# Trastuzumab deruxtecan (breast cancer, after 1 prior therapy) –

## Addendum to Project A22-80 (dossier assessment)[1]

**ADDENDUM**

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## List of abbreviations

| Abbreviation | Meaning |
|---|---|
| AE | adverse event |
| CTCAE | Common Terminology Criteria for Adverse Events |
| EORTC | European Organisation for Research and Treatment of Cancer |
| 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 |
| PT | Preferred Term |
| QLQ-BR23 | Quality of Life Questionnaire-Breast Cancer Module 23 |
| QLQ-C30 | Quality of Life Questionnaire-Core 30 |
| SAE | serious adverse event |
| SGB | Sozialgesetzbuch (Social Code Book) |
| SOC | System Organ Class |
| VAS | visual analogue scale |

# 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 A22-80 (Trastuzumab deruxtecan – Benefit assessment according to § 35a Social Code Book V) [1].

The commission of 6 December 2022 comprises the assessment of the analyses of a new data cut-off of the DESTINY-Breast03 study from 25 July 2022 submitted in the commenting procedure [2] 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 [3].

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 (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and EORTC Quality of Life Questionnaire-Breast Cancer Module 23 (QLQ-BR23) with the response criterion of 10 points from the DESTINY-Breast03 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 data subsequently submitted

The DESTINY-Breast03 study was included for the benefit assessment A22-80 [1] of trastuzumab deruxtecan in adult patients with unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer who have received one prior anti-HER2-based regimen. The DESTINY-Breast03 study is an open-label, randomized, 2-arm study comparing trastuzumab deruxtecan with trastuzumab emtansine.

The benefit assessment was based on the results of the first data cut-off of the DESTINY-Breast03 study from 21 May 2021. In the commenting procedure, the company submitted analyses for a second data cut-off (25 July 2022) for the DESTINY-Breast03 study [4], which are assessed below.

## 2.1 Study characteristics

A detailed description of the DESTINY-Breast03 study can be found in dossier assessment A22-80 [1]. The following text describes only those characteristics for which changes resulted from the second data cut-off.

### Second data cut-off from 25 July 2022

The DESTINY-Breast03 study is an ongoing study. The benefit assessment A22-80 was based on the data cut-off from 21 May 2021. According to the study protocol, this was planned after 234 events in the outcome of progression-free survival (first interim analysis).

In commenting procedure, the company submitted analyses of a second data cut-off from 25 July 2022. This is the second planned interim analysis after 153 deaths.

### Treatment duration and observation period

Table 1 shows the mean and median treatment durations of the patients and the median observation periods for individual outcomes.

Table 1: Information on the course of the study – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine

| **Study**<br>**Duration of the study phase**<br>**Outcome category** | **Trastuzumab deruxtecan**<br>**N = 261** | **Trastuzumab emtansine**<br>**N = 263** |
|---|---|---|
| **DESTINY-Breast03, data cut-off of 25 July 2022** | | |
| Treatment duration [months] | N = 257 | N = 261 |
| Median [min; max] | 18.23 [0.7; 44.0] | 6.90 [0.7; 39.3] |
| Mean (SD) | 19.02 (11.16) | 9.61 (9.03) |
| Observation period [months] | | |
| Overall survival[a] | | |
| Median [95% CI] | 30.9 [30.2; 31.4] | 30.6 [29.5; 31.2] |
| Mean (SD) | ND | ND |
| Morbidity | | |
| Median [min; max] | ND | ND |
| Mean (SD) | ND | ND |
| Health-related quality of life | | |
| Median [min; max] | ND | ND |
| Mean (SD) | ND | ND |
| Side effects | | |
| Median [min; max] | ND | ND |
| Mean (SD) | ND | ND |

a. The observation period is calculated on the basis of the inverse Kaplan-Meier method.

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

At 18.2 months, the median treatment duration in the intervention arm is more than 2.5 times as long as in the control arm (6.9 months).

The median observation period for overall survival is 30.9 months in the intervention arm and 30.6 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 A22-80), 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). The observation periods for these outcomes can only be estimated on the basis of the treatment durations, as the company did not provide any information on observation periods for the outcomes with shorter observation periods for this data cut-off either.

The between-arm differences in treatment duration also result in differences in observation periods of the outcomes. This data situation influences the interpretability of the outcomes with shorter observation period. Detailed reasons can be found in A22-80 [1].

**Subsequent therapies**

Table 2 shows the subsequent therapies patients received after discontinuing the study medication.

Table 2: Information on subsequent antineoplastic therapies – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine

| Study<br>Drug | Patients with subsequent therapy, n (%) | |
|---|---|---|
| | Trastuzumab deruxtecan<br>N = 261 | Trastuzumab emtansine<br>N = 263 |
| **DESTINY-Breast03, data cut-off of 25 July 2022** | | |
| Total | ND | ND |
| Systemic[a] | 130 (49.8) | 191 (72.6) |
| Trastuzumab | 43 (16.5) | 90 (34.2) |
| Trastuzumab deruxtecan | 3 (1.1) | 42 (16.0) |
| Trastuzumab emtansine | 64 (24.5) | 24 (9.1) |
| Pertuzumab | 15 (5.7) | 28 (10.6) |
| Taxane | 13 (5.0) | 32 (12.2) |
| Taxane & trastuzumab | 7 (2.7) | 28 (10.6) |
| Other anti-HER2 (incl. anti-HER2 TKI and other anti-HER2 antibodies or ADC) | 39 (14.9) | 88 (33.5) |
| Anti-HER2 TKI | 38 (14.6) | 87 (33.1) |
| Other anti-HER2 antibodies or ADC | 1 (0.4) | 4 (1.5) |
| Hormone therapy | 25 (9.6) | 30 (11.4) |
| Other systemic therapy[b] | 75 (28.7) | 147 (55.9) |
| Radiotherapy | 20 (7.7) | 38 (14.4) |
| Surgical interventions | 4 (1.5) | 12 (4.6) |

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

ADC: antibody-drug conjugate; HER2: human epidermal growth factor receptor 2; n: number of patients with subsequent therapy; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; TKI: tyrosine kinase inhibitor

In principle, there was no restriction to the administration of subsequent therapies after recurrence in the DESTINY-Breast03 study. By the time of the present data cut-off, 49.8% versus 72.6% of patients had received at least one subsequent systemic antineoplastic therapy. In 24.5% of patients in the intervention arm, this was trastuzumab emtansine. However, the guidelines recommend this drug for use in the second line of treatment. In the

comparator arm, trastuzumab (34.2%), anti-HER2 tyrosine kinase inhibitors (33.1%) and trastuzumab deruxtecan (16.0%) were the most common subsequent therapies used. Furthermore, pertuzumab was used as a subsequent therapy in both treatment arms (5.7% versus 10.6%). According to the approval for pertuzumab, this drug may only be used if no anti-HER2 therapy or chemotherapy has been used before. Thus, pertuzumab as subsequent therapy was not used in compliance with the approval. In addition, other non-HER2-targeted therapies were also used, but no more detailed information is available on these.

Overall, the subsequent therapies used are thus essentially comparable to the first data cut-off. As already described in dossier assessment A22-80, the aspects described above have no influence on the benefit assessment.

## 2.2 Results of the second data cut-off

### 2.2.1 Risk of bias

The risk of bias across outcomes for the DESTINY-Breast03 study is rated as low (see A22-80 [1]).

Table 3 describes the risk of bias for the results of the relevant outcomes.

Table 3: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine

| Study | Study level | 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 | Severe AEs[a] | Discontinuation due to AEs | Cardiac disorders (SOC, severe AEs[a]) | Platelet count decreased (PT, severe AEs[a]) | Further specific AEs[b] |
| DESTINY-Breast03, data cut-off of 25 July 2022 | L | L | H[c, d] | H[c, d] | H[c, d] | H[d] | H[d] | H[e] | H[d] | H[d] | H[d, f] |

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The following events are considered (MedDRA coding): gastrointestinal disorders (SOC, AEs), pyrexia (PT, AEs), malaise (PT, AEs), skin and subcutaneous tissue disorders (SOC, AEs), nose bleed (PT, AEs), neutrophil count decreased (PT, severe AEs), white blood cell count decreased (PT, severe AEs), alanine aminotransferase increased (PT, severe AEs), aspartate aminotransferase increased (PT, severe AEs), general disorders and administration site conditions (SOC, severe AEs), fatigue (PT, severe AEs), and nausea (PT, severe AEs).
c. Lack of blinding in subjective recording of outcomes.
d. Incomplete observations for potentially informative reasons with different follow-up observations.
e. Lack of blinding in subjective decision for discontinuation.
f. Lack of blinding in subjective recording of outcomes (in the case of non-serious/non-severe AEs).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; L: low; 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

For the present second data cut-off, the outcome-specific risk of bias is high for the results of all outcomes except overall survival, as was already the case for the first data cut-off. Depending on the outcome, this is due to the open-label study design and/or incomplete observations for potentially informative reasons.

Irrespective of the aspects described under risk of bias, the certainty of conclusions of study results is reduced due to the uncertainties regarding the pretreatment of the included patients already described in benefit assessment A22-80 [1]. In the present data situation, at most hints, e.g. of an added benefit, can therefore be determined for all outcomes.

### 2.2.2 Results

Table 4 summarizes the results of the data on trastuzumab deruxtecan subsequently submitted, taking into account the second data cut-off of the DESTINY-Breast03 study. Following the oral hearing, the company submitted analyses for the time to first deterioration with a response threshold of 10 points for the EORTC QLQ-C30 and EORTC QLQ-BR23 for the second data cut-off. As in dossier assessment A22-80, these analyses are used for the benefit assessment.

Where available, the Kaplan-Meier curves on the presented event time analyses are presented in Appendix A. Results for common adverse events (AEs), serious AEs (SAEs), severe AEs, and discontinuations due to AEs can be found in Appendix B of this addendum.

Table 4: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine (multipage table)

| Study<br>Outcome category<br>Outcome | Trastuzumab deruxtecan | | Trastuzumab emtansine | | Trastuzumab deruxtecan vs. trastuzumab emtansine |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI]<br>Patients with event n (%) | N | Median time to event in months [95% CI]<br>Patients with event n (%) | HR [95% CI]; p-value |
| **DESTINY-Breast03, data cut-off of 25 July 2022** | | | | | |
| **Mortality** | | | | | |
| Overall survival | 261 | NA [40.5; NC]<br>72 (27.6) | 263 | NA [34.0; NC]<br>97 (36.9) | 0.64 [0.47; 0.87];<br>0.004[a] |
| **Morbidity** | | | | | |
| **Symptoms (EORTC QLQ-C30)[b]** | | | | | |
| Fatigue | 261 | 5.6 [3.0; 9.9]<br>162 (62.1) | 263 | 3.6 [2.8; 5.5]<br>157 (59.7) | 0.83 [0.67; 1.04];<br>0.103[a] |
| Nausea and vomiting | 261 | 2.8 [1.6; 3.0]<br>196 (75.1) | 263 | 9.7 [8.3; 13.9]<br>118 (44.9) | 1.99 [1.58; 2.51];<br>< 0.001[a] |
| Pain | 261 | 8.5 [5.6; 13.8]<br>153 (58.6) | 263 | 6.9 [5.3; 9.8]<br>138 (52.5) | 0.88 [0.70; 1.12];<br>0.297[a] |
| Dyspnoea | 261 | 23.3 [16.6; NC]<br>116 (44.4) | 263 | 15.2 [11.7; 31.8]<br>103 (39.2) | 0.85 [0.65; 1.12];<br>0.237[a] |
| Insomnia | 261 | 19.4 [10.7; 25.1]<br>129 (49.4) | 263 | 12.7 [7.2; NC]<br>115 (43.7) | 0.89 [0.69; 1.15];<br>0.367[a] |
| Appetite loss | 261 | 4.2 [2.9; 5.6]<br>166 (63.6) | 263 | 10.3 [6.6; 20.5]<br>119 (45.2) | 1.41 [1.11; 1.79];<br>0.006[a] |
| Constipation | 261 | 5.6 [4.2; 8.3]<br>160 (61.3) | 263 | 8.5 [5.7; 12.9]<br>125 (47.5) | 1.24 [0.98; 1.57];<br>0.077[a] |
| Diarrhoea | 261 | 27.6 [17.1; NC]<br>116 (44.4) | 263 | NA [22.4; NC]<br>67 (25.5) | 1.69 [1.24; 2.29];<br>< 0.001[a] |
| **Symptoms (EORTC QLQ-BR23)[b]** | | | | | |
| Side effects of systemic therapy | 261 | 5.7 [4.3; 11.0]<br>153 (58.6) | 263 | 11.7 [8.3; 17.0]<br>115 (43.7) | 1.23 [0.97; 1.58];<br>0.094[a] |
| Symptoms in chest region | 261 | NA [36.8; NC]<br>67 (25.7) | 263 | 30.9 [27.9; NC]<br>58 (22.1) | 0.84 [0.59; 1.20];<br>0.340[a] |
| Symptoms in arm region | 261 | 10.3 [7.7; 16.7]<br>147 (56.3) | 263 | 5.6 [4.2; 9.0]<br>139 (52.9) | 0.78 [0.62; 0.99];<br>0.037[a] |
| Upset by hair loss | No usable data[c] | | | | |
| **Health status[d] (EQ-5D VAS)** | 261 | 31.5 [21.7; NC]<br>103 (39.5) | 263 | 15.2 [12.0; NC]<br>96 (36.5) | 0.79 [0.59; 1.05];<br>0.105[a] |

Table 4: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine (multipage table)

| Study<br>Outcome category<br>Outcome | Trastuzumab deruxtecan | | Trastuzumab emtansine | | Trastuzumab deruxtecan vs. trastuzumab emtansine |
|---|---|---|---|---|---|
| | 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 |
| **Health-related quality of life** | | | | | |
| **EORTC QLQ-C30**[e] | | | | | |
| Global health status | 261 | 6.9 [4.4; 10.4]<br>157 (60.2) | 263 | 7.2 [5.7; 10.3]<br>137 (52.1) | 1.00 [0.80; 1.27];<br>0.993[a] |
| Physical functioning | 261 | 22.0 [14.5; 31.5]<br>122 (46.7) | 263 | 17.2 [8.3; NA]<br>105 (39.9) | 0.91 [0.70; 1.19];<br>0.487[a] |
| Role functioning | 261 | 11.6 [6.2; 21.7]<br>144 (55.2) | 263 | 6.3 [4.7; 8.9]<br>142 (54.0) | 0.75 [0.59; 0.96];<br>0.019[a] |
| Emotional functioning | 261 | 18.5 [13.0; 24.9]<br>127 (48.7) | 263 | 11.1 [8.4; 17.9]<br>112 (42.6) | 0.78 [0.60; 1.02];<br>0.064[a] |
| Cognitive functioning | 261 | 10.3 [8.6; 14.8]<br>152 (58.2) | 263 | 8.3 [4.8; 10.3]<br>136 (51.7) | 0.78 [0.62; 1.00];<br>0.045[a] |
| Social functioning | 261 | 7.3 [5.6; 11.8]<br>156 (59.8) | 263 | 8.4 [5.8; 11.7]<br>132 (50.2) | 0.99 [0.78; 1.25];<br>0.893[a] |
| **EORTC QLQ-BR23**[e] | | | | | |
| Body image | 261 | 16.6 [10.7; 32.2]<br>127 (48.7) | 263 | 31.2 [13.6; NC]<br>83 (31.6) | 1.34 [1.01; 1.78];<br>0.040[a] |
| Sexual activity | 261 | NA<br>62 (23.8) | 263 | NA<br>57 (21.7) | 0.93 [0.65; 1.34];<br>0.717[a] |
| Enjoyment of sex | No usable data[c] | | | | |
| Future perspective | 261 | 32.5 [28.6; NC]<br>97 (37.2) | 263 | NA [21.2; NC]<br>74 (28.1) | 1.02 [0.75; 1.38];<br>0.917[a] |
| **Side effects** | | | | | |
| AEs (supplementary information)[f] | 257 | 0.1 [NC]<br>256 (99.6) | 261 | 0.2 [0.1; 0.2]<br>249 (95.4) | – |
| SAEs[f] | 257 | NA<br>65 (25.3) | 261 | 27.4 [22.7; NC]<br>58 (22.2) | 0.65 [0.45; 0.95];<br>0.024[g] |
| Severe AEs[f, h] | 257 | 11.0 [7.0; 16.6]<br>145 (56.4) | 261 | 8.0 [4.2; 13.1]<br>135 (51.7) | 0.77 [0.61; 0.98];<br>0.040[g] |
| Discontinuation due to AEs[f] | 257 | NA [38.2; NC]<br>55 (21.4) | 261 | NA<br>24 (9.2) | 1.19 [0.73; 1.94];<br>0.493[g] |
| Cardiac disorders (SOC, severe AEs[h]) | 257 | ND<br>0 (0) | 261 | ND<br>0 (0) | – |
| Platelet count decreased (PT, severe AEs[h]) | 257 | NA<br>20 (7.8) | 261 | NA<br>52 (19.9) | 0.32 [0.19; 0.54];<br>< 0.001[g] |

Table 4: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine (multipage table)

| Study<br>Outcome category<br>Outcome | Trastuzumab deruxtecan | | Trastuzumab emtansine | | Trastuzumab deruxtecan vs. trastuzumab emtansine |
|---|---|---|---|---|---|
| | 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 |
| Gastrointestinal disorders (SOC, AEs) | 257 | 0.1 [0.1; 0.1]<br>239 (93.0) | 261 | 2.8 [1.4; 6.5]<br>152 (58.2) | 2.87 [2.33; 3.54]; < 0.001[g] |
| Skin and subcutaneous tissue disorders (SOC, AEs) | 257 | 6.0 [2.9; 14.3]<br>155 (60.3) | 261 | 15.1 [12.5; NC]<br>77 (29.5) | 2.07 [1.57; 2.72]; < 0.001[g] |
| Nose bleed (PT, AEs) | 257 | NA<br>35 (13.6) | 261 | NA [21.8; NC]<br>46 (17.6) | 0.42 [0.26; 0.66]; < 0.001[g] |
| Pyrexia (PT, AEs) | 257 | NA<br>39 (15.2) | 261 | NA [28.4; NC]<br>42 (16.1) | 0.46 [0.29; 0.74]; < 0.001[g] |
| Malaise (PT, AEs) | 257 | NA<br>30 (11.7) | 261 | NA<br>9 (3.4) | 2.99 [1.41; 6.34]; 0.003[g] |
| General disorders and administration site conditions (SOC, severe AEs[h]) | 257 | NA<br>31 (12.1) | 261 | NA<br>5 (1.9) | 4.23 [1.63; 11.03]; 0.001[g] |
| Neutrophil count decreased (PT, severe AEs[h]) | 257 | NA<br>41 (16.0) | 261 | NA<br>8 (3.1) | 3.90 [1.82; 8.39]; < 0.001[g] |
| White blood cell count decreased (PT, severe AEs[h]) | 257 | NA<br>16 (6.2) | 261 | NA<br>2 (0.8) | 5.48 [1.25; 24.02]; 0.011[g] |
| Alanine aminotransferase increased (PT, severe AEs[h]) | 257 | NA<br>4 (1.6) | 261 | NA<br>12 (4.6) | 0.31 [0.10; 0.96]; 0.031[g] |
| Aspartate aminotransferase increased (PT, severe AEs[h]) | 257 | NA<br>2 (0.8) | 261 | NA<br>14 (5.4) | 0.12 [0.03; 0.55]; 0.001[g] |
| Fatigue (PT, severe AEs[h]) | 257 | NA<br>15 (5.8) | 261 | NA<br>2 (0.8) | 5.28 [1.19; 23.48]; 0.015[g] |
| Nausea (PT, severe AEs[h]) | 257 | NA<br>18 (7.0) | 261 | NA<br>1 (0.4) | 17.02 [2.27; 127.73]; < 0.001[g] |

Table 4: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine (multipage table)

| Study<br>Outcome category<br>Outcome | Trastuzumab deruxtecan | | Trastuzumab emtansine | | Trastuzumab deruxtecan vs. trastuzumab emtansine |
|---|---|---|---|---|---|
| | 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. Hazard ratio calculated using a stratified Cox proportional hazards regression model and the 95% CI using the Wald test. 2-sided p-value based on a stratified log-rank test. Stratification factors were hormone receptor status, prior treatment with pertuzumab, and history of visceral disease.<br>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).<br>c. Unclear proportion of patients with missing values at baseline and in the course of the study; drastic decrease in the proportion of patients in the analysis already by the first documentation time.<br>d. Time to first deterioration. A decrease by ≥ 15 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).<br>e. Time to first deterioration. A decrease by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).<br>f. For outcomes in the category of side effects, the company presented analyses including progression of the underlying disease.<br>g. Hazard ratio calculated using a stratified Cox proportional hazards regression model with treatment as the only categorical variable and the 95% CI using the Wald test. 2-sided p-value based on a stratified log-rank test.<br>h. Operationalized as CTCAE grade ≥ 3.<br>AE: adverse event; AESI: AE of special interest; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; 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; SOC: System Organ Class; VAS: visual analogue scale | | | | |

On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

### Mortality

#### *Overall survival*

A statistically significant difference in favour of trastuzumab deruxtecan was shown for the outcome of overall survival. There is an effect modification by the characteristic of age for this outcome (see Section 2.2.3). A statistically significant difference in favour of trastuzumab deruxtecan was only shown for patients < 65 years of age. For the outcome of overall survival, this results in a hint of an added benefit of trastuzumab deruxtecan in comparison with trastuzumab emtansine for patients < 65 years of age. No statistically significant difference

between treatment groups was found for patients ≥ 65 years. For patients ≥ 65 years, this results in no hint of added benefit of trastuzumab deruxtecan in comparison with trastuzumab emtansine; an added benefit is therefore not proven for these patients.

**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 are described first.

*Nausea and vomiting, appetite loss, diarrhoea*

Statistically significant differences to the disadvantage of trastuzumab deruxtecan were shown for the outcomes of nausea and vomiting, appetite loss and diarrhoea. Consequently, for each of these outcomes, there is a hint of lesser benefit of trastuzumab deruxtecan in comparison with trastuzumab emtansine.

*Symptoms in arm region*

A statistically significant difference in favour of trastuzumab deruxtecan was shown for the outcome of symptoms in arm region. There is an effect modification by the characteristic of baseline visceral disease for this outcome (see Section 2.2.3).

A statistically significant difference in favour of trastuzumab deruxtecan was only shown for patients without baseline visceral disease. For the outcome of symptoms in arm region, this results in a hint of an added benefit of trastuzumab deruxtecan in comparison with trastuzumab emtansine for patients without baseline visceral disease. For patients with baseline visceral disease, in contrast, there was no statistically significant difference between treatment groups. For patients with baseline visceral disease, this results in no hint of added benefit of trastuzumab deruxtecan in comparison with trastuzumab emtansine; an added benefit is therefore not proven for these patients.

*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; the proportion of patients in the analysis already decreased drastically by the first documentation time. This results in no hint of added benefit of trastuzumab deruxtecan in comparison with trastuzumab emtansine; an added benefit is therefore not proven for this outcome.

*Further symptom outcomes*

No statistically significant differences between treatment groups were shown for the outcomes of fatigue, pain, dyspnoea, insomnia, constipation, side effects of systemic

treatment, and symptoms in chest region. This results in no hints of added benefit of trastuzumab deruxtecan in comparison with trastuzumab emtansine; an added benefit is therefore not proven for these outcomes.

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

There was no statistically significant difference between treatment groups for the outcome of health status recorded with the EQ-5D visual analogue scale (VAS). This results in no hint of added benefit of trastuzumab deruxtecan in comparison with trastuzumab emtansine; an added benefit is therefore not proven for this outcome.

**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.

*Role functioning, cognitive functioning*

A significant difference in favour of trastuzumab deruxtecan was shown for the outcome of role functioning. Consequently, for these outcomes, there is a hint of added benefit of trastuzumab deruxtecan in comparison with trastuzumab emtansine.

*Body image*

A statistically significant difference to the disadvantage of trastuzumab deruxtecan was shown for the outcome of body image. Consequently, for this outcome, there is a hint of lesser benefit of trastuzumab deruxtecan in comparison with trastuzumab emtansine.

*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; the proportion of patients in the analysis already decreased drastically by the first documentation time. This results in no hint of added benefit of trastuzumab deruxtecan in comparison with trastuzumab emtansine; an added benefit is therefore not proven for this outcome.

*Further scales on health-related quality of life*

No statistically significant difference between treatment groups was shown for the outcomes of global health status, physical functioning, emotional functioning, social functioning, sexual activity, and future perspective. This results in no hints of added benefit of trastuzumab deruxtecan in comparison with trastuzumab emtansine; an added benefit is therefore not proven for these outcomes.

**Side effects**

***SAEs, severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] ≥ 3)***

A statistically significant difference in favour of trastuzumab deruxtecan was shown for the outcomes of SAEs and severe AEs (CTCAE ≥ 3). Consequently, for these outcomes, there is a hint of lesser harm of trastuzumab deruxtecan in comparison with trastuzumab emtansine.

***Discontinuation due to AEs***

There was no statistically significant difference between treatment groups for the outcome of discontinuation due to AEs. Consequently, there is no hint of greater or lesser harm from trastuzumab deruxtecan in comparison with trastuzumab emtansine; greater or lesser harm is therefore not proven for this outcome.

***Specific AEs***

*Cardiac disorders (severe AEs)*

For the outcome of cardiac disorders (severe AEs), no events occurred in either treatment group. This results in no hint of greater or lesser harm of trastuzumab deruxtecan in comparison with trastuzumab emtansine; an added benefit is therefore not proven for this outcome.

*Platelet count decreased (severe AEs)*

A statistically significant difference in favour of trastuzumab deruxtecan was shown for the outcome of platelet count decreased (severe AEs). Consequently, for this outcome, there is a hint of lesser harm of trastuzumab deruxtecan in comparison with trastuzumab emtansine.

*General disorders and administration site conditions (severe AEs), neutrophil count decreased (severe AEs), white blood cell count decreased (severe AEs), fatigue (severe AEs), nausea (severe AEs)*

Statistically significant differences to the disadvantage of trastuzumab deruxtecan were shown for the outcomes of general disorders and administration site conditions (severe AEs), neutrophil count decreased (severe AEs), white blood cell count decreased (severe AEs), fatigue (severe AEs), and nausea (severe AEs). Consequently, for each of these outcomes, there is a hint of greater harm of trastuzumab deruxtecan in comparison with trastuzumab emtansine.

*Alanine aminotransferase increased (severe AEs), aspartate aminotransferase increased (severe AEs)*

Statistically significant differences in favour of trastuzumab deruxtecan were shown for the outcomes of alanine aminotransferase increased (severe AEs) and aspartate aminotransferase increased (severe AEs). Consequently, for these outcomes, there is a hint of lesser harm of trastuzumab deruxtecan in comparison with trastuzumab emtansine.

*Gastrointestinal disorders (AEs), skin and subcutaneous tissue disorders (AEs), malaise (AEs)*

Statistically significant differences to the disadvantage of trastuzumab deruxtecan were shown for the outcomes of gastrointestinal disorders (AEs), skin and subcutaneous tissue disorders (AEs), and malaise (AEs). Consequently, for each of these outcomes, there is a hint of greater harm of trastuzumab deruxtecan in comparison with trastuzumab emtansine.

*Nose bleed (AEs), pyrexia (AEs)*

Statistically significant differences in favour of trastuzumab deruxtecan were shown for the outcomes of nose bleed (AEs) and pyrexia (AEs). Consequently, for these outcomes, there is a hint of lesser harm of trastuzumab deruxtecan in comparison with trastuzumab emtansine.

### 2.2.3 Subgroups and other effect modifiers

Analogous to the benefit assessment, the following subgroup characteristics are considered in the present addendum:

- 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. For binary data, there must also 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 only presented if there is a statistically significant and relevant effect in at least one subgroup.

The results are presented in Table 5. The Kaplan-Meier curves on the subgroup results can be found in Appendix A.

Table 5: Subgroups (mortality, morbidity) – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine

| Study<br>Outcome | Trastuzumab deruxtecan | | Trastuzumab emtansine | | Trastuzumab deruxtecan vs. trastuzumab emtansine | |
|---|---|---|---|---|---|---|
| Characteristic<br>Subgroup | 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][a] | p-value[b] |
| **DESTINY-Breast03, data cut-off of 25 July 2022** | | | | | | |
| **Mortality** | | | | | | |
| Age | | | | | | |
| < 65 years | 212 | NA [40.5; NC]<br>55 (25.9) | 206 | 37.7 [30.7; NC]<br>81 (39.3) | 0.54 [0.39; 0.77] | < 0.001 |
| ≥ 65 years | 49 | NA [26.3; NC]<br>17 (34.7) | 57 | NA<br>16 (28.1) | 1.29 [0.65; 2.56] | 0.463 |
| Total | | | | | Interaction: | 0.026[c] |
| **Morbidity** | | | | | | |
| **Symptoms (EORTC QLQ-BR23)[d]** | | | | | | |
| Symptoms in arm region | | | | | | |
| Baseline visceral disease | | | | | | |
| Yes | 195 | 9.5 [7.0; 15.9]<br>114 (58.5) | 189 | 6.9 [4.4; 13.8]<br>91 (48.1) | 0.89 [0.68; 1.18] | 0.430 |
| No | 66 | 12.5 [7.2; NA]<br>33 (50.0) | 74 | 4.2 [2.8; 6.7]<br>48 (64.9) | 0.56 [0.36; 0.87] | 0.009 |
| Total | | | | | Interaction: | 0.036[c] |

a. Unstratified Cox proportional hazards regression model per subgroup with treatment as a factor.
b. Unstratified log-rank test.
c. Interaction test from Cox proportional hazards regression model with treatment, subgroup and interaction term between treatment and subgroup.
d. Time to first deterioration. A score increase by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module 23; RCT: randomized controlled trial

## Mortality

### *Overall survival*

There is an effect modification by the characteristic of age for the outcome of overall survival.

A statistically significant difference in favour of trastuzumab deruxtecan was shown for the age group < 65 years of age. For the outcome of overall survival, this results in a hint of an

added benefit of trastuzumab deruxtecan in comparison with trastuzumab emtansine for patients < 65 years of age.

No statistically significant difference between treatment groups was found for patients ≥ 65 years. For patients ≥ 65 years, this results in no hint of added benefit of trastuzumab deruxtecan in comparison with trastuzumab emtansine; an added benefit is therefore not proven for these patients.

**Morbidity**

***Symptoms (EORTC QLQ-BR23)***

*Symptoms in arm region*

For the outcome of symptoms in arm region, there is an effect modification by the characteristic of baseline visceral disease.

A statistically significant difference in favour of trastuzumab deruxtecan was shown for patients without baseline visceral disease. For the outcome of symptoms in arm region, this results in a hint of an added benefit of trastuzumab deruxtecan in comparison with trastuzumab emtansine for patients without baseline visceral disease.

For patients with baseline visceral disease, in contrast, there was no statistically significant difference between treatment groups. For patients with baseline visceral disease, this results in no hint of added benefit of trastuzumab deruxtecan in comparison with trastuzumab emtansine; an added benefit is therefore not proven for these patients.

## 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 [5].

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 added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Sections 2.2.2 and 2.2.3 (see Table 6).

Table 6: Extent of added benefit at outcome level: trastuzumab deruxtecan vs. trastuzumab emtansine (multipage table)

| **Outcome category**<br>**Outcome**<br>**Effect modifier**<br>**Subgroup** | **Trastuzumab deruxtecan vs. trastuzumab emtansine**<br>**Median time to event (months)**<br>**Effect estimation [95% CI]**<br>**p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| **Total observation period** | | |
| **Mortality** | | |
| Overall survival<br>Age<br>< 65 years | NA vs. 37.7<br>HR: 0.54 [0.39; 0.77]<br>p < 0.001<br>Probability: "hint" | Outcome category: mortality<br>$CI_u$ < 0.85<br>Added benefit, extent: "major" |
| ≥ 65 years | NA vs. NA<br>HR: 1.29 [0.65; 2.56]<br>p = 0.463 | Lesser/added benefit not proven |
| **Shortened observation period** | | |
| **Morbidity** | | |
| **Symptoms (EORTC QLQ-C30)**[c] | | |
| Fatigue | 5.6 vs. 3.6<br>HR: 0.83 [0.67; 1.04];<br>p = 0.103 | Lesser/added benefit not proven |
| Nausea and vomiting | 2.8 vs. 9.7<br>HR: 1.99 [1.58; 2.51]<br>HR: 0.50 [0.40; 0.63][d]<br>p < 0.001<br>Probability: "hint" | Outcome category: non-serious/non-severe symptoms/late complications<br>$CI_u$ < 0.80<br>Lesser benefit, extent: "considerable" |
| Pain | 8.5 vs. 6.9<br>HR: 0.88 [0.70; 1.12]<br>p = 0.297 | Lesser/added benefit not proven |
| Dyspnoea | 23.3 vs. 15.2<br>HR: 0.85 [0.65; 1.12]<br>p = 0.237 | Lesser/added benefit not proven |
| Insomnia | 19.4 vs. 12.7<br>HR: 0.89 [0.69; 1.15]<br>p = 0.367 | Lesser/added benefit not proven |

Table 6: Extent of added benefit at outcome level: trastuzumab deruxtecan vs. trastuzumab emtansine (multipage table)

| **Outcome category**<br>**Outcome**<br>**Effect modifier**<br>**Subgroup** | **Trastuzumab deruxtecan vs. trastuzumab emtansine**<br>**Median time to event (months)**<br>**Effect estimation [95% CI]**<br>**p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| Appetite loss | 4.2 vs. 10.3<br>HR: 1.41 [1.11; 1.79]<br>HR: 0.71 [0.56; 0.90][d]<br>p = 0.006 | Outcome category: non-serious/non-severe symptoms/late complications<br>$0.90 \leq CI_u < 1.00$<br>Lesser/added benefit not proven[e] |
| Constipation | 5.6 vs. 8.5<br>HR: 1.24 [0.98; 1.57]<br>p = 0.077 | Lesser/added benefit not proven |
| Diarrhoea | 27.6 vs. NA<br>HR: 1.69 [1.24; 2.29]<br>HR: 0.59 [0.44; 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" |
| **Symptoms (EORTC QLQ-BR23)**[c] | | |
| Side effects of systemic therapy | 5.7 vs. 11.7<br>HR: 1.23 [0.97; 1.58]<br>p = 0.094 | Lesser/added benefit not proven |
| Symptoms in chest region | NA vs. 30.9<br>HR: 0.84 [0.59; 1.20]<br>p = 0.340 | Lesser/added benefit not proven |
| Symptoms in arm region<br>Baseline visceral disease<br>Yes | 9.5 vs. 6.9<br>HR: 0.89 [0.68; 1.18]<br>p = 0.430 | Lesser/added benefit not proven |
| No | 12.5 vs. 4.2<br>HR: 0.56 [0.36; 0.87]<br>p = 0.009<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" |
| Upset by hair loss | No usable data | Lesser/added benefit not proven |

Table 6: Extent of added benefit at outcome level: trastuzumab deruxtecan vs. trastuzumab emtansine (multipage table)

| **Outcome category**<br>**Outcome**<br>**Effect modifier**<br>**Subgroup** | **Trastuzumab deruxtecan vs. trastuzumab emtansine**<br>**Median time to event (months)**<br>**Effect estimation [95% CI]**<br>**p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| **Health status** | | |
| EQ-5D VAS[f] | 31.5 vs. 15.2<br>HR: 0.79 [0.59; 1.05]<br>p = 0.105 | Lesser/added benefit not proven |
| **Health-related quality of life** | | |
| **EORTC QLQ-C30**[g] | | |
| Global health status | 6.9 vs. 7.2<br>HR: 1.00 [0.80; 1.27]<br>p = 0.993 | Lesser/added benefit not proven |
| Physical functioning | 22.0 vs. 17.2<br>HR: 0.91 [0.70; 1.19]<br>p = 0.487 | Lesser/added benefit not proven |
| Role functioning | 11.6 vs. 6.3<br>HR: 0.75 [0.59; 0.96]<br>p = 0.019<br>Probability: “hint” | Outcome category: health-related quality of life<br>$0.90 \leq CI_u < 1.00$<br>Added benefit, extent: “minor” |
| Emotional functioning | 18.5 vs. 11.1<br>HR: 0.78 [0.60; 1.02]<br>p = 0.064 | Lesser/added benefit not proven |
| Cognitive functioning | 10.3 vs. 8.3<br>HR: 0.78 [0.62; 1.00]<br>p = 0.045<br>Probability: “hint” | Outcome category of health-related quality of life<br>$0.90 \leq CI_u < 1.00$<br>Added benefit, extent: “minor” |
| Social functioning | 7.3 vs. 8.4<br>HR: 0.99 [0.78; 1.25]<br>p = 0.893 | Lesser/added benefit not proven |
| **EORTC QLQ-BR23**[g] | | |
| Body image | 16.6 vs. 31.2<br>HR: 1.34 [1.01; 1.78]<br>HR: 0.75 [0.56; 0.99][d]<br>p = 0.040<br>Probability: “hint” | Outcome category: health-related quality of life<br>$0.90 \leq CI_u < 1.00$<br>Lesser benefit, extent: “minor” |
| Sexual activity | NA vs. NA<br>HR: 0.93 [0.65; 1.34]<br>p = 0.717 | Lesser/added benefit not proven |
| Enjoyment of sex | No usable data | Lesser/added benefit not proven |

Table 6: Extent of added benefit at outcome level: trastuzumab deruxtecan vs. trastuzumab emtansine (multipage table)

| **Outcome category**<br>**Outcome**<br>**Effect modifier**<br>**Subgroup** | **Trastuzumab deruxtecan vs. trastuzumab emtansine**<br>**Median time to event (months)**<br>**Effect estimation [95% CI]**<br>**p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| Future perspective | 32.5 vs. NA<br>HR: 1.02 [0.75; 1.38]<br>p = 0.917 | Lesser/added benefit not proven |
| **Side effects** | | |
| SAEs | NA vs. 27.4<br>HR: 0.65 [0.45; 0.95]<br>p = 0.024<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. 8.0<br>HR: 0.77 [0.61; 0.98]<br>p = 0.040<br>Probability: "hint" | Outcome category: serious/severe side effects<br>$0.90 \leq CI_u < 1.00$<br>Lesser harm; extent: "minor" |
| Discontinuation due to AEs | NA vs. NA<br>HR: 1.19 [0.73; 1.94]<br>p = 0.493 | Greater/lesser harm not proven |
| Cardiac disorders (severe AEs) | ND vs. ND<br>HR: NC<br>p = NC | Greater/lesser harm not proven |
| Platelet count decreased (severe AEs) | NA vs. NA<br>HR: 0.32 [0.19; 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" |
| Gastrointestinal disorders (AEs) | 0.1 vs. 2.8<br>HR: 2.87 [2.33; 3.54]<br>HR: 0.35 [0.28; 0.43][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" |
| Skin and subcutaneous tissue disorders (AEs) | 6.0 vs. 15.1<br>HR: 2.07 [1.57; 2.72]<br>HR: 0.48 [0.37; 0.64][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" |
| Nose bleed (AEs) | NA vs. NA<br>HR: 0.42 [0.26; 0.66]<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" |

Table 6: Extent of added benefit at outcome level: trastuzumab deruxtecan vs. trastuzumab emtansine (multipage table)

| **Outcome category**<br>**Outcome**<br>**Effect modifier**<br>**Subgroup** | **Trastuzumab deruxtecan vs. trastuzumab emtansine**<br>**Median time to event (months)**<br>**Effect estimation [95% CI]**<br>**p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| Pyrexia (AEs) | NA vs. NA<br>HR: 0.46 [0.29; 0.74]<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" |
| Malaise (AEs) | NA vs. NA<br>HR: 2.99 [1.41; 6.34]<br>HR: 0.33 [0.16; 0.71][d]<br>p = 0.003<br>Probability: "hint" | Outcome category: non-serious/non-severe side effects<br>$CI_u$ < 0.80<br>Greater harm, extent: "considerable" |
| General disorders and administration site conditions (severe AEs) | NA vs. NA<br>HR: 4.23 [1.63; 11.03]<br>HR: 0.24 [0.09; 0.61][d]<br>p = 0.001<br>Probability: "hint" | Outcome category: serious/severe side effects<br>$CI_u$ < 0.75, risk ≥ 5%<br>Greater harm, extent: "major" |
| Neutrophil count decreased (severe AEs) | NA vs. NA<br>HR: 3.90 [1.82; 8.39]<br>HR: 0.26 [0.12; 0.55][d]<br>p < 0.001<br>Probability: "hint" | Outcome category: serious/severe side effects<br>$CI_u$ < 0.75, risk ≥ 5%<br>Greater harm, extent: "major" |
| White blood cell count decreased (severe AEs) | NA vs. NA<br>HR: 5.48 [1.25; 24.02]<br>HR: 0.18 [0.04; 0.80][d]<br>p = 0.011<br>Probability: "hint" | Outcome category: serious/severe side effects<br>0.75 ≤ $CI_u$ < 0.90<br>Greater harm, extent: "considerable" |
| Alanine aminotransferase increased (severe AEs) | NA vs. NA<br>HR: 0.31 [0.10; 0.96]<br>p = 0.031<br>Probability: "hint" | Outcome category: serious/severe side effects<br>0.90 ≤ $CI_u$ < 1.00<br>Lesser harm, extent: "minor" |
| Aspartate aminotransferase increased (severe AEs) | NA vs. NA<br>HR: 0.12 [0.03; 0.55]<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" |
| Fatigue (severe AEs) | NA vs. NA<br>HR: 5.28 [1.19; 23.48]<br>HR: 0.19 [0.04; 0.84][d]<br>p = 0.015<br>Probability: "hint" | Outcome category: serious/severe side effects<br>0.75 ≤ $CI_u$ < 0.90<br>Greater harm, extent: "considerable" |

Table 6: Extent of added benefit at outcome level: trastuzumab deruxtecan vs. trastuzumab emtansine (multipage table)

| **Outcome category**<br>**Outcome**<br>**Effect modifier**<br>**Subgroup** | **Trastuzumab deruxtecan vs. trastuzumab emtansine**<br>**Median time to event (months)**<br>**Effect estimation [95% CI]**<br>**p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| Nausea (severe AEs) | NA vs. NA<br>HR: 17.02 [2.27; 127.73]<br>HR: 0.06 [0.01; 0.44][d]<br>p < 0.001<br>Probability: "hint" | Outcome category: serious/severe side effects<br>$CI_u$ < 0.75, risk ≥ 5%<br>Greater harm, extent: "major" |

a. Probability provided if there is a statistically significant and relevant effect.
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 ($CI_u$).
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).
d. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
f. Time to first deterioration. A decrease by ≥ 15 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
g. Time to first deterioration. A decrease by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).

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

Table 7: Positive and negative effects from the assessment of trastuzumab deruxtecan in comparison with trastuzumab emtansine

| **Positive effects** | **Negative effects** |
|---|---|
| **Total observation period** | |
| Mortality<br>▪ Overall survival<br>▫ Age (< 65 years): hint of added benefit – extent: "major" | |
| **Shortened observation period** | |
| Non-serious/non-severe symptoms/late complications<br>Symptoms (EORTC QLQ-BR23)<br>▪ Symptoms in arm region<br>▫ Baseline visceral disease (no): hint of an added benefit – extent: "minor" | Non-serious/non-severe symptoms/late complications<br>Symptoms (EORTC QLQ-C30)<br>▪ Nausea and vomiting: hint of lesser benefit – extent: "considerable"<br>▪ Diarrhoea: hint of lesser benefit – extent: "minor" |
| Health-related quality of life<br>EORTC QLQ-C30<br>▪ Role functioning, cognitive functioning: hint of an added benefit – extent: "minor" | Health-related quality of life<br>EORTC QLQ-BR23<br>▪ Body image: hint of lesser benefit – extent: "minor" |
| Serious/severe side effects<br>▪ SAEs, severe AEs: hint of lesser harm – extent: "minor"<br>▪ Platelet count decreased, aspartate aminotransferase increased (each severe AEs): hint of lesser harm – extent: "major"<br>▪ Alanine aminotransferase increased (severe AE): hint of lesser harm – extent: "minor" | Serious/severe side effects<br>▪ General disorders and administration site conditions, neutrophil count decreased, nausea (severe AEs for each): hint of greater harm – extent: "major"<br>▪ White blood cell count decreased, fatigue (each severe AEs): hint of greater harm – extent: "considerable" |
| Non-serious/non-severe side effects<br>▪ Nose bleed, pyrexia (severe AEs for each): hint of lesser harm – extent: "considerable" | Non-serious/non-severe side effects<br>▪ Gastrointestinal disorders, skin and subcutaneous tissue disorders, malaise (AEs for each): hint of greater harm – extent: "considerable" |
| 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 | |

Overall, the second data cut-off showed both positive and negative effects of trastuzumab deruxtecan in comparison with trastuzumab emtansine (hints in each case).

On the side of the positive effects, there is a hint of major added benefit for the outcome of overall survival for patients < 65 years of age. For patients ≥ 65 years of age, the added benefit is not proven. Due to the effect modification in the outcome of overall survival, the added benefit is derived separately according to age.

For the other outcome categories, both positive and negative effects of trastuzumab deruxtecan are shown with varying, in part major, extent (hints in each case). Overall, the

negative effects do not call into question the major added benefit in the outcome of overall survival.

In summary, for patients < 65 years of age with unresectable or metastatic HER2-positive breast cancer who have received one anti-HER2-based regimen, there is a hint of major added benefit of trastuzumab deruxtecan in comparison with the appropriate comparator therapy trastuzumab emtansine. For patients ≥ 65 years of age, an added benefit of trastuzumab deruxtecan in comparison with the appropriate comparator therapy trastuzumab emtansine is not proven.

## 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 A22-80: For patients < 65 years of age, there is a hint of major added benefit of major added benefit of trastuzumab deruxtecan in comparison with the appropriate comparator therapy trastuzumab emtansine on the basis of the results of the second data cut-off. For patients ≥ 65 years of age, the added benefit is still not proven.

Table 8 below shows the result of the benefit assessment of trastuzumab deruxtecan, taking into account dossier assessment A22-80 and the present addendum.

Table 8: Trastuzumab deruxtecan – probability and extent of added benefit

| **Therapeutic indication** | **ACT[a]** | **Probability and extent of added benefit** |
|---|---|---|
| Patients with unresectable or metastatic HER2-positive breast cancer who have previously received one HER2-targeted therapy[b, c, d] | Trastuzumab emtansine | ▪ Patients < 65 years: hint of major added benefit<br>▪ Patients ≥ 65 years: added benefit not proven |

a. Presented is the respective ACT specified by the GBA.
b. Only patients with an ECOG PS of 0 or 1 were included in the DESTINY-Breast03 study. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2.
c. Only patients whose prior therapy comprised a taxane were included in the DESTINY-Breast03 study. It remains unclear whether the observed effects are transferable to patients who have not received a taxane.
d. According to the G-BA, it is assumed that, at the time of the treatment decision, endocrine therapy is not an option for patients with hormone receptor-positive breast cancer. Moreover, it is assumed that (secondary) resection or radiotherapy with curative intent is not indicated.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2

The G-BA decides on the added benefit.

## 3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Trastuzumab Deruxtecan (Mammakarzinom, nach 1 Vortherapie) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2022 [Accessed: 02.11.2022]. URL: https://www.iqwig.de/download/a22-80_trastuzumab-deruxtecan_nutzenbewertung-35a-sgb-v_v1-0.pdf.

2. Daiichi Sankyo Deutschland. Stellungnahme zum IQWiG-Bericht Nr. 1450: Trastuzumab Deruxtecan (Mammakarzinom, nach 1 Vortherapie). 2022: [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/864/#beschluesse in the document "Zusammenfassende Dokumentation"].

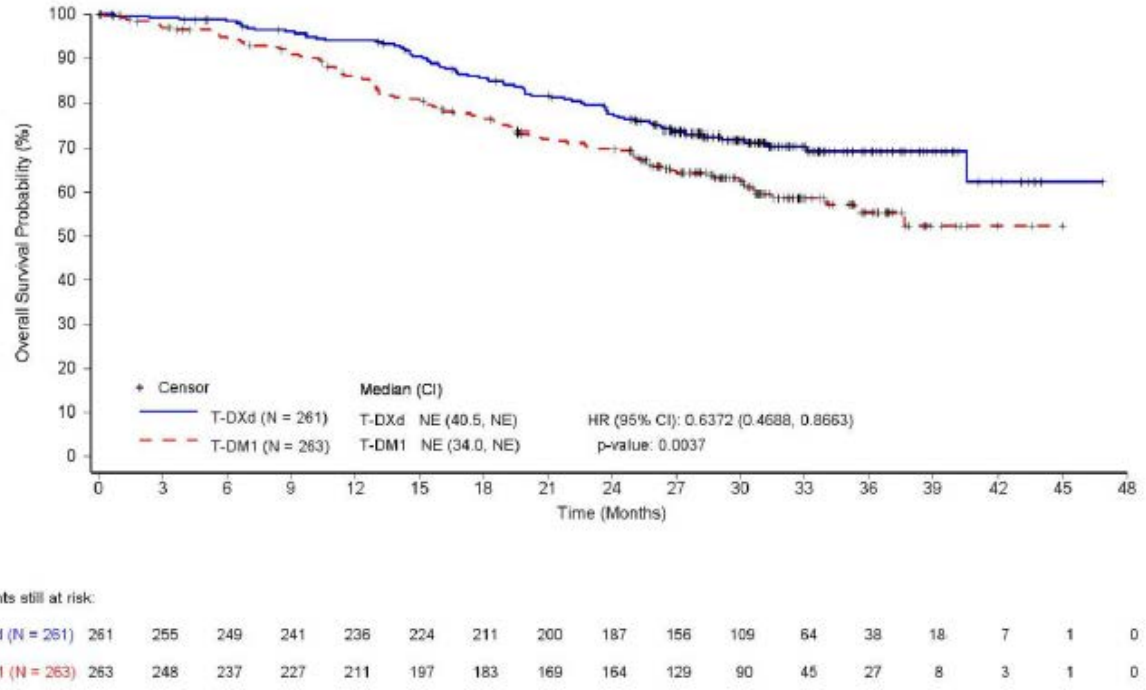
3. Daiichi Sankyo Deutschland. Trastuzumab-Deruxtecan (Enhertu); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2022 [Accessed: 02.11.2022]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/864/#dossier.

4. Daiichi Sankyo Deutschland. Trastuzumab-Deruxtecan (Enhertu); Dossier zur Nutzenbewertung – Modul 4 A; Stand: 21.11.2022; study DESTINY-Breast03; Zusatzanalysen [unpublished]. 2022.

5. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.1 [online]. 2022 [Accessed: 17.08.2022]. URL: https://www.iqwig.de/methoden/general-methods_version-6-1.pdf.

# 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 = 261) | 261 | 255 | 249 | 241 | 236 | 224 | 211 | 200 | 187 | 156 | 109 | 64 | 38 | 18 | 7 | 1 | 0 |
| T-DM1 (N = 263) | 263 | 248 | 237 | 227 | 211 | 197 | 183 | 169 | 164 | 129 | 90 | 45 | 27 | 8 | 3 | 1 | 0 |

Figure 1: Kaplan-Meier curve, outcome of overall survival

## A.2 Morbidity

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

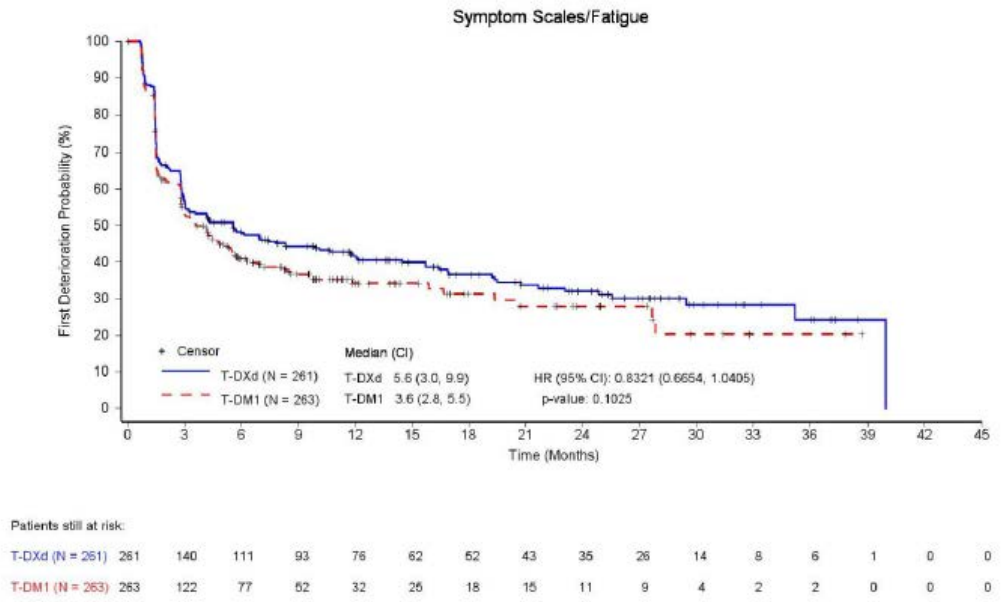



Figure 2: Kaplan-Meier curve for symptoms, outcome of fatigue (EORTC QLQ-C30, first deterioration by ≥ 10 points)

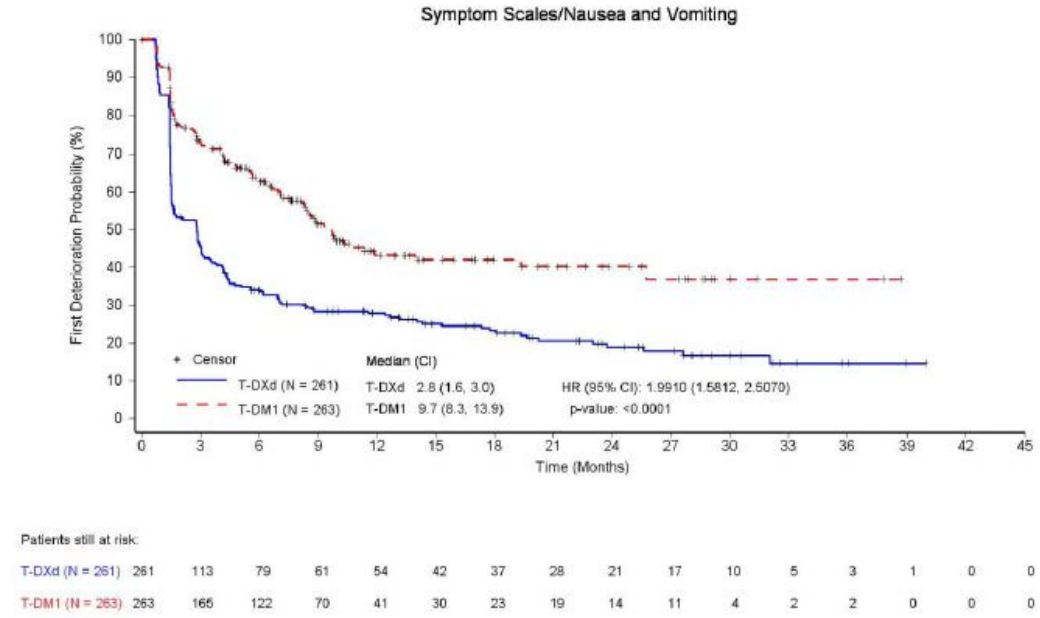



Figure 3: Kaplan-Meier curve for symptoms, outcome auf nausea and vomiting (EORTC QLQ-C30, first deterioration by ≥ 10 points)

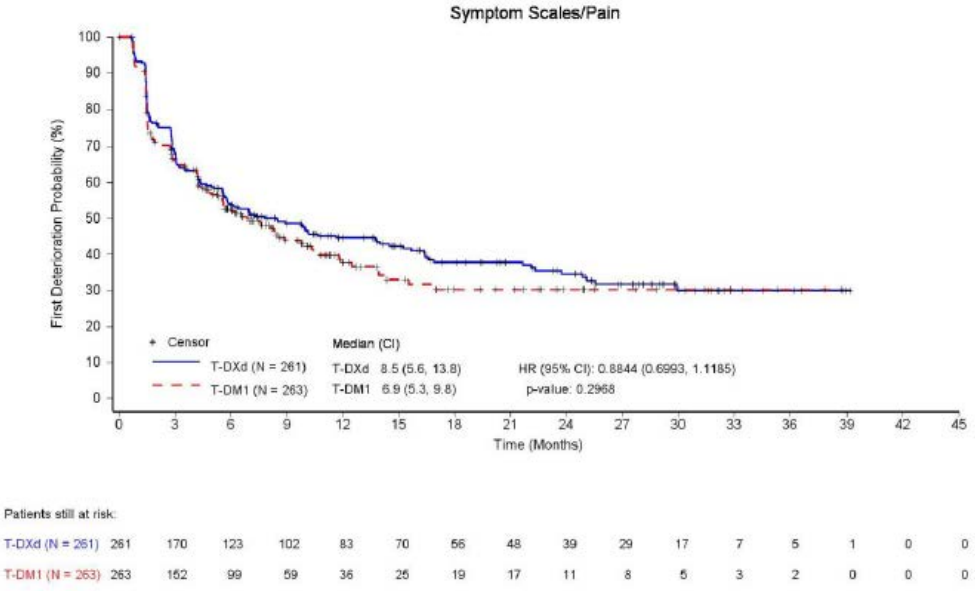



Figure 4: Kaplan-Meier curve for symptoms, outcome of pain (EORTC QLQ-C30, first deterioration by ≥ 10 points)

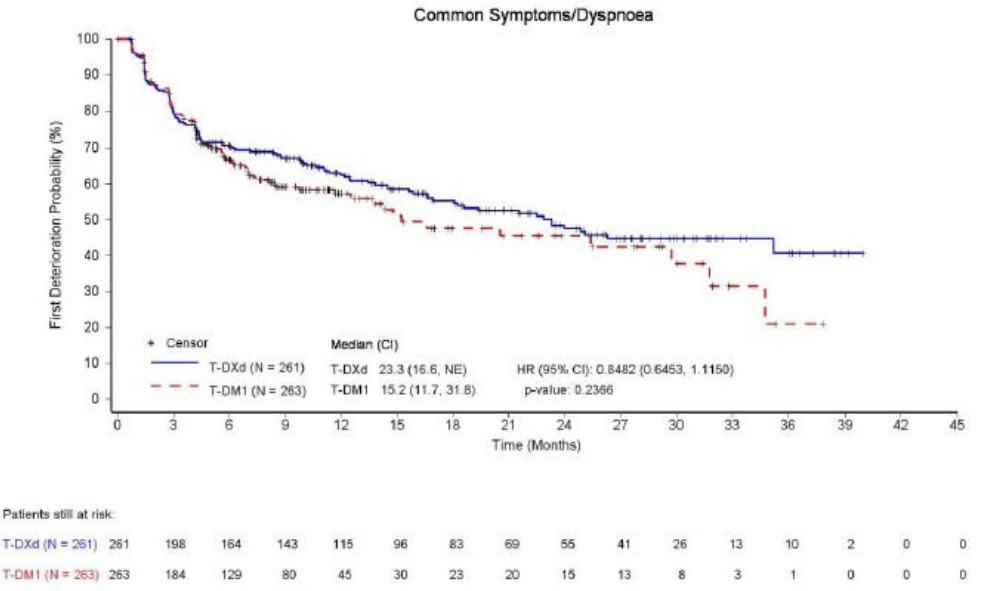



Figure 5: Kaplan-Meier curve for symptoms, outcome of dyspnoea (EORTC QLQ-C30, first deterioration by ≥ 10 points)

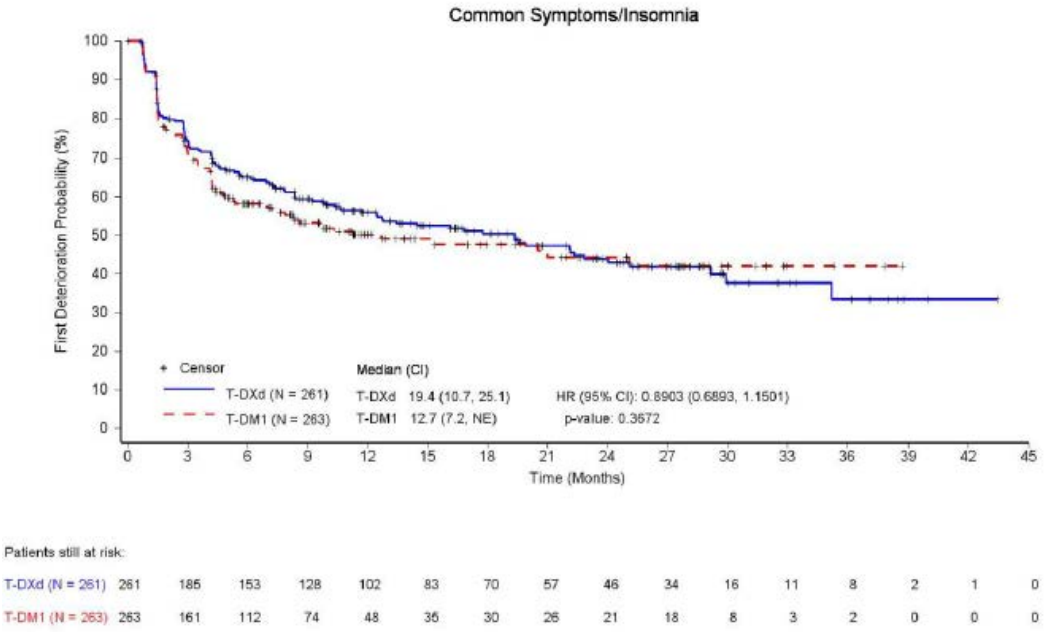



Figure 6: Kaplan-Meier curve for symptoms, outcome of insomnia (EORTC QLQ-C30, first deterioration by ≥ 10 points)

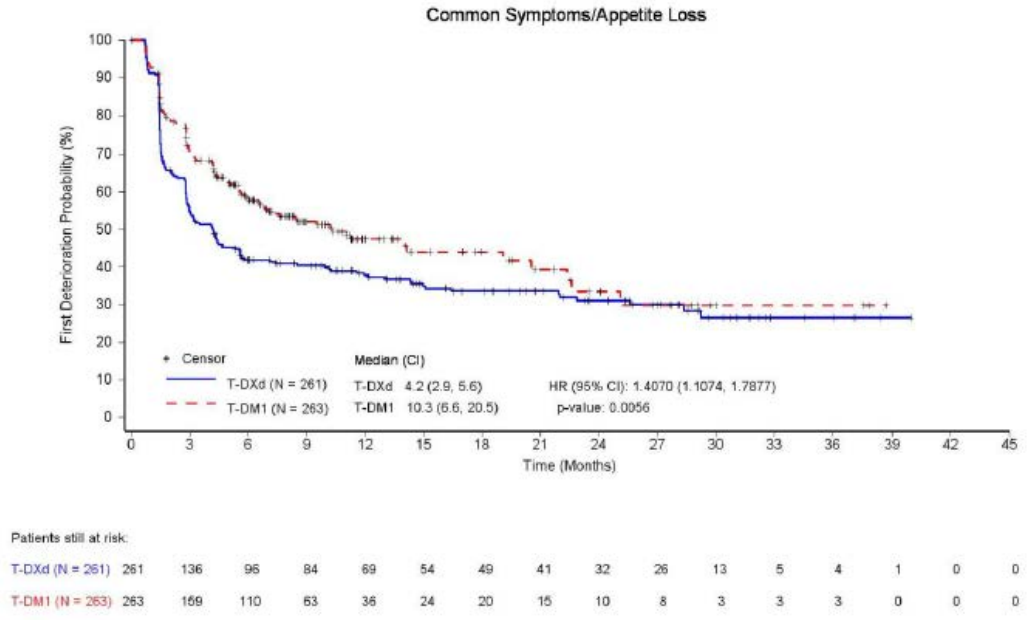



Figure 7: Kaplan-Meier curve for symptoms, outcome of appetite loss (EORTC QLQ-C30, first deterioration by ≥ 10 points)

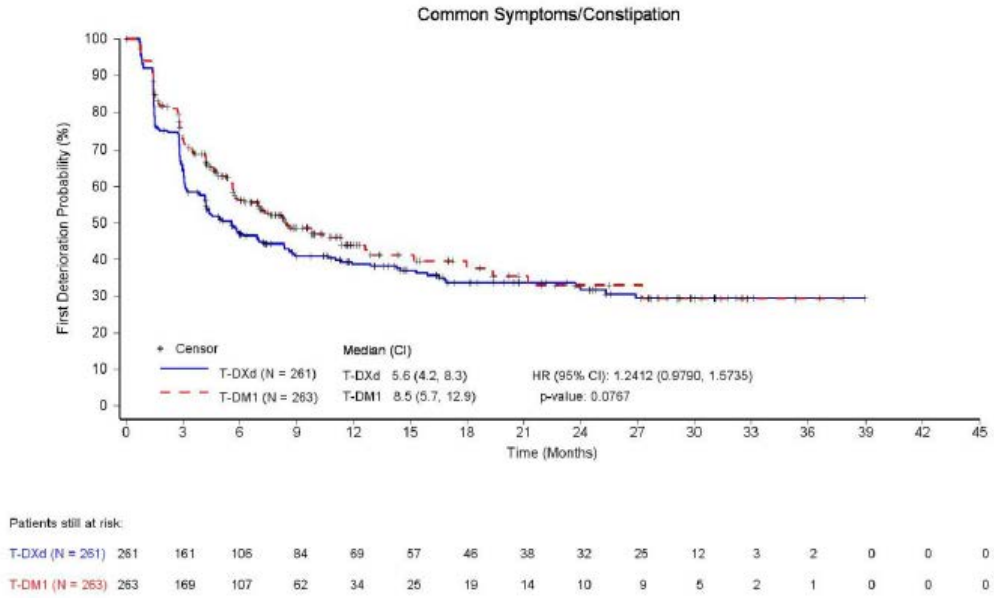



Figure 8: Kaplan-Meier curve for symptoms, outcome of constipation (EORTC QLQ-C30, first deterioration by ≥ 10 points)

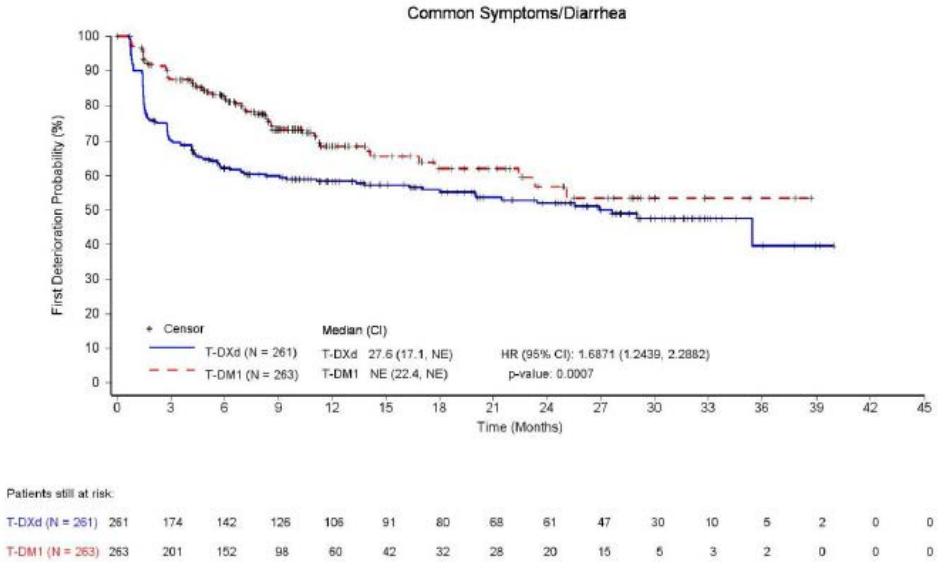



Figure 9: Kaplan-Meier curve for symptoms, outcome of diarrhoea (EORTC QLQ-C30, first deterioration by ≥ 10 points)

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

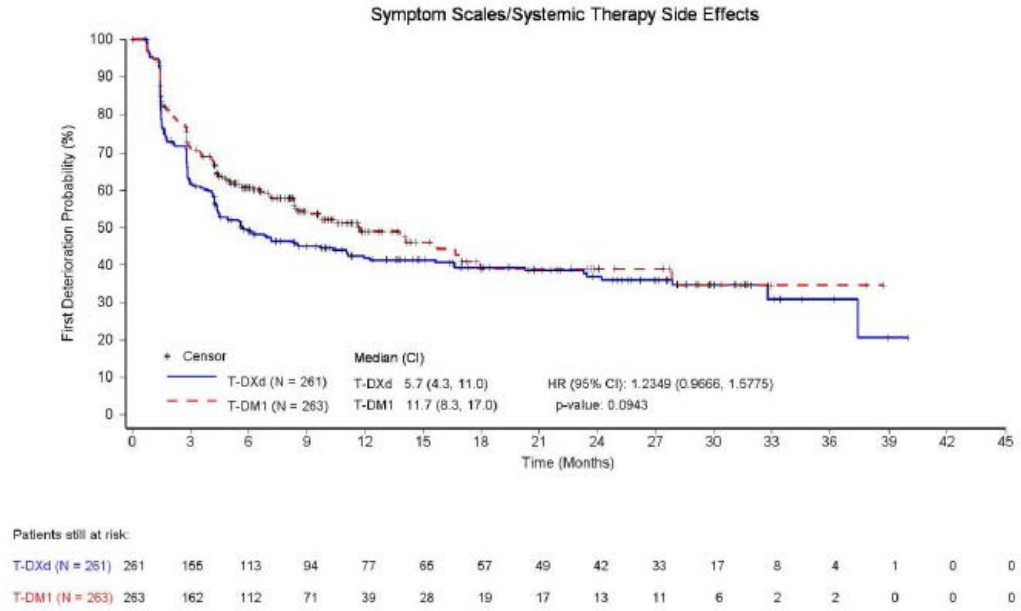



Figure 10: Kaplan-Meier curve for symptoms, outcome of side effects of systemic therapy (EORTC QLQ-BR23, first deterioration by ≥ 10 points)

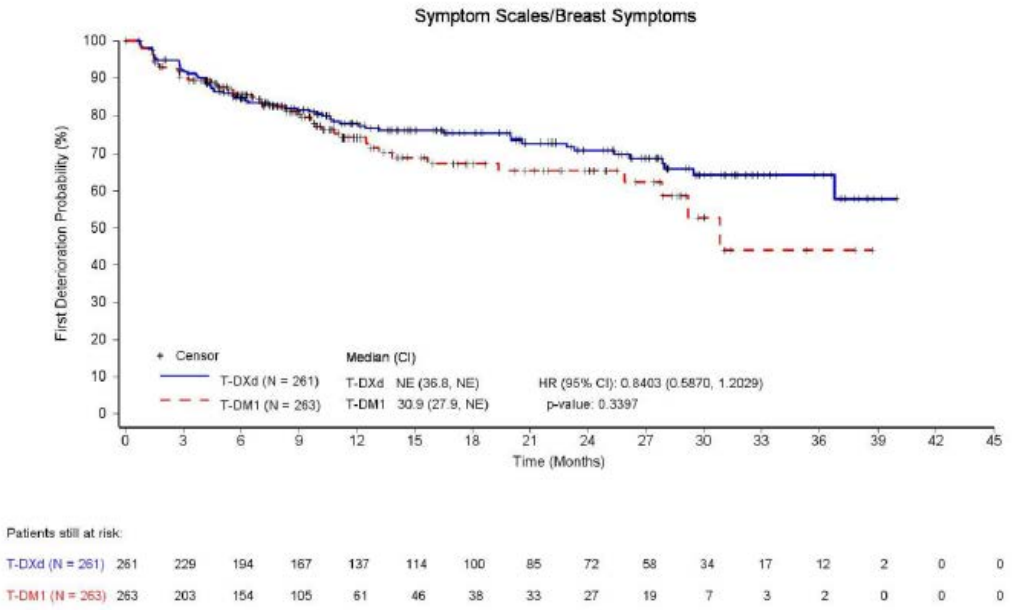



Figure 11: Kaplan-Meier curve for symptoms, outcome of symptoms in chest region (EORTC QLQ-BR23, first deterioration by ≥ 10 points)

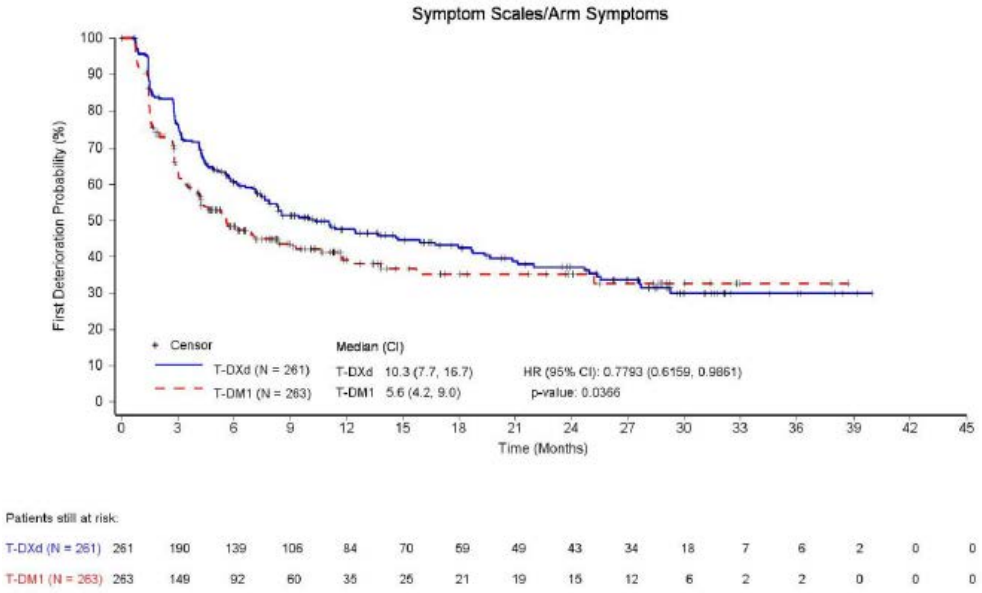



Figure 12: Kaplan-Meier curve for symptoms, outcome of symptoms in arm region (EORTC QLQ-BR23, first deterioration by ≥ 10 points)

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

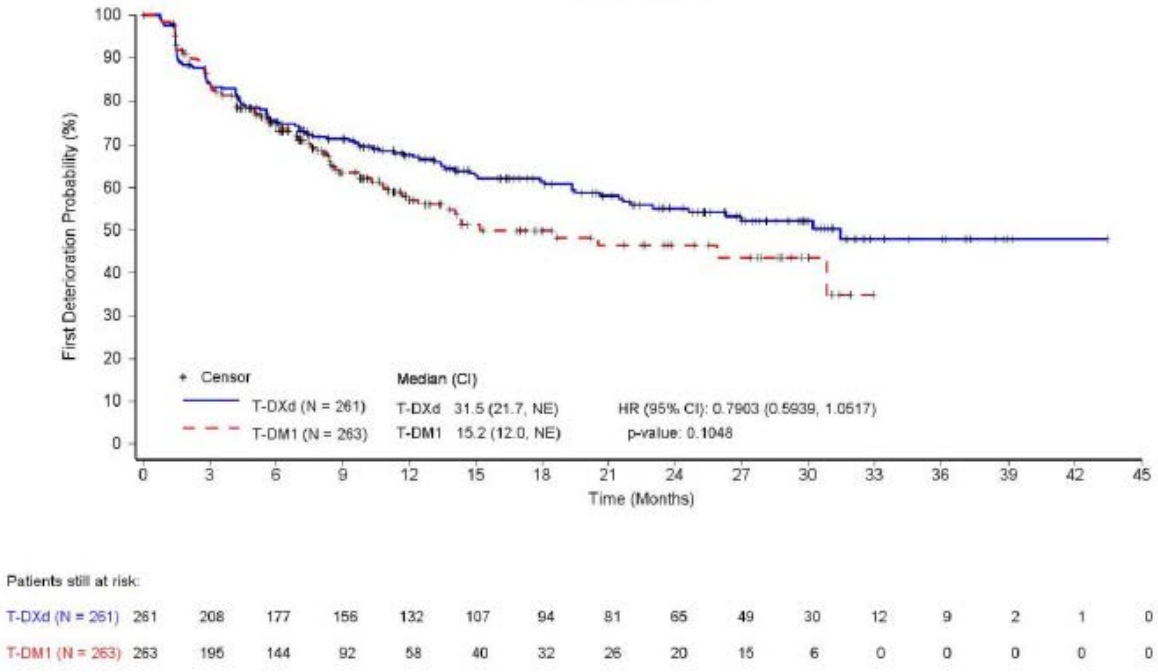



Figure 13: Kaplan-Meier curve, outcome of health status (EQ-5D VAS, first deterioration by ≥ 15 points)

## A.3 Health-related quality of life

### A.3.1 EORTC QLQ-C30

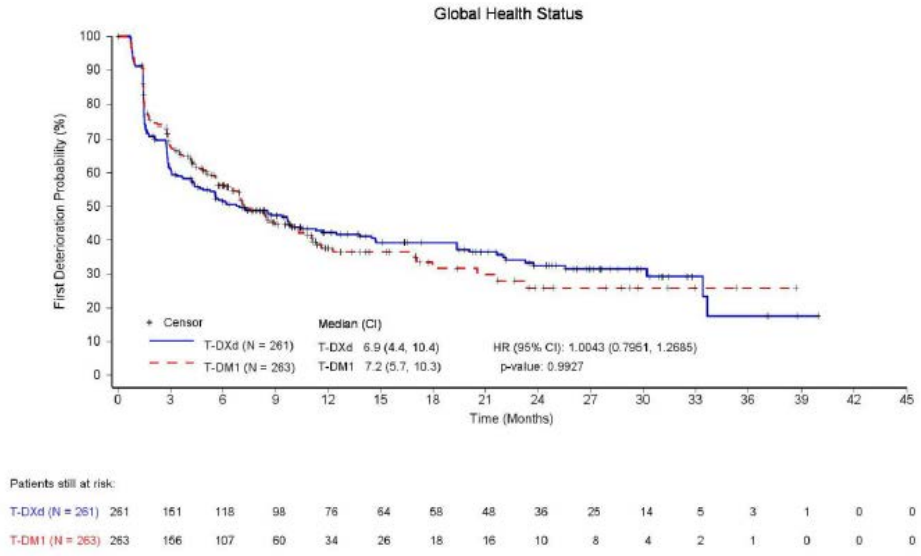



Figure 14: Kaplan-Meier curve for health-related quality of life, outcome of global health status (EORTC QLQ-C30, first deterioration by ≥ 10 points)

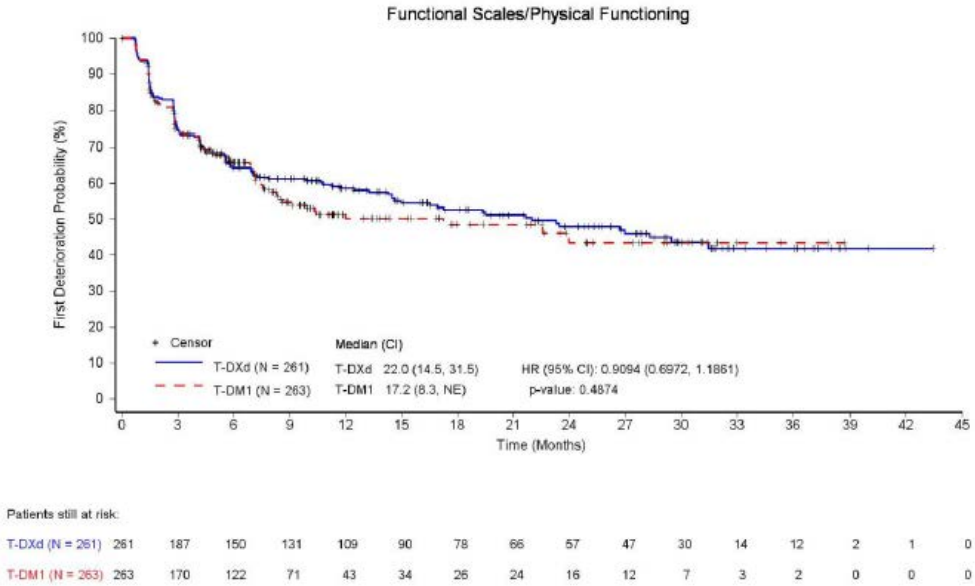



Figure 15: Kaplan-Meier curve for health-related quality of life, outcome of physical functioning (EORTC QLQ-C30, first deterioration by ≥ 10 points)

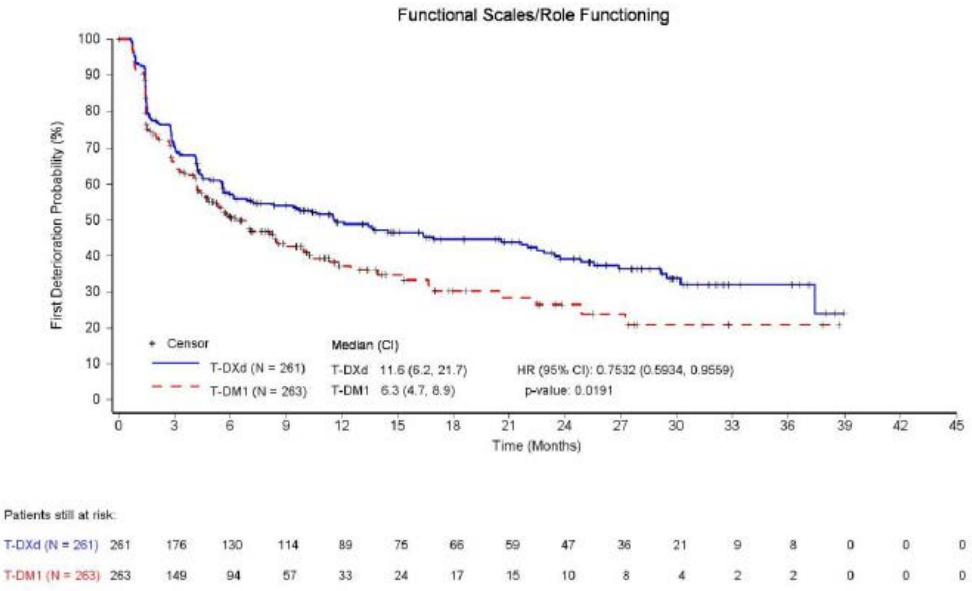



Figure 16: Kaplan-Meier curve for health-related quality of life, outcome of role functioning (EORTC QLQ-C30, first deterioration by ≥ 10 points)

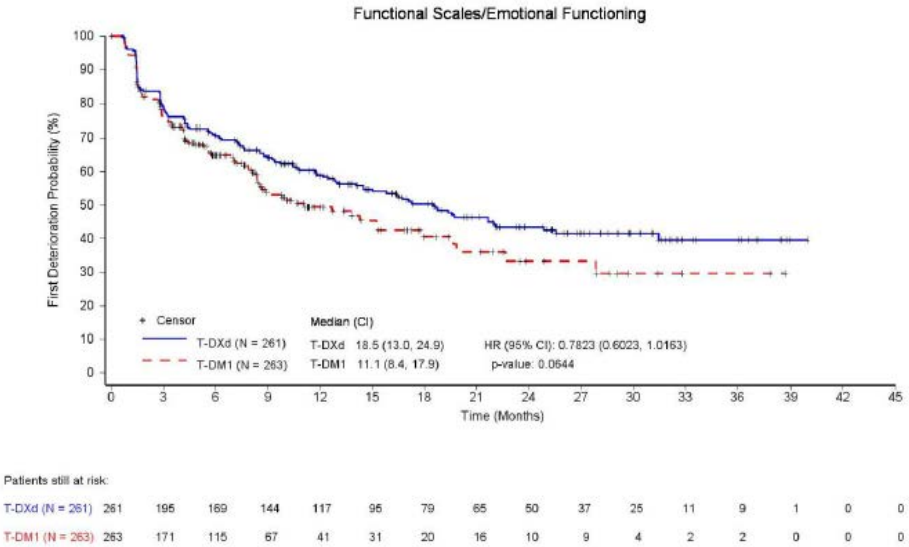



Figure 17: Kaplan-Meier curve for health-related quality of life, outcome of emotional functioning (EORTC QLQ-C30, first deterioration by ≥ 10 points)

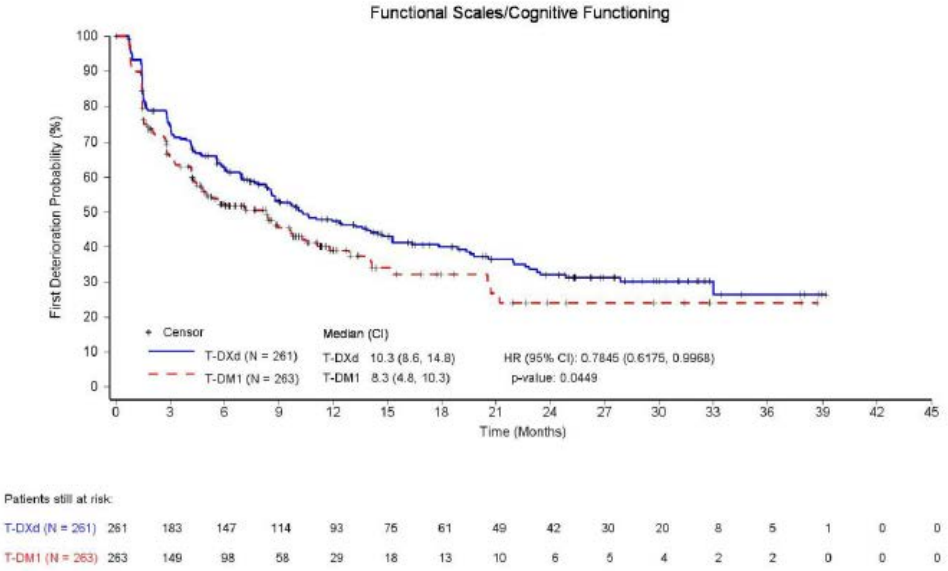



Figure 18: Kaplan-Meier curve for health-related quality of life, outcome of cognitive functioning (EORTC QLQ-C30, first deterioration by ≥ 10 points)

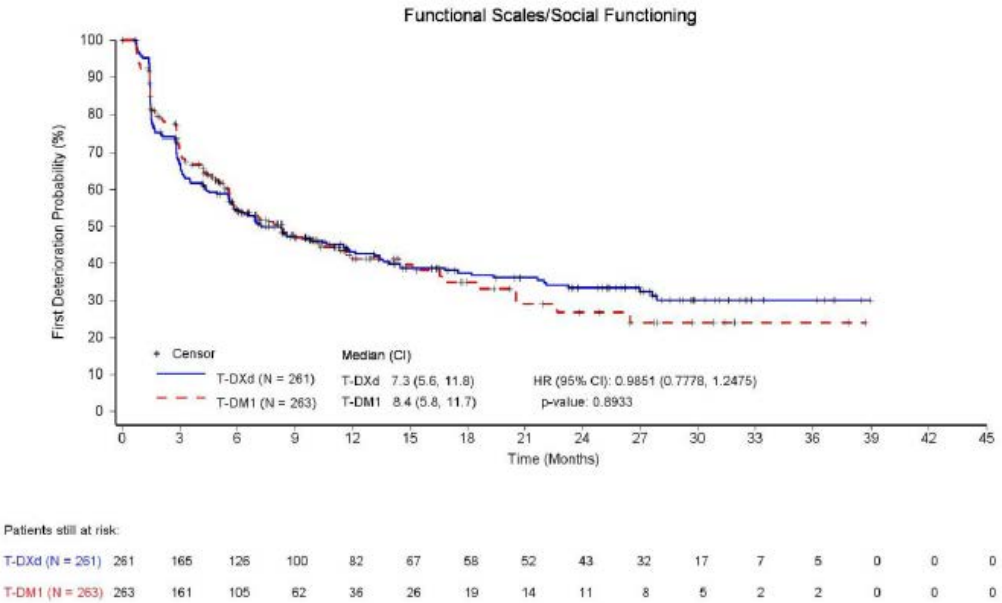



Figure 19: Kaplan-Meier curve for health-related quality of life, outcome of social functioning (EORTC QLQ-C30, first deterioration by ≥ 10 points)

### A.3.2 EORTC QLQ-BR23

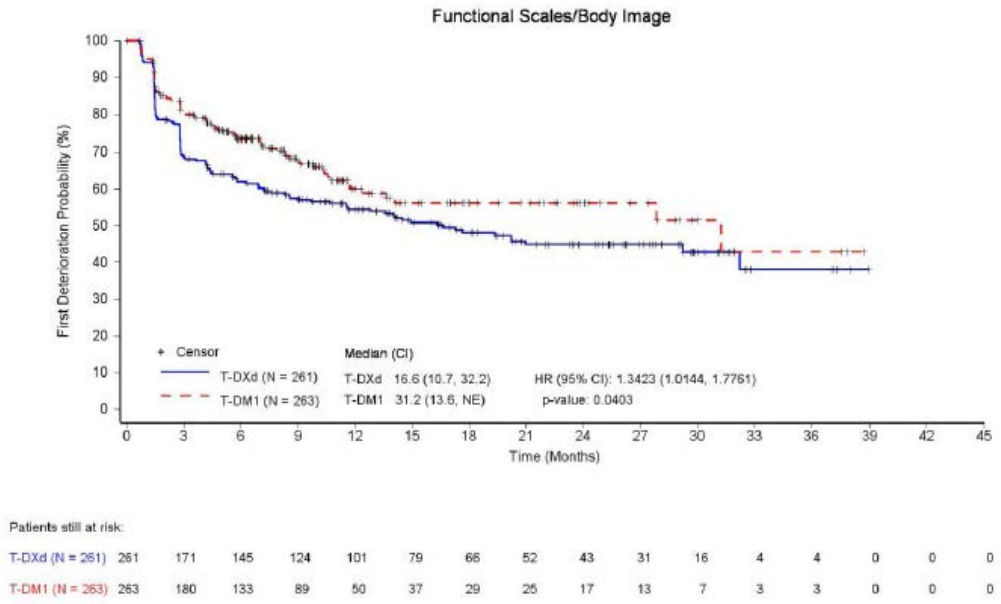



Figure 20: Kaplan-Meier curve for health-related quality of life, outcome of body image (EORTC QLQ-BR23, first deterioration by ≥ 10 points)

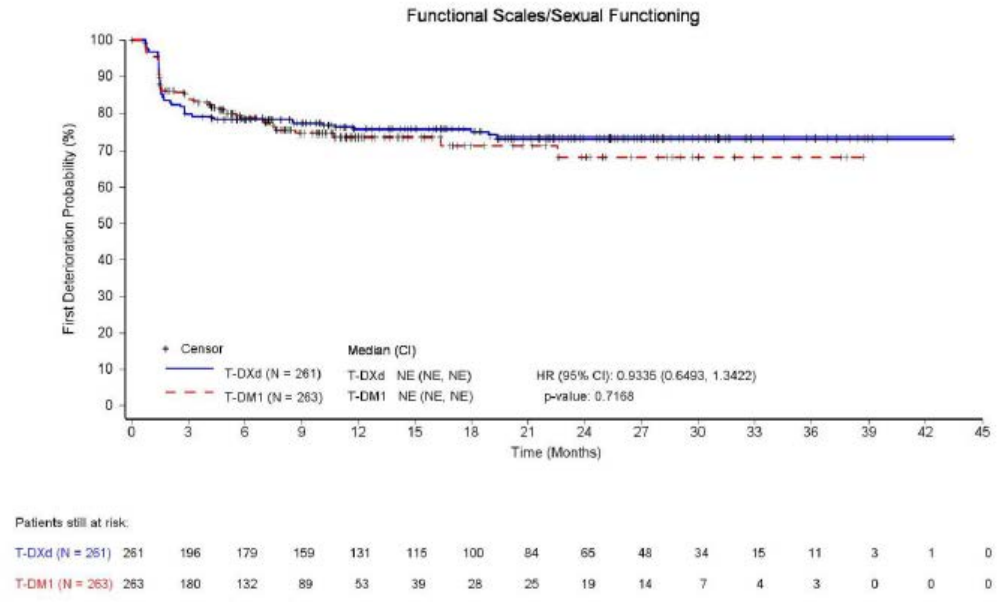



Figure 21: Kaplan-Meier curve for health-related quality of life, outcome of sexual activity (EORTC QLQ-BR23, first deterioration by ≥ 10 points)

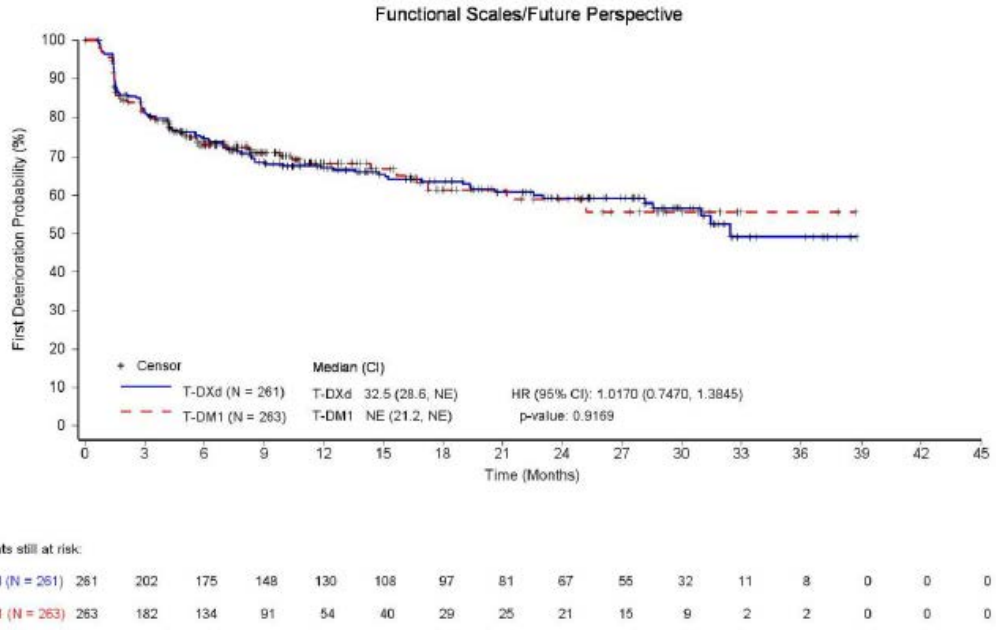



Figure 22: Kaplan-Meier curve for health-related quality of life, outcome of future perspective (EORTC QLQ-BR23, first deterioration by ≥ 10 points)

## A.4 Side effects

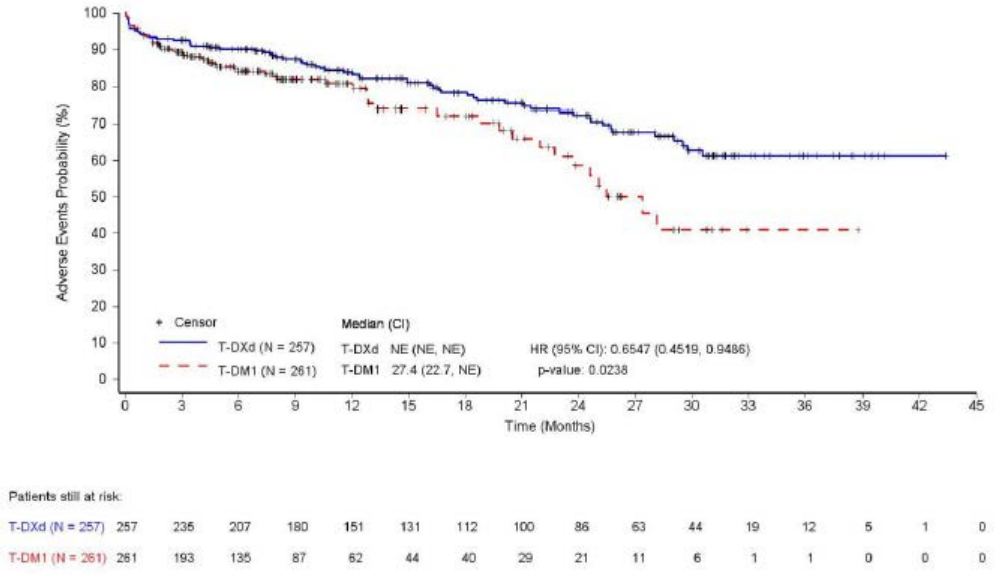



Figure 23: Kaplan-Meier curve, outcome of SAEs

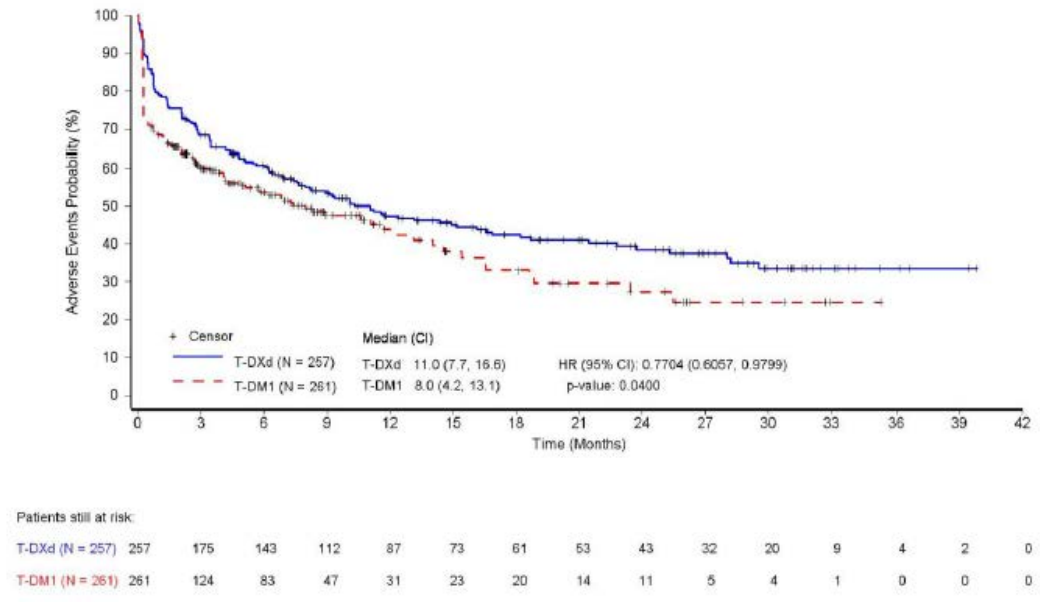



Figure 24: Kaplan-Meier curve, outcome of severe AEs (CTCAE grade ≥ 3)

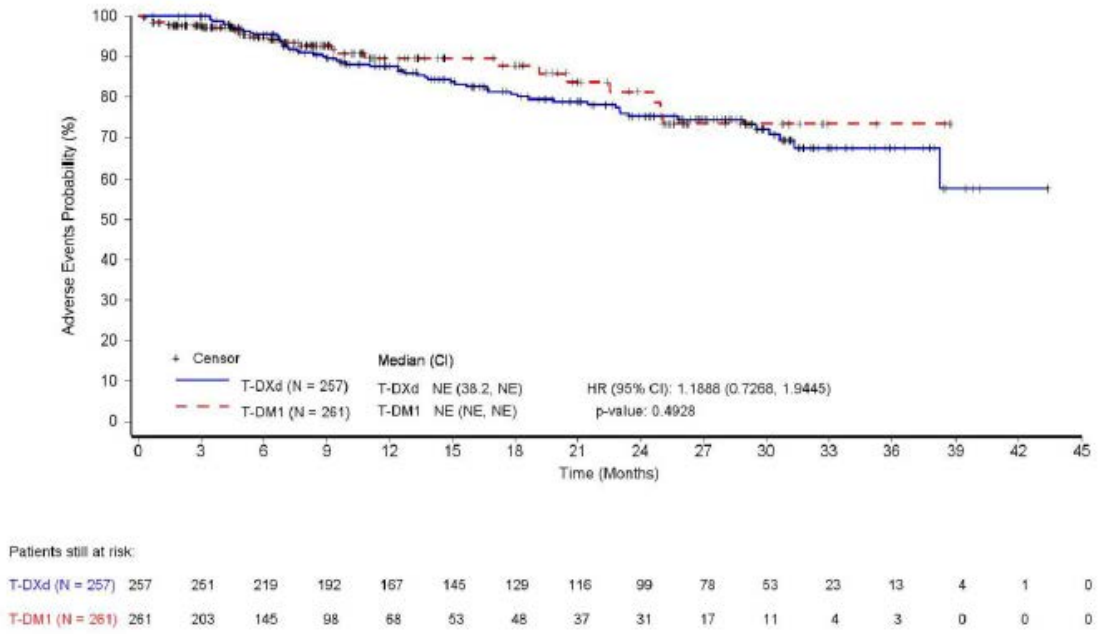



Figure 25: Kaplan-Meier curve, outcome of discontinuation due to AEs

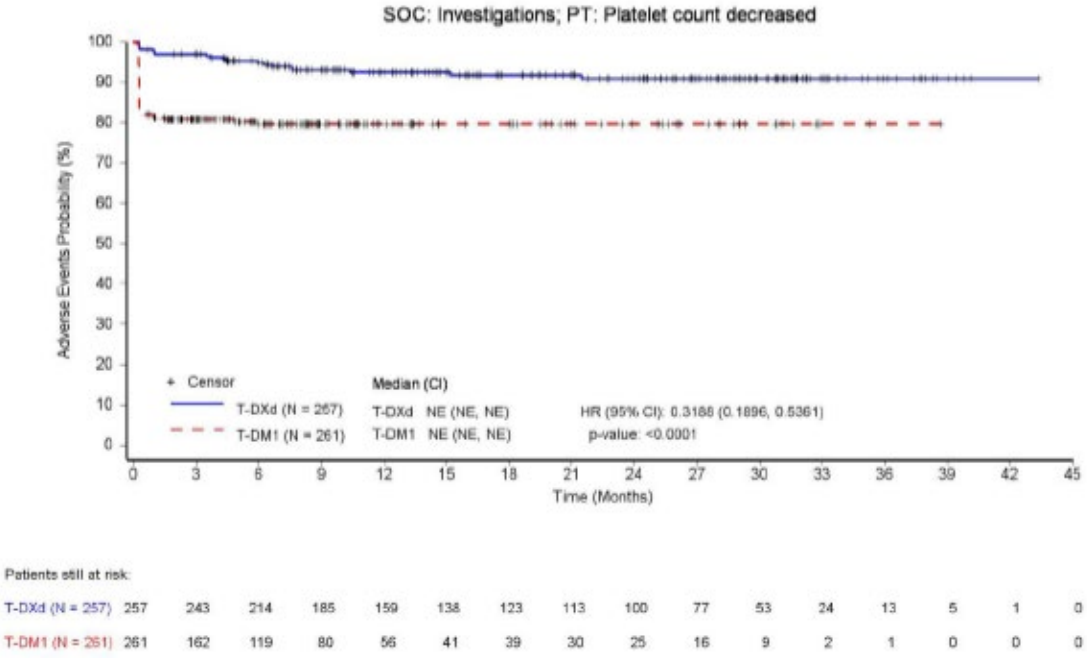



Figure 26: Kaplan-Meier curve, outcome of platelet count decreased (PT, severe AEs)

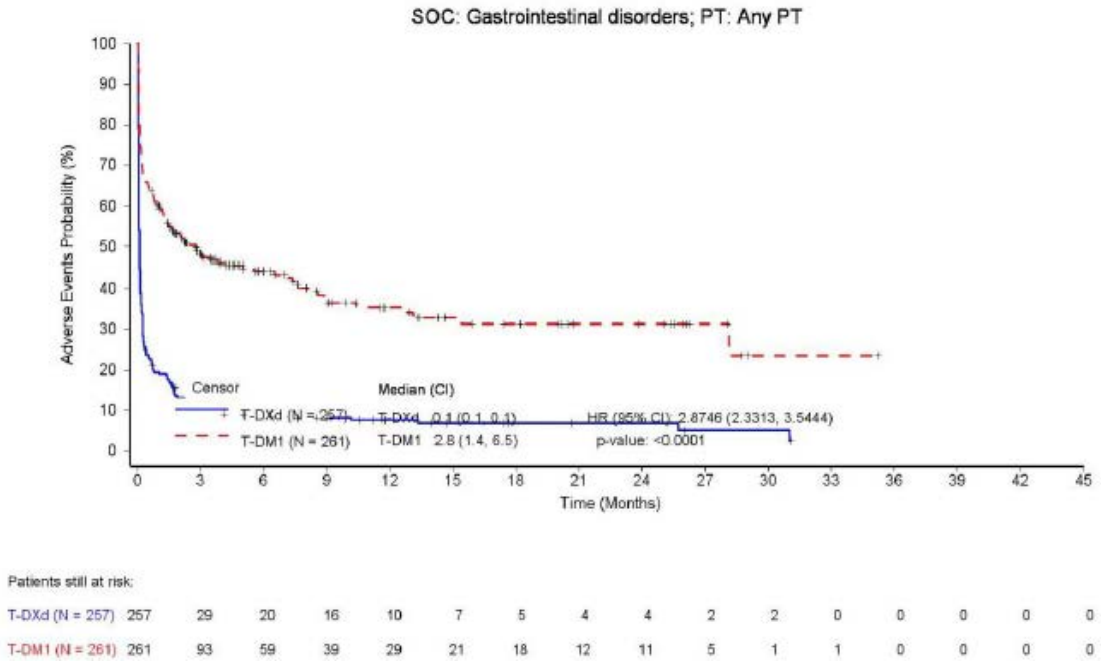



Figure 27: Kaplan-Meier curve, outcome of gastrointestinal disorders (SOC, AEs)

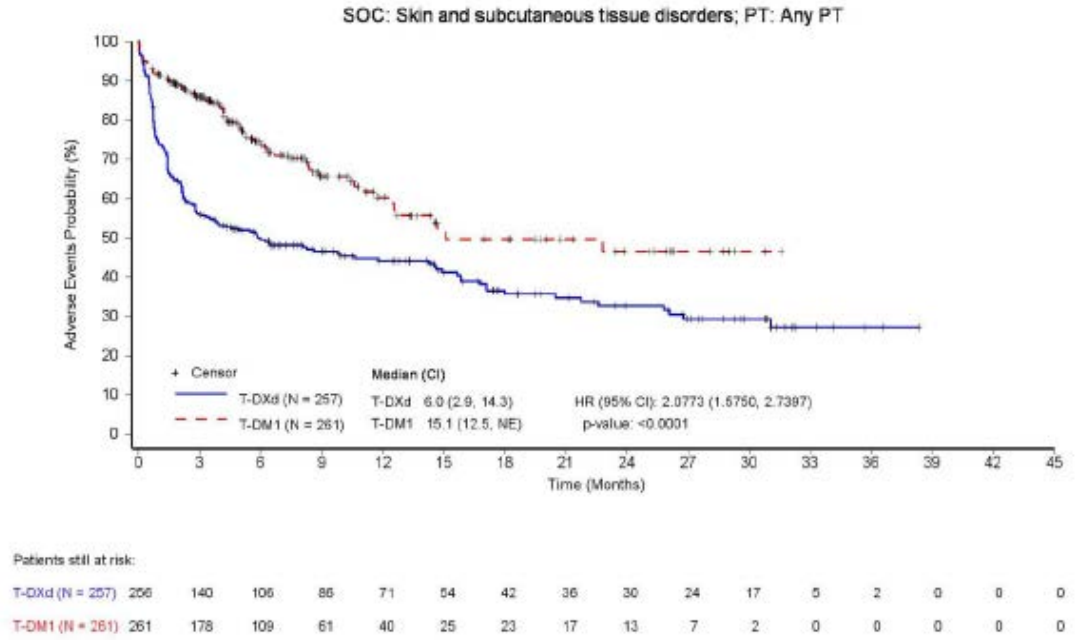



Figure 28: Kaplan-Meier curve, outcome of skin and subcutaneous tissue disorders (SOC, AEs)

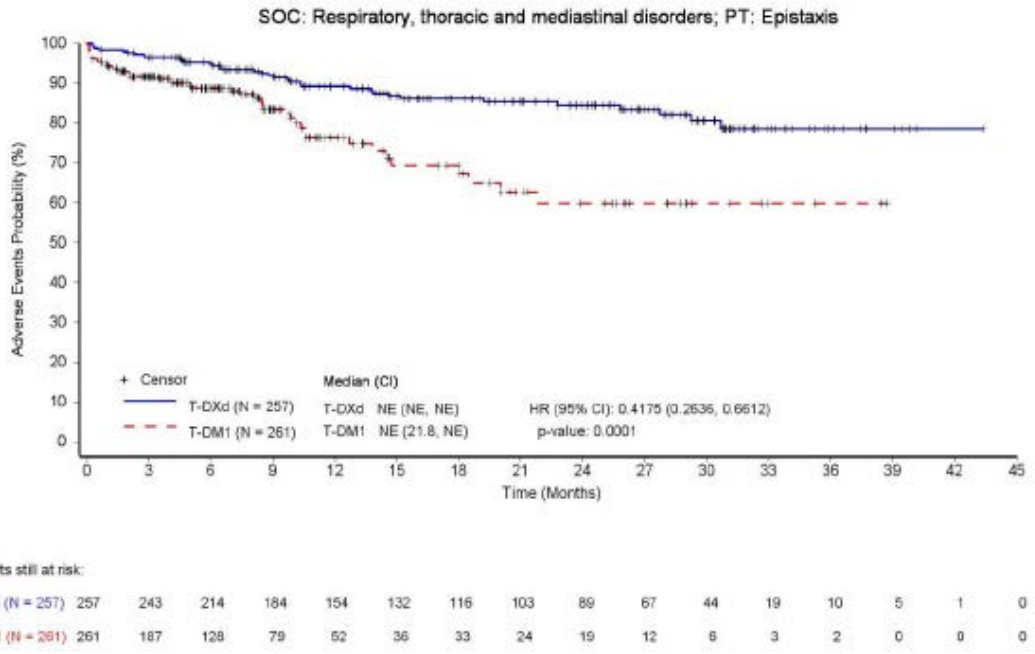



Figure 29: Kaplan-Meier curve, outcome of nose bleed (PT, AEs)

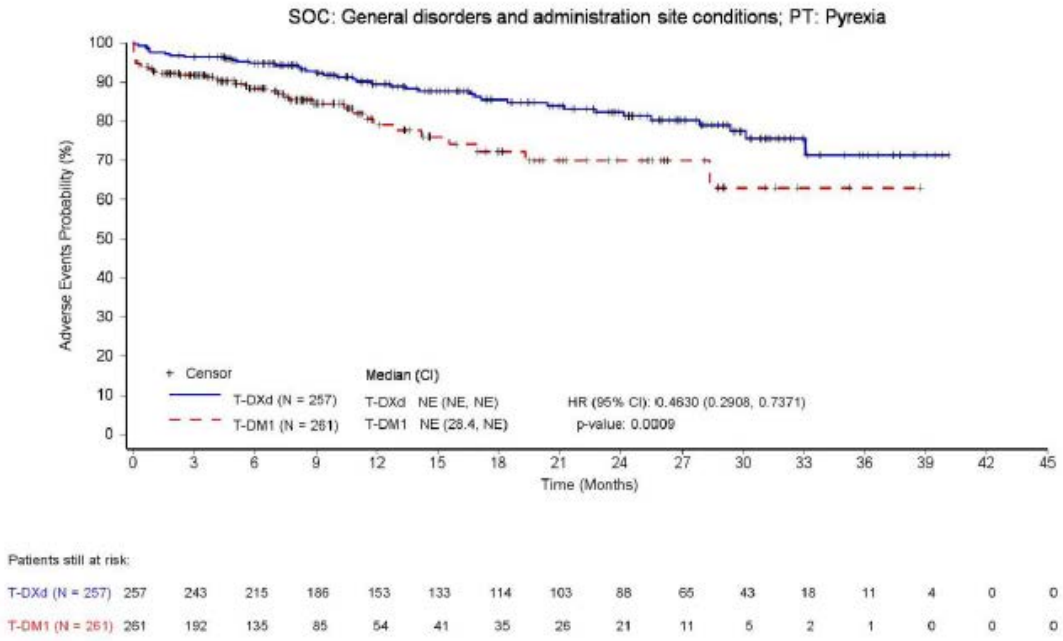



Figure 30: Kaplan-Meier curve, outcome of pyrexia (PT, AEs)

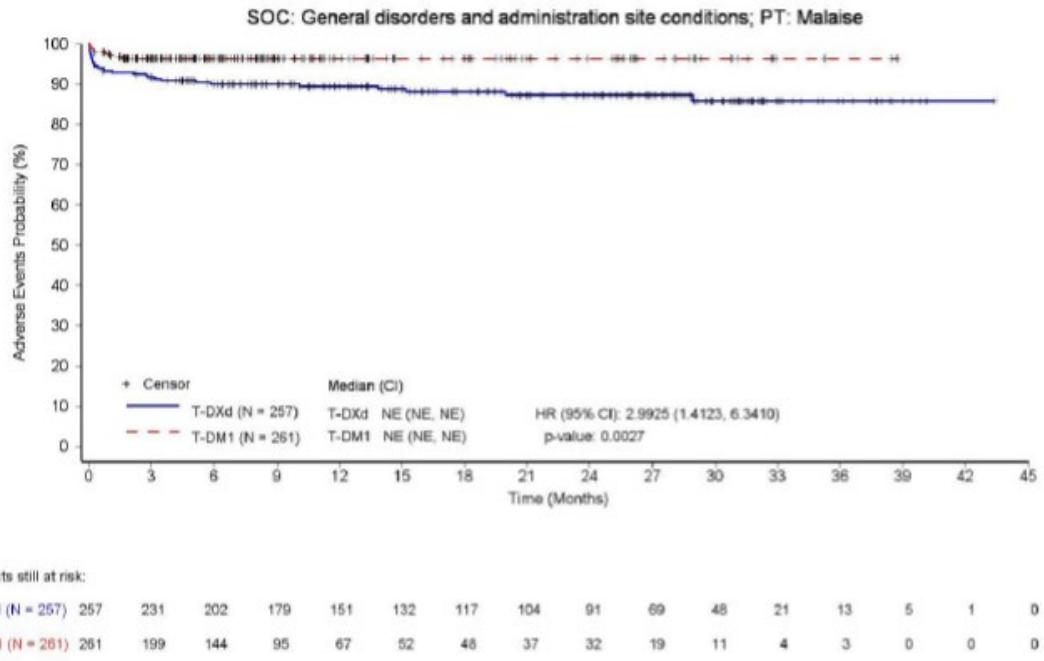



Figure 31: Kaplan-Meier curve, outcome of malaise (PT, AEs)

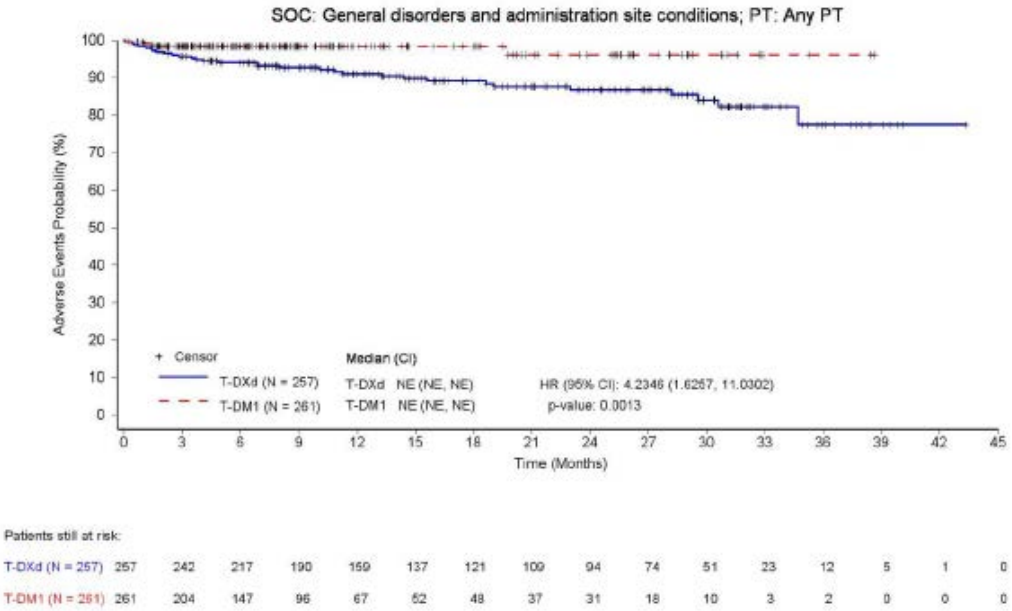



Figure 32: Kaplan-Meier curve, outcome of general disorders and administration site conditions (SOC, severe AEs)

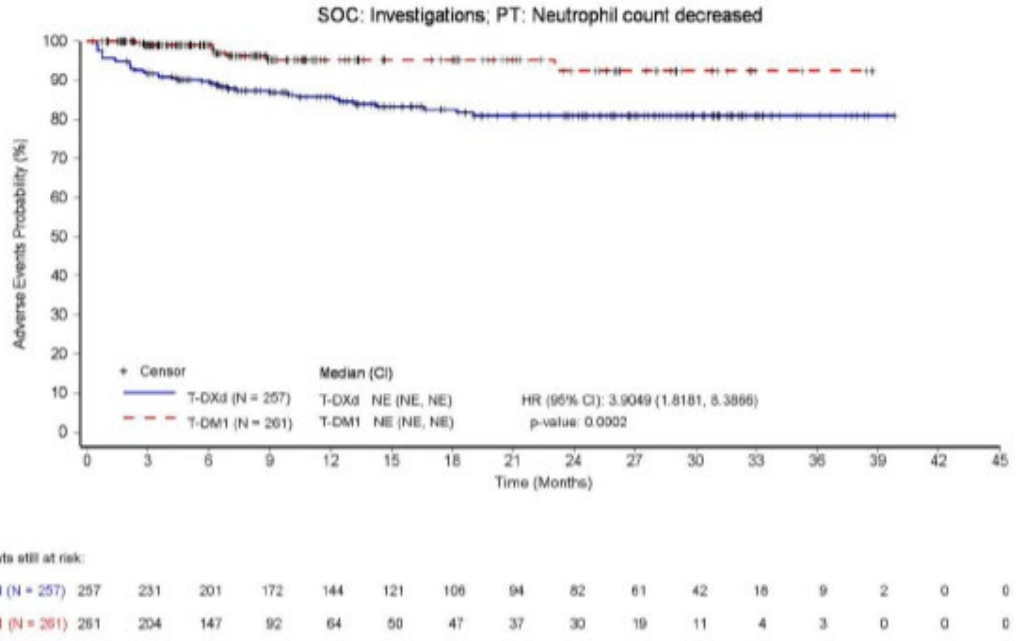



Figure 33: Kaplan-Meier curve, outcome of neutrophil count decreased (PT, severe AEs)

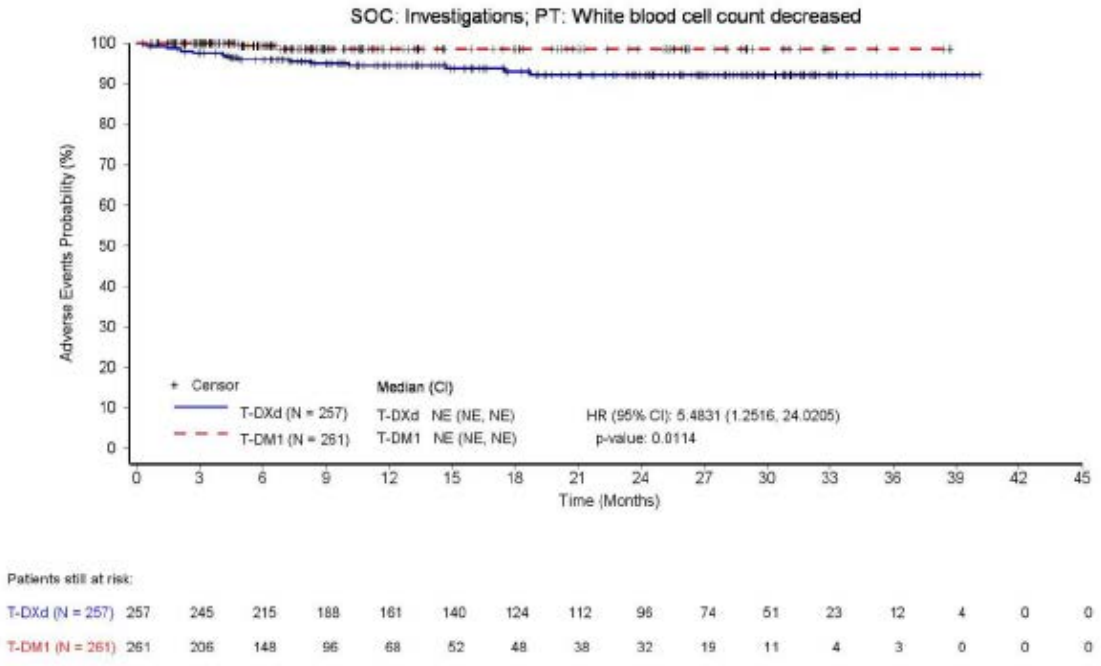



Figure 34: Kaplan-Meier curve, outcome of white blood cell count decreased (PT, severe AEs)

No Kaplan-Meier curves are available for the outcome of alanine aminotransferase increased (PT, severe AEs).

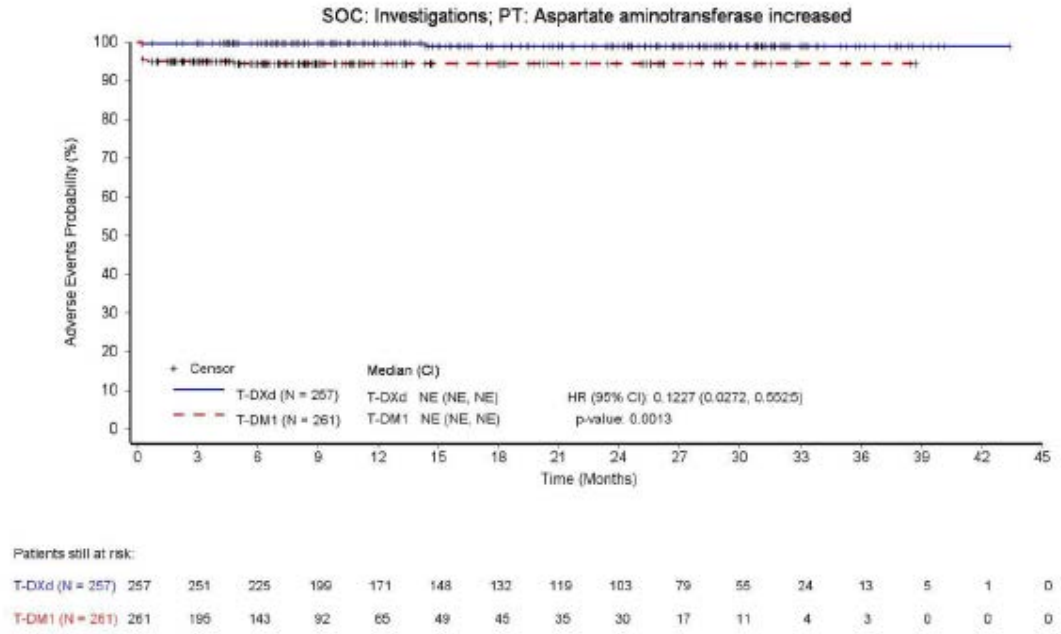



Figure 35: Kaplan-Meier curve, outcome of aspartate aminotransferase increased (PT, severe AEs)

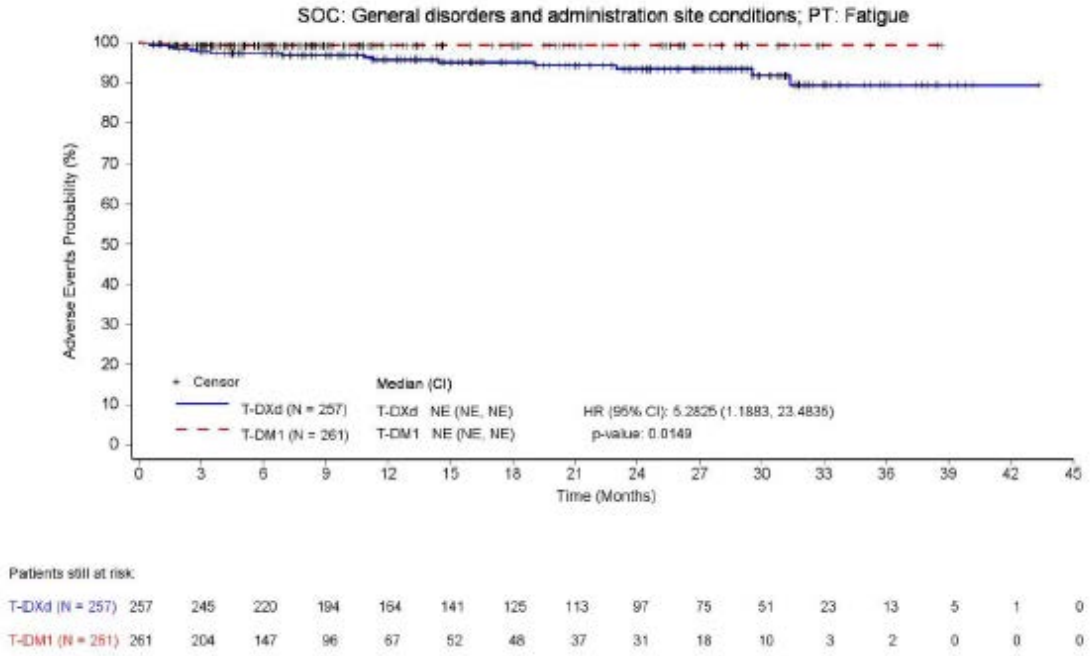



Figure 36: Kaplan-Meier curve, outcome of fatigue (PT, severe AEs)

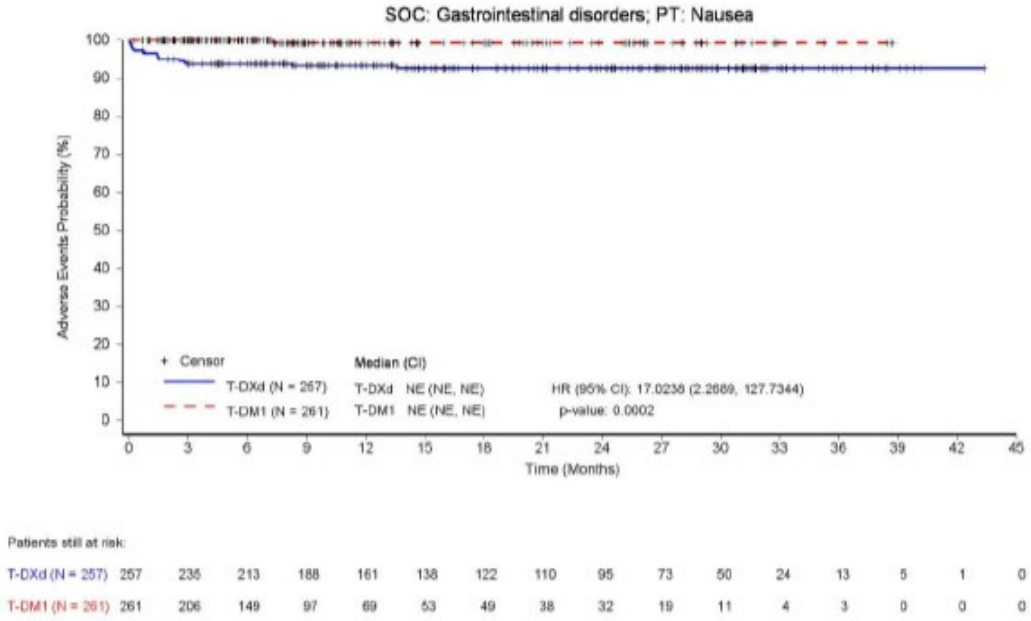



Figure 37: Kaplan-Meier curve, outcome of nausea (PT, severe AEs)

## A.5 Subgroup analyses

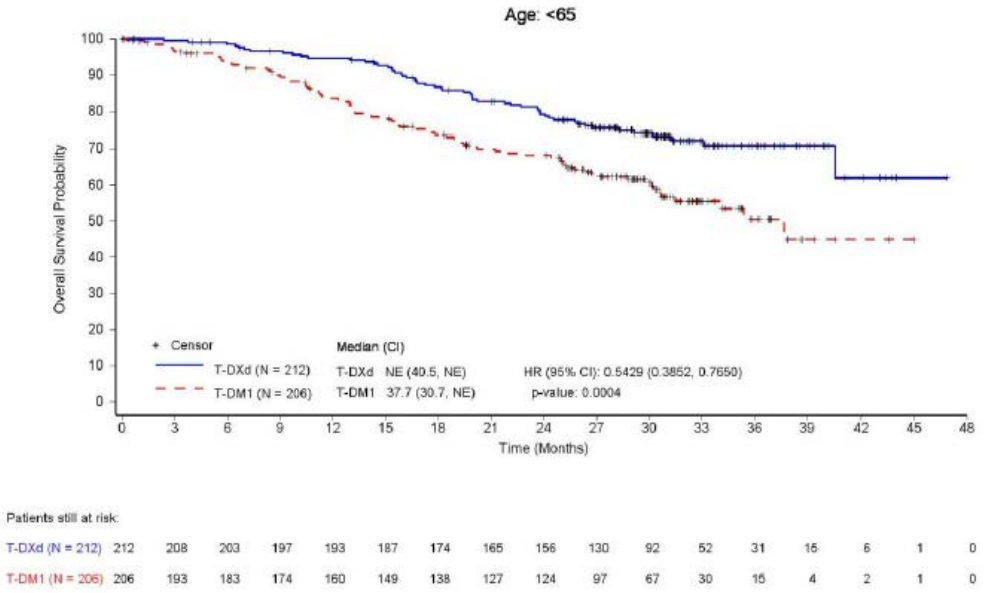



Figure 38: Kaplan-Meier curve, outcome of overall survival, subgroup “age”, category “< 65 years”

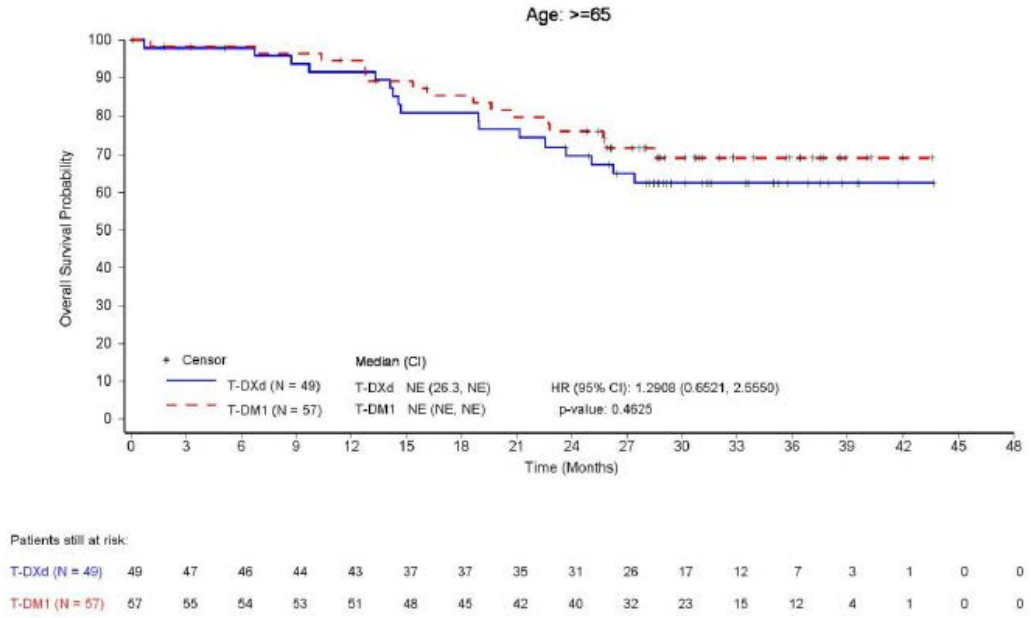



Figure 39: Kaplan-Meier curve, outcome of overall survival, subgroup “age”, category “≥ 65 years”

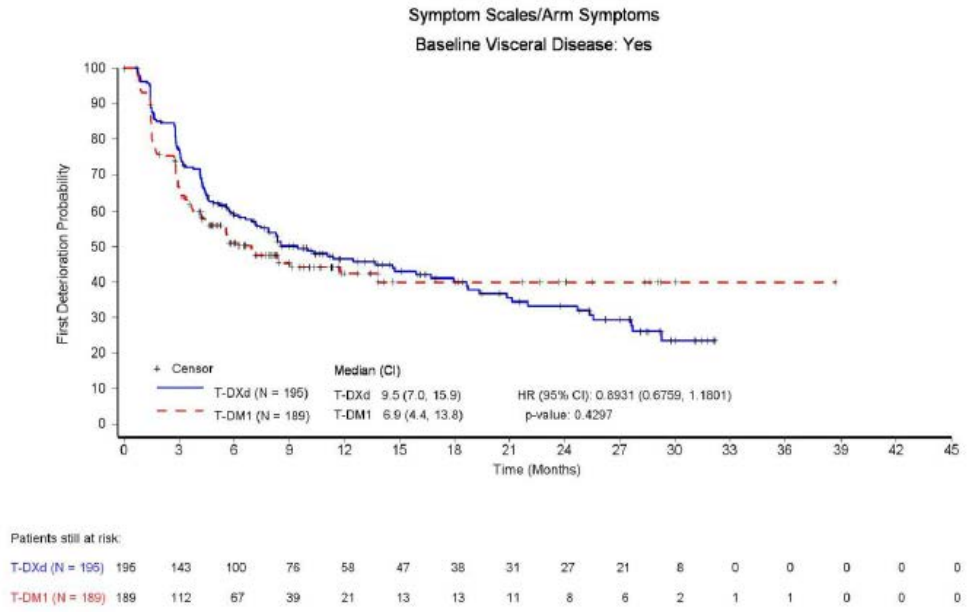



Figure 40: Kaplan-Meier curve, outcome of symptoms in arm region (EORTC QLQ-BR23), subgroup ‘‘baseline visceral disease’’, category ‘‘yes’’

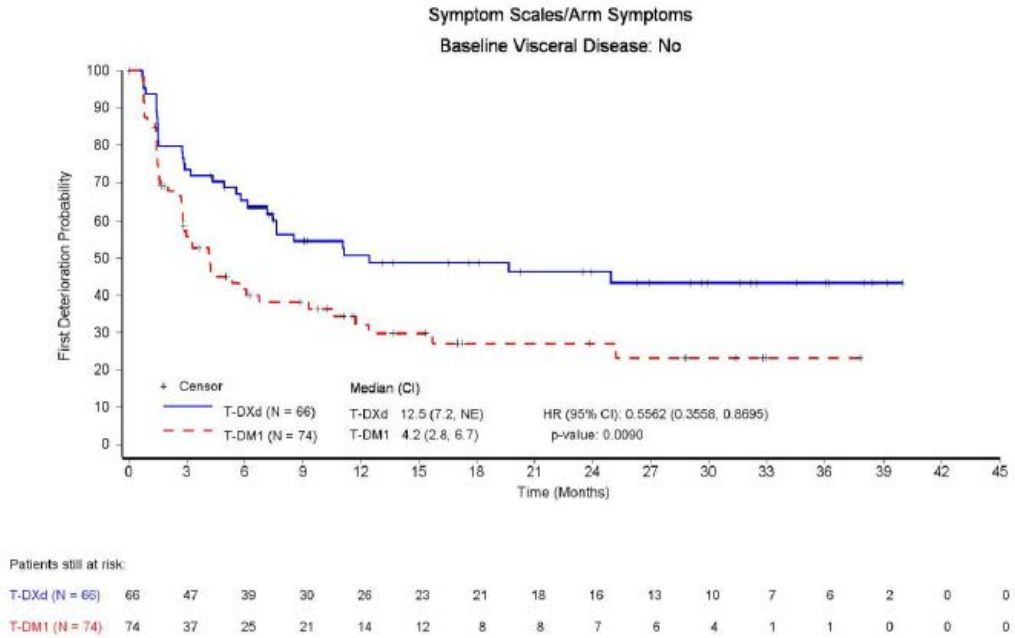



Figure 41: Kaplan-Meier curve, outcome of symptoms in arm region (EORTC QLQ-BR23), subgroup ‘‘baseline visceral disease’’, category ‘‘no’’

## Appendix B Results on side effects

For the overall rates of AEs, SAEs, and severe AEs (CTCAE grade ≥ 3), the following tables present events for System Organ Classes (SOCs) and Preferred Terms (PTs) according to the Medical Dictionary for Regulatory Activities (MedDRA), each on the basis of the following criteria:

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

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

Table 9: Common AEs[a] – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine (multipage table)

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[b]**<br>**PT[b]** | **Trastuzumab deruxtecan**<br>**N = 257** | **Trastuzumab emtansine**<br>**N = 261** |
| **DESTINY-Breast03, data cut-off of 25 July 2022** | | |
| **Overall rate of AEs[c]** | 256 (99.6) | 249 (95.4) |
| Gastrointestinal disorders | 239 (93.0) | 152 (58.2) |
| Nausea | 198 (77.0) | 79 (30.3) |
| Vomiting | 133 (51.8) | 28 (10.7) |
| Constipation | 96 (37.4) | 51 (19.5) |
| Diarrhoea | 83 (32.3) | 21 (8.0) |
| Stomatitis | 46 (17.9) | 10 (3.8) |
| Abdominal pain | 37 (14.4) | 7 (2.7) |
| Dyspepsia | 31 (12.1) | 16 (6.1) |
| Abdominal pain upper | 30 (11.7) | 14 (5.4) |
| Gastrooesophageal reflux disease | 14 (5.4) | 5 (1.9) |
| Abdominal distension | 13 (5.1) | 6 (2.3) |
| Haemorrhoids | 10 (3.9) | 2 (0.8) |
| Dry mouth | 9 (3.5) | 26 (10.0) |
| Investigations | 177 (68.9) | 188 (72.0) |
| Neutrophil count decreased | 79 (30.7) | 30 (11.5) |
| Aspartate aminotransferase increased | 72 (28.0) | 108 (41.4) |
| Platelet count decreased | 64 (24.9) | 114 (43.7) |
| White blood cell count decreased | 60 (23.3) | 16 (6.1) |
| Alanine aminotransferase increased | 59 (23.0) | 83 (31.8) |
| Weight decreased | 58 (22.6) | 23 (8.8) |
| Blood alkaline phosphatase increased | 40 (15.6) | 34 (13.0) |
| Blood lactate dehydrogenase increased | 24 (9.3) | 36 (13.8) |
| Blood bilirubin increased | 22 (8.6) | 14 (5.4) |
| Weight increased | 17 (6.6) | 2 (0.8) |
| Lymphocyte count decreased | 15 (5.8) | 3 (1.1) |
| Blood creatinine increased | 14 (5.4) | 3 (1.1) |
| Gamma-glutamyltransferase increased | 13 (5.1) | 17 (6.5) |
| Electrocardiogram QT prolonged | 11 (4.3) | 15 (5.7) |
| General disorders and administration site conditions | 176 (68.5) | 136 (52.1) |
| Fatigue | 79 (30.7) | 53 (20.3) |
| Pyrexia | 39 (15.2) | 42 (16.1) |
| Asthenia | 38 (14.8) | 31 (11.9) |

Table 9: Common AEs[a] – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine (multipage table)

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[b]**<br>**PT[b]** | **Trastuzumab deruxtecan**<br>**N = 257** | **Trastuzumab emtansine**<br>**N = 261** |
| Malaise | 30 (11.7) | 9 (3.4) |
| Oedema peripheral | 24 (9.3) | 10 (3.8) |
| Influenza like illness | 18 (7.0) | 6 (2.3) |
| Mucosal inflammation | 10 (3.9) | 4 (1.5) |
| Skin and subcutaneous tissue disorders | 155 (60.3) | 77 (29.5) |
| Alopecia | 102 (39.7) | 9 (3.4) |
| Pruritus | 23 (8.9) | 19 (7.3) |
| Rash | 18 (7.0) | 24 (9.2) |
| Dry skin | 14 (5.4) | 5 (1.9) |
| Skin hyperpigmentation | 11 (4.3) | 0 (0) |
| Infections and infestations | 132 (51.4) | 94 (36.0) |
| COVID-19 | 24 (9.3) | 12 (4.6) |
| Upper respiratory tract infection | 23 (8.9) | 16 (6.1) |
| Urinary tract infection | 22 (8.6) | 15 (5.7) |
| Pneumonia | 20 (7.8) | 10 (3.8) |
| Nasopharyngitis | 14 (5.4) | 7 (2.7) |
| Metabolism and nutrition disorders | 128 (49.8) | 85 (32.6) |
| Decreased appetite | 78 (30.4) | 46 (17.6) |
| Hypokalaemia | 40 (15.6) | 29 (11.1) |
| Hypoalbuminaemia | 24 (9.3) | 14 (5.4) |
| Dehydration | 11 (4.3) | 0 (0) |
| Respiratory, thoracic and mediastinal disorders | 128 (49.8) | 87 (33.3) |
| Cough | 40 (15.6) | 29 (11.1) |
| Epistaxis | 35 (13.6) | 46 (17.6) |
| Dyspnoea | 26 (10.1) | 17 (6.5) |
| Pneumonitis | 21 (8.2) | 5 (1.9) |
| Interstitial lung disease | 18 (7.0) | 2 (0.8) |
| Oropharyngeal pain | 14 (5.4) | 7 (2.7) |
| Nervous system disorders | 124 (48.2) | 103 (39.5) |
| Headache | 61 (23.7) | 40 (15.3) |
| Dizziness | 37 (14.4) | 25 (9.6) |
| Peripheral sensory neuropathy | 20 (7.8) | 25 (9.6) |
| Dysgeusia | 16 (6.2) | 9 (3.4) |
| Neuropathy peripheral | 10 (3.9) | 10 (3.8) |
| Blood and lymphatic system disorders | 119 (46.3) | 83 (31.8) |

Table 9: Common AEs[a] – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine (multipage table)

| Study | Patients with event n (%) | |
|---|---|---|
| SOC[b] PT[b] | Trastuzumab deruxtecan N = 257 | Trastuzumab emtansine N = 261 |
| Anaemia | 95 (37.0) | 51 (19.5) |
| Neutropenia | 44 (17.1) | 8 (3.1) |
| Leukopenia | 29 (11.3) | 9 (3.4) |
| Lymphopenia | 21 (8.2) | 10 (3.8) |
| Thrombocytopenia | 17 (6.6) | 36 (13.8) |
| Musculoskeletal and connective tissue disorders | 113 (44.0) | 91 (34.9) |
| Arthralgia | 41 (16.0) | 38 (14.6) |
| Back pain | 27 (10.5) | 15 (5.7) |
| Myalgia | 26 (10.1) | 17 (6.5) |
| Pain in extremity | 25 (9.7) | 21 (8.0) |
| Muscle spasms | 12 (4.7) | 16 (6.1) |
| Eye disorders | 54 (21.0) | 37 (14.2) |
| Dry eye | 13 (5.1) | 10 (3.8) |
| Vision blurred | 11 (4.3) | 3 (1.1) |
| Vascular disorders | 50 (19.5) | 25 (9.6) |
| Hypertension | 16 (6.2) | 8 (3.1) |
| Psychiatric disorders | 49 (19.1) | 37 (14.2) |
| Anxiety | 21 (8.2) | 6 (2.3) |
| Insomnia | 20 (7.8) | 26 (10.0) |
| Injury, poisoning and procedural complications | 42 (16.3) | 29 (11.1) |
| Cardiac disorders | 27 (10.5) | 14 (5.4) |
| Ear and labyrinth disorders | 24 (9.3) | 9 (3.4) |
| Vertigo | 15 (5.8) | 5 (1.9) |
| Hepatobiliary disorders | 24 (9.3) | 32 (12.3) |
| Hepatitis | 6 (2.3) | 10 (3.8) |
| Reproductive system and breast disorders | 24 (9.3) | 21 (8.0) |
| Breast pain | 9 (3.5) | 10 (3.8) |
| Renal and urinary disorders | 19 (7.4) | 12 (4.6) |
| Immune system disorders | 11 (4.3) | 6 (2.3) |

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 25.0; SOC and PT notation taken from Module 4.
c. Including progression of the underlying disease.

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 10: Common SAEs[a] – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[b]** | **Trastuzumab deruxtecan N = 257** | **Trastuzumab emtansine N = 261** |
| **DESTINY-Breast03, data cut-off of 25 July 2022** | | |
| **Overall rate of SAEs[c]** | 65 (25.3) | 58 (22.2) |
| Infections and infestations | 21 (8.2) | 18 (6.9) |
| Gastrointestinal disorders | 14 (5.4) | 7 (2.7) |
| Respiratory, thoracic and mediastinal disorders | 11 (4.3) | 8 (3.1) |
| General disorders and administration site conditions | 10 (3.9) | 3 (1.1) |

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 25.0; SOC notation taken from Module 4.
c. Including progression of the underlying disease.

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

Table 11: Common severe AEs (CTCAE ≥ 3)[a] – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine

| Study | Patients with event n (%) | |
|---|---|---|
| SOC[b] PT[b] | Trastuzumab deruxtecan N = 257 | Trastuzumab emtansine N = 261 |
| **DESTINY-Breast03, data cut-off of 25 July 2022** | | |
| **Overall rate of severe AEs (CTCAE grade ≥ 3)[c]** | 145 (56.4) | 135 (51.7) |
| Investigations | 71 (27.6) | 82 (31.4) |
| Neutrophil count decreased | 41 (16.0) | 8 (3.1) |
| Platelet count decreased | 20 (7.8) | 52 (19.9) |
| White blood cell count decreased | 16 (6.2) | 2 (0.8) |
| Alanine aminotransferase increased | 4 (1.6) | 12 (4.6) |
| Aspartate aminotransferase increased | 2 (0.8) | 14 (5.4) |
| Blood and lymphatic system disorders | 42 (16.3) | 37 (14.2) |
| Anaemia | 24 (9.3) | 17 (6.5) |
| Neutropenia | 12 (4.7) | 1 (0.4) |
| Thrombocytopenia | 2 (0.8) | 16 (6.1) |
| General disorders and administration site conditions | 31 (12.1) | 5 (1.9) |
| Fatigue | 15 (5.8) | 2 (0.8) |
| Gastrointestinal disorders | 30 (11.7) | 8 (3.1) |
| Nausea | 18 (7.0) | 1 (0.4) |
| Metabolism and nutrition disorders | 20 (7.8) | 11 (4.2) |
| Hypokalaemia | 11 (4.3) | 3 (1.1) |
| Infections and infestations | 14 (5.4) | 13 (5.0) |
| Vascular disorders | 12 (4.7) | 7 (2.7) |
| Nervous system disorders | 10 (3.9) | 6 (2.3) |

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 25.0; SOC and PT notation taken from Module 4.
c. Including progression of the underlying disease.

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 12: Discontinuation due to AEs – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine (multipage table)

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[a]**<br>**PT[a]** | **Trastuzumab deruxtecan N = 257** | **Trastuzumab emtansine N = 261** |
| **DESTINY-Breast03, data cut-off of 25 July 2022** | | |
| **Overall rate of discontinuations due to AEs[b]** | 55 (21.4) | 24 (9.2) |
| Respiratory, thoracic and mediastinal disorders | 32 (12.5) | 6 (2.3) |
| Pneumonitis | 15 (5.8) | 3 (1.1) |
| Interstitial lung disease | 13 (5.1) | 2 (0.8) |
| Organizing pneumonia | 2 (0.8) | 0 (0) |
| Pulmonary mass | 1 (0.4) | 0 (0) |
| Nose bleed | 0 (0) | 1 (0.4) |
| Dyspnoea | 1 (0.4) | 0 (0) |
| Infections and infestations | 5 (1.9) | 3 (1.1) |
| Pneumonia | 5 (1.9) | 1 (0.4) |
| COVID-19 | 0 (0) | 2 (0.8) |
| Investigations | 6 (2.3) | 5 (1.9) |
| Platelet count decreased | 3 (1.2) | 4 (1.5) |
| Neutrophil count decreased | 3 (1.2) | 0 (0) |
| Bilirubin value increased | 0 (0) | 1 (0.4) |
| Gastrointestinal disorders | 4 (1.6) | 0 (0) |
| Colitis | 1 (0.4) | 0 (0) |
| Vomiting | 1 (0.4) | 0 (0) |
| Gastric perforation | 1 (0.4) | 0 (0) |
| Pneumatosis intestinalis | 1 (0.4) | 0 (0) |
| General disorders and administration site conditions | 3 (1.2) | 0 (0) |
| Fatigue | 2 (0.8) | 0 (0) |
| Pyrexia | 1 (0.4) | 0 (0) |
| Metabolism and nutrition disorders | 1 (0.4) | 0 (0) |
| Hypokalaemia | 1 (0.4) | 0 (0) |
| Nervous system disorders | 1 (0.4) | 2 (0.8) |
| Epilepsy | 1 (0.4) | 0 (0) |
| Altered state of consciousness | 0 (0) | 1 (0.4) |
| Spinal cord compression | 0 (0) | 1 (0.4) |
| Blood and lymphatic system disorders | 1 (0.4) | 5 (1.9) |
| Thrombocytopenia | 0 (0) | 3 (1.1) |
| Anaemia | 1 (0.4) | 2 (0.8) |

Table 12: Discontinuation due to AEs – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine (multipage table)

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[a]**<br>**PT[a]** | **Trastuzumab deruxtecan**<br>**N = 257** | **Trastuzumab emtansine**<br>**N = 261** |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 2 (0.8) | 0 (0) |
| Pancreatic cancer | 1 (0.4) | 0 (0) |
| Epithelial cancer | 1 (0.4) | 0 (0) |
| Hepatobiliary disorders | 0 (0) | 1 (0.4) |
| Hepatic atrophy | 0 (0) | 1 (0.4) |
| Injury, poisoning and procedural complications | 0 (0) | 1 (0.4) |
| Femoral fracture | 0 (0) | 1 (0.4) |
| Renal and urinary disorders | 0 (0) | 1 (0.4) |
| Acute kidney injury | 0 (0) | 1 (0.4) |

a. MedDRA version 25.0; SOC and PT notation taken from Module 4.
b. Including progression of the underlying disease.

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