IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Eribulin –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment ("Eribulin – Nutzenbewertung gemäß § 35a SGB V" (Version 1.0; Status: 30.01.2012). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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[2] Due to legal data protection regulations, employees have the right not to be named.

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Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
EMBRACE	Eisai Metastatic Breast Cancer Study Assessing Physician's Choice versus Eribulin
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor 2
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
TPC	treatment of physician's choice

2. Benefit assessment

2.1 Executive summary of the benefit assessment

Background

On 01.11.2011, in accordance with § 35a SGB (Social Code Book) V, the Federal Joint Committee (G-BA) wrote to IQWiG to commission the benefit assessment of the drug eribulin. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company").

Research question

The benefit assessment of eribulin was carried out in accordance with the approved therapeutic indication of "Treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapeutic regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane, unless patients were not suitable for these treatments" [1].

The benefit assessment was undertaken in comparison with

- monotherapy with capecitabine, 5-fluorouracil, vinorelbine or,
- if suitable, further treatment containing an anthracycline or taxane.

Results

A total of one relevant study (EMBRACE) was submitted. This was a randomized, open-label, direct comparison (two-arm) approval study in which adult women with locally advanced or metastatic breast cancer were enrolled. For the benefit assessment of eribulin in comparison with the appropriate comparator therapy (ACT) of the G-BA and the company, only the results of a subpopulation of the EMBRACE study were relevant. The main reason was that the patients in the comparator group of the study did not solely receive the specified ACT, but could be given various other treatments as well. The subpopulation relevant for the benefit assessment comprises those patients from the eribulin or comparator group who, if randomized to the comparator group, would have or had received the ACT. Prior to randomization, a physician chose the treatment to be given to each patient if they were allocated to the comparator group. Hence evaluations for the relevant subpopulation of the study are inherently possible. Although the company has not submitted such analyses in its assessment, they are however available for the outcome "overall survival" in the documents of the EMBRACE study.

The risk of bias in the EMBRACE study at study and outcome levels is estimated as low in each case.

Overall survival

Data are available to evaluate the outcome ”overall survival” for patients in the eribulin and comparator group who would have or had received capecitabine, vinorelbine or prior therapy with a taxane or anthracycline if allocated to the comparator group. The results for those patients who, according to the physician’s choice, would have or had received 5-fluorouracil were not evaluated separately in the study. However, from the details in the study it is clear that only one patient in the comparator group received 5-fluorouracil and hence this has no relevant effect on the overall result.

Results are available from analyses carried out at two points in time. The first, primary analysis was initially planned to take place after 411 events (deaths) (approx. 54%). In order to consider results over a longer period, the regulatory authorities requested a second, updated analysis at the time of 75% events (deaths). The results obtained at both these times were used for the benefit assessment

The pooled analyses for the patients of the relevant subpopulation showed no statistically significant result at either time point. However, both analyses displayed a high degree of heterogeneity. Hence an overall conclusion about all drugs did not appear meaningful. On reviewing the analyses, it was apparent that the cause of the heterogeneity can be explained by the option of receiving further treatment with taxanes or anthracyclines. On the basis of this assumption, patients in the relevant subpopulation of the EMBRACE study were divided into the following two subgroups: patients for whom treatment with taxanes or anthracyclines was no longer an option and those in whom further treatment with taxanes or anthracyclines was still possible. Separate evaluations were carried out for these subgroups. In each case, the results of these analyses were homogeneous.

The results of both analyses (initial primary and updated) for the subgroup of patients in whom further treatment with taxanes or anthracyclines was still possible were not statistically significant. Hence there is no proof of added benefit of eribulin for this subgroup. For the other subgroup (patients for whom taxanes or anthracyclines were no longer an option), there was a statistically significant result in favour of eribulin at the primary analysis, which was, however, no longer statistically significant at the updated analysis. Overall, this gives a “hint” of added benefit of eribulin for the subgroup of patients who can no longer be treated with a taxane or anthracycline.

Quality of life

Health-related quality of life was not recorded as an outcome in the study.

Adverse events

There were no results available regarding the complex “adverse events” for the relevant sub-population of the EMBRACE study and hence not for the named subgroups of patients either. The results for the whole population of the study have been shown additionally in order to

give an overall impression of the potential harm from eribulin compared with that from the ACT.

There was a difference to the disadvantage of eribulin in the overall rate of adverse events as well as of severe adverse events (CTCAE Grade 3 and 4). The result was statistically significant in each case.

The proportion of patients with serious adverse events and with adverse events that led to withdrawal from the study did not differ substantially between the eribulin and comparator groups. In each case, the difference was not statistically significant.

In summary, greater harm from eribulin in comparison with the ACT cannot be excluded.

Probability and extent of the added benefit, patient groups with therapeutically important added benefits

Based on the results presented, the extent and probability of an added benefit of the drug eribulin is assessed as follows:

The following two groups of patients are to be considered separately for the overall conclusion about the extent of added benefit:

- **Patients for whom treatment with taxanes or anthracyclines is no longer an option:** In terms of positive effects, there is a “hint” of an added benefit of eribulin for the outcome “overall survival”. Because of the non-uniform results at the two analysis times, the extent is non-quantifiable. However, in view of the statistically significant result at the primary analysis, the added benefit can, at best, be considerable. In terms of the negative effects, a greater harm from eribulin cannot be excluded. The company did not submit any data for the patient group of interest with regard to the complex “adverse events”. Since these also included severe adverse events, it cannot be ruled out that the negative effects outweigh the positive ones. Therefore an added benefit of eribulin for this group of patients is not proven.
- **Patients, in whom further treatment with taxanes or anthracyclines is still possible:** No positive effects of eribulin are shown for this group of patients. However, greater harm from eribulin cannot be excluded because no data on the complex "adverse events" were submitted by the company for this group of patients. Hence a lesser benefit of eribulin in comparison with the ACT cannot be excluded either. An added benefit of eribulin for this group of patients is not proven.

The decision regarding added benefit is made by the G-BA.

2.2 Research question

The benefit assessment of eribulin was carried out in relation to its approved indication of:

"Treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapeutic regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane, unless patients were not suitable for these treatments" [1].

In accordance with the specification of the G-BA, the company designated the following as ACT:

Individual, patient-tailored chemotherapy using the following treatments:

- monotherapy with capecitabine, 5-fluorouracil, vinorelbine, or,
- if suitable, further treatment containing an anthracycline or taxane.

The objective of this report is therefore to assess the added benefit of eribulin compared with the above-mentioned ACT.

The assessment was carried out in respect of patient-relevant outcomes. Only randomized, controlled trials with a direct comparator were included in the assessment.

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

2.3 Information retrieval and study pool

The study pool of the assessment was compiled from the following data:

- Studies on eribulin in breast cancer completed by the company up to 23.08.2011 (company list of studies);
- Results of a bibliographical literature search and a search in trial registries for studies on eribulin (01.09.2011 in trial registries, 02.09.2011 in bibliographical databases, company searches);
- The Institute's own searches in trial registries for studies on eribulin on 21.11.2011 to check the company's search results. No other relevant trial was identified.

The resulting study pool corresponded to that used by the company. However, the single trial discussed by the company was only partly relevant for the benefit assessment (see also Section 2.3.1 below).

Further information about the inclusion criteria for studies in the 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 Studies included in the assessment

The approval study E7389-G000-305 listed in the following table with the study name EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice vs. Eribulin) was included in the benefit assessment.

Table 1: Study pool – RCT with the drug to be assessed; direct comparison of eribulin vs. TPC

Study	Study category		
	Pivotal study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
EMBRACE (E7389-G000-305)	yes	yes	no
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. RCT: randomized controlled trial; TPC: treatment of physician's choice			

The study pool for the benefit assessment of eribulin corresponds to that of the company. However, only the results of a subpopulation of the EMBRACE study are relevant for the assessment of eribulin in comparison with the ACT of the G-BA and the company. The main reason is that the patients in the comparator group of the study did not solely receive the specified ACT, but could be given various other treatments as well. The subpopulation relevant for the benefit assessment comprises those patients from the eribulin or comparator group who, on allocation to the comparator group, would have or had received the ACT. Such evaluations are inherently possible because for all patients, before randomization a physician chose the treatment to be given if they were allocated to the comparator group (see explanations about the study design in Section 2.7.2.4.1 of the full dossier assessment). Such analyses were not, however, submitted by the company in its dossier.

Although the company adhered to the ACT specified by the G-BA, through the wording of its research question and the inclusion criteria of the dossier, it also permitted other treatments as comparator therapy for eribulin. In its benefit assessment, the company therefore considered the results and subgroup analyses for the whole population of the study. There are no data on the relevant subpopulation of patients. The Institute does not accept the company's approach.

For the present benefit assessment, the results concerning the outcome "overall survival" for the relevant subpopulation are shown below. To provide an impression of the results regarding possible harm from eribulin compared to the ACT and to thereby increase the transparency of the assessment, the results on adverse events of the whole population are also shown. No such data are available for the relevant subpopulation.

Peripheral neuropathy was the only specific harmful event outcome whose results are also partially presented by the company for the relevant subpopulation – though these are

restricted to those of patients who would have received taxanes (from the eribulin group) or had received them (from the comparator group). It is insufficient to consider solely this specific outcome in order to derive conclusions about the risk of harm from eribulin.

Section 2.6 contains a list of data sources named by the company for the studies included in its assessment.

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

2.3.2 Study characteristics

Characteristics of the study and the interventions

Table 2 and Table 3 describe the EMBRACE study. EMBRACE was a randomized, open-label study with a direct comparator, in which adult women with locally advanced or metastatic breast cancer were enrolled. The patients had been pretreated with at least 2 and not more than 5 chemotherapy regimens and had shown progression within 6 months of the latest chemotherapy. The previous treatments had to have contained an anthracycline and a taxane, provided these were not contraindicated.

In the study patients were randomly allocated (2:1) to treatment with eribulin (508 patients) or to patient-individualized treatment of physician's choice (TPC, 254 patients). The TPC options were single-agent chemotherapy, hormonal treatment, biological treatment (approved for the treatment of cancer), palliative treatment 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 study treatment was administered according to a regimen corresponding to that described in the Summary of Product Characteristics (Table 3 and [1]). Eribulin treatment consisted of 21-day cycles. The comparator treatments were given according to local practice. 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 or the patient requested to discontinue.

The primary analysis was initially planned for the time when 411 (approx. 54%) of the patients had died. The regulatory authorities requested an additional update analysis for the outcome "overall survival" after 75% of patients had died. This was carried out after 589 deaths (77%).

Overall survival was recorded as the primary outcome of the study. Adverse events were the secondary outcome relevant for the benefit assessment.

Characteristics of the study population

Table 4 shows the characteristics of patients in the EMBRACE study. There were no relevant differences between the treatment groups. The median age of patients was approx. 55 years;

the overwhelming majority of patients (approx. 90%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The HER2 status was negative in approx. 75% of patients.

The risk of bias at study level

The risk of bias at study level is shown in Table 5. It was rated as low for the EMBRACE study included in the assessment. This concurs with the company's assessment.

Table 2: Characteristics of the study included in the assessment – RCT for the direct comparison eribulin vs. TPC

Study	Study design	Population	Interventions (number of randomized patients)	Duration of study	Location and period of study	Primary outcome; secondary outcomes[a]
EMBRACE	RCT, open-label, parallel, active-controlled	Women with locally advanced or metastatic breast cancer, who had been previously treated with at least 2 and not more than 5 chemotherapy regimens and who had shown progression within 6 months of the latest chemotherapy. The previous treatments had to have included an anthracycline and a taxane, provided there were no contraindications.	Eribulin (N = 508) of whom[b]: 77 planned for capecitabine 121 planned for vinorelbine 70 planned for taxanes 73 planned for anthracyclines TPC (N = 254) of whom[b]: 45 capecitabine 65 vinorelbine 41 taxanes 24 anthracyclines	The primary analysis was planned for the time at which 411 patients had died.[c] In addition, an update analysis was carried out for the outcome ”overall survival” (following a request of the regulatory authorities) at 75% deaths; it was undertaken after 589 (77%) deaths	135 centres in 19 countries 11/2006 – 05/2009[c] or 03/2010[d]	Primary: overall survival (OS) Secondary: adverse events

a: Extracted primary outcome criteria contain information without consideration of relevance for this benefit assessment. Extracted secondary outcome criteria contain exclusively information on the relevant available outcomes for this benefit assessment.
b: This subpopulation is relevant for the benefit assessment. The data refer to the ITT population.
c: Original data cut-off.
d: Updating of the analysis of the outcome “overall survival”.
N: number of patients; OS: overall survival; RCT: randomized controlled trial; TPC: treatment of physician’s choice

Table 3: Characteristics of the interventions – RCT for the direct comparison eribulin vs. TPC

Study	Eribulin[a]	TPC[a]
EMBRACE	1.4 mg eribulin mesylate (equiv. to 1.23 mg eribulin)/m^2 body surface area, intravenously, within 2–5 minutes on days 1 and 8 of a 21-day cycle	Patient-individualized treatment ▪ chemotherapy as single agent therapy ▪ hormonal therapy ▪ biological (approved for cancer treatment) therapy ▪ palliative therapy ▪ radiotherapy In each case given according to local practice
a: Patients were treated until unacceptable toxicity or progression occurred or until the physician considered discontinuation was in the patient's interest or the patient requested to discontinue. Participants showing "clinical benefit" could continue treatment as long as this persisted. RCT: randomized controlled trial; TPC: treatment of physician's choice		

Table 4: Characteristics of the study population – RCT for the direct comparison eribulin vs. TPC

Study Characteristic	Eribulin N = 508	TPC N = 254
EMBRACE		
Age (years) Median (range)	55 (28–85)	56 (27–81)
ECOG performance status, n (%)[a]		
0	217 (43 %)	103 (41 %)
1	244 (48 %)	126 (50 %)
2	39 (8 %)	22 (9 %)
HER2 status, n (%)		
Positive	83 (16 %)	40 (16 %)
Negative	373 (73 %)	192 (76 %)
Unknown	4 (1 %)	0 (0 %)
Not done	48 (9 %)	22 (9 %)
a: Information about ECOG performance status only available for 500 patients (eribulin group) and for 251 patients (TPC group). Percentages relate to 508 and 254 patients respectively. ECOG: Eastern Cooperative Oncology Group; HER2: Human Epidermal Growth Factor Receptor 2; N: number of randomized patients; n: number of patients in a category; RCT: randomized controlled trial; TPC: treatment of physician's choice		

Table 5: Risk of bias at study level – RCT for the direct comparison eribulin vs. TPC

Study	Random sequence generation	Allocation concealment	Blinding		Selective reporting	Other sources of bias	Risk of bias at study level
			Participants	Personnel			
EMBRACE	yes	yes	no	no	no	no	low
RCT: randomized controlled trial; TPC: Treatment of Physician´s Choice							

Further information about the study design, study population and risk of bias at study level can be found in Module 4 Sections 4.3.1.2 and 4.3.1.2.2 of the dossier and in Sections 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.

2.4 Results concerning added benefit

This assessment covers the following patient-relevant outcomes (for more detailed reasoning, see Section 2.7.2.4.3):

- Overall survival
- Health-related quality of life
- Adverse events

Table 6 shows the data available for the particular outcomes in the study included in the assessment. Table 7 provides the risk of bias for these outcomes. The risk of bias for the outcomes "overall survival" and "adverse events" was classed as low. In the case of the former outcome, this corresponds to the company’s assessment. For the outcome "adverse events", this deviates from the company’s assessment, which rated the risk of bias as high. An explanation of how the risk of bias was evaluated can be found in Section 2.7.2.4.2 of the full assessment.

Table 6: Outcome matrix – RCT for the direct comparison eribulin vs. TPC

Outcome / Study	Overall survival	Quality of life	Adverse events: Overall rate of AEs	Adverse events: CTCAE Grade 3 and 4 AEs	Adverse events: Serious AEs	Adverse events: Discontinuation due to AE
EMBRACE	yes	no[a]	(yes)[b]	(yes)[b]	(yes)[b]	(yes)[b]

a: The study did not record health-related quality of life.

b: There are no data for the relevant subpopulation of the study and hence not for subgroups of this subpopulation either (see Sections 2.3.1 and 2.4 of this assessment). The benefit assessment additionally presents the results on adverse events for the whole population of the study.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; RCT: randomized controlled trial; TPC: Treatment of Physician´s Choice

Table 7: Risk of bias at study and outcome level – RCT for the direct comparison eribulin vs. TPC

Outcome / Study	Study level	Overall survival	Quality of life	Adverse events: Overall rate of AEs	Adverse events: CTCAE Grade 3 and 4 AEs	Adverse events: Serious AEs	Adverse events: Discontinuation due to AE
EMBRACE	low	low	–[a]	low[b]	low[b]	low[b]	low[b]

a: Outcome was not recorded.

b: There are no data for the relevant subpopulation of the study and hence not for subgroups of this subpopulation either (see Sections 2.3.1 and 2.4 of this assessment). The benefit assessment additionally presents the results on adverse events for the whole population of the study.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; RCT: randomized controlled trial; TPC: Treatment of Physician´s Choice

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

Only results for the outcome “overall survival” are available for the relevant subpopulation of the EMBRACE study. The study did not record the outcome “health-related quality of life”. No results are available for the complex “adverse events” for the relevant subpopulation of the study. Therefore the respective results for the entire study population are additionally

shown, in order to give an overall impression of possible harm from eribulin in comparison with the ACT.

Overall survival

Data for the patients of the eribulin and comparator group who would have received capecitabine, vinorelbine or the previous taxane or anthracycline-containing treatment on allocation to the comparator group were available for evaluating the outcome "overall survival". The results for those patients who, according to the choice of the physician, would have or had received 5-fluorouracil were not evaluated separately in the study, but together with "other treatment options". However, from the details in the study it is clear that only one patient in the comparator group had received 5-fluorouracil and hence this has no relevant effect on the overall result. Therefore the results for the drugs / drug classes capecitabine, vinorelbine, taxanes and anthracyclines are considered below.

The study initially planned to carry out an analysis after 411 events (deaths) (approx. 54%) (primary analysis). The regulatory authorities requested a second, updated analysis at the time of 75% events (deaths) so that results over a longer period could be considered. This updated analysis took place after 589 deaths (77%). The results obtained at both these times were used for the benefit assessment

Table 8 shows the results for the outcome "overall survival" (primary and updated analyses) for the comparison of eribulin with the ACT (relevant subpopulation).

Table 8: Results on overall survival in the relevant subpopulation – RCT for the direct comparison eribulin vs. TPC – results separated according to drug/drug class used

	Eribulin		TPC		Eribulin vs. TPC	
	N[a]	n (%)	N[a]	n (%)	HR[b] [95% CI]	p-value[c]
Overall survival (Primary analysis)						
Capecitabine	77		45			
Dead		35 (45.5)		24 (53.3)		
Censored		42 (54.5)		21 (46.7)		
		KM [95% CI]		**KM [95% CI]**		
Median survival [days]		446.0 [356.0; n. e.]		346.0 [303.0; n. e.]	0.68 [0.38; 1.23]	0.201
Vinorelbine	121		65			
Dead		62 (51.2)		40 (61,5)		
Censored		59 (48.8)		25 (38.5)		
		KM [95% CI]		**KM [95% CI]**		
Median survival [days]		421.0 [288.0; 537.0]		255.0 [191.0; 380.0]	0.63 [0.42; 0.96]	0.030
Taxanes	70		41			
Dead		42 (60.0)		19 (46.3)		
Censored		28 (40.0)		22 (53.7)		
		KM [95% CI]		**KM [95% CI]**		
Median survival [days]		365.0 [261.0; 480.0]		493.0 [272.0; n. e.]	1.48 [0.83; 2.65]	0.184
Anthracyclines	73		24			
Dead		42 (57.5)		14 (58.3)		
Censored		31 (42.5)		10 (41.7)		
		KM [95% CI]		**KM [95% CI]**		
Median survival [days]		373.0 [343.0; 458.0]		319.0 [256.0; n. e.]	0.98 [0.51; 1.88]	0.955

(continued on next page)

Table 8: Results on overall survival in the relevant subpopulation – RCT for the direct comparison eribulin vs. TPC – results separated according to drug/drug class used (continued)

	Eribulin		TPC		Eribulin vs. TPC	
	N[a]	n (%)	N[a]	n (%)	HR[b] [95% CI]	p-value[c]
Overall survival (Updated analysis)						
Capecitabine	77		45			
Dead		47 (61.0)		35 (77.8)		
Alive[d]		27 (35.1)		9 (20.0)		
Unknown[e]		3 (3.9)		1 (2.2)		
		KM [95% CI]		**KM [95% CI]**		
Median survival [days]		482.0 [365.0; 656.0]		340.0 [303.0; 535.0]	0.56 [0.34; 0.92]	0.022
Vinorelbine	121		65			
Dead		98 (81.0)		50 (76.9)		
Alive[d]		22 (18.2)		12 (18.5)		
Unknown[e]		1 (0.8)		3 (4.6)		
		KM [95% CI]		**KM [95% CI]**		
Median survival [days]		384.0 [301.0; 489.0]		255.0 [191.0; 385.0]	0.83 [0.58; 1.19]	0.304
Taxanes	70		41			
Dead		56 (80.0)		31 (75.6)		
Alive[d]		13 (18.6)		10 (24.4)		
Unknown[e]		1 (1.4)		0 (0)		
		KM [95% CI]		**KM [95% CI]**		
Median survival [days]		380.0 [264.0; 480.0]		396.0 [266.0; 527.0]	1.19 [0.75; 1.90]	0.463
Anthracyclines	73		24			
Dead		55 (75.3)		20 (83.3)		
Alive[d]		17 (23.3)		4 (16.7)		
Unknown[e]		1 (1.4)		0 (0)		
		KM [95% CI]		**KM [95% CI]**		
Median survival [days]		410.0 [344.0; 484.0]		333.5 [256.0; 689.0]	0.96 [0.56; 1.67]	0.892

a: Number of patients of the relevant subpopulation. In the eribulin group the treatment shown is that which was planned for patients to receive had they been allocated to the TPC group.
b: Hazard ratio based on Cox model, adjusted for HER2/neu status, previous capecitabine treatment and geographical region.
c: p-value of stratified log-rank test.
d: Up to second (updated) analysis.
e: Patients lost to follow-up or who had withdrawn their consent.
CI: confidence interval; HR: hazard ratio; KM: Kaplan-Meier estimator; N: number of relevant subpopulation; n: number of patients of relevant subpopulation with event; n. e.: not estimable due to insufficient events; TPC: treatment of physician's choice

Out of necessity, the data available for the study from Table 8 were supplemented by the Institute's own calculations. All of these calculations were carried out for the primary as well as the updated analysis. First of all, the results of patients who would have or had received the drugs of the ACT (capecitabine, vinorelbine, taxanes, anthracyclines), were summarized. Figures relating to these analyses are available in Appendix A. There was no statistically significant difference between the eribulin and comparator group at the time of either the primary or the updated analysis. However, both analyses showed a high degree of heterogeneity. Hence an overall conclusion about all drugs did not appear meaningful. On reviewing the analyses, it is apparent that the cause of the heterogeneity can be explained by the option for patients to receive further treatment with taxanes or anthracyclines. On the basis of this assumption, patients in the relevant subpopulation of the EMBRACE study were divided into the following two subgroups: patients for whom treatment with taxanes or anthracyclines was no longer an option and those in whom further treatment with taxanes or anthracyclines was still possible. Separate evaluations were carried out for these subgroups. In each case, the results of these analyses were homogeneous (for Figures, see Appendix A).

The results of both analyses (primary and updated) for the subgroup of patients in whom further treatment with taxanes or anthracyclines was still possible, did not show a statistically significant difference between the eribulin group and the comparator group. Hence there is no proof of added benefit of eribulin for this subgroup. For the subgroup of patients for whom taxanes or anthracyclines was no longer an option, there was a statistically significant result in favour of capecitabine / vinorelbine (hazard ratio 0.65; 95% CI [0.46; 0.91]; p = 0.013) at the primary analysis. However the result was no longer statistically significant at the updated analysis (hazard ratio 0.71; 95% CI [0.49; 1.02]; p = 0.067). Overall, this gives a "hint" of added benefit of eribulin for the subgroup of patients for whom treatment with a taxane or an anthracycline was no longer an option.

In summary, there is no proof of added benefit for the outcome "overall survival" for the subgroup of patients in whom further treatment with taxanes or anthracycline was still possible (comparison of eribulin with taxanes / anthracyclines). For the subgroup of patients for whom this option no longer existed (comparison of eribulin with capecitabine / vinorelbine), there is a "hint" of added benefit of eribulin. This assessment differs markedly from that of the company, which sees proof of a major added benefit of eribulin for the entire target population.

Quality of life

The outcome "quality of life" was not recorded in the study.

Adverse events

There are no relevant results for the complex "adverse events" for the subpopulation of interest for the study (comparison with ACT) and hence not for possible relevant subgroups of patients either. Peripheral neuropathy is an exception for which such data were available and which the company showed solely for the comparison with taxanes in its assessment (see

Section 2.3.1). However the results on peripheral neuropathy are not sufficient by themselves for a consideration of the risk of harm from eribulin in comparison with the ACT.

The report of the EMBRACE study also compared the results on adverse events of the entire eribulin group with the respective results of the individual classes of drugs of the comparator group (capecitabine, vinorelbine, taxanes, anthracyclines). No valid conclusions can be drawn about the risk of harm from eribulin on the basis of these evaluations either. This is because the eribulin group includes patients with different characteristics in terms of the state of the disease or risk. This is also reflected in the fact that before randomization, after assessment by a physician different treatments were specified for patients when allocating them to the comparator group.. Therefore a comparison between the eribulin group, which combines all risk groups, and the individual drug classes of the comparator group is inappropriate.

Therefore the results of the entire study population are discussed in addition below, in order to obtain an impression of possible harm from eribulin compared to the ACT. Table 9 shows the relevant results.

Table 9: Results on adverse events (whole population) – RCT for the direct comparison eribulin vs. TPC

	Eribulin		TPC		Eribulin vs. TPC	
Adverse events[a]	**Total N**	**n (%)**	**Total N**	**n (%)**	**RR[b] [95% CI]**	**p-value[c]**
AEs	503	497 (98.8)	247	230 (93.1)	1.06 [1.02; 1.10]	< 0.001
Severe AEs[d]						
CTCAE Grade 3	503	308 (61.2)	247	114 (46.2)	1.33 [1.14; 1.54]	< 0.001
CTCAE Grade 4	503	148 (29.4)	247	33 (13.4)	2.20 [1.56; 3.11]	< 0.001
SAEs	503	126 (25.0)	247	64 (25.9)	0.97 [0.75; 1.25]	0.818
Discont. due to AEs	503	67 (13.3)	247	38 (15.4)	0.87 [0.60; 1.25]	0.452

a: AEs were recorded during treatment with the study medication and for 30 days afterwards. They were not recorded over the full follow-up period of the study.
b: Own calculation, asymptotic.
c: Own calculation, unconditional exact test (CSZ method according to [2]).
d: AEs of Common Terminology Criteria for Adverse Events (CTCAE) Grades 3 and 4 (Grade 3 = serious and Grade 4 = life-threatening or disabling).

AE: adverse event ; CI: confidence interval; CSZ: convexity, symmetry, z-score; CTCAE: Common Terminology Criteria for Adverse Events; N: number of all patients; n: number of patients with event; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; TPC: treatment of physician's choice;

There was a difference to the disadvantage of eribulin in the overall rate of adverse events and also in severe adverse events (CTCAE Grades 3 and 4). In each case, the result was statistically significant.

The proportion of patients with serious adverse events and adverse events that led to discontinuation of the study did not differ substantially between the eribulin and the comparator group. In each case, the result was not statistically significant.

In summary, greater harm from eribulin compared with the ACT cannot be excluded. There are no relevant evaluations in the company's dossier that would enable definitive conclusions to be drawn about the effect strength or whether there is greater harm for all groups of patients, or whether – as is the case with overall survival – different conclusions must be drawn for the different patient groups.

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

Subgroups

No subgroup analyses are available for the relevant subpopulation of the study included in the assessment or for the relevant subgroups of this subpopulation.

The company presents the results of various pre-defined subgroups for the outcome "overall survival" for the whole study population (see also Section 2.7.2.2). There are no interaction tests. Noteworthy numerical differences in terms of the treatment effect were shown for the following characteristics (information restricted to the second, updated analysis and to characteristics in which the subgroups each contained at least 10% of the total population):

- Age
- Metastatic sites

It would have been meaningful to carry out corresponding subgroup analyses for the relevant subpopulation of the study or for the relevant subgroups of this subpopulation, both for "overall survival" and for the individual outcomes of the complex "adverse events".

2.5 Extent and probability of the added benefit

Derivation of the extent and probability of added benefit is discussed below for each indication at outcome level, taking into account outcome categories and effect sizes. The methods used are explained in Appendix A of Benefit Assessment A11-02 [3].

The procedure for formulating an overall conclusion regarding added benefit based on the aggregation of the conclusions derived at outcome level is a proposal from IQWiG. The decision regarding added benefit is made by the G-BA.

2.5.1 Evaluation of added benefit at outcome level

An assessment of the extent of added benefit at outcome level from the data presented in Section 2.4 can be found in Table 10.

Table 10: Extent of added benefit at outcome level – comparison eribulin vs. TPC

	Effect estimator [95 % CI] / Event proportion eribulin vs. TPC (relevant subpopulation) / p-value / probability[a]	**Derivation of extent[b]**
Overall survival	**Patients for whom taxanes or anthracyclines were no longer an option** **Eribulin vs. capecitabine / vinorelbine** ▪ Primary analysis: HR 0.65 [0.46; 0.91]; p = 0.013 ▪ Updated analysis: HR 0.71 [0.49; 1.02]; p = 0.067 Combined conclusion from both analyses: Probability: "hint" **Patients in whom repeat treatment with taxanes or anthracyclines was still possible** **Eribulin vs. taxanes / anthracyclines** ▪ Primary analysis: HR 1.23 [0.80; 1.90]; p = 0.344 ▪ Updated analysis: HR 1.09 [0.76; 1.55]; p = 0.637	**Eribulin vs. capecitabine / vinorelbine** Combined conclusion from both analyses: added benefit, extent: "non-quantifiable", at best "considerable"[c] **Eribulin vs. taxanes / anthracyclines** added benefit / greater risk of harm not proven
Health-related quality of life	No data available	lesser benefit / added benefit not proven
Adverse events ▪ Overall rate of AEs ▪ Severe AEs CTCAE Grade 3 CTCAE Grade 4 ▪ Serious AEs ▪ Discont. due to AEs	**Results for total population:** RR[d] 1.06 [1.02; 1.10]; p < 0.001[e] RR[d] 1.33 [1.14; 1.54]; p < 0.001[e] RR[d] 2.20 [1.56; 3.11]; p < 0.001[e] RR[d] 0.97 [0.75; 1.25]; p = 0.818[e] RR[d] 0.87 [0.60; 1.25]; p = 0.452[e]	No data on relevant subpopulation available

a: Probability, if statistically significant differences are present.
b: Estimations of effect size are made depending on outcome category with different limits based on upper limit of the confidence interval (CI_0).
c: Added benefit "non-quantifiable", because result is not significant at updated analysis. In view of the result at the primary analysis (upper limit of 95% CI is 0.91) the extent of added benefit can, however, at best be "considerable".
d: Own calculation, asymptotic.
e: Own calculation, unconditional exact test (CSZ method according to [2]) .

2.5.2 Overall conclusion on added benefit

The overall conclusion about the extent of added benefit must compare the positive and negative effects of eribulin. In the process, two subgroups of patients are to be considered separately.

- **Patients for whom treatment with taxanes or anthracyclines is no longer an option:** In respect of the positive effects, there is a "hint" of an added benefit of eribulin for the outcome "overall survival". Because of the heterogeneous results at the two analyses times, the extent is "non-quantifiable". However, in view of the statistically significant result at the primary analysis, the added benefit can at best be "considerable". As regards the negative effects, greater harm from eribulin cannot be excluded. In terms of the complex "adverse events", the company did not present any data for the patient group of interest. Since this also affects severe adverse events, it cannot be ruled out that the negative effects outweigh the positive effects. An added benefit of eribulin is therefore not proven for this group of patients.
- **Patients in whom further treatment with taxanes is still possible:** No positive effects of eribulin are demonstrated for this group of patients. However greater harm from eribulin cannot be excluded, because the company did not present any data on the complex "adverse events" for the patient group of interest. Hence a lesser benefit of eribulin in comparison with the ACT cannot be ruled out. An added benefit of eribulin for this group of patients is not proven.

2.6 List of included studies

EMBRACE Study

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 no E7389-G000-305; clinical study report [unpublished]. 2010.

Eisai. The "EMBRACE" trial: a phase III open label, randomized parallel two-arm multi centre 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 no E7389-G000-305; statistical analysis plan [unpublished]. 2010.

Eisai. The "EMBRACE" trial: Eisai Metastatic Breast Cancer Study Assessing Physician`s Choice Versus E7389; a phase III open label, randomized parallel two-arm multi centre 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 no E7389-G000-305; overall survival update [unpublished]. 2010.

Cortes J, O'Shaughnessy J, Loesch D, Blum JL, Vahdat LT, Petrakova K et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet 2011; 377(9769): 914-923.

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(for English extract; please see full dossier assessment for full reference list)

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3) Institute for Quality and Efficiency in Health Care. Ticagrelor: Benefit assessment according to § 35a Social Code Book V; extract of dossier assessment; Commission No. A11-02 [online]. 29.09.2011 [Accessed on: 05.05.2012]. URL: https://www.iqwig.de/download/A11-02_Extract_of_dossier_assessment_Ticagrelor.pdf

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