



Clinical trial results:

A randomized phase II trial of pertuzumab in combination with trastuzumab with or without chemotherapy, both followed by T-DM1 in case of progression, in patients with HER2-positive metastatic breast cancer

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2012-002556-17 |
| Trial protocol | FR DE NL |
| Global end of trial date | 31 May 2020 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 19 June 2022 |
| First version publication date | 19 June 2022 |

Trial information

Trial identification

| | |
|-----------------------|------------------------|
| Sponsor protocol code | SAKK22/10/UC-0140/1207 |
|-----------------------|------------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01835236 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | UNICANCER |
| Sponsor organisation address | 101 rue de Tolbiac, Paris, France, 75013 |
| Public contact | Nourredine AIT-RAHMOUNE, UNICANCER, 33 1 71 93 67 04, n.ait-rahmoune@unicancer.fr |
| Scientific contact | Jerôme Lemonnier, chef de projets, UNICANCER, 33 1 71 93 67 02, j-lemonnier@unicancer.fr |
| Sponsor organisation name | SAKK |
| Sponsor organisation address | Effingerstrasse 33, Bern, Switzerland, CH-3008 |
| Public contact | Sabrina Chiquet, SAKK - SWISS GROUP FOR CLINICAL CANCER RESEARCH, 41 31 389 91 84, sabrina.chiquet@sakk.ch |
| Scientific contact | Sabrina Chiquet, SAKK - SWISS GROUP FOR CLINICAL CANCER RESEARCH, 41 31 389 91 84, sabrina.chiquet@sakk.ch |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No | No |

| |
|--------------------------------|
| 1901/2006 apply to this trial? |
|--------------------------------|

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 12 October 2020 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 31 May 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial is to evaluate the efficacy in terms of overall survival (OS) at 24 months of a chemotherapy-free dual HER2-inhibition with trastuzumab and pertuzumab (first-line) followed by T-DM1 (second-line) and of a chemotherapy-containing dual HER2-inhibition with trastuzumab and pertuzumab (first-line) followed by T-DM1 (second-line) in patients with HER2-positive metastatic breast cancer.

Protection of trial subjects:

In order to ensure the protection of the rights, safety and well-being of trial subjects, this clinical trial was conducted in accordance with the Declaration of Helsinki (1964) and subsequent amendments, ICH Good Clinical Practice Guidelines (CPMP/ICH/135/95), the European Directive (2001/20/CE) and the applicable local regulatory requirements and laws.

Furthermore, independent Ethics Committees reviewed and gave favorable opinions to the study documents, including the initial protocol and all subsequent amendments, and all information and documents provided to subjects/patients.

Written informed consent was obtained from all patients prior to enrollment.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 01 May 2013 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 4 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------|
| Country: Number of subjects enrolled | Netherlands: 13 |
| Country: Number of subjects enrolled | France: 119 |
| Country: Number of subjects enrolled | Germany: 3 |
| Country: Number of subjects enrolled | Switzerland: 75 |
| Worldwide total number of subjects | 210 |
| EEA total number of subjects | 135 |

Notes:

| Subjects enrolled per age group | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 126 |
| From 65 to 84 years | 84 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Pernetta was an international, multicenter, randomized, open label, phase II trial designed to compare the effect of pertuzumab in combination with trastuzumab with or without chemotherapy, both followed by T-DM1 in case of progression, on overall survival at 2 years in patients with HER2-positive metastatic breast cancer.

Pre-assignment

Screening details:

The trial consisted of a screening phase before randomization to establish eligibility, a treatment phase (3-week treatment cycles; 12 cycles), and a long-term follow-up to monitor overall survival, progression-free survival, time to failure of strategy, objective response, disease control, quality of life, and safety.

Period 1

| | |
|------------------------------|-------------------------|
| Period 1 title | First-line treatment |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Chemotherapy-free dual HER2-inbibition |

Arm description:

Chemotherapy-free dual HER2-inbibition with trastuzumab and pertuzumab:

* Trastuzumab was first administrated (loading dose) at 8 mg/kg by intravenous infusion over 90 min then every 3 weeks at 8 mg/kg by intravenous infusion over 30 to 90 min.

* Pertuzumab was first administrated (loading dose) at 840 mg by intravenous infusion over 60 min then every 3 weeks at 420 mg by intravenous infusion over 30 to 90 min.

Patients with hormone receptor-positive disease should have received endocrine therapy. Treatment was to be prescribed according to the current guidelines.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Trastuzumab |
| Investigational medicinal product code | |
| Other name | Herceptin |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Trastuzumab was first administrated (loading dose) at 8 mg/kg by intravenous infusion over 90 min then every 3 weeks untill disease progression at 8 mg/kg by intravenous infusion over 30 to 90 min.

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Pertuzumab |
| Investigational medicinal product code | |
| Other name | Perjeta |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Pertuzumab was first administrated (loading dose) at 840 mg by intravenous infusion over 60 min then every 3 weeks at 420 mg by intravenous infusion over 30 to 90 min. Pertuzumab was administered after a 30-minute observation period following the administration of trastuzumab.

| | |
|-----------|--|
| Arm title | Chemotherapy-containing dual HER2-inbibition |
|-----------|--|

Arm description:

Chemotherapy-containing dual HER2-inbibition with trastuzumab and pertuzumab:

HER2-inhibition:

* Trastuzumab first administrated (loading dose) at 8 mg/kg by intravenous infusion over 90 min then every 3 weeks at 8 mg/kg by intravenous infusion over 30 to 90 min.

PLUS

* Pertuzumab first administrated (loading dose) at 840 mg by intravenous infusion over 60 min then every 3 weeks at 420 mg by intravenous infusion over 30 to 90 min.

Chemotherapy:

* Paclitaxel administrated by intravenous infusion at 90 mg/m² on day 1, 8, and 15 every 4 weeks for ≥4 months.

OR

* Vinorelbine first administrated by intravenous infusion at 25 mg/m² on day 1, 8 then by intravenous infusion at 30 mg/m² on day 1, 8, and 15 every 3 weeks for ≥4 months.

Patients with hormone receptor-positive disease should have received endocrine therapy. Treatment was to be prescribed according to the current guidelines.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Trastuzumab |
| Investigational medicinal product code | |
| Other name | Herceptin |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Trastuzumab was first administrated (loading dose) at 8 mg/kg by intravenous infusion over 90 min then every 3 weeks until disease progression at 8 mg/kg by intravenous infusion over 30 to 90 min.

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Pertuzumab |
| Investigational medicinal product code | |
| Other name | Perjeta |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Pertuzumab was first administrated (loading dose) at 840 mg by intravenous infusion over 60 min then every 3 weeks at 420 mg by intravenous infusion over 30 to 90 min. Pertuzumab was administered after a 30-minute observation period following the administration of trastuzumab.

| | |
|--|------------------------------------|
| Investigational medicinal product name | Paclitaxel |
| Investigational medicinal product code | |
| Other name | Abraxane |
| Pharmaceutical forms | Powder for dispersion for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Paclitaxel was administrated by intravenous infusion at 90 mg/m² on day 1, 8, and 15 every 4 weeks for ≥4 months.

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Vinorelbine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravascular use |

Dosage and administration details:

Vinorelbine was first administrated by intravenous infusion at 25 mg/m² on day 1, 8 then by intravenous infusion at 30 mg/m² on day 1, 8, and 15 every 3 weeks for ≥4 months.

| Number of subjects in period 1 | Chemotherapy-free dual HER2-inhibition | Chemotherapy-containing dual HER2-inhibition |
|---|--|--|
| | | |
| Started | 105 | 105 |
| Completed | 64 | 47 |
| Not completed | 41 | 58 |
| Physician decision | 7 | 7 |
| Patient never received treatment | - | 2 |
| Secondary malignancy | - | 1 |
| HER2 treatment held for >2 administrations | 2 | 1 |
| Sponsor decision | 10 | 13 |
| Consent withdrawn by subject | 1 | 2 |
| Adverse event, non-fatal | 4 | 5 |
| Symptomatic deterioration during 1st-line therapy | 3 | 2 |
| Death | - | 1 |
| Unknown | - | 2 |
| Radiotherapy of a bone metastasis | - | 1 |
| Patient's refusal to continue the treatment | 7 | 9 |
| Symptomatic after PD under 1st-line therapy | - | 1 |
| Age-related | - | 1 |
| Protocol deviation | 7 | 10 |

Period 2

| | |
|------------------------------|-----------------------|
| Period 2 title | Second-line treatment |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------|-------|
| Arm title | T-DM1 |
|------------------|-------|

Arm description:

Following disease progression under 1st_line treatment, T-DM1 was administrated every 3 weeks until unacceptable toxicity or disease progression at the dose of 3.6 mg/kg by intravenous infusion.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | T-DM1 |
| Investigational medicinal product code | |
| Other name | Kadcyla |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

T-DM1 was administrated at the dose of 3.6 mg/kg by intravenous infusion every 3 weeks until

unacceptable toxicity or disease progression.

| Number of subjects in period 2 | T-DM1 |
|---------------------------------------|--------------|
| Started | 111 |
| Completed | 7 |
| Not completed | 104 |
| Physician decision | 3 |
| Patient decision | 4 |
| Disease progression | 75 |
| Adverse event, non-fatal | 5 |
| Death | 3 |
| Secondary malignancy | 2 |
| Symptomatic deterioration under T-DM1 | 6 |
| Protocol deviation | 6 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Chemotherapy-free dual HER2-inbibition |
|-----------------------|--|

Reporting group description:

Chemotherapy-free dual HER2-inbibition with trastuzumab and pertuzumab:

* Trastuzumab was first administrated (loading dose) at 8 mg/kg by intravenous infusion over 90 min then every 3 weeks at 8 mg/kg by intravenous infusion over 30 to 90 min.

* Pertuzumab was first administrated (loading dose) at 840 mg by intravenous infusion over 60 min then every 3 weeks at 420 mg by intravenous infusion over 30 to 90 min.

Patients with hormone receptor-positive disease should have received endocrine therapy. Treatment was to be prescribed according to the current guidelines.

| | |
|-----------------------|--|
| Reporting group title | Chemotherapy-containing dual HER2-inbibition |
|-----------------------|--|

Reporting group description:

Chemotherapy-containing dual HER2-inbibition with trastuzumab and pertuzumab:

HER2-inhibition:

* Trastuzumab first administrated (loading dose) at 8 mg/kg by intravenous infusion over 90 min then every 3 weeks at 8 mg/kg by intravenous infusion over 30 to 90 min.

PLUS

* Pertuzumab first administrated (loading dose) at 840 mg by intravenous infusion over 60 min then every 3 weeks at 420 mg by intravenous infusion over 30 to 90 min.

Chemotherapy:

* Paclitaxel administrated by intravenous infusion at 90 mg/m² on day 1, 8, and 15 every 4 weeks for ≥4 months.

OR

* Vinorelbine first administrated by intravenous infusion at 25 mg/m² on day 1, 8 then by intravenous infusion at 30 mg/m² on day 1, 8, and 15 every 3 weeks for ≥4 months.

Patients with hormone receptor-positive disease should have received endocrine therapy. Treatment was to be prescribed according to the current guidelines.

| Reporting group values | Chemotherapy-free dual HER2-inbibition | Chemotherapy-containing dual HER2-inbibition | Total |
|--|--|--|-------|
| Number of subjects | 105 | 105 | 210 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | 0 |
| Preterm newborn infants (gestational age < 37 wks) | | | 0 |
| Newborns (0-27 days) | | | 0 |
| Infants and toddlers (28 days-23 months) | | | 0 |
| Children (2-11 years) | | | 0 |
| Adolescents (12-17 years) | | | 0 |
| Adults (18-64 years) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous | | | |
| Units: years | | | |
| median | 59 | 57 | |
| full range (min-max) | 28 to 85 | 26 to 81 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 105 | 105 | 210 |

| | | | |
|------|---|---|---|
| Male | 0 | 0 | 0 |
|------|---|---|---|

| | | | |
|---------------------------|------------|------------|-----|
| WHO performance status | | | |
| Units: Subjects | | | |
| ECOG 0 | 61 | 66 | 127 |
| ECOG 1 | 37 | 38 | 75 |
| ECOG 2 | 7 | 1 | 8 |
| Hormone receptor status | | | |
| Units: Subjects | | | |
| Positive | 68 | 66 | 134 |
| Negative | 37 | 39 | 76 |
| Primary metastatic | | | |
| Units: Subjects | | | |
| Yes | 40 | 36 | 76 |
| No | 65 | 69 | 134 |
| Prior chemotherapy | | | |
| Units: Subjects | | | |
| Yes | 53 | 47 | 100 |
| No | 52 | 57 | 109 |
| Missing | 0 | 1 | 1 |
| Prior anti-HER2 treatment | | | |
| Units: Subjects | | | |
| Yes | 44 | 42 | 86 |
| No | 61 | 62 | 123 |
| Missing | 0 | 1 | 1 |
| Prior endocrine therapy | | | |
| Units: Subjects | | | |
| Yes | 42 | 36 | 78 |
| No | 63 | 68 | 131 |
| Missing | 0 | 1 | 1 |
| Weight | | | |
| Units: Kg | | | |
| median | 66 | 68 | |
| full range (min-max) | 33 to 113 | 43 to 125 | - |
| Height | | | |
| Units: cm | | | |
| median | 162 | 163 | |
| full range (min-max) | 146 to 180 | 146 to 182 | - |
| Body surface | | | |
| Units: m2 | | | |
| median | 1.7 | 1.7 | |
| full range (min-max) | 1.2 to 2.3 | 1.4 to 2.2 | - |

End points

End points reporting groups

| | |
|---|--|
| Reporting group title | Chemotherapy-free dual HER2-inbibition |
| Reporting group description: | |
| Chemotherapy-free dual HER2-inbibition with trastuzumab and pertuzumab: | |
| * Trastuzumab was first administrated (loading dose) at 8 mg/kg by intravenous infusion over 90 min then every 3 weeks at 8 mg/kg by intravenous infusion over 30 to 90 min. | |
| * Pertuzumab was first administrated (loading dose) at 840 mg by intravenous infusion over 60 min then every 3 weeks at 420 mg by intravenous infusion over 30 to 90 min. | |
| Patients with hormone receptor-positive disease should have received endocrine therapy. Treatment was to be prescribed according to the current guidelines. | |
| Reporting group title | Chemotherapy-containing dual HER2-inbibition |
| Reporting group description: | |
| Chemotherapy-containing dual HER2-inbibition with trastuzumab and pertuzumab: | |
| HER2-inhibition: | |
| * Trastuzumab first administrated (loading dose) at 8 mg/kg by intravenous infusion over 90 min then every 3 weeks at 8 mg/kg by intravenous infusion over 30 to 90 min. | |
| PLUS | |
| * Pertuzumab first administrated (loading dose) at 840 mg by intravenous infusion over 60 min then every 3 weeks at 420 mg by intravenous infusion over 30 to 90 min. | |
| Chemotherapy: | |
| * Paclitaxel administrated by intravenous infusion at 90 mg/m ² on day 1, 8, and 15 every 4 weeks for ≥4 months. | |
| OR | |
| * Vinorelbine first administrated by intravenous infusion at 25 mg/m ² on day 1, 8 then by intravenous infusion at 30 mg/m ² on day 1, 8, and 15 every 3 weeks for ≥4 months. | |
| Patients with hormone receptor-positive disease should have received endocrine therapy. Treatment was to be prescribed according to the current guidelines. | |
| Reporting group title | T-DM1 |
| Reporting group description: | |
| Following disease progression under 1st_line treatment, T-DM1 was administrated every 3 weeks until unacceptable toxicity or disease progression at the dose of 3.6 mg/kg by intravenous infusion. | |

Primary: Overall survival at 24 months

| | |
|---|--|
| End point title | Overall survival at 24 months ^[1] |
| End point description: | |
| The primary objective of this trial was to evaluate the efficacy in terms of overall survival at 24 months of a chemotherapy-free dual HER2-inbibition with trastuzumab and pertuzumab (first-line) followed by T-DM1 (second-line) and of a chemotherapy-containing dual HER2-inhibition with trastuzumab and pertuzumab (first-line) followed by T-DM1 (second-line) in patients with HER2-positive metastatic breast cancer. | |
| End point type | Primary |
| End point timeframe: | |
| Overall survival was defined as the amount of patients being alive at least 24 months after randomization. | |
| Notes: | |
| [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. | |
| Justification: Statistical comparisons by hypothesis tests between treatment arms were not planned as the power would be very low. | |

| End point values | Chemotherapy-free dual HER2-inbibition | Chemotherapy-containing dual HER2-inbibition | | |
|-----------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 105 | 105 | | |
| Units: Percent of patients | | | | |
| Alive | 79 | 78 | | |
| Dead | 21 | 22 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival of 1st-line treatment ignoring first CNS lesion

| | |
|-----------------|---|
| End point title | Progression-free survival of 1st-line treatment ignoring first CNS lesion |
|-----------------|---|

End point description:

Progression-free survival (PFS) of first-line treatment ignoring first central nervous system (CNS) lesion was the time from randomization to first event of disease progression (ignoring first CNS lesion event) or death of any cause, whichever occurs first.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Tumor assessment were performed at baseline and after 8, 16, and 24 weeks, thereafter every 12 weeks during 1st-line treatment.

| End point values | Chemotherapy-free dual HER2-inbibition | Chemotherapy-containing dual HER2-inbibition | | |
|----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 105 | 105 | | |
| Units: month | | | | |
| median (confidence interval 95%) | 8.4 (7.9 to 12.0) | 23.3 (18.9 to 33.1) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PFS of second-line treatment

| | |
|-----------------|------------------------------|
| End point title | PFS of second-line treatment |
|-----------------|------------------------------|

End point description:

PFS of second-line treatment was defined as the time from registration to second-line treatment to the first event of disease progression during second-line treatment or death of any cause, whichever occurs first.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Tumor assessment were performed within 3 weeks prior to second-line registration, after 9 and 18

weeks, then every 12 weeks.

| End point values | T-DM1 | | | |
|----------------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 111 | | | |
| Units: month | | | | |
| median (confidence interval 95%) | 6.9 (5.0 to 11.5) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PFS of second-line treatment ignoring first CNS lesion

| | |
|-----------------|--|
| End point title | PFS of second-line treatment ignoring first CNS lesion |
|-----------------|--|

End point description:

PFS of second-line treatment was defined as the time from registration to second-line treatment to the first event of disease progression (ignoring CNS lesion) during second-line treatment or death of any cause, whichever occurs first.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Tumor assessment were performed within 3 weeks prior to second-line registration, after 9 and 18 weeks, then every 12 weeks.

| End point values | T-DM1 | | | |
|----------------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 111 | | | |
| Units: month | | | | |
| median (confidence interval 95%) | 8.9 (5.3 to 11.7) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to failure of strategy of first- plus second-line treatment

| | |
|-----------------|--|
| End point title | Time to failure of strategy of first- plus second-line treatment |
|-----------------|--|

End point description:

Time to failure of strategy (TFS) of first- plus second-line treatment was defined as the time from randomization to a TFS event of first- plus second-line treatment. A TFS event of first- plus second-line treatment was defined as disease progression, CNS progression, or death of any cause, whichever occurred first.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Tumor assessment were performed at baseline and after 8, 16, and 24 weeks, and every 12 weeks thereafter until disease progression then within 3 weeks prior to second-line registration, after 9 and 18 weeks, then every 12 weeks.

| End point values | Chemotherapy-free dual HER2-inhibition | Chemotherapy-containing dual HER2-inhibition | | |
|----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 105 | 105 | | |
| Units: month | | | | |
| median (confidence interval 95%) | 29.0 (18.9 to 63.4) | 48.6 (35.8 to 69.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

| | |
|-----------------|------------------|
| End point title | Overall survival |
|-----------------|------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

OS was defined as the time from randomization until death by any cause.

| End point values | Chemotherapy-free dual HER2-inhibition | Chemotherapy-containing dual HER2-inhibition | | |
|----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 105 | 105 | | |
| Units: month | | | | |
| median (confidence interval 95%) | 60.5 (42.6 to 81) | 68.8 (55.3 to 75) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response of first-line treatment (based on investigator's assessment)

| | |
|-----------------|---|
| End point title | Objective response of first-line treatment (based on investigator's assessment) |
|-----------------|---|

End point description:

Objective response (OR) of first-line treatment was defined as the status complete response (CR) or partial response (PR) succeeded as best response during first-line of treatment.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Tumor assessment were performed at baseline and after 8, 16, and 24 weeks, thereafter every 12 weeks during 1st-line treatment.

| End point values | Chemotherapy-free dual HER2-inbibition | Chemotherapy-containing dual HER2-inbibition | | |
|-----------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 105 | 105 | | |
| Units: Percent of patients | | | | |
| CR | 7 | 25 | | |
| PR | 38 | 36 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control of first-line treatment (based on investigator's assessment)

| | |
|-----------------|--|
| End point title | Disease control of first-line treatment (based on investigator's assessment) |
|-----------------|--|

End point description:

Disease control (DC) of first-line treatment was defined as the status of response CR, PR or stable disease (SD) for a period of 6 months and no progressive disease (PD) at 6 months after randomization. Patients with SD and last evaluation before 6 months after randomization or no assessment within 6 months after randomization were not considered.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Tumor assessment were performed at baseline and after 8, 16, and 24 weeks, thereafter every 12 weeks during 1st-line treatment.

| End point values | Chemotherapy-free dual HER2-inbibition | Chemotherapy-containing dual HER2-inbibition | | |
|-----------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 105 | 105 | | |
| Units: Percent of patients | | | | |
| CR | 7 | 25 | | |
| PR | 38 | 36 | | |
| SD ≥6 months | 17 | 18 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: OR of second-line treatment (based on investigator's assessment)

| | |
|-----------------|--|
| End point title | OR of second-line treatment (based on investigator's assessment) |
|-----------------|--|

End point description:

OR of second-line treatment was defined as the status of response CR or PR succeeded as best response during second-line of treatment.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Tumor assessment were performed within 3 weeks prior to second-line registration, after 9 and 18 weeks, then every 12 weeks.

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | T-DM1 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 111 | | | |
| Units: Percent of patients | | | | |
| CR | 8 | | | |
| PR | 21 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: DC of second-line treatment (based on investigator's assessment)

| | |
|-----------------|--|
| End point title | DC of second-line treatment (based on investigator's assessment) |
|-----------------|--|

End point description:

DC of second-line treatment was defined as the status of response CR, PR or SD for a period of 6 months and no PD at 6 months after registration of second-line treatment. Patients with SD and last evaluation before 6 months after registration to the second-line of treatment or no assessment within 6 months after registration to the second-line of treatment were not considered.

| | |
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| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Tumor assessment were performed within 3 weeks prior to second-line registration, after 9 and 18 weeks, then every 12 weeks.

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | T-DM1 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 111 | | | |
| Units: Percent of patients | | | | |
| CR | 8 | | | |
| PR | 21 | | | |
| SD ≥6 months | 17 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From inclusion until 30 days after end of treatment (up to 7 years).

Adverse event reporting additional description:

For non-serious adverse events, the number of occurrences were not recorded, the number of patient affected were the only value available. Thus, the number of patient affected was entered in both "Subjects affected number" and "Occurrence all number" fields.

| | |
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| Assessment type | Systematic |
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Dictionary used

| | |
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| Dictionary name | MedDRA |
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| | |
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| Dictionary version | 17 |
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Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Chemotherapy-free dual HER2-inbibition |
|-----------------------|--|

Reporting group description: -

| | |
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| Reporting group title | Chemotherapy-containing dual HER2-inbibition |
|-----------------------|--|

Reporting group description: -

| | |
|-----------------------|---------------------|
| Reporting group title | Second-line therapy |
|-----------------------|---------------------|

Reporting group description: -

| Serious adverse events | Chemotherapy-free dual HER2-inbibition | Chemotherapy-containing dual HER2-inbibition | Second-line therapy |
|---|--|--|---------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 46 / 105 (43.81%) | 37 / 103 (35.92%) | 38 / 111 (34.23%) |
| number of deaths (all causes) | 33 | 26 | 39 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Basalioma | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast angiosarcoma | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---------------------------|-----------------|-----------------|
| Leiomyomas of the uterus | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-Hodgkin's lymphoma | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ovarian cyst | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Disease progression | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Vascular disorders | | | |
| Lymphoedema | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thromboembolic event | Additional description: 1 | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 1 / 103 (0.97%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Adnexectomy | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast conserving surgery with ALND | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|-----------------|-----------------|-----------------|
| Hallux valgus requiring surgery subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Persistent exulceration of primary tumor requiring palliative ablation subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary lobectomy (L) with hilar and mediastinal adenectomy subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spine surgery subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Fever | | | |
| subjects affected / exposed | 2 / 105 (1.90%) | 1 / 103 (0.97%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malaise | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neurologic symptom | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-cardiac chest pain | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reduced general condition | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 1 / 103 (0.97%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Allergic reaction | | | |
| subjects affected / exposed | 4 / 105 (3.81%) | 0 / 103 (0.00%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Pelvic organ prolapse | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 1 / 103 (0.97%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thoracic pain | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Confusion | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depression | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| AST and ALT increased | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 3 / 111 (2.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 2 / 103 (1.94%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cranio-cerebral injury | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fracture | | | |
| subjects affected / exposed | 2 / 105 (1.90%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Incisional hernia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seroma | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal fracture | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vertebral compression fracture | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| 3-vessel coronary disease | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericarditis | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 2 / 111 (1.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Parkinson's disease | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral sensory neuropathy | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Transient ischemic attacks | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 3 / 103 (2.91%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast infection | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Optic nerve disorder | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 105 (1.90%) | 4 / 103 (3.88%) | 2 / 111 (1.80%) |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 4 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 105 (1.90%) | 1 / 103 (0.97%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Back pain | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 1 / 103 (0.97%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone pain | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 1 / 103 (0.97%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscle cramps generalized | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pathologic bone fracture | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Bacterial infection | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COVID-19 lung infection | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Catheter-related infection | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 1 / 103 (0.97%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocarditis infective | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fever | | | |

| | | | |
|---|-----------------|-----------------|-------------------|
| subjects affected / exposed | 1 / 105 (0.95%) | 1 / 103 (0.97%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Kidney infection | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung infection | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 2 / 103 (1.94%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Purulent pleurisy | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 1 / 103 (0.97%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin infection | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spondylodiscitis | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 103 (0.00%) | 12 / 111 (10.81%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vulval infection | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 2 / 103 (1.94%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Chemotherapy-free dual HER2-inhibition | Chemotherapy-containing dual HER2-inhibition | Second-line therapy |
|---|--|--|---------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 105 / 105 (100.00%) | 103 / 103 (100.00%) | 111 / 111 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour pain | | | |
| subjects affected / exposed | 6 / 105 (5.71%) | 3 / 103 (2.91%) | 4 / 111 (3.60%) |
| occurrences (all) | 6 | 3 | 4 |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 4 / 105 (3.81%) | 7 / 103 (6.80%) | 2 / 111 (1.80%) |
| occurrences (all) | 4 | 7 | 2 |
| Hot flush | | | |
| subjects affected / exposed | 19 / 105 (18.10%) | 10 / 103 (9.71%) | 13 / 111 (11.71%) |
| occurrences (all) | 19 | 10 | 13 |
| Hypertension | | | |
| subjects affected / exposed | 100 / 105 (95.24%) | 102 / 103 (99.03%) | 104 / 111 (93.69%) |
| occurrences (all) | 100 | 102 | 104 |
| General disorders and administration site conditions | | | |
| Chills | | | |
| subjects affected / exposed | 8 / 105 (7.62%) | 7 / 103 (6.80%) | 7 / 111 (6.31%) |
| occurrences (all) | 8 | 7 | 7 |
| Oedema limbs | | | |

| | | | |
|---|-------------------|-------------------|-------------------|
| subjects affected / exposed | 9 / 105 (8.57%) | 15 / 103 (14.56%) | 12 / 111 (10.81%) |
| occurrences (all) | 9 | 15 | 12 |
| Fatigue | | | |
| subjects affected / exposed | 60 / 105 (57.14%) | 81 / 103 (78.64%) | 79 / 111 (71.17%) |
| occurrences (all) | 60 | 81 | 79 |
| Fever | | | |
| subjects affected / exposed | 24 / 105 (22.86%) | 22 / 103 (21.36%) | 10 / 111 (9.01%) |
| occurrences (all) | 24 | 22 | 10 |
| Flu like symptoms | | | |
| subjects affected / exposed | 18 / 105 (17.14%) | 14 / 103 (13.59%) | 10 / 111 (9.01%) |
| occurrences (all) | 18 | 14 | 10 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 3 / 105 (2.86%) | 9 / 103 (8.74%) | 3 / 111 (2.70%) |
| occurrences (all) | 3 | 9 | 3 |
| Pain | | | |
| subjects affected / exposed | 22 / 105 (20.95%) | 32 / 103 (31.07%) | 18 / 111 (16.22%) |
| occurrences (all) | 22 | 32 | 18 |
| Pharyngitis | | | |
| subjects affected / exposed | 4 / 105 (3.81%) | 10 / 103 (9.71%) | 2 / 111 (1.80%) |
| occurrences (all) | 4 | 10 | 2 |
| Immune system disorders | | | |
| Allergic reaction | | | |
| subjects affected / exposed | 15 / 105 (14.29%) | 10 / 103 (9.71%) | 3 / 111 (2.70%) |
| occurrences (all) | 15 | 10 | 3 |
| Reproductive system and breast disorders | | | |
| Breast pain | | | |
| subjects affected / exposed | 4 / 105 (3.81%) | 6 / 103 (5.83%) | 6 / 111 (5.41%) |
| occurrences (all) | 4 | 6 | 6 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Allergic rhinitis | | | |
| subjects affected / exposed | 11 / 105 (10.48%) | 16 / 103 (15.53%) | 8 / 111 (7.21%) |
| occurrences (all) | 11 | 16 | 8 |
| Cough | | | |
| subjects affected / exposed | 22 / 105 (20.95%) | 23 / 103 (22.33%) | 19 / 111 (17.12%) |
| occurrences (all) | 22 | 23 | 19 |
| Dyspnoea | | | |

| | | | |
|--|-------------------------|-------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 34 / 105 (32.38%) 34 | 23 / 103 (22.33%) 23 | 27 / 111 (24.32%) 27 |
| Epistaxis subjects affected / exposed occurrences (all) | 16 / 105 (15.24%) 16 | 24 / 103 (23.30%) 24 | 19 / 111 (17.12%) 19 |
| Voice alteration subjects affected / exposed occurrences (all) | 4 / 105 (3.81%) 4 | 7 / 103 (6.80%) 7 | 1 / 111 (0.90%) 1 |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 9 / 105 (8.57%) 9 | 7 / 103 (6.80%) 7 | 7 / 111 (6.31%) 7 |
| Depression subjects affected / exposed occurrences (all) | 7 / 105 (6.67%) 7 | 14 / 103 (13.59%) 14 | 11 / 111 (9.91%) 11 |
| Insomnia subjects affected / exposed occurrences (all) | 21 / 105 (20.00%) 21 | 16 / 103 (15.53%) 16 | 11 / 111 (9.91%) 11 |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 41 / 105 (39.05%) 41 | 66 / 103 (64.08%) 66 | 76 / 111 (68.47%) 76 |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 52 / 105 (49.52%) 52 | 54 / 103 (52.43%) 54 | 64 / 111 (57.66%) 64 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 53 / 105 (50.48%) 53 | 66 / 103 (64.08%) 66 | 96 / 111 (86.49%) 96 |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 13 / 105 (12.38%) 13 | 11 / 103 (10.68%) 11 | 17 / 111 (15.32%) 17 |
| Creatinine urine increased subjects affected / exposed occurrences (all) | 34 / 105 (32.38%) 34 | 34 / 103 (33.01%) 34 | 30 / 111 (27.03%) 30 |
| Ejection fraction decreased | | | |

| | | | |
|--|-------------------------|-------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 10 / 105 (9.52%) 10 | 8 / 103 (7.77%) 8 | 1 / 111 (0.90%) 1 |
| Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) | 6 / 105 (5.71%) 6 | 7 / 103 (6.80%) 7 | 16 / 111 (14.41%) 16 |
| Lymphocyte count decreased subjects affected / exposed occurrences (all) | 7 / 105 (6.67%) 7 | 6 / 103 (5.83%) 6 | 4 / 111 (3.60%) 4 |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 19 / 105 (18.10%) 19 | 59 / 103 (57.28%) 59 | 28 / 111 (25.23%) 28 |
| Platelet count decreased subjects affected / exposed occurrences (all) | 15 / 105 (14.29%) 15 | 25 / 103 (24.27%) 25 | 76 / 111 (68.47%) 76 |
| Weight gain subjects affected / exposed occurrences (all) | 33 / 105 (31.43%) 33 | 32 / 103 (31.07%) 32 | 19 / 111 (17.12%) 19 |
| Weight loss subjects affected / exposed occurrences (all) | 38 / 105 (36.19%) 38 | 58 / 103 (56.31%) 58 | 54 / 111 (48.65%) 54 |
| Injury, poisoning and procedural complications Fracture subjects affected / exposed occurrences (all) | 2 / 105 (1.90%) 2 | 6 / 103 (5.83%) 6 | 2 / 111 (1.80%) 2 |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 10 / 105 (9.52%) 10 | 16 / 103 (15.53%) 16 | 6 / 111 (5.41%) 6 |
| Dysesthesia subjects affected / exposed occurrences (all) | 5 / 105 (4.76%) 5 | 11 / 103 (10.68%) 11 | 9 / 111 (8.11%) 9 |
| Dysgeusia subjects affected / exposed occurrences (all) | 15 / 105 (14.29%) 15 | 20 / 103 (19.42%) 20 | 10 / 111 (9.01%) 10 |
| Headache | | | |

| | | | |
|---|-------------------------|-------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 25 / 105 (23.81%) 25 | 31 / 103 (30.10%) 31 | 21 / 111 (18.92%) 21 |
| Paraesthesia subjects affected / exposed occurrences (all) | 13 / 105 (12.38%) 13 | 34 / 103 (33.01%) 34 | 16 / 111 (14.41%) 16 |
| Peripheral motor neuropathy subjects affected / exposed occurrences (all) | 2 / 105 (1.90%) 2 | 5 / 103 (4.85%) 5 | 7 / 111 (6.31%) 7 |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 14 / 105 (13.33%) 14 | 36 / 103 (34.95%) 36 | 24 / 111 (21.62%) 24 |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 48 / 105 (45.71%) 48 | 86 / 103 (83.50%) 86 | 69 / 111 (62.16%) 69 |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 10 / 105 (9.52%) 10 | 10 / 103 (9.71%) 10 | 8 / 111 (7.21%) 8 |
| Eye disorders Blurred vision subjects affected / exposed occurrences (all) | 2 / 105 (1.90%) 2 | 7 / 103 (6.80%) 7 | 2 / 111 (1.80%) 2 |
| Dry eye subjects affected / exposed occurrences (all) | 9 / 105 (8.57%) 9 | 9 / 103 (8.74%) 9 | 8 / 111 (7.21%) 8 |
| Watering eyes subjects affected / exposed occurrences (all) | 5 / 105 (4.76%) 5 | 11 / 103 (10.68%) 11 | 9 / 111 (8.11%) 9 |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) | 18 / 105 (17.14%) 18 | 24 / 103 (23.30%) 24 | 11 / 111 (9.91%) 11 |
| Constipation subjects affected / exposed occurrences (all) | 15 / 105 (14.29%) 15 | 29 / 103 (28.16%) 29 | 26 / 111 (23.42%) 26 |
| Diarrhoea | | | |

| | | | |
|--|-------------------|-------------------|-------------------|
| subjects affected / exposed | 60 / 105 (57.14%) | 77 / 103 (74.76%) | 26 / 111 (23.42%) |
| occurrences (all) | 60 | 77 | 26 |
| Dry mouth | | | |
| subjects affected / exposed | 3 / 105 (2.86%) | 3 / 103 (2.91%) | 11 / 111 (9.91%) |
| occurrences (all) | 3 | 3 | 11 |
| Dyspepsia | | | |
| subjects affected / exposed | 8 / 105 (7.62%) | 14 / 103 (13.59%) | 7 / 111 (6.31%) |
| occurrences (all) | 8 | 14 | 7 |
| Dysphagia | | | |
| subjects affected / exposed | 8 / 105 (7.62%) | 6 / 103 (5.83%) | 2 / 111 (1.80%) |
| occurrences (all) | 8 | 6 | 2 |
| Gastritis | | | |
| subjects affected / exposed | 6 / 105 (5.71%) | 8 / 103 (7.77%) | 4 / 111 (3.60%) |
| occurrences (all) | 6 | 8 | 4 |
| Gastroesophageal reflux disease | | | |
| subjects affected / exposed | 10 / 105 (9.52%) | 10 / 103 (9.71%) | 7 / 111 (6.31%) |
| occurrences (all) | 10 | 10 | 7 |
| Haemorrhoids | | | |
| subjects affected / exposed | 5 / 105 (4.76%) | 6 / 103 (5.83%) | 2 / 111 (1.80%) |
| occurrences (all) | 5 | 6 | 2 |
| Mucositis oral | | | |
| subjects affected / exposed | 12 / 105 (11.43%) | 30 / 103 (29.13%) | 9 / 111 (8.11%) |
| occurrences (all) | 12 | 30 | 9 |
| Nausea | | | |
| subjects affected / exposed | 34 / 105 (32.38%) | 42 / 103 (40.78%) | 39 / 111 (35.14%) |
| occurrences (all) | 34 | 42 | 39 |
| Vomiting | | | |
| subjects affected / exposed | 12 / 105 (11.43%) | 16 / 103 (15.53%) | 8 / 111 (7.21%) |
| occurrences (all) | 12 | 16 | 8 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 8 / 105 (7.62%) | 36 / 103 (34.95%) | 12 / 111 (10.81%) |
| occurrences (all) | 8 | 36 | 12 |
| Dry skin | | | |
| subjects affected / exposed | 16 / 105 (15.24%) | 26 / 103 (25.24%) | 13 / 111 (11.71%) |
| occurrences (all) | 16 | 26 | 13 |

| | | | |
|---|-------------------|-------------------|-------------------|
| Erythema | | | |
| subjects affected / exposed | 7 / 105 (6.67%) | 5 / 103 (4.85%) | 6 / 111 (5.41%) |
| occurrences (all) | 7 | 5 | 6 |
| Nail loss | | | |
| subjects affected / exposed | 5 / 105 (4.76%) | 11 / 103 (10.68%) | 5 / 111 (4.50%) |
| occurrences (all) | 5 | 11 | 5 |
| Pruritus | | | |
| subjects affected / exposed | 15 / 105 (14.29%) | 25 / 103 (24.27%) | 10 / 111 (9.01%) |
| occurrences (all) | 15 | 25 | 10 |
| Rash acneiform | | | |
| subjects affected / exposed | 11 / 105 (10.48%) | 23 / 103 (22.33%) | 3 / 111 (2.70%) |
| occurrences (all) | 11 | 23 | 3 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 11 / 105 (10.48%) | 13 / 103 (12.62%) | 5 / 111 (4.50%) |
| occurrences (all) | 11 | 13 | 5 |
| Endocrine disorders | | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 8 / 105 (7.62%) | 10 / 103 (9.71%) | 9 / 111 (8.11%) |
| occurrences (all) | 8 | 10 | 9 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 16 / 105 (15.24%) | 25 / 103 (24.27%) | 16 / 111 (14.41%) |
| occurrences (all) | 16 | 25 | 16 |
| Back pain | | | |
| subjects affected / exposed | 17 / 105 (16.19%) | 16 / 103 (15.53%) | 20 / 111 (18.02%) |
| occurrences (all) | 17 | 16 | 20 |
| Bone pain | | | |
| subjects affected / exposed | 15 / 105 (14.29%) | 16 / 103 (15.53%) | 16 / 111 (14.41%) |
| occurrences (all) | 15 | 16 | 16 |
| Flank pain | | | |
| subjects affected / exposed | 3 / 105 (2.86%) | 6 / 103 (5.83%) | 3 / 111 (2.70%) |
| occurrences (all) | 3 | 6 | 3 |
| Myalgia | | | |
| subjects affected / exposed | 14 / 105 (13.33%) | 26 / 103 (25.24%) | 15 / 111 (13.51%) |
| occurrences (all) | 14 | 26 | 15 |
| Neck pain | | | |

| | | | |
|---|-------------------------|-------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 7 / 105 (6.67%) 7 | 9 / 103 (8.74%) 9 | 2 / 111 (1.80%) 2 |
| Cramp subjects affected / exposed occurrences (all) | 9 / 105 (8.57%) 9 | 24 / 103 (23.30%) 24 | 8 / 111 (7.21%) 8 |
| Pain in extremity subjects affected / exposed occurrences (all) | 11 / 105 (10.48%) 11 | 16 / 103 (15.53%) 16 | 12 / 111 (10.81%) 12 |
| Infections and infestations | | | |
| Bladder infection subjects affected / exposed occurrences (all) | 2 / 105 (1.90%) 2 | 8 / 103 (7.77%) 8 | 1 / 111 (0.90%) 1 |
| Bronchial infection subjects affected / exposed occurrences (all) | 9 / 105 (8.57%) 9 | 3 / 103 (2.91%) 3 | 3 / 111 (2.70%) 3 |
| Paronychia subjects affected / exposed occurrences (all) | 1 / 105 (0.95%) 1 | 9 / 103 (8.74%) 9 | 2 / 111 (1.80%) 2 |
| Rhinitis infective subjects affected / exposed occurrences (all) | 11 / 105 (10.48%) 11 | 11 / 103 (10.68%) 11 | 3 / 111 (2.70%) 3 |
| Skin infection subjects affected / exposed occurrences (all) | 9 / 105 (8.57%) 9 | 11 / 103 (10.68%) 11 | 4 / 111 (3.60%) 4 |
| Upper respiratory infection subjects affected / exposed occurrences (all) | 12 / 105 (11.43%) 12 | 14 / 103 (13.59%) 14 | 9 / 111 (8.11%) 9 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 5 / 105 (4.76%) 5 | 17 / 103 (16.50%) 17 | 5 / 111 (4.50%) 5 |
| Metabolism and nutrition disorders | | | |
| Anorexia subjects affected / exposed occurrences (all) | 27 / 105 (25.71%) 27 | 19 / 103 (18.45%) 19 | 27 / 111 (24.32%) 27 |
| Hypokalaemia | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 105 (1.90%) | 6 / 103 (5.83%) | 3 / 111 (2.70%) |
| occurrences (all) | 2 | 6 | 3 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

| |
|--|
| A rather good prognosis population included with a greater proportion of patients with primary metastatic disease and less prior adjuvant/neoadjuvant pretreatment like anti-HER2 and endocrine therapy. |
|--|

Notes: