# Trastuzumab deruxtecan (breast cancer)

## Addendum to Project A25-54 (dossier assessment)[1]

**ADDENDUM (DOSSIER ASSESSMENT)**

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# List of abbreviations

| Abbreviation | Meaning |
|---|---|
| ACT | appropriate comparator therapy |
| AE | adverse event |
| AGO | Gynaecological Oncology Group<br>(Arbeitsgemeinschaft Gynäkologische Onkologie) |
| BSA | body surface area |
| BW | body weight |
| CTCAE | Common Terminology Criteria for Adverse Events |
| EORTC QLQ-BR23 | European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire − Breast Cancer 23 |
| EORTC QLQ-BR45 | European Organization for Research and Treatment of Cancer Quality of Life Questionnaire − Breast Cancer 45 |
| EORTC QLQ-C30 | European Organization for Research and Treatment of Cancer Quality of Life Questionnaire − Core 30 |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| HER2 | human epidermal growth factor receptor 2 |
| HR | hormone receptor |
| ILD | interstitial lung disease |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen<br>(Institute for Quality and Efficiency in Health Care) |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PGIC | Patient Global Impression of Change |
| PGIS | Patient Global Impression of Severity |
| PT | Preferred Term |
| RCT | randomized controlled trial |
| SAE | serious adverse event |
| SGB | Sozialgesetzbuch (Social Code Book) |
| SmPC | summary of product characteristics |
| SMQ | Standardized MedDRA Query |
| SOC | System Organ Class |
| VAS | visual analogue scale |

# 1 Background

On 10 September 2025, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A25-54 (Trastuzumab deruxtecan – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprised the assessment of the analyses submitted by the pharmaceutical company (hereinafter referred to as 'the company') in the commenting procedure [2], taking into account the relevant information provided in the dossier [3]:

- Analysis of the entire DESTINY-Breast06 study with the 2nd data cut (from 24 March 2025)

The responsibility for this assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

# 2 Assessment

A subpopulation of the randomized controlled trial (RCT) DESTINY-Breast06 was included for the benefit assessment of trastuzumab deruxtecan in patients with unresectable or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-low or HER2-ultralow breast cancer who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment. The DESTINY-Breast06 study is an ongoing, open-label study on the comparison of trastuzumab deruxtecan with a chemotherapy of physician's choice choosing from capecitabine, paclitaxel or nab-paclitaxel, each as monotherapy.

In Module 4A of its dossier, the company presented results of the total population for the first data cut of the DESTINY-Breast06 study from 18 March 2024 and used them for its assessment [3]. Of the 3 chemotherapies used, only paclitaxel is an appropriate comparator therapy (ACT) option as specified by the G-BA. The benefit assessment was therefore based on the subpopulation of patients for whom, in the event of allocation to the comparator arm, paclitaxel therapy had been determined prior to randomization (hereinafter referred to as the paclitaxel subpopulation). As part of the commenting procedure, the company presented analyses of the total population as well as of the paclitaxel subpopulation for the 2nd data cut of the RCT DESTINY-Breast06 from 24 March 2025 [2]. This was the prespecified 2nd interim analysis of the outcome overall survival, which was planned after 392 events in the group of HER2-low patients.

In accordance with the commission, the following sections contain an assessment of the results of the 2nd data cut from 24 March 2025 for the total population of the DESTINY-Breast06 study.

## 2.1 Study characteristics

A detailed description of the DESTINY-BREAST06 study can be found in the benefit assessment on commission A25-54 [1]. Table 1 shows the characteristics of the intervention and the comparator treatment of the DESTINY-Breast06 study.

Table 1: Characteristics of the intervention – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

| Study | Intervention | Comparison |
|---|---|---|
| DESTINY-Breast06 | trastuzumab deruxtecan 5.4 mg/kg BW[b] IV on Day 1 of a 21-day cycle | capecitabine[c] 1000 or 1250 mg/m$^2$ BSA orally, twice daily on Days 1–14 of a 21-day cycle<br>or<br>paclitaxel 80 mg/m$^2$ BSA, IV, weekly on Day 1 of a 21-day cycle<br>or<br>nab-paclitaxel[d] 100 mg/m$^2$ BSA on Days 1, 8 and 15 of a 28-day cycle |
| | Dose modification:<br>▪ Dose interruption for up to 126 days<br>▪ Dose reductions were allowed as follows[f]:<br>1st dose level: 4.4 mg/kg BW<br>2nd dose level: 3.2 mg/kg BW | ▪ Dose interruption for up to 28 days[e]<br>▪ Dose modifications according to local marketing authorization |
| | **Prior treatment**<br>▪ At least one endocrine therapy with or without targeted therapy in the metastatic setting<br><br>**Disallowed prior treatment**<br>▪ Chemotherapy for advanced or metastatic breast cancer[g]<br>▪ Immunosuppressants within 14 days prior to the 1st study dose, with the exception of intranasal and inhaled corticosteroids or systemic corticosteroids in doses of less than 10 mg/day prednisone or equivalent<br>▪ HER2-directed therapy<br>▪ Antibody-drug conjugate containing an exatecan derivative that is a topoisomerase I inhibitor<br>▪ Completion of whole brain radiotherapy within 2 weeks prior to randomization<br>▪ Hormonal therapy or immunotherapy (non-antibody based) within 3 weeks prior to randomization<br>▪ Major surgery, antibody-based anti-cancer therapy, radiation therapy including palliative stereotactic radiation therapy to the chest within 4 weeks prior to randomization (palliative stereotactic radiation therapy to other areas within 2 weeks prior to randomization)<br>▪ Small molecule drugs within 2 weeks or 5 half-lives prior to treatment with study medication, whichever was longer; (hydroxy-)chloroquine within 14 days prior to randomization<br><br>**Concomitant treatment**<br>▪ For trastuzumab deruxtecan antiemetics such as 5-hydroxytryptamine receptor antagonists, neurokinin-1 receptor antagonists and steroids<br>▪ Anticoagulants<br>▪ Haematopoietic growth factors for prophylaxis or treatment<br>**Prohibited concomitant treatment**<br>▪ Other antineoplastic treatment, monoclonal antibodies against HER2, chemotherapy, targeted therapy, radiotherapy (except palliative radiotherapy of non-targeted lesions), immunotherapy or biologic or hormonal therapy for cancer treatment<br>▪ Immunosuppressants (except for short-term treatment with low- or moderate-dose corticosteroids or long-term treatment with short-acting preparations and for the treatment of AEs) | |

Table 1: Characteristics of the intervention – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

| Study | Intervention | Comparison |
|---|---|---|
| a. In the DESTINY-Breast06 study, therapy could be chosen from capecitabine, paclitaxel and nab-paclitaxel.<br>b. If there is a change in body weight during treatment of ≥ ± 10% of baseline weight compared with baseline, the patient's dose is recalculated based on the updated weight.<br>c. According to the SmPC, the dosage level in this therapeutic indication should be 1250 mg/m$^2$ BSA twice daily on Days 1–14 of a 21-day cycle.<br>d. According to the SmPC, the dosage in this therapeutic indication should be 260 mg/m$^2$ BSA IV on Day 1 of a 21-day cycle.<br>e. In the event of a longer interruption, the resumption of treatment had to be discussed with the study physician.<br>f. Subsequent cycles after dose reduction due to toxicity were to be continued at the lower dose. If toxicity persisted after 2 dose reductions, the study treatment was to be discontinued.<br>g. Patients who received neoadjuvant or adjuvant chemotherapy are eligible to participate, provided they have had a disease-free interval (defined as completion of systemic chemotherapy until diagnosis of advanced or metastatic disease) of more than 12 months.<br>AE: adverse event; BSA: body surface area; BW: body weight; HER2: human epidermal growth factor receptor 2; IV: intravenous; RCT: randomized controlled trial; SmPC: summary of product characteristics | | |

Treatment with trastuzumab deruxtecan was largely in compliance with the specifications of the summary of product characteristics (SmPC) [4]. Treatment with the various treatment options of the comparator arm of the study deviated from the specifications of the respective SmPCs [5-7]. Firstly, the 3 drugs were administered at a dosage deviating from the marketing authorization (see Section 'Dosing of paclitaxel, capecitabine and nab-paclitaxel'). Secondly, only some of the patients in the paclitaxel subpopulation were pretreated with anthracyclines, as required by the marketing authorization [2]. For the 2 other treatment options, capecitabine and nab-paclitaxel, it is unclear to what extent the patients were pretreated with anthracyclines and/or taxanes as per the marketing authorization (see Section 'Pretreatment of patients with anthracyclines and/or taxanes'). There were also deviations in the use of concomitant medication with antiemetics for the prophylaxis of nausea and vomiting. In addition, mandatory pretreatment with corticosteroids, antihistamines and H2 receptor antagonists to prevent hypersensitivity reactions was not specified in the study protocol (see 'Notes on the outcomes in the DESTINY-Breast06 study' in dossier assessment A25-54 [1]).

Treatment with the study medication was conducted until disease progression or unacceptable toxicity. Patients in the comparator arm were not permitted to switch to treatment with trastuzumab deruxtecan.

**Dosing of paclitaxel, capecitabine and nab-paclitaxel**

According to the SmPC, paclitaxel is approved for the treatment of metastatic breast cancer at a dose of 175 mg/m$^2$ body surface area (BSA) every 3 weeks [5]. In the DESTINY-Breast06 study, paclitaxel was administered at an unapproved dose of 80 mg/m$^2$ BSA once a week. In

the study protocol, the company justified the choice of paclitaxel dosage by stating that in a meta-analysis, weekly administration showed an improvement in overall survival and fewer side effects compared to 3-weekly administration. In addition, according to the company, the weekly administration of paclitaxel is common in everyday practice. During the oral hearing on benefit assessment A23-07 (trastuzumab deruxtecan in previously treated HER2-low breast cancer), it was confirmed that the reduced-dose, weekly administration of paclitaxel is common in clinical practice [8]. The current Gynaecological Oncology Group (AGO) guideline also recommends weekly administration of paclitaxel [9]. It was therefore assumed that the patients treated with paclitaxel in the comparator arm received essentially appropriate treatment. Therefore, the paclitaxel dosage deviating from the marketing authorization had no consequences for this benefit assessment.

The drug capecitabine is approved as monotherapy for the treatment of locally advanced or metastatic breast cancer according to the SmPC at a dose of 1250 mg/m$^2$ BSA administered twice daily. In the DESTINY-Breast06 study, treatment with capecitabine could be conducted according to the physician's assessment at a dosage of 1250 mg/m$^2$ BSA twice daily or at a reduced dosage of 1000 mg/m$^2$ BSA twice daily, in accordance with the SmPC. The company justified the dose reduction in the study protocol with a reduction in side effects and referred, among other things, to a meta-analysis by Nishijima 2016 [10]. During the oral hearing on benefit assessment A23-07 (trastuzumab deruxtecan in previously treated HER2-low breast cancer), the use of the reduced dosage was confirmed as common in clinical practice [8]. Therefore, the dosage deviating from the marketing authorization had no consequences for this benefit assessment.

The treatment option nab-paclitaxel is approved according to the SmPC with a dosage of 260 mg/m$^2$ BSA every 3 weeks for the treatment of metastatic breast cancer [7]. In the DESTINY-Breast06 study, treatment was administered at a dose of 100 mg/m$^2$ BSA on Days 1, 8 and 15 of a 28-day cycle. The company justified this deviation in the study protocol by stating that this dosage regimen is the most common in practice due to its better tolerability, and referred to a phase 2 study in patients with previously untreated metastatic breast cancer [11,12]. During the oral hearing on benefit assessment A23-07 (trastuzumab deruxtecan in previously treated HER2-low breast cancer), it was confirmed that the weekly administration of taxanes is common in clinical practice due to better tolerability and effectiveness [8]. Therefore, the dosing regimen deviating from the marketing authorization had no consequences for this benefit assessment.

**Pretreatment of patients with anthracyclines and/or taxanes**

A total of 430 patients were enrolled in the comparator arm of the DESTINY-Breast06 study to receive a chemotherapy of physician's choice selecting from capecitabine (N = 257), paclitaxel (N = 68) and nab-paclitaxel (N = 105).

According to the information in the respective SmPCs, treatment with the different options of the ACT in the comparator arm of the DESTINY-Breast06 study requires varying prior treatments. For example, paclitaxel should only be used if patients have not responded to anthracycline-containing therapy or if it is not suitable for them [5]. Capecitabine should be used if patients have failed previous therapy with anthracyclines and taxanes or if further anthracycline-containing therapy is not indicated [6]. Treatment with nab-paclitaxel requires failure of first-line treatment in metastatic disease, and that standard anthracycline-containing therapy is not indicated [7]. According to the study protocol, neither a lack of response or unsuitability for previous anthracycline-containing therapy nor previous treatment with taxanes (for capecitabine treatment) was a prerequisite for inclusion in the study. The available documentation contained information on previous systemic antineoplastic treatments based on all patients in the comparator arm and separately for the paclitaxel treatment option only. In the comparator arm of the overall population, a total of 206 (48%) patients were treated with anthracyclines and 177 (41%) patients with taxanes in a previous line of treatment (adjuvant/neoadjuvant setting). A total of 28 patients (41%) in the paclitaxel subpopulation were pretreated with anthracyclines [2]. It was unclear whether the patients did not respond to anthracycline-containing therapy or whether this was not an option for them. Furthermore, it was not clear from the study documents whether and to what extent previous therapies played a role in the decision in favour of or against 1 of the 3 drug options in the comparator arm. Overall, it was unclear what effects these prerequisites, which were required according to the SmPCs but were missing for study participation, had on the patient-relevant outcomes.

**Follow-up**

Table 2 shows the planned duration of patient follow-up for the individual outcomes.

Table 2: Planned duration of follow-up – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a]

| **Study**<br>**Outcome category**<br>**Outcome** | **Planned follow-up** |
|---|---|
| **DESTINY-Breast06** | |
| Mortality | |
| Overall survival | Until death or end of study (whichever is first) |
| Morbidity | |
| Symptoms (EORTC QLQ-C30, EORTC QLQ-BR45, PGIS) | Until 2nd disease progression (PFS2)[b], death or end of study (whichever is first) |
| Health status (EQ-5D VAS, PGIC) | Until 2nd disease progression (PFS2)[b], death or end of study (whichever is first) |
| Health-related quality of life | |
| (EORTC QLQ-C30, EORTC QLQ-BR45) | Until 2nd disease progression (PFS2)[b], death or end of study (whichever is first) |
| Side effects | |
| All outcomes in the side effects category | 40 days (+ 7 days) after the last dose of study medication[c] |

a. In the DESTINY-Breast06 study, therapy could be chosen from capecitabine, paclitaxel and nab-paclitaxel.
b. Defined as the earliest progression event after the 1st subsequent therapy.
c. AEs and SAEs that were causally related to the investigational product were also recorded as AEs or SAEs if they occurred 48 days or more after the last dose of the study medication.

AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; PFS: progression-free survival; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; QLQ-BR45: Quality of Life Questionnaire-Breast Cancer Module 45; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The observation periods for the outcomes of the category of side effects were systematically shortened because they were only recorded for the time period of treatment with the study medication plus 40 (+ 7) days. Also systematically shortened were the observation periods for the outcomes in the morbidity and health-related quality of life category recorded using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), EORTC QLQ-Breast Cancer Module 45 (EORTC QLQ-BR45), EQ-5D visual analogue scale (VAS), Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC), as they were only recorded up to maximally the 2nd disease progression. Drawing a reliable conclusion on the total study period or the time to patient death requires recording these outcomes for the total period, as was done for survival.

**Characteristics of the study population**

Table 3 shows the characteristics of the patients in the total population of the DESTINY-Breast06 study.

Table 3: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

| Study<br>Characteristic<br>Category | Trastuzumab deruxtecan<br>N[b] = 436 | Treatment of physician's choice[a]<br>N[b] = 430 |
|---|---|---|
| **DESTINY-Breast06 (2nd data cut from 24 March 2025)** | | |
| Age [years], mean (SD) | 58 (11) | 58 (11) |
| Sex [F/M], % | 100/0 | > 99/< 1 |
| Region, n (%) | | |
| Asia | 149 (34) | 147 (34) |
| North America | 48 (11) | 47 (11) |
| Europe | 227 (52) | 213 (50) |
| Rest of the world | 12 (3) | 23 (5) |
| Family origin, n (%) | | |
| Asian | 154 (35) | 151 (35) |
| Caucasian | 231 (53) | 230 (53) |
| Black or African American | 4 (< 1) | 3 (< 1) |
| Native American or Alaska Native | 1 (< 1) | 0 (0) |
| Other | 7 (2) | 12 (3) |
| Missing | 39 (9) | 34 (8) |
| ECOG PS, n (%) | | |
| 0 | 252 (58) | 257 (60) |
| 1 | 178 (41) | 163 (38) |
| 2 | 1 (< 1) | 1 (< 1) |
| Missing[c] | 5 (1) | 9 (2) |
| Oestrogen receptor/progesterone receptor status, n (%) | | |
| ER positive and PR negative | 167 (38) | 181 (42) |
| ER negative and PR positive | 3 (< 1) | 2 (< 1) |
| ER positive and PR positive | 253 (58) | 237 (55) |
| ER negative and PR negative | 1 (< 1) | 0 (0) |
| ER positive and PR missing | 12 (3) | 10 (2) |
| HER2 expression, n (%) | | |
| IHC 0 | 1 (< 1) | 1 (< 1) |
| IHC > 0 < 1+ | 76 (17) | 76 (18) |
| IHC 1+ | 239 (55) | 234 (54) |
| IHC 2+/ISH negative | 117 (27) | 118 (27) |
| IHC 2+ | 3 (< 1) | 1 (< 1) |
| Baseline CNS metastases, n (%) | 37 (8) | 33 (8) |
| Endocrine resistance, n (%) | | |
| Primary | 128 (29) | 140 (33) |

Table 3: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

| Study<br>Characteristic<br>Category | Trastuzumab deruxtecan<br>N[b] = 436 | Treatment of physician's choice[a]<br>N[b] = 430 |
|---|---|---|
| Secondary | 308 (71) | 288 (67) |
| Missing | 0 (0) | 2 (< 1) |
| Number of previous endocrine monotherapy lines[d], n (%) | | |
| 1 | 65 (15) | 82 (19) |
| 1 and progression in ≤ 6 months after starting endocrine therapy + CDK4/6 inhibitor | 37 (8) | 40 (9) |
| Remaining patients with 1 previous endocrine monotherapy line | 28 (6) | 42 (10) |
| ≥ 2 | 370 (85)[e] | 346 (80)[e] |
| Number of previous lines of treatment with endocrine therapy in combination with CDK4/6 inhibitors, n (%) | | |
| 0 | 48 (11) | 44 (10) |
| 1 | 353 (81) | 358 (83) |
| 2 | 35 (8) | 27 (6) |
| Prior therapies in the adjuvant/neoadjuvant setting, n (%) | | |
| Hormonal therapy | 275 (63) | 256 (60) |
| Cytotoxic chemotherapy | 228 (52) | 234 (54) |
| Taxanes | 179 (41) | 177 (41) |
| Anthracyclines | 197 (45) | 206 (48) |
| Cyclophosphamide | 203 (47) | 213 (50) |
| 5-fluorouracil | 79 (18) | 73 (17) |
| Capecitabine | 4 (< 1) | 2 (< 1) |
| Other | 33 (8) | 20 (5) |
| Visceral disease, n (%) | | |
| Yes | ND | ND |
| No | ND | ND |
| Treatment discontinuation, n (%)[f] | 399 (92) | 407 (98) |
| Study discontinuation, n (%)[g] | 243 (56) | 286 (67) |

Table 3: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

| Study Characteristic Category | Trastuzumab deruxtecan N[b] = 436 | Treatment of physician's choice[a] N[b] = 430 |
|---|---|---|
| a. In the DESTINY-Breast06 study, therapy could be chosen from capecitabine, paclitaxel and nab-paclitaxel.<br>b. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.<br>c. The ECOG PS at the time of screening is derived as the last observed measurement before or at randomization. All 14 patients with missing ECOG PS status at baseline were determined to have an ECOG PS value of 0 or 1 within 6 days of randomization.<br>d. Proportion based on the number of patients with ≥ 1 previous endocrine lines of treatment in the metastatic setting<br>e. Institute's calculation.<br>f. Common reasons for treatment discontinuation in the intervention vs. comparator arm were (percentages refer to randomized patients who received at least one dose of the study medication): disease progression according to RECIST (67% vs. 74%), AEs (16% vs. 10%), patient decision (5% vs. 8%). An additional < 1% vs. 3% of randomized patients never started treatment. The data also include patients who died during treatment with the study medication (intervention arm: 1% vs. comparator arm: 1%).<br>g. A common reason for study discontinuation in the intervention vs. comparator arm was (percentages refer to randomized patients): withdrawal of consent (3% vs. 10%). The data additionally include patients who died during the course of the study (intervention arm: 53% vs. comparator arm: 57%).<br>AE: adverse event; CDK: cyclin-dependent kinase; CNS: central nervous system; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ER: oestrogen receptor; F: female; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; ISH: in situ hybridization; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; PR: progesterone receptor; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours; SD: standard deviation | | |

Both study arms were comparable in terms of patient demographic and clinical characteristics. At the 2nd data cut-off, there were differences between the study arms regarding treatment and study discontinuation, with somewhat higher discontinuation rates in the comparator arm in each case.

**Information on the course of the study**

Table 4 shows the mean/median treatment duration of the total population and the mean/median observation period for individual outcomes.

Table 4: Information on the course of the study – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a]

| **Study**<br>**Duration of the study phase**<br>**Outcome category/outcome** | **Trastuzumab deruxtecan**<br>**N = 436** | **Treatment of physician's choice[a]**<br>**N = 430** |
|---|---|---|
| **DESTINY-Breast06** | | |
| Treatment duration [months][b] | | |
| Median [min; max] | 11.0 [0.4; 49.2] | 5.6 [0.1; 47.7] |
| Mean (SD) | 13.8 (10.1) | 8.2 (7.7) |
| Observation period [months] | | |
| Overall survival[c] | | |
| Median [min; max] | 27.6 [0.1; 52.7] | 25.0 [0.0; 55.1] |
| Mean (SD) | ND | ND |
| Morbidity | | |
| Median [min; max] | ND | ND |
| Mean (SD) | ND | ND |
| Health-related quality of life | | |
| Median [min; max] | ND | ND |
| Mean (SD) | ND | ND |
| Side effects | | |
| Median [min; max] | ND | ND |
| Mean (SD) | ND | ND |

a. In the DESTINY-Breast06 study, therapy could be chosen from capecitabine, paclitaxel and nab-paclitaxel.
b. The data refer to patients who received at least one dose of the study medication (trastuzumab deruxtecan: N = 434, treatment of physician's choice: N = 417).
c. The company defined the observation period as the time between randomization and the last contact date at which the patient was still alive.

max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

The median treatment duration with the study medication was almost twice as long in the intervention arm as in the comparator arm at the 2nd data cut-off.

The median observation period for the outcome overall survival was 27.6 months in the intervention arm and 25 months in the comparator arm. No information was available on the observation period for the outcomes of morbidity, health-related quality of life, and side effects. For the latter, the observation period was linked to the end of treatment (plus 40 [+ 7] days). The median was therefore roughly estimated at approximately 12.4 and 7 months, respectively, and was systematically shorter for these outcomes compared to overall survival.

### Information on subsequent therapies

Table 5 shows the subsequent therapies patients received after discontinuing the study medication.

Table 5: Information on subsequent antineoplastic therapies – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a]

| Study<br>Type of subsequent therapy (all lines of treatment)<br>Drug | Patients with subsequent therapy, n (%) | |
|---|---|---|
| | Trastuzumab deruxtecan<br>N = 436 | Treatment of physician's choice[a]<br>N = 430 |
| **DESTINY-Breast06** | | |
| Subsequent antineoplastic therapies, total[b] | 336 (77.1) | 348 (80.9) |
| CDK4/6 inhibitors with endocrine therapy | 34 (7.8) | 44 (10.2) |
| Endocrine therapy alone | 38 (8.7) | 38 (8.8) |
| Endocrine therapy + targeted therapy (except CDK4/6 inhibitors) | 47 (10.8) | 45 (10.5) |
| Endocrine therapy + mTOR inhibitor | 27 (6.2) | 32 (7.4) |
| Endocrine therapy + PIK3CA inhibitor | 9 (2.1) | 7 (1.6) |
| Endocrine therapy + PARP inhibitor | 2 (0.5) | 0 (0) |
| Targeted therapy alone | 15 (3.4) | 24 (5.6) |
| CDK4/6 inhibitor | 6 (1.4) | 10 (2.3) |
| mTOR inhibitor | 1 (0.2) | 3 (0.7) |
| PI3K inhibitor | 1 (0.2) | 1 (0.2) |
| PARP inhibitor | 5 (1.1) | 7 (1.6) |
| Chemotherapy | 281 (64.4) | 287 (66.7) |
| capecitabine | 203 (46.6) | 112 (26.0) |
| taxane | 161 (36.9) | 115 (26.7) |
| eribulin | 67 (15.4) | 105 (24.4) |
| vinorelbine | 42 (9.6) | 45 (10.5) |
| Other | 117 (26.8) | 155 (36.0) |
| ADC | 50 (11.5) | 132 (30.7) |
| trastuzumab deruxtecan | 15 (3.4) | 117 (27.2) |
| sacituzumab govitecan | 37 (8.5) | 24 (5.6) |
| Other ADC | 1 (0.2) | 15 (3.5) |
| Immunotherapy | 8 (1.8) | 8 (1.9) |
| Gonadotropin-releasing hormone analogues | 7 (1.6) | 4 (0.9) |
| Other | 25 (5.7) | 32 (7.4) |

a. In the DESTINY-Breast06 study, therapy could be chosen from capecitabine, paclitaxel and nab-paclitaxel.
b. Without radiotherapy; patients with endocrine therapy in combination with gonadotropin-releasing hormone analogues are included in the information on endocrine therapy.

ADC: antibody-drug conjugate; CDK: cyclin-dependent kinase; mTOR: mammalian target of rapamycin; n: number of patients with subsequent therapy; N: number of analysed patients; PARP: poly(adenosine diphosphate-ribose) polymerase; PI3K: phosphatidylinositol 3-kinase; PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RCT: randomized controlled trial

After discontinuation of the study medication, 77% (trastuzumab deruxtecan arm) and 81% (chemotherapy arm) of the patients received subsequent therapy. The most common subsequent therapy in both study arms was chemotherapy.

The current guidelines do not provide clear recommendations for the therapy in later lines of treatment in the therapeutic indication in question [9,13]. In addition, there were no substantial differences between the subsequent therapies of the intervention and comparator population. Overall, the aspects described above had no consequence for this benefit assessment.

**Risk of bias across outcomes (study level)**

Table 6 shows the risk of bias across outcomes (bias at study level).

Table 6: Risk of bias across outcomes (study level) – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a]

| Study | Adequate random sequence generation | Allocation concealment | Blinding | | Reporting independent of the results | Absence of other aspects | Risk of bias at study level |
|---|---|---|---|---|---|---|---|
| | | | Patients | Treating staff | | | |
| DESTINY-Breast06 | Yes | Yes | No | No | Yes | Yes | Low |

a. In the DESTINY-Breast06 study, therapy could be chosen from capecitabine, paclitaxel and nab-paclitaxel.
RCT: randomized controlled trial

The risk of bias across outcomes for the DESTINY-Breast06 study was rated as low.

Limitations resulting from the open-label study design are described in Section 2.2.2 under the outcome-specific risk of bias.

## 2.2 Results

### 2.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - Overall survival
- Morbidity
  - Symptoms measured with the EORTC QLQ-C30 symptom scales

- Symptoms recorded using the EORTC QLQ-BR45
- Symptoms recorded using the PGIS
- Health status recorded using the EQ-5D VAS
- Health status recorded using the PGIC

- Health-related quality of life
  - Recorded using the EORTC QLQ-C30 and the EORTC QLQ-BR45
- Side effects
  - Serious adverse events (SAEs)
  - Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - Discontinuation due to AEs
  - Hand-foot syndrome (Preferred Term [PT], AEs)
  - Interstitial lung disease (ILD)/pneumonitis (AEs)
  - Cardiac disorders (System Organ Class [SOC], severe AEs [CTCAE grade ≥ 3])
  - Platelet count decreased (PT, severe AEs [CTCAE grade ≥ 3])
  - Other specific AEs, if any

Table 7 shows for which outcomes data were available in the included study.

Table 7: Matrix of outcomes – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a]

| Study | Outcomes | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Overall survival | Symptoms (EORTC QLQ-C30, EORTC QLQ-BR45, PGIS) | Health status (PGIC) | Health status (EQ-5D VAS) | Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR45) | SAEs | Severe AEs[b] | Discontinuation due to AEs | Cardiac disorders (SOC, severe AEs[b]) | Platelet count decreased (PT, severe AEs[b]) | ILD/pneumonitis[c] (AEs) | Hand-foot syndrome (PT, AEs) | Further specific AEs[d] |
| DESTINY-Breast06 | Yes | No[e] | Yes | No[e] | No[e] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

a. In the DESTINY-Breast06 study, therapy could be chosen from capecitabine, paclitaxel and nab-paclitaxel.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Operationalized as SMQ narrow ILD, selected terms of SMQ broad ILD, respiratory failure (PT) and acute respiratory failure (PT).
d. The following events are considered (coded according to MedDRA): respiratory, thoracic and mediastinal disorders (SOC, AEs), decreased appetite (PT, AEs), constipation (PT, AEs), nausea (PT, AEs), vomiting (PT, AEs), alopecia (PT, AEs), oedema peripheral (PT, AEs), investigations (SOC, severe AEs), musculoskeletal and connective tissue disorders (SOC, severe AEs), nervous system disorders (SOC, severe AEs), anaemia (PT, severe AEs).
e. No suitable data available; see the following text section for reasons.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; ILD: interstitial lung disease; MedDRA: Medical Dictionary for Regulatory Activities; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PT: Preferred Term; QLQ-BR45: Quality of Life Questionnaire-Breast Cancer 45; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized Medical Dictionary for Regulatory Activities Query; SOC: System Organ Class; VAS: visual analogue scale

**Analyses of patient-reported outcomes on morbidity and health-related quality of life**

Detailed explanations of the outcomes included in the DESTINY-Breast06 study, collected using the EORTC QLQ-C30, EORTC QLQ-BR45, EQ-5D VAS, PGIS and PGIC, can be found in benefit assessment A25-54 [1].

***Scales of the EORTC QLQ-BR45***

In the DESTINY-Breast06 study, the company recorded the symptoms and health-related quality of life using the EORTC QLQ-BR45 instrument, among others. Concurrent with the information in the dossier, this instrument comprises 8 scales from the EORTC QLQ-Breast Cancer Module 23 (EORTC QLQ-BR23) and 22 additional items. In the benefit assessment, the company only used the subset of the QLQ-BR23 for the analysis [3]. In the comments, the

company presented results of the EORTC QLQ-BR45 for the 2nd data cut, which included the additional scales ‘endocrine therapy symptoms’, ‘skin mucosis symptom’, ‘endocrine sexual symptoms’ and ‘breast satisfaction’.

**EORTC QLQ-C30, EORTC QLQ-BR45, EQ-5D-VAS and PGIS not usable**

In the comments on the 2nd data cut of the DESTINY-BREAST06 study, the company stated that for the outcomes recorded using the EORTC QLQ-C30, EORTC QLQ-BR45, EQ-5D VAS and PGIS, less than 70% of patients had at least one additional value during the course of the study in addition to a value at baseline. Due to this small proportion, the data presented by the company for the overall population could not be meaningfully interpreted. The information provided in Module 4 A of the dossier for the first data cut already showed that the response rate to the questionnaire was low in both study arms at baseline in the overall population of the DESTINY-Breast06 study. Due to the strongly decreasing and differential response rates over the course of the study, the data presented by the company for the overall population would not have been meaningfully interpretable for the first data cut either (see benefit assessment for commission A25-54 [1]). At the time of the first data cut-off at Week 16 (5th follow-up survey after baseline) the response rate was still around 75% of patients in the intervention arm, while the response rate in the comparator arm was only around 64%. For the 2nd data cut, no information was available for the response rate over the course of the visits.

**Health status assessed using PGIC**

The PGIC consists of a single question asking the patient to rate the change in their health status compared with the time before starting the study medication. There are 7 possible responses (‘very much improved’, ‘much improved’, ‘minimally improved’, ‘no change’, ‘minimally worse’, ‘much worse’, ‘very much worse’). While in Module 4 A of the dossier the company defined the events for the presented time-to-event analyses from the first data cut on time to first and time to confirmed worsening only via the answers ‘much worse’ or ‘very much worse’ [3], the time-to-event analyses presented in the context of the comments also contained the answer ‘minimally worse’ as a relevant worsening. This operationalization of the PGIC was suitable for the benefit assessment [2] and was therefore used.

**Notes on side effect outcomes**

***ILD/pneumonitis***

In the comments, the company presented analyses on predefined AEs of special interest. Analyses were available for these outcomes regardless of severity as well as for serious events and severe events (operationalized as CTCAE grade ≥ 3). According to the study documents, the individual events were adjudicated by an adjudication committee as AEs of special interest ‘ILD/pneumonitis’ [14]. This was done on the basis of a prespecified list of PTs from the Medical Dictionary for Regulatory Activities (MedDRA). This Preferred Term (PT) list consisted

of all PTs of the Standardized MedDRA Query (SMQ) narrow 'ILD', selected terms of the SMQ broad 'ILD' as well as the PTs 'respiratory failure' and 'acute respiratory failure'. Events of CTCAE grade = 1 are in some cases not symptomatic and therefore not relevant to the patient. However, the events presented in the operationalization 'ILD/pneumonitis' (AEs) contained only a minor proportion of CTCAE grade 1 events. The operationalization ILD/pneumonitis (AEs) presented by the company was therefore considered suitable and included.

### 2.2.2 Risk of bias

Table 8 describes the risk of bias for the results of the relevant outcomes.

Table 8: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a]

| Study | | Outcomes | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Study level | Overall survival | Symptoms (EORTC QLQ-C30, EORTC QLQ-BR45, PGIS) | Health status (PGIC) | Health status (EQ-5D VAS) | Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR45) | SAEs | Severe AEs[b] | Discontinuation due to AEs | Cardiac disorders (SOC, severe AEs[b]) | Platelet count decreased (PT, severe AEs[b]) | ILD/pneumonitis[c](AEs) | Hand-foot syndrome (PT, AEs) | Further specific AEs[d] |
| DESTINY-Breast06 | L | L | –[e] | H[f, g] | –[e] | –[e] | H[g] | H[g] | H[h] | H[g] | H[g] | H[g, i] | H[g, i] | H[g, i] |

a. In the DESTINY-Breast06 study, therapy could be chosen from capecitabine, paclitaxel and nab-paclitaxel.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Operationalized as SMQ narrow ILD, selected terms of SMQ broad ILD, respiratory failure (PT) and acute respiratory failure (PT).
d. The following events are considered (coded according to MedDRA): respiratory, thoracic and mediastinal disorders (SOC, AEs), decreased appetite (PT, AEs), constipation (PT, AEs), nausea (PT, AEs), vomiting (PT, AEs), alopecia (PT, AEs), oedema peripheral (PT, AEs), investigations (SOC, severe AEs), musculoskeletal and connective tissue disorders (SOC, severe AEs), nervous system disorders (SOC, severe AEs), anaemia (PT, severe AEs).
e. No suitable data available; see the following text section for reasons.
f. Lack of blinding in subjective recording of outcomes.
g. Incomplete observations for potentially informative reasons in different follow-ups.
h. Lack of blinding in the presence of subjective decision on treatment discontinuation.
i. Lack of blinding in subjective recording of outcomes (in the case of non-serious/non-severe AEs).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; ILD: interstitial lung disease; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PT: Preferred Term; QLQ-BR45: Quality of Life Questionnaire-Breast Cancer 45; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized Medical Dictionary for Regulatory Activities Query; SOC: System Organ Class; VAS: visual analogue scale

The outcome-specific risk of bias was rated as high for the results of all patient-relevant outcomes except overall survival.

No suitable data were available for the outcomes of symptoms and health-related quality of life. This also applied to the outcome health status recorded using EQ-5D VAS (for justification, see Section 'EORTC QLQ-C30, EORTC QLQ-BR45, EQ-5D-VAS and PGIS not usable'). For this reason, the risk of bias for these outcomes was not assessed.

The risk of bias was rated high for the results of the PGIC outcomes and the outcomes in the side effect category. For these outcomes, with the exception of the outcome discontinuation due to AEs, incomplete observations were available for potentially informative reasons in different follow-ups (for the outcomes in the side effects category mainly driven by the end of observation 40 [+ 7] days after treatment discontinuation mainly due to disease progression, see Section 2.1). For the PGIC outcome and non-serious/non-severe AEs, the risk of bias in the results was also increased due to the lack of blinding in subjective outcome recording.

The risk of bias in the results for the outcome of discontinuation due to AEs was rated as high because of lack of blinding in subjective decisions regarding treatment discontinuation. The certainty of results was additionally limited by the fact that treatment might also be discontinued for reasons other than AEs. These reasons represented a competing event for the outcome to be recorded, discontinuation due to AEs. This means that, although AEs that would have led to discontinuation of therapy may occur after discontinuation for other reasons, the criterion of 'discontinuation' is no longer applicable to them. It was impossible to estimate how many AEs this affected.

### 2.2.3 Results

Table 9 summarizes the results of the comparison of trastuzumab deruxtecan with chemotherapy of physician's choice in patients with unresectable or metastatic HR-positive, HER2-low or HER2-ultralow breast cancer who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. The results on common AEs, SAEs, severe AEs and discontinuation due to AEs are presented in Appendix A and the Kaplan-Meier curves on the included outcomes are presented in Appendix B.

Table 9: Results (mortality, morbidity, health-related quality of life and side effects, time to event) – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

| Study<br>Outcome category<br>Outcome | trastuzumab deruxtecan | | Treatment of physician's choice[a] | | trastuzumab deruxtecan vs. treatment of physician's choice[a] |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI]<br>Patients with event n (%) | N | Median time to event in months [95% CI]<br>Patients with event n (%) | HR [95% CI]; p-value |
| **DESTINY-Breast06 (2nd data cut from 24 March 2025)** | | | | | |
| **Mortality** | | | | | |
| Overall survival | 436 | 30.5 [28.4; 33.3]<br>232 (53.2) | 430 | 27.2 [24.7; 29.2]<br>253 (58.8) | 0.79 [0.66; 0.94];<br>0.008[b] |
| **Morbidity** | | | | | |
| Symptoms (EORTC QLQ-C30, EORTC QLQ-BR45, PGIS) | No suitable data[c] | | | | |
| Health status (EQ-5D VAS) | No suitable data[c] | | | | |
| Health status (PGIC, time to first deterioration[d]) | 436 | 24.3 [16.5; NC]<br>158 (36.2) | 430 | 8.9 [7.0; 12.5]<br>177 (41.2) | 0.60 [0.49; 0.751];<br>< 0.001[e] |
| **Health-related quality of life** | | | | | |
| EORTC QLQ-C30, EORTC QLQ-BR45 | No suitable data[c] | | | | |
| **Side effects** | | | | | |
| AEs (supplementary information) | 434 | 0.1 [0.1; 0.1]<br>429 (98.8) | 417 | 0.3 [0.2; 0.3]<br>397 (95.2) | – |
| SAEs | 434 | NA<br>90 (20.7) | 417 | NA<br>67 (16.1) | 0.97 [0.70; 1.34];<br>0.851[e] |
| Severe AEs[f] | 434 | 9.0 [5.7; 12.0]<br>239 (55.1) | 417 | 11.0 [6.2; NC]<br>186 (44.6) | 1.05 [0.87; 1.27];<br>0.626[e] |
| Discontinuation due to AEs | 434 | NA [33.9; NC]<br>71 (16.4) | 417 | NA<br>41 (9.8) | 1.16 [0.79; 1.73];<br>0.458[e] |
| Cardiac disorders (SOC, severe AEs[f]) | 434 | ND<br>2 (0.5) | 417 | ND<br>6 (1.4) | ND |
| Platelet count decreased (PT, severe AEs[f]) | 434 | NA<br>18 (4.1) | 417 | NA<br>0 (0) | NC;<br>< 0.001[g] |
| ILD/pneumonitis (AEs)[h] | 434 | NA<br>59 (13.6) | 417 | NA<br>1 (0.2) | 37.80 [8.31; 668.37]<br>< 0.001[i] |

Table 9: Results (mortality, morbidity, health-related quality of life and side effects, time to event) – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

| Study<br>Outcome category<br>Outcome | trastuzumab deruxtecan | | Treatment of physician's choice[a] | | trastuzumab deruxtecan vs. treatment of physician's choice[a] |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI]<br>Patients with event n (%) | N | Median time to event in months [95% CI]<br>Patients with event n (%) | HR [95% CI]; p-value |
| Hand-foot syndrome (PT, AEs) | 434 | NA<br>5 (1.2) | 417 | NA [12.5; NC]<br>146 (35.0) | 0.02 [0.01; 0.05];<br>< 0.001[e] |
| Respiratory, thoracic and mediastinal disorders (SOC, AEs) | 434 | 12.2 [9.9; 15.3]<br>221 (50.9) | 417 | NA [20.4; NC]<br>109 (26.1) | 1.58 [1.26; 1.99];<br>< 0.001[e] |
| Decreased appetite (PT, AEs) | 434 | NA<br>114 (26.3) | 417 | 39.4 [NC]<br>51 (12.2) | 2.11 [1.53; 2.97];<br>< 0.001[e] |
| Constipation (PT, AEs) | 434 | NA<br>139 (32.0) | 417 | NA<br>62 (14.9) | 2.10 [1.56; 2.85];<br>< 0.001[e] |
| Nausea (PT, AEs) | 434 | 0.2 [0.1; 0.3]<br>307 (70.7) | 417 | NA [23.2; NC]<br>128 (30.7) | 3.37 [2.75; 4.16];<br>< 0.001[e] |
| Vomiting (PT, AEs) | 434 | NA<br>154 (35.5) | 417 | NA<br>50 (12.0) | 3.09 [2.26; 4.30];<br>< 0.001[e] |
| Alopecia (PT, AEs) | 434 | 8.5 [3.7; NC]<br>212 (48.8) | 417 | NA<br>88 (21.1) | 2.51 [1.97; 3.24];<br>< 0.001[e] |
| Oedema peripheral (PT, AEs) | 434 | NA<br>40 (9.2) | 417 | NA [29.5; NC]<br>61 (14.6) | 0.46 [0.30; 0.68];<br>< 0.001[e] |
| Investigations (SOC, severe AEs[f]) | 434 | NA<br>104 (24.0) | 417 | NA<br>47 (11.3) | 1.89 [1.35; 2.70];<br>< 0.001[e] |
| Musculoskeletal and connective tissue disorders (SOC, severe AEs[f]) | 434 | NA<br>5 (1.2) | 417 | NA<br>10 (2.4) | 0.32 [0.10; 0.91];<br>0.040[e] |
| Nervous system disorders (SOC, severe AEs[f]) | 434 | NA<br>9 (2.1) | 417 | NA<br>18 (4.3) | 0.34 [0.14; 0.75];<br>0.009[e] |
| Anaemia (PT, severe AEs[f]) | 434 | NA [40.3; NC]<br>43 (9.9) | 417 | NA<br>18 (4.3) | 1.89 [1.10; 3.37];<br>0.025[e] |

Table 9: Results (mortality, morbidity, health-related quality of life and side effects, time to event) – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

| Study<br>Outcome category<br>Outcome | trastuzumab deruxtecan | | Treatment of physician's choice[a] | | trastuzumab deruxtecan vs. treatment of physician's choice[a] |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI]<br>Patients with event n (%) | N | Median time to event in months [95% CI]<br>Patients with event n (%) | HR [95% CI]; p-value |
| a. In the DESTINY-Breast06 study, therapy could be chosen from capecitabine, paclitaxel and nab-paclitaxel.<br>b. Effect, CI and p-value: Cox proportional hazards model, stratified by previous use of CDK-4/6 inhibitors (yes vs. no) and HER2-IHC expression (IHC > 0 and < 1+ vs. IHC 1+ vs. IHC 2+/ISH-). CI and p-value: profile likelihood method based on this Cox model.<br>c. No suitable data available; see the following text section for reasons.<br>d. An assessment by patients as 'minimally worse', 'much worse' and 'very much worse' compared to baseline is considered a clinically relevant deterioration.<br>e. Effect, CI and p-value: Cox proportional hazards model, unstratified. CI and p-value: profile likelihood method based on this Cox model.<br>f. Severe AEs are operationalized as CTCAE grade ≥ 3.<br>g. Effect, profile likelihood CI and profile likelihood p-value based on an (unstratified) Cox proportional hazards model cannot be estimated here according to the company. The p-value given here is therefore derived from an unstratified log-rank test.<br>h. Operationalized as SMQ narrow ILD, selected terms of SMQ broad ILD, respiratory failure (PT) and acute respiratory failure (PT).<br>i. Effect, CI and p-value: Cox proportional hazards model, presumably unstratified. CI and p-value: profile likelihood method based on this Cox model.<br>AE: adverse event; CDK: cyclin-dependent kinase; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HER2: human epidermal growth factor receptor 2; HR: hazard ratio; IHC: immunohistochemistry; ILD: interstitial lung disease; ISH: in situ hybridization; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; PGIC. Patient Global Impression of Change; PGIS. Patient Global Impression of Severity; PT: Preferred Term; QLQ-BR45: Quality of Life Questionnaire-Breast Cancer Module 45; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale | | | | | |

Overall, for the outcome overall survival, for the outcome health status recorded using PGIC and for the outcomes hand-foot syndrome (AEs), peripheral oedema (AEs), musculoskeletal and connective tissue disorders (severe AEs) and nervous system disorders (severe AEs), there was a statistically significant difference in favour of trastuzumab deruxtecan versus the chemotherapy of physician's choice. There was an effect modification for the outcome of overall survival by the characteristic of age (see Section 2.2.4).

Statistically significant differences to the disadvantage of trastuzumab deruxtecan versus chemotherapy of physician's choice were seen for the outcomes platelet count decreased

(severe AEs), ILD/pneumonitis (AEs), respiratory, thoracic and mediastinal disorders (AEs), decreased appetite (AEs), constipation (AEs), nausea (AEs), vomiting (AEs), alopecia (AEs), investigations (severe AEs) and anaemia (severe AEs).

No hazard ratio data were available for the outcome of cardiac disorders (severe AEs). No statistically significant differences between the treatment arms were shown for the remaining outcomes recorded.

### 2.2.4 Subgroups and other effect modifiers

The following potential effect modifiers were taken into account for this addendum:

- Age (< 65 years versus ≥ 65 years)

This characteristic was prespecified. Sex was not considered as only one man was enrolled in the DESTINY-Breast06 study. There was no suitable characteristic for disease severity.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least 1 subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

The results are presented in Table 10. The Kaplan-Meier curves on the subgroup results are presented in Appendix B.

Table 10: Subgroups (mortality, time to event) – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a]

| Study<br>Outcome<br>Characteristic<br>Subgroup | trastuzumab deruxtecan<br>N | trastuzumab deruxtecan<br>Median time to event in months [95% CI]<br>Patients with event n (%) | Treatment of physician's choice[a]<br>N | Treatment of physician's choice[a]<br>Median time to event in months [95% CI]<br>Patients with event n (%) | trastuzumab deruxtecan vs. treatment of physician's choice[a]<br>HR [95% CI][b] | trastuzumab deruxtecan vs. treatment of physician's choice[a]<br>p-value[c] |
|---|---|---|---|---|---|---|
| **DESTINY-Breast06** | | | | | | |
| **Overall survival** | | | | | | |
| Age | | | | | | |
| < 65 years | 302 | 32.7 [29.9; 36.1]<br>149 (49.3) | 297 | 27.1 [24.2; 29.2]<br>178 (59.9) | 0.70 [0.56; 0.87] | 0.001 |
| ≥ 65 years | 134 | 26.4 [21.2; 31.6]<br>83 (61.9) | 133 | 27.9 [21.9; 36.9]<br>75 (56.4) | 1.03 [0.76; 1.42] | 0.835 |
| Total | | | | | Interaction: | 0.047 |

a. In the DESTINY-Breast06 study, therapy could be chosen from capecitabine, paclitaxel and nab-paclitaxel.
b. Effect: Cox proportional hazards model, unstratified. CI: profile likelihood method based on this Cox model.
c. Subgroup-specific p-values: unstratified log-rank test. Interaction p-value: profile likelihood method based on unstratified Cox proportional hazards model.

CI: confidence interval; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; RCT: randomized controlled trial

For the outcome of overall survival, there was a statistically significant difference in favour of trastuzumab deruxtecan compared to treatment of physician's choice for patients < 65 years of age. There was no statistically significant difference between the treatment arms for patients ≥ 65 years.

## 2.3 Summary

Overall, the DESTINY-Breast06 study for trastuzumab deruxtecan versus chemotherapy of physician's choice, choosing from capecitabine, paclitaxel and nab-paclitaxel, showed the following results for the total population:

- Statistically significant difference in favour of trastuzumab deruxtecan:
  - Overall survival (age [< 65 years])
  - Health status (PGIC)
  - Musculoskeletal and connective tissue disorders (severe AEs)
  - Nervous system disorders (severe AEs)

  - Hand-foot syndrome (AEs)
  - Oedema peripheral (AEs)
- Statistically significant difference to the disadvantage of trastuzumab deruxtecan:
  - Platelet count decreased (severe AEs)
  - Investigations (severe AEs)
  - Anaemia (severe AEs)
  - ILD/pneumonitis (AEs)
  - Respiratory, thoracic and mediastinal disorders (AEs)
  - Decreased appetite (AEs)
  - Constipation (AEs)
  - Nausea (AEs)
  - Vomiting (AEs)
  - Alopecia (AEs)

## 3 References

The reference list contains citations provided by the company in which bibliographical information may be missing.

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## Appendix A Results on side effects

For the overall rates of AEs, SAEs and severe AEs (e.g. CTCAE grade ≥ 3), the following tables present events for SOCs and PTs according to MedDRA, each on the basis of the following criteria:

- Overall rate of AEs (irrespective of severity grade): events that occurred in at least 10% of patients in one study arm
- Overall rate of severe AEs (e.g. CTCAE grade ≥ 3) and SAEs: events that occurred in at least 5% of patients in one study arm
- In addition, for all events irrespective of severity grade: events that occurred in at least 10 patients and in at least 1% of patients in one study arm

For the outcome of discontinuation due to AEs, all events (SOCs/PTs) that resulted in discontinuation are presented.

Table 11: Common AEs[a] – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[b] (multipage table)

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[c]**<br>**PT[c]** | **trastuzumab deruxtecan**<br>**N = 434** | **Treatment of physician's choice[b]**<br>**N = 417** |
| **DESTINY-Breast06** | | |
| **Overall AE rate** | 429 (98.8) | 397 (95.2) |
| Infections and infestations | 235 (54.1) | 163 (39.1) |
| Bronchitis | 11 (2.5) | 6 (1.4) |
| Cellulitis | 2 (0.5) | 10 (2.4) |
| COVID-19 | 109 (25.1) | 55 (13.2) |
| COVID-19 pneumonia | 11 (2.5) | 2 (0.5) |
| Cystitis | 12 (2.8) | 5 (1.2) |
| Influenza | 14 (3.2) | 6 (1.4) |
| Nasopharyngitis | 29 (6.7) | 16 (3.8) |
| Pneumonia | 23 (5.3) | 10 (2.4) |
| Sinusitis | 12 (2.8) | 4 (1.0) |
| Upper respiratory tract infection | 24 (5.5) | 11 (2.6) |
| Urinary tract infection | 32 (7.4) | 20 (4.8) |
| Blood and lymphatic system disorders | 211 (48.6) | 154 (36.9) |
| Anaemia | 168 (38.7) | 109 (26.1) |
| Leukopenia | 31 (7.1) | 17 (4.1) |
| Lymphopenia | 21 (4.8) | 5 (1.2) |
| Neutropenia | 77 (17.7) | 63 (15.1) |
| Thrombocytopenia | 29 (6.7) | 8 (1.9) |
| Immune system disorders | 9 (2.1) | 11 (2.6) |
| Metabolism and nutrition disorders | 201 (46.3) | 112 (26.9) |
| Decreased appetite | 114 (26.3) | 51 (12.2) |
| Hypercalcaemia | 10 (2.3) | 9 (2.2) |
| Hyperglycaemia | 16 (3.7) | 7 (1.7) |
| Hyperuricaemia | 6 (1.4) | 12 (2.9) |
| Hypoalbuminaemia | 26 (6.0) | 13 (3.1) |
| Hypocalcaemia | 18 (4.1) | 16 (3.8) |
| Hypokalaemia | 60 (13.8) | 18 (4.3) |
| Hypomagnesaemia | 13 (3.0) | 9 (2.2) |
| Hyponatraemia | 13 (3.0) | 13 (3.1) |
| Hypophosphataemia | 11 (2.5) | 10 (2.4) |
| Psychiatric disorders | 54 (12.4) | 32 (7.7) |
| Anxiety | 12 (2.8) | 2 (0.5) |
| Depression | 10 (2.3) | 5 (1.2) |

Table 11: Common AEs[a] – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[b] (multipage table)

| Study | Patients with event n (%) | |
|---|---|---|
| **SOC[c]** **PT[c]** | **trastuzumab deruxtecan N = 434** | **Treatment of physician's choice[b] N = 417** |
| Insomnia | 34 (7.8) | 19 (4.6) |
| Nervous system disorders | 174 (40.1) | 192 (46.0) |
| Dizziness | 39 (9.0) | 27 (6.5) |
| Dysgeusia | 51 (11.8) | 24 (5.8) |
| Headache | 76 (17.5) | 43 (10.3) |
| Hypoaesthesia | 5 (1.2) | 13 (3.1) |
| Neuropathy peripheral | 9 (2.1) | 39 (9.4) |
| Paraesthesia | 12 (2.8) | 19 (4.6) |
| Peripheral sensory neuropathy | 15 (3.5) | 48 (11.5) |
| Eye disorders | 92 (21.2) | 59 (14.1) |
| Cataract | 13 (3.0) | 1 (0.2) |
| Dry eye | 29 (6.7) | 18 (4.3) |
| Vision blurred | 17 (3.9) | 8 (1.9) |
| Ear and labyrinth disorders | 19 (4.4) | 18 (4.3) |
| Cardiac disorders | 41 (9.4) | 27 (6.5) |
| Vascular disorders | 60 (13.8) | 52 (12.5) |
| Deep vein thrombosis | 0 (0) | 10 (2.4) |
| Hypertension | 28 (6.5) | 23 (5.5) |
| Hypotension | 11 (2.5) | 4 (1.0) |
| Respiratory, thoracic and mediastinal disorders | 221 (50.9) | 109 (26.1) |
| Cough | 75 (17.3) | 40 (9.6) |
| Dyspnoea | 30 (6.9) | 42 (10.1) |
| Epistaxis | 49 (11.3) | 15 (3.6) |
| Interstitial lung disease | 36 (8.3) | 2 (0.5) |
| Nasal congestion | 11 (2.5) | 4 (1.0) |
| Oropharyngeal pain | 18 (4.1) | 8 (1.9) |
| Pneumonitis | 31 (7.1) | 0 (0) |
| Pulmonary embolism | 9 (2.1) | 10 (2.4) |
| Rhinorrhoea | 13 (3.0) | 9 (2.2) |
| Gastrointestinal disorders | 378 (87.1) | 258 (61.9) |
| Abdominal discomfort | 12 (2.8) | 3 (0.7) |
| Abdominal distension | 23 (5.3) | 16 (3.8) |
| Abdominal pain | 46 (10.6) | 35 (8.4) |
| Abdominal pain upper | 35 (8.1) | 20 (4.8) |

Table 11: Common AEs[a] – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[b] (multipage table)

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[c]** **PT[c]** | **trastuzumab deruxtecan N = 434** | **Treatment of physician's choice[b] N = 417** |
| Constipation | 139 (32.0) | 62 (14.9) |
| Diarrhoea | 152 (35.0) | 115 (27.6) |
| Dry mouth | 25 (5.8) | 16 (3.8) |
| Dyspepsia | 50 (11.5) | 20 (4.8) |
| Flatulence | 10 (2.3) | 4 (1.0) |
| Gastrooesophageal reflux disease | 18 (4.1) | 7 (1.7) |
| Haemorrhoids | 15 (3.5) | 2 (0.5) |
| Nausea | 307 (70.7) | 128 (30.7) |
| Stomatitis | 61 (14.1) | 38 (9.1) |
| Vomiting | 154 (35.5) | 50 (12.0) |
| Hepatobiliary disorders | 26 (6.0) | 16 (3.8) |
| Skin and subcutaneous tissue disorders | 256 (59.0) | 280 (67.1) |
| Alopecia | 212 (48.8) | 88 (21.1) |
| Dry skin | 22 (5.1) | 15 (3.6) |
| Erythema | 7 (1.6) | 12 (2.9) |
| Nail discolouration | 2 (0.5) | 10 (2.4) |
| Nail disorder | 12 (2.8) | 17 (4.1) |
| Palmar-plantar erythrodysaesthesia syndrome | 5 (1.2) | 146 (35.0) |
| Pruritus | 19 (4.4) | 11 (2.6) |
| Rash | 30 (6.9) | 34 (8.2) |
| Musculoskeletal and connective tissue disorders | 137 (31.6) | 134 (32.1) |
| Arthralgia | 35 (8.1) | 45 (10.8) |
| Back pain | 38 (8.8) | 37 (8.9) |
| Bone pain | 6 (1.4) | 10 (2.4) |
| Muscle spasms | 20 (4.6) | 7 (1.7) |
| Musculoskeletal chest pain | 22 (5.1) | 13 (3.1) |
| Musculoskeletal pain | 10 (2.3) | 4 (1.0) |
| Myalgia | 21 (4.8) | 27 (6.5) |
| Neck pain | 10 (2.3) | 2 (0.5) |
| Pain in extremity | 30 (6.9) | 24 (5.8) |
| Renal and urinary disorders | 33 (7.6) | 20 (4.8) |
| Dysuria | 12 (2.8) | 5 (1.2) |
| Reproductive system and breast disorders | 23 (5.3) | 14 (3.4) |

Table 11: Common AEs[a] – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[b] (multipage table)

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[c]** **PT[c]** | **trastuzumab deruxtecan N = 434** | **Treatment of physician's choice[b] N = 417** |
| General disorders and administration site conditions | 280 (64.5) | 234 (56.1) |
| Asthenia | 104 (24.0) | 72 (17.3) |
| Chest discomfort | 10 (2.3) | 7 (1.7) |
| Fatigue | 120 (27.6) | 83 (19.9) |
| Influenza like illness | 14 (3.2) | 5 (1.2) |
| Malaise | 35 (8.1) | 18 (4.3) |
| Mucosal inflammation | 17 (3.9) | 15 (3.6) |
| Oedema peripheral | 40 (9.2) | 61 (14.6) |
| Pyrexia | 55 (12.7) | 33 (7.9) |
| Investigations | 283 (65.2) | 152 (36.5) |
| Alanine aminotransferase increased | 95 (21.9) | 49 (11.8) |
| Aspartate aminotransferase increased | 118 (27.2) | 45 (10.8) |
| Blood alkaline phosphatase increased | 51 (11.8) | 18 (4.3) |
| Blood bilirubin increased | 31 (7.1) | 20 (4.8) |
| Blood lactate dehydrogenase increased | 18 (4.1) | 19 (4.6) |
| Ejection fraction decreased | 39 (9.0) | 12 (2.9) |
| Gamma-glutamyltransferase increased | 40 (9.2) | 9 (2.2) |
| Lymphocyte count decreased | 29 (6.7) | 11 (2.6) |
| Neutrophil count decreased | 100 (23.0) | 66 (15.8) |
| Platelet count decreased | 63 (14.5) | 15 (3.6) |
| Weight decreased | 34 (7.8) | 9 (2.2) |
| Weight increased | 15 (3.5) | 11 (2.6) |
| White blood cell count decreased | 79 (18.2) | 53 (12.7) |
| Injury, poisoning and procedural complications | 52 (12.0) | 39 (9.4) |
| Fall | 11 (2.5) | 10 (2.4) |

a. Events that occurred in ≥ 10 of patients in at least one study arm.
b. In the DESTINY-Breast06 study, therapy could be chosen from capecitabine, paclitaxel and nab-paclitaxel.
c. MedDRA version 27.0; SOC and PT notation adopted without modification from the supplementary submission in the context of the comments.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 12: Common SAEs[a] – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[b]

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[c]** | **trastuzumab deruxtecan N = 434** | **Treatment of physician's choice[b] N = 417** |
| **DESTINY-Breast06** | | |
| **Overall SAE rate** | 90 (20.7) | 67 (16.1) |
| Infections and infestations | 30 (6.9) | 20 (4.8) |
| Respiratory, thoracic and mediastinal disorders | 21 (4.8) | 9 (2.2) |
| Gastrointestinal disorders | 13 (3.0) | 11 (2.6) |

a. Events that occurred in ≥ 10 of patients in at least one study arm.
b. In the DESTINY-Breast06 study, therapy could be chosen from capecitabine, paclitaxel and nab-paclitaxel.
c. MedDRA version 27.0; SOC notation adopted without modification from the supplementary submission in the context of the comments.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 13: Common severe AEs[a] (CTCAE grade ≥ 3) – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[b]

| Study | Patients with event n (%) | |
|---|---|---|
| SOC[c] PT[c] | trastuzumab deruxtecan N = 434 | Treatment of physician's choice[b] N = 417 |
| **DESTINY-Breast06** | | |
| **Overall rate of severe AEs (CTCAE grade ≥ 3)** | 239 (55.1) | 186 (44.6) |
| Infections and infestations | 30 (6.9) | 25 (6.0) |
| Blood and lymphatic system disorders | 77 (17.7) | 53 (12.7) |
| Anaemia | 43 (9.9) | 18 (4.3) |
| Neutropenia | 37 (8.5) | 35 (8.4) |
| Metabolism and nutrition disorders | 34 (7.8) | 14 (3.4) |
| Hypokalaemia | 20 (4.6) | 6 (1.4) |
| Nervous system disorders | 9 (2.1) | 18 (4.3) |
| Vascular disorders | 15 (3.5) | 14 (3.4) |
| Hypertension | 12 (2.8) | 11 (2.6) |
| Respiratory, thoracic and mediastinal disorders | 16 (3.7) | 12 (2.9) |
| Gastrointestinal disorders | 32 (7.4) | 23 (5.5) |
| Diarrhoea | 10 (2.3) | 11 (2.6) |
| Skin and subcutaneous tissue disorders | 0 (0) | 36 (8.6) |
| Palmar-plantar erythrodysaesthesia syndrome | 0 (0) | 31 (7.4) |
| Musculoskeletal and connective tissue disorders | 5 (1.2) | 10 (2.4) |
| General disorders and administration site conditions | 26 (6.0) | 14 (3.4) |
| Asthenia | 11 (2.5) | 5 (1.2) |
| Fatigue | 10 (2.3) | 6 (1.4) |
| Investigations | 104 (24.0) | 47 (11.3) |
| Gamma-glutamyltransferase increased | 10 (2.3) | 2 (0.5) |
| Lymphocyte count decreased | 11 (2.5) | 2 (0.5) |
| Neutrophil count decreased | 61 (14.1) | 36 (8.6) |
| Platelet count decreased | 18 (4.1) | 0 (0) |
| White blood cell count decreased | 25 (5.8) | 20 (4.8) |

a. Events that occurred in ≥ 10 of the patients in at least one study arm.
b. In the DESTINY-Breast06 study, therapy could be chosen from capecitabine, paclitaxel and nab-paclitaxel.
c. MedDRA version 27.0; SOC and PT notation adopted without modification from the supplementary submission in the context of the comments.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 14: Discontinuations due to AEs – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

| Study | Patients with event n (%) | |
|---|---|---|
| **SOC[b]**<br>**PT[b]** | **trastuzumab deruxtecan N = 434** | **Treatment of physician's choice[a] N = 417** |
| **DESTINY-Breast06** | | |
| **Overall rate of discontinuations due to AEs** | 71 (16.4) | 41 (9.8) |
| Infections and infestations | 3 (0.7) | 0 (0) |
| Fracture infection | 1 (0.2) | 0 (0) |
| Pneumocystis jirovecii pneumonia | 1 (0.2) | 0 (0) |
| Pneumonia | 1 (0.2) | 0 (0) |
| Blood and lymphatic system disorders | 2 (0.5) | 0 (0) |
| Anaemia | 1 (0.2) | 0 (0) |
| Pancytopenia | 1 (0.2) | 0 (0) |
| Immune system disorders | 0 (0) | 2 (0.5) |
| Anaphylactic shock | 0 (0) | 1 (0.2) |
| Hypersensitivity | 0 (0) | 1 (0.2) |
| Metabolism and nutrition disorders | 3 (0.7) | 0 (0) |
| Decreased appetite | 1 (0.2) | 0 (0) |
| Hypokalaemia | 2 (0.5) | 0 (0) |
| Nervous system disorders | 2 (0.5) | 13 (3.1) |
| Dysaesthesia | 0 (0) | 1 (0.2) |
| Dysgeusia | 1 (0.2) | 0 (0) |
| Leukoencephalopathy | 1 (0.2) | 0 (0) |
| Neuromuscular toxicity | 0 (0) | 1 (0.2) |
| Neuropathy peripheral | 0 (0) | 3 (0.7) |
| Peripheral motor neuropathy | 0 (0) | 1 (0.2) |
| Peripheral sensory neuropathy | 0 (0) | 6 (1.4) |
| Spinal cord compression | 0 (0) | 1 (0.2) |
| Cardiac disorders | 1 (0.2) | 5 (1.2) |
| Angina pectoris | 0 (0) | 3 (0.7) |
| Atrial fibrillation | 0 (0) | 1 (0.2) |
| Left ventricular dysfunction | 1 (0.2) | 0 (0) |
| Ventricular tachycardia | 0 (0) | 1 (0.2) |
| Vascular disorders | 0 (0) | 1 (0.2) |
| Lymphoedema | 0 (0) | 1 (0.2) |
| Respiratory, thoracic and mediastinal disorders | 44 (10.1) | 1 (0.2) |
| Interstitial lung disease | 19 (4.4) | 0 (0) |
| Nasal inflammation | 0 (0) | 1 (0.2) |

Table 14: Discontinuations due to AEs – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

| Study | Patients with event n (%) | |
|---|---|---|
| **SOC[b]**<br>**PT[b]** | **trastuzumab deruxtecan N = 434** | **Treatment of physician's choice[a] N = 417** |
| Pneumonitis | 24 (5.5) | 0 (0) |
| Pulmonary embolism | 1 (0.2) | 0 (0) |
| Gastrointestinal disorders | 1 (0.2) | 4 (1.0) |
| Ascites | 1 (0.2) | 0 (0) |
| Colitis | 0 (0) | 3 (0.7) |
| Mouth ulceration | 0 (0) | 1 (0.2) |
| Hepatobiliary disorders | 2 (0.5) | 1 (0.2) |
| Acute hepatic failure | 1 (0.2) | 0 (0) |
| Drug-induced liver injury | 0 (0) | 1 (0.2) |
| Hepatic cirrhosis | 1 (0.2) | 0 (0) |
| Skin and subcutaneous tissue disorders | 0 (0) | 6 (1.4) |
| Nail deformation | 0 (0) | 1 (0.2) |
| Nail toxicity | 0 (0) | 1 (0.2) |
| Palmar-plantar erythrodysaesthesia syndrome | 0 (0) | 1 (0.2) |
| Paraneoplastic dermatomyositis | 0 (0) | 1 (0.2) |
| Rash | 0 (0) | 1 (0.2) |
| Skin fissures | 0 (0) | 1 (0.2) |
| Renal and urinary disorders | 0 (0) | 2 (0.5) |
| Cystitis interstitial | 0 (0) | 1 (0.2) |
| Renal colic | 0 (0) | 1 (0.2) |
| General disorders and administration site conditions | 3 (0.7) | 7 (1.7) |
| Asthenia | 1 (0.2) | 3 (0.7) |
| Facial pain | 0 (0) | 1 (0.2) |
| Fatigue | 0 (0) | 2 (0.5) |
| General physical health deterioration | 2 (0.5) | 0 (0) |
| Oedema peripheral | 0 (0) | 1 (0.2) |
| Investigations | 11 (2.5) | 1 (0.2) |
| Blood bilirubin increased | 2 (0.5) | 0 (0) |
| Ejection fraction decreased | 2 (0.5) | 0 (0) |
| Gamma-glutamyltransferase increased | 1 (0.2) | 0 (0) |
| Liver function test increased | 1 (0.2) | 0 (0) |
| Neutrophil count decreased | 1 (0.2) | 1 (0.2) |
| Platelet count decreased | 3 (0.7) | 0 (0) |
| Pulse abnormal | 1 (0.2) | 0 (0) |

Table 14: Discontinuations due to AEs – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

| Study | Patients with event n (%) | |
|---|---|---|
| SOC[b] PT[b] | trastuzumab deruxtecan N = 434 | Treatment of physician's choice[a] N = 417 |
| Injury, poisoning and procedural complications | 1 (0.2) | 3 (0.7) |
| Contusion | 0 (0) | 1 (0.2) |
| Femur fracture | 0 (0) | 1 (0.2) |
| Infusion related reaction | 1 (0.2) | 1 (0.2) |

a. In the DESTINY-Breast06 study, therapy could be chosen from capecitabine, paclitaxel and nab-paclitaxel.
b. MedDRA version 27.0; SOC and PT notation adopted without modification from the supplementary submission in the context of the comments.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

# Appendix B Kaplan-Meier curves for the included outcomes of the total population of the DESTINY-Breast06 study

## B.1 Mortality

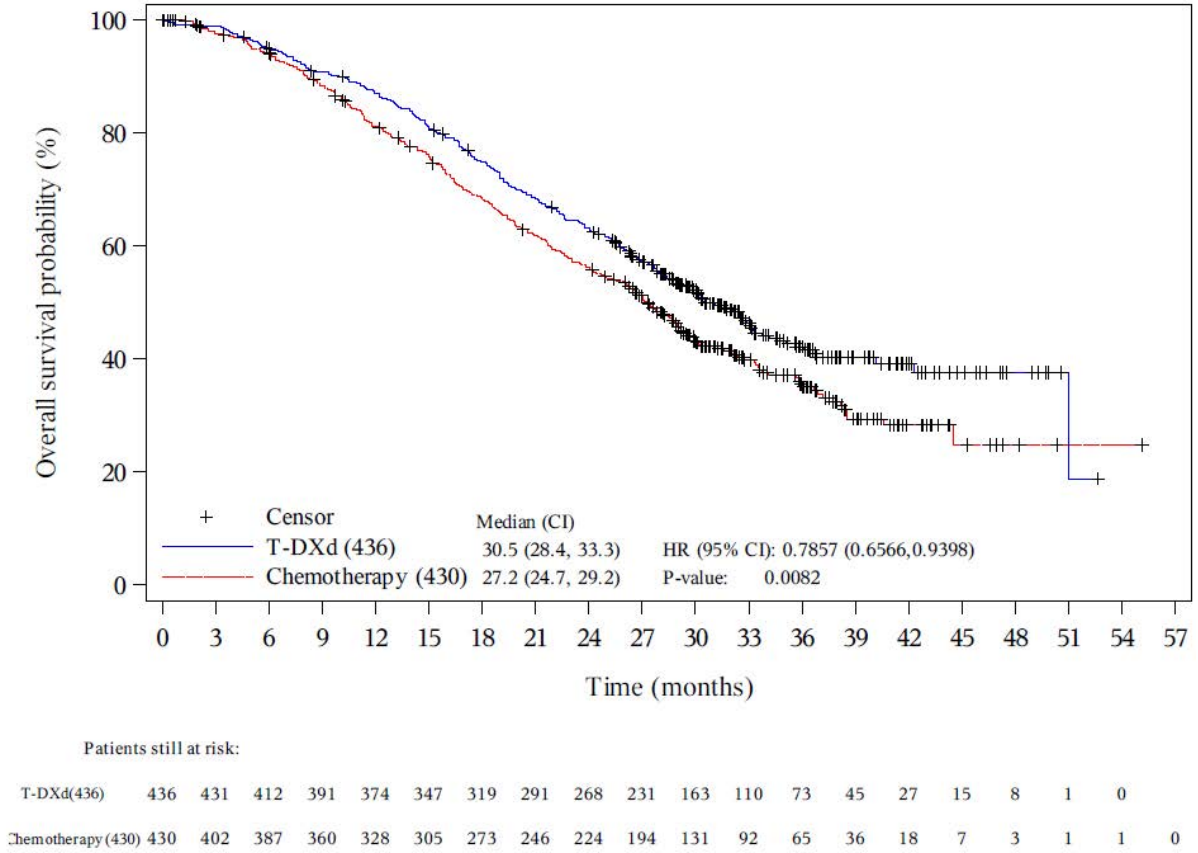



Figure 1: Kaplan-Meier curves for the outcome overall survival – 2nd data cut from 24 March 2025

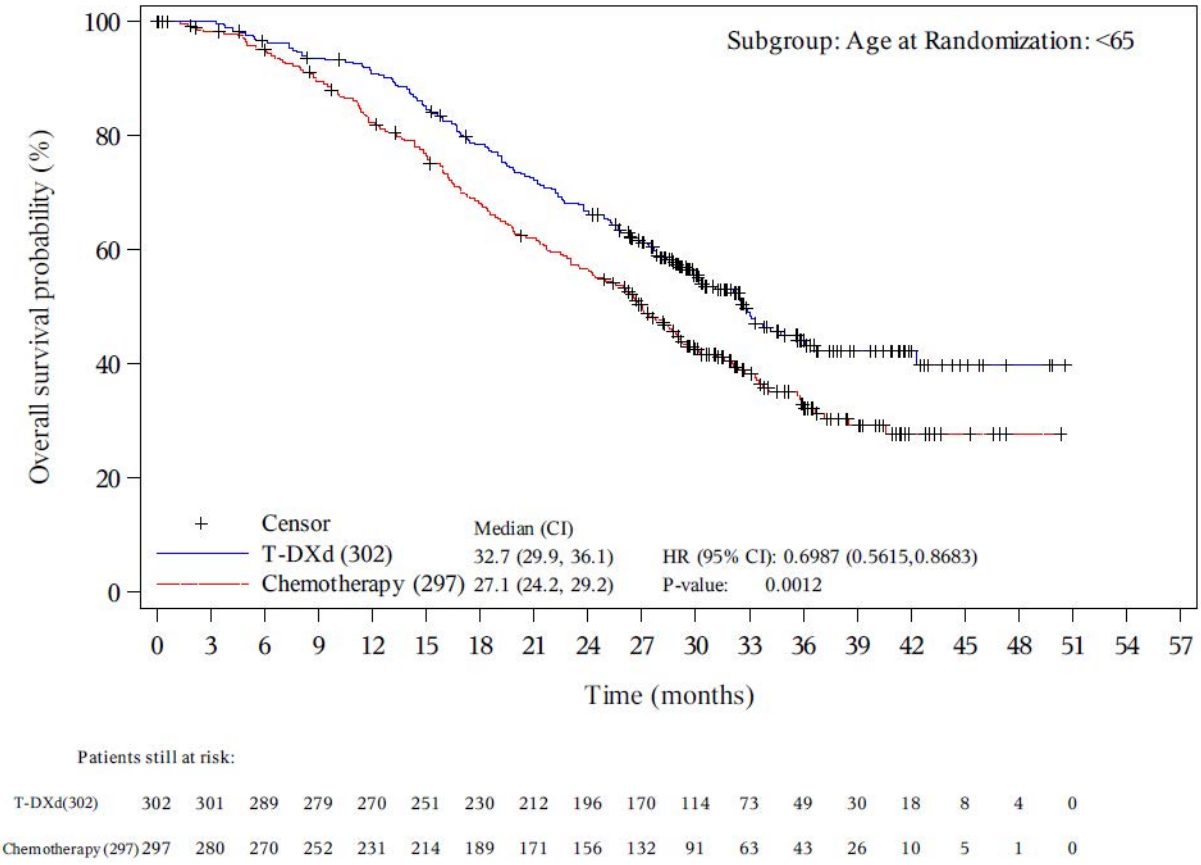



Figure 2: Kaplan-Meier curves for the outcome overall survival – 2nd data cut from 24 March 2025, subgroup < 65 years

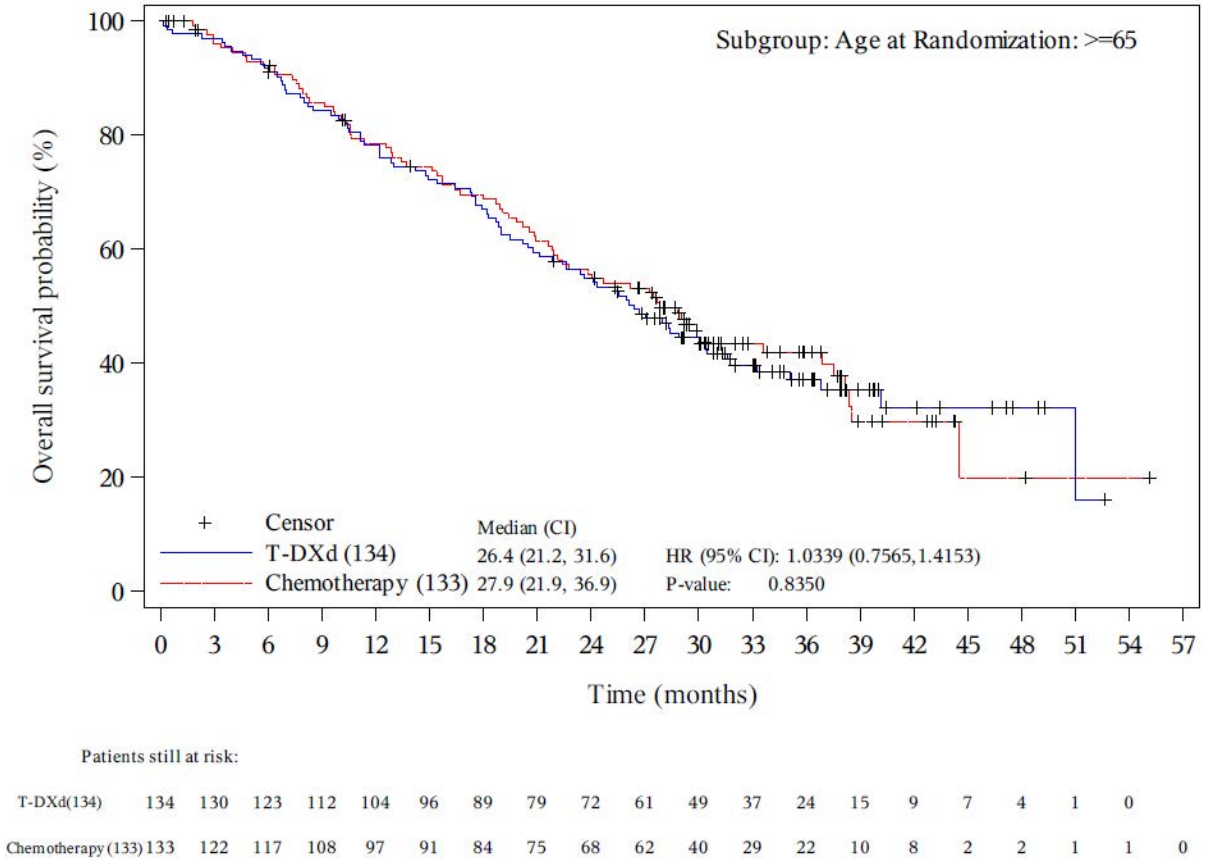



Figure 3: Kaplan-Meier curves for the outcome overall survival – 2nd data cut from 24 March 2025, subgroup ≥ 65 years

## B.2 Morbidity

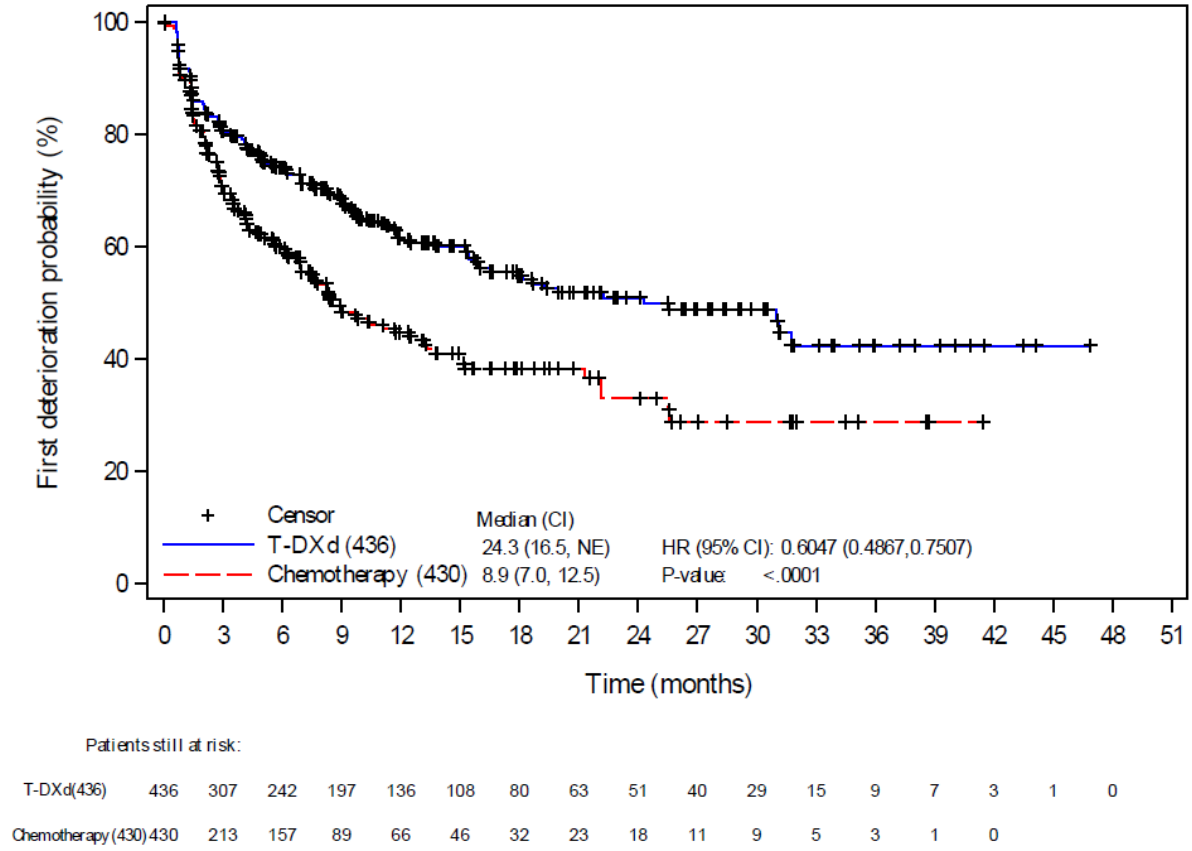



Figure 4: Kaplan-Meier curves for the outcome PGIC (time to first deterioration) – 2nd data cut from 24 March 2025

## B.3 Side effects

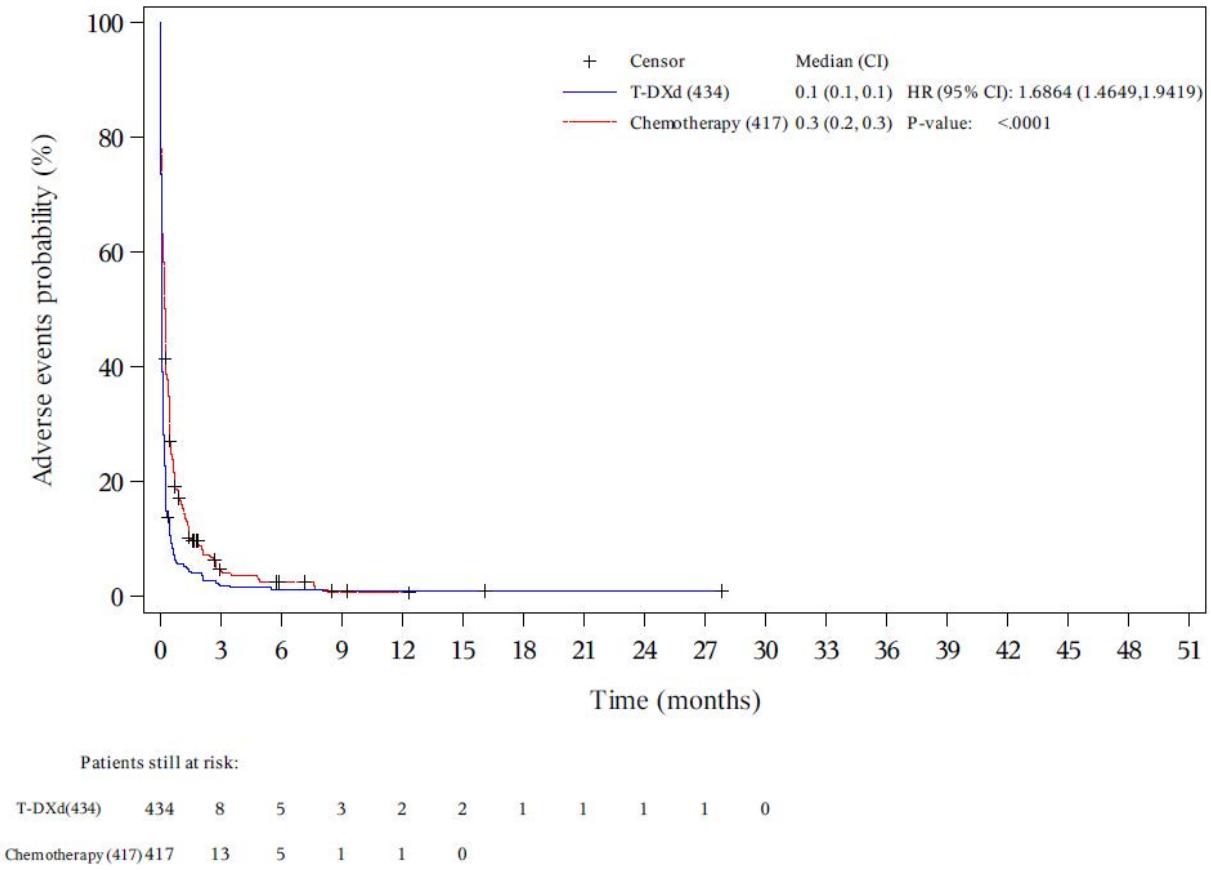
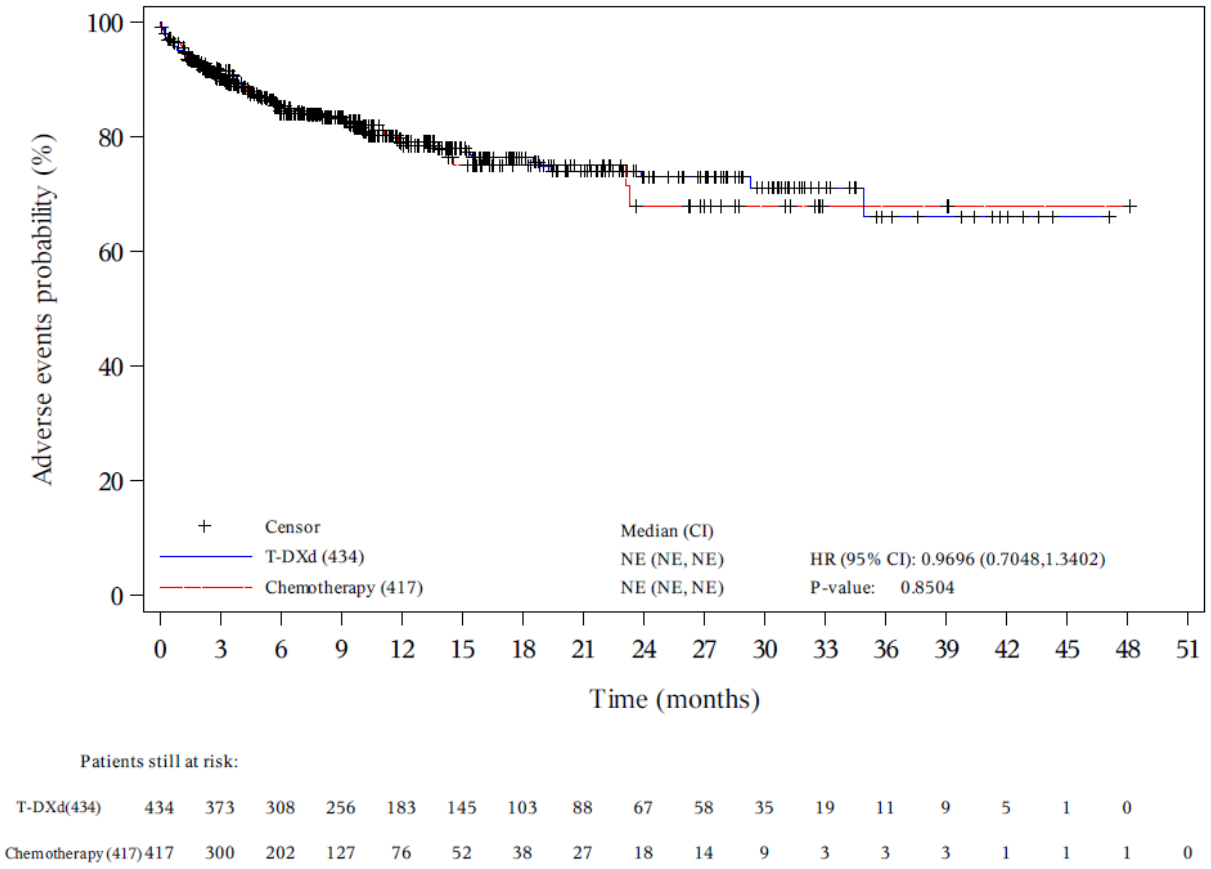



Figure 5: Kaplan-Meier curves for the outcome AEs (presented as supplementary information) – 2nd data cut from 24 March 2025




Patients still at risk:

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T-DXd(434) | 434 | 373 | 308 | 256 | 183 | 145 | 103 | 88 | 67 | 58 | 35 | 19 | 11 | 9 | 5 | 1 | 0 | |
| Chemotherapy (417) | 417 | 300 | 202 | 127 | 76 | 52 | 38 | 27 | 18 | 14 | 9 | 3 | 3 | 3 | 1 | 1 | 1 | 0 |

Figure 6: Kaplan-Meier curves for the outcome SAEs – 2nd data cut from 24 March 2025

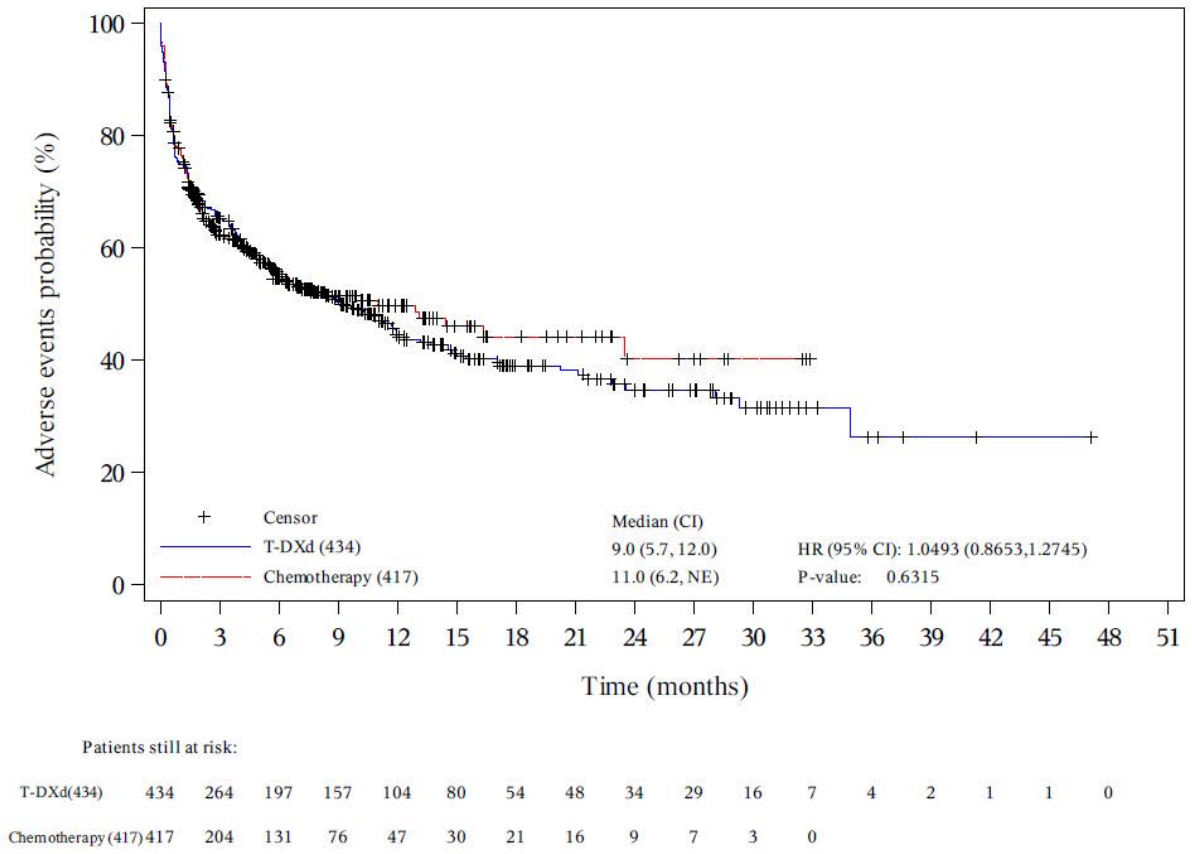



Figure 7: Kaplan-Meier curve for the outcome severe AEs – 2nd data cut from 24 March 2025

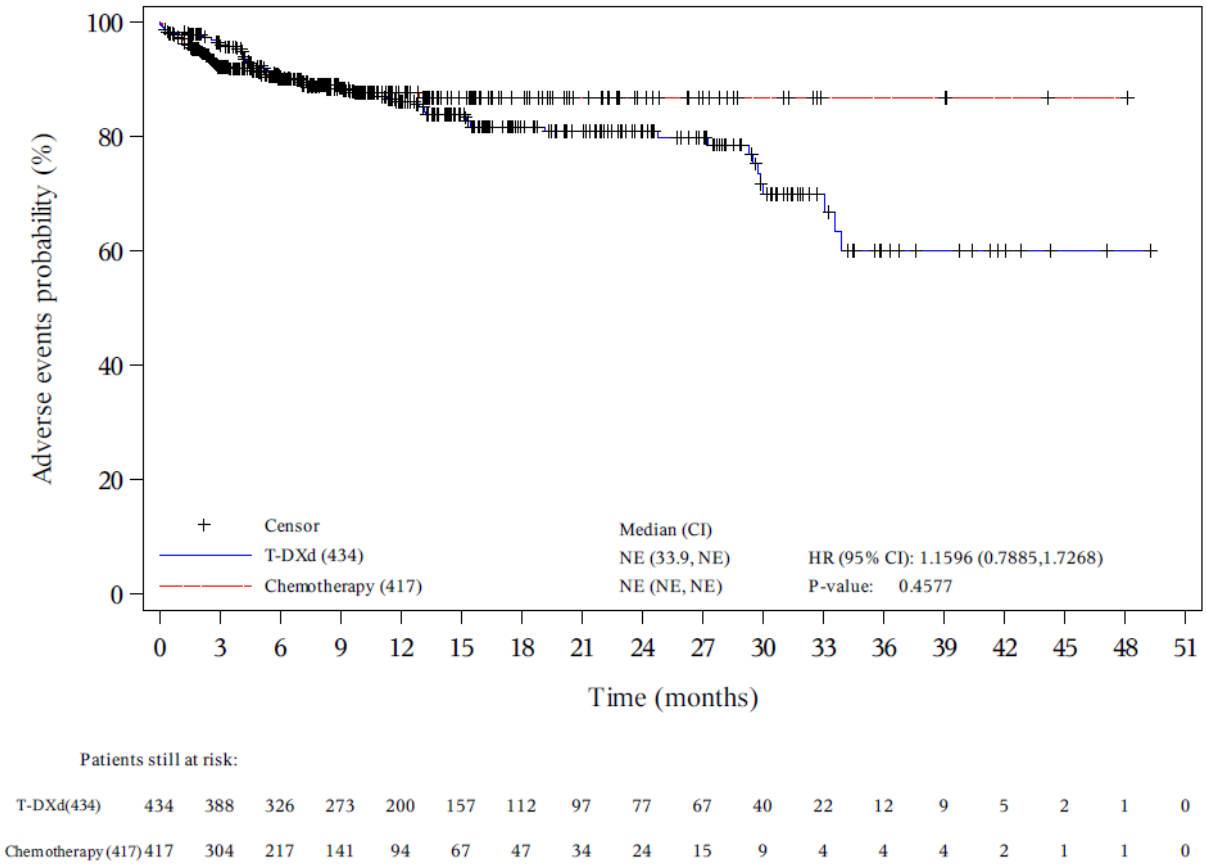



Figure 8: Kaplan-Meier curves for the outcome discontinuation due to AEs – 2nd data cut from 24 March 2025

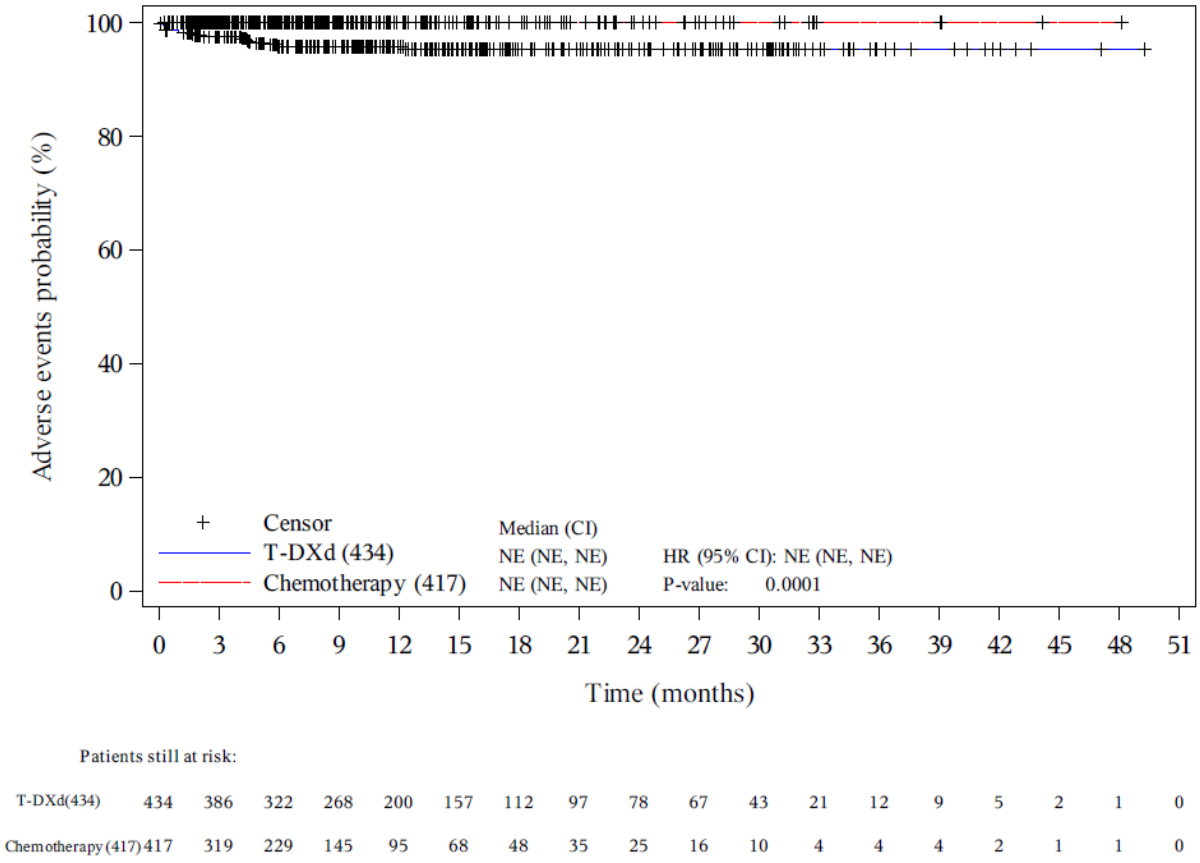
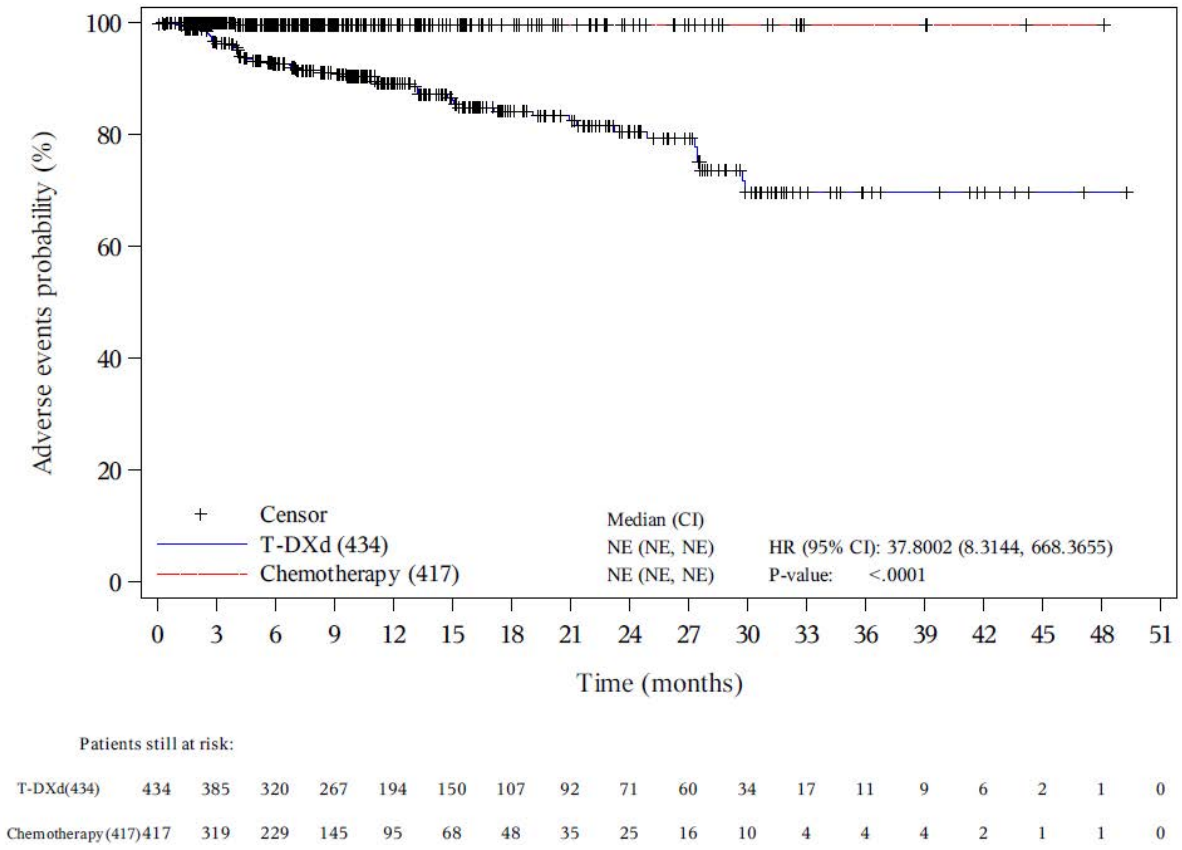


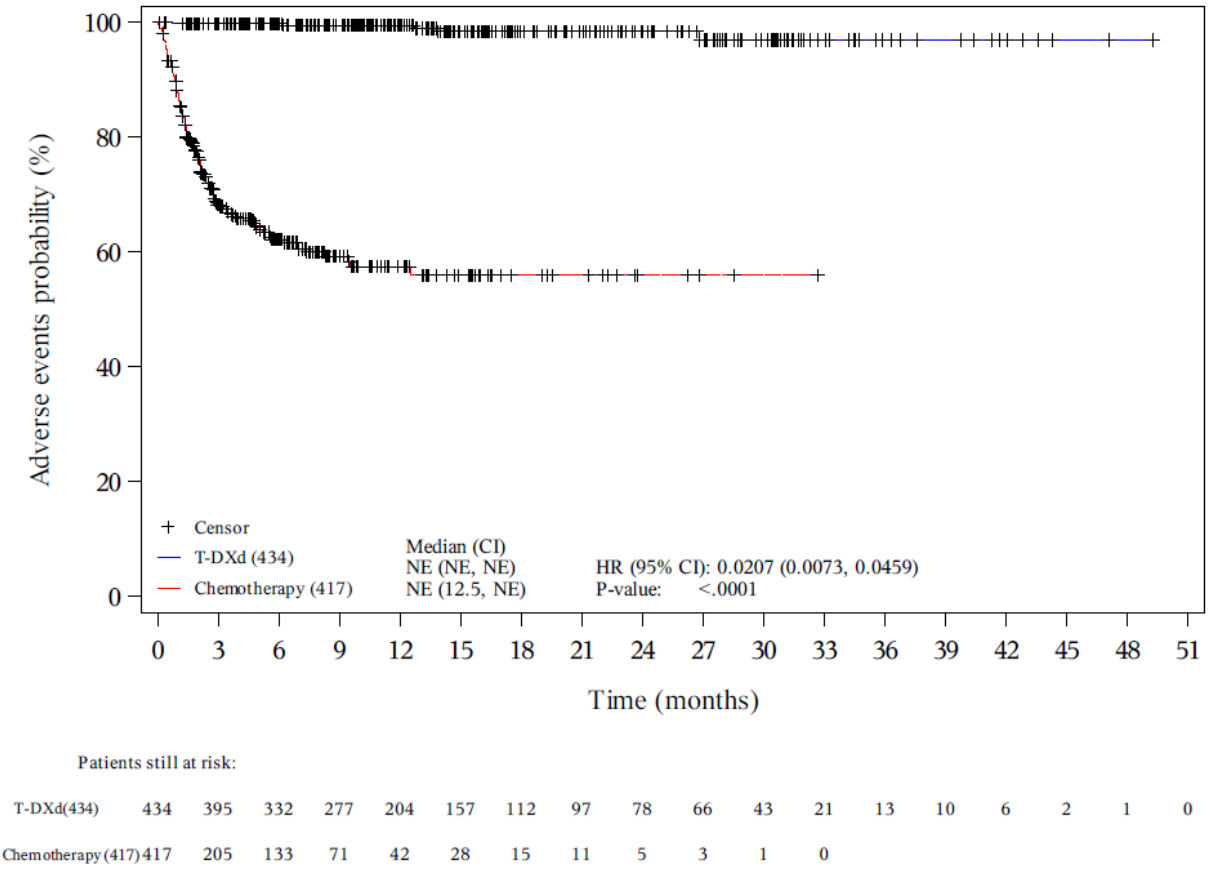

Figure 9: Kaplan-Meier curves for the outcome platelet count decreased (PT, severe AEs) – 2nd data cut from 24 March 2025




Patients still at risk:

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T-DXd(434) | 434 | 385 | 320 | 267 | 194 | 150 | 107 | 92 | 71 | 60 | 34 | 17 | 11 | 9 | 6 | 2 | 1 | 0 |
| Chemotherapy (417) | 417 | 319 | 229 | 145 | 95 | 68 | 48 | 35 | 25 | 16 | 10 | 4 | 4 | 4 | 2 | 1 | 1 | 0 |

Figure 10: Kaplan-Meier curves for the outcome ILD/pneumonitis (AEs) – 2nd data cut from 24 March 2025




Patients still at risk:

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T-DXd(434) | 434 | 395 | 332 | 277 | 204 | 157 | 112 | 97 | 78 | 66 | 43 | 21 | 13 | 10 | 6 | 2 | 1 | 0 |
| Chemotherapy (417) | 417 | 205 | 133 | 71 | 42 | 28 | 15 | 11 | 5 | 3 | 1 | 0 | | | | | | |

Figure 11: Kaplan-Meier curves for the outcome of hand-foot syndrome (PT, AEs) – 2nd data cut from 24 March 2025

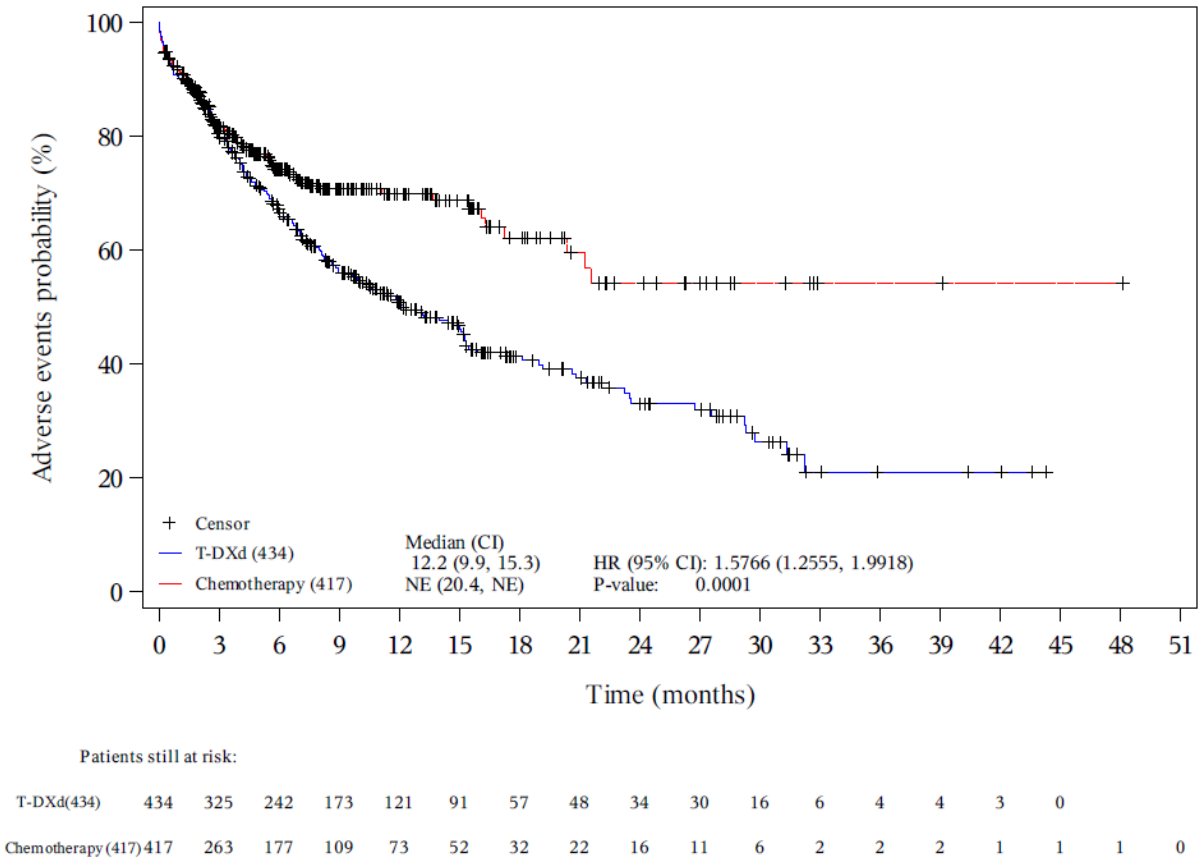



Figure 12: Kaplan-Meier curves for the outcome of respiratory, thoracic and mediastinal disorders (SOC, AEs) – 2nd data cut from 24 March 2025

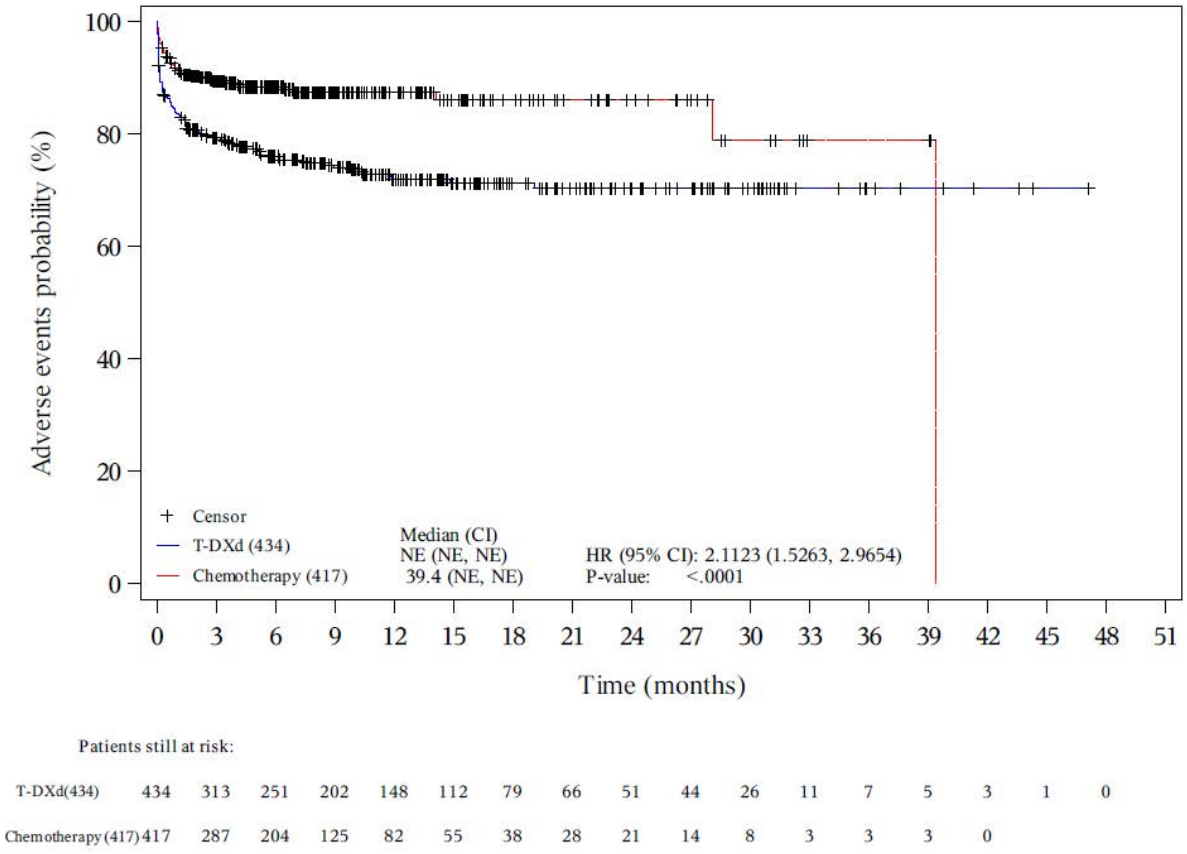



Figure 13: Kaplan-Meier curves for the outcome decreased appetite (PT, AEs) – 2nd data cut from 24 March 2025

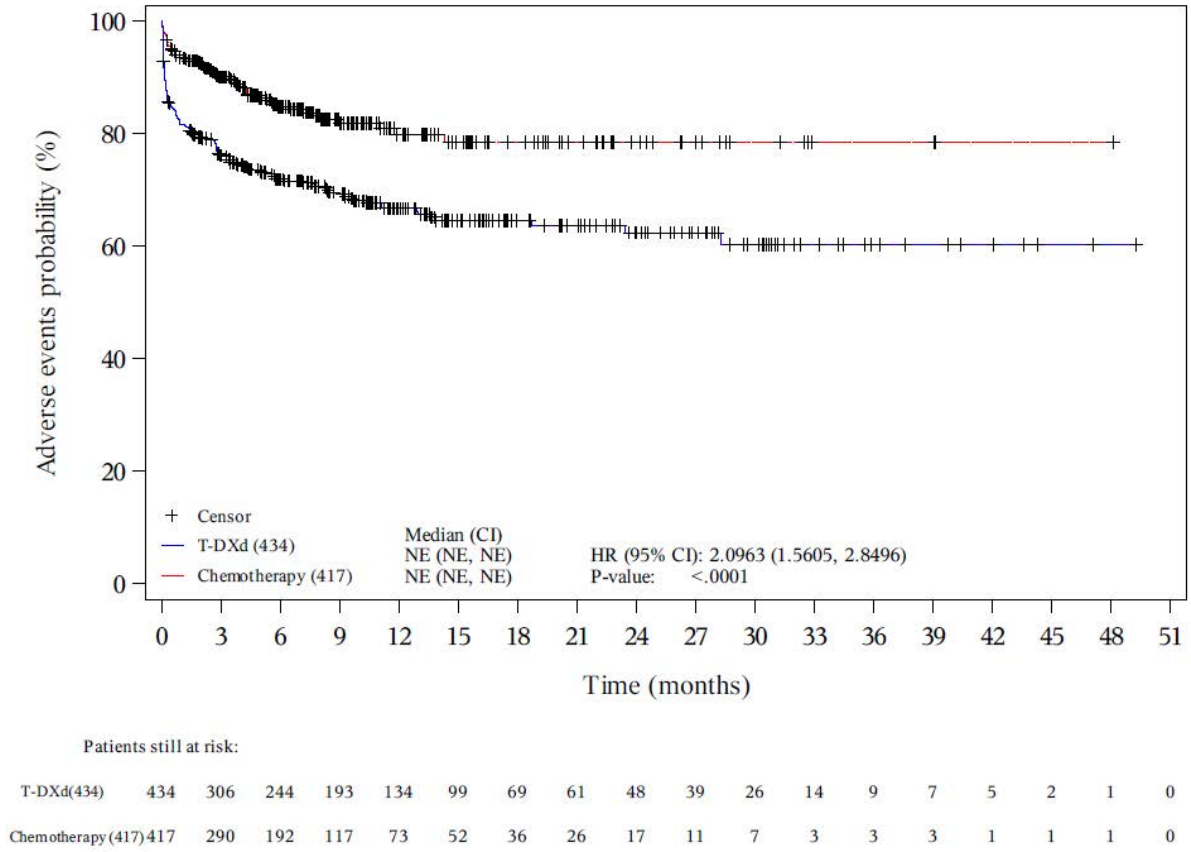



Figure 14: Kaplan-Meier curves for the outcome constipation (PT, AEs) – 2nd data cut from 24 March 2025

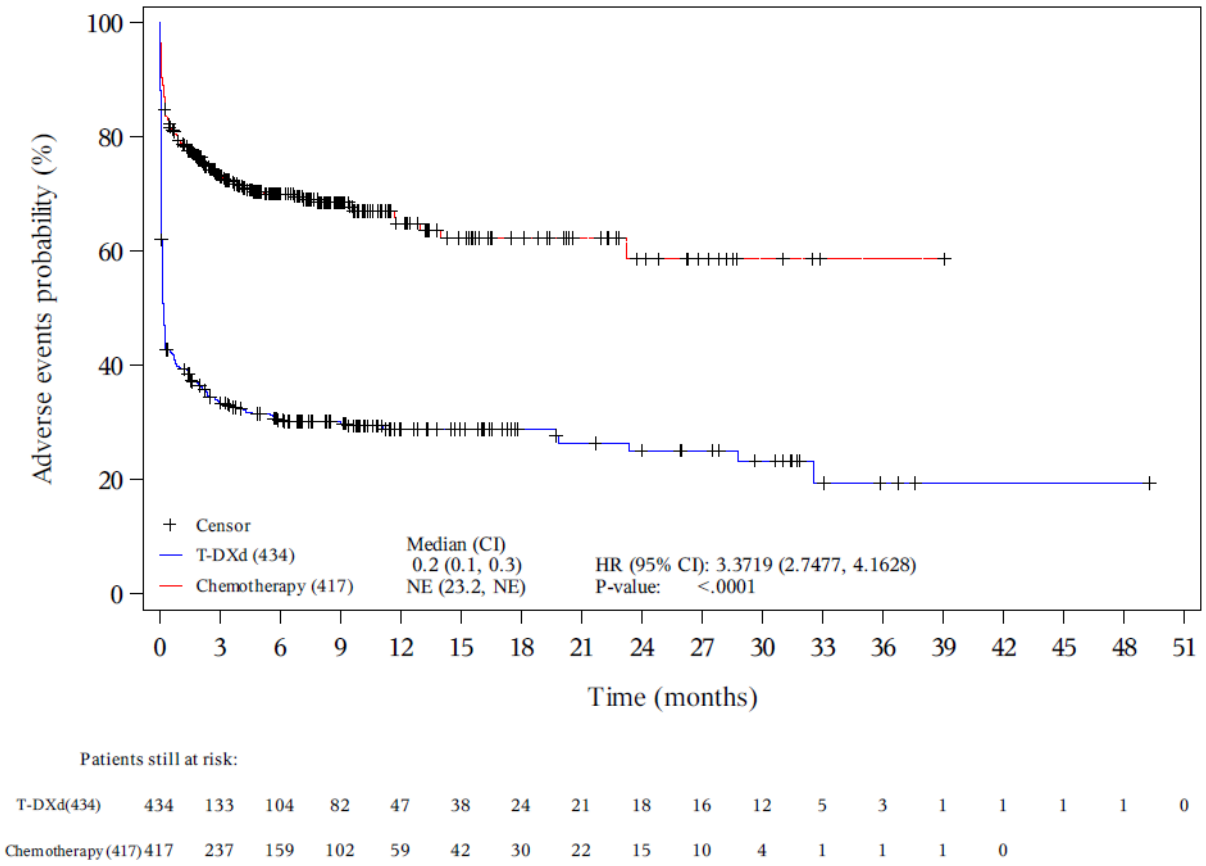
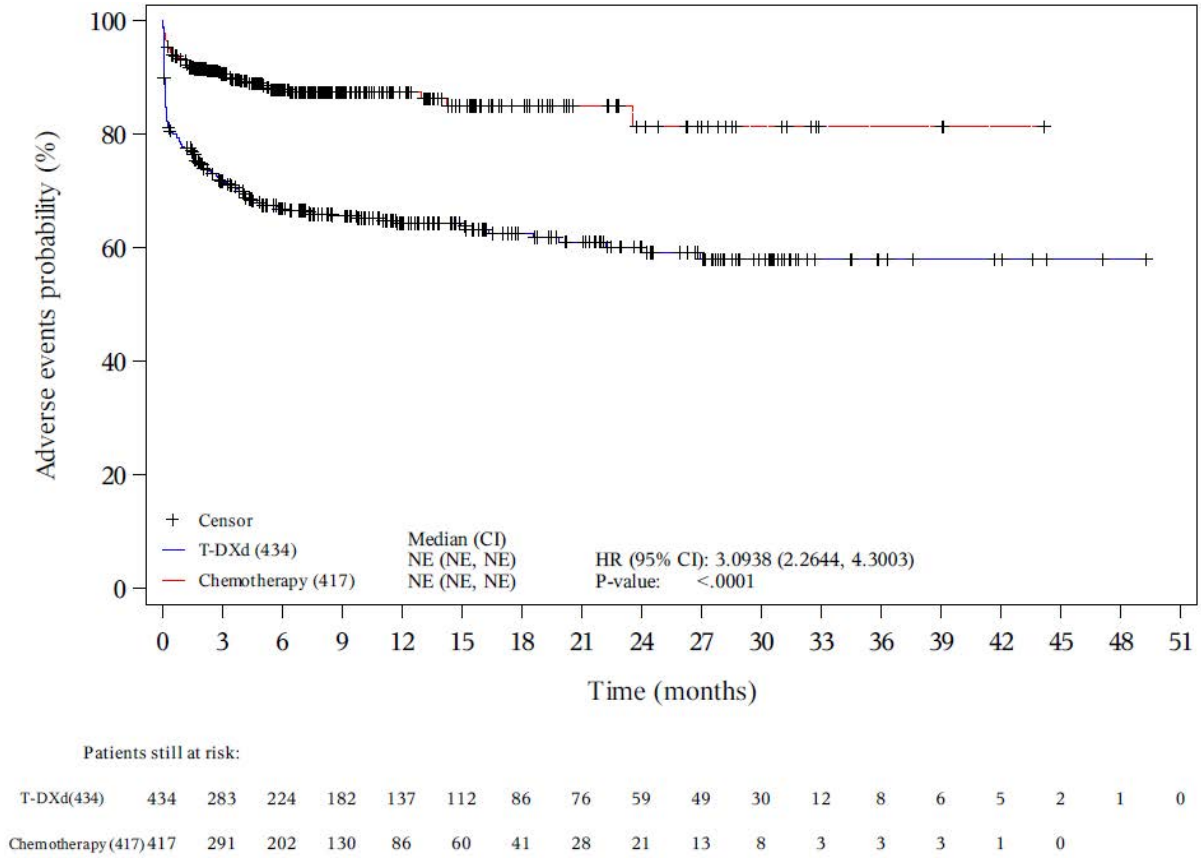



Figure 15: Kaplan-Meier curves for the outcome nausea (PT, AEs) – 2nd data cut from 24 March 2025




Patients still at risk:

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T-DXd(434) | 434 | 283 | 224 | 182 | 137 | 112 | 86 | 76 | 59 | 49 | 30 | 12 | 8 | 6 | 5 | 2 | 1 | 0 |
| Chemotherapy (417) | 417 | 291 | 202 | 130 | 86 | 60 | 41 | 28 | 21 | 13 | 8 | 3 | 3 | 3 | 1 | 0 | | |

Figure 16: Kaplan-Meier curves for the outcome vomiting (PT, AEs) – 2nd data cut from 24 March 2025

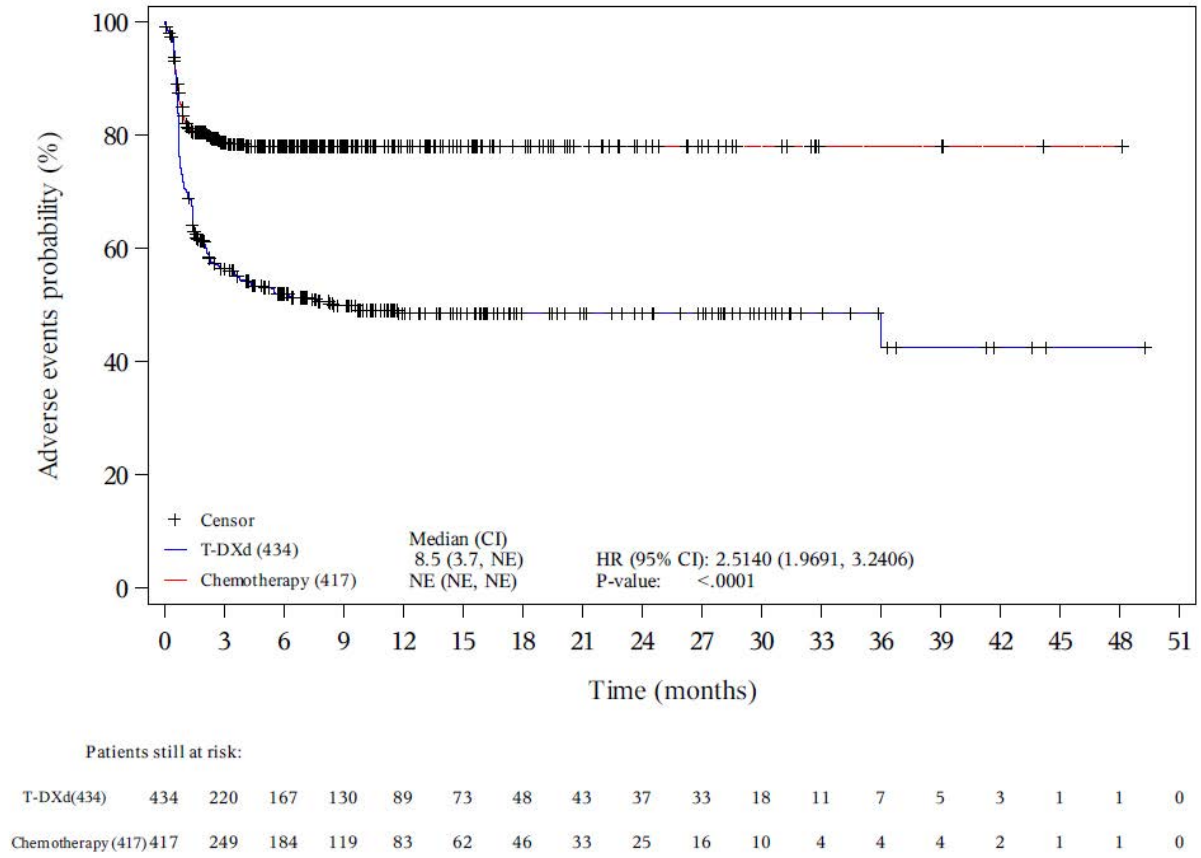
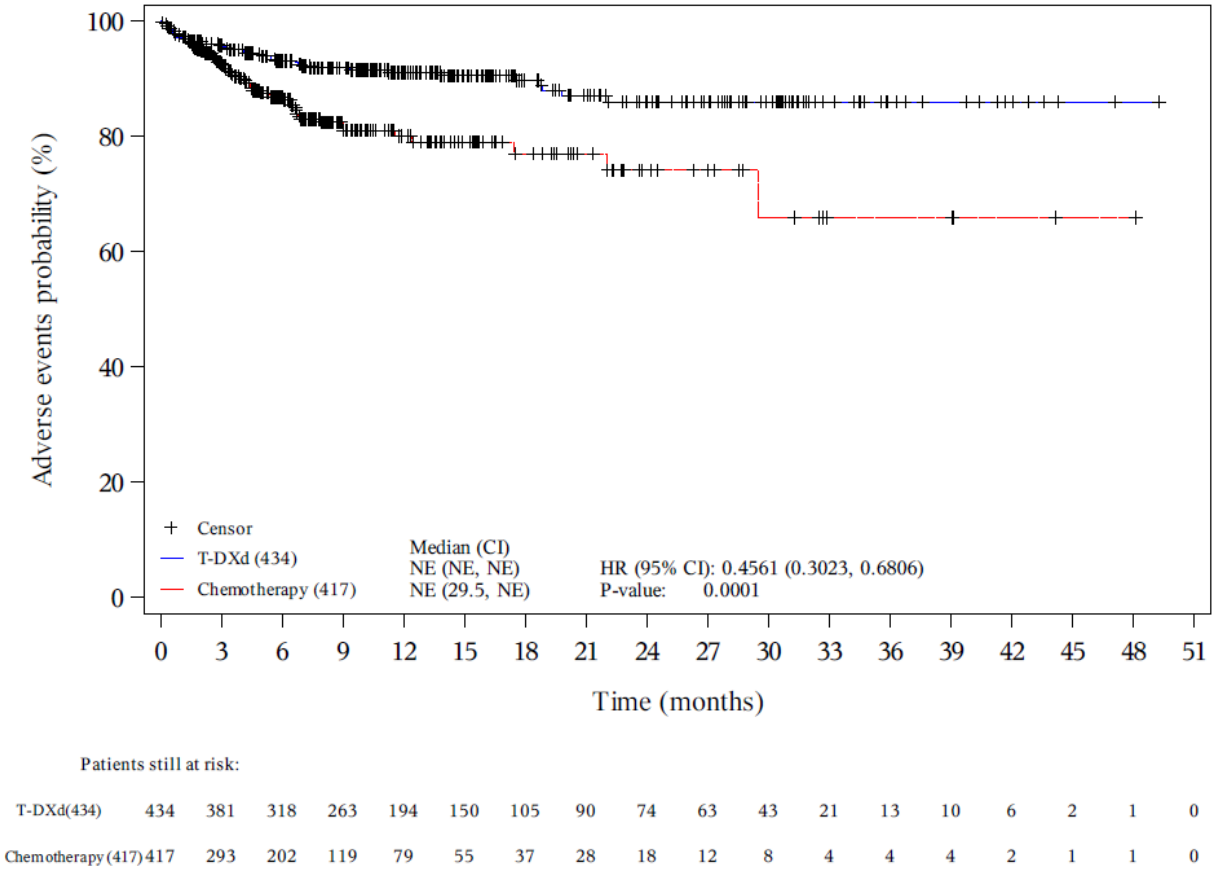



Figure 17: Kaplan-Meier curves for the outcome alopecia (PT, AEs) – 2nd data cut from 24 March 2025




Patients still at risk:

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T-DXd(434) | 434 | 381 | 318 | 263 | 194 | 150 | 105 | 90 | 74 | 63 | 43 | 21 | 13 | 10 | 6 | 2 | 1 | 0 |
| Chemotherapy (417) | 417 | 293 | 202 | 119 | 79 | 55 | 37 | 28 | 18 | 12 | 8 | 4 | 4 | 4 | 2 | 1 | 1 | 0 |

Figure 18: Kaplan-Meier curves for the outcome oedema peripheral (PT, AEs) – 2nd data cut from 24 March 2025

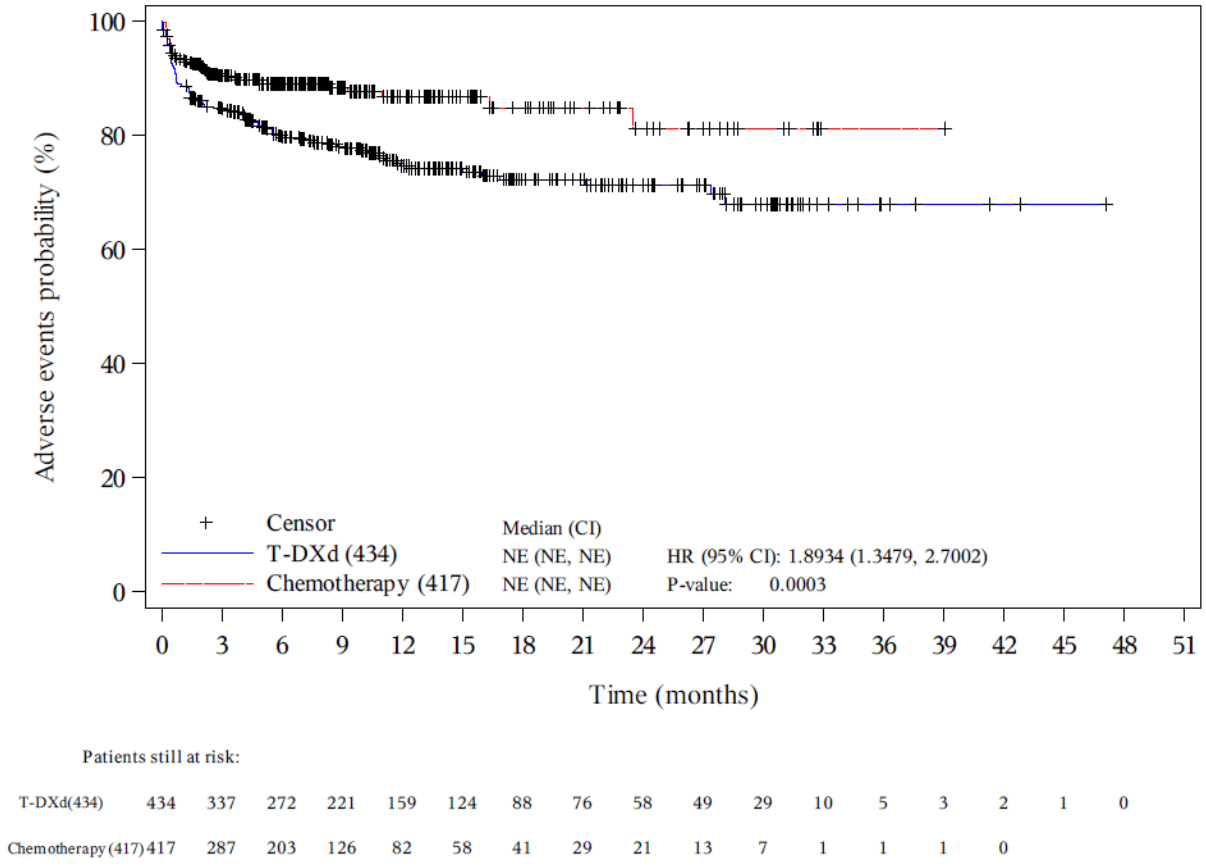



Figure 19: Kaplan-Meier curves for the outcome investigations (SOC, severe AEs) – 2nd data cut from 24 March 2025

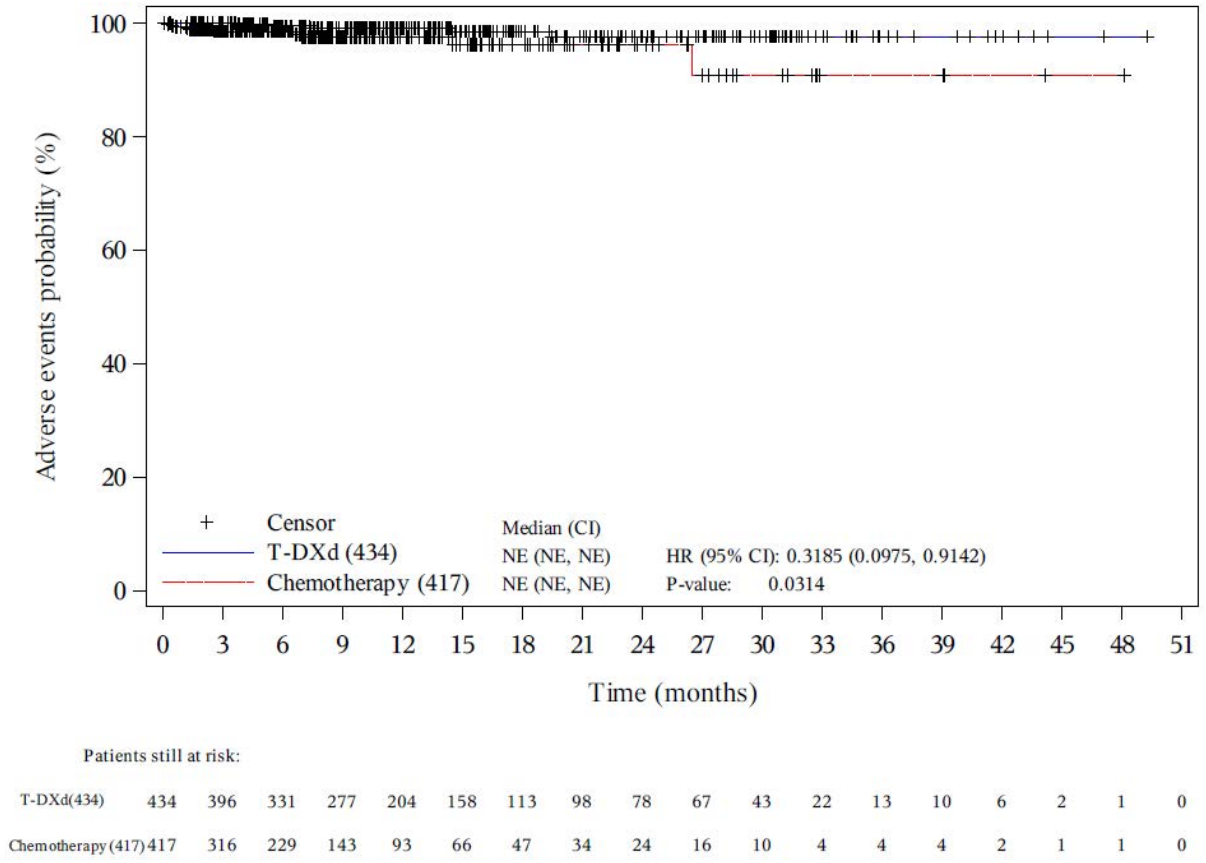



Figure 20: Kaplan-Meier curves for the outcome musculoskeletal and connective tissue disorders (SOC, severe AEs) – 2nd data cut from 24 March 2025

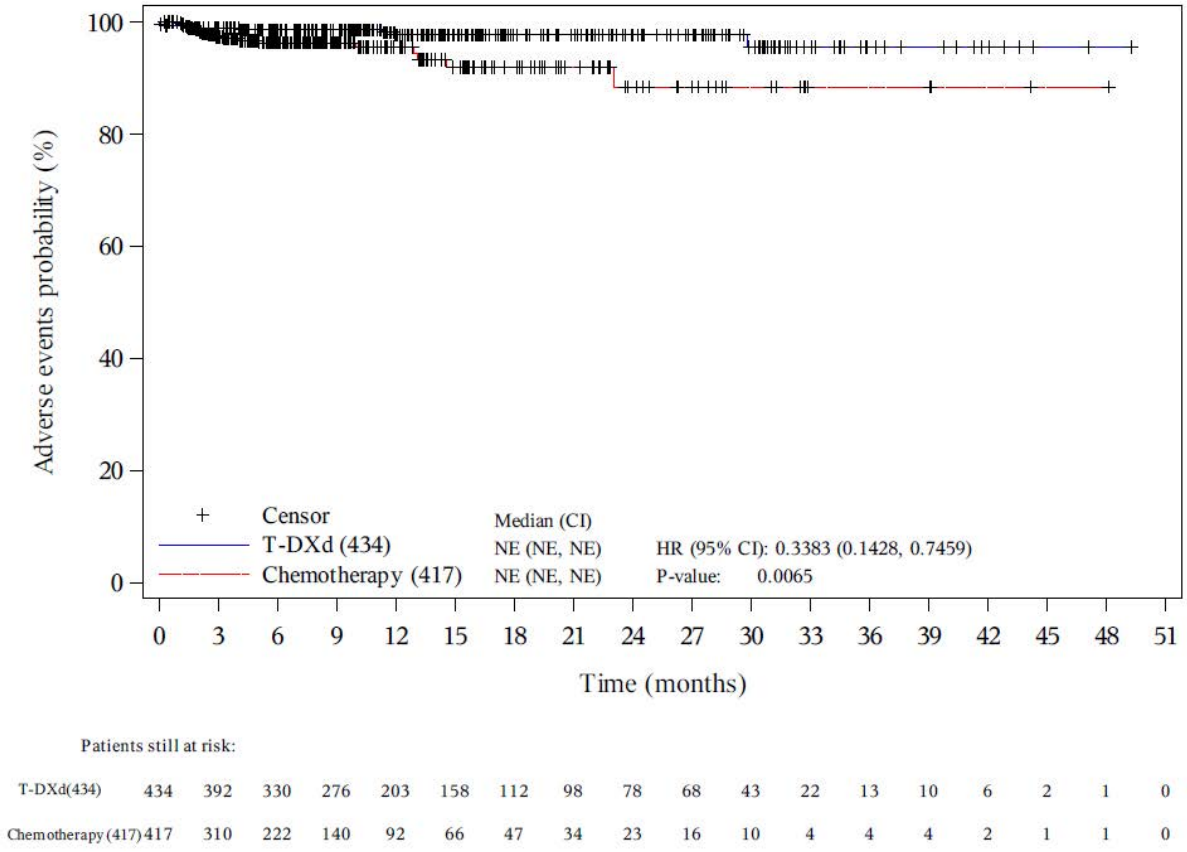
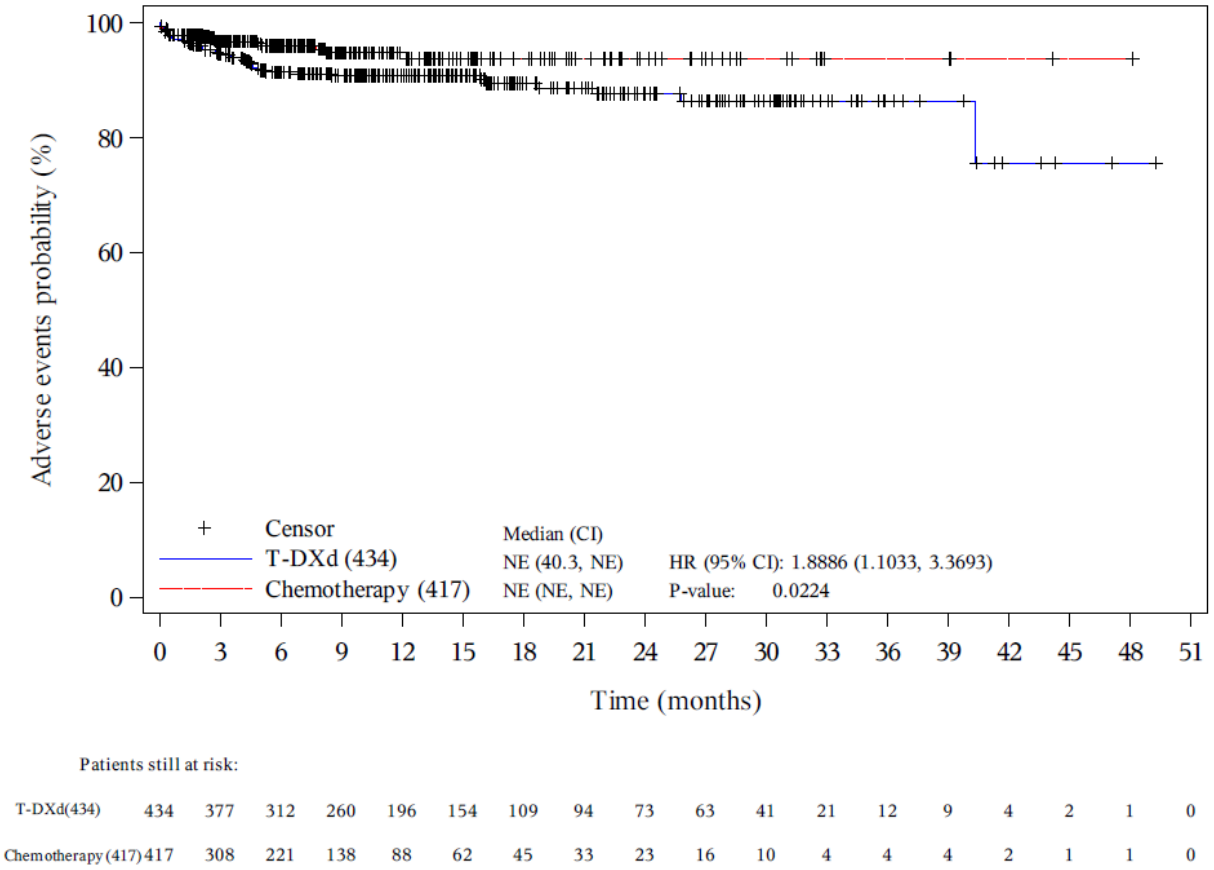



Figure 21: Kaplan-Meier curves for the outcome nervous system disorders (SOC, severe AEs) – 2nd data cut from 24 March 2025




Patients still at risk:

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T-DXd(434) | 434 | 377 | 312 | 260 | 196 | 154 | 109 | 94 | 73 | 63 | 41 | 21 | 12 | 9 | 4 | 2 | 1 | 0 |
| Chemotherapy (417) | 417 | 308 | 221 | 138 | 88 | 62 | 45 | 33 | 23 | 16 | 10 | 4 | 4 | 4 | 2 | 1 | 1 | 0 |

Figure 22: Kaplan-Meier curves for the outcome anaemia (PT, severe AEs) – 2nd data cut from 24 March 2025