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Tucatinib (breast cancer) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Tucatinib (Mammakarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 June 2021). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor 2
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug tucatinib. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 12 March 2021.

Research question

The aim of the present report is to assess the added benefit of tucatinib in combination with trastuzumab and capecitabine versus the appropriate comparator therapy (ACT) in adult patients with human epidermal growth factor receptor 2 (HER2)-positive locally advanced or metastatic breast cancer who have received at least 2 previous anti-HER2 therapy regimens.

The G-BA's specification of the ACT resulted in one research question, which is presented in the following Table 2.

Table 2: Research questions of the benefit assessment of tucatinib in combination with trastuzumab and capecitabine

Therapeutic indication	ACT[a]
Adult patients with HER2-positive locally advanced or metastatic breast cancer who have received at least 2 prior anti-HER2 treatment regimens[b,c]	▪ Lapatinib in combination with capecitabine or ▪ lapatinib in combination with trastuzumab (only for patients with hormone receptor-negative breast cancer)
a. Presentation of the respective ACT specified by the G-BA. b. It is assumed that hormone receptor-positive patients are not eligible for endocrine therapy at the time of the therapeutic decision. d: Moreover, it is assumed that there was no indication for (secondary) resection or radiotherapy with curative intent. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2	

The company did not follow the G-BA's specification of the ACT. From the company's point of view, the ACT presents a HER2-targeted therapy in the present therapeutic indication, preferably in combination with chemotherapy. The choice of the specific treatment was to be based on the general condition and the prior therapies. The company's justification for the deviation from the G-BA's ACT was not followed. This is explained in the following Section. Accordingly, the present assessment was conducted in comparison with the G-BA's ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Deviation of the company from the G-BA's ACT

The company justified the deviation from the ACT specified by the G-BA in Modules 3 A and 4 A by stating that there was no general standard therapy in the therapeutic indication of tucatinib, that numerous therapies were applied in German everyday health care and that a numerical advantage of trastuzumab + capecitabine versus the G-BA's ACT lapatinib + capecitabine had been observed for the outcome "overall survival" in the CEREBEL study.

Overall, the company's justification for the deviation from the G-BA's ACT was not sufficient. National and international guidelines primarily recommend several treatment regimens, however, only lapatinib in combination with capecitabine or trastuzumab (only for patients with hormone receptor-negative breast cancer) is approved in the present therapeutic indication. Moreover, the data from German everyday health care presented by the company are not very meaningful due to the small sample size (N = 85).

The results of the CEREBEL study are not suitable to justify the deviating choice of the ACT in the present therapeutic indication of third-line treatment following at least 2 HER2-targeted therapies. The population of the CEREBEL study was predominantly in earlier lines of therapy than the target population in the present therapeutic indication and in part had not yet received HER2-targeted therapies. Accordingly, conclusions on the ACT in the present therapeutic indication cannot be derived from the CEREBEL study.

Irrespective of the insufficient justification provided by the company for the deviation from the G-BA's ACT, the comparator therapy specified by the company (HER2-targeted therapy, preferably in combination with chemotherapy depending on the general condition and prior therapies of the patients) was not implemented in the HER2CLIMB study presented by the company for the benefit assessment. Consequently, the HER2CLIMB study would not have been relevant for the benefit assessment for a direct comparison of tucatinib with the comparator therapy specified by it, even if the company's reasoning on the ACT would have been sufficient.

Results

The company presented no relevant data for the assessment of the added benefit of tucatinib + trastuzumab + capecitabine versus the ACT.

Direct comparison

The company used the study HER2CLIMB for the assessment of the added benefit of tucatinib + trastuzumab + capecitabine. The HER2CLIMB study includes no comparison with the G-BA's ACT, but with trastuzumab + capecitabine. Overall, the company's justification for the deviation from the G-BA's ACT was insufficient. The present benefit assessment was conducted in comparison with the G-BA's ACT. Therefore, the HER2CLIMB study was not used as direct comparison for the benefit assessment.

Indirect comparison

Although the company takes a different view in defining the ACT, it also presented an adjusted indirect comparison with lapatinib + capecitabine for the assessment of tucatinib + trastuzumab + capecitabine versus the ACT defined by the G-BA. The company conducted the comparison via the common comparator trastuzumab + capecitabine and identified the studies CEREBEL, ELTOP and LANTERN for this purpose. It included the HER2CLIMB study for tucatinib + trastuzumab + capecitabine, and the CEREBEL study for lapatinib + capecitabine. The company did not consider the studies ELTOP and LANTERN for the indirect comparison.

Study HER2CLIMB

The study HER2CLIMB is an ongoing, double-blind phase 2 randomized controlled trial (RCT) comparing tucatinib + trastuzumab + capecitabine with trastuzumab + capecitabine. The study included adult patients with metastatic or unresectable advanced HER2-positive breast cancer that had progressed following the last systemic therapy. Patients with brain metastases could be included if the brain metastases were untreated and did not require immediate local therapy or if the brain metastases had already been treated locally and they were either stable or progressive during the screening phase without the requirement of a renewed immediate therapy. The general condition of the patients had to concur with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. A total of 612 patients were included in the study and assigned to the treatment arms in a 2:1 randomization. 410 patients were randomly assigned to the intervention arm and 202 patients to the comparator arm. Progression-free survival was the primary outcome of the HER2CLIMB study. Relevant secondary outcomes were recorded in the categories “mortality”, “morbidity” and side effects.

Limitation of the HER2CLIMB study – local therapy of brain metastases not permitted

In the HER2CLIMB study, radiotherapy or surgery was only permitted for lesions outside the central nervous system. Only under certain conditions could patients with an isolated radiographic progression of certain brain metastases receive local treatment for their brain metastases after consultation with the medical monitor and then continue to be treated with the study medication until the second progression. However, due to specific criteria, this was only possible in exceptional cases. According to the study protocol, unspecified efforts should principally be made to avoid radiotherapy or surgery. In addition to non-drug treatment options, access to symptomatic treatment of brain metastases using glucocorticoids was also limited in the HER2CLIMB study.

In addition to appropriate drug tumour therapy, local concomitant treatment of brain metastases by means of surgery, stereotactic radiation or whole brain radiation is part of the therapy for HER2-positive locally advanced or metastatic breast cancer currently recommended in guidelines. In the HER2CLIMB study, about 48% of the patients had brain metastases at the start of the study. The limitation of adequate concomitant treatment appears problematic, especially with the high proportion of patients with untreated (approx. 10%) or progressive brain metastases (approx. 18 %) at the start of the study. Overall, only 30 patients (approx. 5%

of the study population) received local therapy for brain metastases. In summary, the extensive prohibition of local therapy for brain metastases in the HER2CLIMB study can be considered a limitation of non-drug treatment options.

Study CEREBEL

The study CEREBEL is a prematurely terminated, open-label phase 3 RCT comparing lapatinib + capecitabine with trastuzumab + capecitabine. The study included adult patients with HER2-positive metastatic breast cancer who had already been treated with anthracyclines and/or taxanes, either (neo)adjuvant or in the metastatic stage. Pretreatment with trastuzumab was optional. Patients with brain metastases were excluded from the study. The ECOG PS of the patients was supposed to be ≤ 2. A total of 540 patients were included in the study and randomly assigned to the treatment arms in a 1:1 ratio. 271 patients were randomly assigned to treatment with lapatinib + capecitabine, and 269 patients to treatment with trastuzumab + capecitabine. Primary outcome of the CEREBEL study was the incidence of brain metastases as first site of recurrence. Relevant secondary outcomes were recorded in the categories "mortality" and "side effects".

Studies excluded by the company

Study ELTOP

The ELTOP study is an open-label phase 2 RCT comparing lapatinib + capecitabine with trastuzumab + capecitabine. The study included adult patients (≥ 20 years) with HER2-positive, metastatic breast cancer whose tumours were progressive under treatment with trastuzumab. Patients with brain metastases could be included if they were asymptomatic. The ECOG PS of the patients was supposed to be ≤ 2. Exclusively patients at Japanese centres were included. The study was terminated prematurely due to slow recruitment. A total of 86 patients were included in the study (originally, the inclusion of 170 patients had been planned) and randomly assigned to the treatment arms in a 1:1 ratio. 43 patients each were randomly assigned to treatment with lapatinib + capecitabine and trastuzumab + capecitabine. Progression-free survival was the primary outcome of the ELTOP study. Relevant secondary outcomes were recorded in the categories "mortality" and "side effects".

Study LANTERN

The LANTERN study is an open-label phase 2 screening RCT comparing lapatinib + capecitabine with trastuzumab + capecitabine. The study included adult patients with HER2-positive metastatic breast cancer who had either newly diagnosed brain metastases or whose brain metastases had progressed within the last 12 months and had a size of at least 10 mm. The prior therapies had to comprise trastuzumab, either taxanes or anthracyclines as well as a completed whole brain radiation therapy or stereotactic radiation. The ECOG PS of the patients was supposed to be ≤ 2. Exclusively patients at centres in Great Britain were included. A total of 30 patients were included in the study and randomly assigned to the treatment arms in a 1:1 ratio. 16 patients were randomly assigned to treatment with lapatinib + capecitabine, and 14 patients to treatment with trastuzumab + capecitabine. Primary outcome of the LANTERN

study was the time to progression of brain metastases. Relevant secondary outcomes were recorded in the categories “mortality”, “morbidity”, “health-related quality of life” and “side effects”.

Indirect comparison is not usable for the benefit assessment

Effects of the limitation of HER2CLIMB on the certainty of results of the indirect comparison

Indirect comparisons are generally subject to a high degree of uncertainty. In order to be able to derive hints, for example of an added benefit, with only 1 study on both sides of the adjusted indirect comparison with only 1 available common comparator, as presented here by the company, both studies must have a high certainty of conclusions. However, the certainty of conclusions of the HER2CLIMB study is limited due to the described limitation in the concomitant treatment of brain metastases. Based on the studies HER2CLIMB and CEREBEL, a hint, for example of an added benefit, can thus not be derived in the adjusted indirect comparison.

Insufficient similarity of the studies HER2CLIMB and CEREBEL

Differences in the line of therapy of the metastatic disease

Due to the different inclusion criteria for the necessary prior therapies in the HER2CLIMB and CEREBEL studies, the patients were in different lines of therapy of their metastatic disease at the start of the study. For example, the patients in the HER2CLIMB study had received at least 1 prior therapy in the metastatic stage before inclusion in the study, with a median of 3 and a maximum of up to 14 prior therapies. In the CEREBEL study, on the other hand, 44% of the patients had not yet received therapy in the metastatic stage at the time of study inclusion.

Differences in the treatment of HER2-positive locally advanced or metastatic breast cancer due to different time periods of study implementation

The studies HER2CLIMB and CEREBEL differ with regard to the period of study. There are about 7 years between the respective last data cut-offs of the two studies. Within this period, there were relevant changes or innovations in the medical care of HER2-positive locally advanced or metastatic breast cancer, which is significantly reflected in differences in the prior therapies administered between the two studies.

Differences and missing data in the characteristics of the studies, patients and interventions

In the HER2CLIMB study, about 48% of the patients had brain metastases at the start of the study. However, patients with brain metastases were excluded from the CEREBEL study. Brain metastases are a relevant prognostic as well as predictive factor in the therapeutic indication of breast cancer and limit both the treatment success and the survival time of the patients. Accordingly, an indirect comparison with the CEREBEL study, which included no patients with the predictive characteristic “brain metastases” cannot be meaningfully interpreted.

Information on treatment and observation periods for the CEREBEL study is missing. Hence, an evaluation of similarity between HER2CLIMB and CEREBEL is not possible for this criterion.

There were relevant differences between the studies HER2CLIMB and CEREBEL in other patient characteristics (family origin white 72.5% vs. 98%, oestrogen receptor status 58.0% vs. 47%, disease stage IV at first diagnosis 35.9% vs. 18%). In addition to the differences described, no statement on the similarity of the two studies can be made for the possibly predictive characteristics "time since diagnosis of the metastatic disease", "previous chemotherapies", "exact number of previous therapies for the metastatic disease" and "duration of the previous trastuzumab therapy". These characteristics were only recorded in one of the two studies. The concomitant treatments in the studies cannot be compared either, as such information is neither available for the HER2CLIMB study nor for the CEREBEL study.

Moreover, there are differences in the dosage of the study medication. In the comparator arm of the HER2CLIMB study, for instance, capecitabine was administered twice daily at a dose of 1000 mg. In the CEREBEL study, by contrast, patients in the comparator arm received 1250 mg twice daily according to the Summary of Product Characteristics (SPC).

Exclusion of the studies ELTOP and LANTERN

The exclusion of the ELTOP study due to the fact that the study was conducted in Japan and only a few patients were included is not appropriate. Compared to the CEREBEL study, the population of the ELTOP study is indeed small (about 16% of the CEREBEL study) and would therefore probably only have a small influence on the results of the indirect comparison. However, it must be noted that the ELTOP study showed an opposite direction of effect in terms of overall survival compared to the CEREBEL study. Information on prior therapies and disease stage were not only lacking for the ELTOP study, but also for CEREBEL. However, irrespective of this, the company included the CEREBEL study for the indirect comparison.

The exclusion of the LANTERN study from the indirect comparison is appropriate.

Summary on the indirect comparison

Due to the limited certainty of results due to the limitation in the HER2CLIMB study, the indirect comparison is not suitable for the benefit assessment. Moreover, the similarity assumption between HER2CLIMB and CEREBEL is not sufficiently fulfilled. In addition, the exclusion of the ELTOP study was not adequately justified by the company. The adjusted indirect comparison of tucatinib + trastuzumab + capecitabine with the ACT presented by the company is thus not usable for the benefit assessment.

There are thus no data for the benefit assessment suitable for a derivation of an added benefit of tucatinib + trastuzumab + capecitabine in comparison with the ACT.

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

Table 3 shows a summary of probability and extent of the added benefit of tucatinib + trastuzumab + capecitabine.

Table 3: Tucatinib in combination with trastuzumab and capecitabine – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adult patients with HER2-positive locally advanced or metastatic breast cancer who have received at least 2 prior anti-HER2 treatment regimens	▪ Lapatinib in combination with capecitabine or ▪ lapatinib in combination with trastuzumab (only for patients with hormone receptor-negative breast cancer)	Added benefit not proven
a. Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2		

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is to assess the added benefit of tucatinib in combination with trastuzumab and capecitabine versus the ACT in adult patients with HER2-positive locally advanced or metastatic breast cancer who have received at least 2 previous anti-HER2 therapy regimens.

The G-BA's specification of the ACT resulted in one research question, which is presented in the following Table 4.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 4: Research questions of the benefit assessment of tucatinib in combination with trastuzumab and capecitabine

Therapeutic indication	**ACT[a]**
Adult patients with HER2-positive locally advanced or metastatic breast cancer who have received at least 2 prior anti-HER2 treatment regimens[b,c]	▪ Lapatinib in combination with capecitabine or ▪ lapatinib in combination with trastuzumab (only for patients with hormone receptor-negative breast cancer)
a. Presentation of the respective ACT specified by the G-BA. b. It is assumed that hormone receptor-positive patients are not eligible for endocrine therapy at the time of the therapeutic decision. c. Moreover, it is assumed that there was no indication for (secondary) resection or radiotherapy with curative intent. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2	

The company did not follow the G-BA's specification of the ACT. From the company's point of view, the ACT presents a HER2-targeted therapy in the present therapeutic indication, preferably in combination with chemotherapy. The choice of the specific treatment was to be based on the general condition and the prior therapies. The company's justification for the deviation from the G-BA's ACT was not followed. This is explained in the following Section. Accordingly, the present assessment was conducted in comparison with the G-BA's ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Deviation of the company from the G-BA's ACT

In the present therapeutic indication, the company specified a HER2-targeted therapy as comparator therapy, preferably in combination with chemotherapy. The selection of the specific therapy should be based on the general condition and previous therapies of the patients. In Modules 3 A and 4 A of the full benefit assessment, it justified the deviation from the G-BA's ACT with the fact that no general standard therapy was available in the therapeutic indication of tucatinib [3-8], that a large number of therapies were used in German everyday health care [9] and that in the CEREBEL study (for a description of the CEREBEL study, see Section 2.3.2.2), a numerical advantage had been observed for trastuzumab + capecitabine compared with the G-BA's ACT lapatinib + capecitabine in the outcome "overall survival".

Overall, the company's justification for the deviation from the G-BA's ACT was not sufficient. National and international guidelines [3-8] recommend several treatment regimens, however, only lapatinib in combination with capecitabine or trastuzumab (only for patients with hormone receptor-negative breast cancer) is approved in the present therapeutic indication [10]. Moreover, the data from German everyday health care [9] presented by the company are not very meaningful due to the small sample size (N = 85).

The results of the CEREBEL study are not suitable to justify the deviating choice of the ACT in the present therapeutic indication of third-line treatment following at least 2 HER2-targeted therapies. The population of the CEREBEL study was predominantly in earlier lines of therapy than the target population in the present therapeutic indication and in part had not yet received HER2-targeted therapies. Accordingly, conclusions on the ACT in the present therapeutic indication cannot be derived from the CEREBEL study.

Irrespective of the insufficient justification provided by the company for the deviation from the G-BA's ACT, the comparator therapy specified by the company (HER2-targeted therapy, preferably in combination with chemotherapy depending on the general condition and prior therapies of the patients) was not implemented in the HER2CLIMB study (for a description of the HER2CLIMB study, see Section 2.3.2.1) presented by the company for the benefit assessment. Consequently, the HER2CLIMB study would not have been relevant for the benefit assessment for a direct comparison of tucatinib with the comparator therapy specified by it, even if the company's reasoning on the ACT would have been sufficient.

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on tucatinib (status: 1 March 2021)
- bibliographical literature search on tucatinib (last search on 11 January 2021)
- search in trial registries/trial results databases for studies on tucatinib (last search on 8 January 2021)
- search on the G-BA website for tucatinib (last search on 15 January 2021)
- bibliographical literature search on the ACT (last search on 11 January 2021)
- search in trial registries/trial results databases for studies on the ACT (last search on 8 January 2021)
- search on the G-BA website for the ACT (last search on 15 January 2021)

To check the completeness of the study pool:

- search in trial registries for studies on tucatinib (last search on 24 March 2021); for search strategies, see Appendix B of the full dossier assessment
- search in trial registries for studies on the ACT (last search on 29 March 2021); for search strategies, see Appendix B of the full dossier assessment

For the ACT, the company searched for studies on trastuzumab + capecitabine + lapatinib. Therefore, the completeness of the study pool on the ACT is not guaranteed.

However, concurring with the company, the check of the completeness of the study pool identified no study relevant for the direct comparison of tucatinib + trastuzumab + capecitabine with the ACT specified by the G-BA.

However, the company used the RCT HER2CLIMB (see Section 2.3.2.1) for a direct comparison of tucatinib + trastuzumab + capecitabine versus trastuzumab + capecitabine for the benefit assessment, although the ACT specified by the G-BA had not been implemented in this study. Moreover, it also presented an adjusted indirect comparison for the assessment of the added benefit of tucatinib + trastuzumab + capecitabine versus one of the treatment options of the ACT specified by the G-BA (lapatinib + capecitabine).

Neither the direct comparison nor the indirect comparison are suitable for the derivation of an added benefit of tucatinib + trastuzumab + capecitabine in comparison with the ACT specified by the G-BA. This is explained below.

2.3.1 Direct comparison

The company used the study HER2CLIMB for the assessment of the added benefit of tucatinib + trastuzumab + capecitabine. A detailed description of the HER2CLIMB study can be found in Section 2.3.2.1. The HER2CLIMB study includes no comparison with the G-BA's ACT, but with trastuzumab + capecitabine. The company justified the deviation from the G-BA's ACT, however, the justification is insufficient (see Section 2.2). The present benefit assessment was conducted in comparison with the G-BA's ACT. Therefore, the HER2CLIMB study was not used as direct comparison for the benefit assessment.

2.3.2 Indirect comparison

No direct comparative studies versus the ACT are available for the present research question. Although the company takes a different view in defining the ACT (see Section 2.2), it also presented an adjusted indirect comparison with lapatinib + capecitabine for the assessment of tucatinib + trastuzumab + capecitabine versus the ACT defined by the G-BA. The company conducted the comparison via the common comparator trastuzumab + capecitabine and identified the studies CEREBEL, ELTOP and LANTERN for this purpose. It included the HER2CLIMB study for tucatinib + trastuzumab + capecitabine, and the CEREBEL study for lapatinib + capecitabine (see Figure 1). The company did not consider the studies ELTOP and LANTERN for the indirect comparison.

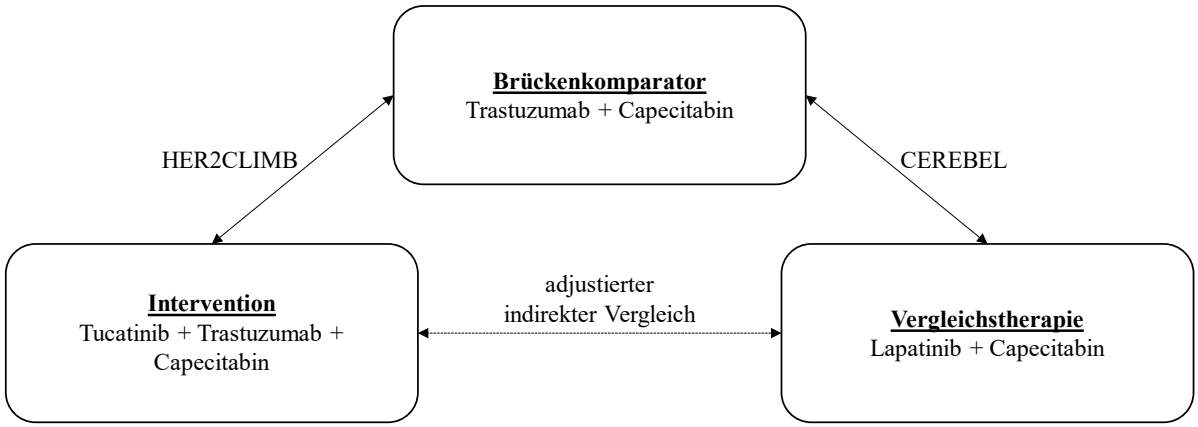

Figure 1: Study pool of the company for the indirect comparison between tucatinib + trastuzumab + capecitabine and lapatinib + capecitabine

Overall, the HER2CLIMB and CEREBEL studies presented by the company for the indirect comparison are not suitable for deriving an added benefit for tucatinib + trastuzumab + capecitabine versus the ACT, because the indirect comparison does not provide sufficient certainty of results due to the limitation of the HER2CLIMB study. Moreover, the included studies HER2CLIMB and CEREBEL are not similar enough. In addition, the exclusion of the ELTOP study from the indirect comparison was not adequately justified.

The studies identified by the company and the missing suitability of the indirect comparison for the benefit assessment are described below. Further information on study, intervention and patient characteristics are presented in Appendix A of the full benefit assessment. Information on subsequent therapies was only available for the HER2CLIMB study and is also presented in Appendix A.

2.3.2.1 Study HER2CLIMB

The HER2CLIMB study [11-15] is an ongoing, double-blind phase 2 RCT comparing tucatinib + trastuzumab + capecitabine versus (hereinafter referred to as "intervention arm") and trastuzumab + capecitabine (hereinafter referred to as "comparator arm"). The study included adult patients with metastatic or unresectable advanced HER2-positive breast cancer that had progressed following the last systemic therapy. Patients should have been treated with trastuzumab, pertuzumab and trastuzumab emtansine before. Previous treatment with lapatinib within the last 12 months was not allowed. Previous therapies with capecitabine as (neo-)adjuvant treatment were allowed up to 12 months before the start of study medication. Patients with brain metastases could be included if the brain metastases were untreated and did not require immediate local therapy or if the brain metastases had already been treated locally and they were either stable or progressive during the screening phase without the requirement of a renewed immediate therapy. Patients who at first received treatment of their brain metastases that had been detected during the screening could be included in the study if there were ≥ 21 days between whole brain radiation therapy, ≥ 7 days between stereotactic radiation or ≥ 28

days between surgery and the first dose of the study medication. At the time of randomization, patients were allowed to receive a maximum of 2 mg dexamethasone equivalent per day for the symptomatic treatment of brain metastases. The general condition of the patients had to concur with an ECOG PS of 0 or 1.

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

Treatment with tucatinib or placebo as well as trastuzumab was in compliance with the specifications of the SPC and the recommendations of the guidelines [4,7,16-18]. However, the dose of 1000 mg capecitabine twice daily administered in the comparator arm deviates from the specifications of the SPC, which specifies 1250 mg twice daily in combination with trastuzumab in the present therapeutic indication [19].

Patients received treatment until disease progression (determined by Response Evaluation Criteria in Solid Tumours [RECIST] version 1.1), unacceptable toxicity, withdrawal of consent or death. A switch from the comparator arm to treatment with tucatinib was only possible after the primary data cut-off of 4 September 2019 and subsequent unblinding.

Progression-free survival was the primary outcome of the HER2CLIMB study. Relevant secondary outcomes were recorded in the categories “mortality”, “morbidity” and side effects.

The patients underwent outcome-specific observation, at most until death, withdrawal of consent or end of the study.

Data cut-offs

Three data cut-offs are available for the HER2CLIMB study:

- First data cut-off of 4 September 2019: analysis of the primary outcome “progression-free survival” predefined in the study protocol
- Second data cut-off of 8 November 2019: unplanned analysis of safety outcomes at the request of the European Medicines Agency (EMA)
- Third data cut-off of 29 May 2020: unplanned analysis of safety outcomes at the request of the EMA

Limitation of the HER2CLIMB study

The HER2CLIMB study had a limitation. This uncertainty is described hereinafter.

Local therapy of brain metastases not permitted

In the HER2CLIMB study, radiotherapy or surgery was only permitted for lesions outside the central nervous system. Only under certain conditions could patients with an isolated

radiographic progression of certain brain metastases receive local treatment for their brain metastases after consultation with the medical monitor and then continue to be treated with the study medication until the second progression. However, due to specific criteria, this was only possible in exceptional cases. Thus, in addition to the isolated intracerebral progression, these patients had to show no worsening of their tumour-related symptoms, had to tolerate the study medication well and had to benefit from the continued drug therapy. According to the study protocol, unspecified efforts should principally be made to avoid radiotherapy or surgery. It is also unclear whether local therapy of brain metastases as subsequent therapy was possible after discontinuation of the study medication. The company provided no information on whether and how many patients received local treatment of brain metastases after discontinuation of the study medication.

The guidelines recommend treatment of brain metastases by surgery, stereotactic radiation or whole brain radiation, depending on the location, size and number of the metastases [4,7]. These recommendations apply regardless of an isolated progression of brain metastases according to RECIST criteria, a worsening of tumour-related symptoms or the tolerability of a current drug treatment. In addition to appropriate drug-based tumour therapy, local concomitant treatment of brain metastases is part of the currently recommended therapy for HER2-positive locally advanced or metastatic breast cancer [7].

In the HER2CLIMB study, about 48% of patients had brain metastases at baseline, but only 30 patients (about 5% of the study population) received local therapy of brain metastases [13]. The limitation of adequate concomitant treatment appears problematic, especially with the high proportion of patients with untreated (approx. 10%) or progressive brain metastases (approx. 18 %) at the start of the study. It can be assumed that local therapy of brain metastases would have been indicated for more patients than those who actually received such therapy and that those patients might have benefited from it. In summary, the extensive prohibition of local therapy for brain metastases in the HER2CLIMB study can be considered a limitation of non-drug treatment options.

In addition to non-drug treatment options, access to symptomatic treatment of brain metastases using glucocorticoids was also limited in the HER2CLIMB study. For example, symptomatic treatment of brain metastases using glucocorticoids required consultation with the medical monitor. This unnecessarily leads to a more difficult and delayed initiation of symptomatic therapy of guideline-compliant brain metastases [4,6].

2.3.2.2 Study CEREBEL

The study CEREBEL [20-22] is a prematurely terminated, open-label phase 3 RCT comparing lapatinib + capecitabine with trastuzumab + capecitabine. The study included adult patients with HER2-positive metastatic breast cancer who had already been treated with anthracyclines and/or taxanes, either (neo)adjuvant or in the metastatic stage. Pretreatment with trastuzumab was optional. Patients with brain metastases were excluded from the study. The ECOG PS of the patients was supposed to be ≤ 2.

A total of 540 patients were included in the study and randomly assigned to the treatment arms in a 1:1 ratio. 271 patients were randomly assigned to treatment with lapatinib + capecitabine, and 269 patients to treatment with trastuzumab + capecitabine. The assignment was stratified by pretreatment with trastuzumab (yes vs. no) and previous therapy in the metastatic stage (yes vs. no).

Treatment in both study arms was conducted according to the recommendations of the SPC [10,16,19].

Patients were treated until disease progression, occurrence of unacceptable toxicity, withdrawal of consent or death. Switching to the treatment of the other treatment arm was not allowed.

Primary outcome of the CEREBEL study was the incidence of brain metastases as first site of recurrence. Relevant secondary outcomes were recorded in the categories "mortality" and "side effects".

The patients underwent outcome-specific observation, at most until death, withdrawal of consent or end of the study.

Data cut-offs

On the recommendation of the Independent Data Monitoring Committee, the CEREBEL study was terminated prematurely on 11 June 2012 after the interim analysis of 475 patients. The last analysis is based on 540 patients.

2.3.2.3 Studies excluded by the company

Study ELTOP

The ELTOP study [23-25] is an open-label phase 2 RCT comparing lapatinib + capecitabine with trastuzumab + capecitabine. The study included adult patients (≥ 20 years) with HER2-positive, metastatic breast cancer whose tumours were progressive under treatment with trastuzumab. Patients with brain metastases could be included if they were asymptomatic. The ECOG PS of the patients was supposed to be ≤ 2. Exclusively patients at Japanese centres were included. The study was terminated prematurely due to slow recruitment.

A total of 86 patients were included in the study (originally, the inclusion of 170 patients had been planned) and randomly assigned to the treatment arms in a 1:1 ratio. 43 patients each were randomly assigned to treatment with lapatinib + capecitabine and trastuzumab + capecitabine. This assignment was stratified by study centre, hormone receptor status (positive versus negative), number of previous chemotherapies in the metastatic stage (0 vs. 1 vs. 2) and the presence of brain metastases (yes vs. no).

Treatment in both study arms was conducted according to the recommendations of the SPC [10,16,19].

Patients were treated until disease progression or occurrence of unacceptable toxicity.

Progression-free survival was the primary outcome of the ELTOP study. Relevant secondary outcomes were recorded in the categories “mortality” and “side effects”.

Data cut-offs

The inclusion of patients in the ELTOP study was prematurely terminated in December 2014. Further information on data cut-offs are not available.

Study LANTERN

The LANTERN study [26-28] is an open-label phase 2 screening RCT comparing lapatinib + capecitabine with trastuzumab + capecitabine. The study included adult patients with HER2-positive metastatic breast cancer who had either newly diagnosed brain metastases or whose brain metastases had progressed within the last 12 months and had a size of at least 10 mm. The prior therapies had to comprise trastuzumab, either taxanes or anthracyclines as well as a completed whole brain radiation therapy or stereotactic radiation. The ECOG PS of the patients was supposed to be ≤ 2. Exclusively patients at centres in Great Britain were included.

A total of 30 patients were included in the study and randomly assigned to the treatment arms in a 1:1 ratio. 16 patients were randomly assigned to treatment with lapatinib + capecitabine, and 14 patients to treatment with trastuzumab + capecitabine.

Treatment in both study arms was conducted according to the recommendations of the SPC [10,16,19].

Initially, the patients were treated for up to 24 weeks. Thereafter, treatment could be continued until disease progression or occurrence of unacceptable toxicity.

Primary outcome of the LANTERN study was the time to progression of brain metastases. Relevant secondary outcomes were recorded in the categories “mortality”, “morbidity”, “health-related quality of life” and “side effects”.

The patients were observed for 24 weeks.

Data cut-offs

In October 2013, patient enrolment was terminated at the end of the planned 2-year randomization phase due to limited recruitment of only 30 patients in total instead of the planned 130. Further information on data cut-offs are not available.

2.3.2.4 Indirect comparison is not usable for the benefit assessment

The exclusion of the adjusted indirect comparison of the two studies HER2CLIMB and CEREBEL from the benefit assessment is justified below.

Effects of the limitation of HER2CLIMB on the certainty of results of the indirect comparison

Indirect comparisons are generally subject to a high degree of uncertainty. In order to be able to derive hints, for example of an added benefit, with only 1 study on both sides of the adjusted indirect comparison with only 1 available common comparator, as presented here by the company, both studies must have a high certainty of conclusions. However, the certainty of conclusions of the HER2CLIMB study is limited due to the limitation in the concomitant treatment of brain metastases described in Section 2.3.2.1. Based on the studies HER2CLIMB and CEREBEL, a hint, for example of an added benefit, can thus not be derived in the adjusted indirect comparison.

Insufficient similarity of the studies HER2CLIMB and CEREBEL

The studies HER2CLIMB and E4599 investigated tucatinib + trastuzumab + capecitabine or one of the options specified as ACT by the G-BA (lapatinib + capecitabine). However, in addition to the high reliability of the individual studies described above, sufficient similarity of the included studies is a prerequisite for an indirect comparison via an adequate bridge comparator. This similarity is missing for several characteristics. Data important for the assessment of the similarity are also missing.

Differences in the line of therapy of the metastatic disease

Due to the different inclusion criteria for the necessary prior therapies in the HER2CLIMB and CEREBEL studies, the patients were in different lines of therapy of their metastatic disease at the start of the study. For example, the patients in the HER2CLIMB study had received at least 1 prior therapy in the metastatic stage before inclusion in the study, with a median of 3 and a maximum of up to 14 prior therapies. In the CEREBEL study, on the other hand, 44% of the patients had not yet received therapy in the metastatic stage at the time of study inclusion.

Differences in the treatment of HER2-positive locally advanced or metastatic breast cancer due to different time periods of study implementation

The studies HER2CLIMB and CEREBEL differ with regard to the period of study. There are about 7 years between the respective last data cut-offs of the two studies (see Table 9 of the full dossier assessment). Within this period, there were relevant changes or innovations in the medical care of HER2-positive locally advanced or metastatic breast cancer, which is significantly reflected in differences in the prior therapies administered between the two studies. Thus, approx. 94% of the patients in the metastatic stage received trastuzumab before being included in the HER2CLIMB study. Moreover, > 90% of the patients in the metastatic stage were pretreated with pertuzumab and trastuzumab emtansine. These therapies are recommended in first- and second-line treatment of HER2-positive metastatic breast cancer [4,6,7]. However, in the CEREBEL study, only 35% of the patients in the metastatic stage received treatment with trastuzumab before being included in the study; none of the patients received pretreatment with pertuzumab or trastuzumab emtansine. This is due to the fact that pertuzumab and trastuzumab emtansine were not yet approved at the time the CEREBEL study

was conducted (2009 to 2012).

From today's perspective, it is to be expected that the patients in the CEREBEL study would accordingly receive other treatments than the study medication administered at that time.

Differences and missing data in the characteristics of the studies, patients and interventions

Brain metastases at baseline

In the HER2CLIMB study, about 48% of the patients had brain metastases at the start of the study. However, patients with brain metastases were excluded from the CEREBEL study. Brain metastases are a relevant prognostic as well as predictive factor in the therapeutic indication of breast cancer and limit both the treatment success and the survival time of the patients [7].

Accordingly, an indirect comparison with the CEREBEL study, which included no patients with the predictive characteristic "brain metastases" cannot be meaningfully interpreted.

Missing data on treatment and observation periods

Information on treatment and observation periods for the CEREBEL study is missing. Hence, an evaluation of similarity between HER2CLIMB and CEREBEL is not possible for this criterion.

Further differences in the patient characteristics as well as missing data on possibly predictive characteristics

Relevant differences in further possibly predictive patient characteristics were shown between the studies HER2CLIMB and CEREBEL (see Table 12 of the full dossier assessment):

- Family origin white: 72.5% vs. 98%
- Oestrogen receptor status positive: 58.0% vs. 47%
- Disease stage IV at initial diagnosis: 35.9% vs 18%

In addition to the differences described, no statement on the similarity of the two studies can be made for the possibly predictive characteristics "time since diagnosis of the metastatic disease", "previous chemotherapies", "exact number of previous therapies for the metastatic disease" and "duration of the previous trastuzumab therapy". These characteristics were only recorded in one of the two studies. The concomitant treatments in the studies cannot be compared either, as such information is neither available for the HER2CLIMB study nor for the CEREBEL study.

Deviating dosage of capecitabine

In the comparator arm of the HER2CLIMB study, capecitabine was administered twice daily at a dose of 1000 mg. In the CEREBEL study, by contrast, patients in the comparator arm received 1250 mg twice daily according to the SPC [10]. This corresponds to a deviation of 25% (see Table 10 of the full dossier assessment).

Exclusion of the studies ELTOP and LANTERN

Study ELTOP

The company excluded the ELTOP study from the indirect comparison. It justified this with the fact that the ELTOP study was conducted exclusively at Japanese study centres, only 86 patients were included and a conclusive assessment of the similarity was not possible due to the lack of information on previous therapies and on the stage of the disease at the time of study inclusion.

The approach of the company was not appropriate. An exclusion of studies solely on the basis of the geographical location of study sites is not justified. Compared to the CEREBEL study, the population of the ELTOP study is indeed small: 86 patients correspond to approx. 16% of the CEREBEL study population and would therefore probably only have a small influence on the results of the indirect comparison. However, it must be noted that the ELTOP study showed an opposite direction of effect in terms of overall survival compared to the CEREBEL study. Information on prior therapies and disease stage were not only lacking for the ELTOP study, but also for CEREBEL (e.g. hormone receptor status, disease stage at baseline, exact number of systemic therapies in the metastatic stage). However, irrespective of this, the company included the CEREBEL study for the indirect comparison.

Study LANTERN

The company excluded the LANTERN study from the indirect comparison. It justified this with the exclusively descriptive presentation of results with a small study population of only 30 patients. This approach is appropriate.

Summary on the indirect comparison

Due to the limited certainty of results due to the limitation in the HER2CLIMB study, the indirect comparison is not suitable for the benefit assessment. Moreover, the similarity assumption between HER2CLIMB and CEREBEL is not sufficiently fulfilled. In addition, the exclusion of the ELTOP study was not adequately justified by the company. The adjusted indirect comparison of tucatinib + trastuzumab + capecitabine with the ACT presented by the company is thus not usable for the benefit assessment.

There are thus no data for the benefit assessment suitable for a derivation of an added benefit of tucatinib + trastuzumab + capecitabine in comparison with the ACT.

2.4 Results on added benefit

The company presented no suitable data for the assessment of the added benefit of tucatinib + trastuzumab + capecitabine. This resulted in no hint of an added benefit of tucatinib + trastuzumab + capecitabine versus the ACT in adult patients with HER2-positive locally advanced or metastatic breast cancer who have received at least 2 previous anti-HER2 therapy regimens. An added benefit is therefore not proven.

2.5 Probability and extent of added benefit

The result of the assessment of the added benefit of tucatinib + trastuzumab + capecitabine in comparison with the ACT is summarized in Table 5.

Table 5: Tucatinib in combination with trastuzumab and capecitabine – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with HER2-positive locally advanced or metastatic breast cancer who have received at least 2 prior anti-HER2 treatment regimens	▪ Lapatinib in combination with capecitabine or ▪ lapatinib in combination with trastuzumab (only for patients with hormone receptor-negative breast cancer)	Added benefit not proven
a. Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2		

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit for tucatinib + trastuzumab + capecitabine.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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