IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Trastuzumab Emtansin – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 March 2014). 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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[3] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
DAS	Diarrhoea Assessment Scale
ECOG PS	Eastern Cooperative Oncology Group Performance Status
FACT-B	Functional Assessment of Cancer Therapy – Breast Cancer
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)
IRC	independent review committee
ORR	objective response rate
PFS	progression-free survival
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
TOI-PFB	Trial Outcomes Index-Physical/Functional/Breast

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 trastuzumab emtansine. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 27 November 2013.

Research question

The aim of the present report is to assess the added benefit of trastuzumab emtansine in patients with human epidermal growth factor receptor 2 (HER2)-positive, unresectable, locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either received prior treatment for locally advanced or metastatic disease, or developed disease recurrence during or within 6 months of completing adjuvant therapy.

The assessment was conducted in comparison with the appropriate comparator therapy (ACT). The G-BA specified the ACT presented in Table 2.

Table 2: Overview of the ACTs for trastuzumab emtansine

Subindication	**ACT specified by the G-BA**	**ACT specified by the company**
Subpopulation a patients with HER2-positive, locally advanced, unresectable breast cancer	Radiotherapy	Lapatinib + capecitabine
Subpopulation b patients with HER2-positive metastatic breast cancer, with prior treatment with anthracyclines, taxanes and trastuzumab	Lapatinib + capecitabine	
Subpopulation c patients with HER2-positive metastatic breast cancer, with prior treatment with taxanes and trastuzumab, but without anthracyclines	Anthracycline (doxorubicin, epirubicin)	
Subpopulation d patients with HER2-positive metastatic breast cancer, with prior treatment with taxanes and trastuzumab, for whom treatment with anthracyclines is not an option	Individual treatment under consideration of the respective approval of the drugs used	
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2		

The company deviated from the G-BA's specification. It used lapatinib + capecitabine as comparator therapy for the total target population. The dossier assessment was conducted

with the ACTs specified by the G-BA because the company did not provide sufficient reasons for deviating from the ACTs.

The assessment was based on patient-relevant outcomes. One direct comparative randomized controlled trial (RCT) was included in the assessment.

Results

Subpopulation a: patients with HER2-positive, locally advanced, unresectable breast cancer

No relevant data were available in the dossier for the assessment of the added benefit of trastuzumab emtansine in patients with HER2-positive, locally advanced, unresectable breast cancer for a comparison of trastuzumab emtansine with radiotherapy. Hence an added benefit of trastuzumab emtansine in comparison with the ACT radiotherapy is not proven for these patients.

Subpopulation b: patients with HER2-positive metastatic breast cancer, with prior treatment with anthracyclines, taxanes and trastuzumab

Study characteristics

One relevant study, the EMILIA study, was available for the assessment. This study is an open-label, randomized, controlled, multinational approval study.

Adult patients with HER2-positive, locally advanced, unresectable breast cancer or with HER2-positive metastatic breast cancer with disease progression after pretreatment were enrolled in the study. The pretreatment had to be conducted in the adjuvant or unresectable, locally advanced or metastatic stage of the disease and had to include a taxane and trastuzumab, in each case separately or in combination with another drug. Disease progression should have occurred during or immediately after treatment for locally advanced or metastatic breast cancer or within 6 months of completing adjuvant therapy. The vast majority of the study population were patients with metastatic breast cancer. Both patients with and without pretreatment with anthracyclines were enrolled in the study. Only the subpopulation of patients after pretreatment with anthracyclines was relevant for the present benefit assessment. With regard to this subpopulation, 605 patients were randomly assigned in a ratio of 1:1, either to treatment with trastuzumab emtansine (303 patients) or to treatment with lapatinib + capecitabine (302 patients). In the study, the drugs trastuzumab emtansine, lapatinib and capecitabine were used in compliance with their approval.

Overall survival, health-related quality of life and adverse events (AEs) were included as patient-relevant outcomes in the benefit assessment. AEs were recorded up to 30 days after the last administration of study medication. Overall survival and health-related quality of life were recorded every 3 months after cessation of the study medication, until death, study discontinuation or end of study.

Risk of bias

The risk of bias at study level was rated as low for the EMILIA study so that, in principle, indications of added benefit or harm could be derived from it.

The risk of bias for the outcome "overall survival" was rated as low. The outcome "time to worsening of health-related quality of life" was rated as potentially highly biased due to the lack of blinding. The risk of bias for the outcomes on AEs was also rated as high because of the different observation periods between the treatment groups and the lack of blinding of patient and treating staff and the generally subjective component in the recording of the outcomes.

Mortality (outcome "overall survival")

Treatment with trastuzumab emtansine produced a statistically significant prolongation of overall survival compared with lapatinib + capecitabine. There is therefore an indication of an added benefit of trastuzumab emtansine for the outcome "overall survival" compared with the ACT lapatinib + capecitabine.

Morbidity

The dossier contained no evaluable data on morbidity. An added benefit of trastuzumab emtansine in comparison with lapatinib + capecitabine is not proven for morbidity.

Health-related quality of life (physical/functional component, measured with the TOI-PFB of the FACT-B)

Treatment with trastuzumab emtansine produced a statistically significant prolongation of the time to worsening of health-related quality of life in comparison with lapatinib + capecitabine. In addition, there was proof of an effect modification by the characteristic "ethnicity". Due to the high risk of bias based on outcomes, for white patients, this results in a hint of an added benefit of trastuzumab emtansine in comparison with the ACT lapatinib + capecitabine regarding the time to worsening of health-related quality of life (physical/functional component). For patients of other ethnicities, an added benefit of trastuzumab emtansine is not proven.

Adverse events

There was no statistically significant difference between the treatment groups for the outcome "serious AEs (SAEs)". Lesser or greater harm from trastuzumab emtansine than from the ACT lapatinib + capecitabine is therefore not proven for this outcome.

For the outcomes "treatment discontinuations due to AEs" and "severe AEs of Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3, there was a statistically significant difference in favour of trastuzumab emtansine. Because of the high risk of bias based on outcomes, this results in a hint of lesser harm from trastuzumab emtansine than from the ACT lapatinib + capecitabine.

There was a statistically significant difference to the disadvantage of trastuzumab emtansine compared with lapatinib + capecitabine for the outcome "bleeding events". Because of the high risk of bias based on outcomes, this results in a hint of greater harm from trastuzumab emtansine than from the ACT lapatinib + capecitabine.

The proportion of patients with severe diarrhoea (CTCAE grade ≥ 3) was statistically significantly smaller under treatment with trastuzumab emtansine than under lapatinib + capecitabine. Overall this results in a hint of lesser harm from trastuzumab emtansine than from the ACT lapatinib + capecitabine.

The proportion of patients with severe hand-foot syndrome (CTCAE grade 3) was statistically significantly smaller under treatment with trastuzumab emtansine than under lapatinib + capecitabine. There was a high risk of bias for this outcome. However, there were no CTCAE grade 3 events in the trastuzumab emtansine arm, and only 5 patients had hand-foot syndrome of a lower severity grade (CTCAE grade 1 and 2). Because of the great difference between the treatment groups and the overall low event rates in the trastuzumab emtansine arm and because of the definitions of the CTCAE severity grades for the outcome "hand-foot syndrome" it was assumed that the influence of the lack of blinding could not raise doubts about the effect or its extent. In summary, this results in an indication of lesser harm from trastuzumab emtansine compared with the ACT lapatinib + capecitabine for the outcome "hand-foot syndrome of CTCAE grade 3".

Subpopulation c: patients with HER2-positive metastatic breast cancer after pretreatment with taxanes and trastuzumab, but without anthracyclines

There were no relevant data for the subpopulation of patients with HER2-positive metastatic breast cancer after pretreatment with taxanes and trastuzumab, but without anthracyclines, in comparison with the ACT (anthracycline [doxorubicin, epirubicin]). Hence an added benefit of trastuzumab emtansine in comparison with the ACT anthracycline (doxorubicin, epirubicin) is not proven for these patients.

Subpopulation d: patients with HER2-positive metastatic breast cancer, pretreated with taxanes and trastuzumab, for whom treatment with anthracyclines is not an option

There were no relevant data for the subpopulation of patients with HER2-positive metastatic breast cancer after pretreatment with taxanes and trastuzumab, for whom treatment with anthracyclines is not an option, in comparison with the ACT (individual treatment). Hence an added benefit of trastuzumab emtansine in comparison with the ACT (individual treatment) is not proven for these patients.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the extent and probability of the added benefit of trastuzumab compared with the ACT is assessed as follows:

Subpopulation a: patients with HER2-positive, locally advanced, unresectable breast cancer

As there were no data for the comparison of trastuzumab emtansine versus the ACT radiotherapy in patients with HER2-positive, locally advanced, unresectable breast cancer, an added benefit of trastuzumab emtansine is not proven in this subpopulation.

Subpopulation b: patients with HER2-positive metastatic breast cancer, with prior treatment with anthracyclines, taxanes and trastuzumab

Overall, there were positive and negative effects for patients with HER2-positive metastatic breast cancer, with prior treatment with anthracyclines, taxanes and trastuzumab. There were positive effects in the outcome categories "mortality", "health-related quality of life" and "serious/severe AEs", and a negative effect in the outcome category "non-serious/non-severe AEs".

For balancing these effects, the positive effects were first considered separately. There was an indication of a considerable added benefit for the outcome "overall survival". In addition, for the time to worsening of health-related quality of life, there was a hint of a considerable added benefit for white patients. For the outcomes on AEs, there were positive effects of different certainty of results for serious/severe AEs. There was a hint of lesser harm with considerable extent for treatment discontinuations due to AEs and for severe AEs of CTCAE grade ≥ 3. The extent of lesser harm was major for diarrhoea (CTCAE grade ≥ 3). Due to the very large effect in hand-foot syndrome (CTCAE grade 3) and due to the fact that hardly any events occurred under trastuzumab emtansine, the certainty of results was greater for this outcome, which resulted in an indication of lesser harm with the extent "major". In the overall assessment of the positive effects, the indication of a major added benefit for this outcome was decisive for the overall conclusion.

The positive effects overall are offset by a hint of greater harm with the extent "considerable" in the category "non-severe/non-serious AEs" in the outcome "bleeding events". As these were mainly mild cases of nose bleed, this does not raise doubts about the overall assessment with regard to the positive effects.

[4] 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), see [1]. 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, no added benefit, or less benefit), see [2].

In summary, for patients with HER2-positive metastatic breast cancer who have been pretreated with anthracyclines, taxanes and trastuzumab, there is an indication of a major added benefit of trastuzumab emtansine versus the ACT lapatinib + capecitabine.

Subpopulation c: patients with HER2-positive metastatic breast cancer after pretreatment with taxanes and trastuzumab, but without anthracyclines

As there were no data for the comparison of trastuzumab emtansine with the ACT anthracycline (doxorubicin, epirubicin) for the subpopulation of patients with HER2-positive metastatic breast cancer after pretreatment with taxanes and trastuzumab, but without anthracyclines, an added benefit of trastuzumab emtansine is not proven for these patients.

Subpopulation d: patients with HER2-positive metastatic breast cancer, pretreated with taxanes and trastuzumab, for whom treatment with anthracyclines is not an option

There were no data for the subpopulation of patients with HER2-positive metastatic breast cancer after pretreatment with taxanes and trastuzumab, for whom treatment with anthracyclines is not an option, on the comparison of trastuzumab emtansine with the ACT individual treatment under consideration of the respective approval of the drugs used. Hence an added benefit of trastuzumab emtansine is not proven for these patients.

Summary

An overview of the assessment of trastuzumab emtansine in comparison with the respective ACT for the 4 subpopulations is given below (see Table 3).

Table 3: Trastuzumab emtansine: extent and probability of added benefit – summary

Subindication	**ACT**	**Extent and probability of added benefit**
Subpopulation a patients with HER2-positive, locally advanced, unresectable breast cancer	Radiotherapy	Added benefit not proven
Subpopulation b patients with HER2-positive metastatic breast cancer, with prior treatment with anthracyclines, taxanes and trastuzumab	Lapatinib + capecitabine	Indication of a major added benefit
Subpopulation c patients with HER2-positive metastatic breast cancer, with prior treatment with taxanes and trastuzumab, but without anthracyclines	Anthracycline (doxorubicin, epirubicin)	Added benefit not proven
Subpopulation d patients with HER2-positive metastatic breast cancer, with prior treatment with taxanes and trastuzumab, for whom treatment with anthracyclines is not an option	Individual treatment under consideration of the respective approval of the drugs used	Added benefit not proven
ACT: appropriate comparator therapy; HER2: human epidermal growth factor receptor 2		

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. 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 trastuzumab emtansine compared with the ACT in patients with HER2-positive, unresectable, locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either received prior treatment for locally advanced or metastatic disease, or developed disease recurrence during or within 6 months of completing adjuvant therapy.

The G-BA derived 4 subpopulations from the therapeutic indication, for which it specified one ACT each. Table 4 shows the patient groups and their respective ACTs.

Table 4: Overview of the ACTs for trastuzumab emtansine

Subindication	**ACT specified by the G-BA**	**ACT specified by the company**
Subpopulation a patients with HER2-positive, locally advanced, unresectable breast cancer	Radiotherapy	Lapatinib + capecitabine
Subpopulation b patients with HER2-positive metastatic breast cancer, with prior treatment with anthracyclines, taxanes and trastuzumab	Lapatinib + capecitabine	
Subpopulation c patients with HER2-positive metastatic breast cancer, with prior treatment with taxanes and trastuzumab, but without anthracyclines	Anthracycline (doxorubicin, epirubicin)	
Subpopulation d patients with HER2-positive metastatic breast cancer, with prior treatment with taxanes and trastuzumab, for whom treatment with anthracyclines is not an option	Individual treatment under consideration of the respective approval of the drugs used	
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2		

The company deviated from the G-BA's specification. It considered the total target population, for which it used lapatinib + capecitabine as comparator therapy. However, it additionally considered – according to the company only for completeness – the subpopulations mentioned in Table 4 compared with their respective ACTs specified by the G-BA.

The dossier assessment was conducted with the ACTs specified by the G-BA because the company did not provide sufficient reasons for deviating from the ACTs (see Section 2.7.1 of the full dossier assessment). The assessment was conducted based on patient-relevant outcomes and on RCTs.

Further information about the research question can be found in Module 3, Section 3.1, and Module 4, Section 4.2.1 of the dossier, and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

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 trastuzumab emtansine (studies completed up to 1 October 2013)
- bibliographical literature search on trastuzumab emtansine (last search on 3 October 2013)
- search in trial registries for studies on trastuzumab emtansine (last search on 14 November 2013)
- bibliographical literature search on the ACT (last search on 1 October 2013)
- search in trial registries for studies on the ACT (last search on 1 October 2013)

The Institute's own search to check the completeness of the study pool:

- bibliographical literature search on trastuzumab emtansine (last search on 16 January 2014)
- search in trial registries for studies on trastuzumab emtansine (last search on 16 January 2014)

No additional relevant study was identified from the check.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.3.1 Subpopulation a: patients with HER2-positive, locally advanced, unresectable breast cancer

No relevant study in comparison with the ACT was available for the assessment of the added benefit of trastuzumab emtansine in patients with HER2-positive, locally advanced, unresectable breast cancer.

This deviated from the company's approach, which included the EMILIA study (see Section 2.3.2.1) on the basis of the total population in its assessment and derived the added benefit of trastuzumab emtansine for the total target population. It did not present any additional separate analyses for the subpopulation of patients with HER2-positive, locally advanced, unresectable breast cancer.

2.3.2 Subpopulation b: patients with HER2-positive metastatic breast cancer after pretreatment with anthracyclines, taxanes and trastuzumab

2.3.2.1 Studies included

The study listed in Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: trastuzumab emtansine vs. lapatinib + capecitabine

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	**Sponsored study[a] (yes/no)**	**Third-party study (yes/no)**
EMILIA	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved.			

Almost exclusively patients with HER2-positive metastatic breast cancer after pretreatment with taxanes and trastuzumab were enrolled in the EMILIA study on the comparison of trastuzumab emtansine with lapatinib + capecitabine. More than half of the patients enrolled (605 of 991 patients, 61.0%) also had received prior treatment with anthracyclines. These patients therefore concur with subpopulation b specified by the G-BA (see Section 2.2). The dossier contained separate analyses for this subpopulation. In the present benefit assessment, the added benefit of trastuzumab emtansine versus the ACT specified by the G-BA (lapatinib + capecitabine) in patients with HER2-positive metastatic breast cancer after pretreatment with anthracyclines, taxanes and trastuzumab was assessed on the basis of this subpopulation of the EMILIA study.

This deviated from the company's approach, which included the EMILIA study on the basis of the total population in its assessment and derived the added benefit of trastuzumab emtansine for the total target population. The company additionally presented the data for the subpopulation of patients with HER2-positive metastatic breast cancer after pretreatment with anthracyclines, taxanes and trastuzumab, but only derived conclusions on the added benefit of trastuzumab emtansine for this subpopulation for completeness.

Section 2.6 contains a reference list for the study included.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment.

2.3.2.2 Study characteristics

Table 6 and Table 7 describe the EMILIA study used for the benefit assessment in patients with HER2-positive metastatic breast cancer after pretreatment with anthracyclines, taxanes and trastuzumab.

Table 6: Characteristics of the study included – RCT, direct comparison: trastuzumab emtansine vs. lapatinib + capecitabine

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
EMILIA	RCT, open-label, active-controlled, parallel, multicentre	Adult patients with HER2-positive, unresectable, locally advanced or metastatic breast cancer after prior treatment with trastuzumab and a taxane who have received prior treatment for locally advanced or metastatic treatment, or developed disease recurrence during or within 6 months of completing adjuvant therapy	Trastuzumab emtansine (N = 495) lapatinib + capecitabine (N = 496) relevant subpopulation with anthracycline pretreatment: trastuzumab emtansine (N = 303) lapatinib + capecitabine (N = 302)	Treatment duration: until disease progression, death or discontinuation of study medication by the patient or observation period: 3-monthly follow-up after cessation of study treatment until death	213 centres in Asia, Europe, North America, South America, New Zealand study start 2/2009 – ongoing First data cut-off 1/2012 after approximately 508 PFS events, final analysis of PFS, interim analysis of overall survival, analysis of AEs Second data cut-off 7/2012 after 316 deaths, planned due to results of the first data cut-off, final analysis of overall survival, additional analysis of PFS and AEs	Primary: PFS, overall survival secondary: health-related quality of life, AEs

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes contain exclusively information on relevant available outcomes for this benefit assessment.

AE: adverse event; HER2: human epidermal growth factor receptor 2; N: number of randomized patients; n: relevant subpopulation; PFS: progression-free survival; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: trastuzumab emtansine vs. lapatinib + capecitabine

Study	Intervention	Comparison	Concomitant medication
EMILIA	Trastuzumab emtansine: 3.6 mg/kg as IV infusion every 3 weeks	Lapatinib: 1250 mg orally, once daily as continuous dose capecitabine: 1000 mg/m^2 orally, twice daily on days 1–14 of a 21-day cycle	Concomitant medications required for the patient's safety and wellbeing were at the investigator's discretion, including bisphosphonates. Approved or investigational treatments for breast cancer, including cytotoxic chemotherapy, immunotherapy, hormonal therapy (except megestrol acetate), biologic agents (except G-CSF and ESA); radiotherapy (except for treating painful bone metastases). Premedication for nausea and anxiety was allowed if they were considered appropriate by the investigator. Drugs that interact with the study medications according to the respective SPC should be avoided.
ESA: erythropoiesis-stimulating agent; G-CSF: granulocyte colony-stimulating factor; IV: intravenous; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; vs.: versus			

The EMILIA study is an open-label, randomized, controlled, multinational phase 3 approval study on the comparison of trastuzumab emtansine with the combination of lapatinib and capecitabine. The study is currently in its third study phase (after the final confirmatory analysis of overall survival). It was conducted in 213 centres in Asia, Europe, North America, South America and New Zealand.

Adult patients with HER2-positive, locally advanced, unresectable breast cancer or with HER2-positive metastatic breast cancer with disease progression after pretreatment were enrolled in the study. The pretreatment had to be conducted in the adjuvant or unresectable, locally advanced or metastatic stage of the disease and had to include a taxane and trastuzumab, in each case separately or in combination with another drug. Disease progression should have occurred during or immediately after treatment for locally advanced breast cancer or metastatic breast cancer or within 6 months of completing adjuvant therapy. The vast majority of the study population were patients with metastatic breast cancer (a total of 976 of 991 patients, 98.5%). Patients were required to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 at the start of the study. Overall, the criteria of the approved therapeutic indication of trastuzumab emtansine were regarded as being fulfilled for the patient population.

Only a subpopulation of the EMILIA study was relevant for the present research question (patients with HER2-positive metastatic breast cancer after pretreatment with anthracyclines, trastuzumab and taxanes). Both patients with and without pretreatment with anthracyclines were enrolled in the study. Lapatinib + capecitabine was the ACT only for patients with

anthracycline pretreatment. For this reason, only this subpopulation was considered, which constituted approximately 61% of the total population of the study.

In the EMILIA study, a total of 991 patients were randomly assigned in a ratio of 1:1, either to treatment with trastuzumab emtansine (495 patients) or to treatment with lapatinib + capecitabine (496 patients). With regard to the relevant subpopulation, these were 605 patients in total, 303 patients in the trastuzumab emtansine arm, and 302 patients in the lapatinib + capecitabine arm. The patients were stratified by region, number of prior chemotherapeutic regimens for locally advanced or metastatic breast cancer and type of disease (visceral, non-visceral). The type of disease was assessed by the investigators at randomization. Visceral disease was defined as metastases in lungs and liver. Because false classifications occurred, an independent review committee (IRC) conducted a blinded assessment of the type of disease based on imaging at the start of the study. This independent assessment formed the basis of a reclassification of the patients. Besides the definition of visceral disease mentioned above, an expanded definition of visceral disease was determined post-hoc. This included metastases of lungs and liver and the presence of ascites or pleural effusion.

In the study, the drugs trastuzumab emtansine, lapatinib and capecitabine were used in compliance with their approval. Patients in the trastuzumab emtansine arm received 3.6 mg/kg intravenously every 3 weeks. Lapatinib was taken orally at a continuous dose of 1250 mg once daily. Capecitabine was taken orally at a dose of 1000 mg/m^2 body surface area twice daily for 2 weeks, followed by 1 week off treatment. According to the Summaries of Product Characteristics (SPCs) of trastuzumab emtansine, lapatinib and capecitabine, in some cases the dose should be reduced or treatment discontinued if severe AEs occur [3-5]. These were mostly implemented in the study. However, the approach in case of severe liver dysfunction under treatment with lapatinib deviated from the specifications in the SPC. Whereas dose reduction to 750 mg is specified in the study protocol, the SPC recommends discontinuation of treatment. However, in the EMILIA study, no dose reduction due to severe liver dysfunction (CTCAE grade ≥ 3) was performed in the lapatinib + capecitabine group.

Treatment with trastuzumab emtansine or lapatinib + capecitabine was continued until the occurrence of either disease progression (defined according to the Response Evaluation Criteria in Solid Tumours [RECIST]), death or the doctor’s or patient’s decision. Patients taking lapatinib + capecitabine could permanently discontinue one of the 2 drugs in case of toxicity without having to leave the study. However, this only applied to a small proportion of patients. In the total population of the study, 17 (3.4%) patients discontinued treatment with capecitabine due to AEs, 6 (1.2%) patients discontinued treatment with lapatinib.

Progression-free survival (PFS) and overall survival were recorded as coprimary outcomes in the study. Of these outcomes, overall survival was included as patient-relevant outcome in the benefit assessment. Further patient-relevant outcomes were health-related quality of life and AEs. AEs were recorded up to 30 days after the last administration of study medication.

Overall survival and health-related quality of life were recorded every 3 months after cessation of the study medication, until death, study discontinuation or end of study.

Two data cut-offs were performed during the study. The first data cut-off (performed in January 2012) was planned after 508 cases of disease progression, but only after enrolment of the last patient in the study. The final confirmatory analysis of the primary outcome "PFS" and the first interim analysis of the coprimary outcome "overall survival" were performed at this time point. The final analysis of overall survival was originally planned after 632 deaths. But because a strong tendency in overall survival was already seen at the first data cut-off, a second data cut-off was performed in accordance with an amendment to the protocol in July 2012, on which the second interim analysis of overall survival was based. This analysis was also the final confirmatory analysis of overall survival because the prespecified significance threshold was undercut at this time point. After this time point, patients could switch from the comparator arm to treatment with trastuzumab emtansine (crossover). This last study phase will probably end in the first quarter of 2014. The data cut-off from July 2012 was decisive for the present benefit assessment because it covered the longest observation period possible. This deviated from the company's approach, which presented the results from the first and second data cut-off for some of the outcomes, and based its conclusions on added benefit for these outcomes on the results of the first data cut-off.

Table 8 shows the characteristics of the patients with HER2-positive metastatic breast cancer, pretreated with anthracyclines, taxanes and trastuzumab (subpopulation b of the G-BA) in the study included.

Table 8: Characteristics of the study populations (subpopulation b) – RCT, direct comparison: trastuzumab emtansine vs. lapatinib + capecitabine

Study characteristics category	Trastuzumab emtansine N = 303	Lapatinib + capecitabine N = 302
EMILIA		
Age [years]: mean (SD)	51 (10)	52 (10)
Sex: [F/M], %	100/0	99/1
Time between diagnosis of LABC/MBC and randomization [months], mean (SD)	24 (25)	26 (28)
ECOG PS, n (%)		
0	189 (62.4)	195 (64.6)
1	113 (37.3)	102 (33.8)
Unknown	1 (0.3)	5 (1.7)
Type of disease (IRC assessment)[a], n (%)		
Visceral	212 (70.0)	200 (66.2)
Non-visceral	91 (30.0)	102 (33.8)
Region, n (%)		
USA	63 (20.8)	56 (18.5)
Western Europe	100 (33.0)	107 (35.4)
Asia	50 (16.5)	50 (16.6)
Others	90 (29.7)	89 (29.5)
Ethnicity, n (%)		
White	228 (75.2)	226 (74.8)
Asian	55 (18.2)	56 (18.5)
Black or Afro-American	10 (3.3)	10 (3.3)
Native Americans or Native Alaskans	4 (1.3)	7 (2.3)
Native Hawaiians or other pacific islanders	1 (0.3)	2 (0.7)
Unknown	5 (1.7)	1 (0.3)
Menopausal status at first diagnosis, n (%)		
Premenopausal	146 (48.2)	150 (49.7)
Perimenopausal	12 (4.0)	12 (4.0)
Postmenopausal	105 (34.7)	107 (35.4)
Unknown	29 (9.6)	26 (8.6)
Not applicable	11 (3.6)	7 (2.3)
Number of prior chemotherapeutic regimens for LABC or MBC		
0-1	164 (54.1)	174 (57.6)
> 1	139 (45.9)	128 (42.4)

(continued)

Table 8: Characteristics of the study populations (subpopulation b) – RCT, direct comparison: trastuzumab emtansine vs. lapatinib + capecitabine (continued)

Study characteristics category	Trastuzumab emtansine N = 303	Lapatinib + capecitabine N = 302
Prior systemic cancer treatment for LABC or MBC, n (%)		
Yes	261 (86.1)	256 (84.8)
No[b]	42 (13.9)	46 (15.2)
Study discontinuations[c, d], n (%)	187 (37.8)	235 (47.4)
Treatment discontinuations[c, e]	391 (79.0)	441 (88.9)

a: The characteristic "type of disease" determined a priori was reassessed in the course of the study on the basis of imaging at the start of the study (see Section 2.3.2.2). Visceral disease was then defined as metastases in the lungs or liver and the presence of ascites or pleural effusion.
b: Patients received the prior systemic cancer treatment at an earlier stage than the metastatic stage.
c: Data for the total population of the study (all randomized patients; 495 patients in the trastuzumab arm and 496 patients in the lapatinib + capecitabine arm).
d: 149 (30.1%) patients in the trastuzumab emtansine arm and 183 (36.9%) patients in the lapatinib + capecitabine arm discontinued the study because they died.
e: The most common reason for treatment discontinuation was disease progression. Approximately 66% of the patients under trastuzumab emtansine and approximately 69% under lapatinib + capecitabine discontinued treatment because of this.
ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; IRC: independent review committee; LABC: locally advanced breast cancer; M: male; MBC: metastatic breast cancer; N: number of randomized patients; n: number of patients in the category; RCT: randomized controlled trial; SD: standard deviation; USA: United States of America; vs.: versus

Both women and men were enrolled in the study. However, the proportion of men was very small (no patient in the trastuzumab emtansine group and 3 (1.0%) patients in the comparator group). The patient characteristics were balanced between the study arms. The mean age of the patients was about 52 years. The mean time since diagnosis of the locally advanced or metastatic disease was 24 and 26 months. Most patients had visceral disease (approximately 68%). The majority of the patients came from Western countries and were therefore of white origin. About 63% of the patients had an ECOG PS of 0, about 36% of the patients had an ECOG-PS of 1. About 85% of the patients had already received systemic cancer treatment for locally advanced or metastatic cancer, the remaining 15% had received systemic cancer treatment at an earlier stage.

In the total population of the study, fewer patients permanently discontinued treatment under trastuzumab emtansine (about 38% in the trastuzumab emtansine arm and about 47% in the lapatinib + capecitabine arm). These numbers also include the patients who died (30.1% under trastuzumab emtansine and 36.9% under lapatinib + capecitabine). The proportion of patients who discontinued treatment was also smaller under trastuzumab emtansine (about 79% of the patients under trastuzumab emtansine and about 89% of the patients under lapatinib + capecitabine). The most common reason for treatment discontinuation was disease progression. Information on the course of the study is provided in Table 9.

Table 9: Information on the course of the study – RCT, direct comparison: trastuzumab emtansine vs. lapatinib + capecitabine

Study	Trastuzumab emtansine N = 495	Lapatinib + capecitabine[a] N = 496
EMILIA		
Observation period[b, c] [months], median (min-max)	19.1 (0 - 40.3)	18.6 (0 - 41.2)
Treatment duration[b] [months], median (min-max)	7.6 (0 - 34.8)	5.5 (0 - 33.3)[d]/ 5.3 (0 - 33.3)[e]

a: Treatment with lapatinib and capecitabine could be discontinued separately in the study.
b: Data for the total population of the study.
c: The observation period applies to the outcomes on overall survival and on health-related quality of life.
d: Median treatment duration for lapatinib.
e: Median treatment duration for capecitabine.
max: maximum; min: minimum; RCT: randomized controlled trial; vs.: versus

The median treatment duration was longer in the trastuzumab emtansine arm than in the lapatinib capecitabine arm. In contrast, the median observation period for overall survival and health-related quality of life was comparable in both arms. No information was available for the actual observation period on AEs. Based on the planned follow-up period of 30 days, a median observation period of 8 to 9 months (trastuzumab emtansine) and 6 to 7 months (lapatinib, capecitabine) was assumed for these outcomes. In the comparator arm, it was therefore between 67% and 88% of the one in the trastuzumab emtansine arm.

Table 10 shows the risk of bias at study level.

Table 10: Risk of bias at study level – RCT, direct comparison: trastuzumab emtansine vs. lapatinib + capecitabine

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
EMILIA	Yes	Yes	No	No	Yes	Yes	Low

The risk of bias at the study level was rated as low for the EMILIA study. This concurs with the company's assessment. Outcome-specific limitations, which resulted from the open-label study design among other things, are described in Section 2.4.2.2 with the outcome-specific risk of bias.

2.3.3 Subpopulation c: patients with HER2-positive metastatic breast cancer after pretreatment with taxanes and trastuzumab, but without anthracyclines

No relevant study in comparison with the ACT anthracyclines was available for the assessment of the added benefit of trastuzumab emtansine in patients with HER2-positive metastatic breast cancer after pretreatment with taxanes and trastuzumab, but without anthracyclines.

This deviated from the company's approach, which included the EMILIA study (see Section 2.3.2.1) on the basis of the total population in its assessment and derived the added benefit of trastuzumab emtansine for the total target population. It additionally presented the data of patients from the EMILIA study who had not received pretreatment with anthracyclines (386 of 991 patients, 39.0%). But the comparator therapy (lapatinib + capecitabine) used in the study did not concur with the ACT specified by the G-BA for this subpopulation (anthracyclines [doxorubicin, epirubicin]). Hence it was not possible to draw conclusions on the added benefit of trastuzumab emtansine versus the ACT specified by the G-BA for this subpopulation.

2.3.4 Subpopulation d: patients with HER2-positive metastatic breast cancer, pretreated with taxanes and trastuzumab, for whom treatment with anthracyclines is not an option

There was also no relevant study in comparison with individual treatment, which the G-BA had specified as the ACT for this group, for the assessment of the added benefit of trastuzumab emtansine in patients with HER2-positive metastatic breast cancer who have been pretreated with taxanes and trastuzumab, but for whom treatment with anthracyclines is not an option.

This deviated from the company's approach, which included the EMILIA study (see Section 2.3.2.1) on the basis of the total population in its assessment and derived the added benefit of trastuzumab emtansine for the total target population. The company presented an analysis of the data on the subpopulation of the patients in the EMILIA study who had not received pretreatment with anthracyclines, and who, according to the company's information based on the recorded medical history and pre-existing conditions, were very likely to have a contraindication to treatment with anthracyclines (14 of 386 patients, 3.6%). But the comparator therapy (lapatinib + capecitabine) used in the study did not concur with the ACT specified by the G-BA for this subpopulation (individual treatment). Hence it was not possible to draw conclusions on the added benefit of trastuzumab emtansine versus the ACT specified by the G-BA.

Further information on study design, study populations and the risk of bias at study level can be found in Module 4, Sections 4.3.1.2.1, 4.3.1.2.2 and 4.3.2.1.2, and in Appendix 4-E of the dossier, and in Sections 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.

2.4 Results on added benefit

2.4.1 Subpopulation a: patients with HER2-positive, locally advanced, unresectable breast cancer

For the subpopulation of patients with HER2-positive, locally advanced, unresectable breast cancer, there were no relevant data in comparison with the ACT (radiotherapy) specified by the G-BA. Hence an added benefit of trastuzumab emtansine versus the ACT is not proven in these patients.

2.4.2 Subpopulation b: patients with HER2-positive metastatic breast cancer after pretreatment with anthracyclines, taxanes and trastuzumab

2.4.2.1 Outcomes included

The following patient-relevant outcomes were considered in this assessment regarding the subpopulation of patients with HER2-positive metastatic breast cancer, pretreated with anthracyclines, taxanes and trastuzumab (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - overall survival
- Health-related quality of life (measured with the Trial Outcomes Index-Physical/Functional/Breast [TOI-PFB] of the Functional Assessment of Cancer Therapy – Breast Cancer [FACT-B] questionnaire)
  - time to worsening
- Adverse events
  - SAEs
  - treatment discontinuations due to AEs
  - severe AEs (CTCAE grade ≥ 3)
  - bleeding events
  - diarrhoea (CTCAE grade ≥ 3)
  - hand-foot syndrome (CTCAE grade 3)

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes or deviating operationalizations in the dossier (Module 4) (see Section 2.7.2.4.3 of the full dossier assessment). These outcomes included PFS, objective response rate (ORR) and patient-reported diarrhoea, recorded with the Diarrhoea Assessment Scale (DAS) as morbidity outcomes, as well as improvement of health-related quality of life recorded with the TOI-PFB subscale of the FACT-B. The outcomes “PFS” and “ORR” were not used for this assessment because neither the patient relevance postulated in the dossier

(both outcomes were exclusively recorded using imaging techniques) nor the validity of a surrogate characteristic was adequately presented. Instead of using the outcome "patient-reported diarrhoea", diarrhoea recorded as AE (CTCAE grade ≥ 3) was used in the present benefit assessment because it is more suitable for reflecting severe diarrhoea. Health-related quality of life was regarded to be sufficiently reflected by the time to worsening so that the improvement was not additionally considered. The specific AEs "bleeding events", "diarrhoea" and "hand-foot syndrome" were chosen based on frequency and differences between the treatment groups in the EMILIA study under consideration of the patient relevance. More explanations on the choice of outcomes can be found in Section 2.7.2.4.3 of the full dossier assessment.

Table 11 shows for which outcomes data were available in the studies included.

Table 11: Matrix of outcomes – RCT, direct comparison: trastuzumab emtansine vs. lapatinib + capecitabine

Study	Outcomes								
	Overall survival	**Morbidity**	**Time to worsening of health-related quality of life[a]**	**SAEs**	**Treatment discontinuation due to AEs**	**Severe AEs CTCAE grade ≥ 3**	**Bleeding events**	**Diarrhoea CTCAE grade ≥ 3**	**Hand-foot syndrome CTCAE grade 3**
EMILIA	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a: Measured with the TOI-PFB subscale of the FACT-B questionnaire. Event refers to the first occurrence of a decrease of 5 points in the TOI-PFB score.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FACT-B: Functional Assessment of Cancer Therapy – Breast Cancer; RCT: randomized controlled trial; SAE: serious adverse event; TOI-PFB: Trial Outcomes Index-Physical/Functional/Breast; vs.: versus

2.4.2.2 Risk of bias at outcome level

Table 12 shows the risk of bias for the outcomes included.

Table 12: Risk of bias at study and outcome level – RCT, direct comparison: trastuzumab emtansine vs. lapatinib + capecitabine

Study	Study level	Outcomes							
		Overall survival	Time to worsening of health-related quality of life[a]	SAEs	Treatment discontinuation due to AEs	Severe AEs CTCAE grade ≥ 3	Bleeding events	Diarrhoea CTCAE grade ≥ 3	Hand-foot syndrome CTCAE grade 3
EMILIA	L	L	H	H	H	H	H	H	H

a: Measured with the TOI-PFB subscale of the FACT-B questionnaire. Event refers to the first occurrence of a decrease of 5 points in the TOI-PFB score.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FACT-B: Functional Assessment of Cancer Therapy – Breast Cancer; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; TOI-PFB (Trial Outcomes Index-Physical/Functional/Breast); vs.: versus

The risk of bias for the outcome "overall survival" was assessed as low. This concurs with the company's assessment. The outcome "time to worsening of health-related quality of life" was rated as potentially highly biased due to the lack of blinding. This also concurs with the company's assessment.

The risk of bias for the outcomes on AEs was rated as high because of the different observation periods between the treatment groups and the lack of blinding of patient and treating staff and the generally subjective component in the recording of the outcomes. This does not with the company's assessment, which rated the risk of bias of the outcomes on AEs as low. More explanations on this can be found in Section 2.7.2.4.2 of the full dossier assessment.

Further information on the choice of outcomes and risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier, and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

2.4.2.3 Results

The following tables summarize the results on the comparison of trastuzumab emtansine with lapatinib + capecitabine in patients with HER2-positive metastatic breast cancer, pretreated with anthracyclines, taxanes and trastuzumab (subpopulation b). Where necessary, the data from the company's dossier were supplemented by the Institute's own calculations.

The EMILIA study did not meet the particular requirements placed on the derivation of proof from a single study (see Section 2.7.2.8.1 of the full dossier assessment). Hence at most indications could be inferred from the data of the study.

Table 13 shows the results on overall survival and on health-related quality of life. Kaplan-Meier curves on the outcomes "overall survival" and "time to worsening of health-related quality of life" can be found in Appendix A of the full dossier assessment.

Table 13: Results on mortality and health-related quality of life (subpopulation b) – RCT, direct comparison: trastuzumab emtansine vs. lapatinib + capecitabine

Study outcome *data cut-off July 2012*	**Trastuzumab emtansine**		**Lapatinib + capecitabine**		**Trastuzumab emtansine vs. lapatinib + capecitabine**	
	N	**Median survival time in months [95% CI]**	**N**	**Median survival time in months [95% CI]**	**HR [95% CI]**	**p-value**
EMILIA						
Mortality						
Overall survival	303	30.9 [25.4; NA]	302	23.7 [20.9; 33.9]	0.70 [0.53; 0.92][a]	0.010
Health-related quality of life (physical/functional component)						
Time to worsening[b]	277	6.6 [5.4; 8.9]	278	5.5 [4.2; 6.9]	0.80 [0.65; 0.999][a]	0.0495

a: Stratified by region (USA, Western Europe, others), number of prior chemotherapeutic regimens for LABC or MBC (0-1, > 1) and type of disease (visceral, non-visceral).
b: Measured with the TOI-PFB subscale of the FACT-B questionnaire. Event refers to the first occurrence of a decrease of 5 points in the TOI-PFB score.
CI: confidence interval; FACT-B: Functional Assessment of Cancer Therapy – Breast Cancer; HR: hazard ratio; LABC: locally advanced breast cancer; MBC: metastatic breast cancer; N: number of analysed patients; NA: not analysed or not evaluable; RCT: randomized controlled trial; TOI-PFB: Trial Outcomes Index-Physical/Functional/Breast; USA: United States of America; vs.: versus

Table 14 summarizes the results on AEs. Additional information on the naive proportion of the events are presented in Table 25 in Appendix B of the full dossier assessment.

The odds ratio offers a good approximation of the relative risk in low numbers of events. Hence in event rates of ≤ 1% (in at least one cell), the Peto odds ratio instead of the relative risk was calculated as effect measure and used for the assessment. This was the case with the outcome "hand-foot syndrome", where the numbers of events in the trastuzumab emtansine arm were very low (≤ 1%).

Table 14: Results on AEs (subpopulation b) – RCT, direct comparison: trastuzumab emtansine vs. lapatinib + capecitabine

Study **outcome category** **outcome** *data cut-off July 2012*	**Trastuzumab emtansine**		**Lapatinib + capecitabine**		**Trastuzumab emtansine vs. lapatinib + capecitabine**
	N	**Median time to first event [95% CI]**	**N**	**Median time to first event [95% CI]**	**HR [95% CI] p-value**
EMILIA					
Adverse events					
SAEs	300	ND	297	ND	0.85 [0.59; 1.23] 0.386[a]
Treatment discontinuations due to AEs	300	ND	297	ND	0.50 [0.29; 0.87] 0.013[a]
Severe AEs of CTCAE grade ≥ 3[b]	300	ND	297	ND	0.61 [0.48; 0.77] < 0.001[a]
Bleeding events[c]	300	ND	297	ND	2.17 [1.52; 3.10] < 0.001[a]
	N	**Patients with events n (%)**	**N**	**Patients with events n (%)**	**RR [95% CI] p-value**
Diarrhoea (CTCAE grade ≥ 3)[d]	300	7 (2.3)	297	59 (19.9)[e]	0.12 [0.05; 0.25][e] < 0.001[f]
Hand-foot syndrome (CTCAE grade 3)[g]	300	0	297	53 (17.8)	Peto-OR[h] 0.11 [0.06; 0.19] < 0.001[f]

a: Institute's calculation, asymptotic.
b: The difference between the treatment groups was largely caused by CTCAE grade 3 AEs (HR [95% CI]: 0.60 [0.48; 0.76]); p < 0.001 [Institute's calculation of p-value, asymptotic]).
c: Based on SMQs "Haemorrhage Laboratory Terms" (narrow) and "Haemorrhage Terms (excluding laboratory terms)" (wide). No events occurred on the SMQ "Haemorrhage Laboratory Terms". Bleeding events are mainly mild AEs of CTCAE grade 1 and 2.
d: The difference between the treatment groups was largely caused by CTCAE grade 3 AEs. For the overall rate of diarrhoea (CTCAE grade 1-5), the difference between the treatment groups was just as pronounced (HR [95% CI]: 0.15 [0.12; 0.20]; p < 0.001 [Institute's calculation of p-value, asymptotic]).
e: Institute's calculation.
f: Institute's calculation, unconditional exact test (CSZ method according to [6]).
g: For the overall rate of hand-foot syndrome (CTCAE grade 1-3), the difference between the treatment groups was just as pronounced (HR [95% CI]: 0.02 [0.01; 0.04]; p < 0.001 [Institute's calculation of p-value, asymptotic]).
h: Peto OR (Institute's calculation) provided in event numbers ≤ 1% in at least one treatment arm.
AE: adverse event; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; ND: no data; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SMQ: Standardized Medical Dictionary for Regulatory Activities Query; vs.: versus

Mortality

Overall survival

Treatment with trastuzumab emtansine produced a statistically significant prolongation of overall survival compared with lapatinib + capecitabine. There is therefore an indication of an added benefit of trastuzumab emtansine for the outcome "overall survival" compared with the ACT lapatinib + capecitabine.

This deviates from the company's assessment, which claimed proof of an added benefit on the basis of the total population of the EMILIA study.

Morbidity

The company did not present any evaluable data on morbidity in its dossier (see Section 2.7.2.4.3 of the full dossier assessment). An added benefit of trastuzumab emtansine in comparison with lapatinib + capecitabine is not proven for morbidity.

This deviates from the company's assessment, which derived proof of an added benefit on the basis of the outcomes "PFS", "ORR" and "patient-reported diarrhoea".

Health-related quality of life (physical/functional component, measured with the TOI-PFB of the FACT-B)

Time to worsening

Treatment with trastuzumab emtansine produced a statistically significant prolongation of the time to worsening of health-related quality of life in comparison with lapatinib + capecitabine. For this outcome, there was a high risk of bias based on outcome.

In addition, there was proof of an effect modification by the characteristic "ethnicity". Due to the high risk of bias, for white patients, there was a hint of an added benefit of trastuzumab emtansine in comparison with the ACT lapatinib + capecitabine regarding the time to worsening of health-related quality of life (physical/functional component). For patients of other ethnicities, an added benefit of trastuzumab emtansine is not proven.

The added benefit was exclusively shown for the physical/functional component of health-related quality of life because only these components are included in the TOI-PFB subscale of the FACT-B. No analyses were presented on the influence of trastuzumab emtansine on psychosocial components or on the FACT-B total score.

This deviates from the company's assessment, which, on the basis of the total population of the EMILIA study, claimed proof of an added benefit for this outcome and did not consider the subgroup.

Adverse events

Serious adverse events

There was no statistically significant difference between the treatment groups for the outcome "SAEs". Lesser or greater harm from trastuzumab emtansine than from the ACT lapatinib + capecitabine is therefore not proven for this outcome.

This concurs with the company's assessment.

Treatment discontinuations due to AEs, severe AEs (CTCAE grade ≥ 3)

For the outcomes "treatment discontinuations due to AEs" and "severe AEs of CTCAE grade ≥ 3, there was a statistically significant difference in favour of trastuzumab emtansine. Because of the high risk of bias for these outcomes, this results in a hint of lesser harm from trastuzumab emtansine than from the ACT lapatinib + capecitabine.

This deviates from the company's assessment, which claimed proof of an added benefit in each case.

Bleeding events

There was a statistically significant difference to the disadvantage of trastuzumab emtansine compared with lapatinib + capecitabine for the outcome "bleeding events". Because of the high risk of bias for this outcome, this results in a hint of greater harm from trastuzumab emtansine than from the ACT lapatinib + capecitabine.

This deviates from the company's assessment, which did not include this outcome in its assessment.

Diarrhoea (CTCAE grade ≥ 3)

The proportion of patients with severe diarrhoea (CTCAE grade ≥ 3) was statistically significantly smaller under treatment with trastuzumab emtansine than under lapatinib + capecitabine. Due to the different observation periods of the treatment groups (the median observation period in the comparator arm was 67% to 88% of the one in the trastuzumab emtansine arm), the relative risks estimated on the basis of naive proportions, which the company presented, were no adequate analysis in this situation. However, as there was an advantage of trastuzumab emtansine for this outcome, due to the known direction of bias to the disadvantage of trastuzumab emtansine, a conclusion can be derived that greater harm from trastuzumab emtansine is excluded. Moreover, it can be assumed that the statistically significant effect in favour of trastuzumab emtansine would remain if the bias was eliminated. Overall this results in a hint of lesser harm from trastuzumab emtansine than from the ACT lapatinib + capecitabine.

This deviates from the company's assessment, which did not include this outcome in its assessment.

Hand-foot syndrome (CTCAE grade 3)

The proportion of patients with severe hand-foot syndrome (CTCAE grade 3) was statistically significantly smaller under treatment with trastuzumab emtansine than under lapatinib + capecitabine. The relative risks estimated on the basis of naive proportions by the company also were no adequate analysis in this situation for this outcome due to the aspects explained for the outcome "diarrhoea". However, as there was also an advantage in favour of trastuzumab emtansine for this outcome, due to the known direction of bias, greater harm from trastuzumab emtansine can be excluded. It can also be assumed that the statistically significant effect in favour of trastuzumab emtansine would remain if the bias was eliminated.

It should also be noted that there were no CTCAE grade 3 events in the trastuzumab emtansine arm, and that only 5 patients had hand-foot syndrome of a lower severity grade (CTCAE grade 1 and 2). Even if these few events had been wrongly categorized as non-severe due to the lack of blinding of patients and investigators, this effect in favour of trastuzumab emtansine could not have been considerably changed. On the other hand, hand-foot syndrome is a known and, according to the SPC, common AE of the combination therapy of lapatinib and capecitabine. Hence misjudging the severity grade of events that occurred in patients in the comparator arm is rather likely. However, more than half of the patients in the lapatinib + capecitabine arm with hand-foot syndrome of CTCAE grade 3 would have to be misclassified for the observed effect to be no longer "major". Because of the definitions of the CTCAE severity grades for the outcome "hand-foot syndrome" (see Table 30 in Appendix B of the full dossier assessment), it was also assumed that the influence of the lack of blinding could not raise doubts about the effect or its extent. In summary, this results in an indication of lesser harm from trastuzumab emtansine compared with the ACT lapatinib + capecitabine for the outcome "hand-foot syndrome of CTCAE grade 3".

This deviates from the company's assessment, which did not include this outcome in its assessment.

2.4.2.4 Subgroups and other effect modifiers

In order to uncover possible effect differences between the patient groups, the following potential effect modifiers were investigated:

- age (< 65 years/≥ 65 years)
- ethnicity (white/Asian/others)
- region (United States of America/Western Europe/others)
- ECOG PS (0/1)
- number of prior chemotherapeutic regimens for locally advanced or metastatic breast cancer (0–1/>1)
- prior systemic cancer treatment for locally advanced or metastatic breast cancer (yes/no)

- hormone receptor status (progesterone receptor positive and/or oestrogen receptor positive/progesterone receptor negative and oestrogen receptor negative)

The prerequisite for proof of different effects is a statistically significant interaction test ($p < 0.05$). A p-value between 0.05 and 0.2 provides an indication of different effects.

Subgroup analyses on all characteristics mentioned above were only available for the outcomes "overall survival" and "health-related quality of life". For the outcomes on AEs, only subgroup analyses on the characteristics "age", "ethnicity" and "region" were available in the dossier. However, these were only conducted using the relative risks estimated on the basis of naive proportions and not using the survival time analyses (hazard ratios) relevant for the present benefit assessment. Because of this, the results of the interaction tests were not evaluable for the outcomes on AEs.

Time to worsening of health-related quality of life

The results of the subgroup analyses for the time to worsening of health-related quality of life according to the characteristic "ethnicity" are presented in Table 15.

Table 15: Subgroups: outcome "time to worsening of health-related quality of life" according to the characteristic "ethnicity" (subpopulation b) – RCT, direct comparison: trastuzumab emtansine vs. lapatinib + capecitabine

Study outcome	**Trastuzumab emtansine**		**Lapatinib + capecitabine**		**trastuzumab emtansine vs. lapatinib + capecitabine**	
characteristic **subgroup** *data cut-off July 2012*	**N**	**Median time to event in months [95% CI]**	**N**	**Median time to event in months [95% CI]**	**HR [95% CI]**	**p-value**
EMILIA						
Time to worsening of health-related quality of life						
Ethnicity						
White	209	8.3 [5.6; 11.7]	205	4.5 [3.5; 6.4]	0.66 [0.51; 0.86]	0.002
Asian + others[a]	68	ND	73	ND	1.47 [0.95; 2.26]	0.081
Asian	*50*	*3.0 [2.8; 5.6]*	*54*	*4.8 [2.8; 8.1]*	*1.36 [0.84; 2.18]*	0.200
Others[b]	*18*	*5.7 [2.8; 8.1]*	*19*	*NA [4.1; ND]*	*2.05 [0.75; 5.56]*	*0.152*
					Interaction[c]:	0.004

Italic type: subgroups (from primary subgroup analyses) that were summarized; see following text for more details.

a: The groups "Asian" and "others" were summarized because heterogeneity could not be demonstrated in pairwise comparison, see following text for more details; Institute's calculation of all values.
b: The subgroup included blacks, African Americans, American Indians, native Alaskans, Native Hawaiians, other pacific islanders and patients of unknown ethnicity.
c: Interaction test relating to the original subgroups (white, Asian, others).

CI: confidence interval; HR: hazard ratio; NA: not analysed or not evaluable; ND: no data; RCT: randomized controlled trial; vs.: versus

In the subgroup analyses on the outcome "time to worsening of health-related quality of life", the investigation for the characteristic "ethnicity" showed proof of an effect modification across all 3 subgroups (interaction test: p = 0.004). The pairwise comparisons of the subgroups neighbouring with regard to the respective effect estimates showed that there was also proof of effect modification between white and Asian patients (interaction test: p = 0.009), but that there was no indication of effect modification between Asian patients and patients of other ethnicities (interaction test: p = 0.468). The subgroups of Asian patients and of patients of other ethnicities were therefore summarized in a meta-analysis to a joint subgroup.

There was a statistically significant advantage of trastuzumab emtansine versus lapatinib + capecitabine in the subgroup of patients of white ethnicity. For these patients, this resulted in an indication of an added benefit of trastuzumab emtansine in comparison with the ACT regarding health-related quality of life (physical/functional component). In the other patients, the time to worsening of health-related quality of life was not statistically significantly different between trastuzumab emtansine and lapatinib + capecitabine. Due to the fact that there is proof of an effect modification, an added benefit of trastuzumab emtansine is not proven for these patients.

As the patients of white origin represent the main ethnicity for the health care area of the present benefit assessment, the subgroup of the other ethnicities are not considered further in the present benefit assessment.

2.4.3 Subpopulation c: patients with HER2-positive metastatic breast cancer after pretreatment with taxanes and trastuzumab, but without anthracyclines

There were no relevant data for the subpopulation of patients with HER2-positive metastatic breast cancer after pretreatment with taxanes and trastuzumab, but without anthracyclines, in comparison with the ACT specified by the G-BA. Hence an added benefit of trastuzumab emtansine versus the ACT is not proven in these patients.

2.4.4 Subpopulation d: patients with HER2-positive metastatic breast cancer, pretreated with taxanes and trastuzumab, for whom treatment with anthracyclines is not an option

There were no relevant data for the subpopulation of patients with HER2-positive metastatic breast cancer after pretreatment with taxanes and trastuzumab, for whom treatment with anthracyclines is not an option, in comparison with the ACT specified by the G-BA. Hence an added benefit of trastuzumab emtansine versus the ACT is not proven in these patients.

Further information on the choice of outcomes, on risk of bias at outcome level, and on outcome results can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit for each subquestion is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Subpopulation a: patients with HER2-positive, locally advanced, unresectable breast cancer

The dossier contained no data for patients with HER2-positive, locally advanced, unresectable breast cancer for a comparison of trastuzumab emtansine with radiotherapy (see Section 2.3.1). Hence an added benefit of trastuzumab emtansine in comparison with the ACT radiotherapy is not proven for these patients.

2.5.2 Subpopulation b: patients with HER2-positive metastatic breast cancer after pretreatment with anthracyclines, taxanes and trastuzumab

2.5.2.1 Assessment of added benefit at outcome level

The data presented in Section 2.4.2 resulted in indications or hints of an added benefit of trastuzumab emtansine in comparison with lapatinib + capecitabine for the outcomes “overall survival” and “health-related quality of life”. Regarding each of the outcomes on harm “treatment discontinuations due to AEs”, “severe AEs of CTCAE grade ≥ 3” and “diarrhoea (CTCAE grade ≥ 3)”, there was a hint of lesser harm; for the outcome “hand-foot syndrome CTCAE grade 3)”, there was an indication of lesser harm from trastuzumab emtansine than from lapatinib + capecitabine. This was offset by a hint of greater harm from trastuzumab emtansine regarding the outcome on harm “bleeding events”.

Moreover, there was proof of an effect modification by the subgroup characteristic “ethnicity” (white/others). The extent of the respective added benefit at outcome level was estimated from these results (see Table 16). In the overall assessment, it was then investigated whether different conclusions on the extent of added benefit arise for the individual patient groups.

Table 16: Extent of added benefit at outcome level (subpopulation b): trastuzumab emtansine vs. lapatinib + capecitabine

Outcome category **outcome** **subgroup characteristic**	**Trastuzumab emtansine vs. lapatinib + capecitabine** **time to event or proportion of events** **effect estimate [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	Median: 30.9 vs. 23.7 months HR: 0.70 [0.53; 0.92] p = 0.010 probability: "indication"	Outcome category "mortality" $0.85 < CI_u < 0.95$ added benefit, extent "considerable"
Morbidity		
	No data	
Health-related quality of life (physical/functional component)		
Time to worsening ethnicity white	Median: 8.3 vs. 4.5 months HR: 0.66 [0.51; 0.86] p = 0.002 probability: "hint"	Outcome category "health-related quality of life $0.75 < CI_u < 0.90$ added benefit, extent "considerable"
Asian + others	Median: ND HR: 1.47 [0.95; 2.26] p = 0.081	Lesser benefit/added benefit not proven

(continued)

Table 16: Extent of added benefit at outcome level (subpopulation b): trastuzumab emtansine vs. lapatinib + capecitabine (continued)

Outcome category **outcome** **subgroup characteristic**	**Trastuzumab emtansine vs. lapatinib + capecitabine** **effect estimate [95% CI]** **p-value** **time to event or proportion of events** **probability**[a]	**Derivation of extent**[b]
Adverse events		
SAEs	Median: ND HR: 0.85 [0.59; 1.23] p = 0.386	Lesser/greater harm not proven
Treatment discontinuations due to AEs	Median: ND HR: 0.50 [0.29; 0.87] p = 0.013 probability: "hint"	Outcome category "serious/severe AEs" $0.75 < CI_u < 0.90$ lesser harm, extent: "considerable"
Severe AEs (CTCAE grade ≥ 3)	Median: ND HR: 0.61 [0.48; 0.77] p < 0.001 probability: "hint"	Outcome category "serious/severe AEs" $0.75 < CI_u < 0.90$ lesser harm, extent: "considerable"
Bleeding events	Median: ND HR: 2.17 [1.52; 3.10] HR[c]: 0.46 [0.32; 0.66] p < 0.001 probability: "hint"	Outcome category "non-serious/non-severe AEs" $CI_u < 0.80$ greater harm, extent: "considerable"
Diarrhoea (CTCAE grade ≥ 3)	2.3% vs. 19.9% RR 0.12 [0.05; 0.25] p < 0.001 probability: "hint"	Outcome category "serious/severe AEs" $CI_u < 0.75$ lesser harm, extent: "major"
Hand-foot syndrome (CTCAE grade 3)	0% vs. 17.8% Peto OR: 0.11 [0.06; 0.19] p < 0.001 probability: "indication"	Outcome category "serious/severe AEs" $CI_u < 0.75$ lesser harm, extent: "major"

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Proportion of events lapatinib + capecitabine vs. trastuzumab emtansine (reversed direction of effect to allow direct use of limits to derive the extent of added benefit).
AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; ND: no data; Peto OR: Peto odds ratio; RR: relative risk; SAE: serious adverse event; vs.: versus

2.5.2.2 Overall conclusion on added benefit

Table 17 summarizes the results that were considered in the overall conclusion on the extent of added benefit for patients with HER2-positive metastatic breast cancer who have been pretreated with anthracyclines, taxanes and trastuzumab.

Table 17: Positive and negative effects from the assessment of trastuzumab emtansine compared with lapatinib + capecitabine (subpopulation b)

Positive effects	**Negative effects**
Mortality: ▪ overall survival indication of added benefit; extent: “considerable”	Non-serious/non-severe AEs: ▪ bleeding events hint of greater harm; extent: “considerable”
Health-related quality of life (physical/functional component): ▪ time to worsening ▫ ethnicity – white hint of added benefit; extent: “considerable”	
Serious/severe AEs: ▪ treatment discontinuations due to AEs hint of lesser harm; extent: “considerable” ▪ severe AEs of CTCAE grade ≥ 3 hint of lesser harm; extent: “considerable” ▪ diarrhoea (CTCAE grade ≥ 3) hint of lesser harm; extent: “major” ▪ hand-foot syndrome (CTCAE grade 3) indication of lesser harm; extent: “major”	
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events	

Overall, there are positive and negative effects. There are positive effects in the outcome categories “mortality”, “health-related quality of life” and “serious/severe AEs”, and a negative effect in the outcome category “non-serious/non-severe AEs”.

For balancing these effects, the positive effects were first considered separately. There was an indication of a considerable added benefit for the outcome “overall survival”. In addition, for the time to worsening of health-related quality of life, there was a hint of a considerable added benefit for white patients. For the outcomes on AEs, there were positive effects of different certainty of results for serious/severe AEs. There was a hint of lesser harm with considerable extent for treatment discontinuations due to AEs and for severe AEs of CTCAE grade ≥ 3. The extent of lesser harm was major for diarrhoea (CTCAE grade ≥ 3). Due to the very large effect in hand-foot syndrome (CTCAE grade 3) and due to the fact that hardly any events occurred under trastuzumab emtansine, the certainty of results was greater for this outcome, which resulted in an indication of lesser harm with the extent “major”. In the overall assessment of the positive effects, the indication of a major added benefit for this outcome was decisive for the overall conclusion.

The positive effects overall are offset by a hint of greater harm with the extent "considerable" in the category "non-severe/non-serious AEs" in the outcome "bleeding events". As these were mainly mild cases of nose bleed, this does not raise doubts about the overall assessment with regard to the positive effects.

In summary, for patients with HER2-positive metastatic breast cancer who have been pretreated with anthracyclines, taxanes and trastuzumab, there is an indication of a major added benefit of trastuzumab emtansine versus the ACT lapatinib + capecitabine.

2.5.3 Subpopulation c: patients with HER2-positive metastatic breast cancer after pretreatment with taxanes and trastuzumab, but without anthracyclines

The dossier contained no data for patients with HER2-positive metastatic breast cancer who have been pretreated with taxanes and trastuzumab – but without anthracyclines – for a comparison of trastuzumab emtansine with anthracycline (doxorubicin, epirubicin) (see Section 2.3.3). Hence an added benefit of trastuzumab emtansine in comparison with the ACT anthracycline (doxorubicin, epirubicin) is not proven for these patients.

2.5.4 Subpopulation d: patients with HER2-positive metastatic breast cancer, pretreated with taxanes and trastuzumab, for whom treatment with anthracyclines is not an option

The dossier contained no data for patients with HER2-positive metastatic breast cancer who have been pretreated with taxanes and trastuzumab – but without anthracyclines – and for whom treatment with anthracyclines is not an option, for a comparison of trastuzumab emtansine with individual treatment under consideration of the respective approval of the drugs used (see Section 2.3.4). Hence an added benefit of trastuzumab emtansine in comparison with the ACT (individual treatment) is not proven for these patients.

2.5.5 Extent and probability of added benefit – summary

An overview of the assessment of trastuzumab emtansine in comparison with the respective ACT for the 4 subpopulations is given below (see Table 18).

Table 18: Trastuzumab emtansine: extent and probability of added benefit – summary

Subindication	**ACT**	**Extent and probability of added benefit**
Subpopulation a patients with HER2-positive, locally advanced, unresectable breast cancer	Radiotherapy	Added benefit not proven
Subpopulation b patients with HER2-positive metastatic breast cancer, with prior treatment with anthracyclines, taxanes and trastuzumab	Lapatinib + capecitabine	Indication of a major added benefit
Subpopulation c patients with HER2-positive metastatic breast cancer, with prior treatment with taxanes and trastuzumab, but without anthracyclines	Anthracycline (doxorubicin, epirubicin)	Added benefit not proven
Subpopulation d patients with HER2-positive metastatic breast cancer, with prior treatment with taxanes and trastuzumab, for whom treatment with anthracyclines is not an option	Individual treatment under consideration of the respective approval of the drugs used	Added benefit not proven
ACT: appropriate comparator therapy; HER2: human epidermal growth factor receptor 2		

The overall assessment deviates considerably from that of the company. The company claimed proof of a major added benefit for the total target population. In the additional consideration of the subpopulations b and c + d, it also claimed proof of a considerable added benefit.

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier, and in Section 2.7.2.8 of the full dossier assessment.

2.6 List of included studies

EMILIA

Genentech, Hoffmann-La Roche. A randomized, multicenter, phase III open-label study of the efficacy and safety of trastuzumab emtansine vs. capecitabine + lapatinib in patients with HER2-positive locally advanced or metastatic breast cancer who have received prior trastuzumab-based therapy: research report no 1044311; study TDM4370g/BO21977; clinical study report [unpublished]. 2012.

Genentech, Hoffmann-La Roche. Trastuzumab emtansine: summary of second overall survival interim analysis in study TDM4370g/BO21977; research report no. 1051968 [unpublished]. 2012.

Genentech, Hoffmann-La Roche. A randomized, multicenter, phase III open-label study of the efficacy and safety of trastuzumab emtansine vs. capecitabine + lapatinib in patients with HER2-positive locally advanced or metastatic breast cancer who have received prior trastuzumab based therapy: research report no. 1053350; study TDM4370g/BO21977; update clinical study report [unpublished]. 2013.

Hoffmann-La Roche. An open-label study of trastuzumab emtansine (T-DM1) vs capecitabine + lapatinib in patients with HER2-positive locally advanced or metastatic breast cancer (EMILIA): full text view [online]. In: Clinicaltrials.gov. April 2013 [accessed: 14 November 2013]. URL: http://clinicaltrials.gov/show/NCT00829166.

Roche. Zusätzliche Analysen zur EMILIA-Studie (BO21977-TDM4370g) [unpublished]. 2013.

Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012; 367(19): 1783-1791.

References for English extract

Please see full dossier assessment for full reference list.

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