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Olaparib (breast cancer) –

Addendum to Commission A19-57[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
BRCA	breast cancer associated gene
EORTC-QLQ C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
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)

1 Background

On 26 November 2019, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A19-57 (Olaparib – Benefit assessment according to §35a Social Code Book V) [1].

The OlympiAD study was used for the benefit assessment of olaparib in 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 [1]. The responder analyses on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), defined as time to clinically relevant deterioration, presented by the pharmaceutical company (hereinafter referred to as "the company") in its dossier [2] were not usable due to insufficient information on patients censored at day 1. Following the oral hearing, the company submitted further information on this.

The G-BA commissioned IQWiG with the assessment of the EORTC QLQ-C30 results under consideration of the information subsequently submitted by the company.

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

In its dossier [2], the company presented analyses on the time to deterioration (without consideration of death as event) for the outcomes “symptoms” and “health-related quality of life”, each measured with the EORTC QLQ-C30. All randomized patients were formally included in these analyses. However, some of the patients were censored on day 1. These patients censored on day 1 do not provide any additional information for the analysis, so that they have the same significance as patients not considered from the outset. The knowledge of these patients censored on day 1 and thus de facto not considered in each study arm is necessary to assess the certainty of results of this outcome. The dossier contained only insufficient information regarding this aspect.

Table 1 presents the information provided by the company following the oral hearing regarding the overall proportions of patients in the analysis who were censored on day 1 in both study arms as well as the difference between the study arms.

Table 1: Number of patients censored on day 1 in the analysis of the time to deterioration (using the EORTC QLQ-C30)

Study Outcome category	Olaparib (N = 205)		Physician's choice chemotherapy[a] (N = 97)		Difference between the study arms (in percentage points)
	Total number of patients censored on day 1	Proportion of patients censored on day 1 in comparison with ITT (%)	Total number of patients censored on day 1	Proportion of patients censored on day 1 in comparison with ITT (%)	
OlympiAD					
EORTC QLQ-C30 symptom scales					
Fatigue	17	8.3	23	23.7	15.4
Pain	15	7.3	26	26.8	19.5
Nausea and vomiting	14	6.8	22	22.7	15.9
Dyspnoea	17	8.3	25	25.8	17.5
Appetite loss	19	9.3	23	23.7	14.4
Insomnia	20	9.8	25	25.8	16.0
Constipation	18	8.8	24	24.7	15.9
Diarrhoea	14	6.8	22	22.7	15.9
EORTC QLQ-C30 functional scales					
Global health status	15	7.3	22	22.7	15.4
Physical functioning	13	6.3	22	22.7	16.4
Role functioning	19	9.3	23	23.7	14.4
Cognitive functioning	14	6.8	24	24.7	17.9
Emotional functioning	15	7.3	24	24.7	17.4
Social functioning	18	8.8	23	23.7	14.9

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

EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; ITT: intention to treat; N: number of analysed patients

The data show that the proportion of patients not considered in the analyses differs by more than 15 percentage points between the treatment groups in almost all symptom and functional scales of the EORTC QLQ-C30. Thus, the certainty of results of the analyses on the EORTC QLQ-C30 is insufficient and the results are therefore not usable for the benefit assessment. An isolated consideration of the scales "appetite loss", "role functioning" and "social functioning", for which the difference between the study arms is just below 15 percentage points, is not meaningful because individual scales are only an inadequate representation of the outcomes considered (symptoms or health-related quality of life). Irrespective of this, there were no statistically significant differences between the treatment groups for these 3 scales.

2.1 Summary

The data subsequently submitted by the company in the commenting procedure did not change the conclusion on the added benefit of olaparib from dossier assessment A19-57.

The following Table 2 shows the result of the benefit assessment of olaparib under consideration of dossier assessment A19-57 and the present addendum.

Table 2: Olaparib – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Olaparib as monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer[b, c]	**Capecitabine** or **vinorelbine** or **eribulin** or, if applicable, anthracycline- or taxane-containing therapy	▪ Patients without prior chemotherapy for metastatic breast cancer: indication of considerable added benefit[d] ▪ Patients with prior chemotherapy for metastatic breast cancer: hint of considerable added benefit[d]

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 previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments.
c: Patients with hormone receptor-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy.
d: The OlympiAD study included only patients with an ECOG PS of 0 or 1 and patients in the metastatic stage. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 or to patients in the locally advanced stage.
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.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Olaparib (Mammakarzinom): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A19-57 [online]. 11.10.2019 [Accessed: 15.10.2019]. (IQWiG-Berichte; Volume 825). URL: https://www.iqwig.de/download/A19-57_Olaparib_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

2. AstraZeneca. Olaparib (Lynparza): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 08.07.2019 [Accessed: 17.10.2019]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/463/#dossier.