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Olaparib (ovarian cancer, first-line maintenance treatment in combination with bevacizumab) –

Addendum to Commission A20-111[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AML	acute myeloid leukaemia
EQ-5D	European Quality of Life-5 Dimensions
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HRD	homologous recombination deficiency
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MDS	myelodysplastic syndrome
MMRM	mixed-effects model repeated measures
RCT	randomized controlled trial
VAS	visual analogue scale

1 Background

On 28 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 A20-111 (Olaparib – Benefit assessment according to §35a Social Code Book V) [1].

The randomized controlled trial (RCT) PAOLA-1 was used for the benefit assessment of olaparib + bevacizumab in comparison with the appropriate comparator therapy (ACT) in adult patients with advanced (Fédération Internationale de Gynécologie et d'Obstétrique -[FIGO] stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status. The PAOLA-1 study compared olaparib + bevacizumab with placebo + bevacizumab.

After the oral hearing [2], the G-BA commissioned IQWiG to assess the following data submitted by the pharmaceutical company (hereinafter referred to as "the company") with its written comments [3] under consideration of the information provided in the dossier [4]:

- Results on the visual analogue scale (VAS) of the European Quality of Life-5 Dimensions (EQ-5D)
- Adverse events: results on myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML)

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

Subsequently submitted results on health status (EQ-5D VAS)

In its dossier, the company on the one hand presented analyses for the outcome "health status (measured using the EQ-5D VAS)" for the time to deterioration with the response criteria 7 and 10 points, and on the other hand it presented analyses on the mean change using a mixed-effects model repeated measures (MMRM). As explained in the *General Methods* of the Institute [5,6], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to a predefined value of at least 15 % of the scale range of an instrument (in post-hoc analyses exactly 15 % of the scale range). This is not the case with the response criteria presented. Therefore, the analyses on the mean change using MMRM analyses were used in the dossier assessment.

With its comments, the company subsequently submitted analyses for the time to deterioration of the health status, measured with the EQ-5D VAS using a response criterion of 15 points. This corresponds to 15% of the scale range of the EQ-5D VAS. These are assessed below.

The risk of bias of the results on health status (EQ-5D VAS) was rated as low.

Table 1 shows the subsequently submitted analysis on health status (EQ-5D VAS) by means of an event time analysis using a response criterion corresponding to 15% of the scale range.

Table 1: Results (morbidity, time to event) – RCT, direct comparison: olaparib + bevacizumab vs. placebo + bevacizumab

Study outcome category outcome	Olaparib + bevacizumab		Placebo + bevacizumab		Olaparib + bevacizumab vs. placebo + bevacizumab
	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
PAOLA-1					
Morbidity					
Health status (EQ-5D VAS)[a]	255	25.3 [17.5; NC] 116 (45.5)	132	26.7 [19.9; NC] 58 (43.9)	1.05 [0.77; 1.46]; 0.749
a. Time to deterioration; defined as decrease of the score by ≥ 15 points compared with baseline. CI: confidence interval; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculable; RCT: randomized controlled trial					

There was no statistically significant difference between the treatment groups for the outcome "health status measured using the EQ-5D VAS". This resulted in no hint of an added benefit of olaparib + bevacizumab in comparison with bevacizumab; an added benefit is therefore not proven.

MDS and AML

The exact operationalization of the submitted outcomes "MDS and AML" and "MDS/AML" was not clear from the company's dossier.

In its comments, the company explained that for the outcome "MDS and AML", all cases of MDS or AML were rated as events, while for the outcome "MDS/ AML" only those cases were considered in which MDS had transformed into AML.

All events of MDS or AML are relevant for the present assessment. Thus, the inclusion of the outcome "MDS and AML" in dossier assessment A20-111 [1] is appropriate. Appendix A shows the analyses on the individual adverse events of MDS or AML subsequently submitted by the company.

2.1 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of the drug combination olaparib + bevacizumab from dossier assessment A20-111.

The following Table 2 shows the result of the benefit assessment of olaparib + bevacizumab under consideration of dossier assessment A20-111 and the present addendum.

Table 2: Olaparib + bevacizumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit[b]**
Maintenance therapy of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian cancer[c] who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with HRD-positive status[d].	Continuation of the treatment with bevacizumab started with first-line platinum-based chemotherapy	▪ Patients without detectable tumour after primary surgery and patients without detectable tumour/with complete response following chemotherapy: indication of considerable added benefit
		▪ Patients without detectable tumour after interval surgery and patients with partial response: indication of lesser benefit

a. Presentation of the respective ACT specified by the G-BA.
b. The PAOLA-1 study included only patients with ECOG PS of 0 or 1 as well as only few patients with non-serous tumour histology (5.6% in the relevant subpopulation). It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 or patients with non-serous tumour histology.
c. This term also includes fallopian tube and primary peritoneal cancer.
d. A positive HRD status is defined by either BRCA 1/2-mutation and/or genomic instability.

ACT: appropriate comparator therapy; BRCA: breast cancer associated gene; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; G-BA: Federal Joint Committee.; HRD: homologous recombination deficiency

The G-BA decides on the added benefit.

3 References

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

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Olaparib (Ovarialkarzinom; Erstlinie Erhaltung in Kombination mit Bevacizumab) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2021 [Accessed: 15.03.2021]. URL: https://www.iqwig.de/download/a20-111_olaparib_nutzenbewertung-35a-sgb-v_v1-0.pdf.

2. Gemeinsamer Bundesausschuss. Mündliche Anhörung gemäß § 35 a Abs. 3 Satz 2 SGB V; hier: Wirkstoff Olaparib (D-616) – Stenografisches Wortprotokoll – [online]. 2021 [Accessed: 04.05.2021]. URL: https://www.g-ba.de/downloads/91-1031-628/2021-04-27_Wortprotokoll_Olaparib_D-616.pdf.

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6. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Dokumentation und Würdigung der Anhörung zum Entwurf der Allgemeinen Methoden 6.0 [online]. 2020 [Accessed: 27.01.2021]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_dwa-entwurf-fuer-version-6-0_v1-0.pdf.

The full report (German version) is published under https://www.iqwig.de/en/projects/a21-55.html.

Appendix A - Supplementary presentation on the individual adverse events "MDS" and "AML"

Table 3: Results (side effects, dichotomous) – RCT, direct comparison: olaparib + bevacizumab vs. placebo + bevacizumab

Study outcome category outcome	Olaparib + bevacizumab		Placebo + bevacizumab		Olaparib + bevacizumab vs. placebo + bevacizumab
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value
PAOLA-1					
Side effects					
MDS	255	1 (0.4)	131	1 (0.8)	0.51 [0.03; 8.15]; 0.637
AML	255	2 (0.8)	131	1 (0.8)	1.03 [0.09; 11.23]; 0.982

CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk