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Trastuzumab emtansine (breast cancer) –

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

Extract

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[2] 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
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
DFS	disease-free survival
DRFI	distant recurrence-free interval
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-BR23	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module
EQ-5D	European Quality of Life-5 Dimensions
ER	oestrogen receptor
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor 2
IDFS	invasive disease-free survival
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PR	progesterone receptor
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

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 14 January 2020.

Research question

The aim of the present report is the assessment of the added benefit of trastuzumab emtansine in comparison with the appropriate comparator therapy (ACT) in patients with human epidermal growth factor receptor 2 (HER2)-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy.

The G-BA specified the continuation of preoperative anti-HER2-targeted therapy with trastuzumab as ACT for the present therapeutic indication. The G-BA additionally noted that patients with positive hormone receptor status should receive additional endocrine therapy and that adjuvant radiotherapy was not part of the ACT, although it could still be used as a patient-specific intervention.

Table 2: Research questions of the benefit assessment of trastuzumab emtansine

Therapeutic indication	**ACT[a]**
Adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy	Continuation of preoperative anti-HER2-targeted therapy with trastuzumab[b]
a. Presentation of the respective ACT specified by the G-BA. b. Patients must have completed preoperative neoadjuvant chemotherapy and started preoperative anti-HER2-targeted therapy with trastuzumab. Trastuzumab should be administered for a total of 1 year. Patients with positive hormone receptor status should receive additional endocrine therapy. Adjuvant radiotherapy can be used as a patient-specific intervention. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2	

The company followed the G-BA's specification on the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of the added benefit.

Results

Study pool and study characteristics

The study KATHERINE was included for the benefit assessment. The KATHERINE study was an open-label, randomized parallel-group study on the comparison of trastuzumab emtansine versus trastuzumab in the adjuvant use. The study included patients with HER2-positive early breast cancer with pathological evidence of residual disease in the breast or axillary lymph nodes. Eligible patients had to have received adequate pretreatment or surgery before the start of the study. For this purpose, patients had to have received neoadjuvant treatment with taxane-based chemotherapy and with trastuzumab-based HER2-targeted therapy. Following completion of the chemotherapy, a complete resection of the tumour had to be performed and there had to be pathological evidence of residual invasive disease in the breast resectate and/or in the lymph nodes.

A total of 1486 patients were included and randomized to treatment with trastuzumab emtansine (N = 743) or to trastuzumab (N = 743) in a 1:1 ratio.

Treatment with trastuzumab emtansine and trastuzumab was in compliance with the Summaries of Product Characteristics (SPCs). Endocrine therapy for patients with positive hormone receptor status, and radiotherapy of the breast and affected lymph nodes were allowed.

Primary outcome of the study was invasive disease-free survival (IDFS). Patient-relevant secondary outcomes were overall survival, recurrence, symptoms, health status, health-related quality of life, and adverse events (AEs).

Risk of bias

The risk of bias across outcomes was rated as low for the KATHERINE study. There was a low risk of bias for the results of the following outcomes: overall survival, recurrence, serious AEs (SAEs), severe AEs (Common Terminology Criteria for Adverse Events [CTCAE grade ≥ 3]) and specific serious/severe AEs. The risk of bias was high for the results of the outcomes on symptoms, health status and health-related quality of life (European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire-Core 30 [QLQ-C30], Quality of Life Questionnaire-Breast Cancer Module [QLQ-BR23]), specific non-serious/non-severe AEs, and discontinuation due to AEs.

Mortality

There was no statistically significant difference between the treatment arms for the outcome “overall survival”. This resulted in no hint of an added benefit of trastuzumab emtansine in comparison with trastuzumab. An added benefit for this outcome is therefore not proven.

The company presented the results of the outcome “disease-free survival (DFS)” as valid surrogate for overall survival. However, the validation study presented is unsuitable to show the validity of DFS as surrogate outcome for “overall survival” in the present therapeutic

indication. In the benefit assessment, DFS was therefore not considered to be a valid surrogate for overall survival.

Morbidity

Recurrence

For the composite outcome "recurrence", a statistically significant difference in favour of trastuzumab emtansine in comparison with trastuzumab was shown between the treatment arms. This resulted in an indication of an added benefit of trastuzumab emtansine in comparison with trastuzumab.

Symptoms

Symptom outcomes were recorded with the symptom scales of the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-BR23. Symptoms were considered at 2 time points. At the end of therapy, the proportions of patients with a deterioration by ≥ 10 points were shown. At the 12-month follow-up, however, the differences in mean values were considered.

Appetite loss, constipation, side effects of systemic therapy

The responder analysis at the end of therapy showed statistically significant differences between the treatment arms to the disadvantage of trastuzumab emtansine for the outcomes "appetite loss", "constipation" and "side effects of systemic therapy". The analysis of continuous data at the 12-month follow-up showed statistically significant differences between the treatment arms to the disadvantage of trastuzumab emtansine for these outcomes. However, the 95% confidence interval (CI) of the standardized mean difference (SMD) (Hedges' g) was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the observed effects at the 12-month follow-up are relevant. Based on the negative effects at the end of therapy, there is overall a hint of lesser benefit of trastuzumab emtansine in comparison with trastuzumab for the outcomes mentioned.

Fatigue, nausea and vomiting, pain, symptoms in arm region

The responder analysis at the end of therapy showed statistically significant differences between the treatment arms to the disadvantage of trastuzumab emtansine for the outcomes "fatigue", "nausea and vomiting", "pain" and "symptoms in arm region". The effect in these outcomes of the category of non-serious/non-severe symptoms/late complications was no more than marginal, however. The analysis of continuous data at the 12-month follow-up showed a statistically significant difference to the disadvantage of trastuzumab emtansine for the outcome "symptoms in arm region". However, the 95% CI of the SMD (Hedges' g) was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the observed effect at the 12-month follow-up is relevant. For the outcomes "fatigue", "nausea and vomiting" and "pain", no statistically significant differences between the treatment arms were shown at the 12-month follow-up. Overall, this resulted in no hint of an added benefit of trastuzumab emtansine in comparison with trastuzumab for the outcomes "fatigue", "nausea and vomiting", "pain" and "symptoms in arm region"; an added benefit is therefore not proven.

Dyspnoea, insomnia, diarrhoea, symptoms in chest region, upset by hair loss

At the end of therapy, no statistically significant differences between the treatment arms were shown for the outcomes "dyspnoea", "insomnia", "diarrhoea" and "symptoms in chest region". The analysis of continuous data at the 12-month follow-up showed statistically significant differences for the outcomes "diarrhoea" and "symptoms in chest region". The difference was in favour of trastuzumab emtansine for the outcome "diarrhoea" and to the disadvantage of trastuzumab emtansine for the outcome "symptoms in chest region". However, the 95% CI of the SMD (Hedges' g) was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the observed effects at the 12-month follow-up are relevant. For the outcomes "dyspnoea" and "insomnia", no statistically significant differences between the treatment arms were shown at the 12-month follow-up. There were no usable data for "upset by hair loss". Overall, this resulted in no hint of an added benefit of trastuzumab emtansine in comparison with trastuzumab; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

At the end of therapy, there was no statistically significant difference between the treatment arms for the outcome "health status" recorded with the European Quality of Life-5 Dimensions (EQ-5D) visual analogue scale (VAS). At the 12-month follow-up, however, there was a statistically significant difference. However, the 95% CI of the SMD (Hedges' g) was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the observed effect at the 12-month follow-up is relevant. Overall, this resulted in no hint of an added benefit of trastuzumab emtansine in comparison with trastuzumab; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life was recorded with the functional scales and with the scale for recording the global health status of the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-C30. Health-related quality of life was considered at 2 time points. At the end of therapy, the proportions of patients with a deterioration by ≥ 10 points were shown. At the 12-month follow-up, however, the differences in mean values were considered.

Physical functioning, social functioning

The responder analyses at the end of therapy showed statistically significant differences between the treatment arms to the disadvantage of trastuzumab emtansine for the outcomes "physical functioning" and "social functioning". The analysis of continuous data at the 12-month follow-up also showed statistically significant differences to the disadvantage of trastuzumab emtansine. However, the 95% CI of the SMD (Hedges' g) was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the observed effects at the 12-month follow-up are relevant. Based on the negative effects at the end of therapy, there is overall a hint of lesser benefit of trastuzumab emtansine in comparison with trastuzumab.

Global health status

For the outcome "global health status", a statistically significant difference between the treatment arms was neither shown at the end of therapy nor in the 12-month follow-up in the total population. However, a statistically significant interaction with the characteristic "age" was shown at the end of therapy. This resulted in a hint of lesser benefit of trastuzumab emtansine in comparison with trastuzumab for patients ≥ 65 years of age. For patients < 65 years of age, there was no hint of an added benefit; an added benefit for these patients is not proven.

Further functional scales and quality of life scales

There were no statistically significant differences between the treatment arms for the outcomes "role functioning", "emotional functioning", "cognitive functioning", "body image" and "future perspective" in the responder analyses at the end of therapy. These responder analyses provided no usable data for the items "sexual activity" and "enjoyment of sex". The analysis of continuous data at the 12-month follow-up showed statistically significant differences for the outcomes "role functioning" and "body image". The difference was to the disadvantage of trastuzumab emtansine for the outcome "role functioning" and in favour of trastuzumab emtansine for the outcome "body image". However, the 95% CI of the SMD (Hedges' g) was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the observed effects at the 12-month follow-up are relevant. For the outcomes "emotional functioning", "cognitive functioning", "future perspective", "sexual activity" and "enjoyment of sex", no statistically significant differences between the treatment arms were shown at the 12-month follow-up. Overall, this resulted in no hint of an added benefit of trastuzumab emtansine in comparison with trastuzumab; an added benefit is therefore not proven.

Side effects

Serious adverse events, severe adverse events (CTCAE grade ≥ 3), discontinuation due to adverse events

A statistically significant difference to the disadvantage of trastuzumab emtansine was shown for each of the outcomes "SAEs", "severe AEs (CTCAE grade ≥ 3)" and "discontinuation due to AEs". This resulted in an indication of greater harm from trastuzumab emtansine in comparison with trastuzumab for each SAEs and severe AEs (CTCAE grade ≥ 3), and in a hint of greater harm for discontinuation due to AEs.

Specific adverse events

For the following AEs, a statistically significant difference to the disadvantage of trastuzumab emtansine in comparison with trastuzumab was shown between the treatment arms:

- Severe or serious AEs:

  platelet count decreased (Preferred Term [PT], severe AEs [CTCAE grade ≥ 3]),
  gastrointestinal disorders (System Organ Class [SOC], severe AEs [CTCAE grade ≥ 3]),

peripheral sensory neuropathy (PT, severe AEs [CTCAE grade ≥ 3]), infections and infestations (SOC, SAE)

- Non-severe/non-serious AEs:

  fatigue (PT), fever (PT), nausea (PT), constipation (PT), dry mouth (PT), stomatitis (PT), headache (PT), respiratory, thoracic and mediastinal disorders (SOC), eye disorders (SOC)

In each case, this resulted in an indication (for severe/serious AEs) or a hint (for non-severe/non-serious AEs) of greater harm from trastuzumab emtansine in comparison with trastuzumab.

No statistically significant difference between the treatment arms was shown for the outcome "cardiac disorders" (SOC, severe AEs [CTCAE grade ≥ 3]). This resulted in no hint of greater or lesser harm from trastuzumab emtansine in comparison with trastuzumab; greater or lesser harm is therefore not proven.

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

Based on the results presented, probability and extent of the added benefit of the drug trastuzumab emtansine in comparison with the ACT are assessed as follows:

In the overall consideration, there was one positive effect and several negative effects of trastuzumab emtansine in comparison with trastuzumab.

The positive effect consisted of an indication of a major added benefit of trastuzumab emtansine in the outcome "recurrence". This was supported by the results on DFS, which had the same direction of effect and were presented as additional information. On the other hand, there were a large number of negative effects in the categories of symptoms, health-related quality of life and side effects with major, considerable and minor extent. For the category of side effects, negative effects were shown both for the overall rates of severe AEs (CTCAE grade ≥ 3), SAEs, and discontinuation due to AEs, and for individual specific serious/severe and non-serious/non-severe AEs.

Overall, the negative effects did not completely call into question the clear effect in recurrences, but led to a downgrading of the extent in the overall conclusion.

[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].

In summary, there was an indication of minor added benefit of trastuzumab emtansine versus trastuzumab for patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy.

Table 3 shows a summary of probability and extent of the added benefit of trastuzumab emtansine.

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

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy	Continuation of preoperative anti-HER2-targeted therapy with trastuzumab	Indication of minor added benefit[b]

a. Presentation of the respective ACT specified by the G-BA.
b. Only patients with an ECOG PS of 0 or 1 were included in the KATHERINE study. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2

The approach for deriving an overall conclusion on the 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 the assessment of the added benefit of trastuzumab emtansine in comparison with the ACT in patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy.

The G-BA specified the continuation of preoperative anti-HER2-targeted therapy with trastuzumab as ACT for the present therapeutic indication (see Table 4). The G-BA additionally noted that patients with positive hormone receptor status should receive additional endocrine therapy and that adjuvant radiotherapy was not part of the ACT, although it could still be used as a patient-specific intervention.

Table 4: Research questions of the benefit assessment of trastuzumab emtansine

Therapeutic indication	**ACT**[a]
Adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy	Continuation of preoperative anti-HER2-targeted therapy with trastuzumab[b]
a. Presentation of the respective ACT specified by the G-BA. b. Patients must have completed preoperative neoadjuvant chemotherapy and started preoperative anti-HER2-targeted therapy with trastuzumab. Trastuzumab should be administered for a total of 1 year. Patients with positive hormone receptor status should receive additional endocrine therapy. Adjuvant radiotherapy can be used as a patient-specific intervention. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2	

The company followed the G-BA's specification on the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of the added benefit.

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 (status: 27 November 2019)
- bibliographical literature search on trastuzumab emtansine (last search on 25 November 2019)
- search in trial registries/trial results databases for studies on trastuzumab emtansine (last search on 16 December 2019)
- search on the G-BA website for trastuzumab emtansine (last search on 16 December 2019)

To check the completeness of the study pool:

- search in trial registries for studies on trastuzumab emtansine (last search on 24 January 2020)

No additional relevant study was identified from the check.

2.3.1 Studies included

The study listed in the following table was included in the benefit assessment.

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

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
BO27938 (KATHERINE[c])	Yes	Yes	No	Yes [3]	Yes [4-8]	Yes [9]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. In the following tables, the study is referred to with this abbreviated form.

CSR: clinical study report; RCT: randomized controlled trial; vs.: versus

2.3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study/studies included – RCT, direct comparison: trastuzumab emtansine vs. trastuzumab

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
KATHERINE	RCT, open-label, parallel	Adult patients with HER2-positive breast cancer, after preoperative taxane-based chemotherapy and trastuzumab-based targeted therapy followed by complete resection of the tumour, with pathological evidence of residual invasive disease in the breast or axillary lymph nodes	Trastuzumab emtansine (N = 743) Trastuzumab (N = 743)	Screening: ≤ 30 days Treatment: 14 cycles Observation[b]: outcome-specific, at most until death, discontinuation of participation in the study or end of study	268 centres in Argentina, Austria, Belgium, Brazil, Canada, China, Colombia, Czech Republic, France, Germany, Greece, Guatemala, Hong Kong, Ireland, Israel, Italy, Mexico, Panama, Peru, Serbia, South Africa, Spain, Sweden, Switzerland, Taiwan, Turkey, United Kingdom, USA 4/2013–ongoing Data cut-offs: ▪ 25 July 2018 (interim analysis IDFS) ▪ 6 December 2018 safety update at the request of the FDA ▪ 6 May 2019 analysis on overall survival at the request of EMA	Primary: IDFS Secondary: recurrence, symptoms, health-related quality of life, overall survival, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Outcome-specific information is provided in Table 8.

AE: adverse event; EMA: European Medicines Agency; FDA: Food and Drug Administration; HER2: human epidermal growth factor receptor 2; IDFS: invasive disease-free survival; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

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

Study	Intervention	Comparison
KATHERINE	Trastuzumab emtansine, 3.6 mg/kg IV on day 1 of a 21-day cycle, 14 cycles in total Dose reduction to ≥ 2.4 mg/kg IV and treatment interruption ≤ 42 days due to AEs possible	Trastuzumab 6 mg/kg IV[a] on day 1 of a 21-day cycle, 14 cycles in total
	Pretreatment ***Allowed*** ▪ preoperative systemic chemotherapy and anti-HER2 therapy: ▫ ≥ 6 cycles of chemotherapy for ≥ 16 weeks, including ≥ 9 weeks trastuzumab and ≥ 9 weeks taxane-based chemotherapy ▫ dose-dense chemotherapy (with ≥ 8 weeks taxane-based chemotherapy and ≥ 8 weeks trastuzumab) ▫ anthracyclines in addition to taxane-based chemotherapy ▫ dose-escalating and dose-dense (225 mg/m² BSA every 2 weeks) treatment with paclitaxel for 6 weeks ▪ surgical removal of all clinically detectable conditions in the breast and lymph nodes ≤ 12 weeks before study start ***Not allowed*** ▪ investigational antineoplastic drugs ≤ 28 days before start of study medication ▪ pretreatment with anthracyclines in the following total doses: ▫ doxorubicin > 240 mg/m² BSA ▫ epirubicin or liposome-encapsulated doxorubicin hydrochloride > 480 mg/m² BSA ▫ other anthracyclines > 240 mg/m² BSA **Concomitant treatment** ***Allowed*** ▪ hormonal therapy (tamoxifen, aromatase inhibitors) in patients with hormone-receptor-positive disease ***Not allowed*** ▪ other chemotherapy, radiotherapy (except adjuvant radiotherapy of the breast and/or affected lymph nodes, starting ≤ 60 days after surgery), immunotherapy and biological or targeted anticancer therapy (e.g. lapatinib, neratinib) ▪ other investigational preparations ▪ avoid use of strong CYP3A4/5 inhibitors (e.g. ketoconazole, itraconazole) with trastuzumab emtansine	

a. A starting dose of 8 mg/kg should be administered if > 6 weeks have passed since the last dose of trastuzumab.

AE: adverse event; BSA: body surface area; CYP: cytochrome P450; HER2: human epidermal growth factor receptor 2; IV: intravenous; RCT: randomized controlled trial; vs.: versus

The KATHERINE study was an open-label, randomized parallel-group study on the comparison of trastuzumab emtansine versus trastuzumab in the adjuvant use. The study included patients with HER2-positive early breast cancer with pathological evidence of residual disease in the breast or axillary lymph nodes. Eligible patients had to have received adequate pretreatment or surgery before the start of the study. For this purpose, patients had to have

received neoadjuvant treatment with taxane-based chemotherapy and with trastuzumab-based HER2-targeted therapy. Following completion of the chemotherapy, a complete resection of the tumour had to be performed and there had to be pathological evidence of residual invasive disease in the breast resectate and/or in the lymph nodes.

A total of 1486 patients were included and randomized to treatment with trastuzumab emtansine (N = 743) or to trastuzumab (N = 743) in a 1:1 ratio. Randomization was stratified by clinical stage at the time of the first diagnosis (operable versus inoperable), hormone receptor status (oestrogen receptor [ER]-positive and/or progesterone receptor [PR]-positive versus ER-negative and PR-negative or unknown), preoperative HER2 therapy (trastuzumab versus trastuzumab and additional HER2-targeted therapy) and pathological lymph node status (positive versus negative or unknown).

In compliance with the SPC [10], treatment with trastuzumab emtansine was conducted over 14 cycles. For the comparator therapy with trastuzumab, treatment was also conducted for 14 cycles. In compliance with the SPC [11], 1 year of treatment with trastuzumab, which had been started neoadjuvantly, was completed. Endocrine therapy for patients with positive hormone receptor status, and radiotherapy of the breast and affected lymph nodes were allowed. Treatment was ended prematurely in case of recurrence, AEs, pregnancy, severe protocol violations, and withdrawal of consent. If treatment with trastuzumab emtansine was discontinued, patients were allowed to complete a total of 14 cycles of anti-HER2 therapy with trastuzumab, provided that the treatment discontinuation was not caused by an AE attributable to the trastuzumab component.

Primary outcome of the study was IDFS. Patient-relevant secondary outcomes were overall survival, recurrence, symptoms, health status, health-related quality of life, and AEs.

Subsequent therapies could be administered without restrictions after completion of the study medication. There is no information on the number of patients who received subsequent antineoplastic therapy. In Module 5, the company presented only proportions of the patients with any subsequent therapy and individual drugs. No relevant imbalances were shown between the treatment arms with regard to antineoplastic drugs. Information on the administered subsequent therapies is presented in Table 27 in Appendix C of the full dossier assessment.

Data cut-offs

In the KATHERINE study, 4 data cut-offs were planned and one data cut-off has been performed in the meantime:

- First data cut-off: interim analysis for IDFS after 257 events. A data cut-off was performed on 25 July 2018 after occurrence of 256 predefined IDFS events. Since the defined efficacy thresholds for this outcome were met in this analysis, a complete analysis of all outcomes was performed at this data cut-off. The company presented analyses on

this data cut-off in its dossier. Since this was the only data cut-off with suitable data, this data cut-off was used in accordance with the company's approach.

- Second data cut-off: final IDFS analysis after 384 events and interim analysis on overall survival
- Third data cut-off: A further analysis on overall survival is to be conducted about 2 years after the second data cut-off.
- Fourth data cut-off: The final analysis of overall survival is to be conducted after 367 deaths or 10 years of follow-up.

Another 2 data cut-offs were conducted at the request of regulatory authorities:

- About 5 months after the first data cut-off (6 December 2018), a new analysis of safety outcomes (safety update) was conducted at the request of the Food and Drug Administration (FDA). This included only AEs recorded in the follow-up observation phase 30 days after the last administration of the study medication.
- Analysis of data on overall survival at the request of the European Medicines Agency (EMA) (6 May 2019). The company presented a document for this data cut-off that only reported the 5-year rate of patients without events as of 6 May 2019 [12].

Follow-up observation

Table 8 shows the planned duration of follow-up observation of the patients for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: trastuzumab emtansine vs. trastuzumab

Study **Outcome category** **Outcome**	**Planned follow-up observation**
KATHERINE	
Mortality	
Overall survival	Until 10 years after the last dose of the study medication
Morbidity	
Recurrence	Until 10 years after the last dose of the study medication
Symptoms (EORTC QLQ-C30, EORTC QLQ-BR23)	12 months after the last dose of the study medication
Health status (EQ-5D VAS)	12 months after the last dose of the study medication
Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23)	12 months after the last dose of the study medication
Side effects	
All outcomes in the category "side effects"	Until 30 days after the last dose of the study medication[a] or until initiation of another antineoplastic treatment, whichever occurred first

a. Except for SAEs and probably treatment-related AEs; these were recorded beyond the 30-day follow-up observation.

AE: adverse event; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Observation of symptoms, health status and health-related quality of life was not over the total study period, but until 12 months after the end of treatment. Side effects (except SAEs) were recorded up to 30 days after the last dose of the study medication or until the start of another subsequent antineoplastic treatment.

The observation periods for the outcomes "symptoms", "health status", "health-related quality of life" and "side effects" (except SAEs) were systematically shortened. To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for survival.

Study population

Table 9 shows the characteristics of the patients in the study included.

Table 9: Characteristics of the study population – RCT, direct comparison: trastuzumab emtansine vs. trastuzumab

Study **Characteristics** **Category**	**Trastuzumab emtansine** **N[a] = 743**	**Trastuzumab** **N[a] = 743**
KATHERINE		
Age [years], mean (SD)	49 (10)	49 (11)
Sex [F/M], %	99.7/0.3	99.6/0.4
Family origin, n (%)		
Asian	65 (8.7)	64 (8.6)
Black/African American	21 (2.8)	19 (2.6)
White	551 (74.2)	531 (71.5)
Other	37 (5.0)	52 (7.0)
Unknown	69 (9.3)	77 (10.4)
Region, n (%)		
North America	170 (22.9)	164 (22.1)
Western Europe	403 (54.2)	403 (54.2)
Other	170 (22.9)	176 (23.7)
ECOG PS		
0	597 (80.3)	613 (82.5)
1	146 (19.7)	130 (17.5)
Female reproductive status, n (%)		
Premenopausal	399 (53.7)	413 (55.6)
Postmenopausal	344 (46.3)	330 (44.4)
Hormone receptor status		
Negative (ER- and PR-negative)	213 (28.7)	210 (28.3)
Positive (ER- and/or PR-positive)	530 (71.3)	533 (71.7)
Type of neoadjuvant chemotherapy		
Anthracycline-containing	579 (77.9)	564 (75.9)
Anthracycline-free	164 (22.1)	179 (24.1)
Preoperative anti-HER2-targeted therapy		
Trastuzumab	601 (80.9)	600 (80.8)
Trastuzumab + additional anti-HER2 therapy	142 (19.1)	143 (19.2)
Time since diagnosis [months], mean (SD)	8.4 (1.7)	8.3 (1.8)
Treatment discontinuation, n (%)	212 (28.5)	135 (18.2)
Study discontinuation, n (%)	108 (14.5)	146 (19.7)

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.

ECOG PS: Eastern Cooperative Oncology Group Performance Status; ER: oestrogen receptor; F: female; HER2: human epidermal growth factor receptor 2; M: male; n: number of patients in the category; N: number of randomized patients; PR: progesterone receptor; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The characteristics of the patients were sufficiently balanced between the treatment arms. The mean age of the patients was 49 years; most of them were white (about 73%) and in good general condition (Eastern Cooperative Oncology Group Performance Status [ECOG PS] of 0 or 1). The vast majority of the patients were female (> 99%) and had a positive hormone receptor status (about 72%).

Treatment duration and observation period

Table 10 shows the median treatment duration of the patients and the median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: trastuzumab emtansine vs. trastuzumab

Study **Duration of the study phase** **Outcome category**	**Trastuzumab emtansine** **N = 740**	**Trastuzumab** **N = 720**
KATHERINE		
Treatment duration [months]		
Median [min; max]	10 [1; 12]	10 [1; 13]
Observation period [months]		
Overall survival		
Median [Q1; Q3][a]	41.4 [35.0; 49.2]	40.9 [33.9; 48.4]
Morbidity	ND	
Health-related quality of life	ND	
Side effects	ND	
a. Calculated with the Kaplan-Meier method.		
max: maximum; min: minimum; N: number of patients; ND: no data; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; vs.: versus		

Both the median treatment duration and the median observation period of overall survival were comparable in both study arms. There is no information on the observation period of morbidity, health-related quality of life and side effects. As the observation period for most of the outcomes of these outcome categories (except for recurrence and SAEs) was linked to the treatment duration (12 months or 30 days after the end of therapy), it is assumed that the observation period was also comparable. Follow-up observation of the patients for recurrences was 10 years. For this outcome, it is not possible to derive the observation period from the treatment duration; corresponding information on the observation period is not available.

Risk of bias across outcomes (study level)

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: trastuzumab emtansine vs. trastuzumab

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
KATHERINE	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias across outcomes was rated as low for the KATHERINE study. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described in Section 2.4 with the outcome-specific risk of bias.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.6.4.3.2 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - recurrence
  - symptoms (EORTC QLQ-C30 and EORTC QLQ-BR23, symptom scales)
  - health status (EQ-5D VAS)
- Health-related quality of life
  - EORTC QLQ-C30 and EORTC QLQ-BR23 (functional scales)
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - cardiac disorders (SOC, severe AEs [CTCAE grade ≥ 3])

- platelet count decreased (PT, severe AEs [CTCAE grade ≥ 3])
- if applicable, further specific AEs

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.6.4.3 of the full dossier assessment).

Continuous deterioration of symptoms and health-related quality of life is not to be expected in the present therapeutic indication. Rather, it can be assumed that the patient-reported outcomes during the treatment phase primarily reflect the burden from side effects of the respective therapy, whereas, in the further course of the study, they reflect the burden from the course of the disease (recurrence). For this reason, the temporal course of deterioration for these outcomes cannot be adequately represented by the presentation of only one time point. For the symptom and functional scales of the questionnaires EORTC QLQ-C30 and -BR23, the results are therefore presented for the time points at the end of anti-HER2 therapy and 12 months after the end of therapy (hereinafter referred to as 12-month follow-up, corresponding to about 22 months after randomization) (see also Section 2.3.2).

Table 12 shows for which outcomes data were available in the study included.

Table 12: Matrix of outcomes – RCT, direct comparison: trastuzumab emtansine vs. trastuzumab

Study	Outcomes										
	Overall survival	**Recurrence[a]**	**Symptoms (EORTC QLQ-C30 and EORTC QLQ-BR23, symptom scales)**	**Health status (EQ-5D VAS)**	**Health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-BR23, functional scales)**	**SAEs**	**Severe AEs (CTCAE grade ≥ 3)**	**Discontinuation due to AEs**	**Cardiac disorders (SOC, severe AEs [CTCAE grade ≥ 3])**	**Platelet count decreased (PT, severe AEs [CTCAE grade ≥ 3])**	**Further specific AEs[b]**
KATHERINE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Includes the events: ipsilateral invasive breast cancer recurrence, ipsilateral invasive regional breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, secondary primary carcinoma (no breast cancer), DCIS (ipsilateral or contralateral) and death from any cause.

b. The following events are considered (MedDRA coding): fatigue (PT, AE), fever (PT, AE), gastrointestinal disorders (SOC, severe AEs [CTCAE grade ≥ 3]), nausea (PT, AE), constipation (PT, AE), dry mouth (PT, AE), stomatitis (PT, AE), headache (PT, AE), peripheral sensory neuropathy (PT, severe AEs [CTCAE grade ≥ 3]), infections and infestations (SOC, SAE), respiratory, thoracic and mediastinal disorders (SOC, AE), eye disorders (SOC, AE).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; DCIS: ductal carcinoma in situ; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.4.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: trastuzumab emtansine vs. trastuzumab

Study		Outcomes										
	Study level	Overall survival	Recurrence[a]	Symptoms (EORTC QLQ-C30 and EORTC QLQ-BR23, symptom scales)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-BR23, functional scales)	SAEs	Severe AEs (CTCAE grade ≥ 3)	Discontinuation due to AEs	Cardiac disorders (SOC, CTCAE grade ≥ 3)	Platelet count decreased (PT, CTCAE grade ≥ 3)	Further specific AEs[b]
KATHERINE	L	L	L	H[c, d]	H[c, d]	H[c, d]	L	L	H[d]	L	L	H/N[e]

a. Includes the events: ipsilateral invasive breast cancer recurrence, ipsilateral invasive regional breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, secondary primary carcinoma (no breast cancer), DCIS (ipsilateral or contralateral) and death from any cause.
b. The following events are considered (MedDRA coding): fatigue (PT, AE), fever (PT, AE), gastrointestinal disorders (SOC, severe AEs [CTCAE grade ≥ 3]), nausea (PT, AE), constipation (PT, AE), dry mouth (PT, AE), stomatitis (PT, AE), headache (PT, AE), peripheral sensory neuropathy (PT, severe AEs [CTCAE grade ≥ 3]), infections and infestations (SOC, SAE), respiratory, thoracic and mediastinal disorders (SOC, AE), eye disorders (SOC, AE).
c.: Large proportion of patients (> 10%) not considered in the analysis.
d. Lack of blinding in subjective recording of outcomes.
e. The risk of bias is rated as low for specific AEs of the outcome category "serious/severe". For specific AEs of the outcome category "non-serious/non-severe", a high risk of bias is assumed due to the lack of blinding in subjective recording of outcomes.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; DCIS: ductal carcinoma in situ; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

There was a low risk of bias for the results of the following outcomes: overall survival, recurrence, SAEs, severe AEs (CTCAE grade ≥ 3) and specific serious/severe AEs. Due to the large proportion of patients not considered in the analysis (> 10%) and the lack of blinding in subjective recording of outcomes, there was a high risk of bias for the results of the outcomes

on symptoms, health status and health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23) and health status (EQ-5D VAS). The results of the specific non-serious/non-severe AEs and discontinuation due to AEs also had a high risk of bias due to the lack of blinding in subjective recording of outcomes or subjective request for treatment discontinuation.

The assessment partly concurs with that of the company. Deviating from the present assessment, the company derived a high risk of bias for severe AEs (CTCAE grade ≥ 3) and SAEs (see Section 2.6.4.2 of the full dossier assessment).

2.4.3 Results

Table 14 and Table 15 summarize the results of the comparison of trastuzumab emtansine and trastuzumab in patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. The available Kaplan-Meier curves on the outcomes included and presented as additional information are presented in Appendix A, the common AEs in Appendix B of the full dossier assessment.

Table 14: Results (mortality, morbidity, side effects) – RCT, direct comparison: trastuzumab emtansine vs. trastuzumab (multipage table)

Study Outcome category Outcome	Trastuzumab emtansine N	Trastuzumab emtansine Patients with event n (%)	Trastuzumab N	Trastuzumab Patients with event n (%)	Trastuzumab emtansine vs. trastuzumab RR [95% CI]; p-value
KATHERINE					
Mortality					
Overall survival	743	42 (5.7) median time to event: NA [NC; NC]	743	56 (7.5) median time to event: NA [NC; NC]	HR[a] 0.70 [0.47; 1.05]; 0.085
Morbidity					
Recurrence	743	98 (13.2)	743	167 (22.5)	0.59 [0.47; 0.74]; < 0.001
Ipsilateral invasive local breast cancer recurrence	743	6 (0.8)	743	30 (4.0)	—[b]
Ipsilateral invasive regional breast cancer recurrence	743	5 (0.7)	743	11 (1.5)	—[b]
Distant recurrence	743	75 (10.1)	743	108 (14.5)	—[b]
Contralateral invasive breast cancer	743	3 (0.4)	743	10 (1.3)	—[b]
Secondary primary carcinoma (no breast cancer)	743	4 (0.5)	743	4 (0.5)	—[b]
DCIS (ipsilateral or contralateral)	743	3 (0.4)	743	1 (0.1)	—[b]
Death from any cause	743	2 (0.3)	743	3 (0.4)	—[b]
Disease-free survival[c] (supplementary information)	743	98 (13.2) median time to event: NA [NC; NC]	743	167 (22.5) median time to event: NA [NC; NC]	HR[a] 0.53 [0.41; 0.68]; < 0.001
Symptoms (EORTC QLQ-C30 symptom scales) – patients with deterioration by ≥ 10 points at the end of therapy					
Fatigue	534	211 (39.5)	536	175 (32.6)	1.21 [1.03; 1.42]; 0.020
Nausea and vomiting	534	89 (16.7)	536	63 (11.8)	1.42 [1.05; 1.91]; 0.022
Pain	534	177 (33.1)	536	146 (27.2)	1.22 [1.01; 1.46]; 0.036
Dyspnoea	534	111 (20.8)	536	111 (20.7)	1.00 [0.79; 1.27]; 0.975
Insomnia	534	140 (26.2)	536	142 (26.5)	0.99 [0.81; 1.21]; 0.919
Appetite loss	534	101 (18.9)	536	58 (10.8)	1.75 [1.30; 2.36]; < 0.001
Constipation	534	159 (29.8)	536	97 (18.1)	1.65 [1.32; 2.05]; < 0.001
Diarrhoea	534	40 (7.5)	536	56 (10.5)	0.72 [0.49; 1.05]; 0.091

Table 14: Results (mortality, morbidity, side effects) – RCT, direct comparison: trastuzumab emtansine vs. trastuzumab (multipage table)

Study Outcome category Outcome	Trastuzumab emtansine N	Trastuzumab emtansine Patients with event n (%)	Trastuzumab N	Trastuzumab Patients with event n (%)	Trastuzumab emtansine vs. trastuzumab RR [95% CI]; p-value
Symptoms (EORTC QLQ-BR23 symptom scales) – patients with deterioration by ≥ 10 points at the end of therapy					
Side effects of systemic therapy	534	144 (27.0)	534	94 (17.6)	1.53 [1.22; 1.93]; < 0.001
Symptoms in chest region	534	99 (18.5)	534	88 (16.5)	1.12 [0.87; 1.46]; 0.376
Symptoms in arm region	534	190 (35.6)	534	150 (28.1)	1.27 [1.06; 1.51]; 0.009
Upset by hair loss				No usable data[d]	
Health-related quality of life					
EORTC QLQ-C30 functional scales – patients with deterioration by ≥ 10 points at the end of therapy					
Global health status	534	123 (23.0)	535	112 (20.9)	1.10 [0.88; 1.38]; 0.408
Physical functioning	534	120 (22.5)	536	91 (17.0)	1.32 [1.04; 1.69]; 0.025
Role functioning	534	141 (26.4)	536	122 (22.8)	1.16 [0.94; 1.43]; 0.167
Emotional functioning	534	208 (39.0)	535	198 (37.0)	1.05 [0.90; 1.23]; 0.513
Cognitive functioning	534	201 (37.6)	535	190 (35.5)	1.06 [0.90; 1.24]; 0.471
Social functioning	534	131 (24.5)	535	102 (19.1)	1.29 [1.02; 1.62]; 0.031
Health-related quality of life					
EORTC QLQ-BR23 functional scales – patients with deterioration by ≥ 10 points at the end of therapy					
Body image	534	91 (17.0)	534	106 (19.9)	0.86 [0.67; 1.11]; 0.237
Sexual activity				No usable data[d]	
Enjoyment of sex				No usable data[d]	
Future perspective	534	106 (19.9)	534	91 (17.0)	1.16 [0.90; 1.50]; 0.237
Side effects[e]					
AEs (supplementary information)	740	731 (98.8)	720	672 (93.3)	–
SAEs	740	94 (12.7)	720	58 (8.1)	1.58 [1.16; 2.15]; 0.004
Severe AEs (CTCAE grade ≥ 3)	740	190 (25.7)	720	111 (15.4)	1.67 [1.35; 2.06]; < 0.001
Discontinuation due to AEs	740	133 (18.0)	720	15 (2.1)	8.63 [5.11; 14.57]; < 0.001
Cardiac disorders (SOC, severe AEs [CTCAE grade ≥ 3])	740	2 (0.3)	720	7 (1.0)	0.28 [0.06; 1.33]; 0.088[f]
Platelet count decreased (PT, severe AEs [CTCAE grade ≥ 3])	740	42 (5.7)	720	2 (0.3)	20.43 [4.96; 84.09]; < 0.001[f]
Fatigue (PT, AE)	740	366 (49.5)	720	243 (33.8)	1.47 [1.29; 1.66]; < 0.001[f]
Fever (PT, AE)	740	77 (10.4)	720	29 (4.0)	2.58 [1.71; 3.91]; < 0.001[f]

Table 14: Results (mortality, morbidity, side effects) – RCT, direct comparison: trastuzumab emtansine vs. trastuzumab (multipage table)

Study Outcome category Outcome	Trastuzumab emtansine		Trastuzumab		Trastuzumab emtansine vs. trastuzumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Gastrointestinal disorders (SOC, severe AEs [CTCAE grade ≥ 3])	740	21 (2.8)	720	7 (1.0)	2.92 [1.25; 6.82]; 0.009[f]
Nausea (PT, AE)	740	308 (41.6)	720	94 (13.1)	3.19 [2.59; 3.92]; < 0.001[f]
Constipation (PT, AE)	740	126 (17.0)	720	59 (8.2)	2.08 [1.55; 2.78]; < 0.001[f]
Vomiting (PT, AE)	740	108 (14.6)	720	37 (5.1)	2.84 [1.98; 4.07]; < 0.001[f]
Dry mouth (PT, AE)	740	100 (13.5)	720	9 (1.3)	10.81 [5.51; 21.22]; < 0.001[f]
Stomatitis (PT, AE)	740	80 (10.8)	720	27 (3.8)	2.88 [1.89; 4.41]; < 0.001[f]
Headache (PT, AE)	740	210 (28.4)	720	122 (16.9)	1.67 [1.37; 2.04]; < 0.001[f]
Peripheral sensory neuropathy (PT, severe AEs [CTCAE grade ≥ 3])	740	10 (1.4)	720	0 (0)	20.43 [1.2; 348.05]; 0.002[f]
Infections and infestations (SOC, SAE)	740	37 (5.0)	720	21 (2.9)	1.71 [1.01; 2.9]; 0.042[f]
Respiratory, thoracic and mediastinal disorders (SOC, AE)	740	329 (44.5)	720	219 (30.4)	1.46 [1.27; 1.68]; < 0.001[f]
Eye disorders (SOC, AE)	740	133 (18.0)	720	63 (8.8)	2.05 [1.55; 2.72]; < 0.001[f]

a. Unstratified Cox model; p-value: 2-sided log-rank test.
b. No presentation of effect estimations. The presented events do not completely represent the outcome. Only events that are relevant for the formation of the composite outcome are presented.
c. Comprises the same components as the outcome "recurrence".
d. Too large or unclear proportion of patients not considered in the analysis.
e. SAEs were recorded beyond the 30-day follow-up observation.
f. Institute's calculation: 95% CI asymptotic; unconditional exact test, (CSZ method according to [13]).

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; DCIS: ductal carcinoma in situ; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 15: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: trastuzumab emtansine vs. trastuzumab (multipage table)

Study Outcome category Outcome	Trastuzumab emtansine			Trastuzumab			Trastuzumab emtansine vs. trastuzumab
	N[a]	Values at baseline mean (SE)	Change mean[b] (SE)	N[a]	Values at baseline mean (SE)	Change mean[b] (SE)	MD [95% CI]; p-value[c]
KATHERINE							
Morbidity							
Health status (EQ-5D VAS[d])							
End of therapy	631	ND	1.66 (0.46)	607	ND	2.55 (0.47)	−0.89 [−2.17; 0.39]; ND
12-month follow-up	618	ND	0.38 (0.47)	600	ND	1.95 (0.48)	−1.57 [−2.89; −0.24]; ND Hedges' g[e] −0.13 [−0.25; −0.02]
Symptoms (EORTC QLQ-C30 symptom scales[f]) – 12-month follow-up							
Fatigue	640	ND	2.48 (0.63)	612	ND	0.76 (0.64)	1.73 [−0.03; 3.48]; ND
Nausea and vomiting	640	ND	1.94 (0.29)	612	ND	1.18 (0.30)	0.75 [−0.06; 1.57]; ND
Pain	640	ND	1.06 (0.66)	612	ND	−0.09 (0.68)	1.15 [−0.71; 3.01]; ND
Dyspnoea	640	ND	3.32 (0.60)	612	ND	3.65 (0.62)	−0.33 [−2.03; 1.37]; ND
Insomnia	640	ND	0.45 (0.84)	612	ND	1.59 (0.86)	−1.14 [−3.50; 1.22]; ND
Appetite loss	640	ND	1.93 (0.48)	612	ND	0.08 (0.49)	1.85 [0.50; 3.20]; ND Hedges' g[e] 0.15 [0.04; 0.26]
Constipation	640	ND	5.54 (0.62)	612	ND	2.89 (0.64)	2.65 [0.90; 4.39]; ND Hedges' g[e] 0.17 [0.06; 0.28]
Diarrhoea	640	ND	−2.62 (0.40)	612	ND	−0.95 (0.41)	−1.67 [−2.78; −0.55]; ND Hedges' g[e] −0.17 [−0.28; −0.05]
Symptoms (EORTC QLQ-BR23 symptom scales[f]) – 12-month follow-up							
Side effects of systemic therapy	638	ND	3.39 (0.42)	610	ND	1.21 (0.43)	2.18 [1.01; 3.35]; ND Hedges' g[e] 0.21 [0.10; 0.32]
Symptoms in chest region	638	ND	−2.51 (0.50)	610	ND	−3.93 (0.52)	1.43 [0.01; 2.84]; ND Hedges' g[e] 0.11 [0.00; 0.22]

Table 15: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: trastuzumab emtansine vs. trastuzumab (multipage table)

Study Outcome category Outcome	Trastuzumab emtansine			Trastuzumab			Trastuzumab emtansine vs. trastuzumab
	N[a]	Values at baseline mean (SE)	Change mean[b] (SE)	N[a]	Values at baseline mean (SE)	Change mean[b] (SE)	MD [95% CI]; p-value[c]
Symptoms in arm region	638	ND	−1.40 (0.60)	610	ND	−3.19 (0.62)	1.80 [0.10; 3.50]; ND Hedges' g[e] 0.12 [0.01; 0.23]
Upset by hair loss	No usable data[g]						
Health-related quality of life							
EORTC QLQ-C30 functional scales[d] – 12-month follow-up							
Global health status	640	ND	0.23 (0.51)	612	ND	1.63 (0.52)	−1.40 [−2.84; 0.04]; ND
Physical functioning	640	ND	−0.31 (0.43)	612	ND	1.32 (0.44)	−1.64 [−2.84; −0.44]; ND Hedges' g[e] −0.15 [−0.26; −0.04]
Role functioning	640	ND	2.00 (0.67)	612	ND	4.20 (0.69)	−2.21 [−4.09; −0.33]; ND Hedges' g[e] −0.13 [−0.24; −0.02]
Emotional functioning	640	ND	−1.27 (0.64)	612	ND	−2.07 (0.65)	0.80 [−0.99; 2.59]; ND
Cognitive functioning	640	ND	−5.67 (0.64)	612	ND	−5.10 (0.65)	−0.57 [−2.36; 1.22]; ND
Social functioning	640	ND	3.83 (0.64)	612	ND	6.21 (0.65)	−2.38 [−4.17; −0.59]; ND Hedges' g[e] −0.15 [−0.26; −0.04]
EORTC QLQ-BR23 functional scales[d] – 12-month follow-up							
Body image	638	ND	5.97 (0.71)	610	ND	3.60 (0.72)	2.38 [0.39; 4.36]; ND Hedges' g[e] 0.13 [0.02; 0.24]
Sexual activity	538	ND	3.57 (0.69)	517	ND	3.95 (0.71)	−0.38 [−2.32; 1.57]; ND
Enjoyment of sex	216	ND	1.00 (1.32)	218	ND	3.05 (1.41)	−2.05 [−5.84; 1.74]; ND
Future perspective	638	ND	6.43 (0.81)	610	ND	6.45 (0.83)	−0.03 [−2.29; 2.24]; ND

Table 15: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: trastuzumab emtansine vs. trastuzumab (multipage table)

Study Outcome category Outcome	Trastuzumab emtansine			Trastuzumab			Trastuzumab emtansine vs. trastuzumab
	N[a]	Values at baseline mean (SE)	Change mean[b] (SE)	N[a]	Values at baseline mean (SE)	Change mean[b] (SE)	MD [95% CI]; p-value[c]
a. Number of patients considered in the analysis for the calculation of the effect estimation; the values at the start of the study (possibly at other time points) may be based on other patient numbers. b. Refers to the change from baseline to the last time point of measurement. c. MMRM with covariables: treatment, time point of study, treatment x time point of study, respective baseline value; effect presents the difference between the treatment groups of the changes averaged over the course of the study between the respective time point of measurement and the start of the study. d. A positive change from baseline to the respective time point of measurement indicates improvement; a positive effect estimation indicates an advantage for the intervention. e. Institute's calculation. f. A positive change from baseline to the respective time point of measurement indicates deterioration of symptoms; a negative effect estimation indicates an advantage for the intervention. g. Too large or unclear proportion of patients not considered in the analysis. CI: confidence interval; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; MD: mean difference; MMRM: mixed effects model repeated measures; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SE: standard error; vs.: versus						

On the basis of the available data, at most indications, e.g. of an added benefit, can be determined for the outcomes "overall survival", "recurrence", "SAEs" and "severe AEs (CTCAE grade ≥ 3)"; and, due to the high risk of bias, at most hints can be determined for the outcomes "symptoms", "health status", "health-related quality of life" and "AEs".

Mortality

There was no statistically significant difference between the treatment arms for the outcome "overall survival". This resulted in no hint of an added benefit of trastuzumab emtansine in comparison with trastuzumab. An added benefit for this outcome is therefore not proven.

The company did not make any statements about the added benefit for this outcome. The company's assessment on mortality was not based on the results for overall survival itself, but on DFS, which the company presented as valid surrogate for overall survival. For this purpose, the company presented a validation study financed by the company [14]. However, this validation study is unsuitable to show the validity of DFS as surrogate outcome for "overall survival" in the present therapeutic indication. In the benefit assessment, DFS was therefore not considered to be a valid surrogate for overall survival. A detailed justification for this and a detailed description of the validation study are presented in Section 2.6.9.4 of the full benefit assessment.

Morbidity

Recurrence

For the composite outcome "recurrence", a statistically significant difference in favour of trastuzumab emtansine in comparison with trastuzumab was shown between the treatment arms. This resulted in an indication of an added benefit of trastuzumab emtansine in comparison with trastuzumab.

This deviates from the assessment of the company insofar as the company derived a clinical benefit of trastuzumab emtansine on the basis of event time analyses on recurrence in general (DFS) and on distant recurrence (distant recurrence-free interval [DRFI]).

Symptoms

Symptom outcomes were recorded with the symptom scales of the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-BR23. Symptoms were considered at 2 time points. At the end of therapy, the proportions of patients with a deterioration by ≥ 10 points were shown. Since the responder analyses on the 12-month follow-up were not usable, the mean differences were considered for this time point (see Section 2.6.4.3.2 of the full dossier assessment). Hereinafter, first the outcomes are described for which statistically significant and relevant group differences were shown for at least one time point.

Appetite loss, constipation, side effects of systemic therapy

The responder analysis at the end of therapy showed statistically significant differences between the treatment arms to the disadvantage of trastuzumab emtansine for the outcomes "appetite loss", "constipation" and "side effects of systemic therapy". The analysis of continuous data at the 12-month follow-up showed statistically significant differences between the treatment arms to the disadvantage of trastuzumab emtansine for these outcomes. However, the 95% CI of the SMD (Hedges' g) was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the observed effects at the 12-month follow-up are relevant. Based on the negative effects at the end of therapy, there is overall a hint of lesser benefit of trastuzumab emtansine in comparison with trastuzumab for the outcomes mentioned.

Fatigue, nausea and vomiting, pain, symptoms in arm region

The responder analysis at the end of therapy showed statistically significant differences between the treatment arms to the disadvantage of trastuzumab emtansine for the outcomes "fatigue", "nausea and vomiting", "pain" and "symptoms in arm region". The effect in these outcomes of the category of non-serious/non-severe symptoms/late complications was no more than marginal, however (see Section 2.5.1). The analysis of continuous data at the 12-month follow-up showed a statistically significant difference to the disadvantage of trastuzumab emtansine for the outcome "symptoms in arm region". However, the 95% CI of the SMD (Hedges' g) was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the observed effect at the 12-month follow-up is relevant. For the outcomes "fatigue", "nausea and vomiting" and "pain", no statistically significant differences between the treatment arms were

shown at the 12-month follow-up. Overall, this resulted in no hint of an added benefit of trastuzumab emtansine in comparison with trastuzumab for the outcomes “fatigue”, “nausea and vomiting”, “pain” and “symptoms in arm region”; an added benefit is therefore not proven.

Dyspnoea, insomnia, diarrhoea, symptoms in chest region, upset by hair loss

At the end of therapy, no statistically significant differences between the treatment arms were shown for the outcomes “dyspnoea”, “insomnia”, “diarrhoea” and “symptoms in chest region”. The analysis of continuous data at the 12-month follow-up showed statistically significant differences for the outcomes “diarrhoea” and “symptoms in chest region”. The difference was in favour of trastuzumab emtansine for the outcome “diarrhoea” and to the disadvantage of trastuzumab emtansine for the outcome “symptoms in chest region”. However, the 95% CI of the SMD (Hedges’ g) was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the observed effects at the 12-month follow-up are relevant. For the outcomes “dyspnoea” and “insomnia”, no statistically significant differences between the treatment arms were shown at the 12-month follow-up. There were no usable data for upset by hair loss (see Section 2.6.4.3.2 of the full dossier assessment). Overall, this resulted in no hint of an added benefit of trastuzumab emtansine in comparison with trastuzumab; an added benefit is therefore not proven.

This deviates from the assessment of the company, which presented responder analyses for all symptom outcomes at both time points. Furthermore, the company presented the results, but did not derive an added benefit or lesser benefit of trastuzumab emtansine from them, as it did not consider there to be persistent deterioration.

Health status (EQ-5D VAS)

At the end of therapy, there was no statistically significant difference between the treatment arms for the outcome “health status” recorded with the EQ-5D VAS. At the 12-month follow-up, however, there was a statistically significant difference. However, the 95% CI of the SMD (Hedges’ g) was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the observed effect at the 12-month follow-up is relevant. Overall, this resulted in no hint of an added benefit of trastuzumab emtansine in comparison with trastuzumab; an added benefit is therefore not proven.

This concurs with the company’s assessment.

Health-related quality of life

Health-related quality of life was recorded with the functional scales and with the scale for recording the global health status of the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-C30. Health-related quality of life was considered at 2 time points. At the end of therapy, the proportions of patients with a deterioration by ≥ 10 points were shown. Since the responder analyses on the 12-month follow-up were not usable, the mean differences were considered for this time point (see Section 2.6.4.3.2 of the full dossier assessment). Hereinafter,

first the outcomes are described for which statistically significant and relevant group differences were shown for at least one time point.

Physical functioning, social functioning

The responder analyses at the end of therapy showed statistically significant differences between the treatment arms to the disadvantage of trastuzumab emtansine for the outcomes "physical functioning" and "social functioning". The analysis of continuous data at the 12-month follow-up also showed statistically significant differences to the disadvantage of trastuzumab emtansine. However, the 95% CI of the SMD (Hedges' g) was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the observed effects at the 12-month follow-up are relevant. Based on the negative effects at the end of therapy, there is overall a hint of lesser benefit of trastuzumab emtansine in comparison with trastuzumab.

Global health status

For the outcome "global health status", a statistically significant difference between the treatment arms was neither shown at the end of therapy nor in the 12-month follow-up in the total population. However, a statistically significant interaction with the characteristic "age" was shown at the end of therapy. This resulted in a hint of lesser benefit of trastuzumab emtansine in comparison with trastuzumab for patients ≥ 65 years of age. For patients < 65 years of age, there was no hint of an added benefit; an added benefit for these patients is not proven.

Further functional scales and quality of life scales

There were no statistically significant differences between the treatment arms for the outcomes "role functioning", "emotional functioning", "cognitive functioning", "body image" and "future perspective" in the responder analyses at the end of therapy. These responder analyses provided no usable data for the items "sexual activity" and "enjoyment of sex" (see Section 2.6.4.3.2 of the full dossier assessment). The analysis of continuous data at the 12-month follow-up showed statistically significant differences for the outcomes "role functioning" and "body image". The difference was to the disadvantage of trastuzumab emtansine for the outcome "role functioning" and in favour of trastuzumab emtansine for the outcome "body image". However, the 95% CI of the SMD (Hedges' g) was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the observed effects at the 12-month follow-up are relevant. For the outcomes "emotional functioning", "cognitive functioning", "future perspective", "sexual activity" and "enjoyment of sex", no statistically significant differences between the treatment arms were shown at the 12-month follow-up. Overall, this resulted in no hint of an added benefit of trastuzumab emtansine in comparison with trastuzumab; an added benefit is therefore not proven.

This deviates from the assessment of the company, which presented responder analyses for all health-related quality of life outcomes at both time points. Furthermore, the company presented

the results, but did not derive an added benefit or lesser benefit of trastuzumab emtansine from them, as it did not consider there to be persistent deterioration.

Side effects

Serious adverse events, severe adverse events (CTCAE grade ≥ 3), discontinuation due to adverse events

A statistically significant difference to the disadvantage of trastuzumab emtansine was shown for each of the outcomes "SAEs", "severe AEs (CTCAE grade ≥ 3)" and "discontinuation due to AEs". This resulted in an indication of greater harm from trastuzumab emtansine in comparison with trastuzumab for each SAEs and severe AEs (CTCAE grade ≥ 3), and in a hint of greater harm for discontinuation due to AEs.

This deviates from the assessment of the company, which presented the results, but did not derive greater or lesser harm of trastuzumab emtansine.

Specific adverse events

For the following AEs, a statistically significant difference to the disadvantage of trastuzumab emtansine in comparison with trastuzumab was shown between the treatment arms:

- Severe AEs or SAEs:

  platelet count decreased (PT, severe AEs [CTCAE grade ≥ 3]), gastrointestinal disorders (SOC, severe AEs [CTCAE grade ≥ 3]), peripheral sensory neuropathy (PT, severe AEs [CTCAE grade ≥ 3]), infections and infestations (SOC, SAE)

- Non-severe/non-serious AEs:

  fatigue (PT), fever (PT), nausea (PT), constipation (PT), vomiting (PT), dry mouth (PT), stomatitis (PT), headache (PT), respiratory, thoracic and mediastinal disorders (SOC), eye disorders (SOC)

In each case, this resulted in an indication (for severe/serious AEs) or a hint (for non-severe/non-serious AEs) of greater harm from trastuzumab emtansine in comparison with trastuzumab.

No statistically significant difference between the treatment arms was shown for the outcome "cardiac disorders" (SOC, severe AEs [CTCAE grade ≥ 3]). This resulted in no hint of greater or lesser harm from trastuzumab emtansine in comparison with trastuzumab; greater or lesser harm is therefore not proven.

2.4.4 Subgroups and other effect modifiers

The following effect modifiers were considered in the present assessment:

- age (< 65 years versus ≥ 65 years)

- geographical region (USA/Canada versus Western Europe versus Asia-Pacific versus Latin America versus other)
- hormone receptor status (ER-positive and/or PR-positive versus ER-negative and PR-negative/unknown)
- pathological lymph node status after preoperative therapy (positive versus negative/unknown)

The characteristics age, hormone receptor status and pathological lymph node status after preoperative surgery, but not the individual subgroups, were prespecified in the planning of the study. No subgroup results were available for the outcome "recurrence", for the mean differences on health status (EQ-5D VAS) and for the mean differences on the 12-month follow-up of the EORTC QLQ-C30 and of the EORTC QLQ-BR23. There were also no subgroup results on the characteristic "hormone receptor status" for AE outcomes. This approach was inadequate. Complete interaction analyses of the relevant outcomes are essential for a comprehensive assessment of subgroup effects.

The characteristic of sex was not considered in the present assessment, as there were only 5 male patients in total.

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there must be 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup. Table 16 shows the results of the subgroup analysis.

Table 16: Subgroups (morbidity, health-related quality of life, side effects) – RCT, direct comparison: trastuzumab emtansine vs. trastuzumab (multipage table)

Study Outcome Characteristic Subgroup	Trastuzumab emtansine		Trastuzumab		Trastuzumab emtansine vs. trastuzumab	
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]	p-value
KATHERINE						
Health-related quality of life						
EORTC QLQ-C30 functional scales – patients with deterioration by ≥ 10 points at the end of therapy						
Global health status (end of therapy)						
Age						
< 65	494	111 (22.5)	484	108 (22.3)	1.01 [0.80; 1.27]	0.954
≥ 65	40	12 (30.0)	51	4 (7.8)	3.82 [1.33; 10.97]	0.013
Total					Interaction:	0.008
Cognitive functioning (end of therapy)						
Geographical region						
USA/Canada	122	50 (41.0)	119	38 (31.9)	1.27 [0.91; 1.78]	0.162
Western Europe	275	116 (42.2)	273	96 (35.2)	1.20 [0.97; 1.48]	0.093
Asia-Pacific	44	15 (34.1)	42	15 (35.7)	0.95 [0.54; 1.70]	0.875
Latin America	48	12 (25.0)	66	25 (37.9)	0.66 [0.37; 1.18]	0.160
Other[a]	45	8 (17.8)	35	16 (45.7)	0.39 [0.19; 0.80]	0.011
Total					Interaction:	0.008
Side effects						
SAEs						
Age						
< 65	683	89 (13.0)	652	48 (7.4)	1.77 [1.27; 2.47]	< 0.001
≥ 65	57	5 (8.8)	68	10 (14.7)	0.60 [0.22; 1.64]	0.318
Total					Interaction:	0.038
Geographical region						
USA/Canada	168	28 (16.7)	157	10 (6.4)	2.62 [1.31; 5.21]	0.006
Western Europe	401	46 (11.5)	391	32 (8.2)	1.40 [0.91; 2.15]	0.123
Asia-Pacific	51	10 (19.6)	49	1 (2.0)	9.61 [1.28; 72.27]	0.028
Latin America	61	4 (6.6)	77	10 (13.0)	0.50 [0.17; 1.53]	0.228
Other[a]	59	6 (10.2)	46	5 (10.9)	0.94 [0.30; 2.87]	0.908
Total					Interaction:	0.010

Table 16: Subgroups (morbidity, health-related quality of life, side effects) – RCT, direct comparison: trastuzumab emtansine vs. trastuzumab (multipage table)

Study Outcome Characteristic Subgroup	Trastuzumab emtansine N	Trastuzumab emtansine Patients with event n (%)	Trastuzumab N	Trastuzumab Patients with event n (%)	Trastuzumab emtansine vs. trastuzumab RR [95% CI]	 p-value
Severe AEs (CTCAE grade ≥ 3)						
Geographical region						
USA/Canada	168	62 (36.9)	157	32 (20.4)	1.81 [1.25; 2.61]	0.002
Western Europe	401	87 (21.7)	391	56 (14.3)	1.51 [1.12; 2.06]	0.008
Asia-Pacific	51	20 (39.2)	49	2 (4.1)	9.61 [2.37; 38.95]	0.002
Latin America	61	11 (18.0)	77	18 (23.4)	0.77 [0.39; 1.51]	0.448
Other[a]	59	10 (16.9)	46	3 (6.5)	2.60 [0.76; 8.90]	0.128
Total					Interaction:	0.002
Fever (PT, AE)						
Age						
< 65	683	72 (10.5)	652	29 (4.4)	2.37 [1.56; 3.60]	< 0.001
≥ 65	57	5 (8.8)	68	0 (0)	13.09 [0.74; 231.71][b]	0.013[c]
Total					Interaction:	0.045
Nausea (PT, AE)						
Geographical region						
USA/Canada	168	94 (56.0)	157	36 (22.9)	2.44 [1.78; 3.35]	< 0.001
Western Europe	401	165 (41.1)	391	43 (11.0)	3.74 [2.76; 5.08]	< 0.001
Asia-Pacific	51	17 (33.3)	49	0 (0)	33.65 [2.08; 544.75][b]	< 0.001[c]
Latin America	61	19 (31.1)	77	10 (13.0)	2.40 [1.21; 4.77]	0.013
Other[a]	59	13 (22.0)	46	5 (10.9)	2.03 [0.78; 5.28]	0.148
Total					Interaction:	0.005

a. No information on which regions are comprised by this group.
b. Institute's calculation of effect (in case of 0 events in one treatment arm with correction factor of 0.5 in both study arms) and 95% CI (asymptotic).
c. Institute's calculation: unconditional exact test (CSZ method according to [13]); discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Morbidity

Health-related quality of life

EORTC QLQ-C30 (functional scales)

Global health status (end of therapy)

For the outcome "global health status", a statistically significant interaction for the characteristic of age was shown at the end of therapy.

There was no statistically significant difference between the treatment groups in the age group < 65 years. This resulted in no hint of an added benefit of trastuzumab emtansine in comparison with trastuzumab. An added benefit for patients < 65 years of age is therefore not proven for this outcome.

A statistically significant difference to the disadvantage of trastuzumab emtansine between the treatment arms was shown for the age group ≥ 65 years. This resulted in a hint of lesser benefit of trastuzumab emtansine in comparison with trastuzumab for patients ≥ 65 years of age for this outcome.

Cognitive functioning (end of therapy)

For the outcome "cognitive functioning", a statistically significant interaction for the characteristic of geographical region was shown at the end of therapy.

A statistically significant difference between the treatment arms was only shown for other regions. This was in favour of trastuzumab emtansine. In other regions, including Western Europe, there was no statistically significant difference between the treatment groups, as was the case for the total population. The region of Western Europe is of particular importance for the present benefit assessment. The conclusion on the added benefit was therefore derived on the basis of the total population.

Side effects

Serious adverse events

For the outcome "SAEs", there was a statistically significant interaction for each of the characteristics of age and of geographical region. The subgroup results could not be meaningfully interpreted because data for the investigation of possible dependencies between the subgroup characteristics were missing. The derivation of the added benefit was therefore conducted on the basis of the results on the total population.

Severe adverse events (CTCAE grade ≥ 3)

For the outcome "severe AEs (CTCAE grade ≥ 3)", there was a statistically significant interaction for the characteristic of geographical region.

A statistically significant difference between the treatment arms was shown for the regions of USA/Canada, Western Europe and Asia-Pacific. This was to the disadvantage of trastuzumab

emtansine. The region of Western Europe is of particular importance for the present benefit assessment. There was a statistically significant effect to the disadvantage of trastuzumab emtansine also for the total population. The derivation of the added benefit was therefore conducted on the basis of the results on the total population.

Fever (PT, AE)

For the outcome "fever", there was a statistically significant interaction for the characteristic of age.

A statistically significant difference between the treatment arms was shown both for the age group ≥ 65 years and for the age group < 65 years. Due to the same direction of effect in the subgroups and the high statistical uncertainty in the effect estimation of the age group ≥ 65 years, the derivation of the added benefit was based on the results of the total population.

Nausea (PT, AE)

For the outcome "nausea", there was a statistically significant interaction for the characteristic of geographical region.

A statistically significant difference between the treatment arms was shown for the regions of USA/Canada, Western Europe, Asia-Pacific and Latin America. This was to the disadvantage of trastuzumab emtansine. The region of Western Europe is of particular importance for the present benefit assessment. There was a statistically significant effect to the disadvantage of trastuzumab emtansine also for the total population. The derivation of the added benefit was therefore conducted on the basis of the results on the total population.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below, 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 the 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 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 17).

Determination of the outcome category for outcomes on symptoms and side effects

It cannot be inferred from the dossier for all outcomes considered in the present benefit assessment whether they were serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

The outcome “recurrence” is considered to be serious/severe. Recurrence of cancer can be potentially fatal, or shows that the curative therapy approach in a potentially fatal disease has not been successful. Besides, the event “death of any cause” was a component of the composite outcome “recurrence”.

The symptom scales of the questionnaires EORTC QLQ-C30 and QLQ-BR23 are considered as non-serious/non-severe outcomes. There is no information on absolute threshold values of the EORTC scales that mark a transition from non-severe to severe manifestation of a symptom or late complication on a scale.

For the outcome “discontinuation due to AEs”, no suitable data are available for the assessment of the outcome category. Therefore, the outcome “discontinuation due to AEs” is allocated to the outcome category of non-serious/non-severe side effects. For outcomes on specific AEs, preference is given to the consideration of events with severe or serious manifestations (CTCAE grade ≥ 3 or SAE). All other outcomes on specific side effects with statistically significant effects are allocated to the category of non-serious/non-severe side effects, as the events included in these outcomes were mostly non-serious/non-severe.

Table 17: Extent of added benefit at outcome level: trastuzumab emtansine vs. trastuzumab (multipage table)

Outcome category **Outcome** **Time point** **Effect modifier** **Subgroup**	**Trastuzumab emtansine vs. trastuzumab** **Proportion of events (%) or MD** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
Overall survival	Median time to event: NA vs. NA HR: 0.70 [0.47; 1.05] p = 0.085	Lesser benefit/added benefit not proven
Morbidity		
Recurrence	13.2% vs. 22.5% RR: 0.59 [0.47; 0.74] p < 0.001 probability: "indication"	Outcome category: serious/severe symptoms/late complications $CI_u < 0.75$, risk ≥ 5% added benefit, extent: "major"
EORTC QLQ-C30 and EORTC QLQ-BR23 symptom scales		
Fatigue		
End of therapy	39.5% vs. 32.6% RR: 1.21 [1.03; 1.42] RR: 0.83 [0.70; 0.97][c] p = 0.020	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[d]
12-month follow-up	mean: 2.48 vs. 0.76 MD: 1.73 [−0.03; 3.48] p = ND	lesser benefit/added benefit not proven
Nausea and vomiting		
End of therapy	16.7% vs. 11.8% RR: 1.42 [1.05; 1.91] RR: 0.70 [0.52; 0.95][c] p = 0.022	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[d]
12-month follow-up	mean: 1.94 vs. 1.18 MD: 0.75 [−0.06; 1.57] p = ND	lesser benefit/added benefit not proven
Pain		
End of therapy	33.1% vs. 27.2% RR: 1.22 [1.01; 1.46] RR: 0.82 [0.68; 0.99][c] p = 0.036	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[d]
12-month follow-up	mean: 1.06 vs. −0.09 MD: 1.15 [−0.71; 3.01] p = ND	lesser benefit/added benefit not proven

Table 17: Extent of added benefit at outcome level: trastuzumab emtansine vs. trastuzumab (multipage table)

Outcome category **Outcome** **Time point** **Effect modifier** **Subgroup**	**Trastuzumab emtansine vs. trastuzumab** **Proportion of events (%) or MD** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Dyspnoea		
End of therapy	20.8% vs. 20.7% RR: 1.00 [0.79; 1.27] p = 0.975	Lesser benefit/added benefit not proven
12-month follow-up	mean: 3.32 vs. 3.65 MD: −0.33 [−2.03; 1.37] p = ND	lesser benefit/added benefit not proven
Insomnia		
End of therapy	26.2% vs. 26.5% RR: 0.99 [0.81; 1.21] p = 0.919	Lesser benefit/added benefit not proven
12-month follow-up	mean: 0.45 vs. 1.59 MD: −1.14 [−3.50; 1.22] p = ND	lesser benefit/added benefit not proven
Appetite loss		
End of therapy	18.9% vs. 10.8% RR: 1.75 [1.30; 2.36] RR: 0.57 [0.42; 0.77][c] p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 lesser benefit, extent: “considerable”
12-month follow-up	mean: 1.93 vs. 0.08 MD: 1.85 [0.50; 3.20] p = ND Hedges’ g: 0.15 [0.04; 0.26][e]	lesser benefit/added benefit not proven
Constipation		
End of therapy	29.8% vs. 18.1% RR: 1.65 [1.32; 2.05] RR: 0.61 [0.49; 0.76][c] p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 lesser benefit, extent: “considerable”
12-month follow-up	mean: 5.54 vs. 2.89 MD: 2.65 [0.90; 4.39] p = ND Hedges’ g: 0.17 [0.06; 0.28][e]	lesser benefit/added benefit not proven

Table 17: Extent of added benefit at outcome level: trastuzumab emtansine vs. trastuzumab (multipage table)

Outcome category **Outcome** **Time point** **Effect modifier** **Subgroup**	**Trastuzumab emtansine vs. trastuzumab** **Proportion of events (%) or MD** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Diarrhoea		
End of therapy	7.5% vs. 10.5% RR: 0.72 [0.49; 1.05] p = 0.091	Lesser benefit/added benefit not proven
12-month follow-up	mean: −2.62 vs. −0.95 MD: −1.67 [−2.78; −0.55] p = ND Hedges' g: −0.17 [−0.28; −0.05][e]	lesser benefit/added benefit not proven
Side effects of systemic therapy		
End of therapy	27.0% vs. 17.6% RR: 1.53 [1.22; 1.93] RR: 0.65 [0.52; 0.82][c] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ lesser benefit, extent: "considerable"
12-month follow-up	mean: 3.39 vs. 1.21 MD: 2.18 [1.01; 3.35] p = ND Hedges' g: 0.21 [0.10; 0.32][e]	lesser benefit/added benefit not proven
Symptoms in chest region		
End of therapy	18.5% vs. 16.5% RR: 1.12 [0.87; 1.46] p = 0.376	Lesser benefit/added benefit not proven
12-month follow-up	mean: −2.51 vs. −3.93 MD: 1.43 [0.01; 2.84] p = ND Hedges' g: 0.11 [0.00; 0.22][e]	lesser benefit/added benefit not proven
Symptoms in arm region		
End of therapy	35.6% vs. 28.1% RR: 1.27 [1.06; 1.51] RR: 0.79 [0.66; 0.94][c] p = 0.009	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[d]
12-month follow-up	mean: −1.40 vs. −3.19 MD: 1.80 [0.10; 3.50] p = ND Hedges' g: 0.12 [0.01; 0.23][e]	lesser benefit/added benefit not proven

Table 17: Extent of added benefit at outcome level: trastuzumab emtansine vs. trastuzumab (multipage table)

Outcome category **Outcome** **Time point** **Effect modifier** **Subgroup**	**Trastuzumab emtansine vs. trastuzumab** **Proportion of events (%) or MD** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Upset by hair loss End of therapy 12-month follow-up	No usable data[f]	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)		
End of therapy	mean: 1.66 vs. 2.55 MD: −0.89 [−2.17; 0.39] p = ND	Lesser benefit/added benefit not proven
12-month follow-up	mean: 0.38 vs. 1.95 MD: −1.57 [−2.89; −0.24] p = ND Hedges' g: −0.13 [−0.25; −0.02][e]	lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-BR23 and EORTC QLQ-BR23 functional scales		
Global health status End of therapy Age < 65	22.5% vs. 22.3% RR: 1.01 [0.80; 1.27] p = 0.954	Lesser benefit/added benefit not proven
≥ 65	30.0% vs. 7.8% RR: 3.82 [1.33; 10.97] RR: 0.26 [0.09; 0.75][c] probability: "hint"	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ lesser benefit, extent: "considerable"
12-month follow-up	mean: 0.23 vs. 1.63 MD: −1.40 [−2.84; 0.04] p = ND	Lesser benefit/added benefit not proven
Physical functioning End of therapy	22.5% vs. 17.0% RR: 1.32 [1.04; 1.69] RR: 0.76 [0.59; 0.96][c] p = 0.025 probability: "hint"	Outcome category: health-related quality of life $90 \leq CI_u < 1.00$ lesser benefit, extent: "minor"
12-month follow-up	mean: −0.31 vs. 1.32 MD: −1.64 [−2.84; −0.44] p = ND Hedges' g: −0.15 [−0.26; −0.04][e]	lesser benefit/added benefit not proven

Table 17: Extent of added benefit at outcome level: trastuzumab emtansine vs. trastuzumab (multipage table)

Outcome category **Outcome** **Time point** **Effect modifier** **Subgroup**	**Trastuzumab emtansine vs. trastuzumab** **Proportion of events (%) or MD** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Role functioning		
End of therapy	26.4% vs. 22.8% RR: 1.16 [0.94; 1.43] p = 0.167	Lesser benefit/added benefit not proven
12-month follow-up	mean: 2.00 vs. 4.20 MD: −2.21 [−4.09; −0.33] p = ND Hedges' g: −0.13 [−0.24; −0.02]	lesser benefit/added benefit not proven
Emotional functioning		
End of therapy	39.0% vs. 37.0% RR: 1.05 [0.90; 1.23] p = 0.513	Lesser benefit/added benefit not proven
12-month follow-up	mean: −1.27 vs. −2.07 MD: 0.80 [−0.99; 2.59] p = ND	lesser benefit/added benefit not proven
Cognitive functioning		
End of therapy	37.6% vs. 35.5% RR: 1.06 [0.90; 1.24] p = 0.471	Lesser benefit/added benefit not proven
12-month follow-up	mean: −5.67 vs. −5.10 MD: −0.57 [−2.36; 1.22] p = ND	lesser benefit/added benefit not proven
Social functioning		
End of therapy	24.5% vs. 19.1% RR: 1.29 [1.02; 1.62] RR: 0.78 [0.62; 0.98][c] p = 0.031 probability: "hint"	Outcome category: health-related quality of life $90 \leq CI_u < 1.00$ lesser benefit, extent: "minor"
12-month follow-up	mean: 3.83 vs. 6.21 MD: −2.38 [−4.17; −0.59] p = ND Hedges' g: −0.15 [−0.26; −0.04]	lesser benefit/added benefit not proven

Table 17: Extent of added benefit at outcome level: trastuzumab emtansine vs. trastuzumab (multipage table)

Outcome category **Outcome** **Time point** **Effect modifier** **Subgroup**	**Trastuzumab emtansine vs. trastuzumab** **Proportion of events (%) or MD** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Body image		
End of therapy	17.0% vs. 19.9% RR: 0.86 [0.67; 1.11] p = 0.237	Lesser benefit/added benefit not proven
12-month follow-up	mean: 5.97 vs. 3.60 MD: 2.38 [0.39; 4.36] p = ND Hedges' g: 0.13 [0.02; 0.24]	lesser benefit/added benefit not proven
Sexual activity		
End of therapy	No usable data[f]	Lesser benefit/added benefit not proven
12-month follow-up	mean: 3.57 vs. 3.95 MD: −0.38 [−2.32; 1.57] p = ND	lesser benefit/added benefit not proven
Enjoyment of sex		
End of therapy	No usable data[f]	Lesser benefit/added benefit not proven
12-month follow-up	mean: 1.00 vs. 3.05 MD: −2.05 [−5.84; 1.74] p = ND	lesser benefit/added benefit not proven
Future perspective		
End of therapy	19.9% vs. 17.0% RR: 1.16 [0.90; 1.50] p = 0.237	Lesser benefit/added benefit not proven
12-month follow-up	mean: 6.43 vs. 6.45 MD: −0.03 [−2.29; 2.24] p = ND	lesser benefit/added benefit not proven
Side effects		
SAEs	12.7% vs. 8.1% RR: 1.58 [1.16; 2.15] RR: 0.63 [0.47; 0.86][c] p = 0.004 probability: "indication"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Severe AEs (CTCAE grade ≥ 3)	25.7% vs. 15.4% RR: 1.67 [1.35; 2.06] RR: 0.60 [0.49; 0.74][c] p < 0.001 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk > 5% greater harm, extent: "major"

Table 17: Extent of added benefit at outcome level: trastuzumab emtansine vs. trastuzumab (multipage table)

Outcome category **Outcome** **Time point** **Effect modifier** **Subgroup**	**Trastuzumab emtansine vs. trastuzumab** **Proportion of events (%) or MD** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Discontinuation due to AEs	18.0% vs. 2.1% RR: 8.63 [5.11; 14.57] RR: 0.12 [0.07; 0.20][c] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Cardiac disorders (SOC, severe AEs [CTCAE grade ≥ 3])	0.3% vs. 1.0% RR: 0.28 [0.06; 1.33] p = 0.088	Greater/lesser harm not proven
Platelet count decreased (PT, severe AEs [CTCAE grade ≥ 3])	5.7% vs. 0.3% RR: 20.43 [4.96; 84.09] RR: 0.05 [0.01; 0.20][c] p < 0.001 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk > 5% greater harm, extent: "major"
Fatigue (PT, AE)	49.5% vs. 33.8% RR: 1.47 [1.29; 1.66] RR: 0.68 [0.60; 0.78][c] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Fever (PT, AE)	10.4% vs. 4.0% RR: 2.58 [1.71; 3.91] RR: 0.39 [0.26; 0.58][c] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Gastrointestinal disorders (SOC, severe AEs [CTCAE grade ≥ 3])	2.8% vs. 1.0% RR: 2.92 [1.25; 6.82] RR: 0.34 [0.15; 0.80][c] p = 0.009 probability: "indication"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Nausea (PT, AE)	41.6% vs. 13.1% RR: 3.19 [2.59; 3.92] RR: 0.31 [0.26; 0.39][c] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Constipation (PT, AE)	17.0% vs. 8.2% RR: 2.08 [1.55; 2.78] RR: 0.48 [0.36; 0.65][c] p = < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"

Table 17: Extent of added benefit at outcome level: trastuzumab emtansine vs. trastuzumab (multipage table)

Outcome category **Outcome** **Time point** **Effect modifier** **Subgroup**	**Trastuzumab emtansine vs. trastuzumab** **Proportion of events (%) or MD** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Vomiting (PT, AE)	14.6% vs. 5.1% RR: 2.84 [1.98; 4.07] RR: 0.35 [0.26; 0.51][c] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Dry mouth (PT, AE)	13.5% vs. 1.3% RR: 10.81 [5.51; 21.22] RR: 0.09 [0.05; 0.18][c] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Stomatitis (PT, AE)	10.8% vs. 3.8% RR: 2.88 [1.89; 4.41] RR: 0.35 [0.23; 0.53][c] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Headache (PT, AE)	28.4% vs. 16.9% RR: 1.67 [1.37; 2.04] RR: 0.60 [0.49; 0.73][c] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Peripheral sensory neuropathy (PT, severe AEs [CTCAE grade ≥ 3])	1.4% vs. 0% RR: 20.43 [1.2; 348.05] RR: 0.05 [0.003; 0.83][c] p = 0.002 probability: "indication"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Infections and infestations (SOC, SAE)	5.0% vs. 2.9% RR: 1.71 [1.01; 2.9] RR: 0.58 [0.34; 0.99][c] p = 0.042 probability: "indication"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
Respiratory, thoracic and mediastinal disorders (SOC, AE)	44.5% vs. 30.4% RR: 1.46 [1.27; 1.68] RR: 0.68 [0.60; 0.79][c] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Eye disorders (SOC, AE)	18.0% vs. 8.8% RR: 2.05 [1.55; 2.72] RR: 0.49 [0.37; 0.65][c] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"

Table 17: Extent of added benefit at outcome level: trastuzumab emtansine vs. trastuzumab (multipage table)

Outcome category **Outcome** **Time point** **Effect modifier** **Subgroup**	**Trastuzumab emtansine vs. trastuzumab** **Proportion of events (%) or MD** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
a. Probability provided if a statistically significant and relevant effect is present. b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u). c. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit. d. The extent of the effect in this non-serious/non-severe outcome was no more than marginal. e. If the CI of Hedges' g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, it cannot be derived that a relevant effect is present. f. Too large or unclear proportion of patients not considered in the analysis. AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; MD: mean difference; PT: Preferred Term; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus		

2.5.2 Overall conclusion on added benefit

Table 18 summarizes the results considered in the overall conclusion on extent of added benefit.

Table 18: Positive and negative effects from the assessment of trastuzumab emtansine in comparison with trastuzumab

Positive effects	**Negative effects**
Morbidity ▪ Recurrence: indication of added benefit – extent: “major”	–
–	Non-serious/non-severe symptoms/late complications ▪ Appetite loss (end of therapy): hint of lesser benefit – extent: “considerable” ▪ Constipation (end of therapy): hint of lesser benefit – extent: “considerable” ▪ Side effects of systemic therapy (end of therapy): hint of lesser benefit – extent: “considerable”
–	Health-related quality of life ▪ Global health status (end of therapy) ▫ age ≥ 65 years hint of lesser benefit – extent: “considerable” ▪ Physical functioning (end of therapy): hint of lesser benefit – extent: “minor” ▪ Social functioning (end of therapy): hint of lesser benefit – extent: “minor”
–	Serious/severe side effects ▪ SAEs: indication of greater harm – extent “considerable” ▫ Infections and infestations (SOC, SAE): indication of greater harm – extent: “minor” ▪ Severe AEs (CTCAE grade ≥ 3): indication of greater harm – extent: “major” ▫ platelet count decreased (PT, severe AEs [CTCAE grade ≥ 3]): indication of greater harm – extent: “major” ▫ gastrointestinal disorders (SOC, severe AEs [CTCAE grade ≥ 3]): indication of greater harm – extent: “considerable” ▫ peripheral sensory neuropathy (PT, severe AEs [CTCAE grade ≥ 3]): indication of greater harm – extent: “considerable”
–	Non-serious/non-severe side effects ▪ Hint of greater harm – extent: “considerable”: ▫ discontinuation due to AEs ▫ fatigue (PT, AE) ▫ fever (PT, AE) ▫ nausea (PT, AE) ▫ constipation (PT, AE) ▫ vomiting (PT, AEs) ▫ dry mouth (PT, AE) ▫ stomatitis (PT, AE) ▫ headache (PT, AE) ▫ respiratory, thoracic and mediastinal disorders (SOC, AE) ▫ eye disorders (SOC, AE)
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; PT: Preferred Term; SAE: serious adverse event; SOC: System Organ Class	

In the overall consideration, there was one positive effect and several negative effects of trastuzumab emtansine.

The positive effect consisted of an indication of a major added benefit of trastuzumab emtansine in the outcome category of morbidity in the outcome "recurrence". This was supported by the results on DFS, which had the same direction of effect and were presented as additional information.

On the other hand, there were a large number of negative effects in the categories of symptoms, health-related quality of life and side effects with major, considerable and minor extent. For the side effect categories, negative effects were shown both for the overall rates of severe AEs (CTCAE grade ≥ 3), SAEs, and discontinuation due to AEs, and for individual specific serious/severe and non-serious/non-severe AEs. Events such as constipation and nausea or vomiting are represented both with symptoms (EORTC QLQ-C30) and with AEs.

All the disadvantages observed were in the treatment phase and were probably mainly due to the burden of the therapy. 12 months after the end of therapy, the continuous analyses used initially showed no differences between the treatment arms. However, this follow-up period was too short to show the changes in symptoms and health-related quality of life resulting from the progression of the disease in the present therapeutic indication. Thus, at the time point of 12 months after the end of therapy (12-month follow-up), recurrence events had only occurred in 27 (3.6%) (trastuzumab-emtansine arm) and in 57 (7.7%) (trastuzumab arm) patients.

Overall, the negative effects did not completely call into question the clear effect in recurrences, but led to a downgrading of the extent in the overall conclusion.

In summary, there was an indication of minor added benefit of trastuzumab emtansine versus trastuzumab for patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy

The result of the assessment of the added benefit of trastuzumab emtansine in comparison with the ACT is summarized in Table 19.

Table 19: Trastuzumab emtansine – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy	Continuation of preoperative anti-HER2-targeted therapy with trastuzumab	Indication of minor added benefit[b]

a. Presentation of the respective ACT specified by the G-BA.
b. Only patients with an ECOG PS of 0 or 1 were included in the KATHERINE study. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2

The assessment described above deviates from that of the company, which derived proof of considerable added benefit.

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. 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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