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Olaparib (prostate cancer) –

Addendum to Commission A20-106[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ADT	androgen deprivation therapy
BPI-SF	Brief Pain Inventory-Short Form
BRCA	breast cancer associated gene
CTCAE	Common Terminology Criteria for Adverse Events
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
mCRPC	metastatic castration-resistant prostate cancer
NHA	new hormonal agent
P	prednisone/prednisolone
PRO	patient-reported outcome
RCT	randomized controlled trial
SAP	statistical analysis plan
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference

1 Background

On 27 April 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A20-106 (Olaparib – Benefit assessment according to §35a Social Code Book V) [1].

The randomized controlled trial (RCT) PROfound was used for the benefit assessment of olaparib in adult patients with metastatic castration-resistant prostate cancer (mCRPC) and breast cancer susceptibility gene (BRCA)1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent (NHA).

After the oral hearing [2], the G-BA commissioned IQWiG to assess the following data presented by the pharmaceutical company (hereinafter referred to as "the company") with its written comments [3]:

- Brief Pain Inventory–Short Form (BPI-SF):
  - subsequently submitted data on the number of censored patients who had not been considered (BPI-SF Item 3)
  - new analyses under consideration of all visits for the outcome "pain interference (BPI-SF Items 9a-g)"
- patient-reported outcome - Common Terminology Criteria for Adverse Events (PRO-CTCAE): review of the data already submitted in the dossier

In addition to the information provided in Modules 1 to 4 and the documentation subsequently submitted in the commenting procedure, it was necessary to use information from Module 5 of the company's dossier for the present addendum. This was information on study methods and study results. The respective information was included in the present addendum.

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 Data subsequently submitted on patient-relevant outcomes

The PROfound study included in the benefit assessment is an RCT in which olaparib is compared with a physician's choice therapy choosing from abiraterone or enzalutamide. The ongoing androgen deprivation therapy (ADT) was also continued in both study arms. Abiraterone was additionally combined with prednisone or, if necessary, prednisolone (P). The results of the relevant subpopulation of patients with BRCA1/2 mutations were used for the benefit assessment. A detailed description of the study design and the results can be found in dossier assessment A20-106 [1].

For dossier assessment A20-106, discrepant analyses on overall survival compared with the European Public Assessment Report (EPAR) [4,5] were available in Module 4 A of the dossier submitted by the company. The reason for this discrepancy was not clear from the information provided in Module 4 A and the EPAR. The analysis from the EPAR was therefore used for the benefit assessment. In its written comments, the company explained why the analysis on overall survival presented in Module 4 A differs from that presented in the EPAR.

Moreover, the information on individual analyses of the BPI-SF was incomplete [4] in Module 4 A. For item 3 of the BPI-SF ("worst pain"), information was missing on the proportion of patients with missing values at baseline and at least 1 subsequent time point. These patients were censored in the event time analysis on day 1 and must therefore be regarded as patients not considered in the analysis. As the data in Module 4 A were contradictory compared to the statistical analysis plan (SAP) it was unclear for items 9a-g (pain interference) of the BPI-SF whether observations were only considered in the analysis if values for the change versus baseline were available for ≥ 25% of patients in both treatment arms at the time of the respective visit. For these and other reasons, such as lack of blinding, the results on BPI-SF item 3 and items 9a-g were rated as potentially highly biased [1]. In its written comments, the company subsequently submitted the missing data on item 3 and further analyses on items 9a-g of the BPI-SF [3,6].

Moreover, the company presented no results for the outcome "PRO-CTCAE" in Module 4 A, although this outcome was recorded in the PROfound study. The company provided no justification for this in Module 4 A [4]. In its comments, the company justifies why it considers the results on the outcome "PRO-CTCAE" unusable and refers to the study report in Module 5 [7] for further details.

In accordance with the G-BA's commission, the data on the BPI-SF subsequently submitted by the company and the analyses of the PRO-CTCAE available in Module 5 of the dossier are assessed below. In addition, the results for the outcome "overall survival" were assessed based on the analysis presented in Module 4 A.

2.2 Results

Mortality

Overall survival

In its written comments, the company explained that the analysis on overall survival presented in Module 4 A is the predefined analysis planned for the main analysis with adjustment for the two stratification factors of the study, whereas the analysis in the EPAR is based on subgroup analyses in which no such adjustment took place. The adjusted analyses are relevant for the benefit assessment. According to the information in Module 4 A, the estimation for the hazard ratio (HR) at the data cut-off of 20 March 2020 is 0.60 and the corresponding 95% CI is [0,40; 0,91]. Deviating from dossier assessment A20-106, this results in a hint of an added benefit of olaparib over individual treatment (abiraterone or enzalutamide) with the extent "considerable" instead of "minor" for this outcome.

Morbidity

Worst pain (BPI-SF Item 3)

The data subsequently submitted by the company show that the proportion of patients who were censored on day 1 because there was either no baseline value and/or no subsequent value, was 25.5% in the intervention arm and 22.4% in the comparator arm. Due to the high proportion of patients who were not considered in the analyses, the results for this outcome are still rated as having a high risk of bias. Consistent with dossier assessment A20-106, a high risk of bias must also be assumed due to the lack of blinding in subjective recording of outcomes.

Pain interference (BPI-SF Items 9a–g)

With its comments, the company clarified that in the analyses for the outcome "pain interference" presented in Module 4 A, observations were only taken into account if values for the change versus baseline at the respective visit were available for ≥ 25% of the patients in both treatment arms. In its comments, the company subsequently submitted analyses in which, according to the company, all visits had been taken into account. These are relevant for the benefit assessment and are presented in Table 1.

The outcome-specific risk of bias was also rated as high for the subsequently submitted analyses. The reason for this is the lack of blinding in subjective recording of outcomes and the high proportion of patients who were not included in the analysis (intervention: 25.5% vs. control: 22.4%).

Table 1: Results (morbidity, continuous) - RCT, direct comparison: olaparib + ADT vs. abiraterone + P + ADT or enzalutamide + ADT

Study outcome category outcome	Olaparib + ADT			Abiraterone + P + ADT or enzalutamide + ADT			Olaparib + ADT vs. abiraterone + P + ADT or enzalutamide + ADT
	N[a]	values at baseline mean (SD)	change at the date of analysis[b] mean (SE)	N[a]	values at baseline mean (SD)	change at the date of analysis[b] mean (SE)	MD [95% CI]; p-value[c]
PROfound							
Morbidity							
Pain interference (BPI-SF item 9a–g)[d]	76	1.68 (2.18)	-0.05 (0.12)	45	1.79 (2.15)	1.13 (0.24)	-1.18 [-1.72; -0.65]; < 0.001 Hedges' g: -0.91 [-1.30; -0.52]

a. Number of patients considered in the analysis for the calculation of the effect estimation.
b. Second data cut-off: 20 March 2020.
c. Effect, CI and p-value: MMRM, additionally adjusted for values at baseline and the stratification factors "previous taxane treatment (yes/no)" and "measurable disease at baseline (yes/no)".
d. Lower (decreasing) values indicate better symptoms; negative effects (intervention–control) indicate an advantage for the intervention.

ADT: androgen deprivation therapy; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; P: prednisone/prednisolone; RCT: randomized controlled trial; SD: standard deviation; SE: standard error

A statistically significant difference in favour of olaparib + ADT versus abiraterone + P + ADT or enzalutamide + ADT was shown between the treatment groups for the outcome "pain interference (BPI-SF Items 9a–g)". The 95% CI of the standardized mean difference (SMD) is fully outside the irrelevance range of −0.2 to 0.2. This was interpreted to be a relevant effect. Consistent with dossier assessment A20-106, this resulted in a hint of an added benefit of olaparib versus individual treatment (abiraterone or enzalutamide) with the extent "non-quantifiable" for this outcome.

Side effects

PRO-CTCAE

The company presented no results on the outcome "PRO-CTCAE" in Module 4 A of the dossier, although this instrument had been recorded in the PROfound study. In its comments, it justified this with the fact that the instrument had only been recorded in countries where a translation into the national language was available. Because of this, the instrument had been recorded in less than half of the study population. The company refers to the IQWiG methods, according to which results are not usable if less than 70% of the patients are included in the analysis.

This rationale is not appropriate. The methods described in IQWiG's General Methods [8] refer to situations in which patients are not included in the analysis for informative reasons, e.g. because they discontinued the study. It can then be assumed that the patients are not randomly missing in the analysis. In the present case, the PRO-CTCAE instrument was not recorded at all in some of the patients of the PROfound study because no translation was available in the respective country. The reason for the missing values is thus independent of the actual missing values; the same distributions of events can be assumed for observed and non-observed patients. Thus, there is no high risk of bias. For this reason, the proportion of patients included in the analysis is to be based on those patients who were randomized in countries for which a translation into the respective national language is available. Based on these patients, the proportion in the total population of the PROfound study was approx. 72%. Thus, the analyses of the PRO-CTCAE were generally usable.

However, for the outcome "PRO-CTCAE", the study report [7] only provides descriptive information, which moreover refers to the entire study population. Information on the relevant subpopulation of patients with BRCA1/2 mutations is not available.

Therefore, usable results on this outcome are still lacking for the benefit assessment.

2.3 Overall conclusion on added benefit

Table 2 summarizes the results of the dossier assessment [1] and the addendum considered in the overall conclusion on the extent of added benefit.

Table 2: Positive and negative effects from the assessment of olaparib + ADT in comparison with abiraterone + P + ADT or enzalutamide + ADT

Positive effects[a]	**Negative effects**[a]
Mortality ▪ overall survival: hint of an added benefit – extent "**considerable**"	–
Serious/severe symptoms/late complications ▪ occurrence of spinal cord compression: hint of an added benefit – extent "minor"	–
Non-serious/non-severe symptoms/late complications ▪ pain ▫ worst pain (BPI-SF item 3): hint of an added benefit - extent: "considerable" ▫ pain interference (BPI-SF items 9a-g): hint of an added benefit - extent: "not quantifiable"	–
–	Serious/severe side effects ▪ anaemia (severe AEs): Hint of greater harm - extent "major"
–	Non-serious/non-severe side effects ▪ nausea (AEs): Hint of greater harm - extent: "considerable"
a. Changes in comparison with dossier assessment A20-106 are printed in **bold**. AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form	

In contrast to dossier assessment A20-106, there is a hint of considerable added benefit for overall survival. The other positive and negative effects have not changed compared with dossier assessment A20-106: In the categories "serious/severe symptoms/ secondary complications" and "non-serious/non-severe symptoms/secondary complications", there are several hints of positive effects with the extents "minor" to "considerable". In contrast, there are hints of negative effects with extents of up to "major". These did not raise doubts about the positive effects, however.

In summary, there is a hint of considerable added benefit of olaparib versus individual therapy (abiraterone or enzalutamide) for adult patients with mCRPC and BRCA1/2 mutations (germline and/or somatic) whose disease is progressive after previous treatment that included an NHA and for whom abiraterone or enzalutamide is best suited on an individual basis within the framework of the appropriate comparator therapy (ACT).

2.4 Summary

The data subsequently submitted by the company in the commenting procedure have changed the conclusion on the added benefit of olaparib from dossier assessment A20-106.

The following Table 3 shows the result of the benefit assessment of olaparib under consideration of dossier assessment A20-106 and the present addendum.

Table 3: Olaparib – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**[b]
Adult patients with mCRPC and BRCA1/2 mutations (germline and/or somatic) whose disease is progressive after previous treatment that included an NHA[c,d]	Individual therapy choosing from abiraterone, enzalutamide, cabazitaxel and docetaxel; taking into account the previous therapies as well as the approval of the respective medicinal products	Patients for whom abiraterone or enzalutamide is the best individual choice: hint of **considerable** added benefit
		Patients for whom docetaxel or cabazitaxel is the best individual choice: added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. Changes in comparison with dossier assessment A20-106 are printed in **bold**.
c. For the present therapeutic indication, it is assumed that ongoing conventional ADT (surgical castration or medical castration using treatment with GnRH agonists or GnRH antagonists) is continued.
d. The G-BA specified the present ACT only for those patients whose disease is progressive after previous treatment with abiraterone and/or enzalutamide.

ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; BRCA: breast cancer associated gene; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; mCRPC: metastatic castration resistant prostate cancer; NHA: new hormonal agent

The G-BA decides on the added benefit.

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