



Clinical trial results:

A Phase 3, multicenter, randomized, open-label, active-controlled study of DS-8201a, an anti-HER2-antibody drug conjugate, versus ado-trastuzumab emtansine (T-DM1) for HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with trastuzumab and taxane

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2018-000222-61 |
| Trial protocol | GB BE FR ES DE IT |
| Global end of trial date | |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 |
| This version publication date | 09 June 2022 |
| First version publication date | 09 June 2022 |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | DS8201-A-U302 |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03529110 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Daiichi Sankyo Inc. |
| Sponsor organisation address | 211 Mt. Airy Rd., Basking Ridge, United States, 07920 |
| Public contact | Global Clinical Director, Daiichi Sankyo Inc., 908 992-6400, CTRinfo@dsi.com |
| Scientific contact | Global Clinical Director, Daiichi Sankyo Inc., 908 992-6400, CTRinfo@dsi.com |

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 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-------------|
| Analysis stage | Interim |
| Date of interim/final analysis | 21 May 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 21 May 2021 |
| Global end of trial reached? | No |

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of DS 8201a to T-DM1 as measured by progression-free survival (PFS).

Protection of trial subjects:

The study protocol, amendments, the informed consent form(s) (ICF[s]), and information sheets were approved by the appropriate and applicable Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs). The study was conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s).

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 09 August 2018 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--|
| Country: Number of subjects enrolled | Australia: 14 |
| Country: Number of subjects enrolled | Belgium: 5 |
| Country: Number of subjects enrolled | Brazil: 63 |
| Country: Number of subjects enrolled | Canada: 2 |
| Country: Number of subjects enrolled | China: 65 |
| Country: Number of subjects enrolled | France: 38 |
| Country: Number of subjects enrolled | Hong Kong: 21 |
| Country: Number of subjects enrolled | Italy: 25 |
| Country: Number of subjects enrolled | Japan: 68 |
| Country: Number of subjects enrolled | Korea, Democratic People's Republic of: 84 |
| Country: Number of subjects enrolled | Spain: 25 |
| Country: Number of subjects enrolled | Taiwan: 71 |
| Country: Number of subjects enrolled | United Kingdom: 11 |
| Country: Number of subjects enrolled | United States: 32 |
| Worldwide total number of subjects | 524 |
| EEA total number of subjects | 93 |

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) | 418 |
| From 65 to 84 years | 106 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

A total of 524 participants were enrolled & treated at study sites in 14 countries. Primary results reported is from first participant randomized up to data cutoff date of 21 May 2021. The results presented are based on primary analysis up to 33 months. Data collection is still on-going & additional results will be provided after study completion.

Pre-assignment

Screening details:

A total of 699 participants were screened and 524 participants enrolled.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|--------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Trastuzumab Deruxtecan (T-DXd) |

Arm description:

Participants with HER2-positive, unresectable and/or metastatic breast cancer participants previously treated with trastuzumab and taxane who received T-DXd as a sterile intravenous (IV) solution at a dose of 5.4 mg/kg every 3 weeks (Q3W).

| | |
|--|----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | trastuzumab deruxtecan |
| Investigational medicinal product code | |
| Other name | T-DXd, DS-8201a, Enhertu® |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

T-DXd is sterile lyophilized powder reconstituted into a sterile aqueous solution (100 mg/5 mL) to be administered intravenously.

| | |
|------------------|-----------------------------------|
| Arm title | Ado-trastuzumab Emtansine (T-DM1) |
|------------------|-----------------------------------|

Arm description:

Participants with HER2-positive, unresectable and/or metastatic breast cancer participants previously treated with trastuzumab and taxane who received T-DM1 in accordance with the approved label.

| | |
|--|---------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | ado-trastuzumab emtansine |
| Investigational medicinal product code | |
| Other name | T-DM1, KADCYLA® |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

The treatment will be in accordance with the approved label.

| Number of subjects in period 1 | Trastuzumab Deruxtecan (T-DXd) | Ado-trastuzumab Emtansine (T-DM1) |
|---------------------------------------|---|--|
| Started | 261 | 263 |
| Completed | 136 | 49 |
| Not completed | 125 | 214 |
| Clinical progression | 4 | 12 |
| Physician decision | 2 | 8 |
| Miscellaneous | 2 | 5 |
| Adverse event | 35 | 17 |
| Progressive disease | 66 | 158 |
| Withdrawal by subject | 13 | 11 |
| Lack of efficacy | 3 | 3 |

Baseline characteristics

Reporting groups

| | |
|---|-----------------------------------|
| Reporting group title | Trastuzumab Deruxtecan (T-DXd) |
| Reporting group description: | |
| Participants with HER2-positive, unresectable and/or metastatic breast cancer participants previously treated with trastuzumab and taxane who received T-DXd as a sterile intravenous (IV) solution at a dose of 5.4 mg/kg every 3 weeks (Q3W). | |
| Reporting group title | Ado-trastuzumab Emtansine (T-DM1) |
| Reporting group description: | |
| Participants with HER2-positive, unresectable and/or metastatic breast cancer participants previously treated with trastuzumab and taxane who received T-DM1 in accordance with the approved label. | |

| Reporting group values | Trastuzumab Deruxtecan (T-DXd) | Ado-trastuzumab Emtansine (T-DM1) | Total |
|--|--------------------------------|-----------------------------------|-------|
| Number of subjects | 261 | 263 | 524 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 212 | 206 | 418 |
| From 65-84 years | 41 | 49 | 90 |
| 85 years and over | 8 | 8 | 16 |
| Age continuous | | | |
| Units: years | | | |
| median | 54.5 | 54.2 | |
| standard deviation | ± 11.11 | ± 11.84 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 260 | 262 | 522 |
| Male | 1 | 1 | 2 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 152 | 162 | 314 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 10 | 9 | 19 |
| White | 71 | 72 | 143 |
| More than one race | 2 | 0 | 2 |
| Unknown or Not Reported | 26 | 20 | 46 |

End points

End points reporting groups

| | |
|---|-----------------------------------|
| Reporting group title | Trastuzumab Deruxtecan (T-DXd) |
| Reporting group description: Participants with HER2-positive, unresectable and/or metastatic breast cancer participants previously treated with trastuzumab and taxane who received T-DXd as a sterile intravenous (IV) solution at a dose of 5.4 mg/kg every 3 weeks (Q3W). | |
| Reporting group title | Ado-trastuzumab Emtansine (T-DM1) |
| Reporting group description: Participants with HER2-positive, unresectable and/or metastatic breast cancer participants previously treated with trastuzumab and taxane who received T-DM1 in accordance with the approved label. | |

Primary: Progression-Free Survival (PFS) Based on Blinded Independent Central Review (BICR) in Participants With HER2-Positive, Unresectable and/or Metastatic Breast Cancer Previously Treated With Trastuzumab and Taxane

| | |
|-----------------|---|
| End point title | Progression-Free Survival (PFS) Based on Blinded Independent Central Review (BICR) in Participants With HER2-Positive, Unresectable and/or Metastatic Breast Cancer Previously Treated With Trastuzumab and Taxane ^[1] |
|-----------------|---|

End point description:

Progression-free survival (PFS) by BICR was defined as the time from the date of enrollment to the earlier of the dates of the first objective documentation of disease progression (as per RECIST v1.1) or death due to any cause. Progressive disease was defined as at least a 20% increase in the sum of diameters of target lesions. Progression-free survival (PFS) was assessed in the Full Analysis Set at data cut-off date of 21 May 2021.

| | |
|--|---------|
| End point type | Primary |
| End point timeframe: Up to 33 months (data cut-off) | |

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: No statistical analysis was performed.

| End point values | Trastuzumab Deruxtecan (T-DXd) | Ado-trastuzumab Emtansine (T-DM1) | | |
|----------------------------------|--------------------------------|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 261 ^[2] | 263 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99.9 (18.5 to 99.9) | 6.8 (5.6 to 8.2) | | |

Notes:

[2] - 99.9=NA, Median and upper CI was not estimable due to insufficient number of events.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) in Participants With HER2-Positive, Unresectable and/or Metastatic Breast Cancer Previously Treated With Trastuzumab and Taxane

| | |
|-----------------|---|
| End point title | Overall Survival (OS) in Participants With HER2-Positive, |
|-----------------|---|

End point description:

Overall survival (OS) was defined as the time from the date of first dose of study drug to the date of death due to any cause. Overall survival (OS) was assessed in the Full Analysis Set at data cut-off date of 21 May 2021.

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

End point timeframe:

Up to 33 months (data cut-off)

| End point values | Trastuzumab Deruxtecan (T-DXd) | Ado-trastuzumab Emtansine (T-DM1) | | |
|----------------------------------|--------------------------------|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 261 ^[3] | 263 ^[4] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99.9 (99.9 to 99.9) | 99.9 (99.9 to 99.9) | | |

Notes:

[3] - 99.9=NA, Median and 95% CI was not estimable due to insufficient number of events.

[4] - 99.9=NA, Median and 95% CI was not estimable due to insufficient number of events.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Objective Response Rate (ORR) Based on BICR and Investigator Assessment in Participants With HER2-Positive, Unresectable and/or Metastatic Breast Cancer Previously Treated With Trastuzumab and Taxane

| | |
|-----------------|---|
| End point title | Percentage of Participants With Objective Response Rate (ORR) Based on BICR and Investigator Assessment in Participants With HER2-Positive, Unresectable and/or Metastatic Breast Cancer Previously Treated With Trastuzumab and Taxane |
|-----------------|---|

End point description:

The Objective Response Rate (ORR) was defined as the percentage of participants who achieved a best overall response of confirmed Complete Response (CR) or Partial Response (PR), assessed by BICR and investigator assessment based on RECIST version 1.1. CR was defined as a disappearance of all target lesions and PR was defined as at least a 30% decrease in the sum of diameters of target lesions. Confirmed ORR is reported. Objective response rate was assessed in the Full Analysis Set at data cut-off date of 21 May 2021.

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

End point timeframe:

Up to 33 months (data cut-off)

| End point values | Trastuzumab Deruxtecan (T-DXd) | Ado-trastuzumab Emtansine (T-DM1) | | |
|-----------------------------------|--------------------------------|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 261 | 263 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | | | | |
| BICR | 79.7 (74.3 to 84.4) | 34.2 (28.5 to 40.3) | | |
| Investigator Assessment | 77.0 (71.2 to 82.0) | 36.9 (31.0 to 43.0) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR) Based on BICR and Investigator Assessment in Participants With HER2-Positive, Unresectable and/or Metastatic Breast Cancer Previously Treated With Trastuzumab and Taxane

| | |
|-----------------|--|
| End point title | Duration of Response (DoR) Based on BICR and Investigator Assessment in Participants With HER2-Positive, Unresectable and/or Metastatic Breast Cancer Previously Treated With Trastuzumab and Taxane |
|-----------------|--|

End point description:

Duration of Response (DoR) was defined as the time from the date of the first documentation of objective response (complete response [CR] or partial response [PR]) to the date of the first objective documentation of progressive disease (PD) or death due to any cause. DoR in participants with confirmed CR/PR based on BICR and investigator assessment is reported. Duration of Response (DoR) was assessed in the Full Analysis Set of participants with confirmed CR/PR at data cut-off date of 21 May 2021.

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

End point timeframe:

Up to 33 months (data cut-off)

| End point values | Trastuzumab Deruxtecan (T-DXd) | Ado-trastuzumab Emtansine (T-DM1) | | |
|----------------------------------|--------------------------------|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 261 ^[5] | 263 ^[6] | | |
| Units: months | | | | |
| median (confidence interval 95%) | | | | |
| BICR | 99.9 (20.3 to 99.9) | 99.9 (12.6 to 99.9) | | |
| Investigator Assessment | 99.9 (20.8 to 99.9) | 99.9 (14.1 to 99.9) | | |

Notes:

[5] - 99.9=NA, Median and upper CI was not estimable due to insufficient number of events.

[6] - 99.9=NA, Median and upper CI was not estimable due to insufficient number of events.

Statistical analyses

Secondary: Progression-Free Survival (PFS) Based on Investigator Assessment in Participants With HER2-Positive, Unresectable and/or Metastatic Breast Cancer Previously Treated With Trastuzumab and Taxane

| | |
|-----------------|--|
| End point title | Progression-Free Survival (PFS) Based on Investigator Assessment in Participants With HER2-Positive, Unresectable and/or Metastatic Breast Cancer Previously Treated With Trastuzumab and Taxane |
|-----------------|--|

End point description:

Progression-free survival (PFS) by investigator assessment was defined as the time from the date of enrollment to the earlier of the dates of the first objective documentation of disease progression (as per RECIST v1.1) or death due to any cause. Progressive disease was defined as at least a 20% increase in the sum of diameters of target lesions. Progression-free survival (PFS) was assessed in the Full Analysis Set at data cut-off date of 21 May 2021.

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

End point timeframe:

Up to 33 months (data cut-off)

| End point values | Trastuzumab Deruxtecan (T-DXd) | Ado-trastuzumab Emtansine (T-DM1) | | |
|----------------------------------|--------------------------------|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 261 ^[7] | 263 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 25.1 (22.1 to 99.9) | 7.2 (6.8 to 8.3) | | |

Notes:

[7] - 99.9=NA, Upper CI was not estimable due to insufficient number of events.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AE) were collected from the date of signing the informed consent form up to 47 days after last dose of the study drug, up 33 months.

Adverse event reporting additional description:

A Treatment-emergent adverse event (TEAE) is defined as an AE that occurs, having been absent before the first dose of study drug, or has worsened in severity or seriousness after the initiating the study drug until 47 days after last dose of the study drug.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|----|
| Dictionary version | 23 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|--------------------------------|
| Reporting group title | Trastuzumab Deruxtecan (T-DXd) |
|-----------------------|--------------------------------|

Reporting group description:

Participants with HER2-positive, unresectable and/or metastatic breast cancer participants previously treated with trastuzumab and taxane who received T-DXd as a sterile intravenous (IV) solution at a dose of 5.4 mg/kg every 3 weeks (Q3W)

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Ado-trastuzumab Emtansine (T-DM1) |
|-----------------------|-----------------------------------|

Reporting group description:

Participants with HER2-positive, unresectable and/or metastatic breast cancer participants previously treated with trastuzumab and taxane who received T-DM1 in accordance with the approved label.

| Serious adverse events | Trastuzumab Deruxtecan (T-DXd) | Ado-trastuzumab Emtansine (T-DM1) | |
|---|--------------------------------|-----------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 49 / 257 (19.07%) | 47 / 261 (18.01%) | |
| number of deaths (all causes) | 33 | 53 | |
| number of deaths resulting from adverse events | 5 | 5 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon cancer | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Hypertension | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angiodysplasia | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arterial haemorrhage | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Seizure | | | |
| subjects affected / exposed | 2 / 257 (0.78%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 4 / 257 (1.56%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 1 | |
| Disease progression | | | |
| subjects affected / exposed | 3 / 257 (1.17%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 5 / 257 (1.95%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Mediastinal cyst | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Investigations | | | |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 3 / 261 (1.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Biopsy lymph gland | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radiation necrosis | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal fracture | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thermal burn | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain herniation | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower limb fracture | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haemorrhage | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vasogenic cerebral oedema | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Altered state of consciousness | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Optic neuritis | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord compression | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 257 (0.78%) | 3 / 261 (1.15%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 2 / 257 (0.78%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Otolithiasis | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Rhegmatogenous retinal detachment | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 5 / 257 (1.95%) | 2 / 261 (0.77%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 2 / 257 (0.78%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 257 (0.39%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Campylobacter gastroenteritis | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal polyp haemorrhage | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematemesis | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Jaundice cholestatic | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic atrophy | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Renal and urinary disorders | | | |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Endocrine disorders | | | |
| Hypercalcaemia of malignancy | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone lesion | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 4 / 257 (1.56%) | 5 / 261 (1.92%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 257 (1.17%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 2 / 257 (0.78%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COVID-19 | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 2 / 261 (0.77%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Breast cellulitis | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cytomegalovirus infection | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis infectious | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tracheobronchitis | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Soft tissue infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 257 (0.78%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lactic acidosis | | | |
| subjects affected / exposed | 1 / 257 (0.39%) | 0 / 261 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 2 / 261 (0.77%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 257 (0.00%) | 1 / 261 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Trastuzumab Deruxtecan (T-DXd) | Ado-trastuzumab Emtansine (T-DM1) | |
|---|---|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 256 / 257 (99.61%) | 249 / 261 (95.40%) | |
| Investigations | | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 75 / 257 (29.18%) | 25 / 261 (9.58%) | |
| occurrences (all) | 75 | 25 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 66 / 257 (25.68%) | 105 / 261 (40.23%) | |
| occurrences (all) | 66 | 105 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 58 / 257 (22.57%) | 14 / 261 (5.36%) | |
| occurrences (all) | 58 | 14 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 56 / 257 (21.79%) | 77 / 261 (29.50%) | |
| occurrences (all) | 56 | 77 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 54 / 257 (21.01%) | 112 / 261 (42.91%) | |
| occurrences (all) | 54 | 112 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 35 / 257 (13.62%) | 30 / 261 (11.49%) | |
| occurrences (all) | 35 | 30 | |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 17 / 257 (6.61%) | 35 / 261 (13.41%) | |
| occurrences (all) | 17 | 35 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 17 / 257 (6.61%) | 13 / 261 (4.98%) | |
| occurrences (all) | 17 | 13 | |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 14 / 257 (5.45%) | 3 / 261 (1.15%) | |
| occurrences (all) | 14 | 3 | |
| Vascular disorders | | | |

| | | | |
|---|-------------------------|-------------------------|--|
| Hypertension subjects affected / exposed occurrences (all) | 14 / 257 (5.45%) 14 | 6 / 261 (2.30%) 6 | |
| Nervous system disorders | | | |
| Headache subjects affected / exposed occurrences (all) | 54 / 257 (21.01%) 54 | 38 / 261 (14.56%) 38 | |
| Dizziness subjects affected / exposed occurrences (all) | 32 / 257 (12.45%) 32 | 22 / 261 (8.43%) 22 | |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 19 / 257 (7.39%) 19 | 25 / 261 (9.58%) 25 | |
| Dysgeusia subjects affected / exposed occurrences (all) | 15 / 257 (5.84%) 15 | 8 / 261 (3.07%) 8 | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 83 / 257 (32.30%) 83 | 43 / 261 (16.48%) 43 | |
| Neutropenia subjects affected / exposed occurrences (all) | 41 / 257 (15.95%) 41 | 7 / 261 (2.68%) 7 | |
| Leukopenia subjects affected / exposed occurrences (all) | 22 / 257 (8.56%) 22 | 8 / 261 (3.07%) 8 | |
| Lymphopenia subjects affected / exposed occurrences (all) | 15 / 257 (5.84%) 15 | 6 / 261 (2.30%) 6 | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 13 / 257 (5.06%) 13 | 31 / 261 (11.88%) 31 | |
| General disorders and administration site conditions | | | |
| Fatigue subjects affected / exposed occurrences (all) | 74 / 257 (28.79%) 74 | 52 / 261 (19.92%) 52 | |

| | | | |
|----------------------------------|--------------------|-------------------|--|
| Asthenia | | | |
| subjects affected / exposed | 32 / 257 (12.45%) | 31 / 261 (11.88%) | |
| occurrences (all) | 32 | 31 | |
| Malaise | | | |
| subjects affected / exposed | 29 / 257 (11.28%) | 10 / 261 (3.83%) | |
| occurrences (all) | 29 | 10 | |
| Pyrexia | | | |
| subjects affected / exposed | 27 / 257 (10.51%) | 39 / 261 (14.94%) | |
| occurrences (all) | 27 | 39 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 17 / 257 (6.61%) | 9 / 261 (3.45%) | |
| occurrences (all) | 17 | 9 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 195 / 257 (75.88%) | 79 / 261 (30.27%) | |
| occurrences (all) | 195 | 79 | |
| Vomiting | | | |
| subjects affected / exposed | 126 / 257 (49.03%) | 26 / 261 (9.96%) | |
| occurrences (all) | 126 | 26 | |
| Constipation | | | |
| subjects affected / exposed | 88 / 257 (34.24%) | 51 / 261 (19.54%) | |
| occurrences (all) | 88 | 51 | |
| Diarrhoea | | | |
| subjects affected / exposed | 75 / 257 (29.18%) | 18 / 261 (6.90%) | |
| occurrences (all) | 75 | 18 | |
| Dyspepsia | | | |
| subjects affected / exposed | 29 / 257 (11.28%) | 16 / 261 (6.13%) | |
| occurrences (all) | 29 | 16 | |
| Abdominal pain | | | |
| subjects affected / exposed | 29 / 257 (11.28%) | 5 / 261 (1.92%) | |
| occurrences (all) | 29 | 5 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 28 / 257 (10.89%) | 12 / 261 (4.60%) | |
| occurrences (all) | 28 | 12 | |
| Gastrooesophageal reflux disease | | | |

| | | | |
|--|------------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 13 / 257 (5.06%) 13 | 4 / 261 (1.53%) 4 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Epistaxis | | | |
| subjects affected / exposed | 29 / 257 (11.28%) | 42 / 261 (16.09%) | |
| occurrences (all) | 29 | 42 | |
| Cough | | | |
| subjects affected / exposed | 27 / 257 (10.51%) | 26 / 261 (9.96%) | |
| occurrences (all) | 27 | 26 | |
| Dyspnoea | | | |
| subjects affected / exposed | 21 / 257 (8.17%) | 13 / 261 (4.98%) | |
| occurrences (all) | 21 | 13 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 20 / 257 (7.78%) | 15 / 261 (5.75%) | |
| occurrences (all) | 20 | 15 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 13 / 257 (5.06%) | 6 / 261 (2.30%) | |
| occurrences (all) | 13 | 6 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 95 / 257 (36.96%) | 8 / 261 (3.07%) | |
| occurrences (all) | 95 | 8 | |
| Pruritus | | | |
| subjects affected / exposed | 21 / 257 (8.17%) | 18 / 261 (6.90%) | |
| occurrences (all) | 21 | 18 | |
| Rash | | | |
| subjects affected / exposed | 16 / 257 (6.23%) | 24 / 261 (9.20%) | |
| occurrences (all) | 16 | 24 | |
| Dry skin | | | |
| subjects affected / exposed | 14 / 257 (5.45%) | 4 / 261 (1.53%) | |
| occurrences (all) | 14 | 4 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 18 / 257 (7.00%) | 6 / 261 (2.30%) | |
| occurrences (all) | 18 | 6 | |
| Insomnia | | | |

| | | | |
|--|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 15 / 257 (5.84%) 15 | 24 / 261 (9.20%) 24 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 24 / 257 (9.34%) | 16 / 261 (6.13%) | |
| occurrences (all) | 24 | 16 | |
| Myalgia | | | |
| subjects affected / exposed | 23 / 257 (8.95%) | 16 / 261 (6.13%) | |
| occurrences (all) | 23 | 16 | |
| Arthralgia | | | |
| subjects affected / exposed | 22 / 257 (8.56%) | 23 / 261 (8.81%) | |
| occurrences (all) | 22 | 23 | |
| Pain in extremity | | | |
| subjects affected / exposed | 21 / 257 (8.17%) | 16 / 261 (6.13%) | |
| occurrences (all) | 21 | 16 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 17 / 257 (6.61%) | 12 / 261 (4.60%) | |
| occurrences (all) | 17 | 12 | |
| Infections and infestations | | | |
| Stomatitis | | | |
| subjects affected / exposed | 40 / 257 (15.56%) | 10 / 261 (3.83%) | |
| occurrences (all) | 40 | 10 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 19 / 257 (7.39%) | 13 / 261 (4.98%) | |
| occurrences (all) | 19 | 13 | |
| Pneumonia | | | |
| subjects affected / exposed | 18 / 257 (7.00%) | 9 / 261 (3.45%) | |
| occurrences (all) | 18 | 9 | |
| Pneumonitis | | | |
| subjects affected / exposed | 18 / 257 (7.00%) | 1 / 261 (0.38%) | |
| occurrences (all) | 18 | 1 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 75 / 257 (29.18%) | 44 / 261 (16.86%) | |
| occurrences (all) | 75 | 44 | |
| Weight decreased | | | |

| | | | |
|-----------------------------|-------------------|------------------|--|
| subjects affected / exposed | 43 / 257 (16.73%) | 16 / 261 (6.13%) | |
| occurrences (all) | 43 | 16 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 33 / 257 (12.84%) | 26 / 261 (9.96%) | |
| occurrences (all) | 33 | 26 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 20 / 257 (7.78%) | 12 / 261 (4.60%) | |
| occurrences (all) | 20 | 12 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 20 June 2018 | Clarified TEAEs section. Updated dose information & modification section and inclusion & exclusion criteria section. Updated definitions of Grade 2, 3, and 4 for specific investigations. Clarified language for timing of signed and dated written consent. Clarified details of urine pregnancy test results. Clarified details of lab procedures. Added details for PK sampling. |
| 08 March 2019 | Clarified the primary objective and updated secondary endpoints. Updated inclusion and exclusion criteria. Updated and clarified AE reporting and follow-up. Updated dose modification, screening, and lab sections. Updated PK sampling times. Updated procedures section. |
| 26 April 2019 | Clarified interstitial lung disease information. |
| 23 April 2020 | Added additional analyses of PFS and OS. Updated the secondary endpoint of OS. Updated the exploratory endpoints. Updated inclusion & exclusion criteria section. Updated general statistical considerations and dose modification sections. Updated screening and lab procedures. Clarified the PK sampling and end of treatment timing. Updated AE of Special Interest. Updated the Schedule of Events section. |
| 25 September 2020 | Updated to incorporate the COVID-19 management procedures. Updated exploratory endpoints to include PFS on next line therapy. Clarified withdrawal of consent language. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported