Trastuzumab deruxtecan (breast cancer)

Addendum to Project A23-07 (dossier assessment)[1]

ADDENDUM

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
EORTC QLQ-BR23	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-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)
PT	Preferred Term
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class

1 Background

On 6 June 2023, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-07 (Trastuzumab deruxtecan – Benefit assessment according to § 35a Social Code Book V) [1].

The commission comprises the assessment of the following data of the DESTINY-Breast04 study subsequently submitted by the pharmaceutical company (hereinafter referred to as the "company") in the commenting procedure, taking into account the information provided in the dossier [2]:

- analyses excluding patients assigned to gemcitabine treatment before randomization
- analyses of the proportions of patients with concomitant anti-emetic treatment

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

Benefit assessment A23-07 [1] used the DESTINY-Breast04 study to assess the added benefit of trastuzumab deruxtecan in comparison with the appropriate comparator therapy (ACT) in patients with unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. The DESTINY-Breast04 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 the drugs capecitabine, eribulin, gemcitabine, paclitaxel or nab-paclitaxel.

The benefit assessment was based on the results of the total population of the DESTINY-Breast04 study. The benefit assessment addressed, among other things, uncertainties regarding the patients' pretreatment with anthracyclines and/or taxanes, the use of concomitant anti-emetic treatment and the administration of the drug gemcitabine, which is not part of the G-BA's ACT, in the comparator arm. This led, among other things, to a limitation of the certainty of conclusions of the DESTINY-Breast04 study, and the consideration of uncertainties in the certainty of conclusions for the results of individual outcomes. In the context of the commenting procedure, the company submitted analyses of a subpopulation without patients who were assigned to gemcitabine treatment prior to randomization, as well as analyses of the proportions of patients with concomitant anti-emetic treatment [3,4]. These analyses are assessed below in compliance with the commission. In addition, the company provided information on pretreatment with anthracyclines and/or taxanes [4].

2.1 Study characteristics

Detailed characteristics of the DESTINY-Breast04 study and of the total study population can be found in dossier assessment A23-07 [1].

Pretreatment of patients with anthracyclines and/or taxanes

The company stated in its comments that, based on the total study population, 89% of patients in the intervention arm and 87% of patients in the comparator arm had received pretreatment with anthracyclines and/or taxanes. However, the proportions of patients per drug option used in the comparator arm are still not clear from this. Furthermore, there is no separate information on how many patients had received pretreatment with anthracyclines, pretreatment with taxanes, or both treatments before the study. As a result, it is still unclear whether the respective prerequisites of pretreatment with taxanes and/or anthracyclines are fulfilled for the use of the drugs capecitabine, eribulin, paclitaxel and nab-paclitaxel according to the Summary of Product Characteristics (SPC). In addition, the company did not address for how many patients anthracycline or taxane therapy was unsuitable or not an option. It is also

not clear from the data whether patients who received paclitaxel or nab-paclitaxel as comparator therapy had not previously received an anthracycline and/or taxane-containing regimen or whether they were eligible for renewed anthracycline or taxane-containing treatment.

Use of concomitant anti-emetic treatment

In its comments, the company subsequently submitted new data on the proportions of patients with concomitant anti-emetic treatment in relation to the total population of the DESTINY-Breast04 study (see Table 1).

Table 1: Information on concomitant anti-emetic treatment – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a]

Study Characteristic Category	Trastuzumab deruxtecan N = 371	Treatment of physician's choice[a] N = 172
DESTINY-Breast04		
Concomitant anti-emetic treatment[b], n (%)		
Yes	307 (83)	99 (58)
No	64 (17)	73 (42)

a. Capecitabine or eribulin or gemcitabine or paclitaxel or nab-paclitaxel.
b. According to the company, anti-emetic medication is defined as any medication in the ATC class "antiemetics and antinauseants", PTs "dexamethasone" or "prednisolone" in the ATC class "corticosteroids for systemic use", PTs "olanzapine" or "haloperidol" in the ATC class "psycholeptics", or PTs "metoclopramide" or "alizapride" in the ATC class "drugs for functional gastrointestinal disorders". According to the company, additional medications with PT "diphenylhydramine" were defined as anti-emetic medication for paclitaxel.

ATC: Anatomical Therapeutic Chemical; n: number of patients in the category; N: number of randomized patients in the safety population; PT: Preferred Term; RCT: randomized controlled trial

The proportions of patients with concomitant anti-emetic treatment are higher in the subsequently submitted data than those summarized under concomitant anti-emetic treatment in the clinical study report. The company justified the changes by stating that the drugs administered as concomitant medication in the DESTINY-Breast04 study were classified according to the Anatomical Therapeutic Chemical (ATC) code and, as a result, some drugs for the treatment of nausea and vomiting, such as systemic dexamethasone or metoclopramide, were not classified in the category of anti-emetics. According to the company, taking into account all additional therapies given, 83% of patients in the intervention arm and 58% of patients in the comparator arm received concomitant anti-emetic treatment.

There are various uncertainties in the subsequently submitted data. On the one hand, according to the SPC, all patients in the intervention arm should have received concomitant anti-emetic treatment [5]. According to the company, the lower proportion of concomitant

anti-emetic treatment in the intervention arm was due to a gain in knowledge during the study, so that concomitant anti-emetic treatment was only included in version 4.0 of the study protocol. Although this is correct based on the information in the study protocol, it cannot be excluded that the lack of concomitant anti-emetic treatment influences the results of the outcomes of nausea and vomiting (patient-reported and adverse events [AEs]). Furthermore, the information on concomitant anti-emetic treatment refers to all patients included in the study and not only to those for whom concomitant anti-emetic treatment is recommended by the SPC (in the comparator arm only for the administration of eribulin and paclitaxel [6,7]). In addition, for some of the ATC classes considered by the company (e.g. “psycholeptics”), it is not clear whether the drugs named in these classes were used as anti-emetics or for other purposes. In summary, the aspects mentioned continue to limit the certainty of conclusions of the results for the outcomes of nausea and vomiting.

Analysis population

In its comments, the company presented results on patient-relevant outcomes of a subpopulation without those patients who were assigned to gemcitabine treatment before randomization. The company’s subpopulation comprises 344 patients in the intervention arm and 165 patients in the comparator arm. The analyses of this subpopulation are considered in the present addendum. Data on the characteristics of the study population, on treatment duration and observation period, and on subsequent antineoplastic therapies for this subpopulation are not included in the subsequently submitted data of the company.

Summary assessment of the certainty of conclusions

The data on the subpopulation subsequently submitted in the commenting procedure resolved the uncertainties regarding gemcitabine administration mentioned in dossier assessment A23-07. The uncertainties regarding the patients’ pretreatment with anthracyclines and/or taxanes are still present. Overall, however, these are no longer considered sufficient to continue to limit the certainty of conclusions of the DESTINY-Breast04 study.

2.2 Results on added benefit

2.2.1 Outcomes included

The choice of patient-relevant outcomes included in the assessment in the present addendum corresponds to the choice made in dossier assessment A23-07. In the subsequently submitted data, the company presented results on common AEs with cut-off values that deviate from those of the dossier template [8]. This means that only a subset of serious AEs (SAEs) and severe AEs are available. As the subpopulation of patients treated with gemcitabine only represents 9% of the total population, the specific AEs considered in dossier assessment

A23-07 are used in the present situation. A descriptive presentation of common AEs for the relevant subpopulation is not provided in the addendum.

2.2.2 Risk of bias

In comparison with dossier assessment A23-07 [1], the classification in the present addendum does not change for both the risk of bias across outcomes and the outcome-specific risk of bias of the DESTINY-Breast04 study. However, due to the analyses subsequently submitted in the commenting procedure, the certainty of conclusions of the DESTINY-Breast04 study is no longer limited.

2.2.3 Results

Table 2 summarizes the results of the comparison of trastuzumab deruxtecan with treatment of physician's choice in patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.

The Kaplan-Meier curves on the presented time-to-event analyses are presented in Appendix A. No Kaplan-Meier curves are available for the outcome of cardiac disorders (System Organ Class [SOC], severe AEs).

Table 2: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

Study Outcome category Outcome	Trastuzumab deruxtecan		Treatment of physician's choice[a]		Trastuzumab deruxtecan vs. treatment of physician's choice[a]
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
DESTINY-Breast04					
Mortality					
Overall survival	344	23.4 [20.0; NC] 137 (39.8)	165	17.0 [15.1; 20.2] 78 (47.3)	0.64 [0.48; 0.85]; 0.002
Morbidity					
Symptoms (EORTC QLQ-C30); time to first deterioration)[c]					
Fatigue	344	4.2 [2.8; 5.5] 220 (64.0)	165	2.8 [1.4; 3.3] 100 (60.6)	0.81 [0.63; 1.03]; 0.081
Nausea and vomiting	344	1.4 [1.4; 1.6] 239 (69.5)	165	8.2 [6.0; 9.8] 68 (41.2)	2.12 [1.61; 2.78]; < 0.001
Pain	344	8.5 [5.9; 10.6] 177 (51.5)	165	4.4 [2.8; 7.2] 86 (52.1)	0.69 [0.53; 0.898]; 0.005
Dyspnoea	344	13.2 [8.3; 21.7] 148 (43.0)	165	6.8 [5.1; NC] 66 (40.0)	0.80 [0.60; 1.08]; 0.148
Insomnia	344	16.0 [11.1; NC] 137 (39.8)	165	5.4 [4.2; 7.1] 76 (46.1)	0.56 [0.42; 0.74]; < 0.001
Appetite loss	344	5.1 [3.2; 6.9] 197 (57.3)	165	7.0 [4.6; 9.8] 74 (44.8)	1.20 [0.92; 1.58]; 0.190
Constipation	344	4.2 [2.9; 5.6] 205 (59.6)	165	5.9 [4.5; 8.4] 73 (44.2)	1.17 [0.89; 1.54]; 0.255
Diarrhoea	344	9.4 [7.0; 15.3] 163 (47.4)	165	13.3 [9.0; NC] 54 (32.7)	1.37 [1.003; 1.87]; 0.049
Symptoms (EORTC QLQ-BR23); time to first deterioration)[c]					
Side effects of systemic therapy	344	4.2 [2.8; 5.9] 193 (56.1)	165	2.8 [1.5; 4.5] 92 (55.8)	0.82 [0.64; 1.06]; 0.131
Breast symptoms	344	NA [20.3; NC] 93 (27.0)	165	NA 37 (22.4)	0.89 [0.60; 1.31]; 0.554
Arm symptoms	344	7.7 [6.7; 11.2] 166 (48.3)	165	5.1 [2.9; NC] 73 (44.2)	0.78 [0.59; 1.03]; 0.079
Upset by hair loss	No suitable data[d]				
Health status (EQ-5D VAS; time to first deterioration)[e]	344	16.4 [11.1; NC] 132 (38.4)	165	8.4 [5.4; NC] 55 (33.3)	0.82 [0.59; 1.13]; 0.220

Table 2: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

Study Outcome category Outcome	Trastuzumab deruxtecan		Treatment of physician's choice[a]		Trastuzumab deruxtecan vs. treatment of physician's choice[a]
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
Health-related quality of life					
EORTC QLQ-C30 (time to first deterioration)[f]					
Global health status	344	5.6 [4.2; 7.9] 190 (55.2)	165	4.0 [2.8; 5.9] 90 (54.5)	0.81 [0.63; 1.04]; 0.097
Physical functioning	344	8.7 [7.1; 11.3] 169 (49.1)	165	4.5 [3.0; 5.8] 87 (52.7)	0.62 [0.47; 0.81]; < 0.001
Role functioning	344	4.2 [2.9; 5.9] 198 (57.6)	165	3.2 [1.6; 4.4] 93 (56.4)	0.81 [0.63; 1.04]; 0.089
Emotional functioning	344	10.4 [8.3; 13.1] 161 (46.8)	165	7.1 [5.7; 11.7] 64 (38.8)	0.89 [0.66; 1.20]; 0.432
Cognitive functioning	344	6.5 [5.0; 7.7] 187 (54.4)	165	4.2 [3.1; 6.3] 90 (54.5)	0.75 [0.58; 0.97]; 0.028
Social functioning	344	5.9 [4.2; 9.7] 194 (56.4)	165	3.4 [2.1; 4.7] 96 (58.2)	0.73 [0.57; 0.94]; 0.014
EORTC QLQ-BR23 (time to first deterioration)[f]					
Body image	344	12.8 [9.6; NC] 143 (41.6)	165	5.1 [2.9; 16.9] 75 (45.5)	0.67 [0.51; 0.897]; 0.006
Sexual functioning	344	NA 73 (21.2)	165	NA 31 (18.8)	0.91 [0.59; 1.39]; 0.651
Sexual enjoyment	No suitable data[d]				
Future perspective	344	16.9 [14.1; NC] 123 (35.8)	165	NA [11.1; NC] 49 (29.7)	0.98 [0.70; 1.38]; 0.916
Side effects					
AEs (supplementary information)	343	0.1 [NC; NC] 341 (99.4)	156	0.1 [0.1; 0.1] 153 (98.1)	–
SAEs	343	NA [24.4; NC] 97 (28.3)	156	NA [9.2; NC] 41 (26.3)	0.66 [0.45; 0.97]; 0.034
Severe AEs[g]	343	7.2 [5.0; 10.5] 184 (53.6)	156	0.9 [0.5; 2.0] 103 (66.0)	0.50 [0.39; 0.64]; < 0.001
Discontinuation due to AEs	343	NA [24.4; NC] 56 (16.3)	156	NA [16.2; NC] 13 (8.3)	1.09 [0.58; 2.04]; 0.784

Table 2: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

Study Outcome category Outcome	Trastuzumab deruxtecan		Treatment of physician's choice[a]		Trastuzumab deruxtecan vs. treatment of physician's choice[a]
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
Hand-foot syndrome (PT, AEs)	343	NA 4 (1.2)	156	NA 24 (15.4)	0.05 [0.02; 0.15]; < 0.001
Cardiac disorders (SOC, severe AEs[g])	343	ND	156	ND	ND
Platelet count decreased (PT, severe AEs[g])	343	NA 19 (5.5)	156	NA 0 (0)	NC; 0.009
Gastrointestinal disorders (SOC, AEs)	343	0.1 [0.1; 0.1] 302 (88.0)	156	0.7 [0.5; 1.5] 106 (67.9)	2.13 [1.69; 2.68]; < 0.001
Infections and infestations (SOC, SAEs)	343	NA 28 (8.2)	156	NA 2 (1.3)	4.22 [0.99; 17.92]; 0.034
Neutropenia (PT, severe AEs[g])	343	NA 20 (5.8)	156	NA 23 (14.7)	0.32 [0.17; 0.59]; < 0.001
Nausea (PT, severe AEs[g])	343	NA 16 (4.7)	156	NA 0 (0)	NC; 0.010

a. Capecitabine or eribulin or paclitaxel or nab-paclitaxel.
b. 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. The stratification factors were HER2 status, number of prior lines of chemotherapy in the metastatic setting, and hormone receptor/CDK status.
c. A score increase by ≥ 10 points from baseline is deemed a clinically relevant deterioration (scale range of 0 to 100).
d. Unclear proportion of patients with missing values at baseline and in the course of the study.
e. A score decrease by ≥ 15 points from baseline is deemed a clinically relevant deterioration (scale range of 0 to 100).
f. A score decrease by ≥ 10 points from baseline is deemed a clinically relevant deterioration (scale range of 0 to 100).
g. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CI: confidence interval; CDK: cyclin-dependent kinase; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HER2: human epidermal growth factor receptor 2; HR: hazard ratio; n: number of patients with 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; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

On the basis of the available information, at most an indication, e.g. of an added benefit, can be derived for the outcome of overall survival, and at most hints can be derived for all other outcomes due to high risk of bias (see Section 2.2.2).

Mortality

Overall survival

A statistically significant difference in favour of trastuzumab deruxtecan in comparison with treatment of physician's choice was shown for the outcome of overall survival. For this outcome, there is an effect modification by the characteristic of visceral disease (see Section 2.2.4). A statistically significant difference in favour of trastuzumab deruxtecan in comparison with treatment of physician's choice was shown both for patients with and for patients without visceral disease. The extent of the effect differs between the subgroups. There is an indication of an added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice for patients with and for patients without visceral disease.

Morbidity

Symptoms

Symptom outcomes were recorded using the instruments European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module 23 (EORTC QLQ-BR23).

EORTC QLQ-C30

Pain and insomnia

A statistically significant difference in favour of trastuzumab deruxtecan in comparison with treatment of physician's choice was shown for each of the outcomes of pain and insomnia. There is a hint of an added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice for each of these outcomes.

Nausea and vomiting

A statistically significant difference to the disadvantage of trastuzumab deruxtecan in comparison with treatment of physician's choice was shown for the outcome of nausea and vomiting. There is a hint of lesser benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice for this outcome.

Diarrhoea

A statistically significant difference to the disadvantage of trastuzumab deruxtecan in comparison with treatment of physician's choice was shown for the outcome of diarrhoea. However, the extent of the effect for this outcome of the category of non-serious/non-severe symptoms/late complications was no more than marginal. There is no hint of added benefit

of trastuzumab deruxtecan in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Fatigue, dyspnoea, appetite loss, and constipation

No statistically significant difference between treatment groups was shown for any of the outcomes of fatigue, dyspnoea, appetite loss, and constipation. In each case, there is no hint of added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice; an added benefit is therefore not proven.

EORTC QLQ-BR23

Side effects of systemic therapy, breast symptoms, and arm symptoms

No statistically significant difference between treatment groups was shown for the outcomes of side effects of systemic therapy, breast symptoms, and arm symptoms. In each case, there is no hint of added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Upset by hair loss

No suitable 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). There is no hint of added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Health status recorded using the EQ-5D VAS

No statistically significant difference between treatment groups was shown for the outcome of health status recorded with the EQ-5D VAS. There is no hint of added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life outcomes were recorded using the instruments EORTC QLQ-C30 and EORTC QLQ-BR23.

EORTC QLQ-C30

Physical functioning, cognitive functioning, and social functioning

A statistically significant difference in favour of trastuzumab deruxtecan in comparison with treatment of physician's choice was shown for each of the outcomes of physical functioning, cognitive functioning, and social functioning. There is a hint of an added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice for each of these outcomes.

Global health status, role functioning, and emotional functioning

No statistically significant difference between treatment groups was shown for either of the outcomes of global health status, role functioning, and emotional functioning. In each case, there is no hint of added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice; an added benefit is therefore not proven.

EORTC QLQ-BR23

Body image

A statistically significant difference in favour of trastuzumab deruxtecan in comparison with treatment of physician's choice was shown for the outcome of body image. There is an effect modification by the characteristic of age for this outcome (see Section 2.2.4). For patients < 65 years of age, there is a hint of added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice. For patients ≥ 65 years, there is no hint of added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice; an added benefit is therefore not proven for these patients.

Sexual enjoyment

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

Sexual functioning and future perspective

No statistically significant difference between treatment groups was shown for either of the outcomes of sexual functioning and future perspective. In each case, there is no hint of added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Side effects

SAEs and severe AEs

A statistically significant difference in favour of trastuzumab deruxtecan in comparison with treatment of physician's choice was shown for each of the outcomes of SAEs and severe AEs. In each case, there is a hint of lesser harm from trastuzumab deruxtecan in comparison with treatment of physician's choice.

Discontinuation due to AEs

No statistically significant difference was found between treatment groups for the outcome of discontinuation due to AEs. There is 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.

Specific AEs

Hand-foot syndrome (AEs) and neutropenia (severe AEs)

A statistically significant difference in favour of trastuzumab deruxtecan in comparison with treatment of physician's choice was shown for each of the outcomes of hand-foot syndrome (AEs) and neutropenia (severe AEs). In each case, there is a hint of lesser harm from trastuzumab deruxtecan in comparison with treatment of physician's choice.

Platelet count decreased, nausea (each severe AEs), gastrointestinal disorders (AEs), and infections and infestations (SAEs)

A statistically significant difference to the disadvantage of trastuzumab deruxtecan in comparison with treatment of physician's choice was shown for each of the outcomes of platelet count decreased, nausea (each severe AEs), gastrointestinal disorders (AEs), and infections and infestations (SAEs). There is a hint of greater harm from trastuzumab deruxtecan in comparison with treatment of physician's choice for each of these outcomes.

Cardiac disorders (severe AEs)

The company presented no analyses for the outcome of cardiac disorders (severe AEs) in its comments. Due to the small number of events in the total population (see dossier assessment A23-07 [1]), it cannot be assumed that there is a statistically significant effect in the present subpopulation. There is 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.

2.2.4 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)
- visceral disease (yes/no)

The characteristic of sex is disregarded because the total study population includes only 2 men (see dossier assessment A23-07 [1]).

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least 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. Subgroup results where the extent did not differ between subgroups are not presented.

The results are presented in Table 3. The Kaplan-Meier curves on the subgroup results are presented in Appendix A.5.

Table 3: Subgroups (mortality, health-related quality of life) – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a]

Study Outcome Characteristic Subgroup	Trastuzumab deruxtecan N	Median time to event in months [95% CI] Patients with event n (%)	Treatment of physician's choice[a] N	Median time to event in months [95% CI] Patients with event n (%)	Trastuzumab deruxtecan vs. treatment of physician's choice[a] HR [95% CI][b]	p-value[c]
DESTINY-Breast04						
Mortality						
Overall survival						
Visceral disease						
Yes	306	21.7 [19.5; 24.7] 130 (42.5)	143	17.1 [15.2; 22.4] 65 (45.5)	0.73 [0.54; 0.99]	0.039
No	38	NA 7 (18.4)	22	15.1 [12.6; 20.6] 13 (59.1)	0.22 [0.09; 0.57]	0.001
Total					Interaction:	0.018[d]
Health-related quality of life						
EORTC QLQ-BR23 – time to first deterioration by ≥ 10 points[e]						
Body image						
Age						
< 65 years	270	13.8 [9.7; NC] 109 (40.4)	122	4.2 [1.7; 6.5] 60 (49.2)	0.55 [0.40; 0.754]	< 0.001
≥ 65 years	74	10.8 [4.2; NC] 34 (45.9)	43	16.9 [4.2; NC] 15 (34.9)	1.17 [0.64; 2.16]	0.600
Total					Interaction:	0.026[d]

a. Capecitabine or eribulin or paclitaxel or nab-paclitaxel.
b. Unstratified Cox proportional hazards regression model.
c. Unstratified log-rank test.
d. Interaction term from Cox proportional hazards regression model with treatment, subgroup and interaction between treatment and subgroup as covariates.
e. A score decrease by ≥ 10 points from baseline is deemed a clinically relevant deterioration (scale range of 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 visceral disease for the outcome of overall survival. A statistically significant difference in favour of trastuzumab deruxtecan in comparison with treatment of physician's choice was shown both for patients with and for patients without visceral disease. The extent of the effect differs between the subgroups. There is an indication of an added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice both for patients with and for patients without visceral disease.

Health-related quality of life

Body image

There is an effect modification by the characteristic of age for the outcome of body image. A statistically significant difference in favour of trastuzumab deruxtecan was found for patients < 65 years of age, whereas no statistically significant difference between treatment groups was shown for patients ≥ 65 years of age. There is a hint of an added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice for patients < 65 years. For patients ≥ 65 years, there is no hint of added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice; 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 [9].

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.

Determination of the outcome category for symptom outcomes

Compared with benefit assessment A23-07 [1], there have been no changes in the determination of the outcome category for the symptom outcomes for the present addendum.

2.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Sections 2.2.3 and 2.2.4 (see Table 4).

Table 4: Extent of added benefit at outcome level: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

Observation period **Outcome category** **Outcome** **Effect modifier** **Subgroup**	**Trastuzumab deruxtecan vs. treatment of physician's choice[a]** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Outcomes with observation over the entire study duration		
Mortality		
Overall survival Visceral disease Yes	21.7 vs. 17.1 HR: 0.73 [0.54; 0.99] p = 0.039 Probability: "indication"	Outcome category: mortality $0.95 \leq CI_u < 1.00$ Added benefit, extent: "minor"
No	NA vs. 15.1 HR: 0.22 [0.09; 0.57] p = 0.001 Probability: "indication"	Outcome category: mortality $CI_u < 0.85$ Added benefit, extent: "major"
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30; time to first deterioration by ≥ 10 points)		
Fatigue	4.2 vs. 2.8 HR: 0.81 [0.63; 1.03] p = 0.081	Lesser/added benefit not proven
Nausea and vomiting	1.4 vs. 8.2 HR: 2.12 [1.61; 2.78] HR: 0.47 [0.36; 0.62][d] p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ Lesser benefit; extent: "considerable"
Pain	8.5 vs. 4.4 HR: 0.69 [0.53; 0.898] p = 0.005 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ Added benefit, extent: "minor"

Table 4: Extent of added benefit at outcome level: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

Observation period **Outcome category** **Outcome** **Effect modifier** **Subgroup**	**Trastuzumab deruxtecan vs. treatment of physician's choice[a]** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Dyspnoea	13.2 vs. 6.8 HR: 0.80 [0.60; 1.08] p = 0.148	Lesser/added benefit not proven
Insomnia	16.0 vs. 5.4 HR: 0.56 [0.42; 0.74] p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ Added benefit, extent: "considerable"
Appetite loss	5.1 vs. 7.0 HR: 1.20 [0.92; 1.58] p = 0.190	Lesser/added benefit not proven
Constipation	4.2 vs. 5.9 HR: 1.17 [0.89; 1.54] p = 0.255	Lesser/added benefit not proven
Diarrhoea	9.4 vs. 13.3 HR: 1.37 [1.003; 1.87] HR: 0.73 [0.53; 0.997][d] p = 0.049	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser benefit/added benefit not proven[e]
Symptoms (EORTC QLQ-BR23; time to first deterioration by ≥ 10 points)		
Side effects of systemic therapy	4.2 vs. 2.8 HR: 0.82 [0.64; 1.06] p = 0.131	Lesser/added benefit not proven
Breast symptoms	NA vs. NA HR: 0.89 [0.60; 1.31] p = 0.554	Lesser/added benefit not proven
Arm symptoms	7.7 vs. 5.1 HR: 0.78 [0.59; 1.03] p = 0.079	Lesser/added benefit not proven
Upset by hair loss	No suitable data[f]	Lesser/added benefit not proven
Health status (EQ-5D VAS; time to first deterioration by ≥ 15 points)	16.4 vs. 8.4 HR: 0.82 [0.59; 1.13] p = 0.220	Lesser/added benefit not proven

Table 4: Extent of added benefit at outcome level: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

Observation period **Outcome category** **Outcome** **Effect modifier** **Subgroup**	**Trastuzumab deruxtecan vs. treatment of physician's choice[a]** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Health-related quality of life		
EORTC QLQ-C30 (time to first deterioration by ≥ 10 points)		
Global health status	5.6 vs. 4.0 HR: 0.81 [0.63; 1.04] p = 0.097	Lesser/added benefit not proven
Physical functioning	8.7 vs. 4.5 HR: 0.62 [0.47; 0.81] p < 0.001 Probability: "hint"	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ Added benefit, extent: "considerable"
Role functioning	4.2 vs. 3.2 HR: 0.81 [0.63; 1.04] p = 0.089	Lesser/added benefit not proven
Emotional functioning	10.4 vs. 7.1 HR: 0.89 [0.66; 1.20] p = 0.432	Lesser/added benefit not proven
Cognitive functioning	6.5 vs. 4.2 HR: 0.75 [0.58; 0.97] p = 0.028 Probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Added benefit, extent: "minor"
Social functioning	5.9 vs. 3.4 HR: 0.73 [0.57; 0.94] p = 0.014 Probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Added benefit, extent: "minor"
EORTC QLQ-BR23 (time to first deterioration by ≥ 10 points)		
Body image Age < 65 years	13.8 vs. 4.2 HR: 0.55 [0.40; 0.754] p < 0.001 Probability: "hint"	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ Added benefit, extent: "considerable"
≥ 65 years	10.8 vs. 16.9 HR: 1.17 [0.64; 2.16] p = 0.600	Lesser/added benefit not proven

Table 4: Extent of added benefit at outcome level: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

Observation period **Outcome category** **Outcome** **Effect modifier** **Subgroup**	**Trastuzumab deruxtecan vs. treatment of physician's choice[a]** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Sexual functioning	NA vs. NA HR: 0.91 [0.59; 1.39] p = 0.651	Lesser/added benefit not proven
Sexual enjoyment	No suitable data[f]	Lesser/added benefit not proven
Future perspective	16.9 vs. NA HR: 0.98 [0.70; 1.38] p = 0.916	Lesser/added benefit not proven
Side effects		
SAEs	NA vs. NA HR: 0.66 [0.45; 0.97] p = 0.034 Probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Lesser harm, extent: "minor"
Severe AEs[g]	7.2 vs. 0.9 HR: 0.50 [0.39; 0.64] p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Lesser harm, extent: "major"
Discontinuation due to AEs	NA vs. NA HR: 1.09 [0.58; 2.04] p = 0.784	Greater/lesser harm not proven
Hand-foot syndrome (AEs)	NA vs. NA HR: 0.05 [0.02; 0.15] p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Lesser harm; extent: "considerable"
Cardiac disorders (severe AEs[g])	ND HR: ND p: ND	Greater/lesser harm not proven
Platelet count decreased (severe AEs[g])	NA vs. NA 19 (5.5) vs. 0 (0) patients HR: NC p = 0.009 Probability: "hint"	Outcome category: serious/severe side effects greater harm, extent: "non-quantifiable"[h]
Gastrointestinal disorders (AEs)	0.1 vs. 0.7 HR: 2.13 [1.69; 2.68] HR: 0.47 [0.37; 0.59][d] p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm, extent: "considerable"

Table 4: Extent of added benefit at outcome level: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

Observation period **Outcome category** **Outcome** **Effect modifier** **Subgroup**	**Trastuzumab deruxtecan vs. treatment of physician's choice[a]** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Infections and infestations (SAEs)	NA vs. NA HR: 4.22 [0.99; 17.92] HR: 0.24 [0.06; 1.01][d] p = 0.034 Probability: "hint"	Outcome category: serious/severe side effects Greater harm, extent: "minor"[i]
Neutropenia (severe AEs[g])	NA vs. NA HR: 0.32 [0.17; 0.59] p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% Lesser harm, extent: "major"
Nausea (severe AEs[g])	NA vs. NA 16 (4.7) vs. 0 (0) patients HR: NC p = 0.010 Probability: "hint"	Outcome category: serious/severe side effects Greater harm, extent: "non-quantifiable"[h]

a. Capecitabine or eribulin or paclitaxel or nab-paclitaxel.
b. Probability provided if a statistically significant and relevant effect is present.
c. 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).
d. Institute's calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit.
e. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
f. See Section 2.2.3 for the reasoning.
g. Operationalized as CTCAE grade ≥ 3.
h. The extent cannot be estimated from the observed data.
i. Discrepancy between p-value (log-rank test) and CI (Cox model) due to different calculation methods; the extent is rated as minor.

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

Table 5: Positive and negative effects from the assessment of trastuzumab deruxtecan compared with treatment of physician's choice[a]

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
Mortality ▪ Overall survival: ▫ Visceral disease (yes): indication of an added benefit – extent: "minor" ▫ Visceral disease (no): indication of an added benefit – extent: "major"	–
Outcomes with shortened observation period	
Morbidity Non-serious/non-severe symptoms/late complications Symptoms (EORTC QLQ-C30): ▪ Pain: hint of an added benefit – extent "minor" ▪ Insomnia: hint of an added benefit – extent: "considerable"	Morbidity Non-serious/non-severe symptoms/late complications Symptoms (EORTC QLQ-C30): ▪ Nausea and vomiting: hint of lesser benefit – extent: "considerable"
Health-related quality of life EORTC QLQ-C30: ▪ Physical functioning: hint of an added benefit – extent: "considerable" ▪ Cognitive functioning: hint of an added benefit – extent: "minor" ▪ Social functioning: hint of an added benefit – extent: "minor" EORTC QLQ-BR23: ▪ Body image: ▫ < 65 years: hint of an added benefit – extent: "considerable"	–
Serious/severe side effects ▪ SAEs: hint of lesser harm – extent: "minor" ▪ Severe AEs: hint of lesser harm – extent: "major", including ▫ neutropenia (severe AE): hint of lesser harm – extent: "major"	Serious/severe side effects ▪ Platelet count decreased (severe AE): hint of greater harm – extent: "non-quantifiable" ▪ Infections and infestations (SAE): hint of greater harm – extent: "minor" ▪ Nausea (severe AE): hint of greater harm – extent: "non-quantifiable"
Non-serious/non-severe side effects ▪ Hand-foot syndrome (AE): hint of lesser harm – extent: "considerable"	Non-serious/non-severe side effects ▪ Gastrointestinal disorders (AE): hint of greater harm – extent: "considerable"
a. Capecitabine or eribulin or paclitaxel or nab-paclitaxel. 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, there are both positive and negative effects of different extents for trastuzumab deruxtecan in comparison with treatment of physician's choice. Only for overall survival are the observed effects based on the entire observation period. For the outcome categories of morbidity, health-related quality of life and side effects, however, they are based exclusively on the shortened observation period of approx. 4.5 months (morbidity, health-related quality of life) and 40 days (side effects) after the end of treatment with the study medication.

For the outcome of overall survival, an effect modification by the characteristic of visceral disease was shown. There is an indication of minor added benefit for patients with visceral disease, and an indication of major added benefit for patients without visceral disease for the outcome of overall survival. Due to this effect modification, the added benefit is derived separately for patients with and without visceral disease.

For non-serious/non-severe symptoms/late complications, as well as for non-serious/non-severe side effects, both positive and negative effects of trastuzumab deruxtecan of different extents, each with the probability of a hint, were shown for all patients. For health-related quality of life, there are exclusively positive effects in several outcomes with the extents “minor” to “considerable”. For the severe/serious side effects, there is, among others, a positive effect in the overall rate of SAEs and severe AEs with the extents “minor” and “major”. However, there are also negative effects in several severe specific AEs with the extents “minor” or “non-quantifiable”.

Overall, the positive effects prevail, so that the negative effects do not call into question the minor or major extent of added benefit in the outcome of overall survival. In summary, the added benefit for patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy is derived as follows: In comparison with treatment of physician’s choice, there is an indication of minor added benefit of trastuzumab deruxtecan for patients with visceral disease, and an indication of major added benefit for patients without visceral disease.

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 A23-07: In comparison with treatment of physician’s choice, there is an indication of minor added benefit of trastuzumab deruxtecan for patients with visceral disease, and an indication of major added benefit for patients without visceral disease.

Table 6 below shows the result of the benefit assessment of trastuzumab deruxtecan, taking into account dossier assessment A23-07 and the present addendum.

Table 6: Trastuzumab deruxtecan – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults[b] with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy[c]	▪ Capecitabine or ▪ eribulin or ▪ vinorelbine or ▪ an anthracycline or taxane-containing regimen (only for patients who have not yet received an anthracycline and/or taxane-containing regimen or who are eligible for renewed anthracycline or taxane-containing treatment)	▪ Patients with visceral disease: indication of minor added benefit[d] ▪ Patients without visceral disease: indication of major added benefit[d]

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, the evidence on treatment options for men with breast cancer is extremely limited. According to the guidelines, the recommendations for the treatment of men are predominantly based on the recommendations for the treatment of women. Within the framework of the benefit assessment, separate consideration of men can be useful.
c. The therapeutic indication may also include patients who are candidates for further endocrine therapy. According to the G-BA, it is assumed that the endocrine treatment options for patients with hormone receptor-positive breast cancer have been exhausted in the present treatment situation. It is also assumed according to the G-BA that, as part of prior therapy, patients typically received taxane and/or anthracycline-containing chemotherapy. Moreover, it is assumed that (secondary) resection or radiotherapy with curative intent is not indicated. According to guideline recommendations, combination therapy should be considered for patients with high remission pressure due to severe symptoms or rapid tumour growth.
d. Only patients with an ECOG PS of 0 or 1 and 2 male patients were included in the DESTINY-Breast04 study. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 and to male patients.

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

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Appendix A Graphic display of the time-to-event analyses presented in the addendum (Kaplan-Meier curves)

A.1 Mortality

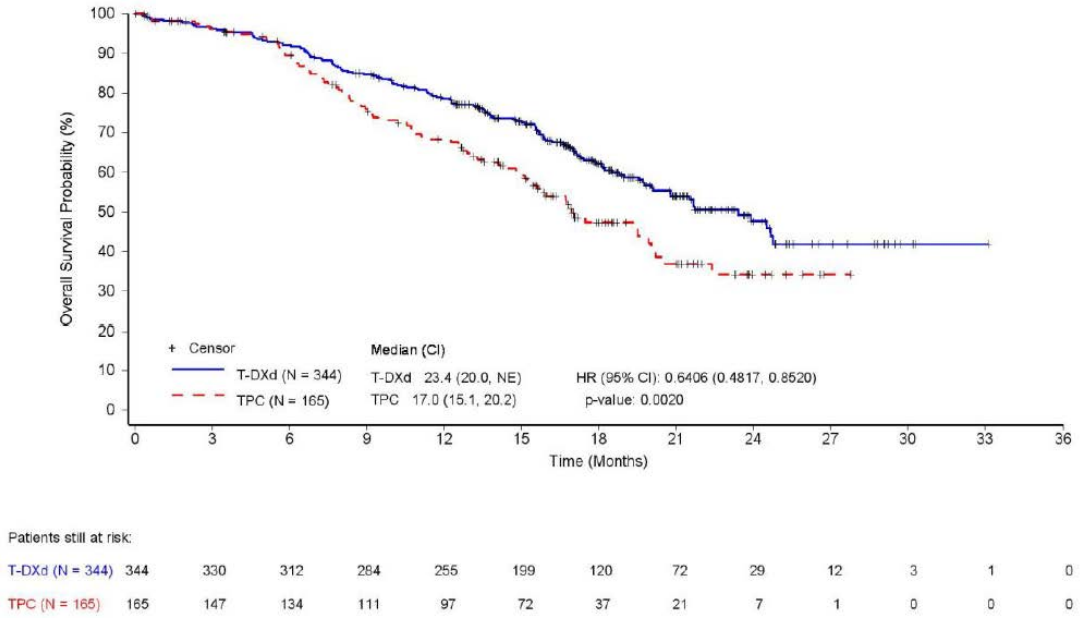

Figure 1: Kaplan-Meier curves for the outcome of overall survival

A.2 Morbidity

A.2.1 Symptoms (EORTC QLQ-C30)

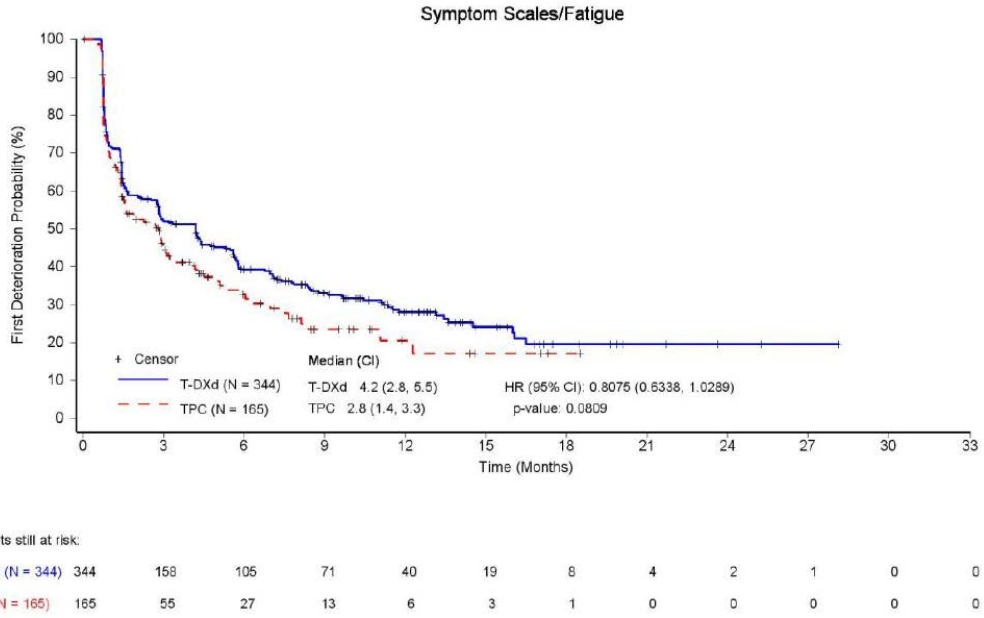

Figure 2: Kaplan-Meier curves the outcome of fatigue (EORTC QLQ-C30, first deterioration by ≥ 10 points)

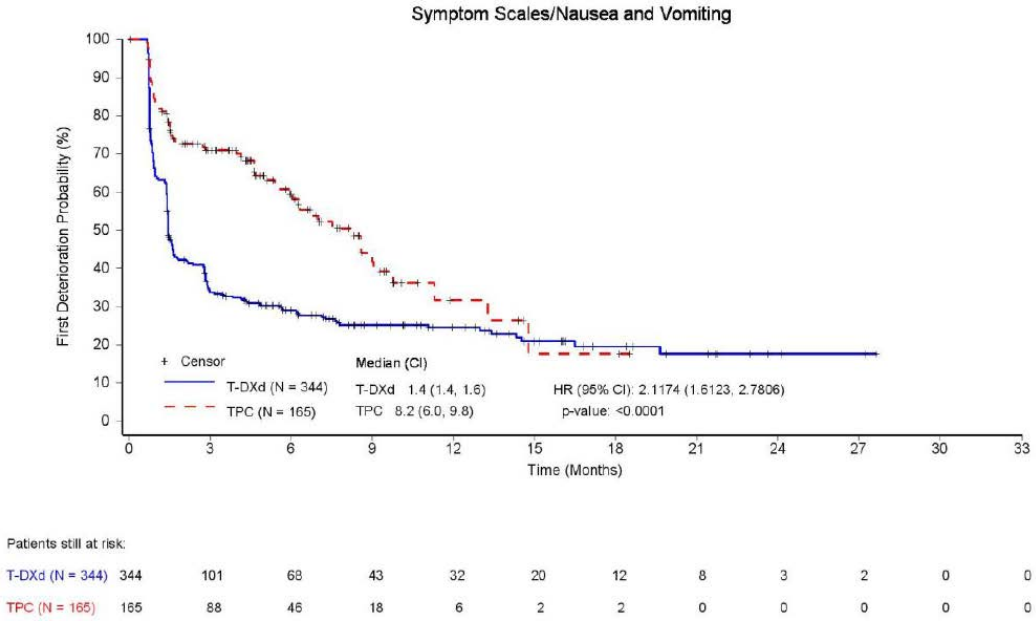

Figure 3: Kaplan-Meier curves for the outcome auf nausea and vomiting (EORTC QLQ-C30, first deterioration by ≥ 10 points)

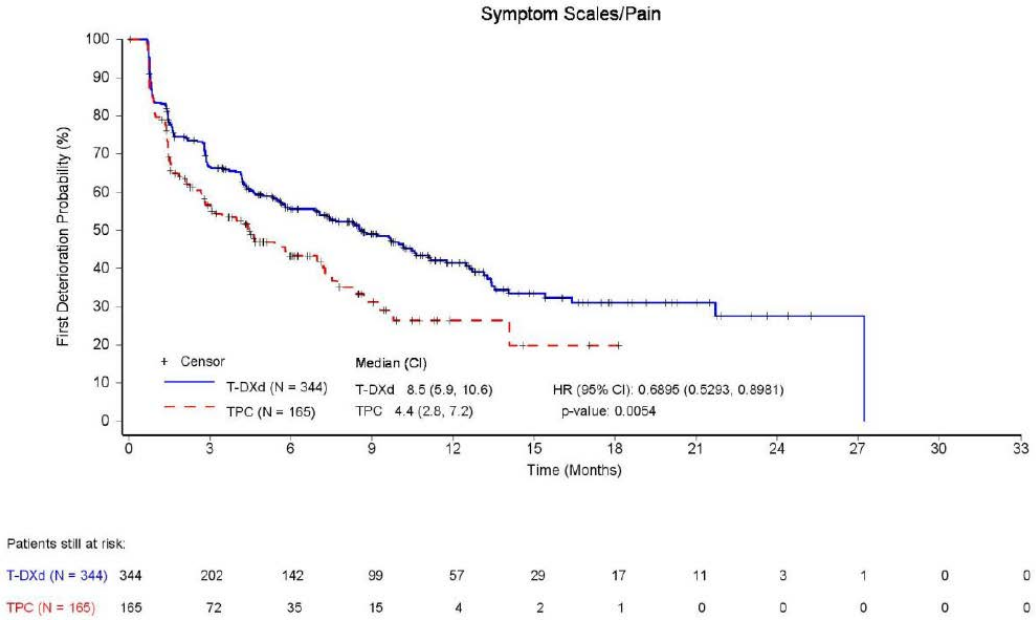

Figure 4: Kaplan-Meier curves for the outcome of pain (EORTC QLQ-C30, first deterioration by ≥ 10 points)

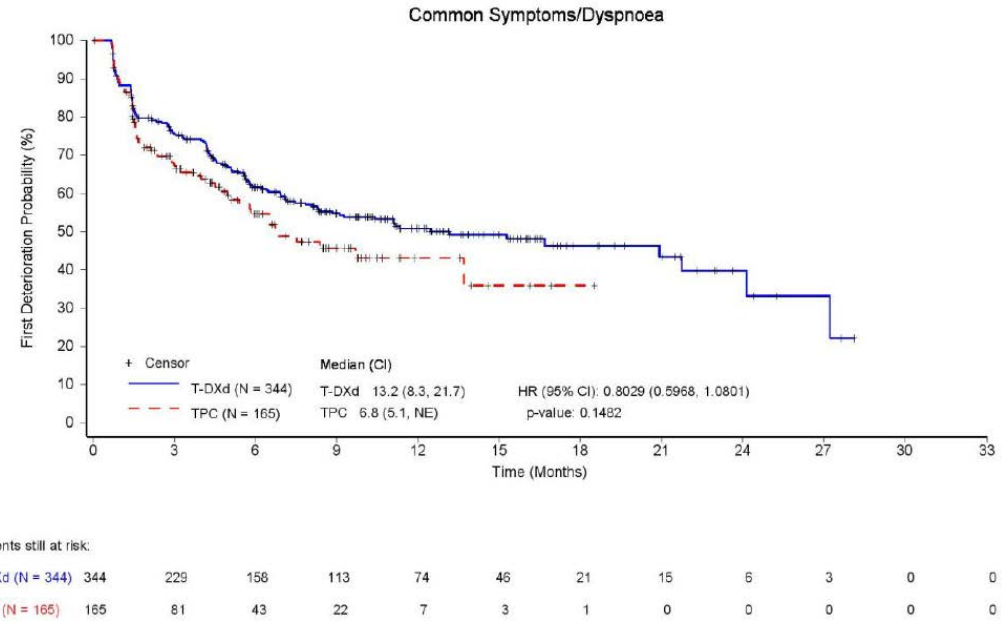

Figure 5: Kaplan-Meier curves for the outcome of dyspnoea (EORTC QLQ-C30, first deterioration by ≥ 10 points)

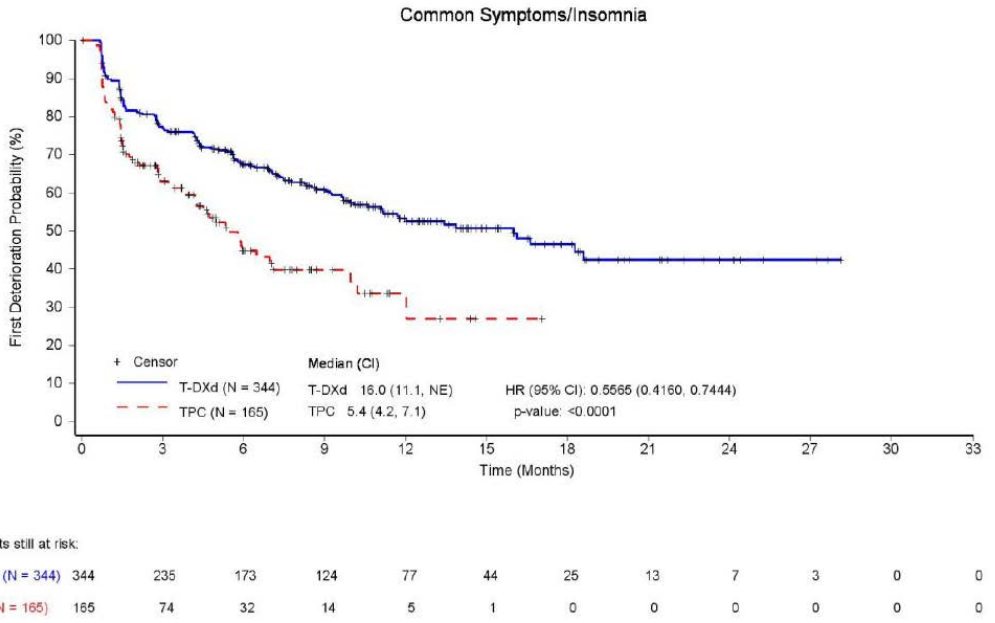

Figure 6: Kaplan-Meier curves for the outcome of insomnia (EORTC QLQ-C30, first deterioration by ≥ 10 points)

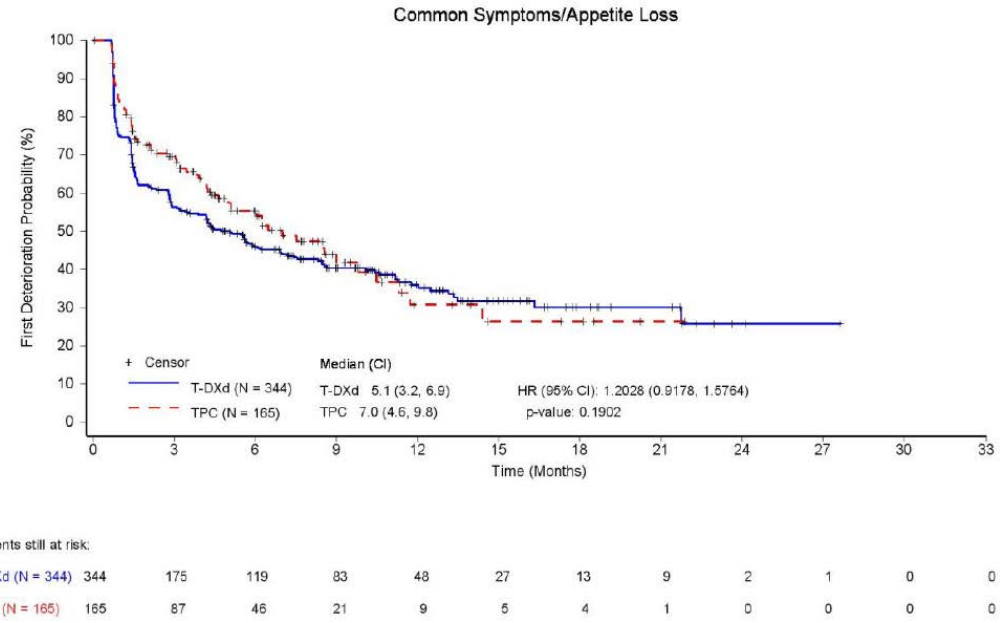

Figure 7: Kaplan-Meier curves for the outcome of appetite loss (EORTC QLQ-C30, first deterioration by ≥ 10 points)

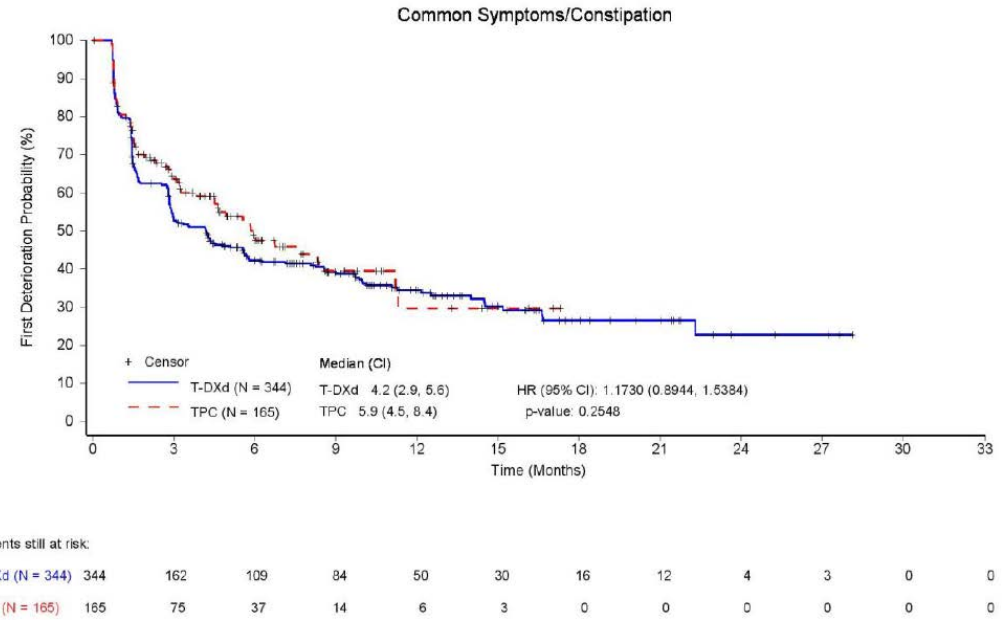

Figure 8: Kaplan-Meier curves for the outcome of constipation (EORTC QLQ-C30, first deterioration by ≥ 10 points)

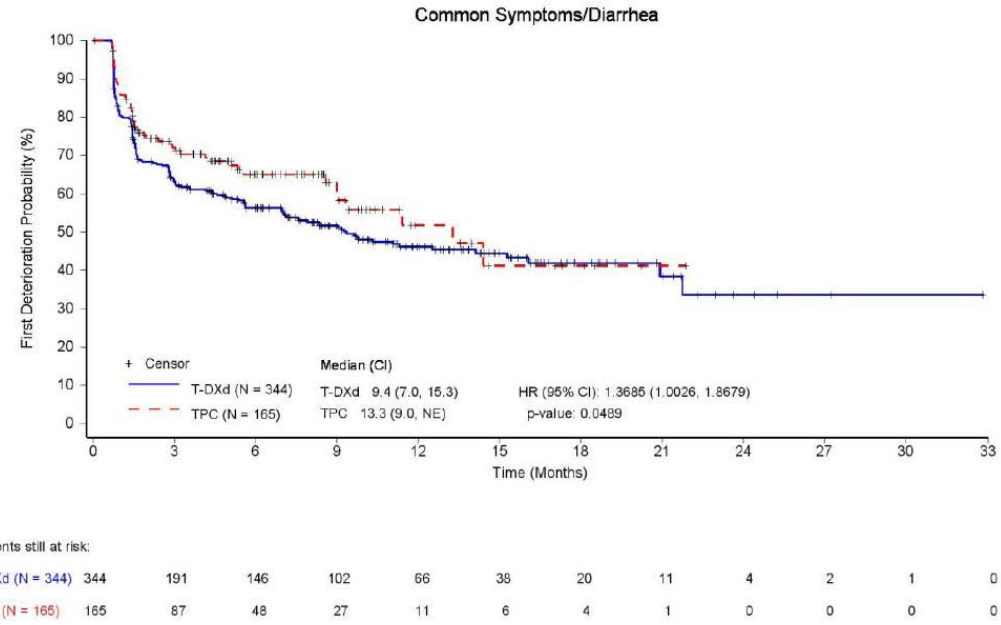

Figure 9: Kaplan-Meier curves for the outcome of diarrhoea (EORTC QLQ-C30, first deterioration by ≥ 10 points)

A.2.2 Symptoms (EORTC QLQ-BR23)

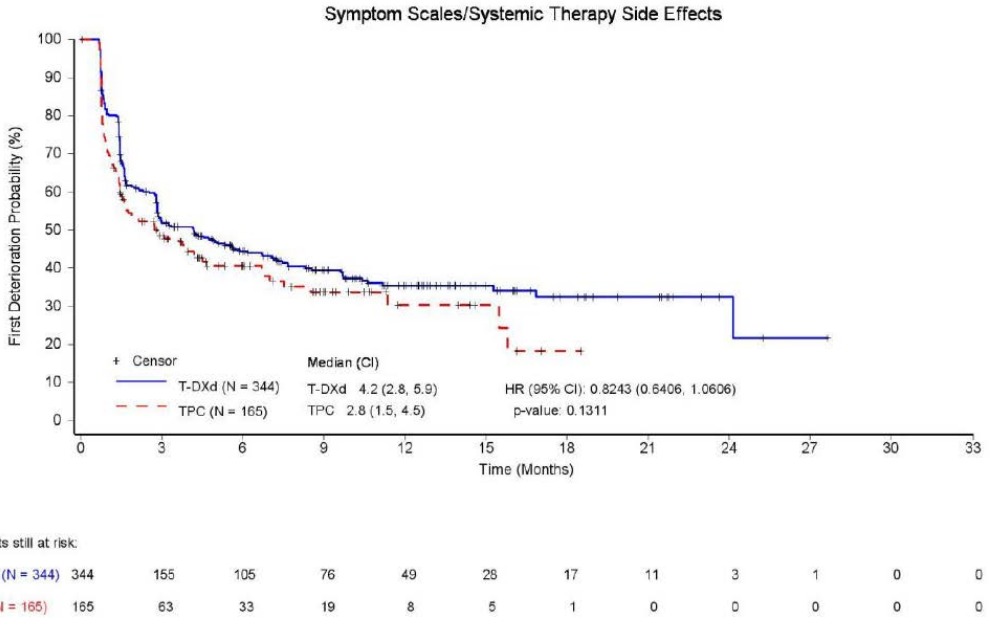

Figure 10: Kaplan-Meier curves for the outcome of systemic therapy side effects (EORTC QLQ-BR23, first deterioration by ≥ 10 points)

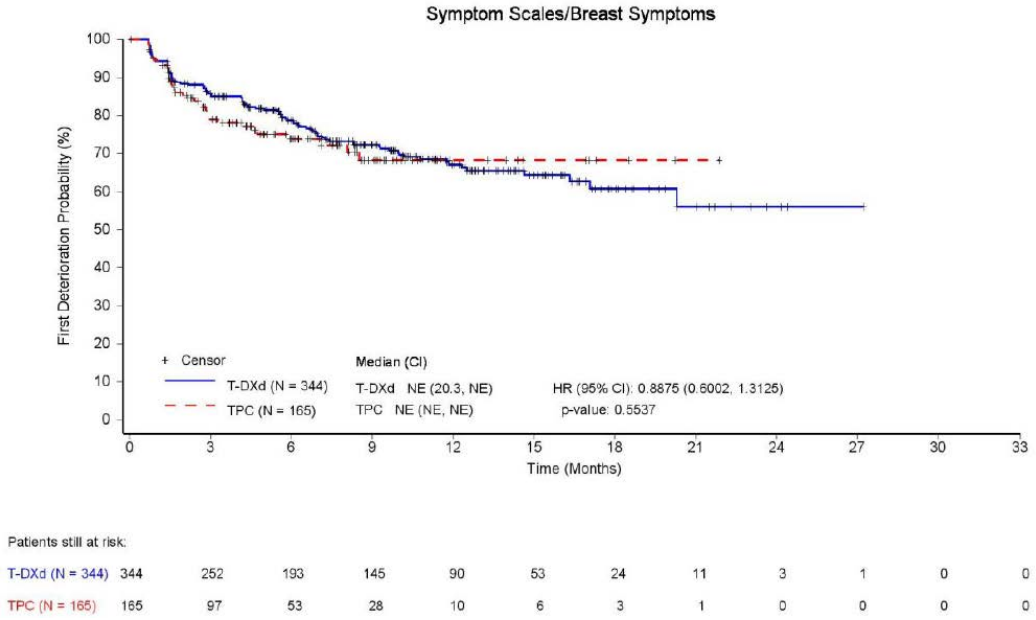

Figure 11: Kaplan-Meier curves for the outcome of breast symptoms (EORTC QLQ-BR23, first deterioration by ≥ 10 points)

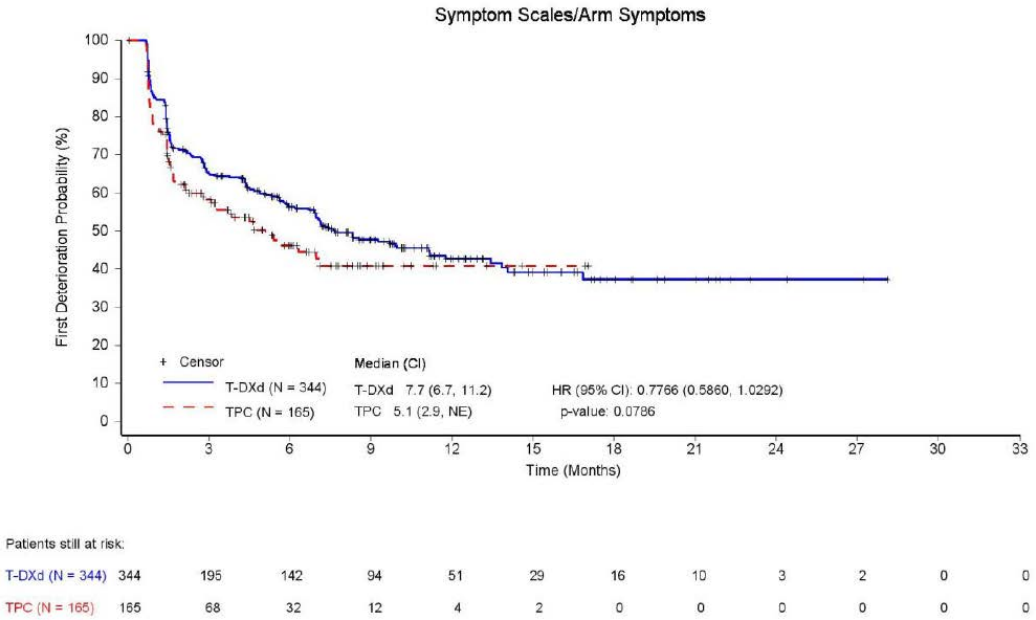

Figure 12: Kaplan-Meier curves for the outcome of arm symptoms (EORTC QLQ-BR23, first deterioration by ≥ 10 points)

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

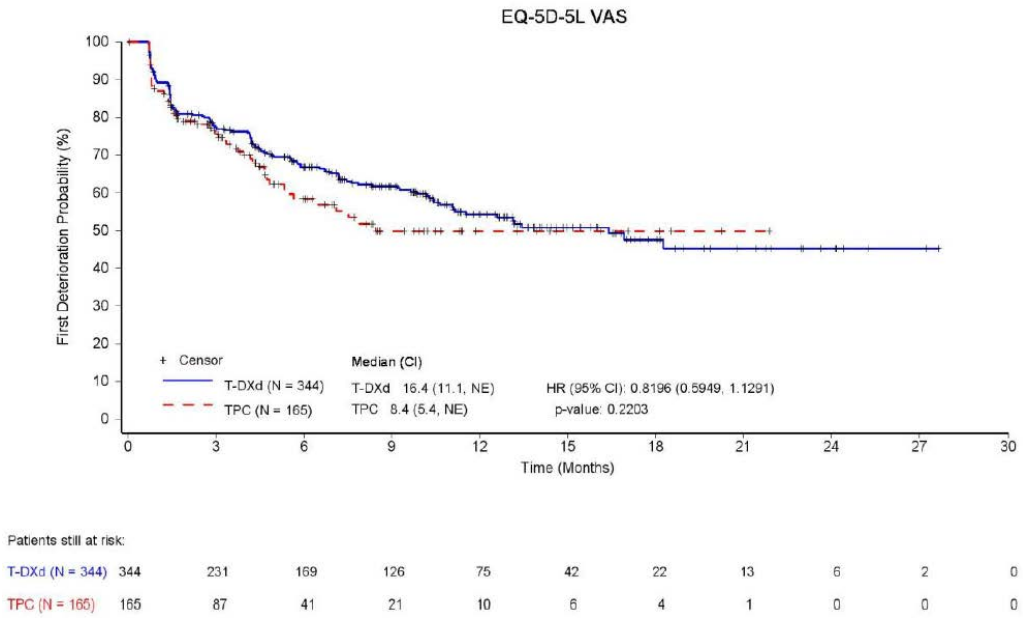

Figure 13: Kaplan-Meier curves for the outcome of health status (EQ-5D VAS, first deterioration by ≥ 15 points)

A.3 Health-related quality of life

A.3.1 EORTC QLQ-C30

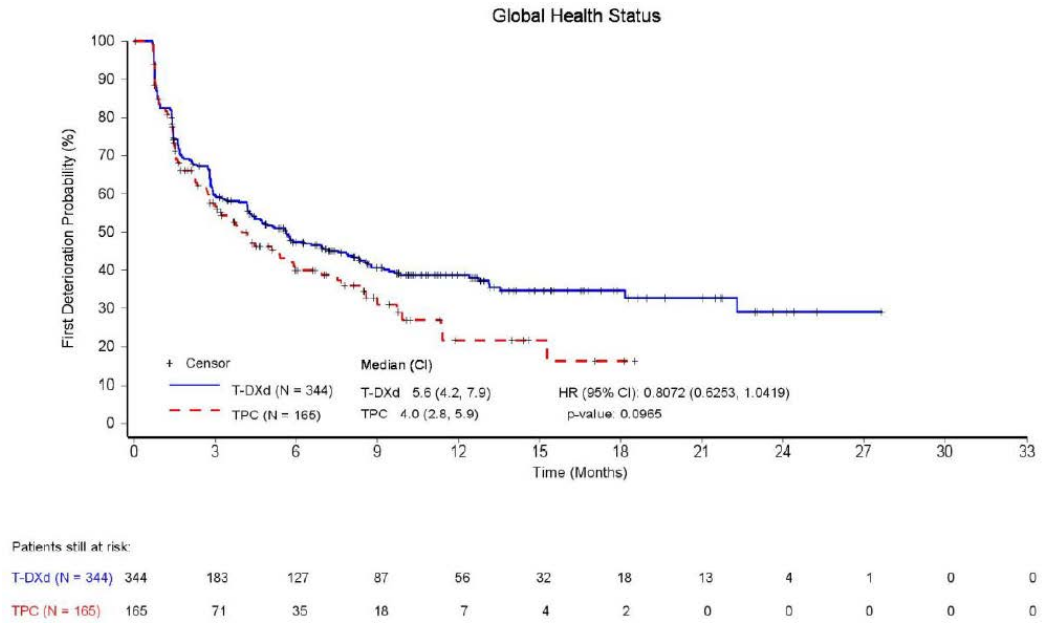

Figure 14: Kaplan-Meier curves for the outcome of global health status (EORTC QLQ-C30, first deterioration by ≥ 10 points)

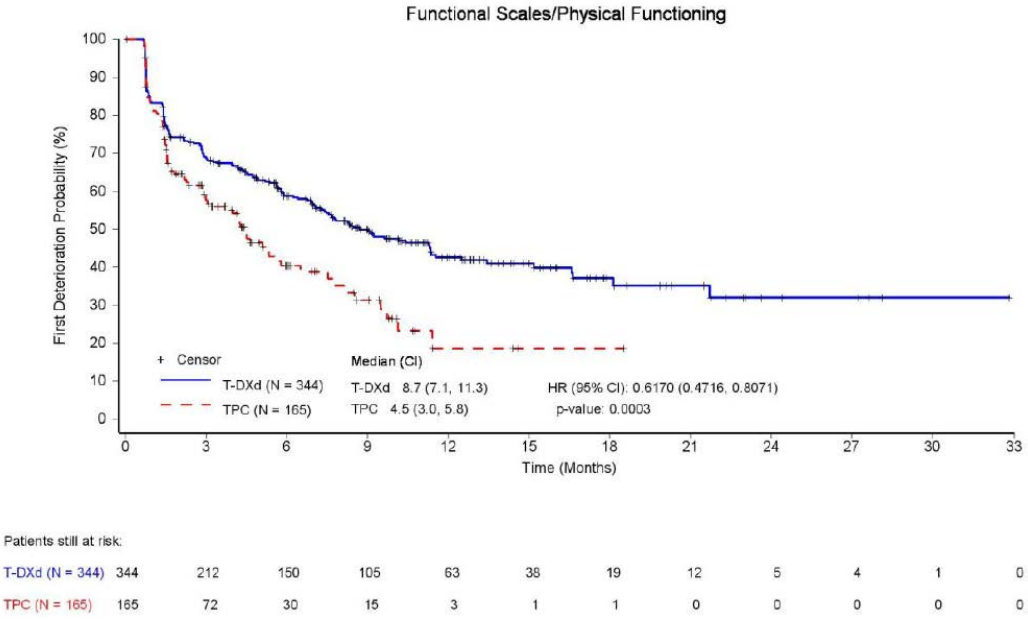

Figure 15: Kaplan-Meier curves for the outcome of physical functioning (EORTC QLQ-C30, first deterioration by ≥ 10 points)

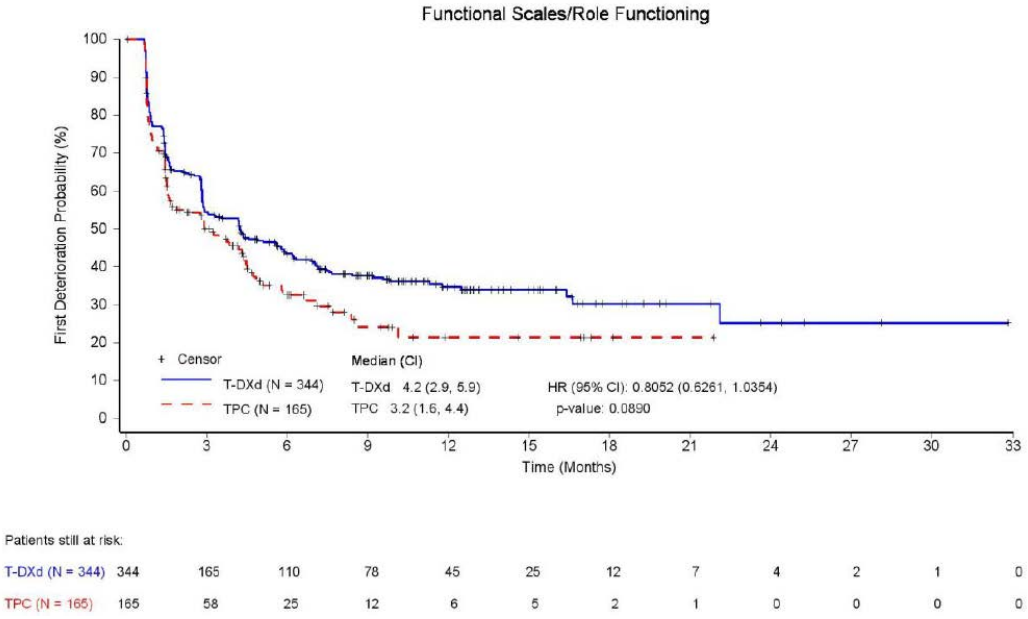

Figure 16: Kaplan-Meier curves for the outcome of role functioning (EORTC QLQ-C30, first deterioration by ≥ 10 points)

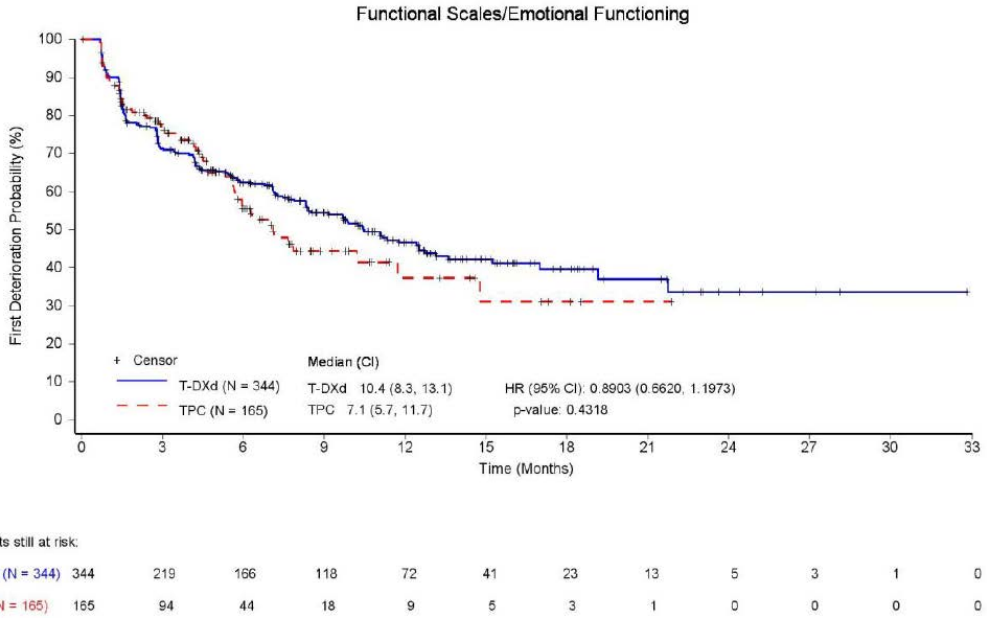

Figure 17: Kaplan-Meier curves for the outcome of emotional functioning (EORTC QLQ-C30, first deterioration by ≥ 10 points)

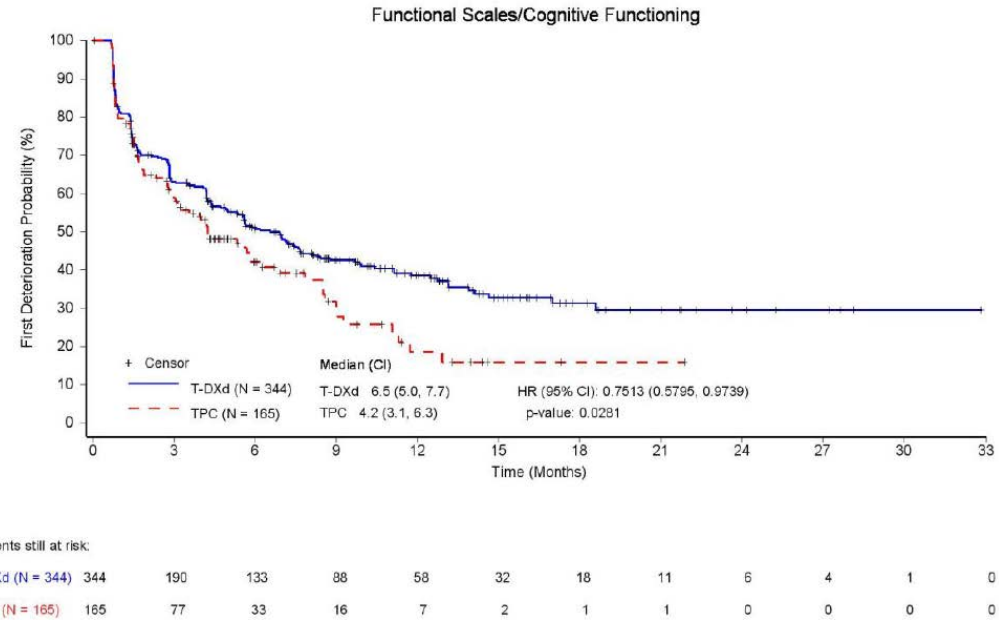

Figure 18: Kaplan-Meier curves for the outcome of cognitive functioning (EORTC QLQ-C30, first deterioration by ≥ 10 points)

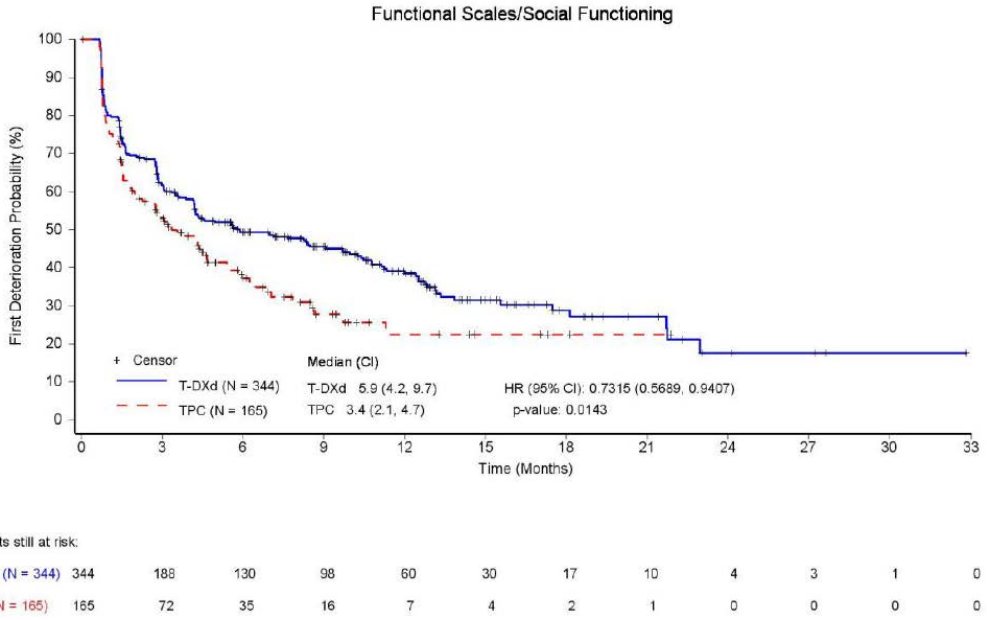

Figure 19: Kaplan-Meier curves for the outcome of social functioning (EORTC QLQ-C30, first deterioration by ≥ 10 points)

A.3.2 EORTC QLQ-BR23

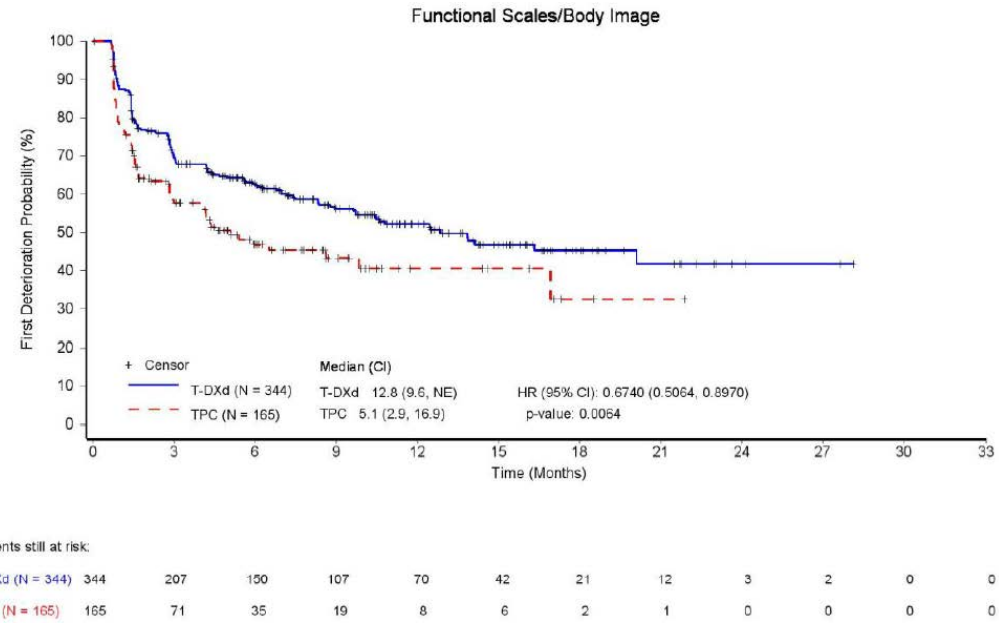

Figure 20: Kaplan-Meier curves for the outcome of body image (EORTC QLQ-BR23, first deterioration by ≥ 10 points)

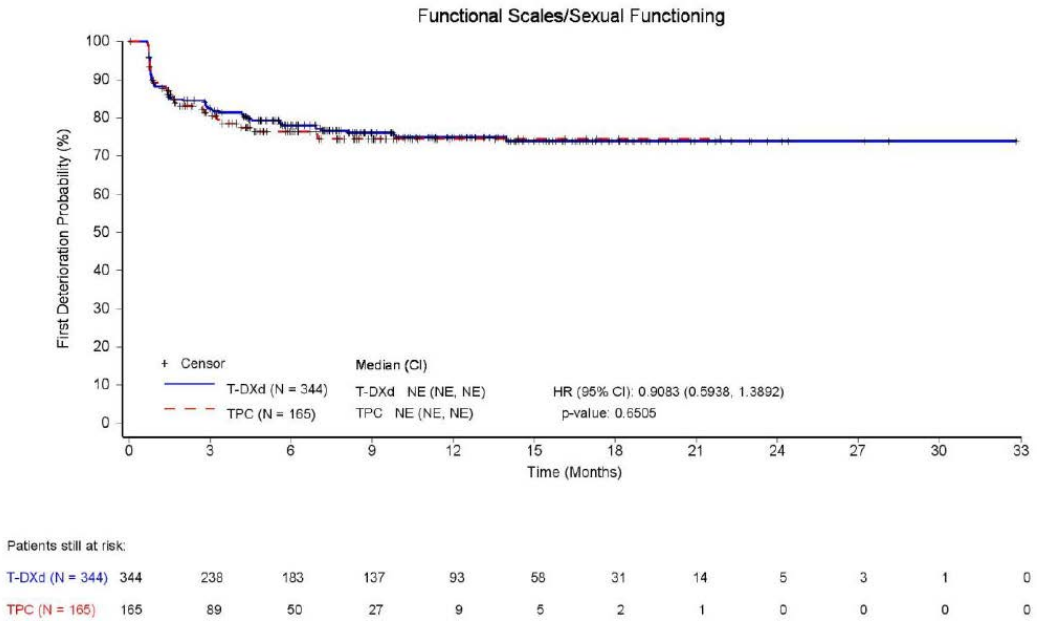

Figure 21: Kaplan-Meier curves for the outcome of sexual functioning (EORTC QLQ-BR23, first deterioration by ≥ 10 points)

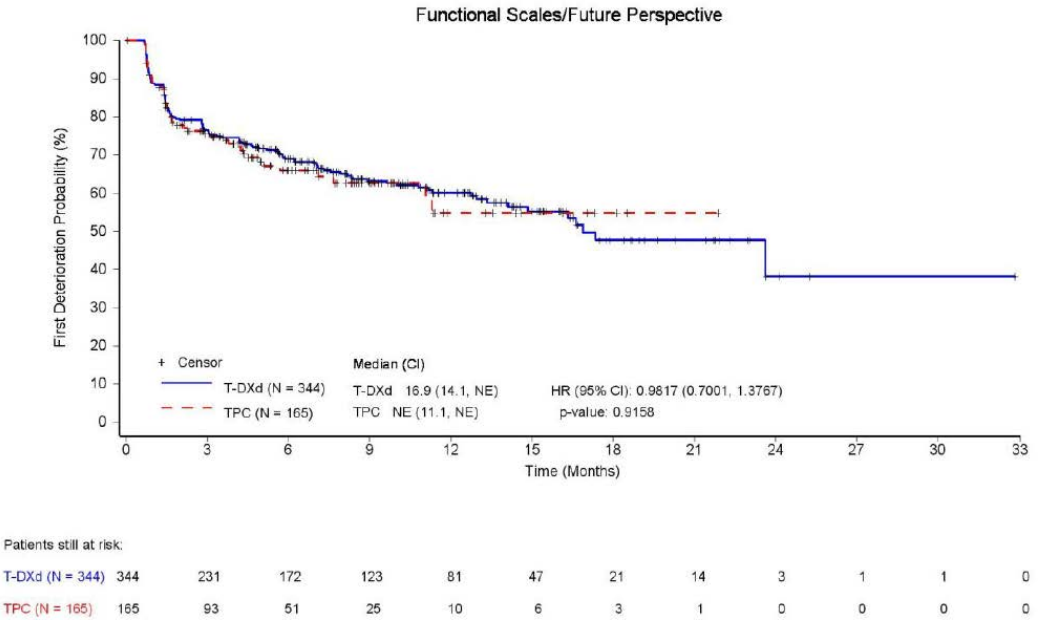

Figure 22: Kaplan-Meier curves for the outcome of future perspective (EORTC QLQ-BR23, first deterioration by ≥ 10 points)

A.4 Side effects

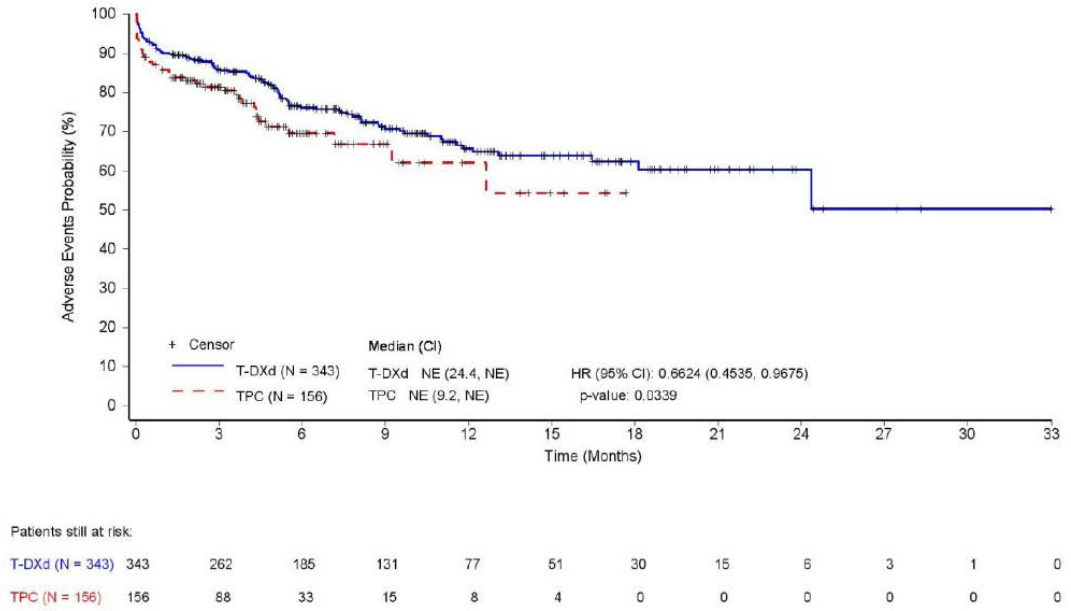

Figure 23: Kaplan-Meier curves for the outcome of SAEs

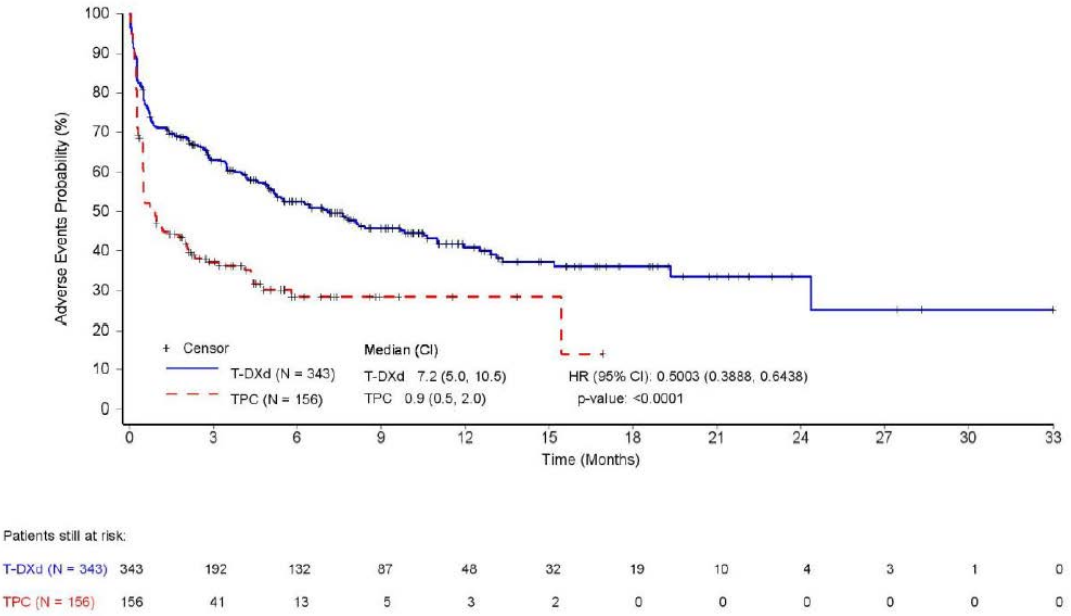

Figure 24: Kaplan-Meier curves for the outcome of severe AEs (Common Terminology Criteria for Adverse Events grade ≥ 3)

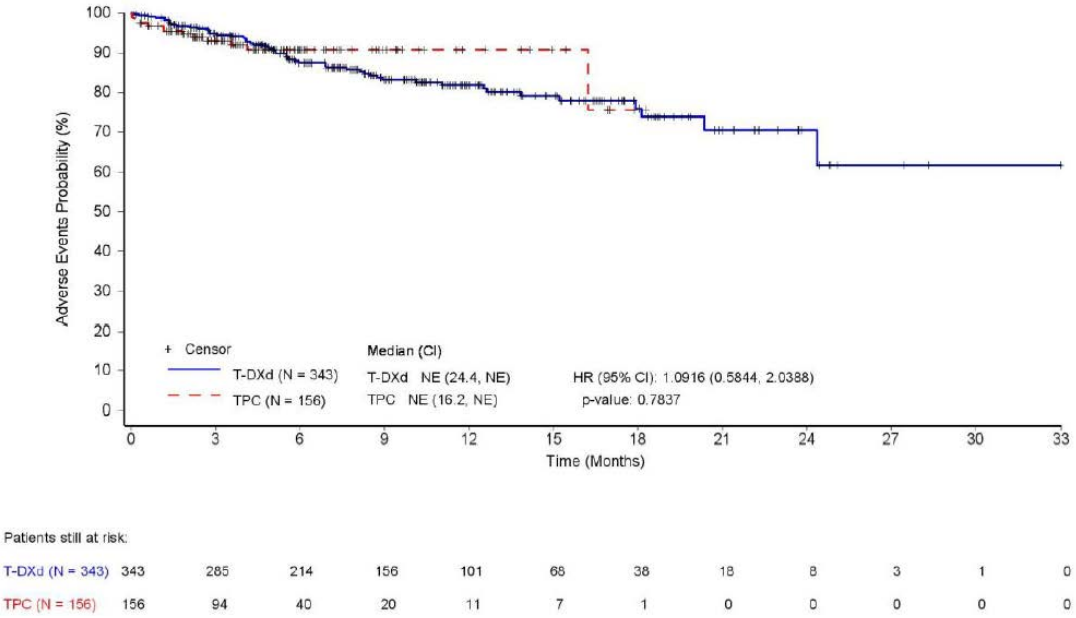

Figure 25: Kaplan-Meier curves for the outcome of discontinuation due to AEs

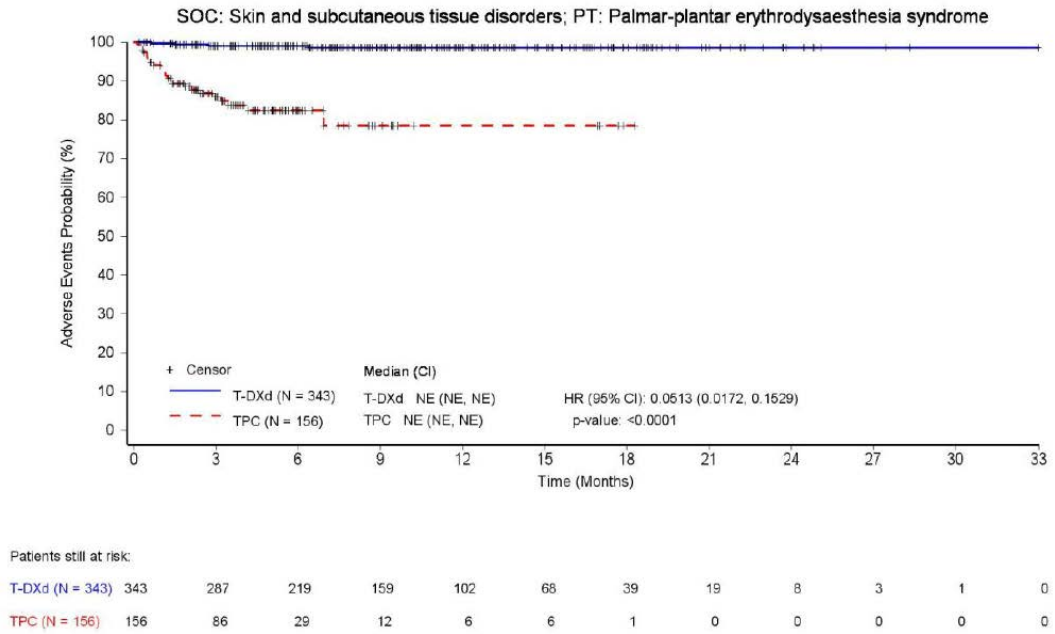

Figure 26: Kaplan-Meier curves for the outcome of hand-foot syndrome (Preferred Term [PT], AEs)

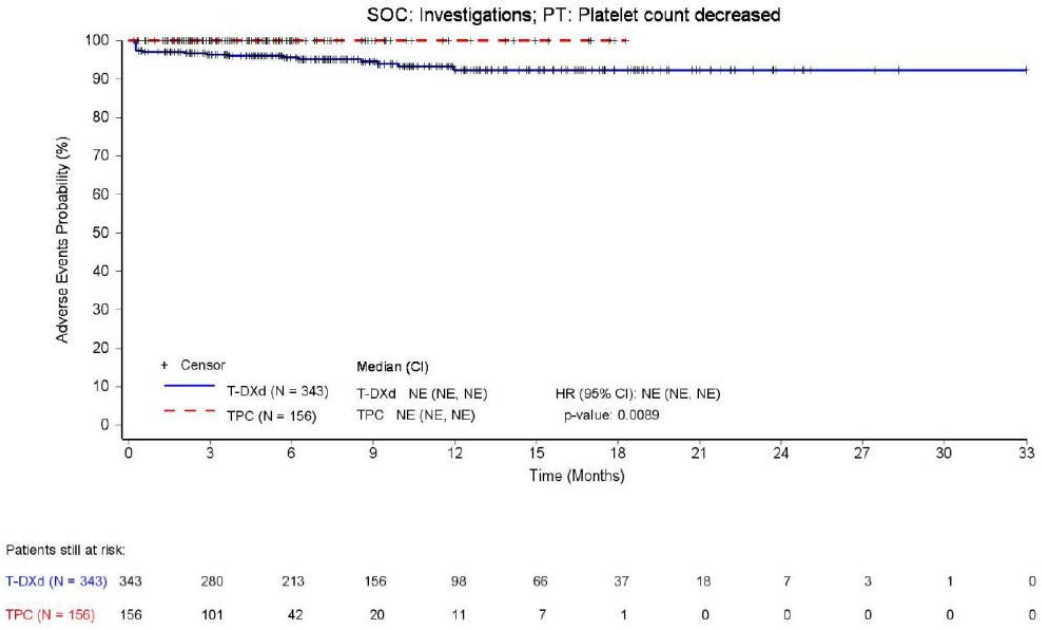

Figure 27: Kaplan-Meier curves for the outcome of platelet count decreased (PT, severe AEs)

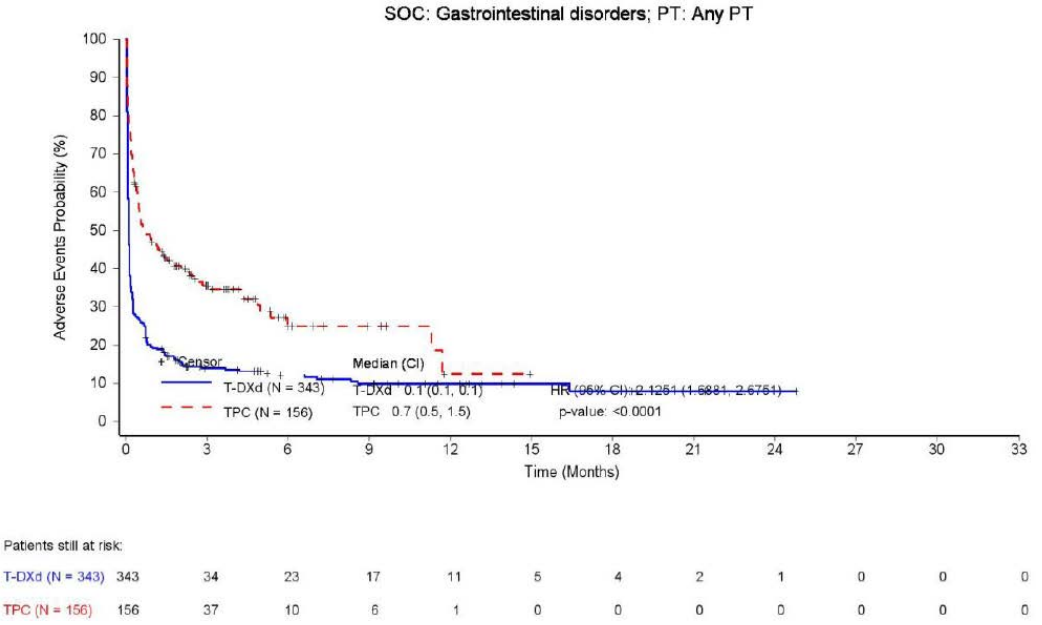

Figure 28: Kaplan-Meier curves for the outcome of gastrointestinal disorders (SOC, AEs)

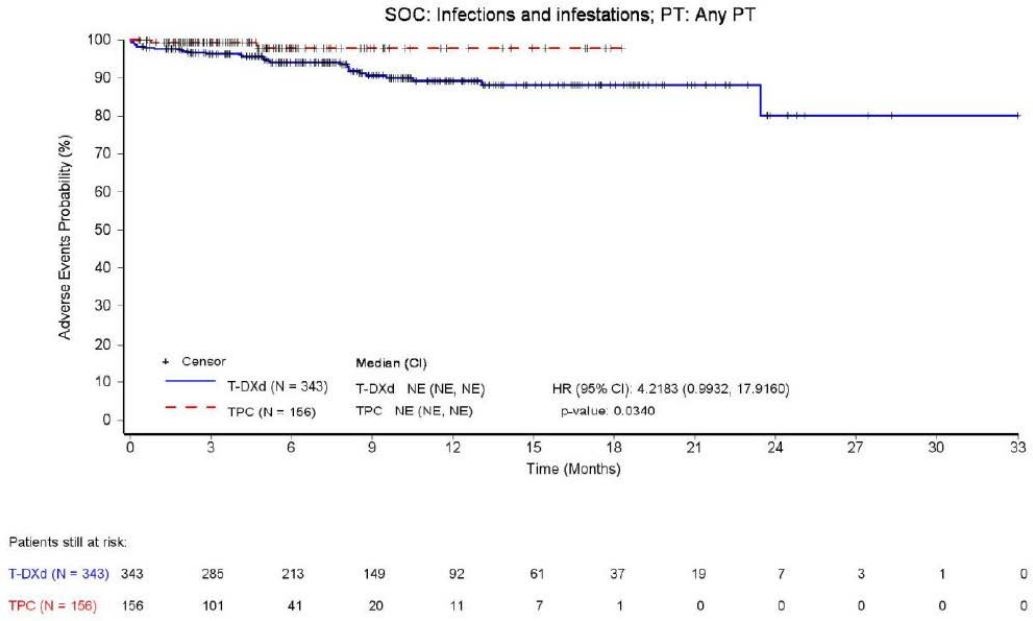

Figure 29: Kaplan-Meier curves for the outcome of infections and infestations (SOC, SAEs)

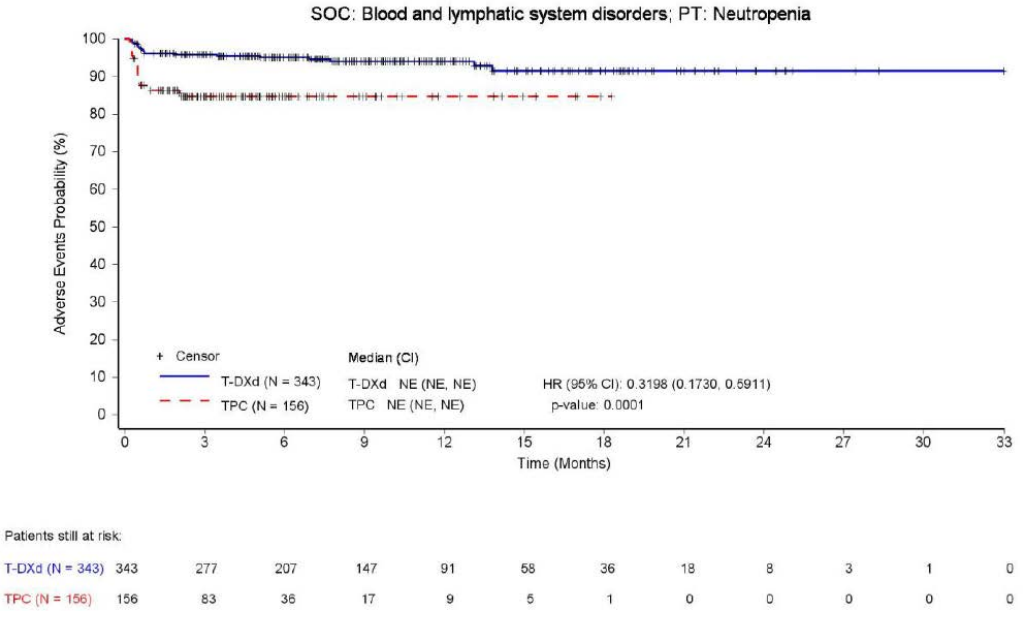

Figure 30: Kaplan-Meier curves for the outcome of neutropenia (PT, severe AEs)

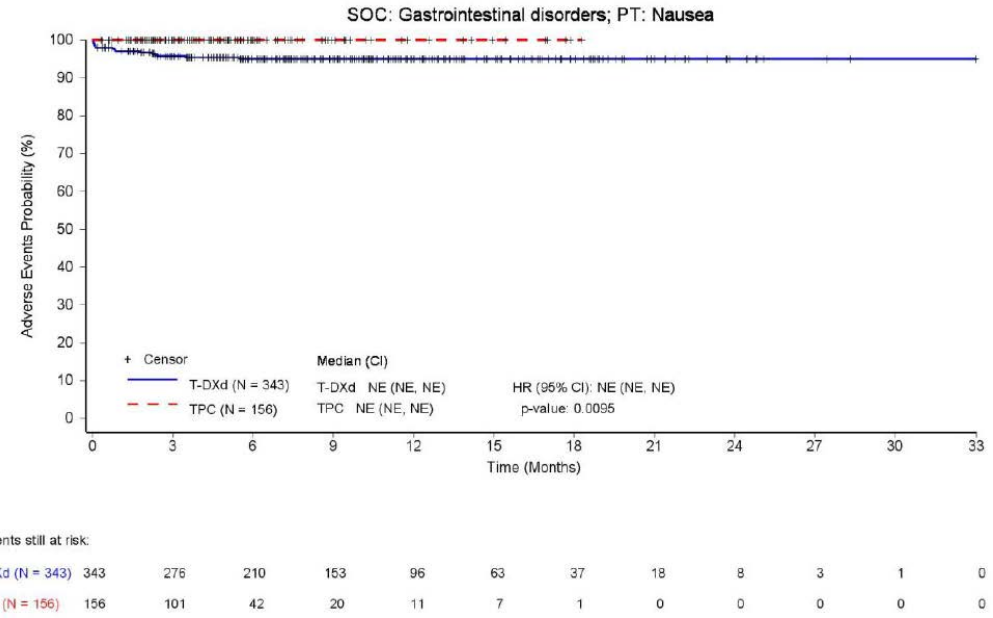

Figure 31: Kaplan-Meier curves for the outcome of nausea (PT, severe AEs)

A.5 Subgroup analyses

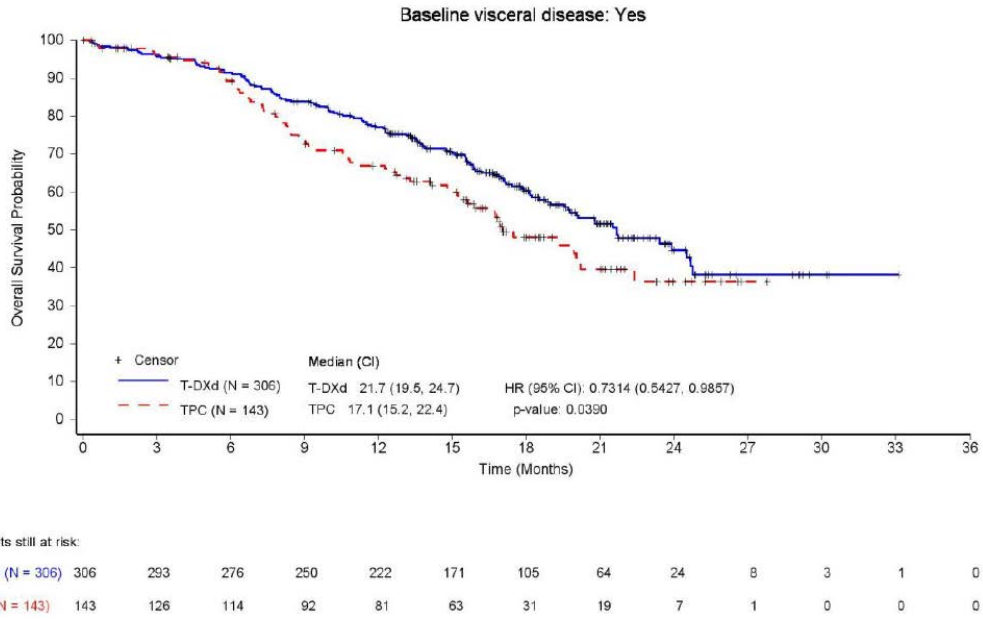

Figure 32: Kaplan-Meier curves for the outcome of overall survival, “visceral disease” subgroup, category of “yes”

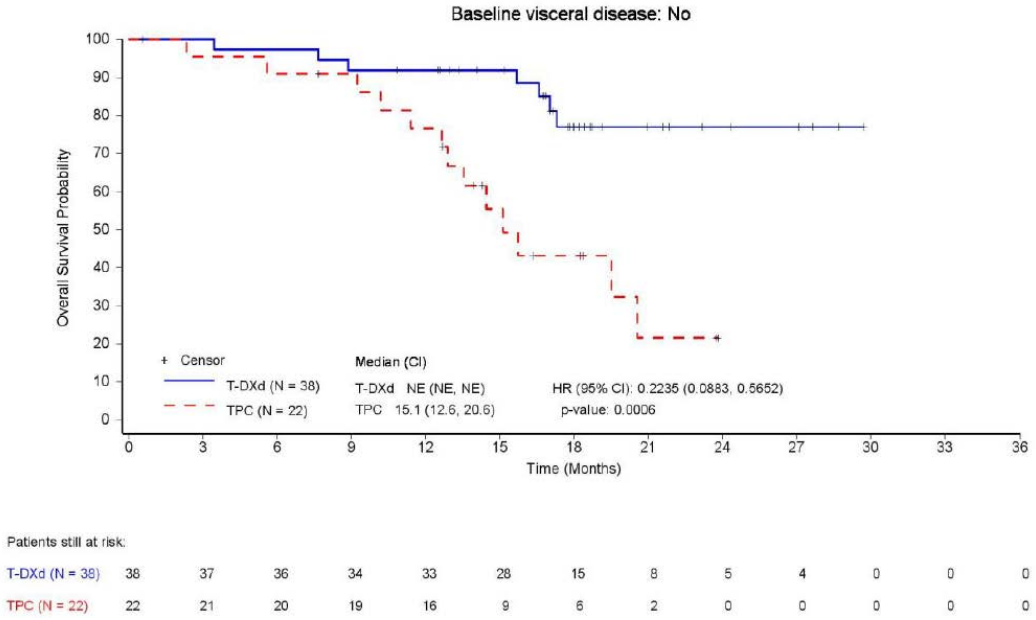

Figure 33: Kaplan-Meier curves for the outcome of overall survival, “visceral disease” subgroup, category of “no”

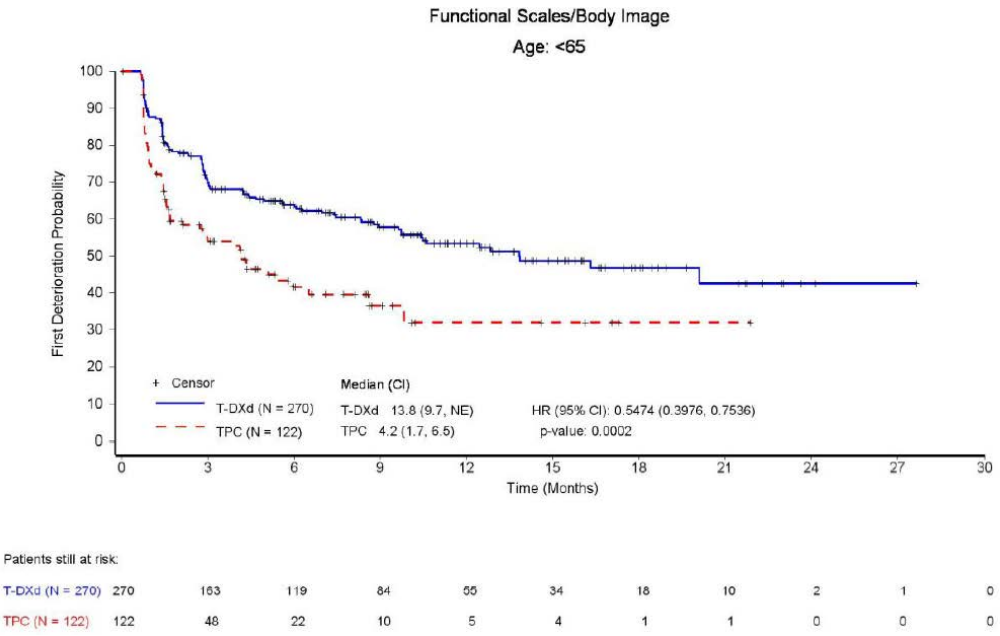

Figure 34: Kaplan-Meier curves for the outcome of body image (EORTC QLQ-BR23, first deterioration by ≥ 10 points), “age” subgroup, category of “< 65 years”

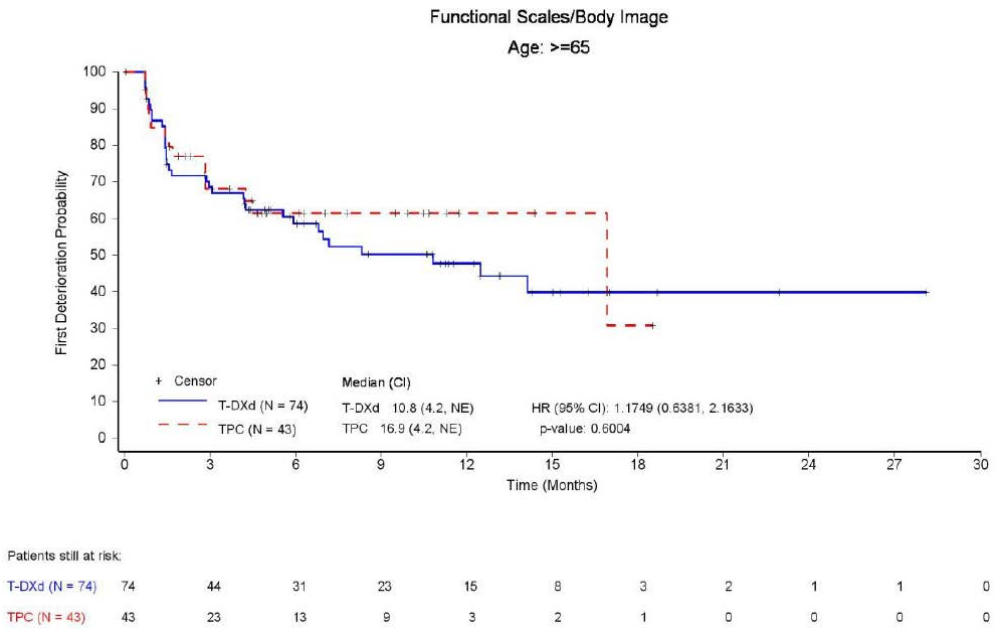

Figure 35: Kaplan-Meier curves for the outcome of body image (EORTC QLQ-BR23, first deterioration by ≥ 10 points), "age" subgroup, category of "≥ 65 years"