IQWiG Institut für Qualität und
Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A14-25

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

Extract

Publishing details

Publisher:

Institute for Quality and Efficiency in Health Care

Topic:

Eribulin – Benefit assessment according to §35a Social Code Book V

Commissioning agency:

Federal Joint Committee

Commission awarded on:

29 July 2014

Internal Commission No.:

A14-25

Address of publisher:

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Keywords: eribulin, breast neoplasms, benefit assessment

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Table of contents

List of tables[3]

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[3] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
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
ER	oestrogen receptor
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2/neu	human epidermal growth factor receptor 2
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PR	progesterone receptor
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
TPC	treatment of physician's choice
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 eribulin. 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 29 July 2014.

Research question

The aim of the present report was to assess the added benefit of eribulin for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease. Prior therapies should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless patients were not suitable for these treatments.

The assessment was conducted separately for 3 research questions versus the appropriate comparator therapy (ACT) specified by the G-BA. The research questions are shown in Table 4.

Table 2: Overview of the research questions and ACTs on eribulin

Therapeutic indication	ACT specified by the G-BA
Research question A patients for whom taxanes or anthracyclines are no longer an option	Individual chemotherapy using monotherapy with the drugs capecitabine, vinorelbine[a]
Research question B patients for whom repeated treatment containing an anthracycline or a taxane is an option	Individual chemotherapy with repeated treatment containing an anthracycline or a taxane[a]
Research question C patients with HER2/neu-positive breast cancer, in whom anti-HER2/neu treatment is indicated, ▪ with advanced or metastatic disease that has progressed after prior treatment including anthracyclines and taxanes as well as, in the metastatic setting, trastuzumab	Lapatinib + capecitabine
▪ with hormone-receptor-negative metastatic disease that has progressed after prior trastuzumab treatment(s) in combination with chemotherapy	lapatinib + trastuzumab
a: It is assumed that, in the treatment of patients with HER2/neu-positive breast cancer, the treatment option of an anti-HER2/neu treatment was carefully considered and assessed as not indicated in the therapeutic decision for treatment with eribulin according to the present therapeutic indication. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2/neu: human epidermal growth factor receptor 2	

The benefit assessment of eribulin in the 3 research questions was conducted versus the ACTs specified by the G-BA. This concurs with the company's approach.

For research questions A and B, the company – like the G-BA (see footnote in Table 2) – assumed that, for patients with human epidermal growth factor receptor 2 (HER2/neu)-positive breast cancer, the treatment option of an anti-HER2/neu treatment was carefully considered and assessed as not indicated before the decision for treatment with eribulin.

Since the company assumed that, for patients with HER2/neu-positive breast cancer, the treatment option of an anti-HER2/neu treatment was carefully considered and assessed as not indicated before the decision for treatment with eribulin, it conducted no detailed analysis of the data of these patients (research question C). This population of patients was considered as a separate subpopulation in the present benefit assessment.

The assessment was conducted based on patient-relevant outcomes and on randomized controlled trials (RCTs).

Results

Research question A: patients for whom treatment with taxanes or anthracyclines is no longer an option

The 2 studies E7389-G000-301 (hereinafter referred to as "Study 301") und E7389-G000-305 (hereinafter referred to as the "EMBRACE" study) were included in the assessment. The EMBRACE study was already included in the first benefit assessment of eribulin (Commission A11-26).

Study characteristics and relevant subpopulations

The studies 301 and EMBRACE were open-label, randomized, controlled, multinational approval studies, which only included women. Only subpopulations of both studies were used for the present benefit assessment.

Patients who had received up to 3 prior chemotherapeutic regimens, and no more than 2 prior regimens for advanced and/or metastatic disease, were included in Study 301 on the comparison of eribulin versus capecitabine. Primarily, only the subpopulation of patients who – according to the approval of eribulin – had received one or several chemotherapeutic regimens for the treatment of advanced or metastatic disease (second or subsequent line of treatment in the advanced setting) was relevant for the present benefit assessment. This applied to the majority of the patients included (882 of 1102 patients, 80.0%). In contrast to the EMBRACE study, Study 301 was not a treatment of physician's choice (TPC) study. This means that, before randomization, it was not individually specified for the patients of Study 301 which treatment they would receive if they were allocated to the comparator group. Instead, the patients of the comparator arm received capecitabine. Nevertheless this study was used for the comparison of eribulin with an individual chemotherapeutic regimen with capecitabine or vinorelbine. Patients who had received at least 2 and up to 5 prior

chemotherapeutic regimens, 2 of which for the treatment of advanced and/or metastatic disease, were included in the EMBRACE study. Hence treatment in this study constituted the third line of treatment in the advanced setting. The patients in the comparator arm were treated with a therapy chosen by the investigator (TPC). Only the subpopulation of patients of the eribulin arm and the comparator arm for whom treatment with capecitabine or vinorelbine was chosen was primarily relevant for the present benefit assessment. This applied to 198 (39.0%) of a total of 508 patients in the eribulin arm, and to 110 (43.3%) of a total of 254 patients in the comparator arm.

Out of the described subpopulations of these studies, only the results of the patients with negative HER2/neu status were relevant for the present benefit assessment (69% of the patients in total). It was not guaranteed for HER2/neu-positive patients that the treatment option of an anti-HER2/neu treatment was carefully considered and assessed as not indicated before the decision for treatment with eribulin. For patients with unknown HER2/neu status it was unclear how large the proportion of patients with positive or negative HER2/neu status was and whether anti-HER2/neu treatment would have been indicated for the patients with positive HER2/neu status. Hence an added benefit is not proven for patients with positive or unknown HER2/neu status.

For the present benefit assessment, the results of the 2 studies were summarized in a meta-analysis. The studies differ in the aspects of comparator therapy and line of treatment (Study 301: comparison with capecitabine; second-line treatment; EMBRACE: comparison with capecitabine or vinorelbine; third-line treatment); however, the influence of these factors on the results of the studies was regarded as low.

Two data cut-offs were performed in the EMBRACE study. The primary data cut-off was conducted on 12 May 2009. 422 patients had died at this time point. The European regulatory authority requested an additional analysis of overall survival at a later time point. This updated analysis was conducted after 589 events on 3 March 2010. In the present benefit assessment, the results of both data cut-offs are presented for the outcome "overall survival". The extent of added benefit was assessed on the basis of the second data cut-off because these data are more informative because of the higher number of events, particularly because the meta-analysis showed considerable heterogeneity between the studies regarding research question A when using the first data cut-off.

Risk of bias

The risk of bias at study level was rated as low for both studies. The risk of bias for all outcomes was rated as high. However, no limitation of the certainty of results was assumed for the outcomes "overall survival" and "adverse events (AEs)" except for the outcome "discontinuation due to AEs". Data from both studies were available for the outcomes "mortality" and "AEs" so that, in principle, the derivation of proof was possible for these outcomes. Only data from one study were available for the outcomes "morbidity" and

"health-related quality of life" (Study 301). At most "indications" of an added benefit were derived for these outcomes.

Mortality (outcome "overall survival")

Based on the meta-analysis of the 2 studies 301 and EMBRACE, treatment with eribulin resulted in a statistically significant prolongation of overall survival in comparison with the individual chemotherapeutic regimen with capecitabine or vinorelbine. There is therefore proof of an added benefit of eribulin for the outcome "overall survival" compared with the ACT individual chemotherapeutic regimen with capecitabine or vinorelbine.

Morbidity (outcome "pain" [VAS])

There were no data for the relevant subpopulations on the outcome "pain" measured with a visual analogue scale (VAS). Hence an added benefit of eribulin in comparison with the ACT is not proven for this outcome.

Morbidity (symptoms)

Aspects of symptoms were recorded in Study 301 using the symptom scales of the disease-specific questionnaire European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 (EORTC QLQ-C30) and the breast-cancer specific supplementary module EORTC QLQ Breast Cancer Module (EORTC QLQ-BR23). The difference in the mean change in values at the time point of 6 weeks was considered for both measurement instruments. There was no statistically significant or relevant difference between the treatment groups for any of the symptom scales. An added benefit of eribulin in comparison with the ACT is not proven with regard to symptoms.

Health-related quality of life

Aspects of health-related quality of life were recorded in Study 301 using the functional scales of the disease-specific questionnaire EORTC QLQ-C30 and the breast-cancer specific supplementary module EORTC QLQ-BR23. The difference in the mean change in values at the time point of 6 weeks was considered for both measurement instruments. There was no statistically significant difference between the treatment groups for any of the scales considered. An added benefit of eribulin in comparison with the ACT is not proven with regard to health-related quality of life.

Adverse events

There was no statistically significant difference between the treatment groups for the outcomes "serious AEs (SAEs)" and "discontinuation due to AEs". Lesser or greater harm from eribulin than from the ACT is not proven for these outcomes.

Based on the meta-analysis of the 2 studies 301 and EMBRACE, there was a statistically significant difference to the disadvantage of eribulin in comparison with the individual chemotherapeutic regimen with capecitabine or vinorelbine for the outcome "severe AEs

(Common Terminology Criteria for Adverse Events [CTCAE] grade 3 and 4)". This results in proof of greater harm from eribulin in comparison with the ACT.

Research question B: patients for whom repeated treatment containing an anthracycline or a taxane is an option

The EMBRACE study was included in the assessment. This study was already presented in the dossier from 27 October 2011 for the first benefit assessment of eribulin (Commission A11-26). For the present benefit assessment, the company presented new analyses of the data already presented in the dossier from 27 October 2011 in its dossier from 28 July 2014. The data underlying the analyses of the EMBRACE study are therefore unchanged.

Study characteristics and relevant subpopulation

In the EMBRACE study, the investigator chose treatment with anthracycline or taxane for 143 (28.1%) of a total of 508 patients in the eribulin arm, and for 65 (25.6%) of a total of 254 patients in the comparator arm. The company used the subpopulation of these patients for the benefit assessment. Out of this subpopulation, only the results of the patients with negative HER2/neu status were relevant for the present benefit assessment (171 [82.2%] of 208 patients). Hereinafter, this patient population is referred to as "relevant subpopulation". Module 4 contained results on this subpopulation relevant for the present benefit assessment in the form of subgroup analyses for the characteristic "HER2/neu status", which the company conducted for the subpopulation it considered. There were no evaluable data for patients with positive or unknown HER2/neu status (24 [11.5%] positive, 13 [6.3%] unknown). Hence an added benefit is not proven for patients with positive or unknown HER2/neu status. The reasons correspond to the reasons provided for research question A.

There were no analyses on subgroups or effect modifiers for the relevant subpopulation. The results of the subgroup analyses of the subpopulation considered by the company could be used, however, because the relevant subpopulation of the patients with negative HER2/neu status comprised more than 80% of the patients of the population considered by the company.

As described in research question A, 2 data cut-offs were performed in the EMBRACE study. In the present benefit assessment, the results of both data cut-offs are presented for the outcome "overall survival" also for research question B. The extent of added benefit was assessed on the basis of the second data cut-off because these data are more informative because of the higher number of events. For research question B, there was no relevantly different result for the first data cut-off.

Risk of bias

The risk of bias at study level and at outcome level is explained in research question A.

Mortality (outcome "overall survival")

In both data cut-offs of the study, there was no statistically significant difference between the treatment groups for the outcome "overall survival". There was an indication of an effect

modification by the characteristic "ethnicity", however. For white patients, there was no statistically significant difference for overall survival in comparison with individual repeated chemotherapy with anthracyclines or taxanes. Hence for this outcome, there is no proof of added benefit of eribulin in comparison with the ACT for this subgroup of patients. For non-white patients, in contrast, there was a statistically significant difference to the disadvantage of eribulin for overall survival in comparison with individual repeated chemotherapy with anthracyclines or taxanes. For the total subpopulation considered, the difference in the same direction of effect was not statistically significant. In consideration of the fact that there was only an indication of an interaction and that there was no statistically significant effect in the total population considered, overall there is a hint of lesser benefit for overall survival for the subgroup of non-white patients.

Morbidity

The dossier contained no evaluable data on morbidity for research question B. An added benefit of eribulin in comparison with the ACT is not proven for this outcome.

Health-related quality of life

The dossier contained no evaluable data on health-related quality of life for research question B. An added benefit of eribulin in comparison with the ACT is not proven for this outcome.

Adverse events

There was no statistically significant difference between the treatment groups for the outcome "SAEs". Lesser or greater harm from eribulin than from the ACT, individual repeated chemotherapy with anthracycline or taxane, is not proven for this outcome.

There was a statistically significant difference in favour of eribulin in comparison with individual repeated chemotherapy with anthracycline or taxane for the outcome "discontinuation due to AEs". Because of the high risk of bias of the outcome, this results in a hint of lesser harm from eribulin in comparison with the ACT.

There was a statistically significant difference to the disadvantage of eribulin in comparison with individual repeated chemotherapy with anthracycline or taxane for the outcome "severe AEs (CTCAE grade 3 and 4)". In addition, there was an indication of an effect modification by the characteristic "number of organs involved". There was also a statistically significant difference to the disadvantage of eribulin for patients with more than 2 organs involved. Hence there is an indication of greater harm from eribulin in comparison with the ACT for this subgroup. In contrast, there was no statistically significant difference between the treatment groups for patients with no more than 2 organs affected by the disease. There is a hint of greater harm from eribulin than from the ACT for this subgroup because there was only an indication of an effect modification and because there was a statistically significant difference between the treatment groups to the disadvantage of eribulin for the total subpopulation considered.

Research question C: patients in whom anti-HER2/neu treatment is indicated

There were no relevant data in comparison with the ACT specified by the G-BA (lapatinib + capecitabine, lapatinib + trastuzumab) for patients with HER2/neu-positive breast cancer in whom anti-HER2/neu treatment is indicated. Hence an added benefit of eribulin in comparison with the ACT is not proven for these patients.

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

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

Research question A: patients for whom treatment with taxanes or anthracyclines is no longer an option

In the overall assessment, there is a positive and a negative effect of equal certainty of results (proof).

On the positive side, there is an added benefit with the extent "considerable" in the category "mortality". On the negative side, there is greater harm with the extent "major" in the category "serious/severe AEs" (severe AEs of CTCAE grade 3 and 4). Even though the extent for severe AEs is "major", this does not completely outweigh the advantage in mortality.

In summary, there is proof of minor added benefit of eribulin versus the ACT individual chemotherapy using monotherapy with the drugs capecitabine, vinorelbine for patients with negative HER2/neu status for whom treatment with taxanes or anthracyclines is no longer an option.

For patients with positive or unknown HER2/neu status for whom treatment with taxanes or anthracyclines is no longer an option and for whom anti-HER2/neu treatment is inadequate, the added benefit of eribulin in comparison with the ACT (individual chemotherapy using monotherapy with the drugs capecitabine, vinorelbine) is not proven.

Research question B: patients for whom repeated treatment containing an anthracycline or a taxane is an option

In the overall assessment, there is a positive effect and there are negative effects of different certainty of results for patients with negative HER2/neu status for whom repeated treatment

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

containing an anthracycline or a taxane is an option. The positive effect was shown in the outcome category "non-serious/non-severe AEs". Negative effects were shown for different subgroups in the outcome categories "mortality" and "serious/severe AEs".

Below, the balancing of positive and negative effects is conducted separately for the 2 severity grades considered (≤ 2 or > 2 organs involved).

Patients with ≤ 2 organs involved

There is a hint of greater harm, the extent of which is "non-quantifiable", but not more than "considerable", for patients with ≤ 2 organs affected by the disease in the category "serious/severe AEs" (severe AEs of CTCAE grade 3 and 4). This is offset by a hint of lesser harm with the extent "minor" in the outcome category "non-serious/non-severe AEs" (discontinuation due to AEs). Greater harm from eribulin regarding severe AEs of CTCAE grade 3 and 4 affected considerably more patients than the advantage regarding discontinuations due to AEs, which were mainly non-serious. Hence, with the same certainty of results, the disadvantage in the category "serious/severe AEs" outweighs the lesser harm in the category "non-serious/non-severe AEs". Moreover, there is a hint of lesser benefit for the outcome "overall survival" for non-white patients (extent: "non-quantifiable", at most "considerable"). Since this effect did not exceed the one on serious/severe AEs with regard to extent or certainty of results, it did not result in a change of the overall conclusion for the group of patients with ≤ 2 organs involved.

Patients with > 2 organs involved

There is an indication of greater harm with the extent "major" for patients with > 2 organs affected by the disease in the category "serious/severe AEs" (severe AEs of CTCAE grade 3 and 4). This is offset by a hint of lesser harm with the extent "minor" in the outcome category "non-serious/non-severe AEs" (discontinuation due to AEs). Hence there is a disadvantage of eribulin, the certainty of results and extent of which outweigh the lesser harm in the category "non-serious/non-severe AEs". Moreover, the hint of lesser benefit for the outcome "overall survival" in non-white patients also has to be considered. The extent and certainty of results of this effect is to be rated as lower than the ones of the effect regarding severe AEs and does not change the overall conclusion for the group of patients with > 2 organs involved.

In summary, there is a hint of lesser benefit of eribulin in comparison with the ACT for patients with ≤ 2 organs affected by the disease. In summary, there is an indication of lesser benefit of eribulin in comparison with the ACT for patients with > 2 organs affected by the disease.

For patients with positive or unknown HER2/neu status for whom repeated treatment containing an anthracycline or a taxane is an option and for whom anti-HER2/neu treatment is inadequate, the added benefit of eribulin in comparison with the ACT (individual chemotherapy with repeated treatment containing an anthracycline or a taxane) is not proven.

Research question C: patients in whom anti-HER2/neu treatment is indicated

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of eribulin in comparison with the ACT specified by the G-BA (lapatinib + capecitabine, lapatinib + trastuzumab) in patients in whom anti-HER2/neu treatment is indicated.

Table 3 presents a summary of the extent and probability of the added benefit of eribulin.

Table 3: Eribulin – extent and probability of added benefit

Therapeutic indication	ACT[a]	Extent and probability of added benefit
Research question A: patients for whom treatment with taxanes or anthracyclines is no longer an option		
HER2/neu status negative	Individual chemotherapy using monotherapy with the drugs capecitabine, vinorelbine	Proof of minor added benefit
HER2/neu status positive/unknown		Added benefit not proven
Research question B: patients for whom repeated treatment containing an anthracycline or a taxane is an option		

HER2/neu status negative
 	
  number of organs involved ≤ 2
  number of organs involved > 2
	Individual chemotherapy with repeated treatment containing an anthracycline or a taxane	Hint of lesser benefit
		
		indication of lesser benefit

HER2/neu status positive/unknown		Added benefit not proven
Research question C: patients with HER2/neu-positive breast cancer in whom anti-HER2/neu treatment is indicated		
Patients with advanced or metastatic disease that has progressed after prior treatment including anthracyclines and taxanes as well as, in the metastatic setting, trastuzumab	Lapatinib + capecitabine	Added benefit not proven
Patients with hormone-receptor-negative metastatic disease that has progressed after prior trastuzumab treatment(s) in combination with chemotherapy	Lapatinib + trastuzumab	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2/neu: human epidermal growth factor receptor 2		

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

2.2 Research questions

The aim of the present report was to assess the added benefit of eribulin for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease. Prior therapies should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless patients were not suitable for these treatments.

The approval of eribulin is not limited with regard to sex. The vast majority of people affected by the disease are women, however.

The assessment was conducted separately for 3 research questions versus the ACT specified by the G-BA. The research questions are shown in Table 4.

Table 4: Overview of the research questions and ACTs on eribulin

Therapeutic indication	ACT specified by the G-BA
Research question A patients for whom taxanes or anthracyclines are no longer an option	Individual chemotherapy using monotherapy with the drugs capecitabine, vinorelbine[a]
Research question B patients for whom repeated treatment containing an anthracycline or a taxane is an option	Individual chemotherapy with repeated treatment containing an anthracycline or a taxane[a]
Research question C patients with HER2/neu-positive breast cancer, in whom anti-HER2/neu treatment is indicated, ▪ with advanced or metastatic disease that has progressed after prior treatment including anthracyclines and taxanes as well as, in the metastatic setting, trastuzumab	Lapatinib + capecitabine
▪ with hormone-receptor-negative metastatic disease that has progressed after prior trastuzumab treatment(s) in combination with chemotherapy	lapatinib + trastuzumab
a: It is assumed that, in the treatment of patients with HER2/neu-positive breast cancer, the treatment option of an anti-HER2/neu treatment was carefully considered and assessed as not indicated in the therapeutic decision for treatment with eribulin according to the present therapeutic indication. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2/neu: human epidermal growth factor receptor 2	

The benefit assessment of eribulin in the 3 research questions was conducted versus the ACTs specified by the G-BA. This concurs with the company's approach.

For research questions A and B, the company – like the G-BA (see footnote in Table 4) – assumed that, for patients with HER2/neu-positive breast cancer, the treatment option of an anti-HER2/neu treatment was carefully considered and assessed as not indicated before the decision for treatment with eribulin

Since the company assumed that, for patients with HER2/neu-positive breast cancer, the treatment option of an anti-HER2/neu treatment was carefully considered and assessed as not indicated before the decision for treatment with eribulin, it conducted no detailed analysis of the data of these patients (research question C). This population of patients was considered as a separate subpopulation in the present benefit assessment.

The assessment of eribulin was based on patient-relevant outcomes. Direct comparative RCTs were included in the assessment.

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

2.3   Research question A: patients for whom treatment with taxanes or anthracyclines is no longer an option

2.3.1   Information retrieval and study pool (research question A)

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 eribulin (studies completed up to 30 May 2014)

- bibliographical literature search on eribulin (last search on 15 May 2014)

- search in trial registries for studies on eribulin (last search on 6 May 2014)

To check the completeness of the study pool:

- search in trial registries for studies on eribulin (last search on 14 August 2014)

No additional relevant study was identified from the check.

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

2.3.1.1   Studies included (research question A)

The studies listed in the following table were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: eribulin vs. capecitabine or vinorelbine

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Study E7389-G000-301[b]	Yes	Yes	No
Study E7389-G000-305 (EMBRACE)[c]	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. b: Hereinafter the study name is abbreviated to "Study 301". c: Hereinafter, the study name "EMBRACE" is used. RCT: randomized controlled trial; vs.: versus			

The 2 studies 301 and EMBRACE were identified. The EMBRACE study was already included in the first benefit assessment of eribulin (Commission A11-26 [3]). Only subpopulations of both studies were used for the present benefit assessment.

Study 301

Patients who had received up to 3 prior chemotherapeutic regimens, and no more than 2 prior regimens for advanced and/or metastatic disease, were included in Study 301 on the comparison of eribulin versus capecitabine. Primarily, only the subpopulation of patients who – according to the approval of eribulin [4] – had received one or several chemotherapeutic regimens for the treatment of advanced or metastatic disease (second or subsequent line of treatment in the advanced setting) was relevant for the present benefit assessment. This applied to the majority of the patients included (882 of 1102 patients, 80.0%).

The company presented the results of this subpopulation in Module 4 and derived the added benefit of eribulin from them. Out of this subpopulation considered by the company, only the population of patients with negative HER2/neu status was relevant for the present benefit assessment (595 [67.5%] of 882 patients). Hereinafter, this patient population is referred to as "relevant subpopulation". There were no evaluable data for patients with positive or unknown HER2/neu status (131 patients [14.9%] and 156 patients [17.7%] of the subpopulation considered by the company). This is due to the fact that, for patients with positive HER2/neu status, it has to be guaranteed that the option of an anti-HER2/neu treatment has been considered and assessed as not indicated when choosing capecitabine or vinorelbine as ACT. There was no information on this (see Section 2.7.2.4.1 of the full dossier assessment). For patients whose HER2/neu status is unknown it was unclear how large the proportion of patients with positive or negative HER2/neu status was and whether anti-HER2/neu treatment would have been indicated for the patients with positive HER2/neu status. Moreover, the

proportion of patients with unknown HER2/neu status is to be regarded as low in the German health care context because, for several years, standard therapy for patients has included regular determination of the HER2/neu status of the primary tumour and a treatment decision based on the result [5]. Further explanation can be found in Section 2.7.2.4.1 of the full dossier assessment.

Module 4 contained results on this relevant subpopulation of patients with negative HER2/neu status in the form of subgroup analyses for the characteristic "HER2/neu status", which the company conducted for the subpopulation it considered.

It should also be noted that, in contrast to the EMBRACE study, Study 301 was not a TPC study. This means that it was not individually specified for the patients of Study 301 before randomization which treatment they would receive if they were allocated to the comparator group. Instead, all patients of the comparator arm received capecitabine. It can still be assumed that the ACT was sufficiently represented in Study 301. This study was used for the comparison of eribulin with an individual chemotherapeutic regimen with capecitabine or vinorelbine. An explanation can be found in Section 2.3.1.2 and in Section 2.7.2.4.1 of the full dossier assessment.

EMBRACE

In the EMBRACE study, the patients in the comparator arm were treated with a therapy chosen by the investigator (TPC). The TPC was defined for all patients before group allocation. Only the subpopulation of patients of the eribulin arm and the comparator arm for whom treatment with capecitabine or vinorelbine was chosen was primarily relevant for the present benefit assessment. This applied to 198 (39.0%) of a total of 508 patients in the eribulin arm, and to 110 (43.3%) of a total of 254 patients in the comparator arm.

The company presented the results of this subpopulation in Module 4 and derived the added benefit of eribulin from them. Out of this subpopulation considered by the company, only the subpopulation of patients with negative HER2/neu status was relevant for the present benefit assessment (226 [73.4%] of 308 patients). Hereinafter, this patient population is referred to as "relevant subpopulation". There were no evaluable data for patients with positive or unknown HER2/neu status (14.3% positive, 12.3% unknown). The reasons correspond to the ones for Study 301.

Module 4 contained results on this subpopulation relevant for the present benefit assessment in the form of subgroup analyses for the characteristic "HER2/neu status", which the company conducted for the subpopulation it considered. These analyses were used for the assessment of the added benefit of eribulin.

This deviates from the company's approach, which included patients with negative, positive and unknown HER2/neu status from both studies in the assessment, and derived an added benefit for all patients for the subpopulations it considered.

Section 2.3.4 contains a reference list for the studies included.

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

2.3.1.2   Study characteristics (research question A)

Characteristics of the studies and of the interventions

Table 6 and Table 7 describe the 2 studies included in the benefit assessment, Study 301 and EMBRACE. Table 8 shows the planned duration of follow-up of the patients for the individual outcomes.

Table 6: Characteristics of the studies included – RCT, direct comparison: eribulin vs. capecitabine or vinorelbine

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Study 301	RCT, open-label, parallel	Patients with locally advanced or metastatic breast cancer who have received up to 3 prior chemotherapeutic regimens (no more than 2 prior regimens for advanced and/or metastatic disease) ▪ prior therapies must have included an anthracycline and a taxane ▪ documented evidence of progression during or after their most recent anticancer therapy ▪ patients with known HER2/neu over-expressing tumours may additionally have been treated with trastuzumab ▪ patients with known oestrogen and/or progesterone receptor-expressing tumours may have additionally been treated with hormonal therapy	Eribulin (N = 554) capecitabine (N = 548) relevant subpopulation thereof[b]: eribulin (n = 290) capecitabine (n = 305)	Screening phase: all screening procedures (except for the ones for assessing the tumour at the start of the study) were performed from day 14 to 0 prior to the start of the treatment treatment phase: until progression of disease, unacceptable toxicity, or treatment discontinuation at the investigator's or the patient's discretion observation phase: ▪ after progression: follow-up for survival every 3 months until death ▪ after discontinuation of the study treatment without progression: follow-up for overall survival, tumour response (in each case, every 3 months) and health-related quality of life (according to defined scheme)	210 centres in North America, Western Europe, Eastern Europe, Latin America, South Africa and Asia 4/2006-ongoing (planned end of study: 2/2015 (final data cut-off for overall survival: 3/2012)	Primary outcomes: overall survival PFS secondary outcomes: morbidity, health-related quality of life, adverse events

(continued)

Table 6: Characteristics of the studies included – RCT, direct comparison: eribulin vs. capecitabine or vinorelbine (continued)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
EMBRACE	RCT, open-label, parallel	Patients with locally recurrent or metastatic breast cancer who have been previously treated with at least 2 and not more than 5 chemotherapeutic regimens (at least 2 of which for the treatment of locally recurrent and/or metastatic disease) ▪ prior therapies must have included treatment with an anthracycline and a taxane, provided there were no contraindications ▪ progression on or after the last chemotherapy (within 6 months) ▪ patients with known HER2/neu over-expressing tumour may additionally have been treated with trastuzumab ▪ patients may have additionally been treated with antihormonal therapy	Eribulin (N = 508) TPC (N = 254) relevant subpopulation A thereof[c]: eribulin (n = 141) capecitabine/ vinorelbine (n = 85) subpopulation B[d] eribulin (n = 114) anthracycline/taxane (n = 57)	Screening: 3 weeks prior to the start of treatment treatment phase: until progression of disease, unacceptable toxicity, or treatment discontinuation at the investigator's discretion observation phase: survival and assessment of tumour every 3 months until death	135 centres in North America, Western Europe, Eastern Europe, Latin America, South Africa, Australia and Asia 11/2006–3/2010 data cut-offs for overall survival: primary analysis: 5/2009 updated analysis: 3/2010	Primary outcome: overall survival secondary outcomes: AEs

(continued)

Table 6: Characteristics of the studies included – RCT, direct comparison: eribulin vs. capecitabine or vinorelbine (continued)

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes exclusively contain information on the relevant available outcomes for this benefit assessment.
b: Patients with negative HER2/neu status who have received at least one prior chemotherapeutic regimen for the treatment of advanced and/or metastatic disease (second and subsequent lines of treatment).
c: Patients with negative HER2/neu status for whom treatment with taxanes or anthracyclines is no longer an option.
d: Patients with negative HER2/neu status for whom repeated treatment containing an anthracycline or a taxane is an option.

HER2/neu: human epidermal growth factor receptor 2; N: number of randomized patients; n: relevant subpopulation; PFS: progression-free survival; RCT: randomized controlled trial; TPC: treatment of physician's choice; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: eribulin vs. capecitabine or vinorelbine

Study	Intervention	Comparison	Concomitant therapies
Study 301	Eribulin mesylate 1.4 mg/m^2 body surface area[a], intravenously, within 2–5 minutes, on days 1 and 8 of a 21-day cycle	Capecitabine 2500 mg/m^2 body surface area twice daily in 2 equal doses, orally, from day 1 to 14 of a 21-day cycle	Allowed treatments: ▪ concomitant medications required for the patient's wellbeing that do not interfere with the study medication ▪ palliative radiotherapy prohibited at any time point: ▪ antitumour treatments such as chemotherapy, hormone therapy, radiotherapy, gene therapy, immunotherapy or biologics ▪ warfarin (except on mini-dose)
EMBRACE	Eribulin mesylate 1.4 mg/m^2 body surface area[a], intravenously, within 2–5 minutes, on days 1 and 8 of a 21-day cycle	TPC, defined as: ▪ chemotherapy as monotherapy ▪ hormonal therapy ▪ biological therapy (approved for cancer treatment) ▪ palliative therapy ▪ radiotherapy in each case given according to local practice relevant treatment for the assessment: research question A: capecitabine or vinorelbine research question B: anthracycline or taxane	Allowed treatments: ▪ concomitant medications required for the patient's wellbeing that do not interfere with the study medication ▪ palliative radiotherapy prohibited in the intervention arm at any time point: ▪ antitumour treatments such as chemotherapy, hormone therapy, radiotherapy (except palliative radiotherapy), gene therapy, immunotherapy or biologics ▪ warfarin (except on mini-dose) prohibited in the comparator arm at any time point: ▪ any other antitumour treatment except TPC ▪ any medication that is not allowed as concomitant medication to the TPC
a: 1.4 mg/m^2 eribulin mesylate is equivalent to 1.23 mg/m^2 eribulin. RCT: randomized controlled trial; TPC: treatment of physician's choice; vs.: versus			

Table 8: Planned duration of follow-up – RCT, direct comparison: eribulin vs. capecitabine or vinorelbine or vs. anthracycline or taxane

Study outcome	Planned follow-up
Study 301	
Overall survival	▪ Every 3 months until death
Morbidity	▪ Weekly up to 30 days after discontinuation of treatment
Health-related quality of life	▪ Until progression or start of a new antitumour treatment
Adverse events	▪ Until final study visit or within 30 days after discontinuation of treatment
EMBRACE	
Overall survival	▪ Every 3 months until death
Morbidity	▪ not recorded
Health-related quality of life	▪ not recorded
Adverse events	▪ Until final study visit or within 30 days after discontinuation of treatment
RCT: randomized controlled trial; vs.: versus	

Study 301

Study 301 is an open-label, randomized, controlled, multinational phase 3 approval study on the comparison of eribulin with capecitabine. In the ClinicalTrials.gov trial registry, the study is marked as ongoing until February 2015. The final data cut-off, was already performed in March 2012, however.

1102 patients with locally advanced or metastatic breast cancer who had received up to 3 prior chemotherapeutic regimens, but no more than 2 prior regimens for advanced or metastatic disease, were included in Study 301. Their disease must have progressed on or after the last cancer treatment. The patients' prior therapies must have included an anthracycline and a taxane. According to the approval of eribulin [4], the majority of the patients (882, 80.0%) had received at least one chemotherapeutic regimen for the treatment of advanced or metastatic disease. However, patients who had not received chemotherapy for the treatment of advanced or metastatic disease were also included in the study (220, 20.0%).

Patients were stratified by geographical region and HER2/neu status and randomized to treatment with either eribulin (554 patients) or capecitabine (548 patients) in a ratio of 1:1. As described in Section 2.3.1.1, only the subpopulation of patients with negative HER2/neu status was used for the present benefit assessment. Out of the 882 patients who had been pretreated with at least one chemotherapeutic regimen for advanced or metastatic disease, this corresponded to 595 patients (67.5%). 290 of these (66.2% of 438 patients) were allocated to the eribulin arm, and 305 (68.7% of 444 patients) to the capecitabine arm.

In the study, the drugs eribulin and capecitabine were used in compliance with their approvals. According to the Summaries of Product Characteristics (SPCs) [4,6], dose

reductions of eribulin and capecitabine or discontinuation of treatment were possible in the study if severe AEs occurred.

Overall survival and progression-free survival were recorded as primary outcomes in the study. Of these outcomes, overall survival was included as patient-relevant outcome in the benefit assessment. Further patient-relevant outcomes were morbidity (pain), health-related quality of life (including components that were recorded under "morbidity" [symptoms] in the present benefit assessment) and AEs. Overall survival was recorded every 3 months after cessation of the study medication. Health-related quality of life was recorded until disease progression or the start of a new cancer treatment at prespecified time points of recording (6 weeks and 3, 6, 12, 18, 24 months). AEs were recorded up to 30 days after the last administration of study medication.

Two planned interim analyses were performed during the study. The independent Data Monitoring Committee recommended in each case that the study should continue unchanged. The study was not stopped prematurely. The planned final data cut-off was conducted on 12 March 2012. 905 patients had died at this time point, and 5 patients were still treated in each treatment arm.

EMBRACE

The EMBRACE study was an open-label, randomized, controlled, multicentre phase 3 approval study on the comparison of eribulin with an individual TPC.

Patients with locally advanced or metastatic breast cancer who had received at least 2 and up to 5 prior chemotherapeutic regimens, 2 of which for the treatment of advanced and/or metastatic disease, were included in the study. Patients had to have proved refractory to the most recent chemotherapy, documented by progression on or within 6 months of therapy.

A total of 762 patients in the study were randomly assigned in a ratio of 2:1 either to treatment with eribulin (508 patients) or to individual TPC (254 patients) (stratified by geographical region, HER2/neu status and pretreatment with capecitabine). The TPC options were single-agent chemotherapy, hormonal treatment, biological therapy (approved for cancer treatment), palliative therapy or radiotherapy. The particular treatment patients were to receive if allocated to the comparator arm of the study was always chosen by a physician prior to randomization. The patients' prior therapies must have included an anthracycline and a taxane. Patients were to receive the study medication until unacceptable toxicity or progression occurred or until the physician considered that discontinuation of the study was in the patient's interest. Capecitabine or vinorelbine was chosen for a total of 308 patients, 198 in the eribulin arm and 110 in the TPC arm. A total of 226 patients (73.4%) of these patients had negative HER2/neu status, 141 (71.2%) in the eribulin arm and 85 (77.3%) in the comparator arm.

As described in Section 2.3.1.1, only data for the subpopulation of patients with negative HER2/neu status were used for the present research question A (patients for whom treatment with taxanes or anthracyclines is no longer an option).

In the study, the drug eribulin was used in compliance with its approval. TPC was to be administered according to the specifications provided in the respective SPC or according to local practice. According to the SPC [4,6], dose reductions of eribulin or discontinuation of treatment were possible if severe AEs occurred.

Overall survival was recorded as primary outcome of the study. AEs were further patient-relevant outcomes. Overall survival was recorded every 3 months after cessation of the study medication. AEs were recorded up to 30 days after the last administration of study medication.

One planned interim analysis was conducted during the study after half of the deaths occurred (206 events). The independent Data Monitoring Committee recommended that the study should continue unchanged. The primary data cut-off planned after 411 deaths was conducted on 12 May 2009. 422 patients had died at this time point. The European regulatory authority requested an additional analysis of overall survival at a later time point. This updated analysis was performed after 589 events (77% of the patients included), the data cut-off date was the 3 March 2010. In the present benefit assessment, the results of both data cut-offs are presented for the outcome "overall survival". The extent of added benefit was assessed on the basis of the second data cut-off because these data are more informative because of the higher number of events.

Comparison of the studies 301 and EMBRACE

The 2 studies 301 and EMBRACE differ in the aspects of comparator therapy and line of treatment (Study 301: comparison with capecitabine; second-line treatment; Study 305: comparison with capecitabine or vinorelbine; third-line treatment); however, the influence of these factors on the results of the studies was regarded as low.

The guidelines do not favour any of the 2 drugs (capecitabine or vinorelbine) [5]. Except for some specific AEs, no concrete operationalizable criteria for favouring the choice of capecitabine or vinorelbine in the existing treatment situation can be derived from the SPCs either [6,7]. Against this background it is assumed that the patient's individual preference was decisive for choosing treatment with capecitabine or vinorelbine. Based on the results of the relevant studies 301 and EMBRACE on the outcomes "overall survival" and "AEs" (SAEs, severe AEs and discontinuation due to AEs), no relevant differences in effects between vinorelbine and capecitabine can be derived either. For the specific AEs, differences between capecitabine and vinorelbine could be detected from the available information (e.g. hand-foot syndrome, neutropenia). However, the dossier contained no complete overview of the specific AEs occurred in the relevant subpopulation (patients with negative HER2/neu status). Hence no comprehensive conclusion can be drawn on potential differences. In summary, the

comparator therapy used in Study 301 is considered to be a sufficient implementation of the ACT.

With regard to the criterion of second- and third-line treatment for the therapy of advanced or metastatic disease it is to be noted that patients in the EMBRACE study received eribulin as third or subsequent line of treatment. Out of the subpopulation considered by the company (irrespective of the HER2/neu status), a total of 65% (573 of 882 patients) of patients were treated in the second line of treatment and 35.0% (309 of 882 patients) of patients in the third or subsequent line of treatment in Study 301. At least for the subpopulation considered by the company, the investigation of the influence of these different uses of the lines of treatment resulted in no proof or indication of an effect modification by this criterion for overall survival (p-value of the interaction test 0.833) and the overall rates of SAEs (p-value 0.301), discontinuation due to AEs (p-value 0.450) and severe AEs (CTCAE grade 3 and 4) (p-value 0.511). It is assumed that these results are transferable with sufficient certainty to the subpopulation relevant for this benefit assessment.

Characteristics of the study populations

Table 9 and Table 10 show the characteristics of the patients of the studies included for the subpopulations considered by the company (Study 301: patients of second and subsequent line of treatment; EMBRACE: patients for whom the investigator chose treatment with capecitabine or vinorelbine prior to randomization).

Table 9: Characteristics of the study populations (demography) – RCT, direct comparison: eribulin vs. capecitabine or vinorelbine for patients for whom treatment with taxanes or anthracyclines is no longer an option

Study group	N	Age [years] median (min; max)	Sex [F/M] %	Ethnicity [white/non-white/ Asian + Pacific Islander/other] n (%)	Geographical region n (%)	Treatment discontin-uations n (%)
Study 301					[Asia/Eastern Europe/Latin America/ North America/South Africa/ Western Europe]	
Eribulin	438	55 (24; 80)	100/0	390 (89.0)/12 (2.7)/17 (3.9)/19 (4.3)	13 (3.0)/252 (57.5)/74 (16.9)/33 (7.5)/ 5 (1.1)/61 (13.9)	ND[a]
Capecitabine	444	54 (26; 80)	100/0	406 (91.4)/10 (2.3)/15 (3.4)/13 (2.9)	9 (2.0)/255 (57.4)/73 (16.4)/34 (7.7)/5 (1.1)/68 (15.3)	ND[a]
EMBRACE					[North America + Western Europe + Australia/ Eastern Europe/Latin America + South Africa]	
Eribulin	198	55 (30; 85)	100/0	178 (89.9)/11 (5.6)/2 (1.0)/7 (3.5)	125 (63.1)/52 (26.3)/21 (10.6)	ND[b]
Capecitabine or vinorelbine	110	55 (30; 81)	100/0	100 (90.9)/9 (8.2)/0 (0.0)/1 (0.9)	67 (60.9)/29 (26.4)/14 (12.7)	ND[b]

a: There were no data for the subpopulation (second and subsequent lines of treatment, HER2/neu status positive + negative + unknown).

b: There were no data for the subpopulation (treatment with capecitabine or vinorelbine planned before randomization, HER2/neu status positive + negative + unknown).

F: female; HER2/neu: human epidermal growth factor receptor 2; M: male; max: maximum; min: minimum; N: number of patients in the subpopulation; n: number of patients in the category; ND: no data; RCT: randomized controlled trial; vs.: versus

Table 10: Characteristics of the study populations (disease characteristics) – RCT, direct comparison: eribulin vs. capecitabine or vinorelbine for patients for whom treatment with taxanes or anthracyclines is no longer an option

Study group	N	ECOG PS [unknown/0/1/2] n (%)	HER2/neu status (FISH and IHC tests) [positive/negative/ unknown] n (%)	Time since first diagnosis [years] mean (SD)/ median (min; max)	Type of disease [visceral/non-visceral/missing values] n (%)	Number of prior chemotherapies n (%)	Number of prior chemotherapies for advanced/metastatic disease [1/≥ 2] n (%)
Study 301						[1/≥ 2]	
Eribulin	438	0 (0)/ 181 (41.3)/ 247 (56.4)/ 10 (2.3)	67 (15.3)/ 290 (66.2)/ 81 (18.5)	4.9 (4.29)/ 3.5 (0.2; 28.3)	369 (84.2)/ 63 (14.4)/ 6 (1.4)	47 (10.7)/ 391 (89.3)	280 (63.9)/ 158 (36.1)[a]
Capecitabine	444	0 (0)/ 174 (39.2)/ 255 (57.4)/ 15 (3.4)	64 (14.4)/ 305 (68.7)/ 75 (16.9)	4.3 (3.81)/ 3.1 (0.2; 21.6)	397 (89.4)/ 44 (9.9)/ 3 (0.7)	55 (12.4)/ 389 (87.6)	293 (66.0)/ 151 (34.0)[a]
EMBRACE						[≤ 3/> 3]	
Eribulin	198	4 (2.0)/ 91 (46.0)/ 89 (44.9)/ 14 (7.1)	31 (15.7)/ 141 (71.2)/ 26 (13.1)	6.5 (4.95)/ 5.2 (0.1; 30.8)	168 (84.8)/ 29 (14.6)/ 1 (0.5)	118 (59.6)/ 79 (39.9)	ND
Capecitabine or vinorelbine	110	2 (1.8)/ 41 (37.3)/ 59 (53.6)/ 8 (7.3)	13 (11.8)/ 85 (77.3)/ 12 (10.9)	6.2 (5.05)/ 4.7 (0.6; 20.5)	91 (82.7)/ 18 (16.4)/ 1 (0.9)	63 (57.3)/ 47 (42.7)	ND

a: Deviating from the inclusion criteria of Study 301, a total of 9 patients (4 patients in the eribulin arm and 5 patients in the comparator arm) were included who had received more than 2 chemotherapeutic regimens for the treatment of advanced or metastatic disease.

ECOG PS: Eastern Cooperative Oncology Group Performance Status; FISH: fluorescence in situ hybridization; HER2/neu: human epidermal growth factor receptor 2; IHC: immunohistochemical; max: maximum; min: minimum; N: number of patients in the subpopulation; n: number of patients in the category; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Data on patient characteristics for the 2 studies 301 and EMBRACE were only available for the subpopulations considered by the company. In Study 301, this subpopulation comprised all patients in the second or subsequent line of treatment in an advanced stage, irrespective of their HER2/neu status. In the EMBRACE study, this subpopulation comprised patients for whom the investigator had chosen treatment with capecitabine or vinorelbine before randomization, also irrespective of their HER2/neu status. There were no data on the subpopulations of these patients (with negative HER2/neu status) relevant for this benefit assessment.

Exclusively women were included in both studies. The characteristics of the patients between the studies and between the treatment arms were largely balanced. The median age was between 54 and 55 years. Most patients were white. In Study 301, most patients were from Eastern Europe (57%); in the EMBRACE study, about 61 to 63% were from Western regions (North America, Western Europe, Australia). The majority of the patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1.

The majority of the patients had a tumour with negative HER2/neu status (67% in Study 301 and 73% in the EMBRACE study). About 15% of the patients in Study 301, and about 14% in the EMBRACE study, had an HER2/neu-positive tumour. The HER2/neu status was unknown in 18% of the patients in Study 301 and in 12% of the patients in the EMBRACE study. Visceral organs were affected by the disease in over 80% of the patients in both studies. The mean time since the first diagnosis was 4.6 years in Study 301 and 6.4 years in the EMBRACE study. During this time, most patients (almost 90%) had received 2 or more chemotherapeutic regimens in Study 301. In the EMBRACE study, most patients (almost 60%) had received up to 3 chemotherapeutic regimens.

There were no data for the subpopulation on the number of patients who discontinued treatment.

Treatment duration and observation period in the studies

Table 11 shows the mean/median treatment duration of the patients and the follow-up period for the individual outcomes.

Table 11: Information on the course of the study – RCT, direct comparison: eribulin vs. capecitabine or vinorelbine

Study characteristics category	Eribulin	Capecitabine or vinorelbine
Study 301 (eribulin vs. capecitabine)		
Mean/median treatment duration [days]	N = 544[a]	N = 546[a]
mean (SD)	169.1 (172.9)	172.6 (182.8)
median (min; max)	125.0 (21; 1372)	119.0 (21; 1442)
Mean/median observation period [days]		
morbidity	ND	ND
health-related quality of life	ND	ND
adverse events	N = 429[b]	N = 442[b]
mean (SD)	190.7 (183.0)	193.0 (183.7)
median (min; max)	138.0 (13; 1372)	131.5 (13; 1422)
EMBRACE (eribulin vs. capecitabine/vinorelbine)		
Mean/median treatment duration [days]	N = 503[c]	N = 247[d]
mean (SD)	137.3 (92.6)	ND
median (min; max)	118.0 (21; 497)	63 (ND)
Mean/median observation period [days]		
morbidity	not recorded	not recorded
health-related quality of life	not recorded	not recorded
adverse events	N = 195[e]	N = 105[e]
mean (SD)	147.5 (88.8)	138.2 (112.0)
median (min; max)	128.0 (8; 506)	93.0 (1; 646)

a: Safety population in the study.
b: Safety population of the subpopulation from the study (second and subsequent lines of treatment, HER2/neu status positive + negative + unknown).
c: Safety population of the total eribulin arm of the study.
d: Safety population of the total TPC arm of the study.
e: Safety population of the subpopulation from the study (treatment with capecitabine or vinorelbine planned before randomization, HER2/neu status positive + negative + unknown).
HER2/neu: human epidermal growth factor receptor 2; max: maximum; min: minimum; N: number of patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; TPC: treatment of physician's choice; vs.: versus

For both studies, data on treatment duration were only available for the respective total study population. The median and the mean treatment duration were comparable in the 2 study arms in Study 301. In the EMBRACE study, the median treatment duration was longer in the eribulin arm (118 days) than in the TPC arm (63 days). For both studies, data on the observation period were available for the subpopulations considered by the company (Study 301: patients in the second or subsequent line of treatment in an advanced stage; EMBRACE: patients for whom treatment with capecitabine or vinorelbine was chosen; in each case irrespective of their HER2/neu status). These were limited to the outcome "AEs", which were

documented for a longer period in Study 301 than in the EMBRACE study. In Study 301, AEs were documented for about the same length of time in both arms. However, in the EMBRACE study, documentation was longer in the eribulin arm (mean 147.5 days; median 128 days) than in the comparator arm (mean 138.2 days; median 93 days). As a consequence, the results for AEs based on raw rates are not evaluable. Survival time analyses are needed instead to account for the differences in the length of observation periods. The company presented such analyses. No data were available in Study 301 for the outcomes "morbidity (symptoms)" and "health-related quality of life".

Risk of bias

Table 12 shows the risk of bias at study level for the studies 301 and EMBRACE.

Table 12: Risk of bias at study level – RCT, direct comparison: eribulin vs. capecitabine or vinorelbine or vs. anthracycline or taxane

| Study | Adequate random sequence generation | Allocation concealment | Blinding | | Reporting independent of the results | No additional aspects | Risk of bias at study level |
			Patient	Treating staff			
Study 301	Yes	Yes	No	No	Yes	Yes	Low
EMBRACE	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level was rated as low for both studies. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described in Section 2.3.2 with the outcome-specific risk of bias.

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

2.3.2   Results on added benefit (research question A)

2.3.2.1   Outcomes included (research question A)

The following patient-relevant outcomes were considered in this assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

▪ Mortality
  ▫ overall survival

- Morbidity

  - pain; recorded using a VAS

  - symptoms; recorded using the symptom scales of the disease-specific instrument EORTC QLQ-C30 and the breast-cancer specific supplementary module EORTC QLQ-BR23

- Health-related quality of life

  - recorded using the functional scales on quality of life of the disease-specific instrument EORTC QLQ-C30 and the breast-cancer specific supplementary module EORTC QLQ-BR23

- Adverse events

  - SAEs

  - treatment discontinuation due to AEs

  - severe AEs (CTCAE Grade 3 and 4)

The choice of patient-relevant outcomes deviates from that of the company (see Section 2.7.2.4.3 of the full dossier assessment). The company did not use the outcome "pain" (recorded using a VAS) in the dossier (Module 4). It used further outcomes on AEs, however.

Further information on the choice of outcomes can be found in Module 4, Sections 4.3.1.3 and 4.3.2.1.3 of the dossier, and in Section 2.7.2.4.3 of the full dossier assessment.

Table 13 shows for which outcomes data were available in the studies included.

Table 13: Matrix of outcomes – RCT, direct comparison: eribulin vs. capecitabine or vinorelbine or vs. anthracycline or taxane

Study	Outcomes						
	Overall survival	Morbidity (symptoms)[a]	Morbidity (pain)[b]	Health-related quality of life[c]	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade 3 and 4)
Study 301	Yes	Yes	No	Yes	Yes	Yes	Yes
EMBRACE	Yes	No	No	No	Yes	Yes	Yes
a: Recorded with the symptom scales of the disease-specific instruments EORTC QLQ-C30 and QLQ-BR23. b: Recorded with visual analogue scale. c: Recorded with the functional scales on quality of life of the disease-specific instruments EORTC QLQ-C30 and QLQ-BR23. AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events, EORTC QLQ-BR23: European Organization 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; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus							

2.3.2.2 Risk of bias (research question A)

Table 14 shows the risk of bias for the relevant outcomes.

Table 14: Risk of bias at study and outcome level – RCT, direct comparison: eribulin vs. capecitabine or vinorelbine or vs. anthracycline or taxane

Study	Study level	Outcomes						
		Overall survival	Morbidity (symptoms)[a]	Morbidity (pain)[b]	Health-related quality of life[c]	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade 3 and 4)
Study 301	L	H[d]	H[e,f]	_[g]	H[e,f]	H[d]	H[d,e]	H[d]
EMBRACE	L	H[d]	_[h]	_[h]	_[h]	H[d]	H[d,e]	H[d]

a: Recorded with the symptom scales of the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-BR23.
b: Recorded with visual analogue scale.
c: Recorded with the functional scales on quality of life of the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-BR23.
d: Data-driven analysis.
e: Patient and treating staff not blinded.
f: ITT principle violated (high proportion of missing values).
g: No data available for the relevant subpopulation.
h: Morbidity and health-related quality of life were not recorded.
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-BR23: European Organization 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; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The risk of bias for all outcomes was rated as high. The risk of bias for the outcomes "morbidity" and "health-related quality of life" was rated as high due to the high proportion of missing values in the analyses and due to the lack of blinding of patients and treating staff. This concurs with the company's assessment. The company, however, considered the high proportion of missing values in the analyses as the sole reason for the bias.

The outcome "overall survival" and the outcomes on AEs were rated as potentially highly biased due to a data-driven approach in the analysis (adjustment of the Cox proportional hazards model after observed imbalances in the baseline characteristics of the patients). The company also presented p-values from unadjusted log-rank tests, however. Since, with the exception of the outcome "discontinuation due to AEs", the p-values of the adjusted analyses only deviated marginally from the unadjusted analyses, no limited certainty of results was assumed. The outcome "discontinuation due to AEs" was also rated as potentially highly biased due to the lack of blinding. This does not concur with the company's assessment, which assumed low risk of bias for the outcomes "overall survival" and "AEs"– with the

exception of the outcome "severe AEs of CTCAE grade 3 and 4 (including neutropenia)". Further explanations on this can be found in Section 2.7.2.4.2 of the full dossier assessment.

Further information on the risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3, and in Appendix 4-F of the dossier and in Section 2.7.2.4.2 of the full dossier assessment.

2.3.2.3   Results (research question A)

2.3.2.3.1   HER2/neu status positive/unknown

There were no data for patients with positive or unknown HER2/neu status for whom treatment with taxanes or anthracyclines is no longer an option and for whom anti-HER2/neu treatment is inadequate. Added benefit has not been proven.

2.3.2.3.2   HER2/neu status negative

The following tables summarize the results on the comparison of eribulin and capecitabine or vinorelbine in patients for whom treatment with taxanes or anthracyclines is no longer an option and whose HER2/neu status is negative.

In the present benefit assessment, the results of the relevant subpopulations of the 2 studies 301 and 305 were summarized in a meta-analysis. The studies differ in the aspects of comparator therapy and line of treatment (Study 301: comparison with capecitabine; second-line treatment; Study 305: comparison with capecitabine or vinorelbine; third-line treatment); however, the influence of these factors on the results of the studies was regarded as low. Further explanations can be found in Section 2.3.1.2.

Since data from 2 studies were available for the outcomes "overall survival" and "AEs", the derivation of proof was principally possible for the different outcomes. Only data from one study were available for the outcomes "morbidity" and "health-related quality of life" (Study 301). These data did not meet the particular requirements placed on the derivation of proof from one study (see Section 2.7.2.8.1 of the full dossier assessment). At most "indications" were derived for these outcomes from Study 301.

The dossier contained results from survival time analyses, which were based on a post-hoc adjusted Cox proportional hazards model (co-factors: number of organs involved and oestrogen receptor [ER] status) and were therefore potentially biased. Prespecified unadjusted analyses were additionally available (log-rank test). However, the survival time analyses from the adjusted Cox hazards model could be used for this benefit assessment because the p-values did not differ substantially from the ones of the unadjusted log-rank test. The results of the studies 301 and EMBRACE were summarized in a meta-analysis for the outcomes for which data from both studies were available. The figures of the meta-analyses of the 2 studies can be found in Appendix C of the full dossier assessment. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations.

Table 15 to Table 17 summarize the results on the comparison of eribulin with the ACT specified by the G-BA (individual chemotherapy using monotherapy with the drugs capecitabine, vinorelbine). Additional information on the naive proportions of AEs are presented in Appendix A of the full dossier assessment. The Kaplan-Meier curve for the outcome "overall survival" for the subpopulation considered by the company irrespective of the HER2/neu status is presented in Appendix B (Figure 1).

Table 15: Results on mortality and AEs – RCT, direct comparison: eribulin vs. capecitabine or vinorelbine for patients for whom treatment with taxanes or anthracyclines is no longer an option, HER2/neu status negative

Outcome category outcome study data cut-off	Eribulin		Capecitabine or vinorelbine		Eribulin vs. capecitabine or vinorelbine	
	N	Median time to event in days [95% CI]	N	Median time to event in days [95% CI]	HR [95% CI][a]	p-value
Overall survival						
Study 301 (3/2012)	290	484 [ND]	305	408 [ND]	0.81 [0.68; 0.97]	0.048[b]
EMBRACE (5/2009)	141	454 [ND]	85	303 [ND]	0.56 [0.39; 0.82]	0.003[b]
EMBRACE (3/2010)	141	444 [ND]	85	304 [ND]	0.74 [0.54; 1.03]	0.063[b]
total[c]					0.79 [0.68; 0.93]	0.004[d]
Adverse events						
AEs						
Study 301 (3/2012)		ND		ND		
EMBRACE (5/2009)		ND		ND		
SAEs						
Study 301 (3/2012)	284	NC	303	NC	0.79 [0.55; 1.13]	0.145[b]
EMBRACE (5/2009)	138	350 [ND]	80	NC	0.82 [0.47; 1.43]	0.562[b]
total					0.80 [0.59; 1.08]	0.145[d]
Discontinuation due to AEs						
Study 301 (3/2012)	284	1079 [ND]	303	NC	0.61 [0.36; 1.04]	0.058[b]
EMBRACE (5/2009)	138	NC	80	NC	1.05 [0.39; 2.81]	0.799[b]
total					0.69 [0.43; 1.10]	0.118[d]
Severe AEs (CTCAE grade 3 and 4)						
Study 301 (3/2012)	284	37 [ND]	303	178 [ND]	1.73 [1.39; 2.16]	< 0.001[b]
EMBRACE (5/2009)	138	36 [ND]	80	99 [ND]	1.41 [0.98; 2.03]	0.067[b]
total					1.64 [1.36; 1.98]	< 0.001[d]

(continued)

Table 15: Results on mortality and AEs – RCT, direct comparison: eribulin vs. capecitabine or vinorelbine for patients for whom treatment with taxanes or anthracyclines is no longer an option, HER2/neu status negative (continued)

a: Cox proportional hazards model with capecitabine pretreatment and geographical region as strata, and number of organs involved and ER status as co-factors defined post-hoc.
b: Log-rank test stratified by capecitabine pretreatment and geographical region (planned analysis).
c: Meta-analysis from values at the 3/2012 data cut-off of Study 301 and values at the 3/2010 data cut-off of the EMBRACE study.
d: Meta-analysis, Institute's calculation.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ER: oestrogen receptor; HER2/neu: human epidermal growth factor receptor 2; HR: hazard ratio; N: number of analysed patients; NC: not calculable; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Table 16: Results on morbidity (symptoms) – RCT, direct comparison: eribulin vs. capecitabine for patients for whom treatment with taxanes or anthracyclines is no longer an option, HER2/neu status negative

Study outcome	Eribulin			Capecitabine or vinorelbine			Eribulin vs. capecitabine or vinorelbine
	N[a]	Baseline values mean [95% CI]	Change week 6[b] mean [95% CI]	N[a]	Baseline values mean [95% CI]	Change week 6[b] mean [95% CI]	Difference in mean changes [95% CI]; p-value
Study 301 (time point 6 weeks)							
Pain (VAS)			No data available				
EORTC QLQ-C30[c]							
Fatigue	217	7.4 [5.6; 9.1]	−1.37 [−4.3; 1.6]	228	8.9 [6.8; 11.0]	5.16 [2.3; 8.0]	−6.53 [−10.0; −3.1]; ND Hedges' g −0.30 [−0.48; −0.11][d]
Nausea and vomiting	219	22.1 [18.9; 25.4]	−2.54 [−6.1; 1.0]	229	26.1 [22.6; 29.5]	−2.11 [−5.6; 1.4]	−0.43 [−4.5; 3.7] ND
Pain	220	71.1 [68.4; 73.8]	5.08 [2.2; 8.0]	233	67.5 [64.8; 70.2]	3.12 [0.3; 5.9]	1.96 [−1.4; 5.3] ND
Dyspnoea	221	35.8 [33.0; 38.7]	−1.88 [−4.9; 1.2]	232	39.2 [36.3; 42.0]	−0.96 [−3.9; 2.0]	−0.92 [−4.4; 2.6] ND
Insomnia	219	29.0 [25.1; 32.9]	−2.75 [−6.8; 1.3]	230	28.4 [24.5; 32.2]	−2.53 [−6.5; 1.4]	−0.22 [−4.9; 4.4] ND
Appetite loss	214	35.3 [31.5; 39.2]	9.11 [4.6; 13.6]	229	31.6 [28.0; 35.2]	7.90 [3.5; 12.3]	1.21 [−4.0; 6.5] ND
Constipation	217	57.7 [55.0; 60.4]	−0.44 [−3.3; 2.5]	229	54.6 [52.2; 57.1]	1.05 [−1.8; 3.9]	−1.49 [−4.9; 1.9] ND
Diarrhoea	220	28.6 [25.1; 32.1]	−4.84 [−8.6; −1.1]	231	32.2 [28.6; 35.8]	−4.55 [−8.2; −0.9]	−0.29 [−4.7; 4.1] ND
Financial difficulties[e]	220	9.0 [6.9; 11.2]	0.12 [−2.4; 2.6]	232	11.2 [8.8; 13.6]	3.17 [0.7; 5.6]	−3.05 [−5.9; −0.2]; ND Hedges' g −0.16 [−0.35; 0.02][d]
EORTC QLQ-BR23[c]							
AEs of systemic treatment			No evaluable data[f]				
Breast symptoms	220	76.4 [73.2; 79.6]	1.98 [−1.6; 5.6]	233	73.3 [70.0; 76.5]	0.59 [−2.9; 4.1]	1.39 [−2.7; 5.4] ND
Arm symptoms	214	20.5 [18.6; 22.5]	2.14 [−0.1; 4.3]	231	23.6 [21.6; 25.5]	−3.59 [−5.7; −1.5]	5.74 [3.2; 8.2]; ND Hedges' g 0.35 [0.16; 0.54][d]
Burden of alopecia			No evaluable data[f]				

(continued)

Table 16: Results on morbidity (symptoms) – RCT, direct comparison: eribulin vs. capecitabine for patients for whom treatment with taxanes or anthracyclines is no longer an option, HER2/neu status negative (continued)

a: Number of patients considered in the analysis for the calculation of the effect estimate (at week 6); the values at the start of the study may be based on other patient numbers.

b: Evaluable data only at week 6.

c: Symptom scales of the EORTC QLQ-C30 and of the breast-cancer specific supplementary module EORTC QLQ-BR23, range 0-100; lower (decreasing) values indicate fewer symptoms; negative values in the group comparison (eribulin – capecitabine or vinorelbine) indicate an advantage of eribulin.

d: Institute's calculation.

e: Financial difficulties are part of the questionnaire, but are not considered to be part of morbidity (symptoms).

f: Because the proportion of patients who were not considered in the analysis was > 30%, the data are not presented.

CI: confidence interval; EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer Module; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; HER2/neu: human epidermal growth factor receptor 2; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

Table 17: Results on health-related quality of life – RCT, direct comparison: eribulin vs. capecitabine for patients for whom treatment with taxanes or anthracyclines is no longer an option, HER2/neu status negative

Study outcome	Eribulin			Capecitabine or vinorelbine			Eribulin vs. capecitabine or vinorelbine
	N[a]	Baseline values mean [95% CI]	Change week 6[b] mean [95% CI]	N[a]	Baseline values mean [95% CI]	Change week 6[b] mean [95% CI]	Difference in mean changes [95% CI]; p-value
Study 301 (time point 6 weeks)							
EORTC QLQ-C30[c]							
Global health status	221	18.0 [14.8; 21.2]	0.59 [−3.1; 4.2]	232	23.5 [20.0; 27.0]	1.65 [−1.9; 5.2]	−1.07 [−5.3; 3.2] ND
Physical functioning	213	22.5 [19.6; 25.3]	−3.04 [−5.8; −0.3]	229	25.8 [22.8; 28.7]	−1.81 [−4.5; 0.9]	−1.23 [−4.4; 1.9] ND
Role functioning	215	68.0 [64.7; 71.3]	3.09 [−0.3; 6.4]	229	64.5 [61.1; 67.9]	4.80 [1.6; 8.0]	−1.71 [−5.5; 2.1] ND
Emotional functioning	210	17.2 [14.7; 19.7]	−2.70 [−5.0; −0.4]	228	20.5 [17.6; 23.5]	−2.49 [−4.7; −0.3]	−0.20 [−2.8; 2.4] ND
Cognitive functioning	220	82.8 [80.5; 85.1]	1.97 [−0.7; 4.6]	233	80.9 [78.5; 83.4]	−0.79 [−3.4; 1.8]	2.76 [−0.3; 5.8] ND
Social functioning	217	12.6 [9.8; 15.3]	0.87 [−2.5; 4.2]	229	15.6 [12.4; 18.7]	0.11 [−3.1; 3.3]	0.76 [−3.1; 4.6] ND
EORTC QLQ-BR23[d]							
Body image	221	29.9 [26.6; 33.3]	−4.15 [−7.6; −0.7]	234	34.2 [30.8; 37.7]	−4.54 [−7.9; −1.2]	0.39 [−3.6; 4.3] ND
Sexual functioning	221	73.1 [70.7; 75.6]	1.60 [−0.9; 4.1]	232	71.0 [68.6; 73.5]	0.20 [−2.3; 2.7]	1.40 [-1.5; 4.3] ND
Sexual pleasure	No evaluable data[e]						
Perspective on the future	No evaluable data[e]						

(continued)

Table 17: Results on health-related quality of life – RCT, direct comparison: eribulin vs. capecitabine for patients for whom treatment with taxanes or anthracyclines is no longer an option, HER2/neu status negative (continued)

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: Valid data only at week 6 (no imputation of missing values).
c: EORTC QLQ-C30 functional scales, range 0–100; higher (increasing) values indicate better functionality; positive effects in the group comparison (eribulin – capecitabine or vinorelbine) indicate an advantage of eribulin.
d: Breast-cancer specific supplementary module of the EORTC questionnaire; EORTC QLQ-BR23 functional scales, range 0–100; higher (increasing) values indicate better functionality; positive effects in the group comparison (eribulin – capecitabine or vinorelbine) indicate advantage of eribulin; exception: sexual functioning and sexual pleasure: lower (decreasing) values indicate better functionality; negative effects in the group comparison (eribulin – capecitabine or vinorelbine) indicate advantage of eribulin.
e: Discrepancies between the main analysis and the subgroup analysis with regard to the patients considered in the analysis.
CI: confidence interval; EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer Module; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; HER2/neu: human epidermal growth factor receptor 2; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

In general it is to be pointed out that the company conducted the assessment of the added benefit for the subpopulation it considered, i.e. the subpopulation of patients for whom treatment with taxanes or anthracyclines is no longer an option, irrespective of the HER2/neu status. In Module 4, the company presented the results for the relevant subpopulation of this benefit assessment (in form of subgroup analyses for the HER2/neu status), but did not derive conclusions on the added benefit for this subpopulation from them.

Mortality

Overall survival

The extent of added benefit was assessed on the basis of the second data cut-off because these data are more informative because of the higher number of events, particularly because the meta-analysis showed considerable heterogeneity between the studies regarding research question A when using the first data cut-off (see Appendix C of the full dossier assessment).

Based on the meta-analysis of the 2 studies 301 and EMBRACE, treatment with eribulin resulted in a statistically significant prolongation of overall survival in comparison with capecitabine or vinorelbine. There is therefore proof of an added benefit of eribulin for the outcome "overall survival" compared with the ACT individual chemotherapeutic regimen with capecitabine or vinorelbine.

Morbidity

Pain

There were no data for the relevant subpopulations on the outcome "pain" measured with a VAS. Hence an added benefit of eribulin in comparison with the ACT is not proven for this outcome.

Symptoms

Aspects of symptoms were recorded in Study 301 using the symptom scales of the disease-specific questionnaire EORTC QLQ-C30 and the breast-cancer specific supplementary module EORTC QLQ-BR23. The difference in the mean change in values at the time point of 6 weeks was considered for both measurement instruments.

There was a statistically significant difference in favour of eribulin for the outcome "fatigue" measured with the EORTC QLQ-C30. However, the 95% confidence interval (CI) of Hedges' g was not completely below the irrelevance threshold of −0.2. Hence an added benefit of eribulin in comparison with the ACT is not proven for this outcome.

There was a statistically significant difference to the disadvantage of eribulin for the outcome "arm symptoms" measured with the EORTC QLQ-BR23. However, the 95% CI of Hedges' g was not completely above the irrelevance threshold of 0.2. Hence an added benefit of eribulin in comparison with the ACT is not proven for this outcome.

There was no statistically significant difference between the treatment groups for the following outcomes: nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and breast symptoms. Hence an added benefit of eribulin in comparison with the ACT is not proven for these outcomes.

For the outcomes "AEs of systemic treatment" and "burden of alopecia", no evaluable data were available due to the low number of patients in the analysis. Hence an added benefit of eribulin in comparison with the ACT is not proven for these outcomes.

Health-related quality of life

Aspects of health-related quality of life were recorded in Study 301 using the functional scales of the disease-specific questionnaire EORTC QLQ-C30 and the breast-cancer specific supplementary module EORTC QLQ-BR23. The difference in the mean change in values at the time point of 6 weeks was considered for both measurement instruments.

There was no statistically significant difference between the treatment groups for the following outcomes: global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, body image, and sexual functioning. Hence an added benefit of eribulin in comparison with the ACT is not proven for these outcomes.

For the outcomes "sexual pleasure" and "perspective on the future", no evaluable data were available due to contradictory data (for more information, see Section 2.7.2.4.3 of the full dossier assessment). Hence an added benefit of eribulin in comparison with the ACT is not proven for this outcome.

Adverse events

Serious adverse events

There was no statistically significant difference between the treatment groups for the outcome "SAEs". Hence lesser or greater harm from eribulin than from the ACT, individual chemotherapy with capecitabine or vinorelbine, is not proven for this outcome.

Discontinuation due to adverse events

There was no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". Hence lesser or greater harm from eribulin than from the ACT, individual chemotherapy with capecitabine or vinorelbine, is not proven for this outcome.

Severe adverse events (CTCAE grade 3 and 4)

Based on the meta-analysis of the 2 studies 301 and EMBRACE, there was a statistically significant difference to the disadvantage of eribulin in comparison with capecitabine or vinorelbine for the outcome "severe AEs (CTCAE grade 3 and 4)". There is therefore proof of greater harm from eribulin in comparison with the ACT individual chemotherapeutic regimen with capecitabine or vinorelbine.

Further information on the outcome results can be found in Module 4, Sections 4.3.1.3 and 4.3.2.1.3 of the dossier, and in Section 2.7.2.4.3 of the full dossier assessment.

2.3.2.4   Subgroups and other effect modifiers (research question A)

The dossier contained no subgroup analyses for the relevant subpopulations.

Further information on subgroup results can be found in Module 4, Sections 4.3.1.3.2 and 4.3.2.1.3.2 of the dossier, and in Section 2.7.2.4.3 of the full dossier assessment.

2.3.3   Extent and probability of added benefit (research question A)

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

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

2.3.3.1 HER2/neu status positive/unknown

There were no data for patients with positive or unknown HER2/neu status for whom treatment with taxanes or anthracyclines is no longer an option and for whom anti-HER2/neu treatment is inadequate. An added benefit of eribulin in these patients in comparison with the ACT (individual chemotherapy using monotherapy with the drugs capecitabine, vinorelbine) is not proven.

2.3.3.2 HER2/neu status negative

2.3.3.2.1 Assessment of added benefit at outcome level

For the outcome "overall survival", the data presented in Section 2.3.2 result in proof of added benefit of eribulin in comparison with individual chemotherapy using the drugs capecitabine or vinorelbine as monotherapy for patients with negative HER2/neu status for whom treatment with taxanes or anthracyclines is no longer an option. In contrast, there is proof of greater harm from eribulin for the outcome "severe AEs (CTCAE grade 3 and 4)". The extent of the respective added benefit at outcome level was estimated from these results (see Table 18).

Table 18: Extent of added benefit at outcome level: eribulin vs. capecitabine or vinorelbine for patients for whom treatment with taxanes or anthracyclines is no longer an option, HER2/neu status negative

Outcome category outcome	Eribulin vs. capecitabine or vinorelbine median time to event/proportion of events/mean change effect estimate [95% CI] p-value probability[a]	Derivation of extent[b]
Mortality		
Overall survival[c]	Median: NC HR: 0.79 [0.68; 0.93] p = 0.004 probability: "proof"	Outcome category "mortality" $0.85 < CI_u < 0.95$ added benefit, extent "considerable"
Morbidity		
Pain (VAS)	No data available	
EORTC QLQ-C30[d]		
Fatigue[e]	−1.37 vs. 5.16 mean: −6.53 [−10.0; −3.1] p = ND Hedges' g: −0.30 [−0.48; −0.11]	Lesser benefit/added benefit not proven
Nausea and vomiting[e]	−2.54 vs. −2.1 mean: −0.43 [−4.5; 3.7] p = ND	Lesser benefit/added benefit not proven
Pain[e]	5.08 vs. 3.12 mean: 1.96 [−1.4; 5.3] p = ND	Lesser benefit/added benefit not proven
Dyspnoea[e]	−1.88 vs. −0.96 mean: −0.92 [−4.4; 2.6] p = ND	Lesser benefit/added benefit not proven
Insomnia[e]	−2.75 vs. −2.53 mean: −0.22 [−4.9; 4.4] p = ND	Lesser benefit/added benefit not proven
Appetite loss[e]	9.11 vs. 7.90 mean: 1.21 [−4.0; 6.5] p = ND	Lesser benefit/added benefit not proven
Constipation[e]	−0.44 vs. 1.05 mean: −1.49 [−4.9; 1.9] p = ND	Lesser benefit/added benefit not proven
Diarrhoea[e]	−4.84 vs. −4.55 mean: −0.29 [−4.7; 4.1] p = ND	Lesser benefit/added benefit not proven

(continued)

Table 18: Extent of added benefit at outcome level: eribulin vs. capecitabine or vinorelbine for patients for whom treatment with taxanes or anthracyclines is no longer an option, HER2/neu status negative (continued)

Outcome category outcome	Eribulin vs. capecitabine or vinorelbine median time to event/proportion of events/mean change effect estimate [95% CI] p-value probability[a]	Derivation of extent[b]
EORTC QLQ-BR23[d]		
AEs of systemic treatment	No evaluable data	
Breast symptoms[e]	1.98 vs. 0.59 mean: 1.39 [−2.7; 5.4] p = ND	Lesser benefit/added benefit not proven
Arm symptoms[e]	−2.14 vs. −3.59 mean: 5.74 [3.2; 8.2] p = ND Hedges' g: 0.35 [0.16; 0.54]	Lesser benefit/added benefit not proven
Burden of alopecia[e]	No evaluable data	
Health-related quality of life		
EORTC QLQ-C30[d]		
Global health status[e]	0.59 vs. 1.65 mean: −1.07 [−5.3; 3.2] p = ND	Lesser benefit/added benefit not proven
Physical functioning[e]	−3.04 vs. −1.81 mean: −1.23 [−4.4; 1.9] p = ND	Lesser benefit/added benefit not proven
Role functioning[e]	3.09 vs. 4.80 mean: −1.71 [−5.5; 2.1] p = ND	Lesser benefit/added benefit not proven
Emotional functioning[e]	−2.70 vs. −2.49 mean: −0.20 [−2.8; 2.4] p = ND	Lesser benefit/added benefit not proven
Cognitive functioning[e]	1.97 vs. −0.79 mean: 2.76 [−0.3; 5.8] p = ND	Lesser benefit/added benefit not proven
Social functioning[e]	0.87 vs. 0.11 mean: 0.76 [−3.1; 4.6] p = ND	Lesser benefit/added benefit not proven

(continued)

Table 18: Extent of added benefit at outcome level: eribulin vs. capecitabine or vinorelbine for patients for whom treatment with taxanes or anthracyclines is no longer an option, HER2/neu status negative (continued)

Outcome category outcome	Eribulin vs. capecitabine or vinorelbine median time to event/proportion of events/mean change effect estimate [95% CI] p-value probability[a]	Derivation of extent[b]
EORTC QLQ-BR23[d]		
Body image[e]	−4.15 vs. −4.54 mean: 0.39 [−3.6; 4.3] p = ND	Lesser benefit/added benefit not proven
Sexual functioning[e]	1.60 vs. 0.20 mean: 1.40 [−1.5; 4.3] p = ND	Lesser benefit/added benefit not proven
Sexual pleasure	No evaluable data	
Perspective on the future	No evaluable data	
Adverse events		
SAEs[f]	Median: NC HR: 0.80 [0.59; 1.08] p = 0.145	Lesser/greater harm not proven
Discontinuation due to AEs[f]	Median: NC HR: 0.69 [0.43; 1.10] p = 0.118	Lesser/greater harm not proven
Severe AEs (CTCAE grade 3 and 4)[f]	Median: NC HR: 1.64 [1.36; 1.98] HR[g]: 0.61 [0.51; 0.74] p = < 0.001 probability: "proof"	Outcome category "serious/severe AEs" $CI_u < 0.75$ greater harm, extent: "major"

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Data of the meta-analysis from values at the 3/2012 data cut-off of Study 301 and values at the 3/2010 data cut-off of the EMBRACE study. Institute's calculation.
d: Data on morbidity and health-related quality of life were only available from Study 301.
e: Mean change after week 6 in comparison with start of study.
f: Data of the meta-analysis from values at the 3/2012 data cut-off of Study 301 and values at the 5/2009 data cut-off of the EMBRACE study. Institute's calculation.
g: Hazard capecitabine/vinorelbine vs. eribulin (reversed direction of effect to enable direct use of limits to derive the extent of added benefit).

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer Module; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; HER2/neu: human epidermal growth factor receptor 2; HR: hazard ratio; NC: not calculable; ND: no data; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.3.3.2.2   Overall conclusion on added benefit

Table 19 summarizes the results that were considered in the overall conclusion on the extent of added benefit for patients with negative HER2/neu status for whom treatment with taxanes or anthracyclines is no longer an option.

Table 19: Positive and negative effects from the assessment of eribulin in comparison with the ACT (research question A, HER2/neu status negative)

Positive effects	Negative effects
Proof of added benefit – extent: "considerable" (mortality: overall survival)	Proof of greater harm – extent: "major" (serious/severe AEs: severe AEs [CTCAE grade 3 and 4])
ACT: appropriate comparator therapy; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; HER2/neu: human epidermal growth factor receptor 2	

In the overall assessment, there is a positive and a negative effect of equal certainty of results (proof).

On the positive side, there is an added benefit with the extent "considerable" in the category "mortality". On the negative side, there is greater harm with the extent "major" in the category "serious/severe AEs" (severe AEs of CTCAE grade 3 and 4). Even though the extent for severe AEs is "major", this does not completely outweigh the advantage in mortality.

In summary, there is proof of minor added benefit of eribulin versus the ACT individual chemotherapy using monotherapy with the drugs capecitabine, vinorelbine for patients with negative HER2/neu status for whom treatment with taxanes or anthracyclines is no longer an option.

The result of the assessment of the added benefit of eribulin in comparison with the ACT is summarized in Table 29 in Section 2.6.

The assessment deviates from that of the company, which derived proof of considerable added benefit for the subpopulation it considered, i.e. the subpopulation of patients for whom treatment with taxanes or anthracyclines is no longer an option, irrespective of the HER2/neu status.

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

2.3.4   List of included studies (research question A)

Eisai. E7389 versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes: full text view [online]. In: Clinicaltrials.gov. 31 July 2013 [accessed: 16 January 2014]. URL: http://clinicaltrials.gov/show/NCT00337103.

Eisai. A phase III open label, randomized two-parallel-arm multicenter study of E7389 versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes: study E7389-G000-301; clinical study report [unpublished]. 2013.

Eisai. E7389 versus treatment of physician's choice in patients with locally recurrent or metastatic breast cancer: full text view [online]. In: Clinicaltrials.gov. 19 March 2012 [accessed: 16 January 2014]. URL: http://clinicaltrials.gov/show/NCT00388726.

Eisai. The EMBRACE trial: Eisai metastatic breast cancer study assessing physician´s choice versus E7389; a phase 3 open label, randomized parallel two-arm multi-center study of E7389 versus "treatment of physician´s choice" in patients with locally recurrent or metastatic breast cancer, previously treated with at least two and a maximum of five prior chemotherapy regimens including an anthracycline and a taxane; study E7389-G000-305; clinical study report [unpublished]. 2010.

Cortes J, Twelves C, Wanders J, Wang W, Vahdat L, Dutcus C. Clinical response to eribulin in patients with metastatic breast cancer is independent of time to first metastatic event. Breast 2011; 20(Suppl 4): S48-S49.

2.4 Research question B: patients for whom repeated treatment containing an anthracycline or a taxane is an option

2.4.1 Information retrieval and study pool (research question B)

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 eribulin (studies completed up to 30 May 2014)

- bibliographical literature search on eribulin (last search on 15 May 2014)

- search in trial registries for studies on eribulin (last search on 6 May 2014)

To check the completeness of the study pool:

- search in trial registries for studies on eribulin (last search on 14 August 2014)

No additional relevant study was identified from the check.

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

2.4.1.1 Studies included (research question B)

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

Table 20: Study pool – RCT, direct comparison: eribulin vs. anthracycline or taxane

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

The EMBRACE study was identified. This study was already presented in the dossier from 27 October 2011 for the first benefit assessment of eribulin (Commission A11-26 [3]). For the present benefit assessment, the company presented new analyses of the data already presented in the dossier from 27 October 2011 in its dossier from 18 July 2014. The data underlying the analyses of the EMBRACE study are therefore unchanged. Only a subpopulation was used from this study for the present benefit assessment.

As already explained in research question A (see Section 2.3.1.1), patients in the comparator arm of the EMBRACE study were treated with a therapy specified by the investigator (TPC),

which had been defined for all patients before group allocation. Treatment with anthracycline or taxane was specified for 143 (28.1%) of a total of 508 patients in the eribulin arm, and for 65 (25.6%) of a total of 254 patients in the comparator arm. The company presented the results of this subpopulation in Module 4 and derived the added benefit of eribulin from them. Out of this subpopulation considered by the company, conclusions for the present benefit assessment can only be drawn for patients with negative HER2/neu status (171 [82.2%] of 208 patients). Hereinafter, this patient population is referred to as "relevant subpopulation". There were no evaluable data for patients with positive or unknown HER2/neu status (24 [11.5%] positive, 13 [6.3%] unknown). The reasons for this are explained in research question A (Section 2.3.1).

Module 4 contained results on the relevant subpopulation in the form of subgroup analyses for the characteristic "HER2/neu status", which the company conducted for the subpopulation it considered. These analyses were primarily used for the assessment of the added benefit of eribulin. If these analyses were not available in the dossier, the results of the subpopulation considered by the company were used. This was possible because more than 80% of the patients with negative HER2/neu status were in the subpopulation considered by the company.

This deviates from the company's approach, which considered the subpopulation of patients for whom the investigator had chosen treatment with anthracycline or taxane before randomization, irrespective of the patients' HER2/neu status.

Section 2.4.4 contains a reference list for the study included.

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

2.4.1.2   Study characteristics (research question B)

Characteristics of the studies and of the interventions

The characteristics of the EMBRACE study and information on the planned duration of follow-up of the patients for the individual outcomes can be found in Section 2.3.1.2 on research question A (Table 6 to Table 8).

Characteristics of the study population

Table 21 shows the characteristics of the patients of the EMBRACE study for the subpopulation considered by the company, i.e. the subpopulation of patients for whom the investigator chose treatment with anthracycline or taxane prior to randomization.

Table 21: Characteristics of the study populations – RCT, direct comparison: eribulin vs. anthracycline or taxane for patients for whom repeated treatment containing an anthracycline or a taxane is an option

Study characteristics category	Eribulin	Anthracycline or taxane
EMBRACE		
N	143	65
Age [years]: median (min; max)	55 (30; 79)	60 (32; 77)
Sex: [F/M], %	100/0	100/0
Ethnicity, n (%)		
white	138 (96.5)	60 (92.3)
non-white	1 (0.7)	3 (4.6)
Asian/Pacific Islander	0	1 (1.5)
other	4 (2.8)	1 (1.5)
Geographical region, n (%)		
North America/Western Europe/Australia	113 (79.0)	53 (81.5)
Eastern Europe	24 (16.8)	10 (15.4)
Latin America/South Africa	6 (4.2)	2 (3.1)
ECOG PS, n (%)		
unknown	3 (2.1)	1 (1.5)
0	58 (40.6)	28 (43.1)
1	71 (49.7)	28 (43.1)
2	11 (7.7)	8 (12.3)
HER2/neu status (FISH and IHC tests), n (%)		
positive	17 (11.9)	7 (10.8)
negative	114 (79.7)	57 (87.7)
unknown	12 (8.4)	1 (1.5)
Time since first diagnosis [years]		
mean (SD)	7.7 (5.6)	7.1 (4.8)
median (min; max)	6.0 (0.8; 37.4)	6.1 (1.4; 22.9)
Type of disease, n (%)		
visceral	124 (86.7)	52 (80.0)
non-visceral	18 (12.6)	12 (18.5)
missing values	1 (0.7)	1 (1.5)
Number of prior chemotherapies, n (%)		
≤ 3	48 (33.6)	20 (30.8)
> 3	94 (65.7)	45 (69.2)
Treatment discontinuations, n (%)[a]	ND	ND

a: There were no data for the subpopulation (treatment with anthracycline or taxane planned before randomization, HER2/neu status positive + negative + unknown).

ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; FISH: fluorescence in situ hybridization; HER2/neu: human epidermal growth factor receptor 2; IHC: immunohistochemical; M: male; max: maximum; min: minimum; N: number of patients in the subpopulation; n: number of patients in the category; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Data on patient characteristics for the EMBRACE study were only available for the subpopulation considered by the company, i.e. the subpopulation of patients for whom the investigator chose treatment with anthracycline or taxane prior to randomization. There were no data on the subpopulation of patients (with negative HER2/neu status) relevant for this benefit assessment.

Exclusively women were included in the study. The characteristics of the patients between the arms were largely balanced. The median age in the eribulin arm (55 years) was slightly lower than in the comparator arm (60 years). Most patients were white and came from Western regions (North America, Western Europe, Australia; approximately 80%). 40.6% and 49.7% of the patients in the eribulin arm had an ECOG PS of 0 or 1 versus 43.1% of the patients in each of the comparator arms (anthracycline or taxane). Approximately 8% of the patients in the eribulin arm and 12% in the comparator arm had an ECOG PS of 2.

The majority of patients had a tumour with negative HER2/neu status (79.7% of the patients in the eribulin arm, and 87.7% of the patients in the comparator arm), approximately 12 and 11% of the patients in the eribulin arm and in the comparator arm had an HER2/neu over-expressing tumour, and the HER2/neu status was unknown in 8.4% and 1.5% of the patients. The mean time since the first diagnosis was 7.5 years. Two thirds of the patients had received more than 3 chemotherapeutic regimens during that time, the remaining patients had received 3 or fewer chemotherapeutic regimens. There were no data on the number of chemotherapeutic regimens for the treatment of advanced or metastatic disease. Visceral organs were affected by the disease in over 80% of the patients.

There were no data on the number of patients who discontinued treatment for the subpopulation.

Table 22 shows the mean/median treatment duration of the patients and the follow-up period for individual outcomes.

Table 22: Information on the course of the study – RCT, direct comparison: eribulin vs. anthracycline or taxane

Study characteristics category	Eribulin	Anthracycline or taxane
EMBRACE		
Mean/median treatment duration [days]	N = 503[a]	N = 247[b]
mean (SD)	137.3 (92.6)	ND
median (min; max)	118.0 (21; 497)	63 (ND)
Mean/median observation period [days]		
morbidity	not recorded	not recorded
health-related quality of life	not recorded	not recorded
adverse events	N = 143[c]	N = 62[c]
mean (SD)	146.2 (88.0)	120.6 (77.5)
median (min; max)	134.0 (1; 470)	92.5 (1; 472)

a: Safety population of the total eribulin arm of the study.
b: Safety population of the total TPC arm of the study.
c: Safety population of the relevant subpopulation from the study (treatment with anthracycline or taxane planned before randomization, HER2/neu status positive + negative + unknown).
HER2/neu: human epidermal growth factor receptor 2; max: maximum; min: minimum; N: number of patients in the subpopulation; ND: no data; RCT: randomized controlled trial; SD: standard deviation; TPC: treatment of physician's choice; vs.: versus

Data on treatment duration were available for the total study population. The median treatment duration was longer in the eribulin arm (118 days) than in the TPC arm (63 days). Data on the observation period of AEs were available for the subpopulation considered by the company, i.e. the subpopulation of patients for whom the investigator chose treatment with anthracycline or taxane prior to randomization, irrespective of the HER2/neu status. AEs were documented for a longer period of time in the eribulin arm (mean 146.2 days; median 134.0 days) than in the comparator arm (mean 120.6 days; median 92.5 days). As a consequence, the results for AEs based on raw rates are not evaluable. Survival time analyses are needed instead to account for the differences in the length of observation periods. The company presented such analyses.

Information on the risk of bias at study level can be found in Table 12 in Section 2.3.1.2 of research question A.

The risk of bias at study level for the EMBRACE study was rated as low. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described in Section 2.4.2.2 with the outcome-specific risk of bias.

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

2.4.2 Results on added benefit (research question B)

2.4.2.1 Outcomes included (research question B)

The following patient-relevant outcomes were considered in this assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - overall survival
- Adverse events
  - SAEs
  - discontinuation due to AEs
  - severe AEs (CTCAE grade 3 and 4)

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4) (see Section 2.7.2.4.3 of the full dossier assessment).

Table 13 in Section 2.3.1.2 (research question A) shows for which outcomes data were available in the included EMBRACE study.

Further information on the choice of outcomes can be found in Module 4, Sections 4.3.1.3 and 4.3.2.1.3 of the dossier, and in Section 2.7.2.4.3 of the full dossier assessment.

2.4.2.2 Risk of bias (research question B)

Table 14 in Section 2.3.2.2 (research question A) shows the risk of bias for the relevant outcomes.

The risk of bias for all outcomes was rated as high. However, no limited certainty of results was assumed, except for the outcome "discontinuation due to AEs". Further explanations can be found in Section 2.3.2.2 (research question A) and in Section 2.7.2.4.2 of the full dossier assessment.

Further information on the risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3, and in Appendix 4-F of the dossier, and in Section 2.7.2.4.2 of the full dossier assessment.

2.4.2.3   Results (research question B)

2.4.2.3.1   HER2/neu status positive/unknown

There were no data for patients with positive or unknown HER2/neu status for whom repeated treatment containing an anthracycline or a taxane is an option and for whom anti-HER2/neu treatment is inadequate. Added benefit has not been proven.

2.4.2.3.2   HER2/neu status negative

Table 23 summarizes the results on the comparison of eribulin with anthracycline or taxane in patients for whom repeated treatment containing an anthracycline or a taxane is an option and who have a negative HER2/neu status. The dossier contained survival time analyses on the results, which were based on a post-hoc adjusted Cox proportional hazards model (co-factors: number of organs involved and ER status) and were therefore potentially biased. Prespecified unadjusted analyses were additionally available (log-rank test). However, the survival time analyses from the adjusted Cox proportional hazards model could be used for this benefit assessment because the p-values did not differ substantially from the ones of the unadjusted log-rank test. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations.

Additional information on the naive proportions of AEs are presented in Appendix A of the full dossier assessment. The Kaplan-Meier curve for the outcome "overall survival" for the subpopulation considered by the company, i.e. the subpopulation of patients for whom the investigator chose treatment with anthracycline or taxane prior to randomization, is presented in Appendix B of the full dossier assessment.

Table 23: Results on mortality and AEs – RCT, direct comparison: eribulin vs. anthracycline or taxane for patients for whom repeated treatment containing an anthracycline or a taxane is an option, HER2/neu status negative

Outcome category outcome	Eribulin		Anthracycline or taxane		Eribulin vs. anthracycline or taxane	
	N	Median time to event in days [95% CI]	N	Median time to event in days [95% CI]	HR [95% CI][a]	p-value[b]
EMBRACE						
Overall survival						
Data cut-off 5/2009	114	394 [ND]	57	444 [ND]	1.18 [0.75; 1.85]	0.433
Data cut-off 3/2010	114	410 [ND]	57	396 [ND]	1.02 [0.70; 1.47]	0.931
Adverse events						
AEs		ND		ND		
SAEs	114	399 [ND]	54	NC	1.01 [0.53; 1.91]	0.888
Discontinuation due to AEs	114	NC	54	NC	0.38 [0.17; 0.86]	0.017
Severe AEs (CTCAE grade 3 and 4)	114	31 [ND]	54	NC	1.95 [1.23; 3.10]	0.003
a: Cox proportional hazards model with capecitabine pretreatment and geographical region as strata, and number of organs involved and ER status as co-factors defined post-hoc. b: Log-rank test stratified by capecitabine pretreatment and geographical region (planned analysis). AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ER: oestrogen receptor; HER2/neu: human epidermal growth factor receptor 2; HR: hazard ratio; N: number of analysed patients; NC: not calculable; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus						

The EMBRACE study did not meet the particular requirements placed on the derivation of proof from one study (see Section 2.7.2.8.1 of the full dossier assessment). Hence at most indications were inferred from the data of the study.

In general it is to be pointed out that the company conducted the assessment of the added benefit for the subpopulation considered by the company, i.e. the subpopulation of patients for whom the investigator chose treatment with anthracycline or taxane prior to randomization, irrespective of the HER2/neu status. In Module 4, the company presented the results for the relevant subpopulation of this benefit assessment (HER2/neu-negative patients) (in form of subgroup analyses for the HER2/neu status), but did not derive conclusions on the added benefit for this subpopulation from them.

Mortality

Overall survival

The extent of added benefit was assessed on the basis of the second data cut-off because these data are more informative because of the higher number of events. There was no relevantly different result for the first data cut-off.

In both data cut-offs, there was no statistically significant difference between the treatment groups for the outcome "overall survival". An added benefit of eribulin in comparison with the ACT, individual repeated chemotherapy with anthracycline or taxane, is not proven for this outcome.

Morbidity

The company presented no data on morbidity in its dossier. An added benefit of eribulin in comparison with the ACT is not proven for this outcome.

Health-related quality of life

The company presented no data on health-related quality of life in its dossier. An added benefit of eribulin in comparison with the ACT is not proven for this outcome.

Adverse events

Serious adverse events

There was no statistically significant difference between the treatment groups for the outcome "SAEs". Lesser or greater harm from eribulin than from the ACT, individual repeated chemotherapy with anthracycline or taxane, is not proven for this outcome.

Discontinuation due to adverse events

There was a statistically significant difference in favour of eribulin in comparison with anthracycline or taxane for the outcome "discontinuation due to AEs". Because of the high risk of bias of the outcome, this results in a hint of lesser harm from eribulin in comparison with the ACT individual repeated chemotherapy with anthracycline or taxane.

Severe adverse events (CTCAE grade 3 and 4)

There was a statistically significant difference to the disadvantage of eribulin in comparison with anthracycline or taxane for the outcome "severe AEs (CTCAE grade 3 and 4)". There is therefore an indication of greater harm from eribulin in comparison with the ACT individual repeated chemotherapy with anthracycline or taxane.

Further information on the outcome results can be found in Module 4, Sections 4.3.1.3 and 4.3.2.1.3 of the dossier, and in Section 2.7.2.4.3 of the full dossier assessment.

2.4.2.4 Subgroups and other effect modifiers (research question B)

The dossier contained no subgroup analyses for the relevant subpopulation of the EMBRACE study (patients with negative HER2/neu status for whom the investigator had chosen treatment with anthracycline or taxane prior to randomization). However, this relevant subpopulation constitutes 82.2% in total of the subpopulation considered by the company, i.e. the subpopulation of patients for whom the investigator chose treatment with anthracycline or taxane prior to randomization. The dossier contained analyses on subgroups and other effect modifiers for this subpopulation. Hence the subgroup analyses of the total subpopulation can

be used for the present assessment. However, potential added benefit was only derived for patients with HER2/neu-negative breast cancer. There were no evaluable data for patients with positive or unknown HER2/neu status.

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

- age (< 40 years/≥ 40 years to < 65 years/≥ 65 years)

- ethnicity (white/non-white)

- hormone receptor status (ER positive or progesterone receptor (PR) positive/ER negative and PR negative/unknown)

- type of disease (visceral/non-visceral)

- number of organs affected by the disease (≤ 2/> 2)

- Number of prior chemotherapeutic regimens (≤ 3/> 3)

- ECOG-PS (0/1/2)

Overall survival

Table 24 shows the subgroups on overall survival with at least an indication of an effect modification.

Table 24: Subgroups: overall survival by the characteristics "number of organs involved" and "ethnicity" – RCT, direct comparison: eribulin vs. anthracycline or taxane for patients for whom repeated treatment containing an anthracycline or a taxane is an option

Study characteristic subgroup	Eribulin		Anthracycline or taxane		Eribulin vs. anthracycline or taxane	
	N	Median time to event in days [95% CI]	N	Median time to event in days [95% CI]	HR[a] [95% CI]	p-value
EMBRACE						
Overall survival (data cut-off 3/2010)						
Number of organs affected by the disease						
≤ 2	73	431 [ND]	31	348 [ND]	0.80 [0.48; 1.33]	0.464[b]
> 2	70	348 [ND]	34	428 [ND]	1.35 [0.81; 2.26]	0.285[b]
					Interaction:	0.176
Ethnicity						
white	138	410 [ND]	60	382 [ND]	1.07 [0.74; 1.54]	0.713[b]
non-white[c]	5	126 [ND]	5	527 [ND]	10.76 [1.08; 107.5]	0.013
					Interaction:	0.112

a: Cox proportional hazards model with HER2/neu status, capecitabine pretreatment and geographical region as strata, and number of organs involved and ER status as co-factors defined post-hoc.
b: Log-rank test stratified by HER2/neu status, capecitabine pretreatment and geographical region (planned analysis).
c: No stratification due to the low number of events. The subgroup of non-whites includes the ethnicities "non-whites", "Asians and Pacific Islanders" and "others".
CI: confidence interval; ER: oestrogen receptor; HER2/neu: human epidermal growth factor receptor 2; HR: hazard ratio; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; vs.: versus

At the final data cut-off, there was an indication of an effect modification by the subgroup characteristics "number of organs affected by the disease" and "ethnicity" for the outcome "overall survival". The following conclusions on added benefit are exclusively based on this data cut-off because this data cut-off was more informative due to the greater number of events.

For patients with no more than 2 or with more than 2 organs affected by the disease, treatment with eribulin resulted in no statistically significant difference for overall survival in comparison with anthracyclines or taxanes. Hence for this outcome, there is no proof of added benefit of eribulin in comparison with the ACT for both subgroups of patients. The effect was also not statistically significant in the total relevant subpopulation (see Table 23).

For white patients, there was no statistically significant difference for overall survival between treatment with eribulin and anthracyclines or taxanes. Hence for this outcome, there is no proof of added benefit of eribulin in comparison with the ACT for this subgroup.

For non-white patients, in contrast, there was a statistically significant difference to the disadvantage of eribulin in comparison with anthracyclines or taxanes for overall survival. For the total subpopulation considered, the difference in the same direction of effect was not statistically significant. Considering the fact that there was only an indication of an interaction, the probability of lesser benefit was downgraded to a hint.

Serious adverse events

Table 25 shows the subgroups on SAEs with at least an indication of an effect modification.

Table 25: Subgroups: SAEs by the characteristic "age" – RCT, direct comparison: eribulin vs. anthracycline or taxane for patients for whom repeated treatment containing an anthracycline or a taxane is an option

Study characteristic subgroup	Eribulin		Anthracycline or taxane		Eribulin vs. anthracycline or taxane	
	N	Median time to event in days [95% CI]	N	Median time to event in days [95% CI]	HR [95% CI][a]	p-value
EMBRACE						
SAEs data cut-off 5/2009						
Age						
< 40 years	8	NC	2	NC	ND	ND
≥ 40 and < 65	112	399 [ND]	42	NC	0.86 [0.42; 1.73]	0.703[b]
≥ 65	23	NC	18	NC	2.27 [0.44; 11.61]	0.288[b]
					Interaction:	0.199

a: Cox proportional hazards model with HER2/neu status, capecitabine pretreatment and geographical region as strata, and number of organs involved and ER status as co-factors defined post-hoc.
b: Log-rank test stratified by HER2/neu status, capecitabine pretreatment and geographical region (planned analysis).
CI: confidence interval; ER: oestrogen receptor; HER2/neu: human epidermal growth factor receptor 2; HR: hazard ratio; N: number of analysed patients; NC: not calculable; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

There was an indication of an effect modification by the subgroup characteristic "age" for the outcome "SAEs". However, the statistically significant result of the interaction test was based on the deviation of the group of patients under 40 years of age. As there was no effect estimate for this subgroup due to the extremely low sample size, the results of this subgroup are subject to high uncertainty and not adequately interpretable. The results of the 2 other age categories (≥ 40 and < 65 years; ≥ 65 years) showed no heterogeneity. Hence no separate conclusions were drawn for the individual subgroups, but the estimate of the total relevant subpopulation was used.

Hence for this outcome, there is no proof of added benefit of eribulin in comparison with the ACT for the characteristic "age" in the age categories considered.

Severe adverse events (CTCAE grade 3 and 4)

Table 26 shows the subgroups on severe AEs (CTCAE grade 3 and 4) with at least an indication of an effect modification.

Table 26: Subgroups: severe AEs (CTCAE grade 3 and 4) by the characteristics "number of organs affected by the disease" and "age" – RCT, direct comparison: eribulin vs. anthracycline or taxane for patients for whom repeated treatment containing an anthracycline or a taxane is an option

Study characteristic subgroup	Eribulin		Anthracycline or taxane		Eribulin vs. anthracycline or taxane	
	N	Median time to event in days [95% CI]	N	Median time to event in days [95% CI]	HR [95% CI][a]	p-value
EMBRACE						
Severe AEs (CTCAE grade 3 and 4) (data cut-off 5/2009)						
Number of organs affected by the disease						
≤ 2	73	34 [ND]	30	54 [ND]	1.42 [0.80; 2.53]	0.316[b]
> 2	70	37 [ND]	32	NC	3.04 [1.50; 6.14]	0.002[b]
					Interaction:	0.075
Age						
< 40 years	8	61 [ND]	2	8 [ND]	NC	0.069[c]
≥ 40 and < 65	112	31 [ND]	42	118 [ND]	1.64 [0.99; 2.72]	0.027[b]
≥ 65	23	43 [ND]	18	NC	2.77 [1.02; 7.56]	0.039[b]
					Interaction:	0.063

a: Cox proportional hazards model with HER2/neu status, capecitabine pretreatment and geographical region as strata, and number of organs involved and ER status as co-factors defined post-hoc.
b: Log-rank test stratified by HER2/neu status, capecitabine pretreatment and geographical region (planned analysis).
c: Log-rank test, no stratification due to the low number of events.
AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ER: oestrogen receptor; HER2/neu: human epidermal growth factor receptor 2; HR: hazard ratio; N: number of analysed patients; NC: not calculable; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

There was an indication of an effect modification by the subgroup characteristics "number of organs affected by the disease" and "age" for the outcome "severe AEs (CTCAE grade 3 and 4)".

For patients with no more than 2 organs affected by the disease, there was no statistically significant difference for severe AEs (CTCAE grade 3 and 4) in comparison with anthracyclines or taxanes. For the total subpopulation considered, however, there was a statistically significant difference between the treatment groups to the disadvantage of eribulin (see Table 23). Since overall there is only an indication of an effect modification, it cannot be assumed for the subgroup of patients with ≤ 2 organs affected by the disease that there is no

effect. Hence the effect observed in the subpopulation considered was included for this subgroup. However, the probability of this effect was downgraded to a "hint".

For the characteristic "age", the statistically significant result of the interaction test was based on the deviation of the group of patients under 40 years of age. As there was no effect estimate for this subgroup due to the extremely low sample size, the results of this subgroup are subject to high uncertainty and not adequately interpretable. The results of the 2 other age categories (≥ 40 and < 65 years; ≥ 65 years) showed no heterogeneity. Hence no separate conclusions were drawn for the individual subgroups, but the estimate of the total relevant subpopulation was used.

Hence for this outcome, there is no proof of added benefit of eribulin in comparison with the ACT for the characteristic "age" in the age categories considered.

Further information on subgroup results can be found in Module 4, Sections 4.3.1.3.2 and 4.3.2.1.3.2 of the dossier, and in Section 2.7.2.4.3 of the full dossier assessment.

2.4.3 Extent and probability of added benefit (research question B)

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

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

2.4.3.1 HER2/neu status positive/unknown

There were no data for patients with positive or unknown HER2/neu status for whom repeated treatment containing an anthracycline or a taxane is an option and for whom anti-HER2/neu treatment is inadequate. An added benefit of eribulin in these patients in comparison with the ACT (individual chemotherapy with repeated treatment containing an anthracycline or a taxane) is not proven.

2.4.3.2 HER2/neu status negative

2.4.3.2.1 Assessment of added benefit at outcome level

For the outcome "discontinuation due to AEs", the data presented in Section 2.3.2 result in a hint of lesser harm from eribulin in comparison with individual chemotherapy with repeated treatment containing an anthracycline or a taxane for patients with negative HER2/neu status for whom repeated treatment containing an anthracycline or a taxane is an option.

In contrast, there are indications or hints of lesser benefit or greater harm from eribulin for different subgroups. For non-white patients, there is a hint of lesser benefit from eribulin for the outcome "overall survival". For the outcome "severe AEs (CTCAE grade 3 and 4)", there

is a hint of greater harm for patients with ≤ 2 organs affected by the disease. For patients with more than 2 organs affected by the disease, there is an indication of greater harm for this outcome. The extent of the respective added benefit at outcome level was estimated from these results (see Table 27).

Table 27: Extent of added benefit at outcome level: eribulin vs. anthracycline or taxane for patients for whom repeated treatment containing an anthracycline or a taxane is an option, HER2/neu status negative

Outcome category outcome subgroup characteristic	Eribulin vs. anthracycline or taxane quantile of time to event or proportion of events/ effect estimate [95% CI] p-value probability[a]	Derivation of extent[b]
Mortality		
Overall survival (data cut-off 3/2010) ethnicity	Median: 410 vs. 396 days HR: 1.02 [0.70; 1.47] p = 0.931	
white	Median: 410 vs. 382 days HR: 1.07 [0.74; 1.54] p = 0.713	Lesser benefit/added benefit not proven
non-white	Median: 126 vs. 527 days HR: 10.76 [1.08; 107.5] HR[c]: 0.09 [0.01; 0.93] p = 0.013 probability: "hint"	Outcome category "mortality" $0.85 < CI_u < 0.95$ Lesser benefit, extent "non-quantifiable" (not more than "considerable")
Morbidity		
	No data	
Health-related quality of life		
	No data	
Adverse events		
Serious adverse events	Median: 399 days vs. NC HR: 1.01 [0.53; 1.91] p = 0.888	Lesser/greater harm not proven
Discontinuation due to AEs	Median: NC HR: 0.38 [0.17; 0.86] p = 0.017 probability: "hint"	Outcome category "non-serious/non-severe AEs" $0.80 < CI_u < 0.90$ lesser harm, extent: "minor"

(continued)

Table 27: Extent of added benefit at outcome level: eribulin vs. anthracycline or taxane for patients for whom repeated treatment containing an anthracycline or a taxane is an option, HER2/neu status negative (continued)

Outcome category outcome subgroup characteristic	Eribulin vs. anthracycline or taxane quantile of time to event or proportion of events/ effect estimate [95% CI] p-value probability[a]	Derivation of extent[b]
Severe AEs (CTCAE grade 3 and 4)	Median: 31 days vs. NC HR: 1.95 [1.23; 3.10] HR[c]: 0.51 [0.32; 0.81] p = 0.003 probability: "indication"	
number of organs involved ≤ 2	Median: 34 vs. 54 days HR: 1.42 [0.80; 2.53] p = 0.316 probability: "hint"	greater harm, extent "non-quantifiable" (not more than "considerable")
> 2	Median: 37 days vs. NC HR: 3.04 [1.50; 6.14] HR[c]: 0.33 [0.16; 0.67] p = 0.002 probability: "indication"	Outcome category "serious/severe AEs" $CI_u < 0.75$ greater harm, extent: "major"

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Hazard anthracycline/taxane vs. eribulin (reversed direction of effect to enable direct use of limits to derive the extent of added benefit).
AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HER2/neu: human epidermal growth factor receptor 2; HR: hazard ratio; NC: not calculable; ND: no data; SAE: serious adverse event; vs.: versus

2.4.3.2.2 Overall conclusion on added benefit

Table 28 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 28: Positive and negative effects from the assessment of eribulin in comparison with the ACT (research question B, HER2/neu status negative)

Positive effects	Negative effects

Non-serious/non-severe AEs
▪ discontinuation due to AEs:
  hint of lesser harm – extent "minor"
	Mortality: overall survival
	  □ ethnicity – non-white
	    hint of lesser benefit – extent "non-quantifiable"
	    (not more than "considerable")

	Serious/severe AEs
	▪ severe AEs (CTCAE grade 3 and 4)
	  number of organs involved
	  □ ≤ 2
	    hint of greater harm – extent "non-quantifiable"
	    (not more than "considerable")
	  □ > 2
	    indication of greater harm – extent "major"

ACT: appropriate comparator therapy; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; HER2/neu: human epidermal growth factor receptor 2	

In the overall assessment, there is a positive effect and there are negative effects of different certainty of results for patients with negative HER2/neu status for whom repeated treatment containing an anthracycline or a taxane is an option. The positive effect was shown in the outcome category "non-serious/non-severe AEs". Negative effects were shown for different subgroups in the outcome categories "mortality" and "serious/severe AEs".

Below, the balancing of positive and negative effects is conducted separately for the 2 severity grades considered (≤ 2 or > 2 organs involved).

Patients with ≤ 2 organs involved

There is a hint of greater harm, the extent of which is "non-quantifiable", but at most "considerable", for patients with ≤ 2 organs affected by the disease in the category "serious/severe AEs" (severe AEs of CTCAE grade 3 and 4). This is offset by a hint of lesser harm with the extent "minor" in the outcome category "non-serious/non-severe AEs" (discontinuation due to AEs). Greater harm from eribulin regarding severe AEs of CTCAE grade 3 and 4 affected considerably more patients than the advantage regarding discontinuations due to AEs, which were mainly non-serious. Hence, with the same certainty of results, the disadvantage in the category "serious/severe AEs" outweighs the lesser harm in the category "non-serious/non-severe AEs". Moreover, there is a hint of lesser benefit for the outcome "overall survival" for non-white patients (extent: "non-quantifiable", at most "considerable"). Since this effect did not exceed the one on serious/severe AEs with regard to

extent or certainty of results, it did not result in a change of the overall conclusion for the group of patients with ≤ 2 organs involved.

Patients with > 2 organs involved

There is an indication of greater harm with the extent "major" for patients with > 2 organs affected by the disease in the category "serious/severe AEs" (severe AEs of CTCAE grade 3 and 4). This is offset by a hint of lesser harm with the extent "minor" in the outcome category "non-serious/non-severe AEs" (discontinuation due to AEs). Hence there is a disadvantage of eribulin, the certainty of results and extent of which outweigh the lesser harm in the category "non-serious/non-severe AEs". Moreover, the hint of lesser benefit for the outcome "overall survival" in non-white patients also has to be considered. The extent and certainty of results of this effect is to be rated as lower than the ones of the effect regarding severe AEs and does not change the overall conclusion for the group of patients with > 2 organs involved.

In summary, there is a hint of lesser benefit of eribulin in comparison with the ACT for patients with ≤ 2 organs affected by the disease, and there is an indication of lesser benefit of eribulin in comparison with the ACT for patients with > 2 organs affected by the disease.

The result of the assessment of the added benefit of eribulin in comparison with the ACT is summarized in Table 29 in Section 2.6.

The assessment deviates from that of the company, which derived an indication of considerable added benefit for the total population of patients for whom repeated treatment containing an anthracycline or a taxane is an option, irrespective of the HER2/neu status.

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

2.4.4 List of included studies (research question B)

Eisai. E7389 versus treatment of physician's choice in patients with locally recurrent or metastatic breast cancer: full text view [online]. In: Clinicaltrials.gov. 19 March 2012 [accessed: 16 January 2014]. URL: http://clinicaltrials.gov/show/NCT00388726.

Eisai. The EMBRACE trial: Eisai metastatic breast cancer study assessing physician´s choice versus E7389; a phase 3 open label, randomized parallel two-arm multi-center study of E7389 versus "treatment of physician´s choice" in patients with locally recurrent or metastatic breast cancer, previously treated with at least two and a maximum of five prior chemotherapy regimens including an anthracycline and a taxane; study E7389-G000-305; clinical study report [unpublished]. 2010.

Cortes J, Twelves C, Wanders J, Wang W, Vahdat L, Dutcus C. Clinical response to eribulin in patients with metastatic breast cancer is independent of time to first metastatic event. Breast 2011; 20(Suppl 4): S48-S49.

2.5   Research question C: patients in whom anti-HER2/neu treatment is indicated

2.5.1   Information retrieval and study pool (research question C)

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 eribulin (studies completed up to 30 May 2014)

- bibliographical literature search on eribulin (last search on 15 May 2014)

- search in trial registries for studies on eribulin (last search on 6 May 2014)

The company identified no direct comparative studies or studies for an indirect comparison on eribulin in patients in whom anti-HER2/neu treatment is indicated versus the ACT specified by the G-BA.

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

2.5.2   Results on added benefit (research question C)

The company presented no relevant data for research question C on eribulin in patients in whom anti-HER2/neu treatment is indicated. Hence the added benefit of eribulin in patients in whom anti-HER2/neu treatment is indicated versus the ACT specified by the G-BA is not proven.

2.5.3   Extent and probability of added benefit (research question C)

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of eribulin in comparison with the ACT specified by the G-BA (lapatinib + capecitabine, lapatinib + trastuzumab) in patients in whom anti-HER2/neu treatment is indicated. Hence there are also no patient groups for whom a therapeutically important added benefit could be derived. This concurs with the company's assessment who claimed no added benefit for this research question.

2.5.4   List of included studies (research question C)

Not applicable as the company did not present any relevant studies in its dossier, from which an added benefit of eribulin in patients in whom anti-HER2/neu treatment is indicated versus the ACT specified by the G-BA (lapatinib + capecitabine, lapatinib + trastuzumab) can be derived.

2.6 Extent and probability of added benefit – summary

The result of the assessment of the added benefit of eribulin in comparison with the ACTs is summarized in Table 29.

Table 29: Eribulin – extent and probability of added benefit

Therapeutic indication	ACT[a]	Extent and probability of added benefit
Research question A: patients for whom treatment with taxanes or anthracyclines is no longer an option		
HER2/neu status negative	Individual chemotherapy using monotherapy with the drugs capecitabine, vinorelbine	Proof of minor added benefit
HER2/neu status positive/unknown		Added benefit not proven
Research question B: patients for whom repeated treatment containing an anthracycline or a taxane is an option		

HER2/neu status negative
 	
  number of organs involved ≤ 2
  number of organs involved > 2
	Individual chemotherapy with repeated treatment containing an anthracycline or a taxane	Hint of lesser benefit
		indication of lesser benefit

HER2/neu status positive/unknown		Added benefit not proven
Research question C: patients with HER2/neu-positive breast cancer in whom anti-HER2/neu treatment is indicated		
Patients with advanced or metastatic disease that has progressed after prior treatment including anthracyclines and taxanes as well as, in the metastatic setting, trastuzumab	Lapatinib + capecitabine	Added benefit not proven
Patients with hormone-receptor-negative metastatic disease that has progressed after prior trastuzumab treatment(s) in combination with chemotherapy	Lapatinib + trastuzumab	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2/neu: human epidermal growth factor receptor 2		

The company conducted no assessment of the added benefit of eribulin versus the ACTs for the respective populations relevant for the assessment.

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier and in Section 2.7.2.8.2 of the full dossier assessment.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General Methods: version 4.1 [online]. 28 November 2013 [accessed: 1 August 2014]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-1.pdf.

2. Institute for Quality and Efficiency in Health Care. Ticagrelor: benefit assessment according to §35a Social Code Book V; extract; commission no. A11-02 [online]. 29 September 2011 [accessed: 5 May 2012]. URL: https://www.iqwig.de/download/A11-02_Extract_of_dossier_assessment_Ticagrelor.pdf.

3. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Eribulin: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A11-26 [online]. 30 January 2012 [accessed: 11 March 2013]. (IQWiG-Berichte; Volume 116). URL: https://www.iqwig.de/download/A11-26_Eribulin_Nutzenbewertung_35a_SGB_V.PDF.

4. Eisai. HALAVEN 0,44mg/ml Injektionslösung: Fachinformation [online]. June 2014 [accessed: 1 August 2014]. URL: http://www.fachinfo.de.

5. Kreienberg R, Albert US, Follmann M, Kopp I, Kühn T, Wöckel A et al. Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms, Langversion 3.0 [online]. July 2012 [accessed: 1 August 2014]. URL: http://www.awmf.org/uploads/tx_szleitlinien/032-045OL_l_S3__Brustkrebs_Mammakarzinom_Diagnostik_Therapie_Nachsorge_2012-07.pdf.

6. Roche. Xeloda: Fachinformation [online]. January 2014 [accessed: 1 August 2014]. URL: http://www.fachinfo.de.

7. Hospira. Vinorelbin Hospira 10 mg/ml Konzentrat zur Herstellung einer Infusionslösung: Fachinformation [online]. December 2013 [accessed: 1 August 2014]. URL: http://www.fachinfo.de.

The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a14-25-eribulin-neues-anwendungsgebiet-nutzenbewertung-gemaess-35a-sgb-v-dossierbewertung.6250.html.