 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 耐糖能障害 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 低ナトリウム血症 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 糖尿病 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 血管障害 | | | |
| - Overall - | - Any Grade - | 58 (23.0%) | 48 (19.4%) |
| | 1 | 40 (15.9%) | 29 (11.7%) |
| | 2 | 16 ( 6.3%) | 14 ( 5.6%) |
| | 3 | 2 ( 0.8%) | 5 ( 2.0%) |
| ほてり | - Any Grade - | 26 (10.3%) | 19 ( 7.7%) |
| | 1 | 20 ( 7.9%) | 17 ( 6.9%) |
| | 2 | 6 ( 2.4%) | 2 ( 0.8%) |
| 高血圧 | - Any Grade - | 4 ( 1.6%) | 9 ( 3.6%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 2 | 3 ( 1.2%) | 3 ( 1.2%) |
| | 3 | 1 ( 0.4%) | 5 ( 2.0%) |
| 潮紅 | - Any Grade - | 7 ( 2.8%) | 3 ( 1.2%) |
| | 1 | 7 ( 2.8%) | 3 ( 1.2%) |
| 低血圧 | - Any Grade - | 5 ( 2.0%) | 5 ( 2.0%) |
| | 1 | 3 ( 1.2%) | 5 ( 2.0%) |
| | 2 | 2 ( 0.8%) | 0 |
| 血腫 | - Any Grade - | 3 ( 1.2%) | 6 ( 2.4%) |
| | 1 | 1 ( 0.4%) | 5 ( 2.0%) |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |
| | 3 | 1 ( 0.4%) | 0 |
| リンパ浮腫 | - Any Grade - | 3 ( 1.2%) | 5 ( 2.0%) |
| | 1 | 2 ( 0.8%) | 2 ( 0.8%) |
| | 2 | 1 ( 0.4%) | 3 ( 1.2%) |
| リンパ嚢腫 | - Any Grade - | 4 ( 1.6%) | 2 ( 0.8%) |
| | 1 | 4 ( 1.6%) | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 血管炎 | - Any Grade - | 3 ( 1.2%) | 1 ( 0.4%) |
| | 1 | 3 ( 1.2%) | 1 ( 0.4%) |
| 深部静脈血栓症 | - Any Grade - | 1 ( 0.4%) | 2 ( 0.8%) |
| | 1 | 1 ( 0.4%) | 0 |
| | 2 | 0 | 2 ( 0.8%) |
| リンパうっ滞 | - Any Grade - | 2 ( 0.8%) | 0 |
| | 1 | 2 ( 0.8%) | 0 |
| 四肢静脈血栓症 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |
| 静脈炎 | - Any Grade - | 2 ( 0.8%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 血栓症 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 塞栓症 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 静脈瘤 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 腸骨動脈閉塞 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 表在性静脈炎 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 末梢冷感 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 精神障害 | | | |
| - Overall - | - Any Grade - | 42 (16.7%) | 53 (21.4%) |
| | 1 | 31 (12.3%) | 34 (13.7%) |
| | 2 | 9 ( 3.6%) | 19 ( 7.7%) |
| | 3 | 1 ( 0.4%) | 0 |
| | 4 | 1 ( 0.4%) | 0 |
| 不眠症 | - Any Grade - | 28 (11.1%) | 37 (14.9%) |
| | 1 | 24 ( 9.5%) | 28 (11.3%) |
| | 2 | 3 ( 1.2%) | 9 ( 3.6%) |
| | 3 | 1 ( 0.4%) | 0 |
| うつ病 | - Any Grade - | 6 ( 2.4%) | 10 ( 4.0%) |
| | 1 | 4 ( 1.6%) | 6 ( 2.4%) |
| | 2 | 1 ( 0.4%) | 4 ( 1.6%) |
| | 4 | 1 ( 0.4%) | 0 |
| 不安 | - Any Grade - | 4 ( 1.6%) | 10 ( 4.0%) |
| | 1 | 2 ( 0.8%) | 6 ( 2.4%) |
| | 2 | 2 ( 0.8%) | 4 ( 1.6%) |
| 抑うつ気分 | - Any Grade - | 4 ( 1.6%) | 1 ( 0.4%) |
| | 1 | 2 ( 0.8%) | 1 ( 0.4%) |
| | 2 | 2 ( 0.8%) | 0 |
| 易刺激性 | - Any Grade - | 3 ( 1.2%) | 0 |
| | 1 | 2 ( 0.8%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 睡眠障害 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| パニック障害 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |

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Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/output/t_ae_ctc_SE_wo40324.out
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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 音恐怖症 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 感情不安定 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 錯乱状態 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 自殺念慮 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 神経過敏 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 精神状態変化 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 双極性障害 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 眼障害 | | | |
| - Overall - | - Any Grade - | 34 (13.5%) | 38 (15.3%) |
| | 1 | 28 (11.1%) | 35 (14.1%) |
| | 2 | 5 ( 2.0%) | 1 ( 0.4%) |
| | 3 | 1 ( 0.4%) | 2 ( 0.8%) |
| 流涙増加 | - Any Grade - | 13 ( 5.2%) | 13 ( 5.2%) |
| | 1 | 13 ( 5.2%) | 12 ( 4.8%) |
| | 3 | 0 | 1 ( 0.4%) |
| ドライアイ | - Any Grade - | 8 ( 3.2%) | 13 ( 5.2%) |
| | 1 | 6 ( 2.4%) | 12 ( 4.8%) |
| | 2 | 2 ( 0.8%) | 0 |
| | 3 | 0 | 1 ( 0.4%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 霧視 | - Any Grade - | 6 ( 2.4%) | 3 ( 1.2%) |
| | 1 | 4 ( 1.6%) | 3 ( 1.2%) |
| | 2 | 2 ( 0.8%) | 0 |
| 視力障害 | - Any Grade - | 4 ( 1.6%) | 3 ( 1.2%) |
| | 1 | 3 ( 1.2%) | 2 ( 0.8%) |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |
| 眼刺激 | - Any Grade - | 2 ( 0.8%) | 1 ( 0.4%) |
| | 1 | 2 ( 0.8%) | 1 ( 0.4%) |
| 眼痛 | - Any Grade - | 1 ( 0.4%) | 2 ( 0.8%) |
| | 1 | 1 ( 0.4%) | 2 ( 0.8%) |
| 眼球乾燥症 | - Any Grade - | 0 | 2 ( 0.8%) |
| | 1 | 0 | 2 ( 0.8%) |
| 白内障 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 3 | 1 ( 0.4%) | 0 |
| 角膜炎 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 眼そう痒症 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 眼充血 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 眼部不快感 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 眼瞼紅斑 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 眼瞼腫脹 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 眼瞼浮腫 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 眼瞼痙攣 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 眼窩周囲浮腫 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 結膜刺激 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 注視麻痺 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 羞明 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 生殖系および乳房障害 | | | |
| - Overall - | - Any Grade - | 30 (11.9%) | 33 (13.3%) |
| | 1 | 16 ( 6.3%) | 22 ( 8.9%) |
| | 2 | 10 ( 4.0%) | 10 ( 4.0%) |
| | 3 | 3 ( 1.2%) | 1 ( 0.4%) |
| | 4 | 1 ( 0.4%) | 0 |
| 乳房痛 | - Any Grade - | 6 ( 2.4%) | 8 ( 3.2%) |
| | 1 | 5 ( 2.0%) | 6 ( 2.4%) |
| | 2 | 1 ( 0.4%) | 2 ( 0.8%) |
| 外陰膣乾燥 | - Any Grade - | 7 ( 2.8%) | 6 ( 2.4%) |
| | 1 | 5 ( 2.0%) | 5 ( 2.0%) |
| | 2 | 2 ( 0.8%) | 1 ( 0.4%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 不規則月経 | - Any Grade - | 7 ( 2.8%) | 4 ( 1.6%) |
| | 1 | 3 ( 1.2%) | 2 ( 0.8%) |
| | 2 | 2 ( 0.8%) | 1 ( 0.4%) |
| | 3 | 2 ( 0.8%) | 1 ( 0.4%) |
| 腟分泌物 | - Any Grade - | 4 ( 1.6%) | 0 |
| | 1 | 2 ( 0.8%) | 0 |
| | 2 | 2 ( 0.8%) | 0 |
| 外陰腟の炎症 | - Any Grade - | 1 ( 0.4%) | 2 ( 0.8%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |
| 不正子宮出血 | - Any Grade - | 2 ( 0.8%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| | 4 | 1 ( 0.4%) | 0 |
| 無月経 | - Any Grade - | 2 ( 0.8%) | 1 ( 0.4%) |
| | 1 | 2 ( 0.8%) | 1 ( 0.4%) |
| 乳房炎症 | - Any Grade - | 0 | 2 ( 0.8%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 乳房血腫 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 3 | 1 ( 0.4%) | 0 |
| 会陰障害 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 外陰部出血 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 外陰腟そう痒症 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 外陰腟不快感 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 月経困難症 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 子宮出血 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 子宮痛 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 性器灼熱感 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 性器出血 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 性器不快感 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 乳頭痛 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 乳房浮腫 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 乳房分泌 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 閉経期症状 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 卵巣嚢胞 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 腟出血 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
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| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 心臓障害 | | | |
| - Overall - | - Any Grade - | 25 ( 9.9%) | 28 (11.3%) |
| | 1 | 15 ( 6.0%) | 19 ( 7.7%) |
| | 2 | 8 ( 3.2%) | 6 ( 2.4%) |
| | 3 | 2 ( 0.8%) | 2 ( 0.8%) |
| | 5 | 0 | 1 ( 0.4%) |
| 頻脈 | - Any Grade - | 7 ( 2.8%) | 11 ( 4.4%) |
| | 1 | 4 ( 1.6%) | 10 ( 4.0%) |
| | 2 | 3 ( 1.2%) | 1 ( 0.4%) |
| 動悸 | - Any Grade - | 8 ( 3.2%) | 6 ( 2.4%) |
| | 1 | 8 ( 3.2%) | 6 ( 2.4%) |
| 左室機能不全 | - Any Grade - | 3 ( 1.2%) | 3 ( 1.2%) |
| | 1 | 2 ( 0.8%) | 2 ( 0.8%) |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |
| 心不全 | - Any Grade - | 2 ( 0.8%) | 2 ( 0.8%) |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |
| | 3 | 1 ( 0.4%) | 1 ( 0.4%) |
| 不整脈 | - Any Grade - | 3 ( 1.2%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 0 |
| | 2 | 2 ( 0.8%) | 0 |
| | 3 | 0 | 1 ( 0.4%) |
| 急性心筋梗塞 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 5 | 0 | 1 ( 0.4%) |
| 狭心症 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 上室性期外収縮 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 上室性頻脈 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 上室性不整脈 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 心筋線維症 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 心室障害 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 心室性期外収縮 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 心室性不整脈 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 3 | 1 ( 0.4%) | 0 |
| 心嚢液貯留 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 心房頻脈 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 心膜炎 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 洞性頻脈 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 頻脈性不整脈 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 腎および尿路障害 | | | |
| - Overall - | - Any Grade - | 17 ( 6.7%) | 22 ( 8.9%) |
| | 1 | 17 ( 6.7%) | 18 ( 7.3%) |
| | 2 | 0 | 2 ( 0.8%) |
| | 3 | 0 | 1 ( 0.4%) |
| | 4 | 0 | 1 ( 0.4%) |
| 排尿困難 | - Any Grade - | 7 ( 2.8%) | 9 ( 3.6%) |
| | 1 | 7 ( 2.8%) | 9 ( 3.6%) |
| 頻尿 | - Any Grade - | 2 ( 0.8%) | 2 ( 0.8%) |
| | 1 | 2 ( 0.8%) | 2 ( 0.8%) |
| 尿路痛 | - Any Grade - | 2 ( 0.8%) | 1 ( 0.4%) |
| | 1 | 2 ( 0.8%) | 1 ( 0.4%) |
| 血尿 | - Any Grade - | 2 ( 0.8%) | 0 |
| | 1 | 2 ( 0.8%) | 0 |
| 腎臓痛 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| 腎不全 | - Any Grade - | 0 | 2 ( 0.8%) |
| | 3 | 0 | 1 ( 0.4%) |
| | 4 | 0 | 1 ( 0.4%) |
| 尿異常 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| 尿失禁 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 0 |
| | 2 | 0 | 1 ( 0.4%) |
| 非感染性膀胱炎 | - Any Grade - | 0 | 2 ( 0.8%) |
| | 1 | 0 | 2 ( 0.8%) |
| 腎仙痛 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |

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| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 腎前性腎不全 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 多尿 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 尿路不快感 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 排尿躊躇 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 白血球尿 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 膀胱痛 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 耳および迷路障害 | | | |
| - Overall - | - Any Grade - | 14 ( 5.6%) | 7 ( 2.8%) |
| | 1 | 12 ( 4.8%) | 6 ( 2.4%) |
| | 2 | 2 ( 0.8%) | 1 ( 0.4%) |
| 回転性めまい | - Any Grade - | 8 ( 3.2%) | 2 ( 0.8%) |
| | 1 | 7 ( 2.8%) | 2 ( 0.8%) |
| | 2 | 1 ( 0.4%) | 0 |
| 耳鳴 | - Any Grade - | 1 ( 0.4%) | 3 ( 1.2%) |
| | 1 | 1 ( 0.4%) | 3 ( 1.2%) |
| 耳痛 | - Any Grade - | 2 ( 0.8%) | 0 |
| | 1 | 2 ( 0.8%) | 0 |
| 難聴 | - Any Grade - | 2 ( 0.8%) | 0 |
| | 1 | 2 ( 0.8%) | 0 |
| メニエール病 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 感音性聴力低下 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 耳不快感 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 聴力低下 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 肝胆道系障害 | | | |
| - Overall - | - Any Grade - | 6 ( 2.4%) | 7 ( 2.8%) |
| | 1 | 3 ( 1.2%) | 4 ( 1.6%) |
| | 2 | 2 ( 0.8%) | 3 ( 1.2%) |
| | 3 | 1 ( 0.4%) | 0 |
| 高トランスアミナーゼ血症 | - Any Grade - | 3 ( 1.2%) | 3 ( 1.2%) |
| | 1 | 2 ( 0.8%) | 2 ( 0.8%) |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |
| 肝細胞損傷 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| 肝毒性 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 3 | 1 ( 0.4%) | 0 |
| 薬物性肝障害 | - Any Grade - | 0 | 2 ( 0.8%) |
| | 2 | 0 | 2 ( 0.8%) |
| 肝機能異常 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 胆汁うっ滞 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |

Investigator text for AEs encoded using MedDRA version 22.0.
All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this patient.
To the SOC Overall row counts, a patient contributes only with the AE occurring with the highest grade within the SOC.
Percentages are based on N in the column headings.
Table includes AEs from Neoadjuvant, Adjuvant and Follow up phase.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/program/t_ae_ctc.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/output/t_ae_ctc_SE_wo40324.out
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Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 免疫系障害 | | | |
| - Overall - | - Any Grade - | 6 ( 2.4%) | 5 ( 2.0%) |
| | 1 | 3 ( 1.2%) | 4 ( 1.6%) |
| | 2 | 2 ( 0.8%) | 1 ( 0.4%) |
| | 3 | 1 ( 0.4%) | 0 |
| 薬物過敏症 | - Any Grade - | 2 ( 0.8%) | 2 ( 0.8%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |
| 過敏症 | - Any Grade - | 2 ( 0.8%) | 1 ( 0.4%) |
| | 1 | 1 ( 0.4%) | 1 ( 0.4%) |
| | 3 | 1 ( 0.4%) | 0 |
| 季節性アレルギー | - Any Grade - | 1 ( 0.4%) | 2 ( 0.8%) |
| | 1 | 1 ( 0.4%) | 2 ( 0.8%) |
| 造影剤反応 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 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） | | | |
| - Overall - | - Any Grade - | 4 ( 1.6%) | 3 ( 1.2%) |
| | 1 | 2 ( 0.8%) | 2 ( 0.8%) |
| | 2 | 1 ( 0.4%) | 1 ( 0.4%) |
| | 3 | 1 ( 0.4%) | 0 |
| 血管腫 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 2 | 1 ( 0.4%) | 0 |
| 子宮平滑筋腫 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 脂漏性角化症 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |

Investigator text for AEs encoded using MedDRA version 22.0.
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To the SOC Overall row counts, a patient contributes only with the AE occurring with the highest grade within the SOC.
Percentages are based on N in the column headings.
Table includes AEs from Neoadjuvant, Adjuvant and Follow up phase.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/program/t_ae_ctc.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/output/t_ae_ctc_SE_wo40324.out
03SEP2020 17:49

Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 腫瘍疼痛 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 腎細胞癌 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 3 | 1 ( 0.4%) | 0 |
| 皮膚乳頭腫 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 1 | 1 ( 0.4%) | 0 |
| 平滑筋腫 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 内分泌障害 | | | |
| - Overall - | - Any Grade - | 1 ( 0.4%) | 2 ( 0.8%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| | 4 | 1 ( 0.4%) | 0 |
| 甲状腺機能低下症 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 2 | 0 | 1 ( 0.4%) |
| 甲状腺腫 | - Any Grade - | 1 ( 0.4%) | 0 |
| | 4 | 1 ( 0.4%) | 0 |
| 自己免疫性甲状腺炎 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 外科および内科処置 | | | |
| - Overall - | - Any Grade - | 0 | 2 ( 0.8%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 3 | 0 | 1 ( 0.4%) |
| デブリードマン | - Any Grade - | 0 | 1 ( 0.4%) |
| | 3 | 0 | 1 ( 0.4%) |

Investigator text for AEs encoded using MedDRA version 22.0.
All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this patient.
To the SOC Overall row counts, a patient contributes only with the AE occurring with the highest grade within the SOC.
Percentages are based on N in the column headings.
Table includes AEs from Neoadjuvant, Adjuvant and Follow up phase.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/program/t_ae_ctc.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/output/t_ae_ctc_SE_wo40324.out
03SEP2020 17:49

Adverse Events by Highest NCI CTCAE Grade by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Pertuzumab IV + Trastuzumab IV Arm (N=252) | Pertuzumab + Trastuzumab FDC SC Arm (N=248) |
|---|---|---|---|
| 医療機器変更 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 3 | 0 | 1 ( 0.4%) |
| 創傷閉鎖 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 先天性、家族性および遺伝性障害 | | | |
| - Overall - | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 0 |
| 表皮融解 | - Any Grade - | 1 ( 0.4%) | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| | 2 | 1 ( 0.4%) | 0 |
| 製品の問題 | | | |
| - Overall - | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |
| 医療機器位置異常 | - Any Grade - | 0 | 1 ( 0.4%) |
| | 1 | 0 | 1 ( 0.4%) |

Investigator text for AEs encoded using MedDRA version 22.0.
All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this patient.
To the SOC Overall row counts, a patient contributes only with the AE occurring with the highest grade within the SOC.
Percentages are based on N in the column headings.
Table includes AEs from Neoadjuvant, Adjuvant and Follow up phase.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/program/t_ae_ctc.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/CTD/prod/output/t_ae_ctc_SE_wo40324.out
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［5.3.5.3-1 t_ae_ctc_SE_wo40324 を再掲］

## 2.7.6.2.1.2 MO40628試験（PHranceSCa 試験）

### 表 2.7.6.2.1.2-1 有害事象の要約（PHranceSCa 試験，主要解析時，試験全体）

Adverse Events by Highest NCI CTCAE Grade by Treatment Period, Safety-Evaluable Patients
Protocol: MO40628
Primary Analysis

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | PH IV<br>Cross-Over<br>(N=160) | PH FDC SC<br>Cross-Over<br>(N=160) | PH IV<br>Continuation<br>(N=21) | PH FDC SC<br>Continuation<br>(N=137) | All Patients<br>(N=160) |
|---|---|---|---|---|---|---|
| - Any adverse events - | - Any Grade - | 113 (70.6%) | 120 (75.0%) | 13 (61.9%) | 70 (51.1%) | 144 (90.0%) |
| | 1 | 68 (42.5%) | 72 (45.0%) | 8 (38.1%) | 41 (29.9%) | 60 (37.5%) |
| | 2 | 39 (24.4%) | 44 (27.5%) | 3 (14.3%) | 25 (18.2%) | 71 (44.4%) |
| | 3 | 6 ( 3.8%) | 4 ( 2.5%) | 2 ( 9.5%) | 4 ( 2.9%) | 13 ( 8.1%) |
| 一般・全身障害および投与部位の状態 | | | | | | |
| - Overall - | - Any Grade - | 18 (11.3%) | 48 (30.0%) | 2 ( 9.5%) | 22 (16.1%) | 69 (43.1%) |
| | 1 | 14 ( 8.8%) | 43 (26.9%) | 0 | 20 (14.6%) | 58 (36.3%) |
| | 2 | 4 ( 2.5%) | 5 ( 3.1%) | 2 ( 9.5%) | 2 ( 1.5%) | 11 ( 6.9%) |
| 注射部位反応 | - Any Grade - | 0 | 36 (22.5%) | 0 | 10 ( 7.3%) | 42 (26.3%) |
| | 1 | 0 | 33 (20.6%) | 0 | 9 ( 6.6%) | 39 (24.4%) |
| | 2 | 0 | 3 ( 1.9%) | 0 | 1 ( 0.7%) | 3 ( 1.9%) |
| 疲労 | - Any Grade - | 9 ( 5.6%) | 9 ( 5.6%) | 1 ( 4.8%) | 4 ( 2.9%) | 17 (10.6%) |
| | 1 | 9 ( 5.6%) | 9 ( 5.6%) | 0 | 4 ( 2.9%) | 16 (10.0%) |
| | 2 | 0 | 0 | 1 ( 4.8%) | 0 | 1 ( 0.6%) |
| 発熱 | - Any Grade - | 0 | 3 ( 1.9%) | 1 ( 4.8%) | 1 ( 0.7%) | 5 ( 3.1%) |
| | 1 | 0 | 3 ( 1.9%) | 1 ( 4.8%) | 1 ( 0.7%) | 5 ( 3.1%) |
| インフルエンザ様疾患 | - Any Grade - | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 2 ( 1.5%) | 4 ( 2.5%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 2 ( 1.5%) | 3 ( 1.9%) |
| | 2 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 疼痛 | - Any Grade - | 0 | 3 ( 1.9%) | 0 | 1 ( 0.7%) | 4 ( 2.5%) |
| | 1 | 0 | 2 ( 1.3%) | 0 | 1 ( 0.7%) | 3 ( 1.9%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 胸痛 | - Any Grade - | 2 ( 1.3%) | 1 ( 0.6%) | 0 | 0 | 3 ( 1.9%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 2 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) |
| 末梢性浮腫 | - Any Grade - | 2 ( 1.3%) | 0 | 0 | 1 ( 0.7%) | 3 ( 1.9%) |
| | 1 | 2 ( 1.3%) | 0 | 0 | 1 ( 0.7%) | 3 ( 1.9%) |
| 悪寒 | - Any Grade - | 0 | 2 ( 1.3%) | 0 | 0 | 2 ( 1.3%) |
| | 1 | 0 | 2 ( 1.3%) | 0 | 0 | 2 ( 1.3%) |
| 肉芽腫 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| 粘膜の炎症 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 2 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 無力症 | - Any Grade - | 2 ( 1.3%) | 0 | 0 | 0 | 2 ( 1.3%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 2 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 腋窩痛 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| インプラント関連被膜拘縮 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| カテーテル留置部位血腫 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| カテーテル留置部位浮腫 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| カテーテル留置部位疼痛 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 温度変化不耐症 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 顔面腫脹 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |

Investigator text for AEs encoded using MedDRA version 22.1. All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term. To the SOC Overall row counts, a patient contributes only with the AE occurring with the highest grade within the SOC. Includes AEs with onset from first dose of any study drug through 28 days after last dose of study treatment. When an AE start date is partially or fully missing, and it is unclear to which treatment period the AE should be assigned, the AE is assigned to all relevant treatment periods.
Extract Date:09APR2020 Cutoff Date:24FEB2020

Program: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD/prod/program/t_ae_ctc.sas
Output: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD/prod/output/t_ae_ctc_SE_mo40628.out
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Adverse Events by Highest NCI CTCAE Grade by Treatment Period, Safety-Evaluable Patients
Protocol: MO40628
Primary Analysis

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | PH IV<br>Cross-Over<br>(N=160) | PH FDC SC<br>Cross-Over<br>(N=160) | PH IV<br>Continuation<br>(N=21) | PH FDC SC<br>Continuation<br>(N=137) | All Patients<br>(N=160) |
|---|---|---|---|---|---|---|
| 顔面痛 | - Any Grade - | 0 | 0 | 1 ( 4.8%) | 0 | 1 ( 0.6%) |
| | 2 | 0 | 0 | 1 ( 4.8%) | 0 | 1 ( 0.6%) |
| 顔面浮腫 | - Any Grade - | 0 | 0 | 1 ( 4.8%) | 0 | 1 ( 0.6%) |
| | 1 | 0 | 0 | 1 ( 4.8%) | 0 | 1 ( 0.6%) |
| 限局性浮腫 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 注射部位紅斑 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 注射部位内出血 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 注射部位疼痛 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 注入部位反応 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 2 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 粘膜乾燥 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 胃腸障害 | | | | | | |
| - Overall - | - Any Grade - | 30 (18.8%) | 30 (18.8%) | 7 (33.3%) | 22 (16.1%) | 61 (38.1%) |
| | 1 | 21 (13.1%) | 21 (13.1%) | 5 (23.8%) | 17 (12.4%) | 41 (25.6%) |
| | 2 | 9 ( 5.6%) | 8 ( 5.0%) | 2 ( 9.5%) | 5 ( 3.6%) | 19 (11.9%) |
| | 3 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 下痢 | - Any Grade - | 16 (10.0%) | 13 ( 8.1%) | 4 (19.0%) | 14 (10.2%) | 35 (21.9%) |
| | 1 | 11 ( 6.9%) | 8 ( 5.0%) | 2 ( 9.5%) | 12 ( 8.8%) | 22 (13.8%) |
| | 2 | 5 ( 3.1%) | 4 ( 2.5%) | 2 ( 9.5%) | 2 ( 1.5%) | 12 ( 7.5%) |
| | 3 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 悪心 | - Any Grade - | 5 ( 3.1%) | 3 ( 1.9%) | 1 ( 4.8%) | 1 ( 0.7%) | 10 ( 6.3%) |
| | 1 | 5 ( 3.1%) | 3 ( 1.9%) | 1 ( 4.8%) | 1 ( 0.7%) | 10 ( 6.3%) |
| 口内炎 | - Any Grade - | 3 ( 1.9%) | 4 ( 2.5%) | 0 | 2 ( 1.5%) | 6 ( 3.8%) |
| | 1 | 2 ( 1.3%) | 2 ( 1.3%) | 0 | 1 ( 0.7%) | 3 ( 1.9%) |
| | 2 | 1 ( 0.6%) | 2 ( 1.3%) | 0 | 1 ( 0.7%) | 3 ( 1.9%) |
| 便秘 | - Any Grade - | 0 | 4 ( 2.5%) | 1 ( 4.8%) | 2 ( 1.5%) | 6 ( 3.8%) |
| | 1 | 0 | 4 ( 2.5%) | 1 ( 4.8%) | 2 ( 1.5%) | 6 ( 3.8%) |
| 嘔吐 | - Any Grade - | 2 ( 1.3%) | 4 ( 2.5%) | 0 | 1 ( 0.7%) | 6 ( 3.8%) |
| | 1 | 2 ( 1.3%) | 4 ( 2.5%) | 0 | 0 | 5 ( 3.1%) |
| | 2 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 嚥下痛 | - Any Grade - | 4 ( 2.5%) | 2 ( 1.3%) | 0 | 0 | 6 ( 3.8%) |
| | 1 | 3 ( 1.9%) | 1 ( 0.6%) | 0 | 0 | 4 ( 2.5%) |
| | 2 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) |
| 腹痛 | - Any Grade - | 1 ( 0.6%) | 2 ( 1.3%) | 0 | 1 ( 0.7%) | 4 ( 2.5%) |
| | 1 | 1 ( 0.6%) | 2 ( 1.3%) | 0 | 1 ( 0.7%) | 4 ( 2.5%) |
| 痔核 | - Any Grade - | 2 ( 1.3%) | 2 ( 1.3%) | 0 | 0 | 3 ( 1.9%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 0 |
| | 2 | 2 ( 1.3%) | 1 ( 0.6%) | 0 | 0 | 3 ( 1.9%) |
| 胃食道逆流性疾患 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 2 ( 1.5%) | 3 ( 1.9%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| | 2 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 消化不良 | - Any Grade - | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 3 ( 1.9%) |
| | 1 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 3 ( 1.9%) |
| 直腸出血 | - Any Grade - | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 3 ( 1.9%) |
| | 1 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 3 ( 1.9%) |
| 裂肛 | - Any Grade - | 1 ( 0.6%) | 2 ( 1.3%) | 0 | 0 | 3 ( 1.9%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 2 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) |

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Extract Date:09APR2020 Cutoff Date:24FEB2020

Adverse Events by Highest NCI CTCAE Grade by Treatment Period, Safety-Evaluable Patients
Protocol: MO40628
Primary Analysis

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | PH IV<br>Cross-Over<br>(N=160) | PH FDC SC<br>Cross-Over<br>(N=160) | PH IV<br>Continuation<br>(N=21) | PH FDC SC<br>Continuation<br>(N=137) | All Patients<br>(N=160) |
|---|---|---|---|---|---|---|
| アフタ性潰瘍 | - Any Grade - | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) |
| | 1 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) |
| 上腹部痛 | - Any Grade - | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 嚥下障害 | - Any Grade - | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) |
| | 1 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) |
| 肛門周囲痛 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 齲歯 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 2 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 肛門直腸不快感 | - Any Grade - | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 2 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 胃炎 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 血便排泄 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 口腔内出血 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 歯の知覚過敏 | - Any Grade - | 0 | 0 | 1 ( 4.8%) | 0 | 1 ( 0.6%) |
| | 1 | 0 | 0 | 1 ( 4.8%) | 0 | 1 ( 0.6%) |
| 歯の発育障害 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 2 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 上部消化管出血 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 食道炎 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 舌潰瘍 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 直腸裂 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 皮膚および皮下組織障害 | | | | | | |
| - Overall - | - Any Grade - | 31 (19.4%) | 24 (15.0%) | 4 (19.0%) | 18 (13.1%) | 61 (38.1%) |
| | 1 | 26 (16.3%) | 16 (10.0%) | 4 (19.0%) | 15 (10.9%) | 47 (29.4%) |
| | 2 | 5 ( 3.1%) | 8 ( 5.0%) | 0 | 3 ( 2.2%) | 14 ( 8.8%) |
| そう痒症 | - Any Grade - | 7 ( 4.4%) | 3 ( 1.9%) | 0 | 5 ( 3.6%) | 13 ( 8.1%) |
| | 1 | 5 ( 3.1%) | 2 ( 1.3%) | 0 | 5 ( 3.6%) | 10 ( 6.3%) |
| | 2 | 2 ( 1.3%) | 1 ( 0.6%) | 0 | 0 | 3 ( 1.9%) |
| 紅斑 | - Any Grade - | 7 ( 4.4%) | 2 ( 1.3%) | 0 | 0 | 9 ( 5.6%) |
| | 1 | 6 ( 3.8%) | 0 | 0 | 0 | 6 ( 3.8%) |
| | 2 | 1 ( 0.6%) | 2 ( 1.3%) | 0 | 0 | 3 ( 1.9%) |
| 発疹 | - Any Grade - | 2 ( 1.3%) | 2 ( 1.3%) | 2 ( 9.5%) | 2 ( 1.5%) | 8 ( 5.0%) |
| | 1 | 1 ( 0.6%) | 2 ( 1.3%) | 2 ( 9.5%) | 1 ( 0.7%) | 6 ( 3.8%) |
| | 2 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| 皮膚反応 | - Any Grade - | 3 ( 1.9%) | 4 ( 2.5%) | 0 | 1 ( 0.7%) | 5 ( 3.1%) |
| | 1 | 2 ( 1.3%) | 3 ( 1.9%) | 0 | 0 | 3 ( 1.9%) |
| | 2 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| ざ瘡 | - Any Grade - | 3 ( 1.9%) | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 4 ( 2.5%) |
| | 1 | 3 ( 1.9%) | 0 | 0 | 1 ( 0.7%) | 3 ( 1.9%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |

Investigator text for AEs encoded using MedDRA version 22.1. All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term. To the SOC Overall row counts, a patient contributes only with the AE occurring with the highest grade within the SOC. Includes AEs with onset from first dose of any study drug through 28 days after last dose of study treatment. When an AE start date is partially or fully missing, and it is unclear to which treatment period the AE should be assigned, the AE is assigned to all relevant treatment periods.
Extract Date:09APR2020 Cutoff Date:24FEB2020

Program: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD/prod/program/t_ae_ctc.sas
Output: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD/prod/output/t_ae_ctc_SE_mo40628.out
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Adverse Events by Highest NCI CTCAE Grade by Treatment Period, Safety-Evaluable Patients
Protocol: MO40628
Primary Analysis

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | PH IV<br>Cross-Over<br>(N=160) | PH FDC SC<br>Cross-Over<br>(N=160) | PH IV<br>Continuation<br>(N=21) | PH FDC SC<br>Continuation<br>(N=137) | All Patients<br>(N=160) |
|---|---|---|---|---|---|---|
| ざ瘡様皮膚炎 | - Any Grade - | 3 ( 1.9%) | 0 | 0 | 1 ( 0.7%) | 4 ( 2.5%) |
| | 1 | 3 ( 1.9%) | 0 | 0 | 1 ( 0.7%) | 4 ( 2.5%) |
| 斑状丘疹状皮疹 | - Any Grade - | 1 ( 0.6%) | 2 ( 1.3%) | 0 | 1 ( 0.7%) | 4 ( 2.5%) |
| | 1 | 1 ( 0.6%) | 2 ( 1.3%) | 0 | 1 ( 0.7%) | 4 ( 2.5%) |
| 皮膚炎 | - Any Grade - | 1 ( 0.6%) | 3 ( 1.9%) | 0 | 0 | 4 ( 2.5%) |
| | 1 | 1 ( 0.6%) | 2 ( 1.3%) | 0 | 0 | 3 ( 1.9%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 多形紅斑 | - Any Grade - | 0 | 3 ( 1.9%) | 0 | 1 ( 0.7%) | 3 ( 1.9%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 2 | 0 | 2 ( 1.3%) | 0 | 0 | 2 ( 1.3%) |
| 爪線状隆起 | - Any Grade - | 0 | 0 | 1 ( 4.8%) | 2 ( 1.5%) | 3 ( 1.9%) |
| | 1 | 0 | 0 | 1 ( 4.8%) | 2 ( 1.5%) | 3 ( 1.9%) |
| 丘疹性皮疹 | - Any Grade - | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 多汗症 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| 脱毛症 | - Any Grade - | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 皮膚乾燥 | - Any Grade - | 1 ( 0.6%) | 0 | 1 ( 4.8%) | 0 | 2 ( 1.3%) |
| | 1 | 1 ( 0.6%) | 0 | 1 ( 4.8%) | 0 | 2 ( 1.3%) |
| 丘疹 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| そう痒性皮疹 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| アレルギー性皮膚炎 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 手掌・足底発赤知覚不全症候群 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 寝汗 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 足底紅斑 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 2 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 爪甲脱落症 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 爪床出血 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 爪変色 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 皮膚障害 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 2 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 皮膚色素過剰 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 皮膚嚢腫 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 皮膚疼痛 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 敏感肌 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 麻疹様発疹 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 2 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 瘢痕痛 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |

Investigator text for AEs encoded using MedDRA version 22.1. All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term. To the SOC Overall row counts, a patient contributes only with the AE occurring with the highest grade within the SOC. Includes AEs with onset from first dose of any study drug through 28 days after last dose of study treatment. When an AE start date is partially or fully missing, and it is unclear to which treatment period the AE should be assigned, the AE is assigned to all relevant treatment periods.
Extract Date:09APR2020 Cutoff Date:24FEB2020

Program: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD/prod/program/t_ae_ctc.sas
Output: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD/prod/output/t_ae_ctc_SE_mo40628.out
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Adverse Events by Highest NCI CTCAE Grade by Treatment Period, Safety-Evaluable Patients
Protocol: MO40628
Primary Analysis

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | PH IV<br>Cross-Over<br>(N=160) | PH FDC SC<br>Cross-Over<br>(N=160) | PH IV<br>Continuation<br>(N=21) | PH FDC SC<br>Continuation<br>(N=137) | All Patients<br>(N=160) |
|---|---|---|---|---|---|---|
| 感染症および寄生虫症 | | | | | | |
| - Overall - | - Any Grade - | 18 (11.3%) | 24 (15.0%) | 4 (19.0%) | 25 (18.2%) | 59 (36.9%) |
| | 1 | 7 ( 4.4%) | 9 ( 5.6%) | 2 ( 9.5%) | 10 ( 7.3%) | 24 (15.0%) |
| | 2 | 7 ( 4.4%) | 14 ( 8.8%) | 2 ( 9.5%) | 13 ( 9.5%) | 29 (18.1%) |
| | 3 | 4 ( 2.5%) | 1 ( 0.6%) | 0 | 2 ( 1.5%) | 6 ( 3.8%) |
| 上気道感染 | - Any Grade - | 5 ( 3.1%) | 7 ( 4.4%) | 0 | 4 ( 2.9%) | 16 (10.0%) |
| | 1 | 2 ( 1.3%) | 2 ( 1.3%) | 0 | 3 ( 2.2%) | 7 ( 4.4%) |
| | 2 | 2 ( 1.3%) | 5 ( 3.1%) | 0 | 1 ( 0.7%) | 8 ( 5.0%) |
| | 3 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 尿路感染 | - Any Grade - | 2 ( 1.3%) | 1 ( 0.6%) | 0 | 4 ( 2.9%) | 7 ( 4.4%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 2 ( 1.5%) | 3 ( 1.9%) |
| | 2 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 2 ( 1.5%) | 4 ( 2.5%) |
| 上咽頭炎 | - Any Grade - | 0 | 2 ( 1.3%) | 1 ( 4.8%) | 2 ( 1.5%) | 5 ( 3.1%) |
| | 1 | 0 | 2 ( 1.3%) | 1 ( 4.8%) | 2 ( 1.5%) | 5 ( 3.1%) |
| インフルエンザ | - Any Grade - | 1 ( 0.6%) | 1 ( 0.6%) | 1 ( 4.8%) | 1 ( 0.7%) | 4 ( 2.5%) |
| | 1 | 1 ( 0.6%) | 1 ( 0.6%) | 1 ( 4.8%) | 1 ( 0.7%) | 4 ( 2.5%) |
| 爪囲炎 | - Any Grade - | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 2 ( 1.5%) | 4 ( 2.5%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 2 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 3 ( 1.9%) |
| 副鼻腔炎 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 3 ( 2.2%) | 4 ( 2.5%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 2 | 1 ( 0.6%) | 0 | 0 | 2 ( 1.5%) | 3 ( 1.9%) |
| 医療機器関連感染 | - Any Grade - | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 3 ( 1.9%) |
| | 3 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 3 ( 1.9%) |
| 帯状疱疹 | - Any Grade - | 0 | 2 ( 1.3%) | 0 | 1 ( 0.7%) | 3 ( 1.9%) |
| | 1 | 0 | 2 ( 1.3%) | 0 | 0 | 2 ( 1.3%) |
| | 2 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 外陰部腟カンジダ症 | - Any Grade - | 2 ( 1.3%) | 0 | 0 | 0 | 2 ( 1.3%) |
| | 1 | 2 ( 1.3%) | 0 | 0 | 0 | 2 ( 1.3%) |
| 気管支炎 | - Any Grade - | 0 | 0 | 1 ( 4.8%) | 1 ( 0.7%) | 2 ( 1.3%) |
| | 2 | 0 | 0 | 1 ( 4.8%) | 1 ( 0.7%) | 2 ( 1.3%) |
| 気道感染 | - Any Grade - | 0 | 2 ( 1.3%) | 0 | 0 | 2 ( 1.3%) |
| | 2 | 0 | 2 ( 1.3%) | 0 | 0 | 2 ( 1.3%) |
| 術後創感染 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| 皮膚感染 | - Any Grade - | 1 ( 0.6%) | 0 | 1 ( 4.8%) | 0 | 2 ( 1.3%) |
| | 2 | 1 ( 0.6%) | 0 | 1 ( 4.8%) | 0 | 2 ( 1.3%) |
| 膀胱炎 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 2 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 丹毒 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 3 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| せつ | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| クロストリジウム・ディフィシレ感染 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 2 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| ヘルペス眼感染 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| レンサ球菌性咽頭炎 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 2 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 咽頭炎 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |

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Extract Date:09APR2020 Cutoff Date:24FEB2020

Program: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD/prod/program/t_ae_ctc.sas
Output: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD/prod/output/t_ae_ctc_SE_mo40628.out
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Adverse Events by Highest NCI CTCAE Grade by Treatment Period, Safety-Evaluable Patients
Protocol: MO40628
Primary Analysis

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | PH IV<br>Cross-Over<br>(N=160) | PH FDC SC<br>Cross-Over<br>(N=160) | PH IV<br>Continuation<br>(N=21) | PH FDC SC<br>Continuation<br>(N=137) | All Patients<br>(N=160) |
|---|---|---|---|---|---|---|
| 外陰部炎 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 2 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 感染性水疱 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 眼感染 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 気管支肺アスペルギルス症 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 2 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 結膜炎 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 2 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 口腔ヘルペス | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 歯感染 | - Any Grade - | 0 | 0 | 1 ( 4.8%) | 0 | 1 ( 0.6%) |
| | 1 | 0 | 0 | 1 ( 4.8%) | 0 | 1 ( 0.6%) |
| 耳感染 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 足部白癬 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 2 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 爪感染 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 爪真菌症 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 2 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 乳腺炎 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 乳房蜂巣炎 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 3 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 膿疱 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 肺炎 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 2 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 皮膚真菌感染 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 鼻炎 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 毛包炎 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 傷害、中毒および処置合併症 | | | | | | |
| - Overall - | - Any Grade - | 38 (23.8%) | 25 (15.6%) | 0 | 4 ( 2.9%) | 59 (36.9%) |
| | 1 | 28 (17.5%) | 19 (11.9%) | 0 | 3 ( 2.2%) | 43 (26.9%) |
| | 2 | 10 ( 6.3%) | 6 ( 3.8%) | 0 | 1 ( 0.7%) | 16 (10.0%) |
| 放射線皮膚損傷 | - Any Grade - | 27 (16.9%) | 17 (10.6%) | 0 | 1 ( 0.7%) | 44 (27.5%) |
| | 1 | 22 (13.8%) | 13 ( 8.1%) | 0 | 1 ( 0.7%) | 35 (21.9%) |
| | 2 | 5 ( 3.1%) | 4 ( 2.5%) | 0 | 0 | 9 ( 5.6%) |
| 注入に伴う反応 | - Any Grade - | 6 ( 3.8%) | 0 | 0 | 0 | 6 ( 3.8%) |
| | 1 | 5 ( 3.1%) | 0 | 0 | 0 | 5 ( 3.1%) |
| | 2 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 漿液腫 | - Any Grade - | 2 ( 1.3%) | 3 ( 1.9%) | 0 | 0 | 5 ( 3.1%) |
| | 1 | 1 ( 0.6%) | 3 ( 1.9%) | 0 | 0 | 4 ( 2.5%) |
| | 2 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 注射に伴う反応 | - Any Grade - | 0 | 3 ( 1.9%) | 0 | 2 ( 1.5%) | 4 ( 2.5%) |
| | 1 | 0 | 3 ( 1.9%) | 0 | 1 ( 0.7%) | 3 ( 1.9%) |
| | 2 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |

Investigator text for AEs encoded using MedDRA version 22.1. All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term. To the SOC Overall row counts, a patient contributes only with the AE occurring with the highest grade within the SOC. Includes AEs with onset from first dose of any study drug through 28 days after last dose of study treatment. When an AE start date is partially or fully missing, and it is unclear to which treatment period the AE should be assigned, the AE is assigned to all relevant treatment periods.
Extract Date:09APR2020 Cutoff Date:24FEB2020

Program: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD/prod/program/t_ae_ctc.sas
Output: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD/prod/output/t_ae_ctc_SE_mo40628.out
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Adverse Events by Highest NCI CTCAE Grade by Treatment Period, Safety-Evaluable Patients
Protocol: MO40628
Primary Analysis

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | PH IV<br>Cross-Over<br>(N=160) | PH FDC SC<br>Cross-Over<br>(N=160) | PH IV<br>Continuation<br>(N=21) | PH FDC SC<br>Continuation<br>(N=137) | All Patients<br>(N=160) |
|---|---|---|---|---|---|---|
| 放射線関連痛 | - Any Grade - | 4 ( 2.5%) | 0 | 0 | 0 | 4 ( 2.5%) |
| | 1 | 2 ( 1.3%) | 0 | 0 | 0 | 2 ( 1.3%) |
| | 2 | 2 ( 1.3%) | 0 | 0 | 0 | 2 ( 1.3%) |
| リコール現象 | - Any Grade - | 2 ( 1.3%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 0 |
| | 2 | 2 ( 1.3%) | 0 | 0 | 0 | 2 ( 1.3%) |
| 創合併症 | - Any Grade - | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) |
| | 1 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) |
| 処置による疼痛 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 2 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 処置後浮腫 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 節足動物刺傷 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 創傷 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 2 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 創部分泌 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 転倒 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 放射線肺臓炎 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 瘢痕 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 腓骨骨折 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 筋骨格系および結合組織障害 | | | | | | |
| - Overall - | - Any Grade - | 22 (13.8%) | 23 (14.4%) | 4 (19.0%) | 9 ( 6.6%) | 47 (29.4%) |
| | 1 | 17 (10.6%) | 17 (10.6%) | 2 ( 9.5%) | 7 ( 5.1%) | 36 (22.5%) |
| | 2 | 5 ( 3.1%) | 6 ( 3.8%) | 0 | 2 ( 1.5%) | 9 ( 5.6%) |
| | 3 | 0 | 0 | 2 ( 9.5%) | 0 | 2 ( 1.3%) |
| 関節痛 | - Any Grade - | 6 ( 3.8%) | 8 ( 5.0%) | 2 ( 9.5%) | 1 ( 0.7%) | 17 (10.6%) |
| | 1 | 4 ( 2.5%) | 8 ( 5.0%) | 2 ( 9.5%) | 1 ( 0.7%) | 15 ( 9.4%) |
| | 2 | 2 ( 1.3%) | 0 | 0 | 0 | 2 ( 1.3%) |
| 筋痙縮 | - Any Grade - | 2 ( 1.3%) | 4 ( 2.5%) | 0 | 5 ( 3.6%) | 11 ( 6.9%) |
| | 1 | 2 ( 1.3%) | 4 ( 2.5%) | 0 | 4 ( 2.9%) | 10 ( 6.3%) |
| | 2 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 筋肉痛 | - Any Grade - | 5 ( 3.1%) | 3 ( 1.9%) | 2 ( 9.5%) | 0 | 10 ( 6.3%) |
| | 1 | 3 ( 1.9%) | 3 ( 1.9%) | 2 ( 9.5%) | 0 | 8 ( 5.0%) |
| | 2 | 2 ( 1.3%) | 0 | 0 | 0 | 2 ( 1.3%) |
| 四肢痛 | - Any Grade - | 1 ( 0.6%) | 4 ( 2.5%) | 1 ( 4.8%) | 2 ( 1.5%) | 7 ( 4.4%) |
| | 1 | 1 ( 0.6%) | 1 ( 0.6%) | 1 ( 4.8%) | 1 ( 0.7%) | 3 ( 1.9%) |
| | 2 | 0 | 3 ( 1.9%) | 0 | 1 ( 0.7%) | 4 ( 2.5%) |
| 骨粗鬆症 | - Any Grade - | 1 ( 0.6%) | 3 ( 1.9%) | 0 | 0 | 4 ( 2.5%) |
| | 1 | 1 ( 0.6%) | 2 ( 1.3%) | 0 | 0 | 3 ( 1.9%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 筋骨格痛 | - Any Grade - | 0 | 1 ( 0.6%) | 1 ( 4.8%) | 1 ( 0.7%) | 3 ( 1.9%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 2 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 3 | 0 | 0 | 1 ( 4.8%) | 0 | 1 ( 0.6%) |
| 頚部痛 | - Any Grade - | 1 ( 0.6%) | 2 ( 1.3%) | 0 | 0 | 3 ( 1.9%) |
| | 1 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |

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Extract Date:09APR2020 Cutoff Date:24FEB2020

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Output: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD/prod/output/t_ae_ctc_SE_mo40628.out
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Adverse Events by Highest NCI CTCAE Grade by Treatment Period, Safety-Evaluable Patients
Protocol: MO40628
Primary Analysis

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | PH IV<br>Cross-Over<br>(N=160) | PH FDC SC<br>Cross-Over<br>(N=160) | PH IV<br>Continuation<br>(N=21) | PH FDC SC<br>Continuation<br>(N=137) | All Patients<br>(N=160) |
|---|---|---|---|---|---|---|
| 滑液嚢腫 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| 関節炎 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| 骨痛 | - Any Grade - | 0 | 0 | 2 ( 9.5%) | 0 | 2 ( 1.3%) |
| | 1 | 0 | 0 | 1 ( 4.8%) | 0 | 1 ( 0.6%) |
| | 3 | 0 | 0 | 1 ( 4.8%) | 0 | 1 ( 0.6%) |
| 背部痛 | - Any Grade - | 2 ( 1.3%) | 0 | 0 | 0 | 2 ( 1.3%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 2 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 関節可動域低下 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 筋緊張 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 筋骨格系胸痛 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 筋骨格硬直 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 筋力低下 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 骨減少症 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 骨軟骨炎 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 尾骨痛 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 変形性関節症 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 腱炎 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 2 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 腱鞘炎 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 呼吸器、胸郭および縦隔障害 | | | | | | |
| - Overall - | - Any Grade - | 11 ( 6.9%) | 13 ( 8.1%) | 1 ( 4.8%) | 13 ( 9.5%) | 35 (21.9%) |
| | 1 | 9 ( 5.6%) | 10 ( 6.3%) | 1 ( 4.8%) | 8 ( 5.8%) | 25 (15.6%) |
| | 2 | 2 ( 1.3%) | 2 ( 1.3%) | 0 | 5 ( 3.6%) | 9 ( 5.6%) |
| | 3 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 咳嗽 | - Any Grade - | 5 ( 3.1%) | 1 ( 0.6%) | 0 | 3 ( 2.2%) | 9 ( 5.6%) |
| | 1 | 4 ( 2.5%) | 1 ( 0.6%) | 0 | 2 ( 1.5%) | 7 ( 4.4%) |
| | 2 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| 鼻漏 | - Any Grade - | 2 ( 1.3%) | 3 ( 1.9%) | 0 | 0 | 5 ( 3.1%) |
| | 1 | 2 ( 1.3%) | 2 ( 1.3%) | 0 | 0 | 4 ( 2.5%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 口腔咽頭痛 | - Any Grade - | 2 ( 1.3%) | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 4 ( 2.5%) |
| | 1 | 2 ( 1.3%) | 1 ( 0.6%) | 0 | 0 | 3 ( 1.9%) |
| | 2 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 鼻乾燥 | - Any Grade - | 0 | 2 ( 1.3%) | 0 | 2 ( 1.5%) | 4 ( 2.5%) |
| | 1 | 0 | 2 ( 1.3%) | 0 | 1 ( 0.7%) | 3 ( 1.9%) |
| | 2 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 鼻出血 | - Any Grade - | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 3 ( 1.9%) |
| | 1 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 3 ( 1.9%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Period, Safety-Evaluable Patients
Protocol: MO40628
Primary Analysis

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | PH IV<br>Cross-Over<br>(N=160) | PH FDC SC<br>Cross-Over<br>(N=160) | PH IV<br>Continuation<br>(N=21) | PH FDC SC<br>Continuation<br>(N=137) | All Patients<br>(N=160) |
|---|---|---|---|---|---|---|
| 鼻閉 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 2 ( 1.5%) | 3 ( 1.9%) |
| | 1 | 0 | 0 | 0 | 2 ( 1.5%) | 2 ( 1.3%) |
| | 2 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| アレルギー性鼻炎 | - Any Grade - | 0 | 2 ( 1.3%) | 0 | 0 | 2 ( 1.3%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 呼吸困難 | - Any Grade - | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) |
| | 1 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) |
| 湿性咳嗽 | - Any Grade - | 0 | 1 ( 0.6%) | 1 ( 4.8%) | 0 | 2 ( 1.3%) |
| | 1 | 0 | 1 ( 0.6%) | 1 ( 4.8%) | 0 | 2 ( 1.3%) |
| 発声障害 | - Any Grade - | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) |
| | 1 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) |
| 労作性呼吸困難 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| 咽頭の炎症 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 2 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 咽頭紅斑 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 急性肺水腫 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 2 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 鼻粘膜障害 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 鼻閉塞 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 鼻痂皮 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 喘息 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 3 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 神経系障害 | | | | | | |
| - Overall - | - Any Grade - | 15 ( 9.4%) | 13 ( 8.1%) | 3 (14.3%) | 4 ( 2.9%) | 31 (19.4%) |
| | 1 | 14 ( 8.8%) | 10 ( 6.3%) | 2 ( 9.5%) | 3 ( 2.2%) | 25 (15.6%) |
| | 2 | 1 ( 0.6%) | 3 ( 1.9%) | 1 ( 4.8%) | 0 | 5 ( 3.1%) |
| | 3 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 頭痛 | - Any Grade - | 3 ( 1.9%) | 5 ( 3.1%) | 2 ( 9.5%) | 1 ( 0.7%) | 10 ( 6.3%) |
| | 1 | 3 ( 1.9%) | 4 ( 2.5%) | 1 ( 4.8%) | 1 ( 0.7%) | 8 ( 5.0%) |
| | 2 | 0 | 1 ( 0.6%) | 1 ( 4.8%) | 0 | 2 ( 1.3%) |
| 浮動性めまい | - Any Grade - | 3 ( 1.9%) | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 5 ( 3.1%) |
| | 1 | 3 ( 1.9%) | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 5 ( 3.1%) |
| 異常感覚 | - Any Grade - | 2 ( 1.3%) | 2 ( 1.3%) | 0 | 0 | 4 ( 2.5%) |
| | 1 | 2 ( 1.3%) | 2 ( 1.3%) | 0 | 0 | 4 ( 2.5%) |
| 錯感覚 | - Any Grade - | 2 ( 1.3%) | 1 ( 0.6%) | 0 | 0 | 3 ( 1.9%) |
| | 1 | 2 ( 1.3%) | 0 | 0 | 0 | 2 ( 1.3%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 記憶障害 | - Any Grade - | 2 ( 1.3%) | 0 | 0 | 0 | 2 ( 1.3%) |
| | 1 | 2 ( 1.3%) | 0 | 0 | 0 | 2 ( 1.3%) |
| 末梢性ニューロパチー | - Any Grade - | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 運動失調 | - Any Grade - | 0 | 0 | 1 ( 4.8%) | 0 | 1 ( 0.6%) |
| | 2 | 0 | 0 | 1 ( 4.8%) | 0 | 1 ( 0.6%) |
| 運動低下 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 2 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Period, Safety-Evaluable Patients
Protocol: MO40628
Primary Analysis

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | PH IV<br>Cross-Over<br>(N=160) | PH FDC SC<br>Cross-Over<br>(N=160) | PH IV<br>Continuation<br>(N=21) | PH FDC SC<br>Continuation<br>(N=137) | All Patients<br>(N=160) |
|---|---|---|---|---|---|---|
| 協調運動異常 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 緊張性頭痛 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 坐骨神経痛 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 失神 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 3 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 神経炎 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 睡眠の質低下 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 頭部不快感 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 平衡障害 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 末梢性感覚ニューロパチー | - Any Grade - | 0 | 0 | 1 ( 4.8%) | 0 | 1 ( 0.6%) |
| | 1 | 0 | 0 | 1 ( 4.8%) | 0 | 1 ( 0.6%) |
| 味覚障害 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 血管障害 | | | | | | |
| - Overall - | - Any Grade - | 10 ( 6.3%) | 14 ( 8.8%) | 0 | 6 ( 4.4%) | 27 (16.9%) |
| | 1 | 8 ( 5.0%) | 11 ( 6.9%) | 0 | 5 ( 3.6%) | 21 (13.1%) |
| | 2 | 2 ( 1.3%) | 2 ( 1.3%) | 0 | 1 ( 0.7%) | 5 ( 3.1%) |
| | 3 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| ほてり | - Any Grade - | 6 ( 3.8%) | 9 ( 5.6%) | 0 | 3 ( 2.2%) | 16 (10.0%) |
| | 1 | 6 ( 3.8%) | 7 ( 4.4%) | 0 | 2 ( 1.5%) | 13 ( 8.1%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| | 3 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| リンパ浮腫 | - Any Grade - | 2 ( 1.3%) | 4 ( 2.5%) | 0 | 1 ( 0.7%) | 7 ( 4.4%) |
| | 1 | 2 ( 1.3%) | 4 ( 2.5%) | 0 | 1 ( 0.7%) | 7 ( 4.4%) |
| 高血圧 | - Any Grade - | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 3 ( 1.9%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 2 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) |
| 血腫 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 血栓症 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 2 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 塞栓症 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 潮紅 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 低血圧 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 臨床検査 | | | | | | |
| - Overall - | - Any Grade - | 9 ( 5.6%) | 9 ( 5.6%) | 1 ( 4.8%) | 5 ( 3.6%) | 18 (11.3%) |
| | 1 | 6 ( 3.8%) | 4 ( 2.5%) | 1 ( 4.8%) | 3 ( 2.2%) | 10 ( 6.3%) |
| | 2 | 2 ( 1.3%) | 5 ( 3.1%) | 0 | 2 ( 1.5%) | 7 ( 4.4%) |
| | 3 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 駆出率減少 | - Any Grade - | 3 ( 1.9%) | 4 ( 2.5%) | 0 | 1 ( 0.7%) | 7 ( 4.4%) |
| | 2 | 2 ( 1.3%) | 4 ( 2.5%) | 0 | 1 ( 0.7%) | 6 ( 3.8%) |
| | 3 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |

Investigator text for AEs encoded using MedDRA version 22.1. All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term. To the SOC Overall row counts, a patient contributes only with the AE occurring with the highest grade within the SOC. Includes AEs with onset from first dose of any study drug through 28 days after last dose of study treatment. When an AE start date is partially or fully missing, and it is unclear to which treatment period the AE should be assigned, the AE is assigned to all relevant treatment periods.
Extract Date:09APR2020 Cutoff Date:24FEB2020

Program: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD/prod/program/t_ae_ctc.sas
Output: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD/prod/output/t_ae_ctc_SE_mo40628.out
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Adverse Events by Highest NCI CTCAE Grade by Treatment Period, Safety-Evaluable Patients
Protocol: MO40628
Primary Analysis

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | PH IV<br>Cross-Over<br>(N=160) | PH FDC SC<br>Cross-Over<br>(N=160) | PH IV<br>Continuation<br>(N=21) | PH FDC SC<br>Continuation<br>(N=137) | All Patients<br>(N=160) |
|---|---|---|---|---|---|---|
| 血中アルカリホスファターゼ増加 | - Any Grade - | 1 ( 0.6%) | 2 ( 1.3%) | 1 ( 4.8%) | 3 ( 2.2%) | 6 ( 3.8%) |
| | 1 | 1 ( 0.6%) | 2 ( 1.3%) | 1 ( 4.8%) | 3 ( 2.2%) | 6 ( 3.8%) |
| 白血球数減少 | - Any Grade - | 2 ( 1.3%) | 3 ( 1.9%) | 0 | 0 | 4 ( 2.5%) |
| | 1 | 2 ( 1.3%) | 2 ( 1.3%) | 0 | 0 | 3 ( 1.9%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 好中球数減少 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 0 |
| | 2 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| アスパラギン酸アミノトランスフェラーゼ増加 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| トランスアミナーゼ上昇 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| リンパ球数減少 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| γ－グルタミルトランスフェラーゼ増加 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 血中クレアチニン増加 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 血中ビリルビン増加 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 体重増加 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 生殖系および乳房障害<br>- Overall - | - Any Grade - | 9 ( 5.6%) | 9 ( 5.6%) | 0 | 3 ( 2.2%) | 20 (12.5%) |
| | 1 | 5 ( 3.1%) | 7 ( 4.4%) | 0 | 3 ( 2.2%) | 15 ( 9.4%) |
| | 2 | 4 ( 2.5%) | 2 ( 1.3%) | 0 | 0 | 5 ( 3.1%) |
| 乳房痛 | - Any Grade - | 3 ( 1.9%) | 2 ( 1.3%) | 0 | 2 ( 1.5%) | 6 ( 3.8%) |
| | 1 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 2 ( 1.5%) | 4 ( 2.5%) |
| | 2 | 2 ( 1.3%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) |
| 外陰腟乾燥 | - Any Grade - | 2 ( 1.3%) | 3 ( 1.9%) | 0 | 0 | 5 ( 3.1%) |
| | 1 | 1 ( 0.6%) | 2 ( 1.3%) | 0 | 0 | 3 ( 1.9%) |
| | 2 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) |
| 腟分泌物 | - Any Grade - | 3 ( 1.9%) | 0 | 0 | 0 | 3 ( 1.9%) |
| | 1 | 2 ( 1.3%) | 0 | 0 | 0 | 2 ( 1.3%) |
| | 2 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 月経過多 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 子宮内膜肥厚 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 性交困難 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 2 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 乳汁漏出症 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 乳房不快感 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 不正子宮出血 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 無月経 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |

Investigator text for AEs encoded using MedDRA version 22.1. All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term. To the SOC Overall row counts, a patient contributes only with the AE occurring with the highest grade within the SOC. Includes AEs with onset from first dose of any study drug through 28 days after last dose of study treatment. When an AE start date is partially or fully missing, and it is unclear to which treatment period the AE should be assigned, the AE is assigned to all relevant treatment periods.
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Adverse Events by Highest NCI CTCAE Grade by Treatment Period, Safety-Evaluable Patients
Protocol: MO40628
Primary Analysis

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | PH IV<br>Cross-Over<br>(N=160) | PH FDC SC<br>Cross-Over<br>(N=160) | PH IV<br>Continuation<br>(N=21) | PH FDC SC<br>Continuation<br>(N=137) | All Patients<br>(N=160) |
|---|---|---|---|---|---|---|
| 血液およびリンパ系障害 | | | | | | |
| - Overall - | - Any Grade - | 9 ( 5.6%) | 6 ( 3.8%) | 0 | 6 ( 4.4%) | 19 (11.9%) |
| | 1 | 7 ( 4.4%) | 4 ( 2.5%) | 0 | 5 ( 3.6%) | 14 ( 8.8%) |
| | 2 | 1 ( 0.6%) | 2 ( 1.3%) | 0 | 0 | 3 ( 1.9%) |
| | 3 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| 貧血 | - Any Grade - | 5 ( 3.1%) | 3 ( 1.9%) | 0 | 4 ( 2.9%) | 10 ( 6.3%) |
| | 1 | 4 ( 2.5%) | 2 ( 1.3%) | 0 | 4 ( 2.9%) | 8 ( 5.0%) |
| | 2 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) |
| リンパ球減少症 | - Any Grade - | 4 ( 2.5%) | 0 | 0 | 0 | 4 ( 2.5%) |
| | 1 | 2 ( 1.3%) | 0 | 0 | 0 | 2 ( 1.3%) |
| | 2 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 3 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 好中球減少症 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 2 ( 1.5%) | 3 ( 1.9%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| | 3 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 白血球減少症 | - Any Grade - | 2 ( 1.3%) | 0 | 0 | 0 | 2 ( 1.3%) |
| | 1 | 2 ( 1.3%) | 0 | 0 | 0 | 2 ( 1.3%) |
| リンパ節症 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| リンパ節痛 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 鉄欠乏性貧血 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 精神障害 | | | | | | |
| - Overall - | - Any Grade - | 3 ( 1.9%) | 5 ( 3.1%) | 1 ( 4.8%) | 7 ( 5.1%) | 14 ( 8.8%) |
| | 1 | 2 ( 1.3%) | 5 ( 3.1%) | 1 ( 4.8%) | 6 ( 4.4%) | 12 ( 7.5%) |
| | 2 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| 不眠症 | - Any Grade - | 2 ( 1.3%) | 3 ( 1.9%) | 0 | 4 ( 2.9%) | 9 ( 5.6%) |
| | 1 | 1 ( 0.6%) | 3 ( 1.9%) | 0 | 3 ( 2.2%) | 7 ( 4.4%) |
| | 2 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| うつ病 | - Any Grade - | 1 ( 0.6%) | 2 ( 1.3%) | 0 | 2 ( 1.5%) | 4 ( 2.5%) |
| | 1 | 1 ( 0.6%) | 2 ( 1.3%) | 0 | 2 ( 1.5%) | 4 ( 2.5%) |
| 不安 | - Any Grade - | 0 | 0 | 1 ( 4.8%) | 1 ( 0.7%) | 2 ( 1.3%) |
| | 1 | 0 | 0 | 1 ( 4.8%) | 1 ( 0.7%) | 2 ( 1.3%) |
| 広場恐怖症 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 代謝および栄養障害 | | | | | | |
| - Overall - | - Any Grade - | 8 ( 5.0%) | 4 ( 2.5%) | 1 ( 4.8%) | 1 ( 0.7%) | 12 ( 7.5%) |
| | 1 | 8 ( 5.0%) | 4 ( 2.5%) | 1 ( 4.8%) | 1 ( 0.7%) | 12 ( 7.5%) |
| 食欲減退 | - Any Grade - | 2 ( 1.3%) | 2 ( 1.3%) | 0 | 0 | 3 ( 1.9%) |
| | 1 | 2 ( 1.3%) | 2 ( 1.3%) | 0 | 0 | 3 ( 1.9%) |
| 低マグネシウム血症 | - Any Grade - | 2 ( 1.3%) | 0 | 1 ( 4.8%) | 0 | 3 ( 1.9%) |
| | 1 | 2 ( 1.3%) | 0 | 1 ( 4.8%) | 0 | 3 ( 1.9%) |
| ビタミンD欠乏 | - Any Grade - | 0 | 2 ( 1.3%) | 0 | 0 | 2 ( 1.3%) |
| | 1 | 0 | 2 ( 1.3%) | 0 | 0 | 2 ( 1.3%) |
| 高血糖 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 脂質異常症 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 体液貯留 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Period, Safety-Evaluable Patients
Protocol: MO40628
Primary Analysis

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | PH IV<br>Cross-Over<br>(N=160) | PH FDC SC<br>Cross-Over<br>(N=160) | PH IV<br>Continuation<br>(N=21) | PH FDC SC<br>Continuation<br>(N=137) | All Patients<br>(N=160) |
|---|---|---|---|---|---|---|
| 脱水 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 低アルブミン血症 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 低ナトリウム血症 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 低リン酸血症 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 低血糖 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 眼障害 | | | | | | |
| - Overall - | - Any Grade - | 3 ( 1.9%) | 2 ( 1.3%) | 1 ( 4.8%) | 2 ( 1.5%) | 8 ( 5.0%) |
| | 1 | 3 ( 1.9%) | 2 ( 1.3%) | 1 ( 4.8%) | 2 ( 1.5%) | 8 ( 5.0%) |
| 流涙増加 | - Any Grade - | 2 ( 1.3%) | 1 ( 0.6%) | 0 | 0 | 3 ( 1.9%) |
| | 1 | 2 ( 1.3%) | 1 ( 0.6%) | 0 | 0 | 3 ( 1.9%) |
| ドライアイ | - Any Grade - | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) |
| | 1 | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) |
| アレルギー性結膜炎 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 角膜炎 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 眼出血 | - Any Grade - | 0 | 0 | 1 ( 4.8%) | 0 | 1 ( 0.6%) |
| | 1 | 0 | 0 | 1 ( 4.8%) | 0 | 1 ( 0.6%) |
| 霧視 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 外科および内科処置 | | | | | | |
| - Overall - | - Any Grade - | 3 ( 1.9%) | 0 | 0 | 2 ( 1.5%) | 5 ( 3.1%) |
| | 1 | 3 ( 1.9%) | 0 | 0 | 2 ( 1.5%) | 5 ( 3.1%) |
| プロテーゼ移植 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 人工乳房移植 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 人工乳房除去 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 腸管手術 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 抜歯 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 心臓障害 | | | | | | |
| - Overall - | - Any Grade - | 1 ( 0.6%) | 2 ( 1.3%) | 0 | 2 ( 1.5%) | 5 ( 3.1%) |
| | 1 | 1 ( 0.6%) | 2 ( 1.3%) | 0 | 2 ( 1.5%) | 5 ( 3.1%) |
| 動悸 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| 頻脈 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| 不整脈 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |

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Adverse Events by Highest NCI CTCAE Grade by Treatment Period, Safety-Evaluable Patients
Protocol: MO40628
Primary Analysis

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | PH IV<br>Cross-Over<br>(N=160) | PH FDC SC<br>Cross-Over<br>(N=160) | PH IV<br>Continuation<br>(N=21) | PH FDC SC<br>Continuation<br>(N=137) | All Patients<br>(N=160) |
|---|---|---|---|---|---|---|
| 耳および迷路障害 | | | | | | |
| - Overall - | - Any Grade - | 2 ( 1.3%) | 2 ( 1.3%) | 0 | 0 | 4 ( 2.5%) |
| | 1 | 2 ( 1.3%) | 1 ( 0.6%) | 0 | 0 | 3 ( 1.9%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 回転性めまい | - Any Grade - | 2 ( 1.3%) | 2 ( 1.3%) | 0 | 0 | 4 ( 2.5%) |
| | 1 | 2 ( 1.3%) | 1 ( 0.6%) | 0 | 0 | 3 ( 1.9%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 腎および尿路障害 | | | | | | |
| - Overall - | - Any Grade - | 2 ( 1.3%) | 1 ( 0.6%) | 1 ( 4.8%) | 0 | 4 ( 2.5%) |
| | 1 | 1 ( 0.6%) | 1 ( 0.6%) | 1 ( 4.8%) | 0 | 3 ( 1.9%) |
| | 2 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 排尿困難 | - Any Grade - | 1 ( 0.6%) | 0 | 1 ( 4.8%) | 0 | 2 ( 1.3%) |
| | 1 | 1 ( 0.6%) | 0 | 1 ( 4.8%) | 0 | 2 ( 1.3%) |
| 頻尿 | - Any Grade - | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 0 | 2 ( 1.3%) |
| | 1 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 2 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 尿路痛 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 内分泌障害 | | | | | | |
| - Overall - | - Any Grade - | 1 ( 0.6%) | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 3 ( 1.9%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 1 ( 0.7%) | 2 ( 1.3%) |
| バセドウ病 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 2 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 甲状腺機能低下症 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 1 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 甲状腺機能亢進症 | - Any Grade - | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| | 2 | 0 | 1 ( 0.6%) | 0 | 0 | 1 ( 0.6%) |
| 甲状腺腫 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 肝胆道系障害 | | | | | | |
| - Overall - | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 肝臓痛 | - Any Grade - | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| | 1 | 1 ( 0.6%) | 0 | 0 | 0 | 1 ( 0.6%) |
| 社会環境 | | | | | | |
| - Overall - | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 2 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| 閉経 | - Any Grade - | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |
| | 2 | 0 | 0 | 0 | 1 ( 0.7%) | 1 ( 0.6%) |

Investigator text for AEs encoded using MedDRA version 22.1. All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term. To the SOC Overall row counts, a patient contributes only with the AE occurring with the highest grade within the SOC. Includes AEs with onset from first dose of any study drug through 28 days after last dose of study treatment. When an AE start date is partially or fully missing, and it is unclear to which treatment period the AE should be assigned, the AE is assigned to all relevant treatment periods.
Extract Date:09APR2020 Cutoff Date:24FEB2020

Program: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD/prod/program/t_ae_ctc.sas
Output: root/clinical_studies/RO7198574/CDPT8076/MO40628/data_analysis/CTD/prod/output/t_ae_ctc_SE_mo40628.out
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［5.3.5.3-1 t_ae_ctc_SE_mo40628 を再掲］

## 2.7.6.2.1.3 BO30185試験

### 表 2.7.6.2.1.3-1 有害事象の要約（BO30185試験, Part 2コホート C）

Summary of Adverse Events by Highest NCI CTCAE Grade: Part 2, Safety Evaluated Population
Protocol: BO30185
Clinical cut-off date: 31MAY2018
Database lock date: 26JUL2018

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Perjeta 600 mg SC + Herceptin 600 mg SC (coformulated)<br>Cohort C<br>(N=20) |
|---|---|---|
| - Any adverse events - | -Any Grade- | 20 |
| | 1 | 20 |
| | 2 | 7 |
| | 3 | 1 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 胃腸障害 | | |
| - Overall - | -Any Grade- | 19 |
| | 1 | 17 |
| | 2 | 4 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 下痢 | -Any Grade- | 17 |
| | 1 | 14 |
| | 2 | 3 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 悪心 | -Any Grade- | 8 |
| | 1 | 7 |
| | 2 | 1 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 嘔吐 | -Any Grade- | 4 |
| | 1 | 3 |
| | 2 | 1 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |

Investigator text for AEs encoded using MedDRA version 21.0.
Only treatment emergent AEs are displayed. All counts represent numbers of patients.
Multiple occurrences of the same preferred term in one individual are counted once at the highest grade for that preferred term.

Program: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/program/t_ae_ctc.sas
Output: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/output/t_ae_ctc_SE_P2_c_bo30185.out
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Summary of Adverse Events by Highest NCI CTCAE Grade: Part 2, Safety Evaluated Population
Protocol: BO30185
Clinical cut-off date: 31MAY2018
Database lock date: 26JUL2018

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Perjeta 600 mg SC + Herceptin 600 mg SC (coformulated)<br>Cohort C<br>(N=20) |
|---|---|---|
| 口腔内潰瘍形成 | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 口内乾燥 | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 舌炎 | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 腹痛 | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 神経系障害 | | |
| - Overall - | -Any Grade- | 15 |
| | 1 | 14 |
| | 2 | 2 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |

Investigator text for AEs encoded using MedDRA version 21.0.
Only treatment emergent AEs are displayed. All counts represent numbers of patients.
Multiple occurrences of the same preferred term in one individual are counted once at the highest grade for that preferred term.

Program: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/program/t_ae_ctc.sas
Output: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/output/t_ae_ctc_SE_P2_c_bo30185.out
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Summary of Adverse Events by Highest NCI CTCAE Grade: Part 2, Safety Evaluated Population
Protocol: BO30185
Clinical cut-off date: 31MAY2018
Database lock date: 26JUL2018

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Perjeta 600 mg SC + Herceptin 600 mg SC (coformulated)<br>Cohort C<br>(N=20) |
|---|---|---|
| 頭痛 | -Any Grade- | 12 |
| | 1 | 11 |
| | 2 | 1 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 味覚異常 | -Any Grade- | 4 |
| | 1 | 4 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 失神寸前の状態 | -Any Grade- | 1 |
| | 1 | 0 |
| | 2 | 1 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 浮動性めまい | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 嗜眠 | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |

Investigator text for AEs encoded using MedDRA version 21.0.
Only treatment emergent AEs are displayed. All counts represent numbers of patients.
Multiple occurrences of the same preferred term in one individual are counted once at the highest grade for that preferred term.

Program: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/program/t_ae_ctc.sas
Output: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/output/t_ae_ctc_SE_P2_c_bo30185.out
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Summary of Adverse Events by Highest NCI CTCAE Grade: Part 2, Safety Evaluated Population
Protocol: BO30185
Clinical cut-off date: 31MAY2018
Database lock date: 26JUL2018

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Perjeta 600 mg SC + Herceptin 600 mg SC (coformulated)<br>Cohort C<br>(N=20) |
|---|---|---|
| 一般・全身障害および投与部位の状態 | | |
| - Overall - | -Any Grade- | 12 |
| | 1 | 12 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 注射部位反応 | -Any Grade- | 7 |
| | 1 | 7 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 疲労 | -Any Grade- | 4 |
| | 1 | 4 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 悪寒 | -Any Grade- | 2 |
| | 1 | 2 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| インフルエンザ様疾患 | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |

Investigator text for AEs encoded using MedDRA version 21.0.
Only treatment emergent AEs are displayed. All counts represent numbers of patients.
Multiple occurrences of the same preferred term in one individual are counted once at the highest grade for that preferred term.

Program: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/program/t_ae_ctc.sas
Output: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/output/t_ae_ctc_SE_P2_c_bo30185.out
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Summary of Adverse Events by Highest NCI CTCAE Grade: Part 2, Safety Evaluated Population
Protocol: BO30185
Clinical cut-off date: 31MAY2018
Database lock date: 26JUL2018

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Perjeta 600 mg SC + Herceptin 600 mg SC (coformulated)<br>Cohort C<br>(N=20) |
|---|---|---|
| 潰瘍 | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 感染症および寄生虫症<br>- Overall - | -Any Grade- | 11 |
| | 1 | 10 |
| | 2 | 0 |
| | 3 | 1 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 上気道感染 | -Any Grade- | 3 |
| | 1 | 3 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 鼻炎 | -Any Grade- | 2 |
| | 1 | 2 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| ウイルス性上気道感染 | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |

Investigator text for AEs encoded using MedDRA version 21.0.
Only treatment emergent AEs are displayed. All counts represent numbers of patients.
Multiple occurrences of the same preferred term in one individual are counted once at the highest grade for that preferred term.

Program: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/program/t_ae_ctc.sas
Output: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/output/t_ae_ctc_SE_P2_c_bo30185.out
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Summary of Adverse Events by Highest NCI CTCAE Grade: Part 2, Safety Evaluated Population
Protocol: BO30185
Clinical cut-off date: 31MAY2018
Database lock date: 26JUL2018

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Perjeta 600 mg SC + Herceptin 600 mg SC (coformulated)<br>Cohort C<br>(N=20) |
|---|---|---|
| 外陰部腟カンジダ症 | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 手足口病 | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 創傷感染 | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 単純ヘルペス | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 尿路感染 | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 蜂巣炎 | -Any Grade- | 1 |
| | 1 | 0 |
| | 2 | 0 |
| | 3 | 1 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |

Investigator text for AEs encoded using MedDRA version 21.0.
Only treatment emergent AEs are displayed. All counts represent numbers of patients.
Multiple occurrences of the same preferred term in one individual are counted once at the highest grade for that preferred term.

Program: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/program/t_ae_ctc.sas
Output: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/output/t_ae_ctc_SE_P2_c_bo30185.out
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Summary of Adverse Events by Highest NCI CTCAE Grade: Part 2, Safety Evaluated Population
Protocol: BO30185
Clinical cut-off date: 31MAY2018
Database lock date: 26JUL2018

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Perjeta 600 mg SC + Herceptin 600 mg SC (coformulated)<br>Cohort C<br>(N=20) |
|---|---|---|
| 毛包炎 | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 皮膚および皮下組織障害<br>- Overall - | -Any Grade- | 8 |
| | 1 | 7 |
| | 2 | 1 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 発疹 | -Any Grade- | 4 |
| | 1 | 3 |
| | 2 | 1 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 皮膚乾燥 | -Any Grade- | 2 |
| | 1 | 2 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| ざ瘡 | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |

Investigator text for AEs encoded using MedDRA version 21.0.
Only treatment emergent AEs are displayed. All counts represent numbers of patients.
Multiple occurrences of the same preferred term in one individual are counted once at the highest grade for that preferred term.

Program: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/program/t_ae_ctc.sas
Output: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/output/t_ae_ctc_SE_P2_c_bo30185.out
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Summary of Adverse Events by Highest NCI CTCAE Grade: Part 2, Safety Evaluated Population
Protocol: BO30185
Clinical cut-off date: 31MAY2018
Database lock date: 26JUL2018

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Perjeta 600 mg SC + Herceptin 600 mg SC (coformulated)<br>Cohort C<br>(N=20) |
|---|---|---|
| ざ瘡様皮膚炎 | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 丘疹性皮疹 | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 爪破損 | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 皮膚剥脱 | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 筋骨格系および結合組織障害<br>- Overall - | -Any Grade- | 7 |
| | 1 | 7 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |

Investigator text for AEs encoded using MedDRA version 21.0.
Only treatment emergent AEs are displayed. All counts represent numbers of patients.
Multiple occurrences of the same preferred term in one individual are counted once at the highest grade for that preferred term.

Program: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/program/t_ae_ctc.sas
Output: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/output/t_ae_ctc_SE_P2_c_bo30185.out
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Summary of Adverse Events by Highest NCI CTCAE Grade: Part 2, Safety Evaluated Population
Protocol: BO30185
Clinical cut-off date: 31MAY2018
Database lock date: 26JUL2018

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Perjeta 600 mg SC + Herceptin 600 mg SC (coformulated)<br>Cohort C<br>(N=20) |
|---|---|---|
| 関節痛 | -Any Grade- | 4 |
| | 1 | 4 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 筋肉痛 | -Any Grade- | 2 |
| | 1 | 2 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 四肢痛 | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 背部痛 | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 呼吸器、胸郭および縦隔障害<br>- Overall - | -Any Grade- | 6 |
| | 1 | 5 |
| | 2 | 1 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |

Investigator text for AEs encoded using MedDRA version 21.0.
Only treatment emergent AEs are displayed. All counts represent numbers of patients.
Multiple occurrences of the same preferred term in one individual are counted once at the highest grade for that preferred term.

Program: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/program/t_ae_ctc.sas
Output: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/output/t_ae_ctc_SE_P2_c_bo30185.out
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Summary of Adverse Events by Highest NCI CTCAE Grade: Part 2, Safety Evaluated Population
Protocol: BO30185
Clinical cut-off date: 31MAY2018
Database lock date: 26JUL2018

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Perjeta 600 mg SC + Herceptin 600 mg SC (coformulated)<br>Cohort C<br>(N=20) |
|---|---|---|
| 鼻出血 | -Any Grade- | 3 |
| | 1 | 3 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 口腔咽頭痛 | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 鼻の炎症 | -Any Grade- | 1 |
| | 1 | 0 |
| | 2 | 1 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 鼻閉 | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 鼻漏 | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |

Investigator text for AEs encoded using MedDRA version 21.0.
Only treatment emergent AEs are displayed. All counts represent numbers of patients.
Multiple occurrences of the same preferred term in one individual are counted once at the highest grade for that preferred term.

Program: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/program/t_ae_ctc.sas
Output: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/output/t_ae_ctc_SE_P2_c_bo30185.out

Summary of Adverse Events by Highest NCI CTCAE Grade: Part 2, Safety Evaluated Population
Protocol: BO30185
Clinical cut-off date: 31MAY2018
Database lock date: 26JUL2018

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Perjeta 600 mg SC + Herceptin 600 mg SC (coformulated)<br>Cohort C<br>(N=20) |
|---|---|---|
| 傷害、中毒および処置合併症 | | |
| - Overall - | -Any Grade- | 4 |
| | 1 | 3 |
| | 2 | 1 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 処置による疼痛 | -Any Grade- | 2 |
| | 1 | 1 |
| | 2 | 1 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 創部炎症 | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 多発性外傷 | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 転倒 | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |

Investigator text for AEs encoded using MedDRA version 21.0.
Only treatment emergent AEs are displayed. All counts represent numbers of patients.
Multiple occurrences of the same preferred term in one individual are counted once at the highest grade for that preferred term.

Program: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/program/t_ae_ctc.sas
Output: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/output/t_ae_ctc_SE_P2_c_bo30185.out
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Summary of Adverse Events by Highest NCI CTCAE Grade: Part 2, Safety Evaluated Population
Protocol: BO30185
Clinical cut-off date: 31MAY2018
Database lock date: 26JUL2018

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Perjeta 600 mg SC + Herceptin 600 mg SC (coformulated)<br>Cohort C<br>(N=20) |
|---|---|---|
| 心臓障害 | | |
| - Overall - | -Any Grade- | 2 |
| | 1 | 2 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 動悸 | -Any Grade- | 2 |
| | 1 | 2 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 眼障害 | | |
| - Overall - | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 眼乾燥 | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 血管障害 | | |
| - Overall - | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |

Investigator text for AEs encoded using MedDRA version 21.0.
Only treatment emergent AEs are displayed. All counts represent numbers of patients.
Multiple occurrences of the same preferred term in one individual are counted once at the highest grade for that preferred term.

Program: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/program/t_ae_ctc.sas
Output: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/output/t_ae_ctc_SE_P2_c_bo30185.out
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Summary of Adverse Events by Highest NCI CTCAE Grade: Part 2, Safety Evaluated Population
Protocol: BO30185
Clinical cut-off date: 31MAY2018
Database lock date: 26JUL2018

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Perjeta 600 mg SC + Herceptin 600 mg SC (coformulated)<br>Cohort C<br>(N=20) |
|---|---|---|
| ほてり | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 精神障害 | | |
| - Overall - | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 不眠症 | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 代謝および栄養障害 | | |
| - Overall - | -Any Grade- | 1 |
| | 1 | 0 |
| | 2 | 1 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 食欲減退 | -Any Grade- | 1 |
| | 1 | 0 |
| | 2 | 1 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |

Investigator text for AEs encoded using MedDRA version 21.0.
Only treatment emergent AEs are displayed. All counts represent numbers of patients.
Multiple occurrences of the same preferred term in one individual are counted once at the highest grade for that preferred term.

Program: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/program/t_ae_ctc.sas
Output: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/output/t_ae_ctc_SE_P2_c_bo30185.out

Summary of Adverse Events by Highest NCI CTCAE Grade: Part 2, Safety Evaluated Population
Protocol: BO30185
Clinical cut-off date: 31MAY2018
Database lock date: 26JUL2018

| MedDRA System Organ Class<br>MedDRA Preferred Term | Grade | Perjeta 600 mg SC + Herceptin 600 mg SC (coformulated)<br>Cohort C<br>(N=20) |
|---|---|---|
| 免疫系障害 | | |
| - Overall - | -Any Grade- | 1 |
| | 1 | 0 |
| | 2 | 1 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 季節性アレルギー | -Any Grade- | 1 |
| | 1 | 0 |
| | 2 | 1 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 臨床検査 | | |
| - Overall - | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |
| 心電図Ｔ波逆転 | -Any Grade- | 1 |
| | 1 | 1 |
| | 2 | 0 |
| | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | Missing | 0 |

Investigator text for AEs encoded using MedDRA version 21.0.
Only treatment emergent AEs are displayed. All counts represent numbers of patients.
Multiple occurrences of the same preferred term in one individual are counted once at the highest grade for that preferred term.

Program: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/program/t_ae_ctc.sas
Output: root/clinical_studies/RO4368451/CDPT3514/BO30185/data_analysis/CTD2/prod/output/t_ae_ctc_SE_P2_c_bo30185.out
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［5.3.5.3-1 t_ae_ctc_SE_P2_c_bo30185 を再掲］

### 2.7.6.2.2 個別症例の詳細

安全性評価に用いた3試験（FeDeriCa 試験，PHranceSCa 試験及び BO30185試験）の個別症例の詳細は，個々の総括報告書（5.3.5.1-1-1 1.NARRATIVES，5.3.5.1-3 1.NARRATIVES 及び 5.3.3.2-1 1.NARRATIVES）に記載した。