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 (breast cancer, HER2+, at least 2 prior therapies)

of 2 February 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 online and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient trastuzumab deruxtecan (Enhertu) 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 29 October 2021, the pharmaceutical company submitted an application for postponement of the date for the start of the benefit assessment procedure for trastuzumab deruxtecan in the therapeutic indication in question here after "two or more prior anti-HER2-based regimens" in accordance with Section 35a paragraph 5b SGB V.

In its session on 16 December 2021, the G-BA approved the application pursuant to Section 35a paragraph 5b SGB V and postponed the relevant date for the start of the benefit assessment and the submission of a dossier for the benefit assessment for the therapeutic indication in question to four weeks after the marketing authorisation of the other therapeutic indication of the therapeutic indication covered by the application, at the latest six months after the first relevant date. The marketing authorisation for the other therapeutic indication

covered by the application according to Section 35a paragraph 5b SGB V were granted within the 6-month period.

Trastuzumab deruxtecan received its first marketing authorisation for the therapeutic indication after "two or more prior anti-HER2-based regimens" on 18 January 2022. Thus, in accordance with the resolution of 16 December 2021, the benefit assessment of the active ingredient trastuzumab deruxtecan in this first approved therapeutic indication started at the latest within four weeks after the approval of trastuzumab deruxtecan in the therapeutic indication for the treatment of patients with "unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens", which took place on 11 July 2022, and 6 months after the first relevant date, i.e. at the latest on 1 August 2022.

On 27 July 2022, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient trastuzumab deruxtecan with the therapeutic indication

"Trastuzumab deruxtecan (Enhertu) as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens."

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 November 2022 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

Trastuzumab deruxtecan (Enhertu) as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens.

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

Therapeutic indication of the resolution (resolution of 02.02.2023):

Trastuzumab deruxtecan (Enhertu) as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with HER2-positive unresectable or metastatic breast cancer previously treated with two or more anti-HER2 based therapies

Appropriate comparator therapy for trastuzumab deruxtecan as monotherapy:

- Therapy according to doctor's instructions

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 terms of authorisation status, the cytotoxic chemotherapies 5-fluououracil, capecitabine, cyclophosphamide, docetaxel, doxorubicin, liposomal doxorubicin, epirubicin, Eribulin, gemcitabine, ifosfamide, methotrexate, mitomycin, mitoxantrone, nab-paclitaxel, paclitaxel, vinblastine, vincristine and vinorelbine, as well as HER2-targeted therapies with lapatinib, neratinib, trastuzumab, trastuzumab emtansine and tucatinib are available for the treatment of pretreated unresectable or metastatic HER2-positive breast cancer.

Medicinal products with explicit marketing authorisation for the treatment of hormone-receptor positive breast cancer or for endocrine 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. The following resolutions or guidelines of the G-BA for medical products and non-medicinal treatments are available:

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

- Eribulin: Resolution of 22 January 2015
- Trastuzumab emtansine: Resolution of 19 June 2014
- Tucatinib: Resolution of 2 September 2021

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 therapeutic indication.

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 health care provision.

It is assumed that hormone receptor-positive patients are not (no longer) eligible for endocrine therapy at the time of the treatment decision.

The treatment regimen for unresectable, locally advanced or metastatic breast cancer is largely determined by the HER2 receptor status. In the presence of a HER2-positive tumour status, according to the guidelines, therapy directed against HER2 is regularly recommended as part of adjuvant or first- and second-line therapy. HER2 antibodies (trastuzumab, pertuzumab, trastuzumab emtansine) as well as chemotherapeutic agents from the taxane group and possibly anthracyclines are used in the therapy. For patients with positive hormone receptor status (in addition to HER2-positive receptor status), the aforementioned targeted HER2 therapies are also recommended.

The evidence base for patients previously treated with at least two HER2-targeted regimens is limited.

The S3 guideline "Diagnosis, therapy and follow-up of breast cancer" of the AWMF does not specifically address this treatment setting.

The American Society of Clinical Oncology (ASCO) guideline for the systemic treatment of patients with advanced HER2-positive breast cancer specifically addresses this treatment setting and recommends further treatment based on HER2-targeted therapy. This recommendation, which according to ASCO is based on limited evidence,

is also shared in the statements of the scientific-medical societies on the benefit assessment in the present procedure. Furthermore, the scientific-medical societies state in their statements that no uniform treatment standard can be named with regard to a specific HER2-targeted therapy, since on the one hand there is insufficient evidence for the recommendation of a specific therapy and on the other hand the heterogeneity of the patient collective must also be taken into account.

Thus, several, different therapy options with HER2-targeted therapy are mentioned in the statements of the scientific-medical societies and also in the ASCO guideline. The combination therapies of lapatinib and capecitabine, trastuzumab and lapatinib as well as trastuzumab in combination with other chemotherapeutic agents are primarily or consistently named as treatment options.

In addition, the ASCO guideline and partly also the statements of the scientific-medical societies recommend the anti-HER2 agent trastuzumab emtansine as well as treatment with the anti-HER2 active ingredient pertuzumab for those patients who have not yet received the respective active ingredient in the pre-treatment. However, the patients in the present therapeutic indication of trastuzumab deruxtecan should have previously received at least 2 treatment regimens directed against HER2, which is why it can be assumed that the patients have already regularly received anti-HER2-directed treatment with pertuzumab as well as with trastuzumab emtansine based on the current therapy recommendations and that these therapies no longer represent regular treatment options in the present treatment setting. In addition, pertuzumab in combination with trastuzumab and docetaxel is not approved for this treatment setting.

With regard to trastuzumab in combination with other chemotherapeutic agents, according to the statements of the scientific-medical societies in the benefit assessment procedure of tucatinib, the combination of trastuzumab and the chemotherapeutic agent capecitabine specifically represents a relevant treatment option. In this regard, the scientific-medical societies state that evidence from a randomised study is available for this combination in comparison to lapatinib plus capecitabine (CEREBEL study), that the combination of trastuzumab plus capecitabine is one of the most frequently used therapies in the reality of care and that, in the view of the scientific-medical societies, it also represents, among others, a suitable comparator therapy for new medicinal treatments in the present therapeutic indication.

However, in terms of authorisation status, trastuzumab in combination with capecitabine is not approved. Therefore, there is a discrepancy between medicinal products approved in the indication and those used in health care/ recommended in guidelines.

For tucatinib in combination with trastuzumab and capecitabine, the benefit assessment identified a hint for a major additional benefit compared to trastuzumab and capecitabine (G-BA resolution of 2 September 2021). However, it cannot be concluded from the current overall evidence that tucatinib in combination with trastuzumab and capecitabine can be recommended in preference to the other comparators in the therapeutic indication. The statements of the scientific-medical societies on the benefit assessment in the present procedure also state that there are no uniform therapy recommendations in the named indication area due to the heterogeneity of the patient population and due to the lack of directly comparative studies between effective therapy alternatives.

In summary, a "therapy according to doctor's instructions" is determined as the appropriate comparator therapy. Within the framework of the therapy according to the doctor's instructions, the treatment options

- lapatinib in combination with capecitabine,
- trastuzumab in combination with lapatinib (only for patients with hormone-receptor negative breast cancer),
- trastuzumab in combination with capecitabine and
- tucatinib in combination with trastuzumab and capecitabine

are considered equally suitable comparators.

The additional benefit can be proven compared to one of the therapy options mentioned; usually, this can be done within the framework of a single-comparator study.

The marketing authorisation and dosage specifications in the product information of the active ingredients must be considered; deviations must be justified separately.

However, regarding trastuzumab in combination with capecitabine the possibility of the off-label use of the active ingredients in a clinical study does not allow any conclusions to be drawn about their appropriateness in the off-label use in the standard care of insured persons in the SHI system. Such an assessment would be reserved for the decision according to Section 35c SGB V. This does not affect an off-label prescription in specific cases according to the criteria of the established case law of the Federal Social Court on off-label use not regulated in the Pharmaceuticals Directive.

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

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.

Change of the appropriate comparator therapy

Originally, the appropriate comparator therapy was determined as follows:

- Therapy according to doctor's instructions

Within the framework of the therapy according to the doctor's instructions, the treatment options

- lapatinib in combination with capecitabine,
- trastuzumab in combination with lapatinib (only for patients with hormone-receptor negative breast cancer),
- trastuzumab in combination with capecitabine

are considered equally suitable comparators.

Compared to the original definition of the comparators considered adequate for patients in the designated therapeutic indication in the context of a clinical study, the therapy option tucatinib in combination with trastuzumab and capecitabine is additionally included. This takes into account the current therapy recommendations and the reality of care.

This change to the appropriate comparator therapy has no effects on the present assessment of the additional benefit, nor does it require the benefit assessment to be carried out again.

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 an additional benefit of trastuzumab deruxtecan compared to therapy according to doctor's instructions, the pharmaceutical company has presented results of the still ongoing, open, randomised and controlled, 2-arm phase III study DESTINY-Breast02. As part of the therapy according to doctor's instructions, the study offers a choice of lapatinib in combination with capecitabine or trastuzumab in combination with capecitabine, whereby the choice for one of these combinations must be made before randomisation.

The ongoing study started in September 2018 is being conducted in 187 study sites across Europe, Asia, North and South America and Australia.

The study included adult patients with unresectable or metastatic HER2-positive breast cancer and previous trastuzumab emtansine treatment.

For patients, according to the inclusion criteria, radiological progression must have been documented either during or after the last pre-treatment or within 6 months after completion of adjuvant therapy. In addition, the patients were not allowed to have received any previous treatment with capecitabine. Another prerequisite for enrolment in the study was a general condition according to ECOG-PS of 0 or 1.

A total of 608 patients were included in the study and allocated in a 2:1 randomisation to treatment arms stratified by hormone-receptor status (positive vs negative), previous treatment with pertuzumab (yes vs no) and history of visceral disease (yes vs no).

Patients were treated until disease progression, death or discontinuation for other reasons (e.g., adverse events or patient decision). Around a quarter of patients in the comparator arm switched to treatment with trastuzumab deruxtecan as part of subsequent therapy.

Patients were observed on an endpoint-specific basis, at most until death, withdrawal of consent, lost to follow-up or end of study.
The primary endpoint of the DESTINY-Breast02 study is progression-free survival (PFS). Other secondary endpoints include endpoints in the categories of mortality, morbidity, health-related quality of life and side effects.

For the ongoing DESTINY-Breast02 study, a data cut-off from 30 June 2022 is currently available, which was used for the benefit assessment.

Extent and probability of the additional benefit

Mortality

The overall survival was operationalised in the DESTINY-Breast02 study as the time from randomisation to death from any cause. For the endpoint of overall survival, there is a statistically significant difference to the advantage of trastuzumab deruxtecan compared to therapy according to doctor's instructions. The hereby achieved prolongation of survival time by the treatment with trastuzumab deruxtecan is evaluated as a significant improvement.

For the assessment of the data on overall survival, it must be taken into account that a high proportion of patients were censored within the first year. It is assumed that the reasons for most early censoring are withdrawal of consent or lost to follow-up, because the study for the last included patient has already been running for at least 1.5 years and censoring is only to be expected later due to the data cut-off. In addition, there is a large difference in the censoring percentages due to withdrawal of consent or lost to follow-up contact termination between the treatment arms in that this censoring percentage is significantly larger in the control group than in the intervention group.

In addition, about 30 % of the patients in the comparator arm received trastuzumab deruxtecan as a subsequent antineoplastic therapy in the sense of treatment switching. For the patients who changed therapy, there is no information on the time of the change and no information on the reasons for the change.

Morbidity

Progression-free survival

Progression-free survival (PFS) is the primary endpoint of the DESTINY-Breast02 study. PFS was defined as the time from randomisation to the earliest of the first objective documentation of radiological tumour progression according to RECIST version 1.1 or the patient's death regardless of the cause of death - whichever occurred earlier.

There was a statistically significant difference between the treatment arms to the advantage of trastuzumab deruxtecan.

The PFS endpoint is a combined endpoint composed of endpoints of the categories "mortality" and "morbidity". The endpoint component "mortality" has already been assessed as an independent endpoint via the endpoint "overall survival". The morbidity component "disease progression" was assessed solely by means of imaging procedures (radiologically determined disease progression according to the RECIST criteria). Thus, morbidity is not primarily assessed based on disease symptoms but solely based on asymptomatic findings that are not directly relevant to the patient.

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 additional benefit remains unaffected.

Symptomatology (collected using EORTC QLQ-C30 and EORTC QLQ-BR23)

Disease symptomatology were assessed in the DESTINY-Breast02 study using the cancer-specific questionnaire EORTC QLQ-C30 and the breast cancer-specific additional module EORTC QLQ-BR23 for the period of treatment with the study medication, plus 40 days and plus an additional 3 months.

The pharmaceutical company submits responder analyses for the proportion of patients with a change of ≥ 10 points and ≥ 15 points each 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 to be presented in the dossier.

With regard to confirmed deterioration, confirmation was operationalised in the DESTINY-Breast02 study such that deterioration was considered confirmed if it was observed on two or more consecutive visits or occurred at the last assessment.

In the study, no data is available on the actual duration of observation for the endpoint symptomatology. The different observation periods for the patient-reported symptomatology

endpoints can be estimated from the large differences in treatment duration, which is more than twice as long in the intervention arm as in the control arm. Furthermore, in the DESTINY-Breast02 study, the questionnaire responses in the comparator arm dropped sharply after only a few observation periods. It is also problematic that the study counted a single deterioration that occurred at the last survey as a confirmed deterioration. There is no information available on how many patients were found to have deteriorated at the last survey time point or how these cases are distributed between the treatment arms. In this situation, potentially a confirmed deterioration in the intervention arm is contrasted with a single deterioration in the comparator arm.

Although both operationalisations ("time to first deterioration" and "time to confirmed deterioration") are considered patient-relevant, the time-to-event analysis for the first deterioration is used against the background of the uncertainties described for the confirmed deterioration, since the evaluations for the confirmed deterioration cannot be interpreted meaningfully.

When analysing time to first deterioration by ≥ 10 points, there is a statistically significant difference between the treatment groups for the endpoints pain, insomnia, diarrhoea, chest symptoms and arm symptoms to the advantage of trastuzumab deruxtecan. For the endpoints nausea and vomiting as well as constipation, there were statistically significant differences between the treatment arms to the disadvantage of trastuzumab deruxtecan. No usable 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, there is an advantage of trastuzumab deruxtecan with regard to symptomatology.

Health status (assessed by EQ-5D VAS)

Health status will be assessed in the DESTINY-Breast02 study using the EQ-5D visual analogue scale (VAS) for the period of treatment with the study medication plus 40 days plus an additional 3 months.

The pharmaceutical company shall submit responder analyses for the endpoint of health status operationalised as time to first deterioration or to confirmed deterioration by ≥ 15 points.

For the present assessment, the evaluations on the responder threshold of 15 points are used to assess the effects on health status.

The results for time to confirmed deterioration are classified as potentially highly biased due to the uncertainties described under the comments on symptomatology. Therefore, the analyses for time to first deterioration are used for the endpoint of health status.

This evaluation shows a statistically significant difference between the treatment arms to the advantage of trastuzumab deruxtecan.

This advantage is considered to be a significant improvement in health status due to treatment with trastuzumab deruxtecan compared to therapy according to doctor's instructions.

<u>Quality of life (collected using EORTC QLQ-C30 and EORTC QLQ-BR23)</u>

Health-related quality of life was assessed in the DESTINY-Breast02 study using the functional scales and the global health status scale of the cancer-specific questionnaire EORTC QLQ-C30 and the breast cancer-specific additional module EORTC QLQ-BR23 for the period of treatment with the study medication plus 40 days and plus an additional 3 months.

The pharmaceutical company submits evaluations for the "time to first deterioration" and for the "time to deterioration confirmed several times" by ≥ 10 points or ≥ 15 points.

For the EORTC questionnaires, only evaluations for the response criterion 10 points are to be presented in the dossier.

For the endpoint of health-related quality of life, the analyses of the "time to first deterioration" are also used in accordance with the above comments on symptomatology.

Analyses of "time to first deterioration" by ≥ 10 points showed statistically significant differences between the treatment arms for the endpoints of global health status, physical functioning, role functioning, cognitive functioning and social functioning, each to the benefit of trastuzumab deruxtecan. No usable data are available for the endpoint of sex pleasure. For the endpoints of emotional functioning, body image, sexual activity and future perspective, there was no statistically significant difference between the treatment arms.

In the overall consideration of the results, an advantage of trastuzumab deruxtecan compared to the therapy according to doctor's instructions is determined for the health-related quality of life.

Side effects

Adverse events (AEs) in total

In the DESTINY-Breast02 study almost all randomised patients experienced at least one adverse event. The results were only presented additionally.

Serious adverse events (SAE)

For the endpoint of serious adverse event, the DESTINY-Breast02 study shows a statistically significant difference between treatment arms to the advantage of trastuzumab deruxtecan. In view of the only marginally statistically significant difference and similar absolute numbers of events in the comparator groups, only minor relevance is attributed to this result.

Severe AEs (CTCAE grade ≥ 3), discontinuation due to AEs

For the endpoints of severe AEs (CTCAE ≥ 3) and discontinuation due to AEs, there was no statistically significant difference between the treatment arms.

Specific adverse events

For the endpoints of diarrhoea (severe AEs) and palmar-plantar erythrodysesthesia syndrome (severe AEs), stomatitis (AEs) and rash (AEs), there were statistically significant differences between the treatment arms in favour of trastuzumab deruxtecan.

For the endpoints of asthenia (severe AE), fatigue (severe AE), leukopenia (severe AE) and neutropenia (severe AE), there were statistically significant differences between the treatment arms to the disadvantage of trastuzumab deruxtecan.

With regard to specific adverse events, positive and negative effects of trastuzumab deruxtecan are available in detail, so that no relevant difference can be determined overall.

In the overall assessment of the results on side effects, there are no relevant difference for the benefit assessment between the treatment arms.

Overall assessment

For the assessment of the additional benefit of trastuzumab deruxtecan for the treatment of unresectable or metastatic HER2-positive breast cancer in adult patients who have already

received at least two or more prior anti-HER2-based regimens, results are available from the randomised, controlled, open-label, DESTINY-Breast02 study on the endpoint categories mortality, morbidity, health-related quality of life and side effects compared to therapy according to doctor's instructions. As part of the therapy according to the doctor's instructions, the study offers a choice of lapatinib in combination with capecitabine or trastuzumab in combination with capecitabine.

In the endpoint category mortality, the endpoint overall survival shows a statistically significant prolongation of survival time through treatment with trastuzumab deruxtecan compared to therapy according to doctor's instructions, which is assessed as a significant improvement.

In the morbidity category, an advantage for the treatment with trastuzumab deruxtecan can be determined for the endpoint health status, which is evaluated as a significant improvement in health status. With regard to symptomatology, treatment with trastuzumab deruxtecan has positive effects on the endpoints pain, insomnia, diarrhoea, chest symptoms and arm symptoms and negative effects on the endpoints "nausea and vomiting" and constipation. Overall, there is an advantage of trastuzumab deruxtecan with regard to symptomatology.

For health-related quality of life, there is also an advantage of trastuzumab deruxtecan compared to therapy according to the doctor's instructions.

In the overall assessment of the results on side effects, there are no relevant difference for the benefit assessment between the treatment arms.

In the overall assessment, the G-BA comes to the conclusion that, in particular due to the extent of the prolongation of survival and in view of the positive effects on morbidity and quality of life, there is a considerable additional benefit for trastuzumab deruxtecan in the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have already received at least two or more prior anti-HER2-based regimens compared to a therapy according to doctor's instructions.

Reliability of data (probability of additional benefit)

This benefit assessment is based on the results of the ongoing, open-label, randomised DESTINY-Breast02 study. The risk of bias at the study level is rated as low.

With regard to the assessment of the risk of bias for the endpoint overall survival, the high proportion of patients who were censored within the first year must be taken into account. It is assumed that most early censoring is due to withdrawal of consent or lost to follow-up. There is a relevant difference between the treatment groups, specifically the percentage of censoring in the control group is greater than in the intervention group. In the control group, approx. 26 % of the patients also received trastuzumab deruxtecan as a subsequent antineoplastic therapy in the sense of treatment switching. Although there is no information in the dossier on the times at which the patients switched therapy and the reasons for the switch, this data constellation can be seen as a hint that a proportion of patients from the control group wanted to switch to treatment with trastuzumab deruxtecan in the course of the unblinded study and that this also results in a difference in the censoring percentages. This results in uncertainty, which, even taking into account the effect magnitude in the endpoint of overall survival, is not considered to be so serious that a high risk of bias can be assumed.

Due to the open study design and the resulting lack of blinding in the case of subjective endpoint assessment, the endpoints on morbidity and health-related quality of life are classified as highly biased.

In summary, the G-BA derives an indication for the identified additional benefit with regard to the significance.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Enhertu with the active ingredient trastuzumab deruxtecan.

Enhertu was approved under special conditions.

Trastuzumab deruxtecan is approved as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens.

The therapeutic indication assessed here is as follows:

Trastuzumab deruxtecan as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens.

The appropriate comparator therapy was determined to be a therapy according to doctor's instructions. In the context of therapy according to doctor's instructions, the treatment options lapatinib in combination with capecitabine, lapatinib in combination with trastuzumab (only for patients with hormone receptor-negative breast cancer), trastuzumab in combination with capecitabine and tucatinib in combination with trastuzumab and capecitabine were named as suitable comparators.

For the benefit assessment, the pharmaceutical company submits the results of the still ongoing, open-label, randomised and controlled phase III DESTINY-Breast02 study.

In the endpoint category mortality, the endpoint overall survival shows a statistically significant prolongation of survival time through treatment with trastuzumab deruxtecan compared to therapy according to doctor's instructions, which is assessed as a significant improvement.

In the morbidity category, an advantage for the treatment with trastuzumab deruxtecan can be determined for the endpoint health status, which is evaluated as a significant improvement in health status. Overall, there is an advantage of trastuzumab deruxtecan with regard to symptomatology.

For health-related quality of life, there is also an advantage of trastuzumab deruxtecan compared to therapy according to the doctor's instructions.

In the overall assessment of the results on side effects, there are no relevant difference for the benefit assessment between the treatment arms.

In the overall assessment, the G-BA comes to the conclusion that, in particular due to the extent of the prolongation of survival time and in view of the positive effects on morbidity and quality of life, there is a considerable additional benefit for trastuzumab deruxtecan in the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have already received at least two or more prior anti-HER2-based regimens compared to a therapy according to doctor's instructions.

The significance is rated as indication.

As a result, the G-BA found an indication of a considerable additional benefit of trastuzumab deruxtecan compared with the appropriate comparator therapy.

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 patient numbers derived by the pharmaceutical company in the dossier are an underestimate. This is due in particular to the possible deviation of the proportion values for staging, to the uncertainty of the progression proportions due to over- and underestimating aspects, to uncertain proportion values for unresectable breast cancer, which are based on outdated data, to the uncertainty of the transferability of a mathematically incomprehensible HER2 positivity rate without staging restriction to metastatic or unresectable breast cancer, proportion values for the receipt of third-line therapy that refer to a deviating population, the inclusion of only incidental instead of prevalent patients and the incomprehensible reduction of the lower limit to 1 patient for the year under review.

Due to the significantly underestimated range of patient numbers by the pharmaceutical company, the G-BA refers to the derivation of the target population in a similar therapeutic indication used as a basis in the resolution on the benefit assessment of tucatinib (resolution of 2 September 2021). The present therapeutic indication differs from present therapeutic indication only formally in that it relates to patients with unresectable or metastatic breast cancer, whereas the therapeutic indication for tucatinib relates to patients with locally advanced or metastatic breast cancer.

The range of patients stated in the resolution on tucatinib (approx. 1,350 to 1,640 patients) was already assessed as an underestimate, so that the range stated by the pharmaceutical company in the present area of application (approx. 1 to 1,530 patients) is even more of an underestimate. Thus, the higher range of approx. 1,350 to 1,640 patients is estimated for the SHI target population in the present procedure.

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: 21 November 2022):

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, obstetrics and gynaecology, and specialists participating in the Oncology Agreement are experienced in the treatment of adults with breast cancer.

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: 15 January 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.

The information on dosages refers to applications in women, as breast cancer is relatively rare in men. For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body weight of adult women: 68.7 kg)2.

Trastuzumab

The data on trastuzumab is based on the intravenous (IV) application.

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				
Therapy according to doctor's instructions[a]				
Lapatinib in combination with capecitabine				
Lapatinib	1 x daily	365	1	365
Capecitabine	on day 1-14 of a 21 day cycle, 2 x day	17.4	14	243.6
Lapatinib in combination with trastuzumab (only for patients with hormone-receptor negative breast cancer)				
Lapatinib	1 x daily	365	1	365
Trastuzumab	1 x every 7 days	52.1	1	52.1
Tucatinib in combination with capecitabine and trastuzumab				
Tucatinib	2 x daily	365	1	365
Capecitabine	on day 1-14 of a 21 day cycle, 2 x day	17.4	14	243.6

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Trastuzumab	1 x every 21 days	17.4	1	17.4
[a] Only costs for lapatinib in combination with capecitabine, lapatinib in combination with trastuzumab and tucatinib in combination with capecitabine and trastuzumab are shown. In addition, trastuzumab in combination with cepacitabine represents a suitable comparator for the present benefit assessment in the context of therapy according to doctor's instructions. However, this medicinal treatment is not approved in the present therapeutic indication and therefore no costs are presented for these medicinal products.				

Consumption:

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					
Therapy according to doctor's instructions[a]					
Lapatinib in combination with capecitabine					
Lapatinib	1250 mg	1250 mg	5 x 250 mg	365	1825 x 250 mg
Capecitabine	1000 mg/m² = 1760 mg	3500 mg	4 x 500 mg +	243.6	974.4 x 500 mg +
			4 x 300 mg +		974.4 x 300 mg +
			2 x 150 mg		487.2 x 150 mg
Lapatinib in combination with trastuzumab (only for patients with hormone-receptor negative breast cancer)					
Lapatinib	1000 mg	1000 mg	4 x 250 mg	365	1460 x 250 mg
Trastuzumab	In cycle 1: 4 mg /kg = 274.8 mg	274.8 mg	2 x 150 mg	52.1	53.1 x 150 mg
	From cycle 2 onwards: 2 mg /kg = 137.4 mg	137.4 mg	1 x 150 mg		
Tucatinib in combination with capecitabine and trastuzumab					
Tucatinib	300 mg	600 mg	4 x 150 mg	365	1460 x 150 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Capecitabine	1000 mg/m² = 1760 mg	3500 mg	4 x 500 mg +	243.6	974.4 x 500 mg +
			4 x 300 mg +		974.4 x 300 mg +
			2 x 150 mg		487.2 x 150 mg
Trastuzumab	Cycle 1: 8 mg/kg	549.6 mg	1 x 420 mg + 1 x 150 mg	17.4	1 x 420 mg + 1 x 150 mg
	from cycle 2 onwards: 6 mg/kg	412.2 mg	1 x 420 mg		16.4 x 420 mg

[a] Only costs for lapatinib in combination with capecitabine, lapatinib in combination with trastuzumab and tucatinib in combination with capecitabine and trastuzumab are shown. In addition, trastuzumab in combination with capecitabine represents a suitable comparator for the present benefit assessment in the context of therapy according to doctor's instructions. However, this medicinal treatment is not approved in the present therapeutic indication and therefore no costs are presented for these medicinal products.

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	1 PIC	€ 2,405.72	€ 1.77	€ 229.89	€ 2,174.06
Appropriate comparator therapy					
Capecitabine 500 mg[2]	120 FCT	€ 151.81	€ 1.77	€ 11.11	€ 138.93
Capecitabine 300 mg[2]	30 FCT	€ 36.33	€ 1.77	€ 0	€ 34.56
Capecitabine 150 mg[2]	120 FCT	€ 54.11	€ 1.77	€ 3.39	€ 48.95
Lapatinib 250 mg	70 FCT	€ 1722.73	€ 1.77	€ 178.65	€ 1542.31
Trastuzumab 420 mg	1 PIC	€ 2216.18	€ 2.00	€ 211.33	€ 2002.85
Trastuzumab 150 mg	1 SFI	€ 798.19	€ 1.77	€ 74.69	€ 721.73
Tucatinib 150 mg	84 FCT	€ 5077.79	€ 1.77	€ 491.49	€ 4584.53
Abbreviations: FCT = film-coated tablets, PIC = powder for the preparation of an infusion solution concentrate					

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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.

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.

Because there are no 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, no costs for additionally required SHI services had to be taken into account.

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 € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71

[2] Fixed reimbursement rate

per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the 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 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 Federal Joint Committee shall designate 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.

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 23 March 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 26 October 2021.

On 27 July 2022, 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 1, sentence 2 VerfO.

By letter dated 29 July 2022 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 27 October 2022, and the written statement procedure was initiated with publication on the G-BA website on 1 November 2022. The deadline for submitting written statements was 22 November 2022.

The oral hearing was held on 19 December 2022.

By letter dated 6 December 2022, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 13 January 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 24 January 2023, and the proposed resolution was approved.

At its session on 2 February 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	23 March 2021	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	26 October 2021	New implementation of the appropriate comparator therapy
Working group Section 35a	29 November 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	19 December 2022	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	3 January 2023 17 January 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	24 January 2023	Concluding discussion of the draft resolution
Plenum	2 February 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 2 February 2023

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

Prof. Hecken