Trastuzumab deruxtecan (breast cancer)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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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
CDK	cyclin-dependent kinase
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
IHC	immunohistochemistry
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ISH	in situ hybridization
PFS	progression-free survival
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug trastuzumab deruxtecan. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 3 February 2023.

Research question

The aim of the present report is to assess the added benefit of trastuzumab deruxtecan in comparison with the appropriate comparator therapy (ACT) in patients with unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

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

Therapeutic indication	**ACT**[a]
Adults[b] with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy[c]	▪ Capecitabine or ▪ eribulin or ▪ vinorelbine or ▪ an anthracycline or taxane-containing regimen (only for patients who have not yet received an anthracycline and/or taxane-containing regimen or who are eligible for renewed anthracycline or taxane-containing treatment)

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

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

The company largely followed the G-BA's specification of the ACT. In addition to the options presented in Table 2, it also cited sacituzumab govitecan as an option for patients with hormone receptor-negative breast cancer. As the company included no study with sacituzumab govitecan as a comparator, the extension of the ACT by the company is of no consequence for the present benefit assessment. The benefit assessment is conducted in comparison with the ACT specified by the G-BA.

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

Study pool and study design

The DESTINY-Breast04 study is used for the benefit assessment of trastuzumab deruxtecan. This is an ongoing open-label, randomized, 2-arm study comparing trastuzumab deruxtecan with treatment of physician's choice. Available options for the treatment of physician's choice in the study are the drugs capecitabine, eribulin, gemcitabine, paclitaxel or nab-paclitaxel. The study enrolled adult patients with unresectable or metastatic HER2-low breast cancer who have been treated with 1 or 2 prior lines of chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Study inclusion was independent from hormone receptor status. If patients had a positive hormone receptor status, the breast cancer had to be refractory to endocrine therapy. At enrolment, patients had to have an Eastern Cooperative Oncology Group-Performance Status (ECOG PS) of 0 or 1.

Overall, 557 patients were included in the study and randomly allocated in a 2:1 ratio either to treatment with trastuzumab deruxtecan (N = 373) or to treatment of physician's choice (N = 184). Randomization was stratified by HER2 status (immunohistochemistry [IHC] 1+ versus IHC 2+/in situ hybridization [ISH]-negative), number of prior lines of chemotherapy in the metastatic setting (1 versus 2), and hormone receptor/cyclin-dependent kinase [CDK] status (hormone receptor-positive with prior CDK4/6 inhibitor treatment versus hormone receptor-positive without prior CDK4/6 inhibitor treatment versus hormone receptor-negative).

Treatment with trastuzumab deruxtecan was largely in compliance with the specifications of the Summary of Product Characteristics (SPC). There were deviations in the concomitant medication with anti-emetics. Treatment with eribulin, capecitabine, gemcitabine, paclitaxel or nab-paclitaxel partly deviated from the specifications in the SPC.

Treatment with the study medication was until disease progression, unacceptable toxicity, withdrawal of consent, or end of study.

The primary outcome of the study was progression-free survival (PFS). Patient-relevant secondary outcomes were outcomes in the mortality, morbidity, health-related quality of life, and adverse events (AEs) categories.

Uncertainties in the implementation of the appropriate comparator therapy in the DESTINY-Breast04 study

Regarding the implementation of the ACT in the DESTINY-Breast04 study, the following uncertainties exist:

- In the DESTINY-Breast04 study, 9% of all patients in the comparator arm received gemcitabine monotherapy. On the one hand, the drug gemcitabine is not part of the G-BA's ACT and, on the other hand, in the present therapeutic indication, is only approved in combination with paclitaxel. Overall, it is unclear to what extent the use of gemcitabine affects the results of patient-relevant outcomes.
- For the use of the drugs capecitabine, eribulin, paclitaxel and nab-paclitaxel, certain requirements of pretreatment with taxanes or anthracyclines must be met. In addition, the G-BA stated that an anthracycline or taxane-containing regimen is an ACT only for those patients who have not yet received an anthracycline and/or taxane-containing regimen or who are eligible for renewed anthracycline or taxane-containing treatment. The study documents provide data on previous systemic cancer therapies only on the basis of all patients in the comparator arm and not per drug option used. However, it is not clear from the study documents which drugs patients had received last before enrolment, or whether they were retreated with anthracyclines or taxanes.
- The DESTINY-Breast04 study partly allowed dosages of capecitabine, paclitaxel and nab-paclitaxel that deviated from the SPC. According to the study protocol, if applicable, administration in a 21-day cycle was to be recommended, however. There is no information in the study documents about which dose regimens were used.

The described uncertainties regarding the administration of gemcitabine, the pretreatment of patients with anthracyclines and/or taxanes and the dosage of capecitabine, paclitaxel and nab-paclitaxel, limits the certainty of conclusions of the DESTINY-Breast04 study.

Risk of bias

The risk of bias across outcomes for the DESTINY-Breast04 study is rated as low.

For the results of the outcomes of symptoms, health status, and health-related quality of life, the risk of bias is rated as high due to the lack of blinding with subjective recording of outcomes and strongly decreasing questionnaire return rates in the course of the study, which differed between the treatment arms. For the results of the outcomes of serious AEs (SAEs) and severe AEs, the risk of bias is rated as high due to the large difference in median treatment

duration (and thus observation period) between the intervention arm (8.2 months) and the control arm (3.5 months) as well as the different reasons for treatment discontinuation. For the results of the non-severe side effects, the lack of blinding with subjective recording of outcomes leads to a high risk of bias. The risk of bias for the outcome of discontinuation due to AEs is rated as high because of lack of blinding with subjective decision on treatment discontinuation.

Irrespective of the aspects described for the risk of bias, the certainty of conclusions of the study results is limited due to the aforementioned uncertainties resulting from the administration of gemcitabine, the pretreatment of the patients, and the dosing of the drugs in the comparator arm. In addition, the certainty of conclusions of the outcomes of nausea and vomiting is limited due to the partial lack of concomitant anti-emetic treatment. Overall, at most hints, e.g. of an added benefit, can be determined for all outcomes.

Results

Mortality

Overall survival

There is an effect modification by the characteristic of visceral disease for the outcome of overall survival. A statistically significant difference in favour of trastuzumab deruxtecan in comparison with treatment of physician's choice was shown both for patients with and for patients without visceral disease. The extent of the effect differs between the subgroups. There is a hint of an added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice both for patients with and for patients without visceral disease.

Morbidity

Symptoms (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30])

Pain and insomnia

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

Nausea and vomiting

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

Fatigue

A statistically significant difference in favour of trastuzumab deruxtecan in comparison with treatment of physician's choice was shown for the outcome of fatigue. However, the extent of the effect for this outcome of the category of non-serious/non-severe symptoms/late complications was no more than marginal. There is no hint of added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Diarrhoea

A statistically significant difference to the disadvantage of trastuzumab deruxtecan in comparison with treatment of physician's choice was shown for the outcome of diarrhoea. However, the extent of the effect for this outcome of the category of non-serious/non-severe symptoms/late complications was no more than marginal. There is no hint of added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Dyspnoea, appetite loss, and constipation

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

Symptoms (EORTC QLQ-Breast Cancer Module 23 [EORTC QLQ-BR23])

Arm symptoms

A statistically significant difference in favour of trastuzumab deruxtecan in comparison with treatment of physician's choice was shown for the outcome of arm symptoms. However, the extent of the effect for this outcome of the category of non-serious/non-severe symptoms/late complications was no more than marginal. There is no hint of added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Upset by hair loss

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

Side effects of systemic therapy and breast symptoms

No statistically significant difference between treatment groups was shown for the outcomes of side effects of systemic therapy and breast symptoms. In each case, there is no hint of

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

Health status (EQ-5D visual analogue scale [VAS])

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

Health-related quality of life

EORTC QLQ-C30

Physical functioning, role functioning, cognitive functioning, and social functioning

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

Global health status and emotional functioning

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

EORTC QLQ-BR23

Body image

A statistically significant difference in favour of trastuzumab deruxtecan in comparison with treatment of physician's choice was shown for the outcome of body image. For this outcome, there is an effect modification by the characteristics of age and visceral disease. The subgroup results cannot be meaningfully interpreted because data for the investigation of possible dependencies between the 2 subgroup characteristics are missing. The added benefit is therefore derived based on the results of the total population. There is a hint of an added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice.

Sexual enjoyment

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

Sexual functioning and future perspective

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

Side effects

Severe AEs

A statistically significant difference in favour of trastuzumab deruxtecan in comparison with treatment of physician's choice was shown for the outcome of severe AEs. There is a hint of lesser harm from trastuzumab deruxtecan in comparison with treatment of physician's choice.

SAEs, discontinuation due to AEs

No statistically significant difference was found between treatment groups for either of the outcomes of SAEs or discontinuation due to AEs. In each case, there is no hint of greater or lesser harm from trastuzumab deruxtecan in comparison with treatment of physician's choice; greater or lesser harm is therefore not proven.

Specific AEs

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

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

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

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

Cardiac disorders (severe AEs)

The company presented no calculations on the hazard ratio and no p-value for the outcome of cardiac disorders (severe AEs). Due to the low number of events, it cannot be assumed that there would be a statistically significant effect in case of suitable analyses. There is no hint of greater or lesser harm from trastuzumab deruxtecan in comparison with treatment of physician's choice; greater or lesser harm is therefore not proven.

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

Overall, there are both positive and negative effects of different extents for trastuzumab deruxtecan in comparison with treatment of physician's choice. Only for overall survival are the observed effects based on the entire observation period. For the outcome categories of morbidity, health-related quality of life and side effects, however, they are based exclusively on the shortened observation period of approx. 4.5 months (morbidity, health-related quality of life) and 40 days (side effects) after the end of treatment.

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

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

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

[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].

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

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

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

The approach for the derivation of an overall conclusion on 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 to assess the added benefit of trastuzumab deruxtecan in comparison with the ACT in patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.

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

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

Therapeutic indication	**ACT**[a]
Adults[b] with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy[c]	▪ Capecitabine or ▪ eribulin or ▪ vinorelbine or ▪ an anthracycline or taxane-containing regimen (only for patients who have not yet received an anthracycline and/or taxane-containing regimen or who are eligible for renewed anthracycline or taxane-containing treatment)
a. Presented is the ACT specified by the G-BA. b. According to the G-BA, the evidence on treatment options for men with breast cancer is extremely limited. According to the guidelines, the recommendations for the treatment of men are predominantly based on the recommendations for the treatment of women. Within the framework of the benefit assessment, separate consideration of men can be useful. c. The therapeutic indication may also include patients who are candidates for further endocrine therapy. According to the G-BA, it is assumed that the endocrine treatment options for patients with hormone receptor-positive breast cancer have been exhausted in the present treatment situation. It is also assumed according to the G-BA that, as part of prior therapy, patients typically received taxane and/or anthracycline-containing chemotherapy. Moreover, it is assumed that (secondary) resection or radiotherapy with curative intent is not indicated. According to guideline recommendations, combination therapy should be considered for patients with high remission pressure due to severe symptoms or rapid tumour growth. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2	

The company largely followed the G-BA's specification of the ACT. In addition to the options presented in Table 4, it also cited sacituzumab govitecan as an option for patients with hormone receptor-negative breast cancer. The company justified this additional option by stating that the medical benefit of sacituzumab govitecan has already been established by the G-BA in a benefit assessment procedure and that sacituzumab govitecan has been included in the recommendations of national and international guidelines relevant to the provision of health care [3-7]. As the company included no study with sacituzumab govitecan as a comparator, the extension of the ACT by the company is of no consequence for the present benefit assessment. The benefit assessment is conducted in comparison with the ACT specified by the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. RCTs are used for the derivation of 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: 3 January 2023)
- bibliographical literature search on trastuzumab deruxtecan (last search on 3 January 2023)
- search in trial registries/trial results databases for studies on trastuzumab deruxtecan (last search on 3 January 2023)
- search on the G-BA website for trastuzumab deruxtecan (last search on 3 January 2023)

To check the completeness of the study pool:

- search in trial registries for studies on trastuzumab deruxtecan (last search on 15 February 2023); 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. treatment of physician's choice[a]

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[b] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[c] (yes/no [citation])	Publication and other sources[d] (yes/no [citation])
DESTINY-Breast04	Yes	Yes	No	Yes [8]	Yes [9-11]	Yes [12]

a. Capecitabine or eribulin or gemcitabine or paclitaxel or nab-paclitaxel.
b. Study for which the company was sponsor.
c. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
d. Other sources: documents from the search on the G-BA website and other publicly available sources.

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

The study pool for the benefit assessment concurs with that of the company.

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. treatment of physician's choice[a]

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
DESTINY-Breast04	RCT, open-label, parallel	Adult patients with pathologically documented breast cancer[c]: ▪ unresectable or metastatic ▪ HER2-low[d] ▪ who have been treated with 1 to 2 prior lines of chemotherapy in the metastatic setting, or developed recurrence during or within 6 months of (neo)adjuvant chemotherapy[e] ▪ ECOG PS 0 or 1	Trastuzumab deruxtecan (N = 373) Treatment of physician's choice[a] (N = 184[f]) ▪ capecitabine (n = 36) ▪ eribulin (n = 89) ▪ gemcitabine (n = 16) ▪ paclitaxel (n = 14) ▪ nab-paclitaxel (n = 17)	Screening: up to 28 days Treatment: until disease progression, unacceptable toxicity, withdrawal of consent, or end of study Observation[g]: outcome-specific, at the longest until death, study discontinuation for any reason, or end of study	161 centres in Austria, Belgium, Canada, China, France, Greece, Hungary, Israel, Italy, Japan, Portugal, Russia, South Korea, Spain, Sweden, Switzerland, Taiwan, UK, USA 12/2018–ongoing Data cut-off: ▪ 11 January 2022[h]	Primary: PFS Secondary: overall survival, morbidity, health-related quality of life, AEs

a. Capecitabine or eribulin or gemcitabine or paclitaxel or nab-paclitaxel.
b. 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.
c. Independent from hormone receptor status. If patients had a positive hormone receptor status, they had to have been pretreated with endocrine therapy and the breast cancer had to be refractory to endocrine therapy.
d. Defined as IHC 1+ or IHC 2+/ISH negative, evaluated by a central laboratory in accordance with the guideline of the American Society of Clinical Oncology – College of American Pathologists (ASCO-CAP) [13].
e. Presence of documented radiological progression.
f. Including 172 patients who received at least one dose of the study medication.
g. Outcome-specific information is provided in Table 8.
h. Final analysis of PFS after 318 events in the group of patients with positive hormone receptor status.

AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; ISH: in situ hybridization; n: number of patients; 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. treatment of physician's choice[a] (multipage table)

Study	Intervention	Comparison
DESTINY-Breast04	Trastuzumab deruxtecan 5.4 mg/kg BW[b] IV on day 1 of a 21-day cycle	Treatment of physician's choice; one of the following chemotherapies was determined for each patient before randomization: ▪ capecitabine: 1000–1250 mg/m^2 BSA orally, twice daily on days 1–14 of a 21-day cycle ▪ eribulin: 1.4 mg/m^2 IV on days 1 and 8 of a 21-day cycle ▪ gemcitabine: 800–1200 mg/m^2 IV on days 1 and 8 of a 21-day cycle, or 800–1200 mg/m^2 IV on days 1, 8 and 15 of a 28-day cycle ▪ paclitaxel: 175 mg/m^2 IV on day 1 of a 21-day cycle, or 80 mg/m^2 IV weekly on day 1 ▪ nab-paclitaxel: 260 mg/m^2 IV every 21 days, or 100 mg/m^2 or 125 mg/m^2 IV on days 1, 8 and 15 of a 28-day cycle
	Dose adjustments ▪ Dose interruption for up to 28 days[c] ▪ Dose reductions were allowed as follows[d]: first dose level: 4.4 mg/kg BW second dose level: 3.2 mg/kg BW	**Dose adjustments** ▪ dose interruption for up to 28 days[c] ▪ dose adjustments according to local approval of the respective drug or the NCCN guideline
	Pretreatment ▪ at least 1 and at most 2 prior lines of chemotherapy in the recurrent or metastatic setting ▪ patients with hormone receptor-positive breast cancer must have received endocrine therapy **Disallowed pretreatment** ▪ ADC that consists of an exatecan derivative that is a topoisomerase I inhibitor ▪ 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 ▪ completion of whole brain radiotherapy within 2 weeks before the start of the study **Concomitant treatment** ▪ haematopoietic growth factors for prophylaxis or treatment ▪ for trastuzumab deruxtecan antiemetics such as 5-hydroxytryptamine receptor antagonists, neurokinin-1 receptor antagonists and/or steroids	

Table 7: Characteristics of the intervention – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

Study	Intervention	Comparison
	Disallowed concomitant treatment ▪ other antineoplastic treatment ▪ treatment with (hydro)chloroquine ▪ other investigational therapy ▪ radiotherapy (except for palliative radiotherapy to known metastatic sites) ▪ chronic systemic corticosteroids (IV or oral) or other immunosuppressants (except for the treatment of AEs) ▪ in the comparator arm: drugs that are not allowed during treatment according to local approval	

a. Capecitabine or eribulin or gemcitabine or paclitaxel or nab-paclitaxel.
b. According to study protocol amendment 6 (12 October 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.
c. If interruption was ≥ 28 days, treatment was permanently discontinued.
d. Subsequent cycles after dose reduction due to toxicity were to be continued at the lower dose. If toxicity persisted after 2 dose reductions, the study treatment was to be discontinued.

ADC: antibody-drug conjugate; AE: adverse event; BSA: body surface area; BW: body weight; IV: intravenously; NCCN: National Comprehensive Cancer Network; RCT: randomized controlled trial

The DESTINY-Breast04 study is an ongoing open-label, randomized, 2-arm study comparing trastuzumab deruxtecan with treatment of physician's choice. Available options for the treatment of physician's choice in the study are the drugs capecitabine, eribulin, gemcitabine, paclitaxel or nab-paclitaxel. The decision for one of these options for the respective patient had to be made before randomization. The study enrolled adult patients with unresectable or metastatic HER2-low breast cancer who have been treated with 1 or 2 prior lines of chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. HER2-low status in the study is defined as low HER2 expression, as determined by VENTANA PATHWAY anti-HER-2/neu (4B5) IHC assay, and is defined as staining intensity of IHC 1+ or 2+. If IHC 2+ is present, ISH must be negative. The approval of trastuzumab deruxtecan in the present therapeutic indication of HER2-low breast cancer is based on this definition of HER2 tumour status [14]. Study inclusion was independent from hormone receptor status. If patients had a positive hormone receptor status, the breast cancer had to be refractory to endocrine therapy. At enrolment, patients had to have an ECOG PS of 0 or 1.

Overall, 557 patients were included in the study and randomly allocated in a 2:1 ratio either to treatment with trastuzumab deruxtecan (N = 373) or to treatment of physician's choice (N = 184). Randomization was stratified by HER2 status (IHC 1+ versus IHC 2+/ISH-negative), number of prior lines of chemotherapy in the metastatic setting (1 versus 2), and hormone receptor/CDK status (hormone receptor-positive with prior CDK4/6 inhibitor treatment versus

hormone receptor-positive without prior CDK4/6 inhibitor treatment versus hormone receptor-negative).

Treatment with trastuzumab deruxtecan was largely in compliance with the specifications of the SPC [14]. There were deviations in the concomitant medication with anti-emetics. Treatment with eribulin, capecitabine, gemcitabine, paclitaxel or nab-paclitaxel partly deviated from the specifications in the SPC [15-19]. These deviations are described below.

Treatment with the study medication was until disease progression, unacceptable toxicity, withdrawal of consent, or end of study. There are no limitations regarding the choice subsequent therapies. In total, only 2 patients in the comparator arm received trastuzumab deruxtecan as subsequent therapy.

The primary outcome of the study was PFS. Patient-relevant secondary outcomes were outcomes in the mortality, morbidity, health-related quality of life, and AEs categories.

Uncertainties in the implementation of the appropriate comparator therapy in the DESTINY-Breast04 study

The G-BA specified capecitabine or eribulin or vinorelbine or an anthracycline or taxane-containing regimen (only for patients who have not yet received an anthracycline and/or taxane-containing regimen or who are eligible for renewed anthracycline or taxane-containing treatment) as ACT. With the exception of vinorelbine, these options were available in the DESTINY-Breast04 study; the drug gemcitabine was an additional option in the comparator arm.

Gemcitabine is not part of the appropriate comparator therapy

In the DESTINY-Breast04 study, 9% of all patients in the comparator arm received gemcitabine monotherapy. On the one hand, the drug gemcitabine is not part of the G-BA's ACT and, on the other, in the present therapeutic indication, is only approved in combination with paclitaxel [19]. Current guidelines recommend gemcitabine also only as part of combination chemotherapy [20,21]. Hence, 9% of all patients in the comparator arm potentially received inadequate therapy. However, these patients are included in the analyses of the company. Overall, it would have been possible for the company to operationalize a corresponding subpopulation while taking into account the ACT and preserving randomization. For this purpose, all patients for whom gemcitabine was selected as a treatment option before randomization would have to be excluded on both the intervention and the comparator side. Overall, it is unclear to what extent the use of gemcitabine affects the results of patient-relevant outcomes.

Pretreatment of patients with anthracyclines and/or taxanes

According to the respective SPCs, the options capecitabine, eribulin, paclitaxel and nab-paclitaxel in the comparator arm of the study, which are relevant for the dossier assessment, should only be used if:

- taxane and anthracycline therapy has failed or further anthracycline treatment is not indicated (capecitabine [16])
- prior therapy included an anthracycline and a taxane, except where they were unsuitable for the patient (eribulin [15])
- patients have not responded to or are not eligible for standard anthracycline-containing therapy (paclitaxel [17])
- first-line therapy for metastatic disease has failed and standard anthracycline-containing therapy is not indicated (nab-paclitaxel [18])

In addition, the G-BA stated that an anthracycline or taxane-containing regimen is an ACT only for those patients who have not yet received an anthracycline and/or taxane-containing regimen or who are eligible for renewed anthracycline or taxane-containing treatment. Overall, the study documents provide data on previous systemic cancer therapies only on the basis of all patients in the comparator arm and not per drug option used. Taxanes and anthracyclines can be found in the listings of prior therapies. However, it is not clear from the study documents which drugs patients had received before enrolment, or whether they were retreated with anthracyclines or taxanes.

Dosing of capecitabine, paclitaxel and nab-paclitaxel

The DESTINY-Breast04 study partly allowed dosages of capecitabine, paclitaxel and nab-paclitaxel that deviated from the SPC. For example, according to the SPC, capecitabine is approved for the treatment of advanced or metastatic breast cancer at a dose of 1250 mg/m^2 twice daily for 14 days [16]. In the DESTINY-Breast04 study, capecitabine could also be used in a partly lower dosage of 1000-1250 mg/m^2 twice daily for 14 days. Besides the approval-compliant dosages of paclitaxel (175 mg/m^2 every 3 weeks) and nab-paclitaxel (260 mg/m^2 every 3 weeks) [17,18] paclitaxel could also be used at 80 mg/m^2 body surface area once weekly, and nab-paclitaxel with 100 mg/m^2 or with 125 mg/m^2 on days 1, 8 and 15 of a 4-week cycle. According to the study protocol, if applicable, administration in a 21-day cycle was to be recommended, however. There is no information in the study documents about which dose regimens were used. Only data on mean dose intensity are available, which was 183 mg/m^2 per dose for paclitaxel and 233 mg/m^2 per dose for nab-paclitaxel. Since this corresponds approximately to the dosage in compliance with the approval, it can be assumed that the patients mainly received the dosage in compliance with the SPC. The mean dose intensity of capecitabine was 963 mg/m^2 per dose, which is lower than the dosage in compliance with the

approval. The deviations in capecitabine dosing may also be based on dose adjustments due to AEs, which occurred in 64% of patients receiving capecitabine treatment. Overall, however, it is unclear whether patients in the study received a dosage of capecitabine that was in compliance with the approval.

Effects on the certainty of conclusions of the DESTINY-Breast04 study

The described aspects regarding the administration of gemcitabine, the pretreatment of patients with anthracyclines and/or taxanes and the dosage of capecitabine, paclitaxel and nab-paclitaxel, limits the certainty of conclusions of the DESTINY-Breast04 study (see Section I 4.2).

Use of concomitant anti-emetic treatment

According to the SPC, patients should receive an anti-emetic before each dose of trastuzumab deruxtecan, eribulin or paclitaxel to prevent nausea and vomiting [14,15,17]. Accordingly, all patients in the intervention arm and at least 60% of patients in the comparator arm (89 patients with eribulin treatment and 14 patients with paclitaxel treatment) should have received concomitant anti-emetic treatment. However, according to the study documents, only 77% of all patients in the intervention arm and 45% in the comparator arm were treated with anti-emetics and anti-nausea medication. Since the proportions of patients with no anti-emetic treatment are similar in both study arms, it is not assumed that the results are not interpretable due to the disadvantage of one study arm. However, it cannot be ruled out either that a lack of concomitant anti-emetic treatment has an influence on the results of the outcomes of nausea and vomiting (patient-reported as well as AEs). This uncertainty is taken into account in the certainty of conclusions of these outcomes (see Section I 4.2).

Data cut-off

The DESTINY-Breast04 study is an ongoing study. The company used an analysis at the data cut-off on 11 January 2022 for the benefit assessment. According to the study protocol, this is the final analysis planned after 318 events for the PFS outcome in the group of patients with hormone receptor-positive breast cancer. According to the statistical analysis plan, this data cut-off is also the final analysis for overall survival.

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. treatment of physician's choice[a]

Study **Outcome category** **Outcome**	**Planned follow-up observation**
DESTINY-Breast04	
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 category of side effects	40 days (+ 7 days) after the last dose of study medication[b]

a. Capecitabine or eribulin or gemcitabine or paclitaxel or nab-paclitaxel.

b. 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; SAE: serious adverse event; VAS: visual analogue scale

In the DESTINY-Breast04 study, only the outcome of overall survival is recorded until study end. The observation periods for the outcomes of morbidity, health-related quality of life, and side effects were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 40 days). For each of the outcomes of the categories of morbidity and health-related quality of life, there is an additional recording after another 3 months. Drawing a reliable conclusion on the total study period or the time to patient death, however, would require surveying these outcomes for the total period, as was done for survival.

Characteristics of the study population

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

Study Characteristic Category	**Trastuzumab deruxtecan N[b] = 373**	**Treatment of physician's choice[a] N[b] = 184**
DESTINY-Breast04		
Age [years], mean (SD)	57 (11)	57 (12)
Sex [F/M], %	99/1	100/0
Region, n (%)		
Asia	147 (39)	66 (36)
North America	60 (16)	33 (18)
Europe and Israel	166 (45)	85 (46)
Family origin, n (%)		
White	176 (47)	91 (49)
Black or African American	7 (2)	3 (2)
Asian	151 (40)	72 (39)
Other	39 (10)[c]	17 (9)
Missing	0 (0)	1 (1)
ECOG PS, n (%)		
0	200 (54)	105 (57)
1	173 (46)	79 (43)
Time from first, histological diagnosis to study treatment [months]		
Mean (SD)	100.5 (78.4)	88.7 (79.4)
Median [min; max]	75.4 [5; 445]	64.0 [4; 358]
HER2 status (EDC), n (%)		
IHC 1+	214 (57)	107 (58)
IHC 2+/ISH negative	159 (43)	77 (42)
Hormone receptor/CDK status (EDC), n (%)		
Positive with prior CDK4/6 inhibitor treatment	235 (63)	118 (64)
Positive without prior CDK4/6 inhibitor treatment	98 (26)	48 (26)
Negative	40 (11)	18 (10)
Visceral disease, n (%)		
Yes	332 (89)	157 (85)
No	41 (11)	27 (15)
CNS metastases, n (%)		
Yes	24 (6)	8 (4)
No	349 (94)	176 (96)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

Study Characteristic Category	Trastuzumab deruxtecan N[b] = 373	Treatment of physician's choice[a] N[b] = 184
Prior lines of chemotherapy in the metastatic setting (EDC), n (%)		
1	218 (58)	102 (55)
2	154 (41)	82 (45)
Missing	1 (0.3)	0 (0)
Prior treatment with anthracyclines, n (%)		
Yes	ND	ND
No	ND	ND
Prior treatment with taxanes, n (%)		
Yes	ND	ND
No	ND	ND
Prior lines of endocrine therapy in the metastatic setting – calculated, n (%)		
0	60 (16)	34 (18)
1	108 (29)	51 (28)
2	115 (31)	54 (29)
≥ 3	90 (24)	45 (24)
Treatment discontinuation, n (%)[d]	313 (84)	169 (98)
Study discontinuation, n (%)[e]	ND	ND

a. Capecitabine or eribulin or gemcitabine or paclitaxel or nab-paclitaxel.
b. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
c. Institute's calculation.
d. Common reasons for treatment discontinuation in the intervention vs. control arm were: disease progression according to mRECIST v1.1 (59.3% vs. 75.6%), AEs (16.2% vs. 8.1%), withdrawal of consent (3.2% vs. 6.4%); data refer to patients who received at least one dose of study medication (371 vs. 172 patients).
e. At least 12 patients in the intervention arm and at least 11 patients in the control arm discontinued the study due to withdrawal of consent.

CDK: cyclin-dependent kinase; CNS: central nervous system; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EDC: electronic data capture; F: female; IHC: immunohistochemistry; ISH: in situ hybridization; M: male; mRECIST: modified Response Evaluation Criteria in Solid Tumours; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

The demographic and clinical characteristics of the patients in both treatment arms are comparable. The study population of the DESTINY-Breast04 study consists almost exclusively of women (2 men in the intervention arm). At enrolment, the patients in the study were on average 57 years old and slightly more than half of the participants (55%) had an ECOG PS of 0.

The majority of patients had visceral disease (88%) and hormone receptor-positive breast cancer (90%). Of the patients with hormone receptor-positive breast cancer, 71% had received prior CDK4/6 inhibitor therapy. Only 10% of all patients had hormone receptor-negative breast cancer. 83% of all patients had received at least one prior line of endocrine therapy in the metastatic setting. 84% of patients in the intervention arm and 98% of those in the control arm discontinued treatment. The most common reason for treatment discontinuation was disease progression (intervention arm: 59%; control arm: 76%) and AEs (intervention arm: 16%; control arm: 8%). No data are available on treatment discontinuation.

Since the study included no patients with ECOG PS ≥ 2 and only 2 men, it remains unclear whether the study results can be transferred to these patients, who are also comprised by the therapeutic indication to be assessed.

Information on the course of the study

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

Table 10: Information on the course of the study – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a]

Study **Duration of the study phase** **Outcome category**	**Trastuzumab deruxtecan** **N = 371**	**Treatment of physician's choice[a]** **N = 172[b]**
DESTINY-Breast04		
Treatment duration [months]		
Median [min; max]	8.2 [0.2; 33.3]	3.5 [0.3; 17.6] Capecitabine: 4.1 [0.3; 17.6] Eribulin: 3.6 [0.3; 17.5] Gemcitabine: 1.6 [1.1; 6.9] Paclitaxel: 4.3 [0.4; 9.0] Nab-paclitaxel: 2.8 [0.7; 16.8]
Mean (SD)	9.2 (6.4)	4.4 (3.7) Capecitabine: 5.8 (5.1) Eribulin: 4.3 (3.4) Gemcitabine: 2.6 (1.8) Paclitaxel: 4.3 (2.4) Nab-paclitaxel: 3.9 (3.8)
Observation period [months]		
Overall survival[c]		
Median [min; max]	16.1 [0.3; 33.1]	13.5 [0; 27.8]
Mean (SD)	15.5 (6.54)	12.5 (7.05)
Morbidity		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Health-related quality of life		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Side effects		
Median [min; max]	ND	ND
Mean (SD)	ND	ND

a. Capecitabine or eribulin or gemcitabine or paclitaxel or nab-paclitaxel.
b. Patients who received at least one dose of the study medication; capecitabine: N = 36; eribulin: N = 89; gemcitabine: N = 16; paclitaxel: N = 14; nab-paclitaxel: N = 17.
c. Defined as the time between randomization and the last contact date at which the patient was still alive.

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

The median treatment duration in the intervention arm is 8.2 months, which is about twice as long as in the control arm (based on the drugs that correspond to the G-BA's ACT). The study documents contain no data on the observation period for the outcomes in the categories of

morbidity, health-related quality of life and side effects. Therefore, these can only be estimated on the basis of the treatment duration.

The median observation period for overall survival is 16.1 months in the intervention arm and 13.5 months in the control arm. For the morbidity, health-related quality of life, and side effects outcomes, whose observation durations are linked to treatment end (see Table 8), the observation durations are markedly shortened when compared to 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 plus another 3 months for morbidity and health-related quality of life). 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).

Information on subsequent therapies

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

Table 11: Information on subsequent antineoplastic therapies (≥ 5% of patients in ≥ 1 treatment arm) – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a] (DESTINY-Breast04 study)

Study **Drug class** **Drug**	**Patients with subsequent therapy n (%)**	
	Trastuzumab deruxtecan **N = 373**	**Treatment of physician's choice[a]** **N = 184**
DESTINY-Breast04		
Total	ND	ND
Systemic	242 (64.9)	142 (77.2)
Targeted therapy	96 (25.7)	68 (37.0)
CDK 4/6 inhibitor	29 (7.8)	23 (12.5)
Abemaciclib	19 (5.1)	14 (7.6)
No subclass specified	68 (18.2)	48 (26.1)
Bevacizumab	20 (5.4)	11 (6.0)
Everolimus	18 (4.8)	15 (8.2)
Endocrine therapy	75 (20.1)	48 (26.1)
Exemestane	24 (6.4)	16 (8.7)
Fulvestrant	33 (8.8)	21 (11.4)
Letrozole	10 (2.7)	11 (6.0)
Chemotherapy	208 (55.8)	117 (63.6)
Capecitabine	53 (14.2)	26 (14.1)
Carboplatin	23 (6.2)	21 (11.4)
Cyclophosphamide	31 (8.3)	16 (8.7)
Doxorubicin	12 (3.2)	11 (6.0)
Eribulin	47 (12.6)	19 (10.3)
Eribulin mesilate	27 (7.2)	5 (2.7)
Gemcitabine	31 (8.3)	23 (12.5)
Paclitaxel	58 (15.5)	23 (12.5)
Nab-paclitaxel	21 (5.6)	6 (3.3)
Doxorubicin hydrochloride (polyethylene glycolized liposomal formulation)	14 (3.8)	14 (7.6)
Vinorelbine	16 (4.3)	20 (10.9)
Vinorelbine bitartrate	13 (3.5)	16 (8.7)
Radiation[b]	25 (6.7)	27 (14.7)
Surgical interventions[b]	4 (1.1)	0 (0)

a. Capecitabine or eribulin or gemcitabine or paclitaxel or nab-paclitaxel.
b. Patients may have been treated with more than one type of subsequent therapy.

CDK: cyclin-dependent kinase; n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

In the DESTINY-Breast04 study, 65% of the patients in the intervention arm and 77% of the patients in the comparator arm received subsequent systemic therapy. With a proportion of approx. 85% of the systemic therapies, chemotherapy was the most frequent subsequent therapy. Of these, 16% of all patients in the intervention arm and 13% in the comparator arm were treated with paclitaxel. In the intervention arm, 20% of all patients in the control arm and 26% in the comparator arm were treated with subsequent endocrine therapy. However, according to the inclusion criteria, only patients whose hormone receptor-positive breast cancer was refractory to endocrine therapy (defined as having progressed on ≥ 1 endocrine therapy and determined by the investigator that they would no longer benefit from further endocrine therapy) were to be included in the study. It is therefore unclear why such a high proportion of patients were treated with subsequent endocrine therapy. Guidelines also recommend monochemotherapy for the metastatic setting as soon as patients have developed resistance or progression under treatment with endocrine therapy [20,21].

However, the current guidelines do not provide clear recommendations for the therapy in later lines of treatment in the present therapeutic indication [20-22]. 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. treatment of physician's choice[a]

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-Breast04	Yes	Yes	No	No	Yes	Yes	Low

a. Capecitabine or eribulin or gemcitabine or paclitaxel or nab-paclitaxel.

RCT: randomized controlled trial

The risk of bias across outcomes for the DESTINY-Breast04 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

In the company's opinion, the results of the DESTINY-Breast04 study are transferable to the German health care context. According to the company, the characteristics of the patients included in the study do not show any important deviations from the corresponding German patient population with regard to sex distribution, with 0.1% men, and to the median age of 57 years. Here, the company referred to patients with HER2-negative breast cancer. According to the company, the transferability of the results to the German health care context is also given due to the high proportion of patients from Europe or from countries with a comparably high health care standard. Although hardly any exact data regarding the disease-specific characteristics exists for the target population in Germany, it can be assumed that the disease-specific characteristics of the study population also essentially correspond to those of patients in Germany, the company added. In addition, the company argued that transferability to the German health care context regarding patients' prior therapies can be assumed.

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

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 (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - hand-foot syndrome (Preferred Term [PT], AEs)
  - cardiac disorders (System Organ Class [SOC], severe AEs [CTCAE grade ≥ 3])
  - platelet count decreased (PT, severe AEs [CTCAE grade ≥ 3])
  - further specific AEs, if any

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

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

Table 13: Matrix of outcomes – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a]

Study	Outcomes										
	Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-BR23)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Hand-foot syndrome (PT, AEs)	Cardiac disorders (SOC, severe AEs[b])	Platelet count decreased (PT, severe AEs[b])	Further specific AEs[b, c]
DESTINY-Breast04	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Capecitabine or eribulin or gemcitabine or paclitaxel or nab-paclitaxel.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. The following events are considered (coded according to MedDRA): gastrointestinal disorders (SOC, AEs), infections and infestations (SOC, SAEs), neutropenia (PT, severe AEs), 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 of patient-reported outcomes on morbidity and health-related quality of life

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

In its dossier, the company presented responder analyses for the proportion of patients with first deterioration or confirmed deterioration by ≥ 10 points and ≥ 15% of the scale range (respective scale range 0 to 100) for the patient-reported outcomes on morbidity and health-related quality of life, recorded with the EORTC QLQ-C30 and EORTC QLQ-BR23 instruments. For the benefit assessment procedure, only analyses for the response criterion of 10 points are to be presented in the dossier for EORTC questionnaires [23]. These are used for the benefit assessment.

Operationalization of deterioration

The company provided analyses of first deterioration and of confirmed deterioration for the patient-reported outcomes on morbidity and health-related quality of life. According to the company, confirmed deterioration is present if clinically relevant deterioration was observed

on at least 2 consecutive visits or if this was first observed on the last visit. 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-Breast04 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 the number of patients for whom this was the case 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. The analyses for the time to first deterioration are used for the benefit assessment.

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. treatment of physician's choice[a]

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[b]	Discontinuation due to AEs	Hand-foot syndrome (PT, AEs)	Cardiac disorders (SOC, severe AEs[b])	Platelet count decreased (PT, severe AEs[b])	Further specific AEs[b, c]
DESTINY-Breast04	L	L	H[d, e]	H[d, e]	H[d, e]	H[f]	H[f]	H[g]	H[d, f]	H[f]	H[f]	H[f, h]

a. Capecitabine or eribulin or gemcitabine or paclitaxel or nab-paclitaxel.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. The following events are considered (coded according to MedDRA): gastrointestinal disorders (SOC, AEs), infections and infestations (SOC, SAEs), neutropenia (PT, severe AEs), nausea (PT, severe AEs).
d. Lack of blinding in subjective recording of outcomes.
e. Strongly decreasing questionnaire return rates in the course of the study, which differed between the treatment arms
f. Large difference in median treatment duration (and hence observation period) between the intervention arm (8.2 months) and the control arm (3.5 months); different reasons for treatment discontinuation.
g. Lack of blinding in the presence of subjective decision on treatment discontinuation.
h. Lack of blinding in the presence of subjective recording of outcomes in specific AEs that are non-severe or non-serious.

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 risk of bias of the results on overall survival is rated as low.

For the results of the outcomes of symptoms, health status, and health-related quality of life, the risk of bias is rated as high due to the lack of blinding with subjective recording of outcomes and strongly decreasing questionnaire return rates in the course of the study, which differed between the treatment arms.

For the results of the outcomes of SAEs and severe AEs, the risk of bias is rated as high due to the large difference in median treatment duration (and thus observation period) between the intervention arm (8.2 months) and the control arm (3.5 months) as well as the different reasons for treatment discontinuation (see Table 9). For the results of the non-severe side effects, the lack of blinding with subjective recording of outcomes leads to a high risk of bias.

The risk of bias for the outcome of discontinuation due to AEs is rated as high because of lack of blinding with subjective decision on treatment discontinuation.

Summary assessment of the certainty of conclusions

Irrespective of the aspects described for the risk of bias, the certainty of conclusions of the study results is limited due to the uncertainties mentioned in Section I 3.2. resulting from the administration of gemcitabine, the pretreatment of the patients, and the dosing of the drugs in the comparator arm. In addition, the certainty of conclusions of the outcomes of nausea and vomiting is limited due to the partial lack of concomitant anti-emetic treatment. Overall, at most hints, e.g. of an added benefit, can be determined for all outcomes.

I 4.3 Results

Table 15 summarizes the results of the comparison of trastuzumab deruxtecan with treatment of physician's choice in patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.

The Kaplan-Meier curves on the time-to-event analyses are presented in I Appendix B, the results on common AEs in I Appendix C of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

Study Outcome category Outcome	Trastuzumab deruxtecan		Treatment of physician's choice[a]		Trastuzumab deruxtecan vs. treatment of physician's choice[a]
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
DESTINY-Breast04					
Mortality					
Overall survival	373	23.4 [20.0; 24.8] 149 (39.9)	184	16.8 [14.5; 20.0] 90 (48.9)	0.64 [0.49; 0.84]; 0.001
Morbidity					
Symptoms (EORTC QLQ-C30); time to first deterioration)[c]					
Fatigue	373	4.2 [2.8; 4.9] 240 (64.3)	184	2.3 [1.4; 3.1] 111 (60.3)	0.78 [0.62; 0.98]; 0.030
Nausea and vomiting	373	1.5 [1.4; 1.7] 258 (69.2)	184	8.2 [6.0; 9.8] 73 (39.7)	2.08 [1.60; 2.70]; < 0.001
Pain	373	9.2 [7.1; 11.1] 188 (50.4)	184	4.4 [2.7; 6.1] 97 (52.7)	0.62 [0.48; 0.803]; < 0.001
Dyspnoea	373	12.5 [8.3; 20.9] 164 (44.0)	184	6.7 [5.1; 13.7] 74 (40.2)	0.80 [0.60; 1.05]; 0.109
Insomnia	373	16.0 [10.6; 18.6] 149 (39.9)	184	5.4 [4.2; 7.0] 85 (46.2)	0.52 [0.40; 0.69]; < 0.001
Appetite loss	373	5.1 [3.5; 7.2] 215 (57.6)	184	6.5 [5.0; 9.8] 80 (43.5)	1.19 [0.92; 1.54]; 0.198
Constipation	373	4.2 [2.9; 5.6] 219 (58.7)	184	5.9 [4.4; 8.4] 82 (44.6)	1.12 [0.87; 1.46]; 0.379
Diarrhoea	373	9.6 [7.0; 16.1] 173 (46.4)	184	13.3 [9.0; NC] 56 (30.4)	1.42 [1.04; 1.92]; 0.025
Symptoms (EORTC QLQ-BR23); time to first deterioration)[c]					
Side effects of systemic therapy	373	4.2 [2.8; 5.9] 211 (56.6)	184	3.1 [1.6; 4.7] 101 (54.9)	0.83 [0.65; 1.05]; 0.117
Breast symptoms	373	NA [20.3; NC] 99 (26.5)	184	NA 38 (20.7)	0.95 [0.65; 1.39]; 0.780
Arm symptoms	373	8.3 [7.0; 11.2] 179 (48.0)	184	5.1 [3.1; 7.0] 81 (44.0)	0.74 [0.56; 0.97]; 0.027
Upset by hair loss				No suitable data[d]	

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

Study Outcome category Outcome	Trastuzumab deruxtecan		Treatment of physician's choice[a]		Trastuzumab deruxtecan vs. treatment of physician's choice[a]
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
Health status (EQ-5D VAS; time to first deterioration)[e]	373	16.4 [11.1; NC] 144 (38.6)	184	8.4 [6.1; NC] 60 (32.6)	0.81 [0.59; 1.10]; 0.169
Health-related quality of life					
EORTC QLQ-C30 (time to first deterioration)[f]					
Global health status	373	5.1 [4.2; 7.0] 210 (56.3)	184	4.2 [2.8; 5.9] 99 (53.8)	0.82 [0.64; 1.05]; 0.110
Physical functioning	373	8.4 [7.0; 11.3] 187 (50.1)	184	4.2 [2.9; 5.6] 99 (53.8)	0.59 [0.46; 0.76]; < 0.001
Role functioning	373	4.2 [2.9; 5.7] 217 (58.2)	184	2.9 [1.5; 4.3] 106 (57.6)	0.76 [0.60; 0.97]; 0.026
Emotional functioning	373	11.1 [8.5; 13.6] 170 (45.6)	184	6.9 [5.7; 10.2] 72 (39.1)	0.81 [0.61; 1.08]; 0.145
Cognitive functioning	373	6.2 [4.7; 7.7] 205 (55.0)	184	4.4 [3.3; 6.3] 97 (52.7)	0.78 [0.61; 1.004]; 0.049
Social functioning	373	5.9 [4.2; 9.7] 211 (56.6)	184	3.8 [2.7; 4.7] 107 (58.2)	0.72 [0.57; 0.91]; 0.006
EORTC QLQ-BR23 (time to first deterioration)[f]					
Body image	373	13.8 [9.7; NC] 152 (40.8)	184	5.1 [3.0; 9.8] 84 (45.7)	0.64 [0.49; 0.84]; 0.001
Sexual functioning	373	NA 78 (20.9)	184	NA 34 (18.5)	0.90 [0.60; 1.36]; 0.612
Sexual enjoyment				No suitable data[d]	
Future perspective	373	17.3 [14.9; NC] 131 (35.1)	184	NA [7.7; NC] 58 (31.5)	0.88 [0.64; 1.21]; 0.439

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

Study Outcome category Outcome	Trastuzumab deruxtecan		Treatment of physician's choice[a]		Trastuzumab deruxtecan vs. treatment of physician's choice[a]
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
Side effects					
AEs (supplementary information)	371	0.1 [NC; NC] 369 (99.5)	172	0.1 [0.1; 0.1] 169 (98.3)	–
SAEs	371	NA [24.4; NC] 103 (27.8)	172	NA [9.2; NC] 43 (25.0)	0.70 [0.48; 1.00]; 0.054
Severe AEs[g]	371	7.6 [5.2; 10.6] 195 (52.6)	172	0.9 [0.5; 1.7] 116 (67.4)	0.47 [0.37; 0.59]; < 0.001
Discontinuation due to AEs	371	NA [24.4; NC] 60 (16.2)	172	NA [16.2; NC] 14 (8.1)	1.12 [0.61; 2.04]; 0.718
Hand-foot syndrome (PT, AEs)	371	NA 5 (1.3)	172	NA 24 (14.0)	0.07 [0.03; 0.18]; < 0.001
Cardiac disorders (SOC, severe AEs[g])	371	ND 3 (0.8)	172	ND 1 (0.6)	ND
Platelet count decreased (PT, severe AEs[g])	371	NA 20 (5.4)	172	NA 1 (0.6)	7.49 [0.999; 56.15]; 0.021
Gastrointestinal disorders (SOC, AEs)	371	0.1 [0.1; 0.1] 328 (88.4)	172	0.7 [0.5; 1.4] 117 (68.0)	2.08 [1.68; 2.59]; < 0.001
Infections and infestations (SOC, SAEs)	371	NA 29 (7.8)	172	NA 2 (1.2)	4.61 [1.08; 19.62]; 0.023
Neutropenia (PT, severe AEs[g])	371	NA 21 (5.7)	172	NA 24 (14.0)	0.33 [0.18; 0.60]; < 0.001
Nausea (PT, severe AEs[g])	371	NA 17 (4.6)	172	NA 0 (0)	NC; 0.007

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

Study Outcome category Outcome	Trastuzumab deruxtecan		Treatment of physician's choice[a]		Trastuzumab deruxtecan vs. treatment of physician's choice[a]
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
a. Capecitabine or eribulin or gemcitabine or paclitaxel or nab-paclitaxel. b. Hazard ratio calculated using a stratified Cox proportional hazards regression model and the 95% CI using the Wald test. 2-sided p-value based on a stratified log-rank test. The stratification factors were HER2 status, number of prior lines of chemotherapy in the metastatic setting, and hormone receptor/CDK status. c. A score increase by ≥ 10 points from baseline is deemed a clinically relevant deterioration (scale range of 0 to 100). d. Unclear proportion of patients with missing values at baseline and in the course of the study. e. A score decrease by ≥ 15 points from baseline is deemed a clinically relevant deterioration (scale range of 0 to 100). f. A score decrease by ≥ 10 points from baseline is deemed a clinically relevant deterioration (scale range of 0 to 100). g. Operationalized as CTCAE grade ≥ 3. AE: adverse event; CI: confidence interval; CDK: cyclin-dependent kinase; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HER2: human epidermal growth factor receptor 2; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; PT: Preferred Term; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module 23; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale					

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Section I 4.2).

Mortality

Overall survival

A statistically significant difference in favour of trastuzumab deruxtecan in comparison with treatment of physician's choice was shown for the outcome of overall survival. There is an effect modification by the characteristic of visceral disease for this outcome (see Section I 4.4). A statistically significant difference in favour of trastuzumab deruxtecan in comparison with treatment of physician's choice was shown both for patients with and for patients without visceral disease. The extent of the effect differs between the subgroups. There is a hint of an

added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice for patients with and for patients without visceral disease.

Morbidity

Symptoms

Symptom outcomes were recorded with the instruments EORTC QLQ-C30 and EORTC QLQ-BR23.

EORTC QLQ-C30

Pain and insomnia

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

Nausea and vomiting

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

Fatigue

A statistically significant difference in favour of trastuzumab deruxtecan in comparison with treatment of physician's choice was shown for the outcome of fatigue. However, the extent of the effect for this outcome of the category of non-serious/non-severe symptoms/late complications was no more than marginal. There is no hint of added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Diarrhoea

A statistically significant difference to the disadvantage of trastuzumab deruxtecan in comparison with treatment of physician's choice was shown for the outcome of diarrhoea. However, the extent of the effect for this outcome of the category of non-serious/non-severe symptoms/late complications was no more than marginal. There is no hint of added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Dyspnoea, appetite loss, and constipation

No statistically significant difference between treatment groups was shown for any of the outcomes of dyspnoea, appetite loss, and constipation. In each case, there is no hint of added

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

EORTC QLQ-BR23

Arm symptoms

A statistically significant difference in favour of trastuzumab deruxtecan in comparison with treatment of physician's choice was shown for the outcome of arm symptoms. However, the extent of the effect for this outcome of the category of non-serious/non-severe symptoms/late complications was no more than marginal. There is no hint of added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Upset by hair loss

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

Side effects of systemic therapy and breast symptoms

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

Health status (EQ-5D VAS)

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

Health-related quality of life

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

EORTC QLQ-C30

Physical functioning, role functioning, cognitive functioning, and social functioning

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

outcomes of physical functioning, role functioning, cognitive functioning, and social functioning.

Global health status and emotional functioning

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

EORTC QLQ-BR23

Body image

A statistically significant difference in favour of trastuzumab deruxtecan in comparison with treatment of physician's choice was shown for the outcome of body image. For this outcome, there is an effect modification by the characteristics of age and visceral disease (see Section I 4.4). The subgroup results cannot be meaningfully interpreted because data for the investigation of possible dependencies between the 2 subgroup characteristics are missing. The added benefit is therefore derived based on the results of the total population. There is a hint of an added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice.

Sexual enjoyment

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

Sexual functioning and future perspective

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

Side effects

Severe AEs

A statistically significant difference in favour of trastuzumab deruxtecan in comparison with treatment of physician's choice was shown for the outcome of severe AEs. There is a hint of lesser harm from trastuzumab deruxtecan in comparison with treatment of physician's choice.

SAEs, discontinuation due to AEs

No statistically significant difference was found between treatment groups for either of the outcomes of SAEs or discontinuation due to AEs. In each case, there is no hint of greater or lesser harm from trastuzumab deruxtecan in comparison with treatment of physician's choice; greater or lesser harm is therefore not proven.

Specific AEs

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

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

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

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

Cardiac disorders (severe AEs)

The company presented no calculations on the hazard ratio and no p-value for the outcome of cardiac disorders (severe AEs). Due to the low number of events, it cannot be assumed that there would be a statistically significant effect in case of suitable analyses. There is no hint of greater or lesser harm from trastuzumab deruxtecan in comparison with treatment of physician's choice; greater or lesser harm is therefore not proven.

I 4.4 Subgroups and other effect modifiers

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

- age (< 65 years/≥ 65 years)
- visceral disease (yes/no)

The characteristic of sex is disregarded because the study population includes only 2 men.

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

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup. Subgroup results where the extent did not differ between subgroups are not presented.

The results are presented in Table 16. The Kaplan-Meier curves on the subgroup results are presented in I Appendix B.5 of the full dossier assessment.

Table 16: Subgroups (mortality, health-related quality of life) – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a]

Study Outcome Characteristic Subgroup	Trastuzumab deruxtecan N Median time to event in months [95% CI] Patients with event n (%)	Treatment of physician's choice[a] N Median time to event in months [95% CI] Patients with event n (%)	Trastuzumab deruxtecan vs. treatment of physician's choice[a] HR [95% CI][b]	p-value[c]
DESTINY-Breast04				
Mortality				
Overall survival				
Visceral disease				
Yes	332 21.7 [19.0; 24.5] 142 (42.8)	157 17.0 [14.8; 20.2] 74 (47.1)	0.69 [0.52; 0.91]	0.009
No	41 NA [NC; NC] 7 (17.1)	27 15.1 [12.9; 20.6] 16 (59.3)	0.22 [0.09; 0.54]	< 0.001
Total			Interaction:	0.015[d]
Health-related quality of life				
EORTC QLQ-BR23 – time to first deterioration by ≥ 10 points[e]				
Body image				
Age				
< 65 years	290 13.9 [9.7; NC] 115 (39.7)	136 4.2 [2.0; 6.1] 68 (50.0)	0.51 [0.38; 0.69]	< 0.001
≥ 65 years	83 10.8 [4.2; NC] 37 (44.6)	48 16.9 [4.2; NC] 16 (33.3)	1.17 [0.65; 2.12]	0.589
Total			Interaction:	0.013[d]
Visceral disease				
Yes	332 13.8 [9.6; NC] 135 (40.7)	157 6.1 [3.9; NC] 66 (42.0)	0.71 [0.53; 0.95]	0.022
No	41 12.8 [3.0; NC] 17 (41.5)	27 1.7 [0.9; 4.5] 18 (66.7)	0.34 [0.17; 0.69]	0.002
Total			Interaction:	0.048[d]

a. Capecitabine or eribulin or gemcitabine or paclitaxel or nab-paclitaxel.
b. Unstratified Cox proportional hazards regression model.
c. Unstratified log-rank test.
d. Interaction term from Cox proportional hazards regression model with treatment, subgroup and interaction between treatment and subgroup as covariates.
e. A score decrease by ≥ 10 points from baseline is deemed a clinically relevant deterioration (scale range of 0 to 100).

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

Mortality

Overall survival

There is an effect modification by the characteristic of visceral disease for the outcome of overall survival. A statistically significant difference in favour of trastuzumab deruxtecan in comparison with treatment of physician's choice was shown both for patients with and for patients without visceral disease. The extent of the effect differs between the subgroups. There is a hint of an added benefit of trastuzumab deruxtecan in comparison with treatment of physician's choice both for patients with and for patients without visceral disease.

Health-related quality of life

Body image

There is an effect modification by the characteristics of age and visceral disease for the outcome of body image. The subgroup results cannot be meaningfully interpreted because data for the investigation of possible dependencies between the 2 subgroup characteristics are missing. The added benefit is therefore derived based on the results of the total population.

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 symptom outcomes

For the symptoms outcomes below, it cannot be inferred from the dossier whether they are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Symptoms

Fatigue, nausea and vomiting, pain, insomnia, diarrhoea (each recorded using EORTC QLQ-C30), arm symptoms (recorded using EORTC QLQ-BR23)

For the outcomes of fatigue, nausea and vomiting, pain, insomnia, diarrhoea, and arm symptoms, 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/late complications.

Table 17: Extent of added benefit at outcome level: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

Observation period **Outcome category** **Outcome** **Effect modifier** **Subgroup**	**Trastuzumab deruxtecan vs. treatment of physician's choice[a]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Outcomes with observation over the entire study duration		
Mortality		
Overall survival Visceral disease Yes	21.7 vs. 17.0 HR: 0.69 [0.52; 0.91] p = 0.009 Probability: "hint"	Outcome category: mortality $0.85 \leq CI_u < 0.95$ Added benefit, extent: "considerable"
No	NA vs. 15.1 HR: 0.22 [0.09; 0.54] p < 0.001 Probability: "hint"	Outcome category: mortality $CI_u < 0.85$ Added benefit, extent: "major"
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30; time to first deterioration by ≥ 10 points)		
Fatigue	4.2 vs. 2.3 HR: 0.78 [0.62; 0.98] p = 0.030	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser/added benefit not proven[d]
Nausea and vomiting	1.5 vs. 8.2 HR: 2.08 [1.60; 2.70] HR: 0.48 [0.37; 0.63][e] p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ Lesser benefit; extent: "considerable"
Pain	9.2 vs. 4.4 HR: 0.62 [0.48; 0.803] p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ Added benefit, extent: "minor"
Dyspnoea	12.5 vs. 6.7 HR: 0.80 [0.60; 1.05] p = 0.109	Lesser/added benefit not proven
Insomnia	16.0 vs. 5.4 HR: 0.52 [0.40; 0.69] p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ Added benefit, extent: "considerable"

Table 17: Extent of added benefit at outcome level: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

Observation period **Outcome category** **Outcome** **Effect modifier** **Subgroup**	**Trastuzumab deruxtecan vs. treatment of physician's choice[a]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Appetite loss	5.1 vs. 6.5 HR: 1.19 [0.92; 1.54] p = 0.198	Lesser/added benefit not proven
Constipation	4.2 vs. 5.9 HR: 1.12 [0.87; 1.46] p = 0.379	Lesser/added benefit not proven
Diarrhoea	9.6 vs. 13.3 HR: 1.42 [1.04; 1.92] HR: 0.71 [0.52; 0.96][e] p = 0.025	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser/added benefit not proven[d]
Symptoms (EORTC QLQ-BR23; time to first deterioration by ≥ 10 points)		
Side effects of systemic therapy	4.2 vs. 3.1 HR: 0.83 [0.65; 1.05] p = 0.117	Lesser/added benefit not proven
Breast symptoms	NA vs. NA HR: 0.95 [0.65; 1.39] p = 0.780	Lesser/added benefit not proven
Arm symptoms	8.3 vs. 5.1 HR: 0.74 [0.56; 0.97] p = 0.027	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser/added benefit not proven[d]
Upset by hair loss	No suitable data[f]	Lesser/added benefit not proven
Health status (EQ-5D VAS; time to first deterioration by ≥ 15 points)	16.4 vs. 8.4 HR: 0.81 [0.59; 1.10] p = 0.169	Lesser/added benefit not proven

Table 17: Extent of added benefit at outcome level: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

Observation period **Outcome category** **Outcome** **Effect modifier** **Subgroup**	**Trastuzumab deruxtecan vs. treatment of physician's choice[a]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Health-related quality of life		
EORTC QLQ-C30 (time to first deterioration by ≥ 10 points)		
Global health status	5.1 vs. 4.2 HR: 0.82 [0.64; 1.05] p = 0.110	Lesser/added benefit not proven
Physical functioning	8.4 vs. 4.2 HR: 0.59 [0.46; 0.76] p < 0.001 Probability: "hint"	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ Added benefit, extent: "considerable"
Role functioning	4.2 vs. 2.9 HR: 0.76 [0.60; 0.97] p = 0.026 Probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Added benefit, extent: "minor"
Emotional functioning	11.1 vs. 6.9 HR: 0.81 [0.61; 1.08] p = 0.145	Lesser/added benefit not proven
Cognitive functioning	6.2 vs. 4.4 HR: 0.78 [0.61; 1.004] p = 0.049 Probability: "hint"	Outcome category: health-related quality of life Added benefit; extent: "minor"[g]
Social functioning	5.9 vs. 3.8 HR: 0.72 [0.57; 0.91] p = 0.006 Probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Added benefit, extent: "minor"
EORTC QLQ-BR23 (time to first deterioration by ≥ 10 points)		
Body image	13.8 vs. 5.1 HR: 0.64 [0.49; 0.84] p = 0.001 Probability: "hint"	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ Added benefit, extent: "considerable"
Sexual functioning	NA vs. NA HR: 0.90 [0.60; 1.36] p = 0.612	Lesser/added benefit not proven
Sexual enjoyment	No suitable data[f]	Lesser/added benefit not proven

Table 17: Extent of added benefit at outcome level: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

Observation period **Outcome category** **Outcome** **Effect modifier** **Subgroup**	**Trastuzumab deruxtecan vs. treatment of physician's choice[a]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Future perspective	17.3 vs. NA HR: 0.88 [0.64; 1.21] p = 0.439	Lesser/added benefit not proven
Side effects		
SAEs	NA vs. NA HR: 0.70 [0.48; 1.00] p = 0.054	Greater/lesser harm not proven
Severe AEs[h]	7.6 vs. 0.9 HR: 0.47 [0.37; 0.59] p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% Lesser harm, extent: "major"
Discontinuation due to AEs	NA vs. NA HR: 1.12 [0.61; 2.04] p = 0.718	Greater/lesser harm not proven
Hand-foot syndrome (AEs)	NA vs. NA HR: 0.07 [0.03; 0.18] p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Lesser harm; extent: "considerable"
Cardiac disorders (severe AEs[h])	ND 3 (0.8) vs. 1 (0.6) patients HR: ND p: ND	Greater/lesser harm not proven
Platelet count decreased (severe AEs[h])	NA vs. NA HR: 7.49 [0.999; 56.15] HR: 0.13 [0.02; 1.001][e] p = 0.021 Probability: "hint"	Outcome category: serious/severe side effects Greater harm, extent: "minor"[g]
Gastrointestinal disorders (AEs)	0.1 vs. 0.7 HR: 2.08 [1.68; 2.59] HR: 0.48 [0.39; 0.60][e] p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm, extent: "considerable"
Infections and infestations (SAEs)	NA vs. NA HR: 4.61 [1.08; 19.62] HR: 0.22 [0.05; 0.92][e] p = 0.023 Probability: "hint"	Outcome category: serious/severe side effects 0.90 ≤ CI_u < 1.00 Greater harm, extent: "minor"

Table 17: Extent of added benefit at outcome level: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

Observation period **Outcome category** **Outcome** **Effect modifier** **Subgroup**	**Trastuzumab deruxtecan vs. treatment of physician's choice[a]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Neutropenia (severe AEs[h])	NA vs. NA HR: 0.33 [0.18; 0.60] p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% Lesser harm, extent: "major"
Nausea (severe AEs[h])	NA vs. NA HR: NC p = 0.007 Probability: "hint"	Outcome category: serious/severe side effects Greater harm, extent: "non-quantifiable"[i]

a. Capecitabine or eribulin or gemcitabine or paclitaxel or nab-paclitaxel.
b. Probability provided if a statistically significant and relevant effect is present.
c. Depending on the outcome category, estimations of effect size and the scale of the outcome are made with different limits based on the upper limit of the confidence interval (CI_u).
d. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
e. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
f. See Section I 4.3 of the present dossier assessment for the reasoning.
g. Discrepancy between p-value (log-rank test) and CI (Cox model) due to different calculation methods; the extent is rated as minor.
h. Operationalized as CTCAE grade ≥ 3.
i. Greater harm results from 17 vs. 0 events. The extent cannot be estimated from the observed data.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NA: not achieved; NC: not calculable; ND: no data; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module 23; QLQ-C30: Quality of Life Questionnaire-Core 30; SAE: serious adverse event; VAS: visual analogue scale

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 compared with treatment of physician's choice[a]

Positive effects	Negative effects
Outcomes with observation over the entire study duration	
Mortality ▪ Overall survival: ▫ Visceral disease (yes): hint of an added benefit – extent: "considerable" ▫ Visceral disease (no): hint of an added benefit – extent: "major"	–
Outcomes with shortened observation period	
Morbidity Non-serious/non-severe symptoms/late complications Symptoms (EORTC QLQ-C30): ▪ Pain: hint of an added benefit – extent "minor" ▪ Insomnia: hint of an added benefit – extent: "considerable"	Morbidity Non-serious/non-severe symptoms/late complications Symptoms (EORTC QLQ-C30): ▪ Nausea and vomiting: hint of lesser benefit – extent: "considerable"
Health-related quality of life EORTC QLQ-C30: ▪ Physical functioning: hint of an added benefit – extent: "considerable" ▪ Role functioning: hint of an added benefit – extent: "minor" ▪ Cognitive functioning: hint of an added benefit – extent: "minor" ▪ Social functioning: hint of an added benefit – extent: "minor" EORTC QLQ-BR23: ▪ Body image: hint of an added benefit – extent: "considerable"	–
Serious/severe side effects ▪ Severe AEs: hint of lesser harm – extent: "major", including ▫ neutropenia (severe AE): hint of lesser harm – extent: "major"	Serious/severe side effects ▪ Platelet count decreased (severe AE): hint of greater harm – extent: "minor" ▪ Infections and infestations (SAE): hint of greater harm – extent: "minor" ▪ Nausea (severe AE): hint of greater harm – extent: "non-quantifiable"
Non-serious/non-severe side effects ▪ Hand-foot syndrome (AE): hint of lesser harm – extent: "considerable"	Non-serious/non-severe side effects ▪ Gastrointestinal disorders (AE): hint of greater harm – extent: "considerable"

a. Capecitabine or eribulin or gemcitabine or paclitaxel or nab-paclitaxel.

AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module 23; QLQ-C30: Quality of Life Questionnaire-Core 30; SAE: serious adverse event

Overall, there are both positive and negative effects of different extents for trastuzumab deruxtecan in comparison with treatment of physician's choice. Only for overall survival are the observed effects based on the entire observation period. For the outcome categories of morbidity, health-related quality of life and side effects, however, they are based exclusively on the shortened observation period of approx. 4.5 months (morbidity, health-related quality of life) and 40 days (side effects) after the end of treatment.

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

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

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

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

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

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

The assessment described above deviates from that by the company, which derived an indication of major added benefit for the total population.

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

I 6 References for English extract

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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