Trastuzumab deruxtecan (breast cancer)

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

EXTRACT

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Trastuzumab deruxtecan, Breast Neoplasms, Benefit Assessment, NCT04494425

Medical and scientific advice

- Volker Heilmann

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

The questionnaire on the disease and its treatment was answered by 2 people.

IQWiG thanks the respondents and the patient organization 'Frauenselbsthilfe Krebs Bundesverband e. V' for participating in the written exchange and for their support. The respondents and the patient organization 'Frauenselbsthilfe Krebs Bundesverband e. V' were not involved in the actual preparation of the 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
AGO	Arbeitsgemeinschaft Gynäkologische Onkologie (Gynaecological Oncology Group)
BRCA	breast cancer-associated gene
CDK	cyclin-dependent kinase
ECOG	Eastern Cooperative Oncology Group
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
HR	hormone receptor
IHC	immunohistochemistry
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ISH	in situ hybridization
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model with repeated measures
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	summary of product characteristics
SOC	System Organ Classes
VAS	visual analogue scale

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book 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 was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the 'company'). The dossier was sent to IQWiG on 28 April 2025.

Research question

The aim of this report is to assess the added benefit of trastuzumab deruxtecan compared with the appropriate comparator therapy (ACT) in patients with unresectable or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-low or HER2-ultralow breast cancer who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment.

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

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

Therapeutic indication	**ACT**[a]
Adult patients[b] with unresectable or metastatic HR-positive, HER2-low or HER2-ultralow breast cancer who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment[c]	An anthracycline- or taxane-containing systemic therapy consisting of[d]: ▪ doxorubicin or ▪ doxorubicin liposomal (only for patients with metastatic breast cancer) or ▪ epirubicin or ▪ docetaxel (only for female patients) or ▪ paclitaxel (only for patients with metastatic breast cancer)
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. According to the G-BA, it is assumed that there is no therapeutic indication for (secondary) resection or radiotherapy with curative intent. It is also assumed as per the G-BA that treatment with trastuzumab deruxtecan is not indicated for patients with BRCA1/2 mutation. d. The ACT specified here comprises several alternative treatment options. However, individual treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets. ACT: appropriate comparator therapy; BRCA: breast cancer associated gene; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor	

The G-BA adjusted the ACT according to Table 2 on 31 March 2025, shortly before the company submitted the dossier. The company deviated from the G-BA's definition of the ACT and referred in its dossier to the outdated definition from the consultation with the G-BA on 29 May 2024, naming the options capecitabine, eribulin, vinorelbine or an anthracycline- or taxane-containing therapy as the ACT. Anthracycline- or taxane-containing therapy is only an option for patients who have not yet received anthracycline- and/or taxane-containing therapy or for whom renewed anthracycline- or taxane-containing therapy is an option. This benefit assessment was conducted in comparison with the ACT currently specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used to derive the added benefit. This concurred with the company's inclusion criteria.

Study pool and study design

The DESTINY-Breast06 study was used for the benefit assessment of trastuzumab deruxtecan. The study is an ongoing, open-label RCT on the comparison of trastuzumab deruxtecan with a chemotherapy of physician's choice choosing from capecitabine, paclitaxel or nab-paclitaxel, each as monotherapy. The study enrolled adult patients with advanced or metastatic HR-positive, HER2-low or HER2-ultralow breast cancer whose disease had progressed during endocrine therapy in combination with a cyclin-dependent kinase (CDK)-4/6 inhibitor within 6 months of starting first-line treatment in the metastatic setting or during ≥ 2 endocrine therapies with or without targeted therapy in the metastatic setting. Only patients with a positive hormone receptor status and an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 were included in the study.

Overall, 866 patients were enrolled in the study and randomly allocated in a 1:1 ratio either to treatment with trastuzumab deruxtecan (N = 436) or to a treatment of physician's choice, selecting from capecitabine, paclitaxel or nab-paclitaxel (N = 430). The decision to use one of these options was made by the investigator for each patient prior to randomization. Randomization was stratified according to previous use of CDK4/6 inhibitors (yes vs. no), HER2-immunohistochemistry (IHC) expression (IHC 2+/in situ hybridization (ISH)- vs. IHC 1+ vs. IHC > 0 and < 1+) and previous use of taxanes in the non-metastatic setting (yes vs. no).

Capecitabine and nab-paclitaxel are not part of the ACT. Therefore, only the subpopulation of patients treated with trastuzumab deruxtecan (n = 67) versus paclitaxel (n = 68) for whom paclitaxel was chosen as therapy prior to allocation to the control arm was relevant for the benefit assessment.

Treatment with trastuzumab deruxtecan was largely in compliance with the specifications of the summary of product characteristics (SmPC). There were deviations in the use of

concomitant medication with antiemetics for the prophylaxis of nausea and vomiting. Treatment with paclitaxel deviated from the specifications in the SmPC. Firstly, paclitaxel was administered in a dosage deviating from the marketing authorization and secondly, it was unclear to what extent the patients had been previously treated with anthracyclines. In addition, mandatory pretreatment with corticosteroids, antihistamines and H2 receptor antagonists to prevent hypersensitivity reactions was not specified in the study protocol.

Treatment with the study medication was conducted until disease progression or unacceptable toxicity. Patients in the control arm were not permitted to switch to treatment with trastuzumab deruxtecan.

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

Results for the relevant subpopulation not suitable

For this benefit assessment, only the subpopulation of patients from the DESTINY-Breast06 study for whom paclitaxel was specified as therapy prior to allocation to the control arm was relevant. For this relevant subpopulation, however, information on patient characteristics, course of the study, subsequent therapies, observation periods and responses to the patient-reported outcomes questionnaires, and subgroup analyses were missing. Due to this lack of information on the course of the study and questionnaire responses, it was not possible to assess whether the data for the patient-reported outcomes on morbidity and health-related quality of life were suitable and which analysis (first-time or confirmed deterioration) was relevant. Additionally, the side effects data for the subpopulation were incomplete, so that no suitable data were available for these outcomes either. Suitable data were available for the outcome of overall survival of the relevant subpopulation. There was no statistically significant difference in overall survival between the treatment arms. The data presented in the dossier submitted by the company were therefore insufficient to derive conclusions about the added benefit of trastuzumab deruxtecan in the given therapeutic indication.

Results on added benefit

No suitable data were available for the assessment of the added benefit of trastuzumab deruxtecan compared with the ACT in adult patients with unresectable or metastatic HR-positive, HER2-low or HER2-ultralow breast cancer who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment. There is no hint of an added benefit of trastuzumab deruxtecan in comparison with the ACT; an added benefit is therefore not proven.

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

The result of the assessment of the added benefit of trastuzumab deruxtecan in comparison with the ACT is summarized in Table 3.

Table 3: Trastuzumab deruxtecan – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adult patients[b] with unresectable or metastatic HR-positive, HER2-low or HER2-ultralow breast cancer who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment[c]	An anthracycline- or taxane-containing systemic therapy consisting of[d]: ▪ doxorubicin or ▪ doxorubicin liposomal (only for patients with metastatic breast cancer) or ▪ epirubicin or ▪ docetaxel (only for female patients) or ▪ paclitaxel (only for patients with metastatic breast cancer)	Added benefit not proven

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. According to the G-BA, it is assumed that there is no therapeutic indication for (secondary) resection or radiotherapy with curative intent. It is also assumed as per the G-BA that treatment with trastuzumab deruxtecan is not indicated for patients with BRCA1/2 mutation.
d. The ACT specified here comprises several alternative treatment options. However, individual treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets.

ACT: appropriate comparator therapy; BRCA: breast cancer associated gene; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor

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.

[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].

I 2 Research question

The aim of this report is to assess the added benefit of trastuzumab deruxtecan compared with the ACT in patients with unresectable or metastatic HR-positive, HER2-low or HER2-ultralow breast cancer who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

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

Therapeutic indication	**ACT[a]**
Adult patients[b] with unresectable or metastatic HR-positive, HER2-low or HER2-ultralow breast cancer who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment[c]	An anthracycline- or taxane-containing systemic therapy consisting of[d]: ▪ doxorubicin or ▪ doxorubicin liposomal (only for patients with metastatic breast cancer) or ▪ epirubicin or ▪ docetaxel (only for female patients) or ▪ paclitaxel (only for patients with metastatic breast cancer)
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. According to the G-BA, it is assumed that there is no therapeutic indication for (secondary) resection or radiotherapy with curative intent. It is also assumed as per the G-BA that treatment with trastuzumab deruxtecan is not indicated for patients with BRCA1/2 mutation. d. The ACT specified here comprises several alternative treatment options. However, individual treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets. ACT: appropriate comparator therapy; BRCA: breast cancer associated gene; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor	

The G-BA adjusted the ACT according to Table 4 on 31 March 2025, shortly before the company submitted the dossier. The company deviated from the G-BA's definition of the ACT and referred in its dossier to the outdated definition from the consultation with the G-BA on 29 May 2024, naming the options capecitabine, eribulin, vinorelbine or an anthracycline- or taxane-containing therapy as the ACT. Anthracycline- or taxane-containing therapy is only an option for patients who have not yet received anthracycline- and/or taxane-containing therapy or for whom renewed anthracycline- or taxane-containing therapy is an option. This benefit assessment was conducted in comparison with the ACT currently specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used to derive the added benefit. This concurred with the company's inclusion criteria.

I 3 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on trastuzumab deruxtecan (status: 18 February 2025)
- Bibliographical literature search on trastuzumab deruxtecan (last search on 18 February 2025)
- Search of trial registries/trial results databases for studies on trastuzumab deruxtecan (last search on 18 February 2025)
- Search on the G-BA website for trastuzumab deruxtecan (last search on 18 February 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on trastuzumab deruxtecan (last search on 15 May 2025); for search strategies, see I Appendix A of the full dossier assessment

Although the review of completeness did not identify any additional relevant studies, the review of the study registry entry did reveal that the results publication Bardia 2024 [3] on the study DESTINY-Breast06 submitted by the company was missing from the dossier. The publication was identified by the company via the information retrieval and then excluded in the title/abstract screening. However, since the study was identified both via the study registry search and via the company's studies, this approach of the company ultimately had no consequences.

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 marketing authorization 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 (yes/no [citation])
D9670C00001 (DESTINY-Breast06[d])	Yes	Yes	No	Yes [4]	Yes [5-7]	Yes [3]

a. In the DESTINY-Breast06 study, therapy could be chosen from capecitabine, paclitaxel and nab-paclitaxel. The option relevant for the dossier assessment is paclitaxel.
b. Study sponsored by the company.
c. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
d. In the following tables, the study is referred to by this acronym.

CSR: clinical study report; RCT: randomized controlled trial

Concurring with the company, the DESTINY-Breast06 study was included in the benefit assessment. In doing so, a subpopulation was considered because the study also allowed the administration of therapies beyond the ACT (see Section I 3.3). Deviating from this, the company considered the entire population of the DESTINY-Breast06 study in its dossier, but presented subgroup analyses on the characteristic 'chemotherapy of physician's choice' (capecitabine vs. nab-paclitaxel vs. paclitaxel) in Appendix 4-G of its dossier. The 'paclitaxel' subgroup was used as the relevant subpopulation for this benefit assessment.

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] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
DESTINY-Breast06	RCT, open-label, parallel	Adult patients with advanced or metastatic HR-positive[c] breast cancer and: ▪ HER2-low or HER2-ultralow[d] ▪ disease progression under endocrine therapy in combination with a CDK4/6 inhibitor within 6 months of starting first-line treatment in the metastatic setting or after ≥ 2 endocrine therapies[e] with or without targeted therapy in the metastatic setting ▪ ECOG PS 0 or 1	trastuzumab deruxtecan (N = 436) Treatment of physician's choice[a] (N = 430) ▪ capecitabine (N = 257) ▪ paclitaxel (N = 68) ▪ nab-paclitaxel (N = 105) Relevant subpopulation thereof[f]: trastuzumab deruxtecan (n = 67) Treatment of physician's choice: ▪ paclitaxel (n = 68)	Screening: up to 28 days Treatment: until disease progression, occurrence of unacceptable toxicity Follow-up: outcome-specific, at most until death	273 centres in Argentina, Australia, Austria, Belgium, Brazil, Canada, China, Denmark, France, Germany, Hungary, India, Israel, Italy, Japan, Mexico, Netherlands, Poland, Portugal, Russia, Saudi Arabia, Singapore, South Korea, Spain, Sweden, Taiwan, United Kingdom, United States 7/2020–ongoing Data cut-off: ▪ 18 March 2024[g]	Primary: PFS Secondary: overall survival, morbidity, health-related quality of life, AEs

a. In the DESTINY-Breast06 study, therapy could be chosen from capecitabine, paclitaxel and nab-paclitaxel. The option relevant for the dossier assessment is paclitaxel.
b. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
c. Evidence of HR status according to the ASCO-CAP guideline [8].
d. Determined using the VENTANA 4B5 IHC test and defined as IHC 1+ or IHC 2+/ISH- (HER2-low) or 0 < IHC < 1+ (HER2-ultralow); evaluated by a central laboratory.
e. The following are counted as one line of treatment: 1) monotherapy with CDK4/6 inhibitors in the metastatic setting, 2) recurrence of the disease within 24 months with adjuvant endocrine therapy (one endocrine therapy line in the metastatic setting is sufficient). The following are not counted as lines of treatment: 1) monotherapy with PARP inhibitors, 2) progression after discontinuation or completion of adjuvant endocrine therapy, 3) changes in dosage or discontinuation/resumption of the same medication or the addition of targeted therapy to endocrine therapy without prior disease progression (e.g. current aromatase inhibitor therapy is combined with a CDK4/6 inhibitor).
f. Subpopulation of patients for whom, prior to randomization, paclitaxel was chosen as the drug to be administered if they were allocated to the control arm. Patients for whom capecitabine or nab-paclitaxel was chosen are not further considered below.
g. Final analysis of PFS (planned after 456 PFS events in the group of patients with HER2-low).

Table 6: Characteristics of the included study – RCT, direct comparison: trastuzumab deruxtecan vs. treatment of physician's choice[a] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
AE: adverse event; ASCO-CAP: American Society of Clinical Oncology – College of American Pathologists; CDK: cyclin-dependent kinase; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; IHC: immunohistochemistry; ISH: in situ hybridization; n: relevant subpopulation; N: number of randomized patients; PARP: poly(adenosine diphosphate-ribose) polymerase; PFS: progression-free survival; RCT: randomized controlled trial						

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

Study	Intervention	Comparison
DESTINY-Breast06	trastuzumab deruxtecan 5.4 mg/kg BW[a] IV on Day 1 of a 21-day cycle	paclitaxel 80 mg/m^2 BSA, IV, weekly on Day 1 of a 21-day cycle
	Dose modification: ▪ Dose interruption for up to 126 days ▪ Dose reductions were allowed as follows[c]: First dose level: 4.4 mg/kg BW Second dose level: 3.2 mg/kg BW	 ▪ Dose interruption for up to 28 days[b] ▪ Dose modifications according to local marketing authorization of paclitaxel
	Prior treatment ▪ At least one endocrine therapy with or without targeted therapy in the metastatic setting **Disallowed prior treatment** ▪ Chemotherapy for advanced or metastatic breast cancer[d] ▪ Immunosuppressants within 14 days prior to the first study dose, with the exception of intranasal and inhaled corticosteroids or systemic corticosteroids in doses of less than 10 mg/day prednisone or equivalent ▪ HER2-directed therapy ▪ Antibody-drug conjugate containing an exatecan derivative that is a topoisomerase I inhibitor ▪ Completion of whole brain radiotherapy within 2 weeks prior to randomization ▪ Hormonal therapy or immunotherapy (non-antibody based) within 3 weeks prior to randomization ▪ Major surgery, antibody-based anti-cancer therapy, radiation therapy including palliative stereotactic radiation therapy to the chest within 4 weeks prior to randomization (palliative stereotactic radiation therapy to other areas within 2 weeks prior to randomization) ▪ Small molecule drugs within 2 weeks or 5 half-lives prior to treatment with study medication, whichever was longer; (hydroxy-)chloroquine within 14 days prior to randomization **Concomitant treatment** ▪ For trastuzumab deruxtecan antiemetics such as 5-hydroxytryptamine receptor antagonists, neurokinin-1 receptor antagonists and steroids ▪ Anticoagulants ▪ Haematopoietic growth factors for prophylaxis or treatment **Prohibited concomitant treatment** ▪ Other antineoplastic treatment, monoclonal antibodies against HER2, chemotherapy, targeted therapy, radiotherapy (except palliative radiotherapy of non-targeted lesions), immunotherapy or biologic or hormonal therapy for cancer treatment ▪ Immunosuppressants (except for short-term treatment with low- or moderate-dose corticosteroids or long-term treatment with short-acting preparations and for the treatment of AEs)	

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

Study	Intervention	Comparison
a. If there is a change in body weight during treatment of ≥ ± 10% of baseline weight compared with baseline, the patient's dose is recalculated based on the updated weight. b. In the event of a longer interruption, the resumption of treatment had to be discussed with the sponsor's study physician. c. 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. d. Patients who received neoadjuvant or adjuvant chemotherapy are eligible to participate, provided they have had a disease-free interval (defined as completion of systemic chemotherapy until diagnosis of advanced or metastatic disease) of more than 12 months. AE: adverse event; BSA: body surface area; BW: body weight; IV: intravenous; HER2: human epidermal growth factor receptor 2; RCT: randomized controlled trial		

Study design

The DESTINY-Breast06 study is an ongoing, open-label RCT on the comparison of trastuzumab deruxtecan with a chemotherapy of physician's choice choosing from capecitabine, paclitaxel or nab-paclitaxel, each as monotherapy. The study enrolled adult patients with advanced or metastatic HR-positive, HER2-low or HER2-ultralow breast cancer whose disease had progressed during endocrine therapy in combination with a CDK4/6 inhibitor within 6 months of starting first-line treatment in the metastatic setting or during ≥ 2 endocrine therapies with or without targeted therapy in the metastatic setting. HER2-low and HER2-ultralow status, determined in the study using the VENTANA 4B5 IHC test, were defined as staining intensities using IHC of 1+ or 2+ (HER2-low) and IHC of > 0 and < 1+ (HER2-ultralow). If IHC 2+ was present, ISH had to be negative. Only patients with a positive hormone receptor status and an ECOG Performance Status of 0 or 1 were enrolled in the study. Patients were not allowed to have received chemotherapy for the treatment of advanced or metastatic breast cancer prior to enrolment in the study. In addition, prior HER2-targeted therapy was excluded. Patients who had received neoadjuvant or adjuvant chemotherapy were eligible for inclusion in the study provided they had had a disease-free interval (defined as the time between completion of systemic chemotherapy and diagnosis of advanced or metastatic disease) of more than 12 months.

Overall, 866 patients were enrolled in the study and randomly allocated in a 1:1 ratio either to treatment with trastuzumab deruxtecan (N = 436) or to a treatment of physician's choice, selecting from capecitabine, paclitaxel or nab-paclitaxel (N = 430). The decision to use one of these options was made by the investigator for each patient prior to randomization. Randomization was stratified according to previous use of CDK4/6 inhibitors (yes vs. no), HER2-IHC expression (IHC 2+/ISH- vs. IHC 1+ vs. IHC > 0 and < 1+) and previous use of taxanes in the non-metastatic setting (yes vs. no).

Capecitabine and nab-paclitaxel are not part of the ACT. Therefore, only the subpopulation of patients treated with trastuzumab deruxtecan (n = 67) versus paclitaxel (n = 68) for whom paclitaxel was chosen as therapy prior to allocation to the control arm was relevant for the benefit assessment, (see Section I 3.3).

Treatment with trastuzumab deruxtecan was largely in compliance with the specifications of the SmPC [9]. There were deviations in the use of concomitant medication with antiemetics for the prophylaxis of nausea and vomiting (see section below). Treatment with paclitaxel deviated from the specifications in the SmPC [10]. Firstly, paclitaxel was administered in a dosage deviating from the marketing authorization and secondly, it was unclear to what extent the patients had been previously treated with anthracyclines (see Sections 'Dosage of paclitaxel' and 'Prior treatment of patients with anthracyclines'). In addition, mandatory pretreatment with corticosteroids, antihistamines and H2 receptor antagonists to prevent hypersensitivity reactions was not specified in the study protocol (see 'Notes on the outcomes in the DESTINY-Breast06 study').

Treatment with the study medication was conducted until disease progression or unacceptable toxicity. Patients in the control arm were not permitted to switch to treatment with trastuzumab deruxtecan.

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

Testing of patients for breast cancer-associated gene (BRCA)1/2 mutation

The information on the ACT indicated that the G-BA assumed that therapy with trastuzumab deruxtecan is not indicated for patients with BRCA1/2 mutations. According to the current guideline of the Gynaecological Oncology Group (AGO) [11], it is recommended to test patients with metastatic breast cancer for BRCA1/2 mutation, as therapy with a poly(adenosine diphosphate-ribose) polymerase inhibitor is recommended for patients with such a mutation. No information was available in the study documents as to whether patients in the DESTINY-Breast06 study were tested for BRCA1/2 mutation. O'Shaughnessy 2020 and Tesch 2020 described that approximately 5 to 10% of patients with HR-positive and HER2-negative breast cancer have a BRCA1/2 mutation [12,13]. It was therefore not assumed that a relevant proportion of patients in this therapeutic indication (HR-positive and HER2-low or HER2-ultralow breast cancer) have a BRCA1/2 mutation. Therefore, the lack of information on testing for BRCA1/2 mutation was of no consequence for this benefit assessment.

Prior treatment of patients with anthracyclines

According to the SmPC, the ACT paclitaxel in the control arm of the DESTINY-Breast06 study, which is relevant for this benefit assessment, should only be used if patients have not

responded to an anthracycline-containing therapy or if this is not suitable for them [10]. According to the study protocol, a lack of response to previous anthracycline-containing therapy or unsuitability for this was not a prerequisite for inclusion in the study. In the study documents, information on previous systemic antineoplastic treatments was only available on the basis of all patients in the control arm and not per treatment option used. According to the study documents, a total of 206 patients (48%) in the control arm were treated with anthracyclines in a previous line of therapy (adjuvant/neoadjuvant setting). However, it was not clear from these documents whether this number included patients who received paclitaxel, nor whether these patients received paclitaxel because they did not respond to anthracycline-containing therapy or because it was not an option for them. Information on the relevant subpopulation is required for the assessment.

Dosing of paclitaxel

According to the SmPC, paclitaxel is approved for the treatment of metastatic breast cancer at a dose of 175 mg/m^2 body surface area every 3 weeks [10]. In the DESTINY-Breast06 study, paclitaxel was administered at an unapproved dose of 80 mg/m^2 body surface area once a week. In the study protocol, the company justified the choice of paclitaxel dosage by stating that in a meta-analysis, weekly administration showed an improvement in overall survival and fewer side effects compared to 3-weekly administration. In addition, according to the company, the weekly administration of paclitaxel is common in everyday practice. During the oral hearing on benefit assessment A23-07 (trastuzumab deruxtecan in previously treated HER2-low breast cancer), it was confirmed that the reduced-dose, weekly administration of paclitaxel is common practice in health care [14]. The current AGO guideline also recommends weekly administration of paclitaxel [11]. It was therefore assumed that the patients treated with paclitaxel in the control arm received essentially appropriate treatment. Therefore, the paclitaxel dosage deviating from the marketing authorization had no consequences for this benefit assessment.

I 3.3 Results for the relevant subpopulation not suitable

As already described, in the DESTINY-Breast06 study, allocation to one of the 3 chemotherapy options capecitabine, paclitaxel and nab-paclitaxel was made by the investigator prior to randomization. Since capecitabine and nab-paclitaxel were not ACT options, the subpopulation relevant for the benefit assessment only comprised patients from the trastuzumab deruxtecan or the control arm who were to receive paclitaxel if assigned to the control arm. As the company referred to a different ACT, in Module 4 A it only presented results for the total population of the study DESTINY-Breast06. Information on the relevant subpopulation were only available in subgroup analyses on the characteristic ‘chemotherapy of physician's choice’ (capecitabine versus nab-paclitaxel versus paclitaxel). However, the available information on the relevant subpopulation was insufficient. An overview of the missing data can be found in Table 8.

Table 8: Missing information on the relevant subpopulation of the study DESTINY-Breast06 – RCT, direct comparison: trastuzumab deruxtecan vs paclitaxel

Results	**Relevant subpopulation**[a]
Characteristics of the relevant subpopulation	ND
Information on the course of the study	ND
Information on subsequent antineoplastic therapies	ND
Outcomes	
Mortality	
Overall survival	Results available
Morbidity	
Symptoms (EORTC QLQ-C30, EORTC QLQ-BR23, PGIS)	Results available ND on observation period and questionnaire responses
Health status	
EQ-5D VAS	Results available ND on observation period and questionnaire responses
PGIC	Results available ND on observation period and questionnaire responses[b]
Health-related quality of life	
EORTC QLQ-C30, EORTC QLQ-BR23	Results available ND on observation period and questionnaire responses
Side effects	Incomplete data
Subgroup analyses	ND

a. Patients who were assigned to the paclitaxel treatment option prior to randomization.
b. No suitable data available; see following text section for reasons.

EORTC: European Organisation for Research and Treatment of Cancer; ND: no data; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module 23; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; VAS: visual analogue scale

The dossier did not contain any information on patient characteristics, study course (treatment duration of patients), subsequent therapies, observation periods and responses to the patient-reported outcomes questionnaires, or subgroup analyses for the relevant subpopulation. The consequences of the missing information for the assessment of the outcomes on morbidity, health-related quality of life and side effects as well as for the overall conclusion on added benefit are explained below.

Notes on the outcomes in the DESTINY-Breast06 study

Patient-reported outcomes on symptoms, health status and health-related quality of life

In the DESTINY-Breast06 study, the company recorded symptoms, health status and health-related quality of life using the instruments European Organisation for Research and

Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), EORTC QLQ-Breast Cancer Module 23 (EORTC QLQ-BR23), EQ-5D visual analogue scale (VAS), Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC). The prespecified operationalization from the statistical analysis plan was, for EORTC QLQ-C30, EORTC QLQ-BR23 and EQ-5D VAS, the change versus baseline using a mixed-effects model with repeated measures (MMRM), as well as responder analyses for the EORTC QLQ-C30 for the time to confirmed deterioration. Operationalization was not prespecified for the PGIS and PGIC instruments. For the relevant subpopulation, the company presented responder analyses in Appendix 4-G of the dossier on the time to the first or time to confirmed deterioration (response criterion ≥ 10 points for EORTC QLQ-C30 and EORTC QLQ-BR23, ≥ 15 points for EQ-5D VAS and ≥ 1 for PGIS; for PGIC, see Section 'Health status assessed using PGIC').

In principle, both the first and the confirmed deterioration are relevant to the patient. The G-BA described which of these 2 operationalizations is suitable for benefit assessment in its 'Answers to frequently asked questions about the benefit assessment procedure' [15]. The selection of the appropriate operationalization depends on the observation periods of the patient-reported outcomes. However, there was a lack of information on the observation period of the patient-reported outcomes. In the overall population of the DESTINY-Breast06 study, the response rate to the questionnaires in both study arms was already low at baseline. Due to the sharp decline and differential response rates over the course of the study, the data presented by the company for the overall population could not be meaningfully interpreted. At Week 16 (5th follow-up survey after baseline) the response rate was still around 75% of patients in the intervention arm, while the response rate in the comparator arm was only around 64%. No information was available on the response rate of the questionnaires for the relevant subpopulation. It was therefore not possible to assess whether the results of the patient-reported outcomes were suitable for the relevant subpopulation.

In order to assess the relevant analysis of the patient-reported outcomes and the suitability of the results for the benefit assessment, information on both the observation period and the response rates for the patient-reported outcomes questionnaires would be required for the relevant subpopulation.

Health status assessed using PGIC

Irrespective of the previously explained limitations for all patient-reported outcomes, the analyses presented by the company (both for first-time and confirmed deterioration) for the PGIC were not suitable for the benefit assessment. This is explained below.

The PGIC consists of a single question asking the patient to rate the change in their health status compared with the time before starting the study medication. There are 7 possible

responses ('very much improved', 'much improved', 'minimally improved', 'no change', 'minimally worse', 'much worse', 'very much worse'). The recording of health status by means of a PGIC is regarded as patient relevant. In Module 4 A, the company presented post hoc time-to-event analyses on the time to first and time to confirmed deterioration, defining only the responses 'much worse' or 'very much worse' as an event. Patients who rated their health status as 'minimally worse' compared to when they started taking the study medication were therefore not classified as patients with deteriorated health status in the company analysis. This is not adequate because even a slight deterioration represents a patient-noticeable and thus patient-relevant change. For the benefit assessment, analyses would therefore be required in which even the answer 'minimally worse' is considered a relevant deterioration.

Outcomes in the category of side effects

Incomplete data on common adverse events

According to the dossier template, in addition to the overall AE rates, results for all AEs (operationalized as System Organ Classes [SOCs] and Preferred Terms [PTs] according to the Medical Dictionary for Regulatory Activities [MedDRA]) must also be presented, provided they exceed a certain minimum frequency [16]. In Appendix 4-G of the dossier, the AEs in the paclitaxel subgroup that occurred in ≥ 10% of patients in at least one study arm were shown. However, the information on AEs at SOC and PT level presented by the company in Appendix 4-G was not complete. In the study documents in Module 5, AEs were presented separately according to the chemotherapy administered in the control arm. A comparison with the study documents in Module 5 showed that approximately 35% of the AEs at SOC and PT level (e.g. PT diarrhoea) that occurred in ≥ 10% of the patients in the control arm of the relevant subpopulation were not shown in Appendix 4-G. Results on these AEs for the intervention arm of the relevant subpopulation were not available. Consequently, it is unclear whether further AEs occurred in ≥ 10% of patients in the intervention arm of the subpopulation that were not presented in Appendix 4-G.

Thus, no complete AE analyses were available for the relevant subpopulation and the AE analyses presented in Appendix 4 G were therefore not suitable for the benefit assessment.

Concomitant treatment for nausea and vomiting (intervention arm)

According to the SmPC, patients should receive a combination regimen of 2 or 3 drugs (e.g. dexamethasone with either a 5-HT3 receptor antagonist and/or an NK1 receptor antagonist and other drugs as per therapeutic indication) before each dose of trastuzumab deruxtecan to prevent chemotherapy-induced nausea and vomiting [9]. The need for antiemetic treatment before each dose of trastuzumab deruxtecan with the combination regimen mentioned in the SmPC was only included in Amendment 3 to the study protocol of 27 April 2022. It is unclear why the necessary antiemetic treatment was not included until Amendment 3 of the study protocol. Overall, 74% of all patients in the intervention arm of the

total population received a 5-HT3 receptor antagonist. However, it was not clear from the information in the study documents how many patients in the intervention arm received dexamethasone as antiemetic treatment. No information was available on the use of NK1 receptor antagonists. However, this information would be required for the assessment. It was therefore unclear how many patients in the intervention arm received antiemetic treatment that concurs with the recommendations in the SmPC. It was therefore not possible to assess the extent to which the non-administration of antiemetic prophylaxis affected the results for the outcomes of morbidity and side effects.

Pretreatment to prevent hypersensitivity reactions (control arm)

According to the SmPC, all patients must be pretreated with corticosteroids, antihistamines and H2 receptor antagonists prior to the use of paclitaxel in order to prevent hypersensitivity reactions [10]. According to the study protocol, pretreatment with corticosteroids, antihistamines and H2 receptor antagonists in order to avoid hypersensitivity reactions was not planned. There was also no separate presentation of the concomitant treatments for the patients in the relevant subpopulation available from the study documents. It was therefore unclear whether and how many patients in the subpopulation in the control arm were treated with the drugs mentioned to prevent hypersensitivity reactions. It was also unclear to what extent a pretreatment that was not carried out affected the results for the outcomes on side effects.

Overall conclusion

For this benefit assessment, only the subpopulation of patients from the DESTINY-Breast06 study for whom paclitaxel was specified as therapy prior to allocation to the control arm was relevant. For this relevant subpopulation, however, information on patient characteristics, course of the study, subsequent therapies, observation periods and responses to the patient-reported outcomes questionnaires, and subgroup analyses were missing. Due to this lack of information on the course of the study and questionnaire responses, it was not possible to assess whether the data for the patient-reported outcomes on morbidity and health-related quality of life were suitable and which analysis (first-time or confirmed deterioration) was relevant. Additionally, the side effects data for the subpopulation were incomplete, so that no suitable data were available for these outcomes either. For the outcome overall survival of the relevant subpopulation, suitable data were available in Appendix 4-G of the dossier and the result is presented in I Appendix B of the full dossier assessment. There was no statistically significant difference in overall survival between the treatment arms. The data presented in the dossier submitted by the company were therefore insufficient to derive conclusions about the added benefit of trastuzumab deruxtecan in the given therapeutic indication.

I 4 Results on added benefit

No suitable data were available for the assessment of the added benefit of trastuzumab deruxtecan compared with the ACT in adult patients with unresectable or metastatic HR-positive, HER2-low or HER2-ultralow breast cancer who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment. There is no hint of an added benefit of trastuzumab deruxtecan in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of trastuzumab deruxtecan in comparison with the ACT is summarized in Table 9.

Table 9: Trastuzumab deruxtecan – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients[b] with unresectable or metastatic HR-positive, HER2-low or HER2-ultralow breast cancer who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment[c]	An anthracycline- or taxane-containing systemic therapy consisting of[d]: ▪ doxorubicin or ▪ doxorubicin liposomal (only for patients with metastatic breast cancer) or ▪ epirubicin or ▪ docetaxel (only for female patients) or ▪ paclitaxel (only for patients with metastatic breast cancer)	Added benefit not proven

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. According to the G-BA, it is assumed that there is no therapeutic indication for (secondary) resection or radiotherapy with curative intent. It is also assumed as per the G-BA that treatment with trastuzumab deruxtecan is not indicated for patients with BRCA1/2 mutation.
d. The ACT specified here comprises several alternative treatment options. However, individual treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets.

ACT: appropriate comparator therapy; BRCA: breast cancer associated gene; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor

The assessment described above deviates from that of the company, which derived an indication of a minor added benefit of trastuzumab deruxtecan for the total population of the DESTINY-Breast06 study.

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.

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