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Rucaparib (ovarian cancer) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Rucaparib (Ovarialkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 May 2019). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

No advisor on medical and scientific questions was available for the present dossier assessment.

IQWiG employees involved in the dossier assessment:

- Anne Hüning
- Christiane Balg
- Anne Catharina Brockhaus
- Florina Kerekes
- Marco Knelangen
- Katrin Nink
- Volker Vervölgyi
- Carolin Weigel

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BRCA	breast cancer associated gene
CSR	clinical study report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) 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 rucaparib. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 26 February 2019.

Research question

The aim of the present report was the assessment of the added benefit of rucaparib as monotherapy treatment of adult patients with platinum-sensitive, relapsed or progressive, breast cancer associated gene (BRCA) mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with 2 or more prior lines of platinum-based chemotherapy, and who are unable to tolerate further platinum-based chemotherapy in comparison with the appropriate comparator therapy (ACT).

The specification of the ACT by the G-BA resulted in the research question presented in Table 2 for the present benefit assessment.

Table 2: Research question of the benefit assessment of rucaparib

Therapeutic indication	**ACT[a]**
Adult patients with platinum-sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian cancer[b], who have been treated with 2 or more prior lines of platinum-based chemotherapy, and who are unable to tolerate further platinum-based chemotherapy	▪ monotherapy with topotecan ▪ monotherapy with pegylated liposomal doxorubicin
a: Presentation of the ACT specified by the G-BA. b: The term "ovarian cancer" also includes fallopian tube and peritoneal cancer. It is assumed that platinum-sensitive, relapsed ovarian cancer involves a response to platinum-containing pretreatment with a relapse-free interval of at least 6 months. This includes partially platinum-sensitive ovarian cancer with relapse between 6 and 12 months after completion of platinum-containing chemotherapy. ACT: appropriate comparator therapy; BRCA: breast cancer associated gene; G-BA: Federal Joint Committee	

In the present dossier assessment, the term "ovarian cancer" includes ovarian, fallopian tube and peritoneal cancer.

The company concurred with the ACT specified by the G-BA. The present assessment was conducted in comparison with the ACT presented in Table 2.

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

Results

The company presented 2 non-controlled rucaparib studies for the derivation of the added benefit: ARIEL2 and Study 10. It additionally identified 2 randomized controlled trials (RCTs) on the ACT: Gordon 2001 and Kaye 2012. The company used the results of both studies on the comparator therapy for a descriptive comparison with those from the rucaparib studies.

The data presented by the company were not relevant for the benefit assessment for the following reasons:

- The considered patient populations of the rucaparib studies and of the studies on the comparator therapy did not concur sufficiently with the approved therapeutic indication.
- There was also no sufficient similarity between the study populations of the rucaparib studies and of the studies on the comparator therapy.
- Comparative data for patient-relevant outcomes were only available for individual adverse events (AEs), but not on patient-relevant outcomes of the categories of mortality, morbidity and health-related quality of life.

In summary, the data presented by the company were unsuitable to prove an advantage or a disadvantage of rucaparib in patients with platinum-sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian cancer, who have been treated with 2 or more prior lines of platinum-based chemotherapy, and who are unable to tolerate further platinum-based chemotherapy in comparison with the ACT. This resulted in no hint of an added benefit of rucaparib 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]

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

[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: Rucaparib – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adult patients with platinum-sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian cancer[b], who have been treated with 2 or more prior lines of platinum-based chemotherapy, and who are unable to tolerate further platinum-based chemotherapy	▪ monotherapy with topotecan ▪ monotherapy with pegylated liposomal doxorubicin	Added benefit not proven

a: Presentation of the ACT specified by the G-BA.
b: The term "ovarian cancer" also includes fallopian tube and peritoneal cancer. It is assumed that platinum-sensitive, relapsed ovarian cancer involves a response to platinum-containing pretreatment with a relapse-free interval of at least 6 months. This includes partially platinum-sensitive ovarian cancer with relapse between 6 and 12 months after completion of platinum-containing chemotherapy.
ACT: appropriate comparator therapy; BRCA: breast cancer associated gene; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was the assessment of the added benefit of rucaparib as monotherapy treatment of adult patients with platinum-sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with 2 or more prior lines of platinum-based chemotherapy, and who are unable to tolerate further platinum-based chemotherapy in comparison with the ACT.

The specification of the ACT by the G-BA resulted in the research question presented in Table 4 for the present benefit assessment.

Table 4: Research question of the benefit assessment of rucaparib

Therapeutic indication	ACT[a]
Adult patients with platinum-sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian cancer[b], who have been treated with 2 or more prior lines of platinum-based chemotherapy, and who are unable to tolerate further platinum-based chemotherapy	▪ monotherapy with topotecan ▪ monotherapy with pegylated liposomal doxorubicin

a: Presentation of the ACT specified by the G-BA.
b: The term "ovarian cancer" also includes fallopian tube and peritoneal cancer. It is assumed that platinum-sensitive, relapsed ovarian cancer involves a response to platinum-containing pretreatment with a relapse-free interval of at least 6 months. This includes partially platinum-sensitive ovarian cancer with relapse between 6 and 12 months after completion of platinum-containing chemotherapy.
ACT: appropriate comparator therapy; BRCA: breast cancer associated gene; G-BA: Federal Joint Committee

According to the S3 guideline "Diagnostics, Therapy and Follow-up of Malignant Ovarian Tumours", cancers of the ovaries, fallopian tubes, and peritoneum are jointly classified due to the same pathogenesis and histomorphology [3]. In the present dossier assessment, the term "ovarian cancer" therefore includes ovarian, fallopian tube and peritoneal cancer.

The company concurred with the ACT specified by the G-BA. The present assessment was conducted in comparison with the ACT presented in Table 4.

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

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on rucaparib (status: 1 February 2019)
- bibliographical literature search on rucaparib (last search on 17 January 2019)
- search in trial registries for studies on rucaparib (last search on 18 December 2018)
- bibliographical literature search on the ACT (last search on 17 January 2019)
- search in trial registries for studies on the ACT (last search on 18 December 2018)

To check the completeness of the study pool:

- search in trial registries for studies on rucaparib (last search on 12 March 2019)

Concurring with the company, the check of the completeness of the study pool produced no relevant studies on the comparison of rucaparib versus the ACT.

For the derivation of the added benefit, however, the company presented 2 non-controlled rucaparib studies under further investigations (Module 4 A, Section 4.3.2.3): ARIEL2 [4-8] and Study CO-338-010 (hereinafter referred to as Study 10) [6,9-12]. It additionally identified 2 RCTs on the ACT: Gordon 2001 [13] and Kaye 2012 [14]. The company used the results of both studies on the comparator therapy for a descriptive comparison with those from the rucaparib studies.

The data presented by the company were not relevant for the benefit assessment for the following reasons:

- The considered patient populations of the rucaparib studies and of the studies on the comparator therapy did not concur sufficiently with the approved therapeutic indication.

- There was also no sufficient similarity between the study populations of the rucaparib studies and of the studies on the comparator therapy.
- Comparative data for patient-relevant outcomes were only available for individual AEs, but not on patient-relevant outcomes of the categories of mortality, morbidity and health-related quality of life.

Hence, overall there were no suitable data to allow a comparison of rucaparib with the ACT. The derivation of an added benefit of rucaparib in comparison with the ACT is therefore impossible in the present benefit assessment. The studies presented by the company and the reasons why the data presented by the company were not relevant to the research question of the benefit assessment are described in more detail below.

Rucaparib studies

ARIEL2

The ARIEL2 study is an ongoing, 2-part, non-randomized, open-label and multicentre phase 2 study. This study is one of the pivotal approval studies for rucaparib in the therapeutic indication under assessment. It enrolled adult patients with relapsed or progressive high-grade serous or grade 2/3 endometrioid epithelial ovarian, fallopian tube or primary peritoneal cancer irrespective of their BRCA mutation status. The 2 study parts are different study arms; and patients were either enrolled in part 1 or in part 2 of the study. The inclusion criteria of both study parts differ with regard to the platinum status of the ovarian cancer and to pretreatment.

Part 1 of the study includes 204 patients with platinum-sensitive ovarian cancer who had at least 1 prior platinum-based regimen. Part 2 includes 111 patients of any platinum status who had 3 or 4 prior chemotherapy regimens. In compliance with the approval, 600 mg rucaparib twice daily was administered in both parts of the study [15]. Primary outcome is progression-free survival in part 1, and objective response in part 2.

Study 10

Study 10 is an ongoing, 3-part, non-randomized, open-label and multicentre phase 1/2 study, which was also submitted for the approval of rucaparib. The patients were included in only one part of the study.

Part 2A (phase 2) enrolled 42 patients with platinum-sensitive, relapsed, high-grade serous or endometrioid epithelial ovarian cancer with BRCA mutation (germline), who had received at least 2, but no more than 4 prior chemotherapeutic regimens. At most 1 of the prior therapies was allowed to be platinum-free. In compliance with the approval, the patients received 600 mg rucaparib twice daily [15]. Primary outcome in part 2A was objective response.

The other parts of the study were either for dose-finding in patients with solid tumours or lymphoma (part 1) or investigations on pharmacokinetics in patients with advanced solid tumours and BRCA mutation (part 3). Part 2B enrolled patients in the therapeutic indication,

but, according to the clinical study report (CSR) from 24 May 2016, no results are available yet as recruitment had only started at this time point.

Consequently, the company considered only data from part 2A of Study 10 for the present assessment.

Patients of the rucaparib studies do not concur sufficiently with the therapeutic indication under assessment

The company used parts 1 and 2 of the ARIEL2 study and part 2A of Study 10 for the present benefit assessment. From both parts of the ARIEL2 study, it considered, in addition to the total populations, subpopulations that exclusively comprised patients with BRCA mutation. These were 40 patients from part 1 and 38 patients from part 2. From Study 10, it used the patients from part 2A completely; exclusively patients with BRCA mutation were included in this part. The company's approach was adequate as BRCA mutation is a criterion within the therapeutic indication.

The patients with BRCA mutation who were included in the 3 parts of the study considered by the company nevertheless did not sufficiently correspond to the therapeutic indication to be investigated:

- In part 1 of the ARIEL2 study, 43% (17 patients) of the BRCA subpopulation had been treated with only 1 prior platinum-containing therapy. However, the approved therapeutic indication comprises only patients who have been treated with 2 or more prior lines of platinum-based chemotherapy.
- In part 2 of the ARIEL2 study, 66% (25 patients) of the BRCA subpopulation have ovarian cancer that is resistant or refractory to platinum. However, the approval comprises only patients with platinum-sensitive tumours.
- The company conducted no further restriction of the patient populations to 2 or more prior lines of platinum-based chemotherapy or to patients with platinum-sensitive tumours for the ARIEL2 study.
- In addition, it was unclear for all 3 parts of the study used by the company to what extent the platinum-sensitive patients of interest do not tolerate further platinum-containing chemotherapy. This criterion is not reflected in the respective requirements on study inclusion. In Module 3 A (Section 3.2.1), the company showed various situations in which platinum-based therapy was not a suitable option despite platinum-sensitive relapse or in which patients rejected this option. Under these situations, the company summarized platinum-induced/cumulative toxicity, hypersensitivity, psychological/social aspects, the desire for a different type of application, or patients with partially platinum-sensitive disease. However, the company did not state in the dossier to what extent these aspects applied to the patients included in the rucaparib studies.

In addition to the separate consideration of the study parts ARIEL2 part 1, ARIEL2 part 2 and Study 10 part 2A, the company carried out an integrated efficacy analysis, as already submitted for the approval of rucaparib. For this purpose, it used all patients with BRCA mutation and at least 2 prior regimens of platinum-based chemotherapy from the above-mentioned study parts. The company neglected to restrict the collective to only patients with platinum-sensitive tumours from part 2 of the ARIEL2 study also in this approach. As for the individual studies, it was also unclear whether patients who do not tolerate further platinum-containing chemotherapy were included in the analysis. The company did not carry out a restriction in this respect. Hence overall, a high proportion of the patients considered did not correspond to the therapeutic indication of rucaparib also in the integrated efficacy analysis.

Further approach of the company – descriptive comparison

With the studies ARIEL2 and Study 10, the company only presented non-comparative studies. The company conducted a descriptive comparison to be able to compare the results on rucaparib from these studies with those on the comparator therapy. To conduct this comparison, the company used the results of the integrated efficacy analysis and results on the comparator therapy of the studies Gordon 2001 [13] and Kaye 2012 [14]. It compared results on the outcomes “progression-free survival”, “objective response rate”, “duration of response” and on individual common AEs.

Studies on the comparator therapy

Gordon 2001

The randomized, multicentre, open-label, 2-arm phase 3 study Gordon 2001 enrolled 481 patients with ovarian cancer whose tumours had relapsed or had not responded to prior first-line treatment with platinum. The patients received either pegylated liposomal doxorubicin or topotecan. Both treatments were options of the comparator therapy.

The included patients did not concur sufficiently with the therapeutic indication of interest, however. The inclusion criteria of the study did not consider the following criteria relevant for the therapeutic indication: platinum-sensitivity of the tumour, pretreatment with at least 2 lines of platinum-based chemotherapy, and presence of BRCA mutation. Depending on the study arm, only 46% to 47% of the included patients had platinum-sensitive tumours. Information on the patients’ BRCA mutation status and the number of prior chemotherapeutic regimens was not available. It was also not considered at study inclusion whether the patients did not tolerate further platinum-containing chemotherapy. It could also not be inferred from the publication whether the tumours of the included patients could be rated as “high-grade”. The included patient population therefore did not sufficiently correspond to the approved therapeutic indication in several criteria, and the data were not relevant for the present assessment.

Kaye 2012

The randomized, multicentre, open-label, 3-arm phase 2 study Kaye 2012 included 125 patients with ovarian cancer and BRCA mutation (germline) who recurred or progressed within

12 months of their most recent platinum-based chemotherapy. Further chemotherapy after the platinum-based treatment and before study inclusion was allowed. The patients received either olaparib (2 arms) or pegylated liposomal doxorubicin, which is one option of the comparator therapy (study arm of interest: 33 patients). Only 79% of the patients in the study arm of interest had a grade 3 tumour and could therefore be defined as "high-grade". The patient characteristics additionally show that 21% of the patients included in the study arm of interest had received only 1 prior therapy. Overall, about 73% of the patients allocated to the arm with administration of pegylated liposomal doxorubicin had received platinum-based treatment as their most recent therapy before study treatment. The number of patients who had received at least 2 prior platinum-based treatments remained unclear, however. It was also not clear from the information provided in the publication to what extent the patients included did not tolerate further platinum-containing chemotherapy. In addition, 42% of the patients receiving pegylated liposomal doxorubicin had platinum-resistant tumours.

Overall, the patient populations in the studies on the ACT do also not concur sufficiently with the therapeutic indication, and the data were not relevant for the present assessment.

Lack of similarity between the study populations

Irrespective of the question of representation of the relevant study population in the individual studies, there is also insufficient similarity between the patient populations of the rucaparib studies and those of the studies on the comparator therapy due to the different inclusion criteria presented. This is another reason why the studies were unsuitable for a descriptive comparison.

Data on patient-relevant outcomes only for individual common adverse events

Even if the study populations were suitable and similar, no results on patient-relevant outcomes of the categories of mortality, morbidity and health-related quality of life are available in the rucaparib studies, the results of which could be compared with those from the studies Gordon 2001 and Kaye 2012, especially since no analyses on overall survival are yet available. The descriptive comparison on patient-relevant outcomes is therefore limited to the comparison of individual common AEs. In addition, the approach of a purely descriptive comparison of results of individual arms from different studies without presentation of effect estimations is inadequate.

Summary

In summary, the data presented by the company were unsuitable to prove an advantage or a disadvantage of rucaparib in patients with platinum-sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian cancer, who have been treated with 2 or more prior lines of platinum-based chemotherapy, and who are unable to tolerate further platinum-based chemotherapy in comparison with the ACT; these data were not used for the present benefit assessment.

2.4 Results on added benefit

In its dossier, the company presented no suitable data for the assessment of the added benefit of rucaparib versus the ACT. This resulted in no hint of an added benefit of rucaparib in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

The company presented no suitable data for the assessment of the added benefit of rucaparib. An added benefit of rucaparib in comparison with the ACT is not proven for adult patients with platinum-sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian cancer, who have been treated with 2 or more prior lines of platinum-based chemotherapy, and who are unable to tolerate further platinum-based chemotherapy.

The result of the assessment of the added benefit of rucaparib in comparison with the ACT is summarized in Table 5.

Table 5: Rucaparib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with platinum-sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian cancer[b], who have been treated with 2 or more prior lines of platinum-based chemotherapy, and who are unable to tolerate further platinum-based chemotherapy	▪ monotherapy with topotecan ▪ monotherapy with pegylated liposomal doxorubicin	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. b: The term “ovarian cancer” also includes fallopian tube and peritoneal cancer. It is assumed that platinum-sensitive, relapsed ovarian cancer involves a response to platinum-containing pretreatment with a relapse-free interval of at least 6 months. This includes partially platinum-sensitive ovarian cancer with relapse between 6 and 12 months after completion of platinum-containing chemotherapy. ACT: appropriate comparator therapy; BRCA: breast cancer associated gene; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company, which derived a hint of a non-quantifiable added benefit of rucaparib on the basis of the studies used by the company.

The G-BA decides on the added benefit.

2.6 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment.

References for English extract

Please see full dossier assessment for full reference list.

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

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