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Talazoparib (breast cancer) –

Addendum to Commission A20-48[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BRCA	Breast Cancer Associated Gene
ECOG PS	Eastern Cooperative Oncology Group Performance Status
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor 2
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SPC	Summary of Product Characteristics

1 Background

On 6 October 2020, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A20-48 (Talazoparib – Benefit assessment according to §35a Social Code Book V) [1].

The randomized controlled trial (RCT) EMBRACA, which compares talazoparib with physician's choice chemotherapy, was used for the benefit assessment 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. A subpopulation was considered here, because the study also allowed administration of therapies going beyond the appropriate comparator therapy (ACT).

In dossier assessment A20-48, it was noted that some data on the characteristics of the study population (including pretreatment) and on follow-up treatments were not available for the relevant subpopulation, so the dossier assessment used information for the total population of the EMBRACA study. The pharmaceutical company (hereinafter referred to as "the company") subsequently submitted the missing data with its comments [2]. With its comments, the company also submitted further data, which, among other things, concern the assessment of the risk of bias across outcomes.

The G-BA commissioned IQWiG with the assessment of the following additional data submitted by the company under consideration of the information provided in the dossier [3]:

- Assessment and presentation of the baseline characteristics submitted subsequently and information on subsequent therapies
- (Methodological) assessment of the sensitivity analysis presented (multiple imputation)

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

2 Assessment

2.1 Assessment and presentation of the subsequently submitted characteristics

In dossier assessment A20-48, some of the data on the characteristics of the study population (including pretreatments) were not available for the relevant subpopulation of the EMBRACA study. The company subsequently submitted these missing data in its comment [2]; Table 1 shows these characteristics of the relevant subpopulation.

Table 1: Characteristics of the study population – RCT, direct comparison: talazoparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin

Study **Characteristic** **Category**	**Talazoparib** **N[a] = 266**	**Physician's choice chemotherapy[b]** **N[a] = 130**
EMBRACA (second data cut-off: 30 September 2019)		
Disease classification, n (%)		
Locally advanced	13 (5)	9 (7)
Metastatic	252 (95)	121 (93)
(Hormone) receptor status, n (%)		
ER- and PR-negative, HER2-negative (TNBC)[c]	123 (46)	53 (41)
ER- and/or PR-positive, HER2-negative[c]	143 (54)	77 (59)
Prior endocrine regimen in any setting[d]		
0	12 (8)	13 (17)
≥ 1	131 (92)	64 (83)
Number of prior endocrine regimen in any setting[d] (eCRF), mean (SD)	2.0 (1.25)	2.0 (1.47)
Prior endocrine therapy in the advanced stage, n (%)		
No	51 (36)[g]	31 (40)[g]
Yes	92 (64[g])	46 (60[g])
Prior treatment with anthracyclines **and** taxanes at any stage, n (%)	205 (77)	95 (73)
Prior treatment with anthracyclines **and/or** taxanes at any stage, n (%)	259 (97)	125 (96)
Treatment discontinuation[e], n (%)	250 (94)	113 (87)
Study discontinuation[f], n (%)	20 (8)[g]	22 (17)[g]

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. These data can already be found in the dossier assessment.
d. Adjuvant and advanced setting. Combination therapies of several endocrine therapies were counted as 1 regimen.
e. The most common reasons for treatment discontinuation were (% in relation to N): progression of the disease (81.2% vs. 65.4%), withdrawal of consent (2.3% vs. 18.5%) and physician's decision (4.9% vs. 8.5%)
f. The reasons for study discontinuation were (% in relation to N): withdrawal of consent (3.4% vs. 12.3%) and loss to follow-up (4.1% vs. 4.6%)
g. Institute's calculation.

eCRF: electronic case report form; ER: oestrogen receptor; HER2: human epidermal growth factor receptor 2; 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

Prior therapy with anthracyclines/taxanes

97% of the patients in the talazoparib arm and 96% of the patients in the control arm received anthracycline- **and/or** taxane-containing prior therapy (at any stage). The requirements for the prior therapy with anthracyclines and/or taxanes according to the Summary of Product Characteristics (SPCs) of talazoparib [4] are thus fulfilled for almost all patients included.

77% of the patients in the talazoparib arm and 73% of the patients in the control arm received anthracycline **and** taxane prior therapy (at any stage), i.e. these patients were pretreated with **both** anthracyclines **and** taxanes. 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.

As a result, about 25% of patients are not pretreated with **both** anthracyclines **and** taxanes, and the company does not provide any information on why such therapy would not have been suitable for these patients in the dossier. In the oral hearing [5] the company explained that in these cases the treating physician had decided that there was a contraindication. The respective side effects and the contraindication were thus given. However, the company confirmed that the reasons were not explicitly recorded in the study.

In the present situation it thus still remains unclear whether the study population of the EMBRACA study included patients for whom a further (anthracycline- or taxane-containing) prior therapy might have been suitable and for whom treatment with one of the drugs listed in the chemotherapy arm would therefore not (yet) have been an option according to the SPC.

Prior therapy with endocrine-based therapies

In the relevant subpopulation, 143 (54%) of the patients in the talazoparib arm and 77 (59%) of the patients in the chemotherapy arm had hormone receptor-positive breast cancer. 92% of the patients with hormone receptor-positive breast cancer in the talazoparib arm and 83% of such patients in the chemotherapy arm had received prior endocrine therapy in any setting.

However, relating to the advanced stage, only 64% (n = 92) of the patients in the talazoparib arm and 60% (n = 46) of the patients in the chemotherapy arm (of the patients with hormone receptor-positive breast cancer) received endocrine therapy in the advanced stage. For the other patients with hormone receptor-positive breast cancer, it is still not possible to tell from the available information whether a further endocrine therapy would 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 [6-8], chemotherapy is only an option when endocrine therapy is no longer suitable; however, information on the exact implementation of this requirement in the EMBRACA study is not available.

Further subsequently submitted data

The majority of patients in the relevant subpopulation of the EMBRACA study (approx. 94%) had metastatic breast cancer.

At the time point of the second data cut-off (30 September 2019), 94% of the patients in the talazoparib arm and 87% of the patients in the chemotherapy arm had discontinued the therapy. 8% of the patients in the talazoparib arm and 17% of the patients in the chemotherapy arm had discontinued the study at this time, withdrawal of consent being the most common reason in the chemotherapy arm (3% vs. 12%).

Certainty of conclusions of the study results

As already described in dossier assessment A20-48, the uncertainties described above with regard to 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.

2.2 Subsequent therapies

Table 2 lists the subsequent therapies at the time point of the second data cut-off.

Table 2: Data on subsequent antineoplastic therapies (≥ 5% of the patients in ≥ 1 treatment arm) – RCT, direct comparison: talazoparib vs. physician's choice chemotherapy using capecitabine or vinorelbine or eribulin

Study	**Patients with subsequent therapy n (%)**	
Drug class[a] **Drug**	**Talazoparib** **N = 266**	**Physician's choice chemotherapy[b]** **N = 130**
EMBRACA (second data cut-off: 30 September 2019)		
Total, n (%)	216 (81.2)	101 (77.7)
Antineoplastic drugs, n (%)	211 (79.3)	101 (77.7)
Carboplatin	104 (39.1)	47 (36.2)
Capecitabine	95 (35.7)	20 (15.4)
Gemcitabine	69 (25.9)	37 (28.5)
Eribulin	71 (26.7)	24 (18.5)
Paclitaxel	43 (16.2)	18 (13.8)
Palbociclib	35 (13.2)	14 (10.8)
Vinorelbine	37 (13.9)	12 (9.2)
Olaparib	6 (2.3)	33 (25.4)
Cyclophosphamide	24 (9.0)	13 (10.0)
Cisplatin	27 (10.2)	9 (6.9)
Paclitaxel albumin	20 (7.5)	12 (9.2)
Methotrexate	18 (6.8)	4 (3.1)
Doxorubicin	15 (5.6)	6 (4.6)
Pegylated liposomal doxorubicin hydrochloride	6 (2.3)	9 (6.9)
Poly ADP-ribose polymerase inhibitor	3 (1.1)	8 (6.2)
Endocrine therapy, n (%)	63 (23.7)	29 (22.3)
Fulvestrant	32 (12.0)	17 (13.1)
Letrozole	26 (9.8)	7 (5.4)
Exemestane	20 (7.5)	8 (6.2)
Investigational preparations	11 (4.1)	11 (8.5)

a. Classification according to "ATC" (coded according to WHO-DD); in the case of multiple occurrences within an ATC class, the patient was counted only once in the drug class line.
b. Capecitabine or vinorelbine or eribulin at the physician's choice.

ADP: adenosine diphosphate; ATC: anatomical therapeutic chemical classification system; n: Number of patients with at least 1 subsequent therapy; N: Number of analysed patients; RCT: randomised controlled trial; WHO-DD: World Health Organization Drug Dictionary; vs.: versus

Carboplatin was the most common subsequent therapy in both treatment arms, followed by capecitabine, eribulin, gemcitabine and endocrine therapy in the talazoparib arm. In the chemotherapy arm, the second most common therapy was gemcitabine, followed by olaparib, endocrine therapy and eribulin. The use of olaparib as subsequent therapy is an approved treatment option.

2.3 Methodological assessment of the sensitivity analysis presented (multiple imputation)

Background

In dossier assessment A20-48, the risk of bias across outcomes was rated as high for the EMBRACA study, since there was a large difference between the study arms in the proportion of patients who discontinued the study before the first administration of the study medication. Based on the relevant subpopulation, this applies to 1 (0.3%) patient in the talazoparib arm and 16 (12.3%) patients in the chemotherapy arm. 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. Also for the outcome "overall survival", censorings at month 0 are shown, especially in the chemotherapy arm.

Presented data

With its comments, the company submitted sensitivity analyses regarding the outcomes of the categories "health-related quality of life" and "serious and severe adverse events" with the aim of checking whether the effects obtained remain stable with regard to the main analysis.

In the framework of a sensitivity analysis, the missing values of patients who discontinued their participation in the study prematurely before the first administration of the study medication were imputed by multiple imputation based on a propensity score matching. To calculate the probability of each patient not receiving study medication (propensity score), the company used a logit model, adjusted for the baseline characteristics "age", "Eastern Cooperative Oncology Group Performance Status (ECOG PS)", "triple-negative status", "time from first breast cancer diagnosis to diagnosis of advanced breast cancer", excluding bone metastases, metastases of the central nervous system in the medical history and patients with ≥ 1 prior chemotherapy for advanced breast cancer. The company did not provide reasons for the selection of the baseline characteristics taken into account. With regard to their propensity score, the company divided the patients into 5 equally sized groups. Thereafter, the company randomly assigned each patient who had not received any medication to one patient with medication who was assigned to the same propensity score group and the same medication. Then, the missing data of the outcome (e.g. censoring status and event time) of the patient without medication was imputed by the data of the patient with medication. This imputation step was repeated 500 times for each outcome. For each imputed data set, the company calculated an effect estimation according to the Cox regression presented in the dossier, from which a pooled effect was reported.

According to the company, these effect estimations point in the same direction with almost the same extent. The positive and negative effects shown were thus to be considered robust and independent of the patients who had discontinued the study (patients who had stopped the study prematurely before the first administration of the medication). A bias could thus be ruled out. According to the company, the risk of bias across outcomes could thus be classified as low and an indication of an added benefit could be derived.

Assessment

The described procedure was used to form pairs of patients with medication and patients without medication who were similar in terms of their considered baseline characteristics. However, there is no information on the extent to which the patients with medication used to form the pairs of individuals were actually similar to the patients without medication for all relevant baseline characteristics. It is therefore not possible to assess whether the formed pairs of individuals were actually sufficiently similar. Moreover, multiple imputation can only provide results with a low risk of bias if the mechanisms that led to the discontinuation of the study can be plausibly explained by the data collected (so-called "missing at random"). However, in its comments, the company does not provide such a plausible explanation.

As the similarity of the pairs of individuals cannot be verified due to a lack of information, the method used cannot be assessed with regard to its validity. Thus, contrary to the assessment of the company, a high risk of bias across outcomes is still assumed, which means that at most hints of an added benefit can be derived.

Irrespective of this, there is a high risk of bias for all considered outcomes except for "overall survival" in the present data situation, which is due to other outcome-specific aspects (see dossier assessment A20-48).

2.4 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of talazoparib from dossier assessment A20-48.

The following Table 3 shows the result of the benefit assessment of talazoparib under consideration of dossier assessment A20-48 and the present addendum.

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 is 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 a renewed 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 G-BA decides on the added benefit.

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