IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. 14-47

Eribulin (Addendum to Commission A14-25)[1]

Addendum

Commission: A14-47
Version: 1.0
Status: 5 January 2015

[1] Translation of addendum A14-47 *Eribulin (Addendum zum Auftrag A14-25*) (Version 1.0; Status: 5 January 2015). 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.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Eribulin (Addendum to Commission A14-25)

Commissioning agency:
Federal Joint Committee

Commission awarded on:
10 December 2014

Internal Commission No.:
A14-47

Address of publisher:
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Keywords: eribulin, breast neoplasms, benefit assessment

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Abbreviation	Meaning
AE	adverse event
DGHO	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (German Society of Haematology and Medical Oncology)
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)
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
TPC	treatment of physician's choice

1 Background

On 10 December 2014, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A14-25 (Eribulin – Benefit assessment according to §35a Social Code Book [SGB] V [1]).

The 2 studies E7389-G000-301 (hereinafter referred to as "Study 301") on the comparison of eribulin versus capecitabine, and E7389-G000-305 (EMBRACE, hereinafter referred to as "EMBRACE" study) on the comparison of eribulin with patient-individualized treatment of physician's choice (TPC) in patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease, were included. The conclusions on the added benefit of eribulin from these studies were limited to the group of human epidermal growth factor receptor 2 (HER2/neu)-negative patients because the results of patients with HER2/neu-positive breast cancer and with unknown HER2/neu status cannot be transferred to the present research questions [1].

The G-BA commissioned IQWiG to conduct an assessment of the study results of the studies 301 and EMBRACE without limiting the subpopulations specified by the G-BA, "patients for whom taxanes or anthracyclines are no longer an option" and "patients for whom repeated treatment containing an anthracycline or a taxane is an option" to HER2-negative patients and without excluding patients with HER2-positive or unknown status. The study results were to be presented without separate consideration of the HER2 status of the patients in the subpopulations.

In the commenting procedure, the pharmaceutical company (hereinafter abbreviated to "the company"), with its comment, additionally submitted supplementary information to the G-BA for the proof of added benefit [2], which went beyond the information in the dossier [3]. On the one hand, this was information subsequently submitted on the outcome "discontinuation due to adverse events (AEs)". In dossier assessment A14-25, this outcome was allocated to the outcome category "non-severe/non-serious AEs" because of the small proportion of serious AEs (SAEs) in the EMBRACE study that resulted in discontinuation. The company subsequently submitted data in the comment, from which it was clear, according to the company, that the outcome "discontinuation due to AEs" is to be allocated to the outcome category "severe/serious". On the other hand, the company presented analyses on the outcome "overall survival" on the basis of a new data cut-off of the EMBRACE study (2 September 2014). The G-BA's commission therefore also comprised the assessment of this information on the outcome "discontinuation due to AEs" subsequently submitted and of the analyses on overall survival of the EMBRACE study subsequently submitted.

The responsibility for the present assessment and the results of the assessment lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Analyses without consideration of the patients' HER2 status

In accordance with the commission, the analyses of the studies 301 and EMBRACE on the research questions A (patients for whom taxanes or anthracyclines are no longer an option) and B (patients for whom repeated treatment containing an anthracycline or a taxane is an option) are presented in the following Sections without consideration of the patients' HER2/neu status. A description of the studies and of the outcomes considered can be found in dossier assessment A14-25 [1].

As specified by the G-BA for research questions A and B, it is assumed for patients with HER2/neu-positive breast cancer that 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. As already described in dossier assessment A14-25 however, presumably a high proportion of HER2/neu-positive patients was included in the 2 studies 301 and EMBRACE in whom the anti-HER2/neu treatment according to current standard of HER2/neu-positive breast cancer treatment was not yet carefully considered. The HER2/neu-positive patients in Study 301 (≥ second line of treatment) and EMBRACE (≥ third line of treatment) partly had been exclusively pretreated with trastuzumab and partly had even received no anti-HER2 treatments at all in their pretreatment. The German Society of Haematology and Medical Oncology (DGHO) has also confirmed the current importance of anti-HER2 treatments. It was clear from its comment on dossier assessment A14-25 that other targeted drugs with good efficacy have become available for HER2/neu-positive patients, and that treatment with eribulin (as described also by the G-BA) should only be conducted after the anti-HER2 treatment options have been used [4]. The results on the HER2/neu-positive patients with limited anti-HER2 treatment who were included in the 2 studies were considered to be not transferable to the ones according to the research question (after using the anti-HER2 treatment options).

Hence, from the Institute's point of view, the analyses without consideration of the HER2/neu status presented below cannot be interpreted in a meaningful way for the assessment of the added benefit of eribulin.

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

The following tables (Table 1 to Table 3) present the results for research question A on the comparison of eribulin with capecitabine or vinorelbine. Their structure corresponds to Tables 15 to 17 of dossier assessment A14-25, but the analyses comprise all patients, irrespective of their HER2/neu status. For Study 301, the results are shown for the population of patients in the target population, presented by the company in Module 4 of the dossier, who had received at least 1 chemotherapeutic regimen for the treatment of advanced or metastatic disease according to the approval of eribulin [5]. For the outcome "overall survival", the results of the EMBRACE study at the data cut-off from 2 September 2014 subsequently

submitted with the comment were supplemented. Correspondingly, the results at this data cut-off were included in the meta-analysis on overall survival for the EMBRACE study.

Table 1: 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

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]	p-value
Overall survival						
Study 301 (3/2012)	438	487 [ND]	444	441 [ND]	0.87 [0.75; 1.01][a]	0.059[b]
EMBRACE (5/2009)	198	421 [ND]	110	321 [ND]	0.65 [0.47; 0.90][a]	0.010[b]
EMBRACE (3/2010)	198	435 [ND]	110	309 [ND]	0.72 [0.54; 0.96][a]	0.024[b]
EMBRACE (9/2014)	198	435 [ND]	110	309 [ND]	0.79 [0.61; 1.02]	0.038[b]
Total[c]					0.85 [0.75; 0.97][d]	0.013[d]
Adverse events						
AEs						
Study 301 (3/2012)		ND		ND	ND	ND
EMBRACE (5/2009)		ND		ND	ND	ND
SAEs						
Study 301 (3/2012)	429	NC	442	NC	0.77 [0.56; 1.05][e]	0.085[b]
EMBRACE (5/2009)	195	NC	105	NC	0.76 [0.47; 1.25][e]	0.306[b]
Total					0.77 [0.59; 1.00][d]	0.049[d]
Discontinuation due to AEs						
Study 301 (3/2012)	429	NC	442	NC	0.67 [0.43; 1.04][e]	0.050[b]
EMBRACE (5/2009)	195	NC	105	NC	0.83 [0.39; 1.77][e]	0.771[b]
Total					0.71 [0.48; 1.04][d]	0.075[d]
Severe AEs (CTCAE grade 3 and 4)						
Study 301 (3/2012)	429	39 [ND]	442	192 [ND]	2.00 [1.66; 2.42][e]	< 0.001[b]
EMBRACE (5/2009)	195	40 [ND]	105	99 [ND]	1.41 [1.02; 1.94][e]	0.035[b]
Total					heterogeneity: Q = 3.38; df = 1; p = 0.066; I^2 = 70.4%[d]	

(continued)

Table 1: 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 (continued)

a: Cox proportional hazards model with HER2/neu status, capecitabine pretreatment and geographical region as strata.
b: Log-rank test stratified by HER2/neu status and geographical region (planned analysis).
c: Meta-analysis from values at the 3/2012 data cut-off of Study 301 and values at the 9/2014 data cut-off of the EMBRACE study.
d: Meta-analysis, Institute's calculation.
e: Cox proportional hazards model with number of organs involved and ER status as co-factors and HER2/neu status and geographical region as strata.

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 2: Results on morbidity (symptoms) – RCT, direct comparison: eribulin vs. capecitabine for patients for whom treatment with taxanes or anthracyclines is no longer an option

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	353	38.1 [35.8; 40.3]	−0.30 [−2.4; 1.8]	344	39.4 [37.1; 41.7]	0.63 [−1.6; 2.8]	−0.93 [−3.8; 1.9] ND
Nausea and vomiting	352	9.9 [8.2; 11.7]	0.44 [−1.3; 2.2]	343	10.7 [8.9; 12.6]	3.95 [2.2; 5.7]	−3.51 [−5.8; −1.2]; ND Hedges' g −0.21 [−0.36; −0.06][d]
Pain	353	31.6 [28.9; 34.2]	−2.79 [−5.2; −0.4]	346	34.5 [31.7; 37.3]	−4.27 [−6.7; −1.8]	1.48 [−1.7; 4.7] ND
Dyspnoea	350	24.8 [22.2; 27.5]	−0.51 [−3.0; 2.0]	338	25.8 [23.0; 28.6]	−1.39 [−4.0; 1.2]	0.88 [−2.5; 4.2] ND
Insomnia	350	30.9 [28.1; 33.8]	−3.30 [−6.0; −0.6]	341	32.3 [29.3; 35.3]	−5.04 [−7.8; −2.3]	1.75 [−1.8; 5.3] ND
Appetite loss	352	20.2 [17.5; 22.8]	1.01 [−1.6; 3.6]	344	24.0 [21.1; 26.8]	2.46 [−0.2; 5.1]	−1.45[−4.9; 2.0]; ND
Constipation	348	13.0 [10.7; 15.2]	0.95 [−1.4; 3.3]	339	14.4 [11.9; 16.9]	0.71 [−1.7; 3.1]	0.25 [−2.9; 3.4] ND
Diarrhoea	346	8.7 [7.0; 10.3]	−0.84 [−2.9; 1.2]	338	8.9 [7.2; 10.6]	5.03 [2.9; 7.1]	−5.87 [−8.7; −3.1]; ND Hedges' g −0.30 [−0.45; −0.15][d]
Financial difficulties[e]	348	32.2 [29.0; 35.5]	−3.05 [−5.9; −0.2]	342	29.9 [26.8; 33.0]	−4.49 [−7.4; −1.6]	1.44 [−2.3; 5.2] ND

(continued)

Table 2: Results on morbidity (symptoms) – RCT, direct comparison: eribulin vs. capecitabine for patients for whom treatment with taxanes or anthracyclines is no longer an option (continued)

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
EORTC QLQ-BR23[c]							
AEs of systemic treatment	346	22.2 [20.6; 23.7]	3.27 [1.7; 4.8]	343	24.6 [22.9; 26.3]	−2.06 [−3.6; −0.5]	5.33 [3.3; 7.4]; ND Hedges' g 0.36 [0.21; 0.51][d]
Breast symptoms	341	18.6 [16.5; 20.8]	−2.74 [−4.3; −1.2]	338	20.6 [18.2; 23.0]	−2.86 [−4.5;-1.2]	0.12 [−2.0; 2.2] ND
Arm symptoms	344	25.0 [22.5; 27.5]	−3.05 [−5.0; −1.1]	340	27.3 [24.7; 29.8]	−2.41 [−4.4; −0.5]	−0.63 [−3.2; 1.9] ND
Burden of alopecia	No evaluable data[f]						

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 3: 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

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	343	56.1 [54.0; 58.3]	−0.58 [−2.6; 1.5]	335	54.0 [52.0; 56.0]	1.38 [−0.7; 3.5]	−1.97 [−4.7; 0.8] ND
Physical functioning	353	71.8 [69.9; 73.8]	0.12 [−1.7; 1.9]	344	71.0 [69.0; 73.0]	−1.09 [−2.9; 0.7]	1.21 [−1.2; 3.6] ND
Role functioning	352	73.0 [70.4; 75.6]	−0.67 [−3.2; 1.8]	343	69.2 [66.4; 72.0]	−2.81 [−5.4; −0.2]	2.14 [−1.2; 5.5] ND
Emotional functioning	351	69.7 [67.5; 71.9]	3.83 [1.8; 5.9]	345	68.1 [65.8; 70.4]	2.92 [0.8; 5.0]	0.92 [−1.8; 3.6] ND
Cognitive functioning	351	81.3 [79.4; 83.2]	0.16 [−1.7; 2.0]	345	80.6 [78.6; 82.6]	−1.06 [−3.0; 0.9]	1.22 [−1.3; 3.7] ND
Social functioning	351	75.7 [73.2; 78.2]	0.03 [−2.5; 2.5]	345	72.9 [70.2; 75.6]	−0.43 [−3.0; 2.1]	0.46 [−2.8; 3.8] ND
EORTC QLQ-BR23[d]							
Body image	347	64.7 [61.9; 67.4]	1.84 [−0.5; 4.2]	340	63.0 [60.1; 65.8]	4.19 [1.8; 6.6]	−2.35 [−5.4; 0.7] ND
Sexual functioning	327	11.9 [10.1; 13.8]	−2.70 [−4.3; −1.1]	312	15.4 [13.3; 17.5]	−0.37 [−2.0; 1.3]	−2.33 [−4.5; −0.1]; ND Hedges' g −0.16 [−0.31; −0.00][e]
Sexual pleasure	No evaluable data[f]						
Perspective on the future	345	32.9 [29.8; 35.9]	8.31 [5.1; 11.5]	340	30.2 [27.3; 33.1]	8.06 [4.8; 11.3]	0.25 [−4.0; 4.5]; ND

(continued)

Table 3: 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 (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: Institute's calculation.
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; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; vs.: versus

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

The following Table 4 presents the results for research question B on the comparison of eribulin with anthracycline or taxane. Its structure corresponds to Table 23 of dossier assessment A14-25, but the analyses comprise all patients, irrespective of their HER2/neu status. For the outcome "overall survival", the results of the EMBRACE study at the data cut-off from 2 September 2014 subsequently submitted with the comment were supplemented.

Table 4: 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

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	143	373 [ND]	65	400 [ND]	1.31 [0.86; 1.99]	0.212[b]
Data cut-off 3/2010	143	399 [ND]	65	390 [ND]	1.07 [0.76; 1.51]	0.705[b]
Data cut-off 9/2014	143	399 [ND]	65	390 [ND]	0.94 [0.69; 1.29]	0.748[b]
Adverse events						
AEs	143	ND	62	ND	ND	ND
SAEs	143	399 [ND]	62	NC	1.04 [0.56; 1.93]	0.826[b]
Discontinuation due to AEs	143	NC	62	NC	0.36 [0.16; 0.80]	0.010[b]
Severe AEs (CTCAE grade 3 and 4)	143	35 [ND]	62	118 [ND]	1.91 [1.24; 2.93]	0.002[b]

a: Cox proportional hazards model with HER2/neu status, capecitabine pretreatment and geographical region as strata.
b: Log-rank test stratified by capecitabine pretreatment, HER2/neu status and geographical region (planned analysis).

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; 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

3 Assessment of the data subsequently submitted with the comment

3.1 Outcome category of the outcome "discontinuation due to AEs"

Based on the information provided in the dossier, the outcome "discontinuation due to AEs" from the EMBRACE study was allocated to the outcome category "non-severe/non-serious AEs" in the dossier assessment A14-25 for research question B (patients for whom repeated treatment containing an anthracycline or a taxane is an option). The fact that only a very small proportion of AEs that led to discontinuation were SAEs was decisive. The dossier contained no information on the proportion of severe AEs (CTCAE grade ≥ 3) that led to discontinuation. The company subsequently submitted this information in its comment.

The following Table 5 shows the proportion of patients who discontinued the EMBRACE study because of severe AEs (CTCAE grade ≥ 3), both for HER2/neu-negative patients (relevant subpopulation in dossier assessment A14-25) and, according to the commission by the G-BA for the present addendum, for the total population, irrespective of the HER2/neu status.

Table 5: Results on the outcome "discontinuation due to AEs" – RCT, direct comparison: eribulin vs. anthracycline or taxane for patients for whom repeated treatment containing an anthracycline or a taxane is an option

Outcome	Eribulin		Anthracycline or taxane	
	N	Proportion of patients with event n (%)	N	Proportion of patients with event n (%)
EMBRACE				
HER2/neu-negative patients				
Discontinuation due to AEs	114	14 (12.3)	54	12 (22.2)
Discontinuation due to severe AEs (CTCAE grade ≥ 3)	114	9 (7.9)[a]	54	9 (16.7)[a]
Total population				
Discontinuation due to AEs	143	15 (10.5)	62	13 (21.0)
Discontinuation due to severe AEs (CTCAE grade ≥ 3)	143	9 (6.3)[a]	62	10 (16.1)[a]

a: Institute's calculation.
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; RCT: randomized controlled trial; vs.: versus

The information in Table 5 shows that, in patients who discontinued the study because of an AE, it was mostly severe AEs (CTCAE grade ≥ 3) that led to discontinuation. The company's assessment that the outcome "discontinuation due to AEs" in the EMBRACE study for research question B is therefore to be allocated to the outcome category "severe/serious AEs" was therefore followed.

This had consequences for the extent of added benefit for the outcome "discontinuation due to AEs" with regard to the subpopulation of HER2/neu-negative patients in research question B relevant for the present assessment. Based on the effect (hazard ratio 0.38, 95% confidence interval [0.17; 0.86], p = 0.017), there was a hint of lesser harm with the extent "considerable" for this outcome (the methods used for the determination of the extent of added benefit can be found in the *General Methods* of IQWiG [6]). For the overall conclusion on the added benefit, in comparison with dossier assessment A14-25, there is therefore the change that an added benefit for the subgroup of patients with ≤ 2 organs involved is not proven when balancing the positive and negative effects.

3.2 Analyses on the outcome "overall survival" of the EMBRACE study

With the comment, the company presented analyses on the outcome "overall survival" on the basis of a third data cut-off (2 September 2014) of the EMBRACE study. The results on the outcome "overall survival" for the relevant subpopulation of HER2/neu-negative patients under consideration of this new data cut-off are presented below. The corresponding analysis on overall survival under consideration of the new data cut-off based on the respective total populations without consideration of the HER2/neu status of the patients, which was in accordance with the approval, was already conducted in Section 2 of the present addendum.

The results on overall survival on research questions A (patients for whom taxanes or anthracyclines are no longer an option, Table 6) and B (patients for whom repeated treatment containing an anthracycline or a taxane is an option, Table 7), which were already included in dossier assessment A14-25, are presented in the following tables. The results of the data cut-off subsequently submitted by the company with the comment are supplemented. The data cut-off of the EMBRACE study on 2 September 2014 was included in the meta-analysis presented in Table 6.

Table 6: Results on mortality – 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]
EMBRACE (9/2014)	141	444 [ND]	85	304 [ND]	0.78 [0.58; 1.05]	0.059[b]
Total[c]					0.80 [0.69; 0.93][d]	0.005[d]

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 9/2014 data cut-off of the EMBRACE study.
d: Meta-analysis, Institute's calculation.
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

Table 7: Results on mortality – 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
Data cut-off 9/2014	114	410 [ND]	57	396 [ND]	0.90 [0.65; 1.25]	0.616

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.
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

Neither for research question A nor for research question B did the consideration of the third data cut-off of the EMBRACE study change the result on overall survival with regard to statistically significant. As a consequence, there were no changes regarding the conclusions on the added benefit for this outcome or for the overall conclusion on the added benefit.

4 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Eribulin: Nutzenbewertung gemäß § 35a SGB V: Dossierbewertung; Auftrag A14-25 [online]. 31 October 2014 [accessed: 10 November 2014]. (IQWiG-Berichte; Volume 253). URL: https://www.iqwig.de/download/A14-25_Eribulin_Nutzenbewertung-35a-SGB-V.pdf.

2. Eisai. Stellungnahme zum IQWiG-Bericht Nr. 253: Eribulin; Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A14-25. [Soon available under: https://www.g-ba.de/informationen/nutzenbewertung/128/#tab/beschluesse in the document "Zusammenfassende Dokumentation"].

3. Eisai. Eribulin (Halaven): Dossier zur Nutzenbewertung gemäß § 35a SGB V; Modul 4A; Patienten mit lokal fortgeschrittenem oder metastasiertem Brustkrebs, bei denen nach mindestens einer Chemotherapie zur Behandlung einer fortgeschrittenen Brustkrebserkrankung eine weitere Progression eingetreten ist. Die Vortherapien sollen ein Anthrazyklin und ein Taxan entweder als adjuvante Therapie oder im Rahmen der Metastasenbehandlung enthalten haben, es sei denn, diese Behandlungen waren ungeeignet für den Patienten; medizinischer Nutzen und medizinischer Zusatznutzen, Patientengruppen mit therapeutisch bedeutsamem Zusatznutzen [online]. 18 July 2014 [accessed: 18 December 2014]. URL: https://www.g-ba.de/informationen/nutzenbewertung/128/.

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