IQWiG Reports – Commission No. A22-80

Trastuzumab deruxtecan (breast cancer, after one prior therapy) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections I 1 to I 5 of the dossier assessment *Trastuzumab Deruxtecan (Mammakarzinom, nach 1 Vortherapie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 October 2022). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-BR23	European Organisation for Research and Treatment of Cancer 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)
PFS	progression-free survival
PT	Preferred Term
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

I 1 Executive summary of the benefit assessment

Background

Trastuzumab deruxtecan as monotherapy is used for the treatment of adult patients with unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer who have received one or more prior anti-HER2-based regimens.

The subject of the present benefit assessment are adults who have received one anti-HER2-based regimen.

Research question

The aim of the present report is the assessment of the added benefit of trastuzumab deruxtecan in comparison with trastuzumab emtansine as appropriate comparator therapy (ACT) in patients with unresectable or metastatic HER2-positive breast cancer who have received one anti-HER2-based regimen.

Table 2: Research question of the benefit assessment of trastuzumab deruxtecan

Therapeutic indication	**ACT[a]**
Adult patients with unresectable or metastatic HER2-positive breast cancer who have previously received one HER2-targeted therapy[b]	Trastuzumab emtansine
a. Presented is the respective ACT specified by the GBA. b. 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; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2	

The pharmaceutical company (hereinafter referred to as “the company”) followed the G-BA’s ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Study pool and study design

The DESTINY-Breast03 study is used for the benefit assessment of trastuzumab deruxtecan.

The DESTINY-Breast03 study is an open-label, randomized, 2-arm study comparing trastuzumab deruxtecan with trastuzumab emtansine. The study included patients with unresectable or metastatic HER2-positive breast cancer who had previously been treated with trastuzumab and a taxane in the advanced/metastatic setting or who had progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen including trastuzumab and taxane.

A total of 524 patients were enrolled in the study. Patients were randomized in a 1:1 ratio, stratified by hormone receptor status (positive versus negative), prior treatment with pertuzumab (yes versus no) and history of visceral disease (yes versus no). The use of trastuzumab deruxtecan or trastuzumab emtansine was in compliance with the respective Summaries of Product Characteristics (SPCs).

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

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

Limitation of the study population

The included population of the DESTINY-Breast03 study are patients with unresectable or metastatic HER2-positive breast cancer who had previously been treated with trastuzumab and a taxane in the advanced/metastatic setting or who had progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen including trastuzumab and taxane. This concurs with the approved therapeutic indication of trastuzumab deruxtecan. However, the research question of the present benefit assessment only comprises patients with unresectable or metastatic HER2-positive breast cancer who have received one anti-HER2 therapy in their pretreatment. Patients who have received 2 or more anti-HER2 therapies in their pretreatment are the subject of benefit assessment A22-81.

In the DESTINY-Breast03 study, almost 20% of the study participants had already received 2 or more lines of anti-HER2 therapy in the metastatic setting. Thus, these patients are not comprised by the research question of the present benefit assessment. However, since at least 80% of the included patients represent the present research question, the total population can be used for the assessment. However, it would have been possible for the company to select the relevant subpopulation taking into account the pretreatment.

In addition, the pretreatment of a large proportion of the included patients deviates from guideline recommendations. According to the inclusion criteria of the DESTINY-Breast03 study, patients had to be pretreated with trastuzumab and a taxane. Guidelines consider a dual blockade of trastuzumab and pertuzumab in combination with a taxane as the option of choice in first-line therapy for patients with metastatic HER2-positive breast cancer. However, only about 60% of patients in the DESTINY-Breast03 study had been pretreated with pertuzumab.

In addition, the study participants had received far more extensive systemic pretreatment in the metastatic setting than the guidelines recommend. 60% of patients had already received ≥ 2 systemic therapies in the metastatic setting, most of which were not anti-HER2 therapies. The inclusion criteria did not allow pretreatment with trastuzumab emtansine, which, according to the guideline, is usually used in the second line. More detailed information on the type of pretreatment is not available. Due to the extensive pretreatment, however, it can be assumed

that the patients included in the study were already in a later stage of the disease than can be expected for the patients in the present research question in German health care. Furthermore, it is unclear whether the extensive pretreatment had an effect on the efficacy as well as the side effects of the administered study medications.

The aspects described above result in uncertainties with regard to the transferability of the study results to the German health care setting, which are taken into account when assessing the certainty of conclusions of the results of the DESTINY-Breast03 study.

Risk of bias

The risk of bias across outcomes for the DESTINY-Breast03 study is rated as low. The outcome-specific risk of bias in the DESTINY-Breast03 study is low only for the results on the outcome of overall survival.

Regardless of the outcome-specific risk of bias, the certainty of conclusions of the study results is reduced due to uncertainties regarding the transferability of the study results to the German health care setting. Overall, no more than a hint, e.g. of an added benefit, is therefore determined for all outcomes.

Results

Mortality

Overall survival

A statistically significant difference in favour of trastuzumab deruxtecan was shown for the outcome of overall survival. There was an effect modification by the characteristic of age for this outcome. 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 in patients ≥ 65 years of age. 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 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). 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. Consequently, for this outcome, there is a hint of added benefit of trastuzumab deruxtecan in comparison with trastuzumab emtansine.

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

Symptom outcomes 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

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

Cognitive functioning

A statistically significant difference in favour of trastuzumab deruxtecan was shown for the outcome of cognitive functioning. For this outcome, there was an effect modification by the characteristic of visceral disease at baseline. A statistically significant difference in favour of trastuzumab deruxtecan was only shown for patients without visceral disease at baseline. For this outcome, this results in a hint of an added benefit of trastuzumab deruxtecan in comparison with trastuzumab emtansine for patients without visceral disease at baseline. No statistically significant difference between treatment groups was shown for patients who had visceral disease at baseline. For these patients, 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.

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 (CTCAE grade ≥ 3), discontinuation due to AEs

No statistically significant difference between treatment groups was shown for the outcomes of serious AEs (SAEs), severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] ≥ 3) and discontinuations due to AEs. Consequently, there are no hints of greater or lesser harm from trastuzumab deruxtecan in comparison with trastuzumab emtansine; greater or lesser harm is therefore not proven for these outcomes.

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), 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), 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.

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.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Based on the results presented, the probability and extent of added benefit of the drug trastuzumab deruxtecan in comparison with the ACT are assessed as follows:

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Overall, there are positive and negative effects of trastuzumab deruxtecan in comparison with trastuzumab emtansine.

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, there are both positive and negative effects of trastuzumab deruxtecan in individual domains of health-related quality of life, as well as in individual specific AEs of different severity categories and with varying, partly major, extent (hints in each case). In addition, there are several negative effects in the category of symptoms for outcomes on gastrointestinal complaint (nausea and vomiting, diarrhoea, and appetite loss), some of which are of considerable extent (hints in each case).

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 considerable added benefit of trastuzumab deruxtecan in comparison with the ACT trastuzumab emtansine. For patients ≥ 65 years of age, an added benefit of trastuzumab deruxtecan in comparison with the ACT trastuzumab emtansine is not proven.

Table 3 shows a summary of probability and extent of the added benefit of trastuzumab deruxtecan.

Table 3: 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 considerable added benefit ▪ 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 approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is the assessment of the added benefit of trastuzumab deruxtecan in comparison with trastuzumab emtansine as ACT in patients with unresectable or metastatic HER2-positive breast cancer who have received one anti-HER2-based regimen.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of trastuzumab deruxtecan

Therapeutic indication	**ACT[a]**
Adult patients with unresectable or metastatic HER2-positive breast cancer who have previously received one HER2-targeted therapy[b]	Trastuzumab emtansine
a. Presented is the respective ACT specified by the GBA. b. 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; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2	

The company followed the G-BA's ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on trastuzumab deruxtecan (status: 6 July 2022)
- bibliographical literature search on trastuzumab deruxtecan (last search on 24 June 2022)
- search in trial registries/trial results databases for studies on trastuzumab deruxtecan (last search on 6 July 2022)
- search on the G-BA website for trastuzumab deruxtecan (last search on 6 July 2022)

To check the completeness of the study pool:

- search in trial registries for studies on trastuzumab deruxtecan (last search on 9 August 2022); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 3.1 Studies included

The study presented in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
DS8201-A-U302 (DESTINY-Breast03[d])	Yes	Yes	No	Yes [3]	Yes [4-6]	Yes [7,8]

a. Study for which the company was sponsor.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to by this acronym.

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

I 3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the included study – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
DESTINY-Breast03	RCT, open-label, parallel	Adult patients[b] with pathologically documented breast cancer: ▪ unresectable or metastatic ▪ HER2-positive[c] ▪ pretreated with trastuzumab and a taxane in the advanced/metastatic setting, or with progression within 6 months after neoadjuvant or adjuvant treatment involving trastuzumab or a taxane[d] ▪ ECOG PS 0 or 1	▪ Trastuzumab deruxtecan (N = 261) ▪ trastuzumab emtansine (N = 263)	▪ Screening: up to 28 days ▪ Treatment: until disease progression, death, or study discontinuation for any reason ▪ Observation[e]: outcome-specific, at the longest until death, study discontinuation for any reason, or end of the study[f]	172 study centres in Australia, Belgium, Brazil, Canada, China, France, Germany, Hong Kong, Italy, Japan, Republic of Korea, Spain, Taiwan, United Kingdom, USA 8/2018–ongoing Data cut-off: ▪ 21 May 2021[g]	▪ Primary: progression-free survival (BICR) ▪ Secondary: overall survival, morbidity, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Men or women aged ≥ 20 years in Japan and Korea, and ≥ 18 years in the other countries.
c. According to the American Society of Clinical Oncology/College of American Pathologists guideline, HER2-positive tumour status is determined either by an IHC value of 3+ or by confirmation using ISH or FISH [9].
d. Presence of documented radiological progression.
e. Outcome-specific information is described in Table 8.
f. According to final protocol version amendment 6 (25 September 2020): after reaching approx. 250 events for the outcome of overall survival.
g. First interim analysis after 234 PFS events.

AE: adverse event; BICR: blinded independent central review; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FISH: fluorescence in situ hybridization; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; ISH: in situ hybridization; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine (multipage table)

Study	Intervention	Comparison
DESTINY-Breast03	Trastuzumab deruxtecan 5.4 mg/kg BW[a] IV on day 1 of a 21-day cycle	Trastuzumab emtansine 3.6 mg/kg BW[a] IV on day 1 of a 21-day cycle
	Dose adjustments[b] Dose interruption up to 28 days[c] and dose reduction[d] were allowed as follows: first dose level: 4.4 mg/kg BW second dose level: 3.2 mg/kg BW	**Dose adjustments[b]** Dose interruption up to 28 days[c] and dose reduction[c] were allowed as follows: first dose level: 3.0 mg/kg BW second dose level: 2.4 mg/kg BW
	Pretreatment ▪ Patients had to be pretreated with trastuzumab and a taxane. **Non-permitted pretreatment** ▪ treatment with an anti-HER2-targeted ADC (such as T-DM1) in the metastatic setting treatment in the adjuvant/neoadjuvant phase was permitted if progression had not occurred within 12 months of completion of adjuvant therapy ▪ therapeutic radiotherapy or major surgery within 4 weeks before randomization or palliative stereotactic radiotherapy within 2 weeks before randomization ▪ systemic treatment with anticancer therapy (immunotherapy [not antibody-based therapy]), retinoid therapy or hormonal therapy within 3 weeks before randomization; antibody-based anticancer therapy within 4 weeks before randomization, or treatment with nitrosourea compounds or mitomycin C within 6 weeks before randomization; or treatment with small-molecule targeted agents within 2 weeks or 5 half-lives before study drug treatment, whichever was longer ▪ treatment with strong CYP3A4 inhibitors (a washout phase of ≥ 3 elimination half-lives was required)[e] **Concomitant treatment** ▪ at the discretion of the investigator[f] **Non-permitted concomitant treatment** ▪ other antineoplastic therapy ▪ treatment with (hydro)chloroquine[g] ▪ chronic systemic corticosteroids (IV or oral) or other immunosuppressants (except for the treatment of AEs) ▪ other investigational therapy ▪ radiotherapy[h]	

a. According to study protocol amendment 5 (23 April 2020): If there is a change in body weight of ≥ ± 10% of baseline weight compared with baseline during treatment, the patient's dose is recalculated based on the updated weight.
b. Dose adjustment is in compliance with the recommendations of the corresponding SPC.
c. Treatment pauses are possible up to a duration of 28 days from the planned date of application. If the patient requires a longer delay of the next dose than 28 days (48 days since the last infusion), the patient will permanently discontinue treatment with the study medication and will be followed up for overall survival.
d. Once the dose of study medication has been reduced due to toxicity, all subsequent cycles are to be administered at reduced dose level unless further dose reduction is required. If the toxicities persist > 2 weeks after 2 dose reductions, the study medication is discontinued. Dose increase is not allowed in the study.
e. According to study protocol amendment 5 (23 April 2020): CYP3A4, OATP and foods containing grapefruit were removed from the list of prohibited medications in the exclusion criteria, due to new study findings showing no clinical impact of these substances.
f. E.g.: for prophylaxis: haematopoietic growth factors, antiemetics.
g. Inclusion as prohibited concomitant medication according to study protocol amendment 5 (23 April 2020).
h. Excluding palliative radiotherapy of pre-existing metastatic region.

Table 7: Characteristics of the intervention – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine (multipage table)

Study	Intervention	Comparison
ADC: antibody-drug conjugate; AE: adverse event; BW: body weight; CYP3A4: cytochrome P450; HER2: human epidermal growth factor receptor 2; OATP: organic anion transporting polypeptide; RCT: randomized controlled trial; T-DM1: trastuzumab emtansine		

The DESTINY-Breast03 study is an open-label, randomized, 2-arm study comparing trastuzumab deruxtecan with trastuzumab emtansine. The study included patients with unresectable or metastatic HER2-positive breast cancer who had previously been treated with trastuzumab and a taxane in the advanced/metastatic setting or who had progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen including trastuzumab and taxane. Patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 at study entry.

A total of 524 patients were enrolled in the study. Patients were randomized in a 1:1 ratio, stratified by hormone receptor status (positive versus negative), prior treatment with pertuzumab (yes versus no) and history of visceral disease (yes versus no). The use of trastuzumab deruxtecan and trastuzumab emtansine was in compliance with the respective SPC [10,11].

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

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

Data cut-offs

The DESTINY-Breast03 study is an ongoing study. The company used an analysis at the first data cut-off (21 May 2021) for the benefit assessment. This is the first interim analysis, which was planned to occur after 234 PFS events, according to the study protocol.

Planned duration of follow-up observation

Table 8 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine

Study **Outcome category** **Outcome**	**Planned follow-up observation**
DESTINY-Breast03	
Mortality	
Overall survival	▪ Until death, withdrawal of consent, lost to follow-up, or end of study (whichever is first)
Morbidity	
Symptoms (EORTC QLQ-C30 and QLQ-BR23)	▪ 40 days (+ 7 days) after the last dose of study medication, and another documentation time 3 months (± 14 days) later
Health status (EQ-5D VAS)	▪ 40 days (+ 7 days) after the last dose of study medication, and another documentation time 3 months (± 14 days) later
Health-related quality of life (EORTC QLQ-C30 and QLQ-BR23)	▪ 40 days (+ 7 days) after the last dose of study medication, and another documentation time 3 months (± 14 days) later
Side effects	
All outcomes in the side effects category	▪ 40 days (+ 7 days) follow-up after the last dose of study medication, or initiation of a new antineoplastic treatment (whichever is first)[a]
a. SAEs that the investigator judged to be causally related to the investigational product were also recorded as SAEs if their first occurrence was later than 48 days after the last dose of study medication or their severity had increased.	
EORTC: European Organisation for Research and Treatment of Cancer; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module 23; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; VAS: visual analogue scale	

In the DESTINY-Breast03 study, only the outcome of overall survival is recorded until study end. The observation periods for the outcomes of morbidity, health-related quality of life and side effects were systematically shortened because they were only recorded for the time period of treatment with the study medication, plus 40 days. For each of the outcomes of the categories of morbidity and health-related quality of life, there is an additional recording after another 3 months. However, to be able to draw a reliable conclusion on the total study period or the time to patient death, it would be necessary to record these outcomes as well for the total period, as was done for survival.

Table 9 shows the characteristics of the patients in the included study.

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine (multipage table)

Study **Characteristic** **Category**	**Trastuzumab deruxtecan** **N[a] = 261**	**Trastuzumab emtansine** **N[a] = 263**
DESTINY-Breast03		
Age [years], mean (SD)	55 (11)	54 (12)
Sex [F/M], %	> 99/< 1	> 99/< 1
Region, n (%)		
Asia	149 (57)	160 (61)
North America	17 (7)	17 (7)
Europe	54 (21)	50 (19)
Rest of the world	41 (16)	36 (14)
ECOG PS, n (%)		
0	154 (59)	175 (67)
1	106 (41)	87 (33)
Missing	1 (< 1)	1 (< 1)
Family origin n (%)		
White	71 (27)	72 (27)
Black or African American	10 (4)	9 (3)
Asian	152 (58)	162 (62)
Multiple	2 (1)	0 (0)
Other	26 (10)	20 (8)
Hormone receptor status (EDC), n%		
Positive	128 (49)	139 (53)
Negative	132 (51)	123 (47)
Missing	1 (< 1)	1 (< 1)
Baseline visceral disease, n (%)		
Yes	195 (75)	189 (72)
No	66 (25)	74 (28)
Baseline CNS metastases, n (%)		
Yes	43 (17)	39 (15)
No	218 (84)	224 (85)
HER2 expression[b] (IHC), n (%)		
0	0 (0)	0 (0)
1+	1 (< 1)	0 (< 1)
2+	25 (10)	30 (11)
3+	234 (90)	232 (88)
Not evaluable	1 (< 1)	1 (< 1)
HER2 gene amplification[b] (ISH), n (%)		
Amplified	24 (9)	29 (11)
Non-amplified	2 (1)	2 (1)
Missing	235 (90)	232 (88)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine (multipage table)

Study **Characteristic** **Category**	**Trastuzumab deruxtecan** **N[a] = 261**	**Trastuzumab emtansine** **N[a] = 263**
Lines of prior anti-HER2 therapy in metastatic setting, n (%)		
≤ 1[c]	215 (82)	211 (80)
≥ 2	46 (18)	52 (20)
Lines of prior systemic therapy in metastatic setting, n (%)		
0[d]	1 (< 1)	1 (< 1)
1	108 (41)	102 (39)
2	60 (23)	64 (24)
3	44 (17)	45 (17)
4	15 (6)	23 (9)
≥ 5	33 (13)	28 (11)
Mean (SD)	2.4 (2.0)	2.5 (2.0)
Median [min; max]	2.0 [0; 16]	2.0 [0; 15]
Prior treatment with pertuzumab (EDC), n (%)		
Yes	159 (61)	156 (59)
No	101 (39)	106 (40)
Missing	1 (< 1)	1 (< 1)
Time from first, histological diagnosis to study treatment [months]	N = 257	N = 261
Mean (SD)	59.5 (56.5)	57.3 (55.8)
Median [min; max]	38.8 [4; 346]	40.7 [5; 325]
Treatment discontinuation, n (%)[e]	125 (49)	214 (82)
Study discontinuation, n (%)	13 (5)	11 (4)

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. According to the SPC, HER2-positive tumour status is determined either by an IHC value of 3+ or by confirmation using ISH or FISH [10,11]. 25 (9.6%) patients in the intervention arm and 30 (11.4%) patients in the comparator arm had an IHC value of 2+ in combination with a positive ISH result [7].
c. According to the inclusion criteria, patients were also included if they had not received their previous anti-HER2 therapy in the metastatic setting, but had progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen including trastuzumab and taxane (see Table 6). According to the EPAR, this applies to 25 patients in the trastuzumab deruxtecan arm and 32 patients in the trastuzumab emtansine arm [12]. Differentiated information on the number of patients within the respective treatment settings is not available in the study documents.
d. For 2 patients who were erroneously randomized but not treated, the pages with information on previous systemic cancer therapies were not completed.
e. Common reasons for treatment discontinuation in the trastuzumab deruxtecan arm vs. the trastuzumab emtansine arm were: disease progression according to mRECIST v1.1 (26% vs. 61%), AEs (14% vs. 7%), withdrawal of consent (5% vs. 4%).

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine (multipage table)

Study Characteristic Category	Trastuzumab deruxtecan N[a] = 261	Trastuzumab emtansine N[a] = 263
AE: adverse event; CNS: central nervous system; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EDC: electronic data capture; F: female; FISH: fluorescence in situ hybridization; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; ISH: in situ hybridization; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours; SD: standard deviation; SPC: Summary of Product Characteristics		

The demographic and clinical characteristics of the patients in both treatment arms are comparable. The mean age of the patients in the DESTINY-Breast03 study was 54 years at study entry. 59% of the patients in the intervention arm had an ECOG PS of 0, compared with 67% in the comparator arm. About 3 quarters of the patients had visceral disease at baseline. In addition, about 60% of the patients included in the study had received ≥ 2, and about 20% of the patients ≥ 4 systemic therapies in the metastatic setting. About 60% of the patients had received prior pertuzumab.

Limitation of the study population

The included population of the DESTINY-Breast03 study are patients with unresectable or metastatic HER2-positive breast cancer who had previously been treated with trastuzumab and a taxane in the advanced/metastatic setting or who had progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen including trastuzumab and taxane. This concurs with the approved therapeutic indication of trastuzumab deruxtecan. However, the research question of the present benefit assessment only comprises patients with unresectable or metastatic HER2-positive breast cancer who have received one anti-HER2 therapy in their pretreatment (see Table 4). Patients who have received 2 or more anti-HER2 therapies in their pretreatment are the subject of benefit assessment A22-81 [13].

In the DESTINY-Breast03 study, almost 20% of the study participants had already received 2 or more lines of anti-HER2 therapy in the metastatic setting (see Table 9). Thus, these patients are not comprised by the research question of the present benefit assessment. However, since at least 80% of the included patients represent the present research question, the total population can be used for the assessment. However, it would have been possible for the company to select the relevant subpopulation taking into account the pretreatment.

In addition, the pretreatment of a large proportion of the included patients deviates from guideline recommendations. According to the inclusion criteria of the DESTINY-Breast03 study, patients had to be pretreated with trastuzumab and a taxane. Guidelines consider a dual blockade of trastuzumab and pertuzumab in combination with a taxane as the option of choice in first-line therapy for patients with metastatic HER2-positive breast cancer [14,15]. However,

only about 60% of patients in the DESTINY-Breast03 study had been pretreated with pertuzumab.

In addition, the study participants had received far more extensive systemic pretreatment in the metastatic setting than the guidelines recommend. 60% of patients had already received ≥ 2 systemic therapies in the metastatic setting, most of which were not anti-HER2 therapies. The inclusion criteria did not allow pretreatment with trastuzumab emtansine, which, according to the guideline, is usually used in the second line. More detailed information on the type of pretreatment is not available. Due to the extensive pretreatment, however, it can be assumed that the patients included in the study were already in a later stage of the disease than can be expected for the patients in the present research question in German health care. Furthermore, it is unclear whether the extensive pretreatment had an effect on the efficacy as well as the side effects of the administered study medications.

The aspects described above result in uncertainties with regard to the transferability of the study results to the German health care setting, which are taken into account when assessing the certainty of conclusions of the results of the DESTINY-Breast03 study. A summary assessment of the certainty of conclusions can be found in Section I 4.2.

In addition, the approval also covers patients who have received only anti-HER2 therapy but no taxane in their pretreatment. These patients were not included in the study, so that no conclusions on added benefit can be drawn for them on the basis of the available data.

Table 10 shows the mean and median treatment durations of the patients and the median observation periods for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine

Study **Duration of the study phase** **Outcome category**	**Trastuzumab deruxtecan** **N = 261**	**Trastuzumab emtansine** **N = 263**
DESTINY-Breast03		
Treatment duration [months]	N = 257	N = 261
Median [min; max]	14.30 [0.7; 29.8]	6.90 [0.7; 25.1]
Mean (SD)	13.68 (6.29)	8.02 (6.03)
Study duration [months]		
Median [min; max]	16.2 [0.0; 32.7]	15.3 [0.0; 31.3]
Mean (SD)	16.3 (5.7)	14.9 (6.1)
Observation period [months]		
Overall survival[a]		
Median [95% CI]	16.7 [16.2; 17.2]	16.5 [16.0; 17.1]
Mean (SD)	ND	ND
Morbidity		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Health-related quality of life		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Side effects		
Median [min; max]	ND	ND
Mean (SD)	ND	ND

a. 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

The median treatment duration in the intervention arm is 14.3 months, almost twice as long as in the control arm (6.9 months).

The median observation period for overall survival is 16.7 months in the intervention arm and 16.5 months in the control arm. For the outcomes of the categories of morbidity, health-related quality of life, and side effects, whose observation duration is linked to treatment end (see Table 8), the observation durations are markedly shorter in comparison with overall survival, particularly in the comparator arm. Therefore, for these outcomes, conclusions can only be drawn about the time under treatment (plus 40 days for side effects, and for morbidity and health-related quality of life plus another 3 months). In addition, the between-arm differences in treatment duration also result in differences in observation periods of the outcomes. This data situation has consequences regarding the interpretability of the outcomes which were observed for a shorter period (see Section I 4.1).

Table 11 shows the subsequent therapies patients received after discontinuing the study medication.

Table 11: Information on subsequent antineoplastic therapies – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine

Study Drug	Patients with subsequent therapy, n (%)	
	Trastuzumab deruxtecan N = 261	Trastuzumab emtansine N = 263
DESTINY-Breast03		
Total	78 (29.9)	164 (62.4)
Systemic[a]	78 (29.9)	164 (62.4)
Trastuzumab	23 (8.8)	66 (25.1)
Trastuzumab deruxtecan	0 (0)	30 (11.4)
Trastuzumab emtansine	43 (16.5)	17 (6.5)
Pertuzumab	11 (4.2)	25 (9.5)
Taxane	5 (1.9)	16 (6.1)
Taxane & trastuzumab	3 (1.1)	15 (5.7)
Other anti-HER2 (incl. anti-HER2 TKI and other anti-HER2 antibodies or ADC)	16 (6.1)	73 (27.8)
Anti-HER2 TKI	13 (5.0)	66 (25.1)
Other anti-HER2 antibodies or ADC	3 (1.1)	13 (4.9)
Hormone therapy	13 (5.0)	21 (8.0)
Other systemic therapy[b]	40 (15.3)	126 (47.9)
Radiotherapy	10 (3.8)	25 (9.5)
Surgical interventions	2 (0.8)	10 (3.8)

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; 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. 29.9% versus 62.4% of the patients had received at least one subsequent antineoplastic therapy by the time of the present data cut-off. 16.5% of those patients who were treated with trastuzumab deruxtecan in the intervention arm of the study received trastuzumab emtansine as subsequent therapy. However, the guidelines recommend this drug for use in the second line of treatment. The most common subsequent therapies used in the comparator arm were trastuzumab (25.1%) and anti-HER2 tyrosine kinase inhibitors (27.8%), as well as trastuzumab deruxtecan (11.4%). Furthermore, pertuzumab was used as a subsequent therapy in both treatment arms (4.2% versus 9.5%). According to the approval for pertuzumab, this drug may only be used if no anti-HER2 therapy or chemotherapy has been used before [16]. Accordingly, 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.

The current guidelines do not provide clear recommendations for the therapy starting from the third line of treatment in the present therapeutic indication [12,14,15]. In addition, there are no substantial differences between the subsequent therapies of the intervention and comparator population. Overall, the aspects described above have no consequence for the present benefit assessment.

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
DESTINY-Breast03	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes for the DESTINY-Breast03 study is rated as low.

Limitations resulting from the open-label study design are described in Section I 4.2 with the outcome-specific risk of bias.

Transferability of the study results to the German health care context

The company stated that it assumed unlimited transferability of the results of the DESTINY-Breast03 study to the German health care context. According to the company, the characteristics of the patients included in the study did not differ substantially in terms of age from the population of breast cancer patients in the unresectable or metastatic setting in the current German health care context. It added that there was also no impediment from diagnosis and implementation of the therapy, as these corresponded to international standards, which were also used in Germany, or to the respective SPCs.

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

Aspects that influence the transferability of the study results to the German health care context were also discussed at the beginning of the section under the heading *Limitation of the study population*.

I 4 Results on added benefit

I 4.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - symptoms recorded using the EORTC QLQ-C30
  - symptoms recorded using the EORTC QLQ-BR23
  - health status recorded using the EQ-5D VAS
- Health-related quality of life
  - recorded using the EORTC QLQ-C30 and the EORTC QLQ-BR23
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - cardiac disorders (System Organ Class [SOC], severe AEs [CTCAE grade ≥ 3])
  - platelet count decreased (Preferred Term [PT], severe AEs [CTCAE grade ≥ 3])
  - further specific AEs, if any

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

Table 13 shows for which outcomes data are available in the included study.

Table 13: Matrix of outcomes – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine

Study	Outcomes									
	Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-BR23)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23)	SAEs[b]	Severe AEs[a, b]	Discontinuation due to AEs[b]	Cardiac disorders (SOC, severe AEs[a])	Platelet count decreased (PT, severe AEs[a])	Further specific AEs[c]
DESTINY-Breast03	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. For outcomes in the category of side effects, the company presented analyses including progression of the underlying disease.
c. The following events are considered (MedDRA coding): gastrointestinal disorders (SOC, AEs), skin and subcutaneous tissue disorders (SOC, AEs), nose bleed (PT, AEs), pyrexia (PT, AEs), malaise (PT, AEs), general disorders and administration site conditions (SOC, severe AEs), neutrophil count decreased (PT, severe AEs), white blood cell count decreased (PT, severe AEs), and nausea (PT, severe AEs).

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

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

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

Response criteria for the scales of the EORTC QLQ-C30, EORTC QLQ-BR23, and the EQ-5D VAS

The company presented responder analyses for the proportion of patients with a deterioration by ≥ 10 points or ≥ 15 points (scale range 0 to 100) for the EQ-5D VAS. As explained in the *General Methods* of the Institute [1], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to at least 15% of the scale range of an instrument if prespecified (in post-hoc analyses exactly 15% of the scale range). The analysis with a response threshold of 15 points (corresponds to 15% of the scale range) is therefore used for the benefit assessment.

The company present responder analyses for the proportion of patients with a deterioration by ≥ 10 or ≥ 15 points (respective scale range 0 to 100) also for the EORTC QLQ-C30 and the

EORTC QLQ-BR23. The analysis with a response threshold of 10 points is considered a sufficient approximation to an analysis with a 15% threshold (15 points) and is used for the benefit assessment (for an explanation, see [17]).

Operationalization of deterioration

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

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

For the symptom and health-related quality of life outcomes as well as for the outcome of health status, no information is available on the actual observation period in the study. However, the observation period for these outcomes is linked to the treatment duration and thus, on the one hand, systematically shorter compared with overall survival and, on the other, notably different between the treatment arms (see Table 8 and Table 10). The different observation periods for the patient-reported outcomes can be estimated from the large differences in treatment duration, which is about twice as long in the intervention arm as in the control arm (see Section I 3.2). Also, in the DESTINY-Breast03 study, the responses to the questionnaires in the comparator arm decreased sharply after only a few observation points. Another problem is that the study counted a single deterioration that occurred at the last recording as confirmed deterioration. There is no information available on how many patients were found to have deteriorated at the last documentation time or how these cases were distributed between the treatment arms. In this situation, confirmed deterioration in the intervention arm is potentially compared with a single deterioration in the comparator arm. For this reason, the analyses for the time to first deterioration are used for the benefit assessment.

Outcomes in the category of side effects

In deviation from the specification in the dossier template [18], besides treatment-related AEs, the analyses of the overall rates of AEs, SAEs, severe AEs and discontinuations due to AEs also include AEs that can be attributed to progression of the underlying disease. In Module 4 A, the company explained this with the lack of a complete and valid definition of disease-related events in the present therapeutic indication to clearly differentiate disease-related AEs from other AEs. This is not appropriate. Since the overall rates of the outcomes in the category of side effects in the DESTINY-Breast03 study only include a few events that can potentially be attributed to progression of the underlying disease, the available data on side effects are used for the benefit assessment without restrictions, however.

I 4.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: 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	L	L	H[c, d]	H[c, d]	H[c, d]	H[d]	H[d]	H[e]	H[d]	H[d]	H[d]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The following events are considered (MedDRA coding): gastrointestinal disorders (SOC, AEs), skin and subcutaneous tissue disorders (SOC, AEs), nose bleed (PT, AEs), pyrexia (PT, AEs), malaise (PT, AEs), general disorders and administration site conditions (SOC, severe AEs), neutrophil count decreased (PT, severe AEs), white blood cell count decreased (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.

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

The outcome-specific risk of bias in the DESTINY-Breast03 study is low only for the results on the outcome of overall survival.

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

For the side effects outcomes, except for the outcomes of discontinuation due to AEs and platelet count decreased, the risk of bias of is rated high due to incomplete observations for potentially informative reasons. Despite the high risk of bias, there is a high certainty of results for the outcome of platelet count decreased, due to the size of the effect, which is already seen at an early point in the course of the study (see the Kaplan-Meier curve in I Appendix B.3 of the full dossier assessment). For the outcome of discontinuation due to AEs, the risk of bias is rated as high due to lack of blinding in subjective recording of outcomes.

Summary assessment of certainty of results

Irrespective of the aspects described under risk of bias, the certainty of conclusions of study results is reduced due to the uncertainties described in Section I 3.2, which resulted from the pretreatment of the included patients. For the reasons described above, no more than hints can be derived in the DESTINY-Breast03 study for all outcomes except overall survival and platelet count decreased. Due to the limitations regarding pretreatment, no more than hints, e.g. of an added benefit, are also determined for these 2 outcomes.

I 4.3 Results

Table 15 summarizes the results of the comparison of trastuzumab deruxtecan with trastuzumab emtansine in patients with unresectable or metastatic HER2-positive breast cancer who have received one anti-HER2-based regimen. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The Kaplan-Meier curves on the presented event time analyses are presented in I Appendix B of the full dossier assessment. Results on common AEs, SAEs, severe AEs, and discontinuations due to AEs are presented in I Appendix C of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine (multipage table)

Study Outcome category Outcome	Trastuzumab deruxtecan		Trastuzumab emtansine		Trastuzumab deruxtecan vs. trastuzumab emtansine
	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
DESTINY-Breast03					
Mortality					
Overall survival	261	NA 33 (12.6)	263	NA 53 (20.2)	0.55 [0.36; 0.86]; 0.007[a]
Morbidity					
Symptoms (EORTC QLQ-C30)[b]					
Fatigue	261	5.6 [3.0; 9.9] 150 (57.5)	263	3.6 [2.8; 5.5] 153 (58.2)	0.84 [0.67; 1.05]; 0.126[a]
Nausea and vomiting	261	2.8 [1.6; 3.0] 191 (73.2)	263	9.7 [8.3; 13.9] 116 (44.1)	1.98 [1.56; 2.49]; < 0.001[a]
Pain	261	8.5 [5.6; 14.5] 142 (54.4)	263	6.9 [5.3; 9.8] 137 (52.1)	0.87 [0.69; 1.10]; 0.238[a]
Dyspnoea	261	NA [15.8; NC] 101 (38.7)	263	15.2 [11.7; NC] 98 (37.3)	0.84 [0.63; 1.11]; 0.210[a]
Insomnia	261	19.4 [10.7; NC] 115 (44.1)	263	12.7 [7.2; NC] 112 (42.6)	0.86 [0.66; 1.11]; 0.243[a]
Appetite loss	261	4.2 [2.9; 5.6] 160 (61.3)	263	10.3 [6.6; 20.5] 115 (43.7)	1.44 [1.13; 1.83]; 0.003[a]
Constipation	261	5.6 [4.2; 8.3] 154 (59.0)	263	8.5 [5.7; 12.6] 122 (46.4)	1.24 [0.97; 1.58]; 0.083[a]
Diarrhoea	261	NA [17.1; NC] 106 (40.6)	263	NA [17.8; NC] 62 (23.6)	1.73 [1.26; 2.38]; < 0.001[a]
Symptoms (EORTC QLQ-BR23)[b]					
Side effects of systemic therapy	261	5.7 [4.3; 11.0] 145 (55.6)	263	11.7 [8.3; 16.7] 113 (43.0)	1.23 [0.96; 1.58]; 0.100[a]
Symptoms in chest region	261	NA 56 (21.5)	263	NA 52 (19.8)	0.85 [0.58; 1.24]; 0.403[a]
Symptoms in arm region	261	10.3 [7.7; 16.7] 134 (51.3)	263	5.6 [4.2; 9.0] 137 (52.1)	0.74 [0.58; 0.94]; 0.014[a]
Upset by hair loss	No usable data[c]				
Health status[d] (EQ-5D VAS)	261	24.6 [19.4; NC] 91 (34.9)	263	14.4 [12.0; NC] 93 (35.4)	0.75 [0.56; 1.01]; 0.061[a]

Table 15: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine (multipage table)

Study Outcome category Outcome	Trastuzumab deruxtecan		Trastuzumab emtansine		Trastuzumab deruxtecan vs. trastuzumab emtansine
	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
Health-related quality of life					
EORTC QLQ-C30[e]					
Global health status	261	6.9 [4.4; 10.4] 146 (55.9)	263	7.2 [5.7; 10.3] 135 (51.3)	0.99 [0.78; 1.25]; 0.885[a]
Physical functioning	261	NA [14.3; NC] 109 (41.8)	263	12.0 [8.3; NC] 104 (39.5)	0.87 [0.66; 1.15]; 0.326[a]
Role functioning	261	11.6 [6.2; 23.7] 130 (49.8)	263	6.3 [4.7; 8.9] 138 (52.5)	0.75 [0.59; 0.96]; 0.022[a]
Emotional functioning	261	16.7 [12.9; 19.4] 117 (44.8)	263	11.1 [8.4; 15.2] 107 (40.7)	0.80 [0.61; 1.05]; 0.101[a]
Cognitive functioning	261	10.3 [8.6; 14.5] 138 (52.9)	263	8.3 [4.8; 10.3] 135 (51.3)	0.78 [0.61; 0.99]; 0.041[a]
Social functioning	261	7.3 [5.6; 11.8] 147 (56.3)	263	8.4 [5.8; 11.7] 126 (47.9)	1.04 [0.82; 1.32]; 0.774[a]
EORTC QLQ-BR23[e]					
Body image	261	17.3 [10.7; 21.0] 121 (46.4)	263	NA [12.4; NC] 81 (30.8)	1.35 [1.02; 1.80]; 0.039[a]
Sexual activity	261	NA 60 (23.0)	263	NA [22.6; NC] 57 (21.7)	0.93 [0.65; 1.34]; 0.707[a]
Enjoyment of sex				No usable data[c]	
Future perspective	261	NA [19.4; NC] 88 (33.7)	263	21.2 [16.7; NC] 73 (27.8)	0.98 [0.72; 1.35]; 0.920[a]
Side effects					
AEs (supplementary information)[f]	257	ND 256 (99.6)	261	ND 249 (95.4)	–
SAEs[f]	257	ND 49 (19.1)	261	ND 47 (18.0)	0.74 [0.49; 1.11]; 0.146[g]
Severe AEs[f, h]	257	ND 134 (52.1)	261	ND 126 (48.3)	0.79 [0.62; 1.02]; 0.084[g]
Discontinuation due to AEs[f]	257	ND 35 (13.6)	261	ND 19 (7.3)	1.12 [0.64; 1.98]; 0.684[g]
Cardiac disorders (SOC, severe AEs[h])	257	ND 0 (0)	261	ND 0 (0)	–

Table 15: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine (multipage table)

Study Outcome category Outcome	Trastuzumab deruxtecan		Trastuzumab emtansine		Trastuzumab deruxtecan vs. trastuzumab emtansine
	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
Platelet count decreased (PT, severe AEs[h])	257	ND 17 (6.6)	261	ND 52 (19.9)	0.27 [0.16; 0.47]; < 0.001
Gastrointestinal disorders (SOC, AEs)	257	ND 237 (92.2)	261	ND 152 (58.2)	2.86 [2.33; 3.52]; < 0.001[g]
Skin and subcutaneous tissue disorders (SOC, AEs)	257	ND 139 (54.1)	261	ND 75 (28.7)	1.96 [1.48; 2.60]; < 0.001[g]
Nose bleed (PT, AEs)	257	ND 29 (11.3)	261	ND 42 (16.1)	0.41 [0.25; 0.67]; < 0.001[g]
Pyrexia (PT, AEs)	257	ND 27 (10.5)	261	ND 39 (14.9)	0.45 [0.27; 0.74]; 0.001[g]
Malaise (PT, AEs)	257	ND 29 (11.3)	261	ND 10 (3.8)	2.64 [1.28; 5.45]; 0.006[f, g]
General disorders and administration site conditions (SOC, severe AEs[h])[i]	257	ND 23 (8.9)	261	ND 4 (1.5)	4.38 [1.51; 12.76]; 0.003[g]
Neutrophil count decreased (PT, severe AEs[h])	257	ND 39 (15.2)	261	ND 7 (2.7)	4.49 [2.00; 10.08]; < 0.001
White blood cell count decreased (PT, severe AEs[h])	257	ND 15 (5.8)	261	ND 1 (0.4)	11.24 [1.48; 85.45]; 0.003
Nausea (PT, severe AEs[h])	257	ND 17 (6.6)	261	ND 1 (0.4)	15.62 [2.08; 117.54]; < 0.001[f]

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.
b. Time to first deterioration. A score increase by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
c. Unclear proportion of patients with missing values at baseline and in the course of the study; drastic decrease in the proportion of patients in the analysis already by the first documentation time.
d. Time to first deterioration. A decrease by ≥ 15 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
e. Time to first deterioration. A decrease by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
f. For outcomes in the category of side effects, the company presented analyses including progression of the underlying disease.
g. Hazard ratio calculated using an unstratified Cox proportional hazards regression model and the 95% CI using the Wald test. 2-sided p-value based on a log-rank test.
h. Operationalized as CTCAE grade ≥ 3.
i. Including the PTs “fatigue“ and “asthenia“ as most common manifestations.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine (multipage table)

Study Outcome category Outcome	Trastuzumab deruxtecan		Trastuzumab emtansine		Trastuzumab deruxtecan vs. trastuzumab emtansine
	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
AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; 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 I 4.4). 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 in patients ≥ 65 years of age. 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. Consequently, for this outcome, there is a hint of added benefit of trastuzumab deruxtecan in comparison with trastuzumab emtansine.

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 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

Symptom outcomes 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

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

Cognitive functioning

A statistically significant difference in favour of trastuzumab deruxtecan was shown for the outcome of cognitive functioning. There is an effect modification by the characteristic of baseline visceral disease for this outcome (see Section I 4.4). A statistically significant

difference in favour of trastuzumab deruxtecan was only shown for patients without visceral disease at baseline. For this outcome, this results in a hint of an added benefit of trastuzumab deruxtecan in comparison with trastuzumab emtansine for patients without visceral disease at baseline. No statistically significant difference between treatment groups was shown for patients who had visceral disease at baseline. For these patients, 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.

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 (CTCAE grade ≥ 3), discontinuation due to AEs

No statistically significant difference between treatment groups was shown for the outcomes of SAEs, severe AEs (CTCAE ≥ 3) and discontinuations due to AEs. Consequently, there are no hints of greater or lesser harm from trastuzumab deruxtecan in comparison with trastuzumab emtansine; greater or lesser harm is therefore not proven for these outcomes.

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), 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), 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.

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.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics are considered in the benefit assessment:

- age (< 65 years/≥ 65 years)
- visceral disease at baseline (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 16. The Kaplan-Meier curves on the subgroup results are presented in I Appendix B.4 of the full dossier assessment.

Table 16: Subgroups (mortality, morbidity, health-related quality of life, time to event) – RCT, direct comparison: trastuzumab deruxtecan vs. trastuzumab emtansine

Study Outcome	Trastuzumab deruxtecan		Trastuzumab emtansine		Trastuzumab deruxtecan vs. trastuzumab emtansine	
Characteristic Subgroup	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][a]	p-value[b]
DESTINY-Breast03						
Mortality						
Overall survival						
Age						
< 65 years	212	NA 24 (11.3)	206	NA 47 (22.8)	0.43 [0.27; 0.71]	< 0.001
≥ 65 years	49	NA 9 (18.4)	57	NA 6 (10.5)	1.74 [0.62; 4.88]	0.289
Total					Interaction:	0.014[c]
Health-related quality of life (EORTC QLQ-C30)[e]						
Cognitive functioning						
Baseline visceral disease						
Yes	195	8.8 [6.0; 13.6] 109 (55.9)	189	8.4 [4.8; 11.1] 94 (49.7)	0.88 [0.67; 1.17]	0.380
No	66	NA [9.0; NC] 29 (43.9)	74	5.0 [3.0; 12.9] 41 (55.4)	0.49 [0.31; 0.80]	0.004
Total					Interaction:	0.040[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).
e. Time to first deterioration. A decrease 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; QLQ-C30: Quality of Life Questionnaire-Core 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.

Health-related quality of life

Cognitive functioning

For the outcome of cognitive functioning, there is an effect modification by the characteristic of visceral disease at baseline.

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

No statistically significant difference between treatment groups was shown for patients who had visceral disease at baseline. For these patients, 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.

I 5 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 [1].

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.

I 5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section I 4 (see Table 17).

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

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

Symptoms

Nausea and vomiting, appetite loss, diarrhoea (each assessed using EORTC QLQ-C30), symptoms in arm region (assessed using EORTC QLQ-BR23)

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

Table 17: Extent of added benefit at outcome level: trastuzumab deruxtecan vs. trastuzumab emtansine (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Trastuzumab deruxtecan vs. trastuzumab emtansine** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Total observation period		
Mortality		
Overall survival Age < 65 years	NA vs. NA HR: 0.43 [0.27; 0.71] p < 0.001 Probability: "hint"	Outcome category: serious/severe symptoms/late complications $CI_u < 0.75$, risk ≥ 5% Added benefit, extent: "major"
≥ 65 years	NA vs. NA HR: 1.74 [0.62; 4.88] p = 0.289	Lesser/added benefit not proven
Shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30)[c]		
Fatigue	5.6 vs. 3.6 HR: 0.84 [0.67; 1.05] p = 0.126	Lesser/added benefit not proven
Nausea and vomiting	2.8 vs. 9.7 HR: 1.98 [1.56; 2.49] HR: 0.51 [0.40; 0.64][d] p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ Lesser benefit, extent: "considerable"
Pain	54.4% vs. 52.1% HR: 0.87 [0.69; 1.10] p = 0.238	Lesser/added benefit not proven
Dyspnoea	38.7% vs. 37.3% HR: 0.84 [0.63; 1.11] p = 0.210	Lesser/added benefit not proven
Insomnia	19.4 vs. 12.7 HR: 0.86 [0.66; 1.11] p = 0.243	Lesser/added benefit not proven
Appetite loss	4.2 vs. 10.3 HR: 1.44 [1.13; 1.83] HR: 0.69 [0.55; 0.88][d] p = 0.003 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ Lesser benefit, extent: "minor"

Table 17: Extent of added benefit at outcome level: trastuzumab deruxtecan vs. trastuzumab emtansine (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Trastuzumab deruxtecan vs. trastuzumab emtansine** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Constipation	5.6 vs. 8.5 HR: 1.24 [0.97; 1.58] p = 0.083	Lesser/added benefit not proven
Diarrhoea	NA vs. NA HR: 1.73 [1.26; 2.38] HR: 0.58 [0.42; 0.79][d] p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ Lesser benefit, extent: "considerable"
Symptoms (EORTC QLQ-BR23)[c]		
Side effects of systemic therapy	5.7 vs. 11.7 HR: 1.23 [0.96; 1.58] p = 0.100	Lesser/added benefit not proven
Symptoms in chest region	NA vs. NA HR: 0.85 [0.58; 1.24] p = 0.403	Lesser/added benefit not proven
Symptoms in arm region	10.3 vs. 5.6 HR: 0.74 [0.58; 0.94] p = 0.014	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser benefit/added benefit not proven[e]
Upset by hair loss	No usable data	Lesser/added benefit not proven
Health status		
EQ-5D VAS[f]	24.6 vs. 14.4 HR: 0.75 [0.56; 1.01] p = 0.061	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30[g]		
Global health status	6.9 vs. 7.2 HR: 0.99 [0.78; 1.25] p = 0.885	Lesser/added benefit not proven
Physical functioning	NA vs. 12.0 HR: 0.87 [0.66; 1.15] p = 0.326	Lesser/added benefit not proven
Role functioning	11.6 vs. 6.3 HR: 0.75 [0.59; 0.96] p = 0.022 Probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Added benefit, extent: "minor"

Table 17: Extent of added benefit at outcome level: trastuzumab deruxtecan vs. trastuzumab emtansine (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Trastuzumab deruxtecan vs. trastuzumab emtansine** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Emotional functioning	16.7 vs. 11.1 HR: 0.80 [0.61; 1.05] p = 0.101	Lesser/added benefit not proven
Cognitive functioning		
Baseline visceral disease		
Yes	8.8 vs. 8.4 HR: 0.88 [0.67; 1.17] p = 0.380	Lesser/added benefit not proven
No	NA vs. 5.0 HR: 0.49 [0.31; 0.80] p = 0.004 Probability: "hint"	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ Added benefit, extent: "considerable"
Social functioning	7.3 vs. 8.4 HR: 1.04 [0.82; 1.32] p = 0.774	Lesser/added benefit not proven
EORTC QLQ-BR23[g]		
Body image	17.3 vs. NA HR: 1.35 [1.02; 1.80] HR: 0.74 [0.56; 0.98][d] p = 0.039 Probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Lesser benefit, extent: "minor"
Sexual activity	NA vs. NA HR: 0.93 [0.65; 1.34] p = 0.707	Lesser/added benefit not proven
Enjoyment of sex	No usable data	Lesser/added benefit not proven
Future perspective	NA vs. 21.2 HR: 0.98 [0.72; 1.35] p = 0.920	Lesser/added benefit not proven
Side effects		
SAEs	ND vs. ND HR: 0.74 [0.49; 1.11] p = 0.146	Greater/lesser harm not proven
Severe AEs	ND vs. ND HR: 0.79 [0.62; 1.02] p = 0.084	Greater/lesser harm not proven
Discontinuation due to AEs	ND vs. ND HR: 1.12 [0.64; 1.98] p = 0.684	Greater/lesser harm not proven

Table 17: Extent of added benefit at outcome level: trastuzumab deruxtecan vs. trastuzumab emtansine (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Trastuzumab deruxtecan vs. trastuzumab emtansine** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Cardiac disorders (severe AEs)	ND vs. ND HR: NC p = NC	Greater/lesser harm not proven
Platelet count decreased (severe AEs)	ND vs. ND HR: 0.27 [0.16; 0.47] p < 0.001 Probability: "hint"	Outcome category: serious/severe symptoms/late complications CI_u < 0.75, risk ≥ 5% Lesser harm, extent: "major"
Gastrointestinal disorders (AEs)	ND vs. ND HR: 2.86 [2.33; 3.52] HR: 0.35 [0.28; 0.43][d] p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 Greater harm, extent: "considerable"
Skin and subcutaneous tissue disorders (AEs)	ND vs. ND HR: 1.96 [1.48; 2.60] HR: 0.51 [0.38; 0.68][d] p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 Greater harm, extent: "considerable"
Nose bleed (AEs)	ND vs. ND HR: 0.41 [0.25; 0.67] p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 Lesser harm, extent: "considerable"
Pyrexia (AEs)	ND vs. ND HR: 0.45 [0.27; 0.74] p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 Lesser harm, extent: "considerable"
Malaise (AEs)	ND vs. ND HR: 2.64 [1.28; 5.45] HR: 0.38 [0.18; 0.78][d] p = 0.006 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 Greater harm, extent: "considerable"
General disorders and administration site conditions (severe AEs)	ND vs. ND HR: 4.38 [1.51; 12.76] HR: 0.23 [0.08; 0.66][d] p = 0.003 Probability: "hint"	Outcome category: serious/severe symptoms/late complications CI_u < 0.75, risk ≥ 5% Greater harm; extent: "major"

Table 17: Extent of added benefit at outcome level: trastuzumab deruxtecan vs. trastuzumab emtansine (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Trastuzumab deruxtecan vs. trastuzumab emtansine** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Neutrophil count decreased (severe AEs)	ND vs. ND HR: 4.49 [2.00; 10.08] HR: 0.22 [0.10; 0.50][d] p < 0.001 Probability: "hint"	Outcome category: serious/severe symptoms/late complications CI_u < 0.75, risk ≥ 5% Greater harm; extent: "major"
White blood cell count decreased (severe AEs)	ND vs. ND HR: 11.24 [1.48; 85.45] HR: 0.09 [0.01; 0.68][d] p = 0.003 Probability: "hint"	Outcome category: serious/severe symptoms/late complications CI_u < 0.75, risk ≥ 5% Greater harm; extent: "major"
Nausea (severe AEs)	ND vs. ND HR: 15.62 [2.08; 117.54] HR: 0.06 [0.01; 0.48][d] p < 0.001 Probability: "hint"	Outcome category: serious/severe symptoms/late complications CI_u < 0.75, risk ≥ 5% 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; 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

I 5.2 Overall conclusion on added benefit

Table 18 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of trastuzumab deruxtecan in comparison with trastuzumab emtansine

Positive effects	Negative effects
Total observation period	
Mortality ▪ Overall survival ▫ Age (< 65 years): hint of added benefit – extent: "major"	
Shortened observation period	
	Non-serious/non-severe symptoms/late complications Symptoms (EORTC QLQ-C30) ▪ Nausea and vomiting: hint of lesser benefit – extent: "considerable" ▪ Appetite loss: hint of lesser benefit – extent: "minor" ▪ Diarrhoea: hint of lesser benefit – extent: "considerable"
Health-related quality of life EORTC QLQ-C30 ▪ Role functioning: hint of an added benefit – extent: "minor" ▪ Cognitive functioning ▫ Baseline visceral disease (no): hint of an added benefit – extent: "considerable"	Health-related quality of life EORTC QLQ-BR23 ▪ Body image: hint of lesser benefit – extent: "minor"
Serious/severe side effects ▪ Platelet count decreased (severe AEs): hint of lesser harm – extent: "major"	Serious/severe side effects ▪ General disorders and administration site conditions, neutrophil count decreased, white blood cell count decreased, nausea (severe AEs for each): hint of greater harm – extent: "major"
Non-serious/non-severe side effects ▪ Nose bleed, pyrexia (severe AEs for each): hint of lesser harm – extent: "considerable"	Non-serious/non-severe side effects ▪ 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	

Overall, there are positive and negative effects of trastuzumab deruxtecan in comparison with trastuzumab emtansine.

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, there are both positive and negative effects of trastuzumab deruxtecan in individual domains of health-related quality of life, as well as in individual specific AEs of different severity categories and with varying, partly major, extent (hints in each case). In addition, there are several negative effects in the category of symptoms for

outcomes on gastrointestinal complaint (nausea and vomiting, diarrhoea, and appetite loss), some of which are of considerable extent (hints in each case).

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 considerable added benefit of trastuzumab deruxtecan in comparison with the ACT trastuzumab emtansine. For patients ≥ 65 years of age, an added benefit of trastuzumab deruxtecan in comparison with the ACT trastuzumab emtansine is not proven.

The result of the assessment of the added benefit of trastuzumab deruxtecan in comparison with the ACT is summarized in Table 19.

Table 19: 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 considerable added benefit ▪ 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 assessment described above deviates from that of the company, which derived an indication of considerable added benefit for all patients.

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

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Please see full dossier assessment for full reference list.

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

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