Rucaparib (Rubraca®) as monotherapy for the maintenance treatment of advanced high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer

General information

Drug description [1]

Rucaparib (Rubraca®) is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP-1, PARP-2, and PARP-3.

Indication [2]

Rucaparib (Rubraca®) is indicated as monotherapy for the maintenance treatment of adult patients with advanced (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.

Incidence

In Austria, in 2020, 689 women were newly diagnosed with ovarian cancer. The age-standardised[1] incidence rate was 13.8 per 100,000 women [3].
The median age at diagnosis is 69 years, disease rates increase continuously until the age of 85. The majority of ovarian cancers (approximately 75%) are diagnosed at an advanced stage (FIGO stage III/IV) [4].

Current treatment [4]

- **For maintenance therapy after systemic therapy at initial diagnosis, Onkopedia recommends the following:**
  - Maintenance therapy in stages III and IV with partial or complete remission after chemotherapy is standard of care. In low-grade carcinomas, bevacizumab is used; in high-grade carcinomas, depending on the BRCA/HRD status and the question of the feasibility of bevacizumab therapy, the options available today are monotherapy with either bevacizumab or one of the PARP inhibitors olaparib or niraparib or the combination therapy with olaparib and bevacizumab.
  - Bevacizumab:
    - Bevacizumab is given concurrently with chemotherapy, carboplatin and paclitaxel and subsequently as maintenance therapy for a maximum of 15 months in stages FIGO IIIA1 and IIIB-IV according to the current FIGO classification (corresponding to stages IIIB, IIIC and IV according to the 2009 FIGO classification). It leads to a prolongation of PFS. Prolongation of OS was only observed in cases of high tumour burden, residual tumour, stage IV or high-grade serous subtype.
  - PARP inhibitors:
    - The PARP inhibitor olaparib can be used in BRCA1/2 mutation (germline and/or somatic), according to the SOLO1 study, and the PARP inhibitor niraparib independent of BRCA1/2
      status and HRD status (PRIMA study). A significant prolongation of PFS was observed for both agents, and a benefit in OS was also demonstrated for olaparib, although not statistically significant.
  - The combination of olaparib and bevacizumab can be used after completion of first-line platinum-containing chemotherapy in responding patients whose tumour has a positive HRD status, defined by BRCA1-/2 mutation and/or increased genomic instability. In the PAOLA-1 trial, the combination was shown to achieve a benefit in PFS and PFS2 over placebo + bevacizumab. Whether the combination of olaparib with bevacizumab provides a survival benefit over olaparib alone cannot be assessed based on current study data.
  - The value of endocrine maintenance therapy in low-grade, hormone receptor-positive carcinomas has not been definitively evaluated (ongoing trials for anti-estrogenic therapy with aromatase inhibitors: MATAO/ENGOT-ov54/Swiss-GO2).

Regulatory status

EMA [2]	FDA [1]
Approval status for this indication: On 12 October 2023, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Rubraca®. The CHMP adopted a new indication for Rubraca® as follows:	**Approval status for this indication**: not approved **Other indications**: Rubraca® is indicated

[1] European Standard Population 2013.

- ❖ Rubraca® is indicated as monotherapy for the maintenance treatment of adult patients with advanced (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.

Other indications:

- ❖ Rubraca® is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

✓ **Medicine under additional monitoring**

- ❖ for the maintenance treatment of adult patients with a deleterious BRCA mutation (germline and/or somatic)- associated recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy.
- ❖ for the treatment of adult patients with a deleterious BRCA mutation (germline and/or somatic)-associated metastatic castration-resistant prostate cancer who have been treated with androgen receptor-directed therapy and taxane-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Rubraca®. This indication is approved under accelerated approval based on ORR and DOR.

Manufacturer

Rubraca® is manufactured by pharmaand GmbH.

Costs

Currently, there is no cost information available.

Warnings and precautions [5]

- ❖ **Haematological toxicity**
  - During treatment with rucaparib, events of myelosuppression (anaemia, neutropenia, thrombocytopenia) may be observed and are typically first observed after 8 to 10 weeks of treatment with rucaparib. These reactions are manageable with routine medical treatment and/or dose adjustment for more severe cases.
  - Complete blood count testing prior to starting treatment with Rubraca®, and monthly thereafter, is advised. Patients should not start Rubraca® treatment until they have recovered from haematological toxicities caused by previous chemotherapy (≤ CTCAE Grade 1).
  - Supportive care and institutional guidelines should be implemented for the management of low blood counts for the treatment of anaemia and neutropenia. Rubraca® should be interrupted or dose reduced according to product information and blood counts monitored weekly until recovery. If the levels have not recovered to CTCAE Grade 1 or better after 4 weeks, the patient should be referred to a haematologist for further investigations.
- ❖ **Myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML)**
  - MDS/AML, including cases with fatal outcomes, have been reported in patients who received rucaparib. The duration of therapy with rucaparib in patients who developed MDS/AML varied from < 2 months to approximately 6 years.
  - If MDS/AML is suspected, the patient should be referred to a haematologist for further investigations, including bone marrow analysis and blood sampling for cytogenetics. If following investigation for prolonged haematological toxicity, MDS/AML is confirmed, Rubraca should be discontinued.
- ❖ **Photosensitivity**
  - Photosensitivity has been observed in patients treated with rucaparib. Patients should avoid spending time in direct sunlight because they may burn more easily during rucaparib treatment; when outdoors, patients should wear a hat and protective clothing, and use sunscreen and lip balm with a sun protection factor of 50 or greater.
- ❖ **Gastrointestinal toxicities**
  - Gastrointestinal toxicities (nausea and vomiting) are frequently reported with rucaparib, are generally low grade (CTCAE Grade 1 or 2) and may be managed with dose reduction or interruption.
  - Antiemetics, such as 5-HT3 antagonists, dexamethasone, aprepitant and fosaprepitant, can be used as a treatment for nausea/vomiting and may also be considered for prophylactic (i.e., preventative) use prior to starting Rubraca®. It is important to proactively manage these events to avoid prolonged or more severe events of nausea/vomiting which have the potential to lead to complications such as dehydration or hospitalisation.
- ❖ **Intestinal obstruction**

- Cases of intestinal obstruction have been observed in ovarian cancer patients treated with rucaparib in clinical trials; 4.5% of patients experienced a serious event of intestinal obstruction, with a fatal outcome of less than 0.1%. The underlying disease may play a role in the development of intestinal obstruction in patients with ovarian cancer. In the event of suspected intestinal obstruction, a prompt diagnostic evaluation should be conducted, and the patient should be treated appropriately.

❖ **Embryo-foetal toxicity**
- Rubraca can cause foetal harm when administered to a pregnant woman based on its mechanism of action and findings from animal studies.

❖ **Pregnancy/contraception**
- Pregnant women should be informed of the potential risks to a foetus. Women of reproductive potential should be advised to use effective contraception during treatment and for 6 months following the last dose of Rubraca®. A pregnancy test before initiating treatment is recommended in women of reproductive potential.

❖ **Excipients**
- This medicine contains less than 1 mmol sodium (23 mg) per tablet, essentially 'sodium-free'.

Study characteristics [6, 7]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up (I vs. C)	Characteristics	Biomarker	Funding	Publication(s)
ATHENA (GOG-3020/ ENGOT-ov45) NCT03522246	538 (4:1)	oral rucaparib 600 mg twice a day	placebo	PFS per RECIST (investigator-assessed)	26.1 vs. 26.2 months	**ongoing**[2], international, multicentre, randomized, double-blind, phase III trial	BRCA	Clovis Oncology Inc; supported in part by the NIHR Cambridge Biomedical Research Centre	ATHENA trial [6]

Inclusion criteria[3]	Exclusion criteria	Patient characteristics at baseline, ITT population (I vs. C, n=427 vs. 111)
❖ ≥18 years and had newly diagnosed, histologically confirmed, advanced (FIGO stage III-IV), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer. ❖ Patients had completed cytoreductive surgery (R0/complete resection was permitted) before chemotherapy or following neoadjuvant chemotherapy; had completed 4-8 cycles of first-line platinum-doublet treatment, including a minimum of 4 cycles of a platinum/taxane combination (bevacizumab was only allowed during the chemotherapy phase), and achieved an investigator-assessed response. ❖ Sufficient formalin-fixed paraffin-embedded tumour tissue is available for planned analyses and a known BRCA mutation result	❖ Non-epithelial tumours (pure sarcomas) or ovarian tumours with low malignant potential or mucinous tumours. Mixed mullerian tumours/carcinosarcomas are allowed. ❖ Active second malignancy. ❖ Patients with a history of malignancy that has been completely treated, with no evidence of active cancer for 3 years prior to enrolment, or patients with surgically cured low-risk tumours, such as early-stage cervical or endometrial cancer are allowed to enrol. ❖ Known CNS brain metastases. ❖ Any prior treatment for ovarian cancer, other than the first-line platinum regimen, including any maintenance treatment between completion of the platinum regimen and initiation of the study drug in this study. Ongoing hormonal treatment for previously treated breast cancer is permitted. Hormonal maintenance treatment for ovarian cancer is not allowed. ❖ Evidence of interstitial lung disease, active pneumonitis, myocarditis, or a history of myocarditis.	❖ Median age (range): 61.0 (30-83) vs. 61.0 (31-80) ❖ Race: • White: 76.8% vs. 78.4% • Asian: 18.7% vs. 14.4% • Other: 2.6% vs. 5.4% • Unknown: 1.9% vs. 1.8% ❖ ECOG PS: • 0: 69.1% vs. 68.5% • 1: 30.7% vs. 31.5% ❖ FIGO stage: • III: 75.6% vs. 70.3% • IV: 24.4% vs. 29.7% ❖ Type of cancer: • Epithelial ovarian: 78.7% vs. 76.6% • Fallopian tube: 11.7% vs. 16.2% • Primary peritoneal: 9.6% vs. 7.2% ❖ Histology • Serous: 89.9% vs. 95.5%

[2] The ATHENA trial is currently ongoing; the estimated study completion date is 12/2023.
[3] For detailed in- and exclusion criteria, please see trial protocol.

(either positive or negative) via central testing. ❖ ECOG PS of 0-1. ❖ Have adequate organ function confirmed by the following laboratory values obtained within 14 days of randomization: • Bone Marrow Function: ANC ≥ 1.5 × 109/L, platelets ≥ 100 × 109/L, haemoglobin ≥ 9 g/dL • Hepatic Function: AST and ALT ≤ 1.5 × ULN, bilirubin ≤ 1.5 × ULN; < 2 × ULN if hyperbilirubinemia is due to Gilbert's syndrome, serum albumin ≥ 30 g/L (3.0 g/dL) • Renal Function: Serum creatinine ≤ 1.5 × ULN unless estimated GFR ≥ 30 mL/min using the Cockcroft Gault formula.	❖ Patients with an active, known, or suspected autoimmune disease. ❖ Patients with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enrol. ❖ Patients with a condition requiring systemic treatment with either corticosteroids or other immunosuppressive medications within 14 days of randomization. ❖ Drainage of ascites during the final 2 cycles of treatment with the platinum regimen. ❖ Pre-existing duodenal stent and/or any gastrointestinal disorder or defect that would, in the opinion of the investigator, interfere with absorption of study treatment. ❖ Known history of a positive test for (HIV) or known acquired immunodeficiency syndrome (AIDS). ❖ Any positive test result for hepatitis B and/or known history of hepatitis B. ❖ Pregnant, or breastfeeding. ❖ Received chemotherapy within 14 days prior to first dose of study drug and/or ongoing adverse effects from such treatment NCI-CTCAE v.5.0 grade1. ❖ Hospitalization for bowel obstruction within 12 weeks prior to enrolment.	• Endometrioid: 3.0% vs. 0.9% • Clear cell: 3.0% vs. 1.8% • Mixed: 2.3% vs. 0.9% • Other: 1.6% vs. 0.9% ❖ Surgical outcome: • Complete resection: 61.6% vs. 65.8% • Microscopic residual disease: 19.0% vs. 13.5% • Macroscopic residual disease (≥1 cm): 19.4% vs. 20.7% ❖ Radiologic response after first-line platinum-doublet chemotherapy: • No disease after surgery: 52.5% vs. 57.7% • CR: 17.1% vs. 9.9% • PR: 17.8% vs. 19.8% • Inevaluable/other: 12.6% vs. 12.6% ❖ No. of cycles of first-line platinum-doublet chemotherapy, • median (range): 6 (4-8) vs. 6 (4-8) • 4 to <6 cycles: 6.1% vs. 7.2% • 6-8 cycles: 93.9% vs. 92.8% ❖ Prior bevacizumab: 19.7% vs. 10.8% ❖ Measurable disease at baseline: 9.6% vs. 9.9% ❖ CA-125 within normal limits at baseline by central or local: 86.9% vs. 90.1%

Efficacy (I vs. C)	**Safety** (I vs. C, n=425 vs. n=110)
<u>Data cutoff 23 March 2022</u> **HRD population (n=185 vs. n=49)** **Median PFS:** 28.7 months (95% CI, 23.0-NR) vs. 11.3 months (95% CI, 9.1-22.1); log-rank p=0.0004; HR 0.47; 95% CI, 0.31-0.72 **OS**: results were immature at the data cutoff **ORR:** 58.8% (95% CI, 32.9-81.6) vs. 20.0% (95% CI, 0.5-71.6) **Median DOR**: 16.7 months (95% CI, 5.7-NR) vs. 5.5 months (95% CI, NE) **ITT population (n=427 vs. n=111)** **Median PFS**: 20.2 months (95% CI, 15.2-24.7) vs. 9.2 months (95% CI, 8.3-12.2); log-rank p=0.0001; HR 0.52; 95% CI, 0.40-0.68 **PFS at 24 months**: 45.1% vs. 25.4% **OS**: results were immature at data cutoff; 24.7% of death events had occurred **ORR:** 48.8% (95% CI, 32.9-64.9) vs. 9.1% (95% CI, 0.2-41.3) **Median DOR**: 22.1 months (95%CI, 8.4-NR) vs. 5.5 months (95% CI, NE)	**TEAEs of any grade:** 96.7% vs. 92.7% **TEAEs of grade ≥3**: 60.5% vs. 22.7% **TEAEs leading to discontinuation**: 11.8% vs. 5.5% **Death due to a TEAE:** 0.5%[4] vs. 0

[4] N=1 because of myocardial infarction and pulmonary embolism and n=1 because of multiple organ dysfunction syndrome; neither was considered related to rucaparib.

Patient-reported outcomes

- Changes from baseline in Functional Assessment of Cancer Therapy—Ovarian Trial Outcome Index scores were similar between rucaparib and placebo in the ITT population.

ESMO-MCBS version 1.1 [8]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2B	>6 months	PFS: +11 months	0.52 (0.40-0.68)	≤0.65 AND gain ≥3 months	3	-	No improvement	-	3
Adapted	NC	2B	>6 months	PFS: +11 months	0.52 (0.40-0.68)	≤0.65 AND gain ≥3 months	3	TEAEs grade ≥3: +37.8%	No improvement	-1[5]	2

Risk of bias (RCT) [9]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes low risk	unclear unclear risk	yes low risk	unclear[6] unclear risk	yes[7] high risk	unclear

Ongoing trials [10]

NCT number/trial name	Description	Estimated study completion date
NCT03522246/ATHENA	Please see above.	12/2030
NCT04227522/MAMOC	Rucaparib maintenance after bevacizumab maintenance following carboplatin-based first-line chemotherapy in ovarian cancer patients.	01/2025

Available assessments

- In February 2022, a Health Technology Briefing "Rucaparib maintenance therapy for ovarian, fallopian tube or primary peritoneal cancer after frontline platinum-based chemotherapy" was published by NIHR [11].
- No further assessments were identified via NICE, CADTH, ICER and G-BA.

Other aspects and conclusions

- In October 2023, the **CHMP adopted a new indication** for Rubraca®, indicated as monotherapy for the maintenance treatment of adult patients with advanced (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. This indication is currently **not approved by the FDA.**
- **ATHENA** (NCT03522246) is an **ongoing**, international, multicentre, randomized, double-blind, phase III trial comparing rucaparib maintenance treatment vs. placebo. Eligible patients were ≥18 years old and had newly diagnosed, histologically confirmed, advanced (FIGO stage III-IV), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer. Patients had completed cytoreductive surgery
  before chemotherapy or following neoadjuvant chemotherapy; had completed 4-8 cycles of first-line platinum-doublet treatment, achieved an investigator-assessed response and had an ECOG of 0-1 and adequate organ function. Patients with non-epithelial tumours or ovarian tumours with low malignant potential or mucinous tumours, an active second malignancy, or known CNS brain metastases were excluded.
- The **primary endpoint** was investigator-assessed **PFS in the HRD population and the ITT population**. Median PFS was 28.7 months vs. 11.3 months in the HRD population (log-rank p=.0004; HR 0.47; 95% CI, 0.31-0.72) and 20.2 months vs. 9.2 months in the ITT population (log-rank p=.0001; HR 0.52; 95% CI, 0.40-0.68).
- Analysis of **patient-reported outcomes** among patients of the ITT population showed that changes from baseline in Functional Assessment of Cancer Therapy—Ovarian Trial Outcome Index scores were **similar** between rucaparib and placebo.

[5] Downgrade 1 level due to +37.8% TEAEs in the rucaparib group.
[6] The ATHENA trial is ongoing; currently,
[7] Industry-funded.

- The **original and adapted ESMO-MCBS** were applied, resulting in a final adjusted magnitude of clinical benefit **grade of 3 and 2**, respectively.
- Due to the ongoing status of the ATHENA trial, the **risk of bias is considered unclear**. However, it is increased by its industry-funded background.
- Besides the ATHENA trial, one further ongoing trial, assessing rucaparib maintenance after bevacizumab maintenance following carboplatin-based first-line chemotherapy in ovarian cancer patients, was identified.
- Analysis of the ATHENA trial data is **limited** due to the **small number of placebo group patients,** as patients were randomized in a 4:1 ratio to both treatment arms. Moreover, an improvement of 38.7% of TEAEs in patients treated with rucaparib as compared to placebo group patients raises safety concerns. Hence, final and robust phase 3 data is required.

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Abbreviations: ADP=adenosine diphosphate, AE=adverse event, AIDS=acquired immunodeficiency syndrome, AJ=adjustment, AML=acute myeloid leukemia, ANC=absolute neutrophil count, BRCA=breast cancer susceptibility gene, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS=central nervous system, CTCAE=Common Terminology Criteria for Adverse Events, DOR=duration of response, ECOG PS=Eastern Cooperative Oncology Group performance status, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FIGO=International Federation of Gynecology and Obstetrics, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, GFR=glomerular filtration rate, HIV=human immunodeficiency virus, HR=hazard ratio, HRD=homologous recombination deficiency, I=intervention, ICER=Institute for Clinical and Economic Review, Int.=intention, MDS=myelodysplastic syndrome, MG=median gain, n=number of patients, NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events, NE=not evaluable, NICE=National Institute for Health Care Excellence, NIHR=National Institute for Health Research, NR=not reached, ORR=objective response rate, OS=overall survival, PARP=poly adenosine diphosphate-ribose polymerase, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, RECIST=Response Evaluation Criteria in Solid Tumors, SAE=serious adverse event, ST=standard treatment, TEAE=treatment-emergent adverse event, ULN=upper limit of normal

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