# Trastuzumab deruxtecan (breast cancer, after ≥ 2 prior therapies) –

## Addendum to Project A22-81 (dossier assessment)[1]

**ADDENDUM**

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## List of abbreviations

| Abbreviation | Meaning |
|---|---|
| ACT | appropriate comparator therapy |
| AE | adverse event |
| CSR | clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ECOG PS | Eastern Cooperative Oncology Group Performance Status |
| EORTC QLQ-BR23 | European Organisation for Research and Treatment of Cancer-Breast Cancer Module 23 |
| EORTC QLQ-C30 | European Organisation 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 |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MID | minimal important difference |
| PFS | progression-free survival |
| PT | Preferred Term |
| RCT | randomized controlled trial |
| SAE | serious adverse event |
| SGB | Sozialgesetzbuch (Social Code Book) |
| SOC | System Organ Class |
| SPC | Summary of Product Characteristics |

# 1 Background

On 6 December 2022 and on 23 December 2022, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments on Commission A22-81 (Trastuzumab deruxtecan – Benefit assessment according to § 35a Social Code Book V) [1].

The commission of 6 December 2022 comprises the assessment of the analyses [2] of the DESTINY-Breast02 study submitted in the commenting procedure [3] by the pharmaceutical company (hereinafter referred to as the "company"), the results of which were not available at the time of submission of the dossier [4].

In a follow-up commission dated 23 December 2022, the G-BA additionally commissioned IQWiG to evaluate the analyses of the measurement instruments European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and EORTC QLQ-Breast Cancer Module 23 (EORTC QLQ-BR23) with the response criterion of 10 points from the DESTINY-Breast02 study. These were submitted by the company in the follow-up to the oral hearing on 19 December 2022.

The responsibility for the present 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 of the DESTINY-Breast02 study

The research question of the benefit assessment was the assessment of the added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice as ACT in adults with unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer who have previously received 2 or more HER2-targeted therapies.

The research question presented in Table 1 results from the ACT specified by the G-BA.

Table 1: Research question of the benefit assessment of trastuzumab deruxtecan

| **Therapeutic indication** | **ACT**[a] |
|---|---|
| Adults with unresectable or metastatic HER2-positive breast cancer who have previously received 2 or more HER2-targeted therapies | Treatment of physician's choice[b] |

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, the following treatment options are considered equally suitable comparators in the context of treatment of physician's choice: lapatinib in combination with capecitabine, trastuzumab in combination with lapatinib (only for patients with hormone receptor-negative breast cancer) and trastuzumab in combination with capecitabine.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2

### Study pool and evidence presented by the company

In the dossier [4], the company presented comparisons of individual arms of different studies for this research question. These were unsuitable for a benefit assessment. Detailed reasons for this can be found in dossier assessment A22-81 [1].

In its information retrieval, the company additionally identified the randomized controlled trial (RCT) DESTINY-Breast02 conducted by the company. However, the results of the DESTINY-Breast02 study were not available at the time of submission of the dossier [4] and could therefore not be used for the benefit assessment. In the commenting procedure [3], the company presented the results for the first data cut-off of the DESTINY-Breast02 study [2] performed on 30 June 2022, as well as the most recent version of the study protocol and the statistical analysis plan. A clinical study report (CSR) for the study was not presented by the company (see Table 2). The assessment of the DESTINY-Breast02 study is based on the analyses presented by the company and the information in the study protocol and statistical analysis plan.

The DESTINY-Breast02 study is relevant to the present benefit assessment and is included in the assessment.

Table 2: Study pool – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice

| Study | Study category | | | Available sources | | |
|---|---|---|---|---|---|---|
| | Study for the approval of the drug to be assessed (yes/no) | Sponsored study[a] (yes/no) | Third-party study (yes/no) | CSR (yes/no [citation]) | Registry entries[b] (yes/no [citation]) | Publication and other sources[c] (yes/no [citation]) |
| DESTINY-Breast02 | Yes | Yes | No | No[d] | Yes [5-7] | Yes [2] |

a. Study for which the company was sponsor.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. Results of the DESTINY-Breast02 study presented by the company in the comments and in the follow-up to the hearing.
d. The company presented the most recent version of the study protocol [8] and of the statistical analysis plan [9], but no CSR.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

## 2.1 Study characteristics

Table 3 and Table 4 describe the study used for the benefit assessment.

Table 3: Characteristics of the included study – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice

| Study | Study design | Population | Interventions (number of randomized patients) | Study duration | Location and period of study | Primary outcome; secondary outcomes[a] |
|---|---|---|---|---|---|---|
| DESTINY-Breast02 | RCT, open-label, parallel | Adult patients (≥ 18 years[b]) with pathologically documented breast cancer:<br>▪ unresectable or metastatic<br>▪ HER2-positive[c]<br>▪ previously treated with trastuzumab emtansine<br>▪ progression during or after most recent treatment or within 6 months after completing adjuvant therapy[d]<br>▪ ECOG PS 0 or 1 | Trastuzumab deruxtecan (N = 406)<br>Treatment of physician's choice[e] (N = 202)<br>▪ Trastuzumab + capecitabine (n = 91)<br>▪ lapatinib + capecitabine (n = 111) | Screening: up to 28 days<br>Treatment: until disease progression, death, AEs, withdrawal of consent, lost to follow-up, or end of study<br>Observation[f]: outcome-specific, at the longest until death, study discontinuation for any reason, or end of study[g] | 187 study centres in Australia, Belgium, Brazil, Czech Republic, France, Germany, Greece, Israel, Italy, Japan, Republic of Korea, Spain, Turkey, United Kingdom, USA<br>9/2018–ongoing<br>Data cut-off:<br>▪ 30 June 2022[h] | Primary: PFS<br>Secondary: overall survival, morbidity, health-related quality of life, AEs |

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. In countries where the age of consent for study participation is > 18 years, local regulatory requirements must be followed.
c. Evaluated by a central laboratory in accordance with the guideline of the American Society of Clinical Oncology – College of American Pathologists (ASCO-CAP) [10].
d. Presence of documented radiological progression.
e. The choice of therapy had to be determined before randomization.
f. Outcome-specific information is provided in Table 5.
g. Final analysis to take place after reaching approx. 434 events for the outcome of overall survival.
h. Primary analysis after reaching approx. 372 events for the outcome of PFS according to BICR or 18 months after randomization of the last patient, whichever was to occur first.

AE: adverse event; BICR: blinded independent central review; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HER2: human epidermal growth factor receptor 2; n: relevant subpopulation; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial

Table 4: Characteristics of the intervention – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice (multipage table)

| Study | Intervention | Comparison |
|---|---|---|
| DESTINY-Breast02 | Trastuzumab deruxtecan 5.4 mg/kg BW[a, b] IV on day 1 of a 21-day cycle | Trastuzumab 8 mg/kg BW IV on day 1 followed by 6 mg/kg BW IV every 21 days<br>+<br>capecitabine 1250 mg/m$^2$ BSA orally, twice daily on days 1–14 of a 21-day cycle<br>**or**<br>lapatinib 1250 mg orally, on days 1–21 of a 21-day cycle<br>+<br>capecitabine 1000 mg/m$^2$ BSA orally, twice daily on days 1–14 of a 21-day cycle |
| | **Dose adjustments**<br>▪ Dose interruption for up to 28 days[c]<br>▪ Dose reductions for toxicity was allowed as follows[d]:<br>first dose level: 4.4 mg/kg BW<br>second dose level: 3.2 mg/kg BW | **Dose adjustments**<br>▪ Dose interruption for up to 28 days[c]<br>▪ dose adjustments in accordance with local approvals of the respective drug<br>▪ discontinuation: the treatment components could each be discontinued individually |
| | **Pretreatment**<br>▪ Patients had to be pretreated with trastuzumab emtansine.<br>**Non-permitted pretreatment**<br>▪ capecitabine<br>▪ any treatment that is not permitted as concomitant treatment in the respective SPC of capecitabine, trastuzumab and lapatinib<br>▪ therapeutic radiotherapy or major surgery within 4 weeks or palliative stereotactic radiotherapy within 2 weeks before randomization<br>▪ systemic treatment with anticancer therapy (not antibody-based immunotherapy, retinoid therapy or hormonal therapy) within 3 weeks, antibody-based anticancer therapy within 4 weeks, or treatment with nitrosourea compounds or mitomycin C within 6 weeks before randomization; or treatment with small-molecule targeted agents within 2 weeks or 5 half-lives before study drug treatment, whichever was longer<br>**Permitted concomitant treatment**<br>▪ for trastuzumab deruxtecan antiemetics such as 5-hydroxytryptamine receptor antagonists, neurokinin-1 receptor antagonists and/or steroids<br>▪ haematopoietic growth factors for prophylaxis or treatment<br>▪ bisphosphonates or RANKL pathway inhibitors for the prevention or treatment of skeletal-related events<br>**Non-permitted concomitant treatment**<br>▪ other antineoplastic therapy<br>▪ treatment with (hydro)chloroquine<br>▪ chronic systemic corticosteroids (IV or oral) or other immunosuppressants (except for the treatment of AEs)<br>▪ other investigational therapy<br>▪ radiotherapy (exception: palliative radiotherapy of metastases)<br>▪ in the comparator arm: concomitant treatment not permitted according to local approval | |

Table 4: Characteristics of the intervention – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice (multipage table)

| Study | Intervention | Comparison |
|---|---|---|
| a. If there is a change in body weight of ≥ ± 10% of baseline weight compared with baseline during treatment, the patient's dose is recalculated based on the updated weight.<br>b. The initial dose of trastuzumab deruxtecan was to be infused over 90 minutes. In the absence of infusion reactions, the duration of the infusion could be reduced to 30 minutes from cycle 2.<br>c. If interruption was ≥ 28 days (of both components in the comparator arm), treatment was permanently discontinued.<br>d. 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>AE: adverse event; BSA: body surface area; BW: body weight; RANKL: receptor activator of nuclear factor kappa-B ligand; RCT: randomized controlled trial | | |

The DESTINY-Breast02 study is an open-label, randomized, 2-arm study comparing trastuzumab deruxtecan with treatment of physician's choice. Available options for the treatment of physician's choice in the study are lapatinib in combination with capecitabine or trastuzumab in combination with capecitabine. The decision for one of these combinations had to be made before randomization.

The study included adult patients with unresectable or metastatic HER2-positive breast cancer and prior trastuzumab emtansine treatment. According to the inclusion criteria, patients had to have documented radiographic progression of disease during or after the last pretreatment or within 6 months after completion of adjuvant therapy. In addition, previous capecitabine treatment was not allowed. Patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 at study entry.

A total of 608 patients were enrolled in the study. Patients were randomized in a 2:1 ratio, stratified by hormone receptor status (positive versus negative), prior treatment with pertuzumab (yes versus no) and history of visceral disease (yes versus no). The use of trastuzumab deruxtecan as well as trastuzumab in combination with capecitabine or lapatinib in combination with capecitabine was in compliance with the respective Summary of Product Characteristics (SPC) [11-14].

Treatment with the study medication was until disease progression, death, or discontinuation for other reasons (e.g. adverse events [AEs] or patient request).

The primary outcome of the study was progression-free survival (PFS). Relevant secondary outcomes were overall survival, symptoms, health status, health-related quality of life, and AEs.

**Implementation of the appropriate comparator therapy in the DESTINY-Breast02 study**

The G-BA specified treatment of physician's choice as the ACT, and its notes list the following combination therapies as treatment options:

- lapatinib in combination with capecitabine,
- trastuzumab in combination with lapatinib (only for patients with hormone receptor-negative breast cancer)
- trastuzumab in combination with capecitabine

In the DESTINY-Breast02 study presented by the company, trastuzumab + capecitabine or lapatinib + capecitabine was used in the comparator arm. No comparison with trastuzumab + lapatinib is available.

The current guidelines do not provide clear recommendations for the therapy starting from the third line of treatment in the present therapeutic indication [15-17]. Overall, the comparator therapies used in the DESTINY-Breast02 study represent relevant treatment options in the present therapeutic indication.

**Data cut-offs**

The DESTINY-Breast02 study is an ongoing study, for which the primary data cut-off from 30 June 2022 is currently available. According to the study protocol, this is the primary analysis planned after 372 PFS events or 18 months after randomization of the last patient, whichever is first.

**Planned duration of follow-up observation**

Table 5 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 5: Planned duration of follow-up observation – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice

| **Study**<br>**Outcome category**<br>**Outcome** | **Planned follow-up observation** |
|---|---|
| **DESTINY-Breast02** | |
| Mortality | |
| Overall survival | Until death, withdrawal of consent, lost to follow-up, or end of study (whichever is first) |
| Morbidity | |
| Symptoms (EORTC QLQ-C30 and QLQ-BR23) | 40 days (+ 7 days) after the last dose of study medication or before the start of a new antineoplastic therapy (whichever was first) and another time point of documentation 3 months (± 14 days) later |
| Health status (EQ-5D VAS) | 40 days (+ 7 days) after the last dose of study medication or before the start of a new antineoplastic therapy (whichever was first) and another time point of documentation 3 months (± 14 days) later |
| Health-related quality of life (EORTC QLQ-C30 and QLQ-BR23) | 40 days (+ 7 days) after the last dose of study medication or before the start of a new antineoplastic therapy (whichever was first) and another time point of documentation 3 months (± 14 days) later |
| Side effects | |
| All outcomes in the category of side effects | 40 days (+ 7 days) after the last dose of study medication, or before initiation of a new antineoplastic treatment (whichever was first)[a] |

a. SAEs that the investigator judged to be causally related to the investigational product were also recorded as SAEs if they occurred later than 47 days after the last dose of study medication.

EORTC: European Organisation for Research and Treatment of Cancer; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module 23; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

In the DESTINY-Breast02 study, only the outcome of overall survival is recorded until study end. The observation periods for the outcomes of morbidity, health-related quality of life and side effects were systematically shortened because they were only recorded for the time period of treatment with the study medication, plus 40 days. For each of the outcomes of the categories of morbidity and health-related quality of life, there is an additional recording after another 3 months. Drawing a reliable conclusion on the total study period or the time to patient death, however, would require surveying these outcomes for the total period, as was done for survival.

**Patient characteristics**

Table 6 shows the characteristics of the patients in the included study.

Table 6: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice (multipage table)

| **Study Characteristic Category** | **Trastuzumab deruxtecan N[a] = 406** | **Treatment of physician's choice N[a] = 202** |
|---|---|---|
| **DESTINY-Breast02** | | |
| Age [years], mean (SD) | 55 (12) | 55 (11) |
| Sex [F/M], % | > 99/< 1 | 99/1 |
| Region, n (%) | | |
| Asia | 112 (28) | 52 (26) |
| North America | 41 (10) | 23 (11) |
| Europe | 152 (37) | 78 (39) |
| Rest of the world | 101 (25) | 49 (24) |
| Family origin, n (%) | | |
| White | 257 (63) | 127 (63) |
| Black or African American | 10 (2) | 7 (3) |
| Asian | 122 (30) | 56 (28) |
| Other | 17 (4)[b] | 12 (6)[b] |
| ECOG PS, n (%) | | |
| 0 | 228 (56) | 121 (60) |
| 1 | 177 (44) | 81 (40) |
| 2 | 1 (< 1) | 0 (0) |
| Time from first, histological diagnosis to study treatment [months] | | |
| Mean (SD) | 69.5 (57.5) | 70.4 (54.9) |
| Median [min; max] | 53.7 [6; 381] | 54.9 [7; 326] |
| Hormone receptor status (EDC), n (%) | | |
| Positive | 229 (59) | 116 (57) |
| Negative | 177 (44) | 86 (43) |
| Baseline visceral disease, n (%) | | |
| Yes | 316 (78) | 160 (79) |
| No | 90 (22) | 42 (21) |
| Baseline CNS metastases, n (%) | | |
| Yes | 74 (18) | 36 (18) |
| No | 332 (82) | 166 (82) |

Table 6: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice (multipage table)

| **Study Characteristic**<br>**Category** | **Trastuzumab deruxtecan**<br>**N[a] = 406** | **Treatment of physician's choice**<br>**N[a] = 202** |
|---|---|---|
| HER2 expression (IHC)[c], n (%) | | |
| 1+ | 0 (0) | 1 (< 1) |
| 2+ | 80 (20) | 42 (21) |
| 3+ | 326 (80) | 159 (79) |
| HER2 gene amplification (ISH) [c], n (%) | | |
| Amplified | 79 (19) | 42 (21) |
| Non-amplified | 1 (< 1) | 0 (0) |
| Not evaluable | 0 (0) | 1 (< 1) |
| Missing | 326 (80) | 159 (79) |
| Lines of prior anti-HER2 therapy in metastatic setting, n (%) | | |
| ≤ 1 | ND | ND |
| ≥ 2 | ND | ND |
| Lines of prior systemic therapy in the metastatic/locally advanced setting (no hormonal therapies), n (%) | | |
| 0 | 2 (< 1) | 0 (0) |
| 1 | 18 (4) | 12 (6) |
| 2 | 192 (47) | 92 (46) |
| 3 | 123 (30) | 63 (31) |
| 4 | 42 (10) | 13 (6) |
| ≥ 5 | 29 (7) | 22 (11) |
| Prior systemic anticancer therapies, n (%) | | |
| Trastuzumab | 404 (100) | 202 (100) |
| Trastuzumab emtansine | 404 (100) | 202 (100) |
| Taxanes | 386 (95) | 197 (98) |
| Pertuzumab | 318 (78) | 156 (77) |
| Other systemic therapy | 289 (71) | 157 (78) |
| Hormones | 164 (40) | 87 (43) |
| HER2 TKI | 26 (6) | 17 (8) |
| Other HER2 (without TKI) | 11 (3) | 6 (3) |
| Anthracyclines | ND | ND |
| Treatment discontinuation, n (%)[d] | 310 (77) | 190 (97) |
| Study discontinuation, n (%) | ND | ND |

Table 6: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice (multipage table)

| Study Characteristic Category | Trastuzumab deruxtecan N[a] = 406 | Treatment of physician's choice N[a] = 202 |
|---|---|---|
| a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.<br>b. Institute's calculation.<br>c. According to the SPC, HER2-positive tumour status is determined either by an IHC value of 3+ or by confirmation using ISH or FISH [11,12].<br>d. Common reasons for treatment discontinuation in the intervention vs. control arm were: disease progression (49% vs. 80%), AEs (18% vs. 7%), withdrawal of consent (7% vs. 9%); data refer to patients who received at least one dose of study medication (404 vs. 195).<br>AE: adverse event; CNS: central nervous system; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EDC: electronic data capture; F: female; FISH: fluorescence in situ hybridization; 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; RCT: randomized controlled trial; SD: standard deviation; SPC: Summary of Product Characteristics; TKI: tyrosine kinase inhibitor | | |

Both treatment arms are very similar in terms of the demographic and clinical characteristics of the patients in the DESTINY-Breast02 study. The mean age of the patients was 55 years at study entry. 56% of patients in the intervention arm and 60% of patients in the comparator harm had an ECOG PS of 0. About 79% of patients in the study had visceral disease at baseline. Almost all patients had received ≥ 2 systemic therapies in the metastatic or locally advanced setting and were treated with the HER2 antibody drugs trastuzumab and trastuzumab emtansine. Thus, all patients had received ≥ 2 HER2-targeted therapies. 95% of patients in the intervention arm and 98% of patients in the comparator arm had received a taxane in their pretreatment. About 78% of patients had received prior pertuzumab.

The company did not provide any information on study discontinuation and on the reasons that led to study discontinuation.

**Data on treatment and observation periods**

Table 7 shows the mean and median treatment durations of the patients and the median observation periods for individual outcomes.

Table 7: Information on the course of the study – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice

| **Study**<br>**Duration of the study phase**<br>**Outcome category** | **Trastuzumab deruxtecan**<br>**N = 404** | **Treatment of physician's choice**<br>**N = 195[a]** |
|---|---|---|
| **DESTINY-Breast02** | | |
| Treatment duration [months] | | |
| Median [min; max] | 11.3 [0.7; 45.1] | Capecitabine: 4.6 [0.1; 42.3]<br>Lapatinib: 4.5 [0.2; 28.7]<br>Trastuzumab: 4.4 [0.1; 43.0] |
| Mean (SD) | 14.1 (9.8) | Capecitabine: 6.7 (6.4)<br>Lapatinib: 7.3 (6.5)<br>Trastuzumab: 6.2 (6.3) |
| Observation period [months] | | |
| Overall survival [b] | | |
| Median [Q1; Q3] | 26.5 [ND] | 25.2 [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. Capecitabine: N = 195; lapatinib: N = 108; trastuzumab: N = 87.
b. The observation period is calculated on the basis of the inverse Kaplan-Meier method.

max: maximum; min: minimum; N: number of analysed patients; ND: no data; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation

The median treatment duration in the intervention arm (11.3 months) was more than twice as long as in the control arm (ranging from 4.4 months for trastuzumab to 4.6 months for capecitabine).

The median observation period for overall survival was 26.5 months in the intervention arm and 25.2 months in the control arm. For the outcomes of the categories of morbidity, health-related quality of life, and side effects, whose observation duration was linked to treatment end (see Table 5), the observation durations are markedly shorter in comparison with overall survival, particularly in the comparator arm. Therefore, for these outcomes, conclusions can only be drawn about the time under treatment (plus 40 days for side effects, and for morbidity and health-related quality of life plus another 3 months). In addition, the between-arm

differences in treatment duration also result in differences in observation periods of the outcomes. This data situation has consequences regarding the interpretability of the outcomes which were observed for a shorter period (see Section 2.2.1).

Table 8 shows the subsequent therapies patients received after discontinuing the study medication.

Table 8: Information on subsequent antineoplastic therapies[a] – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice

| Study<br>Drug | Patients with subsequent therapy n (%) | |
|---|---|---|
| | Trastuzumab deruxtecan<br>N = 406 | Treatment of physician's choice<br>N = 202 |
| **DESTINY-Breast02** | | |
| Total | 220 (54.2) | 140 (69.3) |
| Systemic | 220 (54.2) | 140 (69.3) |
| Trastuzumab | 126 (31.0) | 94 (46.5) |
| HER2 TKI | 124 (30.5) | 42 (20.8) |
| Taxane | 30 (7.4) | 20 (9.9) |
| Pertuzumab | 20 (4.9) | 18 (8.9) |
| Trastuzumab deruxtecan | 18 (4.4) | 52 (25.7) |
| Trastuzumab emtansine | 3 (0.7) | 5 (2.5) |
| Other HER2 therapies (except HER2 TKIs) | 2 (0.5) | 8 (4.0) |
| Hormonal therapy | 37 (9.1) | 14 (6.9) |
| Other systemic therapy[b] | 188 (46.3) | 107 (53.0) |
| Radiotherapy | 29 (7.1) | 20 (9.9) |
| Surgical interventions | 8 (2.0) | 5 (2.5) |

a. Patients may have been treated with more than one subsequent therapy.
b. No information is available on what these other systemic therapies are.

HER2: human epidermal growth factor receptor 2; n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial TKI: tyrosine kinase inhibitor

In the DESTINY-Breast02 study, 54.2% of the patients in the intervention arm and 69.3% of the patients in the comparator arm received ≥ 1 subsequent antineoplastic therapy. In the intervention arm, the most frequently used subsequent systemic therapies were trastuzumab (31.0%) and anti-HER2 tyrosine kinase inhibitors (30.5%). In the comparator arm, the most frequently used therapies were trastuzumab (46.5%) and trastuzumab deruxtecan (25.7%), followed by anti-HER2 tyrosine kinase inhibitors (20.8%). This means that about a quarter of the patients in the comparator arm switched to treatment with trastuzumab deruxtecan. Furthermore, pertuzumab was used as a subsequent therapy in both treatment arms (4.9% versus 8.9%). According to the approval for pertuzumab, this drug may only be used if no anti-

HER2 therapy or chemotherapy has been used before [18]. Accordingly, pertuzumab as subsequent therapy was not used in compliance with the approval. In addition, about half of the patients received other systemic therapies (46.3% versus 53.0%), for which no detailed information is available, however.

The current guidelines do not provide clear recommendations for the therapy starting from the third line of treatment in the present therapeutic indication [15-17]. In addition, there are no substantial differences between the subsequent therapies of the intervention and comparator population. With the exception of the use of trastuzumab deruxtecan as subsequent therapy in the comparator arm, the aspects described above have no influence on the present benefit assessment. This is considered in the assessment of the risk of bias (see Section 2.2.2).

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

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice

| Study | Adequate random sequence generation | Allocation concealment | Blinding | | Reporting independent of the results | No additional aspects | Risk of bias at study level |
|---|---|---|---|---|---|---|---|
| | | | Patients | Treating staff | | | |
| DESTINY-Breast02 | Yes | Yes | No | No | Yes | Yes | Low |
| RCT: randomized controlled trial | | | | | | | |

The risk of bias across outcomes for the DESTINY-Breast02 study is rated as low.

**Transferability of the study results to the German health care context**

From the point of view of the company, the results of the international DESTINY-Breast02 study can be transferred without restriction to the German health care context, as the origin of the patients has no influence on the course of the disease. The company added that the mean age of the study population (54.8 years) and the sex distribution (0.8% men) are comparable to the corresponding German patient population. It also pointed out that the vast majority of patients had received pretreatment in compliance with German guidelines and that the care context in the certified study centres can be considered sufficiently uniform. The company added that the DESTINY-Breast02 study used trastuzumab deruxtecan in compliance

with the valid SPC, and that the diagnostics and medication of the patients in the study centres were in accordance with international standards.

The company did not provide any further information on the transferability of the study results to the German health care context.

## 2.2 Results on added benefit

### 2.2.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - symptoms recorded using the EORTC QLQ-C30
  - symptoms recorded using the EORTC QLQ-BR23
  - health status recorded using the EQ-5D visual analogue scale (VAS)
- Health-related quality of life
  - recorded using the EORTC QLQ-C30 and the EORTC QLQ-BR23
- Side effects
  - serious AEs (SAEs)
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - diarrhoea (Preferred Term [PT], severe AEs [CTCAE grade ≥ 3])
  - cardiac disorders (System Organ Class [SOC], severe AEs [CTCAE grade ≥ 3])
  - palmar-plantar erythrodysaesthesia syndrome (PT, severe AE [CTCAE grade ≥ 3])
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that made by the company, which used further outcomes in the dossier (Module 4 B).

Table 10 shows the outcomes for which data are available in the included study.

Table 10: Matrix of outcomes – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice

| Study | Outcomes | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Overall survival | Symptoms (EORTC QLQ-C30, EORTC QLQ-BR23) | Health status (EQ-5D VAS) | Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23) | SAEs[a] | Severe AEs[a, b] | Discontinuation due to AEs[a] | Diarrhoea (PT, severe AEs[a]) | Cardiac disorders (SOC, severe AEs[a]) | Palmar-plantar erythrodysaesthesia syndrome (PT, severe AEs[a]) | Further specific AEs[c] |
| DESTINY-Breast02 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No[d] | Yes | Yes |

a. For outcomes in the category of side effects, the company presented analyses including progression of the underlying disease.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. The following events are considered (MedDRA coding): asthenia (PT, severe AEs), fatigue (PT, severe AEs), white blood cell count decreased (PT, severe AEs), neutrophil count decreased (PT, severe AEs), nausea (PT, AEs), vomiting (PT, AEs), constipation (PT, AEs), stomatitis (PT, AEs), alopecia (PT, AEs), rash (PT, AEs), headache (PT, AEs).
d. No usable results; the company did not present any effect estimate or event time analyses.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module 23; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

## Notes on outcomes

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

The company presented responder analyses for the outcomes on symptoms and health-related quality of life (recorded with the scales of the EORTC QLQ-C30 and the EORTC QLQ-BR23) and for the outcome of health status (recorded with the EQ-5D VAS). These are operationalized as time to "first deterioration" or to "confirmed deterioration" by ≥ 10 or ≥ 15 points.

*Response criteria for the EORTC QLQ-C30 and EORTC QLQ-BR23 scales*

In its comments and after the hearing, the company presented responder analyses for the proportion of patients with a deterioration by ≥ 10 or ≥ 15 points (respective scale range 0 to

100) for the EORTC QLQ-C30 and the EORTC QLQ-BR23. According to the ‘‘Answers to frequently asked questions about the benefit assessment procedure’’ [19] provided by the G-BA, only analyses of the currently accepted minimal important difference (MID) of 10 points are to be presented in the dossier for analyses of the EORTC QLQ-C30 questionnaire and the corresponding validated supplementary disease-specific modules. The present assessment uses the analyses of the response threshold of 10 points.

*Operationalization of deterioration*

The company presented analyses on first deterioration and confirmed deterioration for the symptom and health-related quality of life outcomes as well as for the outcome of health status. In the DESTINY-Breast02 study, confirmation is operationalized by considering a deterioration as confirmed if it was observed on 2 or more consecutive visits or occurred at the last recording.

In principle, both operationalizations are patient-relevant. However, the analyses on confirmed deterioration cannot be interpreted meaningfully. This is explained below.

For the symptom and health-related quality of life outcomes as well as for the outcome of health status, no information is available on the actual observation period in the study. However, the observation period for these outcomes is linked to the treatment duration and thus, on the one hand, systematically shorter compared with overall survival and, on the other, notably different between the treatment arms (see Table 5 and Table 7). The different observation periods for the patient-reported outcomes can be estimated from the large differences in treatment duration, which is more than twice as long in the intervention arm as in the control arm (see Section 2.1). Also, in the DESTINY-Breast02 study, the responses to the questionnaires in the comparator arm decreased sharply after only a few observation points. Another problem is that the study counted a single deterioration that occurred at the last recording as confirmed deterioration. There is no information available on how many patients were found to have deteriorated at the last documentation time or how these cases were distributed between the treatment arms. In this situation, confirmed deterioration in the intervention arm is potentially compared with a single deterioration in the comparator arm. For this reason, the analyses for the time to first deterioration are used for the benefit assessment.

***Outcomes in the category of side effects***

In deviation from the specification in the dossier template [20], besides treatment-related AEs, the analyses of the overall rates of AEs, SAEs, severe AEs and discontinuations due to AEs also include AEs that can be attributed to progression of the underlying disease. In the addendum to Module 4 B, the company explained this with the lack of a complete and valid definition of disease-related events in the present therapeutic indication to clearly

differentiate disease-related AEs from other AEs. This is not appropriate. Since the overall rates of the outcomes in the category of side effects in the DESTINY-Breast02 study include only few events that can potentially be attributed to progression of the underlying disease, the available data on side effects are used for the benefit assessment without restrictions, however.

For the outcome of cardiac disorders (SOC, severe AEs), no usable results are available. In this situation, a meaningful interpretation of results would require event time analyses. Said analyses are not available for this outcome.

### 2.2.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice

| Study | | Outcomes | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Study level | Overall survival | Symptoms (EORTC QLQ-C30, EORTC QLQ-BR23) | Health status (EQ-5D VAS) | Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23) | SAEs | Severe AEs[a] | Discontinuation due to AEs | Diarrhoea (PT, severe AEs[a]) | Cardiac disorders (SOC, severe AEs[a]) | Palmar-plantar erythrodysaesthesia syndrome (PT, severe AEs[d]) | Further specific AEs[a, b] |
| DESTINY-Breast02 | L | H[c, d] | H[e, f] | H[e, f] | H[e, f] | H[f] | H[f] | H[g] | H[f] | – | H[f] | H[f, h] |

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The following events are considered (MedDRA coding): asthenia (PT, severe AEs), fatigue (PT, severe AEs), white blood cell count decreased (PT, severe AEs), neutrophil count decreased (PT, severe AEs), nausea (PT, AEs), vomiting (PT, AEs), constipation (PT, AEs), stomatitis (PT, AEs), alopecia (PT, AEs), rash (PT, AEs), headache (PT, AEs).
c. High proportion of patients who were censored early. In addition, there is a large difference in censoring proportions between the treatment arms.
d. High proportion of patients in the comparator arm who received trastuzumab deruxtecan as a subsequent antineoplastic therapy in the sense of a treatment switch; no information on the time points and reasons for the switch.
e. Lack of blinding in subjective recording of outcomes.
f. Incomplete observations for potentially informative reasons with different follow-up observations.
g. Lack of blinding in the presence of subjective decision on treatment discontinuation.
h. For non-severe AEs, the following also applies: lack of blinding in subjective recording of outcomes.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module 23; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Deviating from the company, the risk of bias for the outcome of overall survival is rated as high. The reason for this is the high proportion of patients who were censored within the first year (see Kaplan-Meier curve for overall survival in Section A.1). It is assumed that the reasons for most early censorings are withdrawal of consent or lost to follow-up because the study for the last included patient has already been running for at least 1.5 years (randomization of the last included patient: 31 December 2020; date of data cut-off: 30 June 2022) and censorings due to the data cut-off are expected to occur later. In addition, there is a large difference in the proportions of censoring due to withdrawal of consent or lost to follow-up between the treatment arms (11.8% versus 19.3%). Besides, approximately 26% of the patients in the comparator arm received trastuzumab deruxtecan as subsequent antineoplastic therapy in the sense of a treatment switch. There is no information available regarding the times at which the patients switched treatment or reasons for the treatment switch.

For the results of the outcomes of symptoms, health-related quality of life and health status, the risk of bias is rated as high due to the open-label study design with subjective reporting of outcomes and incomplete observations for potentially informative reasons.

For the side effects outcomes, the risk of bias of the results is rated high due to incomplete observations for potentially informative reasons. For non-severe side effects, the lack of blinding in subjective recording of outcomes also leads to a high risk of bias. The risk of bias for the outcome of discontinuation due to AEs is rated as high because of lack of blinding with subjective decision on treatment discontinuation.

In summary, based on the DESTINY-Breast02 study, at most hints, e.g. of an added benefit, can be derived for all outcomes presented.

### 2.2.3 Results

Table 12 summarizes the results of the comparison of trastuzumab deruxtecan with treatment of physician’s choice as ACT in adults with unresectable or metastatic HER2-positive breast cancer who have previously received 2 or more HER2-targeted therapies.

Kaplan-Meier curves for event time analyses can be found in Appendix A, results for common AEs in Appendix B.

Table 12: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice (multipage table)

| Study<br>Outcome category<br>Outcome | Trastuzumab deruxtecan | | Treatment of physician's choice | | Trastuzumab deruxtecan vs. treatment of physician's choice |
|---|---|---|---|---|---|
| | 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] |
| **DESTINY-Breast02** | | | | | |
| **Mortality** | | | | | |
| Overall survival | 406 | 39.2 [32.7; NC]<br>143 (35.2) | 202 | 26.5 [21.0; NC]<br>86 (42.6) | 0.66 [0.50; 0.86]; 0.002 |
| **Morbidity** | | | | | |
| **Symptoms (EORTC QLQ-C30)[b]** | | | | | |
| Fatigue | 406 | 2.9 [2.8; 4.2]<br>279 (68.7) | 202 | 1.9 [1.5; 2.9]<br>129 (63.9) | 0.82 [0.66; 1.01]; 0.060 |
| Nausea and vomiting | 406 | 1.5 [1.5; 1.8]<br>296 (72.9) | 202 | 3.0 [1.7; 4.4]<br>111 (55.0) | 1.30 [1.04; 1.62]; 0.022 |
| Pain | 406 | 8.5 [6.0; 11.2]<br>222 (54.7) | 202 | 2.8 [1.9; 3.5]<br>117 (57.9) | 0.58 [0.46; 0.73]; < 0.001 |
| Dyspnoea | 406 | 15.6 [12.6; 21.7]<br>180 (44.3) | 202 | 11.6 [8.0; NC]<br>74 (36.6) | 0.86 [0.65; 1.13]; 0.286 |
| Insomnia | 406 | 13.4 [9.9; 16.7]<br>193 (47.5) | 202 | 5.8 [4.3; 9.2]<br>91 (45.0) | 0.68 [0.52; 0.87]; 0.003 |
| Appetite loss | 406 | 5.5 [3.0; 7.3]<br>252 (62.1) | 202 | 2.9 [1.7; 4.4]<br>108 (53.5) | 0.83 [0.66; 1.04]; 0.107 |
| Constipation | 406 | 5.5 [4.3; 6.3]<br>251 (61.8) | 202 | 18.7 [8.1; NC]<br>69 (34.2) | 1.62 [1.24; 2.13]; < 0.001 |
| Diarrhoea | 406 | 9.7 [7.8; 13.0]<br>218 (53.7) | 202 | 1.5 [1.5; 1.8]<br>128 (63.4) | 0.40 [0.32; 0.51]; < 0.001 |
| **Symptoms (EORTC QLQ-BR23)[b]** | | | | | |
| Side effects of systemic therapy | 406 | 5.1 [4.2; 6.9]<br>239 (58.9) | 202 | 5.8 [3.3; 1.26]<br>90 (44.6) | 1.07 [0.84; 1.37]; 0.613 |
| Symptoms in chest region | 406 | NA [27.8; NC]<br>109 (26.8) | 202 | 18.4 [12.5; NC]<br>60 (29.7) | 0.58 [0.42; 0.81]; 0.001 |
| Symptoms in arm region | 406 | 10.0 [6.9; 13.9]<br>206 (50.7) | 202 | 4.4 [2.8; 6.1]<br>102 (50.5) | 0.62 [0.48; 0.79]; < 0.001 |
| Upset by hair loss | No usable data[c] | | | | |

Table 12: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice (multipage table)

| Study<br>Outcome category<br>Outcome | Trastuzumab deruxtecan | | Treatment of physician's choice | | Trastuzumab deruxtecan vs. treatment of physician's choice |
|---|---|---|---|---|---|
| | 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] |
| **Health status (EQ-5D VAS)[d]** | 406 | 19.4 [17.1; 24.9]<br>158 (38.9) | 202 | 7.3 [5.6; 11.3]<br>85 (42.1) | 0.56 [0.43; 0.74]; < 0.001 |
| **Health-related quality of life** | | | | | |
| **EORTC QLQ-C30[e]** | | | | | |
| Global health status | 406 | 7.0 [5.0; 10.0]<br>232 (57.1) | 202 | 2.9 [1.9; 4.2]<br>123 (60.9) | 0.58 [0.46; 0.72]; < 0.001 |
| Physical functioning | 406 | 11.4 [8.6; 15.4]<br>211 (52.0) | 202 | 4.3 [3.1; 6.0]<br>109 (54.0) | 0.61 [0.48; 0.79]; < 0.001 |
| Role functioning | 406 | 5.6 [4.3; 8.6]<br>240 (59.1) | 202 | 2.9 [1.8; 4.2]<br>116 (57.4) | 0.68 [0.54; 0.86]; < 0.001 |
| Emotional functioning | 406 | 10.2 [7.9; 13.9]<br>206 (50.7) | 202 | 7.2 [5.5; 10.6]<br>86 (42.6) | 0.91 [0.70; 1.17]; 0.453 |
| Cognitive functioning | 406 | 6.9 [5.5; 9.7]<br>229 (56.4) | 202 | 3.3 [2.8; 5.7]<br>111 (55.0) | 0.71 [0.56; 0.898]; 0.004 |
| Social functioning | 406 | 7.2 [5.6; 10.4]<br>225 (55.4) | 202 | 3.3 [1.9; 6.1]<br>109 (54.0) | 0.72 [0.57; 0.91]; 0.005 |
| **EORTC QLQ-BR23[e]** | | | | | |
| Body image | 406 | 13.5 [8.1; 22.9]<br>187 (46.1) | 202 | 10.6 [5.5; 17.1]<br>75 (37.1) | 0.91 [0.69; 1.20]; 0.507 |
| Sexual activity | 406 | NA<br>110 (27.1) | 202 | NA<br>44 (21.8) | 1.07 [0.75; 1.53]; 0.700 |
| Enjoyment of sex | No usable data[c] | | | | |
| Future perspective | 406 | 32.5 [20.7; NC]<br>158 (38.9) | 202 | 12.5 [6.9; NC]<br>71 (35.1) | 0.82 [0.62; 1.09]; 0.170 |
| **Side effects** | | | | | |
| AEs (supplementary information)[f] | 404 | 0.1 [0.1; 0.1]<br>403 (99.8) | 195 | 0.2 [0.2; 0.3]<br>185 (94.9) | – |
| SAEs[f] | 404 | NA [35.4; NC]<br>103 (25.5) | 195 | NA [15.7; NC]<br>46 (23.6) | 0.70 [0.49; 0.9994]; 0.049 |
| Severe AEs[f, g] | 404 | 11.0 [7.0; 16.3]<br>213 (52.7) | 195 | 9.9 [5.1; 15.7]<br>86 (44.1) | 0.92 [0.71; 1.18]; 0.493 |

Table 12: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice (multipage table)

| **Study**<br>**Outcome category**<br>**Outcome** | **Trastuzumab deruxtecan** | | **Treatment of physician's choice** | | **Trastuzumab deruxtecan vs. treatment of physician's choice** |
|---|---|---|---|---|---|
| | **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]** |
| Discontinuation due to AEs[f] | 404 | NA<br>80 (19.8) | 195 | NA<br>19 (9.7) | 1.08 [0.65; 1.81]; 0.757 |
| Diarrhoea (PT, severe AEs[g]) | 404 | NA<br>11 (2.7) | 195 | NA<br>14 (7.2) | 0.23 [0.10; 0.54]; < 0.001 |
| Cardiac disorders (SOC, severe AEs[g]) | 404 | ND<br>2 (0.5) | 195 | ND<br>4 (2.1) | –[h] |
| Palmar-plantar erythrodysaesthesia syndrome (PT, severe AEs[g]) | 404 | NA<br>1 (0.2) | 195 | NA<br>20 (10.3) | 0.02 [0.003; 0.14]; < 0.001 |
| Further specific AEs | | | | | |
| Asthenia (PT, severe AEs[g]) | 404 | NA<br>20 (5.0) | 195 | NA<br>1 (0.5) | 7.92 [1.06; 59.23]; 0.017 |
| Fatigue (PT, severe AEs[g]) | 404 | NA<br>16 (4.0) | 195 | NA<br>1 (0.5) | 6.48 [0.86; 49.03]; 0.038 |
| White blood cell count decreased (PT, severe AEs[g]) | 404 | NA<br>21 (5.2) | 195 | NA<br>0 (0) | NC [0.00; NC]; 0.007 |
| Neutrophil count decreased (PT, severe AEs[g]) | 404 | NA<br>43 (10.6) | 195 | NA<br>4 (2.1) | 3.93 [1.40; 11.02]; 0.005 |
| Nausea (PT, AEs) | 404 | 0.2 [0.2; 0.4]<br>293 (72.5) | 195 | NA [12.1; NC]<br>73 (37.4) | 2.70 [2.09; 3.50]; < 0.001 |
| Vomiting (PT, AEs) | 404 | NA [24.0; NC]<br>152 (37.6) | 195 | NA<br>25 (12.8) | 2.89 [1.89; 4.42]; < 0.001 |
| Constipation (PT, AEs) | 404 | NA [22.8; NC]<br>142 (35.1) | 195 | NA<br>21 (10.8) | 2.93 [1.85; 4.64]; < 0.001 |
| Stomatitis (PT, AEs) | 404 | NA<br>45 (11.1) | 195 | NA<br>36 (18.5) | 0.36 [0.23; 0.58]; < 0.001 |
| Alopecia (PT, AEs) | 404 | NA<br>150 (37.1) | 195 | NA<br>8 (4.1) | 9.72 [4.77; 19.81]; < 0.001 |
| Rash (PT, AEs) | 404 | NA<br>27 (6.7) | 195 | NA<br>22 (11.3) | 0.45 [0.25; 0.798]; 0.005 |

Table 12: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice (multipage table)

| Study<br>Outcome category<br>Outcome | Trastuzumab deruxtecan | | Treatment of physician's choice | | Trastuzumab deruxtecan vs. treatment of physician's choice |
|---|---|---|---|---|---|
| | 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] |
| Headache (PT, AEs) | 404 | NA [38.9; NC]<br>80 (19.8) | 195 | NA<br>12 (6.2) | 2.55 [1.38; 4.71]; 0.002 |

a. Cox proportional hazards model (HR, 95% CI) and log-rank test (p-value) stratified by hormone receptor status (positive/negative), prior treatment with pertuzumab (yes/no) and history of visceral disease (yes/no).
b. Time to first deterioration. A score increase by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
c. Unclear proportion of patients with missing values at baseline and in the course of the study.
d. Time to first deterioration. A decrease by ≥ 15 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
e. Time to first deterioration. A decrease by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
f. For outcomes in the category of side effects, the company presented analyses including progression of the underlying disease.
g. Operationalized as CTCAE grade ≥ 3.
h. The company did not present any calculations on HR, CI and p-value.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; 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; PT: Preferred Term; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module 23; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; VAS: visual analogue scale

## Mortality

### *Overall survival*

A statistically significant difference in favour of trastuzumab deruxtecan was shown for the outcome of overall survival. This results in a hint of an added benefit of trastuzumab deruxtecan in comparison with the ACT.

**Morbidity**

***Symptoms***

Symptom outcomes were recorded with the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-BR23. Below, the symptom outcomes with statistically significant differences between the treatment arms are described first.

*Pain, insomnia, diarrhoea, symptoms in chest region, symptoms in arm region*

Statistically significant differences between the treatment arms in favour of trastuzumab deruxtecan were shown for each of the outcomes of pain, insomnia, diarrhoea, symptoms in chest region and symptoms in arm region. For these outcomes, this results in a hint of added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice.

*Nausea and vomiting, constipation*

Statistically significant differences between the treatment arms to the disadvantage of trastuzumab deruxtecan were shown for each of the outcomes of nausea and vomiting and constipation. For these outcomes, this results in a hint of lesser benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice.

*Upset by hair loss*

No usable data are available for the outcome of upset by hair loss. The proportion of patients with missing values at baseline and in the course of the study is unclear for this scale (one item). This results in no hint of added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice; an added benefit is therefore not proven for this outcome.

*Further symptom outcomes*

There was no statistically significant difference between the treatment arms for each of the outcomes of fatigue, dyspnoea, appetite loss, and side effects of systemic therapy. This results in no hints of added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice; an added benefit is therefore not proven for these outcomes.

***Health status (EQ-5D VAS)***

A statistically significant difference between the treatment arms in favour of trastuzumab deruxtecan was shown for the outcome of health status recorded with the EQ-5D VAS. For this outcome, this results in a hint of added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice.

**Health-related quality of life**

Outcomes of health-related quality of life were recorded with the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-BR23. Below, the outcomes with statistically significant differences are described first.

*Global health status, physical functioning, role functioning, cognitive functioning, social functioning*

Statistically significant differences between the treatment arms in favour of trastuzumab deruxtecan were shown for each of the outcomes of global health status, physical functioning, role functioning, cognitive functioning, and social functioning. For these outcomes, this results in a hint of added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice.

*Enjoyment of sex*

No usable data are available for the outcome of enjoyment of sex. The proportion of patients with missing values at baseline and in the course of the study is unclear for this scale (one item). This results in no hint of added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice; an added benefit is therefore not proven for this outcome.

*Further outcomes on health-related quality of life*

No statistically significant difference between the treatment arms was shown for the outcomes of emotional functioning, body image, sexual activity, and future perspective. This results in no hints of added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice; an added benefit is therefore not proven for these outcomes.

**Side effects**

***SAEs***

A statistically significant difference between the treatment arms in favour of trastuzumab deruxtecan was shown for the outcome of SAEs. For this outcome, this results in a hint of lesser harm of trastuzumab deruxtecan in comparison with treatment of physician's choice.

***Severe AEs (CTCAE ≥ 3), discontinuation due to AEs***

No statistically significant difference between the treatment arms was shown for the outcomes of severe AEs (CTCAE ≥ 3) and discontinuation due to AEs. This results in no hints of greater or lesser harm from trastuzumab deruxtecan in comparison with treatment of physician's choice; greater or lesser harm is therefore not proven for these outcomes.

***Specific AEs***

*Diarrhoea (severe AEs), palmar-plantar erythrodysaesthesia syndrome (severe AEs)*

Statistically significant differences between the treatment arms in favour of trastuzumab deruxtecan were shown for each of the outcomes of diarrhoea (severe AEs) and palmar-plantar erythrodysaesthesia syndrome (severe AEs). For these outcomes, this results in a hint of lesser harm of trastuzumab deruxtecan in comparison with treatment of physician's choice.

*Cardiac disorders (severe AEs)*

The company presented no calculations on hazard ratio and p-value for this outcome. Due to the low number of events, it cannot be assumed that a statistically significant effect will result if suitable analyses are available. This results in no hint of greater or lesser harm from trastuzumab deruxtecan in comparison with treatment of physician's choice; greater or lesser harm is therefore not proven for this outcome.

*Asthenia (severe AEs), fatigue (severe AEs), white blood cell count decreased (severe AEs), neutrophil count decreased (severe AEs)*

Statistically significant differences between the treatment arms to the disadvantage of trastuzumab deruxtecan were shown for each of the outcomes of asthenia (severe AEs), fatigue (severe AEs), white blood cell count decreased (severe AEs), and neutrophil count decreased (severe AEs). For these outcomes, this results in a hint of greater harm of trastuzumab deruxtecan in comparison with treatment of physician's choice.

*Stomatitis (AEs), rash (AEs)*

Statistically significant differences between the treatment arms in favour of trastuzumab deruxtecan were shown for each of the outcomes of stomatitis (AEs) and rash (AEs). For these outcomes, this results in a hint of lesser harm of trastuzumab deruxtecan in comparison with treatment of physician's choice.

*Nausea (AEs), vomiting (AEs), constipation (AEs), alopecia (AEs), headache (AEs)*

Statistically significant differences between the treatment arms to the disadvantage of trastuzumab deruxtecan were shown for each of the outcomes of nausea (AEs), vomiting (AEs), constipation (AEs), alopecia (AEs), and headache (AEs). For these outcomes, this results in a hint of greater harm of trastuzumab deruxtecan in comparison with treatment of physician's choice.

### 2.2.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account for the present benefit assessment:

- age (≤ 65 years/> 65 years)
- baseline visceral disease (yes/no)

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there have to be at least 10 events in at least one 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 presented only if there is a statistically significant and relevant effect in at least one subgroup.

Using the methods described above, the available subgroup results do not reveal any effect modifications.

## 2.3 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [21].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

### 2.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.2.3 (see Table 13).

**Determination of the outcome category for outcomes on symptoms and side effects**

It cannot be inferred from the dossier whether the following outcomes were serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

***Symptoms***

*Nausea and vomiting, pain, insomnia, constipation, diarrhoea (each recorded using EORTC QLQ-C30), symptoms in chest region, symptoms in arm region (recorded using EORTC QLQ-BR23)*

For the outcomes of nausea and vomiting, pain, insomnia, constipation, diarrhoea, symptoms in chest region, and symptoms in arm region, there is insufficient information available to classify the severity category as serious/severe. Therefore, these outcomes are assigned to the outcome category of non-serious/non-severe symptoms.

Table 13: Extent of added benefit at outcome level: trastuzumab deruxtecan vs. treatment of physician's choice (multipage table)

| **Outcome category**<br>**Outcome**<br>**Effect modifier**<br>**Subgroup** | **Trastuzumab deruxtecan vs. treatment of physician's choice**<br>**Median time to event (months)**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| **Mortality** | | |
| Overall survival | 39.2 vs. 26.5<br>HR: 0.66 [0.50; 0.86]<br>p = 0.002<br>Probability: "hint" | Outcome category: mortality<br>$0.85 \leq CI_u < 0.95$<br>Added benefit, extent: "considerable" |
| **Morbidity** | | |
| **Symptoms (EORTC QLQ-C30)**[c] | | |
| Fatigue | 2.9 vs. 1.9<br>HR: 0.82 [0.66; 1.01]<br>p = 0.060 | Lesser/added benefit not proven |
| Nausea and vomiting | 1.5 vs. 3.0<br>HR: 1.30 [1.04; 1.62]<br>HR: 0.77 [0.62; 0.96][d]<br>p = 0.022<br>Probability: "hint" | Outcome category: non-serious/non-severe symptoms/late complications<br>$0.90 \leq CI_u < 1.00$<br>Lesser/added benefit not proven[e] |
| Pain | 8.5 vs. 2.8<br>HR: 0.58 [0.46; 0.73]<br>p = < 0.001<br>Probability: "hint" | Outcome category: non-serious/non-severe symptoms/late complications<br>$CI_u < 0.80$<br>Added benefit, extent: "considerable" |
| Dyspnoea | 15.6 vs. 11.6<br>HR: 0.86 [0.65; 1.13]<br>p = 0.286 | Lesser/added benefit not proven |
| Insomnia | 13.4 vs. 5.8<br>HR: 0.68 [0.52; 0.87]<br>p = 0.003<br>Probability: "hint" | Outcome category: non-serious/non-severe symptoms/late complications<br>$0.80 \leq CI_u < 0.90$<br>Added benefit, extent: "minor" |
| Appetite loss | 5.5 vs. 2.9<br>HR: 0.83 [0.66; 1.04]<br>p = 0.107 | Lesser/added benefit not proven |
| Constipation | 5.5 vs. 18.7<br>HR: 1.62 [1.24; 2.13]<br>HR: 0.62 [0.47; 0.81][d]<br>p < 0.001<br>Probability: "hint" | Outcome category: non-serious/non-severe symptoms/late complications<br>$0.80 \leq CI_u < 0.90$<br>Lesser benefit, extent: "minor" |

Table 13: Extent of added benefit at outcome level: trastuzumab deruxtecan vs. treatment of physician's choice (multipage table)

| **Outcome category**<br>**Outcome**<br>**Effect modifier**<br>**Subgroup** | **Trastuzumab deruxtecan vs. treatment of physician's choice**<br>**Median time to event (months)**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| Diarrhoea | 9.7 vs. 1.5<br>HR: 0.40 [0.32; 0.51]<br>p < 0.001<br>Probability: "hint" | Outcome category: non-serious/non-severe symptoms/late complications<br>$CI_u < 0.80$<br>Added benefit, extent: "considerable" |
| **Symptoms (EORTC QLQ-BR23)**[c] | | |
| Side effects of systemic therapy | 5.1 vs. 5.8<br>HR: 1.07 [0.84; 1.37]<br>p = 0.613 | Lesser/added benefit not proven |
| Symptoms in chest region | NA vs. 18.4<br>HR: 0.58 [0.42; 0.81]<br>p = 0.001<br>Probability: "hint" | Outcome category: non-serious/non-severe symptoms/late complications<br>$0.80 \leq CI_u < 0.90$<br>Added benefit, extent: "minor" |
| Symptoms in arm region | 10.0 vs. 4.4<br>HR: 0.62 [0.48; 0.79]<br>p < 0.001<br>Probability: "hint" | Outcome category: non-serious/non-severe symptoms/late complications<br>$CI_u < 0.80$<br>Added benefit, extent: "considerable" |
| Upset by hair loss | No usable data | Lesser/added benefit not proven |
| **Health status** | | |
| EQ-5D VAS[f] | 19.4 vs. 7.3<br>HR: 0.56 [0.43; 0.74]<br>p < 0.001<br>Probability: "hint" | Outcome category: non-serious/non-severe symptoms/late complications<br>$CI_u < 0.80$<br>Added benefit, extent: "considerable" |
| **Health-related quality of life** | | |
| **EORTC QLQ-C30**[g] | | |
| Global health status | 7.0 vs. 2.9<br>HR: 0.58 [0.46; 0.72]<br>p < 0.001<br>Probability: "hint" | Outcome category: health-related quality of life<br>$CI_u < 0.75$, risk ≥ 5%<br>Added benefit, extent: "major" |
| Physical functioning | 11.4 vs. 4.3<br>HR: 0.61 [0.48; 0.79]<br>p < 0.001<br>Probability: "hint" | Outcome category: health-related quality of life<br>$0.75 \leq CI_u < 0.90$<br>Added benefit; extent: "considerable" |
| Role functioning | 5.6 vs. 2.9<br>HR: 0.68 [0.54; 0.86]<br>p < 0.001<br>Probability: "hint" | Outcome category: health-related quality of life<br>$0.75 \leq CI_u < 0.90$<br>Added benefit; extent: "considerable" |

Table 13: Extent of added benefit at outcome level: trastuzumab deruxtecan vs. treatment of physician's choice (multipage table)

| **Outcome category**<br>**Outcome**<br>**Effect modifier**<br>**Subgroup** | **Trastuzumab deruxtecan vs. treatment of physician's choice**<br>**Median time to event (months)**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| Emotional functioning | 10.2 vs. 7.2<br>HR: 0.91 [0.70; 1.17]<br>p = 0.453 | Lesser/added benefit not proven |
| Cognitive functioning | 6.9 vs. 3.3<br>HR: 0.71 [0.56; 0.898]<br>p = 0.004<br>Probability: "hint" | Outcome category: health-related quality of life<br>$0.75 \leq CI_u < 0.90$<br>Added benefit; extent: "considerable" |
| Social functioning | 7.2 vs. 3.3<br>HR: 0.72 [0.57; 0.91]<br>p = 0.005<br>Probability: "hint" | Outcome category: health-related quality of life<br>$0.90 \leq CI_u < 1.00$<br>Added benefit, extent: "minor" |
| **EORTC QLQ-BR23**[g] | | |
| Body image | 13.5 vs. 10.6<br>HR: 0.91 [0.69; 1.20]<br>p = 0.507 | Lesser/added benefit not proven |
| Sexual activity | NA vs. NA<br>HR: 1.07 [0.75; 1.53]<br>p = 0.700 | Lesser/added benefit not proven |
| Enjoyment of sex | No usable data | Lesser/added benefit not proven |
| Future perspective | 32.5 vs. 12.5<br>HR: 0.82 [0.62; 1.09]<br>p = 0.170 | Lesser/added benefit not proven |
| **Side effects** | | |
| SAEs | NA vs. NA<br>HR: 0.70 [0.49; 0.9994]<br>p = 0.049<br>Probability: "hint" | Outcome category: serious/severe side effects<br>$0.90 \leq CI_u < 1.00$<br>Lesser harm; extent: "minor" |
| Severe AEs | 11.0 vs. 9.9<br>HR: 0.92 [0.71; 1.18]<br>p = 0.493 | Greater/lesser harm not proven |
| Discontinuation due to AEs | NA vs. NA<br>HR: 1.08 [0.65; 1.81]<br>p = 0.757 | Greater/lesser harm not proven |

Table 13: Extent of added benefit at outcome level: trastuzumab deruxtecan vs. treatment of physician's choice (multipage table)

| **Outcome category**<br>**Outcome**<br>**Effect modifier**<br>**Subgroup** | **Trastuzumab deruxtecan vs. treatment of physician's choice**<br>**Median time to event (months)**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability[a]** | **Derivation of extent[b]** |
|---|---|---|
| Diarrhoea (severe AE) | NA vs. NA<br>HR: 0.23 [0.10; 0.54]<br>p < 0.001<br>Probability: "hint" | Outcome category: serious/severe side effects<br>$CI_u$ < 0.75, risk ≥ 5%<br>Lesser harm, extent: "major" |
| Cardiac disorders (severe AE) | ND<br>HR: –[h]<br>p: –[h] | Greater/lesser harm not proven |
| Palmar-plantar erythrodysaesthesia syndrome (severe AE) | NA vs. NA<br>HR: 0.02 [0.003; 0.14]<br>p < 0.001<br>Probability: "hint" | Outcome category: serious/severe side effects<br>$CI_u$ < 0.75, risk ≥ 5%<br>Lesser harm, extent: "major" |
| Asthenia (severe AE) | NA vs. NA<br>HR: 7.92 [1.06; 59.23]<br>HR: 0.13 [0.17; 0.94][d]<br>p = 0.017<br>Probability: "hint" | Outcome category: serious/severe side effects<br>0.90 ≤ $CI_u$ < 1.00<br>Greater harm, extent: "minor" |
| Fatigue (severe AE) | NA vs. NA<br>HR: 6.48 [0.86; 49.03]<br>HR: 0.15 [0.02; 1.16][d]<br>p = 0.038<br>Probability: "hint" | Outcome category: serious/severe side effects<br>Greater harm, extent: "minor"[i] |
| White blood cell count decreased (severe AE) | NA vs. NA<br>HR: NC [0.00; NC]<br>p = 0.007<br>Probability: "hint" | Outcome category: serious/severe side effects<br>Greater harm[j], extent: "minor"[k] |
| Neutrophil count decreased (severe AE) | NA vs. NA<br>HR: 3.93 [1.40; 11.02]<br>HR: 0.25 [0.09; 0.71][d]<br>p = 0.005<br>Probability: "hint" | Outcome category: serious/severe side effects<br>$CI_u$ < 0.75, risk ≥ 5%<br>Greater harm, extent: "major" |
| Nausea (AE) | 0.2 vs. NA<br>HR: 2.70 [2.09; 3.50]<br>HR: 0.37 [0.29; 0.48][d]<br>p < 0.001<br>Probability: "hint" | Outcome category: non-serious/non-severe side effects<br>$CI_u$ < 0.80<br>Greater harm, extent: "considerable" |

Table 13: Extent of added benefit at outcome level: trastuzumab deruxtecan vs. treatment of physician's choice (multipage table)

| **Outcome category**<br>**Outcome**<br>**Effect modifier**<br>**Subgroup** | **Trastuzumab deruxtecan vs. treatment of physician's choice**<br>**Median time to event (months)**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability[a]** | **Derivation of extent[b]** |
|---|---|---|
| Vomiting (AE) | NA vs. NA<br>HR: 2.89 [1.89; 4.42]<br>HR: 0.35 [0.23; 0.53][d]<br>p < 0.001<br>Probability: "hint" | Outcome category: non-serious/non-severe side effects<br>$CI_u$ < 0.80<br>Greater harm, extent: "considerable" |
| Constipation (AE) | NA vs. NA<br>HR: 2.93 [1.85; 4.64]<br>HR: 0.34 [0.22; 0.54][d]<br>p < 0.001<br>Probability: "hint" | Outcome category: non-serious/non-severe side effects<br>$CI_u$ < 0.80<br>Greater harm, extent: "considerable" |
| Stomatitis (AE) | NA vs. NA<br>HR: 0.36 [0.23; 0.58]<br>p < 0.001<br>Probability: "hint" | Outcome category: non-serious/non-severe side effects<br>$CI_u$ < 0.80<br>Lesser harm, extent: "considerable" |
| Alopecia (AE) | NA vs. NA<br>HR: 9.72 [4.77; 19.81]<br>HR: 0.10 [0.05; 0.21][d]<br>p < 0.001<br>Probability: "hint" | Outcome category: non-serious/non-severe side effects<br>$CI_u$ < 0.80<br>Greater harm, extent: "considerable" |
| Rash (AE) | NA vs. NA<br>HR: 0.45 [0.25; 0.798]<br>p = 0.005<br>Probability: "hint" | Outcome category: non-serious/non-severe side effects<br>$CI_u$ < 0.80<br>Lesser harm, extent: "considerable" |
| Headache (AE) | NA vs. NA<br>HR: 2.55 [1.38; 4.71]<br>HR: 0.39 [0.21; 0.72][d]<br>p = 0.002<br>Probability: "hint" | Outcome category: non-serious/non-severe side effects<br>$CI_u$ < 0.80<br>Greater harm, extent: "considerable" |

Table 13: Extent of added benefit at outcome level: trastuzumab deruxtecan vs. treatment of physician's choice (multipage table)

| **Outcome category**<br>**Outcome**<br>**Effect modifier**<br>**Subgroup** | **Trastuzumab deruxtecan vs. treatment of physician's choice**<br>**Median time to event (months)**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability[a]** | **Derivation of extent[b]** |
|---|---|---|
| a. Probability provided if there is a statistically significant and relevant effect.<br>b. Depending on the outcome category, estimations of effect size and the scale of the outcome are made with different limits based on the upper limit of the confidence interval ($CI_u$).<br>c. Time to first deterioration. A score increase by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).<br>d. Institute's calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit.<br>e. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.<br>f. Time to first deterioration. A decrease by ≥ 15 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).<br>g. Time to first deterioration. A decrease by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).<br>h. The company did not present any calculations on HR, CI and p-value.<br>i. Discrepancy between CI and p-value; the extent is rated as minor.<br>j. Greater harm results from 21 vs. 0 events.<br>k. It is assumed that the CI of the HR includes the zero effect. Thus, there is a discrepancy between CI and p-value. Its extent is rated as "minor".<br>AE: adverse event; CI: confidence interval; $CI_u$: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NA: not achieved; NC: not calculable; ND: no data; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module 23; QLQ-C30: Quality of Life Questionnaire-Core 30; SAE: serious adverse event; VAS: visual analogue scale | | |

### 2.3.2 Overall conclusion on added benefit

Table 14 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 14: Positive and negative effects from the assessment of trastuzumab deruxtecan compared with treatment of physician's choice (multipage table)

| **Positive effects** | **Negative effects** |
|---|---|
| **Total observation period** | |
| Mortality<br>▪ Overall survival: hint of an added benefit – extent: "considerable" | |
| **Shortened observation period** | |
| Non-serious/non-severe symptoms/late complications<br>Symptoms (EORTC QLQ-C30)<br>▪ Pain: hint of an added benefit – extent: "considerable"<br>▪ Insomnia: hint of an added benefit – extent: "minor"<br>▪ Diarrhoea: hint of an added benefit – extent: "considerable"<br>Symptoms (EORTC QLQ-BR23)<br>▪ Symptoms in chest region: hint of an added benefit – extent: ''minor''<br>▪ Symptoms in arm region: hint of an added benefit – extent: "considerable"<br>Health status<br>▪ EQ-5D VAS: hint of an added benefit – extent: ''considerable'' | Non-serious/non-severe symptoms/late complications<br>Symptoms (EORTC QLQ-C30)<br>▪ Constipation: hint of lesser benefit – extent: ''minor'' |
| Health-related quality of life<br>EORTC QLQ-C30<br>▪ Global health status: hint of an added benefit – extent: ''major''<br>▪ Physical functioning: hint of an added benefit – extent: ''considerable''<br>▪ Role functioning: hint of an added benefit – extent: "considerable"<br>▪ Cognitive functioning: hint of an added benefit – extent: ''considerable''<br>▪ Social functioning: hint of an added benefit – extent: ''minor'' | – |
| Serious/severe side effects<br>▪ SAEs: hint of lesser harm – extent: "minor"<br>▪ Diarrhoea, palmar-plantar erythrodysaesthesia syndrome (each severe AE): hint of lesser harm – extent: "major" | Serious/severe side effects<br>▪ Asthenia, fatigue, white blood cell count decreased (each severe AE): hint of greater harm – extent: "minor"<br>▪ Neutrophil count decreased (severe AE): hint of greater harm – extent: "major" |
| Non-serious/non-severe side effects<br>Stomatitis, rash (each AE): hint of lesser harm – extent: ''considerable'' | Non-serious/non-severe side effects<br>▪ Nausea, vomiting, constipation, alopecia, headache (each AE): hint of greater harm – extent: "considerable" |

Table 14: Positive and negative effects from the assessment of trastuzumab deruxtecan compared with treatment of physician's choice (multipage table)

| Positive effects | Negative effects |
|---|---|
| AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module 23; QLQ-C30: Quality of Life Questionnaire Core-30; SAE: serious adverse event; VAS: visual analogue scale | |

Overall, there are positive and negative effects of trastuzumab deruxtecan in comparison with treatment of physician's choice.

In terms of positive effects, there is a hint of considerable added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice for the outcome of overall survival.

For the other outcome categories of morbidity, health-related quality of life and side effects, there are both positive and negative effects of trastuzumab deruxtecan of varying extent, all with probability of a hint. For the outcome category of symptoms, there are positive effects in several outcomes with the extents "minor" to "considerable", and there is a negative effect in the outcome of constipation with minor extent. Likewise, there is a considerable added benefit for the outcome of health status, recorded with EQ-5D VAS. In health-related quality of life, there are exclusively positive effects in several outcomes with an extent ranging from "minor" (social functioning) to "major" (global health status). In the category of side effects, there are positive effects in the overall rate of SAEs with the extent "minor" and individual severe and non-severe specific AEs with the extent "major" or "considerable". On the other hand, there are negative effects in several severe specific AEs with the extents "minor" or "major", and in non-severe specific AEs with the extent "considerable". Overall, the negative effects do not call into question the considerable extent of the added benefit in the outcome of overall survival. In addition, the results of the outcomes on patient-reported outcomes with shortened observation, particularly in several domains of health-related quality of life, support a considerable added benefit.

In summary, there is a hint of considerable added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice for adults with unresectable or metastatic HER2-positive breast cancer who have previously received 2 or more HER2-targeted therapies.

## 2.4 Summary

The data subsequently submitted by the company in the commenting procedure have changed the conclusion on the added benefit of trastuzumab deruxtecan from dossier assessment A22-81. Table 15 below shows the result of the benefit assessment of

trastuzumab deruxtecan taking into account dossier assessment A22-81 [1] and the present addendum.

Table 15: Trastuzumab deruxtecan – probability and extent of added benefit

| **Therapeutic indication** | **ACT[a]** | **Probability and extent of added benefit** |
|---|---|---|
| Adults with unresectable or metastatic HER2-positive breast cancer who have previously received 2 or more HER2-targeted therapies | Treatment of physician's choice[b] | Hint of considerable added benefit[c] |

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, the following treatment options are considered equally suitable comparators in the context of treatment of physician's choice: lapatinib in combination with capecitabine, trastuzumab in combination with lapatinib (only for patients with hormone receptor-negative breast cancer) and trastuzumab in combination with capecitabine.
c. In the DESTINY-Breast02 study, only the treatment options of lapatinib in combination with capecitabine and trastuzumab in combination with capecitabine were used. No data are available in comparison with trastuzumab in combination with lapatinib.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2

The G-BA decides on the added benefit.

## 3 References

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

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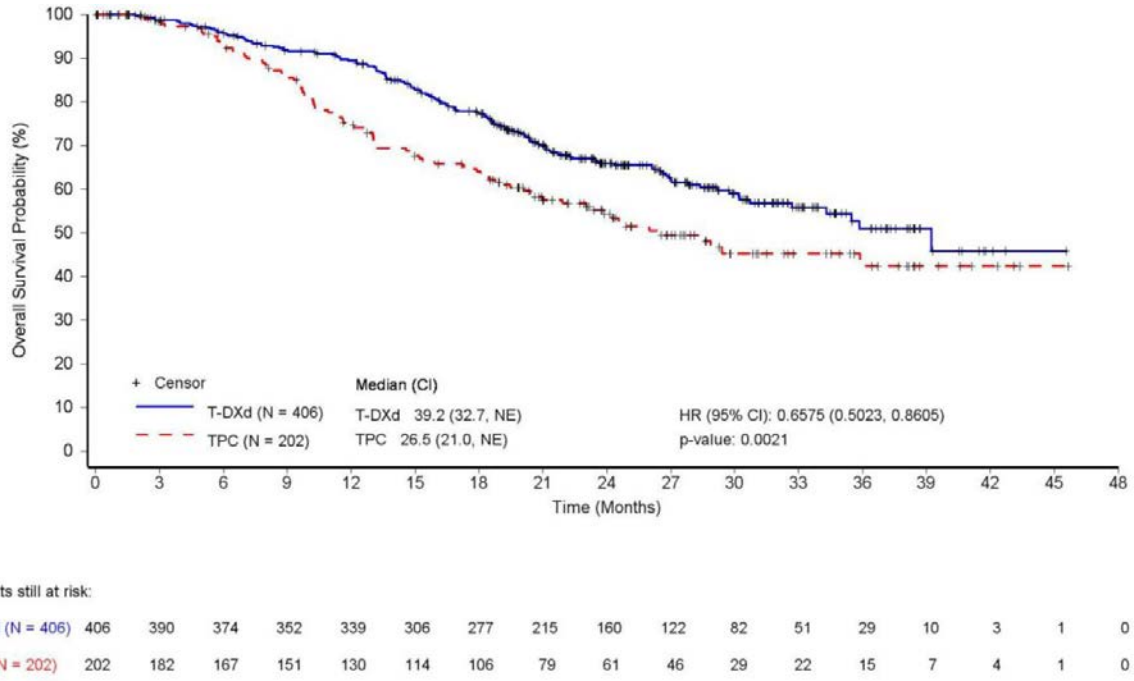
# Appendix A Graphic display of the event time analyses presented in the benefit assessment (Kaplan-Meier curves)

## A.1 Mortality




Patients still at risk:

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T-DXd (N = 406) | 406 | 390 | 374 | 352 | 339 | 306 | 277 | 215 | 160 | 122 | 82 | 51 | 29 | 10 | 3 | 1 | 0 |
| TPC (N = 202) | 202 | 182 | 167 | 151 | 130 | 114 | 106 | 79 | 61 | 46 | 29 | 22 | 15 | 7 | 4 | 1 | 0 |

Figure 1: Kaplan-Meier analyses for the outcome of overall survival

## A.2 Morbidity

### A.2.1 Symptoms (EORTC QLQ-C30)

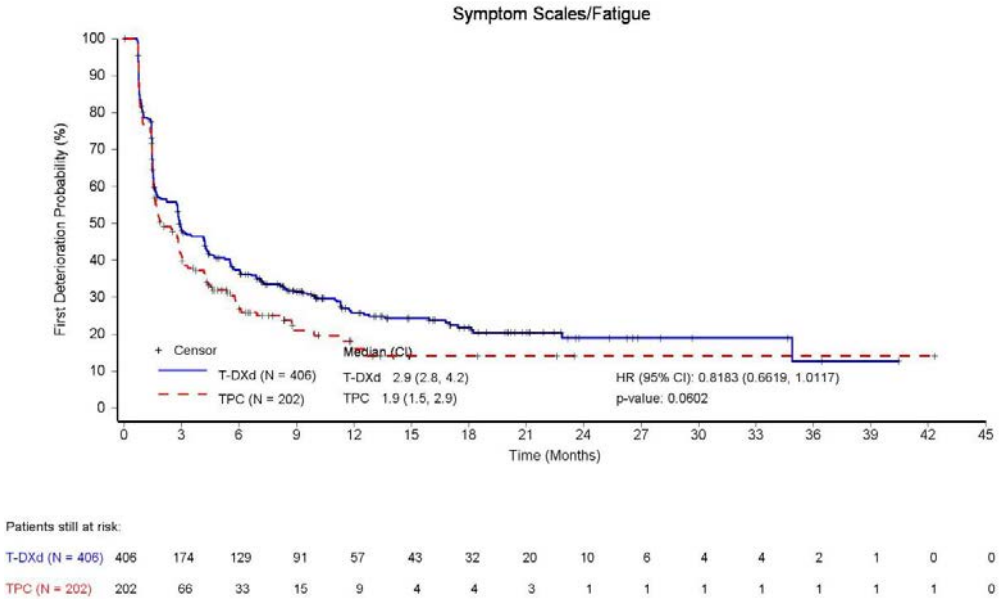



Figure 2: Kaplan-Meier curve for symptoms, outcome of fatigue (EORTC QLQ-C30, first deterioration by ≥ 10 points)

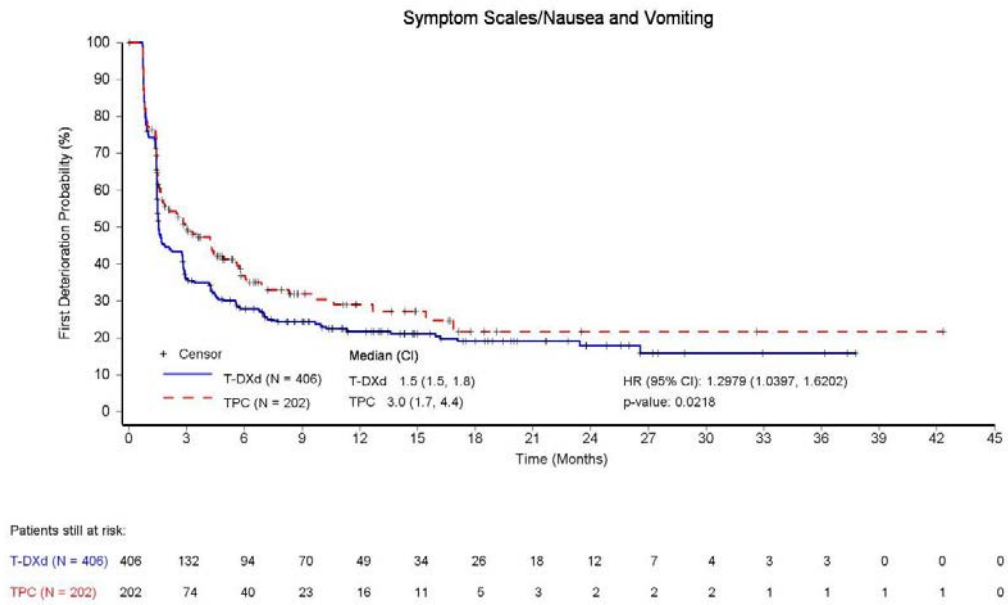



Figure 3: Kaplan-Meier curve for symptoms, outcome auf nausea and vomiting (EORTC QLQ-C30, first deterioration by ≥ 10 points)

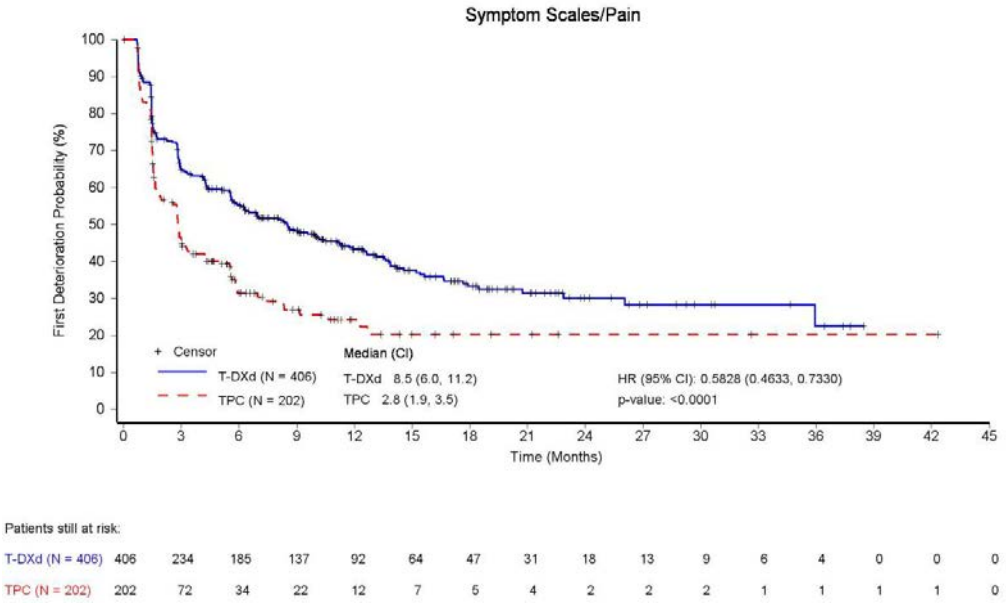



Figure 4: Kaplan-Meier curve for symptoms, outcome of pain (EORTC QLQ-C30, first deterioration by ≥ 10 points)

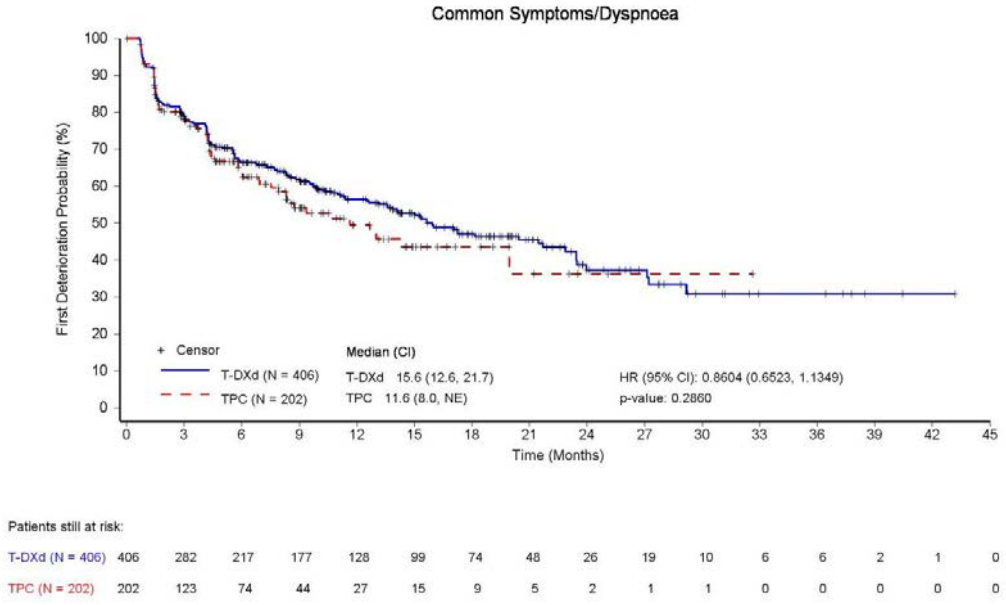



Figure 5: Kaplan-Meier curve for symptoms, outcome of dyspnoea (EORTC QLQ-C30, first deterioration by ≥ 10 points)

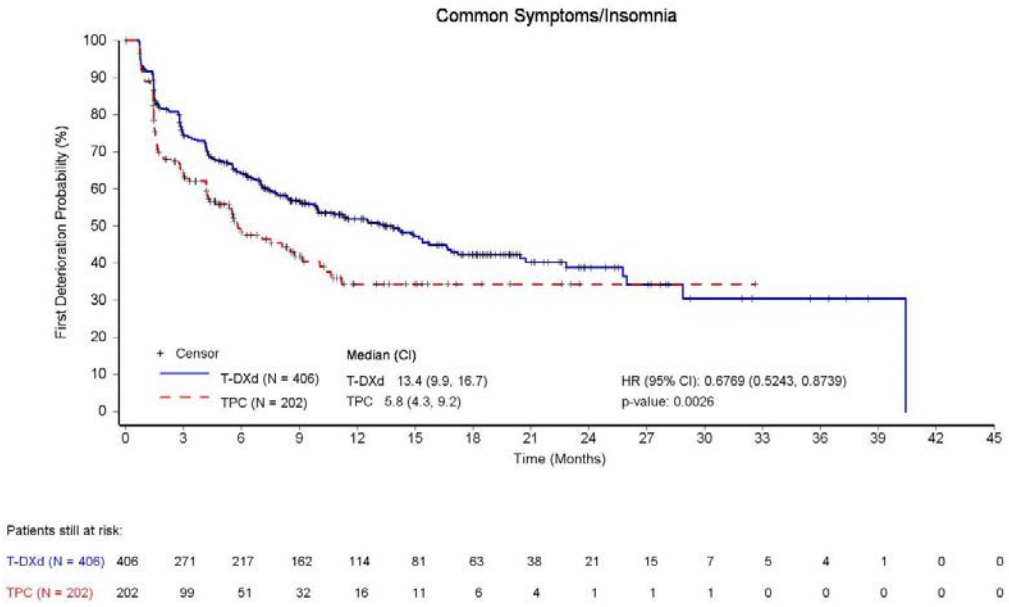



Figure 6: Kaplan-Meier curve for symptoms, outcome of insomnia (EORTC QLQ-C30, first deterioration by ≥ 10 points)

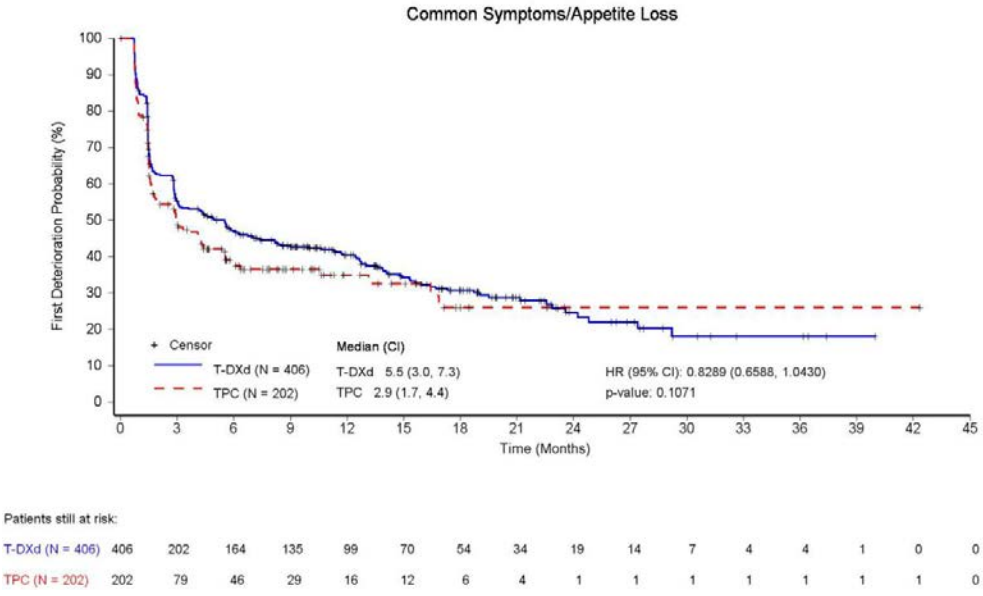



Figure 7: Kaplan-Meier curve for symptoms, outcome of appetite loss (EORTC QLQ-C30, first deterioration by ≥ 10 points)

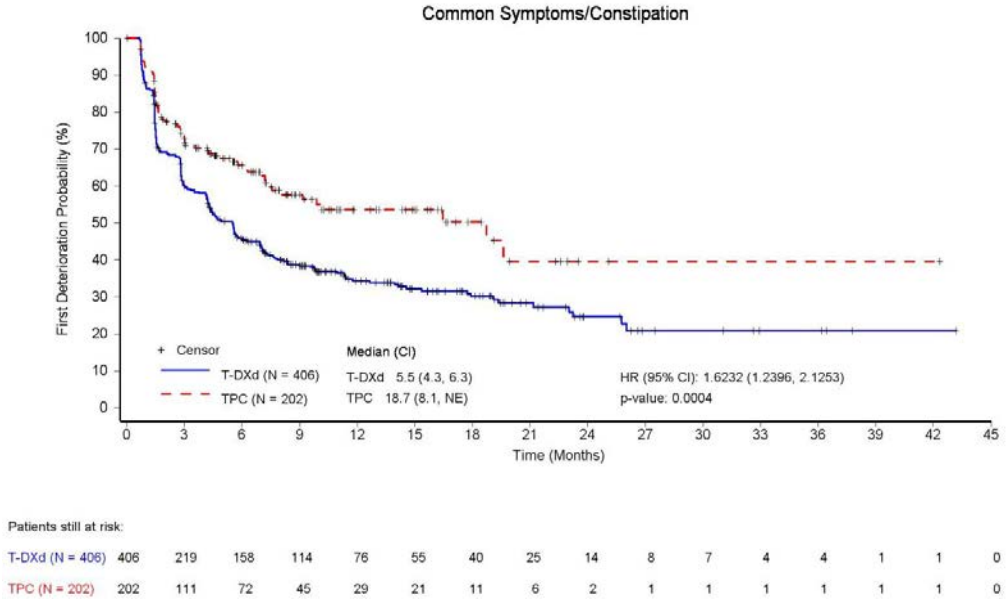



Figure 8: Kaplan-Meier curve for symptoms, outcome of constipation (EORTC QLQ-C30, first deterioration by ≥ 10 points)

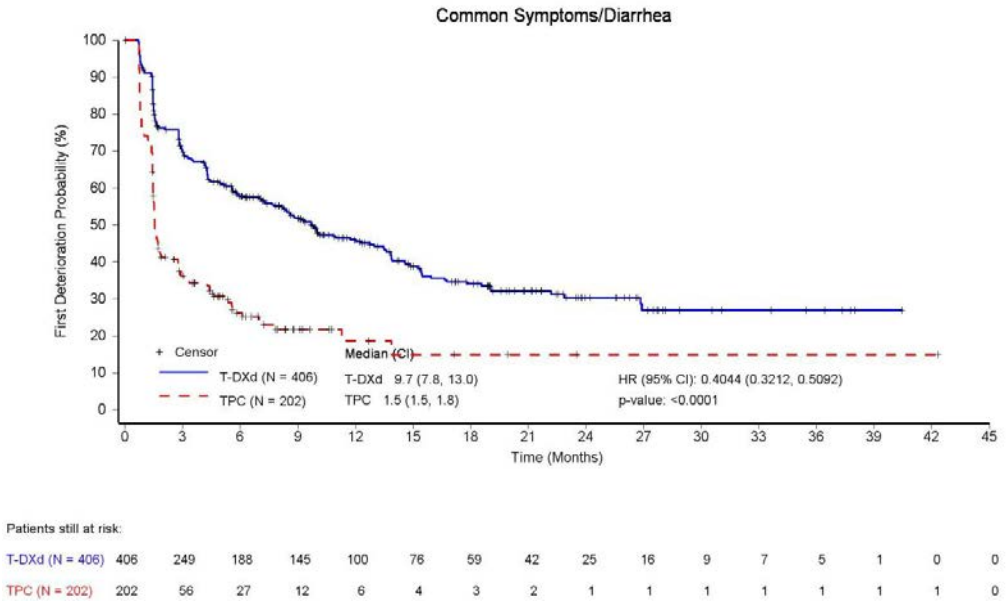



Figure 9: Kaplan-Meier curve for symptoms, outcome of diarrhoea (EORTC QLQ-C30, first deterioration by ≥ 10 points)

### A.2.2 Symptoms (EORTC QLQ-BR23)

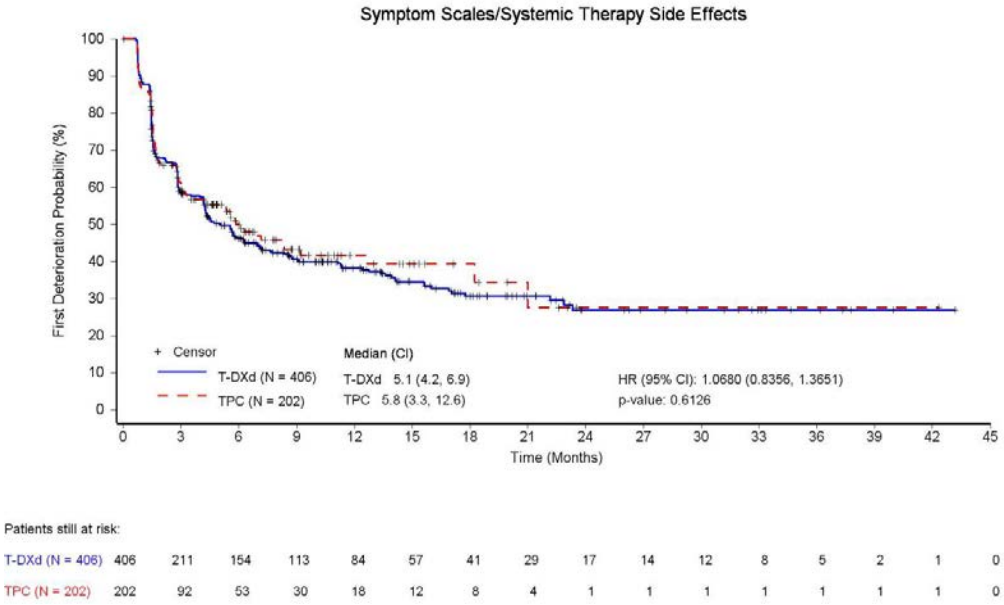



Figure 10: Kaplan-Meier curve for symptoms, outcome of side effects of systemic therapy (EORTC QLQ-BR23, first deterioration by ≥ 10 points)

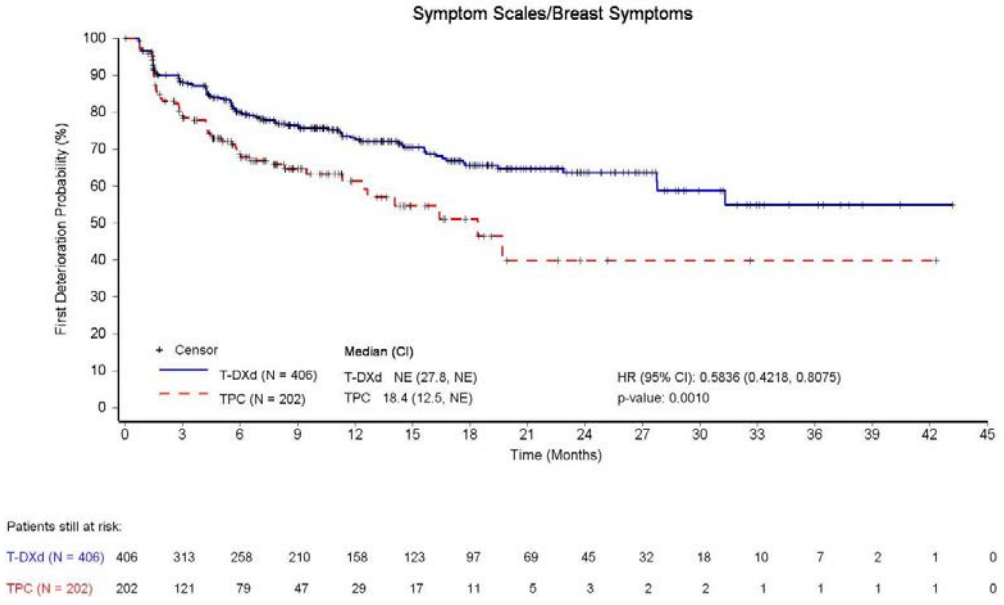



Figure 11: Kaplan-Meier curve for symptoms, outcome of symptoms in chest region (EORTC QLQ-BR23, first deterioration by ≥ 10 points)

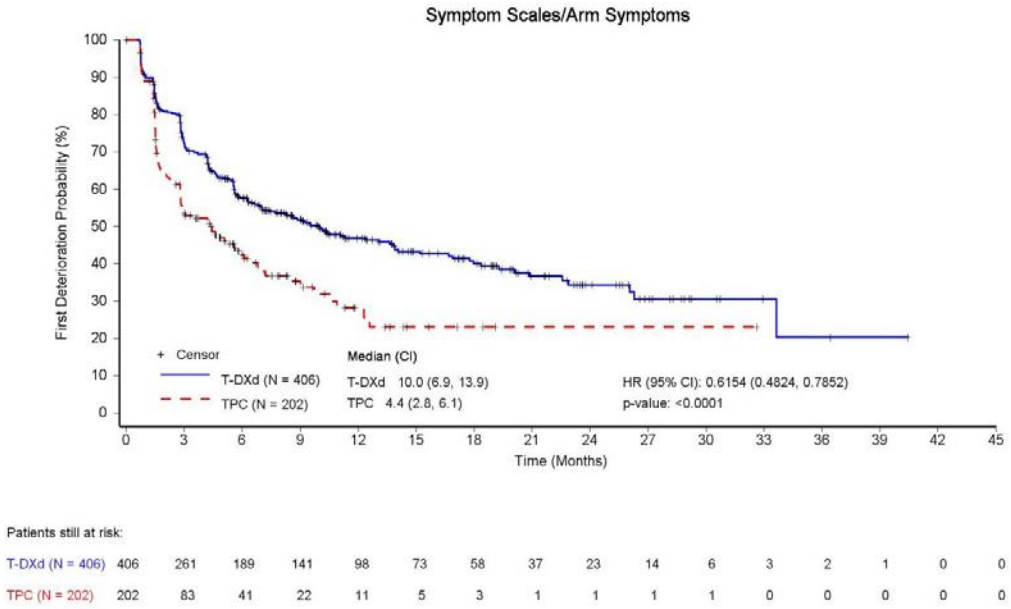



Figure 12: Kaplan-Meier curve for symptoms, outcome of symptoms in arm region (EORTC QLQ-BR23, first deterioration by ≥ 10 points)

### A.2.3 Health status (EQ-5D VAS)

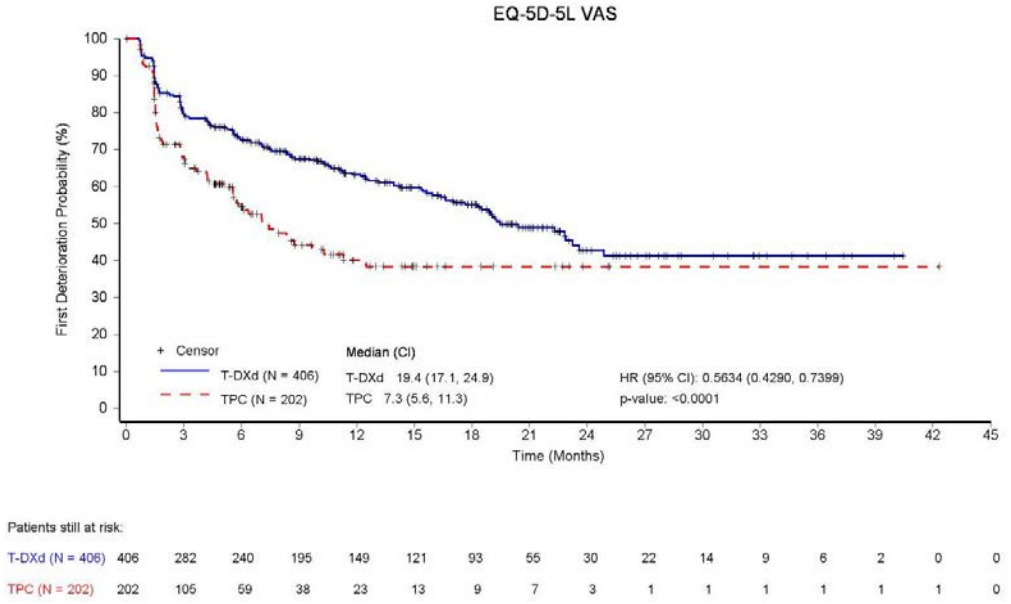



Figure 13: Kaplan-Meier curve, outcome of health status (EQ-5D VAS, first deterioration by ≥ 15 points)

## A.3 Health-related quality of life

### A.3.1 EORTC QLQ-C30

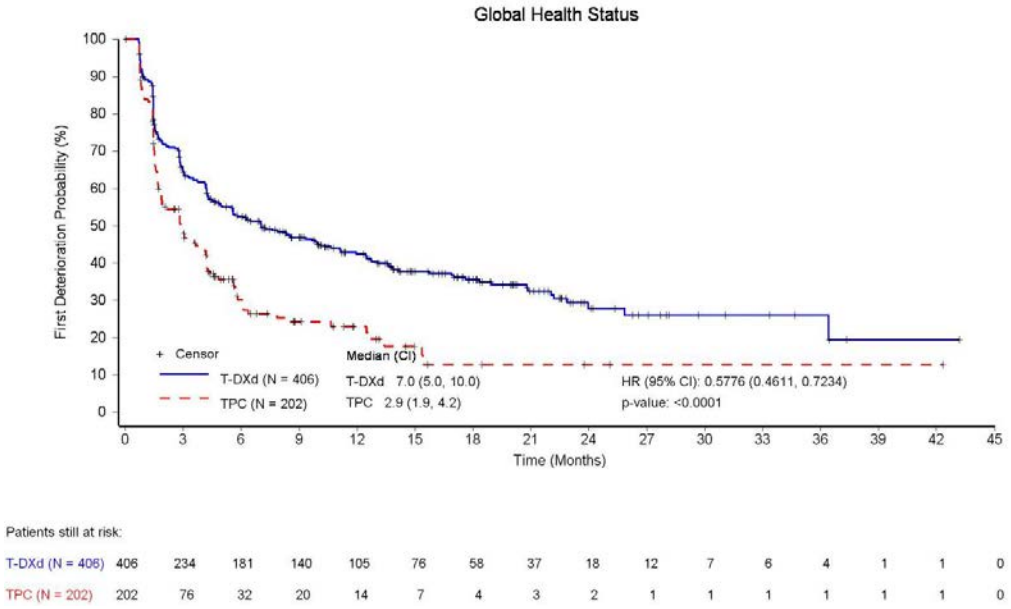



Figure 14: Kaplan-Meier curve for health-related quality of life, outcome of global health status (EORTC QLQ-C30, first deterioration by ≥ 10 points)

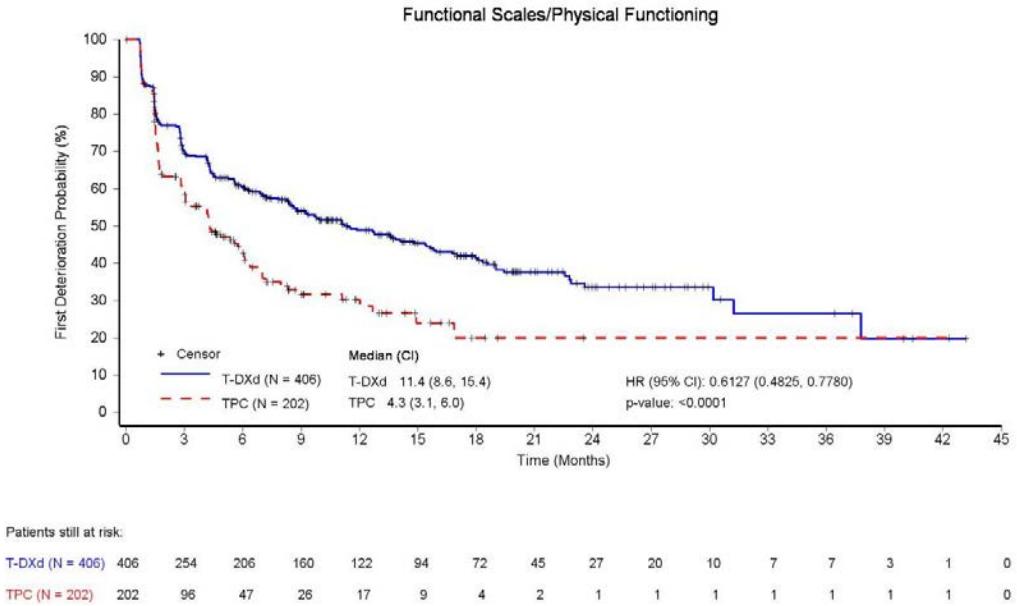



Figure 15: Kaplan-Meier curve for health-related quality of life, outcome of physical functioning (EORTC QLQ-C30, first deterioration by ≥ 10 points)

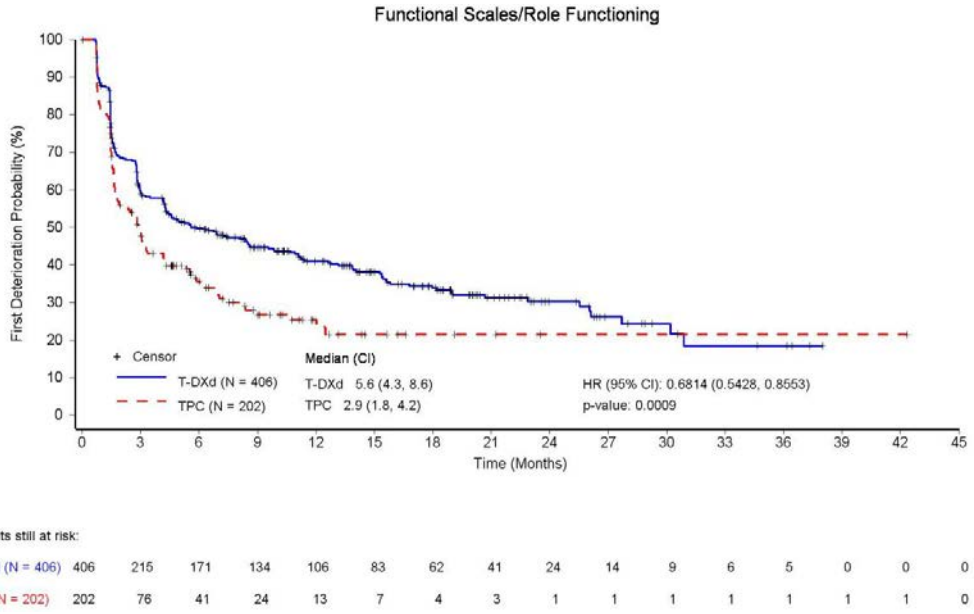



Figure 16: Kaplan-Meier curve for health-related quality of life, outcome of role functioning (EORTC QLQ-C30, first deterioration by ≥ 10 points)

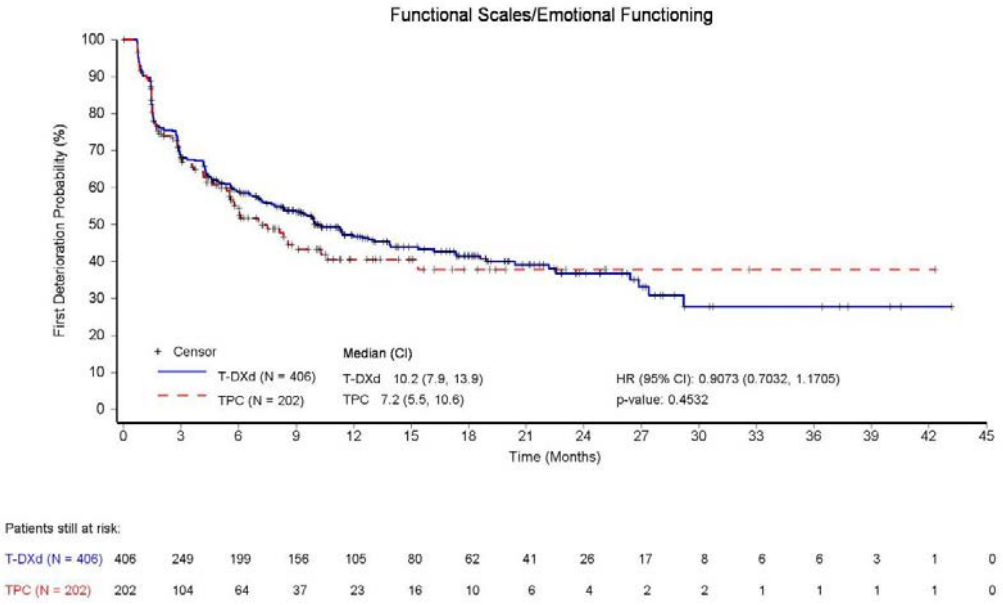



Figure 17: Kaplan-Meier curve for health-related quality of life, outcome of emotional functioning (EORTC QLQ-C30, first deterioration by ≥ 10 points)

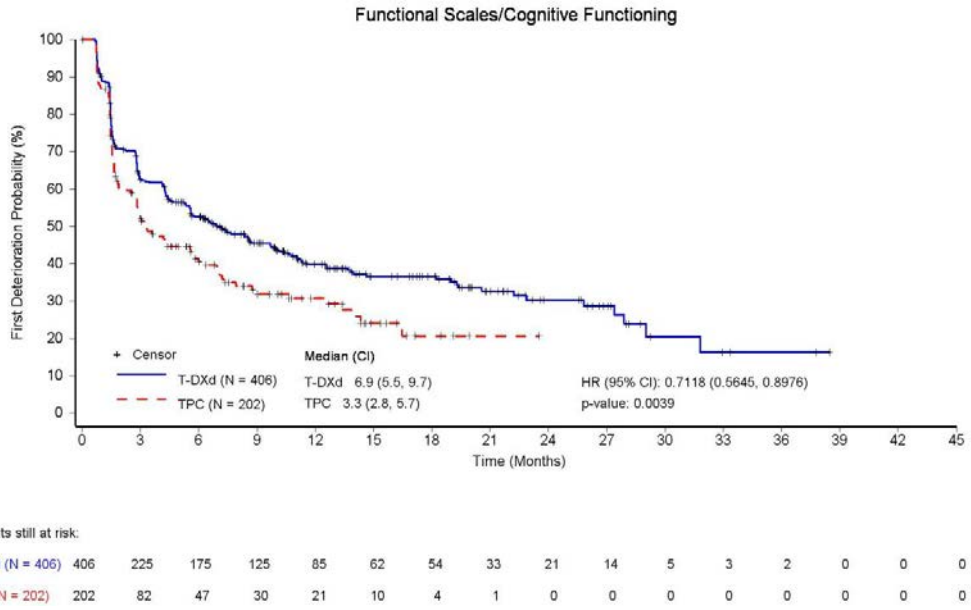



Figure 18: Kaplan-Meier curve for health-related quality of life, outcome of cognitive functioning (EORTC QLQ-C30, first deterioration by ≥ 10 points)

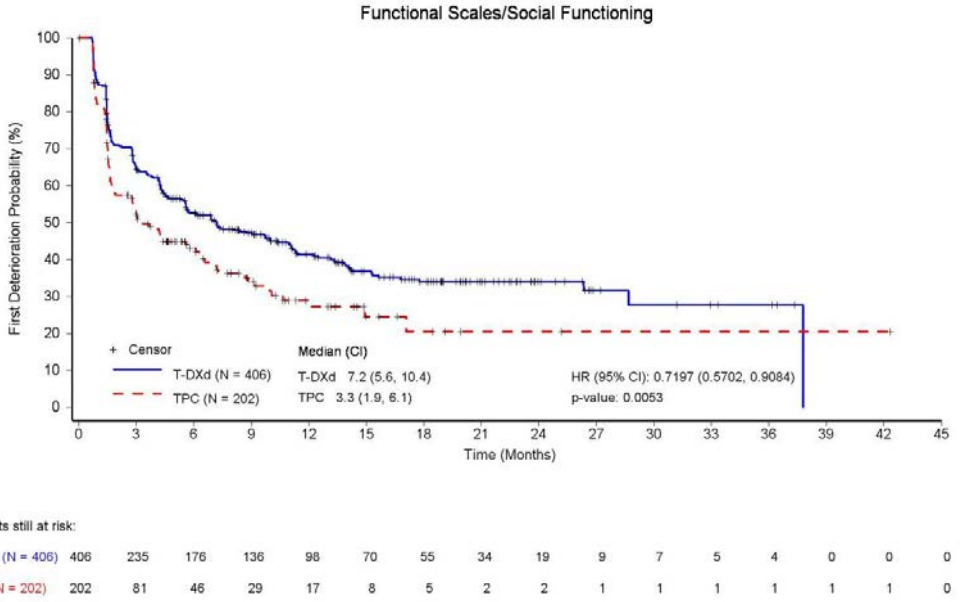



Figure 19: Kaplan-Meier curve for health-related quality of life, outcome of social functioning (EORTC QLQ-C30, first deterioration by ≥ 10 points)

### A.3.2 EORTC QLQ-BR23

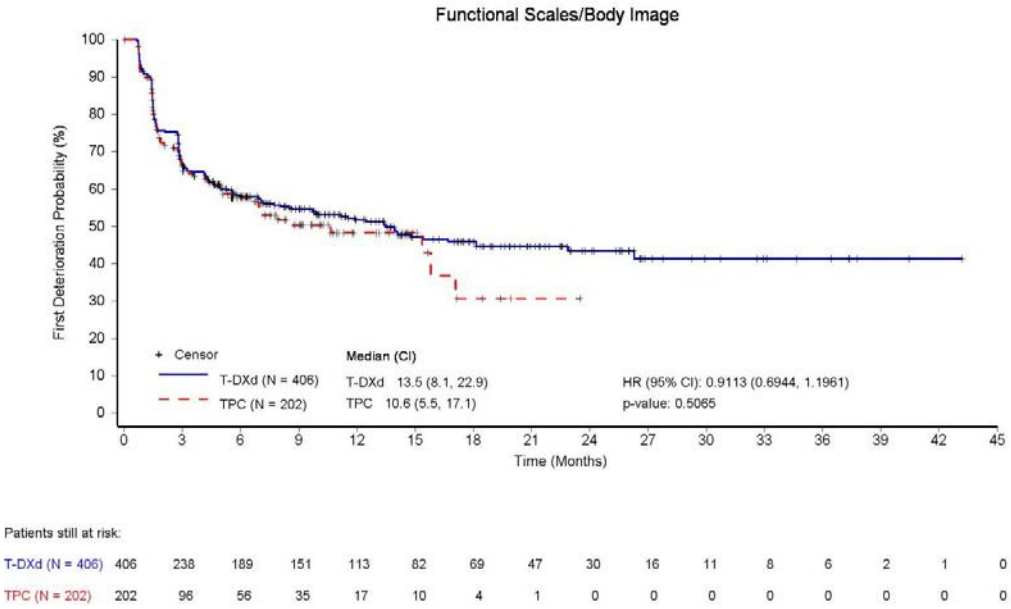



Figure 20: Kaplan-Meier curve for health-related quality of life, outcome of body image (EORTC QLQ-BR23, first deterioration by ≥ 10 points)

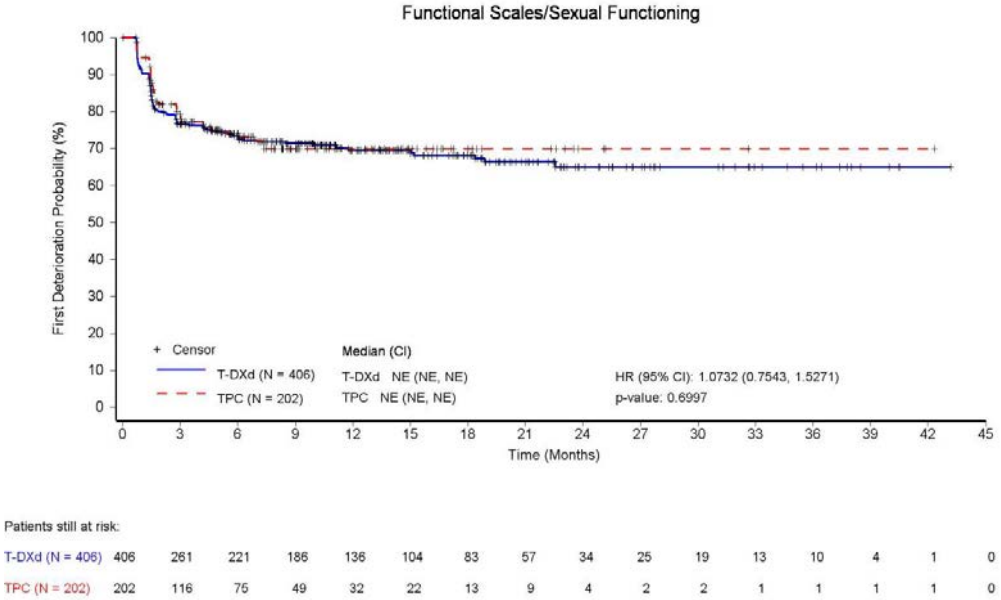



Figure 21: Kaplan-Meier curve for health-related quality of life, outcome of sexual activity (EORTC QLQ-BR23, first deterioration by ≥ 10 points)

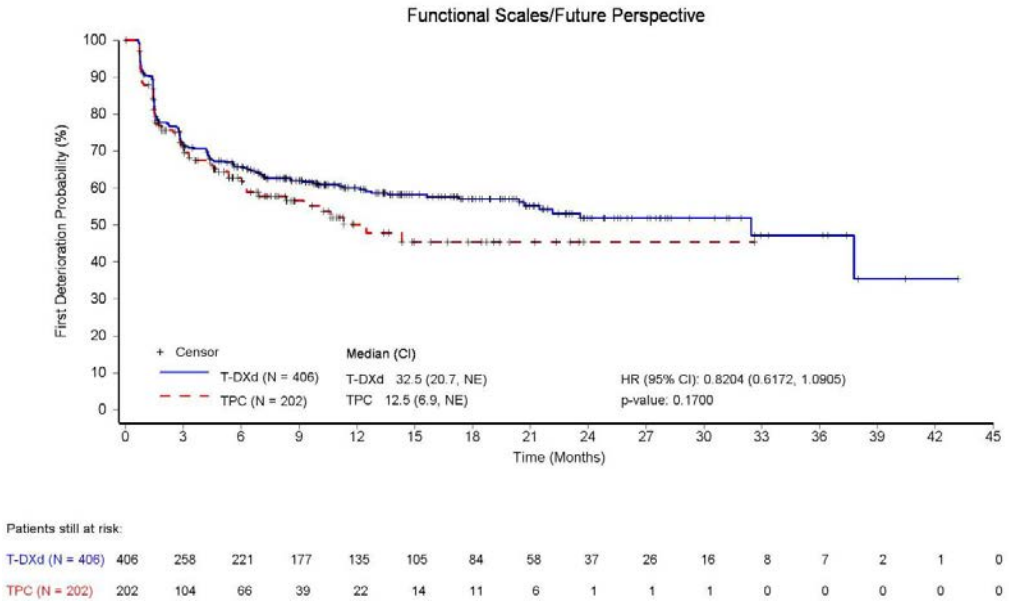



Figure 22: Kaplan-Meier curve for health-related quality of life, outcome of future perspective (EORTC QLQ-BR23, first deterioration by ≥ 10 points)

## A.4 Side effects

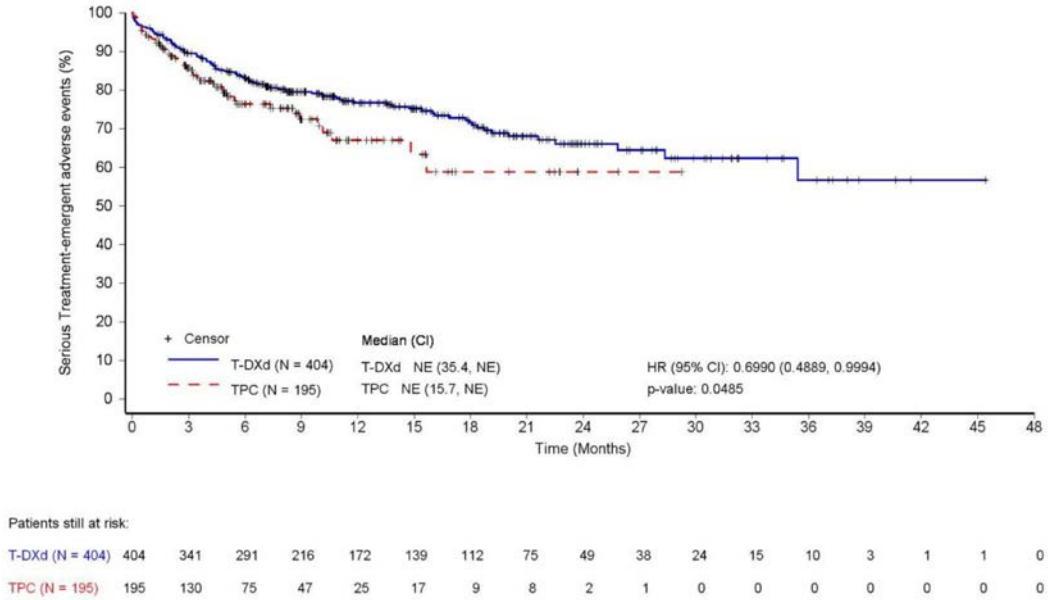
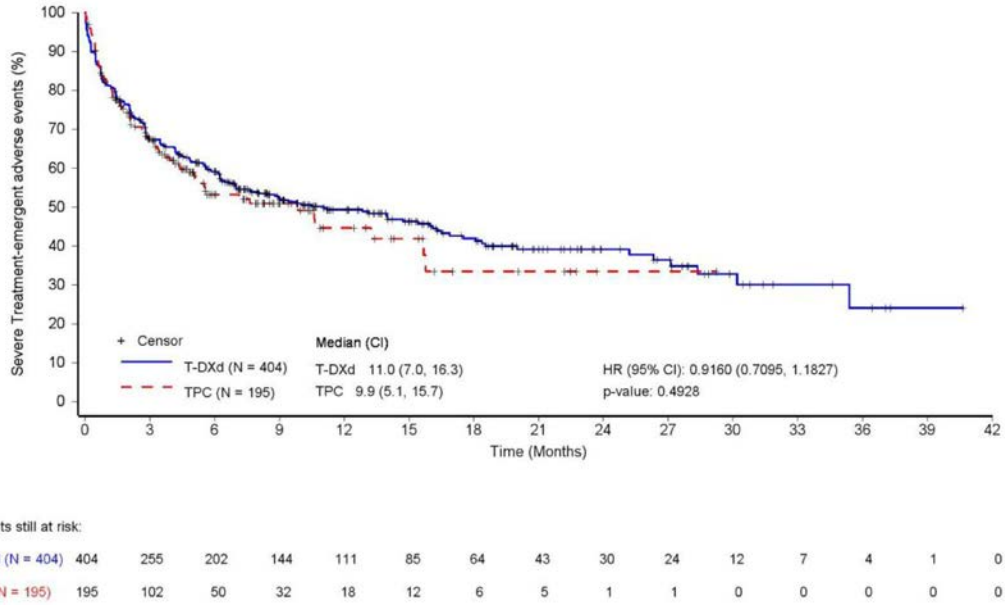


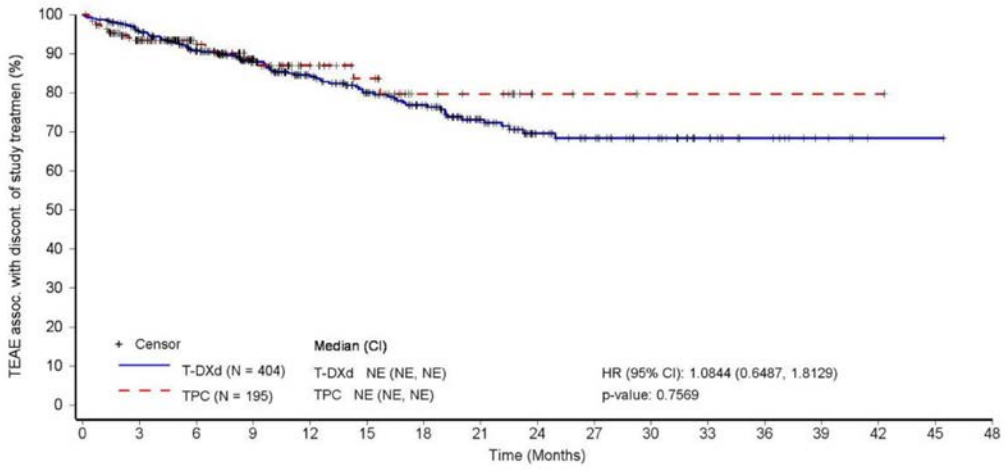

Figure 23: Kaplan-Meier curve, outcome of SAEs




Patients still at risk:

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T-DXd (N = 404) | 404 | 255 | 202 | 144 | 111 | 85 | 64 | 43 | 30 | 24 | 12 | 7 | 4 | 1 | 0 |
| TPC (N = 195) | 195 | 102 | 50 | 32 | 18 | 12 | 6 | 5 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |

Figure 24: Kaplan-Meier curve, outcome of severe AEs (CTCAE grade ≥ 3)




Patients still at risk:

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T-DXd (N = 404) | 404 | 363 | 318 | 248 | 201 | 164 | 136 | 93 | 61 | 48 | 33 | 21 | 13 | 5 | 1 | 1 | 0 |
| TPC (N = 195) | 195 | 138 | 84 | 55 | 33 | 24 | 13 | 11 | 3 | 2 | 1 | 1 | 1 | 1 | 1 | 0 | 0 |

Figure 25: Kaplan-Meier curve, outcome of discontinuation due to AEs

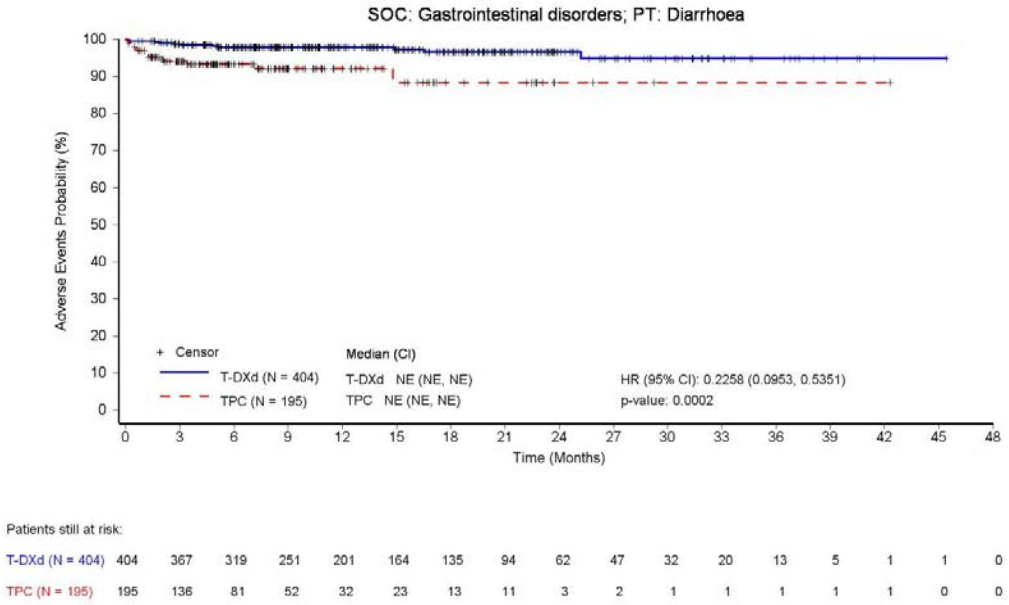



Figure 26: Kaplan-Meier curve, outcome of diarrhoea (PT, severe AEs)

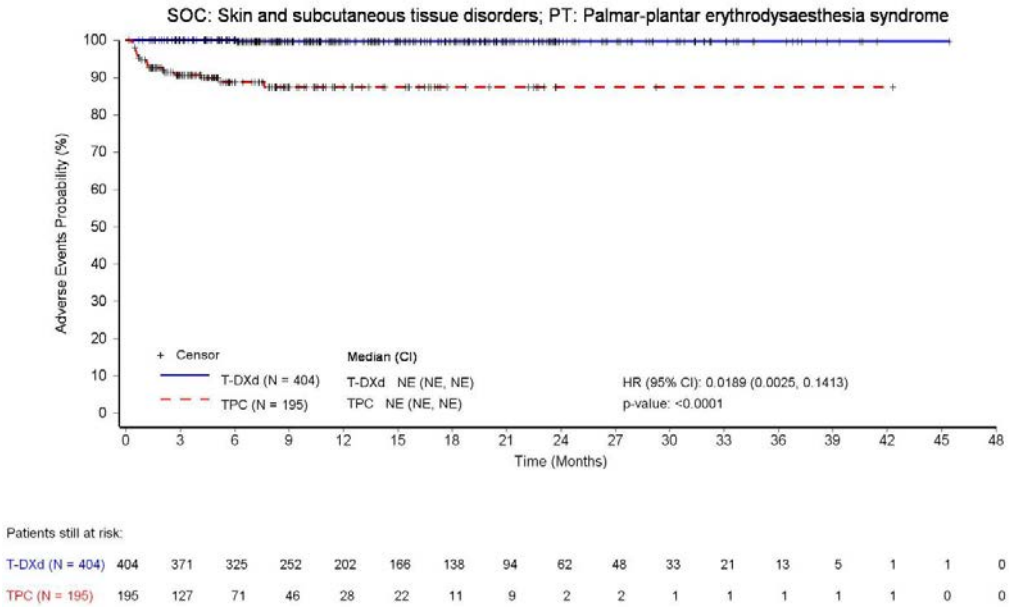



Figure 27: Kaplan-Meier curve, outcome of palmar-plantar erythrodysaesthesia syndrome (PT, severe AEs)

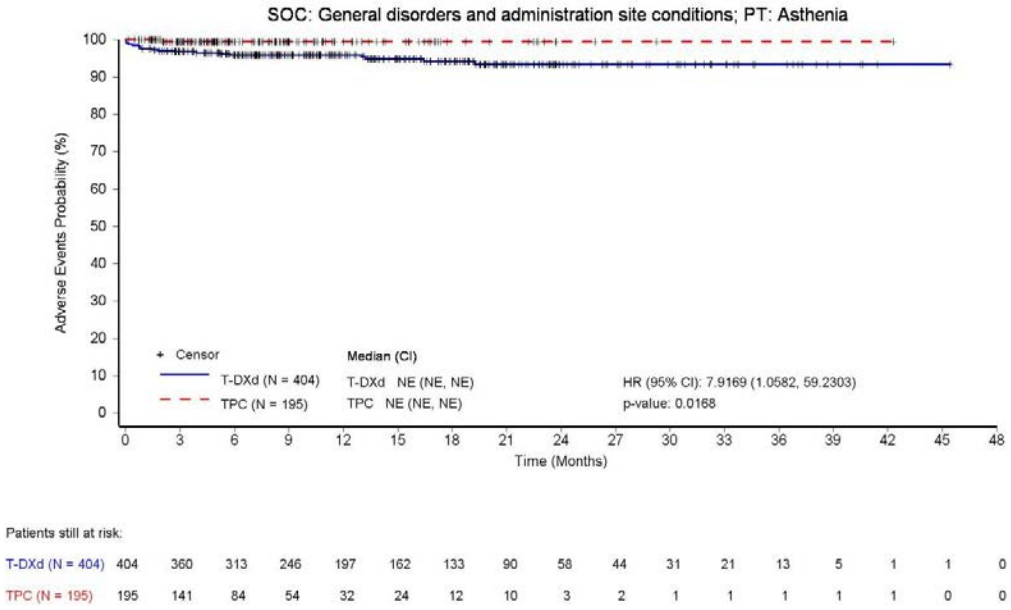



Figure 28: Kaplan-Meier curve, outcome of asthenia (PT, severe AEs)

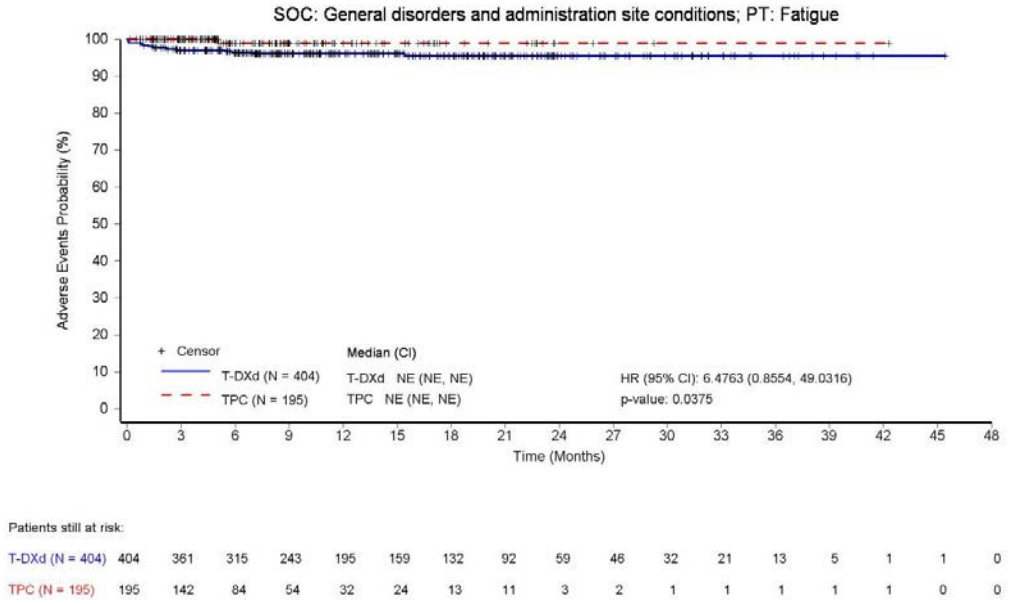
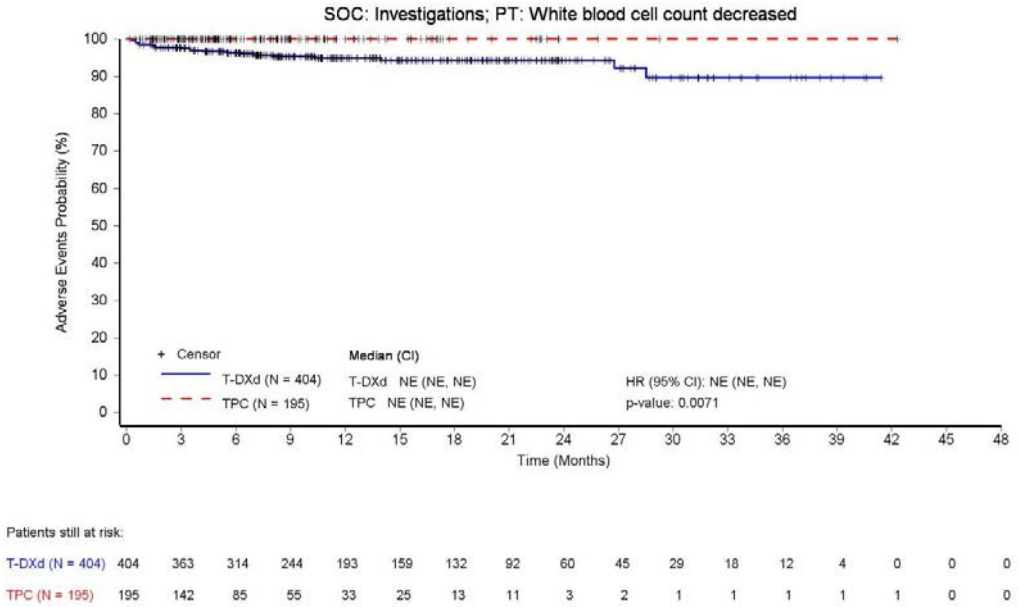


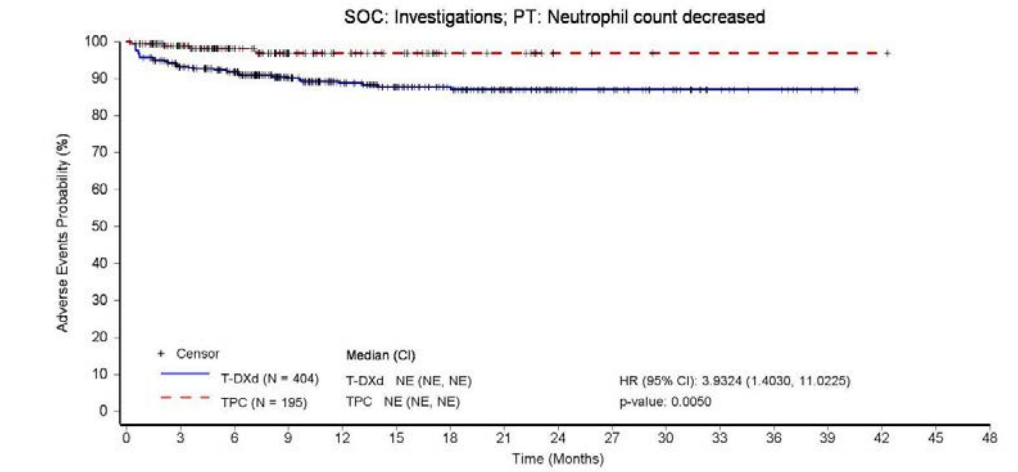

Figure 29: Kaplan-Meier curve, outcome of fatigue (PT, severe AEs)




Patients still at risk:

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T-DXd (N = 404) | 404 | 363 | 314 | 244 | 193 | 159 | 132 | 92 | 60 | 45 | 29 | 18 | 12 | 4 | 0 | 0 | 0 |
| TPC (N = 195) | 195 | 142 | 85 | 55 | 33 | 25 | 13 | 11 | 3 | 2 | 1 | 1 | 1 | 1 | 1 | 0 | 0 |

Figure 30: Kaplan-Meier curve, outcome of white blood cell count decreased (PT, severe AEs)




Patients still at risk:

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T-DXd (N = 404) | 404 | 347 | 301 | 229 | 181 | 146 | 121 | 84 | 54 | 41 | 27 | 15 | 10 | 3 | 0 | 0 | 0 |
| TPC (N = 195) | 195 | 140 | 84 | 53 | 33 | 25 | 13 | 11 | 3 | 2 | 1 | 1 | 1 | 1 | 1 | 0 | 0 |

Figure 31: Kaplan-Meier curve, outcome of neutrophil count decreased (PT, severe AEs)

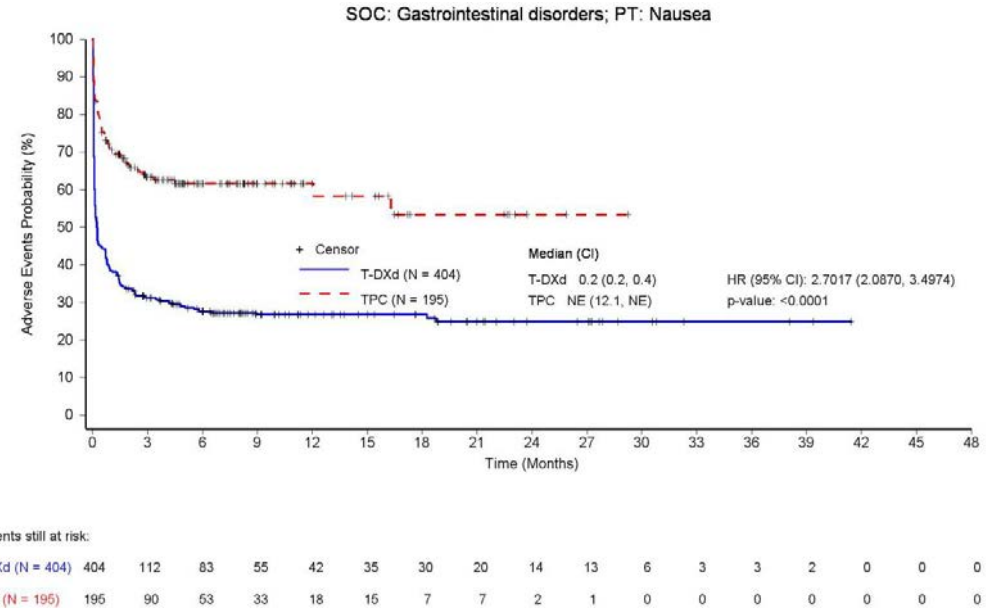



Figure 32: Kaplan-Meier curve, outcome of nausea (PT, AEs)

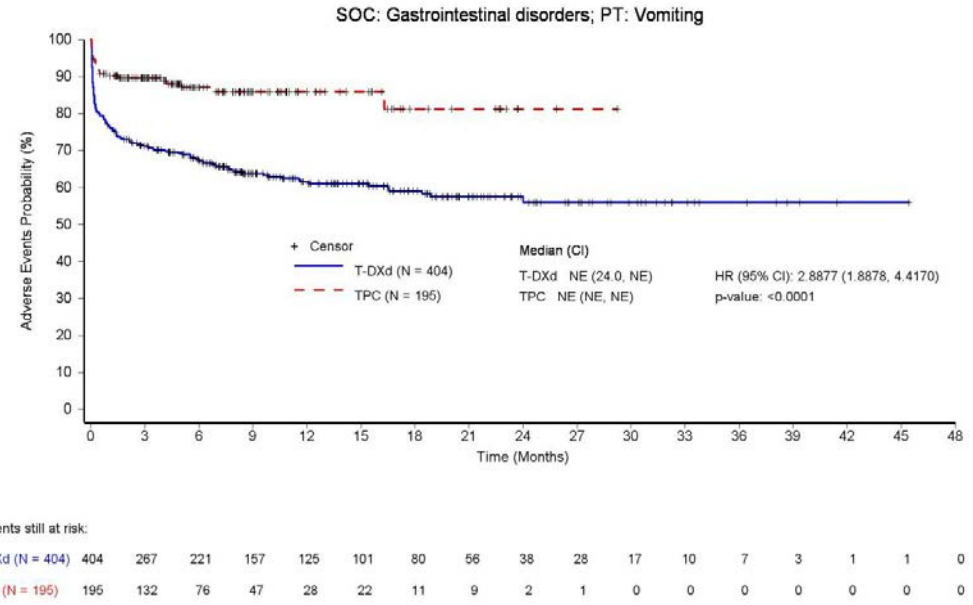
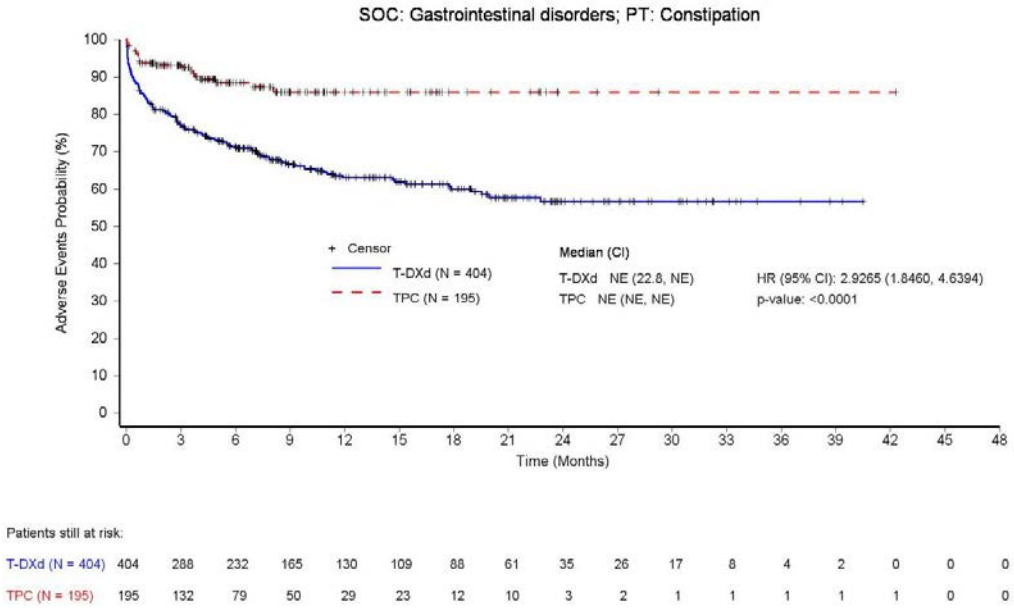


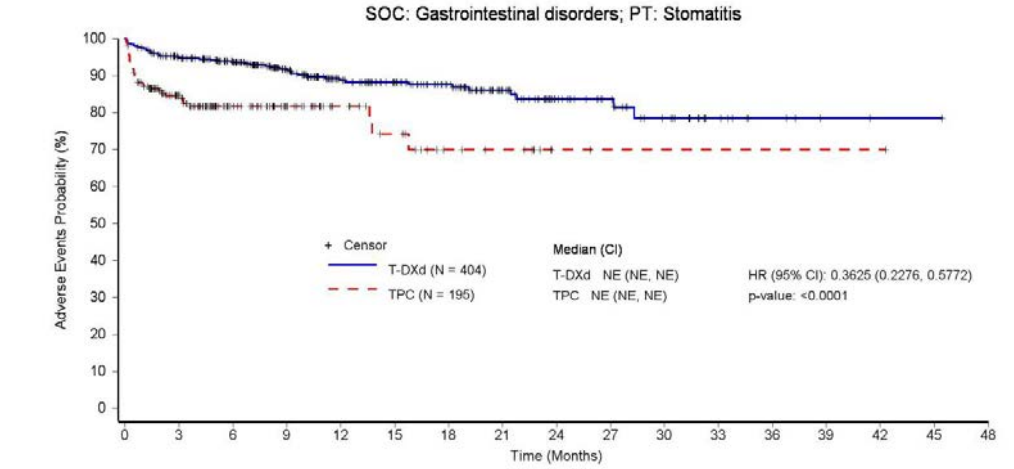

Figure 33: Kaplan-Meier curve, outcome of vomiting (PT, AEs)




Patients still at risk:

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T-DXd (N = 404) | 404 | 288 | 232 | 165 | 130 | 109 | 88 | 61 | 35 | 26 | 17 | 8 | 4 | 2 | 0 | 0 | 0 |
| TPC (N = 195) | 195 | 132 | 79 | 50 | 29 | 23 | 12 | 10 | 3 | 2 | 1 | 1 | 1 | 1 | 1 | 0 | 0 |

Figure 34: Kaplan-Meier curve, outcome of constipation (PT, AEs)




Patients still at risk:

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T-DXd (N = 404) | 404 | 354 | 305 | 230 | 177 | 145 | 121 | 81 | 51 | 38 | 23 | 12 | 6 | 2 | 1 | 1 | 0 |
| TPC (N = 195) | 195 | 118 | 66 | 44 | 26 | 19 | 11 | 9 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 |

Figure 35: Kaplan-Meier curve, outcome of stomatitis (PT, AEs)

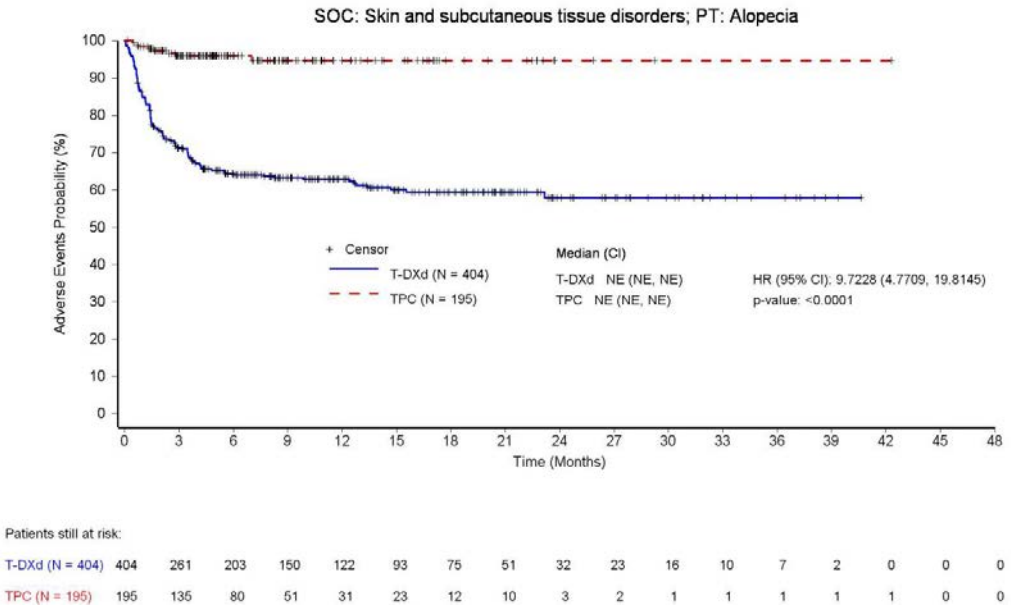



Figure 36: Kaplan-Meier curve, outcome of alopecia (PT, AEs)

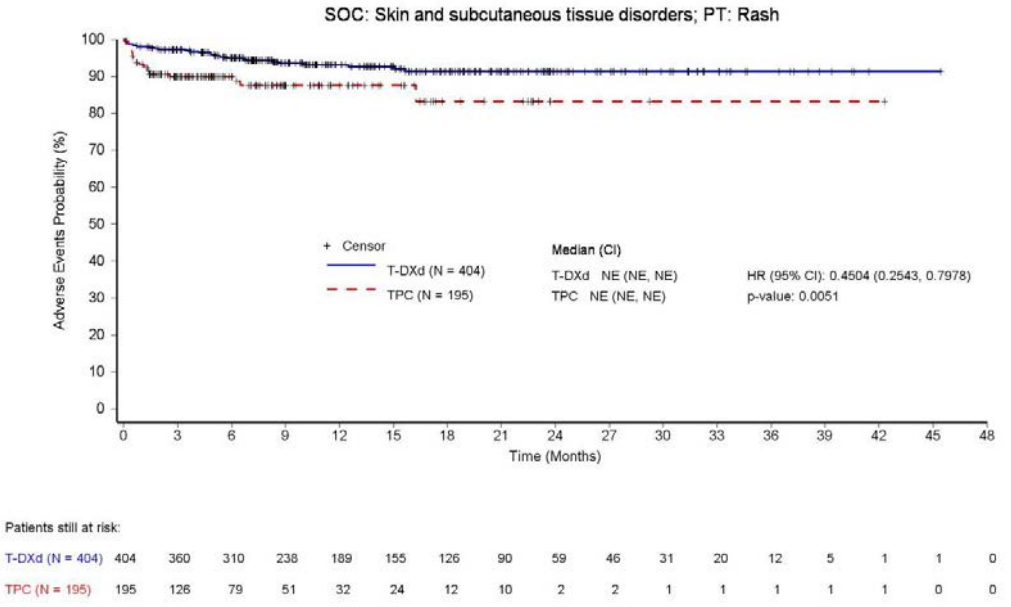
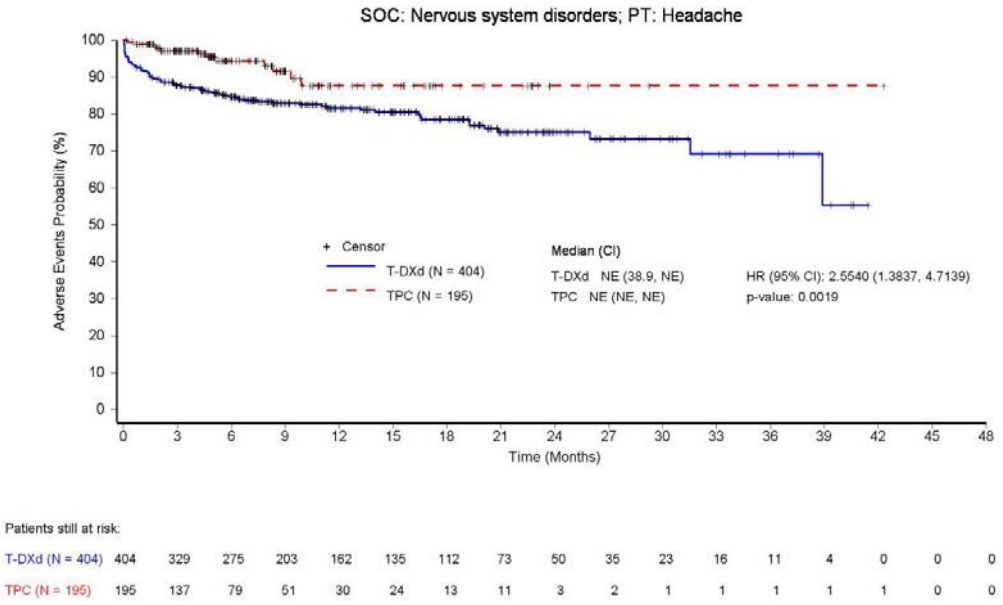



Figure 37: Kaplan-Meier curve, outcome of rash (PT, AEs)




Patients still at risk:

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T-DXd (N = 404) | 404 | 329 | 275 | 203 | 162 | 135 | 112 | 73 | 50 | 35 | 23 | 16 | 11 | 4 | 0 | 0 | 0 |
| TPC (N = 195) | 195 | 137 | 79 | 51 | 30 | 24 | 13 | 11 | 3 | 2 | 1 | 1 | 1 | 1 | 1 | 0 | 0 |

Figure 38: Kaplan-Meier curve, outcome of headache (PT, AEs)

## Appendix B Results on side effects

The tables below present events for Medical Dictionary for Regulatory Activities (MedDRA) SOCs and PTs for the overall rates of AEs and SAEs, each on the basis of the following criteria:

- overall rate of AEs (irrespective of severity): events which occurred in at least 10% of patients in one study arm
- SAEs: events which occurred in at least 5% of patients in one study arm
- additionally, for all events irrespective of severity: events which occurred in at least 10 patients and at least 1% of patients in one study arm

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

Table 16: Common AEs[a] – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice (multipage table)

| Study | Patients with event n (%) | |
|---|---|---|
| SOC[b] PT[b] | Trastuzumab deruxtecan N = 404 | Treatment of physician's choice N = 195 |
| **DESTINY-Breast02** | | |
| **Overall AE rate** | 403 (99.8) | 185 (94.9) |
| Gastrointestinal disorders | 358 (88.6) | 148 (75.9) |
| Nausea | 293 (72.5) | 73 (37.4) |
| Vomiting | 152 (37.6) | 25 (12.8) |
| Constipation | 142 (35.1) | 21 (10.8) |
| Diarrhoea | 109 (27.0) | 105 (53.8) |
| Dyspepsia | 48 (11.9) | 18 (9.2) |
| Abdominal pain | 47 (11.6) | 19 (9.7) |
| Stomatitis | 45 (11.1) | 36 (18.5) |
| Upper abdominal pain | 38 (9.4) | 18 (9.2) |
| Dry mouth | 16 (4.0) | 8 (4.1) |
| Gastrooesophageal reflux disease | 16 (4.0) | 3 (1.5) |
| Gastritis | 11 (2.7) | 3 (1.5) |
| General disorders and administration site conditions | 283 (70.0) | 98 (50.3) |
| Fatigue | 147 (36.4) | 52 (26.7) |
| Asthenia | 99 (24.5) | 19 (9.7) |
| Pyrexia | 54 (13.4) | 13 (6.7) |
| Oedema peripheral | 28 (6.9) | 9 (4.6) |
| Malaise | 16 (4.0) | 2 (1.0) |
| Mucosal inflammation | 15 (3.7) | 15 (7.7) |
| Chills | 12 (3.0) | 1 (0.5) |
| Non-cardiac chest pain | 12 (3.0) | 3 (1.5) |
| Influenza like illness | 10 (2.5) | 3 (1.5) |
| Investigations | 240 (59.4) | 75 (38.5) |
| Neutrophil count decreased | 79 (19.6) | 14 (7.2) |
| Weight decreased | 71 (17.6) | 7 (3.6) |
| AST increased | 66 (16.3) | 23 (11.8) |
| ALT increased | 61 (15.1) | 20 (10.3) |
| White blood cell count decreased | 59 (14.6) | 9 (4.6) |
| Platelet count decreased | 49 (12.1) | 12 (6.2) |
| Lymphocyte count decreased | 30 (7.4) | 4 (2.1) |
| Blood alkaline phosphatase increased | 24 (5.9) | 8 (4.1) |
| Bilirubin increased | 20 (5.0) | 21 (10.8) |

Table 16: Common AEs[a] – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice (multipage table)

| Study | Patients with event n (%) | |
|---|---|---|
| SOC[b] PT[b] | Trastuzumab deruxtecan N = 404 | Treatment of physician's choice N = 195 |
| Gamma-glutamyltransferase increased | 19 (4.7) | 2 (1.0) |
| Weight increased | 19 (4.7) | 5 (2.6) |
| Ejection fraction decreased | 17 (4.2) | 1 (0.5) |
| Electrocardiogram QT prolonged | 13 (3.2) | 7 (3.6) |
| Blood lactate dehydrogenase increased | 12 (3.0) | 2 (1.0) |
| Skin and subcutaneous tissue disorders | 206 (51.0) | 143 (73.3) |
| Alopecia | 150 (37.1) | 8 (4.1) |
| Rash | 27 (6.7) | 22 (11.3) |
| Pruritus | 22 (5.4) | 8 (4.1) |
| Skin hyperpigmentation | 14 (3.5) | 6 (3.1) |
| Dry skin | 11 (2.7) | 9 (4.6) |
| Palmar-plantar erythrodysaesthesia syndrome | 7 (1.7) | 100 (51.3) |
| Dermatitis acneiform | 2 (0.5) | 10 (5.1) |
| Infections and infestations | 200 (49.5) | 71 (36.4) |
| COVID-19 | 57 (14.1) | 4 (2.1) |
| Urinary tract infection | 36 (8.9) | 6 (3.1) |
| Nasopharyngitis | 21 (5.2) | 5 (2.6) |
| Upper respiratory tract infection | 21 (5.2) | 6 (3.1) |
| Pneumonia | 16 (4.0) | 2 (1.0) |
| Cystitis | 15 (3.7) | 2 (1.0) |
| Influenza | 10 (2.5) | 2 (1.0) |
| Paronychia | 10 (2.5) | 14 (7.2) |
| Blood and lymphatic system disorders | 177 (43.8) | 48 (24.6) |
| Anaemia | 115 (28.5) | 27 (13.8) |
| Neutropenia | 65 (16.1) | 10 (5.1) |
| Thrombocytopenia | 41 (10.1) | 11 (5.6) |
| Leukopenia | 23 (5.7) | 4 (2.1) |
| Lymphopenia | 21 (5.2) | 2 (1.0) |
| Metabolism and nutrition disorders | 176 (43.8) | 55 (28.2) |
| Decreased appetite | 125 (30.9) | 35 (17.9) |
| Hypokalaemia | 29 (7.2) | 13 (6.7) |
| Hypomagnesaemia | 15 (3.7) | 4 (2.1) |
| Dehydration | 11 (2.7) | 3 (1.5) |
| Hypocalcaemia | 11 (2.7) | 1 (0.5) |
| Nervous system disorders | 170 (42.1) | 53 (27.2) |

Table 16: Common AEs[a] – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice (multipage table)

| Study | Patients with event n (%) | |
|---|---|---|
| SOC[b] PT[b] | Trastuzumab deruxtecan N = 404 | Treatment of physician's choice N = 195 |
| Headache | 80 (19.8) | 12 (6.2) |
| Dizziness | 33 (8.2) | 14 (7.2) |
| Dysgeusia | 33 (8.2) | 4 (2.1) |
| Peripheral sensory neuropathy | 15 (3.7) | 5 (2.6) |
| Peripheral neuropathy | 12 (3.0) | 10 (5.1) |
| Paraesthesia | 10 (2.5) | 3 (1.5) |
| Respiratory, thoracic and mediastinal disorders | 166 (41.1) | 50 (25.6) |
| Cough | 53 (13.1) | 20 (10.3) |
| Dyspnoea | 34 (8.4) | 13 (6.7) |
| Pneumonitis | 34 (8.4) | 1 (0.5) |
| Epistaxis | 33 (8.2) | 12 (6.2) |
| Interstitial lung disease | 20 (5.0) | 0 (0) |
| Oropharyngeal pain | 13 (3.2) | 2 (1.0) |
| Musculoskeletal and connective tissue disorders | 137 (33.9) | 48 (24.6) |
| Arthralgia | 44 (10.9) | 14 (7.2) |
| Back pain | 36 (8.9) | 8 (4.1) |
| Pain in extremity | 25 (6.2) | 8 (4.1) |
| Myalgia | 23 (5.7) | 8 (4.1) |
| Muscle spasms | 13 (3.2) | 11 (5.6) |
| Eye disorders | 67 (16.6) | 22 (11.3) |
| Dry eye | 23 (5.7) | 9 (4.6) |
| Psychiatric disorders | 61 (15.1) | 13 (6.7) |
| Insomnia | 25 (6.2) | 11 (5.6) |
| Depression | 15 (3.7) | 1 (0.5) |
| Anxiety | 13 (3.2) | 2 (1.0) |
| Vascular disorders | 55 (13.6) | 19 (9.7) |
| Hot flush | 18 (4.5) | 0 (0) |
| Lymphoedema | 11 (2.7) | 1 (0.5) |
| Hypertension | 10 (2.5) | 7 (3.6) |
| Injury, poisoning and procedural complications | 45 (11.1) | 16 (8.2) |
| Reproductive system and breast disorders | 33 (8.2) | 10 (5.1) |
| Breast pain | 12 (3.0) | 4 (2.1) |
| Hepatobiliary disorders | 31 (7.7) | 7 (3.6) |
| Hyperbilirubinaemia | 12 (3.0) | 5 (2.6) |

Table 16: Common AEs[a] – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice (multipage table)

| Study | Patients with event n (%) | |
|---|---|---|
| SOC[b] PT[b] | Trastuzumab deruxtecan N = 404 | Treatment of physician's choice N = 195 |
| Renal and urinary disorders | 27 (6.7) | 10 (5.1) |
| Dysuria | 10 (2.5) | 5 (2.6) |
| Cardiac disorders | 19 (4.7) | 11 (5.6) |
| Ear and labyrinth disorders | 17 (4.2) | 1 (0.5) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 10 (2.5) | 4 (2.1) |

a. Events which occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 25.0; SOCs and PTs taken from Module 4.

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

| Study | Patients with event n (%) | |
|---|---|---|
| SOC[b] PT[b] | Trastuzumab deruxtecan N = 404 | Treatment of physician's choice N = 195 |
| **DESTINY-Breast02** | | |
| **Overall SAE rate** | 103 (25.5) | 46 (23.6) |
| Infections and infestations | 30 (7.4) | 12 (6.2) |
| COVID-19 | 11 (2.7) | 1 (0.5) |
| Gastrointestinal disorders | 23 (5.7) | 10 (5.1) |
| Respiratory, thoracic and mediastinal disorders | 22 (5.4) | 7 (3.6) |
| Pneumonitis | 10 (2.5) | 1 (0.5) |
| General disorders and administration site conditions | 12 (3.0) | 6 (3.1) |
| Nervous system disorders | 11 (2.7) | 1 (0.5) |

a. Events that occurred in ≥ 10 patients in the intervention arm, or in ≥ 5% of patients in the comparator arm.
b. MedDRA version 25.0; SOCs and PTs taken from Module 4.

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; SAE: serious adverse event; SOC: System Organ Class

Table 18: Common severe AEs (CTCAE grade ≥ 3)[a] – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice

| Study | Patients with event n (%) | |
|---|---|---|
| SOC[b] PT[b] | Trastuzumab deruxtecan N = 404 | Treatment of physician's choice N = 195 |
| **DESTINY-Breast02** | | |
| **Overall rate of severe AEs** | 213 (52.7) | 86 (44.1) |
| Investigations | 78 (19.3) | 16 (8.2) |
| Neutrophil count decreased | 43 (10.6) | 4 (2.1) |
| White blood cell count decreased | 21 (5.2) | 0 (0) |
| Lymphocyte count decreased | 11 (2.7) | 1 (0.5) |
| Blood and lymphatic system disorders | 69 (17.1) | 13 (6.7) |
| Anaemia | 32 (7.9) | 6 (3.1) |
| Neutropenia | 31 (7.7) | 4 (2.1) |
| Gastrointestinal disorders | 55 (13.6) | 24 (12.3) |
| Nausea | 27 (6.7) | 5 (2.6) |
| Vomiting | 15 (3.7) | 2 (1.0) |
| Diarrhoea | 11 (2.7) | 14 (7.2) |
| General disorders and administration site conditions | 43 (10.6) | 11 (5.6) |
| Asthenia | 20 (5.0) | 1 (0.5) |
| Fatigue | 16 (4.0) | 1 (0.5) |
| Infections and infestations | 30 (7.4) | 12 (6.2) |
| Metabolism and nutrition disorders | 23 (5.7) | 7 (3.6) |
| Hypokalaemia | 11 (2.7) | 5 (2.6) |
| Nervous system disorders | 14 (3.5) | 5 (2.6) |
| Respiratory, thoracic and mediastinal disorders | 13 (3.2) | 7 (3.6) |
| Skin and subcutaneous tissue disorders | 2 (0.5) | 21 (10.8) |
| Palmar-plantar erythrodysaesthesia syndrome | 1 (0.2) | 20 (10.3) |

a. Events that occurred in ≥ 10 patients in the intervention arm, or in ≥ 5% of patients in the comparator arm.
b. MedDRA version 25.0; SOCs and PTs taken from Module 4.

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

| Study | Patients with event n (%) | |
|---|---|---|
| SOC[a]<br>PT[a] | Trastuzumab deruxtecan<br>N = 404 | Treatment of physician's choice<br>N = 195 |
| **DESTINY-Breast02** | | |
| **Overall rate of discontinuations due to AEs** | 80 (19.8) | 19 (9.7) |
| Respiratory, thoracic and mediastinal disorders | 45 (11.1) | 1 (0.5) |
| Pneumonitis | 25 (6.2) | 1 (0.5) |
| Interstitial lung disease | 15 (3.7) | 0 (0) |
| Idiopathic interstitial pneumonia | 1 (0.2) | 0 (0) |
| Lung disorder | 1 (0.2) | 0 (0) |
| Pleural effusion | 1 (0.2) | 0 (0) |
| Pulmonary fibrosis | 1 (0.2) | 0 (0) |
| Pulmonary toxicity | 1 (0.2) | 0 (0) |
| Infections and infestations | 11 (2.7) | 2 (1.0) |
| COVID-19 | 4 (1.0) | 0 (0) |
| Pneumonia | 3 (0.7) | 0 (0) |
| Atypical pneumonia | 1 (0.2) | 0 (0) |
| COVID-19 pneumonia | 1 (0.2) | 0 (0) |
| Hepatitis B | 1 (0.2) | 0 (0) |
| Pneumocystis jirovecii pneumonia | 1 (0.2) | 0 (0) |
| Abdominal sepsis | 0 (0) | 1 (0.5) |
| Atypical mycobacterial infection | 0 (0) | 1 (0.5) |
| General disorders and administration site conditions | 4 (1.0) | 1 (0.5) |
| Asthenia | 3 (0.7) | 0 (0) |
| Fatigue | 1 (0.2) | 0 (0) |
| Disease progression | 0 (0) | 1 (0.5) |
| Investigations | 4 (1.0) | 3 (1.5) |
| Ejection fraction decreased | 2 (0.5) | 0 (0) |
| ALT increased | 1 (0.2) | 0 (0) |
| AST increased | 1 (0.2) | 0 (0) |
| ECG QT prolonged | 1 (0.2) | 0 (0) |
| Blood bilirubin increased | 0 (0) | 2 (1.0) |
| Platelet count decreased | 0 (0) | 1 (0.5) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 4 (1.0) | 0 (0) |
| Brain neoplasm | 1 (0.2) | 0 (0) |
| Malignant pleural effusion | 1 (0.2) | 0 (0) |
| Metastases to meninges | 1 (0.2) | 0 (0) |

Table 19: Discontinuations due to AEs[a] – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice (multipage table)

| Study | Patients with event n (%) | |
|---|---|---|
| SOC[a] PT[a] | Trastuzumab deruxtecan N = 404 | Treatment of physician's choice N = 195 |
| Pulmonary tumour thrombotic microangiopathy | 1 (0.2) | 0 (0) |
| Blood and lymphatic system disorders | 3 (0.7) | 0 (0) |
| Haemolysis | 1 (0.2) | 0 (0) |
| Neutropenia | 1 (0.2) | 0 (0) |
| Thrombocytopenia | 1 (0.2) | 0 (0) |
| Nervous system disorders | 2 (0.5) | 1 (0.5) |
| Peripheral sensory neuropathy | 1 (0.2) | 0 (0) |
| Vasogenic cerebral oedema | 1 (0.2) | 0 (0) |
| Facial paralysis | 0 (0) | 1 (0.5) |
| Skin and subcutaneous tissue disorders | 2 (0.5) | 4 (2.1) |
| Skin hyperpigmentation | 2 (0.5) | 0 (0) |
| Drug eruption | 0 (0) | 1 (0.5) |
| Palmar-plantar erythrodysaesthesia syndrome | 0 (0) | 3 (1.5) |
| Gastrointestinal disorders | 1 (0.2) | 3 (1.5) |
| Ascites | 1 (0.2) | 0 (0) |
| Diarrhoea | 0 (0) | 2 (1.0) |
| Dysphagia | 0 (0) | 1 (0.5) |
| Vomiting | 0 (0) | 1 (0.5) |
| Hepatobiliary disorders | 1 (0.2) | 0 (0) |
| Liver cirrhosis | 1 (0.2) | 0 (0) |
| Metabolism and nutrition disorders | 1 (0.2) | 0 (0) |
| Hypercalcaemia | 1 (0.2) | 0 (0) |
| Reproductive system and breast disorders | 1 (0.2) | 0 (0) |
| Breast haemorrhage | 1 (0.2) | 0 (0) |
| Vascular disorders | 1 (0.2) | 0 (0) |
| Haemorrhage | 1 (0.2) | 0 (0) |
| Cardiac disorders | 0 (0) | 3 (1.5) |
| Cardiac arrest | 0 (0) | 1 (0.5) |
| Cardiac failure | 0 (0) | 1 (0.5) |
| Pericardial effusion | 0 (0) | 1 (0.5) |
| Injury, poisoning and procedural complications | 0 (0) | 1 (0.5) |
| Craniocerebral injury | 0 (0) | 1 (0.5) |

Table 19: Discontinuations due to AEs[a] – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice (multipage table)

| Study | Patients with event n (%) | |
|---|---|---|
| SOC[a] PT[a] | Trastuzumab deruxtecan N = 404 | Treatment of physician's choice N = 195 |
| a. MedDRA version 25.0; SOCs and PTs taken from Module 4. | | |
| 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 | | |