IQWiG Reports – Commission No. A18-36

Olaparib (ovarian cancer) –

Benefit assessment according to §35a Social Code Book V[1] (extension of approval/ expiry of decision)

Extract

[1] Translation of the executive summary of the dossier assessment *Olaparib (Ovarialkarzinom) – Nutzenbewertung gemäß § 35a SGB V (Zulassungserweiterung / Ablauf Befristung)* (Version 1.0; Status: 13 September 2018). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Olaparib (ovarian cancer) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:
Federal Joint Committee

Commission awarded on:
5 June 2018

Internal Commission No.:
A18-36

Address of publisher:
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Keywords: olaparib, ovarian neoplasms, benefit assessment, NCT00753545, NCT01874353

Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SBG) 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 olaparib. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 05/06/2018. This was commissioned for assessing 2 procedures synchronized upon the company's request.

- On 16/12/2014, the drug olaparib was initially approved as an orphan drug. After approval of the drug to be assessed, the company submitted a dossier for early benefit assessment in this original therapeutic indication as per 01/06/2015. With its decision dated 27/11/2015, the G-BA specified for the decision on this procedure to expire on 01/12/2018.
- On 08/05/2018, the approval of olaparib was extended and its orphan drug status lifted.

The assessment was commissioned by the G-BA for the entire therapeutic indication after extension of approval as well as for the therapeutic indication added by the extension and the original therapeutic indication.

Research question

The aim of this report is to assess the added benefit of olaparib monotherapy as maintenance therapy in adult patients with platinum-sensitive recurrence of high-grade epithelial ovarian cancer, fallopian tube or primary peritoneal carcinoma who respond to platinum-based chemotherapy (either complete response [CR] or partial response [PR]) in comparison with watchful waiting as the appropriate comparator therapy (ACT) (entire therapeutic indication).

The original therapeutic indication and the newly added therapeutic indication each comprise the following patient groups:

Original therapeutic indication

Adult patients with platinum-sensitive recurrence of a breast cancer susceptibility gene (BRCA)-mutated (BRCAm) (germline and/or somatic) high-grade serous epithelial ovarian carcinoma, fallopian tube or primary peritoneal carcinoma who respond to platinum-based chemotherapy (CR or PR).

Newly added therapeutic indication

Adult patients with platinum-sensitive recurrence of a BRCA-mutated (germline and/or somatic) high-grade – non-serous – epithelial ovarian carcinoma, fallopian tube or primary peritoneal carcinoma, as well as patients with platinum-sensitive recurrence of a BRCA wild-type (BRCAwt) (not BRCA-mutated) – serous or non-serous – ovarian carcinoma, fallopian tube or primary peritoneal carcinoma who respond to platinum-based chemotherapy.

The fact that the original therapeutic indication and the newly added therapeutic indication are subsets of the entire therapeutic indication led to the research question presented in Table 2 and the two sub-questions 1a and 1b.

Table 2[2]: Research questions of the benefit assessment of olaparib

Research question	Indication	ACT[a]
1	**Entire therapeutic indication** Patients with platinum-sensitive recurrence of high-grade epithelial ovarian carcinoma[b], regardless of BRCA mutation status and histology	Watchful waiting
1a	**Newly added therapeutic indication** Patients with platinum-sensitive recurrence of a BRCA wild-type (not BRCA mutated) high-grade serous epithelial ovarian carcinoma[b] as well as patients with a platinum-sensitive recurrence of a high-grade non-serous epithelial ovarian carcinoma[b] regardless of BRCA mutation status	Watchful waiting
1b	**Original therapeutic indication** Patients with platinum-sensitive recurrence of a BRCA-mutated (germline and/or somatic) high-grade serous epithelial ovarian carcinoma[b]	Watchful waiting
a: Presentation of the ACT specified by the G-BA. b: This also includes fallopian tube carcinoma and primary peritoneal carcinoma. ACT: appropriate comparator therapy; BRCA: Breast cancer susceptibility gene; G-BA: Federal Joint Committee		

In this dossier assessment, the term ovarian carcinoma collectively refers to ovarian, fallopian tube, and primary peritoneal carcinomas.

From among the research questions specified by the G-BA, the company discussed only research question 1 (BRCAwt/m, serous/non-serous – entire therapeutic indication).

In accordance with the commission received from the G-BA, this benefit assessment assesses the added benefit for the entire therapeutic indication, the newly added therapeutic indication, and the original therapeutic indication. Accordingly, the studies relevant for the entire therapeutic indication are assessed first. The process also included a review as to whether these studies cover the sub-questions and if so, whether there are any relevant differences compared to the overall result.

The company used the ACT watchful waiting, thus following the G-BA's specification.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

Results

Research question 1: BRCAwt/m, serous/non-serous (entire therapeutic indication)

Study pool

Study 19 and the SOLO2 study were included in the benefit assessment.

Study design

Study 19

Study 19 is a randomized, double-blind, parallel-group study to compare olaparib with placebo. The study included adult female patients with platinum-sensitive recurrence of high-grade serous ovarian carcinoma who had completely or partially responded to previous platinum-containing chemotherapy. Patients were included regardless of BRCA mutation status. At the start of the study, patients were to be in good to fair general health (Eastern Cooperative Oncology Group Performance Status [ECOG-PS] of 0 to 2).

The study included a total of 265 female patients and randomly allocated them to treatment with olaparib (N = 136) or placebo (N = 129) in a 1:1 ratio. Olaparib treatment was administered in accordance with the German approval status.

The primary outcome of the study was progression-free survival (PFS). Patient-relevant secondary outcomes were overall survival, health-related quality of life, and adverse events (AEs).

SOLO2 study

The SOLO2 study is also a randomized, double-blind, parallel-group study to compare olaparib with risperidone. Unlike Study 19, this study included only patients with known BRCA mutation as well as patients with non-serous (endometrioid) histology. In the SOLO2 study, the general-health-related inclusion criterion was an ECOG-PS between 0 and 1.

The study included a total of 295 female patients and randomly allocated them to treatment with olaparib (N = 196) or a placebo (N = 99) in a 2:1 ratio. Olaparib treatment was administered in accordance with the German approval status.

Data from a SOLO2 Chinese cohort, which started later and was therefore studied separately, was not taken into account for the benefit assessment, because this data is not expected to provide any relevant additional information, particularly regarding long-term effects.

The primary outcome of the study was PFS. Patient-relevant secondary outcomes were overall survival, health status, health-related quality of life, and AEs.

Populations studied in Study 19 and SOLO2

For the assessment of the added benefit of olaparib in patients with platinum-sensitive recurrence regardless of BRCA mutation status and histology (research question 1, entire therapeutic indication), the total populations of Study 19 and SOLO2 were used. However, the

total populations of the two studies, either taken alone or in combination, did not represent the target population of all patients with platinum-sensitive recurrence regardless of BRCA status and histology. Patients with non-serous histology plus BRCA wild-type were not investigated in the study, and patients with non-serous histology plus BRCA mutation only to a minor extent.

Implementation of the ACT in Study 19 and SOLO2

The included studies, Study 19 and SOLO2, were not designed for comparison with watchful waiting. With some limitations, the studies are nevertheless suitable for such a comparison.

The fact that both studies allowed for the decision about treatment discontinuation or continuation after progression in accordance with Responsive Evaluation Criteria in Solid Tumors (RECIST) – and hence about the timing of initiating subsequent treatment – to be made based on symptoms and at the physician's discretion can be seen as an approximation of watchful waiting. In addition, patients in both studies were able to choose to be unblinded to facilitate decision-making with their physicians about follow-up treatment.

The ACT of watchful waiting is not fully implemented due to the incomplete investigation of adverse events, morbidity, and health-related quality of life beyond the end of treatment. For the continued follow-up strategy, the information on patient-relevant outcomes is therefore incomplete. Furthermore, examinations along with imaging were to be performed at regular intervals to diagnose disease progression. The S3 Guideline, in contrast, recommends a symptom-oriented approach without regular examination intervals.

Risk of bias and reliability

The risk of bias across outcomes was rated as low for the SOLO2 study. For Study 19, in contrast, it was rated high due to a high percentage of patients in both treatment arms being incorrectly classified in the stratified block randomization. On an outcome-specific level, the results of all outcomes from Study 19 and SOLO2 are rated as potentially highly biased, except for the outcome discontinuation due to AEs in the SOLO2 study.

Irrespective of the above, the insufficient implementation of the ACT leads to low reliability of all outcomes in both included studies for all research questions.

On the basis of the available data for all outcomes, at most hints, e.g. of an added benefit, can therefore be derived. Furthermore, neither study allows for any conclusions on patients with non-serous histology since they were either not included in the studies at all (patients with BRCA wild-type) or only in very small numbers (patients with BRCA mutation).

Results

Mortality

Overall survival

For the outcome overall survival, the meta-analysis of the studies shows a statistically significant difference between treatment groups in favour of olaparib in comparison with

placebo. After an observation period of about 8 years, Study 19 shows about 2 months' longer survival for olaparib. For the outcome overall survival, this results in a hint of an added benefit of olaparib in comparison with the ACT of watchful waiting.

Morbidity

Health status (Visual Analogue Scale [VAS] of the EuroQoL (European Quality of Life Questionnaire [EQ-5D VAS])

Health status, as surveyed by EQ-5D VAS, was investigated only in the SOLO2 study. Surveys continued for some time after progression as well. In the SOLO2 study, no statistically significant difference between treatment groups was found over a period of 24 months. Consequently, there is no hint of added benefit of olaparib in comparison with the ACT of watchful waiting; an added benefit is therefore not proven.

Health-related quality of life

Functional Analysis of Cancer Therapy – Ovarian (FACT-O) total score

In both studies (Study 19 and SOLO2), health-related quality of life was measured by the total score of the FACT-O questionnaire. The studies differed in their survey periods. In the SOLO2 study, the survey also included a period after disease progression, while Study 19 limited it to the time until progression. Analyses over a period of 24 months are only available for the SOLO2 study. For Study 19, analyses over a period of 12 months are available. No statistically significant difference between treatment groups was found in Study 19 or SOLO2. Consequently, neither study has resulted in a hint of added benefit of olaparib in comparison with the ACT of watchful waiting; an added benefit is therefore not proven.

Adverse events

Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3), serious AEs (SAEs), and discontinuation due to AEs

The outcomes severe AEs (CTCAE grade ≥ 3), SAEs, and discontinuation due to AEs each show differences between treatment arms to the disadvantage of olaparib in comparison with placebo. For the outcome severe AEs (CTCAE grade ≥ 3), this difference is statistically significant in the meta-analysis of the studies. Consequently, for the outcome severe AEs (CTCAE grade ≥ 3), there is a hint of greater harm of olaparib in comparison with the ACT of watchful waiting. For the outcomes SAEs and discontinuation due to AEs, the difference is not statistically significant in the meta-analysis of the studies. For each of these outcomes, there is consequently no hint of greater or lesser harm of olaparib in comparison with watchful waiting; therefore, greater or lesser harm is therefore not proven.

Specific AEs

Anaemia (CTCAE grade ≥ 3), nausea and vomiting

The specific AEs nausea and vomiting are categorized as non-serious/non-severe adverse events since the events associated with these outcomes were predominantly non-serious/non-severe. Only anaemia events of CTCAE grade ≥ 3 were used to derive an added benefit.

For each of these specific AEs, the meta-analysis of the studies shows a statistically significant difference to the disadvantage of olaparib in comparison with the placebo. For these outcomes, there is consequently a hint of greater harm of olaparib in comparison with the ACT of watchful waiting.

Myelodysplastic syndrome, acute myeloid leukaemia and pneumonitis

For the specific AEs myelodysplastic syndrome, acute myeloid leukaemia and pneumonitis, no statistically significant difference between treatment groups was found. For these outcomes, there is consequently no hint of greater or lesser harm of olaparib in comparison with the ACT of watchful waiting; therefore, greater or lesser harm is not proven for these outcomes.

Sub-questions 1a (newly added therapeutic indication: BRCAwt, serous and BRCAwt/m, non-serous) and 1b (original therapeutic indication: BRCAm, serous)

Regarding sub-questions 1a and 1b of this benefit assessment (assessment of the newly added therapeutic indication and the original therapeutic indication), the following can be derived from the assessment of the entire therapeutic indication (research question 1):

- In patients with serous histology, there were no relevant differences (influencing the overall assessment) between patients with and without BRCA mutation. On the basis of the available data, it is therefore assumed that there is no relevant interaction due to the BRCA mutation status. The above results were consequently used for patients with serous histology regardless of mutation status.
- For patients with non-serous histology, no relevant data are available. Consequently, there are also no data on which to base the transferability of the results observed in patients with serous histology. For patients with non-serous histology, regardless of mutation status, there is consequently no hint of an added benefit of olaparib in comparison with the ACT; an added benefit is therefore not proven.

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

On the basis of the results presented, the probability and extent of the added benefit of the drug olaparib compared with the ACT is assessed as follows:

In summary for the entire therapeutic indication, a positive effect for overall survival is contrasted by various adverse events (including severe AEs). Data are incomplete on adverse events, morbidity, and health-related quality of life during continued care, for example on subsequent therapies, after disease progression.

The major effects from adverse events curb the added benefit in overall survival, but do not fundamentally put it into question.

In summary, for patients with platinum-sensitive recurrence of ovarian carcinoma of any BRCA mutation status with serous histology (entire therapeutic indication without patients with non-serous ovarian carcinoma), there is a hint of minor added benefit of olaparib in comparison with the ACT of watchful waiting.

This added benefit applies to all research questions for patients with serous histology regardless of BRCA mutation status since the available data show no relevant differences (affecting the overall assessment) between patients with and without BRCA mutation. For patients with non-serous histology, no relevant data are available. For this population, there is no hint of added benefit; an added benefit is therefore not proven.

Table 3 presents a summary of the probability and extent of the added benefit of olaparib.

[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: Olaparib – probability and extent of added benefit

Research question	Indication	ACT[a]	Probability and extent of added benefit
1	**Entire therapeutic indication**		
	Patients with platinum-sensitive recurrence of a high-grade **serous** epithelial ovarian carcinoma[b], regardless of BRCA mutation status[c] Among them: 1a Patients with platinum-sensitive recurrence of a BRCA wild-type (not BRCA-mutated) high-grade serous epithelial ovarian carcinoma[b] (newly added therapeutic indication) 1b Patients with platinum-sensitive recurrence of a BRCA-mutated (germline and/or somatic) high-grade serous epithelial ovarian carcinoma[b] (original therapeutic indication)	Watchful waiting	Hint of minor added benefit
	Patients with platinum-sensitive recurrence of a high-grade **non-serous** epithelial ovarian carcinoma[b], regardless of BRCA mutation status Among them: 1a Patients with platinum-sensitive recurrence of a high-grade non-serous epithelial ovarian carcinoma[b], regardless of BRCA mutation status (newly added therapeutic indication)	Watchful waiting	Added benefit not proven

a: Presentation of the ACT specified by the G-BA.
b: This collectively refers also to fallopian tube carcinoma and primary peritoneal carcinoma.
c: Patients with an ECOG-PS of 0 or 1 were investigated in the included studies only to a minor degree. It remains unclear whether the observed effects also apply to patients with an ECOG-PS ≥ 2.
ACT: appropriate comparator therapy; BRCA: Breast cancer susceptibility gene; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee

The approach for deriving the overall conclusion on added benefit is a suggestion from IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-36-olaparib-ovarian-fallopian-tube-peritoneal-cancer-benefit-assessment-according-to-35a-social-code-book-v.10099.html.