Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a (SGB V) Trastuzumab Deruxtecan (New Therapeutic Indication: Breast Cancer, HER2-low, Unresectable or Metastatic, Pretreated)

of 20 July 2023

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient (trastuzumab deruxtecan) was listed for the first time on 1 February 2022 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 23 January 2023, trastuzumab deruxtecan received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7).

On 31 January 2023, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, No.2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient trastuzumab deruxtecan with the new

therapeutic indication in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication): "Enhertu as monotherapy is indicated for the treatment of adult 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 G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 2 May 2023 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of trastuzumab deruxtecan compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of trastuzumab deruxtecan.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of Trastuzumab Deruxtecan (Enhertu) in accordance with the product information

Enhertu as monotherapy is indicated for the treatment of adult 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.

Therapeutic indication of the resolution (resolution of 20.07.2023):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults 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

Appropriate comparator therapy for trastuzumab deruxtecan as monotherapy:

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

– Capecitabine

or

– Eribulin

or

– Vinorelbine

or

– an anthracycline or taxane-containing therapy (only for patients who have not yet received anthracycline and/or taxane-containing therapy or who are eligible for renewed anthracycline or taxane-containing treatment).

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5 Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO:

on 1. In addition to trastuzumab deruxtecan, the following active ingredients are approved for the present therapeutic indication:

5-fluorouracil, capecitabine, cyclophosphamide, docetaxel, doxorubicin, doxorubicin (liposomal), epirubicin, eribulin, ifosfamide, methotrexate, mitomycin, mitoxantrone, paclitaxel, nab-paclitaxel, vinblastine, vincristine, vinorelbine, olaparib, talazoparib and sacituzumab govitecan.

Medicinal products with explicit marketing authorisation for HER2-positive breast cancer and for endocrine-based therapy were not included.

on 2. A radiotherapy is generally considered as a non-medicinal treatment in the present therapeutic indication. However, it is assumed that there is no indication for (secondary) resection or radiotherapy with a curative objective.

on 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Eribulin: Resolution of 22 January 2015
- Olaparib: Resolution of 16 January 2020
- Talazoparib: Resolution of 20 November 2020
- Sacituzumab govitecan: Resolution of 19 May 2022

Annex VI to Section K of the Pharmaceuticals Directive – Active ingredients that cannot be prescribed in applications beyond the scope of the approval (off-label use); last revised 17 October 2019:

- Gemcitabine in monotherapy for breast cancer in women

Methods Hospital Treatment Policy - Section 4 Excluded Methods, effective 19 December 2019:

- Proton therapy for breast cancer

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

Among the approved active ingredients listed under 1., only certain active ingredients named below will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of care.

The present therapeutic indication includes patients with low HER2 expression (defined as ICH1+ or ICH2+/ISH- according to the product information). For these patients, no targeted therapeutic alternative currently exists, and treatment of these patients is carried out according to the current guidelines and written statements of the scientific-medical societies in accordance with the therapy recommendations for HER2-negative breast cancer. Therapies that are indicated exclusively for HER2-positive breast cancer were therefore not considered for determining the appropriate comparator therapy.

It is assumed that patients with HR-positive breast cancer have exhausted the endocrine therapy options in the present treatment setting.

Furthermore, it is assumed that the patients have usually received taxane and/or anthracycline-based chemotherapy as part of the prior therapy.

In addition, it is assumed that patients with germline BRCA1/2 mutation will not be eligible for BRCA-specific therapy at the time of treatment with trastuzumab deruxtecan.

According to current guidelines, further cytotoxic chemotherapy is the current treatment standard for patients with HER2-negative, advanced / metastatic breast cancer who previously received chemotherapy in case of disease progression or relapse. According to the guidelines, primarily monotherapies should be used with regard to cytotoxic chemotherapies. According to the guideline recommendations, polychemotherapy is only considered indicated in patients with high remission pressure due to more severe conditions, rapid tumour growth and aggressive tumour behaviour.

Treatment with anthracyclines and taxanes can be considered as a therapeutic alternative for patients who have not yet received anthracycline and/or taxane-containing therapy or also as re-therapy in the case of corresponding individual conditions.

Of the active ingredients primarily mentioned in various guidelines, besides taxanes and anthracyclines, capecitabine, vinorelbine and eribulin are approved for use as monotherapy in the present therapeutic indication.

For the treatment of patients who have experienced further progression after at least one course of chemotherapy for the treatment of advanced breast cancer, the G-BA identified a hint for a considerable additional benefit of eribulin compared to monotherapy with capecitabine or vinorelbine for patients who can no longer be treated with taxanes or anthracyclines (resolution of 22 January 2015).

Taking into account the importance of eribulin in the current guideline recommendations in relation to other treatment options and in view of the restriction of the additional benefit to a part of the approved therapeutic indication, eribulin is considered to be an equally appropriate treatment option alongside capecitabine and vinorelbine.

Furthermore, sacituzumab govitecan is approved for the treatment of unresectable or metastatic triple-negative breast cancer in patients who have received two or more prior systemic therapies, including at least one for advanced disease. By resolution of 19 May 2022, the G-BA identified an indication of major additional benefit of sacituzumab govitecan over capecitabine, eribulin or vinorelbine. The scientific-medical societies consider sacituzumab govitecan to be a possible treatment option for patients with triple-negative breast cancer after at least 2 previous systemic therapies. In contrast, sacituzumab govitecan is currently not mentioned in the German S3 guideline. In addition, it must be taken into account that the approved therapeutic indication of sacituzumab govitecan and the present therapeutic indication relevant to the assessment only overlap to a small extent with regard to the target population. Sacituzumab govitecan is therefore not considered as an appropriate comparator therapy.

Overall, the G-BA determined capecitabine, eribulin, vinorelbine and an anthracycline or taxane-containing therapy as equally appropriate comparator therapies (only for patients who have not yet received anthracycline and/or taxane-containing therapy or who are eligible for renewed anthracycline or taxane-containing treatment).

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of trastuzumab deruxtecan is assessed as follows:

Indication of a considerable additional benefit

Justification:

For the proof of additional benefit of trastuzumab deruxtecan, the pharmaceutical company presented the results of the DESTINY-Breast04 study.

DESTINY-Breast04 is a multicentre, open-label, randomised controlled trial comparing trastuzumab deruxtecan with a therapy according to doctor's instructions selecting capecitabine, eribulin, gemcitabine, paclitaxel or nab-paclitaxel. The study enrolled adult patients with unresectable or metastatic HER2-low breast cancer who had previously received 1 or 2 lines of chemotherapy in the metastatic setting or who had relapsed during or within 6 months of completing adjuvant chemotherapy.

HER2-low status is defined in the DESTINY-Breast04 study as low HER2 expression in terms of a staining intensity of 1+ or 2+ determined by immunohistochemistry (IHC). If IHC 2+ is present, in situ hybridisation (ISH) must be negative at the same time. The marketing authorisation of trastuzumab deruxtecan in the present therapeutic indication is based on this definition of HER2 tumour status.

Enrolment in the study was independent of hormone receptor status. If patients had a positive hormone receptor status, the breast cancer had to be refractory to endocrine therapy.

Furthermore, patients should have an Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) of 0 or 1 for enrolment in the study.

The 557 patients included were randomised 2:1 to treatment with trastuzumab deruxtecan (N = 373) or to therapy according to doctor's instructions (N = 184). Prior to randomisation, the patients had to decide which of the available therapy options they would be treated with in the case of randomisation into the comparator arm.

Stratification was by HER2 status (IHC 1+ vs IHC 2+/ISH negative), number of prior chemotherapies in the metastatic setting (1 vs 2) and hormone receptor/ cyclin-dependent kinase (CDK) status (hormone receptor positive with prior CDK4/6 inhibitor therapy vs hormone receptor positive without prior CDK4/6 inhibitor therapy vs hormone receptor negative).

Treatment was given in the DESTINY-Breast04 study until disease progression, unacceptable toxicity, withdrawal of informed consent or study termination.

DESTINY-Breast04 is conducted in 161 study sites across Asia, Europe and North America. The study was launched in December 2018 and is currently ongoing.

For the benefit assessment, the data cut-off from 11.01.2022 was submitted. This is the final analysis planned after 318 events for the PFS endpoint in the group of patients with hormone receptor-positive breast cancer. At the same time, this data cut-off represents the final analysis for the endpoint of overall survival. For the present benefit assessment, the results of this data cut-off are used.

For the implementation of the appropriate comparator therapy in DESTINY-Breast04

IQWiG's dossier assessment noted that for the administration of the active ingredients capecitabine, eribulin, paclitaxel and nab-paclitaxel, certain prerequisites of pretreatment

with taxanes or anthracyclines must be fulfilled according to the respective product information. According to the appropriate comparator therapy determined by the G-BA, an anthracycline or taxane-containing therapy only represents an appropriate comparator therapy for those patients who have not yet received an anthracycline and/or taxane-containing therapy or who are eligible for a renewed anthracycline or taxane-containing treatment. In this regard, IQWiG pointed out in the dossier assessment that the study documents only contained information on prior systemic cancer therapies on the basis of all patients in the comparator arm and not per active ingredient option used. Furthermore, no information was available on the active ingredients the patients had received prior to enrolment in the study or whether they had been re-treated with anthracyclines or taxanes.

Furthermore, IQWiG's dossier assessment stated that in the DESTINY-Breast04 study, doses deviating from the product information were possible in some cases. Capecitabine could be used in a partly lower dosage, paclitaxel and nab-paclitaxel could be used in a weekly dosage in addition to the 3-weekly dosage in accordance with the marketing authorisation. IQWiG pointed out that no information was available in the study documents on the dose regimens that were actually applied.

According to the product information, the recommended dose for paclitaxel as monotherapy in the second line is 175 mg/m² BSA every 3 weeks. There is no consistent information in the guidelines. In the studies referenced in the guidelines, a dosing scheme of 175 mg/m² BSA paclitaxel every 3 weeks or 80 to 90 mg/m² BSA paclitaxel weekly was most commonly used.

The statements made by clinical experts critically discussed both the dosages used in the DESTINY-Breast04 study and the treatment regimens of nab-paclitaxel or paclitaxel used. However, with regard to toxicities and associated therapy discontinuations, a reduced dosage with weekly administration could be better tolerated as well as more effective and would be used accordingly in clinical practice.

Overall, it can be deduced that the lower dosage of capecitabine and the weekly administration of the taxanes also correspond to the therapeutic standard in clinical practice.

On the relevant sub-population of the DESTINY-Breast04 study

In the DESTINY-Breast04 study, 9% of all patients in the comparator arm received gemcitabine as monotherapy. Gemcitabine is not part of the appropriate comparator therapy and is only approved in combination with paclitaxel in the present therapeutic indication. IQWiG's dossier assessment pointed out a resulting uncertainty.

As part of the written statement procedure on the present assessment, additional analyses were submitted by the pharmaceutical company excluding patients assigned to gemcitabine treatment prior to randomisation. This sub-population includes 344 patients in the intervention arm and 165 in the control arm. The present assessment is based on the results for this sub-population.

Extent and probability of the additional benefit

Mortality

Overall survival is defined in the DESTINY-Breast04 study as the time between randomisation and death, regardless of the underlying cause of death.

For the endpoint of overall survival, a statistically significant prolongation of survival time was shown in the relevant sub-population by treatment with trastuzumab deruxtecan compared

to capecitabine, eribulin, paclitaxel or nab-paclitaxel, the extent of which is assessed as a significant improvement.

For this endpoint, there was an effect modification by the characteristic "visceral disease (yes/no)". There was a statistically significant difference to the advantage of trastuzumab deruxtecan for both patients with visceral disease and those without visceral disease. However, the magnitude of the effect differed between the subgroups. Accordingly, patients without visceral disease showed a positive effect of greater magnitude than patients with visceral disease.

In the overall analysis of the available results from the DESTINY-Breast04 study, this effect modification by the characteristic "visceral disease" is considered insufficient to derive corresponding separate statements on the additional benefit in the overall assessment. The data on the subgroups "with visceral disease" and "without visceral disease" are nevertheless considered a relevant outcome of the benefit assessment and are therefore shown in the study results.

Morbidity

Progression-free survival (PFS)

PFS was operationalised in the DESTINY-Breast04 study as the time between randomisation and disease progression (determined using mRECIST criteria version 1.1) or death regardless of the underlying cause, whichever event occurs first.

Based on the relevant sub-population, there was a statistically significant prolonged PFS in favour of trastuzumab deruxtecan over capecitabine, eribulin, paclitaxel or nab-paclitaxel.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. The endpoint component "mortality" has already been assessed as an independent endpoint via the endpoint "overall survival". The morbidity component "disease progression" was not assessed in a symptom-related manner but exclusively by means of imaging (disease progression assessed by radiology according to the RECIST 1.1 criteria). Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient-relevance of the endpoint PFS. The overall statement on the extent of the additional benefit remains unaffected.

Symptomatology

Symptomatology was assessed in the DESTINY-Breast04 study using the symptom scales of the disease-specific questionnaire EORTC QLQ-C30 and the breast cancer-specific additional module QLQ-BR23.

In the dossier for the benefit assessment, the pharmaceutical company submits responder analyses for the percentage of patients with a change of ≥ 10 points and ≥ 15% of the scale range for the time to first deterioration and for the time to confirmed deterioration. For the EORTC questionnaires, only evaluations for the response criterion 10 points are used. The analyses of time to first deterioration are used for the present assessment.

In the analysis of time to first deterioration by ≥ 10 points, a statistically significant difference to the advantage of trastuzumab deruxtecan was shown in relation to the relevant sub-population for the endpoints of pain and insomnia respectively. For the endpoints of nausea and vomiting as well as diarrhoea, there were statistically significant differences between the treatment groups to the disadvantage of trastuzumab deruxtecan. No suitable data are

available for the endpoint "burden due to hair loss". For all other endpoints no statistically significant difference was detected between the treatment groups.

In the overall assessment of the results, no predominant advantage or disadvantage was found with regard to the symptomatology.

Health status

General health status is assessed in the DESTINY-Breast04 study using the EQ-5D visual analogue scale (VAS).

In the dossier for the benefit assessment, the pharmaceutical company submits responder analyses for the percentage of patients with a change of ≥ 15 points for the time to first deterioration and for the time to confirmed deterioration. The analyses of time to first deterioration are used for the present assessment.

For the endpoint of health status, there was no statistically significant difference between the treatment groups.

Thus, there are neither positive nor negative effects of trastuzumab deruxtecan with regard to the health status.

Quality of life

Health-related quality of life was assessed in the DESTINY-Breast04 study using the functional scales of the disease-specific questionnaire EORTC QLQ-C30 and the breast cancer-specific additional module QLQ-BR23.

In the dossier for the benefit assessment, the pharmaceutical company submits responder analyses for the percentage of patients with a change of ≥ 10 points and ≥ 15% of the scale range for the time to first deterioration and for the time to confirmed deterioration. For the EORTC questionnaires, only evaluations for the response criterion 10 points are used. The analyses of time to first deterioration are used for the present assessment.

In the analysis of time to first deterioration by ≥ 10 points, there was a statistically significant difference to the advantage of trastuzumab deruxtecan for the endpoints of physical functioning, cognitive functioning, social functioning and body image in the relevant sub-population. No suitable data are available for the endpoint of sex pleasure. For all other endpoints no statistically significant difference was detected between the treatment groups.

Overall, there are advantages of trastuzumab deruxtecan in terms of quality of life.

Side effects

Adverse events (AEs)

In the DESTINY-Breast04 study, almost all patients in the relevant sub-population experienced AEs in both study arms. The results were only presented additionally.

Serious adverse events (SAE)

For serious adverse events, there was a statistically significant difference to the advantage of trastuzumab deruxtecan in the relevant sub-population.

Severe AEs (CTCAE grade ≥ 3)

For severe adverse events with CTCAE grade ≥ 3, there was a statistically significant difference to the advantage of trastuzumab deruxtecan in relation to the relevant sub-population.

Discontinuation due to AEs

For the endpoint of "discontinuation due to AEs", no statistically significant difference was found between the treatment groups.

Specific AEs

In relation to the relevant sub-population, there was a statistically significant difference to the advantage of trastuzumab deruxtecan for each of the specific AEs hand-foot syndrome (PT, AE) and neutropenia (PT, severe AE). For the specific AE thrombocytopenia (PT, severe AE), nausea (PT, severe AE), gastrointestinal disorders (SOC, AE) and infections and infestations (SOC, SAE), there was a statistically significant difference to the disadvantage of trastuzumab deruxtecan in each case. For the endpoint of cardiac disorders (SOC, severe AE), no hazard ratio calculations and no p value were provided by the pharmaceutical company. Due to the low number of events, however, it cannot be assumed that a statistically significant effect will result if suitable analyses are available.

In summary, an advantage of treatment with trastuzumab deruxtecan over capecitabine, eribulin, paclitaxel or nab-paclitaxel can be found in the side effects due to the positive effects in SAEs and severe AEs. With regard to specific adverse events, both advantages and disadvantages of trastuzumab deruxtecan were present in detail.

Overall assessment

For the benefit assessment of trastuzumab deruxtecan, data from the open-label, randomised, controlled trial DESTINY-Breast04 on mortality, morbidity, quality of life and side effects are available in comparison with therapy according to doctor's instructions selecting capecitabine, eribulin, gemcitabine, paclitaxel or nab-paclitaxel.

The present assessment is based on the evaluations submitted by the pharmaceutical company in the written statement procedure, which excluded patients with treatment with gemcitabine, which is not part of the appropriate comparator therapy.

For the endpoint of overall survival, a statistically significant prolongation of survival time is shown by treatment with trastuzumab deruxtecan compared to capecitabine, eribulin, paclitaxel or nab-paclitaxel, which is assessed as a significant improvement.

With regard to symptomatology (assessed using EORTC QLQ-C30 and -BR23), no predominant advantage or disadvantage of trastuzumab deruxtecan is found in the overall assessment. With regard to health status (assessed by EQ-5D VAS), there are neither positive nor negative effects.

In terms of quality of life (assessed by EORTC QLQ-C30 and -BR23), there are advantages of trastuzumab deruxtecan over capecitabine, eribulin, paclitaxel or nab-paclitaxel.

In terms of side effects, trastuzumab deruxtecan has advantages in serious AEs and severe AEs. There are no statistically significant differences between the treatment groups in terms of therapy discontinuations due to AEs. In detail, there are both advantages and disadvantages of trastuzumab deruxtecan for the specific AEs.

In the overall analysis, the G-BA comes to the conclusion that, in particular due to the clear positive effects on the prolongation of survival time and in view of the advantages with regard to quality of life and side effects, there is a considerable additional benefit of trastuzumab

deruxtecan compared with capecitabine, eribulin, paclitaxel or nab-paclitaxel in the treatment of adult patients with unresectable or metastatic HER2-low breast cancer, who have received prior chemotherapy in the metastatic setting or who have had a recurrence during or within 6 months of completing adjuvant chemotherapy.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the randomised, open-label, controlled phase III DESTINY-Breast04 study.

At the study level, the risk of bias is considered low.

The risk of bias for the endpoint of overall survival is assessed as low. For the endpoints in the areas of symptomatology, health status and health-related quality of life, the risk of bias is classified as high due to the lack of blinding and the strongly decreasing return of questionnaires over the course of the study, which is differential between the therapy arms.

There are also uncertainties regarding the implementation of the appropriate comparator therapy in the DESTINY-Breast04 study. In this regard, the extent to which the patients in the comparator arm of the study had received prior therapy with anthracyclines or taxanes in accordance with the respective specifications of the product information remained unclear on the basis of the information provided by the pharmaceutical company in the dossier. It also remained unclear to what extent an anthracycline or taxane-containing therapy was used in the study according to the specifications determined by the G-BA with regard to the appropriate comparator therapy. Even on the basis of the information provided by the pharmaceutical company as part of the written statement procedure, the uncertainties mentioned could not be eliminated.

Overall, the available data basis is subject to uncertainties. However, these uncertainties are not rated so high as to justify a downgrading of the reliability of data of the overall assessment. Thus, the reliability of data for the additional benefit determined is classified in the category "indication".

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient trastuzumab deruxtecan:

"Enhertu as monotherapy is indicated for the treatment of adult 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".

Enhertu was approved under special conditions.

The G-BA determined capecitabine or eribulin or vinorelbine or anthracycline or taxane-containing therapy as the appropriate comparator therapy (only for patients who have not yet received anthracycline and/or taxane-containing therapy or who are eligible for renewed anthracycline or taxane-containing treatment) .

The open-label RCT DESTINY-Breast04 is available for assessment, comparing trastuzumab deruxtecan with therapy according to doctor's instructions selecting capecitabine, eribulin, gemcitabine, paclitaxel or nab-paclitaxel.

The assessment is based on evaluations on a sub-population assigned to treatment with capecitabine, eribulin, paclitaxel or nab-paclitaxel prior to randomisation.

For the endpoint of overall survival, a statistically significant prolongation of the survival time is shown by trastuzumab deruxtecan, which is assessed as a significant improvement.

With regard to symptomatology, no predominant advantage or disadvantage of trastuzumab deruxtecan is found in the overall assessment. With regard to health status, there are neither positive nor negative effects.

In terms of quality of life, there are advantages of trastuzumab deruxtecan.

In terms of side effects, trastuzumab deruxtecan has advantages in serious AEs and severe AEs. In detail, both advantages and disadvantages are evident for the specific AEs.

Overall, especially in view of the lack of blinding, the data basis is fraught with uncertainties. However, these are not rated to be so high as to justify a downgrading of the reliability of data of the overall assessment.

As a result, the G-BA finds an indication of considerable additional benefit of trastuzumab deruxtecan compared to capecitabine, eribulin, paclitaxel or nab-paclitaxel, in particular due to the clear positive effects on the prolongation of survival time and in view of the advantages with regard to quality of life and side effects.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The G-BA bases its resolution on the information from the dossier of the pharmaceutical company. It must be taken into account that the patient numbers presented are subject to uncertainties. On the one hand, this results from the fact that patients whose breast cancer was first diagnosed at an earlier stage more than 10 years ago and who have shown a progression to the unresctable or metastasised stage by the current year were not taken into account. On the other, instead of limiting to patients with recurrence during or within 6 months of completing adjuvant chemotherapy, patients who experience progression to locoregional recurrence within 10 years of diagnosis were included. Furthermore, the transferability of percentage values for the receipt of chemotherapy to the current care setting is unclear.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Enhertu (active ingredient: trastuzumab deruxtecan) at the following publicly accessible link (last access: 27 April 2023):

https://www.ema.europa.eu/en/documents/product-information/enhertu-epar-product-information_en.pdf

Treatment with trastuzumab deruxtecan should only be initiated and monitored by specialists in internal medicine, haematology, and oncology who are experienced in the treatment of patients with breast cancer, as well as specialists in obstetrics and gynaecology, and other specialists participating in the Oncology Agreement.

This medicinal product was approved under "special conditions". This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 July 2023).

The annual treatment costs shown refer to the first year of treatment.

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Trastuzumab deruxtecan	1 x per 21-day cycle	17.4	1	17.4
Appropriate comparator therapy				
Capecitabine	2 x on day 1-14 of a 21-day cycle	17.4	14	243.6
Eribulin	Day 1 and 8 of a 21-day cycle	17.4	2	34.8
Vinorelbine	1 x weekly	52.1	1	52.1
Anthracycline or taxane-containing treatment regimens				
Docetaxel	1 x per 21-day cycle	17.4	1	17.4
Paclitaxel	1 x per 21-day cycle	17.4	1	17.4
nab-paclitaxel	1 x per 21-day cycle	17.4	1	17.4
Doxorubicin	1 x per 21-day cycle	5 - 11 [2]	1	5.0 - 11.0

[2] The maximum total doxorubicin dose of 450-550 mg/m² body surface area should not be exceeded to avoid cardiac toxicity.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Pegylated liposomal doxorubicin	1 x per 28-day cycle	13.0	1	13.0
Eprirubicin	1 x per 21-day cycle	10 - 16 [3]	1	10.0 - 16.0

Consumption:

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments, e.g. because of side effects or comorbidities, are not taken into account when calculating the annual treatment costs.

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

The information on dosages refers to applications in women, as breast cancer is relatively rare in men. The average body measurements of adult females were applied for dosages, depending on body weight (BW) or body surface area (BSA) (average body height: 1.66 m; average body weight: 68.7 kg). This results in a body surface area of 1.76 m² (calculated according to Du Bois 1916).[4]

For doxorubicin and epirubicin, the total cumulative dose was considered (450 - 550 mg/m² for doxorubicin or 900 - 1,000 mg/m² for epirubicin). Product information with different dosage recommendations is available for doxorubicin and epirubicin (doxorubicin: 50 - 80 mg/m² and 60 - 75 mg/m²; epirubicin: 75 - 90 mg/m² and 60 - 90 mg/m². The dosage recommendations with the largest range were used for the cost calculation: Doxorubicin 50 - 80 mg/m² and epirubicin: 60 - 90 mg/m². In the table "Consumption", only the dosing schemes that result in the range of annual treatment costs when calculated are shown.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Trastuzumab deruxtecan	5.4 mg/kg = 370.98 mg	370.98 mg	4 x 100 mg	17.4	69.6 x 100 mg
Appropriate comparator therapy					
Capecitabine	1250 mg/m² = 2200 mg	2 x 2200 mg	8 x 500 mg + 2 x 150 mg	243.6	1948.8 x 500 mg +

[3] The total cumulative epirubicin dose of 900 - 1000 mg/m² should not be exceeded to avoid cardiac toxicity.
[4] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
					487.2 x 150 mg
Eribulin	1.23 mg/m² = 2.17 mg	2.17 mg	5 x 0.44 mg	34.8	174 x 0.44 mg
Vinorelbine	25 mg/m² - 30 mg/m² = 44 mg - 52.8 mg	44 mg - 52.8 mg	1 x 50 mg - 1 x 50 mg + 1 x 10 mg	52.1	52.1 x 50 mg - 52.1 x 50 mg + 52.1 x 10 mg -
Anthracycline or taxane-containing treatment regimens					
Docetaxel	100 mg/m² = 176 mg	176 mg	1 x 160 mg + 1 x 20 mg	17.4	17.4 x 160 mg + 17.4 x 20 mg
Paclitaxel	175 mg/m² = 308 mg	308 mg	1 x 300 mg + 1 x 30 mg	17.4	17.4 x 300 mg + 17.4 x 30 mg
nab-paclitaxel	260 mg/m² = 457.6 mg	457.6 mg	5 x 100 mg	17.4	87 x 100 mg
Doxorubicin	50 mg/m² 80 mg/m² = 88 mg - 140.8 mg	88 mg - 140.8 mg	1 x 100 mg - 1 x 150 mg	5.0 - 11.0	11 x 100 mg - 5 x 150 mg
Pegylated liposomal doxorubicin	50 mg/m² = 88 mg	88 mg	1 x 50 mg - 2 x 20 mg	13.0 - 26.0	13.0 x 50 mg + 26.0 x 20 mg
Eprirubicin	60 mg/m² - 90 mg/m² = 105.6 mg - 158.4 mg	105.6 - 158.4 mg	1 x 100 mg + 1 x 10 mg - 1 x 100 mg + 1 x 50 mg + 1 x 10 mg	10.0 - 16.0	16 x 100 mg + 16 x 10 mg - 10 x 100 mg + 10 x 50 mg + 10 x 10 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of

the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy		Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed						
Trastuzumab deruxtecan	100 mg	1 PCI	€ 2,405.72	€ 2.00	€ 229.89	€ 2,173.83
Appropriate comparator therapy						
Capecitabine [5]	500 mg	120 FCT	€ 54.11	€ 2.00	€ 3.39	€ 48.72
Capecitabine [5]	150 mg	120 FCT	€ 151.81	€ 2.00	€ 11.11	€ 138.70
Eribulin	0.44 mg	6 SFI	€ 2,429.93	€ 2.00	€ 232.26	€ 2,195.67
Vinorelbine	50 mg	10 CIS	€ 1,424.53	€ 2.00	€ 67.07	€ 1,355.46
Vinorelbine	10 mg	10 CIS	€ 293.98	€ 2.00	€ 13.42	€ 278.56
Docetaxel	160 mg	1 CIS	€ 820.45	€ 2.00	€ 38.40	€ 780.05
	20 mg	1 CIS	€ 112.43	€ 2.00	€ 4.80	€ 105.63
Paclitaxel	300 mg	1 CIS	€ 847.45	€ 2.00	€ 39.68	€ 805.77
	30 mg	1 CIS	€ 94.12	€ 2.00	€ 3.93	€ 88.19
nab-paclitaxel	100 mg	1 PIS	€ 429.33	€ 2.00	€ 19.84	€ 407.49
Doxorubicin [5]	100 mg	1 CIS	€ 285.75	€ 2.00	€ 0.00	€ 283.75
	150 mg	1 SFI	€ 418.32	€ 2.00	€ 0.00	€ 416.32
Pegylated liposomal doxorubicin	20 mg	1 CIS	€ 721.45	€ 2.00	€ 89.87	€ 629.58
	50 mg	1 CIS	€ 1,778.86	€ 2.00	€ 224.69	€ 1,552.17
Eprirubicin	100 mg	1 SFI	€ 300.81	€ 2.00	€ 13.74	€ 285.07
	50 mg	1 SFI	€ 155.41	€ 2.00	€ 6.84	€ 146.57
	10 mg	1 SFI	€ 39.47	€ 2.00	€ 1.34	€ 36.13

Abbreviations:
FCT = film-coated tablets; CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; PIS = powder for the preparation of an infusion suspension; PCI = powder for a concentrate for the preparation of a solution for infusion

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Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

[5] Fixed reimbursement rate

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Cost/ patient/ year
Appropriate comparator therapy							
Paclitaxel							
Dexamethasone[5] 2 x 20 mg	20 TAB x 40 mg	€ 81.55	€ 2.00	€ 0.00	€ 79.55	17.4	€ 69.21
Dimetindene IV 1 mg/10 kg = 6.87 mg	5 x 4 mg SFI	€ 23.67	€ 2.00	€ 5.53	€ 16.14	17.4	€ 112.33
Cimetidine IV 300 mg	10 AMP each 200 mg	€ 19.77	€ 2.00	€ 0.40	€ 17.37	17.4	€ 60.45
Abbreviations: AMP = ampoules; SFI = solution for injection; TAB = tablets							

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Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131, paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs do not add to the pharmacy sales price but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe). The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

2.5 Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with Trastuzumab Deruxtecan

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 6 December 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 31 January 2023, the pharmaceutical company submitted a dossier for the benefit assessment of trastuzumab deruxtecan to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2, sentence 1 VerfO.

By letter dated 3 February 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient trastuzumab deruxtecan.

The dossier assessment by the IQWiG was submitted to the G-BA on 26 April 2023, and the written statement procedure was initiated with publication on the G-BA website on 2 May 2023. The deadline for submitting statements was 23 May 2023.

The oral hearing was held on 5 June 2023.

By letter dated 6 June 2023, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 30 June 2023.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 11 July 2023, and the proposed resolution was approved.

At its session on 20 July 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	06 December 2022	Determination of the appropriate comparator therapy
Working group Section 35a	30 May 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	5 June 2023	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	13 June 2023 20 June 2023 5 July 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	11 July 2023	Concluding discussion of the draft resolution
Plenum	20 July 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 20 July 2023

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken