Medicinrådet

Bilag til direkte indplacering af rucaparib i Medicinrådets behandlingsvejledning vedrørende lægemidler til BRCA-muteret kræft i æggestokkene, æggelederne eller primær kræft i bughinden

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. rucaparib
2. Forhandlingsnotat fra Amgros vedr. rucaparib
3. Ansøgers endelige ansøgning vedr. rucaparib

Comments on tBRCA assessment for Rucaparib in Denmark

Page	Comment	Detail
11	Type II variation on: 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 was appoved 30. Nov 2023; EMA Rubraca-H-C-4272-II-0036 : Assessment report - Variation	The reference to the assessment report variation should be added to the end of the statement
16	ATHENA-Mono included R0 patients: No requirement for patients with FIGO Stage III to have measurable disease prior to receiving platinum-based chemotherapy, i.e. R0 disease allowed.	Important to note here that ATHENA-MONO has includes R0 patients, which allows the ATHENA-MONO study population to be close to the real-world setting.
17	This is incorrect; the HR quoted in table 3-2 and figure 3-1 are for the tBRCA population, not the HRD population. These are extracted from the type ii variation report	The HR in table 3-2 is for the tBRCA population.
19	This is incorrect; number should be 91 (number of patient in tBRCA subgroup)	The table has the HR for the tBRCA population but the patient numbers for the HRD population
19	This is incorrect, number should be 24 (number of patients in tBRCA subgroup)	The table has the HR for the tBRCA population but the patient numbers for the HRD population
22	This is incorrect, the numbers quoted in the tables are actually for the tBRCA population from the EPAR.	The statement should be corrected since table 3-2 has the HR for the tBRCA population.
30	Rucaparib has immature OS data.	Statement should mention that the reason why rucaparib does not have statistical significant or clinically relevant increase in survival may be due to immature OS data, which is in contrast with niraparib, which has already conducted their final overall survival analysis in PRIMA. OS HR 1.01 [95% confidence interval (CI) 0.84-1.23; P = 0.8834] for niraparib: Monk BJ, Barretina-Ginesta MP, Pothuri B, Vergote I, Graybill W, Mirza MR, McCormick CC, Lorusso D, Moore RG, Freyer G, O'Cearbhaill RE, Heitz F, O'Malley DM, Redondo A, Shahin MS, Vulsteke C, Bradley WH, Haslund CA, Chase DM, Pisano C, Holman LL, Pérez MJR, DiSilvestro P, Gaba L, Herzog TJ, Bruchim I, Compton N, Shtessel L, Malinowska IA, González-Martín A. Niraparib first-line maintenance therapy in patients with newly diagnosed advanced ovarian cancer: final overall survival results from the PRIMA/ENGOT-OV26/GOG-3012 trial. Ann Oncol. 2024 Nov;35(11):981-

		992. doi: 10.1016/j.annonc.2024.08.2241. Epub 2024 Sep 14. PMID: 39284381; PMCID: PMC11934258.
32	3-step dose reduction is possible	This statement should emphasise that there is a 3-step dose reduction possible for rucaparib. Rucaparib is the only PARPi for which a 3-step dose reduction is possible
33	Monitoring states in 5.3 reflects what is in niraparib SmPC (weekly blood tests). niraparib requires blood pressure tests as well on weekly basis for the first 8 weeks. For rubraca, complete blood count testing prior to starting treatment with Rubraca, and monthly thereafter, is advised (see SmPC)	Monitoring statement should be clarified in terms of differences in monitoring for rucaparib compared to niraparib based on what is in the respective SmPCs. See below an overview of the difference of monitoring requirements and costs for each treatment.

We believe that not taking into account the costs differences in direct monitoring costs for each treatment would be an incorrect comparison of treatment costs.

According to SmPC of Zejula and Rubraca following monitoring requirements are advised for each of the product treatment:

Monitored parameters	**Monitoring frequency**	
	Rubraca (rucaparib)	**Zejula (niraparib)**
Blood pressure	**- No requirements**	- Before treatment - Weekly during first 2 months (first 2 treatment cycles) - Monthly during 3rd to 12th month (3rd to 12th treatment cycles)
Blood cell counts	- Before treatment - Monthly during 1st to 12th month (1st to 12th treatment cycles)	- Before treatment - Weekly during first month (first treatment cycle) - Monthly during 2nd to 12th month (2nd to 12th treatment cycles)
Source: Rubraca SmPC from 15.03.2024; Zejula SmPC from 03.01.2024		

The above listed monitoring requirements would require following frequency of visits and transport to and from Health Care centra for each product treatment:

Number of Health Care visits & Transport to and from HealthCare centra	**Before treatment start**	**Treatment cycle 1**	**Treatment cycle 2**	**Treatment cycle 3 - 12**	**Total no. of visits (1-12 treatment cycles)**
Zejula patients	1	4	4	10	**19**
Rubraca patients	1	1	1	10	**13**

The difference of monitoring requirements will also result in costs difference for the activity and frequency for each product treatment:

Activity	**Cost difference**	**Rubraca**	**Zejula**

Visit at/Review of sampling result by healthcare professional	46% higher personnel costs for time spent of each healthcare professional due to higher frequency of visits for Zejula (13 vs 19 visits)	Every time a monitoring activity is required; - 1 before treatment; - 1 during treatment cycle 1, - 1 during treatment cycle 2, and - 1 every month during treatment cycle 3-12. - in total 13 visits at healthcare specialist	Every time a monitoring activity is required; - 1 before treatment; - 4 during treatment cycle 1, - 4 during treatment cycle 2, and - 1 every month during treatment cycle 3-12. - in total 19 visits at healthcare specialist
CT-scanning	Equal costs	4 during 12 months treatment (every 3rd month)	4 during 12 months treatment (every 3rd month)
Blood Pressure Check	No costs for Rubraca vs. costs for 19 blood pressure checks during 1st year of treatment (1-12 treatment cycles)	No requirements	- 1 time before treatment, - 4 each during 1st and 2nd treatment cycle (weekly, total 8 checks for 2 treatment cycles), - 1 every month during treatment cycle 3-12 (10 checks during 10 treatment cycles); - in total 19 blood pressure checks during one year treatment.
Blood Cell Counts	23% higher costs for blood cell counts testing for Zejula due to higher frequency of testing (13 vs 16 testings)	- 1 time before treatment, - 1 every month during treatment cycle 1-12 (12 checks during 12 treatment cycles); - in total 13 blood pressure checks during one year treatment.	- 1 time before treatment, - 4 each during 1st treatment cycle (weekly, total 4 checks), - 1 every month during treatment cycle 2-12 (11 checks during 11 treatment cycles); - in total 16 blood pressure checks during one year treatment.
Transport to and from healthcare centra	46% higher costs for transport to and from healthcare centra due to higher frequency of visits for Zejula (13 vs 19 visits)	- 1 time before treatment, - 1 every month during treatment cycle 1-12 (12 checks during 12 treatment cycles); - in total 13 blood pressure checks during one year treatment.	- 1 time before treatment, - 4 each during 1st and 2nd treatment cycle (weekly, total 8 checks for 2 treatment cycles), - 1 every month during treatment cycle 3-12 (10 checks during 10 treatment cycles); - in total 19 blood pressure checks during one year treatment.

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08.04.2025

MBA/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	21.05.2025
Leverandør	GHN Pharma
Lægemiddel	Rubraca (rucaparib)
Ansøgt indikation	BRCA-muteret kræft i æggestokkene, æggelederne eller primær kræft i bughinden
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel - Direkte indplacering

Prisinformation

Amgros har forhandlet følgende pris på Rubraca (rucaparib)

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Rubraca	200 mg (60 stk.)	18.075,00	[redacted]	[redacted]
Rubraca	250 mg (60 stk.)	19.075,00	[redacted]	[redacted]
Rubraca	300 mg (60 stk.)	20.075,00	[redacted]	[redacted]

Aftaleforhold

Amgros vil indgå en aftale med leverandøren, som gælder fra [redacted]. Herefter vil Rubraca indgå i et nyt udbud sammen med Lynparza (olaparib) og Zejula (niraparib), og dermed får alle tre lægemidler de samme betingelser.

Konkurrencesituationen

[redacted] Rubraca bliver ligeledes vurderet af Medicinrådet til HRD+/BRCAwt patienter. Forventet dato for beslutning om anbefaling til denne patientgruppe er 29. oktober 2025.

Tabel 2 viser en sammenligning af lægemiddeludgifter pr. patient pr. år i relation til de andre lægemidler.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandling/år (SAIP, DKK)
Rubraca	300 mg (60 stk.)	600 mg 2 gange dagligt	[redacted]	[redacted]
Lynparza	150 mg (56 stk.)	300 mg 2 gange dagligt	[redacted]	[redacted]
Zejula	100 mg (84 stk.)	200 mg dagligt	[redacted]	[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Ikke anbefalet	Link til anbefaling
England	Anbefalet	Link til anbefaling
Sverige	Delvis anbefalet	Link til anbefaling

Opsummering

[redacted]

Application for the assessment of Rubraca® by updating Medicinrådet's recommendation and treatment guideline for medical products for BRCA-mutated ovarian, fallopian tube or primary peritoneal cancer

Contact information

Contact information	
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[If a company wishes to use external representation in relation to the application for evaluation of a new pharmaceutical / extension of indications, the following power of attorney must be completed and sent to medicinraadet@medicinraadet.dk.]

Table of contents

Tables and Figures

Abbreviations

AE	Adverse event
AML	Acute Myeloid Leukaemia
BICR	Blinded independent central review
BRCA	BReast CAncer gene
BRCAm	BRCA-mutated
CI	Confidence Interval
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Cancer
EORTC QLQ-OV28	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Ovarian Cancer
EMA	European Medicines Agency
EPAR	European Public Assessment Report
FACT-O TOI	Functional Assessment of Cancer Therapy – Ovarian Trial Outcome Index
FIGO	International Federation of Gynecology and Obstetrics
FOSI	Functional Assessment of Cancer Therapy Ovarian Cancer Symptom Index
HRD	Homologous Recombination Deficiency
ITT	Intention to treat
MDS	Myelodysplastic Syndrome
OS	Overall survival
PFS	Progression-free survival
TEAEs	Treatment-Emergent Adverse Events

1. Regulatory information on the pharmaceutical

Overview of the pharmaceutical	
Proprietary name	Rubraca
Generic name	Rucaparib
Therapeutic indication as defined by EMA	Rubraca is indicated as monotherapy for the maintenance treatment of adult patients with advanced (International Federation of Gynecology and Obstetrics [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(1). 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(1).
Marketing authorization holder in Denmark	pharmaand GmbH, Taborstrasse 1, 1020 Vienna, Austria
ATC code	L01XK03
Combination therapy and/or co-medication	Not applicable
(Expected) Date of EC approval	EC approved in their meeting on 15th November 2023 following CHMP positive opinion 12th Oct 2023. EPAR updated on EMA website 30th November 2023.
Has the pharmaceutical received a conditional marketing authorization?	Not applicable, unconditional authorization
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	No other EMA indication other than mentioned above

Overview of the pharmaceutical	
Other indications that have been evaluated by the DMC (yes/no)	No
Dispensing group	BEGR/NBS
Packaging – types, sizes/number of units and concentrations	Rubraca 200 mg film-coated tablets – each bottle* of 60 tablets Rubraca 250 mg film-coated tablets – each bottle* of 60 tablets Rubraca 300 mg film-coated tablets – each bottle* of 60 tablets *HDPE bottle, with a polypropylene (PP) induction seal closure, containing 60 tablets. Each carton contains one bottle(1).

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	1st line maintenance therapy for newly diagnosed patients with advanced BRCA-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer(1). The therapeutic indication relevant for this assessment is a subset of the EMA indication, restricted to patients with a BRCA mutation.
Dosage regiment and administration:	The recommended dose of Rubraca is 600 mg taken twice daily (oral pills to be taken at home), equivalent to a total daily dose of 1200 mg*. Patients should start the maintenance treatment with Rubraca no later than 8 weeks after completion of their final dose of the platinum containing regimen. Method of administration: Rubraca is for oral use and can be taken with or without food. The doses should be taken approximately 12 hours apart. *In line with SmPC, dose adjustments recommended if prescribed by the doctor: • Starting dose 600 mg twice daily (two 300 mg tablets twice daily) • First dose reduction 500 mg twice daily (two 250 mg tablets twice daily) • Second dose reduction 400 mg twice daily (two 200 mg tablets twice daily)

Summary	
	Third dose reduction 300 mg twice daily (one 300 mg tablet twice daily(1)
Choice of comparator [if any]	Niraparib (Zejula)(2) and olaparib (Lynparza)(3)
Most important efficacy endpoints (Difference/gain compared to comparator)	Efficacy endpoints included in the guideline were progression-free survival (PFS), overall survival (OS), and quality of life(4-6). There is no direct comparison of the comparators available. A meaningful indirect treatment comparison could not be performed due to differences in data availability, study design, target population, and baseline characteristics for prognostic factors and potential effect modifiers(6). For rucaparib, data from the ATHENA-MONO trial demonstrated a significant improvement in PFS among BRCAm patients compared to placebo (median PFS not reached vs 16.7 months in rucaparib and placebo arms, respectively) with a hazard ratio of 0.47 (95% CI, 0.26 to 0.84)(7). OS, median OS was not reached in either rucaparib or placebo arms after 37 months of follow-up(1, 8). Quality of life was measured using FACT-O TOI and showed no difference between rucaparib and placebo arms (mean difference 0.0 [95% CI: -4.0 to 4.0](9)). For niraparib, data from the PRIMA and PRIME studies demonstrated a significant improvement in PFS among BRCAm patients compared to placebo (median PFS for niraparib and placebo arms, respectively: PRIMA 30.1 vs. 11.5 based on 5-year follow-up data(10), PRIME not reached vs. 10.8 months(11)) yielding similar hazard ratios of 0.43 (95% CI, 0.31 to 0.59) and 0.40 (95% CI, 0.23 to 0.68), respectively. OS among BRCAm patients was reported in PRIMA following 74 months median follow-up showing no difference between treatment groups (HR 0.94 [95% CI, 0.63 to 1.41])(10). In the PRIMA study, quality of life was measured using the FOSI, EORTC QLQ-C30, and EORTC QLQ-OV28 instruments. Differences between niraparib and placebo were not reported; change from baseline values were comparable between niraparib and placebo arms, suggesting no difference in quality of life between arms(12). For olaparib, results from the SOLO-1 trial demonstrated a significant improvement in PFS among BRCAm patients compared to placebo (median PFS: 56.0 vs 13.8 months in olaparib and placebo arms, respectively) with a hazard ratio of 0.33 (95% CI, 0.25 to 0.43)(13). For OS, olaparib demonstrated significant improvement after 7 years follow-up compared to placebo (median OS: not reached vs. 75.2 months in olaparib and placebo arms, respectively) with a hazard ratio of 0.55 (95% CI, 0.40 to 0.76)(14). Quality of life as measured using FAT-O TOI showed significant worsening in the olaparib arm compared to placebo (mean difference -3.00 [95% CI: -4.78 to -1.22, p = 0.001]. However, this difference was not considered clinically meaningful(15).

Summary

Most important serious adverse events for the intervention and comparator	Key safety outcomes included in the guidelines are treatment discontinuations due to adverse events and grade 3-4 adverse events. In addition, there were key serious adverse events relevant for each of the treatments considered. For rucaparib, treatment discontinuations due to adverse events in the ATHENA-MONO trial were higher in the rucaparib arm vs. placebo (11.8% compared to 5.5%); the proportion of patients experiencing a grade 3 or 4 adverse event was higher in the rucaparib arm (60.5%) compared to the placebo arm (23.6%)(16). The most frequently reported reason for discontinuation was thrombocytopenia, nausea, anaemia, and fatigue/asthenia. The SmPC includes special warnings and precautions for use for haematological toxicity, MDS/AML, photosensitivity, gastrointestinal toxicities, intestinal obstruction, embryofoetal toxicity, and pregnancy / contraception(1). For niraparib, treatment discontinuations due to adverse events in the PRIMA(10) and PRIME(11) studies were higher in the niraparib arm vs. placebo (PRIMA: 16.3% vs. 3.7%; PRIME: 6.7% vs. 5.4%); the proportion of patients experiencing a grade 3 or 4 adverse event was higher in the niraparib arm (PRIMA: 73.8%; PRIME: 54.5%) compared to the placebo arm (PRIMA: 23.8%; PRIME 17.8%). The most common serious adverse reactions > 1% (treatment-emergent frequencies) were thrombocytopenia and anaemia. The SmPC includes special warnings and precautions for use for haematologic adverse reactions, MDS/AML, hypertension, including hypertensive crisis, posterior reversible encephalopathy syndrome, pregnancy / contraception, and hepatic impairment(2). For olaparib, treatment discontinuations due to adverse events in the SOLO1 study were higher in the olaparib arm vs. placebo (11.9% compared to 3.1%); the proportion of patients experiencing a grade 3 or 4 adverse event was higher in the olaparib arm (39.6%) compared to the placebo arm (20.0%)(14). Adverse reactions that most commonly led to permanent discontinuation were anaemia (1.7%), nausea (0.9%), fatigue/asthenia (0.8%), thrombocytopenia (0.7%), neutropenia (0.6%) and vomiting (0.5%). The SmPC includes special warnings and precautions for use for haematological toxicity, MDS/AML, venous thromboembolic events, pneumonitis, hepatotoxicity, embryofoetal toxicity, pregnancy / contraceptions, and interactions with strong or moderate CYP3A(3).

3. The patient population, intervention and relevant outcomes

3.1 The medical condition, patient population, current treatment options and choice of comparator(s)

Standard treatment involves treating the disease through surgery and/or chemotherapy, which is gruelling and causes many long- and short-term side effects and related hospital visits. Patients are then under a “watch and wait” approach to see whether the cancer recurs or offered maintenance treatments if they are eligible.

In Danish guidelines, olaparib or niraparib are recommended as treatments the first-line maintenance treatment of newly diagnosed patients with advanced BRCA-mutated high-grade epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer(4).

Treatment criteria need to be met before patients can start treatment with olaparib or niraparib. Patients may begin treatment 4-6 weeks after completing chemotherapy:

- Either genetic or somatic BRCA mutation (in tumor tissue)
- Disease stage should reach FIGO III or IV
- Complete or partial response to chemotherapy (carboplatin and taxane) should be reached
- Residual disease < 1cm from surgical outcome
- Patients must be assessed as capable of taking tablets and completing treatment.

3.2 The intervention

Overview of intervention	
Therapeutic indication relevant for the assessment	Newly diagnosed patients with advanced BRCA-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer (1st line maintenance therapy). The therapeutic indication relevant for this assessment is a subset of the EMA indication, restricted to patients with a BRCA mutation in 1st line maintenance. Below is the EMA indication with no deviations: 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

Overview of intervention	
	partial) following completion of first-line platinum-based chemotherapy. 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(1).
Method of administration	Rubraca is for oral use and can be taken with or without food. The doses should be taken approximately 12 hours apart(1).
Dosing	The recommended dose of Rubraca is 600 mg taken twice daily, equivalent to a total daily dose of 1200 mg*. Patients should start the maintenance treatment with Rubraca no later than 8 weeks after completion of their final dose of the platinum containing regimen. Method of administration: Rubraca is for oral use and can be taken with or without food. The doses should be taken approximately 12 hours apart. *In line with SmPC, dose adjustments recommended if prescribed by the doctor: • Starting dose 600 mg twice daily (two 300 mg tablets twice daily) • First dose reduction 500 mg twice daily (two 250 mg tablets twice daily) • Second dose reduction 400 mg twice daily (two 200 mg tablets twice daily) Third dose reduction 300 mg twice daily (one 300 mg tablet twice daily(1)
Should the pharmaceutical be administered with other medicines?	Not as per SmPC.
Treatment duration / criteria for end of treatment	In 1st line maintenance treatment of advanced ovarian cancer, patients can continue treatment until disease progression, unacceptable toxicity or completion of 2 years treatment(1).
Necessary monitoring, both during administration and during the treatment period	None as per SmPC, except if particular patient populations make additional monitoring necessary (e.g. patients with hepatic empairment)
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	None as per SmPC.

Overview of intervention	
Package size(s)	Each pack consists of 60 film-coated tablets.

3.2.1 The intervention in relation to Danish clinical practice

The addition of rucaparib (Rubraca) as an alternative for the 1st line maintenance treatment of newly diagnosed patients with advanced BRCA1/2 mutated high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer into current Danish guidelines does not lead to any changes in current practices or routines. Criteria for treatment initiation is anticipated to remain the same as for existing options(4).

Importantly, diagnostic tests and methods are not currently required as per SmPC for the initiation of treatment with rucaparib, which may facilitate treatment initiation compared to alternative treatment options.

4. Overview of literature

A systematic literature review was conducted to identify relevant studies. Detailed information in the SLR is provided in Appendix D.

Characteristics of identified studies relevant for the clinical questions are presented in Table 1. Four studies were identified: one for rucaparib (ATHENA-MONO)(7, 9, 16-22), 2 for niraparib (PRIMA(10, 23-40), PRIME(11, 41-47)), and 1 for olaparib (SOLO-1) (13-15, 48-52) with a total of 44 publications.

Table 1 Relevant literature included in the assessment of efficacy and safety

Trial name, NCT identifier and reference (Full citation incl. reference number)*	Study design	Study duration	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Patient population (specify if a subpopulation in the relevant study)	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
ATHENA-MONO NCT03522246 (17): Monk BJ et al. Clin Oncol. 2022 Dec 1; 40(34): 3952–3964 (16): O'Malley, et al. Journal of clinical oncology. 2024;42(16). (7): Kristeleit et al. ESMO open. 2024 Jun 1;9.	A 4:1 randomised, double-blind, dual placebo-controlled, randomized study	Rucaparib treatment could continue until 24 months, disease progression, death, or unacceptable toxicity.	Start: 14-May-2018 Expected Completed: 30-Dec-2030 PFS cut-off 01-MAR-2024 Safety cut-off 9-MAR-2024	Patients with stage III-IV high-grade ovarian cancer undergoing surgical cytoreduction (R0/complete resection permitted) and responding to first-line platinum-doublet chemotherapy including those without BRCA1 or BRCA2 (BRCA)mutations or other evidence of homologous recombination deficiency (HRD), or high-risk clinical characteristics such as residual disease. Relevant subpopulation: BRCA mutation: n=91 (49.2%) and n=24 (49.0%) patients in the rucaparib	Oral rucaparib (600 mg) administered twice a day + IV placebo administered once every 4 weeks.	Oral placebo administered twice a day + IV placebo administered once every 4 weeks	Clinical question 1 & Clinical question 2	HRD sub-population [includes all patients with BRCA mutation (n=115) or tBRCAwt / LOHhigh (n=119)]: - OS (median follow-up 37 months)(1) - Treatment discontinuation due to AE (cut-off 9-MAR-2023, mean treatment duration 15 months)(16); - Grade 3-4 AE (cut-off 9-MAR-2023, mean treatment duration 15 months)(16); - FACT-O (26.1 and 26.2 months follow-up in rucaparib and placebo, respectively)(9) Relevant subpopulation (BRCA mutation): - PFS (4.0 and 3.5 yrs follow-up in rucaparib and placebo, respectively)(7)* *PFS data cut-off of 17-MAY-2024 also available as data on file

Trial name, NCT identifier and reference (Full citation incl. reference number)*	Study design	Study duration	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Patient population (specify if a subpopulation in the relevant study)	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
(1): Rubraca EU SmPC (9): ATHENA-MONO interim clinical study report				and placebo arm, respectively.				
PRIMA NCT02655016 (23): González-Martín A et al., N Engl J Med. 2019 Dec 19;381(25):2391-2402. (37): Monk, B.J. et al. Annals of Oncology, 2024, Volume	A 2:1 randomized, double-blind, placebo-controlled phase 3 trial (20 countries, 181 clinical sites)	36 months or until disease progression Median follow-up 73.9 months in overall population	Start: 11-Jul-2016 Completion: 8-APR-24	Patients With Advanced Ovarian Cancer (Stage III or IV) Following Response on Front-Line Platinum-Based Chemotherapy Relevant subpopulation: BRCA mutation: n=152 and n=71 patients in the niraparib and placebo arm, respectively.	Niraparib 200mg QD or 300mg QD (based on baseline body weight or baseline platelet count) 200mg incorporated in 27-NOV-2017 amendment	Placebo QD	Clinical question 1 & Clinical question 2	Reported in BRCA mutated subpopulation(37): 1) BICR-assessment PFS, 2) OS Reported in overall population (ITT): 1) treatment discontinuation due to adverse events(37), 2) adverse events grade 3-4(37), 3) FOSI (12), 4) EORTC QLQ-C30 (12), 5) EORTC QLQ-OV28 (12) Follow-up period: 73.9 months median follow-up

Trial name, NCT identifier and reference (Full citation incl. reference number)*	Study design	Study duration	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Patient population (specify if a subpopulation in the relevant study)	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
35, Issue 11, 981 – 992 (12): ClinicalTrials.gov register NCT02655016								
PRIME NCT03709316 (11): Li N, Zhu J, Yin R, et al. JAMA Oncol. 2023;9(9):1230–1237. doi:10.1001/jamaoncol.2023.2283	A 2:1 randomized, double-blind, placebo-controlled study	Approximately 36 months from first subject enrolled Median follow-up: niraparib 27.5 months; PBO: 27.6 months	Study start (actual): 30-JUN-2018 Primary completion (estimated): 29-JAN-2023 Cut-off 30-SEP-2021	Patients With Advanced (FIGO Stage III or IV) Ovarian Cancer, Fallopian Tube Carcinoma or Primary Peritoneal Cancer Who Have Achieved Effective Response After First-line Platinum-containing Chemotherapy. Relevant subpopulation: Germline BRCA variant status: 33.3% (n=85) and 31.0% (n=40) patients in the niraparib and placebo arm, respectively.	Niraparib 200mg QD or 300mg QD (based on baseline body weight or baseline platelet count)	Placebo QD	Clinical question 1 & Clinical question 2	Reported in BRCA mutated subpopulation: - BICR-assessment PFS Reported in HRD subpopulation: - OS Reported in overall population (ITT): - Treatment discontinuation due to AE - AE grade 3-4 Not included/reported: - QoL Follow-up period: approximately 36 months from first subject enrolled (11)

Trial name, NCT identifier and reference (Full citation incl. reference number)*	Study design	Study duration	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Patient population (specify if a subpopulation in the relevant study)	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
SOLO 1 (15): Moore et al. N Engl J Med. 2018;379(26): 2495-2505. doi: 10.1056/NEJMoa1810858. (14): DiSilvestro et al., JCO 41, 609-617(2023).DOI :10.1200/JCO.22.01549 (13): Banerjee et al. The Lancet Oncology, Volume 22,	A 2:1 Randomized, Double Blind, Placebo Controlled, Phase III study	Treatment duration of up to 2 years Most recent data cut at 7 years follow-up	Study Start: 26-08-2013 Primary Completion: 17-05-2017 Planned Study Completion: 29-08-2028	Newly diagnosed, histologically confirmed advanced (FIGO stage III or IV) high-grade serous or endometrioid ovarian, primary peritoneal, and/or fallopian tube cancer, with a germline or somatic BRCA1 and/or BRCA2 mutation	Olaparib 300mg twice daily	Placebo twice daily	Clinical question 1 & Clinical question 2	OS (7-years follow-up) (14); PFS (5-year follow-up) (13); Treatment discontinuation due to AE (7-year follow-up) (14); Grade 3-4 AE (7-year follow-up) (14); FACT-O (median follow-up 41 months) (53)

Trial name, NCT identifier and reference (Full citation incl. reference number)*	Study design	Study duration	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Patient population (specify if a subpopulation in the relevant study)	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
Issue 12, 1721 – 1731 (53): ClinicalTrials.gov register NCT01844986								

OS: overall survival; PFS: progression-free survival; QD: once daily; QoL: quality of life * If there are several publications connected to a trial, include all publications used.

5. Clinical question(s) 1&2

Are there clinically meaningful differences between rucaparib, olaparib and niraparib for maintenance treatment of newly diagnosed patients with advanced BRCA1/2 mutated high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer?

5.1 Efficacy of rucaparib compared to olaparib and niraparib for maintenance treatment of newly diagnosed patients with advanced BRCA1/2 mutated high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer

5.1.1 Relevant studies

All relevant studies are summarized in Table 1 with full details provided in Appendix A. Four relevant studies were included: ATHENA-MONO(17) (rucaparib), PRIME(11) (niraparib), PRIMA(23) (niraparib), and SOLO1(15) (olaparib). The primary patient population varied across studies: in SOLO1, only patients with BRCA mutations were included in the study. In contrast, ATHENA-MONO, PRIME, and PRIMA included all patients with newly diagnosed advanced ovarian cancer regardless of BRCA mutation and HRD status.

To align most closely with the relevant population in the Danish guideline(4) of patients with BRCA1/2 mutation, data reported for the BRCA1/2 mutated subgroup, where available, were extracted. Otherwise, data reported for the HRD positive subgroup were extracted. Finally, if data were not available for the BRCA1/2 mutated or HRD subgroup, data for the full population of the trial were extracted.

In the ATHENA-MONO study, HRD and BRCA status were predefined subgroups. The analysis of the primary endpoint (PFS) among HRD positive patients was tested first in the hierarchical testing procedure, followed by the full ITT population.

In the PRIMA study, HRD and BRCA status were pre-defined subgroups. The analysis of the primary endpoint (PFS) among HRD positive patients was tested first in the hierarchical testing procedure. In the PRIME study. HRD and BRCA status were included as pre-specified subgroups in the secondary analyses; and were not included in the hierarchical testing procedure.

BRCA and HRD status were included as randomization stratification factors in all studies, except for SOLO1 (olaparib), which included only patients with BRCA mutations.

5.1.2 Comparability of studies

Key differences were noted in terms of population, inclusion/exclusion criteria and regional distribution.

Population

Overall, studies had similarities in inclusion / exclusion criteria, with some key differences.

- SOLO1(15) only included patients with BRCA mutations, whereas ATHENA-MONO(17), PRIME(11), and PRIMA(23) included a broader population of patients regardless of BRCA mutations and HRD status.
- SOLO1, PRIMA, and ATHENA-MONO were global studies; PRIME included study sites in China only. ATHENA-MONO and PRIMA were the only studies to include study sites in Denmark
- The PRIMA study (niraparib) was not initially designed with the intent of studying different starting doses and hence the study did not have the statistical power to allow any firm conclusions to be drawn regarding the 200mg starting dose.
- Variation in terms of inclusion criteria relating to cytoreductive surgery outcomes were present across trials. For example, in the PRIMA study patients who received primary or interval debulking surgery were eligible regardless of cytoreductive surgery outcome. In the overall population, 40% of patients has no visible residual disease following primary or interval debulking surgery(34). In contrast, 76% of patients in SOLO1 were reported as having no gross residual disease(50), with 77% of patients in the ATHENA-MONO BRCAm population reported with complete resection or microscopic residual(9). In PRIME, Stage III patients who have undergone primary tumor reductive surgery with postoperative status of R0-complete resection (with no residual lesion) were excluded(11).

Endpoints

Overall, the endpoints assessed across studies were consistent in definition.

- The primary endpoint across all studies was progression-free survival defined as the time from randomization to disease progression or death from any cause. Disease progression was assessed according to the RECIST v1.1 criteria as primary either by BICR (e.g. PRIMA(23)) or investigator assessed (e.g. ATHINA-MONO(17)). However, in SOLO1(15), the primary method was changed from BICR to investigator assessment.
- Overall survival was included as a secondary endpoint and was defined as the time from randomization to death from any cause.

5.1.3 Comparability of patients across studies and with Danish patients eligible for treatment

Available data for the patient population relevant for clinical research question 1 & 2(4), i.e. patients with BRCA-mutations, was not consistently available for the identified studies. Baseline characteristics for this population were available for the ATHENA-MONO(9) and SOLO-1(15) trials, but not for the PRIMA(23) and PRIME(11) studies. Therefore, comparability of baseline characteristics was challenging due to inconsistencies in patient populations.

There were notable differences in prognostic factors and potential effect modifiers across studies.

- Response following platinum-based chemotherapy and cytoreproductive surgery outcomes were not consistently reported across studies; differences were observed in the proportion of patients with complete response and complete resection, respectively.
- Due to discrepancies in the populations where baseline characteristics were reported; there were differences in HRD status, BRCA mutation status as baseline characteristics for the relevant population were not available in PRIMA and PRIME.

The ATHENO-MONO study population is comparable to the Danish patients eligible for treatment according to the recommendation and guideline treatment(4) and relevant appendices (5, 6). Specifically, the patient population included in the ATHENA-MONO study(17) is closely aligned with the relevant population within the Danish treatment guidelines for clinical questions 1 & 2:

- The relevant patient population within guidelines, i.e. patients with BRCA-mutations as the target population, was a pre-specified subgroup in the ATHENA-MONO study
- ATHENA-MONO includes patients with FIGO stage III or IV in line with Danish treatment guidelines
- Rucaparib treatment is administered as maintenance therapy after responding to platinum-based chemotherapy in line with current Danish treatment guidelines for olaparib and niraparib

Table 2 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	ATHENA-MONO (9)		PRIMA (23)		PRIME (11)		SOLO-1 (15, 50)	
	Rucaparib (n = 91)	Placebo (n = 24)	Niraparib (n = 247)	Placebo (n = 126)	Niraparib (n = 255)	Placebo (n = 129)	Olaparib (n = 260)	Placebo (n = 131)
Population with available baseline characteristics	Relevant subgroup (Patients with BRCA1/BRCA2 mutation)		HRD subpopulation (Patients with homologous-recombination deficiency))		ITT population (Patients With Advanced (FIGO Stage III or IV))		Patients with BRCA1/BRCA2 mutation	
N	91	24	247	126	255	129	260	131
Age (years), median [range]	59 [30-78]	60 [38-78]	58 [32-83]	58 [33-82]	53 [32-77]	54 [33-77]	53.0 [29-82]	53.0 [31-84]
Weight (kg), median [range]	65.2 [41-115]	62.1 [49-82]			59.0 [40-100]	57.0 [37-97]		
ECOG performance status, n (%)								
0	70 (77%)	16 (67%)	182 (74%)	97 (77%)	98 (38%)	52 (40%)	200 (77%)	105 (80%)
1	21 (23%)	8 (33%)	65 (26%)	29 (23%)	157 (62%)	77 (60%)	60 (23%)	25 (19%)
Missing							0	1 (1%)
Primary tumor location, n (%)								
Ovary	76 (84%)	19 (79%)	201 (81%)	105 (83%)	229 (90%)	117 (91%)	220 (85%)	113 (86%)
Fallopian Tube	9 (10%)	3 (13%)	32 (13%)	13 (10%)	19 (8%)	9 (7%)	22 (9%)	11 (8%)
Primary Peritoneal	6 (7%)	2 (8%)	14 (6%)	8 (6%)	7 (3%)	3 (2%)	15 (6%)	7 (5%)
Other							3 (1%)	0
FIGO stage, n(%)								
III	65 (71%)	12 (50%)	161 (65%)	78 (62%)	182 (71%)	94 (73%)	220 (85%)	105 (80%)
IV	26 (29%)	12 (50%)	86 (35%)	48 (38%)	73 (29%)	35 (27%)	40 (15%)	26 (20%)
BRCA mutation, n(%)	91 (100%)	24 (100%)	152 (62%)	71 (56%)	85 (33%)	40 (31%)	260 (100%)	260 (100%)
BRCA1 mutation	60 (66%)	15 (62.5%)	105 (43%)	43 (34%)			191 (73%)	91 (69%)
BRCA2 mutation	31 (34%)	9 (37.5%)	47 (19%)	28 (22%)			66 (25%)	40 (31%)
Both BRCA1 and BRCA2							3 (1%)	0
BRCA mutation status, n(%)								
Germline	56 (62%)	12 (50%)			85 (33%)	40 (31%)	257 (99%)	131 (100%)

	ATHENA-MONO (9)		PRIMA (23)		PRIME (11)		SOLO-1 (15, 50)	
	Rucaparib (n = 91)	Placebo (n = 24)	Niraparib (n = 247)	Placebo (n = 126)	Niraparib (n = 255)	Placebo (n = 129)	Olaparib (n = 260)	Placebo (n = 131)
Somatic	25 (28%)	8 (33%)					2 (1%)	0
Unknown	10 (11%)	4 (17%)					0	0
Non-Germline					170 (67%)	89 (69%)		
HRD positive	91 (100%)	24 (100%)	247 (100%)	126 (100%)	170 (67%)	87 (67%)		
Prior use of bevacizumab, n(%)	15 (17%)	2 (8%)						
Cycles of previous platinum-based chemotherapy								
4	4 (4%)	2 (8%)					2 (1%)	0
5							2 (1%)	1 (1%)
6	87 (96%)	22 (92%)	165 (67%)	84 (67%)			198 (76%)	106 (81%)
7			52 (21%)	28 (22%)			17 (7%)	10 (8%)
8							18 (7%)	7 (5%)
9							23 (9%)	7 (5%)
Missing			30 (12%)	14 (11%)				
Response after platinum-based chemotherapy								
Complete response	22 (24%)	1 (4%)	185 (75%)	93 (74%)	212 (83%)	103 (80%)	213 (82%)	107 (82%)
Partial Response	17 (19%)	4 (17%)	62 (25%)	33 (26%)	43 (17%)	26 (20%)	47 (18%)	24 (18%)
No disease post-surgery	41 (45%)	15 (63%)						
Inevaluable	11 (12%)	4 (17%)						
Cytoreproductive surgery outcome, n(%)								
Complete resection = R0	48 (53%)	17 (71%)						
Microscopic Residual <1 cm	21 (23%)	2 (8%)						
Macroscopic Residual >= 1cm	22 (24%)	5 (21%)						
Optimal debulking (R0/R1)*					193 (76%)	105 (81%)		
Suboptimal debulking (R2)*					36 (14%)	14 (11%)		
Missing					26 (10%)	10 (8%)		
Upfront surgery							161 (62%)	85 (65%)

	ATHENA-MONO (9)		PRIMA (23)		PRIME (11)		SOLO-1 (15, 50)	
	Rucaparib (n = 91)	Placebo (n = 24)	Niraparib (n = 247)	Placebo (n = 126)	Niraparib (n = 255)	Placebo (n = 129)	Olaparib (n = 260)	Placebo (n = 131)
Residual macroscopic disease							37 (23%)	22 (26%)
No gross residual disease							123 (76%)	62 (73%)
Unknown							1 (<1%)	1 (1%)
Interval cytoreductive surgery							94 (36%)	43 (33%)
Residual macroscopic disease							18 (19%)	7 (16%)
No gross residual disease							76 (81%)	36 (84%)
No surgery before random assignment							4 (1%)	3 (2%)

*R1: residual <2.5mm; R2 residual between 2.5mm and 2.5cm

5.2 Comparative analyses of efficacy and safety

5.2.1 Efficacy and safety – results per study

Key efficacy and safety outcomes for the most relevant population per study are included in Table 3.

For rucaparib, data from the ATHENA-MONO trial demonstrated a significant improvement in PFS among BRCAm patients compared to placebo (median PFS not reached vs 16.7 months in rucaparib and placebo arms, respectively) with a hazard ratio of 0.47 (95% CI, 0.26 to 0.84)(7). For OS, median OS was not reached in either rucaparib or placebo arms after 37 months of follow-up(1). Quality of life was measured using FACT-O TOI and showed no difference between rucaparib and placebo arms (mean difference 0.0 [95% CI: -4.0 to 4.0])(9). Treatment discontinuations due to adverse events were higher in the rucaparib arm vs. placebo (11.8% compared to 5.5%); the proportion of patients experiencing a grade 3 or 4 adverse event was higher in the rucaparib arm (60.5%) compared to the placebo arm (23.6%)(16).

For niraparib, data from the PRIMA and PRIME studies demonstrated a significant improvement in PFS among BRCAm patients compared to placebo (median PFS for niraparib and placebo arms, respectively: PRIMA(37) 30.1 vs. 11.5, PRIME(11) not reached vs. 10.8 months) yielding similar hazard ratios of 0.43 (95% CI, 0.31 to 0.59) and 0.40 (95% CI, 0.23 to 0.68), respectively. Overall survival among BRCAm patients was reported in PRIMA following 74 months median follow-up showing no difference between treatment groups (median OS not reported, HR 0.94 [95% CI, 0.63 to 1.41])(37); and in PRIME for the HRD subpopulation following 36 months median follow-up, with an HR of 0.88 (95% CI, 0.43 to 1.78) (11). In the PRIMA study, quality of life was measured using the FOSI, EORTC QLQ-C30, and EORTC QLQ-OV28 instruments. Differences between niraparib and placebo were not reported; change from baseline values were comparable between niraparib and placebo arms, suggesting no difference in quality of life between arms(12). In both studies, treatment discontinuations due to adverse events were higher in the niraparib arm vs. placebo (PRIMA: 16.3% vs. 3.7%; PRIME: 6.7% vs. 5.4%); the proportion of patients experiencing a grade 3 or 4 adverse event was higher in the niraparib arm (PRIMA: 73.8%; PRIME: 54.5%) compared to the placebo arm (PRIMA: 23.8%; PRIME 17.8%)(11, 37).

For olaparib, results from the SOLO-1 trial demonstrated a significant improvement in PFS among BRCAm patients compared to placebo (median PFS: 56.0 vs 13.8 months in olaparib and placebo arms, respectively) with a hazard ratio of 0.33 (95% CI, 0.25 to 0.43)(13). For OS, olaparib demonstrated significant improvement after 7 years follow-up compared to placebo (median OS: not reached vs. 75.2 months in olaparib and placebo arms, respectively) with a hazard ratio of 0.55 (95% CI, 0.40 to 0.76)(14). Quality of life as measured using FAT-O TOI showed significant worsening in the olaparib arm compared to placebo (mean difference -3.00 [95% CI: -4.78 to -1.22, p = 0.001])(53). However, this difference was not considered clinically meaningful. Treatment discontinuations due to adverse events were higher in the olaparib arm vs. placebo (11.9% compared to 3.1%); the

proportion of patients experiencing a grade 3 or 4 adverse event was higher in the olaparib arm (39.6%) compared to the placebo arm (20.0%)(14).

Further details on key efficacy and safety findings are provided in Appendix B.

5.2.2 Please provide a qualitative description of safety data. Differences in definitions of outcomes between studies

All relevant treatments (rucaparib, niraparib, olaparib) were associated with higher grade 3-4 adverse events and discontinuations due to adverse events compared to placebo. Broadly, there were no differences between treatments.

A meaningful comparison of safety findings between rucaparib, niraparib and olaparib was not possible. In addition to differences in study design, geography, target populations, and baseline characteristic for prognostic factors and potential effect modifiers, large discrepancies in follow-up time also made comparisons challenging. For example, treatment discontinuation due to AEs in the niraparib arm was over 2 times higher in the PRIMA study compared to the PRIME study; this difference may be in part due to length of follow-up, which was 6.2 years in PRIMA compared to 3 years in PRIME. Similarly for grade 3-4 adverse events, longer exposure to study drug would likely contribute to a higher proportion of patients with at least one grade 3-4 adverse event.

5.2.3 Method of synthesis

In line with the Danish Medicines Council's expert committee observations (100404) and clinical comparability between olaparib and niraparib stated in the Addendum to treatment guidelines (122849), there was limited basis for a meaningful indirect comparison between rucaparib, olaparib, and niraparib due to differences between studies. Therefore, in a narrative review of the data, the efficacy and safety profile of rucaparib, olaparib and niraparib was conducted.

5.2.4 Results from the comparative analysis

Due to lack of data available, differences in study design, geography, target populations, baseline characteristic for prognostic factors and potential effect modifiers, as well as follow-up times, a meaningful indirect comparison was not deemed feasible. This was further justified when comparing results observed in the placebo arms of trials included in this review, confirming the considerable potential for lack of transitivity / similarity across trials. A narrative review of the data was therefore performed.

Rucaparib, niraparib, and olaparib were all associated with significant improvements in progression-free survival, demonstrated through significant hazard ratios ranging from 0.33 to 0.47. Comparisons of these results however would be considerably biased, as demonstrated by the variability of median PFS in the placebo arms ranging from 10.8 in the PRIME study to 16.7 months in the ATHENA-MONO study.

Mature OS data was only available in the SOLO-1(14) and PRIMA(37) study following a median follow-up period of 7 years and 6 years (73.9 months), respectively. In contrast,

OS data from other studies lacked maturity and failed to show meaningful differences between treatments. In addition to challenges already identified with comparing study results, there was up to a 5 year gap between the start of SOLO-1 in 2013 and other studies, and therefore differences in standard of care and availability of treatment alternatives could also contribute to differences in study outcomes.

Quality of life outcomes were reported in three (ATHENA-MONO(9), PRIMA(12), SOLO1(53)) out of four studies, although instruments included varied across studies. ATHENA-MONO and SOLO1 included one common instrument: FACT-O. PRIMA includes FOSI, EORTC QLQ-C30 and EORTC QLQ-OV28. With the exception of a statistically significant but not clinically meaningful worsening in FACT-O TOI (a difference of 10 is considered clinically meaningful) reported in SOLO1, results reported for across studies showed no differences between treatment and placebo.

The comparability of safety findings is discussed in section 5.2.2. Although an indirect treatment comparison cannot be performed; the EMA provided the following remarks on the safety of rucaparib in the EPAR: Medicine Overview (p2): *"Rubraca has been shown to delay worsening or return of the disease in patients whose cancer had cleared partially or completely after treatment with platinum-based chemotherapy. Regarding safety, side effects occur frequently but are generally not serious and are manageable with appropriate treatment. In addition, fewer liver and blood-related problems occur with Rubraca than with other existing treatments for these patients.(8)."* Thus, treatment with rucaparib may offer a more favorable safety profile for patients in comparison to existing treatments.

Table 3 Review of rucaparib, niraparib, and olaparib outcomes for maintenance treatment of newly diagnosed patients with advanced BRCA1/2 mutated high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer

Outcome measure	Intervention [rucaparib vs Placebo]	Comparator 1 [niraparib vs Placebo]		Comparator 2 [olaparib vs Placebo]
Study	ATHENA-MONO	PRIMA	PRIME	SOLO-1
Overall survival (OS): median (months)	HRD Group (1) rucaparib (n=185): NR placebo (n=49): NR **HR:** 0.84 (95% CI, 0.44 to 1.58)	BRCAm (37) niraparib (n=152): not reported (71.9 in HRD subgroup) placebo (n=71): not reported (69.8 in HRD subgroup) **HR:** 0.94 (95% CI, 0.63 to 1.41)	HRD subgroup (11) niraparib (n=170): NR placebo (n=87): NR **HR:** 0.88 (95% CI, 0.43 to 1.78)	BRCAm (14) olaparib (n=260): NR placebo (n=131): 75.2 **HR:** 0.55 (95% CI, 0.40 to 0.76)
Progression-free survival (PFS)	BRCAm (7) rucaparib (n=91): NR placebo (n=24): 16.7 **HR:** 0.47 (95% CI, 0.26 to 0.84)	BRCAm (37) niraparib (n=152): 30.1 placebo (n=71): 11.5 **HR:** 0.43 (95% CI, 0.31 to 0.59)	BRCAm (11) niraparib (n=85): NR placebo (n=40): 10.8 **HR:** 0.40 (95%CI, 0.23 to 0.68)	BRCAm (14) olaparib (n=260): 56.0 placebo (n=131): 13.8 **HR:** 0.33 (95% CI, 0.25 to 0.43)
Treatment discontinuation due to adverse events, n (%)	ITT (16) rucaparib (n=425): 11.8% placebo (n=110): 5.5%	ITT (37) niraparib (n=484): 79 (16.3%) placebo (n=244): 9 (3.7%)	ITT (11) niraparib (n=255): 17 (6.7%) placebo (n=129): 7 (5.4%)	BRCAm (14) olaparib (n=260): 31 (11.9%) placebo (n=131): 4 (3.1%)

Outcome measure	Intervention [rucaparib vs Placebo]	Comparator 1 [niraparib vs Placebo]		Comparator 2 [olaparib vs Placebo]
Grade 3-4 adverse events, n (%)	ITT (16) rucaparib (n=425): 60.5% placebo (n=110): 23.6%	ITT (37) niraparib (n=484): 357 (73.8%) placebo (n=244): 58 (23.8%)	ITT (11) niraparib (n=255): 139 (54.5%) placebo (n=129): 23 (17.8%)	BRCAm (14) olaparib (n=260): 103 (39.6%) placebo (n=131): 26 (20.0%)
FACT-O TOI	HRD Group (9) rucaparib (n=185): -2.0 (-3.9, -0.2) placebo (n=49): -2.0 (-5.6, 1.5) Mean difference 0.0 (-4.0; 4.0) p=0.9911	Not included in study	Not included in study	BRCAm (53) olaparib (n=260): 0.30 (-0.72; 1.32) placebo (n=131): 3.30 (1.84; 4.76) Mean difference -3.00 (-4.78; -1.22) p=0.001
FOSI change from baseline least squares mean (SE)	Not included in study	ITT (12) niraparib (n=479): -0.4 (0.15) placebo (n=240): -0.3 (0.22)	Not included in study	Not included in study
EORTC QLQ-C30: change from baseline least squares mean (SE)	Not included in study	ITT (12) niraparib (n=478): 1.01 (0.690) placebo (n=243): 1.18 (1.001)	Not included in study	Not included in study
EORTC QLQ-OV28: change from baseline least squares mean (SE)	Not included in study	ITT (12) Functional scales *Body image* niraparib (n=475): 8.49 (1.014) placebo (n=244): 10.07 (1.482) *Sexuality*	Not included in study	Not included in study

Outcome measure	Intervention [rucaparib vs Placebo]	Comparator 1 [niraparib vs Placebo]		Comparator 2 [olaparib vs Placebo]
		niraparib (n=471): 3.63 (0.800) placebo (n=240): 3.26 (1.189) *Attitude to disease/treatment* niraparib (n=475): 13.66 (0.931) placebo (n=244): 12.22 (1.326) <u>Symptoms scale:</u> *abdominal/GI* niraparib (n=481) 2.19 (0.57) placebo (n=244) 0.83 (0.811) *peripheral neuropathy* niraparib (n=480) -8.22 (0.930) placebo (n=244) -9.64 (1.322) *hormonal/menopausal symptoms* niraparib (n=480) 1.50 (0.880) placebo (n=244) -2.52 (1.307) *other chemo side effects* niraparib (n=480) -2.22 (0.558) placebo (n=244) -3.02 (0.836) *hair loss* niraparib (n=477) -23.36 (0.982) placebo (n=242) -20.74 (1.369)		

NR: Not reached

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Appendix A. Main characteristics of studies included

Trial name: ATHENA	NCT number: NCT03522246
Objective	ATHENA is a randomized, multinational, double-blind, dual placebo-controlled, 4-arm, Phase 3 study evaluating rucaparib and nivolumab as monotherapy and in combination as maintenance treatment following response to first-line treatment (surgery and platinum-based chemotherapy) in newly diagnosed ovarian cancer patients. The study has two separate and fully independently powered comparisons evaluating rucaparib monotherapy (ATHENA–MONO) and rucaparib + nivolumab (ATHENA–COMBO). This overview describes only the 2 arms of the study that were part of the ATHENA-MONO comparison, ie, rucaparib (oral rucaparib + IV placebo) versus placebo (oral placebo + IV placebo).
Publications – title, author, journal, year	PRIMARY: (17) Monk B, Parkinson C, Lim M, et al. A Randomized, Phase III Trial to Evaluate Rucaparib Monotherapy as Maintenance Treatment in Patients With Newly Diagnosed Ovarian Cancer (ATHENA-MONO/GOG-3020/ENGOT-ov45). Journal of Clinical Oncology. 2022;381. doi:10.1200/jco.22.01003. SECONDARY: (18) Fujiwara K, Kristeleit R, Ghamande S, et al. Rucaparib maintenance treatment in patients (pts) with newly diagnosed ovarian cancer (OC): defining benefit according to disease risk subgroups within the phase III ATHENA-MONO study. Annals of oncology. 1505;33:S1505-S1506. doi:10.1016/j.annonc.2022.10.214. (19) Kristeleit R, Ghamande S, Lim M, et al. 527MO Rucaparib maintenance treatment in patients (pts) with newly diagnosed ovarian cancer (OC): defining benefit according to disease risk subgroups within the phase 3 ATHENA-MONO study. Annals of oncology. 2022;33:S786-S787. doi:10.1016/j.annonc.2022.07.655.

Trial name: ATHENA	NCT number: NCT03522246
	(20) Oaknin A, Kristeleit R, Mahdi H, et al. Patients with Newly Diagnosed Ovarian Cancer Treated with Maintenance Rucaparib: Exploratory Biomarker Analysis from the Phase 3 Athena-Mono Study (Gog-3020/ Engot-Ov45; Nct03522246). International journal of gynecological cancer. 2022;32:2022-10. doi:10.1136/ijgc-2022-esgo.1018. (21) O'Malley D, Christopoulou A, Lim M, et al. Efficacy Analysis by Disease Risk Subgroup for the Phase 3 Athena-Mono Study (Gog-3020/Engot-Ov45) Evaluating Rucaparib Maintenance Treatment in Patients with Newly Diagnosed Ovarian Cancer. International journal of gynecological cancer. 2022;32:2022-09. doi:10.1136/ijgc-2022-igcs.28. (22) Monk B, Parkinson C, Lim M, et al. ATHENA-MONO (GOG-3020/ENGOT-ov45): a randomized, double-blind, phase 3 trial evaluating rucaparib monotherapy versus placebo as maintenance treatment following response to first-line platinum-based chemotherapy in ovarian cancer. Journal of clinical oncology. 2022;40(17):2022-06. doi:10.1200/jco.2022.40.17suppl.lba5500. (16) O'Malley D, Monk B, Lim M, et al. Final safety results from ATHENA-MONO (GOG-3020/ENGOT-ov45), a randomized, placebo-controlled, double-blind, phase 3 trial evaluating rucaparib monotherapy as maintenance treatment in patients with newly diagnosed ovarian cancer. Journal of clinical oncology. 2024;42(16). (7) Kristeleit R, O'Malley D, Lim MC, McNeish I, Herzog TJ, Wilson M, Fehm TN, Coleman RL, Van Gorp T, Oza AM, Mikheeva O. 49MO Updated progression-free survival (PFS) in patients (pts) with newly diagnosed advanced ovarian cancer (OC) treated with rucaparib (RUC) in ATHENA-MONO. ESMO open. 2024 Jun 1;9. (9): Pharma&; ATHENA-MONO Interim clinical study report [CONFIDENTIAL], 2022
Study type and design	A randomised, international, double-blind, placebo-controlled, multicentre, phase III study. The study consisted of a Screening Phase, a Treatment Phase, and a Post-treatment Phase. Randomization:

Trial name: ATHENA	NCT number: NCT03522246
	Randomisation in a 4:1 ratio, central, computer-generated (block size of 10), using *interactive response technology*; Stratification factors: ▪ Disease status after CTh (residual disease vs no residual disease); ▪ timing of surgery (primary cytoreduction vs deferred cytoreduction); ▪ Homologous recombination deficit [HRD] assessment (BRCA [tBRCA] mutation, BRCA wild-type/high heterozygosity loss [non-tBRCA LOH^{high}] [heterozygosity loss ≥16%], BRCA wild-type/low heterozygosity loss [non-tBRCA LOH^{low}] [heterozygosity loss <16%], BRCA wild-type/loss of heterozygosity undetermined [non-tBRCA ^{LOHunknown}]) in a central laboratory, next-generation sequencing-based test Blinding: Blinding - double; investigators, clinical staff, patients, sponsor-related staff had no information about the intervention used; active intervention and placebo (infusion solution and oral substances) identical in appearance, delivered in identical containers
Sample size (n)	*538*
Main inclusion criteria	• Newly diagnosed advanced (FIGO stage III-IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer. • Completed cytoreductive surgery, including at least a bilateral salpingo-oophorectomy and partial omentectomy, either prior to chemotherapy (primary surgery) or following neoadjuvant chemotherapy (interval debulking) • Completed first-line platinum-based chemotherapy and surgery with a response, in the opinion of the Investigator • Sufficient tumor tissue for planned analysis • ECOG performance status of 0 or 1

Trial name: ATHENA	NCT number: NCT03522246
	• Patients must be 20 years of age to consent in Japan, Taiwan and South Korea; in all other participating countries patients must be 18 years of age to consent
Main exclusion criteria	• Pure sarcomas or borderline tumors or mucinous tumors • Active second malignancy • Known central nervous system brain metastases • Any prior treatment for ovarian cancer, other than the first-line platinum regimen • Evidence of interstitial lung disease or active pneumonitis • Active, known or suspected autoimmune disease • Condition requiring active systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications
Intervention	Patients received rucaparib (n=427) 600 mg orally twice a day starting on cycle 1 day 1 and placebo IV every 4 weeks starting on cycle 2 day 1 in 28-day cycles. Rucaparib treatment could continue until 24 months after initiation of placebo IV administration, disease progression, death, or unacceptable toxicity.
Comparator(s)	Patients received placebo (n=111) 600 mg orally twice a day starting on cycle 1 day 1 and placebo IV every 4 weeks starting on cycle 2 day 1 in 28-day cycles. Rucaparib treatment could continue until 24 months after initiation of placebo IV administration, disease progression, death, or unacceptable toxicity.
Follow-up time	Most recent cut-off at 01-MAR-2024 includes median follow-up time of 4.0 and 3.5 yrs in rucaparib and placebo arms, respectively. A new cut-off for PFS on 17-MAY-2024 is available as data on file.

Trial name: ATHENA	NCT number: NCT03522246
Primary, secondary and exploratory endpoints	Primary efficacy endpoint The primary endpoint was analyzed in the HRD and ITT Populations: To evaluate PFS by RECIST, as assessed by the investigator (invPFS) The time to invPFS was calculated in months as the time from randomization to disease progression +1 day, according to RECIST v1.1 criteria, or death due to any cause, whichever occurred first. Only scans or deaths prior to and on the start of any subsequent anticancer treatment were used in the PFS analysis. The stratified log-rank test of invPFS between the randomized treatment groups together with a graphical presentation of unstratified invPFS distributions, median invPFS with 95% CI, and event rates were presented. Furthermore, the probability of being progression-free at 6, 12, 18, and 24 months was summarized by treatment group by using the Kaplan Meier estimates, both unstratified and stratified, at each time point with 95% CI using a log-log distribution. In addition, the primary endpoint was also analyzed using the stratified Cox proportional hazards methodology, presenting the HR with 95% CI between the randomized treatment groups. In order to ensure that the results in the HRD Population (tBRCA and non-tBRCA LOHhigh) and the ITT Population (HRD, non-tBRCA LOHlow, and non-tBRCA LOHunknown) were not solely driven by the results in the tBRCA subgroup, invPFS was assessed in the tBRCA as well as the other non-nested molecular subgroups. Other randomization stratification factors such as disease status post-chemotherapy (no residual disease versus residual disease), and timing of surgery (primary surgery versus interval debulking) were included in the primary analysis of invPFS. <u>Secondary efficacy endpoints</u> The following secondary endpoints were analyzed in the HRD and ITT Populations: PFS by RECIST v1.1, as assessed by the blinded independent central review (bicrPFS). It was defined as the time from randomization to disease progression, according to RECIST v.1.1 criteria as assessed by BICR or death due to any cause.

Trial name: ATHENA	NCT number: NCT03522246
	overall survival (OS): OS was defined as the time from randomization to death by any cause. It was anticipated that the data for OS would be immature at the time of the primary endpoint analysis. In order to adjust for multiple analyses of OS at a later stage, a stopping rule was applied. The Haybittle-Peto stopping rule was applied where any interim (early) OS with a p-value < 0.001 could be used to claim superiority. This meant that a p-value < 0.025 two-sided could still be utilized at the final analysis, which is projected to be once 70% of the death events have been collected. Objective response rate (OOR) by RECIST v1.1 as assessed by the investigator, in patients with measurable disease at baseline. The ORR of confirmed response by RECIST v1.1 was defined as the proportion of patients with a confirmed CR or PR on subsequent tumor assessment at least 28 days after first response documentation Duration of response (DOR) as assessed by the investigator, in patients who had a confirmed response (ie., completer or partial) by RECIST v1.1. DOR was calculated in months as the time from the first date of the scan showing a response to the first scan with disease progression + 1 day. <u>Exploratory endpoints:</u> The exploratory endpoints were: PFS2 (PFS on the subsequent line of treatment) defined as the time from randomization to the second event of disease progression as assessed by the investigator, or death due to any cause. Efficacy and safety in the tBRCA subgroup for the comparison of rucaparib vs placebo (invPFS, bicrPFS, OS, ORR, DOR, and safety). This subgroup was explored in order to ensure that the results in the HRD and ITT Populations were not solely driven by the results in the tBRCA subgroup. Health-related Quality of Life (HRQoL) as assessed by the TOI of the FACT-O. Analyses of changes from baseline were analyzed for each scheduled post-baseline visit and for the final visit for each subscale, total score, and FACT-O TOI. Patients that did not have both a baseline measurement and at least 1 post-baseline measurement were not included. A change of at least 10 points in the FACT-O TOI was considered as clinically relevant and minimally important difference and was summarized categorically.

Trial name: ATHENA	NCT number: NCT03522246
	EQ-5D-5L: changes from baseline were analyzed for each scheduled post-baseline visit and for the final visit for the EQ-5D-5L instrument and the EQ-VAS. Patients who did not have both a baseline measurement and at least 1 post-baseline measurement were not included. The following post-progression efficacy endpoints were also analyzed: Chemotherapy-free interval Time to first subsequent anticancer treatment (TFST) Time to second subsequent anticancer treatment (TSST) Time to treatment discontinuation of oral dose After treatment discontinuation, subsequent anticancer treatments were collected for all patients every 12 or 24 weeks (± 14 days), until death, loss to follow-up, withdrawal of consent from study, or closure of the study.
Method of analysis	The predefined analysis populations used to analyse the ATHENA-MONO trial data are listed below ('Subgroup analyses'). In order to preserve the overall type 1 error rate, while testing the primary and secondary endpoints for ATHENA–MONO, a hierarchical step-down procedure was specified. Statistical significance was only declared for any of the endpoints if the previous endpoints were also statistically significant at the significance level of two-sided 0.025. The step-down procedure is outlined in Figure 3.49 invPFS in the HRD population was tested first at a one-sided 0.0125 significance level. If invPFS in the HRD population was statistically significant, then invPFS was tested in the ITT population. If both the HRD and ITT populations reached statistical significance for the primary endpoint, then the first secondary endpoint of OS was to be tested at the one-sided 0.0125 significance level in the HRD and ITT populations for that treatment comparison and testing continued to the last key secondary endpoint of

Trial name: ATHENA	NCT number: NCT03522246
	ORR. Once statistical significance was not achieved for one test, the statistical significance was not declared for all subsequent analyses in the ordered step-down procedure for the comparison of the rucaparib arm to placebo.
Subgroup analyses	The following analysis populations were defined in the SAP for the ATHENA-MONO treatment comparison: ITT Population: The ITT Population consisted of all randomized patients. The ITT Population consisted of all mutually exclusive HRD status groups (tBRCA, non-tBRCA LOH^{high}, non-tBRCA LOH^{low}, and non-tBRCA LOH^{unknown}). HRD Population: The HRD population consisted of all randomized patients that were either tBRCA or non-tBRCA LOH^{high}. Safety Population: The Safety Population consisted of all patients who received at least one dose of protocol-specified treatment of oral study drug. tBRCA cohort: Patients with deleterious BRCA1/2 mutation in tumour tissue Non-tBRCA/LOH$_{high}$: Patients without a tBRCA mutation and with percent of tumour genome LOH ≥16% Non-tBRCA/LOH$_{low}$: Patients without a tBRCA mutation and with percent of tumour genome LOH <16% Non-tBRCA/LOH$_{unknown}$: Patients without a tBRCA mutation and with percent of tumour genome LOH unknown
Other relevant information	

Trial name: PRIMA	NCT number: NCT02655016
Objective	The primary objective of this study is to evaluate the efficacy of niraparib versus placebo as maintenance treatment in patients with Stage III or IV ovarian cancer (including fallopian and peritoneal cancers) with a homologous recombination deficiency (HRD)-positive tumor and a complete response (CR) or partial response (PR) following front-line platinum-based chemotherapy treatment as assessed by the prolongation of progression-free survival (PFS).
Publications – title, author, journal, year	PRIMARY: (23) González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, McCormick C, Lorusso D, Hoskins P, Freyer G, Baumann K, Jardon K, Redondo A, Moore RG, Vulsteke C, O'Cearbhaill RE, Lund B, Backes F, Barretina-Ginesta P, Haggerty AF, Rubio-Pérez MJ, Shahin MS, Mangili G, Bradley WH, Bruchim I, Sun K, Malinowska IA, Li Y, Gupta D, Monk BJ; PRIMA/ENGOT-OV26/GOG-3012 Investigators. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med. 2019 Dec 19;381(25):2391-2402. doi: 10.1056/NEJMoa1910962. Epub 2019 Sep 28. PMID: 31562799. SECONDARY: (24) Barretina-Ginesta M, Monk B, Han S, et al. Quality-adjusted time without symptom or toxicity (QA-TWiST) and quality-adjusted progression-free survival (QA-PFS) of first-line (1L) maintenance niraparib in patients with advanced ovarian cancer (OC): results from the PRIMA trial. Annals of oncology. 2021;32:S736-S737. doi:10.1016/j.annonc.2021.08.1180. (25) Barretina-Ginesta M, Monk B, Han S, et al. Quality-adjusted time without symptoms of disease or toxicity and quality-adjusted progression-free survival with niraparib maintenance in first-line ovarian cancer in the PRIMA trial. Therapeutic Advances in Medical Oncology. 2022;14:17588359221126149. doi:10.1177/17588359221126149. (26) Bhavana P, Sileny H, Dana C, et al. Patient-reported outcomes (PROs) in patients (pts) receiving niraparib in the PRIMA/ENGOT-OV26/GOG-3.012 trial. Journal of obstetrics and gynaecology research. 2021;Vol.47(8):2803p. doi:10.1111/jog.14876. (28) Chase D, Marin M, Backes F, et al. Impact of disease progression on health-related quality of life of advanced ovarian cancer patients - Pooled analysis from the PRIMA trial. Gynecologic Oncology. 2022;166(3):494-502. doi:10.1016/j.ygyno.2022.06.028.

Trial name: PRIMA	NCT number: NCT02655016
	(27) Chase D, Romeo Marin M, Backes F, et al. Impact of disease progression on healthrelated quality of life of advanced ovarian cancer (AOC) patients-pooled analysis from the prima trial. International journal of gynecological cancer. 2021;Vol.31(SUPPL 1):A284p. doi:10.1136/ijgc-2021-esgo.494. (29) Gonzalez M.A., et al. Progression-free survival and safety at 3.5years of follow-up: results from the randomised phase 3 PRIMA/ENGOT-OV26/GOG-3012 trial of niraparib maintenance treatment in patients with newly diagnosed ovarian cancer. European journal of cancer. 2023;189(112908). doi:10.1016/j.ejca.2023.04.024. (30) Gonzalez Martin A, Pothuri B, Vergote I, et al. PRIMA/ENGOT-OV26/GOG-3012 study: updated long-term PFS and safety. Annals of oncology. 2022;33:2022-09. doi:10.1016/j.annonc.2022.07.658. (31) Gonzalez Martin A, Pothuri B, Vergote I, et al. 33O PRIMA/ENGOT-OV26/GOG-3012 study: long-term conditional PFS. ESMO open. 2023;8(1). doi:10.1016/j.esmoop.2023.100813. (32) Mirza M, Gonzalez-Martin A, Graybill W, et al. Prospective evaluation of the tolerability and efficacy of niraparib dosing based on baseline body weight and platelet count: Results from the PRIMA/ENGOT-OV26/GOG-3012 trial. Cancer. 2023;129(12):1846-1855. doi:10.1002/cncr.34706. (33) O'Cearbbhaill R, Perez-Fidalgo J, Monk B, et al. Efficacy of niraparib by timing of surgery and residual disease: a Post Hoc analysis of patients in the PRIMA/ENGOT-OV26/GOG-3012 Study. Tumori. 2021;Vol.107(2 SUPPL):36p. doi:10.1177/03008916211041664. (34) O'Cearbhaill R, Grabowski J, Perez-Fidalgo J, et al. Efficacy of niraparib by timing of surgery and residual disease: a post-hoc analysis of patients in the PRIMA/ENGOT-OV26/ GOG-3012 study. Oncology research and treatment. 2022;45:120-121. doi:10.1159/000521004. (35) Herzog TJ, Wahab SA, Mirza MR, et al. Optimizing disease progression assessment using blinded central independent review and comparing it with investigator assessment in the PRIMA/ENGOT-ov26/GOG-3012 trial: challenges and solutions. Int J Gynecol Cancer 2023;33:1733–1742

Trial name: PRIMA	NCT number: NCT02655016
	(10) Gonzalez-Martin A, Pothuri B, Barretina Ginesta M, et al. LBA29 Final overall survival (OS) in patients (pts) with newly diagnosed advanced ovarian cancer (aOC) treated with niraparib (nir) first-line (1L) maintenance: Results from PRIMA/ENGOT-OV26/GOG-3012. Annals of Oncology. 2024;35(Supplement 2):S1222-S1223. doi:10.1016/j.annonc.2024.08.2268. (36) Gonzalez-Martin A, Pothuri B, Vergote I, et al. Progression-free survival and safety at 3.5 years of follow-up: results from the randomized phase 3 PRIMA/ENGOT-OV26/GOG-3012 trial of niraparib maintenance treatment in patients with newly diagnosed ovarian cancer - a plain language summary. Future oncology (London, England). 2024;:1-14. doi:10.2217/fon-2023-0782. (37) Monk B, Barretina-Ginesta M, Pothuri B, et al. Niraparib first-line maintenance therapy in patients with newly diagnosed advanced ovarian cancer: final overall survival results from the PRIMA/ENGOT-OV26/GOG-3012 trial. Annals of oncology : official journal of the European Society for Medical Oncology. 2024;doi:10.1016/j.annonc.2024.08.2241. (38) Pothuri B, Han S, Chase D, et al. Health-related quality of life in patients with newly diagnosed advanced ovarian cancer treated with niraparib vs placebo: Results from the phase 3 randomized PRIMA/ENGOT-OV26/GOG-3012 trial. Gynecologic oncology. 2024;184:168-177. doi:10.1016/j.ygyno.2024.01.021. (39) Valabrega G, Pothuri B, Oaknin A, et al. Efficacy and safety of niraparib in patients aged 65 years and older with advanced ovarian cancer: Results from the PRIMA/ENGOT-OV26/GOG-3012 trial. Gynecologic oncology. 2024;187:128-138. doi:10.1016/j.ygyno.2024.03.009. (40) Vulsteke C, Chambers S, Perez M, et al. Tolerability of the niraparib individualized starting dose in the PRIMA/ENGOT-OV26/GOG-3012 trial of niraparib first-line maintenance therapy. European journal of cancer (Oxford, England : 1990). 2024;208:114157. doi:10.1016/j.ejca.2024.114157.
Study type and design	This study is a double-blind, randomized (2:1 niraparib:placebo), placebo-controlled study in patients with ovarian cancer who have HRD-positive tumors, as identified with a centralized HRD test, and are at high risk for progressive disease (PD), as identified by the stage of cancer and previous response to surgery. Patients must have received at least 4 cycles of a front-line platinum-based regimen with a physician-assessed response of CR or PR (no measurable lesion >2 cm). Additionally, patients must have a normal or >90% decrease in cancer antigen 125 (CA-125) following front-line platinum treatment. The study will assess whether maintenance

Trial name: PRIMA	NCT number: NCT02655016
	treatment with niraparib will extend PFS in this population. Stratification factors will include best response during the front-line platinum regimen (CR and PR).
Sample size (n)	*733*
Main inclusion criteria	• Participants must have histologically diagnosed high-grade serous or endometrioid, or high-grade predominantly serous or endometrioid ovarian cancer, fallopian tube cancer, or primary peritoneal cancer that is Stage III or IV according to FIGO criteria. • Participants with inoperable Stage III and IV disease; All Stage IV participants with operable disease; Participants with stage III or IV disease treated with neoadjuvant chemotherapy and interval debulking surgery; and Participants with stage III disease who have visible residual disease after primary debulking surgery. • Participants who have received intraperitoneal chemotherapy; All participants must have had more than or equal to (>=)6 and less than or equal to (<=)9 cycles of platinum-based therapy; Participants must have had >=2 post-operative cycles of platinum-based therapy following interval debulking surgery; Participants must have physician assessed complete or partial response after >=3 cycles of therapy; and Participants must have either CA-125 in the normal range or CA-125 decrease by more than 90 percent(%) during their front-line therapy that is stable for at least 7 days (no increase more than (>)15% from nadir). • Participants must be randomized within 12 weeks of the first day of the last cycle of chemotherapy. • All participants must agree to undergo central tumor HRD testing. • Participants of childbearing potential must have a negative serum or urine pregnancy test (beta human chorionic gonadotropin) within 7 days prior to receiving the first dose of study treatment.

Trial name: PRIMA	NCT number: NCT02655016
Main exclusion criteria	• Participant has mucinous or clear cell subtypes of epithelial ovarian cancer, carcinosarcoma or undifferentiated ovarian cancer. • Participants with Stage III disease who have had complete cytoreduction (no visible residual disease) after primary debulking surgery. • Participant has undergone more than two debulking surgeries for the study disease. • Participant is pregnant, breastfeeding, or expecting to conceive children while receiving study treatment and for up to 180 days after the last dose of study treatment. • Participant has a known hypersensitivity to the components of niraparib or its excipients. • Participant has received prior treatment with a known PARP inhibitor or has participated in a study where any treatment arm included administration of a known PARP inhibitor. • Participant is to receive bevacizumab as maintenance treatment. • Participant has had investigational therapy administered within 4 weeks, or within a time interval less than at least 5 half-lives of the investigational agent, whichever is longer, prior to the first scheduled day of dosing in this study. • Participant has had any known >=Grade 3 anemia, neutropenia or thrombocytopenia due to prior chemotherapy that persisted >4 weeks. • Participant has a condition (such as transfusion dependent anemia or thrombocytopenia), therapy, or laboratory abnormality that might confound the study results or interfere with the participation for the full duration of the study treatment, including: 1. Participant received a transfusion (platelets or red blood cells) within 2 weeks of the first dose of study treatment.

Trial name: PRIMA	NCT number: NCT02655016
	2. Participant received colony-stimulating factors (e.g., granulocyte colony stimulating factor, granulocyte macrophage colony-stimulating factor or recombinant erythropoietin) within 2 weeks prior to the first dose of study treatment. • Participant has been diagnosed and/or treated for invasive cancer less than 5 years prior to study enrollment.
Intervention	Niraparib. 300mg* administered once daily in 28-day cycles for 36 months or until disease progression. *In the initial protocol, all the patients started at a fixed dose of 300 mg once daily (FSD; fixed starting dose). The trial was amended on November 27, 2017, to incorporate an individualized starting dose (ISD) of 200 mg once daily for patients with a baseline body weight of less than 77 kg, a platelet count of less than 150,000 per cubic millimeter, or both.
Comparator(s)	Placebo. Administered once daily in 28-day cycles for 36 months or until disease progression.
Follow-up time	Median follow-up time was 11.2 months
Primary, secondary and exploratory endpoints	Primary: Progression Free Survival. Progression free survival was defined as the time from the date of treatment randomization to the date of first documentation of disease progression or death due to any cause in the absence of documented progression, whichever occurs first. It was assessed by the blinded independent central review (BICR). Median and 95% CI are presented. Up to 34 months. Secondary: Overall survival. Overall survival was defined as the time from the date of randomization to the date of death by any cause. Median and 95% CI are presented for overall survival interim analysis. Up to 34 months. Time to First Subsequent Therapy (TFST). Time to first subsequent therapy was defined as the time from the date of randomization to the date of the first subsequent anti-cancer therapy or death, whichever occurs first. Median and 95% CI are presented. Up to 34 months.

Trial name: PRIMA	NCT number: NCT02655016
	Progression-Free Survival-2 (PFS2). PFS2 was defined as the time from the date of randomization to the date of progression on the next anti-cancer therapy following study treatment or death by any cause, whichever occurs first. Median and 95% CI are presented. Up to 34 months. Change From Baseline in Participant Reported Outcome (PRO): Functional Assessment of Cancer Therapy-Ovarian Symptom Index (FOSI). FOSI is a validated, 8-item measure of symptom response to treatment for ovarian cancer. Participants responded to their symptom experience over the past 7 days using a 5-point Likert scale scored from "not at all" (0) to "very much" (4). FOSI score was calculated as (sum of item scores)*8 divided by (number of items answered). The FOSI score ranged from 0 (severely symptomatic) to 32 (asymptomatic). A higher score indicated a better quality of life (QoL). Change from Baseline was calculated by subtracting Baseline value from the post-dose visit value. Baseline was defined as the latest pre-dose assessment (Day 1 pre-dose). Baseline (Day 1, Pre-dose) and Up to Week 24. Change From Baseline in PRO: European Quality of Life Scale, 5-dimensions, 5-levels of Severity (EQ-5D-5L) Utility Score. The EQ-5D-5L is a well-validated general preference-based, health-related QoL instrument. The five-item measure has 1 question assessing each of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression and 5 levels for each dimension including 1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems and 5=extreme problems. The health state is defined by combining the levels of answers from each of the 5 questions. Each health state is referred to in terms of a 5 digit code. Health state 5 digit code is translated into utility score, which is valued up to 1 (perfect health) with lower values meaning worse state. EQ-5D-5L utility score ranges from -0.281 to 1. Higher scores indicate better health. Change from Baseline was calculated by subtracting Baseline value from the post-dose visit value. Baseline was defined as the latest pre-dose assessment (Day 1 pre-dose). Baseline (Day 1, Pre-dose) and Up to Week 24. Change From Baseline in Functional Scales of European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC-QLQ-C30). EORTC-QLQ-C30 incorporates 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea/vomiting), a global health status/QoL scale (global health status, QoL), and 6 single items (dyspnea, appetite loss, insomnia, constipation, diarrhea, and financial difficulty) assessing additional symptoms commonly reported by participants with cancer. Five functional scales had total 15 items (physical-5, role-2, cognitive-4, emotional-2, and social-2). Each functional scales score was calculated by averaging scores of all scale items and transforming average scores linearly (1 minus [average score minus 1] divided by 3*100). All of the functional scales range in score from 0 to 100. Higher score

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	represents a higher ("better") level of functioning. Change from Baseline was calculated by subtracting Baseline value from the post-dose visit value. Baseline was defined as the latest pre-dose assessment (Day 1 pre-dose). Baseline (Day 1, Pre-dose) and Up to Week 24. Change From Baseline in Global Health Status/QoL of EORTC-QLQ-C30. EORTC-QLQ-C30 incorporates 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea/vomiting), a global health status/QoL scale (global health status, QoL), and 6 single items (dyspnea, appetite loss, insomnia, constipation, diarrhea, and financial difficulty) assessing additional symptoms commonly reported by participants with cancer. A global health status/QoL scale had total 2 items. Each global health status/QoL scales score was calculated by averaging scores of all scale items and transforming average scores linearly ([average score minus 1] divided by 6*100). The global health status/QoL scales range in score from 0 to 100. Higher score represents a higher ("better") level of health status/QoL. Change from Baseline was calculated by subtracting Baseline value from the post-dose visit value. Baseline was defined as the latest pre-dose assessment (Day 1 pre-dose). Baseline (Day 1, Pre-dose) and Up to Week 24. Change From Baseline in Symptoms Scales and Symptoms Items (Dyspnea, Appetite Loss, Insomnia, Constipation, Diarrhea and Financial Difficulty) of EORTC-QLQ-C30. EORTC-QLQ-C30 incorporates 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea/vomiting), a global health status/QoL scale, and 6 single items (dyspnea, appetite loss, insomnia, constipation, diarrhea, and financial difficulty) assessing additional symptoms commonly reported by participants with cancer. Symptom scale had total 7 items (fatigue-3, pain-2, nausea/vomiting-2). Each symptoms scales and 6 single additional symptoms items score was calculated by averaging scores of all scale items and transforming average scores linearly ([average score minus 1] divided by 3*100). All of the symptoms scales and 6 single additional symptoms scales range in score from 0 to 100. Higher score represents a higher ("worse") level of symptoms. Change from Baseline was calculated by subtracting Baseline value from the post-dose visit value. Baseline was defined as the latest pre-dose assessment (Day 1 pre-dose). Baseline (Day 1, Pre-dose) and Up to Week 24 Change From Baseline in Functional Scales of European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Ovarian Cancer Module (EORTC-QLQ-OV28). EORTC-QLQ-OV28 is supplement to EORTC-QLQ-C30. It includes 3 functional scales (body image, sexuality, attitude to disease/treatment) and 5 symptom scales/items (abdominal/gastrointestinal [GI] symptoms, peripheral neuropathy, hormonal/menopausal symptoms, other chemotherapy side-effects, and hair loss).

Trial name: PRIMA	NCT number: NCT02655016
	Functional scales score (body Image and attitude to disease/treatment) was calculated by averaging scores of all scale items and transforming average scores linearly (1 minus [average score minus 1] divided by 3*100). Functional scales score (sexuality) was calculated by averaging scores of all scale items and transforming average scores linearly ([average score minus 1] divided by 3*100). All of the functional scales range in score from 0 to 100. Higher score represents a higher ("better") level of functioning. Change from Baseline was calculated by subtracting Baseline value from the post-dose visit value. Baseline was defined as the latest pre-dose assessment (Day 1 pre-dose). Baseline (Day 1, Pre-dose) and Up to 34 months Change From Baseline in Symptoms Scale of EORTC-QLQ-OV28. EORTC-QLQ-OV28 is supplement to EORTC-QLQ-C30. It includes 3 functional scales (body image, sexuality, attitude to disease/treatment) and 5 symptom scales/items (abdominal/GI symptoms, peripheral neuropathy, hormonal/menopausal symptoms, other chemotherapy side-effects, and hair loss). Symptoms scales score was calculated by averaging scores of all scale items and transforming average scores linearly ([average score minus 1] divided by 3*100). All of the symptoms scales range in score from 0 to 100. Higher score represents a higher ("worse") level of symptoms. Change from Baseline was calculated by subtracting Baseline value from the post-dose visit value. Baseline was defined as the latest pre-dose assessment (Day 1 pre-dose). Baseline (Day 1, Pre-dose) and Up to 34 months Other Outcomes: Number of Participants With Any Non-serious Adverse Event (Non-SAE) or Any SAE. An adverse event is any untoward medical occurrence that occurs in a participant or clinical investigation participant administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with study treatment. Any untoward event resulting in death, life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, congenital anomaly or birth defect or any other situation according to medical or scientific judgment was categorized as SAE. Up to 34 months Area Under the Curve (AUC) From 0 to the Last Quantifiable Concentration (AUC[0-last]). Blood samples were planned to be collected for assessment of AUC(0-last). Up to 34 months. Peak Plasma Concentration. Blood samples were planned to be collected for assessment of Cmax. Up to 34 months.

Trial name: PRIMA	NCT number: NCT02655016
	Number of Participants With Positive HRD Test. Number of participants with positive HRD test was planned to be assessed. Up to 34 months.
Method of analysis	The PFS analysis will be performed using a 1-sided log-rank test, stratified for best response during the first platinum regimen (CR or PR), high-risk characteristic (Stage III with neoadjuvant treatment, Stage III with adjuvant/first line treatment and suboptimal cytoreduction, or Stage IV), intraperitoneal or intravenous first-line platinum therapy, and geographic region. In addition, a stratified Cox proportional hazards model will be used to estimate the treatment HR and its 95% CI. PFS will also be descriptively summarized using Kaplan-Meier methodology.
Subgroup analyses	Subgroups will also be explored for the primary efficacy endpoint based on: age, race, geographic region, and best response during the first platinum regimen (CR and PR). Subgroups involving BRCA mutation markers may also be explored for the primary efficacy endpoint.
Other relevant information	

Trial name: PRIME	NCT number: NCT03709316
Objective	The primary objective of this study is to evaluate the efficacy of niraparib versus placebo as maintenance treatment, as assessed by PFS, in patients with stage III or IV ovarian cancer with a CR or PR following first-line platinum-based chemotherapy. The study population includes patients with high-grade serous/endometrioid or predominantly high-grade serous/endometrioid epithelial ovarian cancer (no histological restriction for patients with germline BRCA mutation) with Stage III or IV according to FIGO criteria. Eligible patients will be randomized in a 2: 1 ratio to receive niraparib or placebo.
Publications – title, author, journal, year	PRIMARY: (11) Li N, Zhu J, Yin R, et al. Treatment With Niraparib Maintenance Therapy in Patients With Newly Diagnosed Advanced Ovarian Cancer: A Phase 3 Randomized Clinical Trial. JAMA Oncology. 2023;13:13. doi:10.1001/jamaoncol.2023.2283. SECONDARY: (41) Li N, Zhu J, Yin R, et al. Efficacy and safety of niraparib as maintenance treatment in patients with newly diagnosed advanced ovarian cancer using an individualized starting dose (PRIME Study): a randomized, double-blind, placebo-controlled, phase 3 trial. Asia Pacific journal of clinical oncology. 2022;18:132-133. doi:10.1111/ajco.13869. (42) Li N, Zhu J, Yin R, et al. Efficacy and safety of niraparib as maintenance treatment in patients with newly diagnosed advanced ovarian cancer using an individualized starting dose (PRIME Study): a randomized, double-blind, placebo-controlled, phase 3 trial (LBA 5). Gynecologic oncology. 2022;166:S50-S51. doi:10.1016/s0090-8258(22)01298-7. (43) Pan L, Wu L, Zhu J, et al. 37MO Niraparib maintenance therapy in patients with newly diagnosed advanced ovarian cancer: a post hoc analysis on efficacy by surgical timing and residual disease status in the phase III PRIME trial. ESMO open. 2023;8(1):2023-02. doi:10.1016/j.esmoop.2023.100817. (44) Wang J, Wu L, Zhu J, et al. Impact of Initiation Timing of Niraparib Maintenance Treatment in Newly Diagnosed Advanced Ovarian Cancer. International journal of gynecological cancer. 2022;32:A174-A175. doi:10.1136/ijgc-2022-igcs.391. (45) Yin R, Li N, Wu L, et al. Efficacy of niraparib maintenance therapy in patients with newly diagnosed advanced ovarian cancer in phase 3 PRIME study: A subgroup analysis by response to first-line platinum-based chemotherapy. Journal of Clinical Oncology.

Trial name: PRIME	NCT number: NCT03709316
	Conference: Annual Meeting of the American Society of Clinical Oncology, ASCO. 2022;40(16 Supplement 1). doi:10.1200/jco.2022.40.16_suppl.5551. (46) Zhu J, Wu L, Yin R, et al. Impact of dose modifications due to treatment-emergent adverse events (TEAEs) on the efficacy of niraparib maintenance treatment with an individualized starting dose in patients (Pts) with newly diagnosed advanced ovarian cancer (aOC) (1266). 2023;176:S168. doi:10.1016/j.ygyno.2023.06.175. (47) Kong B, Wu L, Zhu J, Yin R, Wang J, Pan L, Zheng H, Liu J, Wu X, Wang L, Huang Y. Efficacy and safety of niraparib maintenance therapy in patients with newly diagnosed advanced ovarian cancer who had measurable residual disease: A post-hoc subgroup analysis of the PRIME study..J Clin Oncol 41, 2023 (suppl 16; abstr 5562)
Study type and design	A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Phase III Clinical Trial Evaluating the Efficacy and Safety of ZL-2306 (Niraparib) for Maintenance Treatment in Patients With Advanced Ovarian Cancer, Fallopian Tube Carcinoma or Primary Peritoneal Cancer (Collectively Referred to as Ovarian Cancer) Who Have Achieved Effective Response After First-line Platinum-containing Chemotherapy
Sample size (n)	*384*
Main inclusion criteria	• The subject shall be a female, aged 18 years or older. • Histologically confirmed high-grade serous/endometrioid or dominantly high-grade serous/endometrioid epithelial ovarian cancer, fallopian tube carcinoma or primary peritoneal carcinoma (no histological restriction for patients carrying germline BRCA mutations). Note: Patients who have received neoadjuvant chemotherapy can also be enrolled if their tumors after chemotherapy cannot be pathologically graded. • 5. FIGO staging is Stage III or IV. • Criteria for previous surgery (meeting any of these): Inoperable Stage III or IV patients, Stage IV patients, regardless of postoperative residual lesion status, Stage III patients who have undergone primary tumor reductive surgery with postoperative residual lesion status of R1 (microscopic residual lesions) or R2 (macroscopic residual lesions), Stage III or IV

Trial name: PRIME	NCT number: NCT03709316
	patients who have undergone intermittent tumor reductive surgery (patients who have used neoadjuvant therapy) regardless of postoperative residual lesion status • Criteria for previous chemotherapy: ○ It is allowed to enroll patients who have received intraperitoneal chemotherapy ○ Patients have completed at least 6 cycles yet no more than 9 cycles of first-line platinum-containing chemotherapy (preferably carboplatin, but cisplatin is also acceptable) ○ Patients undergoing intermittent tumor reductive surgery should respectively receive at least 2 cycles of platinum-containing chemotherapy preoperatively and postoperatively, and receive a total of at least 6 cycles yet no more than 9 cycles of chemotherapy (preferably carboplatin, but cisplatin is also acceptable) preoperatively and postoperatively ○ Patients are assessed by the investigator to have achieved complete response (CR) or partial response (PR) after first-line platinum-containing chemotherapy, and the efficacy assessment should be performed after the end of at least 3 cycles of chemotherapy ○ CA-125 level must be within the normal range after the end of chemotherapy or has decreased by more than 90% during the course of first-line chemotherapy and remains so for at least 7 days (the elevation of CA-125 prior to enrollment shall not exceed 15% compared with the CA-125 level after the end of chemotherapy) ○ Patients must be randomized within 12 weeks since Day 1 of the last cycle of chemotherapy 8. Patients must be able to submit formalin-fixed, paraffin-embedded tumor tissue samples. • ECOG physical condition score of the patient shall be 0 or 1. • Organ function is in good condition, including: ○ Neutrophil count ≥1.5×109/L

Trial name: PRIME	NCT number: NCT03709316
	○ Platelet count ≥100×109/L ○ Hemoglobin ≥100 g/L ○ Serum creatinine is not more than 1.5 times the normal upper limit, or creatinine clearance rate is not less than 60 mL/min (calculated with Cockcroft-Gault formula) ○ Total bilirubin is not more than 1.5 times the normal upper limit, or direct bilirubin is not more than 1.0 time the normal upper limit. ○ AST and ALT are not more than 2.5 times their normal upper limit, and with existence of hepatic metastasis, these values must not be more than 5 times their normal upper limit.
Main exclusion criteria	• Patients diagnosed with mucinous, clear cell subtypes of epithelial ovarian cancer, carcinosarcoma, or undifferentiated ovarian cancer. • Stage III patients who have undergone primary tumor reductive surgery with postoperative status of R0-complete resection (with no residual lesion). • Patients who have undergone tumor reductive surgery more than twice. • Patients who plan to or have used bevacizumab as maintenance therapy after first-line platinum-containing chemotherapy. If the patient received bevacizumab in platinum-containing chemotherapy but did not receive bevacizumab as maintenance therapy, and the last dose of bevacizumab was used ≥ 28 days before signing the master informed consent form, the patient can be enrolled. • Patients who are known to be allergic to active or inactive ingredients of ZL-2306 (niraparib) or other drugs with similar chemical structures to ZL-2306 (niraparib). • Patients who have previously been treated with PARP inhibitors (including niraparib).

Trial name: PRIME	NCT number: NCT03709316
	• Patients who have received other study drug treatment within 4 weeks prior to the first administration or < 5 elimination half-lives of the study drug (whichever is longer). • Patients with ≥ grade 3 anemia, neutropenia or thrombocytopenia due to prior chemotherapy for more than 4 weeks.
Intervention	Niraparib: the starting dose is 300mg or 200mg QD based on the subject's baseline body weight or baseline platelet count
Comparator(s)	Placebo
Follow-up time	36 months (first analysis)
Primary, secondary and exploratory endpoints	• BICR-assessed progression-free survival (PFS) [Time Frame: Approximately 36 months since the first subject enrolled]: the time from randomization to progressive disease or death due to various causes assessed by the BICR according to RECIST 1.1, whichever occurs first • Overall survival (OS) [Time Frame: Approximately 36 months since the first subject enrolled]: the time from the date of randomization to the date of death caused by any reason. • Time to first subsequent anti-tumor treatment (TFST) [Time Frame: Approximately 36 months since the first subject enrolled]: the time from the date of randomization in the study to the date when the first subsequent anti-tumor treatment starts ○ PFS and OS assessed by BICR in patients with HRD (homologous recombination defects) [Time Frame: Approximately 36 months since the first subject enrolled]
Method of analysis	• The following statistical analyses will be performed for the primary efficacy endpoint, PFS assessed by BICR: ○ Stratified Log-Rank test: to compare the differences in survival curves between treatment groups, and to provide the two-sided p-value.

Trial name: PRIME	NCT number: NCT03709316
	○ Kaplan-Meier estimation: ▪ To estimate the median and 95% confidence interval, upper and lower quartiles, and range including the censored observations (minimum and maximum) of PFS by the Kaplan-Meier method; ▪ To estimate PFS at 6 months, 12 months, 18 months, 24 months and 30 months as data allow. ▪ To plot the Kaplan-Meier curves of the two treatment groups. ○ Hazard ratio (HR) estimation: ▪ To estimate the HR between treatment groups and its 95% confidence interval using the stratified COX proportional hazard model which includes treatment • The statistical analysis of secondary efficacy endpoints (OS and TFST) will be performed using the similar methods as for the primary efficacy endpoint of PFS. • Safety Endpoints: ○ Treatment emergent adverse events (TEAEs) and concomitant medications will be summarized separately by treatment group. ○ Clinical laboratory values, vital signs and ECG findings will be summarized by treatment group and visit. The observed values at post-baseline as well as change from baseline will be presented. Changes in the worst post-baseline from baseline will be summarized using shift tables by CTCAE grade and/or normal range.
Subgroup analyses	Subgroup analyses of PFS assessed by BICR: • HRD status (positive or negative);

Trial name: PRIME	NCT number: NCT03709316
	• Administration of neoadjuvant chemotherapy (yes or no); • Best overall response (CR and PR) following the first-line platinum-based chemotherapy; • gBRCA mutation status (presence or absence); • Age (18-64 years, ≥ 65 years); • History of intraperitoneal chemotherapy (yes or no); • Satisfactory surgical cytoreduction for ovarian cancer (yes or no); • Tumor staging (III or IV). • PFS assessed by BICR in HRDpos subgroup (including gBRCAmut patients)
Other relevant information	

Trial name: SOLO-1	NCT number: NCT01844986
Objective	To determine the efficacy by progression free survival (PFS) using blinded independent central review (BICR) according to modified Response Evaluation Criteria in Solid Tumours (RECIST 1.1) of olaparib maintenance monotherapy compared to placebo in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy.
Publications – title, author, journal, year	PRIMARY: (15) Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, Lisyanskaya A, Floquet A, Leary A, Sonke GS, Gourley C, Banerjee S, Oza A, González-Martín A, Aghajanian C, Bradley W, Mathews C, Liu J, Lowe ES, Bloomfield R, DiSilvestro P. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med. 2018 Dec 27;379(26):2495-2505. doi: 10.1056/NEJMoa1810858. Epub 2018 Oct 21. PMID: 30345884. SECONDARY: (13) Banerjee S, Moore K, Colombo N, et al. Maintenance olaparib for patients with newly diagnosed advanced ovarian cancer and a BRCA mutation (SOLO1/GOG 3004): 5-year follow-up of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncology. 2021;22(12):1721-1731. doi:10.1016/s1470-2045(21)00531-3. (48) Bradley W, Moore K, Colombo N, et al. Maintenance olaparib for patients with newly diagnosed, advanced ovarian cancer and a BRCA mutation: 5-year follow-up from SOLO1. Gynecologic oncology. 2021;162:S25-S26. doi:10.1016/s0090-8258(21)00694-6. (49) Colombo N, Moore K, Scambia G, et al. Tolerability of maintenance olaparib in newly diagnosed patients with advanced ovarian cancer and a BRCA mutation in the randomized phase III SOLO1 trial. Gynecologic Oncology. 2021;163(1):41-49. doi:10.1016/j.ygyno.2021.07.016.

Trial name: SOLO-1	NCT number: NCT01844986
	(14) DiSilvestro P, Banerjee S, Colombo N, et al. Overall Survival With Maintenance Olaparib at a 7-Year Follow-Up in Patients With Newly Diagnosed Advanced Ovarian Cancer and a BRCA Mutation: The SOLO1/GOG 3004 Trial. Journal of Clinical Oncology. 2023;41(3):609-617. doi:10.1200/jco.22.01549. (50) DiSilvestro P, Colombo N, Scambia G, et al. Efficacy of Maintenance Olaparib for Patients With Newly Diagnosed Advanced Ovarian Cancer With a BRCA Mutation: Subgroup Analysis Findings From the SOLO1 Trial. Journal of Clinical Oncology. 2020;38(30):3528-3537. doi:10.1200/jco.20.00799. (51) Friedlander M, Moore K, Colombo N, et al. Patient-centred outcomes and effect of disease progression on health status in patients with newly diagnosed advanced ovarian cancer and a BRCA mutation receiving maintenance olaparib or placebo (SOLO1): a randomised, phase 3 trial. Lancet Oncology. 2021;22(5):632-642. doi:10.1016/s1470-2045(21)00098-x. (52) Wu L, Zhu J, Yin R, et al. Olaparib maintenance therapy in patients with newly diagnosed advanced ovarian cancer and a BRCA1 and/or BRCA2 mutation: SOLO1 China cohort. Gynecologic Oncology. 2021;160(1):175-181. doi:10.1016/j.ygyno.2020.10.005.
Study type and design	A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Patients with BRCA Mutated Advanced (FIGO Stage III-IV) Ovarian Cancer following First Line Platinum Based Chemotherapy.
Sample size (n)	*391*
Main inclusion criteria	• Female patients with newly diagnosed, histologically confirmed, high risk advanced (FIGO stage III - IV) BRCA mutated high grade serous or high grade endometrioid ovarian cancer, primary peritoneal cancer and / or fallopian - tube cancer who have completed first line platinum based chemotherapy (intravenous or intraperitoneal). • Stage III patients must have had one attempt at optimal debulking surgery (upfront or interval debulking). Stage IV patients must have had either a biopsy and/or upfront or interval debulking surgery. • Documented mutation in BRCA1 or BRCA2 that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function).

Trial name: SOLO-1	NCT number: NCT01844986
	• Patients who have completed first line platinum (e.g. carboplatin or cisplatin), containing therapy (intravenous or intraperitoneal) prior to randomisation: • Patients must have, in the opinion of the investigator, clinical complete response or partial response and have no clinical evidence of disease progression on the post treatment scan or rising CA-125 level, following completion of this chemotherapy course. Patients with stable disease on the post-treatment scan at completion of first line platinum-containing therapy are not eligible for the study. • Patients must be randomized within 8 weeks of their last dose of chemotherapy
Main exclusion criteria	• Female patients with newly diagnosed, histologically confirmed, high risk advanced (FIGO stage III - IV) BRCA mutated high grade serous or high grade endometrioid ovarian cancer, primary peritoneal cancer and / or fallopian - tube cancer who have completed first line platinum based chemotherapy (intravenous or intraperitoneal). • Stage III patients must have had one attempt at optimal debulking surgery (upfront or interval debulking). Stage IV patients must have had either a biopsy and/or upfront or interval debulking surgery. • Documented mutation in BRCA1 or BRCA2 that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function). • Patients who have completed first line platinum (e.g. carboplatin or cisplatin), containing therapy (intravenous or intraperitoneal) prior to randomisation: • Patients must have, in the opinion of the investigator, clinical complete response or partial response and have no clinical evidence of disease progression on the post treatment scan or rising CA-125 level, following completion of this chemotherapy course. Patients with stable disease on the post-treatment scan at completion of first line platinum-containing therapy are not eligible for the study. • Patients must be randomized within 8 weeks of their last dose of chemotherapy

Trial name: SOLO-1	NCT number: NCT01844986
Intervention	• Olaparib 300mg tablets: Olaparib tablets 300mg twice daily for up to 3 years or until objective radiological disease progression as per RECIST as assessed by the Investigator. Patients with evidence of stable disease (or those who have progressed), may continue on treatment beyond 2 years, if in the patient's best interest. Dose reduction to 250mg and subsequently 200mg is permitted following confirmation of toxicity
Comparator(s)	• Placebo tablets p.o. twice daily: placebo tablets p.o 300mg twice daily for up to 3 years or until objective radiological disease progression as per RECIST as assessed by the Investigator. Patients with evidence of stable disease (or those who have progressed), may continue on treatment beyond 2 years, if in the patient's best interest. Dose reduction to 250mg and subsequently 200mg is permitted following confirmation of toxicity
Follow-up time	Minimum follow-up period of **24 months**
Primary, secondary and exploratory endpoints	PRIMARY • Progression Free Survival (PFS) Using Investigator Assessment According to Modified Response Evaluation Criteria in Solid Tumours (RECIST 1.1) [Time Frame: Radiologic scans performed at baseline then every 12 weeks up to 156 weeks, then every 24 weeks thereafter until objective radiological disease progression. DCO: 17 May 2018] ○ To determine the efficacy by progression free survival (PFS) using investigator assessment according to modified Response Evaluation Criteria in Solid Tumours (RECIST 1.1) of olaparib maintenance monotherapy compared to placebo in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy. SECONDARY • Efficacy in Patients Following First Line Platinum Based Chemotherapy by Assessment of Overall Survival [Time Frame: Assessed every 4 weeks until treatment discontinues (up to a max of 156 weeks), then as per protocol. Analysis performed

Trial name: SOLO-1	NCT number: NCT01844986
	with DCO: 17May2018. Further analyses will be performed at 7 years (descriptive), after 206 events and after 60% maturity.] ○ To determine the efficacy of olaparib maintenance monotherapy compared to placebo in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy by assessment of overall survival (OS). Reports results of a pre-specified interim analysis; results for final OS analysis (235 OS events) anticipated 2029. • Efficacy in Patients Following First Line Platinum Based Chemotherapy by Assessment of Time to Earliest Progression by RECIST or Cancer Antigen (CA-125) or Death [Time Frame: CA-125 performed at baseline + every 4 weeks. Radiologic scans performed at baseline + every 12 weeks up to 156 weeks, then every 24 weeks until objective radiological disease progression. DCO:17May2018] ○ To determine the efficacy of olaparib maintenance monotherapy compared to placebo in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy by assessment of time to earliest progression by RECIST or Cancer Antigen-125 (CA-125) or death • Efficacy in Patients Following First Line Platinum Based Chemotherapy by Assessment of Time From Randomization to Second Progression [Time Frame: Following first progression disease then assessed per local practice every 12 weeks until second progression.] ○ To determine the efficacy of olaparib maintenance monotherapy compared to placebo in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy by assessment of time from randomisation to second progression (PFS2) • Change From Baseline in Health-Related Quality of Life (HRQoL) as Assessed by the the Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy - Ovarian (FACT-O) [Time Frame: Questionnaires will be given to the patient at

Trial name: SOLO-1	NCT number: NCT01844986
	baseline, at Day 29 and then every 12 weeks for 156 weeks, then every 24 weeks or until the data cut off for the PFS analysis, change in TOI over 24 months reported] ○ To compare the effects of olaparib maintenance monotherapy compared to placebo on Health-related Quality of Life (HRQoL) as assessed by the trial outcome index (TOI) of the Functional Assessment of Cancer Therapy - Ovarian (FACT-O) in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy. The TOI ranges from 0-100 and a higher score indicates a higher HRQoL. • Efficacy in Patients Following First Line Platinum Based Chemotherapy by Assessment of Time to First Subsequent Therapy or Death (TFST) [Time Frame: Assessed every 12 weeks following treatment discontinuation. Analysis performed with DCO: 17May2018. Further analyses will be performed at 7 years (descriptive), after 206 events and after 60% maturity.] ○ To determine the efficacy of olaparib maintenance monotherapy compared to placebo in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy by assessment of time from randomisation to first subsequent therapy or death (TFST). Reports results of a pre-specified interim analysis; final analysis results will later be added at time of final OS analysis (anticipated 2029). • Efficacy in Patients Following First Line Platinum Based Chemotherapy by Assessment of Time to Second Subsequent Therapy or Death (TSST) [Time Frame: Assessed every 12 weeks following treatment discontinuation. Analysis performed with DCO: 17May2018. Further analyses will be performed at 7 years (descriptive), after 206 events and after 60% maturity.] ○ To determine the efficacy of olaparib maintenance monotherapy compared to placebo in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy by assessment of time from randomisation to second subsequent therapy or death (TSST). Reports results of a pre-specified interim analysis; final analysis results will later be added at time of final OS analysis (anticipated 2029).

Trial name: SOLO-1	NCT number: NCT01844986
	• Efficacy in Patients Following First Line Platinum Based Chemotherapy by Assessment of Time From Randomization to Study Treatment Discontinuation or Death (TDT) [Time Frame: Time elapsed from randomization to study treatment discontinuation or death. Analysis performed with DCO: 17May2018. Further analyses will be performed at 7 years (descriptive), after 206 events and after 60% maturity.] ○ To determine the efficacy of olaparib maintenance monotherapy compared to placebo in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy by assessment of time from randomisation to study treatment discontinuation or death (TDT). Reports results of a pre-specified interim analysis; final analysis results will later be added at time of final OS analysis (anticipated 2029). • Efficacy in Patients With a Deleterious or Suspected Deleterious Variant in Either of the BRCA Genes by Assessment of PFS [Time Frame: Radiologic scans performed at baseline then every 12 weeks for the first 156 weeks, then every 24 weeks thereafter, assessed until disease progression. Analysis of data assessed up to a maximum of 54 months.] ○ To assess efficacy of olaparib in patients identified as having a deleterious or suspected deleterious variant in either of the BRCA genes using variants identified with current and potential future BRCA mutation assays (gene sequencing and large rearrangement analysis)
Method of analysis	PFS will be analysed using a log-rank test stratified by response to first line platinum chemotherapy (in the opinion of the investigator, clinical complete response (CR) or partial response (PR)) for generation of the p-value and using the Breslow approach for handling ties. The hazard ratio (HR) and confidence interval (CI) will be estimated from a Cox Proportional Hazards model (with ties = Efron and the stratification variable as a covariate) and the CI will be calculated using a profile likelihood approach. Stratification variables will be defined according to data from the randomisation. If there are any patients who were mis-stratified, a sensitivity analysis will be carried out using the (correct) baseline data collected in the eCRF. Although not anticipated, if patients are randomised in error when they have not previously had a response to first line platinum chemotherapy, they will be categorised in the “PR” category for the sensitivity analysis using eCRF stratification data. The HR (olaparib versus placebo) together with its

Trial name: SOLO-1	NCT number: NCT01844986
	corresponding 95% CI and p-value will be presented (a HR less than 1 represents the reduction in risk for those patients allocated olaparib). OS data will be analysed at the time of the primary analysis of PFS and will use the same methodology and model (provided there are sufficient events available for a meaningful analysis [≥20 deaths], if not descriptive summaries will be provided). A further analysis of OS will be performed when the OS data are approximately 60% mature. Time to first subsequent therapy or death (TFST) and time to second subsequent therapy or death (TSST) will be analysed at the same time as the primary analysis of PFS and using the same methodology and model. The HRs for the treatment effect together with 95% CIs will be presented. KM plots will be presented by treatment arm. In addition, the number of patients who received further therapy relative to progression (before, after, no progression) will also be presented by treatment arm. Time to study treatment discontinuation or death (TDT) will be analysed at the same time as the primary analysis of PFS and using the same methodology and model. The HR for the treatment effect together with 95% CIs will be presented. A KM plot will be presented by treatment arm. No multiplicity adjustment will be applied as this is viewed as a supportive endpoint. Change from baseline in TOI score will be regarded as the primary analysis of the FACT-O questionnaire and will be analysed using a mixed model for repeated measures (MMRM) analysis of the change from baseline (defined as prior to first dose) in TOI scores for each visit.
Subgroup analyses	The following subgroups of the full analysis set will be analysed for PFS: • Response to previous platinum chemotherapy (obtained from the randomisation schedule) • gBRCAm status-confirmed by Myriad test or gBRCAwildtype (wt) or gBRCA variant of uncertain significance (VUS) or missing by Myriad test]*.This will be determined from the Myriad central laboratory tests.

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	• ECOG performance status at baseline (normal activity [PSTAT=0] or restricted activity [PSTAT=1]). This will be determined from the response to “Performance status” (PSTAT module) on the eCRF at screening. • Baseline CA-125 value (≤ ULN or > ULN). The baseline CA-125 value will be defined as the measurement nearest to but prior to date of randomisation. • BRCA mutation type (BRCA1 or BRCA2 or BRCA1/2 (both)). • Age (<65 or ≥ 65) • Stage of disease at initial diagnosis (III [FIGO_STG=30 or 31 or 32 or 33] or IV [FIGO_STG=40]) • Residual macroscopic disease following debulking surgery prior to entry into the study [HISPOUT=1] or no residual macroscopic disease [HISPOUT=2]. • Region 1 (North America or Rest of World). • Region 2 (Brazil, Poland, Russia, Japan, Korea or Rest of World) • Race (White or Black/African-American or Asian or Native Hawaiian/Pacific Islander or American Indian/Alaska Native or Others).
Other relevant information	

Appendix B. Efficacy results per study

Results from ATHENA-MONO (NCT03522246)												
Outcome	**Cohort**	**Study arm**	**N**	**Result (CI)**	**Estimate absolute difference in effect**			**Estimated relative difference in effect**			**Description of methods used for estimation**	**Ref**
					Difference	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
PFS	**BRCAm**	rucaparib	91	Not reached	Not estimable			0.47	0.26 to 0.84	NR	PFS in the BRCAm subgroup was analyzed using stratified log-rank test and stratified Cox proportional hazard model comparing the treatment groups stratified by the randomization stratification factors, ie, disease status (no residual disease versus residual disease), and timing of surgery (primary surgery vs. interval debulking). At time of analysis, median follow-up was 4.0 and 3.5 yrs in rucaparib and placebo, respectively.	(7)
		placebo	24	16.7 months								
OS	**HRD group**	Rucaparib	185	Not reached	Not estimable			0.84	0.44 to 1.58	0.581	OS was analyzed using stratified log-rank test and stratified Cox proportional hazard model comparing the treatment groups stratified by the randomization stratification factors, ie, HRD classification (tBRCA, non-tBRCA LOHhigh, non-tBRCA LOHlow, and non-tBRCA LOHunknown), disease status (no residual disease versus residual disease), and timing of surgery (primary surgery vs. interval debulking). At time of analysis, median follow-up was 26 months.	(1)
		placebo	49	Not recahed								
Treatment discontinuation due to adverse events	**ITT**	rucaparib	425	(11.8%)							Data from all patients who receive at least 1 dose of study drug was included in the safety analyses. The number and percentage of patients who experienced TEAEs leading to discontinuation will be summarized. TEAEs are defined as AEs with onset date on or after the date of first dose of study drug until 28 days after the last dose	(16)
		placebo	110	(5.5%)								

Results from ATHENA-MONO (NCT03522246)												
Outcome	**Cohort**	**Study arm**	**N**	**Result (CI)**	**Estimate absolute difference in effect**			**Estimated relative difference in effect**			**Description of methods used for estimation**	**Ref**
					Difference	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
											of oral study drug or 5 months after the last dose of IV study drug, whichever occurs later.	
Grade 3-4 adverse events	**ITT**	rucaparib	425								Only treatment-emergent adverse events (TEAEs) were collected: TEAEs are defined as AEs with onset date on or after the date of first dose of study drug until 28 days after the last dose of oral study drug or 5 months after the last dose of IV study drug, whichever occurs later. Multiple instances of the TEAE in each SOC and multiple occurrences of the same preferred term were counted only once per patient. The number and percentage of patients with at least one grade 3-4 TEAE was summarized.	(16)
		placebo	110									
FACT-O TOI change from baseline (final visit)	**HRD group**	rucaparib	185	-2.0 (-3.9 to 0.2)	0.0	-4.0 to 4.0	0.991	NA			Analyses of changes from baseline were analyzed for each scheduled post-baseline visit and for the final visit. Patients that did not have both a baseline measurement and at least 1 post-baseline measurement were not included. The final visit was defined as the last assessment within 28 days after date of last dose of oral study drug for those that discontinued oral treatment or prior to the visit cutoff date for those still ongoing. At a given visit, the change from baseline was analyzed for the treatment comparisons using an ANCOVA with treatment and stratification variable as a categorical factors and baseline measurement for the parameter as a continuous covariate. A change of at least 10 points in the FACT-O TOI was considered as clinically relevant and	(9)
		placebo	49	-2.0 (-5.6 to 1.5)								

Results from ATHENA-MONO (NCT03522246)												
Outcome	**Cohort**	**Study arm**	**N**	**Result (CI)**	**Estimate absolute difference in effect**			**Estimated relative difference in effect**			**Description of methods used for estimation**	**Ref**
					Difference	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
											minimally important difference and was summarized categorically. Results are reported for the final visit.	

NR: not reported

Results from PRIMA (NCT02655016)												
Outcome	**Cohort**	**Study arm**	**N**	**Result (CI)**	**Estimate absolute difference in effect**			**Estimated relative difference in effect**			**Description of methods used for estimation**	**Ref**
					Difference	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
PFS	**BRCAm**	niraparib	152	30.1 months	18.6 months			0.43	0.31 to 0.59	NR	PFS was analysed with a stratified log-rank test using stratification factors from randomisation and summarised using Kaplan-Meier methodology. Hazard ratios with 95% CIs were estimated using a stratified Cox proportional hazards model, with stratification factors used in randomisation. In the final analysis, median follow-up was 73.9 months.	(37)
		placebo	71	11.5 months								

Results from PRIMA (NCT02655016)												
Outcome	**Cohort**	**Study arm**	**N**	**Result (CI)**	**Estimate absolute difference in effect**			**Estimated relative difference in effect**			**Description of methods used for estimation**	**Ref**
					Difference	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
OS	**HRD group**	niraparib	152	Not reached	Not estimable			0.94	0.63 to 1.41	NR	OS was analysed with a stratified log-rank test using stratification factors from randomisation and summarised using Kaplan-Meier methodology. Hazard ratios with 95% CIs were estimated using a stratified Cox proportional hazards model, with stratification factors used in randomisation. In the final analysis, median follow-up was 73.9 months.	(37)
		placebo	71	Not recahed								
Treatment discontinuation due to adverse events	**ITT**	niraparib	484	79 (16.3%)	NR			NR			Data from all patients who received at least one dose of investigational drug was included and was based on the treatment actually received. The number and percentage of patients who experienced TEAEs leading to discontinuation will be summarized. TEAEs are defined as AEs with onset date on or after the date of first dose of study drug until 28 days after the last dose of oral study drug or 5 months after the last dose of IV study drug, whichever occurs later.	(37)
		placebo	244	9 (3.7%)								
Grade 3-4 adverse events	**ITT**	niraparib	484	357 (73.8%)	NR			NR			Only treatment-emergent adverse events (TEAEs) were collected: TEAE is defined as any new AE that occurs on or after the first dose of the study drug until 30 days after the last dose of the study drug or initiation of new anti-cancer therapy (whichever occurs first), or any AE with increasing CTCAE grade. Multiple instances of the TEAE in each SOC and multiple occurrences of the same preferred term were counted only once per patient. The number and percentage	(37)
		placebo	244	58 (23.8%)								

Results from PRIMA (NCT02655016)												
Outcome	**Cohort**	**Study arm**	**N**	**Result (CI)**	**Estimate absolute difference in effect**			**Estimated relative difference in effect**			**Description of methods used for estimation**	**Ref**
					Difference	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
											of patients with at least one grade 3-4 TEAE was summarized.	
FOSI CFB (final visit)	**ITT**	niraparib	479	-0.4 (0.15)	NR			NA			Change from Baseline was calculated by subtracting Baseline value from the post-dose visit value. Baseline was defined as the latest pre-dose assessment (Day 1 pre-dose).	(12)
		placebo	240	-0.3 (0.22)								
EORTC QLQ-C30 CFB	**ITT**	niraparib	478	1.01 (0.690)	NR			NR			Change from Baseline was calculated by subtracting Baseline value from the post-dose visit value. Baseline was defined as the latest pre-dose assessment (Day 1 pre-dose).	(12)
		placebo	243	1.18 (1.001)								
EORTC QLQ-OV28 Functional scale – Body Image - CFB	**ITT**	niraparib	475	8.49 (1.014)	NR			NR			Change from Baseline was calculated by subtracting Baseline value from the post-dose visit value. Baseline was defined as the latest pre-dose assessment (Day 1 pre-dose).	(12)
		placebo	244	10.07 (1.482)								
EORTC QLQ-OV28 Functional scale – Sexuality - CFB	**ITT**	niraparib	471	3.63 (0.800)	NR			NR				(12)

Results from PRIMA (NCT02655016)												
Outcome	**Cohort**	**Study arm**	**N**	**Result (CI)**	**Estimate absolute difference in effect**			**Estimated relative difference in effect**			**Description of methods used for estimation**	**Ref**
					Difference	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
		placebo	240	3.26 (1.189)							Change from Baseline was calculated by subtracting Baseline value from the post-dose visit value. Baseline was defined as the latest pre-dose assessment (Day 1 pre-dose).	
EORTC QLQ-OV28 Functional scale – Attitude to disease/treatment - CFB	**ITT**	niraparib	475	13.66 (0.931)	NR			NR			Change from Baseline was calculated by subtracting Baseline value from the post-dose visit value. Baseline was defined as the latest pre-dose assessment (Day 1 pre-dose).	(12)
		placebo	244	12.22 (1.326)								
EORTC QLQ-OV28 Symptoms scale – abdominal/GI - CFB	**ITT**	niraparib	481	2.19 (0.57)	NR			NR			Change from Baseline was calculated by subtracting Baseline value from the post-dose visit value. Baseline was defined as the latest pre-dose assessment (Day 1 pre-dose).	(12)
		placebo	244	0.83 (0.811)								
EORTC QLQ-OV28 Symptoms scale – peripheral neuropathy - CFB	**ITT**	niraparib	480	-8.22 (0.930)	NR			NR			Change from Baseline was calculated by subtracting Baseline value from the post-dose visit value. Baseline was defined as the latest pre-dose assessment (Day 1 pre-dose).	(12)
		placebo	244	-9.64 (1.322)								

Results from PRIMA (NCT02655016)												
Outcome	**Cohort**	**Study arm**	**N**	**Result (CI)**	**Estimate absolute difference in effect**			**Estimated relative difference in effect**			**Description of methods used for estimation**	**Ref**
					Difference	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
EORTC QLQ-OV28 Symptoms scale – hormonal/menopausal symptoms - CFB	**ITT**	niraparib	480	1.50 (0.880)	NR			NR			Change from Baseline was calculated by subtracting Baseline value from the post-dose visit value. Baseline was defined as the latest pre-dose assessment (Day 1 pre-dose).	(12)
		placebo	244	-2.52 (1.307)								
EORTC QLQ-OV28 Symptoms scale - other chemo side effects- CFB	**ITT**	niraparib	480	-2.22 (0.588)	NR			NR			Change from Baseline was calculated by subtracting Baseline value from the post-dose visit value. Baseline was defined as the latest pre-dose assessment (Day 1 pre-dose).	(12)
		placebo	244	-3.02 (0.836)								
EORTC QLQ-OV28 Symptoms scale – hair loss-CFB	**ITT**	niraparib	477	-23.36 (0.982)	NR			NR			Change from Baseline was calculated by subtracting Baseline value from the post-dose visit value. Baseline was defined as the latest pre-dose assessment (Day 1 pre-dose).	(12)
		placebo	242	-20.74 (1.369)								

*CFB: change from baseline NR: not reported

Results from PRIME												
Outcome	**Cohort**	**Study arm**	**N**	**Result (CI)**	**Estimate absolute difference in effect**			**Estimated relative difference in effect**			**Description of methods used for estimation**	**Ref**
					Difference	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
PFS	**BRCAm**	rucaparib	85	Not reached	Not estimable			0.40	0.23 to 0.68	NR	PFS was analysed with a stratified log-rank test using stratification factors from randomisation and summarised using Kaplan-Meier methodology. Hazard ratios with 95% CIs were estimated using a stratified Cox proportional hazards model, with stratification factors used in randomisation. At the time of analysis, median follow-up was approximately 3 years.	(11)
		placebo	40	10.8								
OS	**HRD group**	Rucaparib	170	Not reached				0.88	0.43 to 1.78	NR	OS was analysed with a stratified log-rank test using stratification factors from randomisation and summarised using Kaplan-Meier methodology. Hazard ratios with 95% CIs were estimated using a stratified Cox proportional hazards model, with stratification factors used in randomisation. At the time of analysis, median follow-up was approximately 3 years.	(11)
		placebo	87	Not reached								
Treatment discontinuation due to adverse events	**ITT**	rucaparib	255	31 (11.9%)	NR						Data from all patients who received at least one dose of investigational drug was included and was based on the treatment actually received. The number and percentage of patients who experienced TEAEs leading to discontinuation will be summarized. TEAEs are defined as AEs with onset date on or after the date of first dose of study drug until 28 days after the last dose of oral study drug or 5 months after the last dose of IV study drug, whichever occurs later. At the time of analysis, median follow-up was approximately 3 years.	(11)
		placebo	129	4 (3.1%)								

Results from PRIME												
Outcome	**Cohort**	**Study arm**	**N**	**Result (CI)**	**Estimate absolute difference in effect**			**Estimated relative difference in effect**			**Description of methods used for estimation**	**Ref**
					Difference	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Grade 3-4 adverse events	**ITT**	rucaparib	255	103 (39.6%)	NR						Only treatment-emergent adverse events (TEAEs) were collected: TEAE is defined as any new AE that occurs on or after the first dose of the study drug until 30 days after the last dose of the study drug or initiation of new anti-cancer therapy (whichever occurs first), or any AE with increasing CTCAE grade. Multiple instances of the TEAE in each SOC and multiple occurrences of the same preferred term were counted only once per patient. The number and percentage of patients with at least one grade 3-4 TEAE was summarized. At the time of analysis, median follow-up was approximately 3 years.	(11)
		placebo	129	26 (20.0%)								

*NR: not reported

Results from SOLO1											
Outcome	**Cohort**	**Study arm**	**N**	**Result (CI)**	**Estimate absolute difference in effect**			**Estimated relative difference in effect**			**Description of methods used for estimation**	**Ref**
					Difference	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
PFS	**BRCAm**	olaparib	260	56.0 months	NR			0.33	0.25 to 0.43	NR	PFS was analysed using a log-rank test stratified by response to first line platinum chemotherapy (in the opinion of the investigator, clinical complete response (CR) or partial response (PR)) for	(13)

Results from SOLO1												
Outcome	**Cohort**	**Study arm**	**N**	**Result (CI)**	**Estimate absolute difference in effect**			**Estimated relative difference in effect**			**Description of methods used for estimation**	**Ref**
					Difference	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
		Placebo	131	13.8 months							generation of the p-value and using the Breslow approach for handling ties. The hazard ratio (HR) and confidence interval (CI) will be estimated from a Cox Proportional Hazards model (with ties = Efron and the stratification variable as a covariate) and the CI will be calculated using a profile likelihood approach. Stratification variables will be defined according to data from the randomisation. If there are any patients who were mis-stratified, a sensitivity analysis will be carried out using the (correct) baseline data collected in the eCRF. This final analysis included median follow-up of 5 years.	
OS	**BRCAm**	olaparib	260	Not reached	NR			0.55	0.40 to 0.76	NR	OS was analyzed using a log-rank test stratified by response to first-line platinum-based chemotherapy, with HRs and 95% CIs estimated using a Cox proportional hazards model, including the stratification variable as a covariate. OS was not adjusted for subsequent PARP inhibitor therapy. This final analysis included median follow-up of 7 years.	(14)
		placebo	131	75.2 months								
Treatment discontinuation due to adverse events	**BRCAm**	olaparib	260	31 (11.9%)	NR			NR			Any patient who received an initial dose of olaparib will be included in the olaparib group, even if the patient was planned to receive placebo. Similarly, any patient who received an initial dose of placebo will be included in the placebo group, even if the patient was planned to receive olaparib. The summary tables will include all AEs that occurred after the start of treatment up until the end of the 30 day follow-up period. The 30 day follow-up period will be defined	(14)
		placebo	131	4 (3.1%)								

Results from SOLO1												
Outcome	**Cohort**	**Study arm**	**N**	**Result (CI)**	**Estimate absolute difference in effect**			**Estimated relative difference in effect**			**Description of methods used for estimation**	**Ref**
					Difference	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
											as 30 days following discontinuation of olaparib/placebo treatment. This final analysis included median follow-up of 7 years.	
Grade 3-4 adverse events	**BRCAm**	olaparib	260	103 (39.6%)	NR			NR			Any patient who received an initial dose of olaparib will be included in the olaparib group, even if the patient was planned to receive placebo. Similarly, any patient who received an initial dose of placebo will be included in the placebo group, even if the patient was planned to receive olaparib. The summary tables will include all AEs that occurred after the start of treatment up until the end of the 30 day follow-up period. The 30 day follow-up period will be defined as 30 days following discontinuation of olaparib/placebo treatment. This final analysis included median follow-up of 7 years.	(14)
		placebo	131	26 (20.0%)								
FACT-O TOI change from baseline (final visit)	**BRCAm**	olaparib	260	0.30 (-0.72 to 1.32)	-3.00	-4.78 to -1.22	0.001	NA			Change from baseline in TOI score was analysed using a mixed model for repeated measures (MMRM) analysis of the change from baseline (defined as prior to first dose) in TOI scores for each visit. The MMRM model will include patient, treatment, visit (analysis) and treatment by visit interaction as explanatory variables, the baseline TOI score as a covariate along with the baseline TOI score by visit interaction. Treatment, visit and treatment by visit interaction will be fixed effects in the model; patient will be included as a random effect. Restricted maximum likelihood (REML) estimation will be used. An overall adjusted mean estimate will be derived that will estimate the average treatment effect over visits giving each visit equal weight. For this overall treatment comparison, adjusted mean estimates per treatment group and	(53)
		placebo	131	3.30 (1.84 to 4.76)								

Results from SOLO1												
Outcome	**Cohort**	**Study arm**	**N**	**Result (CI)**	**Estimate absolute difference in effect**			**Estimated relative difference in effect**			**Description of methods used for estimation**	**Ref**
					Difference	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
											corresponding 95% CIs will be presented along with an estimate of the treatment difference, 95% CI and p-value. The treatment by visit interaction will remain in the model regardless of significance. An unstructured covariance matrix will be used to model the within-subject error and the Kenward-Roger approximation will be used to estimate the degrees of freedom.	

*NR: not reported

Appendix C. Literature searches for the clinical assessment

D.1 Efficacy and safety of the intervention and comparator(s)

Objective of the literature search:

To meet the objectives of the SLR, the following primary research question was addressed:

- What is the clinical efficacy, safety, and utility values of rucaparib and relevant comparators as a first-line maintenance therapy in randomized controlled trials (RCT) involving previously treated patients with locally advanced or metastatic OC, fallopian tube or primary peritoneal carcinomas who have responded to prior platinum-based therapy?

Systematic searches were conducted to identify peer-reviewed studies of interest, published in the electronic literature databases listed in Appendix Table 1.

Appendix Table 1 Bibliographic databases included in the literature

Database	Platform/source	Relevant period for the search	Date of search completion
Embase (including Embase in-process)	OVID	1974 to 24 September 2024	25SEP2024
MEDLINE (including MEDLINE in-process)	OVID	1946 to 24 September 2024	25SEP2024
CENTRAL	Cochrane Library	2005 to 24 September 2024	25SEP2024
CDSR	Cochrane Library	August 2024	25SEP2024

Abbreviations: CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials

Tabel 1 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
HTA International	https://www.cambridge.org/core/journals/international-journal-of-technology-assessment-in-health-care		25SEP2024

Source name	Location/source	Search strategy	Date of search
Clinical Trials Register	https://clinicaltrials.gov/		25SEP2024
International Trials Register	http://apps.who.int/trialsearch/		25SEP2024

Abbreviations:

To identify the most recent research that may not have been published in peer-reviewed journals, proceedings from 2023 onwards of key conferences were screened for abstracts of relevant studies (Appendix Table 2). Conference proceedings were captured and screened via the electronic online database searches if indexed within them. For conference proceedings which were not indexed in Embase or Medline, the relevant online medium was searched using keywords similar to those used in the electronic literature database searches, and the results were screened. The abstracts were screened according to the criteria detailed in Appendix Table 7. In addition, any abstracts of RCTs reporting on efficacy and safety outcomes that were identified from the conference searches were included in the review as grey literature.

Appendix Table 2 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ASCO Annual Meeting	OVID	Same as a database searches	Same as a database searches	25SEP2024
ESGO Biennial Meeting	OVID	Same as a database searches	Same as a database searches	25SEP2024
ESMO Congress	OVID	Same as a database searches	Same as a database searches	25SEP2024
IGCS Biennial Meeting	OVID	Same as a database searches	Same as a database searches	25SEP2024
ISPOR Conference (all locations)	OVID	Same as a database searches	Same as a database searches	25SEP2024

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
SGO Annual Meeting	OVID	Same as a database searches	Same as a database searches	25SEP2024

Abbreviations: ASCO = American Society of Clinical Oncology; ESGO = European Society of Gynaecological Oncology; ESMO = European Society for Medical Oncology; IGCS = International Gynecologic Cancer Society; PRO = patient-reported outcome; SGO = Society of Gynecologic Oncology

D.1.2 Search strategies

Search strategies for each electronic literature database interface included a combination of free-text search terms and controlled vocabulary terms. Search terms were validated by checking previous relevant HTAs, and published SLRs. Searches were designed to ensure studies of patients who are diagnosed with locally advanced or metastatic ovarian cancer, fallopian tube or primary peritoneal carcinomas receiving maintenance therapy after first line treatment are captured. The searches were restricted to references published in English. The abstracts and full-text articles were screened according to the criteria detailed in Appendix Table 7. Bibliographies of relevant SLRs identified in the search were for additional relevant references.

Appendix Table 3 Embase (OVID): 1974 to August 22, 2024. Date Searched: 23 August 2024

No.	Query	Results
1	exp ovary cancer/ or exp ovary/ or ovary disease/	342100
2	(ovar$ adj6 (cancer$ or neoplas$ or tumo?r$ or malignan$ or metasta$ or carcino$ or adenocarcino$ or adeno-carcino$ or onco$)).ti,ab.	173046
3	uterine tube tumor/ or exp Fallopian tube/ or exp uterine tube disease/	15235
4	((fallopian tube? or fallopian tubal) adj6 (neoplas$ or tumo?r$ or cancer$ or carcino$ or adenocarcino$ or adeno-carcino$ or malignan$ or metast$ or onco$)).ti,ab.	5364
5	exp peritoneum tumor/ or exp peritoneum/	107157
6	((periton$ adj6 (neoplas$ or tumo?r$ or cancer$ or carcino$ or adenocarcino$ or adeno-carcino$ or malignan$ or metast$ or onco$)) or (psammomacarcino$ or psammoma-carcino$)).ti,ab.	39168
7	or/1-6	505658
8	olaparib/ or rucaparib/ or niraparib/ or bevacizumab/	90712

No.	Query	Results
9	(olaparib or AZD 2281 or AZD2281 or lynparza or AZD221 or rucaparib or rubraca or PF-01367338 or AG014699 or "AG 014699" or niraparib or MK4827 or MK 4827 or bevacizumab or avastin).ti,ab.	46798
10	or/8-9	93488
11	(maintain or maintenance or consolidat$).ti,ab,tw.	885173
12	exp randomized controlled trial/ or phase 3 clinical trial/ or phase 4 clinical trial/	880150
13	(exp clinical trial/ or prospective study/) and random$.ti,ab.	877180
14	randomization/ or single blind procedure/ or double blind procedure/ or triple blind procedure/ or placebo/	668419
15	((singl$ or doubl$ or tripl$) adj3 (blind$3 or mask$3 or dummy)).ti,ab.	298288
16	(random$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).ti,ab.	540435
17	(((phase II or phase 2 or clinic$) adj3 trial$) and random$).ti,ab.	295061
18	(placebo$ or (allocat$ adj2 random$)).ti,ab.	435196
19	((random$ adj3 trial$) or "clinicaltrials.gov" or (systematic adj (review$ or overview$)) or meta-analy$ or metaanaly$).ti,ab.	1196001
20	single arm.ti,ab.	32858
21	(nonrandom$ or non random$ or quasi random$ or quasirandom$).ti,ab.	75225
22	or/12-21	2302554
23	7 and 10 and 11 and 22	1028
24	animal/ or animal experiment/ or (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw.	7929400
25	exp human/ or human experiment/	27010683
26	24 not (24 and 25)	5899378

No.	Query	Results
27	letter/ or case study/ or (letter or editorial or note or erratum or short survey).pt.	3953384
28	or/26-27	9746103
29	23 not 28	991
30	("conference abstract" or "conference review" or "conference paper").pt. or conference$.so,st.	6045220
31	29 not 30	419
32	limit 30 to yr="2021 -Current"	1060916
33	29 and 32	242
34	**31 or 33**	**661**

Appendix Table 4 MEDLINE ALL (OVID): 1946 to August 22, 2024. Date Searched: 23 August 2024

No.	Query	Results
1	exp Ovarian Neoplasms/ or exp Ovary/ or Ovarian Diseases/	195067
2	(ovar$ adj6 (cancer$ or neoplas$ or tumo?r$ or malignan$ or metasta$ or carcino$ or adenocarcino$ or adeno-carcino$ or onco$)).ti,ab.	119913
3	Fallopian Tube Neoplasms/ or Fallopian Tubes/ or Fallopian Tube Diseases/	17560
4	((fallopian tube? or fallopian tubal) adj6 (neoplas$ or tumo?r$ or cancer$ or carcino$ or adenocarcino$ or adeno-carcino$ or malignan$ or metast$ or onco$)).ti,ab.	3227
5	Peritoneal Neoplasms/ or Peritoneum/	32187
6	((periton$ adj6 (neoplas$ or tumo?r$ or cancer$ or carcino$ or adenocarcino$ or adeno-carcino$ or malignan$ or metast$ or onco$)) or (psammomacarcino$ or psammoma-carcino$)).ti,ab.	25715
7	or/1-6	288486
8	Bevacizumab/	15021
9	(olaparib or AZD 2281 or AZD2281 or lynparza or AZD221 or rucaparib or rubraca or PF-01367338 or AG014699 or "AG	24943

No.	Query	Results
	014699" or niraparib or MK4827 or MK 48274827 or bevacizumab or avastin).ti,ab.	
10	or/8-9	27495
11	(maintain or maintenance or consolidat$).ti,ab,kw.	653809
12	exp Randomized Controlled Trial/ or Clinical Trial, Phase III/ or Clinical Trial, Phase IV/	626012
13	(exp Clinical Trial/ or Prospective Studies/) and random$.ti,ab.	539562
14	Random Allocation/ or Single-Blind Method/ or Double-Blind Method/ or Placebos/	330809
15	((singl$ or doubl$ or tripl$) adj3 (blind$3 or mask$3 or dummy)).ti,ab.	209692
16	(random$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).ti,ab.	366504
17	(((phase II or phase 2 or clinic$) adj3 trial$) and random$).ti,ab.	219589
18	(placebo$ or (allocat$ adj2 random$)).ti,ab.	299682
19	((random$ adj3 trial$) or "clinicaltrials.gov").ti,ab.	561922
20	single arm.ti,ab.	15607
21	(nonrandom$ or non random$ or quasi random$ or quasirandom$).ti,ab.	58142
22	((systematic adj (review$ or overview$)) or meta-analy$ or metaanaly$).ti,ab.	484197
23	limit 22 to yr="2018 -Current"	299566
24	or/12-21,23	1538101
25	7 and 10 and 11 and 24	299
26	exp animals/ not humans/	5251228
27	(comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case reports or historical article).pt. or Letter/ or Case Reports/	5039099
28	or/26-27	10157561

No.	Query	Results
29	**25 not 28**	**288**

Appendix Table 5 Cochrane Database of Systematic Reviews. EBM Reviews (OVID): 2005 to August 22, 2024. Date Searched: 23 August 2024

No.	Query	Results
1	(ovar$ adj6 (cancer$ or neoplas$ or tumo?r$ or malignan$ or metasta$ or carcino$ or adenocarcino$ or adeno-carcino$ or onco$)).ti,ab,kw.	70
2	((fallopian tube? or fallopian tubal) adj6 (neoplas$ or tumo?r$ or cancer$ or carcino$ or adenocarcino$ or adeno-carcino$ or malignan$ or metast$ or onco$)).ti,ab,kw.	9
3	((periton$ adj6 (neoplas$ or tumo?r$ or cancer$ or carcino$ or adenocarcino$ or adeno-carcino$ or malignan$ or metast$ or onco$)) or (psammomacarcino$ or psammoma-carcino$)).ti,ab,kw.	11
4	or/1-3	75
5	(olaparib or Lynparza or rucaparib or Rubraca or niraparib or bevacizumab or avastin).ti,ab,kw.	35
6	(maintain or maintenance or consolidat$).ti,ab,kw.	533
7	4 and 5 and 6	1
8	(202312$ or 2024$).up.	2400
9	**7 and 8**	**1**

Appendix Table 6 CENTRAL (OVID): July 2024. Date Searched: 23 August 2024

No.	Query	Results
1	exp Ovarian Neoplasms/ or exp Ovary/ or Ovarian Diseases/ or Fallopian Tube Neoplasms/ or Fallopian Tubes/ or Fallopian Tube Diseases/ or Peritoneal Neoplasms/ or Peritoneum/	5961
2	(ovar$ adj6 (cancer$ or neoplas$ or tumo?r$ or malignan$ or metasta$ or carcino$ or adenocarcino$ or adeno-carcino$ or onco$)).ti,ab,kw.	8932

No.	Query	Results
3	((fallopian tube? or fallopian tubal) adj6 (neoplas$ or tumo?r$ or cancer$ or carcino$ or adenocarcino$ or adeno-carcino$ or malignan$ or metast$ or onco$)).ti,ab,kw.	1061
4	((periton$ adj6 (neoplas$ or tumo?r$ or cancer$ or carcino$ or adenocarcino$ or adeno-carcino$ or malignan$ or metast$ or onco$)) or (psammomacarcino$ or psammoma-carcino$)).ti,ab,kw.	2689
5	or/1-4	12676
6	Bevacizumab/	3081
7	(olaparib or Lynparza or rucaparib or Rubraca or niraparib or bevacizumab or avastin).ti,ab,kw.	8813
8	or/6-7	9086
9	(maintain or maintenance or consolidat$).ti,ab,kw.	85314
10	5 and 8 and 9	655
11	conference proceeding.pt.	243939
12	10 not 11	316
13	limit 11 to yr="2021 -Current"	51080
14	10 and 13	132
15	**12 or 14**	**448**

D.1.3 Systematic selection of studies

The eligibility criteria for the SLR are detailed in the Appendix Table 7. In addition to these criteria, the following subgroups will be included during the screening phase:

<u>The broad population of interest</u>

- FIGO Stage III vs. stage IV
- Germline and somatic BRCA1/BRCA 2 mutations
- BRCA1 vs BRCA2 mutation
- BRCA wildtype
- Homologous recombination DNA repair deficiency (HRD) scores or tests for HRD, including LOH, if data is available

- Residual disease at study entry vs no residual disease

Appendix Table 7 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Women with de novo locally advanced or metastatic OC or fallopian tube or primary peritoneal carcinomas who, have platinum-sensitive* disease, have responded to a prior first-line platinum therapy	Women in the following categories: - Early OC (stage I) - Without previous platinum-based chemotherapy - Prior maintenance treatment - With central nervous system metastasis that remains untreated
Intervention	Targeted treatments: PARP inhibitors (e.g., rucaparib, olaparib, niraparib), monoclonal antibodies (bevacizumab)	Non-pharmacologic treatments, such as surgery or radiotherapy alone Alternative doses, schedules, or formulations of the intervention as the only comparator arms
Comparators	Targeted treatments: PARP inhibitors (e.g., rucaparib, olaparib, niraparib), monoclonal antibodies (bevacizumab), chemotherapy (platinum-based and non-platinum-based), no treatment/placebo/"wait-and-see" approach, best supportive care	Non-pharmacologic treatments, such as surgery or radiotherapy alone Alternative doses, schedules, or formulations of the intervention as the only comparator arms
Outcomes	Efficacy: PFS using RECIST criteria, time on treatment, time to treatment discontinuation, ORR, OS, and duration of response, time to progression to first treatment, PFS on the subsequent line of treatment. Safety/tolerability: any adverse event, adverse events by grade, discontinuation due to adverse events, including tolerability for dose. HRQoL and PROs, including symptom assessment (for example, FACT-O, FOSI, and TOI)	Publications that do not report data on relevant outcomes Publications that report only interim trial results
Study design/publication type	Systematic reviews and meta-analyses of RCTs^	Non-randomized, single-arm, or observational (non-

	RCTs in any country (phases II/III) for efficacy, safety, and PROs	interventional) studies for efficacy, safety, PROs Open-label extension phases of RCTs Pre-clinical studies (animal, in vitro) Case reports, expert opinion articles, letters, narrative (non-systematic reviews) Publications of the following types: - Narrative publications - Non-systematic reviews - Case studies - Case reports - Editorials
Language restrictions	Only English-language articles/conference abstracts will be included	Journal articles and conference abstracts without English full text
Timeframe for the SLR	2021 onwards for conference abstracts No time restrictions for other publications	

* Defined as disease progression greater than six months after completion of their penultimate platinum regimen (from last dose) ^Published SLRs will not be included in the results of this review, but will be used for citation-chasing purposes

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
ATHENA-MONO	Assess efficacy & safety of rucaparib	Ph3, randomizer, double-blind, multiregional, 4:1 ratio	Broad incl. HRD +/- & BRCAm and wt	Rucaparib vs. placebo	PFS (4.0y rucaparib and 3.5y placebo	OS (37m)

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
PRIMA	Assess efficacy & safety of niraparib	Ph3, randomize d, double-blind, multiregion al, 2:1 ratio	Broad incl. HRD +/- and BRCAm/wt	Niraparib vs. placebo	PFS (73.9m)	OS (73.9m)
PRIME	Assess efficacy & safety of niraparib	Ph3, randomize d, double-blind, China only, 2:1 ratio	Broad incl. HRD +/- and BRCAm/wt	Niraparib vs. placebo	PFS (3y)	OS (3y)
SOLO1	Assess efficacy & safety of olaparib	Ph3, randomize d, double-blind, multiregion al, 2:1 ratio	BRCAm only	Olaparib vs. placebo	PFS (5y)	OS (7y)

D.1.4 Quality assessment

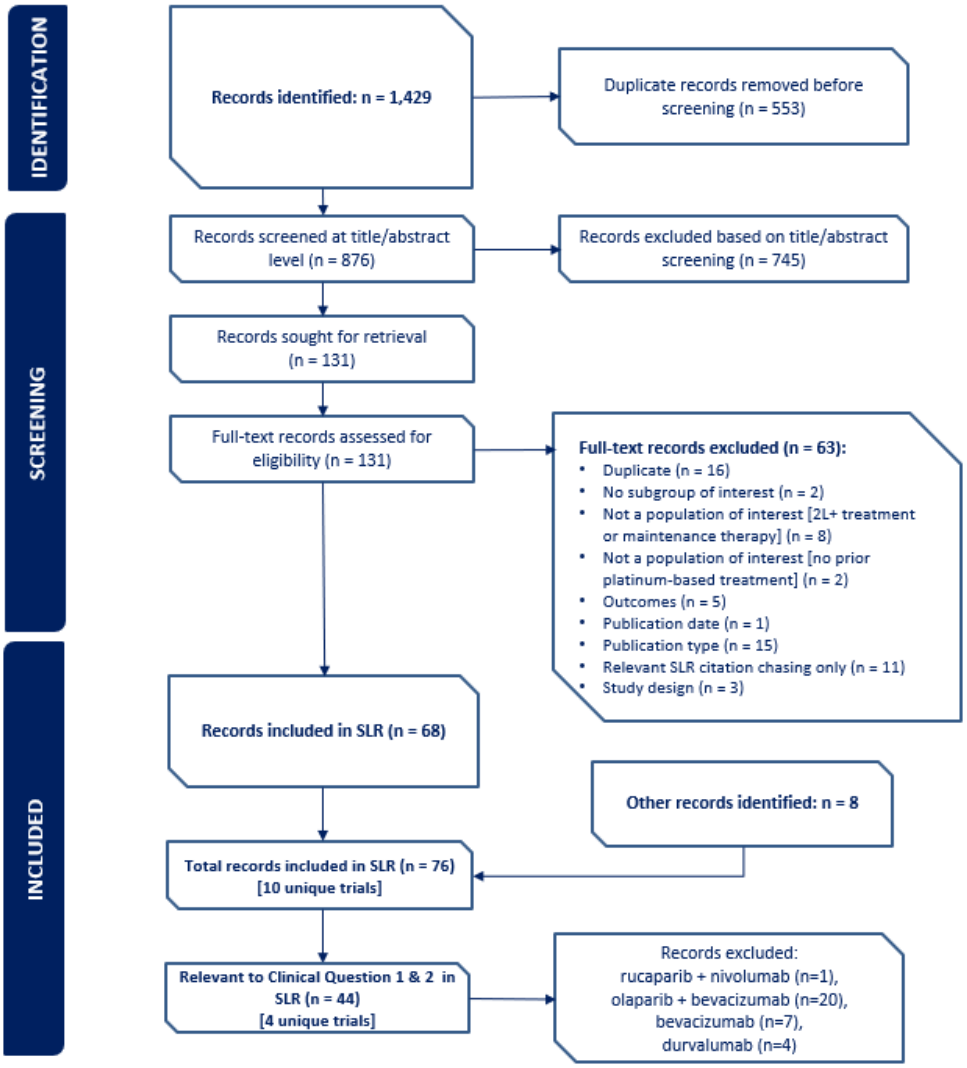
The quality assessment of the RCTs included in the SLR was conducted using the Cochrane Risk of Bias Tool. Risk of bias was assessed independently by two reviewers. The risk of bias was low across all studies included.

Appendix Table 8 Risk of Bias assessment

	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
ATHENA-MONO	Low	Low	Low	Low	Low	Low
PRIMA	Low	Low	Low	Low	Low	Low
PRIME	Low	Low	Low	Low	Low	Low
SOLO-1	Low	Low	Low	Low	Low	Low

D.1.5 Unpublished data

The SLR included the ATHENA-MONO interim clinical study report.



Appendix Figure 1 PRISMA flow diagram (searches conducted on 25th September 2024)

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