IQWiG Reports – Commission No. A20-48

Talazoparib (breast cancer) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Talazoparib (Mammakarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 August 2020). 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] 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
BRCA	Breast Cancer Associated Gene
CHMP	Committee for Medicinal Products for Human Use
CNS	central nervous system
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 23
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EPAR	European Public Assessment Report
ER	oestrogen receptor
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)
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities (Medizinisches Wörterbuch für Aktivitäten im Rahmen der Arzneimittelzulassung)
mITT	modified intention to treat
PARP	poly(adenosine diphosphate-ribose) polymerase
PFS	progression-free survival
P-gp	P-glycoprotein
PR	progesterone recepto
PT	Preferred Term (bevorzugter Begriff)
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
SOC	System Organ Class
TNBC	triple-negative breast cancer

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 talazoparib. 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 May 2020.

Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

Research question

The aim of the present report is the assessment of the added benefit of talazoparib as monotherapy in adult patients with germline breast cancer associated gene (BRCA) 1/2-mutations, who have human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer, in comparison with the appropriate comparator therapy (ACT). Patients should have been pretreated with an anthracycline and/or a taxane in the neoadjuvant, adjuvant, locally advanced or metastatic setting, unless these treatments were unsuitable for them. Moreover, patients with hormone receptor-positive breast cancer should have been pretreated with an endocrine-based therapy, or this therapy should have been unsuitable for them.

For the benefit assessment, the research question presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of talazoparib

Therapeutic indication	**ACT**[a]
Monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative, locally advanced or metastatic breast cancer[b, c, d]	**Capecitabine** or **eribulin** or **vinorelbine** or an anthracycline- or taxane-containing therapy[e]
a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b. Patients should have been pretreated with an anthracycline and/or a taxane in the neoadjuvant, adjuvant, locally advanced or metastatic setting, unless these treatments were unsuitable for them. c. Moreover, patients with hormone receptor-positive breast cancer should have received prior endocrine-based therapy, or this therapy should have been unsuitable for them. d: For the present therapeutic indication, it is assumed that there was no indication for (secondary) resection or radiotherapy with curative intent. e. The G-BA defines anthracycline- or taxane-containing therapy as a treatment option only for those patients who have not yet received anthracycline- and taxane-containing therapy or who are candidates for retreatment with an anthracycline- or taxane-containing therapy. ACT: appropriate comparator therapy; BRCA: breast cancer associated gene; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2	

The G-BA specified capecitabine or vinorelbine or eribulin or, if applicable, anthracycline- or taxane-containing therapy as ACT. The company deviates from the G-BA's specification insofar as it cited monotherapy with capecitabine, eribulin or vinorelbine chosen by the physician on an individual basis as ACT and did not list anthracycline- or taxane-containing therapy as part of the ACT. The lack of consideration of anthracycline- or taxane-containing therapy options by the company has no consequence for the present assessment, since the company claimed having considered anthracycline- or taxane-containing therapy to be part of the ACT when selecting relevant studies, and stated that the check of the completeness of the study pool produced no additional relevant study with talazoparib versus an anthracycline- or taxane-containing therapy. The present benefit assessment of talazoparib was conducted versus the G-BA's ACT.

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

Results

Study pool and study characteristics

A subpopulation of the EMBRACA study is relevant for the benefit assessment. The EMBRACA study is an open-label, multicentre, randomized, active-controlled study on the comparison of talazoparib with physician's choice chemotherapy using capecitabine or vinorelbine or eribulin or gemcitabine. The study included adult patients with HER2-negative, locally advanced or metastatic breast cancer, provided they had germline BRCA1/2-mutation.

For patients with locally advanced breast cancer, it had to be ensured that curative radiation or curative resection was not an option for them.

Monotherapy with one of the drugs listed in the chemotherapy arm had to be suitable for all patients to be included, and pretreatment with an anthracycline and/or taxane in the neoadjuvant, adjuvant, locally advanced or metastatic setting had to be carried out, unless there was a contraindication. Patients were only included in the study if they had received prior adjuvant chemotherapy or if the investigator confirmed that the patient also would be offered one of the drugs available in the chemotherapy arm as a treatment option outside of the study. In total, at most 3 prior chemotherapy regimens for locally advanced or metastatic disease were allowed. Further restrictions existed for patients who had received prior platinum-based chemotherapy. These patients could only participate in the study if, as a result of adjuvant or neoadjuvant treatment, no recurrence had occurred within 6 months after the last dose, or if there was no proof of disease progression during the treatment when received in the locally advanced or metastatic stage. All patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0, 1 or 2.

The mentioned inclusion criteria were taken from Amendment 1 of 14 December 2015 and are extended inclusion criteria compared to the initial protocol of 17 July 2013. At the time of the amendment, approximately 50% of patients had already been included. The extension was to allow the inclusion of a broader patient population.

A total of 431 patients were included in the study. Prior to randomization, the physician determined which of the chemotherapy options (capecitabine or vinorelbine or eribulin or gemcitabine) each patient should receive if assigned to the chemotherapy arm. The patients were then randomized either to treatment with talazoparib (N = 287) or to the corresponding physician’s choice chemotherapy (N = 144) in a 2:1 ratio. In total, 1 (0.3%) patient in the talazoparib arm and 18 (12.5%) patients in the chemotherapy arm withdrew their consent immediately after randomization and thus received no study medication. Of the 126 patients in the chemotherapy arm who were treated with the study medication, n = 55 received capecitabine, n = 9 received vinorelbine, n = 50 received eribulin and n = 12 received gemcitabine. Treatment with gemcitabine is not relevant for the present benefit assessment and is therefore not considered further.

Treatment with talazoparib and with the chemotherapies capecitabine, vinorelbine and eribulin was in compliance with the Summary of Product Characteristics (SPC); dose adjustments in accordance with the local guidelines were permitted in the chemotherapy arm.

Patients were treated until confirmed disease progression (Response Evaluation Criteria in Solid Tumours [RECIST] criteria version 1.1, modified), unless one of the other criteria for treatment discontinuation applied previously: unacceptable toxicity, withdrawal of consent, physician's decision or termination of the study by the sponsor.

Primary outcome of the study is “progression-free survival (PFS)”; patient-relevant secondary outcomes include “overall survival” and outcomes on symptoms, health-related quality of life and adverse events (AEs).

Two preplanned data cut-offs are available for the study:

- first data cut-off of 15 September 2017: primary analysis, planned after occurrence of about 288 PFS events.
- second data cut-off of 30 September 2019: final analysis of the study, planned to be conducted after about 321 deaths.

This preplanned, final analysis of the EMBRACA study served as a basis for the present benefit assessment.

Subpopulation relevant for the research question and implementation of the ACT

EMBRACA is a multi-comparator study. Prior to randomization, the physician determined on an individual basis which of the chemotherapy options each patient should receive in the study if randomly assigned to the chemotherapy arm. In doing so, the physician could freely chose from the following chemotherapy options: capecitabine or vinorelbine or eribulin or gemcitabine. In the dossier, the company submitted analyses on what it calls the modified intention to treat (mITT) population, for which it excluded those patients from both treatment arms who had been assigned to the chemotherapy option gemcitabine by their physician prior to randomization; gemcitabine is not a treatment option in accordance with the ACT specified by the G-BA. All therapies considered through the formation of the relevant subpopulation in the chemotherapy arm (capecitabine, vinorelbine, eribulin) are thus possible treatment options of the ACT specified by the G-BA. Studies on talazoparib in comparison with further treatment options specified by the G-BA were not identified.

Overall, the chemotherapy arm of the relevant subpopulation from the EMBRACA study (physician’s choice chemotherapy using capecitabine or vinorelbine or eribulin) was assessed as adequate implementation of the ACT. The subpopulation formed by the company (mITT population) was considered as relevant population for the present benefit assessment.

However, in the EMBRACA study, there are uncertainties regarding the prior therapies, which also apply to the relevant subpopulation.

Comments on the prior therapies in the relevant subpopulation

In the present situation it is unclear whether the study population of the EMBRACA study comprised patients for whom anthracycline- or taxane-containing therapy might have been suitable and for whom treatment with one of the drugs listed in the chemotherapy arm would therefore not have been an option. It is also unclear whether the study included patients with hormone receptor-positive breast cancer for whom endocrine therapy might still have been suitable at an advanced stage.

Risk of bias

The risk of bias across outcomes as well as the risk of bias for the results on all outcomes was rated as high. Therefore, at most hints, e.g. of an added benefit, could be derived for all outcomes.

Mortality

Overall survival

No statistically significant difference between the treatment groups was shown for the outcome "overall survival". This resulted in no hint of an added benefit of talazoparib in comparison with the ACT; an added benefit is therefore not proven.

Morbidity - symptoms (symptom scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23 (EORTC QLQ-BR23)

In the EMBRACA study, outcomes on symptoms were recorded using the EORTC QLQ-C30 and EORTC QLQ-BR23 symptom scales. In each case, the time to first deterioration by ≥ 10 points was considered.

Fatigue (EORTC QLQ-C30), side effects of the systemic therapy and symptoms in arm region (EORTC QLQ-BR23)

For the EORTC QLQ-C30 symptom scale “fatigue”, as well as for the symptom scales “side effects of systemic therapy” and “symptoms in arm region” of the EORTC QLQ-BR23, there is a statistically significant difference in favour of talazoparib versus physician’s choice chemotherapy (capecitabine or vinorelbine or eribulin). However, the extent of the effect was no more than marginal. This resulted in no hint of an added benefit of talazoparib in comparison with the ACT for any of these symptom scales; an added benefit is therefore not proven.

Nausea and vomiting, dyspnoea, constipation and diarrhoea (EORTC QLQ-C30)

No statistically significant difference between the treatment groups was shown for any of the EORTC QLQ-C30 symptom scales on nausea and vomiting, dyspnoea, constipation and diarrhoea. This resulted in no hint of an added benefit of talazoparib in comparison with the ACT for each of these symptom scales; an added benefit is therefore not proven.

Pain, insomnia, appetite loss (EORTC QLQ-C30) and symptoms in chest region (EORTC QLQ-BR23)

For the EORTC QLQ-C30 symptom scales “pain”, “insomnia” and "appetite loss”, as well as for the symptom scale “symptoms in chest region” of the EORTC QLQ-BR23, there is a statistically significant difference in favour of talazoparib versus physician’s choice chemotherapy (capecitabine or vinorelbine or eribulin). This resulted in a hint of an added benefit of talazoparib in comparison with the ACT for each of these symptom scales.

Upset by hair loss (EORTC QLQ-BR23)

There were no usable analyses for the symptom scale "upset by hair loss" of the EORTC QLQ-BR23, because the company's approach does not ensure that the burden of patients who only develop hair loss in the course of the treatment is also recorded. This resulted in no hint of an added benefit of talazoparib in comparison with the ACT; an added benefit is therefore not proven.

Health-related quality of life – EORTC QLQ-C30 (functional scales, scale on the global health status) and EORTC QLQ-BR23 (functional scales)

Health-related quality of life was recorded using the global health status and the EORTC QLQ-C30 functional scales as well as the EORTC QLQ-BR23 functional scales. The time to first deterioration by ≥ 10 points was considered in each case.

Global health status, physical functioning, role functioning, cognitive functioning, emotional functioning, social functioning (EORTC QLQ-C30), body image (EORTC QLQ-BR23)

For the global health status and for the functional scales "physical functioning", "role functioning", "cognitive functioning", "emotional functioning" and "social functioning" recorded using the EORTC QLQ-C30, and for the EORTC QLQ-BR23 functional scale "body image", there is a statistically significant difference each in favour of talazoparib versus a physician's choice chemotherapy (capecitabine or vinorelbine or eribulin). For the scale "global health status" and for each of the cited functional scales, there is one hint of an added benefit in favour of talazoparib in comparison with the ACT.

Sexual activity and future perspective (EORTC QLQ-BR23)

No statistically significant difference between the treatment groups was shown for the functional scales "sexual activity" and "future perspective" recorded with the EORTC QLQ-BR23. For these functional scales, this resulted in no hint of an added benefit of talazoparib in comparison with the ACT; an added benefit is therefore not proven.

Enjoyment of sex (EORTC QLQ-BR23)

There were no usable analyses for the functional scale "enjoyment of sex" of the EORTC QLQ-BR23, because the company's approach does not ensure that the burden of patients who only become sexually active in the course of treatment is also recorded. This resulted in no hint of an added benefit of talazoparib in comparison with the ACT; an added benefit is therefore not proven.

Side effects

Serious adverse event (SAEs)

No statistically significant difference between the treatment groups was shown for the outcome "SAEs". This resulted in no hint of greater or lesser harm from talazoparib in comparison with the ACT; greater or lesser harm is therefore not proven.

Severe adverse events (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)

For the outcome "severe AEs (CTCAE grade ≥ 3)", there was a statistically significant difference in favour of talazoparib versus physician's choice chemotherapy (capecitabine or vinorelbine or eribulin). This resulted in a hint of lesser harm from talazoparib in comparison with the ACT.

Discontinuation due to AEs

There was no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from talazoparib in comparison with the ACT; greater or lesser harm is therefore not proven.

Specific AEs

In both arms, no events occurred in the specific AEs "myelodysplastic syndrome" and "acute myeloid leukaemia", both CTCAE grade ≥ 3. Hence, there was no hint of greater or lesser harm from talazoparib in comparison with the ACT for any of these outcomes; greater or lesser harm is therefore not proven.

For the specific AEs "skin and subcutaneous tissue disorders", "neutropenia" and "diarrhoea" (each of them CTCAE grade ≥ 3)", there was a statistically significant difference in favour of talazoparib versus physician's choice chemotherapy (capecitabine or vinorelbine or eribulin). This resulted in a hint of lesser harm from talazoparib in comparison with the ACT for each of the mentioned specific AEs.

For the specific AEs "anaemia" and "thrombocytopenia" (each of them CTCAE grade ≥ 3), there was a statistically significant difference to the disadvantage of talazoparib versus physician's choice chemotherapy (capecitabine or vinorelbine or eribulin). This resulted in a hint of greater harm from talazoparib in comparison with the ACT for each of the mentioned specific AEs.

For the specific AEs "eye disorders", "hand-foot syndrome" and "paraesthesia", there was a statistically significant difference in favour of talazoparib versus physician's choice chemotherapy (capecitabine or vinorelbine or eribulin). This resulted in a hint of lesser harm from talazoparib in comparison with the ACT for each of the mentioned specific AEs.

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

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

In the overall consideration, there were mostly positive and only few negative effects of talazoparib in comparison with the ACT.

Advantages are shown in "health-related quality of life", here in "global health status", all EORTC QLQ-C30 functional scales and the functional scale "body image" of the EORTC QLQ-BR23, most of them of considerable extent.

In the category "non-serious/non-severe symptoms/late complications", advantages are also found in the EORTC QLQ-C30 symptom scales "pain", "insomnia" and "appetite loss", as well as in the EORTC QLQ-BR23 symptoms scale "symptoms in chest region", with an extent of "minor to considerable".

Besides the positive ones, there were also negative effects of talazoparib in comparison with the ACT in "serious/severe side effects". An advantage with the extent "minor" was shown in the severe AEs (CTCAE grade ≥ 3). These include the specific AEs "neutropenia", "skin and subcutaneous tissue disorders" and "diarrhoea", where advantages up to the extent "major" were shown in some cases. Disadvantages up to the extent "major" were shown in the specific AEs "anaemia" and "thrombocytopenia" (each of them CTCAE grade ≥ 3).

In the category "non-serious/non-severe side effects", the advantages of talazoparib are found in the specific AEs "hand-foot syndrome", "eye disorders" and "paraesthesia", each with the extent "considerable".

In summary, there is a hint of considerable added benefit of talazoparib versus the ACT for adult patients with germline BRCA1/2-mutations who have HER2-negative, locally advanced or metastatic breast cancer.

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

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

Table 3: Talazoparib – probability and extent of added benefit

Therapeutic Indication	ACT[a]	Probability and extent of added benefit
Monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative, locally advanced or metastatic breast cancer[b, c, d]	**Capecitabine** or **eribulin** or **vinorelbine** or an anthracycline- or taxane-containing therapy[e]	Hint of considerable added benefit[f]

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. Patients should have been pretreated with an anthracycline and/or a taxane in the neoadjuvant, adjuvant, locally advanced or metastatic setting, unless these treatments were unsuitable for them.
c. Moreover, patients with hormone receptor-positive breast cancer should have received prior endocrine-based therapy, or this therapy should have been unsuitable for them.
d. For the present therapeutic indication, it is assumed that there was no indication for (secondary) resection or radiotherapy with curative intent.
e. The G-BA defines anthracycline- or taxane-containing therapy as a treatment option only for those patients who have not yet received anthracycline- and taxane-containing therapy or who are candidates for retreatment with an anthracycline- or taxane-containing therapy.
f. Only few patients with an ECOG PS of 2 were included in the EMBRACA study, almost all patients had an ECOG PS of 0 or 1. It thus remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.

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

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

2.2 Research question

The aim of the present report is the assessment of the added benefit of talazoparib as monotherapy in adult patients with germline BRCA 1/2-mutations, who have HER2-negative, locally advanced or metastatic breast cancer, in comparison with the ACT. Patients should have been pretreated with an anthracycline and/or a taxane in the neoadjuvant, adjuvant, locally advanced or metastatic setting, unless these treatments were unsuitable for them. Moreover, patients with hormone receptor-positive breast cancer should have been pretreated with an endocrine-based therapy, or this therapy should have been unsuitable for them.

For the benefit assessment, the research question presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of talazoparib

Therapeutic indication	**ACT**[a]
Monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative, locally advanced or metastatic breast cancer[b, c, d]	**Capecitabine** or **eribulin** or **vinorelbine** or an anthracycline- or taxane-containing therapy[e]
a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b. Patients should have been pretreated with an anthracycline and/or a taxane in the neoadjuvant, adjuvant, locally advanced or metastatic setting, unless these treatments were unsuitable for them. c. Moreover, patients with hormone receptor-positive breast cancer should have received prior endocrine-based therapy, or this therapy should have been unsuitable for them. d. For the present therapeutic indication, it is assumed that there was no indication for (secondary) resection or radiotherapy with curative intent. e. The G-BA defines anthracycline- or taxane-containing therapy as a treatment option only for those patients who have not yet received anthracycline- and taxane-containing therapy or who are candidates for retreatment with an anthracycline- or taxane-containing therapy. ACT: appropriate comparator therapy; BRCA: breast cancer associated gene; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2	

The G-BA specified capecitabine or vinorelbine or eribulin or, if applicable, anthracycline- or taxane-containing therapy as ACT. The company deviates from the G-BA's specification insofar as it cited monotherapy with capecitabine, eribulin or vinorelbine chosen by the physician on an individual basis as ACT and did not list anthracycline- or taxane-containing therapy as part of the ACT. The lack of consideration of anthracycline- or taxane-containing therapy options by the company has no consequence for the present assessment, since the company claimed having considered anthracycline- or taxane-containing therapy to be part of the ACT when selecting relevant studies, and stated that the check of the completeness of the study pool produced no additional relevant study with talazoparib versus an anthracycline- or taxane-containing therapy. The present benefit assessment of talazoparib was conducted versus the G-BA's ACT.

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

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on talazoparib (status: 19 March 2020)
- bibliographical literature search on talazoparib (last search on 16 March 2020)
- search in trial registries/trial results databases for studies on talazoparib (last search on 19 March 2020)

- search on the G-BA website for talazoparib (last search on 19 March 2020)

To check the completeness of the study pool:

- search in trial registries for studies on talazoparib (last search on 9 June 2020)

The check did not identify any additional relevant studies.

2.3.1 Studies included

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

Table 5: Study pool – RCT, talazoparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
Study 673-301 (EMBRACA[d])	Yes	Yes	No	No[e]	Yes [3-7]	Yes [8-12]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: EPAR.
d. In the following tables, the study is referred to with this abbreviated form.
e. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

EPAR: European Public Assessment Report; RCT: randomized controlled trial

The study EMBRACA is used for the benefit assessment. Thereby, a subpopulation is considered because the study also allowed the administration of therapies going beyond the ACT (see Section 2.3.2). This concurs with the company's approach.

2.3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: talazoparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
EMBRACA	RCT, open-label, parallel	Adult patients (≥ 18 years of age) with HER2-negative locally advanced or metastatic breast cancer[b] and documented germline BRCA1/2-mutation[c] ▪ pretreatment with an anthracycline and/or a taxane[d] unless patients had contraindications to these treatments[e] ▪ ≤ 3 prior chemotherapy regimens in the locally advanced and/or metastatic stage[e] ▪ ECOG PS ≤ 2[e]	▪ Talazoparib (n = 287[f]) ▪ physician's choice chemotherapy[g] (N = 144), thereof: ▫ capecitabine (N = 55) ▫ vinorelbine (N = 9) ▫ eribulin (N = 50) ▫ gemcitabine (N = 12) relevant subpopulation thereof[h]: ▪ talazoparib (n = 266) ▪ physician's choice chemotherapy using capecitabine or vinorelbine or eribulin (n = 130)	Screening: up to 28 days before randomization treatment: until radiologically confirmed disease progression[i], unacceptable toxicity, withdrawal of consent, treatment discontinuation following the decision by the physician, termination of study by the sponsor observation[j]: outcome-specific, at most until death	145 study centres in Australia, Belgium, Brazil, France, Germany, Ireland, Israel, Italy, Poland, Russia, South Korea, Spain, Taiwan, Ukraine, United Kingdom, USA 10/2013–ongoing data cut-offs: ▪ first data cut-off: 15 September 2017 ▪ second data cut-off: 30 September 2019	Primary: PFS secondary: overall survival, symptoms, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: talazoparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Patients with locally advanced breast cancer were only included in the study if curative radiation or curative resection was not an option for them. Patients with active inflammatory breast cancer could not participate in the study. Monotherapy with one of the drugs listed in the chemotherapy arm had to be suitable for all patients to be included.
c. The test had to be performed by Myriad Genetics or another laboratory approved by the sponsor. At the time of screening, blood samples were collected from the patients to test the BRCA mutation status retrospectively or prospectively.
d. Pretreatment with an anthracycline and/or a taxane could have been neoadjuvant or adjuvant or could have been performed in the locally advanced or metastatic stage. Within the framework of the study, treatment without prior adjuvant chemotherapy was only allowed if the treating physician confirmed that the patient would have been offered one of the drugs available in the chemotherapy arm as a treatment option also outside of the study.
e. Compared to the initial protocol, these inclusion criteria are extended inclusion criteria, which were formulated only after an amendment in December 2015 (after approx. 50% of the patients had already been included) and were to enable the inclusion of a broader patient population (see further explanations in the text). The results of the ABRAZO study were the reason for this. Moreover, patients with an ECOG PS of 2 were included according to recommendations of the CHMP.
f. One patient in the talazoparib arm and 18 patients in the chemotherapy arm received no study medication after randomization.
g. Patients in the chemotherapy arm of the study received the chemotherapy determined for them by the treating physician prior to randomization. In doing so, the physician could chose between capecitabine, vinorelbine, eribulin and gemcitabine.
h. Subpopulation of patients for whom, prior to randomization, capecitabine, vinorelbine or eribulin was determined as the drug to be administered if they were allocated to the chemotherapy arm. The other treatment option gemcitabine is not considered further in the following.
i. Determined by an independent review committee in accordance with modified RECIST criteria, version 1.1.
j. Outcome-specific data are described in Table 8.

AE: adverse event; BRCA: breast cancer associated gene; CHMP: Committee for Medicinal Products for Human Use; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HER2: human epidermal growth factor receptor 2; n: relevant subpopulation; N: number of randomized (included) patients; PFS: progression-free survival; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria In Solid Tumours; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: talazoparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin (multipage table)

Study	Intervention	Comparison
EMBRACA	▪ Talazoparib, 1 mg/day, orally ▪ recommended treatment interruptions[a] and dose reductions due to side effects comply with the specifications of the SPC	▪ One of the following chemotherapies chosen by the physician for the individual patient before randomization: ▫ capecitabine 1250 mg/m^2 BSA: twice daily, orally, administered for 14 days, repeated every 21 days ▫ vinorelbin 30 mg/m^2 BSA: IV on day 1, day 8 and day 15, repeated every 21 days ▫ eribulin mesylate 1.4 mg/m^2 BSA or eribulin (active substance) 1.23 mg/m^2 BSA: IV on day 1 and day 8, repeated every 21 days ▪ dose adjustment in accordance with SPC and local guidelines
	Pretreatment ▪ with an anthracycline and/or a taxane[b], unless patients had contraindications to these treatments[c] ▪ with adjuvant chemotherapy, unless the investigator decided that the patient would be offered one of the drugs in the chemotherapy arm as treatment option also outside of the study[c] ▪ at most 3 regimens of a chemotherapy in the locally advanced and/or metastatic stage[c, d] ▪ patients who had previously received adjuvant or neoadjuvant platinum-containing chemotherapy could participate in the study unless they had a relapse within 6 months after the last dose[c] **Non-permitted pretreatment** ▪ treatment with a PARP inhibitor (except for iniparib) ▪ chemotherapy, endocrine therapy, other targeted therapies, investigational drugs, radiotherapy or major surgery ≤ 14 days[c] prior to randomization ▪ platinum-containing chemotherapy in the locally advanced or metastatic stage (however, patients could participate in the study if there was no proof of disease progression during platinum-containing chemotherapy. Patients who had received low-dose platinum-containing chemotherapy in combination with radiotherapy could also join the study)[c] **Permitted concomitant treatment** ▪ any supportive medication at the physician's discretion (e.g. blood products[e], antiemetics, antidiarrhoeal drugs, appetite stimulants) ▪ bisphosphonates and denosumab for the prevention or treatment of bone metastases ▪ G-CSF only as rescue medication ▪ radiotherapy was allowed after consultation with the clinical monitor ▪ resection of metastases if in the patient's best interest and after consultation with the clinical monitor **Non-permitted concomitant treatment** ▪ further (systemic) anticancer therapies and investigational drugs ▪ in the talazoparib arm: strong P-gp inhibitors/inducers or BCRP inhibitors should be avoided	

Table 7: Characteristics of the intervention – RCT, direct comparison: talazoparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin (multipage table)

Study	Intervention	Comparison
a. The proportion of patients with treatment interruption due to AEs was higher in the talazoparib arm (60.1%; data for the total population) than in the chemotherapy arm (32.7%; data for the total population) b. Pretreatment with an anthracycline and/or a taxane could have been neoadjuvant or adjuvant or could have been performed in the locally advanced or metastatic stage. c. Compared to the initial protocol, the requirements for the pretreatment are adapted requirements, which were formulated only after an amendment in December 2015 (after approx. 50% of the patients had already been included) and were to enable the inclusion of a broader patient population. d. Pretreatment with endocrine or targeted therapy was possible without limitation. e. According to the SPC of talazoparib, occurring thrombocytopenia and anaemia can be counteracted with blood transfusions in addition to dose adjustments (interruption and reduction). According to EPAR data, approximately 3% of the patients in the total population of the talazoparib arm received platelet transfusions and approximately 38% received erythrocyte transfusions (number of erythrocyte transfusions: n = 2 [median] per patient). In the chemotherapy arm, none of the patients received platelet transfusion, and 5.6% of the patients received erythrocyte transfusion (number of erythrocyte transfusions: n = 1 [median] per patient). According to a publication on the EMBRACA study [9] it is unclear whether more transfusions were administered in the study than usual in clinical practice. AE: adverse event; BCRP: breast cancer resistance protein; BSA: body surface area; EPAR: European Public Assessment Report; G-CSF: granulocyte colony-stimulating factor; PARP: poly(adenosine diphosphate-ribose) polymerase; P-gp: P-glycoprotein; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; vs.: versus		

The EMBRACA study is an open-label, multicentre, randomized, active-controlled study on the comparison of talazoparib with physician's choice chemotherapy using capecitabine or vinorelbine or eribulin or gemcitabine. The study included adult patients with HER2-negative, locally advanced or metastatic breast cancer, provided they had germline BRCA1/2-mutation. For patients with locally advanced breast cancer, it had to be ensured that curative radiation or curative resection was not an option for them.

Monotherapy with one of the drugs listed in the chemotherapy arm had to be suitable for all patients to be included, and pretreatment with an anthracycline and/or taxane in the neoadjuvant, adjuvant, locally advanced or metastatic setting had to be completed, unless there was a contraindication. Patients were only included in the study if they had received prior adjuvant chemotherapy or if the investigator confirmed that the patient would be offered one of the drugs available in the chemotherapy arm as a treatment option also outside of the study. In total, at most 3 prior chemotherapy regimens for locally advanced or metastatic disease were allowed. Further restrictions existed for patients who had received prior platinum-based chemotherapy. These patients could only participate in the study if, as a result of adjuvant or neoadjuvant treatment, no recurrence had occurred within 6 months after the last dose, or if there was no proof of disease progression during the treatment when received in the locally advanced or metastatic stage. All patients had to have an ECOG-PS of 0, 1 or 2.

The mentioned inclusion criteria were taken from Amendment 1 of 14 December 2015 and are extended inclusion criteria compared to the initial protocol of 17 July 2013. At the time of the

amendment, approximately 50% of patients had already been included. The extension was to allow the inclusion of a broader patient population and took place on the basis of intermediate results of the ABRAZO study [13]. The major changes included:

- Extension of the number of allowed prior chemotherapy regimens in the advanced stage from 2 to 3
- Deviating from the initial protocol, prior platinum-containing therapy in advanced stages was allowed under certain conditions (if there was no proof of disease progression during platinum-based chemotherapy; prior low-dose platinum-containing chemotherapy in combination with radiotherapy without limitation)
- prior platinum-containing therapy in the neoadjuvant/adjuvant setting was allowed, unless a relapse had occurred within 6 months (initially: 12 months) after the last dose
- Extension of the inclusion criterion for pretreatment with anthracyclines and/or taxanes in the adjuvant or advanced setting by the neoadjuvant setting, as well as the possibility that pretreatment with anthracyclines and/or taxanes was no prerequisite in case of contraindications
- Deletion of the requirement of prior adjuvant chemotherapy, if the investigator decided that the patient would be offered one of the drugs in the chemotherapy arm as a treatment option also outside of the study
- Extension of ECOG PS ≤ 1 to ≤ 2 (corresponds to recommendation of the CHMP)

The study included a total of 431 patients for whom monotherapy with capecitabine or vinorelbine or eribulin or gemcitabine was suitable according to the inclusion criteria. Prior to randomization, the physician determined which of the cited chemotherapy options each patient should receive if assigned to the chemotherapy arm. The patients were then randomized either to treatment with talazoparib (N = 287) or to the corresponding physician's choice chemotherapy (N = 144) in a 2:1 ratio. In total, 1 (0.3%) patient in the talazoparib arm and 18 (12.5%) patients in the chemotherapy arm withdrew their consent immediately after randomization and thus received no study medication. Of the 126 patients in the chemotherapy arm who were treated with the study medication, n = 55 received capecitabine, n = 9 received vinorelbine, n = 50 received eribulin and n = 12 received gemcitabine. Randomization was stratified according to the number of prior chemotherapy regimens for locally advanced and/or metastatic disease (0/1, 2 or 3), the receptor status (triple-negative breast cancer [TNBC]: oestrogen receptor [ER]-/ progesterone receptor [PgR]-/HER2-negative) based on the last biopsy (TNBC: yes/no), and the presence of metastases in the central nervous system (CNS) during the course of the medical history (yes/no).

Treatment with talazoparib was in compliance with the SPC [14]. In the chemotherapy arm, the therapies capecitabine, vinorelbine and eribulin were also used in accordance with the respective SPCs [15-17], whereby dose adjustments were possible in the chemotherapy arm in accordance with the local guidelines. Treatment with gemcitabine is not relevant for the present

benefit assessment (see subsequent section on the relevant subpopulation) and is therefore not considered further.

Patients were treated until confirmed disease progression (RECIST criteria version 1.1, modified), unless one of the other criteria for treatment discontinuation applied previously: unacceptable toxicity, withdrawal of consent, physician's decision or termination of the study by the sponsor.

Primary outcome of the study was "progression-free survival (PFS)"; patient-relevant secondary outcomes include "overall survival" and outcomes on symptoms, health-related quality of life and AEs.

Subpopulation relevant for the research question and implementation of the ACT

EMBRACA is a multi-comparator study. Prior to randomization, the physician determined on an individual basis which of the chemotherapy options each patient should receive in the study if randomly assigned to the chemotherapy arm. In doing so, the physician could freely chose from the following chemotherapy options: capecitabine or vinorelbine or eribulin or gemcitabine. 3 of these 4 chemotherapies to be used in the study were possible treatment options of the ACT specified by the G-BA: capecitabine, vinorelbine and eribulin. Accordingly, the company submitted analyses on what it calls the mITT population in the dossier, for which it excluded those patients from both treatment arms who had been assigned to the chemotherapy option gemcitabine by their physician prior to randomization; gemcitabine is not a treatment option according to the ACT specified by the G-BA. Exclusion of these patients resulted in a number of 266 patients in the talazoparib arm and 130 patients in the chemotherapy arm. All therapies considered through the formation of the relevant subpopulation in the chemotherapy arm (capecitabine, vinorelbine, eribulin) are thus possible treatment options of the ACT specified by the G-BA. Studies on talazoparib in comparison with further treatment options specified by the G-BA were not identified (see Section 2.2 and Section 2.3).

According to current guideline recommendations, combination therapy should be considered for patients with high remission pressure due to severe symptoms or rapid tumour growth [18-20]. A publication on the EMBRACA study [11] states that combination therapies were not yet part of the health care standard at the time the EMBRACA study was planned (2013). It is not clear from the available information whether such patients were included in the EMBRACA study. In the dossier, the company does not discuss whether combination therapies would have been an option for patients from the EMBRACA study under current health care standards.

Overall, the chemotherapy arm of the relevant subpopulation from the EMBRACA study (physician's choice chemotherapy using capecitabine or vinorelbine or eribulin) was assessed as sufficient implementation of the ACT. The subpopulation formed by the company (mITT population) was considered as relevant population for the present benefit assessment. Subgroup analyses to investigate any differential effects of talazoparib versus the chemotherapy chosen by the physician (capecitabine or vinorelbine or eribulin) would have been desirable to

determine whether the effects differed between the different treatment options. However, such analyses were not available for the relevant subpopulation.

However, in the EMBRACA study and also for the relevant subpopulation there are uncertainties regarding the prior therapies, which are described hereinafter.

Comments on the prior therapies in the relevant subpopulation

Prior therapy with anthracyclines/taxanes

Talazoparib should only be used if patients had previously been treated with an anthracycline and/or a taxane in the neoadjuvant, adjuvant, locally advanced or metastatic setting, unless these treatments were unsuitable for them. This restriction of the therapeutic indication corresponds to the inclusion criteria of the EMBRACA study. For the relevant subpopulation, there is a list of drugs received within the framework of the prior therapies in the advanced stage (see Appendix A of the full dossier assessment). However, data on patients with anthracycline- and/or taxane-containing prior therapy (at any stage) are not available. However, the data in the European Public Assessment Report (EPAR) show that 97.2% of the patients in the total population of the EMBRACA study received anthracycline- and/or taxane-containing prior therapy (any stage). The requirements for the prior therapy with anthracyclines and/or taxanes according to the SPCs of talazoparib [14] are thus fulfilled.

However, the SPCs of the 3 drugs in the chemotherapy arm of the relevant subpopulation (eribulin, capecitabine and vinorelbine) require that patients should have been pretreated with both anthracyclines and taxanes if such treatment is suitable for these patients. EPAR data show that 331 patients (76.8%) of the total EMBRACA study population received both anthracycline- and taxane-containing prior therapy at any stage (41 [9.5%] advanced stage patients). These data are not available for the relevant subpopulation. In the present situation it remains unclear whether the study population of the EMBRACA study included patients for whom anthracycline- or taxane-containing therapy would have been suitable and for whom treatment with one of the drugs listed in the chemotherapy arm would therefore not have been an option.

Prior therapy with endocrine-based therapies

In patients with hormone receptor-positive breast cancer, talazoparib should only be used if these patients have already received endocrine-based therapy or if this therapy is not suitable for the patient. There was no corresponding inclusion criterion for prior endocrine treatment in the EMBRACA study. In the relevant subpopulation, 143 (53.8%) of the patients in the talazoparib arm and 77 (59.2%) of the patients in the chemotherapy arm had hormone-receptor-positive breast cancer. Data on the proportion of patients with hormone receptor-positive breast cancer in the relevant subpopulation who have received prior endocrine therapy in any setting are not available. In the total population of the EMBRACA study, 9.6% of the patients with hormone receptor-positive breast cancer in the talazoparib arm and 16.7% of such patients in the chemotherapy arm had not received prior endocrine therapy in the neoadjuvant, adjuvant or advanced setting. However, based on the relevant subpopulation and the advanced stage, only

64.3% (n = 92) of the patients in the talazoparib arm and 59.7% (n = 46) of the patients in the chemotherapy arm (of the patients with hormone receptor-positive breast cancer) received endocrine therapy (see Table 9). For the other patients with hormone receptor-positive breast cancer, it is not possible to tell from the available information whether endocrine therapy would still have been suitable for them in an advanced stage. The study protocol indicates that monotherapy with one of the drugs listed in the chemotherapy arm should have been an option for patients according to the exclusion and inclusion criteria of the EMBRACA study. According to guidelines [18-20], chemotherapy is only an option when endocrine therapy is no longer suitable; however, information on the exact implementation of these guidelines in the EMBRACA study is not available.

However, the described uncertainties regarding the prior therapies have no consequence for the present benefit assessment, since the certainty of conclusions of the study results is already reduced by a high risk of bias across outcomes (see the section on risk of bias across outcomes). In the dossier, the company does not discuss the extent to which an anthracycline- or taxane-containing therapy or an endocrine therapy would have been suitable for the patients in the EMBRACA study.

Data cut-offs

Two preplanned data cut-offs are available for the study:

- first data cut-off of 15 September 2017: primary analysis, planned after occurrence of about 288 PFS events
- second data cut-off of 30 September 2019: final analysis of the study, planned to be conducted after about 321 deaths

The company presented results on all patient-relevant outcomes for the second data cut-off for the relevant subpopulation. This preplanned, final analysis of the EMBRACA study served as a basis for the present benefit assessment.

This concurs with the company's approach, which also used the analyses on second data cut-off for the derivation of the added benefit for all outcomes considered by it except PFS.

Planned duration of follow-up observation

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

Table 8: Planned duration of follow-up observation – RCT, direct comparison: talazoparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin

Study **Outcome category** **Outcome**	**Planned follow-up observation**
EMBRACA	
Mortality	
Overall survival	Until death
Morbidity	
Symptoms (EORTC QLQ-C30 and QLQ-BR23)	Until 30 days after the last dose of the study medication
Health-related quality of life (EORTC QLQ-C30 and QLQ-BR23)	Until 30 days after the last dose of the study medication
All outcomes in the category of side effects	Up to 30 days after the last dose of the study medication or initiation of new antineoplastic treatment

EORTC: European Organisation for Research and Treatment of Cancer; QLQ-BR23: Quality of Life-5 Dimensions; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; vs.: versus

The observation periods for the outcomes "morbidity", "health-related quality of life" and "side effects" were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 30 days). To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for survival.

Patient characteristics

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

Table 9: Characteristics of the study population – RCT, talazoparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin (multipage table)

Study Characteristic Category	Talazoparib N[a] = 266	Physician's choice chemotherapy[b] N[a] = 130
EMBRACA (second data cut-off: 30 September 2019)		
Age [years], mean (SD)	47 (11)	50 (12)
Age groups, n (%)		
< 50 years	171 (64.3)	62 (47.7)
≥ 50 to < 65 years	70 (26.3)	58 (44.6)
≥ 65 years	25 (9.4)	10 (7.7)
Sex [female/male], n (%)	263 (98.9)/3 (1.1)	127 (97.7)/3(2.3)
Region, n (%)		
North America	86 (32.3[c])	46 (35.4[c])
Europe	129 (48.5[c])	54 (41.5[c])
Rest of the world	51 (19.2[c])	30 (23.1[c])
Family origin[d], n (%)		
Asian	29 (10.9)	16 (12.3)
Black or African American	10 (3.8)	1 (0.8)
White	175 (65.8)	95 (73.1)
Other	5 (1.9)	1 (0.8)
Not reported	47 (17.7)	17 (13.1)
ECOG PS, n (%)		
0	142 (53.4)	75 (57.7)
1	117 (44.0)	52 (40.0)
2	6 (2.3)	2 (1.5)
No data	1 (0.4)	1 (0.8)
BRCA mutation status, n (%)		
BRCA1 mutation		
Central laboratory analysis	116 (43.6[c])	53 (40.8[c])
Local laboratory analysis	8 (3.0[c])	3 (2.3[c])
BRCA2 mutation		
Central laboratory analysis	135 (50.8[c])	71 (54.6[c])
Local laboratory analysis	7 (2.6[c])	3 (2.3[c])
(Hormone) receptor status, n (%)		
ER- and/or PR-positive, HER2-negative	143 (53.8)	77 (59.2)
ER- and PR-negative, HER2-negative (TNBC)	123 (46.2)	53 (40.8)
Disease duration: time between first diagnosis and randomization [years], mean (SD)	6.0 (5.7)	6.6 (5.9)

Table 9: Characteristics of the study population – RCT, talazoparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin (multipage table)

Study **Characteristic** **Category**	**Talazoparib** **N[a] = 266**	**Physician's choice chemotherapy[b]** **N[a] = 130**
Disease duration: time between diagnosis of an advanced stage and randomization [years], mean (SD)	2.4 (3.8)	2.4 (3.3)
Disease classification, n (%)		
Locally advanced	ND[e]	ND[e]
Metastatic	ND[e]	ND[e]
Number of locations of the metastases, n (%)		
1	64 (24.1)	38 (29.2)
2	84 (31.6)	38 (29.2)
≥ 3	118 (44.4)	54 (41.5)
Location of metastases, n (%)		
Bone	147 (55.3)	72 (55.4)
Brain	30 (11.3)	14 (10.8)
Breast	38 (14.3)	13 (10.0)
Liver	108 (40.6)[d]	54 (41.5)
Lungs	101 (38.0)	58 (44.6)
Lymph nodes	129 (48.5)	60 (46.2)
Mediastinum	20 (7.5)	5 (3.8)
Other	84 (31.6)	39 (30.0)
CNS metastases in the medical history (eCRF), n (%)		
Yes	40 (15.1)	17 (13.1)
No	226 (85.0)	113 (87.0)
Prior neoadjuvant/adjuvant therapy, n (%)		
Yes	218 (82.0[c])	109 (83.8[c])
No	48 (18.0[c])	21 (16.2[c])
Prior systemic therapy in the advanced stage[f], n (%)		
Yes	187 (70.3)	91 (70.0)
No	79 (29.7)[c]	39 (30.0)[c]
Prior chemotherapy in the advanced stage (eCRF)[d, f], n (%)		
Yes	159 (59.8[c])	79 (60.8[c])
1	98 (36.8[c])	49 (37.7[c])
≥ 2	61 (22.9[c])	30 (23.1[c])
No	107 (40.2[c])	51 (39.2[c])

Table 9: Characteristics of the study population – RCT, talazoparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin (multipage table)

Study Characteristic Category	Talazoparib N[a] = 266	Physician's choice chemotherapy[b] N[a] = 130
Prior endocrine therapy in the advanced stage[d, f], n (%)		
Yes	92 (34.6)	46 (35.4)
No	174 (65.4)[c]	84 (64.6)[c]
Prior platinum therapy (any stage)[f]		
Yes	42 (15.8[e])	27 (20.8[e])
No	224 (84.2[e])	103 (79.2[e])
Treatment discontinuation, n (%)	ND[g]	ND[g]
Study discontinuation, n (%)	ND[h]	ND[h]

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Capecitabine or vinorelbine or eribulin at the physician's choice.
c. Institute's calculation.
d. Discrepancy between information in the main section of Module 4 A and Appendix 4-G.
e. In the total population of the EMBRACA study, 15 (5.2%) patients in the talazoparib and 9 (6.2%) patients in the chemotherapy arm had locally advanced breast cancer, and 271 (94.4%) patients in the talazoparib arm and 135 (93.8%) patients in the chemotherapy arm had metastatic breast cancer.
f. For more detailed information on the administration of individual drugs in the advanced stage see Appendix A of the full dossier assessment.
g. At the time point of the first data cut-off (15 September 2017), 222 (77.4%) patients in the talazoparib arm and 119 (82.6%) patients in the chemotherapy arm had discontinued the study treatment in the total population. The majority of treatment discontinuations was due to disease progression. This applied to 197 (68.6%) patients in the talazoparib arm and to 87 (60.4%) patients in the chemotherapy arm.
h. In the total population, 14 (4.9%) patients in the talazoparib arm and 26 (18.1%) patients in the chemotherapy arm had discontinued the study prematurely at the time of the first data cut-off (15 September 2017) (reasons for discontinuation: "lost to follow-up" or "withdrawal of consent").

BRCA: breast cancer associated gene; CNS: central nervous system; ECOG PS: Eastern Cooperative Oncology Group Performance Status; eCRF: electronic case report form; ER: oestrogen receptor; HER2: human epidermal growth factor receptor 2; ND: no data; n: number of patients in the category; N: number of analysed patients; PR: progesterone receptor; RCT: randomized controlled trial; SD: standard deviation; TNBC: triple-negative breast cancer; vs.: versus

The demographic and clinical characteristics of the patients in both treatment arms were largely comparable. In relation to age, however, there were slight differences. On average, the patients in the talazoparib arm were 47 years old, and the majority (64.3%) was younger than 50 years of age, while the mean age of the patients in the chemotherapy arm was 50 years, and less than half of them (47.7%) were younger than 50 years. Besides women, the study also included a small proportion of men (3 patients each in the talazoparib and chemotherapy arms). In terms of general condition, approx. 43% of the patients had an ECOG PS of 1 and only few patients (approx. 2%) had an ECOG PS of 2. Their inclusion was only from Amendment 1 of the study protocol, after approx. 50% of the study population had already been included. About 45% of the patients had germline BRCA1 mutation and thus about 55% of the patients had germline

BRCA2 mutation. In the majority of patients, the BRCA mutation status had been confirmed by the Myriad Genetics BRACAnalysis CDx test.

Information on the proportion of patients with locally advanced or metastatic breast cancer is not available for the relevant subpopulation. The majority of patients in the total population (approx. 94%) of the EMBRACA study had metastatic breast cancer. The majority (approx. 70%) of patients had already received treatment in the advanced stage, with small differences between treatment arms being shown for individual drugs (see Appendix A of the full dossier assessment). Information on patients who discontinued treatment or the study is not available.

Treatment duration and observation period

Table 10 shows the available information on the mean/median treatment duration of the patients and on the observation periods for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: talazoparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin

Study **Duration of the study phase** **Outcome category**	**Talazoparib** **N = 266**	**Physician's choice chemotherapy[a]** **N = 130**
EMBRACA (second data cut-off: 30 September 2019)		
Treatment duration [months]		
Median [min; max]	6.9 [0.0; 61.4]	3.1 [0.0; 36.1]
Mean (SD)	ND	ND
Observation period [months]		
Overall survival	ND	ND
Morbidity	ND	ND
Health-related quality of life	ND	ND
Side effects	ND	ND

a. Capecitabine or vinorelbine or eribulin at the physician's discretion.

max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

In the EMBRACA study, median treatment duration in the talazoparib arm was 6.9 months and thus about twice as long as in the chemotherapy arm (3.1 months).

There was no information on the observation period for the relevant subpopulation for any of the outcomes. According to the study protocol, the outcomes on morbidity, health-related quality of life as well as side effects were recorded until 30 days after the end of treatment (for information on the planned follow-up observation, see Table 8), so that for the observation period of these outcomes a similarly large difference between the treatment arms as in the treatment duration can be assumed.

Subsequent therapies

Follow-up therapies after discontinuation of the study medication were not specified in the study protocol, and a planned switch of patients from the chemotherapy arm to treatment with talazoparib was not planned in the study. A list of received subsequent therapies for the total population at the time of the first data cut-off (15 September 2017) is shown in Appendix B of the full dossier assessment. Carboplatin was the most common subsequent therapy in both treatment arms, followed by capecitabine, gemcitabine, endocrine therapy and eribulin in the talazoparib arm. In the chemotherapy arm, the second most common therapy was gemcitabine, followed by endocrine therapy, olaparib and eribulin. Information on the second data cut-off is not available. There is no such list of received subsequent therapies for the relevant subpopulation. The data in Module 4 A only show that at the time of the second data cut-off (30 September 2019) 4.5% of the patients in the talazoparib arm and 32.6% of the patients in the chemotherapy arm were treated with a poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor as subsequent therapy after the study medications, the vast majority received olaparib. The use of olaparib as subsequent therapy is an approved treatment option.

Risk of bias across outcomes (study level)

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

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: talazoparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
EMBRACA	Yes	Yes	No	No	Yes	No[a]	High

a. Large difference between the treatment groups regarding the proportion of patients who discontinued the study before the first treatment with the study medication: 1 (0.4%) patient in the talazoparib arm and 16 (12.3%) patients in the chemotherapy arm in the relevant subpopulation. This applies to all outcomes.

RCT: randomized controlled trial; vs.: versus

The risk of bias across outcomes was rated as high for the EMBRACA study, since there was a large difference (approx. 12 percentage points) between the two study arms in the proportion of patients who had discontinued the study before the first administration of the study medication. Upon the analysis of all outcomes, this results in a high difference between the treatment groups (> 5 percentage points) regarding the proportion of patients not included in the analysis. Especially in the chemotherapy arm, censorings at month 0 are also shown for the outcome "overall survival". The company addresses this aspect neither at study level nor for any of the outcomes and rates the risk of bias as low.

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

Transferability of the study results to the German health care context

The company points out that the patient characteristics of the population in the EMBRACA study largely reflect the situation in the German population in terms of family origin, proportion of men, pretreatment, weight, height and age and refers to registry data of the Robert Koch Institute [21]. With regard to prior therapies, the company further states that the treatment status of the population in the EMBRACA study corresponds to the guideline recommendations [18,19,22] and to the current registry data of German healthcare research [23,24]. Moreover, from the company's point of view, treatment in both study arms corresponds to the treatment standard in the present therapeutic indication [18,19,22]. In addition, the company states that the subgroup analyses in the EMBRACA study did not show any effect-modifying influences relevant for the conclusion that may indicate significant uneven distribution between the study arms.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
  - overall survival
- Morbidity
  - symptoms recorded with the symptom scales of the instruments EORTC QLQ-C30 and EORTC QLQ-BR23
- Health-related quality of life
  - recorded with the global health status and the functional scales of the EORTC QLQ-C30 as well as the functional scales of the EORTC QLQ-BR23
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - myelodysplastic syndrome (preferred term [PT], CTCAE grade ≥ 3)
  - acute myeloid leukaemia (PT, CTCAE grade ≥ 3)

- hand-foot syndrome (PT, AEs)
- if applicable, further specific AEs

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

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

Table 12: Matrix of outcomes – RCT, direct comparison: talazoparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin

Study	Outcomes									
	Overall survival	**Symptoms (EORTC QLQ-C30, EORTC QLQ-BR23)**	**Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23)**	**SAEs**	**Severe AEs (CTCAE grade ≥ 3)**	**Discontinuation due to AEs**	**Myelodysplastic syndrome (PT, CTCAE grade ≥ 3)**	**Acute myeloid leukaemia (PT, CTCAE grade ≥ 3)**	**Hand-foot syndrome (PT, AEs)**	**Further specific AEs[a]**
EMBRACA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. The following events are considered (MedDRA coding): "anaemia (PT, CTCAE grade ≥ 3)", "thrombocytopenia (PT, CTCAE grade ≥ 3)", "neutropenia (PT, CTCAE grade ≥ 3)", "diarrhoea (PT, CTCAE grade ≥ 3)", "skin and subcutaneous tissue disorders (SOC, CTCAE grade ≥ 3)", "eye disorders (SOC, AEs)" and "paraesthesia (PT, AEs)".

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

For the outcomes "symptoms" and "health-related quality of life", the company presented responder analyses for the time to first and definitive deterioration. The corresponding response criterion was a deterioration by at least 10 points versus baseline. Deterioration was considered to be definitive if the response criterion was also met in all subsequent observations. Both operationalizations are patient-relevant. In the present data situation, however, the analyses on definitive deterioration are not suitable to make a statement on definitive deterioration; this is described below:

With regard to all randomized patients, the proportion of patients with completed questionnaires is lower in the chemotherapy arm than in the talazoparib arm already at the beginning. Because progression (and thus the end of treatment and observation) occurred earlier in the chemotherapy arm than in the intervention arm (see Module 4A, Section 4.3.1.3.1.2.1), the response rate to questionnaires decreased more strongly in the chemotherapy arm than in the talazoparib arm in the further course. Thus, there is a clear difference between the treatment arms in the proportion of patients with available documentation at an early stage. Moreover, for the analysis on definitive deterioration it finally remains unclear whether patients who did not have subsequent recordings after the observation of a first deterioration were classified as patients with an event or censored. For the present benefit assessment, the analyses on first deterioration are used for the reasons mentioned above.

For the outcomes “SAEs”, “severe AEs” and “discontinuation due to AEs”, the analyses are based on the respective overall rates. The company also considers the overall rate, excluding disease-specific progression events. However, for these analyses the information provided by the company in the dossier does not indicate which events the company classified as disease-specific progression events. In the present data situation, it can be assumed, e.g. due to the low proportion of events in the System Organ Class (SOC) “benign, malignant and unspecified neoplasms (including cysts and polyps)” in the AEs (see Table 23 of the full dossier assessment), that the disease-specific progression events have no relevant effect on the results for the overall rates of severe AEs, SAEs and discontinuation due to AEs.

2.4.2 Risk of bias

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

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: talazoparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin

Study		Outcomes									
	Study level	Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-BR23)	Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23)	SAEs	Severe AEs (CTCAE grade ≥ 3)	Discontinuation due to AEs	Myelodysplastic syndrome (PT, CTCAE grade ≥ 3)	Acute myeloid leukaemia (PT, CTCAE grade ≥ 3)	Hand-foot syndrome (PT, AEs)	Further specific AEs[a]
EMBRACA	H	H[b]	H[b, c, d]	H[b, c, d]	H[b, d]	H[b, d]	H[b, c]	H[b, d]	H[b, d]	H[b, c, d]	H[b, c, d]

a. The following events are considered (MedDRA coding): "anaemia (PT, CTCAE grade ≥ 3)", "thrombocytopenia (PT, CTCAE grade ≥ 3)", "neutropenia (PT, CTCAE grade ≥ 3)", "diarrhoea (PT, CTCAE grade ≥ 3)", "skin and subcutaneous tissue disorders (System Organ Class [SOC], CTCAE grade ≥ 3)", "eye disorders (SOC, AEs)" and "paraesthesia (PT, AEs)".
b. High risk of bias across outcomes.
c. Lack of blinding in subjective recording of outcomes (except for specific AEs with CTCAE grade ≥ 3) or subjective request for treatment discontinuation (discontinuation due to AEs)
d. Incomplete observations for potentially informative reasons.

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

There is a high risk of bias for the results on all outcomes, as there is already a high risk of bias across outcomes (see Section 2.3.2 on the risk of bias across outcomes).

Apart from the outcomes "overall survival" and "discontinuation due to AEs", the high risk of bias for the results on all outcomes is additionally due to the fact that the observation of outcomes was incomplete for potentially informative reasons. Moreover, the results for the outcomes "symptoms", "health-related quality of life", "discontinuation due to AEs" as well as the specific AEs "hand-foot syndrome", "eye disorders" and "paraesthesia" have a high risk of bias due to the lack of blinding in subjective recording of outcomes or subjective request for treatment discontinuation.

Deviating from this, the company rated the risk of bias for the result on the outcome "overall survival" as low. For the results on symptoms, health-related quality of life and side effects, the company assessed the risk of bias as high due to the lack of blinding.

2.4.3 Results

Table 14 summarizes the results on the comparison of talazoparib with the ACT in patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Results on common AEs, SAEs and severe AEs (CTCAE grade ≥ 3) are presented in Appendix C of the full dossier assessment. Kaplan-Meier curves on the included outcomes are presented in Appendix D of the full dossier assessment.

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: talazoparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin (multipage table)

Study Outcome category Outcome	Talazoparib		Physician's choice chemotherapy[a]		Talazoparib vs. physician's choice chemotherapy[a]
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
EMBRACA (second data cut-off: 30 September 2019)					
Mortality					
Overall survival	266	19.6 [16.7; 22.7] 199 (74.8)	130	19.8 [17.6; 22.4] 97 (74.6)	0.86 [0.67; 1.10]; 0.236
Morbidity					
Symptoms					
EORTC QLQ-C30 – symptom scales, time to first deterioration[c]					
Fatigue	243	2.1 [1.5; 2.8] 166 (68.3)	104	1.5 [1.4; 1.9] 69 (66.3)	0.74 [0.55; 0.99]; 0.043
Nausea and vomiting	243	3.8 [2.3; 7.5] 139 (57.2)	104	3.0 [1.5; 11.3] 51 (49.0)	0.93 [0.66; 1.30]; 0.659
Pain	243	5.7 [4.0; 9.7] 130 (53.5)	104	2.9 [1.6; 4.9] 61 (58.7)	0.55 [0.40; 0.75]; < 0.001
Dyspnoea	243	8.4 [5.6; 10.8] 122 (50.2)	104	7.8 [5.1; NC] 36 (34.6)	0.99 [0.67; 1.45]; 0.940
Insomnia	243	10.4 [7.0; 17.1] 109 (44.9)	104	3.2 [1.8; 8.1] 53 (51.0)	0.54 [0.38; 0.76]; < 0.001
Appetite loss	243	7.4 [4.9; 11.9] 128 (52.7)	104	2.3 [1.5; 4.2] 58 (55.8)	0.60 [0.44; 0.84]; 0.002
Constipation	243	7.2 [5.7; 10.1] 118 (48.6)	104	10.1 [3.7; NC] 37 (35.6)	1.03 [0.70; 1.50]; 0.884
Diarrhoea	243	10.7 [8.2; 16.0] 103 (42.4)	104	NA [3.5; NC] 34 (32.7)	0.79 [0.53; 1.19]; 0.256
EORTC QLQ-BR23 – symptom scales, time to first deterioration[c]					
Side effects of systemic therapy	243	9.3 [5.8; 12.5] 119 (49.0)	104	3.5 [2.1; 10.6] 50 (48.1)	0.65 [0.46; 0.92]; 0.013
Symptoms in chest region	243	37.4 [23.5; NC] 59 (24.3)	104	12.5 [8.8; NC] 29 (27.9)	0.54 [0.34; 0.86]; 0.008
Symptoms in arm region	243	6.9 [4.2; 14.9] 122 (50.2)	104	3.9 [2.1; 11.9] 49 (47.1)	0.70 [0.50; 0.99]; 0.044
Upset by hair loss	No usable data[d]				

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: talazoparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin (multipage table)

Study Outcome category Outcome	Talazoparib		Physician's choice chemotherapy[a]		Talazoparib vs. physician's choice chemotherapy[a]
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
Health-related quality of life					
EORTC QLQ-C30 – global health status and functional scales, time to first deterioration[e]					
Global health status	243	5.7 [3.8; 7.8] 130 (53.5)	104	3.3 [2.1; 5.0] 55 (52.9)	0.61 [0.44; 0.85]; 0.003
Physical functioning	243	9.3 [7.7; 14.9] 109 (44.9)	104	2.8 [2.1; 6.6] 53 (51.0)	0.51 [0.36; 0.72]; < 0.001
Role functioning	243	4.6 [3.5; 6.6] 135 (55.6)	104	1.7 [1.1; 3.0] 64 (61.5)	0.56 [0.41; 0.77]; < 0.001
Cognitive functioning	243	4.4 [3.0; 7.5] 141 (58.0)	104	2.8 [1.7; 3.7] 56 (53.8)	0.71 [0.51; 0.98]; 0.038
Emotional functioning	243	10.7 [6.4; 24.3] 101 (41.6)	104	3.5 [2.3; 9.9] 49 (47.1)	0.54 [0.38; 0.77]; < 0.001
Social functioning	243	8.2 [4.9; 12.5] 122 (50.2)	104	2.3 [1.6; 4.9] 54 (51.9)	0.60 [0.43; 0.84]; 0.003
EORTC QLQ-BR23 – functional scales, time to first deterioration[e]					
Body image	243	17.7 [11.5; NC] 88 (36.2)	104	4.9 [2.8; NC] 42 (40.4)	0.56 [0.38; 0.81]; 0.002
Sexual activity	243	32.8 [7.5; NC] 92 (37.9)	104	14.0 [3.6; NC] 33 (31.7)	0.95 [0.63; 1.42]; 0.799
Enjoyment of sex	No usable data[d]				
Future perspective	243	NA [24.8; NC] 68 (28.0)	104	NA [6.1; NC] 27 (26.0)	0.70 [0.44; 1.11]; 0.129
Side effects					
AEs (supplementary information)	265	0.2 [0.1; 0.3] 261 (98.5)	114	0.1 [0.1; 0.2] 111 (97.4)	–
SAEs[f]	265	20.7 [15.3; 31.1] 95 (35.8)	114	NA [6.7; NC] 33 (28.9)	0.75 [0.49; 1.13]; 0.162
Severe AEs (CTCAE grade ≥ 3)[f]	265	3.5 [2.8; 4.0] 183 (69.1)	114	2.0 [1.3; 3.5] 72 (63.2)	0.73 [0.55; 0.97]; 0.027
Discontinuation due to AEs[f]	265	NA 21 (7.9)	114	NA 10 (8.8)	0.59 [0.27; 1.27]; 0.169
Myelodysplastic syndrome[g] (PT, CTCAE grade ≥ 3)	265	0 (0)[h]	114	0 (0)[h]	NC[i]
Acute myeloid leukaemia (PT, CTCAE grade ≥ 3)	265	0 (0)[h]	114	0 (0)[h]	NC[i]

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: talazoparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin (multipage table)

Study Outcome category Outcome	Talazoparib		Physician's choice chemotherapy[a]		Talazoparib vs. physician's choice chemotherapy[a]
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
Hand-foot syndrome (PT, AEs)[k]	265	NA 4 (1.5)	114	NA 28 (24.6)	0.05 [0.02; 0.14]; < 0.001
Anaemia (PT, CTCAE grade ≥ 3)	265	18.1 [11.6; NC] 103 (38.9)	114	NA 5 (4.4)	7.23 [2.93; 17.79]; < 0.001
Thrombocytopenia (PT, CTCAE grade ≥ 3)	265	NA 22 (8.3)	114	NA 1 (0.9)	8.34 [1.12; 61.98]; 0.013
Neutropenia (PT, CTCAE grade ≥ 3)	265	NA 50 (18.9)	114	NA 26 (22.8)	0.61 [0.38; 0.99]; 0.044
Diarrhoea (PT, CTCAE grade ≥ 3)	265	NA 2 (0.8)	114	NA [11.8; NC] 6 (5.3)	0.12 [0.02; 0.58]; 0.002
Skin and subcutaneous tissue disorders (SOC, CTCAE grade ≥ 3)	265	NA 2 (0.8)	114	NA [16.5; NC] 8 (7.0)	0.04 [0.01; 0.32]; < 0.001
Eye disorders (SOC, AEs)	265	NA 35 (13.2)	114	20.0 [20.0; NC] 21 (18.4)	0.38 [0.21; 0.68]; < 0.001
Paraesthesia (PT, AEs)	265	NA 13 (4.9)	114	NA 14 (12.3)	0.23 [0.10; 0.53]; < 0.001

a. Capecitabine or vinorelbine or eribulin at the physician's choice.
b. HR and CI: Cox proportional hazards model; p-value: log-rank test; each stratified according to the number of prior lines of chemotherapy for locally advanced and/or metastatic disease (0/1–3), TNBC status of the last biopsy (yes/no) and CNS metastases in the medical history (yes/no).
c. An increase of the respective score by at least 10 points was considered as clinically relevant deterioration.
d. At baseline, about 75% and 63% of the patients had no hair loss and no sexual activity. These patients were censored by the company at month 0. The approach of the company does not ensure that the burden of patients who only develop hair loss or become sexually active in the course of the treatment is recorded.
e. A decrease of the respective score by ≥ 10 points was considered as clinically relevant deterioration.
f. In Module 4 A, the company additionally considered analyses excluding disease-specific progression events, whereby it is not apparent which events the company assessed as disease-specific progression events. The results on the analyses under exclusion of disease-specific progression events are consistent with the results presented above (see Module 4 A, Section 4.3.1.3.1.4.1 of the full dossier assessment).
g. The company considered the SMQ "MDS" for MDS, which presents no sufficiently specific operationalization for the present benefit assessment. The results on the SMQ "MDS" show that 1 (0.4%) patient in the talazoparib arm and no patient in the chemotherapy arm had a severe event (CTCAE grade ≥ 3).
h. Institute's calculation
i. Since no event occurred, the HR cannot be estimated.

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: talazoparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin (multipage table)

Study Outcome category Outcome	Talazoparib		Physician's choice chemotherapy[a]		Talazoparib vs. physician's choice chemotherapy[a]
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
j. The company stated that it was to consider the SMQ "AML", although this is not an SMQ according to MedDRA, but rather a compilation of PTs predefined by the company, which present no sufficiently specific operationalization for the present benefit assessment. In the compilation of PTs on AML considered by the company, no patient in the talazoparib arm and one (0.9%) patient in the chemotherapy arm had a severe event (CTCAE grade ≥ 3). k. 1 (0.4%) patient in the talazoparib arm and 3 (2.6%) patients in the chemotherapy arm had a severe hand-foot syndrome (CTCAE grade ≥ 3). AE: adverse event; AML: acute myeloid leukaemia; CI: confidence interval; CNS: central nervous system; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organization for Research and Treatment of Cancer; HR: Hazard Ratio; MDS: myelodysplastic syndrome; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; PT: Preferred Term; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: standardized MedDRA Query; SOC: System Organ Class; TNBC: triple-negative breast cancer; vs.: versus					

Based on the available data, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

Mortality

Overall survival

No statistically significant difference between the treatment groups was shown for the outcome "overall survival". This resulted in no hint of an added benefit of talazoparib in comparison with the ACT; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Symptoms (symptom scales of EORTC QLQ-C30 and EORTC-QLQ-BR23)

In the EMBRACA study, outcomes on symptoms were recorded using the EORTC QLQ-C30 and EORTC QLQ-BR23 symptom scales. In each case, the time to first deterioration by ≥ 10 points was considered (see Section 2.4.1).

This deviates from the approach of the company, which considered both the time to first deterioration and the time to definitive deterioration.

Fatigue (EORTC QLQ-C30), side effects of the systemic therapy and symptoms in arm region (EORTC QLQ-BR23)

For the EORTC QLQ-C30 symptom scale "fatigue", as well as for the symptom scales "side effects of systemic therapy" and "symptoms in arm region" of the EORTC QLQ-BR23, there is a statistically significant difference in favour of talazoparib versus physician's choice chemotherapy (capecitabine or vinorelbine or eribulin). However, the extent of the effect was no more than marginal (see Section 2.5.1). This resulted in no hint of an added benefit of talazoparib in comparison with the ACT for any of these symptom scales; an added benefit is therefore not proven.

This deviates from the assessment of the company, which derived an indication of an added benefit for each of these symptom scales.

Nausea and vomiting, dyspnoea, constipation and diarrhoea (EORTC QLQ-C30)

No statistically significant difference between the treatment groups was shown for any of the EORTC QLQ-C30 symptom scales on nausea and vomiting, dyspnoea, constipation and diarrhoea. This resulted in no hint of an added benefit of talazoparib in comparison with the ACT for each of these symptom scales; an added benefit is therefore not proven.

This deviates from the assessment of the company, which derived an indication of an added benefit for each of these symptom scales.

Pain, insomnia, appetite loss (EORTC QLQ-C30) and symptoms in chest region (EORTC QLQ-BR23)

For the EORTC QLQ-C30 symptom scales "pain", "insomnia" and "appetite loss", as well as for the symptom scale "symptoms in chest region" of the EORTC QLQ-BR23, there is a statistically significant difference in favour of talazoparib versus physician's choice chemotherapy (capecitabine or vinorelbine or eribulin). This resulted in a hint of an added benefit of talazoparib in comparison with the ACT for each of these symptom scales.

This concurs with the assessment of the company insofar as the company also derived an added benefit for each of the symptom scales mentioned, but assessed the certainty of conclusions as an indication despite the high risk of bias.

Upset by hair loss (EORTC QLQ-BR23)

There were no usable analyses for the symptom scale "upset by hair loss" of the EORTC QLQ-BR23, because the company's approach does not ensure that the burden of patients who develop hair loss in the course of the treatment is also recorded. This resulted in no hint of an added benefit of talazoparib in comparison with the ACT; an added benefit is therefore not proven.

This concurs with the assessment of the company insofar as the company arrived at the same result on the basis of the analyses used by it.Health-related quality of life

EORTC QLQ-C30 (functional scales, scale on global health status) and EORTC QLQ-BR23 (functional scales)

Health-related quality of life was recorded using the global health status and the EORTC QLQ-C30 functional scales as well as the EORTC QLQ-BR23 functional scales. In each case, the time to first deterioration by ≥ 10 points was considered (see Section 2.4.1).

This deviates from the approach of the company, which considered both the time to first deterioration and the time to definitive deterioration.

Global health status, physical functioning, role functioning, cognitive functioning, emotional functioning, social functioning (EORTC QLQ-C30), body image (EORTC QLQ-BR23)

For the global health status and for the functional scales "physical functioning", "role functioning", "cognitive functioning", "emotional functioning" and "social functioning" recorded using the EORTC QLQ-C30, and for the EORTC QLQ-BR23 functional scale "body image", there is a statistically significant difference each in favour of talazoparib versus a physician's choice chemotherapy (capecitabine or vinorelbine or eribulin). For the scale "global health status" and for each of the cited functional scales, there is a hint of an added benefit in favour of talazoparib.

This concurs with the assessment of the company insofar as the company also derived an added benefit for the scale "global health status" and for each of the mentioned functional scales, but assessed the certainty of conclusions as an indication despite the high risk of bias.

Sexual activity and future perspective (EORTC QLQ-BR23)

No statistically significant difference between the treatment groups was shown for the functional scales "sexual activity" and "future perspective" recorded with EORTC QLQ-BR23. For these functional scales, this resulted in no hint of an added benefit of talazoparib in comparison with the ACT; an added benefit is therefore not proven.

The assessment on the functional scale "sexual activity" deviates from that of the company, which derived an indication of an added benefit for this scale. The assessment on the functional scale "future perspective" concurs with that of the company insofar as the company arrived at the same result on the basis of the analyses used by it.

Enjoyment of sex (EORTC QLQ-BR23)

There were no usable analyses for the functional scale "enjoyment of sex" of the EORTC QLQ-BR23, because the company's approach does not ensure that the burden of patients who become sexually active in the course of treatment is also recorded. This resulted in no hint of an added benefit of talazoparib in comparison with the ACT; an added benefit is therefore not proven.

This concurs with the assessment of the company insofar as the company arrived at the same result on the basis of the analyses used by it.

Side effects

SAEs

No statistically significant difference between the treatment groups was shown for the outcome "SAEs". This resulted in no hint of greater or lesser harm from talazoparib in comparison with the ACT; greater or lesser harm is therefore not proven.

This concurs with the assessment of the company insofar as the company arrived at the same result on the basis of the analyses used by it.

Severe AEs (CTCAE grade ≥ 3)

For the outcome "severe AEs (CTCAE grade ≥ 3)", there was a statistically significant difference in favour of talazoparib versus physician's choice chemotherapy (capecitabine or vinorelbine or eribulin). This resulted in a hint of lesser harm from talazoparib in comparison with the ACT.

This concurs with the assessment of the company insofar as the company also derived an added benefit on the basis of the analyses used by it; however, the company assessed the certainty of conclusions as an indication despite the high risk of bias.

Discontinuation due to AEs

There was no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from talazoparib in comparison with the ACT; greater or lesser harm is therefore not proven.

This concurs with the assessment of the company insofar as the company arrived at the same result on the basis of the analyses used by it.

Specific AEs

Myelodysplastic syndrome and acute myeloid leukaemia (each CTCAE grade ≥ 3)

In both arms, no events occurred in the specific AEs "myelodysplastic syndrome" and "acute myeloid leukaemia", both CTCAE grade ≥ 3. Hence, there was no hint of greater or lesser harm from talazoparib in comparison with the ACT for any of these outcomes; greater or lesser harm is therefore not proven.

This concurs with the assessment of the company insofar as the company arrived at the same result on the basis of the analyses used by it.

Skin and subcutaneous tissue disorders, neutropenia and diarrhoea (each CTCAE grade ≥ 3)

For the specific AEs "skin and subcutaneous tissue disorders", "neutropenia" and "diarrhoea" (each of them CTCAE grade ≥ 3)", there was a statistically significant difference in favour of

talazoparib versus physician's choice chemotherapy (capecitabine or vinorelbine or eribulin). This resulted in a hint of lesser harm from talazoparib in comparison with the ACT for each of the mentioned specific AEs.

For the specific AE "skin and subcutaneous tissue disorders (CTCAE grade ≥ 3)", the assessment concurs with that of the company insofar as the company derived an added benefit for the SOC, irrespectitve of the severity. For the specific AEs "neutropenia" and "diarrhoea" (both CTCAE grade ≥ 3), the company performed no separate derivation of greater or lesser harm, but derived a lesser benefit for the SOC "blood and lymphatic system disorders" (including neutropenia) and an added benefit of talazoparib versus the ACT for the SOC "gastrointestinal disorders" (including diarrhoea), irrespective of the severity. The company only commented on the certainty of conclusions when an added benefit was derived and assessed this as an indication despite the high risk of bias.

Anaemia, thrombocytopenia (each CTCAE grade ≥ 3)

For the specific AEs "anaemia" and "thrombocytopenia" (each of them CTCAE grade ≥ 3), there was a statistically significant difference to the disadvantage of talazoparib versus physician's choice chemotherapy (capecitabine or vinorelbine or eribulin). This resulted in a hint of greater harm from talazoparib in comparison with the ACT for each of the mentioned specific AEs.

For the specific AEs "anaemia" and "thrombocytopenia" (both CTCAE grade ≥ 3), the company performed no separate derivation of greater or lesser harm, but derived a lesser benefit of talazoparib versus the ACT for the SOC "blood and lymphatic system disorders" (including anaemia and thrombocytopenia), irrespective of the severity, without making any statement on the certainty of conclusions.

Eye disorders, hand-foot syndrome and paraesthesia

For the specific AEs "eye disorders", "hand-foot syndrome" and "paraesthesia", there was a statistically significant difference in favour of talazoparib versus physician's choice chemotherapy (capecitabine or vinorelbine or eribulin). This resulted in a hint of lesser harm from talazoparib in comparison with the ACT for each of the mentioned specific AEs.

For the specific AE eye disorders, the assessment concurs with that of the company insofar as the company derived an added benefit instead of lesser harm, but assessed the certainty of conclusions as an indication despite the high risk of bias. For the specific AEs "hand-foot syndrome" and "paraesthesia", the company performed no separate derivation of greater or lesser harm, but derived an added benefit of talazoparib versus the ACT for the SOC "skin and subcutaneous tissue disorders (including hand-foot syndrome)" and for the SOC "nervous system disorders (including paraesthesia)"; in doing so, the company assessed the certainty of conclusions as an indication despite the high risk of bias.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics were considered in the present benefit assessment:

- age (< 50 years, ≥ 50 years)
- sex (female, male)

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

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

In accordance with the methods described, no relevant effect modification by age or sex was identified for the outcomes for which usable analyses were available.

2.5 Probability and extent of added benefit

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

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

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 15).

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

The dossier does not provide information for every outcome considered in the present benefit assessment whether it was serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Fatigue, pain, insomnia and appetite loss (EORTC QLQ-C30 [symptom scales]), as well as side effects of the systemic therapy, symptoms in chest region and symptoms in arm region (EORTC QLQ-BR23 [symptom scales])

The dossier contains no information that would allow an assignment of the severity category for the symptom scales "fatigue", "appetite loss", "pain" and "insomnia" of the EORTC QLQ-C30, as well as “side effects of systemic treatment”, “symptoms in chest region” and

"symptoms in arm region" of the EORTC QLQ-BR23. Therefore, these symptom scales were each assigned to the outcome category "non-serious/non-severe symptoms/late complications".

The company did not assign the mentioned symptom scales to a severity category, but regarding fatigue and pain as well as symptoms recorded with the symptom scales of the EORTC QLQ-BR23 it stated that the mentioned symptoms affected the patients.

Specific AEs

Hand-foot syndrome

The majority of the events that occurred in this outcome were non-severe (CTCAE grade < 3). Only 1 (0.4%) patient in the talazoparib arm and 3 (2.6%) patients in the chemotherapy arm had a severe hand-foot syndrome (CTCAE grade ≥ 3). The outcome "hand-foot syndrome" was therefore allocated to the category of non-serious/non-severe side effects.

For this outcome, the company did not assign the effects to a severity category, but explained that this was a particularly distressing side effect with varying severity degrees.

Eye disorders and paraesthesia

For these two outcomes, no data are available on severe (CTCAE grade ≥ 3) or serious AEs, therefore the two specific AEs "eye disorders" and "paraesthesia" will each be assigned to the outcome category "non-serious/non-severe side effects".

The company did not assign the mentioned outcomes to a severity category.

Table 15: Extent of added benefit at outcome level: talazoparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin (multipage table)

Outcome category **Outcome**	**Talazoparib vs. physician's choice chemotherapy[a]** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI]; p-value** **probability[b]**	**Derivation of extent[c]**
Mortality		
Overall survival	19.6 vs. 19.8 months HR: 0.86 [0.67; 1.10]; p = 0.236	Lesser benefit/added benefit not proven
Morbidity		
Symptoms		
EORTC QLQ-C30 – symptom scales, time to first deterioration		
Fatigue	2.1 vs. 1.5 months HR: 0.74 [0.55; 0.99]; p = 0.043	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[d]
Nausea and vomiting	3.8 vs. 3.0 months HR: 0.93 [0.66; 1.30]; p = 0.659	Lesser benefit/added benefit not proven
Pain	5.7 vs. 2.9 months HR: 0.55 [0.40; 0.75]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
Dyspnoea	8.4 vs. 7.8 months HR: 0.99 [0.67; 1.45]; p = 0.940	Lesser benefit/added benefit not proven
Insomnia	10.4 vs. 3.2 months HR: 0.54 [0.38; 0.76]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
Appetite loss	7.4 vs. 2.3 months HR: 0.60 [0.44; 0.84]; p = 0.002 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: "minor"
Constipation	7.2 vs. 10.1 months HR: 1.03 [0.70; 1.50]; p = 0.884	Lesser benefit/added benefit not proven
Diarrhoea	10.7 months vs. NA HR: 0.79 [0.53; 1.19]; p = 0.256	Lesser benefit/added benefit not proven
EORTC QLQ-BR23 – functional scales, time to first deterioration		
Side effects of systemic therapy	9.3 vs. 3.5 months HR: 0.65 [0.46; 0.92]; p = 0.013	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[d]

Table 15: Extent of added benefit at outcome level: talazoparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin (multipage table)

Outcome category **Outcome**	**Talazoparib vs. physician's choice chemotherapy[a]** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI]; p-value** **probability[b]**	**Derivation of extent[c]**
Symptoms in chest region	37.4 vs. 12.5 months HR: 0.54 [0.34; 0.86]; p = 0.008 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: "minor"
Symptoms in arm region	6.9 vs. 3.9 months HR: 0.70 [0.50; 0.99]; p = 0.044	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[d]
Upset by hair loss	No usable data	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 – global health status and functional scales, time to first deterioration		
Global health status	5.7 vs. 3.3 months HR: 0.61 [0.44; 0.85]; p = 0.003 probability: "hint"	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ added benefit, extent: "considerable"
Physical functioning	9.3 vs. 2.8 months HR: 0.51 [0.36; 0.72]; p < 0.001 probability: "hint"	Outcome category: health-related quality of life $CI_u < 0.75$ and risk ≥ 5% added benefit, extent: "major"
Role functioning	4.6 vs. 1.7 months HR: 0.56 [0.41; 0.77]; p < 0.001 probability: "hint"	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ added benefit, extent: "considerable"
Cognitive functioning	4.4 vs. 2.8 months HR: 0.71 [0.51; 0.98]; p = 0.038 probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
Emotional functioning	10.7 vs. 3.5 months HR: 0.54 [0.38; 0.77]; p < 0.001 probability: "hint"	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ added benefit, extent: "considerable"
Social functioning	8.2 vs. 2.3 months HR: 0.60 [0.43; 0.84]; p = 0.003 probability: "hint"	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ added benefit, extent: "considerable"
EORTC QLQ-BR23 – functional scales, time to first deterioration		
Body image	17.7 vs. 4.9 months HR: 0.56 [0.38; 0.81]; p = 0.002 probability: "hint"	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ added benefit, extent: "considerable"
Sexual activity	32.8 vs. 14.0 months HR: 0.95 [0.63; 1.42]; p = 0.799	Lesser benefit/added benefit not proven
Enjoyment of sex	No usable data	Lesser benefit/added benefit not proven

Table 15: Extent of added benefit at outcome level: talazoparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin (multipage table)

Outcome category **Outcome**	**Talazoparib vs. physician's choice chemotherapy[a]** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI]; p-value** **probability[b]**	**Derivation of extent[c]**
Future perspective	NA vs. NA HR: 0.70 [0.44; 1.11]; p = 0.129	Lesser benefit/added benefit not proven
Side effects		
SAEs	20.7 months vs. NA HR: 0.75 [0.49; 1.13]; p = 0.162	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)	3.5 vs. 2.0 months HR: 0.73 [0.55; 0.97]; p = 0.027 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ lesser harm, extent: "minor"
Discontinuation due to AEs	NA vs. NA HR: 0.59 [0.27; 1.27]; p = 0.169	Greater/lesser harm not proven
Myelodysplastic syndrome (PT, CTCAE grade ≥ 3)	Proportions of events: 0 % vs. 0 % HR: NC	Greater/lesser harm not proven
Acute myeloid leukaemia (PT, CTCAE grade ≥ 3)	Proportions of events: 0 % vs. 0 % HR: NC	Greater/lesser harm not proven
Hand-foot syndrome (PT, AEs)	NA vs. NA HR: 0.05 [0.02; 0.14]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Anaemia (PT, CTCAE grade ≥ 3)	18.1 months vs. NA HR: 7.23 [2.93; 17.79]; p < 0.001 HR: 0.14 [0.06; 0.34][e] probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% greater harm, extent: "major"
Thrombocytopenia (PT, CTCAE grade ≥ 3)	NA vs. NA HR: 8.34 [1.12; 61.98]; p = 0.013 HR: 0.12 [0.02; 0.89][e] probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Neutropenia (PT, CTCAE grade ≥ 3)	NA vs. NA HR: 0.61 [0.38; 0.99]; p = 0.044 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ lesser harm, extent: "minor"
Diarrhoea (PT, CTCAE grade ≥ 3)	NA vs. NA HR: 0.12 [0.02; 0.58]; p = 0.002 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% lesser harm, extent: "major"
Skin and subcutaneous tissue disorders (SOC, CTCAE grade ≥ 3)	NA vs. NA HR: 0.04 [0.01; 0.32]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% lesser harm, extent: "major"

Table 15: Extent of added benefit at outcome level: talazoparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin (multipage table)

Outcome category **Outcome**	**Talazoparib vs. physician's choice chemotherapy[a]** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI]; p-value** **probability[b]**	**Derivation of extent[c]**
Eye disorders (SOC, AEs)	NA vs. 20.0 months HR: 0.38 [0.21; 0.68]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: "considerable"
Paraesthesia (PT, AEs)	NA vs. NA HR: 0.23 [0.10; 0.53]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: "considerable"

a. Capecitabine or vinorelbine or eribulin at the physician's choice.
b. Probability provided if a statistically significant and relevant effect is present.
c. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
d. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
e. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of CI; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NA: not achieved; NC: not calculable; ND: no data; PT: Preferred Term; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module; QLQ-C30: Quality of Life Questionnaire-Lung Cancer 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 16 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 16: Positive and negative effects from the assessment of talazoparib in comparison with the ACT

Positive effects	Negative effects
Health-related quality of life ▪ global health status, role functioning, emotional functioning, social functioning, body image: hint of an added benefit – extent: considerable ▪ physical functioning: hint of an added benefit – extent: "major" ▪ cognitive functioning: hint of an added benefit – extent: "minor"	–
Serious/severe side effects ▪ severe AEs (CTCAE grade ≥ 3): hint of lesser harm – extent: "minor" ▫ specific AEs (CTCAE grade ≥ 3): - neutropenia: hint of lesser harm – extent: "minor" - skin and subcutaneous tissue disorders, diarrhoea: hint of lesser harm, extent: "major"	Serious/severe side effects ▪ specific AEs (CTCAE grade ≥ 3): ▫ anaemia, hint of greater harm – extent: "major" ▫ thrombocytopenia: hint of greater harm – extent: "considerable"
Non-serious/non-severe symptoms/late complications ▪ pain, insomnia: hint of an added benefit – extent "considerable" ▪ appetite loss, symptoms in chest region: hint of an added benefit – extent: "minor"	–
Non-serious/non-severe side effects ▪ specific AEs: ▫ hand-foot syndrome, eye disorders, paraesthesia: hint of lesser harm – extent: "considerable"	–
ACT: appropriate comparator therapy; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events	

In the overall consideration, there were mostly positive and only few negative effects of talazoparib in comparison with the ACT.

Advantages are shown in “health-related quality of life”, here in “global health status”, all EORTC QLQ-C30 functional scales and the functional scale “body image” of the EORTC QLQ-BR23, most of them of considerable extent.

In the category “non-serious/non-severe symptoms/late complications”, advantages are also found in the EORTC QLQ-C30 symptom scales “pain”, “insomnia” and “appetite loss”, as well as in the EORTC QLQ-BR23 symptoms scale “symptoms in chest region”, with an extent of “minor to considerable”.

Besides the positive ones, there were also negative effects of talazoparib in comparison with the ACT in “serious/severe side effects”. An advantage with the extent “minor” was shown in the severe AEs (CTCAE grade ≥ 3). These include the specific AEs “neutropenia”, “skin and subcutaneous tissue disorders” and “diarrhoea”, where advantages up to the extent “major”

were shown in some cases. Disadvantages up to the extent "major" were shown in the specific AEs "anaemia" and "thrombocytopenia" (each of them CTCAE grade ≥ 3).

In the category "non-serious/non-severe side effects", the advantages of talazoparib are found in the specific AEs "hand-foot syndrome", "eye disorders" and "paraesthesia", each with the extent "considerable".

In summary, there is a hint of considerable added benefit of talazoparib versus the ACT for adult patients with germline BRCA1/2-mutations who have HER2-negative, locally advanced or metastatic breast cancer.

Table 17 summarizes the result of the assessment of the added benefit of talazoparib in comparison with the ACT.

Table 17: Talazoparib – probability and extent of added benefit

Therapeutic Indication	**ACT[a]**	**Probability and extent of added benefit**
Monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative, locally advanced or metastatic breast cancer[b, c, d]	**Capecitabine** or **eribulin** or **vinorelbine** or an anthracycline- or taxane-containing therapy[e]	Hint of considerable added benefit[f]

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. Patients should have been pretreated with an anthracycline and/or a taxane in the neoadjuvant, adjuvant, locally advanced or metastatic setting, unless these treatments were unsuitable for them.
c. Moreover, patients with hormone receptor-positive breast cancer should have received prior endocrine-based therapy, or this therapy should have been unsuitable for them.
d. For the present therapeutic indication, it is assumed that there was no indication for (secondary) resection or radiotherapy with curative intent.
e. The G-BA defines anthracycline- or taxane-containing therapy as a treatment option only for those patients who have not yet received anthracycline- and taxane-containing therapy or who are candidates for retreatment with an anthracycline- or taxane-containing therapy.
f. Only few patients with an ECOG PS of 2 were included in the EMBRACA study, almost all patients had an ECOG PS of 0 or 1. It thus remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.

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

The assessment described above deviates from that of the company, insofar as the company overall derived an indication of a considerable added benefit.

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

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Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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