Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Tucatinib (breast cancer, HER2-positive, at least 2 prior therapies, combination with trastuzumab and capecitabine)

of 2 September 2021

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 studies 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 benefits,
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. Costs of therapy for the statutory health insurance,
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 forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the (German) market of the combination of active ingredient tucatinib in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 March 2021. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 12 March 2021.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de), on 15 June 2021, thus initiating the written statement procedure. In addition, an oral hearing was also held.

The G-BA came to a resolution on whether an additional benefit of tucatinib 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 addenda 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 tucatinib.

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 tucatinib (Tukysa) in accordance with the product information

TUKYSA is indicated in combination with trastuzumab and capecitabine for the treatment of adult patients with HER2-positive locally advanced or metastatic breast cancer who have received at least 2 prior anti-HER2 treatment regimens.

Therapeutic indication of the resolution (resolution from the 2 September 2021):

see approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with HER2-positive locally advanced or metastatic breast cancer who have received at least 2 prior anti-HER2 treatment regimens

Appropriate comparator therapy for tucatinib in combination with trastuzumab and capecitabine:

- 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

1 General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2. If a non-medicinal treatment is considered 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 Federal Joint Committee has already determined the patient-relevant benefit shall be preferred.
4. The comparative therapy should be part of the appropriate therapy in the therapeutic indication according to the generally accepted state of medical knowledge.

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

on 1. In terms of authorisation status, the following active ingredients are available for the treatment of pre-treated HER2-positive locally advanced unresectable or metastatic breast cancer: 5-fluorouracil, capecitabine, cyclophosphamide, docetaxel, doxorubicin, doxorubicin (liposomal), epirubicin, eribulin, gemcitabine, ifosfamide, methotrexate, mitomycin, mitoxantrone, paclitaxel, nab-paclitaxel, vinblastine, vincristine, vinorelbine, lapatinib, trastuzumab and trastuzumab emtansine. Regarding the respective application requirements in relation to the prior therapies, restrictions may arise in relation to the present therapeutic indication, which is the subject of the assessment.

Medicinal products with explicit marketing authorisation for the treatment of hormone-receptor positive breast cancer or endocrine therapy were not included.

on 2. Radiotherapy is generally considered 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 aim.

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

Annex VI to Section K of the Medicinal Products Guideline - Active ingredients that are not prescribable in off-label uses; last revised 17 October 2019:

- Gemcitabine in monotherapy for female breast cancer

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

- Proton therapy for breast cancer

on 4. The general state of medical knowledge, on which the finding of the G-BA is based, was illustrated by systematic research for guidelines as well as reviews of clinical studies in the present therapeutic indication.

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 (or no longer) eligible for endocrine therapy at the time of the treatment decision.

The evidence on treatment options for men with breast cancer is extremely limited. According to the guidelines, the recommendations for the treatment of men are predominantly based on the recommendations for the treatment of women.

The HER2 receptor status largely determines the treatment concept of locally advanced unresectable or metastatic breast cancer. In the presence of HER2-positive tumour status, the guidelines normally recommend therapy directed against HER2 in the context of adjuvant or first- and second-line therapy. HER2 antibodies (trastuzumab, pertuzumab, trastuzumab emtansin) and chemotherapeutic agents of 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 subsequent lines of therapy, i.e. 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 therapy situation.

The American Society of Clinical Oncology (ASCO) guideline for the systemic treatment of patients with advanced HER2-positive breast cancer specifically addresses this therapy situation and recommends further treatment based on HER2-targeted therapy. According to ASCO, this recommendation is based on limited evidence, is also unanimously shared in the statements of the scientific-medical societies on the benefit assessment in the present procedure. As already stated in the ASCO guideline, the scientific-medical societies also state in their statements that no uniform standard of treatment can be named concerning a specific HER2-targeted therapy, since on the one hand, there is insufficient evidence for the recommendation of specific therapy, and on the other hand the heterogeneity of the patient population must also be taken into account.

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

In addition, in the ASCO guideline and partly also in the statements of the scientific-medical societies, the anti-HER2 agent trastuzumab emtansine as well as treatment with the anti-HER2 agent pertuzumab is recommended for those patients who have not yet received the respective active ingredient in the pre-treatment. However, patients in the present therapeutic indication of tucatinib are expected to have received at least 2 prior anti-HER2 treatment regimens, so it can be assumed that patients have already received regular anti-HER2 treatment with both pertuzumab and trastuzumab emtansine based on current treatment recommendations and that these therapies no longer represent regular treatment options in the present therapy situation. In addition, pertuzumab in combination with trastuzumab and docetaxel is not approved in the present therapeutic indication of tucatinib.

About trastuzumab in combination with other chemotherapeutic agents, the combination of trastuzumab and the chemotherapeutic agent capecitabine represents a relevant treatment option according to the statements of the scientific-medical societies. In this regard, the scientific-medical societies state that evidence is available for this combination from a randomised study 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 medical care and that, in the view of the professional societies, it also represents, among others, a suitable comparative therapy for new medicinal products therapies in the present therapeutic indication.

In the product information of lapatinib (invented name: Tyverb) is stated in section 4.4 "Special warnings and precautions for use": "Data have shown that Tyverb combined with chemotherapy is less effective than trastuzumab when
ombined with chemotherapy." Section 5.1 presents the results of the CEREBEL randomised study of lapatinib plus capecitabine compared with trastuzumab plus capecitabine.

About the authorisation status of the medicinal products, lapatinib in combination with capecitabine and lapatinib in combination with trastuzumab are approved in the present therapeutic indication. The combination of trastuzumab plus capecitabine is not approved for use in the present therapeutic indication. There is a discrepancy between medicinal therapies approved in the therapeutic indications and those recommended by guidelines or used in care.

For these reasons, the G-BA considers it appropriate to recognise the combination of trastuzumab plus capecitabine as a further suitable comparator for demonstrating an additional benefit, although this is not approved in the present therapeutic indication according to the authorisation status of the medicinal products.

Thus, 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 are

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

are considered to be equally suitable comparators.

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

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

Change of the appropriate comparator therapy

Originally, the appropriate comparator therapy was determined as follows:

- Lapatinib in combination with capecitabine

  or
- Lapatinib in combination with trastuzumab (only for patients with hormone-receptor negative breast cancer)

The determination of therapy according to the doctor's instructions as an appropriate comparator therapy considers that other treatment options in the therapeutic indication under consideration are recommended in guidelines and are used in health care. In particular, this considers the scientific-medical societies' statements on the reality of care and on the current therapy recommendations submitted in the benefit assessment procedure.

This change in the appropriate comparator therapy means that the results of the HER2CLIMB study presented by the pharmaceutical company in the dossier can be used for the present assessment. The HER2CLIMB study was assessed in the addendum prepared by IQWiG. In addition, the results of the HER2CLIMB study were the subject of the statements, which is why the change in the appropriate comparator therapy does not require a new benefit assessment procedure.

2.1.3 Extent and probability of the additional benefit

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

Adult patients with HER2-positive locally advanced or metastatic breast cancer who have received at least 2 prior anti-HER2 treatment regimens

A hint of a considerable additional benefit

Justification:

For the proof of the additional benefit of tucatinib in combination with trastuzumab and capecitabine compared to trastuzumab and capecitabine, the pharmaceutical company presented results from the ongoing double-blind, randomised controlled study HER2CLIMB.

The study included adult patients with metastatic or unresectable advanced HER2-positive breast cancer that was progressive after the last systemic therapy.

Patients with brain metastases were eligible for inclusion if the brain metastases were untreated and did not require immediate local therapy or if the brain metastases had already been treated locally and were either stable or progressive during the screening period without a renewed indication for immediate therapy.

Another requirement for study enrolment was a general condition according to ECOG-PS of 0 or 1.

A total of 612 patients were enrolled in the study and assigned to treatment arms in a 2:1 randomisation. 410 patients were randomly assigned to the intervention arm and 202 patients to the comparator arm. This was stratified by history or baseline brain metastases (yes vs no), ECOG-PS (0 vs 1), and region (US vs Canada vs rest of the world).

Patients were treated until disease progression, the occurrence of unacceptable toxicity, withdrawal of consent, or death. A switch from the comparator arm to therapy with tucatinib was possible after the primary data cut-off of 04.09.2021 and subsequent unblinding.

Patients were followed endpoint-specifically, maximally until death, withdrawal of consent, or end of the study.

The primary endpoint of the HER2CLIMB study was progression-free survival. Secondary patient-specific endpoints were assessed in the categories of mortality, morbidity and side effects.

For the HER2CLIMB study, analyses are available for the following data cut-offs:

- 1. Data cut-offs from 04.09.2019: analysis of the primary endpoint progression-free survival predefined in the study protocol
- 2. Data cut-off from 08.11.2019: unplanned analysis of safety endpoints at the request of the European Medicines Agency
- 3. Data cut-off from 29.05.2020: unplanned analysis of safety endpoints at the request of the European Medicines Agency
- 4. Data cut-off of 08.02.2021: final analysis predefined in the statistical analysis plan for overall survival after approximately 361 events.

For the evaluation of the HER2CLIMB study, only the 1st data cut-off of 04.09.2019 is used, as complete evaluations are only available for this data cut-off. The pharmaceutical company does not present evaluations for the 2nd data cut-off from 08.11.2019. For the 3rd data cut-off of 29.05.2020, the company only presents evaluations on adverse events (AEs) in the dossier. In the evaluations submitted with its statements on the 4th data cut-off from 08.02.2021 missing results on AE overall rates without progression events, on specific AEs, subgroup analyses on AEs as well as Kaplan-Meier curves on time-to-event analysis.

Extent and probability of the additional benefit

Mortality

Overall survival was one of the secondary efficacy endpoints in the HER2CLIMB study and was defined as the time between randomisation and death from any cause.

Overall survival was statistically significantly prolonged in the tucatinib + trastuzumab + capecitabine treatment group compared with the control group (trastuzumab + capecitabine) at the 04.09.2019 data cut-off.

Treatment with tucatinib + trastuzumab + capecitabine shows a prolongation of survival compared to treatment with trastuzumab + capecitabine, which is assessed as a significant improvement.

Morbidity

Progression-free survival

Progression-free survival (PFS) was the endpoint in the HER2CLIMB study. It was defined as the time between randomisation and the time of first disease progression or death from any cause, whichever occurred earlier. Disease progression was assessed according to the RECIST criteria v1.1.

PFS was statistically significantly prolonged in the tucatinib + trastuzumab + capecitabine treatment group compared with the control group.

The PFS endpoint is a combined endpoint composed of endpoints of the Mortality and Morbidity categories. The endpoint component "Mortality" was collected in the HER2CLIMB study via the endpoint "overall survival" as an independent endpoint. The morbidity component "Disease progression" was assessed solely employing 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 patient-relevant.

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.

Health status (EQ-5D VAS)

In the HER2CLIMB study, health status was assessed using the EQ-5D VAS questionnaire.

Only patients included in the study from protocol version 7 onwards are included in the evaluations submitted by the pharmaceutical company for the endpoint health status (EQ-5D VAS). These evaluations included 217 (52.9%) patients in the intervention arm and 112 (55.4%) patients in the comparator arm. It is assumed that the populations randomised before or from protocol version 7 onward do not differ significantly. The results for the endpoint health status are therefore transferable to the entire study population.

In the dossier, the pharmaceutical company presented responder analyses operationalised as the time to first deterioration, defined as a decrease in score by ≥ 7 points and ≥ 10 points compared with baseline. These responder analyses are used for the benefit assessment.

For patients in the HER2CLIMB study, there was no statistically significant difference between treatment groups for both a ≥ 7 point and ≥ 10 point decrease in score.

Thus, concerning the endpoint health status, there is neither an advantage nor a disadvantage for tucatinib in combination with trastuzumab and capecitabine.

Quality of life

No data on health-related quality of life were collected in the HER2CLIMB study.

Side effects

Adverse events

In the HER2CLIMB study, 99.3% of patients experienced an adverse event in the intervention arm. In the comparator arm, this was 97.0% of patients. The results for the endpoint Total adverse events are only presented additionally.

SAEs, severe AEs (CTCAE grade ≥ 3), discontinuation due to AEs

There was no statistically significant difference between the treatment groups for the endpoints SAEs, severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs.

Specific AE

In detail, the specific AEs show an advantage in the endpoint "dyspnoea" (PT, severe AEs [CTCAE grade ≥ 3]), which is offset by a disadvantage in other specific AEs.

Disadvantages are evident in the endpoints "gastrointestinal disorders" (system organ class [SOC], AEs) and the endpoint "diarrhoea" contained therein (preferred term [PT], AEs) and for the endpoints "alanine aminotransferase elevated" (PT, severe AEs [CTCAE grade ≥ 3]) and "aspartate aminotransferase elevated" (PT, severe AEs [CTCAE grade ≥ 3])

In the overall assessment of the endpoint category side effects, neither an advantage nor a disadvantage can be identified for tucatinib + trastuzumab + capecitabine compared to trastuzumab + capecitabine. There are statistically significant differences only in the specific adverse events. There are both advantages and disadvantages for tucatinib + trastuzumab + capecitabine compared to trastuzumab + capecitabine.

Overall assessment

For the evaluation of the additional benefit of tucatinib + trastuzumab + capecitabine versus trastuzumab + capecitabine in the treatment of patients with HER2-positive, locally advanced or metastatic breast cancer who have received at least two prior HER2-targeted therapy regimens, results on mortality (overall survival), morbidity (health status) and side effects available from the ongoing, double-blind, randomised controlled HER2CLIMB study.

In the endpoint category mortality, the present results for the endpoint overall survival show a statistically significant prolongation of survival of treatment with tucatinib + trastuzumab + capecitabine compared to trastuzumab + capecitabine, which is assessed as a significant improvement.

For the endpoint category morbidity, neither positive nor negative effects of treatment with tucatinib + trastuzumab + capecitabine compared to treatment with trastuzumab + capecitabine were found for the endpoint health status.

No data are available regarding health-related quality of life, as health-related quality of life was not assessed in the HER2CLIMB study.

About side effects, neither an advantage nor a disadvantage can be identified for tucatinib + trastuzumab + capecitabine compared to trastuzumab + capecitabine. There are statistically significant differences in specific adverse events alone, demonstrating both an advantage and disadvantages.

In the overall consideration of the present results on the patient-relevant endpoints, the advantage in overall survival is not offset by any disadvantages in morbidity and side effects.

The G-BA concluded that tucatinib + trastuzumab + capecitabine for treating patients with HER2-positive, locally advanced or metastatic breast cancer who have received at least two prior HER2-targeted therapy regimens, provides considerable additional benefit compared to the appropriate comparator therapy.

Reliability of data (probability of additional benefit)

The present benefit assessment is based on the results of the ongoing, double-blind, randomised and controlled phase 2 study HER2CLIMB.

Since the benefit assessment is based on the results of only one study, only indications of an additional benefit can be derived concerning the reliability of data.

The risk of bias at study level and at endpoint level for overall survival is rated as low.

No data on disease-specific symptomatology are available from the HER2CLIMB study. Thus, it is not possible to assess the effect on the symptomatology of tucatinib in combination with trastuzumab and capecitabine compared to trastuzumab and capecitabine. Furthermore, it

cannot be assessed to what extent the positive effect on overall survival also corresponds to corresponding effects on symptomatology.

In addition, no data on health-related quality of life are available from the HER2CLIMB study. Thus, it cannot be assessed to what extent therapy with tucatinib in combination with trastuzumab and capecitabine impacts patients' quality of life compared to trastuzumab and capecitabine. Data on health-related quality of life are of great importance, especially in the palliative therapy situation with advanced disease.

The reliability of data on the adverse event categories SAEs, severe AEs (CTCAE grade 3 or 4) is assessed as high, on the endpoint discontinuation due to AEs assessed as limited due to possible competing events (reasons for discontinuation other than AEs with different treatment and observation durations).

Overall, these limitations lead to the reliability of data on the additional benefit being classified as "hint".

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Tukysa in combination with trastuzumab and capecitabine.

Tukysa is approved in combination with trastuzumab and capecitabine for the treatment of adult patients with HER2-positive locally advanced or metastatic breast cancer who have received at least 2 prior anti-HER2 treatment regimens.

The appropriate comparator therapy was determined to be a therapy according to the doctor's instructions.

In the context of treatment, according to the 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) and trastuzumab in combination with capecitabine were designated as suitable comparators.

For the benefit assessment, the pharmaceutical company submits the results of the still ongoing, double-blind randomised and controlled study HER2CLIMB.

In the endpoint category mortality, the present results for the endpoint overall survival show a statistically significant prolongation of survival of treatment with tucatinib + trastuzumab + capecitabine compared to trastuzumab + capecitabine, which is assessed as a significant improvement.

For the endpoint category morbidity, neither positive nor negative effects of treatment with tucatinib + trastuzumab + capecitabine compared to treatment with trastuzumab + capecitabine were found for the endpoint health status.

No data are available regarding health-related quality of life, as no data on health-related quality of life were collected in the HER2CLIMB study.

About side effects, neither an advantage nor a disadvantage can be identified for tucatinib + trastuzumab + capecitabine compared to trastuzumab + capecitabine. There are statistically significant differences in specific adverse events alone, demonstrating both an advantage and disadvantages.

In the overall consideration of the present results on the patient-relevant endpoints, the advantage in overall survival is not offset by any disadvantages in morbidity and side effects.

The G-BA concluded that tucatinib + trastuzumab + capecitabine for treating patients with HER2-positive, locally advanced or metastatic breast cancer who have received at least two prior HER2-targeted therapy regimens provides considerable additional benefit compared to the appropriate comparator therapy.

No data on disease-specific symptomatology and health-related quality of life are available from the HER2CLIMB study. Overall, these limitations lead to the reliability of data regarding the additional benefit being classified as "hint".

As a result, the G-BA found hint of considerable additional benefit for tucatinib in combination with trastuzumab and capecitabine 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 number of patients in the SHI target population calculated by the company in the present study is underestimated because patients diagnosed before the period under review and patients with advanced breast cancer were not included, and it is unclear whether all patients with metastases were included. In addition, an underestimation of the patient numbers results from the fact that, about the setting of the upper limit, on the one hand, only patients were included who had not previously been diagnosed with metastases for at least 1 year and, on the other hand, patients in the target population were potentially excluded by setting the individual follow-up period to 3 years.

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 Tukysa (active ingredient: tucatinib) at the following publicly accessible link (last access: 2 June 2021):

https://www.ema.europa.eu/documents/product-information/tukysa-epar-product-information_de.pdf

Treatment with tucatinib should only be initiated and monitored by specialists in internal medicine, haematology, oncology, obstetrics and gynaecology, and specialists participating in the Oncology Agreement are experienced in treating adults with breast cancer.

2.4 Treatment costs

The treatment costs are based on the product information and the information in the LAUER-TAXE® (last revised: 15 August 2021).

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 is patient-individual 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 the maximum treatment duration, if specified in the product information.

For dosages depending on body weight or body surface, the average body measurements of adult women were applied (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).[2]

Trastuzumab

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

2 Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				
Tucatinib	2 x daily	365	1	365
Capecitabine	on day 1-14 of an 21 day cycle 2 x daily	17.4	14	243.6
Trastuzumab	1 x every 21 days	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 an 21 day cycle 2 x daily	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
[a] Only costs for lapatinib in combination with capecitabine and lapatinib in combination with 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 the doctor's instructions. However, this medicinal product therapy 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	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Tucatinib	300 mg	600 mg	4 x 150 mg	365	1,460 x 150 mg
Capecitabine	1,000 mg/m2 = 1,760 mg	3,500 mg	4 x 500 mg + 4 x 300 mg + 2 x 150 mg	243.6	974.4 x 500 mg + 974.4 x 300 mg + 487.2 x 150 mg
Trastuzumab	Cycle 1: 8 mg/kg From cycle 2 onwards: 6 mg/kg	549.6 mg 412.2 mg	1 x 420 mg + 1 x 150 mg 1 x 420 mg	17.4	1 x 420 mg + 1 x 150 mg 16.4 x 420 mg
Appropriate comparator therapy					
Therapy according to doctor's instructions[a]					
Lapatinib in combination with capecitabine					
Lapatinib	1,250 mg	1,250 mg	5 x 250 mg	365	1825 x 250 mg
Capecitabine	1,000 mg/m^2 = 1,760 mg	3,500 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

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
Lapatinib in combination with trastuzumab (only for patients with hormone-receptor negative breast cancer)					
Lapatinib	1,000 mg	1,000 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		
[a] Only costs for lapatinib in combination with capecitabine and lapatinib in combination with 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 the doctor's instructions. However, this medicinal product therapy 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 Sections 130 and 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. The required number of packs of a particular potency was first determined based on consumption to calculate the annual treatment costs. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated based on 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					
Tucatinib 150 mg	84 FCT	€ 8,021.98	€ 1.77	€ 454.86	€ 7,565.35
Capecitabine 500 mg[3]	120 FCT	€ 151.57	€ 1.77	€ 11.12	€ 138.68
Capecitabine 300 mg[3]	30 FCT	€ 36.09	€ 1.77	€ 1.98	€ 32.34
Capecitabine 150 mg[3]	120 FCT	€ 53.87	€ 1.77	€ 3.39	€ 48.71
Trastuzumab 420 mg	1 PIC	€ 2,173.65	€ 1.77	€ 120.86	€ 2,051.02
Trastuzumab 150 mg	1 PIC	€ 790.66	€ 1.77	€ 43.16	€ 745.73
Appropriate comparator therapy					
Capecitabine 500 mg[3]	120 FCT	€ 151.57	€ 1.77	€ 11.12	€ 138.68
Capecitabine 300 mg[3]	30 FCT	€ 36.09	€ 1.77	€ 1.98	€ 32.34
Capecitabine 150 mg[3]	120 FCT	€ 53.87	€ 1.77	€ 3.39	€ 48.71
Lapatinib 250 mg	70 FCT	€ 1,722.49	€ 1.77	€ 149.10	€ 1,571.62
Trastuzumab 150 mg	1 PIC	€ 790.66	€ 1.77	€ 43.16	€ 745.73
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 considered as costs for additionally required SHI services.

3Fixed 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 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 per ready-to-use unit are to be payable. These additional 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 sales 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.

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 5 May 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy defined by the G-BA was carried out. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 6 October 2020.

On 12 March 2021, the pharmaceutical company submitted a dossier for the benefit assessment of tucatinib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 12 March 2021 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits 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 tucatinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 11 June 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 15 June 2021. The deadline for submitting written statements was 6 July 2021.

The oral hearing was held on 26 July 2021.

By letter dated 27 July 2021, the IQWiG was commissioned with a supplementary assessment. The addenda prepared by IQWiG was submitted to the G-BA on 12 August 2021.

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 the 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 were discussed at the session of the subcommittee on 24 August 2021, and the proposed resolution was approved.

At its session on 2 September 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation

Subcommittee Medicinal product	18.08.2021	Determination of the appropriate comparator therapy
Subcommittee Medicinal product	18.08.2021	New implementation of the appropriate comparator therapy
Working group Section 35a	18.08.2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	18.08.2021	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	18.08.2021 18.08.2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal product	18.08.2021	Concluding consultation of the draft resolution
Plenum	18.08.2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 2 September 2021

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

Prof. Hecken