12 October 2023
EMA/CHMP/503870/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rubraca

International non-proprietary name: rucaparib

Procedure No. EMEA/H/C/004272/II/0036

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADR(s) adverse drug reaction(s)

AE(s) adverse event(s)

AESI(s) adverse event(s) of special interest

ALT alanine aminotransferase

AML acute myeloid leukaemia

AST aspartate aminotransferase

AUC0-24h area under the concentration-time curve from 0 to 24 hours

AUCavg,ss* averaged steady-state area under the concentration-time curve

BICR blinded independent central review

bicrPFS progression-free survival as assessed by blinded independent central review (disease progression according to RECIST v1.1 as assessed by blinded central radiology review, or death from any cause; also known as irrPFS)

BID twice a day

BRCA breast cancer gene, includes BRCA1 and BRCA2

BRCA1 breast cancer gene 1

BRCA2 breast cancer gene 2

BCRP breast cancer resistance protein

CA-125 cancer antigen 125

CI confidence interval

CLcr creatinine clearance

CMA Conditional Marketing Authorization

COVID-19 coronavirus disease 2019

CR complete response

CSR clinical study report

CTCAE Common Terminology Criteria for Adverse Events

CYP cytochrome P450

DOR duration of response

EC European Commission

ECG electrocardiogram

ECOG Eastern Cooperative Oncology Group

EMA European Medicines Agency

EOC epithelial ovarian cancer

EQ-5D-5L Euro-Quality of Life - 5 Dimensions - 5 Levels

ER exposure-response

EU European Union

FACT-O Functional Assessment of Cancer Therapy - Ovarian

FDA Food and Drug Administration

FTC fallopian tube cancer

FIGO International Federation of Gynecology and Obstetrics

gBRCA germline BRCA

HR hazard ratio

HRD homologous recombination deficiency

HRQoL Health-related Quality of Life

IC50 50% inhibitory concentration

Inc. Incorporated

invPFS investigator-assessed progression-free survival

irrPFS independent radiology review of progression-free survival

IRT interactive response technology

ISS Integrated Summary of Safety

ITT intent-to-treat

IV intravenous

KM Kaplan-Meier

LOH loss of heterozygosity

MAA Marketing Authorization Application

MAH Marketing Authorization Holder

mCRPC metastatic castration-resistant prostate cancer

MDS myelodysplastic syndrome

MedDRA Medical Dictionary for Regulatory Activities

mPFS median progression-free survival

NGS next-generation sequencing

NR not reached

ORR objective response rate

OS overall survival

PARP poly (adenosine diphosphate-ribose) polymerase

PFI progression-free interval

PFS progression-free survival

PFS2 progression-free survival on a subsequent line of treatment

PK pharmacokinetics

PPC primary peritoneal cancer

PPK population pharmacokinetics

PR partial response

PRO patient-reported outcomes

PS performance status

PSUR Periodic Safety Update Report

PT Preferred Term

QT time from the beginning of the Q wave to the end of the T wave

R0 complete resection

RECIST Response Evaluation Criteria in Solid Tumours

SAE(s) serious adverse event(s)

SAP statistical analysis plan

sBRCA somatic BRCA

SCE Summary of Clinical Efficacy

SCS Summary of Clinical Safety

SEER Surveillance, Epidemiology, and End Results

SmPC Summary of Product Characteristics

SOB Specific Obligation

SOC System Organ Class

T2V Type II variation

TEAE(s) treatment-emergent adverse event(s)

UK United Kingdom

US United States

USPI United States Prescribing Information

v Version

WBC white blood cell

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Clovis Oncology Ireland Limited submitted to the European Medicines Agency on 27 August 2022 an application for a Type II variation for the above medicinal product. During the procedure the marketing authorisation holder was changed to pharmaand GmbH (previously named zr pharma& GmbH).

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include maintenance treatment of adult patients with advanced (FIGO Stages III and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to first-line platinum-based chemotherapy for RUBRACA, based on interim results from study CO-338-087 (ATHENA); this is a Phase III, randomised, double-blind, dual placebo controlled study of rucaparib as monotherapy and in combination with nivolumab in patients with newly diagnosed EOC, FTC, or PPC who have responded to their first-line treatment (surgery and platinum-based chemotherapy). As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 6.3 of the RMP has also been submitted. As part of the application the MAH is requesting a 1-year extension of the market protection.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0242/2020 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

MAH request for additional market protection

Initially the MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication. The request was withdrawn during the procedure.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Carolina Prieto Fernandez Co-Rapporteur: Peter Mol

Timetable	Actual dates
Submission date	27 August 2022
Start of procedure:	17 September 2022
CHMP Rapporteur's preliminary assessment report circulated on	21 November 2022
PRAC Rapporteur's preliminary assessment report circulated on	18 November 2022
CHMP Co-Rapporteur Assessment circulated on	29 November 2022
PRAC RMP advice and assessment overview adopted by PRAC on	1 December 2022
CHMP Rapporteur(s) updated (joint) assessment report circulated on	10 December 2022
Request for supplementary information adopted by the CHMP on	15 December 2022
MAH's responses submitted to the CHMP on	23 March 2023
CHMP Rapporteur(s) preliminary (joint) assessment report on the MAH's responses circulated on	26 April 2023
CHMP Rapporteur(s) updated (joint) assessment report on the MAH's responses circulated on	19 May 2023
2nd request for supplementary information adopted by the CHMP on	25 May 2023
MAH's responses submitted to the CHMP on	14 July 2023
CHMP Rapporteur(s) preliminary (joint) assessment report on the MAH's responses circulated on	14 August 2023
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	17 August 2023
PRAC RMP advice and assessment overview adopted by PRAC	31 August 2023
CHMP Rapporteur(s) updated (joint) assessment report on the MAH's responses circulated on	8 September 2023
3rd request for supplementary information adopted by the CHMP on	14 September 2023
MAH's responses submitted to the CHMP on	18 September 2023
CHMP Rapporteur(s) preliminary (joint) assessment report on the MAH's responses circulated on	27 September 2023
CHMP Rapporteur(s) updated (joint) assessment report on the MAH's responses circulated on	5 October 2023
CHMP opinion adopted on	12 October 2023
The CHMP adopted a report on similarity of Rubraca with Zejula on	12 October 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Ovarian cancer is the eighth most common cancer and the eighth leading cause of cancer death among women. In Europe, the estimated age standardised rate of newly diagnosed ovarian cancer cases in 2020 is 15.5/100,000 and the mortality is 10.3/100,000 (ECIS 2020).

Ovarian cancer is classified primarily as stages I to IV using the International Federation of Gynaecology and Obstetrics (FIGO) staging system (NCCN 2022). More than two-thirds of patients are diagnosed at an advanced stage (FIGO stage III and IV) and these women have particularly poor outcomes.

Epithelial ovarian cancer (EOC) represents the majority of malignant ovarian neoplasms (about 90%). EOC has four main subtypes, including serous, endometrioid, mucinous, and clear cell. The most common is serous carcinoma (about 70%). Grade is an additional prognostic determinant. Low grade (grade 1, well differentiated) serous ovarian carcinoma is considered a distinct type of disease compared with high grade (grade 2 and 3 – moderately and poorly differentiated) serous carcinoma based on a number of clinical and molecular features, thus serous ovarian cancer is now often referred to as either low grade (most grade 1 serous tumours) or high grade (most grade 2 or 3 serous tumours).

Management

First-line treatment of newly diagnosed ovarian cancer includes a combination of surgery and chemotherapy: either primary debulking surgery (PDS) followed by adjuvant platinum-doublet chemotherapy (platinum plus a taxane) or neoadjuvant platinum-based chemotherapy with subsequent interval debulking surgery followed by additional platinum-containing chemotherapy (NCCN 2022). The goal of this approach is to minimise residual tumour to no visible residual disease, a major prognostic indicator for improved survival.

Despite optimal upfront surgery and the administration of front-line platinum-taxane chemotherapy, approximately 70% of patients will relapse in the first 3 years and become largely incurable (Ledermann 2013).

Maintenance therapy following a response to standard treatment provides an opportunity to extend the disease-free period. Three agents are currently approved for maintenance treatment in the first-line setting; the anti-angiogenesis inhibitor antibody bevacizumab and two poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors, olaparib (± bevacizumab) and niraparib.

The anti-angiogenesis antibody, bevacizumab, given with chemotherapy in the first-line setting and then as maintenance showed significant improvements in PFS in two studies (GOG-0218 and ICON7), and as a result bevacizumab was incorporated into the standard of care for first-line ovarian cancer. However, this observed PFS benefit did not translate into an OS benefit.

PARP inhibitor maintenance therapy was initially evaluated as a strategy for improving outcomes in recurrent, second-line and beyond, platinum-sensitive ovarian cancer. In this setting, at least three randomised, double-blind studies have demonstrated statistically significant improvements in median progression free survival (mPFS) for PARP inhibitors when compared to placebo in their ITT populations regardless of BRCA1/2 mutation or HRD status. These are studies 19, NOVA and ARIEL3 for olaparib, niraparib and rucaparib, respectively.

Following results observed in the second-line setting, PARP inhibitor switch maintenance therapy in ovarian cancer was evaluated in the first-line setting following cytoreductive surgery and platinum-based chemotherapy. Both olaparib and niraparib are approved to be used as monotherapy in that setting based on observed statistically significant improvements in PFS compared to placebo. Of note, the use of olaparib as maintenance treatment in 1L is limited to BRCA-mutated ovarian cancer

patients, based on the results from the SOLO-1 study, while niraparib is approved for patients irrespective of HRD status, based on results from the PRIMA study. Main results from these two pivotal studies are outlined below.

In the SOLO-1 study an improvement in PFS as assessed by the investigator (invPFS) was shown in patients with advanced ovarian cancer and a BRCA1/2 mutation who, after achieving a response following completion of first-line platinum-based chemotherapy, were treated with olaparib compared to those who received placebo (mPFS 56.0 versus 13.8 months; HR 0.33 [95% CI, 0.25-0.43]).

In the PRIMA study a statistically significant improvement in PFS by BICR was observed with niraparib versus placebo in the HRD population (mPFS 21.9 versus 10.4 months; HR 0.43 [95% CI, 0.31-0.59; p < 0.001]), and in the overall unselected patient population (mPFS 13.8 versus 8.2 months; HR 0.62 [95% CI, 0.50-0.76; p < 0.001]).

In addition, olaparib in combination with bevacizumab is also indicated for maintenance treatment in 1L of HRD positive ovarian cancer patients (defined by either a BRCA1/2 mutation and/or genomic instability). This approval was based on the results from the PAOLA-1 study where the combination of olaparib and bevacizumab demonstrated an improvement in invPFS over bevacizumab alone in the HRD population (mPFS 37.2 versus 17.7 months; HR 0.33 [95% CI, 0.25-0.45]) and in the overall unselected patient population (mPFS 22.1 versus 16.6 months; HR 0.59 [95% CI, 0.49-0.72; p < 0.001]). However, in the 277 patients with HRD-negative tumours, the mPFS was 16.6 months in the olaparib and bevacizumab group and 16.2 months in the bevacizumab group (HR 1.00 [95% CI, 0.75-1.35]) so the combination was only approved in HRD positive patients.

Despite recent advances, there remains a significant need for improved treatment options in the first-line setting for patients with newly diagnosed advanced ovarian cancer. In this context, rucaparib can be an additional option to the treatment armamentarium.

2.1.2. About the product

Rucaparib (CO-338) is a small molecule inhibitor of poly (adenosine diphosphate [ADP] ribose) polymerase (PARP)enzymes, including PARP-1, PARP-2, and PARP-3, which play a role in DNA repair.

In the EU Rubraca is currently approved for the following indication:

"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."

The CHMP adopted the following indication: "As monotherapy for the maintenance treatment of adult patients with advanced (FIGO Stages III and IV) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy."

The recommended dose is 600 mg Rubraca taken twice daily, equivalent to a total daily dose of 1,200 mg. This is the same as the currently approved dose in the second line maintenance setting (see Rubraca SmPC).

For this new indication patients can continue treatment until disease progression, unacceptable toxicity or completion of 2 years treatment.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH did not seek scientific advice at the CHMP concerning the current procedure.

2.1.4. General comments on compliance with GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.2. Non-clinical aspects

2.2.1. Introduction

The MAH provided an updated environmental risk assessment of rucaparib 200 mg, 250 mg and 300 mg film-coated tablets addressing the following indication: "The maintenance treatment of adult patients with advanced (FIGO Stages III and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to first-line platinum-based chemotherapy."

The recommended dose is 600 mg Rubraca taken twice daily, equivalent to a total daily dose of 1,200 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.

No new non-clinical data have been submitted in this application.

An environmental risk assessment (ERA) report has been submitted. The non-clinical evaluation will focus on this ERA.

2.2.2. Pharmacology

No new data was submitted in this application.

2.2.3. Pharmacokinetics

No new data was submitted in this application.

2.2.4. Toxicology

No new data was submitted in this application.

2.2.5. Ecotoxicity/environmental risk assessment

In support of this application, the predicted concentration of rucaparib in surface water ($PEC_{SURFACEWATER}$) was calculated according to the *Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use* (EMEA/CHMP/SWP/4447/00 corr 2), and *Questions and Answers on the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use* (EMA/CHMP/SWP/44609/2010 Rev 1) and reassessed after refinement of the Fpen based on the prevalence of patients in the EU-27

with ovarian cancer, eligible for maintenance treatment with rucaparib.

Since an updated $PEC_{SURFACEWATER}$ has been calculated, an ERA summary table has been provided. See Table 1.

Table 1 Summary of main study results

Substance (INN/Invented Name): Rucaparib					
CAS-number (if available): 1859053-21-6					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 (Study 14101.6105)	0.71 (Ph =7)			Potential PBT (N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	0.71			not B
	BCF	Not required			B/not B
Persistence	DT50 or ready biodegradability	Not required			P/not P
Toxicity	NOEC or CMR	Not required			T/not T
PBT-statement:	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC surfacewater , refined (e.g. prevalence, literature)	10.4	µg/L			> 0.01 threshold (Y)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 (Study 14101.6106)	Sludge: Koc = 3409, 751 L/kg (n=2, geometric mean 2080) Soil: Koc = 31191, 166488, 226141 L/kg (n=3, geometric mean 140856)			Koc values indicated Rucaparib as having slight mobility in sludge and immobile in soils.
Ready Biodegradability Test	OECD 301B (Study 14101.6107)	Not readily biodegradable			Phase IIb terrestrial assessment not required
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308 (Study 14101.6109)	DT50, water, 20°C = 1.8 days (S1) & 1.5 days (S2) DT50, sediment, 20°C = >10,000 days (S1) & (S2) DT50, total system, 20°C = 50.7 days (S1) & 17.5 days (S2) >10% shifting to sediment			S1: Taunton River System S2: Weweantic River System Phase IIb sediment assessment required
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201 (Study 14101.6110)	NOEC	510	µg/L	*Raphidocelis subcapitata*
Daphnia sp. Reproduction Test	OECD 211 (Study 14101.6112)	NOEC	59	µg/L	$PEC_{SURFACEWATER}$ / $PNEC_{SURFACEWATER}$ = 0.0018 (<1) $PEC_{SURFACEWATER}$ / $PNEC_{GROUNDWATER}$ = 0.0018 (<1)

Fish, Early Life Stage Toxicity Test/*Species*	OECD 210 (Study 14101.6111)	NOEC	170	µg/L	Fathead minnows (*Pimephales promelas*)
Activated Sludge, Respiration Inhibition Test	OECD 209 (Study 14101.6113)	EC_{10}	590	µg/L	*NOEC <1.0 mg/mL. Exact NOEC could not be defined, EC10 can be considered equivalent* $PEC_{SURFACEWATER}$ / $PNEC_{MICROORGANISM}$ = 0.00018 (<0.1)
Phase IIb Studies					
Sediment dwelling organism	OECD 218 (Study 14101.6115)	NOEC LOEC 28-day	170 >170 >170	mg/kg mg/kg mg/kg	*Chironomous riparius* RCR = 0.002 (<1)

2.2.6. Discussion on non-clinical aspects

The MAH has calculated a $PEC_{SURFACEWATER}$ in compliance with the guideline on the environmental risk assessment for rucaparib, due to the proposed extension of indication to include 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 for Rubraca, based on interim results from study CO-338-087 (ATHENA). For this, the MAH has used an F_{pen} refined by the prevalence data for the disease in Latvia, which is the country that has the highest prevalence of ovarian cancer in the European Union according to GLOBOCAN of the IARC. This is in line with the Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use'.

The $PEC_{SURFACEWATER}$ value for rucaparib was 0.0104 µg/L.

. A Phase I (screening) and Phase II environmental risk assessment for rucaparib was evaluated previously (Environmental Risk Assessment version 3 (April 2019)), which was acceptable, and rucaparib is unlikely to pose a risk to the aquatic environment and does not present a risk to sediment-dwelling organisms.

2.2.7. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted in this application which is acceptable.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of rucaparib.

Considering the above data, rucaparib is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Type of Study/ Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Patients/ Subjects	Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Reports of Efficacy and Safety Studies								
Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication								
CO-338-087 **(ATHENA-MONO)** Phase 3 Ovarian Cancer	Section 5.3.5.1 CO-338-087 Interim CSR	**Primary:** To evaluate PFS by Response Evaluation Criteria in Solid Tumors (RECIST), as assessed by the investigator (invPFS). **Secondary:** To evaluate PFS by RECIST, as assessed by BICR; bicrPFS To evaluate survival benefit To evaluate ORR and DOR, as assessed by the investigator, in patients with measurable disease at baseline To evaluate safety **Exploratory:** To evaluate PFS2 (PFS on the subsequent line of treatment) To evaluate efficacy and safety in the tBRCA subgroup for the comparison of rucaparib vs placebo (invPFS, bicrPFS, OS, ORR, DOR, safety) To evaluate Health-related Quality of Life (HRQoL) as assessed by the trial outcome index (TOI) of the Functional Assessment of Cancer Therapy - Ovarian (FACT O) To evaluate patient-reported outcome (PRO) utilizing the Euro-Quality of Life 5D-5L (EQ-5D-5L) To characterize pharmacokinetics (PK) of rucaparib as monotherapy	Randomized, double-blind, dual placebo-controlled	Randomized 4:1 Oral rucaparib or matching placebo 600 mg BID; AND IV placebo on Day 1 of every 28-day cycle, starting with Cycle 2.	538 patients	Patients with high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancer who completed first-line platinum-based chemotherapy and surgery, and who achieved a response	Up to 24 months following first dose of IV placebo or until other protocol-defined criteria for removal from study are met.	Enrollment complete, study ongoing. Interim CSR

2.3.2. Pharmacokinetics

The primary objective of the current analysis was to update the existing population pharmacokinetics (PopPK) model and characterize the exposure-response (ER) relationships for efficacy and safety for rucaparib 600 mg twice a day (BID) in the first-line maintenance setting in ATHENA-MONO.

This pharmacokinetic-pharmacodynamic (PKPD) report describes 2 of the 4 arms of the study ATHENA: Arm B (oral rucaparib + intravenous (IV) placebo) versus Arm D (oral placebo + IV placebo), that were part of the ATHENA-MONO comparison, i.e. rucaparib vs. placebo. The schema of the ATHENA-MONO portion of the study is included in section 2.4.2 below.

The objectives of this analyses were to:

• Determine if the existing PopPK model adequately describes rucaparib pharmacokinetics (PK) from ATHENA-MONO and update the model as appropriate, if needed;

• Characterize the rucaparib exposure-efficacy relationship;

• Characterize the rucaparib exposure-safety relationship.

Pharmacokinetics in target population

The data included in this analysis comprised of 500 randomised patients, with 400 randomised to receive rucaparib (Arm B) and 100 randomised to receive placebo (Arm D) for the ATHENA-MONO comparison. The remaining arms (Arms A and C) will be evaluated at a later date.

The treatment phase consisted of 28-day treatment cycles. In Cycle 1, patients received treatment with oral rucaparib or placebo only, beginning on Day 1. Oral rucaparib or placebo was taken BID continuously thereafter.

Oral study drug was taken with or without food. Study drug treatment continued in 28-day cycles until 24 months after initiating oral rucaparib/ IV placebo combination study treatment, disease progression, or unacceptable toxicity, whichever occurred first.

PK samples for rucaparib were collected approximately 12 hours after the last dose, but prior to the next dose (ie, within 1 hour). If dosing was held for toxicity or any other reason, PK sample was still collected at the end of treatment in Cycles 1, 2, 3, and 5.

Population PK Model Development

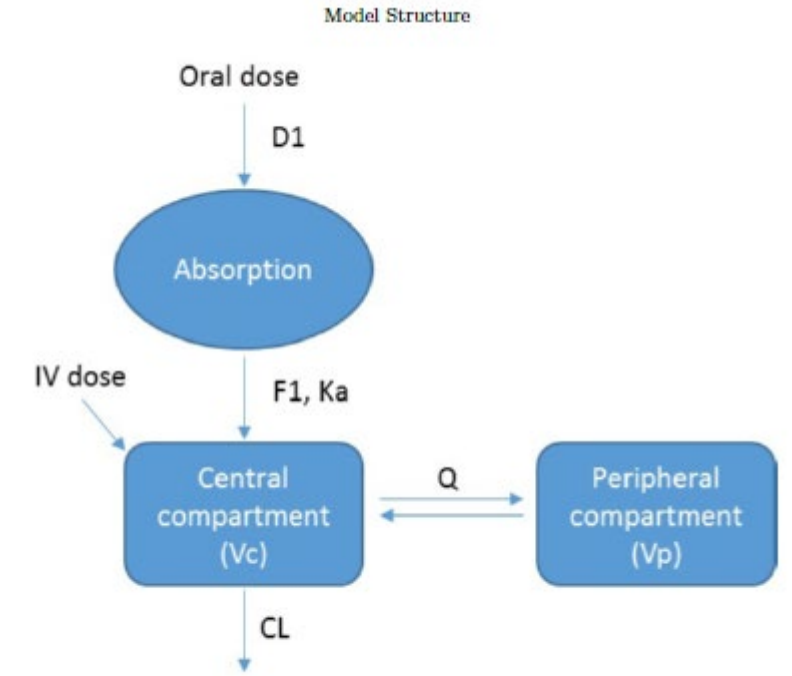
The population PK analysis was conducted with the following steps:

1. External validation of the final PK model (existing model) with the Study ATHENA-MONO dataset via prediction-corrected visual predictive check (VPC).
2. Estimation of individual post hoc PK parameters for Study ATHENA-MONO patients based on the existing PopPK model parameters (with MAXEVAL=0).
3. Evaluation of a study effect for Study ATHENA-MONO in the PopPK model. A study effect was tested on CL, central volume of distribution (Vc), and F1 in a univariate fashion with all other model parameters (THETAs, OMEGAs, and SIGMAs)

Previous modelling experience

A PopPK model was previously established using rucaparib PK data based on IV and oral data from Study 1014, and oral data from Studies 10 and ARIEL2. The overall rucaparib PK was well described by a two-compartment model with sequential zero-order release, first-order absorption, and first-order elimination. The model structure and parameters are provided in Figure 1 and Table 2.

Figure 1 Structure of existing PopPK Model



CL = clearance, Cp = plasma concentration, D1 = duration of the zero-order absorption process, F1 = bioavailability in the central compartment, Ka = absorption rate constant, Vc = volume of the central compartment, Vp = volume of the peripheral compartment.

Table 2 Parameters of existing PopPK Model

Final QS-CLV-006 Model (613)

Description	NONMEM Estimate	Bootstrap Estimate	Bootstrap 95% CI	%CV	Shrinkage
θ_1 CL, L/hr	10.26	10.36	(8.573, 12.82)	48.8	8.84
θ_2 Vc, L	16.92	16.98	(13.73, 20.33)	-	-
θ_3 Q, L/hr	17.44	17.9	(14.55, 22.96)	-	-
θ_4 Vp, L	165.9	164.7	(132.5, 199.7)	-	-
θ_5 Ka, hr^{-1}	0.07175	0.0732	(0.05712, 0.0891)	63.5	5.21
θ_6 D1, hr	0.6188	0.6195	(0.4771, 0.812)	111	11.8
θ_7 LF1	-0.5234	-0.5175	(-0.828, -0.1276)	-	-
F1	0.3720	0.3734	(0.3041, 0.4681)	-	-
θ_8 ResErr(Prop), all patients	0.3821	0.3772	(0.3573, 0.3991)	-	-
θ_9 ResErr(Add), intensively sampled patients	0.8314	0.8364	(0.5435, 3.082)	-	-
θ_{10} ResErr(Add), sparsely sampled patients	378.9	377.2	(269.1, 458)	-	-
θ_{11} F1, fasted or a high-fat meal, ≤480 mg	-0.3802	-0.3768	(-0.7392, -0.09048)	-	-
θ_{12} F1, fasted, >480 mg	-0.2017	-0.2686	(-0.7004, 0.1833)	-	-
θ_{13} F1, high-fat, >480 mg	0.5903	0.5518	(0.05534, 1.086)	-	-
θ_{14} Ka, fasted	0.4009	0.4501	(0.1151, 1.072)	-	-
θ_{16} dose on Ka	-0.3249	-0.3012	(-0.4082, -0.1776)	-	-
θ_{17} albumin on CL	0.7202	0.7226	(0.2873, 1.159)	-	-
θ_{18} CLCR on CL	0.3130	0.3213	(0.1969, 0.4463)	-	-
η_1 IIV D1, intensively sampled patients	1.241	1.192	(0.9131, 1.608)	-	-
η_2 IIV KA, intensively sampled patients	0.4035	0.3975	(0.2809, 0.5237)	-	-
η_3 IIV CL, all patients	0.2386	0.2332	(0.1692, 0.3357)	-	-

CL = clearance, CV = coefficient of variation, D1 = duration of the zero-order absorption, F1 = absolute bioavailability, IIV = inter individual variability, LF1 = logit of bioavailability, Ka = absorption rate, Vc = central volume of distribution, Q = inter-compartmental clearance, ResErr(Prop) = proportional residual error, ResErr(Add) = additive residual error, Vp = peripheral volume

External validation of the model with sparsely sampled data from two additional studies (ARIEL3 in second line maintenance patients, and TRITON2 and TRITON3 in mCRPC patients) showed no clinically meaningful differences in PK across indication or sex.

Model development

Model development was mostly based on a preliminary PopPK dataset. The final model was re-estimated using the final dataset. Changes in PK data between the two were minimal. The final dataset for PopPK model development included 1 482 observation records from 403 patients treated with rucaparib in ATHENA-MONO. The preliminary dataset included 1481 observation records from 403 patients. Of the 1482 observations in the final dataset, 60 (4.05%) were BQL. In addition to the BQL observations, 103 non-BQL samples collected more than 150 hours after dose were excluded from the analysis as potential

data errors, given the expected 36 hour half-life for rucaparib. An additional 1 record where the sample was missing and 19 outliers were also excluded. All data records excluded from the analysis were kept in the dataset and flagged for exclusion.

After the exclusions listed, 396 patients with at least one adequately documented rucaparib dose administration and at least one non-BQL, non-excluded PopPK concentration after the dose were evaluable for PopPK, with 1299 observations. A summary of patients and observations is provided in Table 3.

Table 3 Number (%) of Subjects and Observations in the PopPK Population

	Oral Rucaparib + IV Placebo
	(N = 425)
PK Data Available	
has PK data	403 (94.8%)
no PK data	22 (5.2%)
Evaluable	
PK-evaluable	396 (98.3%)
Not PK-evaluable	7 (1.7%)
Number of Non-Missing, Non-BLQ Observations	1482
Number of BLQ	60
Number of Missing Observations	1
Number of Observations with TAD>150 hrs	103
Number of Outliers	19
Total Number of Observations in Analysis Dataset	1299

IV = intravenous; BLQ = below the limit of quantification; PK = pharmacokinetics; TAD = time after dose

The median rucaparib concentration in ATHENA-MONO was similar to the medians observed in the OC maintenance and mCRPC study, and lower than the median observed in ARIEL2. Estimates of variability (coeficient of variation(CV)) were comparable across the four studies, and observed PK concentrations were largely overlapping.

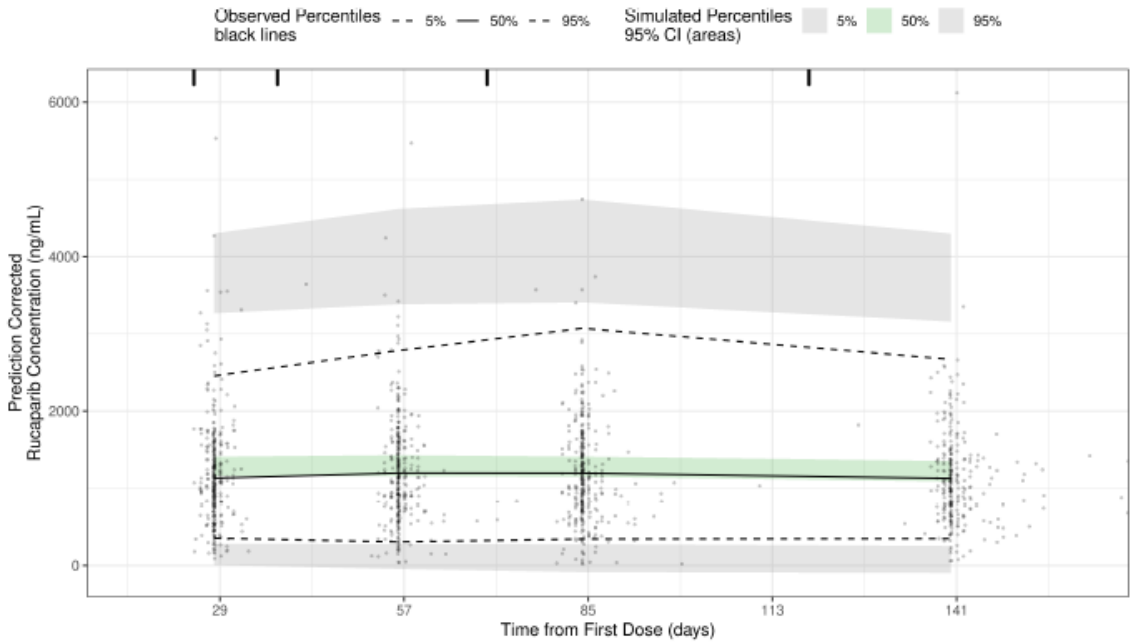
External Validation of the Existing PopPK Model

The ability of the existing model to describe the ATHENA-MONO data was evaluated by prediction corrected visual predictive check (pcVPC).

The VPC was plotted versus nominal time since first dose (Figure 2). The VPC was also plotted versus time after dose and stratified by PK sampling visit to allow more detailed evaluation of the time course of the post-dose samples (Figure 3 and Figure 4).

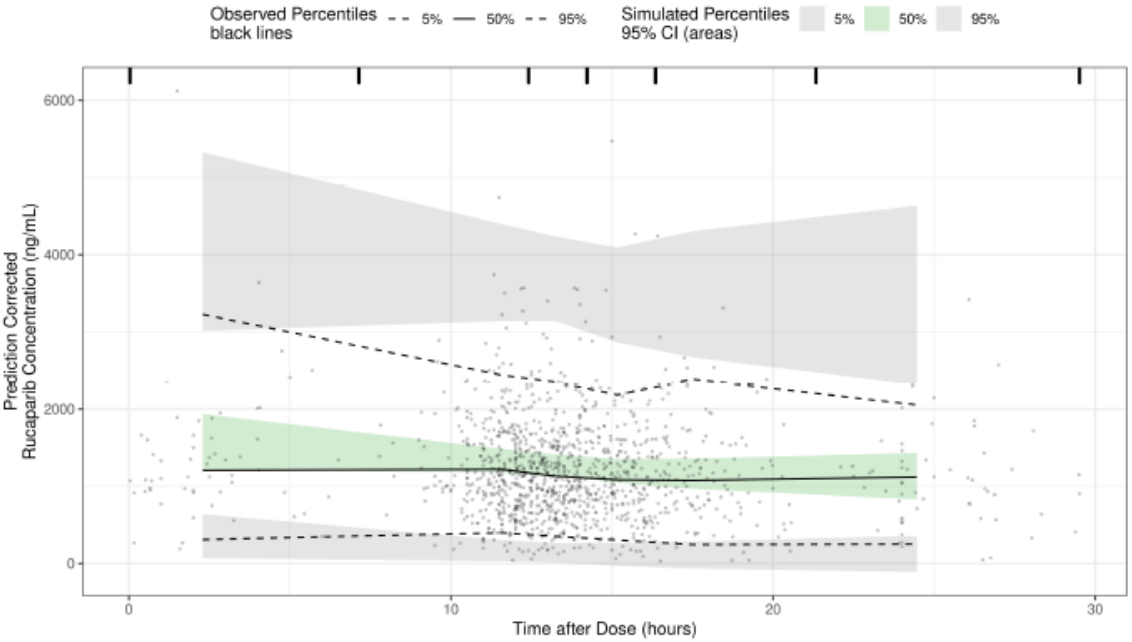
The VPC as a function of Time from First Dose (Figure 2) shows that while the median ATHENA-MONO PK data were well described (i.e., the solid black line falls within the green shaded region), the variability was overestimated (i.e., the dashed lines fall outside the grey shaded regions). When plotted as a function of time after dose (Figure 3), the trends are similar; however, the variability at the 5th percentile (lower dashed line) is mostly contained within the appropriate grey shaded region. Trends are similar when stratified by study visit (Figure 4).

Figure 2 External Validation of the Existing PopPK Model, Time Since First Dose



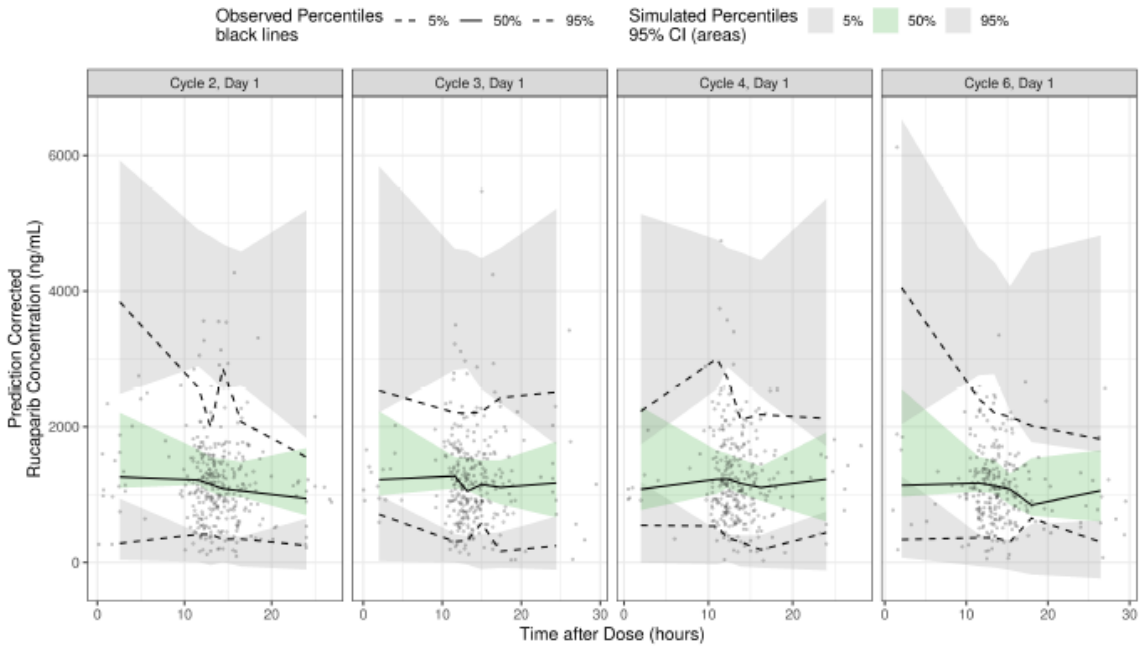
Note: The solid black line represents the median of the observed data. The dashed black lines represent the 5^{th} and 95^{th} percentiles of the observed data. The shaded regions encompass 95% of the simulated values (n=1000) of the predicted medians (green), 5^{th} (gray), and 95^{th} (gray) percentiles. Data points (dots) represent the individual observations.

Figure 3 External Validation of the Existing PopPK Model, Time After Dose



Note: The solid black line represents the median of the observed data. The dashed black lines represent the 5^{th} and 95^{th} percentiles of the observed data. The shaded regions encompass 95% of the simulated values (n=1000) of the predicted medians (green), 5^{th} (gray), and 95^{th} (gray) percentiles. Data points (dots) represent the individual observations.

Figure 4 External Validation of the Existing PopPK Model, Time After Dose, Stratified by Visit



Note: The solid black line represents the median of the observed data. The dashed black lines represent the 5th and 95th percentiles of the observed data. The shaded regions encompass 95% of the simulated values (n=1000) of the predicted medians (green), 5th (gray), and 95th (gray) percentiles. Data points (dots) represent the individual observations.

Additional Model Evaluation

To address the potential misfit in the variance model observed in the external validation of run003, the residual error model parameters were re-estimated. Table 4provides a summary of the key steps in the model development process.

Table 4 Summary of Key Models Evaluated

Run	Ref	OFV	ΔOFV	CondNum	Description	Selected
001	613	32650.4	–	39.0	estimate posthocs only maxeval=0, no outlier exclusions	yes
002	001	17798.4	–		estimate posthocs only MAXEVAL=0; exclude 14 outliers	yes
003	002	17754.6	-43.8		estimate post hocs only MAXEVAL=0 (remove addl outliers from subject 30010004)	yes
005	003	17340.6	-414.1	9.0	estimate residual error parameters	yes
012	005	17323.2	-17.4	9.0	estimate study effect on CL	no
013	005	17300.9	-39.7	6.0	estimate study effect on V2	no
014	005	17299.1	-41.5	8.0	estimate study effect on F1	no

Note: run613 is the final model from the previous analysis
OFV = Objective Function Value, ΔOFV = change in OFV, MAXEVAL= maximum number of evaluation steps, CL = clearance, V2 = central volume, F1 = bioavailability

When the additive and proportional error parameters were re-estimated, the OFV of the model was reduced by 414 points (run005). Model diagnostic plots also showed improvement in predictions at the highest exposures (Table 5). The additive residual error was reduced from 379 ng/mL to 200 ng/mL. The proportional residual error was reduced from 38.2% to 22.6%.

Next, study effects were tested separately on estimates of CL, Vc, and F1 in the resulting model. All models were tested with existing covariate effects fixed and random effects constrained to their estimates for the existing model (run613). A comparison of relevant model parameter estimates is provided in Appendix A.5. Each study effect was estimated as a multiplicative effect on the parameter of interest. In each model, the study effect was statistically significant with $p<0.001$.

The study effect on Vc (run013) was well estimated (multiplicative factor of 16.2, 95% CI 4.04 to 28.4); however, the resulting estimate of Vc was very large, suggesting a substantial increase in Vc for the ATHENA-MONO population (274 L vs 16.9 L). Given that post-dose PK samples were not collected in ATHENA-MONO, thus containing little information of central volume, the study effect on Vc was not accepted.

The study effects on F1 (run014) and CL (run012) were also well estimated, with estimates of 0.830 (2.8% relative standard error (RSE)) for F1 and 1.11 (2.4% RSE) for CL. The 95% CI of the multipliers for F1 and CL were 0.784 to 0.876 and 1.06 to 1.17, respectively. The estimates of F1 and CL for ATHENA-MONO were 30.9% and 11.4 L/hr, respectively, compared to 37.2% and 10.3 L/hr for the existing PopPK model. Both of these effects were statistically significant and well estimated; however, neither met the criteria for clinical significance (20% change in the typical value). Hence, both study effects were rejected.

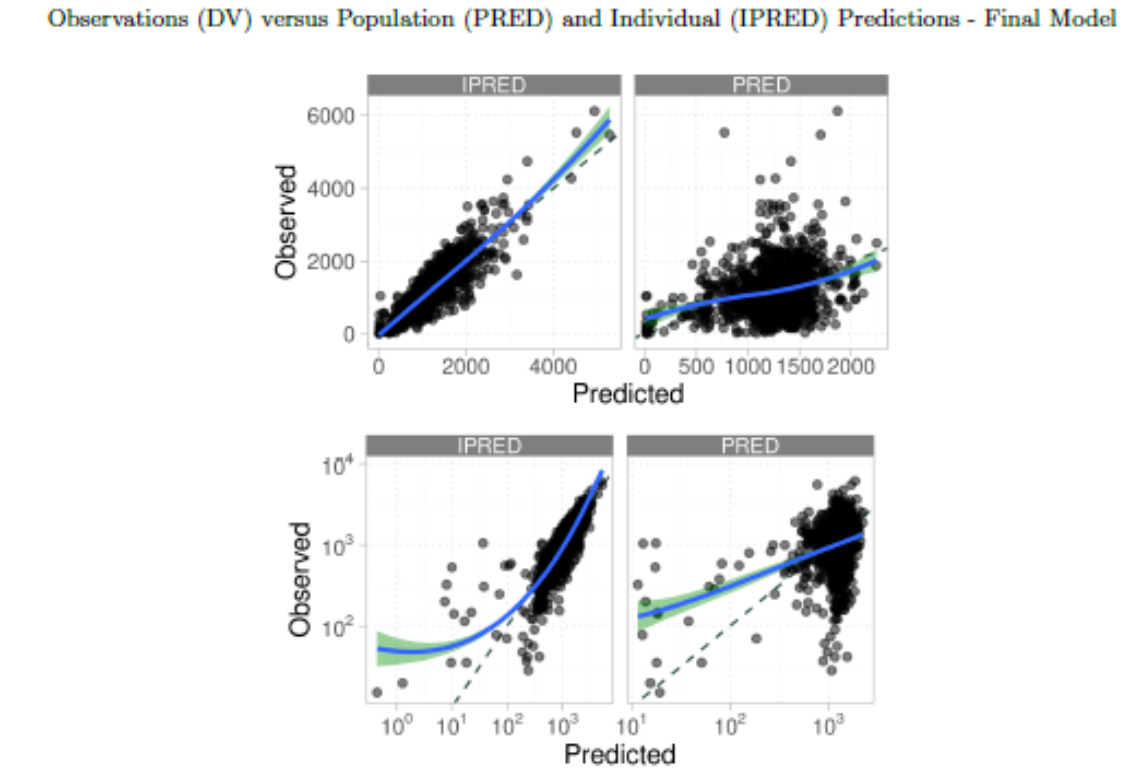
Run005 was selected as the preliminary final PopPK model for ATHENA-MONO. When the final PopPK dataset became available, the analysis dataset was used to re-estimate the preliminary final model (run005). Final residual error estimates for run102 were consistent with those from run005. The model parameters for run102 are provided in Table 5.

Table 5 Final Model (run102) Parameters

Parameter	Descriptor	NONMEM Estimate	%CV
θ_1	CL, L/hr	10.3	.....
θ_2	Vc, L	16.9	.....
θ_3	Q, L/hr	17.4	.....
θ_4	Vp, L	166.	.....
θ_5	Ka, 1/hr	0.0717	.....
θ_6	D1, hr	0.619	.....
θ_7	F1	0.372	.....
θ_8	ResErr, proportional (all patients)	0.224 (7.5 RSE)	7.5
θ_9	ResErr, ng/mL, additive (intensive)	0.831	.....
θ_{10}	ResErr, ng/mL, additive (sparse)	199. (12.5 RSE)	12.5
θ_{11}	fasted or high-fat meal on F1, <=480 mg	-0.380	.....
θ_{12}	fasted on F1, >480 mg	-0.202	.....
θ_{13}	high-fat meal on F1, >480 mg	0.590	.....
θ_{14}	Ka, fasted, 1/hr	0.401	.....
θ_{16}	dose on Ka	-0.325	.....
θ_{17}	albumin on CL (power model)	0.720	.....
θ_{18}	CLCR on CL (power model)	0.313	.....
$\omega_{1.1}$	$\omega^2 IIV_{D1}$, intensive	1.24	.....
$\omega_{2.2}$	$\omega^2 IIV_{Ka}$, intensive	0.404	.....
$\omega_{3.3}$	$\omega^2 IIV_{CL}$, all patients	0.239	.....

Note: CL = clearance, CLCR = creatinine clearance, CV = coefficient of variation, D1 = duration of the zero-order absorption, F1 = bioavailability, IIV = inter individual variability, Ka = absorption rate, Q = inter-compartmental clearance, ResErr = residual error, RSE = relative standard error (in %) Vc = central volume, Vp = peripheral volume

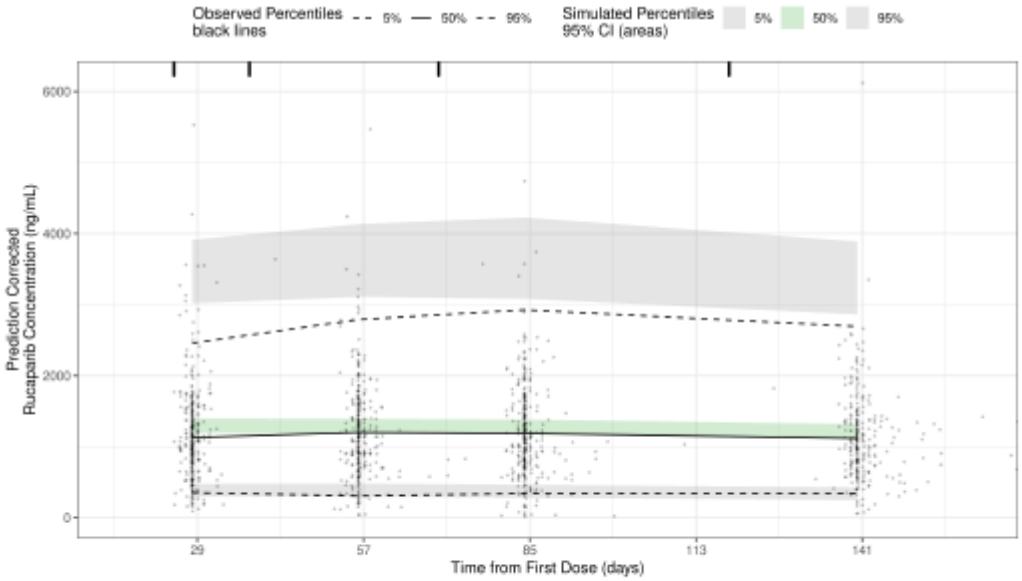
Figure 5 GOF Plots - Final Model



The ability of run102 to describe the ATHENA-MONO data was again evaluated by pcVPC (Figure 6). Similar to run005, the median of the observed data fell within the 95% simulated CI for the median. The position of the observed median on the lower edge of the CI suggests that although the model generally describes the central tendency, there may be a slight trend toward overprediction of the median trough concentration. The overprediction is consistent with the study effect on CL (run012) or F1 (run014), each of which was statistically significant, but not clinically meaningful. The 95th percentile of the observed

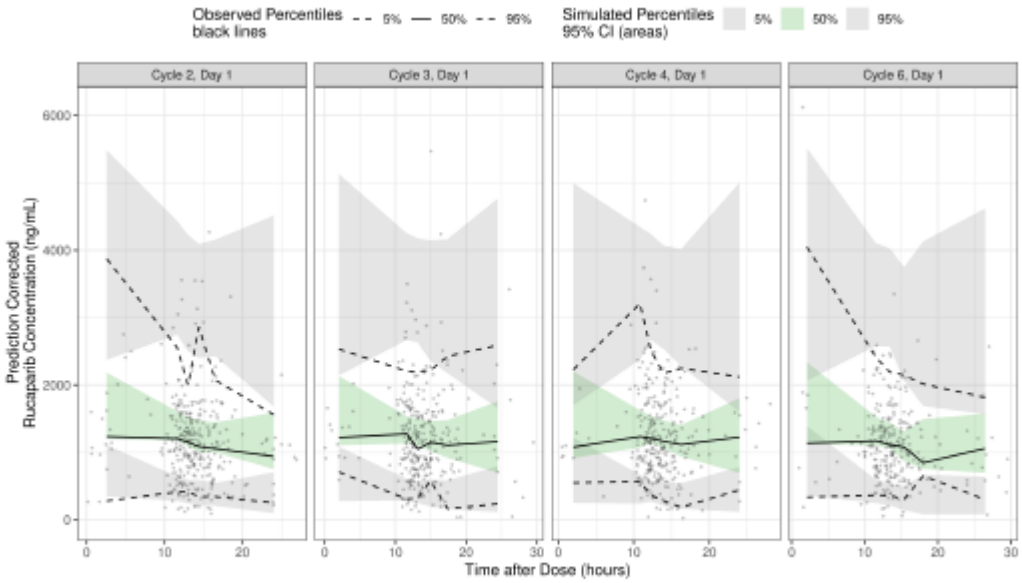
data also falls just below the corresponding 95% CI. However, the 5th percentile of the observed data falls within the corresponding 95% CI. When plotted as a function of time after dose (Figure 7), the observed median and 5th percentile fall within the corresponding 95% CI at each nominal visit. The overprediction of the 95th percentile of the observed data near 12 hours after dose persists across each nominal visit. Overall, the model describes the central tendency of the data reasonably well, but may overestimate the upper end of variability. The re-estimated model (run102) was selected as the final model for this analysis.

Figure 6 pcVPC of the Updated PopPK Model, Time from First Dose



Note: The solid black line represents the median of the observed data. The dashed black lines represent the 5th and 95th percentiles of the observed data. The shaded regions encompass 95% of the simulated values (n=1000) of the predicted medians (green), 5th (gray), and 95th (gray) percentiles. Data points (dots) represent the individual observations.

Figure 7 pcVPC of the Updated PopPK Model, Stratified by Visit



Note: The solid black line represents the median of the observed data. The dashed black lines represent the 5th and 95th percentiles of the observed data. The shaded regions encompass 95% of the simulated values (n=1000) of the predicted medians (green), 5th (gray), and 95th (gray) percentiles. Data points (dots) represent the individual observations.

Individual PK parameter estimates from the final re-estimated model (run102) were used to simulate exposures for the ER analyses of efficacy and safety.

2.3.3. Pharmacodynamics

Not applicable.

2.3.4. PK/PD modelling

Exposure-response

All placebo and PK-evaluable rucaparib treated patients were included in the ER datasets for efficacy and safety. Placebo subjects were included to allow assessment of the magnitude of treatment effects in addition to rucaparib exposure effects. Hence, both the exposure-efficacy and the exposure-safety analysis datasets included 506 patients, including 396 PK evaluable rucaparib patients and 110 placebo patients.

Exposure variables were calculated from individual PK parameter estimates from the population PK analysis, the nominal dose and frequency, and actual dosing information. The steady-state daily area under the concentration vs. time curve at steady state (AUCss), minimum concentration at steady state (Cmin;ss), and maximum concentration at steady state (Cmax;ss) were calculated for each patient using standard equations. Placebo patients had no rucaparib exposure, i.e., AUCss and Cmax;ss exposures were 0.

To account for dose adjustments and/or dose holds, the steady-state average PK parameters were calculated by multiplying the steady-state PK parameters by an average dose ratio.

Efficacy analysis

The exposure-efficacy analysis tested one endpoint: progression free survival (PFS) by RECIST v1.1 as assessed by the investigator.

The invPFS endpoint was modeled using cox-regression. Efficacy covariates included the following variables:

• HRD analysis group (tBRCA, non-tBRCA LOH high (+), non-tBRCA LOH low (-), and non-tBRCA LOH unknown)

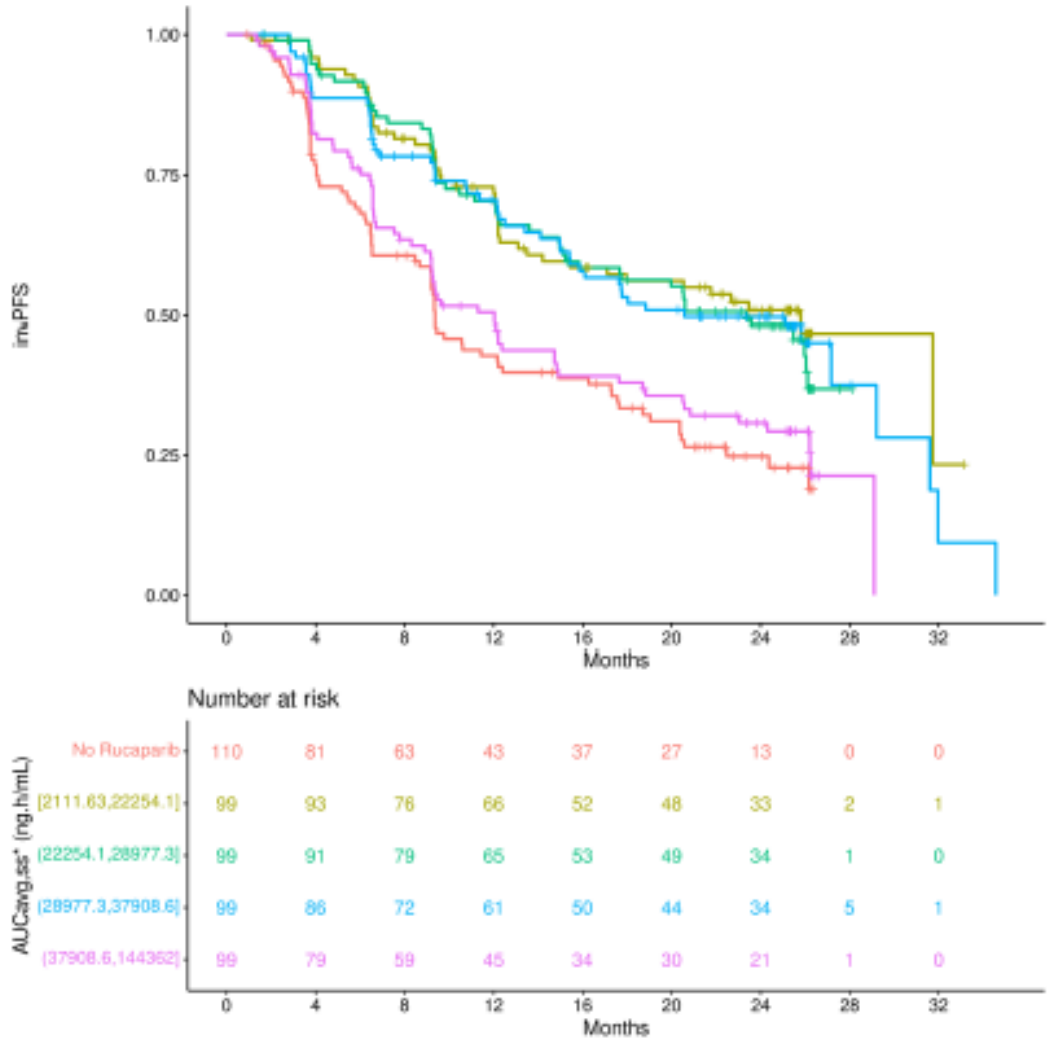
• Disease status post chemotherapy (no residual disease vs residual disease)

• Time of surgery (primary vs interval debulking)

Exposure-efficacy relationship

Figure 8 shows the Kaplan-Meier (KM) survival curve for invPFS stratied by exposure quartiles. Although the difference between the placebo and rucaparib treated groups was found to be statistically significant, no significant ER relationships were detected within the range of rucaparib exposures.

Figure 8 Exposure-Response Relationship for invPFS



invPRS = Progression-free survival by investigator; $AUC_{avg,ss}$ = average steady-state area under the concentration-time curve. The upper panel shows the Kaplan-Meier curves stratified by exposure quartile (colored from lowest exposure to highest: yellow, green, blue, purple). The plus signs (+) indicate censored patients. The number of patients per quartile at risk is indicated in the lower panel.

Exposure-efficacy covariate effects

Table 6 provides a summary of the linear exposure-response relationships for invPFS with or without adjustment for statistically significant covariates. The fits with no covariate adjustment are displayed graphically in Figure 8.

As shown in Table 5, two of the tested covariates were found to be significant for both the treatment and ER model: HRD analysis group and time of surgery. Disease status post frontline treatment was not found to be significant.

The covariate model parameter estimates for invPFS are provided in Table 7. For the HRD analysis group, all three non-tBRCA populations (LOH+, LOH-, and LOH Unknown) had increased relative risk compared to the tBRCA population. For time of surgery analysis group, the relative risk of progression was lower in the primary surgery group compared to the interval debulking group.

Table 6 Exposure-Efficacy Relationships with Covariates

Model	Efficacy Endpoint	p-value for model[a]		Significant Covariates (p<0.05)
		No covariate	Covariate adjusted	
Treatment	invPFS	<0.001	<0.001	· HRD analysis group[b] · Time of Surgery analysis group[c]
AUCavg,ss	invPFS	1.0	1.0	· HRD analysis group[b] · Time of Surgery analysis group[c]

Model = Treatment effect or exposure-response; invPRS = Progression-free survival by investigator; AUC,avg,ss = average steady-state area under the concentration-time curve; HRD = homologous recombination deficiency; – Not applicable;

[a] For a treatment effect model, the p-value is the significance level for the treatment effect in the model (compared to the null model). For an exposure-response model, the p-value is the significance level for the exposure-response relationship in the model (compared to the treatment effect model).

[b] HRD analysis groups include tBRCA, non-tBRCA LOH+, non-tBRCA LOH-, and non-tBRCA LOH unknown.

[c] Time of Surgery analysis groups include Primary Surgery and Interval Debulking.

Note: "Covariate adjusted" means that the model includes significant covariates. The p-value is the significance level for the exposure variable.

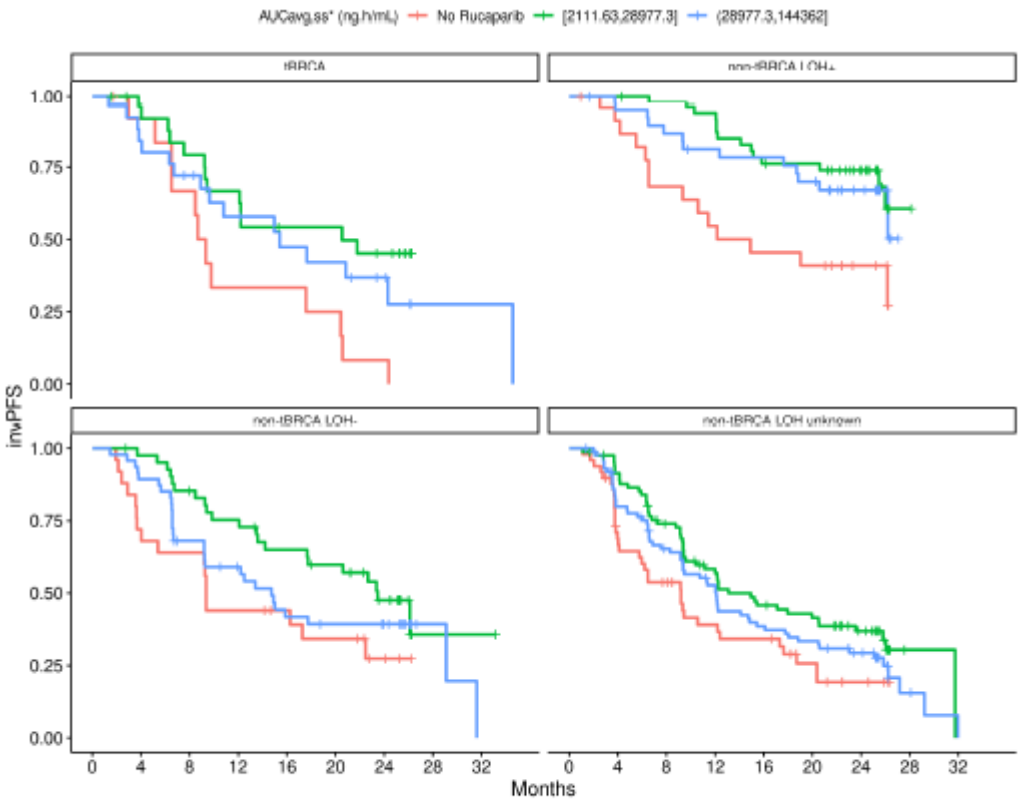
Table 7 Model Parameter Estimates for invPFS

Parameter	Estimate	HR	SE, estimate	z	Pr(>|z|)
slope, (AUCavg,ss* - median)	-3.87e-06	1.00e+00	3.81e-06	-1.02e+00	3.10e-01
Non-tBRCA LOH+	7.52e-01	2.12e+00	2.00e-01	3.76e+00	1.68e-04
Non-tBRCA LOH-	9.90e-01	2.69e+00	1.77e-01	5.58e+00	2.35e-08
Non-tBRCA LOH Unknown	6.61e-01	1.94e+00	2.25e-01	2.94e+00	3.32e-03
Primary Surgery	-5.63e-01	5.70e-01	1.23e-01	-4.58e+00	4.63e-06

invPRS = Progression-free survival by investigator; HR = hazard ratio; SE = standard error; z = Wald statistic; AUC,avg,ss = average steady-state area under the concentration-time curve; tBRCA = deleterious germline or somatic BRCA mutation; LOH = loss of heterozygosity.

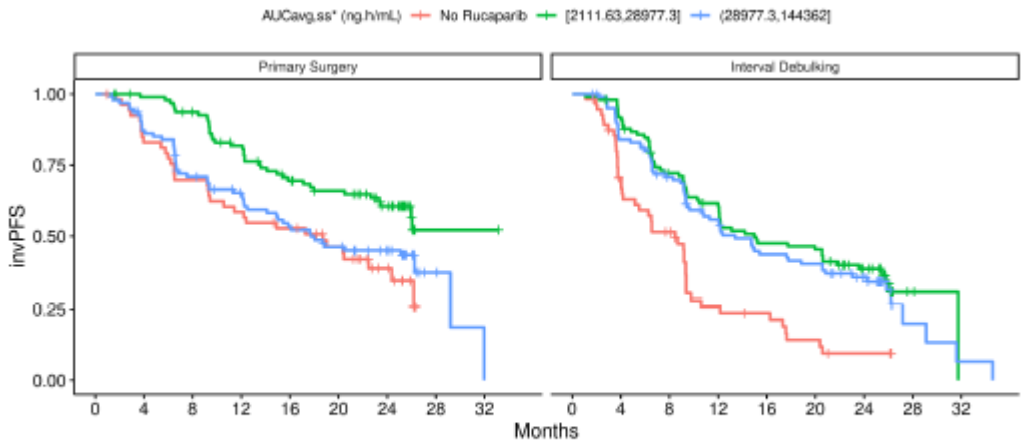
Multivariate relationships for invPFS with exposure and each of the two significant covariates are shown in Figure 9 and Figure 10. Each Figure shows the KM survival curves for invPFS stratified by exposure (placebo, low AUCavg,ss, and high AUCavg,ss) and stratified by one of the statistically significant covariates.

Figure 9 Exposure-Response Relationship for invPFS Stratified by HRD Analysis Group



invPRS = Progression-free survival by investigator; $AUC_{avg,ss}$ = average steady-state area under the concentration-time curve. tBRCA = deleterious germline or somatic BRCA mutation; LOH = loss of heterozygosity. Kaplan-Meier curves stratified by high or low exposure (green: below median exposure, blue: above median exposure). The plus signs (+) indicate censored patients.

Figure 10 Exposure-Response Relationship for invPFS Stratified by Time of Surgery



invPRS = Progression-free survival by investigator; $AUC_{avg,ss}$ = average steady-state area under the concentration-time curve. Kaplan-Meier curves stratified by high or low exposure (green: below median exposure, blue: above median exposure). The plus signs (+) indicate censored patients.

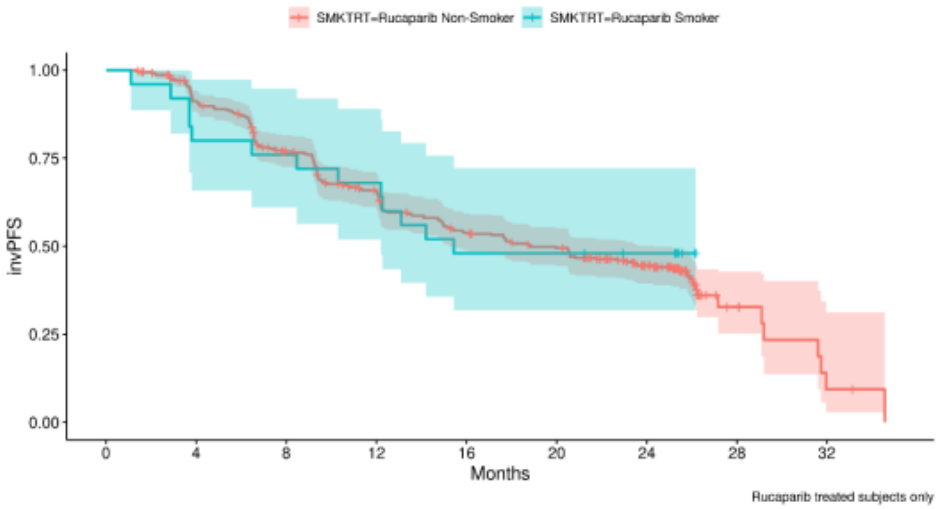
Impact of exposure on invPFS in current smokers and non-current smokers

Exposure variables were calculated from individual pharmacokinetic (PK) parameter estimates from the final population PK (PopPK) model (run106). Parameter estimates were calculated based on the nominal dose and frequency and actual dosing information.

Exploratory and exposure-response (ER) analyses evaluating the impact of exposure on invPFS in current smokers and non-current smokers (i.e., former smokers, patients who never smoked, and patients with

unknown smoking status) and exposure-efficacy relationships in each population were completed. Figure 1 shows the Kaplan-Meier (KM) survival curve for invPFS in rucaparib-treated subjects for current smokers and non-current smokers.

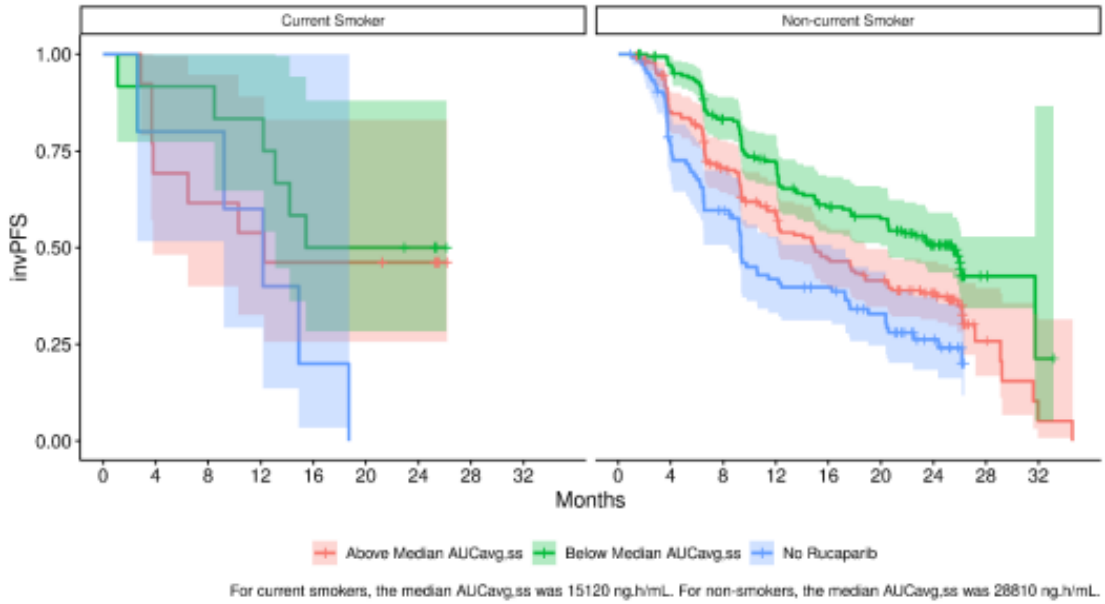
Figure 11 Kaplan-Meyer Curve for invPFS by Smoking Status in Rucaparib-Treated Subjects



Note: Rucaparib Non-Smokers includes PK-evaluable former smokers (N=79 rucaparib-treated), subjects who never smoked (N=283 rucaparib-treated), and subjects with unknown smoking status (N=9 rucaparib-treated). There were 25 rucaparib-treated PK-evaluable current smokers. The definition of "PK-evaluable" is provided in Section 3.3 of Clovis Oncology, 2022.
invPFS = Progression-free survival by investigator

Figure 12 shows the KM curve stratified by both exposure and smoking status. Given the limited number of rucaparib-treated current smokers (N=25), exposures were categorized as above or below the median of the average steady-state area under the concentration-time curve (AUCavg,ss) in the subpopulation (i.e., smokers vs non-smokers), rather than as exposure quartiles. Subjects in the placebo arm are included for comparison.

Figure 12 Exposure-Response Relationship for invPFS Stratified by Smoking Status



Note: "Non-current Smoker" panel includes former smokers, subjects who never smoked, and subjects with unknown smoking status. invPFS = Progression-free survival by investigator; AUC,avg,ss = average steady-state area under the concentration-time curve

Table 8 Exposure-Efficacy Relationships by Population

Population	Model	p-value	AIC
All subjects	Null model	--	3348.0
	Treatment effect	<0.001	3331.4
	AUCavg,ss	1.0	3350.0
Non-current smokers	Null model	--	3105.1
	Treatment effect	<0.001	3090.6
	AUCavg,ss	1.0	3107.0
Current smokers	Null model	--	109.3
	Treatment effect	0.123	109.0
	AUCavg,ss	1.0	109.7

Note: The p-value for the "Treatment effect" model compares the null model to a model with a treatment effect. The p-value for the AUCavg,ss model compares the ER model to the treatment effect model. AIC = Akaike Information Criterion; AUCavg,ss = average steady-state area under the concentration-time curve

The impact of smoking status on the ER relationship in the full population was also evaluated by testing smoking status as a covariate on the intercept and on the slope of the relationship. As in the original analysis, rucaparib exposure was forced into the model regardless of statistical significance. No statistically significant relationships were identified for smoking status on either the intercept or the slope of the relationship and no statistically significant ER relationships were observed (data not shown).

Safety analysis

The primary exposure-safety analysis tested treatment-emergent laboratory variables:

- Grade 3+ alanine aminotransferase (ALT) increase
- Grade 3+ neutrophil decrease

- Grade 3+ platelet decrease
- Grade 3+ leukocyte decrease
- Grade 3+ hemoglobin decrease
- hemoglobin maximum reduction from baseline
- Grade 2+ creatinine increase

Continuous endpoints (i.e., hemoglobin, maximum change from baseline) were modeled using linear or nonlinear regression. All other endpoints were binary and were modeled using linear logistic regression.

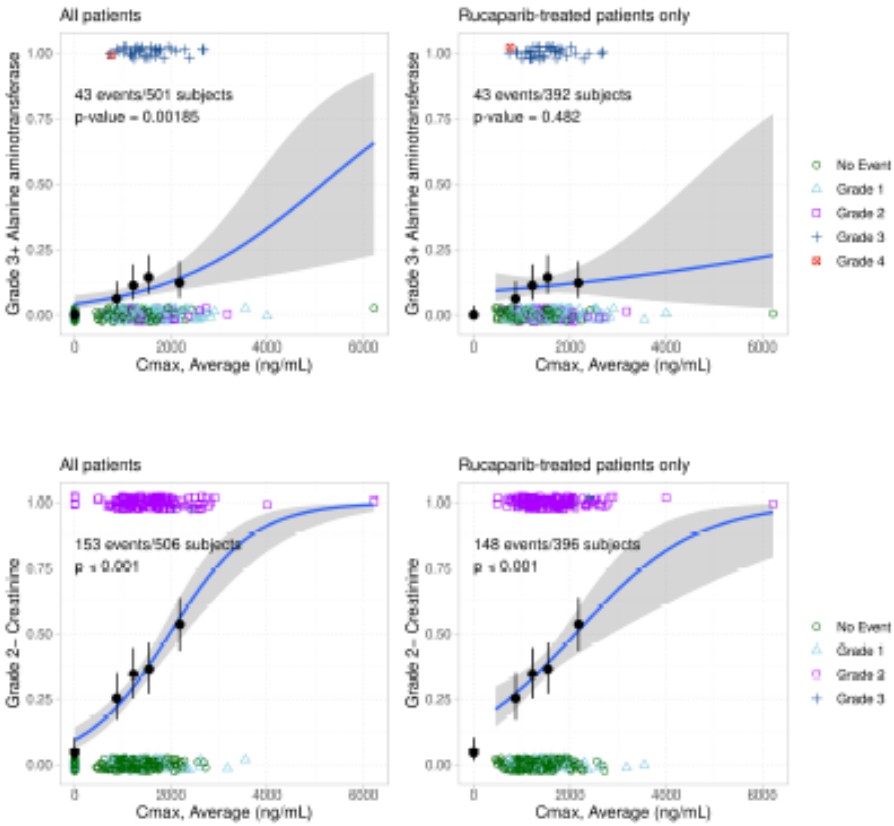
Safety covariates included only HRD analysis group (tBRCA, non-tBRCA LOH high (+), non-tBRCA LOH low (-), and non-tBRCA LOH unknown).

Models were compared to assess whether the exposure-response model provided a better fit to the data than the treatment effect model.

Exposure-safety relationship

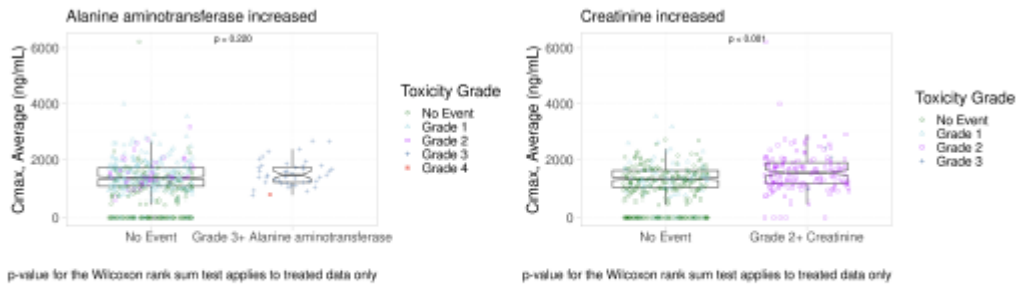
Figure 13 and Figure 14 show ER relationships between ALT or creatinine and exposure and boxplots of exposure in patients with or without events, respectively. The incidences of Grade 3+ ALT and Grade 2+ creatinine were greater in the rucaparib treated patients than in the placebo patients.

Figure 13 Logistic Regression Relationships for ALT and Creatinine for All Patients and Rucaparib-Treated Patients Only



Note: The solid black points represent the mean exposure and event rates in the placebo treated patients or patients stratified by rucaparib exposure quartile. Vertical black bars represent the 5th to 95th percentile CI on the event rate. The solid blue line indicates the logistic regression model fit (regardless of p-value). The shaded gray region represents the 95% CI on the modeled event rate. The p-value for the slope is indicated. The data points for patients with and without an event are shown at the top and bottom of the plots, respectively. The maximum concentration (C_{max}), Average is the daily steady-state C_{max} adjusted from the nominal dose to the average dose.

Figure 14 Boxplots of Average Cmax in Rucaparib-Treated Patients Stratified Based on Grade 3+ ALT or Grade 2+ Creatinine Events



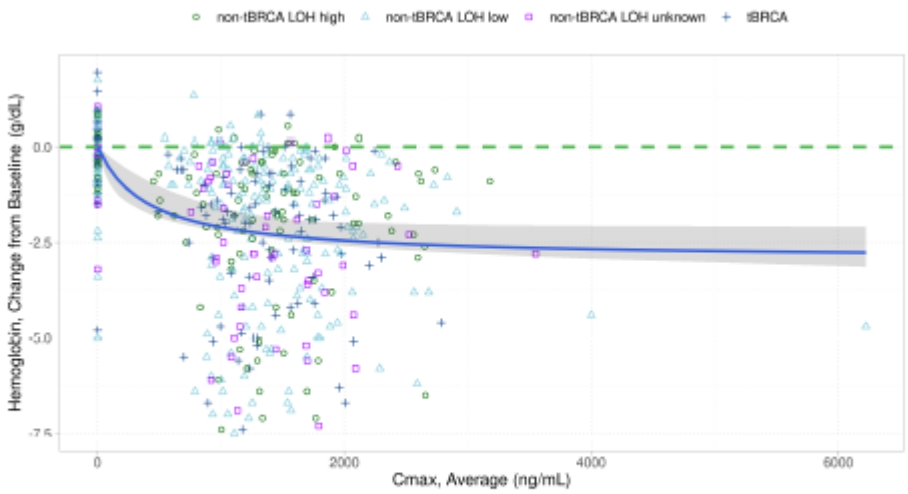
Note: Boxplots show the C_{max} distributions, stratified by response in rucaparib-treated patients. The C_{max}, Average is the daily steady-state C_{max} adjusted from the nominal dose to the average dose. The boxes denote the interquartile range and median, the whiskers extend to 1.5 times the interquartile range, and the dots represent the raw data.

For Grade 3+ lymphocytes, Grade 3+ neutrophils, and Grade 3+ platelets, the relationship with average Cmax is not statistically significant with or without placebo patients. Consistent with the logistic regression results, exposure estimates were not statistically different for patients with or without Grade 3+ lymphocytes or Grade 3+ platelets. The average Cmax was statistically lower in patients with Grade 3+ neutrophil events than in patients without Grade 3+ neutrophil events.

Relationships between Grade 3+ white blood cell (WBC) events and average Cmax were not statistically significant with or without placebo patients and the average Cmax was not statistically different in patients with and without Grade 3+ WBC events. For Grade 3+ anemia, the relationship with exposure was statistically significant with placebo patients, but was not significant when limited to rucaparib patients. The rucaparib treatment effect was predictive of Grade 3+ anemia, but the ER relationship was not. Exposures in patients with Grade 3+ anemia were not statistically higher than patients without Grade 3+ anemia.

The nonlinear relationship between exposure and the maximum Hb change from baseline (CFB) was also statistically significant, as shown in Figure 15. Linear and maximal response (Emax) models were compared with and without placebo patients. The Emax model shown was selected over a linear model based on the model fit, and the saturable relationship with average Cmax was confirmed excluding placebo patients (Appendix A.11.8). The model fit shown estimated the concentration producing the half-maximal response (EC50) to be 400 ng/mL (95% CI 106 to 1510 ng/mL), with an Emax of -2.94 g/dL (95% CI -3.84 to -2.04 g/dL) Hb CFB. Following 600 mg rucaparib BID, the median average Cmax was 1370 ng/mL. At the median exposure, the mean maximum Hb CFB was -2.28 g/dL with the 5th to 95th percentile CI of -2.39 to -1.88 g/dL.

Figure 15 CFB Hb as a Function of Average Cmax in All Patients



Note: The solid blue line in the plot is the nonlinear regression model fit and the shaded blue region represents the 95% CI for the model fit. The green dashed line indicates 0 g/dL CFB Hb.

Exposure-safety covariate effects

The impact of HRD on the intercept of the ER relationships with safety endpoints was also assessed. The effect of HRD was not statistically significant for any of the endpoints. Additionally, the inclusion of the covariate effect in the model did not increase the statistical significance of the ER relationship.

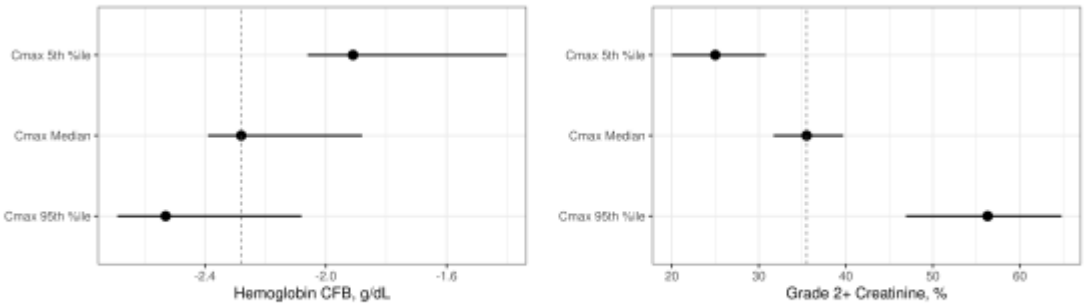
Exposure-safety predicted effects

Figure 16 shows forest plots for Grade 2+ creatinine in rucaparib-treated patients and CFB Hb in all patients. For these two endpoints, there was a significant ER. The nominal response for each safety

endpoint with a statistically significant ER relationship was estimated at the median average Cmax following 600 mg rucaparib BID.

The predicted incidence and 90% CI of Grade 2+ creatinine was 35.5% (31.7 to 39.7%). The predicted maximum Hb CFB at the median rucaparib Cmax was -2.28 g/dL (-2.39 to -1.88 g/dL).

Figure 16 Forest Plots Showing Effects of Exposure on Safety Endpoints



Note: Cmax = the daily steady-state C_{max} adjusted from the nominal dose to the average dose. HRD was not statistically significant for any endpoint.

2.3.5. Discussion on clinical pharmacology

The clinical pharmacology update include data from the ATHENA-MONO, Arm B (oral rucaparib + IV placebo) and Arm D (oral placebo + IV placebo).

The final dataset for the current Population PK model development included 1482 observation records from 403 patients treated with rucaparib in ATHENA-MONO.

PK samples of rucaparib below the lower limit of quantification (LLQ) were low (3.89 %) and were excluded from the analysis. M1 method for handling BLQ-data is considered acceptable.

The population PK model development of rucaparib includes the re-use of the PPK model previously established in the initial marketing authorisation application (EMEA/H/C/004272) based on a pool dataset from Study A4991014, Study 10, and ARIEL2 to support the treatment as monotherapy of patients with BRCA-mutated, recurrent ovarian cancer. The initial PPK model was retested (procedure EMEA/H/C/0004272/II/0001) to support the second-line maintenance treatment of recurrent ovarian cancer with data form Study ARIEL3 (model 613). However, several concerns were raised regarding model structure and variability by the regulatory authorities, which have been also identified in the current analysis (model misspecification of inter-individual random effects, large variability, empirical and confusing covariate effects). The model was updated following the recommendations (procedure EMEA/H/C/0004272/II/0002). The new model (2031a) provides a more rational description of rucaparib absorption, considering a saturable absorption through Michaelis-Menten kinetics and transit absorption compartments following first-order kinetics, which represents a more mechanistic pharmacokinetic framework enabling the identification of complex absorption mechanisms that are affecting rucaparib. The Applicant states that the initial model was selected in this analysis because in the ATHENA-MONO there were not post-dose pharmacokinetic samples that could inform the semi-mechanistic absorption model and also because the benefit of a third compartment in this new model is minimal when no IV data is included. Therefore, the use of this model could lead to an unstable and over-parameterized model, which is accepted.

Both models initial and new were re-estimated using the ATHENA-MONO dataset with all parameters fixed other than the residual error to model 613 (run 102) and model 2031a (run 201), respectively. The minimal difference between the OFV revealed no statistical difference in model fit to the observed data. VPC showed that run102 (model 613) provides a better description of the data as the media 50% percentile is within the 50% simulated percentile, but very little differences in longitudinal PK profile prediction were observed across both models. Furthermore, comparison of steady-state exposures from both models appear to be similar. Therefore, the overall performance of the updated model provides very similar performance compared to the initial model for the ATHENA-MONO dataset.

The covariate analysis demonstrates the statistical significance of smoking status on CL and study effect on F1. A drop of 82 units in the OFV from the base model was observed when both covariates were included in the population PK model. The Applicant justified the exclusion of the significant covariates (study effect on bioavailability and smoking status on clearance) due to several reasons. The study effect on bioavailability was removed based on the analysis plan established for the development of the original popPK model in ovarian cancer (QS-CLV-006), where categorical covariates with less than 20% difference with the reference population value were removed. The rationale could be accepted.

The impact of covariates was evaluated on simulated steady-state exposure metrics from the final model (AUC,ss, Cmax,ss and Cmin,ss) and observed Cmin for 396 patients from the ATHENA-MONO. The covariates evaluated included patients demographics, smoking status, ECOG group, baseline albumin, disease status and organ function. Based on the graphical evaluation, relevant PK differences due to smoking status, age, albumin, creatinine clearance and renal impairment were observed. However, this simulation analysis does not represent a formal clinical relevance assessment because it does not allow to understand quantitatively the predicted magnitude of change associate to each covariate effect (without including inter-individual random effects) over exposure endpoints. Subsequently, the Applicant provided a formal forest plot analysis including the covariates evaluated in order to understand whether differences in PK are expected. No clinically relevant changes in exposure were predicted due to changes in albumin, creatinine clearance and study effect. However, approximately half of the exposure is expected in smoking vs non-smoking patients.

The exposure-response analysis included 506 patients, including 396 PK evaluable rucaparib patients and 110 placebo patients.

In the efficacy analysis, the area under the concentration at steady state (AUCss) vs. time was calculated for each patient derived from the PPK analysis and the average exposure parameters were calculated based on actual doses.

PFS by RECIST v1.1 as assessed by the investigator was used as efficacy outcome in the exposure efficacy analysis which is endorsed. No statistically significant exposure-efficacy relationship was established. Kaplan-Meier curves stratified by exposure quartiles (Figure 8) showed that fourth quartile and placebo have similar invPFS, however, first, second and third quartiles have similar and longer invPFS. Same results were observed when patients were stratified by time of surgery, larger invPFS with lower exposure was found in patients in primary surgery. Although, it seems that there was a trend towards rucaparib exposure, the addition of an exposure-response relationship in the Cox regression analysis for invPFS was not statistically significant. Therefore, this trend could be due to confounding factor, patients who progressed quickly have less chances to have dose reductions and it could lead to misleading results.

In order to investigate the impact of smoking status, the Rucaparib Pop PK model was updated and the statistically significant effect of smoking status on CL was incorporated. Subsequently, exposure parameters (AUCavg,ss) were calculated from individual PK parameter estimates using the final model.

The exploratory exposure-efficacy evaluating the effect of the efficacy variable invPFS over time and stratified by smoking status showed that the 95% confidence intervals of both curves overlap. Kaplan-Meier curves stratified as above or below the median of AUVavg,ss and smoking status showed no significant differences over the range of rucaparib exposures for the full population, current smokers or non-current smokers, similar to previous reported results with the full population.

The exposure-efficacy relationships by population showed a statistically significant treatment effect for all subjects and in non-current smokers populations. Although, the effect on the smokers population should be interpreted with caution due to the small number of subjects in the study.

The MAH also evaluated the impact of smoking status as a covariate on the intercept and on the slope of the exposure-response relationship and no statistically significant relationship was identified. In spite of the fact that the data from this analysis has not been included in this submission.

Taking into account the results from the exploratory and exposure-response analysis, the differences observed in exposure in smoking patients does not seem to impact the efficacy profile of the drug. Therefore, no dose adjustments seems to be necessary in this subgroup of patients.

In the safety analysis, the maximum concentration at steady state (Cmax;ss) vs. time were calculated for each patient derived from the PPK analysis as the measure of exposure and the average exposure parameters were calculated.

The exposure-safety analysis demonstrated statistically significant relationships ($p < 0.05$) between Cmax,ss* and Grade 2+ creatinine increase and maximum Hb change from baseline even when rucaparib patients are evaluated alone. The model-predicted incidences of 35.5% of grade 2 + creatinine and a change in Hb of -2.28 g/dL for the typical patient (50^{th} percentile). Patients with higher exposure (95^{th} percentile) would show a change in Hb >2.5 g/dL and incidences of >55% of grade 2+ creatinine.

2.3.6. Conclusions on clinical pharmacology

Clinical pharmacology properties of rucaparib have been characterized in 403 patients treated with rucaparib in ATHENA-MONO and are supportive of the extension of indication as monotherapy for the maintenance treatment of adult patients with advanced (FIGO Stages III and IV) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to following completion of first-line platinum-based chemotherapy.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

In the ATHENA study rucaparib was administered at an initial dosage of 600 mg BID. This starting dosage of 600 mg BID rucaparib was selected as the recommended dose for Phase 2 and Phase 3 studies based on safety, tolerability, overall PK, and the efficacy profile observed in Study CO-338-010 (Study 10), which evaluated rucaparib as monotherapy in patients with advanced solid tumours. No new dose-finding studies have been conducted in conjunction with this application.

This is the currently approved dosage for rucaparib in the maintenance setting.

2.4.2. Main study(ies)

Title of Study

Study CO-338-087 (ATHENA): A multicenter, randomised, double-blind, placebo-controlled Phase 3 study in ovarian cancer patients evaluating Rucaparib and Nivolumab as maintenance treatment following response to front-line platinum-based chemotherapy

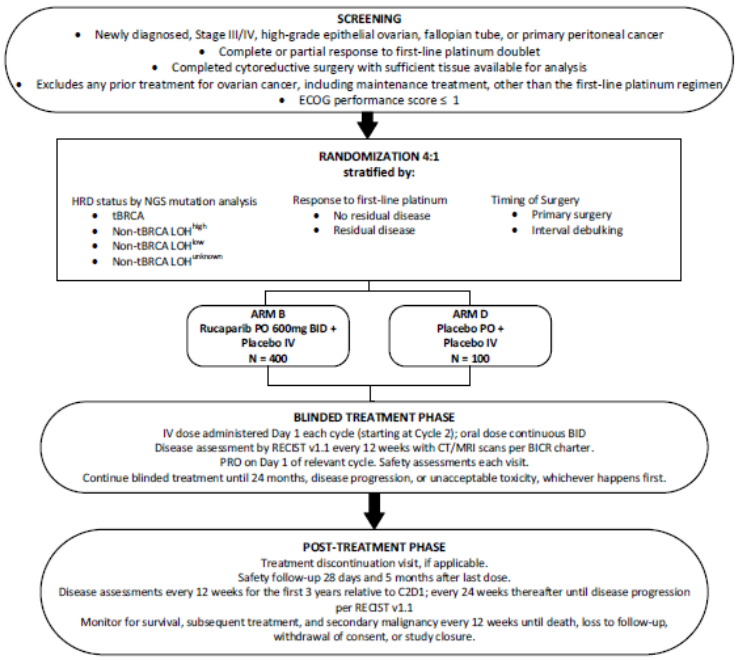
Methods

This is a randomised, multinational, double-blind, dual placebo-controlled, 4-arm, study evaluating rucaparib and nivolumab in combination and alone as maintenance therapy in newly diagnosed ovarian cancer patients who have completed first-line chemotherapy and who had a response. Only data for patients who were randomised to rucaparib monotherapy or placebo (ATHENA-MONO treatment comparison) were analysed and have been provided. This comparison was pre-planned.

The study consisted of a Screening Phase, a Treatment Phase, and a Post-treatment Phase. A schema of the ATHENA–MONO treatment comparison portion of the study is presented below in Figure 17.

In the Screening Phase, patients underwent screening assessments, including submission of tumour tissue for determining BRCA mutation status and percent LOH, within 120 days prior to randomisation. Eligible patients were enrolled/randomised within 8 weeks of the first day of the last cycle of chemotherapy.

Figure 17 Study Schema for ATHENA–MONO



Abbreviations: BID = twice a day; BRCA = breast cancer gene; CA-125 = cancer antigen 125; ECOG = Eastern Cooperative Oncology Group; gBRCA = germline BRCA; HRD = homologous recombination deficiency; IDMC = Independent Data Monitoring Committee; IV = intravenous; LOH = loss of heterozygosity; MRI = magnetic resonance imaging; NGS = next-generation sequencing; PO = oral; PRO = patient-reported outcome; Q4W = every 4 weeks; sBRCA = somatic BRCA; tBRCA = tumor tissue mutation in BRCA1 or BRCA2, includes gBRCA and sBRCA.

Prior to enrolment, patients were required to provide archival tumour tissue or a screening biopsy for central laboratory analysis of HRD status. A BRCA result (positive or negative) was required and non-tBRCA patients could have a result of LOH-high (LOH≥16%), LOH-low (LOH<16%), or LOH-unknown.

Study participants

Inclusion criteria

1. Had signed an Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved Informed Consent Form (ICF) prior to any study-specific evaluation.
2. Been ≥ 18 years of age at the time the ICF was signed (patients enrolled in South Korea, Taiwan, and Japan must have been ≥ 20 years of age at the time the ICF was signed).

   Patients enrolled in the open-label safety cohort in Japan must have been of Japanese ethnicity (i.e. both parents were native Japanese and were born in Japan).
3. Had **newly diagnosed**, histologically confirmed, **advanced** (FIGO Stage III-IV), **high-grade** epithelial ovarian, fallopian tube, or primary peritoneal cancer.
4. **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).
5. Had received **4 to 8 cycles** of **first line platinum-doublet treatment** per standard clinical practice, including a minimum of 4 cycles of platinum/taxane combination.
   a. A patient with best response of PR must have received at least 6 cycles.
   b. Bevacizumab was allowed during the chemotherapy phase, but not during maintenance i.e., during therapy directed by this protocol.
6. Had completed **first-line platinum-based chemotherapy and surgery** with a **response**, in the opinion of the investigator, defined as no evidence of disease progression radiologically or through rising CA-125 (per GCIG guidelines) at any time during front-line treatment; and:
   a. No evidence of measurable disease by RECIST v1.1 (if complete resection/R0 at primary or interval cytoreductive surgery); or
   b. A partial or complete response per RECIST v1.1 (if measurable disease was present after surgery and prior to chemotherapy); or
   c. A GCIG CA-125 response (if only non-measurable disease was present after surgery and prior to chemotherapy).
7. Pre-treatment CA-125 measurements must have met criterion specified below:
   a. If the first value was within ULN the patient was eligible to be randomised and a second sample was not required;
   b. If the first value was greater than ULN a second assessment must have been performed at least 7 days after the first. If the second assessment was ≥ 15% than the first value the patient was not eligible.
8. Patient must have been randomised within 8 weeks of the first day of the last cycle of chemotherapy.
9. Had sufficient formalin-fixed paraffin-embedded (FFPE) tumour tissue available for planned analyses.

a. Submission of a tumour block was preferred; if sections were provided, these must all have been from the same tumour sample.

b. Tumour tissue from the cytoreductive surgery was required.

c. Sample must have been received at the central laboratory at least 3 weeks prior to planned start of treatment to enable stratification for randomisation.

10. Had adequate organ function confirmed by the following laboratory values obtained within 14 days of randomisation:

    a. Bone Marrow Function: ANC ≥ 1.5 × 109/L; platelets ≥ 100 × 109/L; haemoglobin ≥ 9 g/dL.
    b. Hepatic Function: AST and ALT ≤ 1.5 × ULN; bilirubin ≤ 1.5 × ULN; < 2 × ULN if hyperbilirubinemia was due to Gilbert's syndrome; serum albumin ≥ 30 g/L (3.0 g/dL).
    c. Renal Function: serum creatinine ≤ 1.5 × ULN unless GFR ≥ 30 mL/min using the Cockcroft-Gault formula.

11. Had an ECOG performance status of 0 to 1.

Exclusion criteria

1. Non-epithelial tumours (pure sarcomas) or ovarian tumours with low malignant potential (ie, borderline tumours) or mucinous tumours. Mixed mullerian tumours/carcinosarcomas were allowed.

2. Active second malignancy, ie, patient known to have potentially fatal cancer present for which she may have been (but not necessarily) currently receiving treatment.

   Patients with a history of malignancy that had been completely treated, with no evidence of active cancer for 3 years prior to enrolment, or patients with surgically cured low-risk tumours, such as early-stage cervical or endometrial cancer were allowed to enrol.

3. Known central nervous system brain metastases.

4. Any prior treatment for ovarian cancer, other than the first-line platinum regimen, including any maintenance treatment between completion of the platinum regimen and initiation of study drug in this study.

   Ongoing hormonal treatment for previously treated breast cancer was permitted. Hormonal maintenance treatment for ovarian cancer was not allowed.

5. Had evidence of interstitial lung disease, active pneumonitis, myocarditis, or a history of myocarditis.

6. Patients with an active, known or suspected autoimmune disease (e.g., autoimmune hepatitis). Patients with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger were permitted to enrol.

7. Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomisation. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, were permitted in the absence of active autoimmune disease.

8. Drainage of ascites during the final 2 cycles of treatment with the platinum regimen.

9. Pre-existing duodenal stent and/or any gastrointestinal disorder or defect that would have, in the opinion of the investigator, interfered with absorption of study treatment.
10. Known history of a positive test for HIV or known AIDS.
11. Any positive test result for hepatitis B and/or known history of hepatitis B infection including patients with undetectable hepatitis B virus (HBV) DNA and inactive carriers; positive test result for hepatitis C antibody (anti-HCV; except if HCV-RNA negative).
12. Received chemotherapy within 14 days prior to first dose of study drug and/or ongoing adverse effects from such treatment > NCI-CTCAE v5.0 Grade 1, with the exception of Grade 2 non-hematologic toxicity such as alopecia, peripheral neuropathy, Grade 2 anaemia with haemoglobin ≥ 9 g/dL, and related effects of prior chemotherapy that were unlikely to be exacerbated by treatment with study drug.
13. Pregnant, or breastfeeding. All study participants must have avoided pregnancy achieved through assisted reproductive technology for the duration of study treatment and for a minimum of 6 months following the last dose of study drug (oral or IV, whichever was later).
14. Non-study related minor surgical procedure (e.g. placement of a central venous access port) ≤ 5 days, or major surgical procedure ≤ 21 days, prior to first dose of study drug; in all cases, the patient must have been sufficiently recovered and stable before treatment administration.
15. Presence of any other condition that may have increased the risk associated with study participation or may have interfered with the interpretation of study results, and, in the opinion of the investigator, would have made the patient inappropriate for entry into the study.
16. Hospitalization for bowel obstruction within 12 weeks prior to enrolment.

Treatments

Patients in the ATHENA–MONO treatment comparison were randomised 4:1 to the following treatment arms:

- Arm B: oral rucaparib + IV placebo; or
- Arm D: oral placebo + IV placebo.

Rucaparib was administered at an initial dosage of 600 mg. Rucaparib 600 mg, or matching placebo, was administered orally BID. IV placebo was administered via a 30 minute IV infusion (100 mL total volume per infusion) on Day 1 of every 28 day cycle, starting on Cycle 2. This regimen was selected to match the dosing regimen for nivolumab.

In the Treatment Phase, patients received oral study treatment BID starting on C1D1 and IV placebo Q4W starting on C2D1 in continuous 28-day treatment cycles. Patients continued treatment until 24 months after initiating IV placebo treatment in Arm B (oral rucaparib + IV placebo) or Arm D (oral placebo + IV placebo), disease progression, or unacceptable toxicity, whichever occurred first.

If a patient receiving study drug met criteria for confirmed radiologic disease progression by RECIST v.1 criteria, but the patient continued to derive clinical benefit per the investigator, then continuation of treatment was permitted.

Doses of oral study drug and/or IV study drug were interrupted or delayed for toxicity and other protocol-specified criteria. Dose reductions were permitted for oral study drug but not for IV study drug.

Patients were assessed for disease status per RECIST v1.1 by the investigator every 12 calendar weeks relative to C2D1 for the first 3 years and then every 24 weeks thereafter until objective radiological disease progression, as assessed by the investigator. All CT scans (and other imaging, as appropriate) performed during the treatment period and at treatment discontinuation were collected for and read by blinded independent central review (BICR).

Patients who discontinued treatment for a reason other than disease progression or death continued to have tumour scans performed at 12 week intervals relative to C2D1 for the first 3 years and then every 24 weeks thereafter until objective radiological disease progression by RECIST v1.1, as assessed by the investigator, was documented. An optional tumour biopsy was collected from patients who experienced disease progression/randomised treatment discontinuation and provided appropriate consent.

Patients were followed long-term for survival, subsequent treatments, and monitoring for secondary malignancy every 12 weeks (± 14 days) after SFU1 until death, loss to follow-up, withdrawal of consent, or study closure. If a patient began subsequent anticancer therapy, the sponsor terminated collection of SAEs, with the exception of the AESIs of MDS and AML.

Objectives

Primary objective

The primary objective was analysed in the HRD and ITT Populations:

- To evaluate progression free survival (PFS) by RECIST, as assessed by the investigator (invPFS)

Secondary objectives

The following secondary objectives were analysed in the HRD and ITT Populations:

- To evaluate PFS by RECIST, as assessed by the blinded independent central review (BICR) (bicrPFS)
- To evaluate survival benefit.
- To evaluate objective response rate (ORR) and duration of response (DOR), as assessed by the investigator, in patients with measurable disease at baseline
- To evaluate safety

Exploratory objectives

The exploratory objectives are:

- To evaluate PFS2 (PFS on the subsequent line of treatment)
- To evaluate efficacy and safety in the tBRCA subgroup for the comparison of rucaparib vs placebo (invPFS, bicrPFS, OS, ORR, DOR, and safety)
- To evaluate Health-related Quality of Life (HRQoL) as assessed by the trial outcome index (TOI)
- To evaluate Health-related Quality of Life (HRQoL) as of the Functional Assessment of Cancer Therapy – Ovarian (FACT O)
- To evaluate patient-reported outcome (PRO) utilizing the EQ-5D-5LTo characterize PK of rucaparib as monotherapy

Outcomes/endpoints

Primary endpoint

The primary efficacy endpoint is invPFS.

Secondary endpoints included in the step-down analysis

- OS
- ORR by RECIST v1.1 in patients with measurable disease at baseline

Secondary endpoints not included in the step-down analysis

- bicrPFS
- DOR by RECIST v1.1 in patients with measurable disease at baseline

Exploratory endpoints

- PFS of study treatment followed by the subsequent line of treatment (PFS2), defined as the time from randomisation to the second event of disease progression or death, as assessed by the investigator.
- To evaluate efficacy and safety in the tBRCA subgroup for the comparison of rucaparib vs placebo (invPFS, bicrPFS, OS, ORR, DOR, and safety)
- HRQoL as assessed by the TOI of the FACT-O
- PRO utilizing the EQ-5D
- To explore rucaparib PK in ATHENA-MONO

Sample size

Three separate comparisons of the treatment arms were planned to be evaluated independently in the original protocol:

1. Arm A (oral rucaparib + IV nivolumab) versus Arm B (oral rucaparib + IV placebo);
2. Arm A (oral rucaparib + IV nivolumab) versus Arm D (placebo [oral and IV]); and
3. Arm B (oral rucaparib + IV placebo) versus Arm D (placebo [oral and IV]).

The level of statistical significance was to be split into 3 so that each of the above comparisons were made independently at a one-sided 0.0083 significance level.

The table below provides the sample size and power for comparison 3 of Arm B (rucaparib monotherapy) to Arm D (placebo) for the tBRCA, HRD, and ITT Populations.

Table 9 Monotherapy Treatment Comparison: Arm B (oral rucaparib + IV placebo) vs Arm D (placebo [oral and IV]), randomisation allocation 4:1

Group	Hazard Ratio	Cumulative N (4:1)	Number of Events	Median PFS (months)	Power	One-sided Alpha
tBRCA	0.50	170 (135:34)	120	36 vs 18	90%	0.008
HRD	0.60	340 (270:68)	230	25 vs 15	90%	0.008
ITT	0.65	500 (400:100)	340	17 vs 12	90%	0.008

Abbreviations: HRD = homologous recombination deficient (tBRCA + non-tBRCA LOH^{high}); ITT =intent-to-treat; PFS = progression free survival; tBRCA = tumor tissue alteration in BRCA1 or BRCA2, includes gBRCA and sBRCA.

Based on the recently established standard of care of PARP inhibitor monotherapy in the first-line maintenance setting, the treatment comparison of Arm A (oral rucaparib + IV nivolumab) vs Arm D (placebo [oral and IV]) from the original protocol was no longer necessary.

Therefore, the comparison of Arm A vs Arm D was moved from the primary endpoint to an exploratory endpoint leaving 2 separate comparisons ATHENA–MONO and ATHENA–COMBO, which were designed to be evaluated independently and at different time points based on the maturity of the respective study arms:

- ATHENA–MONO: Arm B (oral rucaparib + IV placebo) vs Arm D (placebo [oral and IV]); and
- ATHENA–COMBO: Arm A (oral rucaparib + IV nivolumab) vs Arm B (oral rucaparib + IV placebo).

As such, in this amended protocol, the level of statistical significance was split into two so that each of the above comparisons were made at a one-sided 0.0125 (two-sided 0.025) significance level.

The proposed timing of sufficient maturity for the monotherapy treatment comparison was assumed to be at as early as 15 months from the last patient randomised, and once approximately 60% of the events have occurred.

The enrolment of tBRCA was lower than originally anticipated in the sample size assumptions in the original protocol. Thus, the monotherapy treatment comparison, comparing Arm B (oral rucaparib + IV placebo) versus Arm D (placebo [oral and IV]), started with the HRD analysis subpopulation, then ITT Population for the step-down hierarchical testing and the tBRCA population was explored as an exploratory endpoint.

Table 10 Monotherapy Treatment Comparison: Arm B (oral rucaparib + IV placebo) vs Arm D (placebo [oral and IV]), randomisation allocation 4:1. Original Protocol and Amendment 1 version and Amendment 2 version.

Protocol Version	Group	Cumulative N (4:1)	Number of Events	HR Median PFS	Power	One-sided Alpha
Original Protocol and Amendment 1	tBRCA	170 (135:34)	120	HR 0.50 18 vs 36 months	90%	0.008
	HRD	340 (270:68)	230	HR 0.60, 15 vs 25 months	90%	0.008
	ITT	500 (400:100)	340	HR 0.65 12 vs 17 months	90%	0.008
Amendment 2	HRD	205 (164:41)	123	HR 0.45[80] 12 vs 26.7 months	90%	0.0125
	ITT	500 (400:100)	300	HR 0.60[80] 12 vs 20 months	90%	0.0125

Abbreviations: HR = hazard ratio; HRD = homologous recombination deficiency (tBRCA + non-tBRCA LOH^{high}); ITT = intent-to-treat, IV = intravenous; PFS = progression-free survival.

Randomisation

For the Double-Treatment Phase, eligible patients were randomised 4:1 to Arm B (oral rucaparib + IV placebo) or Arm D (placebo oral and IV).

Randomisation occurred by a central randomisation procedure using an interactive response technology (IRT). The following were included as randomisation stratification factors at study entry to ensure treatment groups were balanced:

- HRD status (tBRCA, non-tBRCA LOH-high, non-tBRCA LOH-low, or non-tBRCA LOH-unknown) by central laboratory analysis.
- Disease status post-chemotherapy (residual disease vs no residual disease)
- Timing of surgery (primary surgery vs interval debulking)

Blinding (masking)

The study was double-blind.

Investigators and patients were blinded to study treatments, which for the full, 4-arm study included monotherapy and combination therapy with oral rucaparib and IV nivolumab, as well as matching placebos. To maintain the blind, patients received both an oral and an IV administration of study drug and/or placebo.

Statistical methods

Populations analysed

The following analysis populations were defined in the SAP for the ATHENA–MONO treatment comparison:

- **ITT Population**: The ITT Population consisted of all randomised 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 randomised patients that were either tBRCA or non-tBRCA LOH-high.
- **Safety Population**: The Safety Population consisted of all patients who received at least 1 dose of protocol-specified treatment of oral study drug.

Efficacy analyses were analysed in the HRD and ITT Populations. All safety analyses were based on the Safety Population. Only patients who were randomised to Arm B (rucaparib monotherapy) and Arm D (placebo) are included in the analyses.

In addition to the population definitions above, exploratory efficacy analyses were performed in subgroups including the mutually exclusive (non-nested) molecular subgroups within the ITT Population as outlined below.

- **tBRCA**: Patient 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%; and
- **Non-tBRCA LOH-unknown**: Patients without a tBRCA mutation and with percent of tumour genome LOH unknown.

Efficacy analyses

Primary efficacy endpoint

The primary efficacy endpoint was PFS as assessed by the investigator (invPFS). The time to invPFS was calculated in months as the time from randomisation to disease progression +1 day, as determined by 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 PFS analysis. Any deaths or progression events occurring within 2 missing expected scan assessments were included in the analysis. Two missed scans or visits was defined as a duration of 26 weeks (12 × 2 + 2) for the first 3 years and 50 weeks (2 × 24 + 2), thereafter. Events occurring immediately after 2 consecutive missed scans were censored as described below.

The stratified log-rank test was the official test used for the hierarchical testing. In addition, the primary endpoint was also analysed using the stratified Cox proportional hazards methodology, presenting the hazard ratio with 95% CI between the randomised treatment groups. The randomisation stratification factors were included in the primary analysis of invPFS.

Censoring rule: Any patients who did not experience an event of either disease progression or death were censored on the last on-study tumour assessment prior to start of any subsequent anticancer treatment. Any patient with an event of either disease progression or death following 2 or more missed expected consecutive scans was censored on the date of the last on-study tumour assessment prior to the gap in scan collection. If a patient did not have any on-study tumour assessments, then the patient was censored on the date of randomisation (ie, Day 1).

Sensitivity analyses

A sensitivity analysis of invPFS was performed using the actual supportive data from FMI's NGS-based test and EDC to derive the randomisation strata groups: HRD status based on FMI's NGS-based test; disease status (no residual disease vs residual disease post-chemotherapy) based on EDC data; and timing of surgery (primary surgery vs interval debulking) based on EDC data.

Sensitivity analyses for invPFS were performed to evaluate the impact of censored patients. The following sensitivity analyses were performed:

- All scans and data: A sensitivity analysis was performed in which all tumour scans or death events were included for assessment of PFS even if the patient discontinued study treatment or initiated a subsequent anticancer therapy. This was in accordance to the EMA guidelines.
- Clinical progression or withdrawal: A sensitivity analysis was performed in which patients who discontinued oral study drug due to clinical progression or who withdrew consent from treatment were also considered events of invPFS on the date of the last dose of study drug.

Secondary efficacy endpoints

Following the primary endpoint, secondary efficacy endpoints were analysed in the HRD and ITT Populations in the following order in accordance with the hierarchical step-down procedure:

1. OS
2. ORR by RECIST v1.1 in patients with measurable disease at baseline.

Overall survival was defined as the time from randomisation to death by any cause, and was calculated in months as the time from randomisation to death +1 day. Patients who had not died were censored on the date the patient was last known to be alive or last visit. Interim OS was analysed using the stratified Cox proportional hazards methodology and a stratified log-rank test. The stratified HR from the Cox proportional hazards model was used to estimate the HR between the randomised treatment groups. The stratified log-rank test was the official test used for the hierarchical testing.

It was anticipated that the data for OS would be immature and thus heavily censored 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 was projected to be once 70% of the death events had been collected. Any additional interim analyses of OS conducted was to be adjusted for at the time of final OS.

The ORR as assessed by the investigator was analysed in the subgroup of patients who were response evaluable (ie, measurable target lesions) at baseline. The ORR of confirmed response by RECIST v1.1 was summarized, and 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. The ORR was compared between treatments by using a chi-square test of proportions.

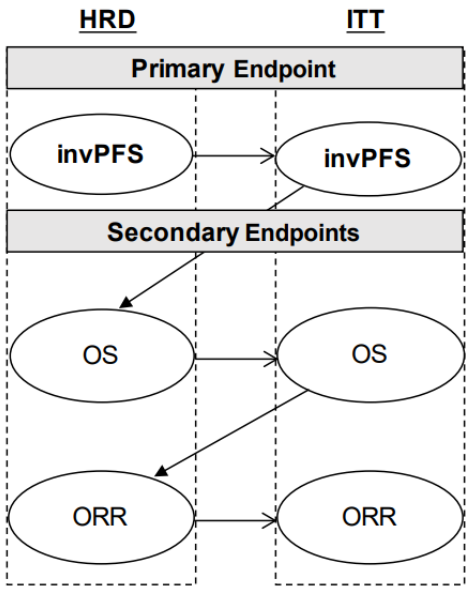
The bicrPFS was evaluated as a stand-alone secondary endpoint and was not part of the hierarchical step-down procedure described. The bicrPFS was used as a supportive analysis to the primary endpoint. The secondary endpoint of DOR was also evaluated as a stand-alone secondary endpoint and was not part of the hierarchical step-down procedure.

Multiple comparison/Multiplicity

In order to preserve the overall type 1 error rate, the primary and key secondary endpoints for ATHENA-MONO were tested using a pre-specified hierarchical step-down procedure.

The primary endpoint of invPFS and key secondary endpoints of OS and ORR were tested among the HRD Population first and then the ITT Population using a one-sided alpha of 0.0125 (two-sided alpha = 0.025). That is, the invPFS in the HRD Population was tested first at a one-sided 0.0125 (two-sided p = 0.025) 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 tested at the one-sided 0.0125 (two-sided p = 0.025) significance level in the HRD and ITT Populations for that treatment comparison and testing continued to the last key secondary endpoint of 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.

Figure 18 Ordered Step-Down Procedure for ATHENA-MONO



Abbreviations: HRD = homologous recombination deficiency; invPFS = investigator-assessed progression-free survival; ITT = intent-to-treat; ORR = objective response rate; OS = overall survival.

Results

Data are available from a total of 538 patients randomised to receive either rucaparib monotherapy (n = 427; Arm B: oral rucaparib + IV placebo [rucaparib]) or placebo (n = 111; Arm D: oral placebo + IV placebo [placebo]) for the ATHENA–MONO treatment comparison.

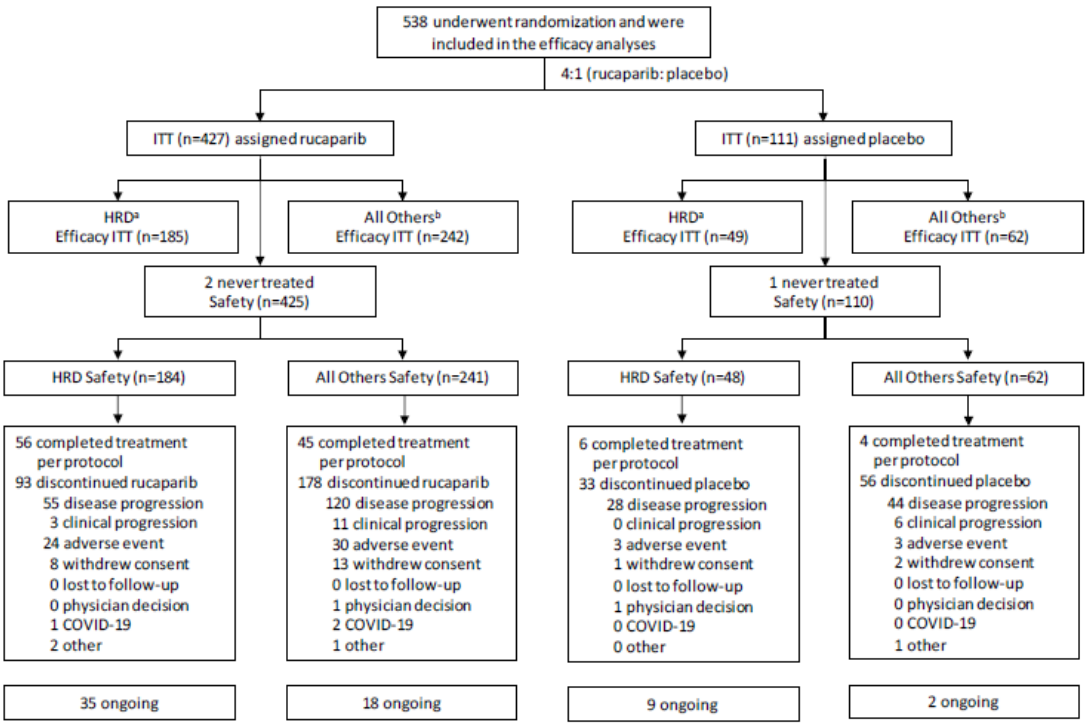
Participant flow

There were 538 patients randomised into the ATHENA–MONO treatment comparison (i.e. the ITT Population); 427 patients in the rucaparib group and 111 patients in the placebo group. Three patients who were randomised (rucaparib, n = 2; placebo, n = 1) discontinued prior to receiving any oral study drug. Therefore, the Safety Population consisted of 535 patients (99.4% of the ITT Population) who initiated treatment with either 600 mg BID rucaparib (n = 425) or placebo (n = 110).

As of the visit cut-off, 111 patients (rucaparib, n = 101; placebo, n = 10) had completed treatment with oral study drug (24 months from the time of initiating IV placebo), 360 patients (rucaparib, n = 271, placebo, n = 89) had discontinued treatment early, and 64 patients (rucaparib, n = 53; placebo, n = 11) were ongoing. The primary reason for early discontinuation of study drug, regardless of

treatment group, was disease progression (rucaparib, 175/427 [41.0%]; placebo, 72/111 [64.9%]).

Figure 19 Patient Disposition Flow Chart for ATHENA–MONO



Source: Table 14.1.1.1 (t-disp-itt); Table 14.1.1.1.1 (t-disp-hrd); Table 14.1.1.1.2 (t-disp-nhrd); Table 14.1.1.1.3 (t-disp-hrdsf); Table 14.1.1.1.4 (t-disp-nhrdsf).
Abbreviations: AE = adverse event; BRCA = breast cancer gene; COVID-19 = coronavirus disease 2019; HRD = homologous recombination deficiency; ITT = intent-to-treat; LOH = loss of heterozygosity; LOH^{high} = LOH ≥ 16%; LOH^{low} = LOH < 16%; $LOH^{unknown}$ = LOH that is unknown; non-tBRCA = BRCA wild-type; tBRCA = tumor tissue mutation in BRCA.

[a] HRD includes tBRCA + non-tBRCA LOH^{high}.

[b] All others include non-tBRCA LOH^{low} + non-tBRCA $LOH^{unknown}$.

Table 11 Patient disposition – ITT population

	Arm B Oral Rucaparib + IV Placebo	Arm D Oral Placebo + IV Placebo
End of Oral Treatment Status		
Oral Study Drug Never Initiated	2 (0.5%)	1 (0.9%)
Oral Study Drug Never Initiated Due to COVID-19	0	0
Ongoing	53 (12.4%)	11 (9.9%)
Discontinued	372 (87.1%)	99 (89.2%)
Primary Reason for Discontinuation of Oral Study Drug [1]		
Adverse Event	54 (14.5%)	6 (6.1%)
Disease Progression	175 (47.0%)	72 (72.7%)
Clinical Progression	14 (3.8%)	6 (6.1%)
Subject Completed Protocol Specified Duration on Study Drug	101 (27.2%)	10 (10.1%)
Physician Decision	1 (0.3%)	1 (1.0%)
Lost to Follow-up	0	0
Subject Withdrew Consent to Treatment	21 (5.6%)	3 (3.0%)
Protocol Violation	0	0
Study Terminated by Sponsor	0	0
Study Drug Permanently Discontinued Due to COVID-19	3 (0.8%)	0
Other	3 (0.8%)	1 (1.0%)

[1] Percentages based on the number of subject who discontinued oral study drug.
Data cutoff is 23MAR2022.

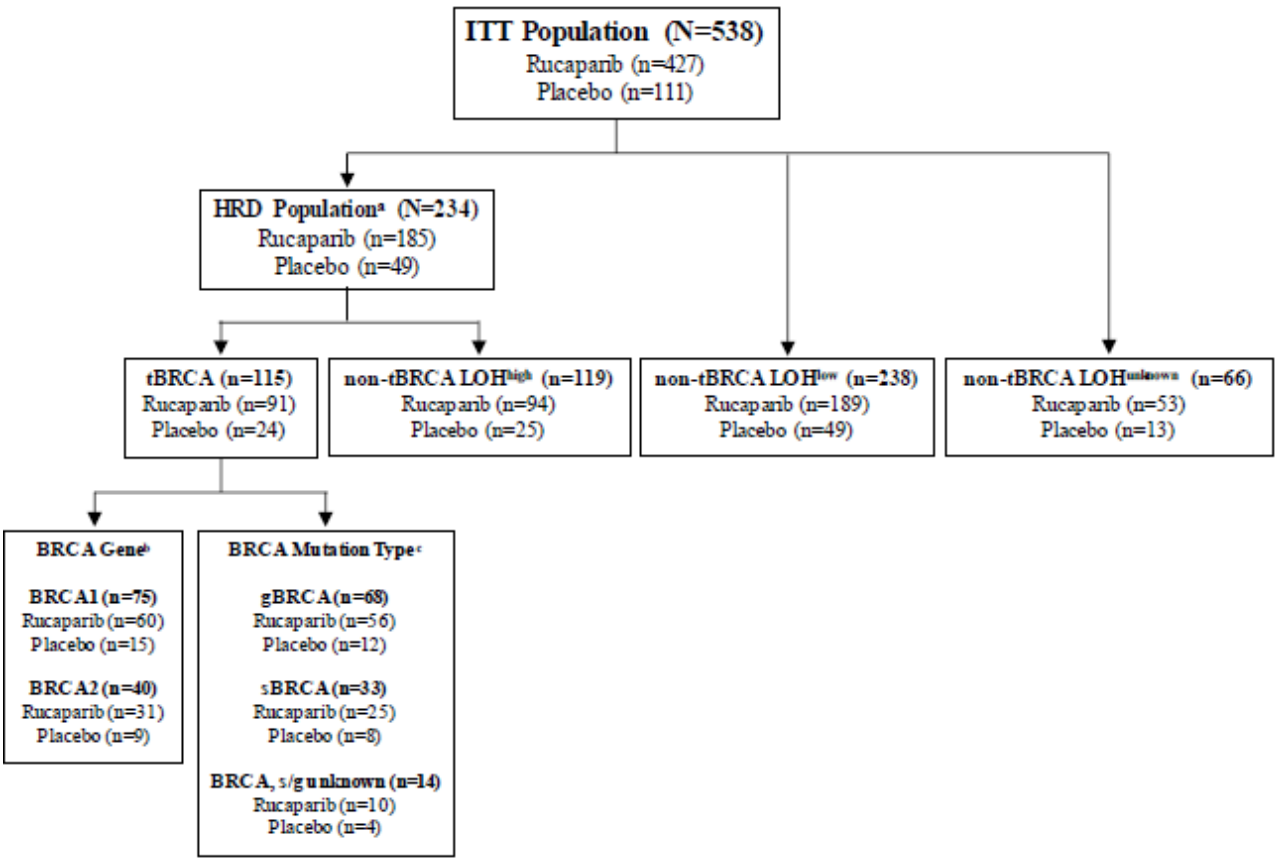
HRD status

Evidence of a deleterious BRCA (includes BRCA1 and BRCA2) mutation was determined from local or central genomic testing prior to randomisation. For central confirmation of deleterious BRCA mutations, tumour tissues were sent from the study sites directly to Foundation Medicine, Inc. (FMI; Cambridge, MA, US) for testing using the NGS-based Foundation One DX1 assay. Laboratory kits were made available via ICON Clinical Research, Ltd. (ICON; Farmingdale, NY, US).

Patients were screened for BRCA mutation and percent LOH to determine HRD status, based on an archival tumour tissue sample or a screening biopsy prior to enrolment, by FMI's NGS-based test. LOH of ≥ 16% was the pre-specified cut-off for inclusion in the non-tBRCA LOH-high subgroup. In addition, a central laboratory (Ambry Genetics) test result of a blood samples and/or a local test result of blood or buccal samples were used to determine germline and somatic BRCA mutation status using the CancerNext Expanded assay.

A flow diagram illustrating patient disposition of the ITT Population based on HRD status (non-nested molecular subgroup) and BRCA mutation status is provided in Figure 20.

Figure 20 Patient Disposition Flow Chart of ITT Population by HRD Status and BRCA Test Results for ATHENA–MONO



Source: Table 14.1.4.3.1 (t-hrd-itt).

Abbreviations: BRCA = breast cancer gene; HRD = homologous recombination deficiency; FMI = Foundation Medicine, Inc.; LOH = loss of heterozygosity; LOH^{high} = LOH ≥ 16%; LOH^{low} = LOH < 16%; $LOH^{unknown}$ = LOH that is unknown; ITT = intent-to-treat; NGS = next-generation sequencing; tBRCA = tumor tissue mutation in BRCA.

[a] HRD status and percent LOH were determined by FMI's NGS-based test result.

[b] BRCA gene was determined by FMI's NGS-based test result (a BRCA result [positive or negative] was required for enrollment).

[c] BRCA mutation type was determined by Ambry Genetics or a local test result.

The tumour-based NGS-based test cannot distinguish whether a detected BRCA mutation is of germline or somatic origin; therefore, the NGS-based test results were compared to the central blood germline BRCA results in order to derive the BRCA mutation type used for analysis. A majority of the tBRCA patients (68/115 [59.1%]) were identified as having a germline BRCA mutation: 56 patients in the rucaparib group (56/91 [61.5%]) and 12 patients in the placebo group (12/24 [50.0%]). Approximately 30% of tBRCA patients in either treatment group were identified as having a somatic BRCA mutation. A smaller percentage of patients with a BRCA mutation as detected by the tumour NGS-based test were identified as having a BRCA mutation of unknown origin (14/115 [12.2%]) due to the lack of a central blood germline BRCA test result.

Of the patients with a tBRCA mutation as detected by the NGS-based test (n = 115 overall), 75/115 (65.2%) were designated as having a mutation in BRCA1 and 40/115 (34.8%) were designated as having a mutation in BRCA2, with similar incidences in either treatment group.

Table 12 Summary of Local and Central BRCA and HRD Testing. ITT Population

	Arm B Oral Rucaparib + IV Placebo (N=427)	Arm D Oral Placebo + IV Placebo (N=111)	Total (N=538)
Randomization Strata: HRD Classification			
tBRCA	91 (21.3%)	24 (21.6%)	115 (21.4%)
non-tBRCA LOH^{high}	94 (22.0%)	25 (22.5%)	119 (22.1%)
non-tBRCA LOH^{low}	189 (44.3%)	49 (44.1%)	238 (44.2%)
non-tBRCA LOH^{unknown}	53 (12.4%)	13 (11.7%)	66 (12.3%)
FMI [1] HRD Classification			
tBRCA	91 (21.3%)	24 (21.6%)	115 (21.4%)
non-tBRCA LOH^{high}	94 (22.0%)	25 (22.5%)	119 (22.1%)
non-tBRCA LOH^{low}	189 (44.3%)	48 (43.2%)	237 (44.1%)
non-tBRCA LOH^{unknown}	53 (12.4%)	14 (12.6%)	67 (12.5%)
Local Lab BRCA Mutation Results			
BRCA1	23 (5.4%)	6 (5.4%)	29 (5.4%)
BRCA2	11 (2.6%)	2 (1.8%)	13 (2.4%)
Non-BRCA	201 (47.1%)	50 (45.0%)	251 (46.7%)
Unknown	192 (45.0%)	53 (47.7%)	245 (45.5%)
FMI [1] BRCA Mutation Results			
BRCA1	60 (14.1%)	15 (13.5%)	75 (13.9%)
BRCA2	31 (7.3%)	9 (8.1%)	40 (7.4%)
Non-BRCA	336 (78.7%)	87 (78.4%)	423 (78.6%)
Central Germline BRCA Mutation Results (Ambry)			
BRCA1	35 (8.2%)	8 (7.2%)	43 (8.0%)
BRCA2	17 (4.0%)	4 (3.6%)	21 (3.9%)
Non-BRCA	28 (6.6%)	8 (7.2%)	36 (6.7%)
Unknown	347 (81.3%)	91 (82.0%)	438 (81.4%)
tBRCA Mutation Type [2]			
Germline	56 (61.5%)	12 (50.0%)	68 (59.1%)
Somatic	25 (27.5%)	8 (33.3%)	33 (28.7%)
Unknown	10 (11.0%)	4 (16.7%)	14 (12.2%)

[1] Foundation Medicine Inc. CTA Testing.
[2] Percentages based on tBRCA population.
Data cutoff is 23MAR2022.

Recruitment

Patients were randomised into the study from 01 October 2018 through 30 September 2020. The visit cut-off date of 23 March 2022 is approximately 1.5 years after the last patient was randomised.

The 538 patients were recruited from 200 study sites in 24 countries: Australia, Belgium, Canada, the Czech Republic, Denmark, Finland, Germany, Greece, Ireland, Israel, Italy, Japan, New Zealand, Poland, Romania, Russia, Singapore, South Korea, Spain, Sweden, Taiwan, Turkey, the UK, and the US. This study is currently ongoing in 238 active sites across these 24 countries.

Conduct of the study

Protocol amendments

The original protocol was dated 02 March 2018. As of 23 March 2022 cut-off date there have been 4 global protocol amendments and 2 country-specific protocol addenda. There were also clarification memos regarding aspects of the study during the COVID-19 pandemic and classification of pneumonitis as an AESI.

Table 13 Summary of Protocol Amendments and Addenda for Study CO-338-087 (ATHENA)

Number	Date	Details of Amendment/Addendum
Amendment 1	05 July 2018	Amendment 1 of the CO-338-087 study protocol replaced the original protocol dated 02 March 2018. Significant changes included in this amendment are summarized as follows: • The study design was revised to define patients who responded as those who had a PR or CR to first-line treatment. The use of a placebo comparator for patients who had achieved a PR to their first platinum-based regimen was justified. • The Safety Follow-up Visit after discontinuation of IV study drug was revised from 100 days to 5 months, consistent with the nivolumab SmPC. • Myocarditis or a history of myocarditis was added as exclusion criteria to align with the nivolumab SmPC. In addition, discontinuation of IV study drug for patients who experience ≥ Grade 3 myocarditis was specified. • Within the exclusion criteria, autoimmune hepatitis was added as an example of an autoimmune disease in order to bring this to the investigators' attention. • Referral of patients with visual complaints to an ophthalmologist was specified in accordance with the nivolumab IB. • Interruption of IV study drug for drug-related Grade 2 adrenal insufficiency or hypophysitis was specified in alignment with the nivolumab SmPC, which indicates withholding nivolumab treatment for these Grade 2 events. • Language was added to specify that if pancreatitis is suspected clinically, serum lipase and amylase should be analyzed. The use of strong CYP3A4 inhibitors and inducers was clarified to help inform investigators regarding CYP drug-drug interactions.
Addendum 1 (Germany-specific)	19 June 2020	In response to guidance documents issued by the US FDA and EMA on study conduct during the COVID-19 Pandemic, Clovis Oncology developed guidance for key aspects of study conduct to address the challenges facing all clinical study site personnel and study patients in the COVID-19 pandemic environment. The protocol addendum was not meant to change the requirements of Protocol CO-338-087, but rather to provide guidance that was applicable as a temporary measure during the timeframe that a clinical study site and/or the respective clinical study patients were adversely affected by the pandemic.
Amendment 2	26 October 2020	Amendment 2 of the study CO-338-087 protocol replaced Amendment 1 of the protocol. Significant changes included in this amendment are summarized as follows: • Updated the statistical methods to include an additional analysis population of the ITT Population, and to build in a hierarchical step-down procedure for the analysis populations for primary and secondary endpoints. • Updated the AESIs to include pneumonitis and similar events, including management guidance and Clovis Oncology PV reporting and follow-up requirements to align with the rucaparib IB and other Clovis Oncology study protocols. • Included guidance for management of anemia for consistency with the rucaparib IB. • Updated the End-of-Study language to allow flexibility for continuing treatment and/or follow up via other mechanisms. • Updated the PRO collection formats to include other options, as appropriate (ie, paper form). • Updated the statistical design, including: (1) moving the original comparison of rucaparib + nivolumab vs placebo from the primary endpoint analysis to an exploratory endpoint analysis due to the current standard of care of PARP inhibitors in first-line maintenance. The alpha was split between the remaining 2 independent comparisons of combination (rucaparib + nivolumab vs rucaparib) and monotherapy (rucaparib vs placebo) treatment; (2) clarifying that the 2 remaining independent comparisons will mature at different time points, and will therefore be read out separately; and (3) updated the step-down analysis for the monotherapy comparison (rucaparib vs placebo), from tBRCA → HRD → ITT to HRD → ITT, due to a low proportion of tBRCA patients enrolled to the study.
		• Incorporated language from Clarification memos issued for Amendment 1 (see above), including (1) that 24 months of treatment was reached after initiation of combination oral/IV treatment, not C2D1; (2) that tumor scan/disease assessment interval was anchored to C2D1, not from the start of combination treatment; (3) that LTFU for overall survival, subsequent treatments, and monitoring for secondary malignancy every 12 weeks was anchored to the first Safety Follow-up Visit; (4) updated hepatitis language; (5) updated CA-125 level language per GCIG guidelines; and (6) updated age of signing consent for Taiwan and S. Korea, consistent with Amendment 1 Memos to File. • Updated NCI-CTCAE grading from v4.03 or higher to v5.0, to reflect the version that sites had been trained on and that had been/will be in use throughout the lifetime of the study. • Updated AE management algorithms for immuno-oncology agents, and PRO assessment questionnaires, to current versions. • Incorporated safety language related to the AESI of pneumonitis. • Revised the reporting requirement for progression of a patient's underlying cancer. Events of progression of the patient's underlying cancer as well as events clearly related to progression of the patient's cancer (signs and symptoms of progression) should not be reported.

Addendum (Turkey-specific)	09 January 2021	Details of the addendum are the same as those presented above for Addendum 1 (Germany-specific)
Amendment 3	08 September 2021	Amendment 3 of the study CO-338-087 protocol replaced Amendment 2 of the protocol. Significant changes included in this amendment are summarized as follows: • Updated the statistical design with the following changes: - The step-down for combination treatment comparison (Arm A: rucaparib + nivolumab vs Arm B: rucaparib + placebo) was changed from an HRD → ITT analysis to an ITT analysis only. No changes to sample size and power assumptions were made. - Added an exploratory analysis for tBRCA, HRD, and PD-L1 subgroups of the combination comparison. - Added graphic representation of the step-down for each of the 2 independent comparisons (monotherapy and combination). • Updated safety guidelines with the following changes: - The IV drug hold guidance was modified to add back text regarding management of IV drug for cases of concurrent AST or ALT > 3 × ULN and total bilirubin > 2 × ULN that had been inadvertently omitted during Amendment 2. - The CYP450 Isoenzyme inhibitors, inducers and substrates text was modified to reflect the current rucaparib IB. - The AE/SAE/AESI reporting language was edited for clarity.
Number	**Date**	**Details of Amendment/Addendum**
		- The rucaparib safety data overview in the protocol introduction was updated to align with the current USPI. - Nivolumab indications and safety data overview in the protocol introduction were updated to align with the current nivolumab IB and USPI. • Updated operational procedures with the following changes: - Text was added to clarify that prevention of disclosure of confidential patient information includes that by unauthorized external entities. - Text was added to describe remote study monitoring to allow more flexibility.
Amendment 4	29 November 2021	The following changes were made per US FDA request: • Removed bicrPFS from the hierarchical step-down and added bicrPFS as a stand-alone secondary endpoint. Per FDA request, it was not necessary to have bicrPFS in the step-down due to this endpoint being supportive of the primary endpoint of invPFS. - For clarity, secondary efficacy endpoints were split out by (1) those in the step-down, and (2) those not in the step-down procedure. - Added language clarifying the key secondary endpoints in the step-down analysis are OS and ORR. - Added language clarifying that secondary endpoints of bicrPFS and DOR were outside of the step-down procedure. • Included further details on methodology around PFS events for the primary endpoint to only include disease progression and death within 2 missed expected visits as events.

Abbreviations: AESI = adverse event of special interest; ALT = alanine aminotransferase; AST = aspartate aminotransferase; bicrPFS = progression-free survival as assessed by blinded independent review; BRCA = breast cancer gene; C2D1 = Cycle 2 Day 1; CA-125 = cancer antigen-125; COVID-19 = coronavirus disease 2019; CR = complete response; CYP = cytochrome P450; DOR = duration of response; EMA = European Medicines Agency; EOT = end of treatment; FDA = Food and Drug Administration; GCIG = Gynecologic Cancer InterGroup; HBeAg = hepatitis antigen envelope antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HRD = homologous recombination deficiency; IB = Investigator's Brochure; invPFS = progression-free survival as assessed by investigator; IRT = interactive response technology; ITT = intent-to-treat; IV = intravenous; LTFU = Long-term Follow-up; NCI-CTCAE = National Cancer Institute – Common Terminology Criteria for Adverse Events; ORR = objective response rate; PD-L1 = ligand of PD-1; PR = partial response; PARP = poly (adenosine diphosphate [ADP]-ribose) polymerase; PRO = patient-reported outcome; PV = pharmacovigilance; QoL = quality of life; SmPC = Summary of Product Characteristics; tBRCA = tumor tissue mutation in BRCA; ULN = upper limit of normal; US = United States; USPI = United States Prescribing Information.

Protocol deviations

One patient (0.2%) in the rucaparib group had taken more than the prescribed dose leading to a major protocol deviation, with no observed safety issues due to the overdose. Six patients (1.4%) in the rucaparib group were given incorrect study drug during 1 treatment cycle. None of these incorrect drug administrations were associated with any observed safety issues. These six cases occurred at six unique sites across five countries.

Table 14 Important Protocol Deviations for ATHENA–MONO (ITT Population)

	Rucaparib (N = 427)	Placebo (N = 111)	Total (N = 538)
Number of Patients With at Least One Deviation, n (%)	**16 (3.7)**	**6 (5.4)**	**22 (4.1)**
Deviation Category, n (%)			
Inclusion/Exclusion Criteria	4 (0.9)	4 (3.6)	8 (1.5)
Incorrect IP given	6 (1.4)	0	6 (1.1)
Oral Treatment started > 3 days Randomization	4 (0.9)	2 (1.8)	6 (1.1)
Overdose (IP Oral)	1 (0.2)	0	1 (0.2)
Prohibited Medications	1 (0.2)	0	1 (0.2)

Source: Table 14.1.9.2 (t-dv-itt).
Abbreviations: IP = investigational product; ITT = intent-to-treat; IV = intravenous.

In addition, one patient received treatment beyond the pre specified 2 years cap, following the treating investigator judgement that the patient was still deriving clinical benefit, and local requirement to provide treatment beyond the end of the study. This case is not reflected in Table 14 since the deviation reporting was pending at the time of the CSR.

No pregnancies were reported. No patients were excluded from safety or efficacy analyses because of a protocol deviation.

Baseline data

Table 15 Patient Demographics (ITT Population)

	Rucaparib (N = 427)	Placebo (N = 111)	Total (N = 538)
Age (yr)			
Mean (StD)	60.3 (10.24)	61.1 (9.65)	60.4 (10.12)
Median	61.0	61.0	61.0
Min, Max	30, 83	31, 80	30, 83
Age Group (yr), n (%)			
< 65	270 (63.2)	68 (61.3)	338 (62.8)
65-74	130 (30.4)	33 (29.7)	163 (30.3)
≥ 75	27 (6.3)	10 (9.0)	37 (6.9)
Sex, n (%)			
Female	427 (100.0)	111 (100.0)	538 (100.0)
Race, n (%)			
American Indian or Alaska Native	1 (0.2)	1 (0.9)	2 (0.4)
Asian	80 (18.7)	16 (14.4)	96 (17.8)
Black or African American	5 (1.2)	3 (2.7)	8 (1.5)
Native Hawaiian or Other Pacific Islander	3 (0.7)	1 (0.9)	4 (0.7)
White	328 (76.8)	87 (78.4)	415 (77.1)
Multiple	2 (0.5)	1 (0.9)	3 (0.6)
Not Reported	8 (1.9)	2 (1.8)	10 (1.9)
Race Group, n (%)			
White	328 (76.8)	87 (78.4)	415 (77.1)
Other	91 (21.3)	22 (19.8)	113 (21.0)
Unknown	8 (1.9)	2 (1.8)	10 (1.9)
Ethnicity, n (%)			
Hispanic or Latino	17 (4.0)	1 (0.9)	18 (3.3)
Not Hispanic or Latino	397 (93.0)	107 (96.4)	504 (93.7)
Not Reported	13 (3.0)	3 (2.7)	16 (3.0)

	Rucaparib (N = 427)	Placebo (N = 111)	Total (N = 538)
Geographical Region, n (%)			
US/Canada	144 (33.7)	38 (34.2)	182 (33.8)
Europe	127 (29.7)	40 (36.0)	167 (31.0)
Eastern Europe	59 (13.8)	12 (10.8)	71 (13.2)
Asia	72 (16.9)	14 (12.6)	86 (16.0)
Australia/New Zealand	25 (5.9)	7 (6.3)	32 (5.9)
BMI (kg/m^2)			
Mean (StD)	25.94 (5.666)	25.98 (5.749)	25.95 (5.678)
Median	24.69	24.60	24.65
Min, Max	13.9, 60.5	16.9, 49.6	13.9, 60.5
ECOG PS at Baseline, n (%)			
0	295 (69.1)	76 (68.5)	371 (69.0)
1	131 (30.7)	35 (31.5)	166 (30.9)
2	1 (0.2)[a]	0	1 (0.2)
Smoking Status, n (%)			
Current Smoker	26 (6.1)	5 (4.5)	31 (5.8)
Former Smoker	87 (20.4)	28 (25.2)	115 (21.4)
Never Smoked	305 (71.4)	77 (69.4)	382 (71.0)
Unknown	9 (2.1)	1 (0.9)	10 (1.9)

Source: Table 12, ATHENA-MONO CSR.
Abbreviations: BMI = body mass index; ECOG PS = Eastern Cooperative Oncology Group performance status; ITT = intent-to-treat; Max = maximum; Min = minimum; StD = standard deviation; US = United States; yr= years.
[a] This patient had an ECOG PS of 1 during Screening and was thus eligible for the study.

Disease characteristics

Table 16 Cancer History (ITT Population)

	Rucaparib (N = 427)	Placebo (N = 111)	Total (N = 538)
Time Since Cancer Diagnosis (months)			
Mean (StD)	7.43 (1.404)	7.49 (1.778)	7.44 (1.487)
Median	7.20	7.30	7.20
Min, Max	3.0, 12.2	4.5, 17.6	3.0, 17.6
Time Since Cancer Diagnosis Group (months)			
0-3	1 (0.2)	0	1 (0.2)
> 3-6	62 (14.5)	19 (17.1)	81 (15.1)
> 6-9	307 (71.9)	79 (71.2)	386 (71.7)
> 9-12	55 (12.9)	11 (9.9)	66 (12.3)
> 12	2 (0.5)	2 (1.8)	4 (0.7)
Type of Ovarian Cancer, n (%)			
EOC	336 (78.7)	85 (76.6)	421 (78.3)
FTC	50 (11.7)	18 (16.2)	68 (12.6)
PPC	41 (9.6)	8 (7.2)	49 (9.1)
Histological Classification, n (%)			
Serous	384 (89.9)	106 (95.5)	490 (91.1)
Endometrioid	13 (3.0)	1 (0.9)	14 (2.6)
Clear Cell	13 (3.0)	2 (1.8)	15 (2.8)
Mixed	10 (2.3)	1 (0.9)	11 (2.0)
Other	7 (1.6)	1 (0.9)	8 (1.5)
Histological Grade, n (%)			
High Grade	427 (100.0)	111 (100.0)	538 (100.0)
Low Grade	0	0	0
FIGO Stage at Diagnosis, n (%)			
FIGO Stage IIIA	31 (7.3)	9 (8.1)	40 (7.4)
FIGO Stage IIIB	40 (9.4)	9 (8.1)	49 (9.1)
FIGO Stage IIIC	252 (59.0)	60 (54.1)	312 (58.0)
FIGO Stage IV	104 (24.4)	33 (29.7)	137 (25.5)

Source: Table 13, ATHENA-MONO CSR.
Abbreviations: EOC = epithelial ovarian cancer; FIGO = International Federation of Gynecology and Obstetrics; FTC = fallopian tube cancer; ITT = intent-to-treat; Max = maximum; Min = minimum; PPC = primary peritoneal cancer; StD = standard deviation.

Table 17 Prior Anticancer Treatment (ITT Population)

	Rucaparib (N = 427)	Placebo (N = 111)	Total (N = 538)
Prior Cycles of Doublet (Platinum/Taxane)			
Mean (StD)	6.4 (0.92)	6.4 (0.89)	6.4 (0.91)
Median	6.0	6.0	6.0
Min, Max	4, 8	4, 8	4, 8
Prior Cycles of Doublet (Platinum/Taxane), n (%)			
< 4 Cycles	0	0	0
4 to < 6 Cycles	26 (6.1)	8 (7.2)	34 (6.3)
6 to 8 Cycles	401 (93.9)	103 (92.8)	504 (93.7)
> 8 Cycles	0	0	0
Prior Cycles of Platinum			
Mean (StD)	6.5 (0.89)	6.5 (0.85)	6.5 (0.88)
Median	6.0	6.0	6.0
Min, Max	4, 8	5, 8	4, 8
Prior Cycles of Platinum, n (%)			
< 4 Cycles	0	0	0
4 to < 6 Cycles	13 (3.0)	4 (3.6)	17 (3.2)
6 to 8 Cycles	414 (97.0)	107 (96.4)	521 (96.8)
> 8 Cycles	0	0	0
Number of Patients With Prior Bevacizumab[a] During First-line Chemotherapy, n (%)			
Yes	84 (19.7)	12 (10.8)	96 (17.8)
No	343 (80.3)	99 (89.2)	442 (82.2)
Duration Since Last Dose of Chemotherapy (weeks), n (%)			
< 2 Weeks	1 (0.2)	0	1 (0.2)
2 to < 4 Weeks	26 (6.1)	4 (3.6)	30 (5.6)
4 to < 6 Weeks	113 (26.5)	33 (29.7)	146 (27.1)
6 to < 8 Weeks	217 (50.8)	61 (55.0)	278 (51.7)
8 Weeks	65 (15.2)	10 (9.0)	75 (13.9)
> 8 Weeks	5 (1.2)	3 (2.7)	8 (1.5)

	Rucaparib (N = 427)	Placebo (N = 111)	Total (N = 538)
Route of Administration for Chemotherapy, n (%)			
IV only without HIPEC	395 (92.5)	107 (96.4)	502 (93.3)
IP only without HIPEC	2 (0.5)	0	2 (0.4)
IV only with HIPEC	12 (2.8)	0	12 (2.2)
IP only with HIPEC	0	0	0
IV and IP without HIPEC	17 (4.0)	4 (3.6)	21 (3.9)
IV and IP with HIPEC	1 (0.2)	0	1 (0.2)
Number of Prior Surgeries, n (%)			
0	0	0	0
1	404 (94.6)	104 (93.7)	508 (94.4)
2	23 (5.4)	7 (6.3)	30 (5.6)
> 2	0	0	0
Best Response to Chemotherapy, n (%)			
Radiological			
Complete Response	73 (17.1)	11 (9.9)	84 (15.6)
Partial Response	76 (17.8)	22 (19.8)	98 (18.2)
No Disease Post Surgery	224 (52.5)	64 (57.7)	288 (53.5)
Inevaluable	53 (12.4)	14 (12.6)	67 (12.5)
Other	1 (0.2)	0	1 (0.2)
CA-125 Response			
Response	390 (91.3)	104 (93.7)	494 (91.8)
No Response	11 (2.6)	1 (0.9)	12 (2.2)
Inevaluable	23 (5.4)	6 (5.4)	29 (5.4)
Other	3 (0.7)	0	3 (0.6)
Disease Free After Chemotherapy With Normal CA-125, n (%)			
Yes	270 (63.2)	69 (62.2)	339 (63.0)
No	157 (36.8)	42 (37.8)	199 (37.0)
Type of Surgery, n (%)			
Bilateral salpingo-oophorectomy	422 (98.8)	111 (100.0)	533 (99.1)
Hysterectomy	367 (85.9)	102 (91.9)	469 (87.2)
Partial Omentectomy	66 (15.5)	21 (18.9)	87 (16.2)
Full Omentectomy	364 (85.2)	93 (83.8)	457 (84.9)
Other	233 (54.6)	57 (51.4)	290 (53.9)
Cytoreductive Surgery Outcome, n (%)			
Complete Resection = R0	263 (61.6)	73 (65.8)	336 (62.5)
Microscopic Residual < 1 cm	81 (19.0)	15 (13.5)	96 (17.8)
Macroscopic Residual ≥ 1 cm	83 (19.4)	23 (20.7)	106 (19.7)

	Rucaparib (N = 427)	Placebo (N = 111)	Total (N = 538)
Not Applicable	0	0	0
Randomization Stratification of Disease Status Post-chemotherapy, n (%)			
No Residual Disease	322 (75.4)	82 (73.9)	404 (75.1)
Residual Disease	105 (24.6)	29 (26.1)	134 (24.9)
Disease Status Based on EDC, n (%)			
No Residual Disease	308 (72.1)	77 (69.4)	385 (71.6)
Residual Disease	119 (27.9)	34 (30.6)	153 (28.4)
Randomization Stratification of Timing of Surgery, n (%)			
Primary Surgery	209 (48.9)	54 (48.6)	263 (48.9)
Interval Debulking	218 (51.1)	57 (51.4)	275 (51.1)
Timing of Surgery Based on EDC, n (%)			
Primary Surgery	208 (48.7)	51 (45.9)	259 (48.1)
Interval Debulking	219 (51.3)	60 (54.1)	279 (51.9)

Source: Table 14, ATHENA-MONO CSR.
Abbreviations: CA-125 = cancer antigen 125; EDC = electronic data capture; HIPEC = hyperthermic intraperitoneal chemotherapy; IP = intraperitoneal; ITT = intent-to-treat; IV = intravenous; Max = maximum; Min = minimum; StD = standard deviation.
[a] Maintenance bevacizumab was not permitted.

Table 18 Disease Burden (ITT Population)

	Rucaparib (N = 427)	Placebo (N = 111)	Total (N = 538)
Measurable Disease at Baseline per Investigator, n (%)			
Yes	41 (9.6)	11 (9.9)	52 (9.7)
No	386 (90.4)	100 (90.1)	486 (90.3)
Only Non-measurable Disease at Baseline per Investigator, n (%)			
Yes	73 (17.1)	23 (20.7)	96 (17.8)
No	354 (82.9)	88 (79.3)	442 (82.2)
Without Disease at Baseline per Investigator, n (%)			
Yes	313 (73.3)	77 (69.4)	390 (72.5)
No	114 (26.7)	34 (30.6)	148 (27.5)
CA-125 within Normal Limits at Baseline, per Central Lab, n (%)			
Yes	371 (86.9)	100 (90.1)	471 (87.5)
No	56 (13.1)	11 (9.9)	67 (12.5)

Source: Table 14.1.4.4.2 (t-disb-itt).
Abbreviations: CA-125 = cancer antigen 125; ITT = intent-to-treat.

Concomitant medications

The highest incidence of concomitant medication usage coded by ATC class included anilides, proton pump inhibitors, serotonin (5HT3) antagonists, propionic acid derivatives, and osmotically acting laxatives.

The most commonly used concomitant medications included paracetamol, ondansetron, ibuprofen, omeprazole, gabapentin, and cholecalciferol.

Subsequent therapies

At the time of the visit cut-off, the majority of patients were still being followed. There were 287/538 patients (53.3%) in the ITT Population who initiated at least 1 regimen of subsequent anticancer therapy. Of these, 24/208 (11.5%) patients in the rucaparib group and 26/79 (32.9%) patients in the placebo group received subsequent PARP inhibitor therapy including olaparib, niraparib, veliparib, and rucaparib. Other subsequent anticancer therapy included liposomal doxorubicin/doxorubicin, bevacizumab, cisplatin, carboplatin, gemcitabine, and paclitaxel.

Table 19 Overall Subsequent Anticancer Treatment in the ITT Population

	ITT		
	Rucaparib (N=427)	**Placebo (N=111)**	**Overall (N=538)**
Number of Patients With At Least One Subsequent Therapy for Ovarian Cancer Reported at Data Cut	208 (48.7)	79 (71.2)	287 (53.3)
Chemotherapy	197 (94.7)	77 (97.5)	274 (95.5)
Platinum-based Chemotherapy	171 (82.2)	61 (77.2)	232 (80.8)
Non-Platinum Chemotherapy	95 (45.7)	37 (46.8)	132 (46.0)
Non-Chemotherapy	46 (22.1)	24 (30.4)	70 (24.4)

Table 20 Summary of First Subsequent Therapy for Ovarian Cancer by ITT and HRD, Populations

Anticancer Treatment	ITT		HRD	
	Rucaparib (N=427) n (%)	**Placebo (N=111) n (%)**	**Rucaparib (N=185) n (%)**	**Placebo (N=49) n (%)**
At Least One Subsequent Anticancer Therapy	**208 (48.7)**	**79 (71.2)**	**73 (39.5)**	**29 (59.2)**
Any Chemotherapy	189 (90.9)	76 (96.2)	67 (91.8)	28 (96.6)
Platinum-based Chemotherapy	159 (76.4)	51 (64.6)	61 (83.6)	19 (65.5)
w/ PARPi maintenance	5 (2.4)	10 (12.7)	2 (2.7)	4 (13.8)
w/Bevacizumab	61 (29.3)	19 (24.1)	27 (37.0)	9 (31.0)
w/Bevacizumab and PARPi maintenance	0 (0.0)	3 (3.8)	0 (0.0)	2 (6.9)
All Other	93 (44.7)	19 (24.1)	32 (43.8)	4 (13.8)
Non-Platinum Chemotherapy	30 (14.4)	25 (31.6)	6 (8.2)	9 (31.0)
Non-Chemotherapy	19 (9.1)	3 (3.8)	6 (8.2)	1 (3.4)
PARPi	8 (3.8)	0 (0.0)	4 (5.5)	0 (0.0)
Monoclonal Antibody	2 (1.0)	1 (1.3)	0 (0.0)	1 (3.4)
Hormonal Therapy	9 (4.3)	1 (1.3)	2 (2.7)	0 (0.0)
Other	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)

Data cutoff is 23MAR2022.
Source: Table 12.2.1

Abbreviations: HRD=homologous recombination deficient, ITT=Intent to Treat, PARPi=PARP inhibitor

Numbers analysed

There were **538 patients** randomised into the ATHENA–MONO treatment comparison (i.e. the **ITT Population**); 427 patients in the rucaparib group and 111 patients in the placebo group. The ITT

Population consisted of all the non-nested molecular subgroups: tBRCA, non-tBRCA LOH-high, non-tBRCA LOH-low, and non-tBRCA LOH unknown. The **HRD Population** (tBRCA and non-tBRCA LOH-high) included **234 patients** overall (43.5% of the ITT Population), with 185 patients in the rucaparib group and 49 patients in the placebo group.

Three patients who were randomised (rucaparib, n = 2; placebo, n = 1) discontinued prior to receiving any oral study drug. Therefore, the **Safety Population** consisted of **535 patients** (99.4% of the ITT Population) who initiated treatment with either 600 mg BID rucaparib (n = 425) or placebo (n = 110).

Outcomes and estimation

The study is ongoing, and the data presented herein are based on a visit cut-off date of **23 March 2022** unless otherwise specified. Randomisation was complete as of 30 September 2020.

Table 21 Summary of efficacy results

Analysis Population/Subgroup	Events/N (%)		Kaplan-Meier Analysis[a] Rucaparib vs Placebo	Cox Proportional Hazard[b] Rucaparib vs Placebo
PRIMARY ENDPOINT				
invPFS[c]	**Rucaparib**	**Placebo**	**Medians (months) Log-rank p-value**	**Hazard Ratio (95% CI) p-value**
HRD	80/185 (43.2)	31/49 (63.3)	28.7 vs 11.3 p = 0.0004	0.47 (0.31, 0.72) p = 0.0005
ITT	230/427 (53.9)	78/111 (70.3)	20.2 vs 9.2 p = <.0001	0.52 (0.40, 0.68) p = <.0001
tBRCA	30/91 (33.0)	14/24 (58.3)	NR vs 14.7 p = 0.0041	0.40 (0.21, 0.75) p = 0.0045
Non-tBRCA LOH^{high}	50/94 (53.2)	17/25 (68.0)	20.3 vs 9.2 p = 0.0584	0.58 (0.33, 1.01) p = 0.0524
Non-tBRCA LOH^{low}	120/189 (63.5)	35/49 (71.4)	12.1 vs 9.1 p = 0.0284	0.65 (0.45, 0.95) p = 0.0260
Non-tBRCA LOH^{unknown}	30/53 (56.6)	12/13 (92.3)	17.5 vs 8.9 p = 0.0068	0.39 (0.20, 0.78) p = 0.0072
KEY SECONDARY AND EXPLORATORY ENDPOINTS				
bicrPFS[c]	**Rucaparib**	**Placebo**	**Medians (months) Log-rank p-value**	**Hazard Ratio (95% CI) p-value**
HRD	63/185 (34.1)	27/49 (55.1)	NR vs 9.9 p = 0.0004	0.44 (0.28, 0.70) p = 0.0005

Analysis Population/Subgroup	Events/N (%)		Kaplan-Meier Analysis[a] Rucaparib vs Placebo	Cox Proportional Hazard[b] Rucaparib vs Placebo
ITT	192/427 (45.0)	70/111 (63.1)	25.9 vs 9.1 p = <.0001	0.47 (0.36, 0.63) p = <.0001
tBRCA	24/91 (26.4)	10/24 (41.7)	NR vs NR p = 0.0566	0.48 (0.23, 1.00) p = 0.0512
Non-tBRCA LOH^{high}	39/94 (41.5)	17/25 (68.0)	27.8 vs 9.1 p = 0.0072	0.46 (0.26, 0.81) p = 0.0074
Non-tBRCA LOH^{low}	103/189 (54.5)	32/49 (65.3)	12.0 vs 6.4 p = 0.0119	0.60 (0.40, 0.89) p = 0.0113
Non-tBRCA LOH^{unknown}	26/53 (49.1)	11/13 (84.6)	17.4 vs 6.5 p = 0.0020	0.33 (0.16, 0.68) p = 0.0026
OS[d]	**Rucaparib**	**Placebo**	**Medians (months) Log-rank p-value**	**Hazard Ratio (95% CI) p-value**
HRD	46/185 (24.9)	12/49 (24.5)	NR vs NR p = 0.6470	0.84 (0.44, 1.58) p = 0.5811
ITT	144/427 (33.7)	42/111 (37.8)	NR vs 46.2 p = 0.3015	0.83 (0.58, 1.17) p = 0.2804
tBRCA	18/91 (19.8)	3/24 (12.5)	NR vs NR p = 0.3835	1.51 (0.47, 4.86) p = 0.4919[c]
Non-tBRCA LOH^{high}	28/94 (29.8)	9/25 (36.0)	NR vs 41.0 p = 0.2370	0.61 (0.29, 1.30) p = 0.2019[c]
Non-tBRCA LOH^{low}	79/189 (41.8)	26/49 (53.1)	42.9 vs 32.4 p = 0.2271	0.75 (0.48, 1.17) p = 0.2064[c]
Non-tBRCA LOH^{unknown}	19/53 (35.8)	4/13 (30.8)	NR vs NR p = 0.7533	1.08 (0.38, 3.09) p = 0.8797[c]
PFS2[d]	**Rucaparib**	**Placebo**	**Medians (months) Log-rank p-value**	**Hazard Ratio (95% CI) p-value**
HRD	71/185 (38.4)	20/49 (40.8)	NR vs 39.9 p = 0.2992	0.75 (0.46, 1.24) p = 0.2682
ITT	207/427 (48.5)	59/111 (53.2)	36.0 vs 26.8 p = 0.2606	0.84 (0.63, 1.13) p = 0.2441
tBRCA	27/91 (29.7)	9/24 (37.5)	NR vs NR p = 0.4617	0.73 (0.34, 1.54) p = 0.4045
Non-tBRCA LOH^{high}	44/94 (46.8)	11/25 (44.0)	39.0 vs NR p = 0.6575	0.83 (0.43, 1.60) p = 0.5855
Non-tBRCA LOH^{low}	109/189 (57.7)	33/49 (67.3)	24.4 vs 20.0 p = 0.2102	0.77 (0.52, 1.14) p = 0.1918
Non-tBRCA LOH^{unknown}	27/53 (50.9)	6/13 (46.2)	29.0 vs NR p = 0.8100	1.05 (0.44, 2.50) p = 0.9158

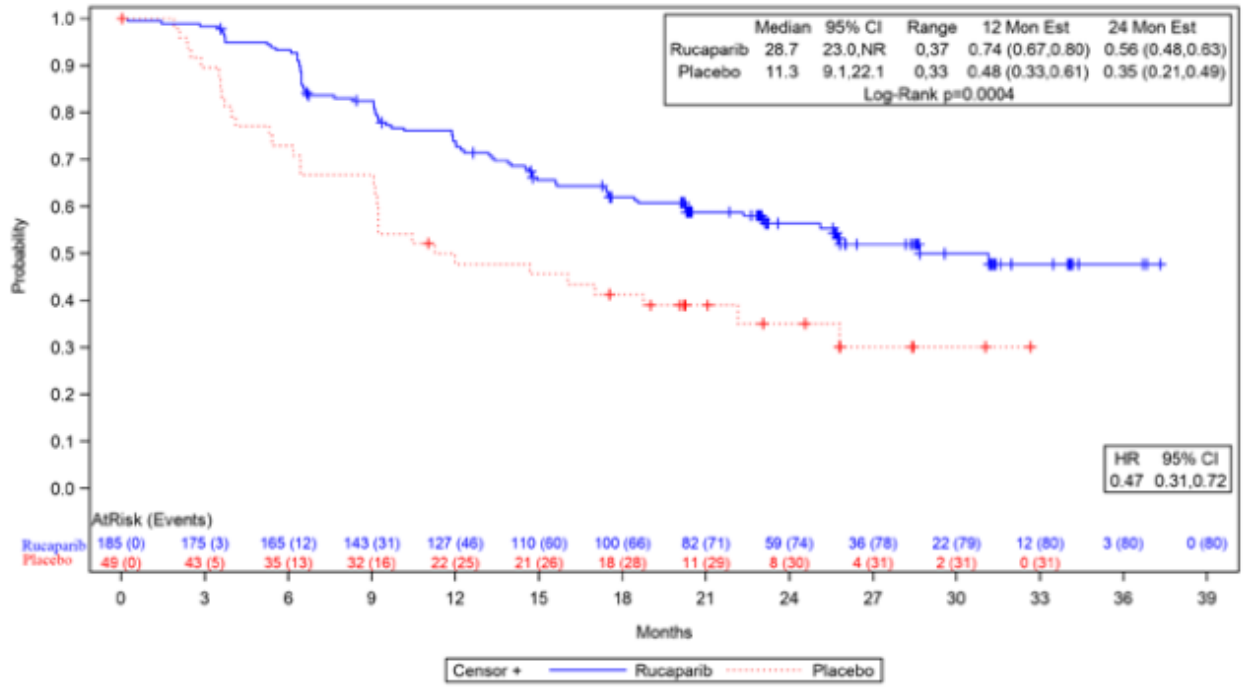
[a]Log-rank analysis performed by randomization strata for the ITT and HRD Populations and unstratified for the non-nested subgroups.
[b]Cox proportional hazards method performed by randomization strata for the ITT and HRD Populations and unstratified for the non-nested subgroups.
[c]Data cutoff is 23MAR2022.
[d]Data cutoff is 09 March 2023
NR=not reached

Primary endpoint – PFS as assessed by Investigator

The first step of the procedure showed a statistically significant improvement in invPFS with rucaparib treatment compared to placebo (log-rank, p = 0.0004) for the **HRD Population**.

The stratified Cox proportional hazards model showed a statistically significant improvement in invPFS with rucaparib treatment compared to placebo (HR 0.47 [95% CI, 0.31-0.72; p = 0.0005]).

Figure 21 PFS per Investigator (HRD Population)

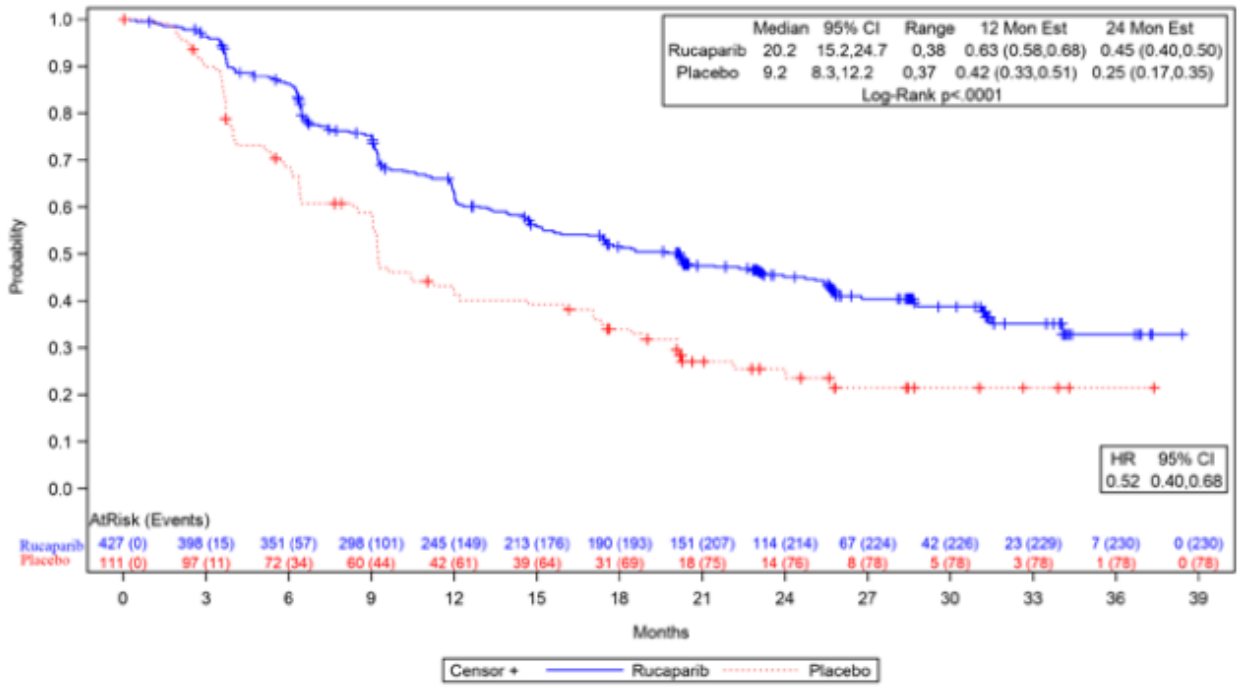


Source: Table 14.2.1.1.1 (t-pfs-hrd); Table 14.2.1.1.3 (t-pfsmo-hrd); Figure 14.2.1.1.1 (f-pfs-hrd).
Abbreviations: CI = confidence interval; HR = hazard ratio; HRD = homologous recombination deficiency; NR = not reached; PFS = progression-free survival.

There was a statistically significant improvement in invPFS with rucaparib treatment compared to placebo group (log-rank, $p < 0.0001$) for the **ITT Population**.

The stratified Cox proportional hazards model showed a statistically significant improvement in invPFS with rucaparib treatment compared to placebo (HR 0.52 [95% CI, 0.40-0.68]; $p < 0.0001$).

Figure 22 PFS per Investigator (ITT Population)



Source: Table 14.2.1.1.2 (t-pfs-itt); Table 14.2.1.1.4 (t-pfsmo-itt); Figure 14.2.1.1.2 (f-pfs-itt).
Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; PFS = progression-free survival.

Table 22 Summary of Events- Progression Free Survival by Investigator and BICR

Event Information	Rucaparib	Placebo	Rucaparib	Placebo
	PFS by Investigator		PFS BICR	
HRD				
Number of Events				
Total	80	31	63	27
Disease Progression	76	31	59	27
Death	4	0	4	0
Rate of Patients Event-Free[a], % (95% CI)				
6 Months	93.2 (88.4, 96.1)	72.9 (58.0, 83.3)	89.8 (84.3, 93.4)	72.9 (58.0, 83.3)
12 Months	73.8 (66.6, 79.7)	47.7 (33.1, 61.0)	73.7 (66.4, 79.7)	45.7 (31.3, 59.0)
18 Months	62.0 (54.3, 68.7)	41.2 (27.2, 54.7)	66.6 (58.8, 73.2)	43.2 (28.9, 56.7)
24 Months	56.3 (48.3, 63.5)	35.0 (21.1, 49.3)	62.6 (54.5, 69.6)	43.2 (28.9, 56.7)
ITT				
Number of Events				
Total	230	78	192	70
Disease Progression	224	78	185	70
Death	6	0	7	0
Rate of Patients Event-Free[a], % (95% CI)				
6 Months	86.2 (82.4, 89.1)	68.4 (58.7, 76.3)	83.8 (79.9, 87.1)	64.3 (54.4, 72.6)
12 Months	63.0 (58.1, 67.5)	42.1 (32.6, 51.4)	61.9 (56.9, 66.6)	36.1 (26.9, 45.4)
18 Months	51.5 (46.5, 56.3)	34.0 (25.0, 43.2)	53.1 (47.9, 58.1)	31.7 (22.8, 41.0)
24 Months	45.1 (40.0, 50.0)	25.4 (17.1, 34.6)	50.1 (44.7, 55.2)	31.7 (22.8, 41.0)

[a] The proportion of patients progression free at each time point is estimated using the Kaplan-Meier (KM) methodology and the 95% confidence intervals are estimated using Greenwood's estimate of the variance of the KM proportion.
NR=not reached
Data cutoff is 23MAR2022.

Table 23 Summary of Reasons for Censoring Progression Free Survival by Investigator by ITT, HRD and tBRCA Populations

	ITT		HRD		tBRCA	
	Rucaparib (N=427)	Placebo (N=111)	Rucaparib (N=185)	Placebo (N=49)	Rucaparib (N=91)	Placebo (N=24)
Progression Free Survival by Investigator Status						
Had Event	230 (53.9%)	78 (70.3%)	80 (43.2%)	31 (63.3%)	30 (33.0%)	14 (58.3%)
Censored	197 (46.1%)	33 (29.7%)	105 (56.8%)	18 (36.7%)	61 (67.0%)	10 (41.7%)
Reason for Censoring [1]						
Study drug never initiated	2 (1.0%)	1 (3.0%)	1 (1.0%)	1 (5.6%)	0 (0.0%)	1 (10.0%)
Treatment ongoing						
Ongoing with oral and IV treatment	48 (24.4%)	9 (27.3%)	30 (28.6%)	7 (38.9%)	19 (31.1%)	4 (40.0%)
Ongoing with oral treatment	2 (1.0%)	1 (3.0%)	2 (1.9%)	1 (5.6%)	1 (1.6%)	1 (10.0%)
Treatment discontinued						
Ongoing in LTFU (Alive)[2]	113 (57.4%)	13 (39.4%)	59 (56.2%)	8 (44.4%)	34 (55.7%)	4 (40.0%)
Started subsequent treatment[3]	16 (8.1%)	6 (18.2%)	6 (5.7%)	0 (0.0%)	4 (6.6%)	0 (0.0%)
Gap in assessments	2 (1.0%)	1 (3.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
No scan data available	8 (4.1%)	1 (3.0%)	5 (4.8%)	0 (0.0%)	2 (3.3%)	0 (0.0%)
Withdrew consent	5 (2.5%)	0 (0.0%)	2 (1.9%)	0 (0.0%)	1 (1.6%)	0 (0.0%)
Lost to follow-up	1 (0.5%)	1 (3.0%)	0 (0.0%)	1 (5.6%)	0 (0%)	0 (0%)

[1] Denominator includes patients that were censored.
[2] Ongoing with no progression event
[3] No progression event prior to starting subsequent treatment
Data cutoff is 23MAR2022.

Table 24 PFS by Investigator Review in the Primary Analysis Populations and Non-nested Molecular Subgroups

Analysis Population	Median invPFS (95% CI) Months Rucaparib vs Placebo[a]	Hazard Ratio (95% CI)[b]
Primary Analysis Populations		
HRD Rucaparib n = 185 Placebo n = 49	28.7 (23.0, NR) vs 11.3 (9.1, 22.1) p = 0.0004	0.47 (0.31, 0.72) p = 0.0005
ITT Rucaparib n = 427 Placebo n = 111	20.2 (15.2, 24.7) vs 9.2 (8.3, 12.2) p < 0.0001	0.52 (0.40, 0.68) p < 0.0001
Exploratory Analysis of Non-nested Molecular Subgroups		
tBRCA Rucaparib n = 91 Placebo n = 24	NR (25.8, NR) vs 14.7 (6.4, NR) p = 0.0041	0.40 (0.21, 0.75) p = 0.0045
Non-tBRCA LOH^{high} Rucaparib n = 94 Placebo n = 25	20.3 (13.4, 31.1) vs 9.2 (4.0, 22.1) p = 0.0584	0.58 (0.33, 1.01) p = 0.0524
Non-tBRCA LOH^{low} Rucaparib n = 189 Placebo n = 49	12.1 (11.1, 17.7) vs 9.1 (4.0, 12.2) p = 0.0284	0.65 (0.45, 0.95) p = 0.0260
Non-tBRCA $LOH^{unknown}$ Rucaparib n = 53 Placebo n = 13	17.5 (10.6, 34.1) vs 8.9 (5.1, 20.1) p = 0.0068	0.39 (0.20, 0.78) p = 0.0072

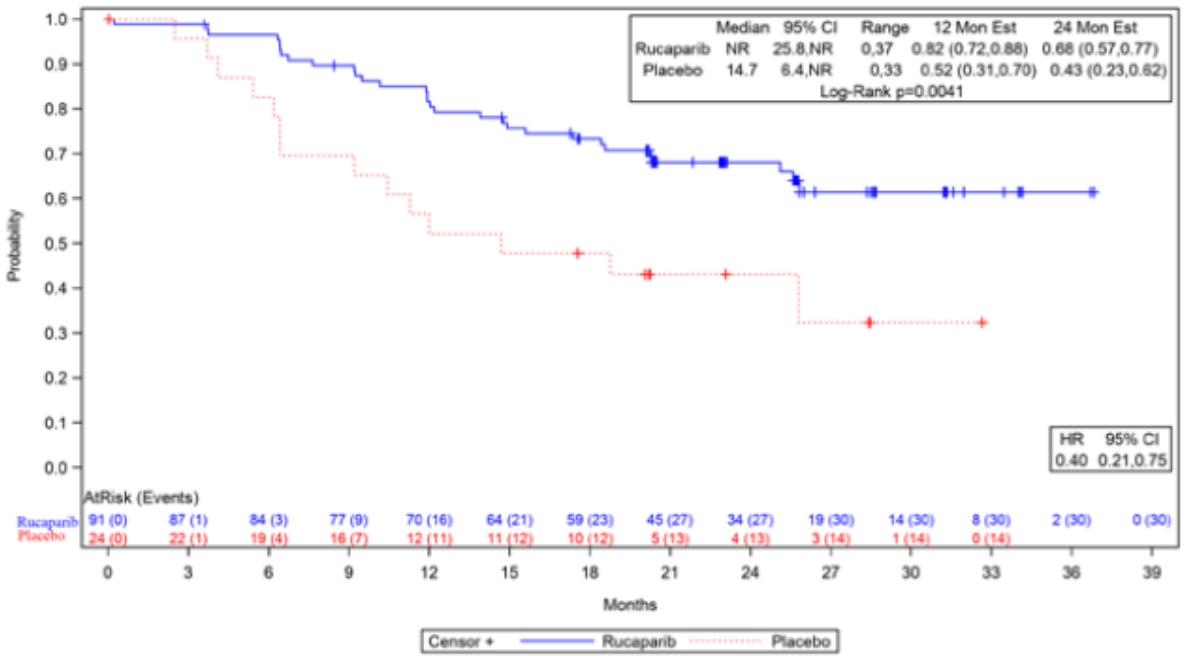
Source: Table 27, ATHENA-MONO CSR.

Abbreviations: BRCA = breast cancer gene; CI = confidence interval; HRD = homologous recombination deficiency; invPFS = investigator-assessed progression-free survival; ITT = intent-to-treat; LOH = loss of heterozygosity; LOH^{high} = LOH ≥ 16%; LOH^{low} = LOH< 16%; $LOH^{unknown}$ = LOH that is unknown; non-tBRCA = BRCA wild-type; NR = not reached; PFS = progression-free survival; tBRCA = tumor tissue mutation in BRCA; vs = versus.

[a] Stratified log-rank analysis was used for HRD and ITT Populations; the non-nested subgroups were tested with an unstratified analysis.

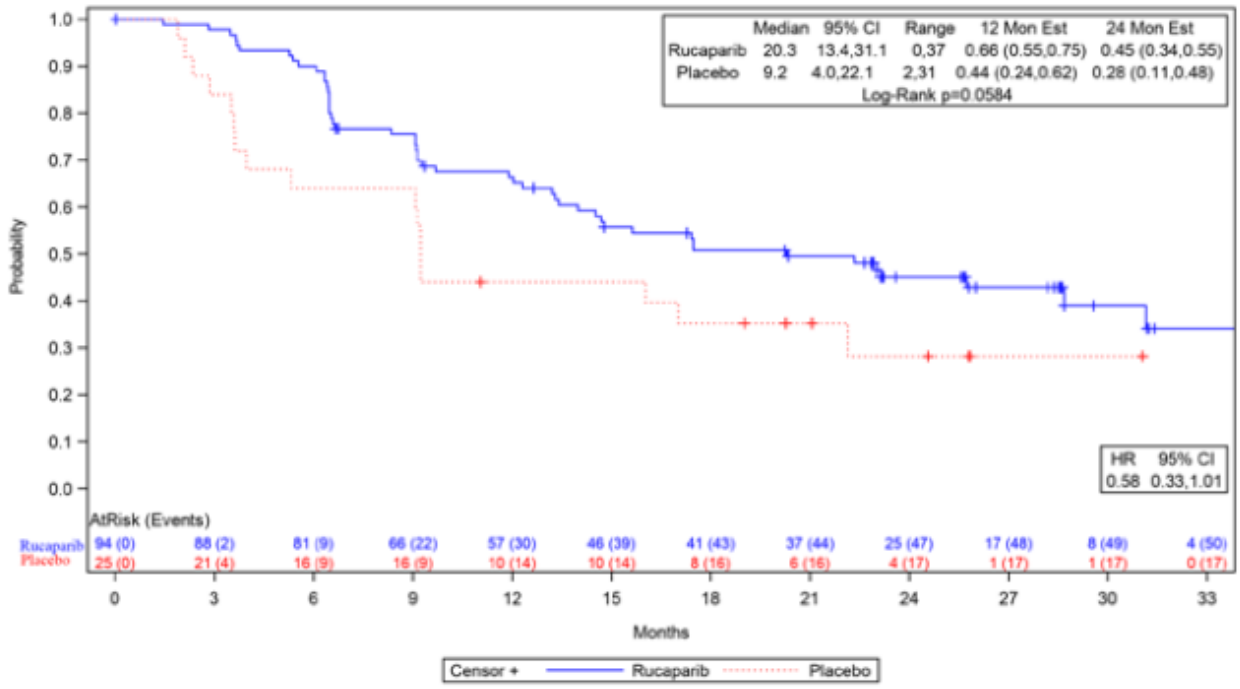
[b] Stratified Cox proportional hazards model was used for HRD and ITT Populations; the non-nested subgroups were tested with an unstratified analysis.

Figure 23 PFS per Investigator (tBRCA Subgroup)



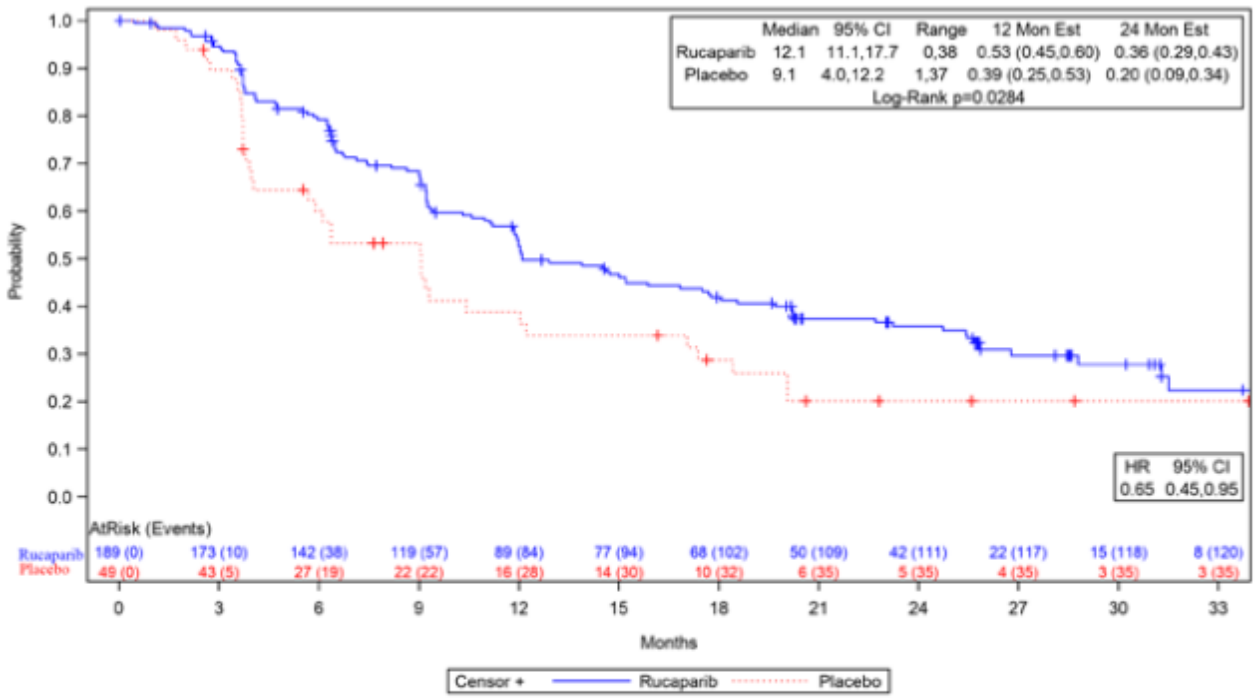
Source: Table 14.2.1.5.2 (t-pfs-sghrd); Table 14.2.1.1.5 (t-pfsmo-tbrca); Figure 14.2.1.5.1 (f-pfs-tbrca).
Abbreviations: BRCA = breast cancer gene; CI = confidence interval; HR = hazard ratio; PFS = progression-free survival; tBRCA = tumor tissue mutation in BRCA.

Figure 24 PFS per Investigator (non-tBRCA LOH-high Subgroup)



Source: Table 14.2.1.5.2 (t-pfs-sghrd); Table 14.2.1.1.6 (t-pfsmo-lohp); Figure 14.2.1.5.2 (f-pfs-lohp).
Abbreviations: BRCA = breast cancer gene; CI = confidence interval; HR = hazard ratio; LOH = loss of heterozygosity; non-tBRCA LOH^{high} = BRCA wild-type with LOH ≥ 16%; PFS = progression-free survival; tBRCA = tumor tissue mutation in BRCA.

Figure 25 PFS per Investigator (non-tBRCA LOH-low Subgroup)



Source: Table 14.2.1.5.2 (t-pfs-sghrd); Table 14.2.1.1.7 (t-pfsmo-lohn); Figure 14.2.1.5.3 (f-pfs-lohn).
Abbreviations: BRCA = breast cancer gene; CI = confidence interval; HR = hazard ratio; LOH = loss of heterozygosity; non-tBRCA LOH^{low} = BRCA wild-type with LOH < 16%; PFS = progression-free survival; tBRCA = tumor tissue mutation in BRCA.

Sensitivity analyses

- invPFS Adjusted by Actual Stratification

A sensitivity analysis of invPFS was performed using the actual supportive data in the eCRF for the corresponding stratification groups: HRD population: HR 0.49 [95% CI: 0.32, 0.75]; ITT population: HR 0.54 [95% CI: 0.41, 0.70].

- invPFS Adjusted to Evaluate the Impact of Censored Patients

Sensitivity analyses for invPFS were performed to evaluate the impact of censored patients.

A sensitivity analysis for invPFS was performed in which all scans and data were used for assessment of PFS even if the patient discontinued study treatment or initiated a subsequent anticancer therapy: HRD population: HR 0.48 [95% CI: 0.48 0.31, 0.73]; ITT population: HR 0.52 [95% CI: 0.40, 0.68].

A second sensitivity analysis of invPFS with respect to censoring was performed in which patients who discontinued oral study drug due to clinical progression or who withdrew consent from treatment were also considered events of invPFS on the date of the last dose of study drug: HRD population: HR 0.54 [95% CI: 0.36, 0.81]; ITT population: HR 0.56 [95% CI: 0.44, 0.72].

Secondary efficacy endpoints

- Overall survival (OS)

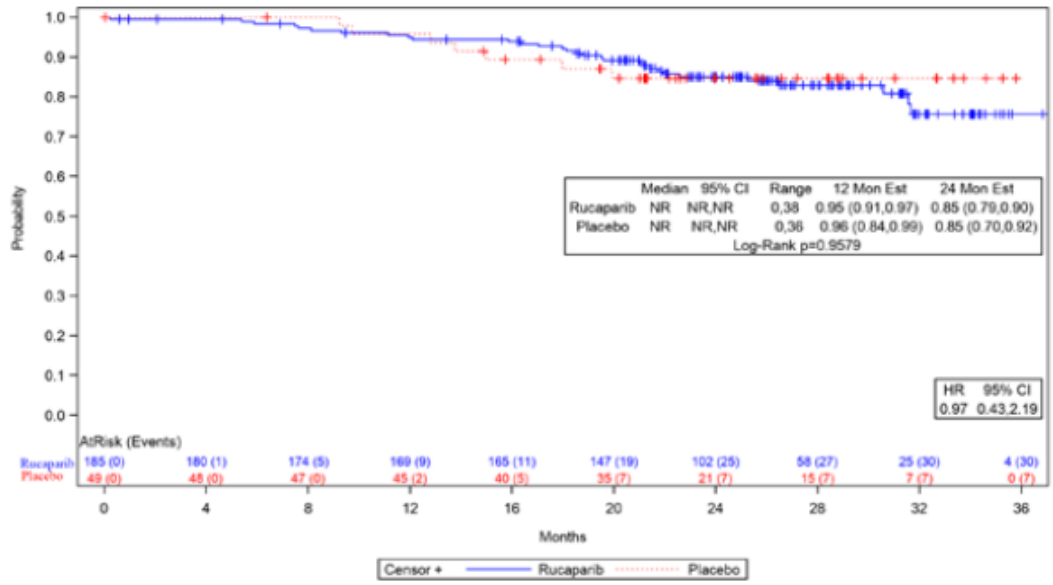
The first secondary endpoint in the step-down multiple comparisons procedure was OS; however, due to the immaturity of these data at the time of the primary endpoint analysis (death events: HRD

Population, 37/234 [15.8%]; ITT Population, 133/538 [24.7%]), an interim analysis of OS was performed.

For the HRD Population, the estimated KM probability of survival at 24 months was 85% for each treatment group.

For all patients in the HRD Population, the median duration of follow-up was 26.0 months (95% CI, 25.2-27.0) for rucaparib and 24.5 months (95% CI, 21.3-28.4) for placebo.

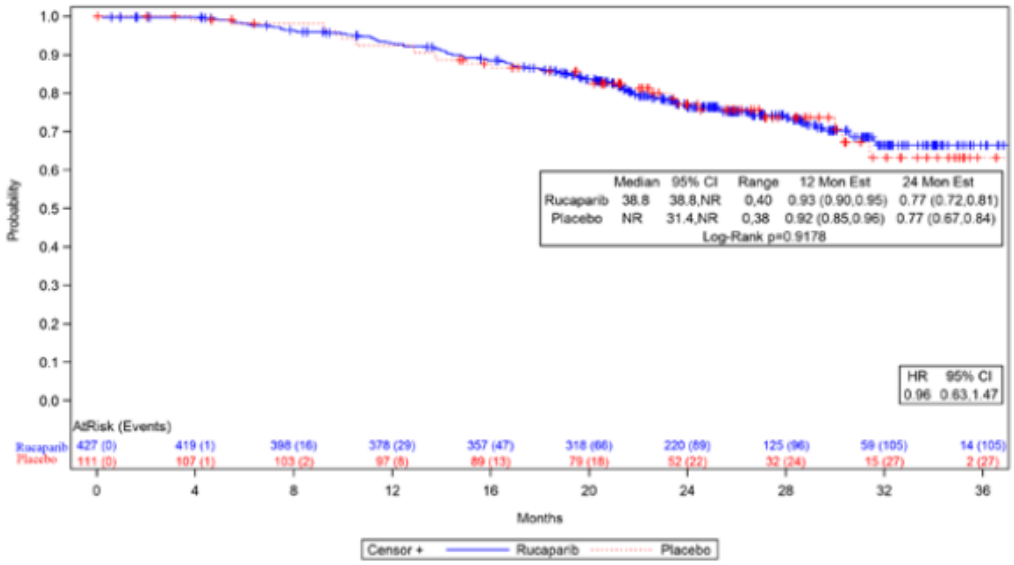
Figure 26 Interim OS (HRD Population)



Source: Table 14.2.3.1.1 (t os-hrd); Figure 14.2.3.1 (f-os-hrd).
Abbreviations: CI = confidence interval; Est = estimate; HR = hazard ratio; HRD = homologous recombination deficiency; Mon = month; NR = not reached; OS = overall survival.

For the ITT Population, the estimated KM probability of survival at 24 months was 77% for each treatment group. For all patients in the ITT Population, the median duration of follow-up was 26.1 months (95% CI, 25.8-26.9) for rucaparib and 26.2 months (95% CI, 24.0-27.7) for placebo.

Figure 27 Interim OS (ITT Population)



Source: Table 14.2.3.1.2 [t-os-itt]; Figures 14.2.3.2 (f-os-itt).
Abbreviations: CI = confidence interval; Est = estimate; HR = hazard ratio; ITT = intent-to-treat; Mon = month; NR = not reached; OS = overall survival.

Table 25 Interim OS – All Populations and Subgroups

Analysis Population/ Subgroup	Events/N (%)		Kaplan-Meier Analysis[a] Rucaparib vs Placebo	Cox Proportional Hazard[b] Rucaparib vs Placebo
	Rucaparib	Placebo	Medians (months) Log-rank p-value	Hazard Ratio (95% CI) p-value
HRD	30/185 (16.2)	7/49 (14.3)	NA vs NA p = 0.9579	0.97 (0.43, 2.19) p = 0.9431
ITT	106/427 (24.8)	27/111 (24.3)	38.8 vs NA p = 0.9178	0.96 (0.63, 1.47) p = 0.8688
tBRCA	12/91 (13.2)	1/24 (4.2)	NA vs NA p = 0.2340	2.24 (0.39, 12.99) p = 0.3688
Non-tBRCA LOH^{high}	18/94 (19.1)	6/25 (24.0)	NA vs NA p = 0.3946	0.64 (0.25, 1.59) p = 0.3331
Non-tBRCA LOH^{low}	63/189 (33.3)	17/49 (34.7)	38.8 vs 30.3 p = 0.8269	0.92 (0.54, 1.57) p = 0.7667
Non-tBRCA LOH^{unknown}	13/53 (24.5)	3/13 (23.1)	NA vs NA p = 0.8122	1.04 (0.31, 3.50) p = 0.9530

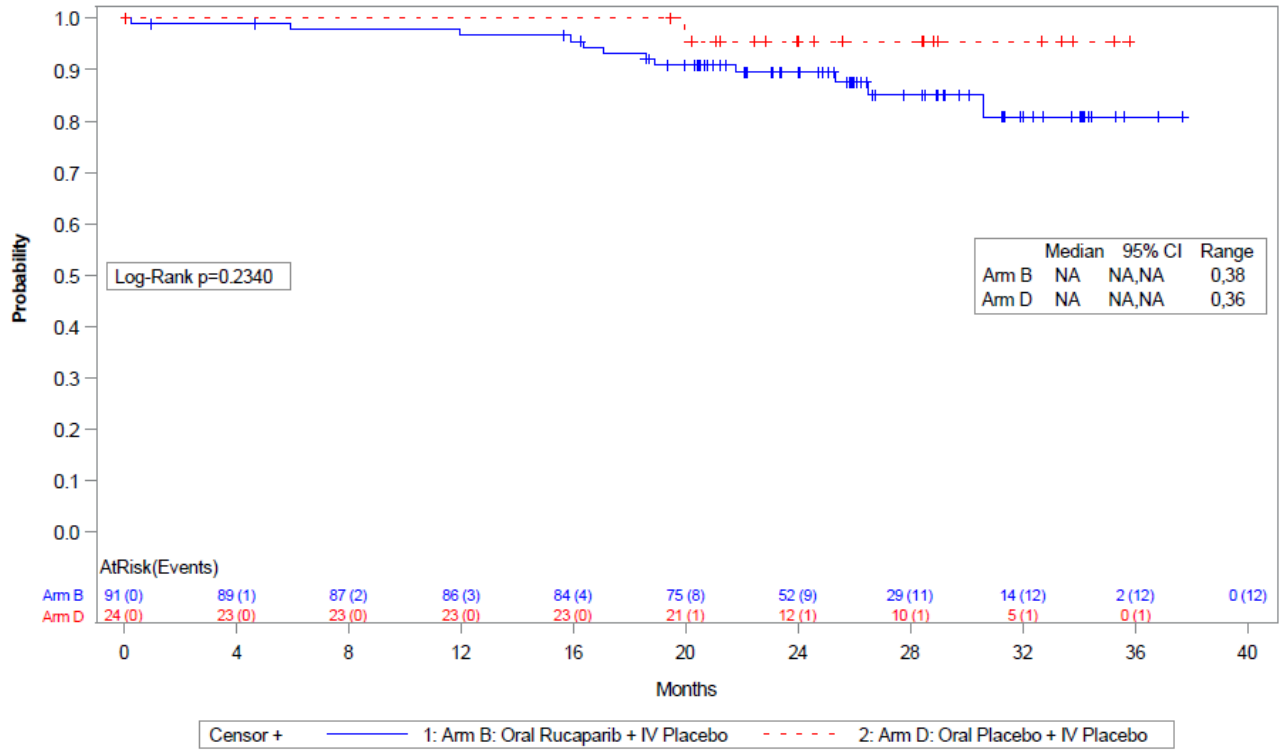
Source: Table 14.2.3.1.1 [t os-hrd]; Table 14.2.3.1.2 [t-os-itt]; Table 14.2.3.1.3 (t-os-tbrca), Table 14.2.3.1.5 (t-os-lohp), Table 14.2.3.1.6 (t-os-lohn), Table 14.2.3.1.7 (t-os-lohu), Figure 14.2.3.1 [f-os-hrd]; Figure 14.2.3.2 [f os-itt]; Figure 14.2.3.3 (f-os-tbrca) to Figure 14.2.3.6 (f-os-lohu), ATHENA-MONO CSR.
Abbreviations: BRCA = breast cancer gene; CI = confidence interval; HRD = homologous recombination deficiency; invPFS = investigator-assessed progression-free survival; ITT = intent-to-treat; LOH = loss of heterozygosity; LOH^{high} = LOH ≥ 16%; LOH^{low} = LOH< 16%; LOH^{unknown} = LOH that is unknown; NA = not available; non-tBRCA = BRCA wild-type; OS = overall survival; tBRCA = tumor tissue mutation in BRCA; vs = versus.

[a] Log-rank analysis performed by randomization strata for the ITT and HRD Populations and unstratified for the non-nested subgroups.

[b] Cox proportional hazards method performed by randomization strata for the ITT and HRD Populations and unstratified for the non-nested subgroups.

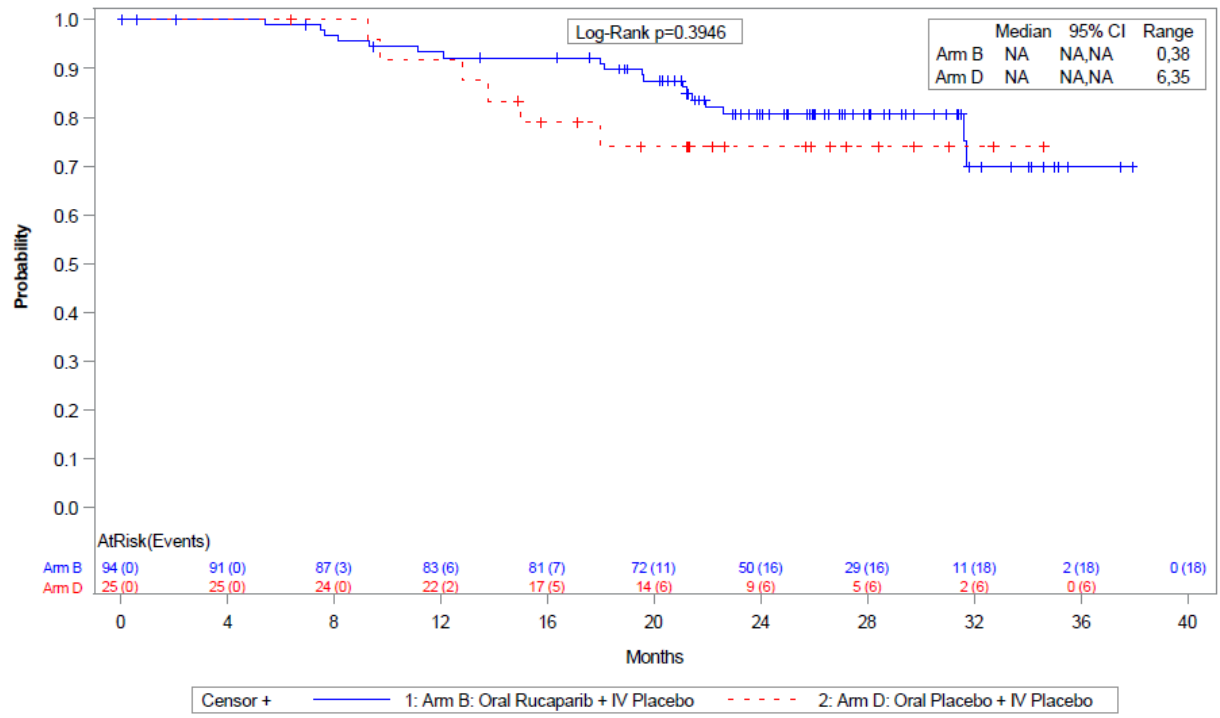
The analysis of OS in the non-nested molecular subgroups were exploratory.

Figure 28 Secondary Endpoint: Interim Overall Survival – tBRCA Population



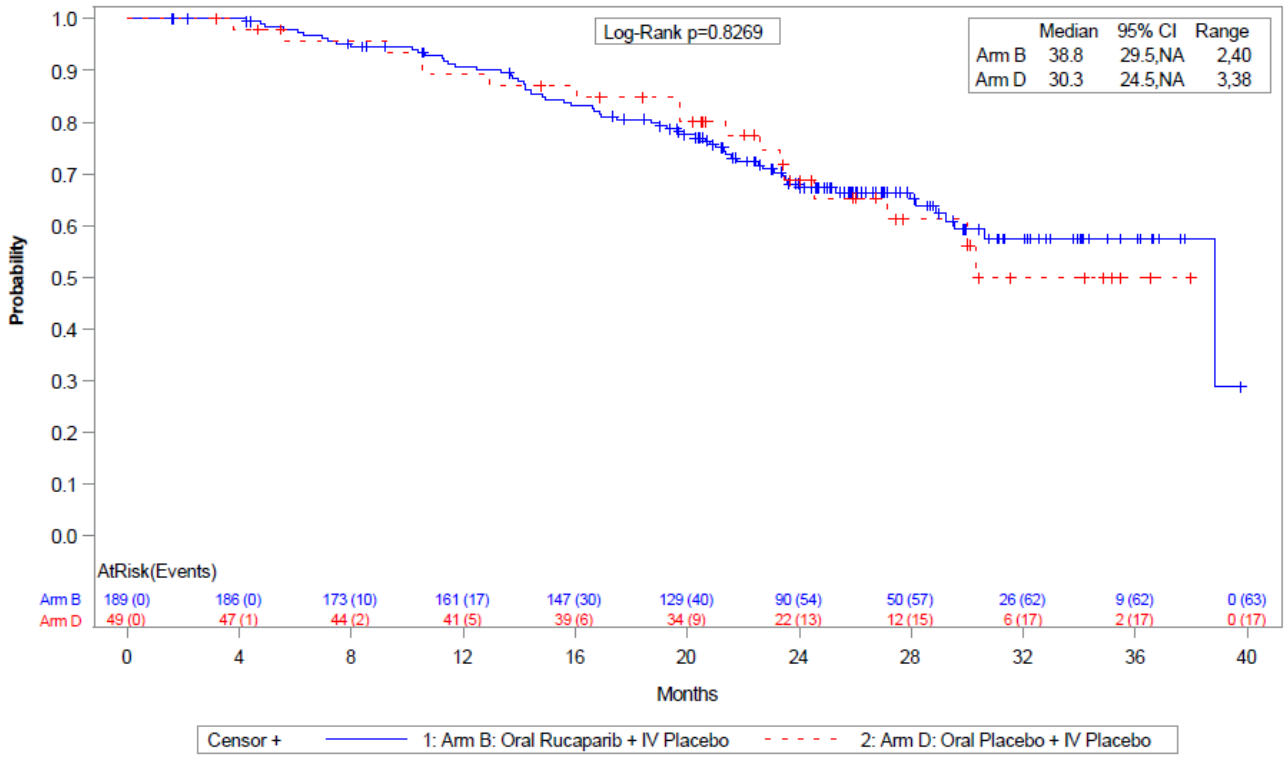
Data cutoff is 23MAR2022.

Figure 29 Secondary Endpoint: Interim Overall Survival – non-tBRCA LOH- high Population



Data cutoff is 08FEB2022.

Figure 30 Secondary Endpoint: Interim Overall Survival - non-tBRCA LOH-low Population



Data cutoff is 08FEB2022.

Updated OS data (data cut-off of 09 March 2023)

At the 09 March 2023 data cut, OS maturity had increased to 35% (186/538), versus 25% (133/538) at the 23 March 2022 data cut for the ITT population. With the additional approximately 1 year follow up, the hazard ratio decreased numerically in the ITT population (HR 0.83 [95%: CI 0.58-1.17]) and HRD population (HR 0.84 [95% CI: 0.44, 1.58]), as well as in all nested, non-nested and non-tBRCA groups, other than the small non-tBRCA LOH-unknown subgroup.

Table 26 Interim OS Analysis for Nested, Non-Nested, and non-tBRCA Groups (09 March 2023 vs 23 March 2022 Data Cut-off)

Analysis Population/Subgroup	23 March 2022 Data Cutoff (CSR)				09 March 2023 Data-Cutoff			
	Events/N (%)		Kaplan-Meier Analysis[a] Rucaparib vs Placebo	Cox Proportional Hazard[b] Rucaparib vs Placebo	Events/N (%)		Kaplan-Meier Analysis[a] Rucaparib vs Placebo	Cox Proportional Hazard[b] Rucaparib vs Placebo
OS	Rucaparib	Placebo	Medians (months) Log-rank p-value	Hazard Ratio (95% CI) p-value	Rucaparib	Placebo	Medians (months) Log-rank p-value	Hazard Ratio (95% CI) p-value
Primary Analysis Populations								
HRD	30/185 (16.2%)	7/49 (14.3%)	NR vs NR; p=0.9579	0.97 (0.43, 2.19); p=0.9431	46/185 (24.9)	12/49 (24.5)	NR vs NR p = 0.6470	0.84 (0.44, 1.58) p = 0.5811
ITT	106/427 (24.8%)	27/111 (24.3%)	38.8 vs NR p=0.9178	0.96 (0.63, 1.47); p=0.8688	144/427 (33.7)	42/111 (37.8)	NR vs 46.2 p = 0.3015	0.83 (0.58, 1.17) p = 0.2804
Exploratory Analysis Populations								
tBRCA	12/91 (13.2%)	1/24 (4.2%)	NR vs NR; p=0.2340[c]	2.24 (0.39, 12.99); p=0.3688[c]	18/91 (19.8)	3/24 (12.5)	NR vs NR p = 0.3835	1.51 (0.47, 4.86) p = 0.4919[c]
Non-tBRCA LOH^{high}	18/94 (19.1%)	6/25 (24.0%)	NR vs NR; p=0.3946[c]	0.64 (0.25, 1.59); p=0.3331[c]	28/94 (29.8)	9/25 (36.0)	NR vs 41.0 p = 0.2370	0.61 (0.29, 1.30) p = 0.2019[c]
Non-tBRCA LOH^{low}	63/189 (33.3%)	17/49 (34.7%)	38.8 vs 30.3; p=0.8269[c]	0.92 (0.54, 1.57); p=0.7667[c]	79/189 (41.8)	26/49 (53.1)	42.9 vs 32.4 p = 0.2271	0.75 (0.48, 1.17) p = 0.2064[c]
Non-tBRCA LOH^{unknown}	13/53 (24.5%)	3/13 (23.1%)	NR vs NR; p=0.8122[c]	1.04 (0.31, 3.50); p=0.9530[c]	19/53 (35.8)	4/13 (30.8)	NR vs NR p = 0.7533	1.08 (0.38, 3.09) p = 0.8797[c]
Non-tBRCA	94/336 (28.0)	26/87 (29.9)	38.8 vs NR p = 0.5641	87 (0.56, 1.34) p = 0.522	126/336 (37.5)	39/87 (44.8)	NR vs 38.8 p = 0.1356	0.75 (0.53, 1.08) p = 0.1238[c]

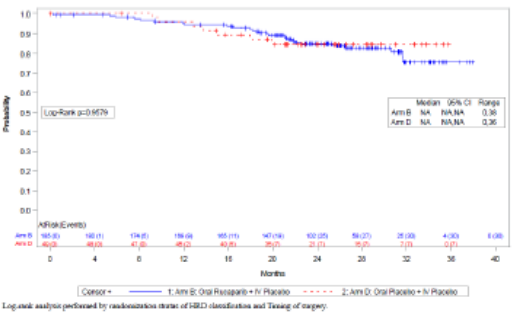
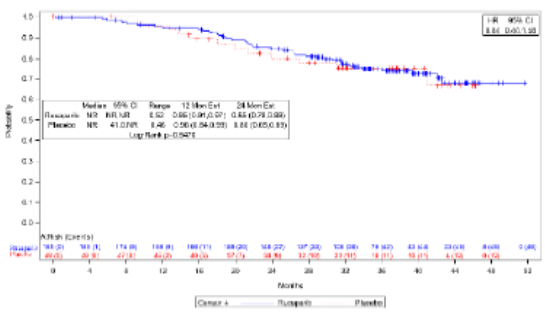
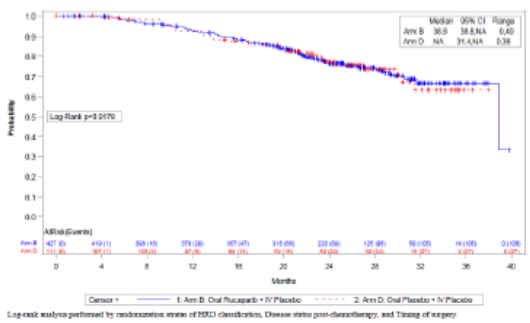
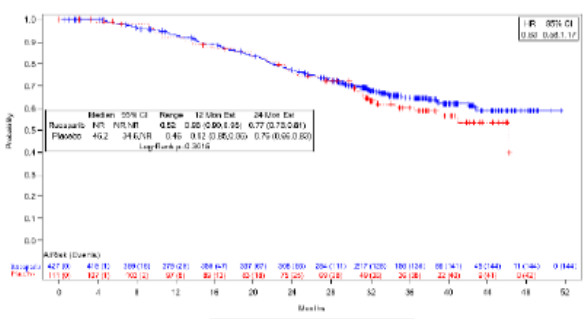
Abbreviations: BRCA = breast cancer gene; CI = confidence interval; HR = hazard ratio; HRD = homologous recombination deficiency (ie, tBRCA or non- tBRCA LOH^{high}); ITT = intent-to-treat; LOH= loss of heterozygosity; NR = not reached; tBRCA = tumor tissue mutation in BRCA.

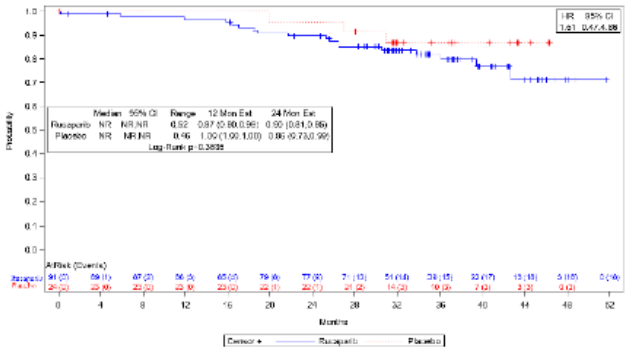
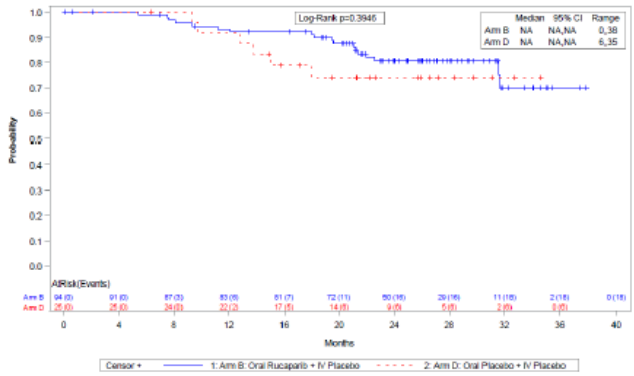
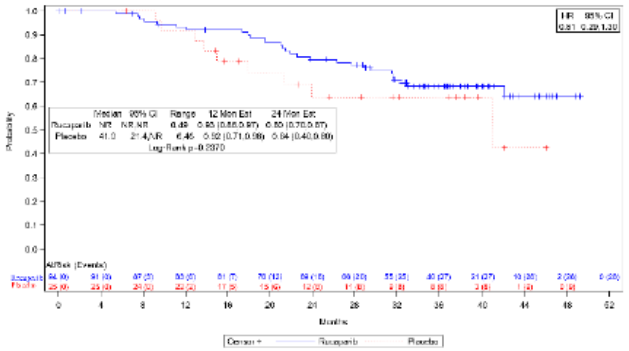
[a] Log-rank analysis performed by randomization strata for ITT, and HRD and unstratified for the non-nested subgroups.

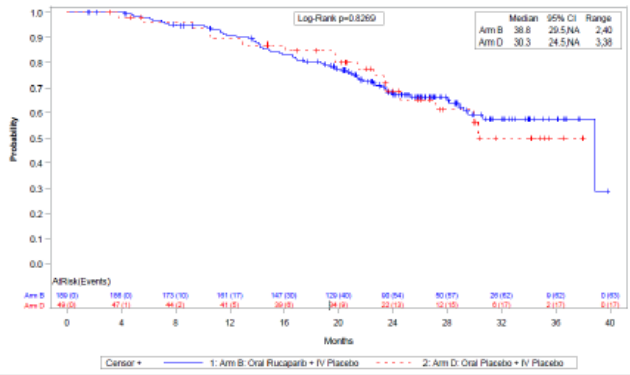
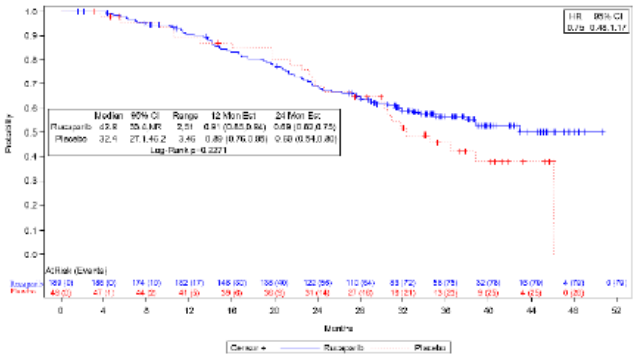
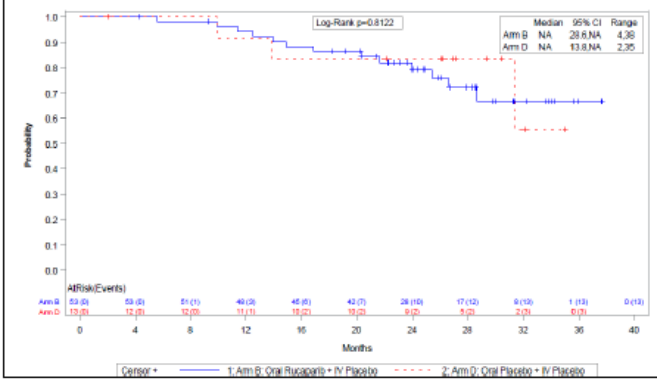
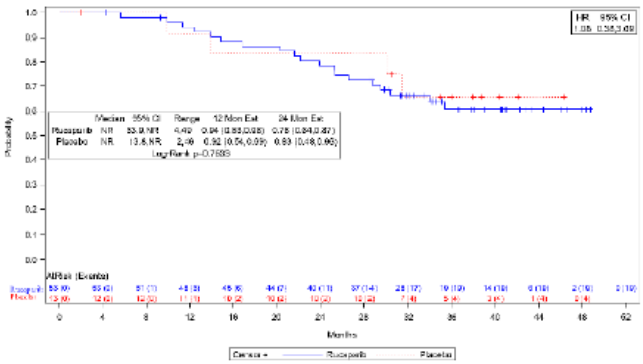
[b] Cox proportional hazard method performed by randomization strata for ITT, and HRD and unstratified for the non-nested subgroups.

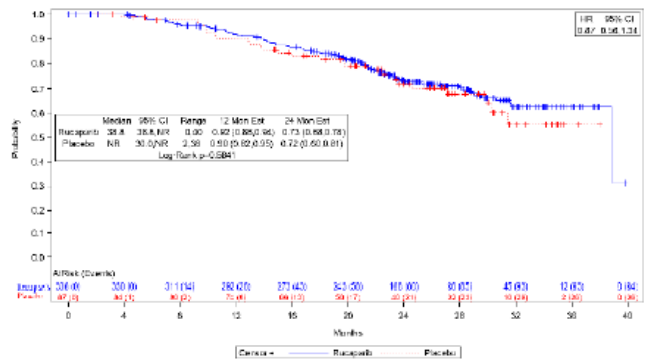
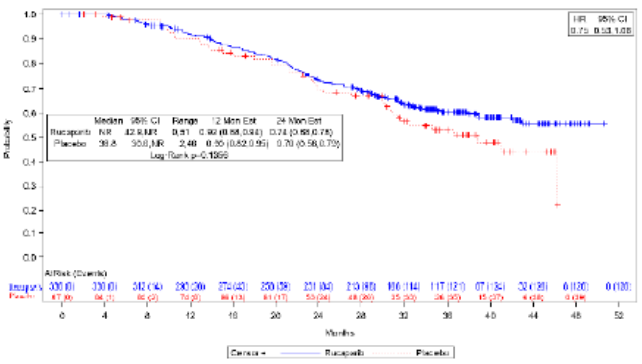
[c] Nominal p-value; not adjusted for multiplicity.

Table 27 Interim OS Kaplan Meier Curves for Nested, Non-Nested, and non-tBRCA Groups (09 March 2023 vs 23 March 2022 Data Cut-off)

Interim Overall Survival Data Cutoff 23 March 2022	Interim Overall Survival Data Cutoff 09 March 2023
Nested Subgroups	
Figure 1 HRD Population 	*Figure 2 HRD Population* 
Figure 3 ITT Population 	*Figure 4 ITT Population* 

Interim Overall Survival Data Cutoff 23 March 2022	Interim Overall Survival Data Cutoff 09 March 2023
Non-nested Subgroups	
Figure 5 tBRCA Population 	*Figure 6 tBRCA Population* 
Figure 7 Non-tBRCA LOH^{high} Population 	*Figure 8 Non-tBRCA LOH^{high} Population* 

Interim Overall Survival Data Cutoff 23 March 2022	Interim Overall Survival Data Cutoff 09 March 2023
Non-nested Subgroups (Continued)	
Figure 9 Non-tBRCA LOH^{low} Population 	*Figure 10 Non-tBRCA LOH^{low} Population* 
Figure 11 Non-tBRCA LOH^{unknown} Population 	*Figure 12 Non-tBRCA LOH^{unknown} Population* 

Interim Overall Survival Data Cutoff 23 March 2022	Interim Overall Survival Data Cutoff 09 March 2023
Non-nested Subgroups (Continued)	
Figure 13 Non-tBRCA Population 	*Figure 14 Non-tBRCA Population* 

- Objective Response Rate (ORR)

The ORR per RECIST v1.1, as assessed by the investigator, was analysed in the subgroup of patients (~10%) who were response evaluable (i.e., measurable target lesions) at baseline.

Table 28 Confirmed Response Rate by Investigator (Patients with measurable disease at baseline)

	ITT Population		HRD Population	
	Rucaparib (N = 41)	Placebo (N = 11)	Rucaparib (N = 17)	Placebo (N = 5)
Confirmed Response Rate, n (%)	**20 (48.8)**	**1 (9.1)**	**10 (58.8)**	**1 (20.0)**
95% CI, %	32.9, 64.9	0.2, 41.3	32.9, 81.6	0.5, 71.6
p-value	**0.0172**		**0.1269**	
Best Overall Confirmed Response, n (%)				
CR	1 (2.4)	0	0	0
PR	19 (46.3)	1 (9.1)	10 (58.8)	1 (20.0)
SD	10 (24.4)	4 (36.4)	6 (35.3)	2 (40.0)
PD	10 (24.4)	6 (54.5)	1 (5.9)	2 (40.0)
NE	1 (2.4)	0	0	0

Source: Table 18, Table 19, ATHENA-MONO CSR.
Abbreviations: CI = confidence interval; CR = complete response; HRD = homologous recombination deficiency; ITT = intent-to-treat; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

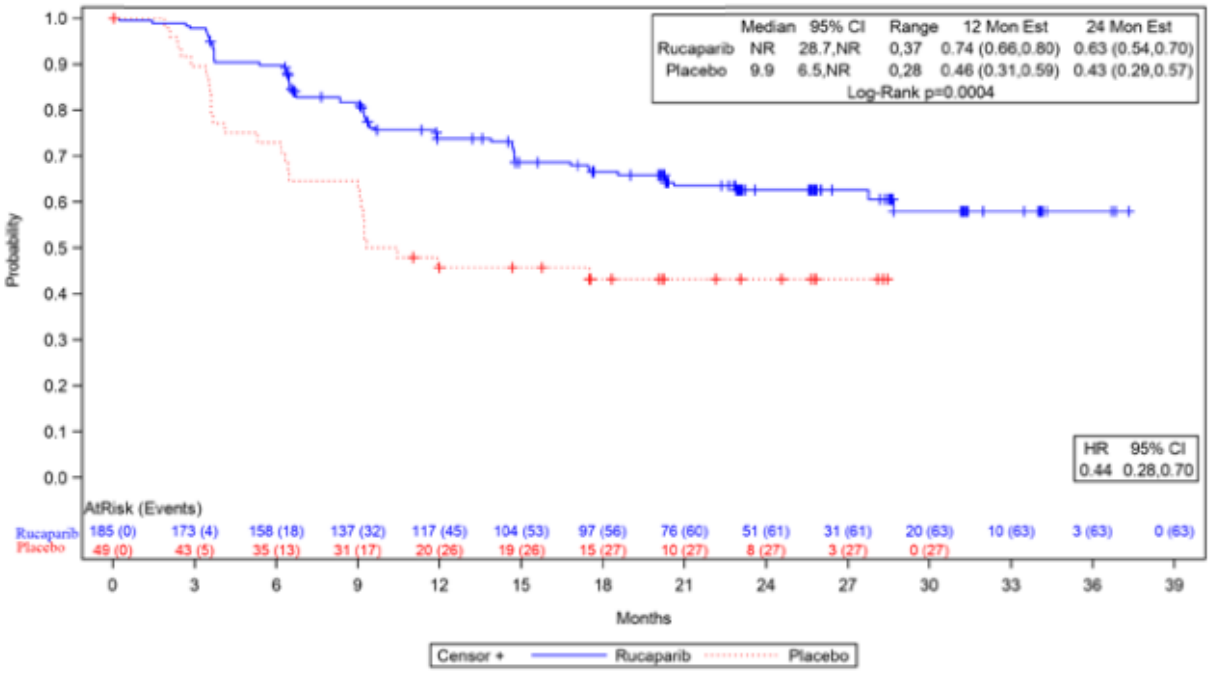
In the exploratory tBRCA subgroup, there were also similar percentages of patients in the rucaparib group (8/91 [8.8%]) and placebo group (2/24 [8.3%]) with measurable disease at baseline. The confirmed ORR was 62.5% (5/8) for rucaparib and 50.0% (1/2) for placebo in the tBRCA subgroup (p = 0.7469).

- Duration of response

For the **HRD Population**, the median DOR for rucaparib was 16.7 months (95% CI, 5.7-NR; n = 10) compared to 5.5 months (95% CI, NR-NR; n = 1) for placebo (log-rank, p = 0.0016). For the **ITT Population**, the median DOR for rucaparib was 22.1 months (95% CI, 8.4-NR; n = 20) compared to 5.5 months (95% CI, NR-NR; n = 1) for placebo.

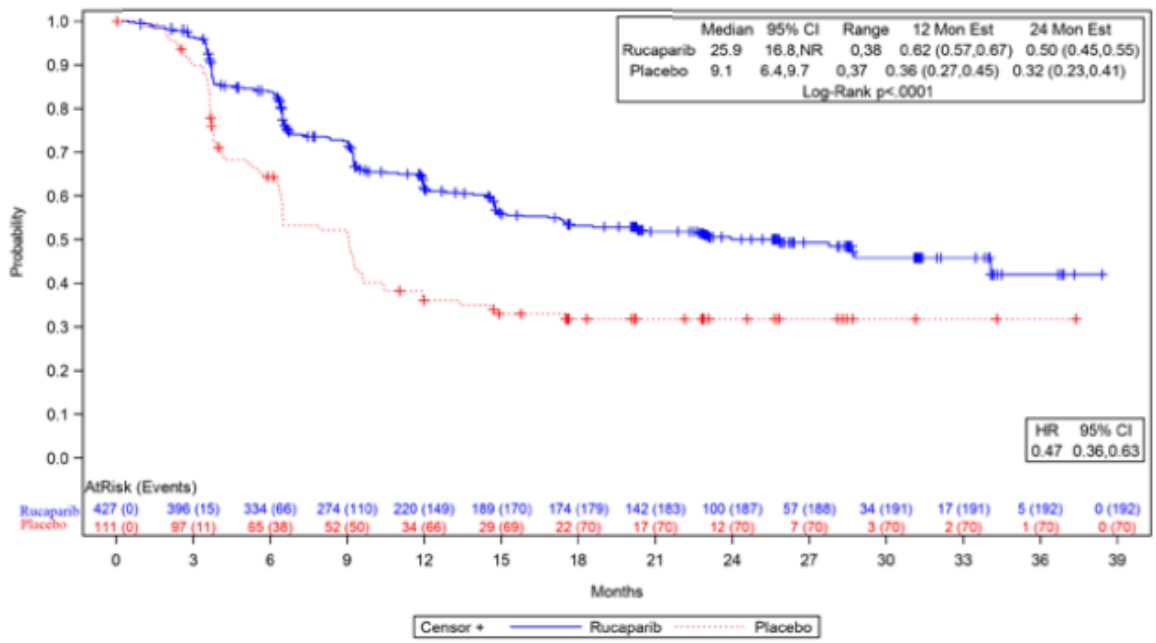
- Progression-free Survival by Blinded Independent Central Review (BICR)

Figure 31 PFS by BICR (HRD Population)



Source: Table 14.2.2.1.1 (t-pfsbicr-hrd); Table 14.2.2.1.4 (t-pfsmo-bicr-hrd); Figure 14.2.2.1 (f-pfsbicr-hrd).
Abbreviations: BICR = blinded independent central review; CI = confidence interval; HR = hazard ratio; HRD = homologous recombination deficiency; PFS = progression-free survival.

Figure 32 PFS by BICR (ITT Population)



Source: Table 14.2.2.1.2 (t-pfsbicr-itt); Table 14.2.2.1.5 (t-pfsmo-bicr-itt); Figure 14.2.2.2 (f-pfsbicr-itt).
Abbreviations: BICR = blinded independent central review; CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; PFS = progression-free survival.

Table 29 PFS by BICR in Primary Analysis Populations and Non-nested Molecular Subgroups

Analysis Population	Median bicrPFS (95% CI) Months[a] Rucaparib vs Placebo	Hazard Ratio (95% CI)[b]
Primary Analysis Populations		
HRD Rucaparib n = 185 Placebo n = 49	NR (28.7, NR) vs 9.9 (6.5, NR) p = 0.0004	0.44 (0.28, 0.70) p = 0.0005
ITT Rucaparib n = 427 Placebo n = 111	25.9 (16.8, NR) vs 9.1 (6.4, 9.7) p < 0.0001	0.47 (0.36, 0.63) p < 0.0001
Exploratory Analysis of Non-nested Subgroups		
tBRCA Rucaparib n = 91 Placebo n = 24	NR (NR, NR) vs NR (9.0, NR) p = 0.0566	0.48 (0.23, 1.00) p = 0.0512
Non-tBRCA LOH^{high} Rucaparib n = 94 Placebo n = 25	27.8 (16.8, NR) vs 9.1 (3.6, 17.5) p = 0.0072	0.46 (0.26, 0.81) p = 0.0074
Non-tBRCA LOH^{low} Rucaparib n = 189 Placebo n = 49	12.0 (9.3, 17.3) vs 6.4 (3.9, 9.6) p = 0.0119	0.60 (0.40, 0.89) p = 0.0113
Non-tBRCA $LOH^{unknown}$ Rucaparib n = 53 Placebo n = 13	17.4 (9.2, NR) vs 6.5 (3.6, 14.6) p = 0.0020	0.33 (0.16, 0.68) p = 0.0026

Source: Table 27, ATHENA-MONO CSR.
Abbreviations: BICR = blinded independent central review; bicrPFS = progression-free survival as assessed by BICR; BRCA = breast cancer gene; CI = confidence interval; HRD = homologous recombination deficiency; invPFS = investigator-assessed progression-free survival; ITT = intent-to-treat; LOH = loss of heterozygosity; LOH^{high} = LOH ≥ 16%; LOH^{low} = LOH< 16%; $LOH^{unknown}$ = LOH that is unknown; non-tBRCA = BRCA wild-type; NR = not reached; PFS = progression-free survival; tBRCA = tumor tissue mutation in BRCA.

[a] Stratified log-rank analysis was used for HRD and ITT Populations; the non-nested subgroups were tested with an unstratified analysis.

[b] Cox proportional hazards model was used for HRD and ITT Populations; the non-nested subgroups were tested with an unstratified analysis.

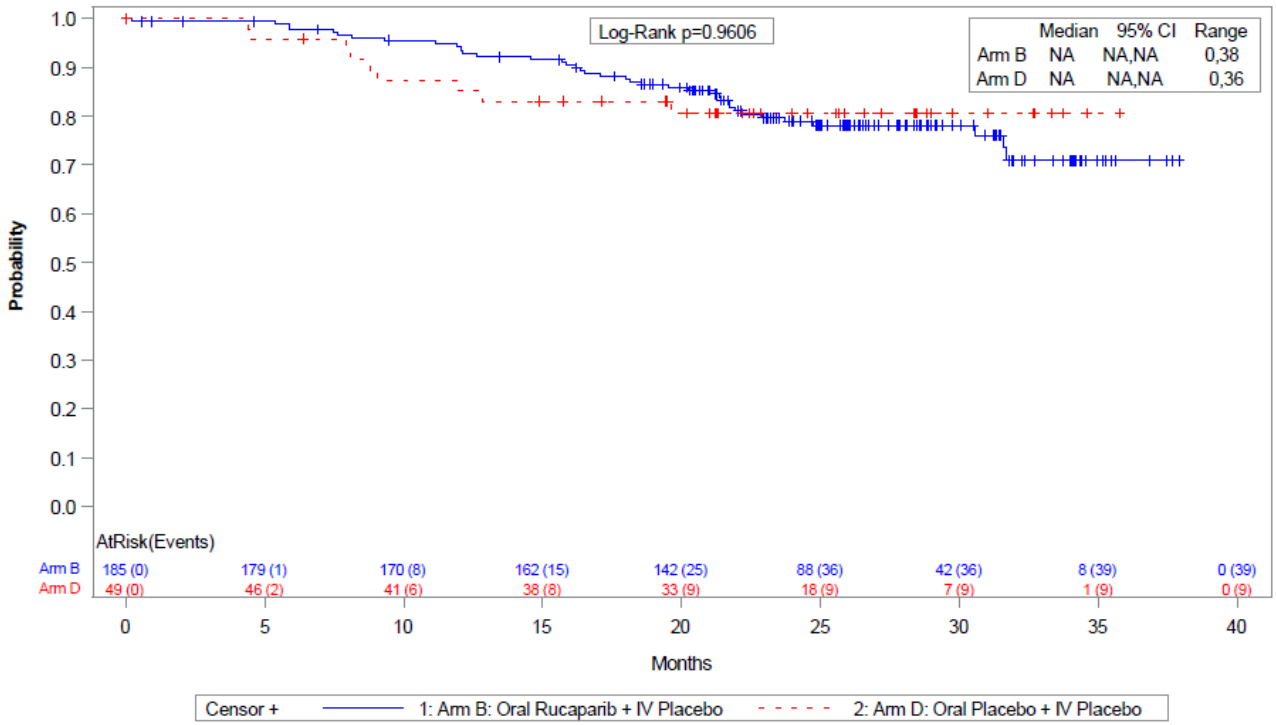
Exploratory endpoints

- PFS2

Data for PFS2 were heavily censored at the time of the visit cut-off for the primary endpoint analysis. The number of PFS2 events in the rucaparib and placebo groups in the HRD and ITT Populations was small (HRD, 48/234 [20.5%]; ITT, 162/538 [30.1%]).

Cox Proportional Hazard Model of PFS2 by Investigator – HRD Population: HR 0.94 (95% CI: 0.46, 1.93).

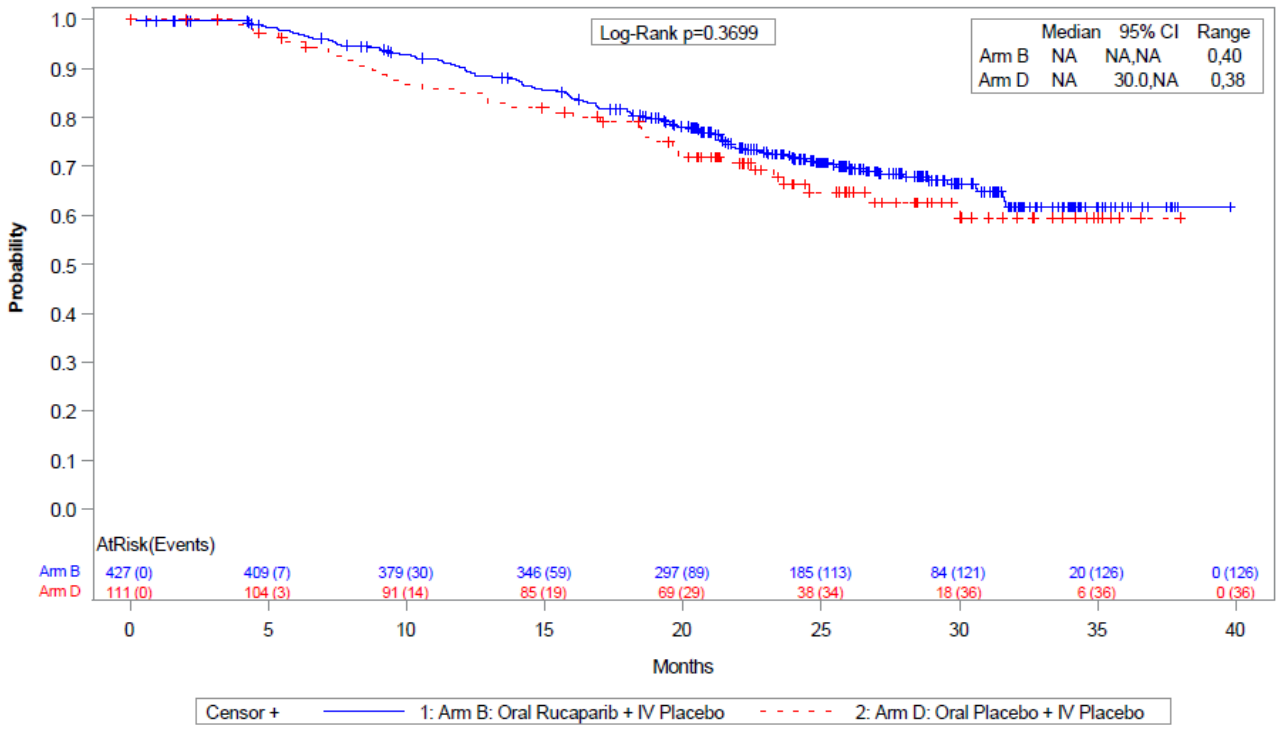
Figure 33 PFS2 HRD Population



Log-rank analysis performed by randomization stratas of HRD classification and Timing of surgery.
Data cutoff is 23MAR2022.

Cox Proportional Hazard Model of PFS2 by Investigator - ITT Population: HR 0.84 (95% CI: 0.58, 1.21).

Figure 34. PFS2 - ITT Population



Log-rank analysis performed by randomization stratas of HRD classification, Disease status post-chemotherapy, and Timing of surgery.
Data cutoff is 23MAR2022.

- Chemotherapy-free Interval (CFI)

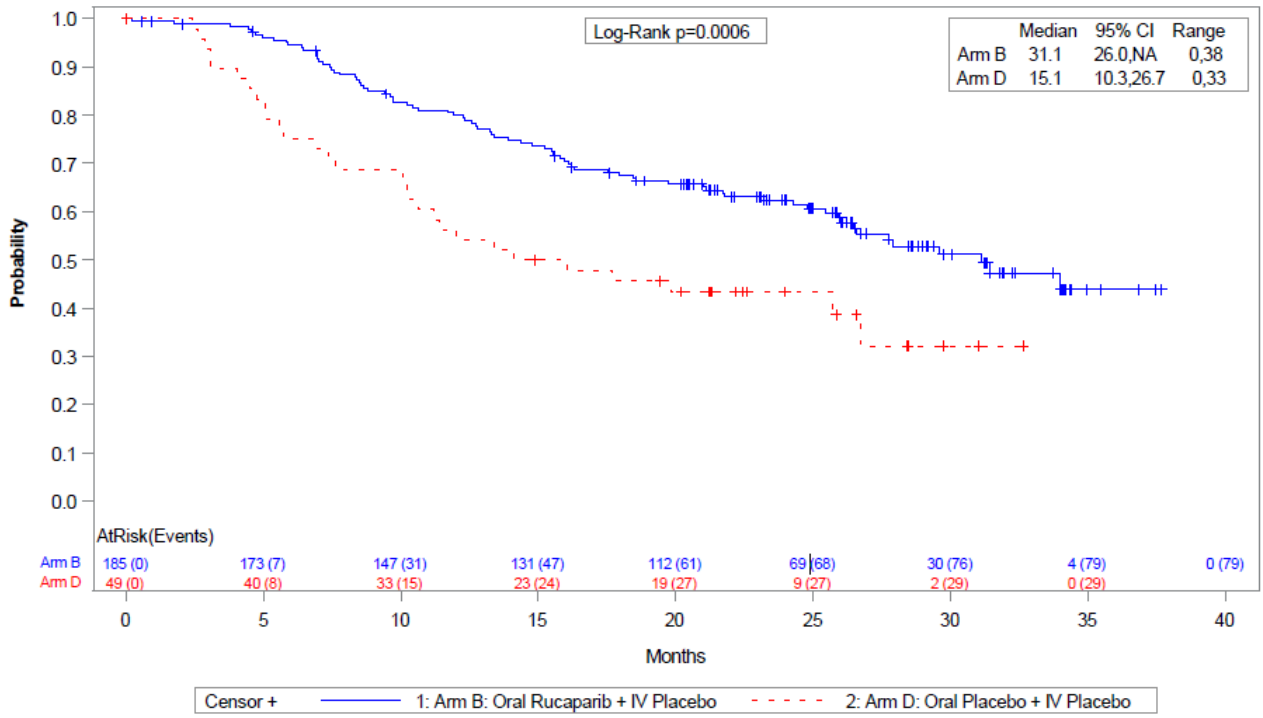
Data for CFI were heavily censored at the time of the visit cut-off for the primary endpoint analysis (HRD Population, 126/234 [53.8%]; ITT Population, 235/538 [43.7%]). For the HRD Population, the median CFI was 32.3 months (95% CI, 27.7-NR]) for rucaparib compared to 16.2 months (95% CI, 11.8-28.3) for placebo (log-rank; p = 0.0005). The stratified Cox proportional hazards model was consistent with the log-rank results (HR 0.47 [95% CI, 0.30-0.72]; p < 0.0006). For the ITT Population, results of CFI were similar to those observed for the HRD Population (HR 0.52 [95% CI: 0.40, 0.67]; Median was 25.4 months for rucaparib and 13.7 months for placebo).

- Time to First Subsequent Anticancer Treatment (TFST)

The results for TFST are similar to those for CFI, including high censoring rates analysis (HRD Population, 126/234 [53.8%]; ITT Population, 235/538 [43.7%]).

For the HRD Population, the stratified Cox proportional hazards model was consistent with the log-rank results (HR 0.47 [95% CI, 0.30-0.72]; p = 0.0006).

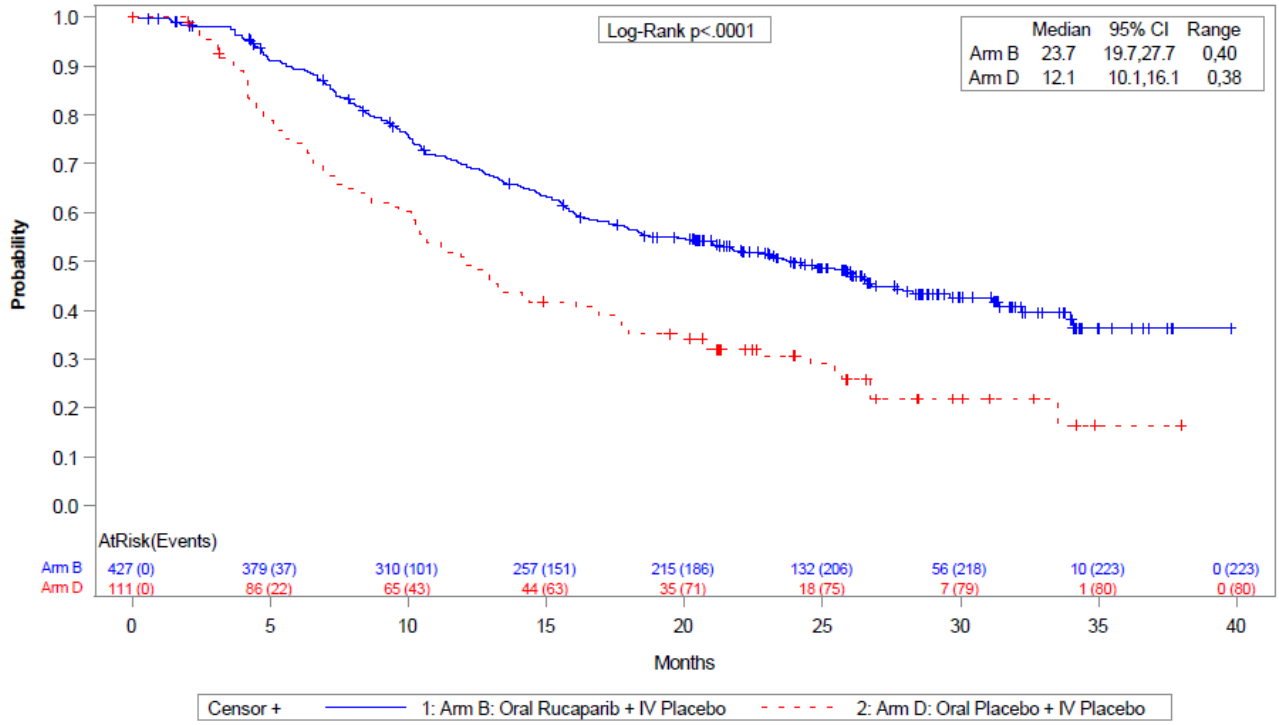
Figure 35 Time to First Subsequent Ovarian Treatment - HRD Population



Log-rank analysis performed by randomization stratas of HRD classification and Timing of surgery.
Data cutoff is 23MAR2022.

For the ITT Population, results for TFST were similar to those observed for the HRD Population.

Figure 36 Time to First Subsequent Ovarian Treatment - ITT Population



Log-rank analysis performed by randomization stratas of HRD classification, Disease status post-chemotherapy, and Timing of surgery.
Data cutoff is 23MAR2022.

- Time to Second Subsequent Anticancer Treatment (TSST)

For the HRD Population, the median TSST was not reached for either treatment group. The HR was 0.65 (95% CI, 0.37-1.14; p = 0.1341) by stratified Cox proportional hazards model.

For the ITT Population, the median TSST was 37.5 months (95% CI, 30.6-NR) for rucaparib compared to 26.5 months (95% CI, 20.5-30.9) for placebo (log-rank, p = 0.0077), and the HR was 0.65 (95% CI, 0.48-0.89; p = 0.0073) by stratified Cox proportional hazards model.

- Time to Treatment Discontinuation of Oral Dose (TDT)

For the HRD Population, the median TDT was 23.6 months (95% CI, 18.4-24.8) for rucaparib compared to 12.5 months (95% CI, 8.6-18.5) for placebo (log-rank, p = 0.0146). The stratified Cox proportional hazards model was consistent with the log-rank results (HR 0.64 [95% CI, 0.44-0.91]; p = 0.0140). For the ITT Population, the median TDT was 14.7 months (95% CI, 12.1-17.5) for rucaparib compared to 9.9 months (95% CI, 7.6-12.1) for placebo (log-rank, p = 0.0027). The stratified Cox proportional hazards model was consistent with the log-rank results (HR 0.71 [95% CI, 0.56-0.89]; p = 0.0028).

Updated PFS2, CFI, FST, TSST and TDT data (data cut-off of 09 March 2023)

Updated interim PFS2, CFI, TFST, TSST, and TDT analyses were provided for the primary analysis populations, non-nested molecular subgroups, and the pooled subgroup of patients without a BRCA mutation (ITT minus tBRCA patients, n=423) using a data cut-off of 09 March 2023 with a side by side comparison of values.

Table 30 Interim PFS2, CFI, TFST, TSST, and TDT for Nested, Non-Nested, and non-tBRCA populations

Table 18.3	23 March 2022 Data Cut-off	09 March 2023 Data-Cut-off			
Analysis Population/Subgroup	Cox Proportional Hazard[b] Rucaparib vs Placebo	Events/N (%)		Kaplan-Meier Analysis[a] Rucaparib vs Placebo	Cox Proportional Hazard[b] Rucaparib vs Placebo
EXPLORATORY ENDPOINTS					
	Hazard Ratio (95% CI) p-value	Rucaparib	Placebo	Medians (months) Log-rank p-value	Hazard Ratio (95% CI) p-value
PFS2					
Primary Analysis Populations					
HRD	0.95 (0.51, 1.77) p = 0.8641	71/185 (38.4)	20/49 (40.8)	NR vs 39.9 p = 0.2992	0.75 (0.46, 1.24) p = 0.2682
ITT	0.88 (0.63, 1.22) p = 0.4396	207/427 (48.5)	59/111 (53.2)	36.0 vs 26.8 p = 0.2606	0.84 (0.63, 1.13) p = 0.2441
Exploratory Analysis Populations					
tBRCA	Not performed	27/91 (29.7)	9/24 (37.5)	NR vs NR p = 0.4617	0.73 (0.34, 1.54) p = 0.4045
Non-tBRCA LOH^{high}		44/94 (46.8)	11/25 (44.0)	39.0 vs NR p = 0.6575	0.83 (0.43, 1.60) p = 0.5855
Non-tBRCA LOH^{low}		109/189 (57.7)	33/49 (67.3)	24.4 vs 20.0 p = 0.2102	0.77 (0.52, 1.14) p = 0.1918
Non-tBRCA LOH^{unknown}		27/53 (50.9)	6/13 (46.2)	29.0 vs NR p = 0.8100	1.05 (0.44, 2.50) p = 0.9158
Non-tBRCA		180/336 (53.6)	50/87 (57.5)	29.3 vs 23.9 p = 0.2420	0.82 (0.60, 1.13) p = 0.2243
CFI					
Primary Analysis Populations					
HRD	0.46 (0.29, 0.71) p = 0.0005	87/185 (47.0)	32/49 (65.3)	43.3 vs 16.2 p = 0.0003	0.47 (0.31, 0.71) p = 0.0003
ITT	0.51 (0.40, 0.67) p = <.0001	242/427 (56.7)	84/111 (75.7)	25.6 vs 14.0 p = <.0001	0.52 (0.41, 0.67) p = <.0001
Exploratory Analysis Populations					
tBRCA	Not performed	33/91 (36.3)	14/24 (58.3)	NR vs 26.7 p = 0.0124	0.45 (0.24, 0.84) p = 0.0121
Non-tBRCA LOH^{high}		54/94 (57.4)	18/25 (72.0)	28.0 vs 13.5 p = 0.0282	0.54 (0.32, 0.93) p = 0.0253
Non-tBRCA LOH^{low}		122/189 (64.6)	41/49 (83.7)	18.8 vs 11.7 p = 0.0013	0.56 (0.39, 0.80) p = 0.0013
Non-tBRCA LOH^{unknown}		33/53 (62.3)	11/13 (84.6)	20.4 vs 14.2 p = 0.0805	0.53 (0.27, 1.05) p = 0.0690
Non-tBRCA		209/336 (62.2)	70/87 (80.5)	20.3 vs 12.2 p = <.0001	0.55 (0.42, 0.73) p = <.0001
TFST					
Primary Analysis Populations					
HRD	0.47 (0.30, 0.72) p = 0.0006	91/185 (49.2)	32/49 (65.3)	32.7 vs 15.1 p = 0.0010	0.50 (0.33, 0.76) p = 0.0010
ITT	0.52 (0.40, 0.67) p = <.0001	248/427 (58.1)	85/111 (76.6)	23.3 vs 12.1 p = <.0001	0.52 (0.40, 0.67) p = <.0001
Exploratory Analysis Populations					
tBRCA	Not performed	37/91 (40.7)	14/24 (58.3)	NR vs 25.7 p = 0.0425	0.52 (0.28, 0.96) p = 0.0380
Non-tBRCA LOH^{high}		54/94 (57.4)	18/25 (72.0)	26.1 vs 12.0 p = 0.0340	0.55 (0.33, 0.95) p = 0.0303
Non-tBRCA LOH^{low}		124/189 (65.6)	41/49 (83.7)	16.2 vs 10.4 p = 0.0015	0.56 (0.40, 0.80) p = 0.0014
Non-tBRCA LOH^{unknown}		33/53 (62.3)	12/13 (92.3)	19.4 vs 12.0 p = 0.0209	0.45 (0.23, 0.88) p = 0.0193
Non-tBRCA		211/336 (62.8)	71/87 (81.6)	18.5 vs 10.7 p = <.0001	0.55 (0.42, 0.72) p = <.0001

Table 18.3	23 March 2022 Data Cut-off	09 March 2023 Data-Cut-off			
Analysis Population/Subgroup	Cox Proportional Hazard[b] Rucaparib vs Placebo	Events/N (%)		Kaplan-Meier Analysis[a] Rucaparib vs Placebo	Cox Proportional Hazard[b] Rucaparib vs Placebo
EXPLORATORY ENDPOINTS					
	Hazard Ratio (95% CI) p-value	Rucaparib	Placebo	Medians (months) Log-rank p-value	Hazard Ratio (95% CI) p-value
TSST					
Primary Analysis Populations					
HRD	0.65 (0.37, 1.14) p = 0.1341	67/185 (36.2)	21/49 (42.9)	NR vs 40.4 p = 0.1180	0.67 (0.41, 1.09) p = 0.1048
ITT	0.65 (0.48, 0.89) p = 0.0073	199/427 (46.6)	63/111 (56.8)	37.9 vs 24.9 p = 0.0301	0.72 (0.54, 0.97) p = 0.0279
Exploratory Analysis Populations					
tBRCA	Not performed	24/91 (26.4)	9/24 (37.5)	NR vs NR p = 0.2931	0.64 (0.30, 1.38) p = 0.2552
Non-tBRCA LOH^{high}		43/94 (45.7)	12/25 (48.0)	36.9 vs 29.0 p = 0.3218	0.70 (0.37, 1.33) p = 0.2796
Non-tBRCA LOH^{low}		105/189 (55.6)	36/49 (73.5)	27.7 vs 21.4 p = 0.0254	0.64 (0.44, 0.94) p = 0.0231
Non-tBRCA LOH^{unknown}		27/53 (50.9)	6/13 (46.2)	35.1 vs 31.0 p = 0.8629	1.02 (0.43, 2.42) p = 0.9699
Non-tBRCA		175/336 (52.1)	54/87 (62.1)	31.8 vs 23.6 p = 0.0258	0.70 (0.52, 0.95) p = 0.0237
TDT					
Primary Analysis Populations					
HRD	0.64 (0.44, 0.91) p = 0.0140	184/185 (99.5)	48/49 (98.0)	23.4 vs 12.5 p = 0.0071	0.64 (0.46, 0.89) p = 0.0074
ITT	0.71 (0.56, 0.89) p = 0.0028	425/427 (99.5)	110/111 (99.1)	14.7 vs 9.9 p = 0.0072	0.74 (0.60, 0.92) p = 0.0076
Exploratory Analysis Populations					
tBRCA	Not performed	91/91 (100.0)	23/24 (95.8)	24.8 vs 15.3 p = 0.1620	0.71 (0.45, 1.13) p = 0.1526
Non-tBRCA LOH^{high}		93/94 (98.9)	25/25 (100.0)	14.3 vs 9.8 p = 0.0237	0.59 (0.38, 0.93) p = 0.0224
Non-tBRCA LOH^{low}		189/189 (100.0)	49/49 (100.0)	10.3 vs 8.0 p = 0.1570	0.79 (0.58, 1.09) p = 0.1470
Non-tBRCA LOH^{unknown}		52/53 (98.1)	13/13 (100.0)	12.1 vs 9.9 p = 0.2730	0.70 (0.38, 1.28) p = 0.2474
Non-tBRCA		334/336 (99.4)	87/87 (100.0)	12.0 vs 9.2 p = 0.0085	0.73 (0.57, 0.92) p = 0.0085

[a]Log-rank analysis performed by randomization strata for the ITT and HRD Populations and unstratified for the non-nested subgroups.
[b]Cox proportional hazards method performed by randomization strata for the ITT and HRD Populations and unstratified for the non-nested subgroups.

- Health-related QoL – FACT-O

Health-related QoL as assessed by the Functional Assessment of Cancer Therapy – Ovarian (FACT-O) was assessed at Screening, on Day 1 (Cycle 1 through Cycle 3, and Cycle 5), then every 12 weeks (aligning with CT scans) until treatment discontinuation or until the data cut-off for the primary analysis, whichever comes first. In addition, PRO assessments were performed at End of Treatment, and at the SFU1 (28-day Safety Follow-up) and the SFU2 (5-month Safety Follow-up) for all patients.

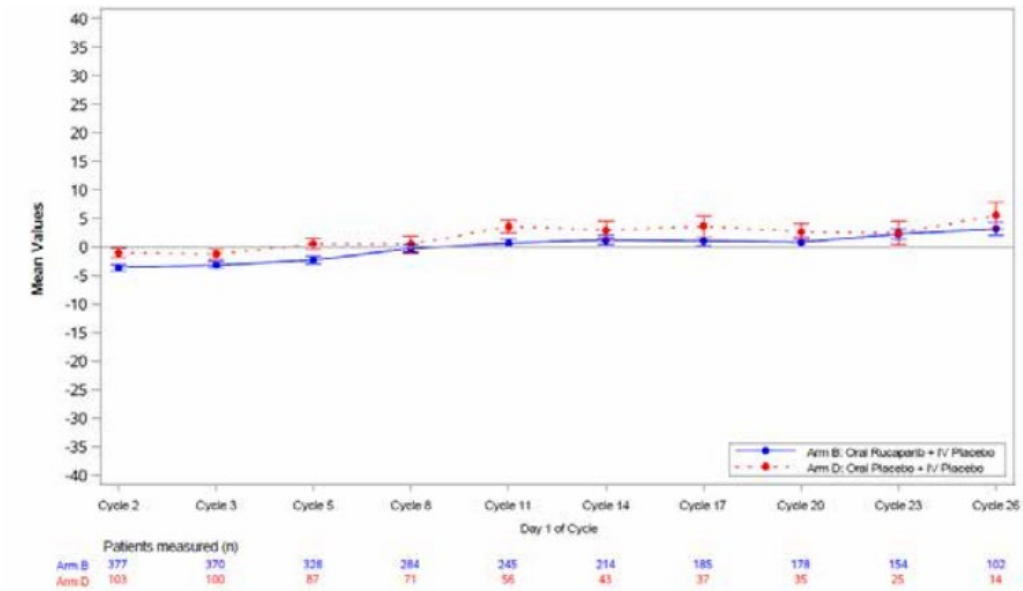
The FACT-O subscales values and total score together with the TOI were calculated. A change of at least 10 points in the FACT-O TOI was considered as clinically relevant.

The completion rates for FACT-O using either electronic or paper questionnaires were approximately 90% in both treatment groups for the first 12 months of treatment.

The mean change from baseline over time of FACT-O TOI is presented by treatment group for the ITT Population in Figure 37. Baseline scores were similar for all patients (mean [± StD] scores were 76.4 ± 12.54 and 74.9 ± 13.79 for rucaparib and placebo, respectively). The mean (± StD) TOI scores ranged from 72.7 (± 13.50) to 78.9 (± 11.69) for rucaparib, and 72.4 (± 15.36) to 79.1 (± 7.19) for placebo,

while on-treatment, with higher scores indicating better HRQoL and clinically meaningful difference defined as ± 10 points. The mean (± StD) change from baseline ranged from -3.6 (± 10.48) to 3.1 (± 11.52) for rucaparib and -1.3(± 9.22) to 5.5 (± 8.57) for placebo, and thus neither treatment group met criteria for a clinically meaningful change in FACT-O TOI scores. Mean change from baseline assessed by FACT-O was statistically significantly higher in placebo at Cycle 2 compared to rucaparib, and similar during all other time points on-treatment for the ITT Population.

Figure 37 Change From Baseline by Cycle for FACT-O TOI (ITT Population)



Source: Figure 14.2.7.1 (f-qolfact).
Abbreviations: FACT-O= Functional Assessment of Cancer Therapy - Ovarian; ITT = intent-to-treat; TOI = Trial Outcome Index.

- Patient-reported Outcome of EQ-5D-5L

The completion rates for EQ-5D-5L using either electronic or paper questionnaires were approximately 90% in both treatment groups for the first 12 months of treatment.

Baseline scores for EQ-5D-5L index (US) were similar for all patients (the mean [± StD] scores were 0.86 [± 0.151] and 0.83 (± 0.207) for rucaparib and placebo, respectively). Mean (± StD) EQ-5D-5L index scores (US) ranged from 0.83 (± 0.183) to 0.87 (± 0.153) for rucaparib, and 0.79 (± 0.210) to 0.90 (± 0.112) for placebo, while on-treatment. The mean (± StD) change from baseline for EQ-5D-5L index scores (US) ranged from -0.04 (± 0.186) to 0.02 (± 0.137) for rucaparib and -0.03 (± 0.175) to 0.05 (± 0.185) for placebo. The EQ-5D-5L index analyses were done with both the US and UK population norms, and the results of both analyses were similar for the ITT Population.

For the ITT Population, baseline scores for EQ-5D-5L VAS were also similar for all patients (mean [± StD] scores were 79.6 [± 14.38] and 78.7 (± 16.39) for rucaparib and placebo, respectively). The mean (± StD) EQ-5D-5L VAS scores ranged from 76.0 (± 17.77) to 83.6 (± 11.05) for rucaparib, and 74.4 (± 17.69) to 80.5 (± 10.92) for placebo, while on treatment. The mean (± StD) change from baseline for EQ-5D-5L VAS scores ranged from -3.8 (± 17.12) to 3.7 (± 12.85) for rucaparib and -4.4 (± 18.80) to 3.7 (± 15.72) for placebo.

Patients treated with rucaparib did not show statistically significantly mean change from baseline for EQ-5D-5L index score and VAS score as compared to placebo for the ITT Population.

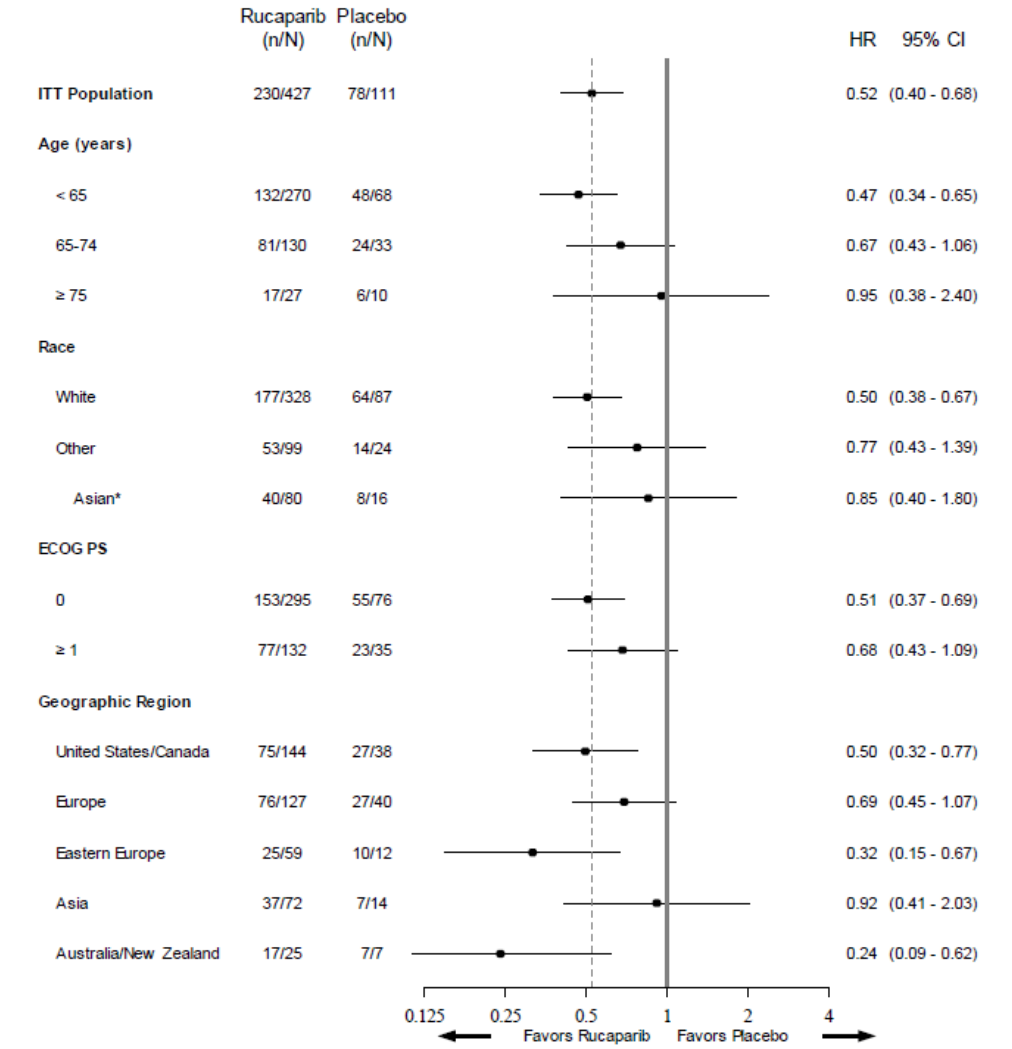
Ancillary analyses

Subgroup analyses

The exploratory subgroup analyses of invPFS were analysed using the Cox proportional hazards methodology and a log-rank test. The HR from the Cox proportional hazards model was used to estimate the HR between the randomised treatment groups. In addition, an interaction test of the subgroup-by-treatment interaction term in the Cox proportional hazards model was done.

For these exploratory subgroup analyses, no adjustments for multiple comparisons have been made and statistical significance refers to a nominal p-value < 0.025 for ATHENA–MONO.

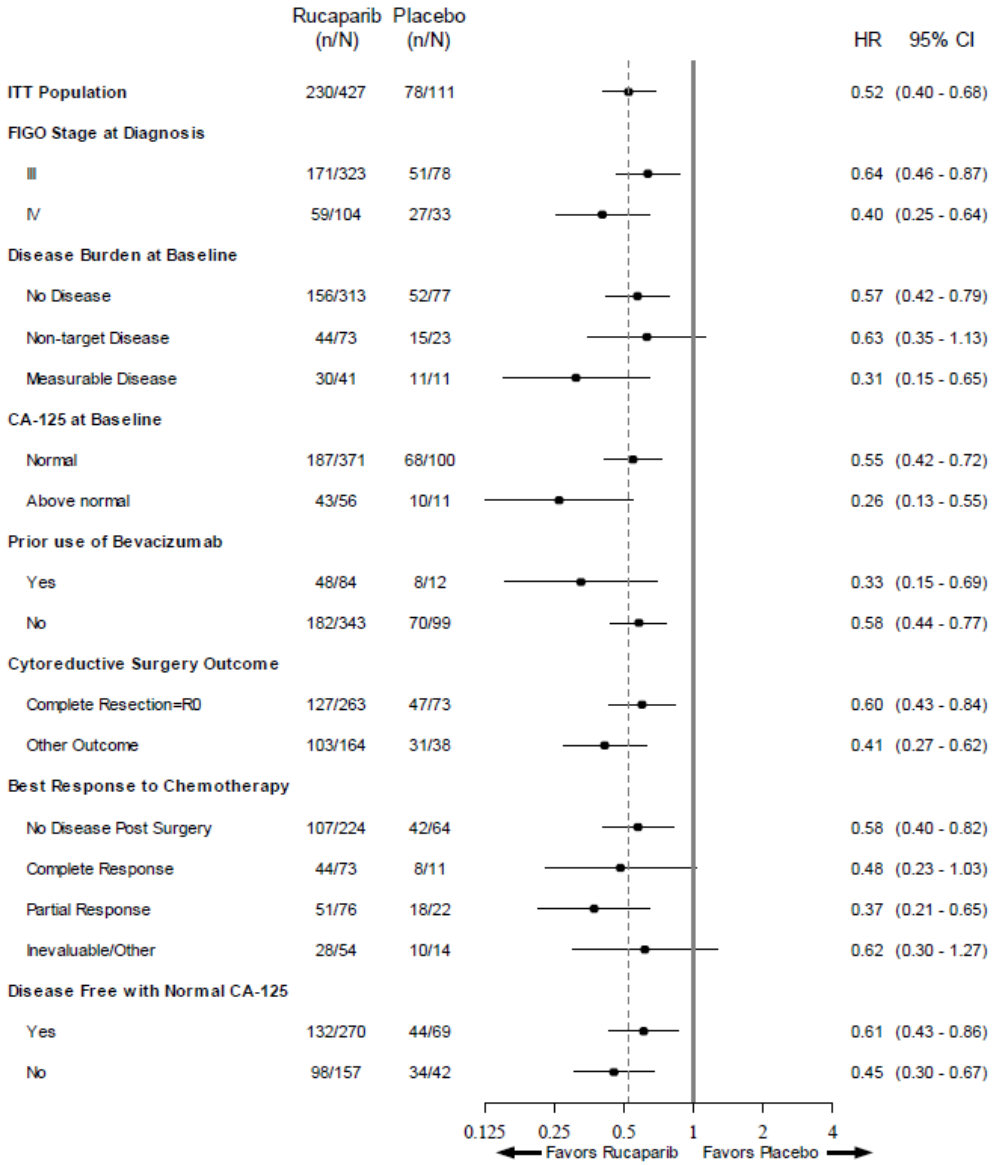
Figure 38 Forest Plot of invPFS by Demographics (ITT Population)



Source: Table 14.2.1.1.2 (t-pfs-itt); Table 14.2.1.8.2 (t-pfs-age); Table 14.2.1.9.2 (t-pfs-race); Table 14.2.1.10.2 (t-pfs-ecog); Table 14.2.1.13.2 (t-pfs-geo); Table 14.2.1.22.2 (t-pfs-asian).
Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; invPFS = progression-free survival assessed by investigator; ITT = intent-to-treat.
* Asian is a subgroup of 'Other' race.

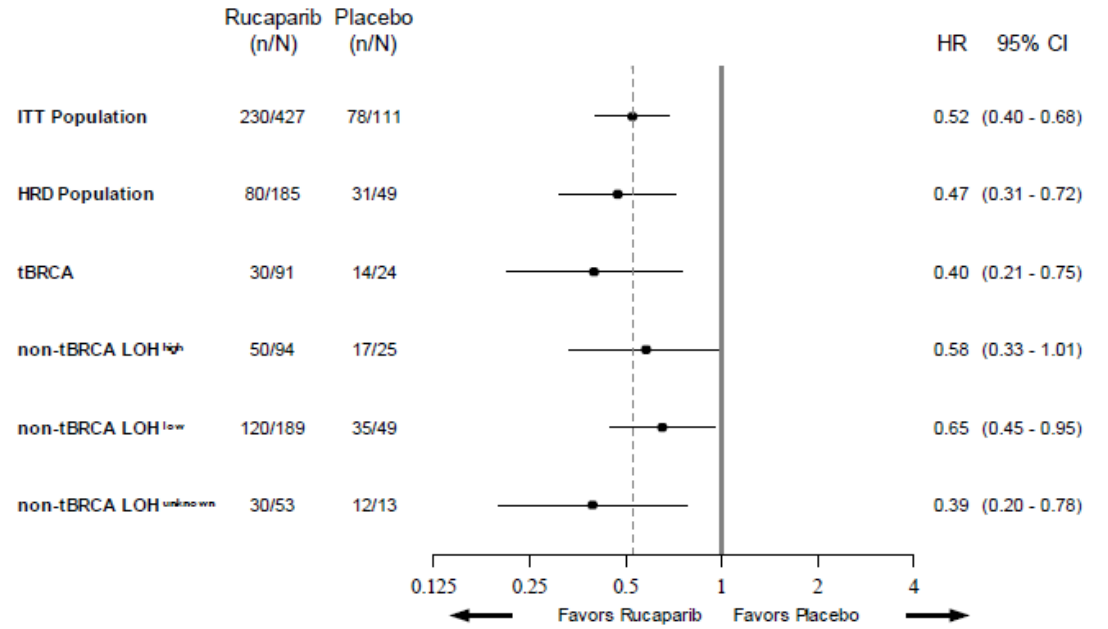
The Cox proportional hazards model showed a statistically significant improvement in invPFS with rucaparib treatment compared to placebo in many of the demographic subgroups. The placebo arms in some of the demographic subgroups (Asian race, Asia region, and ≥ 75 years old) performed better than expected leading to higher HRs.

Figure 39 invPFS by Ovarian Cancer History and Disease Burden (ITT Population)



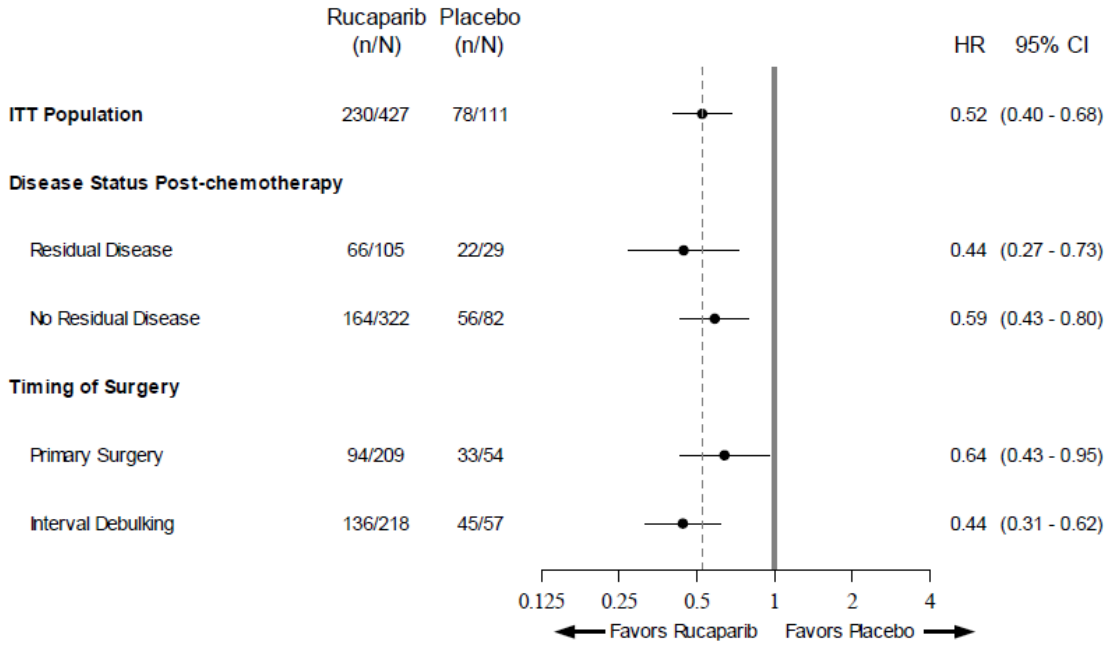
Source: Table 14.2.1.1.2 (t-pfs-itt); Table 14.2.1.11.2 (t-pfs-figo); Table 14.2.1.17.2 (t-pfs-disburd); Table 14.2.1.14.2 (t-pfs-ca125); Table 14.2.1.12.2 (t-pfs-bev); Table 14.2.1.15.2, (t-pfs-surg); Table 14.2.1.18.2 (t-pfs-bresp); Table 14.2.1.16.2 (t-pfs-df125).
Abbreviations: CA-125 = cancer antigen 125; CI = confidence interval; FIGO = International Federation of Gynecology and Obstetrics; HR = hazard ratio; ITT = intent-to-treat; R0 = complete resection.

Figure 40 Forest Plot of invPFS by Randomisation Stratification of HRD Status (ITT Population)



Source: Table 14.2.1.1.2 (t-pfs-itt); Table 14.2.1.5.2 (t-pfs-sghrd).
Abbreviations: BRCA = breast cancer gene; HRD = homologous recombination deficiency; CI = confidence interval; HR = hazard ratio; invPFS = progression-free survival assessed by investigator; ITT = intent-to-treat; LOH = loss of heterozygosity; LOH^{high} = LOH ≥ 16%; LOH^{low} = LOH< 16%; $LOH^{unknown}$ = LOH that is unknown; non-tBRCA = BRCA wild-type; tBRCA = tumor tissue mutation in BRCA.

Figure 41 Forest Plot of invPFS by Randomisation Stratification of Disease Status and Timing of Surgery (ITT Population)



Source: Table 14.2.1.1.2 (t-pfs-itt); Table 14.2.1.6.2 (t-pfs-strat2); Table 14.2.1.7.2 (t-pfs-strat3).
Abbreviations: CI = confidence interval; HR = hazard ratio; invPFS = progression-free survival assessed by investigator; ITT = intent-to-treat.

Summary of main study

Table 31 Summary of Efficacy for trial CO-338-087 (ATHENA) – ATHENA-MONO

Title: A multicenter, randomised, double-blind, placebo-controlled Phase 3 study in ovarian cancer patients evaluating rucaparib and nivolumab as maintenance treatment following response to front-line platinum-based chemotherapy			
Study identifier	EudraCT number 2017-004557-17		
Design	Randomised, double-blind, Phase 3 study.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 months not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Rucaparib		Rucaparib 600 mg BID in continuous 28-day treatment cycles. Until disease progression, or unacceptable toxicity or up to 24 months whichever occurred first. 427 patients randomised.
	Placebo		Matching placebo. Until disease progression, or unacceptable toxicity or up to 24 months whichever occurred first. 111 patients randomised.
Endpoints and definitions	Primary endpoint: Progression free survival	PFS	Time from randomisation to disease progression +1 day, as determined by RECIST v1.1 criteria (by the investigator) or death due to any cause, whichever occurred first.
	Key secondary endpoint: Overall survival	OS	Time from randomisation to death by any cause
	Key secondary endpoint: Objective response rate	ORR	The proportion of patients with a confirmed CR or PR on subsequent tumour assessment at least 28 days after first response documentation as determined by RECIST v1.1 criteria (by the investigator). The ORR was analysed in the subgroup of patients who were response evaluable (ie, measurable target lesions) at baseline.
Database lock	23 March 2022		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	**HRD population**		
Descriptive statistics and estimate variability	Treatment group	Rucaparib	Placebo
	Number of subjects	185	49
	PFS (Median, months)	28.7	11.3
	95% CI	23.0, NR	9.1, 22.1
	OS (Median, months)	38.8	NR

	95% CI	(38.8, NR)	(31.4, NR)
	ORR (%)	58.8 (10/17)	20 (1/5)
	95% CI	32.9, 81.6	0.5, 71.6
Analysis population and time point description	**Intent to treat**		
Descriptive statistics and estimate variability	Treatment group	Rucaparib	Placebo
	Number of subjects	427	111
	PFS (Median, months)	20.2	9.2
	95% CI	15.2, 24.7	8.3, 12.2
	OS (Median, months)	NR	NR
	95% CI	NR, NR	NR, NR
	ORR (%; n)	48.8 (20/41)	9.1 (1/11)
	95% CI	32.9, 64.9	0.2, 41.3
Effect estimate per comparison **HRD population**	Primary endpoint: PFS	Comparison groups	Rucaparib vs Placebo
		HR	0.47
		95% CI	0.31, 0.72
		p-value	0.0005
	Secondary: OS	Comparison groups	Rucaparib vs Placebo
		HR	0.97
		95% CI	0.43, 2.19
		p-value	0.9431
Effect estimate per comparison **ITT population**	Primary endpoint: PFS	Comparison groups	Rucaparib vs Placebo
		HR	0.52
		95% CI	0.40, 0.68
		p-value	0.0001
	Secondary: OS	Comparison groups	Rucaparib vs Placebo
		HR	0.96
		95% CI	0.63, 1.47
		p-value	0.8688

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Clinical studies in special populations

Not applicable.

Supportive study(ies)

Not applicable.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Currently approved treatment options in the (first-line) maintenance setting include bevacizumab, olaparib either as monotherapy (for BRCA mutated patients) or in combination with bevacizumab (for HRD positive patients), and niraparib (for all comers). The choice of placebo as comparator was justified by the lack of products approved in both EU and US at the time of protocol development and study start (March 2018). Bevacizumab was approved for maintenance treatment in the EU in January 2011 and in the US in June 2018. Even if the use of bevacizumab may not have been widespread in all regions at the time when the study began, it could have been considered as a treatment option under discretion of investigator and according to local practice. Having said that, the choice of placebo as comparator is acknowledged.

The study included newly diagnosed patients with advanced (FIGO III-IV), high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who had completed cytoreductive surgery, either prior to chemotherapy (primary surgery) or following neoadjuvant chemotherapy (interval debulking), and 4 to 8 cycles of first-line platinum-doublet chemotherapy with a response. Only patients with an ECOG 0 or 1 were included in the study. Any prior treatment for ovarian cancer, other than first-line chemotherapy was not allowed. The use of bevacizumab was allowed during the chemotherapy phase but not as maintenance treatment (i.e. between completion of the platinum regimen and initiation of study drug or during study treatment). Of note, palliative radiotherapy on lesions not considered target lesions for tumour evaluation was permitted during the study. There are several exclusion criteria that are the common ones of clinical trials with immunotherapy.

Patients must have been randomised within 8 weeks of the first day of the last cycle of chemotherapy.

All patients were tested for HRD status (i.e. BRCA mutation and LOH) prior to randomisation by a central laboratory using the NGS-based Foundation One DX1 assay. Patients with non-BRCA tumours were categorized in three HRD groups: non-tBRCA LOH-high (LOH ≥16%), non-tBRCA LOH-low (LOH < 16%), or non-tBRCA LOH-unknown. The choice of a cut-off of 16% was based on results of prior clinical trials with rucaparib and it was also used in the ARIEL3 study and considered acceptable at the time of assessment (EMEA/H/C/004272/II/0001). Moreover, since the FMI´s test does not allow the discrimination between somatic and germline mutations, a central germline blood test was carried out to identify germline and somatic BRCA mutations.

In the ATHENA-MONO, patients were randomised to receive rucaparib 600 mg BID (plus IV placebo) or placebo (oral placebo + IV placebo). Treatment continued until disease progression, unacceptable toxicity or up to 24 months. The rucaparib duration of treatment was chosen to align with the duration of treatment for nivolumab (or IV placebo). Continuation of treatment after radiographic progression was permitted. Twenty-five (5.9%) patients in the rucaparib arm and 7 (6.3%) patients in the placebo arm received treatment beyond progression. Median duration of treatment was of 134 (range: 34, 496) weeks in the rucaparib arm and 168 (range: 88, 552) weeks in the placebo arm. Considering the low number of patients, it is not expected that this could have had an impact on the efficacy results.

Cross-over of patients from the placebo to the rucaparib arm was not allowed and patients in the placebo arm with disease progression were to be treated with appropriate therapy per standard clinical practice, including second-line chemotherapy.

Randomisation was stratified by HRD status by central laboratory analysis (tBRCA, non-tBRCA LOH-high, non-tBRCA LOH-low, or non-tBRCA LOH-unknown), disease status post-chemotherapy (residual disease vs no residual disease) and timing of surgery (primary surgery vs interval debulking).

The primary endpoint of the study was PFS by RECIST v1.1. as assessed by the investigator. PFS has been considered an acceptable primary endpoint in clinical trials in this setting provided that the treatment effect is large and clearly outweighs the toxicity of maintenance therapy (compared to no treatment). Considering the double-blind design of the study, PFS as assessed by the investigator is acceptable. Moreover, PFS by an independent central review (BICR) was a secondary endpoint of the study. Tumour responses were assessed using RECIST v1.1. Patients who met GCIG CA-125 criteria for disease progression had a radiologic assessment and were assessed by RECIST v1.1.

OS and ORR by RECIST v1.1 in patients with measurable disease at baseline were key secondary endpoints. In the maintenance treatment setting being able to disregard a detrimental effect on survival is of particular relevance, even more considering that the comparator is placebo. DOR was another secondary endpoint. PFS2 was an exploratory endpoint.

The primary PFS analysis was in accordance with FDA rules. In addition, two sensitivity analyses were conducted to evaluate the impact of censoring.

The primary and key secondary endpoints were tested using a pre-specified hierarchical step-down procedure in order to preserve the overall type 1 error rate, among the HRD population (patients tBRCA and non-tBRCA LOH-high) first and then in the ITT population, using a one-sided alpha of 0.0125. OS was the first key secondary endpoint to be tested. OS data provided so far are based on an interim analysis at the time of the final PFS analysis (planned at 60% maturity,). According to the SAP, the final analysis for OS is projected to be done once 70% of events have occurred. The MAH will submit the results of the final OS analysis as a PAES by Q4 2026 (see Annex II).

The sample size estimations were based on PFS in the HRD and ITT populations and adjusted with protocol amendment 2. The sample size after amendment 2 (26 October 2020) was of 500 subjects for the ITT population and 205 for the HRD population with a power of 90% per population which is coherent with the simple size and power assumptions presented in the original protocol and amendment 1 (5 July 2018).

There were 4 global amendments to the protocol. Amendment 2 (26 October 2020) introduced important changes including the removal of the tBRCA population from the step-down analysis, due to a lower than expected proportion of tBRCA patients enrolled in the study, resulting from the approval of other PARPi in this setting. Further, one of the original comparisons initially planned (i.e. rucaparib + nivolumab vs placebo) was removed from the primary analysis to an exploratory endpoint analysis and therefore the alpha was split between the remaining 2 independent comparisons. Of note, at the time of amendment 2 almost all patients were already enrolled. In amendment 4 (29 November 2021) the MAH removed bicrPFS from the hierarchical step-down analysis and added it as a stand-alone secondary endpoint. This change was made following the request from the US FDA (since bicrPFS is supportive of the primary endpoint of invPFS). Overall, the amendments performed regarding the ATHENA-MONO comparison are justified and would not entail important methodological issues in the context of a double-blind study.

The number of important protocol deviations was low and comparable between treatment arms (16 [3.7%] rucaparib and 6 [5.4%] placebo). Of note, there was one patient that received treatment with rucaparib beyond the 24 months defined in the protocol.

Efficacy data and additional analyses

A total of 1611 patients were enrolled in the study, of whom 544 were randomised to Arm A or C (ATHENA-COMBO) and **538 patients** were randomised to receive either rucaparib (Arm B; n=427) or placebo (Arm D; n=111). The HRD population (i.e. tBRCA and non-BRCA LOH-high) was comprised of

234 patients (43.5%), of whom 115 (21.4%) were tBRCA and 119 (22.1%) were non-tBRCA^{high}. Among patients with tBRCA mutation, the majority were BRCA1 (65%) and germline (59.1%).

As per inclusion criteria all patients had high grade advanced disease (58% FIGO Stage IIIC and 25.5% FIGO Stage IV). Since all patients included in the study had "high grade" disease, this has been reflected in the indication. Further, the fact that patients should have completed their first line platinum-based chemotherapy before starting their treatment with Rubraca has been explicitly reflected in the wording of the indication, in line with other PARP inhibitors approved in this treatment setting.

As per protocol, all patients had received prior chemotherapy (platinum/taxane) treatment, with a median of 6 cycles (range: 4, 8), which is in line with current clinical practice. The vast majority received between 6 and 8 cycles (94%).

Regarding the use of concomitant medications, ondansetron and omeprazole were administered at a higher percentage to patients in the rucaparib group as compared to placebo.

In general, there was a higher use of concomitant medications in the rucaparib group, which is consistent with the AE profile.

There were discrepancies for stratification factors between the randomisation stratification factors and the data collected (electronic data captured) but they were overall balanced between treatment arms. There were discrepancies in the HRD status in one patient, disease status post-chemotherapy in 51 (9.5%) patients and timing of surgery in 12 (2.2%) patients. Moreover, a sensitivity analysis of invPFS using the actual supportive data in the eCRF showed consistent results to the primary efficacy analysis.

Efficacy outcomes

The data provided are based on a DCO of **23 March 2022**, in addition, an updated analysis for OS, PFS2 and other exploratory endpoints (i.e. CFI, FST, TSST and TDT) with DCO **09 March 2023** was provided during the procedure. Of note, enrolment of patients was completed as of 30 September 2020.

The **primary endpoint** of the study (invPFS) was met, both in the HRD population (HR 0.47; 95% CI: 0.31, 0.72) and the ITT population (HR 0.52; 95% CI: 0.40, 0.68), with early separation of the KM curves. The number of invPFS events in the ITT population was 53.9% in the rucaparib arm and 70.3% in the placebo arm (43.2% and 63.2%, respectively, in the HRD population), with a median follow-up of 26.1 months (95% CI, 25.8-26.9) for rucaparib and 26.2 months (95% CI, 24.0-27.7) for placebo. At the time of the DCO, 46.1% patients in the rucaparib arm and 29.7% in the placebo arm were censored, being the main reason for censoring treatment discontinuation but ongoing with no progression in LTFU (57.4% rucaparib vs 39.4% placebo).

Exploratory analyses of non-nested molecular subgroups showed consistent results in patients with tBRCA (HR 0.40; 95% CI: 0.21, 0.75), non-BRCA LOH-high (HR 0.58; 95% CI: 0.33, 1.01), non-tBRCA low (HR 0.65; 95% CI: 0.45, 0.95) and in those whose LOH status was unknown (HR 0.39; 95% CI: 0.20, 0.78). In addition, results in the pooled subgroup of patients without a BRCA mutation (ITT minus tBRCA; n=423) also favoured the rucaparib arm (HR 0.59; 95% CI: 0.44, 0.78). As expected, the effect appears higher in the subgroup of tBRCA.

Two sensitivity analysis of invPFS to evaluate the impact of censoring were provided. One in which all scans and data were considered for assessment and another one in which discontinuation due to clinical progression or withdrawal of consent were considered events. Both sensitivity analyses were consistent with the primary analysis.

There were three patients with tumour assessments conducted outside of the protocol defined schedule. Results of a sensitivity analysis of invPFS with progression determined at the next scheduled scan have been provided and were consistent with the primary analysis.

PFS by BICR (bicrPFS), which was a secondary endpoint in the study, showed consistent results in terms of benefit of rucaparib over placebo. There was concordance in PFS between the investigator and the BICR of 85%. However, there were differences in the reported PFS medians, with better results according to the BICR compared with the investigator, particularly in the rucaparib arm for the HRD and ITT populations. Of note, a similar pattern has been observed in previous trials with rucaparib (i.e. ARIEL3) and with other PARP inhibitors.

Overall, subgroup analyses were consistent with the primary analysis. In the subgroup of very elderly patients (≥75 years) and Asian patients the benefit is less clear. However, these results may be attributed to low patient numbers within these subgroups, as well as imbalances in baseline prognostic factors.

Moreover, a particularly higher efficacy is observed in the subgroup of Asian patients with placebo (20.2 months rucaparib vs 25.8 placebo).

The first **secondary endpoint** to be analysed in the hierarchical step-down procedure was OS. However, at the time of interim analysis, with a median follow-up of around 26 months, the number of OS events was low, (i.e. 37 [15.8%] in the HRD population and 133 [24.7%] in the ITT population) and no differences in survival were observed between treatment arms in the HRD population (HR 0.97; 95% CI: 0.43, 2.19) and ITT population (HR 0.96; 95% CI: 0.63, 1.47). No separation is observed in the KM curves. Of note, in the subgroup of tBRCA patients, expected to be those benefiting most from the treatment with PARP inhibitors, an unexpected HR for OS of 2.24 (95% CI: 0.39, 12.99) has been reported, evidencing the immaturity of OS data available, with wide CI. There were imbalances in baseline prognosis factors between treatment arms in favour of the placebo arm. The number of patients with R0 was 52.7% in the rucaparib arm vs. 70.8% in the placebo arm and the number of patients with Stage IIIC/IV was higher in the rucaparib arm (92.3% vs 83.3%). However, the proportion of patients with FIGO Stage IV was higher in the placebo arm (28.6% vs 50%), as well as the number of patients with ECOG 1 (23.1% rucaparib vs. 33.3% placebo) which somehow may favour the rucaparib arm. In addition, differences were observed in the proportion of patients that received bevacizumab (16.5% vs 8.3%). Whether these differences may explain the results in the tBRCA subgroup is difficult to ascertain with the available data. As noted above, interpretation of OS results is hampered by the immaturity of the data. As a consequence, a potential detrimental effect on OS in the overall population or specific subgroups could not be ruled out based on initially available data. Updated OS data were therefore requested during the assessment. The MAH provided updated OS data from an IA based on a data cut-off date of 9 March 2023, with 35% (186/538) of events reported. OS data have been provided for the ITT population, non-nested molecular subgroups and the subgroup of patients with non-BRCA mutation. At the time of this IA statistical significance was not reached, neither in the ITT population (HR 0.83; 95% CI 0.58-1.17), nor in the HRD population (HR 0.84; 95% CI: 0.44, 1.58) although overall the HRs look better than in the previous IA. Similar trends are observed for the different populations analysed, with improved results compared with the previous DCO, although not statistically significant. As stated above, the final OS is expected to be performed when 70% of events are available. The MAH has committed to submit the final OS analysis by Q2 2027 as a PAES (Annex II condition, PAES), in line with criterion stated in Article 1 paragraph 2.(a) of commission delegated regulation (EU) No 357/2014.

Since OS did not reach statistical significance, ORR could not be formally tested. Of note, ORR was analysed in the subgroup of patients with measurable disease, which represents 10% of the patient

population. The ORR was higher in patients treated with rucaparib compared with placebo in both the HRD population (10/17 [58.8%] vs. 1/5 [20%]) and ITT population (20/41 [48.8%] vs. 1/11 [9.1%]). A similar pattern was observed in the tBRCA stratified subgroup.

No statistically significant differences were observed in PFS2 (investigator), neither in the HRD population (HR 0.94; 95% CI: 0.46, 1.93), nor in the ITT population (HR 0.84; 95% CI: 0.58, 1.21). Data were immature at the time of analysis (20.5% events in the HRD population and 30.1% in the ITT population).

Positive results in favour of the rucaparib arm were observed regarding other exploratory endpoints such as CFI, FST and TSST.

Updated data for all the above-mentioned exploratory endpoints, i.e. PFS2, CFI, FST and TSST were submitted based on a data cut-off date of 9 March 2023. Regarding PFS2, although statistical significance was not reached, a trend in favour of the rucaparib arm was observed in the ITT (HR 0.84; 95% CI: 0.63, 1.13) and HRD (HR 0.75; 95% CI: 0.46, 1.24) populations. Similar results were observed in the subgroup of tBRCA and non-BRCA, as well as non-nested molecular subgroups (Non-tBRCA LOH-high and Non-tBRCA LOH-low). Positive results in favour of the rucaparib arm were also observed for CFI, TFST, TSST and TDT in all the populations analysed.

Patients treated with rucaparib did not show statistically significantly mean change from baseline for EQ-5D-5L index score and VAS score as compared to placebo for the ITT Population.

2.4.4. Conclusions on the clinical efficacy

Rucaparib has demonstrated a statistically significant improvement in invPFS when given as maintenance treatment in patients with newly diagnosed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.

This said, interpretation of OS results is hampered by the immaturity of the data and it is therefore not possible to ascertain, based on currently available results, whether this prolongation of invPFS translates into an overall survival benefit, although a trend in favour of the rucaparib arm is observed.

The following measures are considered necessary to address issues related to efficacy:

Annex II.D Condition: PAES: In order to further investigate the efficacy of rucaparib monotherapy in 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, the MAH should submit the final analysis of OS of the phase 3, randomized, double-blind, placebo controlled study CO-338-087.

With a due date on 30 June 2027.

2.5. Clinical safety

The data provided aims to support the safety of rucaparib monotherapy in the maintenance treatment of adult patients with advanced EOC, FTC, or PPC who are in complete or partial response to first-line platinum-based chemotherapy.

The primary safety evaluation is based on the results from Study CO-338-087 (ATHENA), an ongoing, Phase 3, randomized, double-blind, dual placebo-controlled study of rucaparib as monotherapy and in

combination with nivolumab in patients with newly diagnosed EOC, FTC, or PPC who have responded to their first-line treatment (surgery and platinum-based chemotherapy). Only data for patients in ATHENA who were randomized to rucaparib monotherapy or placebo (ATHENA-MONO treatment comparison) are presented.

Adverse events (AE) data from ATHENA-MONO have also been integrated with the data from Studies CO-338-010 (Study 10), CO-338-17 (ARIEL2), CO-338-014 (ARIEL3), and CO-338-043 (ARIEL4), including patients with ovarian cancer who received treatment with at least one dose of oral study drug (rucaparib 600 mg BID or placebo as appropriate).

Safety data from these five studies (referred to as the "Pooled Ovarian Cancer Safety Population" or only "the Pool") are being used to support the comprehensive safety evaluation of rucaparib monotherapy in patients with ovarian cancer (N=1,594).

Patient exposure

Patients in ATHENA-MONO and the Pooled Ovarian Cancer Safety Population received study drug until confirmed radiologic disease progression as assessed by the investigator using RECIST v1.1 criteria, unacceptable toxicity or inability to tolerate further treatment, loss to follow-up, death, or withdrawal of consent. In ATHENA-MONO, treatment of rucaparib was capped at 24 months after beginning IV placebo if none of these conditions was met.

Table 32. Study Drug Exposure: Pooled Ovarian Cancer Safety Population

	ATHENA-MONO		Overall	
	Rucaparib (N = 425)	Placebo (N = 110)	Rucaparib (N = 1,594)	Placebo (N = 299)
Duration of Treatment (months)				
Mean (StD)	14.7 (9.14)	11.9 (8.17)	12.2 (13.78)	8.8 (8.59)
Median	14.7	9.9	7.4	5.7
Min, Max	0, 33	1, 26	0, 89	0, 91
Duration of Treatment (months), n (%)				
0 to < 6 months	98 (23.1)	33 (30.0)	675 (42.3)	151 (50.5)
6 to < 12 months	95 (22.4)	31 (28.2)	377 (23.7)	85 (28.4)
12 to < 24 months	114 (26.8)	33 (30.0)	293 (18.4)	46 (15.4)
≥ 24 months[a]	118 (27.8)	13 (11.8)	249 (15.6)	17 (5.7)
Dose Intensity[b]				
N	425	110	1,593	299
Mean (StD)	0.82 (0.195)	0.96 (0.104)	0.87 (0.172)	0.98 (0.069)
Median	0.88	1.00	0.94	1.00
Min, Max	0.1, 1.1	0.1, 1.0	0.1, 1.9	0.1, 1.0
Dose Reductions, n (%)				
Any Dose Reduction	210 (49.4)	9 (8.2)	779 (48.9)	18 (6.0)
1 Dose Reduction	92 (21.6)	3 (2.7)	416 (26.1)	12 (4.0)
≥ 2 Dose Reductions	118 (27.8)	6 (5.5)	363 (22.8)	6 (2.0)

Abbreviations: BID = twice a day; IV = intravenous; Max = maximum; Min = minimum; StD = standard deviation.

[a] In ATHENA-MONO, the protocol-specified treatment cap of 24 months is anchored to the start of combination treatment, ie when IV placebo started in the ATHENA-MONO portion.

[b] Dose intensity is defined as the actual total dose over time divided by the protocol-specified starting dose of 600 mg BID.

Demographics and baseline patient characteristics

Table 33. Patient Demographics at Baseline: Pooled Ovarian Cancer Safety Population

	ATHENA-MONO		Overall	
	Rucaparib (N = 425)	**Placebo (N = 110)**	**Rucaparib (N = 1,594)**	**Placebo (N = 299)**
Age (yr)				
Mean (StD)	60.2 (10.26)	61.1 (9.69)	60.6 (9.86)	60.9 (9.69)
Median	61.0	61.5	61.0	62.0
Min, Max	30, 83	31, 80	30, 91	31, 85
Age Group (yr), n (%)				
< 65	269 (63.3)	67 (60.9)	1,014 (63.6)	184 (61.5)
65 to 74	129 (30.4)	33 (30.0)	454 (28.5)	97 (32.4)
≥ 75	27 (6.4)	10 (9.1)	126 (7.9)	18 (6.0)
Sex, n (%)				
Female	425 (100.0)	110 (100.0)	1,594 (100.0)	299 (100.0)
Race, n (%)				
American Indian or Alaska Native	1 (0.2)	1 (0.9)	7 (0.4)	2 (0.7)
Asian	80 (18.8)	16 (14.5)	128 (8.0)	23 (7.7)
Black or African American	5 (1.2)	3 (2.7)	24 (1.5)	5 (1.7)
Native Hawaiian or Other Pacific Islander	3 (0.7)	1 (0.9)	4 (0.3)	1 (0.3)
White	326 (76.7)	86 (78.2)	1,268 (79.5)	230 (76.9)
Other	2 (0.5)	1 (0.9)	20 (1.3)	9 (3.0)
Unknown	8 (1.9)	2 (1.8)	143 (9.0)	29 (9.7)
Race Group, n (%)				
White	326 (76.7)	86 (78.2)	1,268 (79.5)	230 (76.9)
Other	91 (21.4)	22 (20.0)	183 (11.5)	40 (13.4)
Unknown	8 (1.9)	2 (1.8)	143 (9.0)	29 (9.7)
Ethnicity, n (%)				
Hispanic or Latino	17 (4.0)	1 (0.9)	84 (5.3)	13 (4.3)
Not Hispanic or Latino	395 (92.9)	106 (96.4)	1,332 (83.6)	247 (82.6)
Unknown	13 (3.1)	3 (2.7)	178 (11.2)	39 (13.0)
Geographical Region, n (%)				
US/Canada	143 (33.6)	37 (33.6)	630 (39.5)	107 (35.8)
Europe	127 (29.9)	40 (36.4)	596 (37.4)	139 (46.5)
Eastern Europe	58 (13.6)	12 (10.9)	164 (10.3)	12 (4.0)
Latin America	0	0	34 (2.1)	0
Asia	72 (16.9)	14 (12.7)	72 (4.5)	14 (4.7)
Australia/New Zealand	25 (5.9)	7 (6.4)	98 (6.1)	27 (9.0)
BMI (kg/m^2)				
n	425	110	1,591	297
Mean (StD)	25.94 (5.671)	25.92 (5.741)	27.23 (6.475)	26.32 (5.397)
Median	24.69	24.59	26.05	25.24
Min, Max	13.9, 60.5	16.9, 49.6	13.9, 113.1	16.2, 50.5

Table 33. Patient Demographics at Baseline: Pooled Ovarian Cancer Safety Population

	ATHENA-MONO		Overall	
	Rucaparib (N = 425)	Placebo (N = 110)	Rucaparib (N = 1,594)	Placebo (N = 299)
ECOG PS at Baseline, n (%)				
0	294 (69.2)	75 (68.2)	1,005 (63.0)	211 (70.6)
1	130 (30.6)	35 (31.8)	586 (36.8)	88 (29.4)
≥ 2	1 (0.2)[a]	0	3 (0.2)[b]	0
BRCA Status, n (%)				
BRCA	95 (22.4)	24 (21.8)	677 (42.5)	98 (32.8)
Non-BRCA	330 (77.6)	86 (78.2)	917 (57.5)	201 (67.2)

Abbreviations: BMI = body mass index; BRCA = breast cancer gene, type 1 or 2; ECOG PS = Eastern Cooperative Oncology Group performance status; Max = maximum; Min = minimum; StD = standard deviation; US = United States; yr = year.

[c] This patient had an ECOG PS of 1 during Screening and was thus eligible for the study.

[d] Two patients in ARIEL2 had a baseline ECOG PS ≥ 2; however, inclusion criterion 11 stipulated an ECOG PS of 0 to 1.

Adverse events

Overview of adverse events

Table 34. Overall Summary of TEAEs: Pooled Ovarian Cancer Safety Population

	ATHENA-MONO		Overall	
	Rucaparib (N = 425)	Placebo (N = 110)	Rucaparib (N = 1,594)	Placebo (N = 299)
	n (%)	n (%)	n (%)	n (%)
Patients with one or more TEAEs	411 (96.7)	102 (92.7)	1,577 (98.9)	284 (95.0)
Patients with one or more treatment-related TEAEs	391 (92.0)	75 (68.2)	1,500 (94.1)	215 (71.9)
Patients with one or more TEAEs of Grade 3 or higher	257 (60.5)	25 (22.7)	997 (62.5)	56 (18.7)
Patients with one or more treatment-related TEAEs of Grade 3 or higher	208 (48.9)	5 (4.5)	756 (47.4)	14 (4.7)
Patients with one or more TEAEs leading to death	3 (0.7)	0	55 (3.5)	2 (0.7)
Patients with one or more treatment-related TEAEs leading to death	0	0	7 (0.4)	0
Patients with one or more serious TEAEs	90 (21.2)	7 (6.4)	421 (26.4)	27 (9.0)
Patients with one or more serious treatment-related TEAEs	34 (8.0)	1 (0.9)	173 (10.9)	4 (1.3)
Patients with one or more TEAEs leading to study drug discontinuation	50 (11.8)	6 (5.5)	269 (16.9)	10 (3.3)
Patients with one or more treatment-related TEAEs leading to study drug discontinuation	40 (9.4)	4 (3.6)	165 (10.4)	5 (1.7)
Patients with one or more TEAEs of Grade 3 or higher that led to study drug discontinuation	23 (5.4)	2 (1.8)	169 (10.6)	5 (1.7)
Patients with one or more treatment-related TEAEs of Grade 3 or higher that led to study drug discontinuation	18 (4.2)	1 (0.9)	85 (5.3)	1 (0.3)

	ATHENA-MONO		Overall	
	Rucaparib (N = 425)	Placebo (N = 110)	Rucaparib (N = 1,594)	Placebo (N = 299)
	n (%)	n (%)	n (%)	n (%)
Patients with one or more TEAEs leading to study drug dose reduction	210 (49.4)	9 (8.2)	764 (47.9)	17 (5.7)
Patients with one or more treatment-related TEAEs leading to study drug dose reduction	203 (47.8)	9 (8.2)	737 (46.2)	16 (5.4)
Patients with one or more TEAEs leading to study drug interruption	258 (60.7)	22 (20.0)	964 (60.5)	41 (13.7)
Patients with one or more treatment-related TEAEs leading to study drug interruption	230 (54.1)	10 (9.1)	831 (52.1)	19 (6.4)
Patients with one or more TEAEs leading to dose reduction or interruption	271 (63.8)	24 (21.8)	1,035 (64.9)	44 (14.7)
Patients with one or more treatment-related TEAEs leading to dose reduction or interruption	245 (57.6)	12 (10.9)	925 (58.0)	23 (7.7)
Patients with one or more TEAEs leading to interruption, reduction, or discontinuation of study drug	285 (67.1)	24 (21.8)	1,093 (68.6)	45 (15.1)
Patients with one or more treatment-related TEAEs leading to interruption, reduction, or discontinuation of study drug	254 (59.8)	12 (10.9)	960 (60.2)	23 (7.7)

Abbreviation: TEAE = treatment-emergent adverse event.

Common TEAEs

Table 35. Treatment-emergent AEs Reported in ⩾ 20% of overall rucaparib-treated patients: Pooled Ovarian Cancer Safety Population

	ATHENA-MONO		Overall	
System Organ Class Preferred Term	**Rucaparib (N = 425)**	**Placebo (N = 110)**	**Rucaparib (N = 1,594)**	**Placebo (N = 299)**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Number of Patients With At Least One TEAE	**411 (96.7)**	**102 (92.7)**	**1,577 (98.9)**	**284 (95.0)**
Combined Preferred Terms				
ALT and AST increased	148 (34.8)	6 (5.5)	490 (30.7)	7 (2.3)
ALT/AST increased	181 (42.6)	9 (8.2)	622 (39.0)	15 (5.0)
Anemia/Hemoglobin decreased	198 (46.6)	10 (9.1)	728 (45.7)	19 (6.4)
Asthenia/Fatigue	237 (55.8)	41 (37.3)	1,050 (65.9)	126 (42.1)
Asthenia/Fatigue/Lethargy	238 (56.0)	41 (37.3)	1,070 (67.1)	128 (42.8)
Neutropenia/Neutrophil count decreased	118 (27.8)	8 (7.3)	331 (20.8)	17 (5.7)
Thrombocytopenia/Platelet count decreased	101 (23.8)	1 (0.9)	410 (25.7)	6 (2.0)
Blood and lymphatic system disorders				
Anaemia	193 (45.4)	10 (9.1)	705 (44.2)	19 (6.4)
Gastrointestinal disorders				
Abdominal pain	106 (24.9)	31 (28.2)	468 (29.4)	81 (27.1)
Constipation	82 (19.3)	17 (15.5)	480 (30.1)	61 (20.4)
Diarrhoea	102 (24.0)	23 (20.9)	467 (29.3)	66 (22.1)
Nausea	239 (56.2)	33 (30.0)	1,089 (68.3)	103 (34.4)
Vomiting	100 (23.5)	13 (11.8)	582 (36.5)	42 (14.0)

	ATHENA-MONO		Overall	
System Organ Class Preferred Term	**Rucaparib (N = 425)**	**Placebo (N = 110)**	**Rucaparib (N = 1,594)**	**Placebo (N = 299)**
General disorders and administration site conditions				
Fatigue	183 (43.1)	31 (28.2)	781 (49.0)	97 (32.4)
Investigations				
Alanine aminotransferase increased	173 (40.7)	7 (6.4)	582 (36.5)	11 (3.7)
Aspartate aminotransferase increased	156 (36.7)	8 (7.3)	530 (33.2)	11 (3.7)
Metabolism and nutrition disorders				
Decreased appetite	76 (17.9)	16 (14.5)	438 (27.5)	41 (13.7)
Nervous system disorders				
Dysgeusia	90 (21.2)	6 (5.5)	390 (24.5)	17 (5.7)

ATHENA-MONO data cutoff date: 23 March 2022

Overall: Incorporates total pooled data with data cutoffs as follows: study 010: complete and closed, ARIEL2: 01Feb2019, ARIEL3: 04Apr2022, ARIEL4: 10Apr2022 and ATHENA: 23Mar2022

Treatment-related TEAEs

Table 36. Treatment-related TEAEs Reported in ≥ 20% of Overall Rucaparib-treated Patients: Pooled Ovarian Cancer Safety Population

	ATHENA-MONO		Overall	
System Organ Class	**Rucaparib (N = 425)**	**Placebo (N = 110)**	**Rucaparib (N = 1,594)**	**Placebo (N = 299)**
Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number of Patients With at Least One Treatment-related TEAE	**391 (92.0)**	**75 (68.2)**	**1,500 (94.1)**	**215 (71.9)**
Combined Preferred Terms				
ALT and AST increased	133 (31.3)	4 (3.6)	452 (28.4)	4 (1.3)
ALT/AST increased	166 (39.1)	7 (6.4)	582 (36.5)	12 (4.0)
Anemia/Hemoglobin decreased	179 (42.1)	6 (5.5)	654 (41.0)	13 (4.3)
Asthenia/Fatigue	198 (46.6)	32 (29.1)	902 (56.6)	92 (30.8)
Asthenia/Fatigue/Lethargy	200 (47.1)	32 (29.1)	921 (57.8)	93 (31.1)
Thrombocytopenia or Platelet count decreased	89 (20.9)	1 (0.9)	374 (23.5)	5 (1.7)
Blood and lymphatic system disorders				
Anaemia	174 (40.9)	6 (5.5)	634 (39.8)	13 (4.3)
Gastrointestinal disorders				
Nausea	211 (49.6)	21 (19.1)	981 (61.5)	72 (24.1)
Vomiting	74 (17.4)	5 (4.5)	411 (25.8)	14 (4.7)
General disorders and administration site conditions				
Fatigue	157 (36.9)	23 (20.9)	675 (42.3)	69 (23.1)
Investigations				
Alanine aminotransferase increased	160 (37.6)	6 (5.5)	541 (33.9)	9 (3.0)
Aspartate aminotransferase increased	139 (32.7)	5 (4.5)	493 (30.9)	7 (2.3)
Metabolism and nutrition disorders				
Decreased appetite	60 (14.1)	5 (4.5)	348 (21.8)	18 (6.0)

System Organ Class Preferred Term	ATHENA-MONO		Overall	
	Rucaparib (N = 425) n (%)	Placebo (N = 110) n (%)	Rucaparib (N = 1,594) n (%)	Placebo (N = 299) n (%)
Nervous system disorders				
Dysgeusia	84 (19.8)	4 (3.6)	366 (23.0)	15 (5.0)

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; TEAE = treatment-emergent adverse event.

Grade 3 or higher TEAEs

Table 37. Grade 3 or Higher TEAEs Reported in ≥ 2% of Overall Rucaparib-treated Patients: Pooled Ovarian Cancer Safety Population

System Organ Class Preferred Term	ATHENA-MONO		Overall	
	Rucaparib (N = 425) n (%)	Placebo (N = 110) n (%)	Rucaparib (N = 1,594) n (%)	Placebo (N = 299) n (%)
Number of Patients With At Least One Grade 3 or Higher TEAE	**257 (60.5)**	**25 (22.7)**	**997 (62.5)**	**56 (18.7)**
Combined Preferred Terms				
ALT and AST increased	19 (4.5)	1 (0.9)	43 (2.7)	1 (0.3)
ALT/AST increased	45 (10.6)	1 (0.9)	164 (10.3)	1 (0.3)
Anemia/Hemoglobin decreased	122 (28.7)	0	401 (25.2)	1 (0.3)
Asthenia/Fatigue	21 (4.9)	1 (0.9)	136 (8.5)	6 (2.0)
Asthenia/Fatigue/Lethargy	21 (4.9)	1 (0.9)	138 (8.7)	6 (2.0)
Leukopenia/White blood cell count decreased	15 (3.5)	0	38 (2.4)	0
Neutropenia/Neutrophil count decreased	62 (14.6)	1 (0.9)	165 (10.4)	3 (1.0)
Thrombocytopenia/Platelet count decreased	30 (7.1)	0	108 (6.8)	0
Blood and lymphatic system disorders				
Anaemia	121 (28.5)	0	386 (24.2)	1 (0.3)
Neutropenia	33 (7.8)	1 (0.9)	103 (6.5)	2 (0.7)
Thrombocytopenia	16 (3.8)	0	71 (4.5)	0
Gastrointestinal disorders				
Abdominal pain	2 (0.5)	2 (1.8)	47 (2.9)	3 (1.0)
Nausea	8 (1.9)	0	58 (3.6)	1 (0.3)
Vomiting	6 (1.4)	0	57 (3.6)	2 (0.7)
General disorders and administration site conditions				
Asthenia	6 (1.4)	0	52 (3.3)	1 (0.3)
Fatigue	15 (3.5)	1 (0.9)	87 (5.5)	5 (1.7)
Investigations				
Alanine aminotransferase increased	44 (10.4)	1 (0.9)	157 (9.8)	1 (0.3)
Aspartate aminotransferase increased	20 (4.7)	1 (0.9)	50 (3.1)	1 (0.3)
Neutrophil count decreased	30 (7.1)	0	64 (4.0)	1 (0.3)
Platelet count decreased	14 (3.3)	0	37 (2.3)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Malignant neoplasm progression	1 (0.2)	0	45 (2.8)	2 (0.7)

ATHENA-MONO data cutoff date: 23 March 2022

Overall: Incorporates total pooled data with data cutoffs as follows: study 010: complete and closed, ARIEL2: 01Feb2019, ARIEL3: 04Apr2022, ARIEL4: 10Apr2022 and ATHENA: 23Mar2022

Serious adverse events

Table 38. Treatment-emergent SAEs Reported in ⩾ 1% of Overall Rucaparib-treated Patients: Pooled Ovarian Cancer Safety Population

	ATHENA-MONO		Overall	
System Organ Class Preferred Term	**Rucaparib (N = 425)**	**Placebo (N = 110)**	**Rucaparib (N = 1,594)**	**Placebo (N = 299)**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Number of Patients With At Least One Serious TEAE	**90 (21.2)**	**7 (6.4)**	**421 (26.4)**	**27 (9.0)**
Combined Preferred Terms				
Anemia/Hemoglobin decreased	17 (4.0)	0	81 (5.1)	1 (0.3)
Neutropenia/Neutrophil count decreased	6 (1.4)	0	17 (1.1)	0
Thrombocytopenia/Platelet count decreased	5 (1.2)	0	21 (1.3)	0
Blood and lymphatic system disorders				
Anaemia	17 (4.0)	0	80 (5.0)	1 (0.3)
Febrile neutropenia	3 (0.7)	0	17 (1.1)	0
Neutropenia	6 (1.4)	0	16 (1.0)	0
Thrombocytopenia	4 (0.9)	0	16 (1.0)	0
Gastrointestinal disorders				
Abdominal pain	3 (0.7)	0	18 (1.1)	0
Intestinal obstruction	3 (0.7)	0	21 (1.3)	2 (0.7)
Small intestinal obstruction	4 (0.9)	0	32 (2.0)	3 (1.0)
Vomiting	3 (0.7)	0	26 (1.6)	2 (0.7)
Infections and infestations				
Urinary tract infection	4 (0.9)	0	17 (1.1)	1 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Malignant neoplasm progression	1 (0.2)	0	37 (2.3)	0
Renal and urinary disorders				
Acute kidney injury	1 (0.2)	0	16 (1.0)	0

ATHENA-MONO data cutoff date: 23 March 2022

Overall: Incorporates total pooled data with data cutoffs as follows: study 010: complete and closed, ARIEL2: 01Feb2019, ARIEL3: 04Apr2022, ARIEL4: 10Apr2022 and ATHENA: 23Mar2022

Deaths

In ATHENA-MONO, 3 (0.7%) patients treated with rucaparib experiencing fatal TEAEs. The cause of death in one patient was reported as possible myocardial infarction or possible pulmonary embolism due to pre-existing comorbidities. The cause of death in another patient was reported as multiple organ failure associated with COVID-19 pneumonia. The death of the third patient was attributed to malignant neoplasm progression. No TEAE that led to death was assessed as related to rucaparib by the investigator. No patients in the placebo group experienced a TEAE that led to death.

Upon implementation of Protocol Amendment 2, events of malignant neoplasm progression were no longer collected as TEAEs in ATHENA-MONO.

Table 39. Treatment-emergent AEs with an outcome of death: Pooled Ovarian Cancer Safety Population

	ATHENA-MONO		Overall	
System Organ Class Preferred Term	**Rucaparib (N = 425)**	**Placebo (N = 110)**	**Rucaparib (N = 1,594)**	**Placebo (N = 299)**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Number of Patients With At Least One TEAE Leading to Death	**3 (0.7)**	**0**	**55 (3.5)**	**2 (0.7)**
Combined Preferred Terms				
MDS/AML	0	0	5 (0.3)	0
Neutropenia/Neutrophil count decreased	0	0	1 (0.1)	0
Thrombocytopenia/Platelet count decreased	0	0	1 (0.1)	0
Blood and lymphatic system disorders				
Neutropenia	0	0	1 (0.1)	0
Thrombocytopenia	0	0	1 (0.1)	0
Cardiac disorders				
Cardiac arrest	0	0	1 (0.1)	0
Cardiac disorder	0	0	1 (0.1)	0
Myocardial infarction	1 (0.2)	0	1 (0.1)	0
Gastrointestinal disorders				
Intestinal obstruction	0	0	1 (0.1)	0
Large intestine perforation	0	0	1 (0.1)	0
General disorders and administration site conditions				
Death	0	0	2 (0.1)	0
General physical health deterioration	0	0	4 (0.3)	0
Multiple organ dysfunction syndrome	1 (0.2)	0	1 (0.1)	0
Immune system disorders				
Haemophagocytic lymphohistiocytosis	0	0	1 (0.1)	0
Infections and infestations				
COVID-19	0	0	1 (0.1)	0
Pneumonia	0	0	1 (0.1)	0
Sepsis	0	0	1 (0.1)	0
Septic shock	0	0	2 (0.1)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Acute myeloid leukaemia	0	0	1 (0.1)	0
B-cell type acute leukaemia	0	0	1 (0.1)	0
B-cell unclassifiable lymphoma high grade	0	0	1 (0.1)	0
Malignant neoplasm progression	1 (0.2)	0	24 (1.5)	0
Metastases to meninges	0	0	0	1 (0.3)
Metastatic neoplasm	0	0	1 (0.1)	0
Myelodysplastic syndrome	0	0	4 (0.)	0
Neoplasm malignant	0	0	1 (0.1)	0
Nervous system disorders				

	ATHENA-MONO		Overall	
System Organ Class Preferred Term	**Rucaparib (N = 425)**	**Placebo (N = 110)**	**Rucaparib (N = 1,594)**	**Placebo (N = 299)**
Cerebrovascular accident	0	0	1 (0.1)	0
Respiratory, thoracic and mediastinal disorders				
Pulmonary embolism	1 (0.2)	0	3 (0.2)	1 (0.3)

ATHENA-MONO data cutoff date: 23 March 2022

Overall: Incorporates total pooled data with data cutoffs as follows: study 010: complete and closed, ARIEL2: 01Feb2019, ARIEL3: 04Apr2022, ARIEL4: 10Apr2022 and ATHENA: 23Mar2022

Table 40. Summary of primary cause of death (ITT Population)

	Rucaparib (N=427)	Placebo (N=111)	Total (N=538[1])
Overall Survival Status			
Died	106 (24.9%)	27 (24.5%)	133 (24.7%)
Censored [1]	321 (75.1%)	84 (75.5%)	405 (75.3%)
Primary Cause of Death [2]			
Disease Under Study	90 (84.9%)	25 (92.6%)	115 (86.5%)
Serious Adverse Event (terms below)	5 (4.7%)	0 (0.0%)	5 (3.8%)
Cardiac arrest	1 (0.9%)	0 (0.0%)	1 (0.8%)
Malignant neoplasm progression	1 (0.9%)	0 (0.0%)	1 (0.8%)
Multiple organ failure	1 (0.9%)	0 (0.0%)	1 (0.8%)
Ovarian cancer progression	1 (0.9%)	0 (0.0%)	1 (0.8%)
Myelodysplastic syndrome	1 (0.9%)	0 (0.0%)	1 (0.8%)
Unknown	9 (8.5%)	2 (7.4%)	11 (8.3%)
Other (reasons below)	2 (1.9%)	0 (0.0%)	2 (1.5%)
Admitted for sepsis and passed away in hospital	1 (0.9%)	0 (0.0%)	1 (0.8%)
Progression	1 (0.9%)	0 (0.0%)	1 (0.8%)

[1] Includes 3 patients who were never dosed (2 patients randomised to rucaparib and 1 patient to placebo)
[2] Denominator includes patients that died.
Data cutoff is 23MAR2022

Other significant events (Adverse Events of Special Interest)

Myelodysplastic syndrome and Acute Myeloid Leukemia

Myelodysplastic syndrome and AML are considered AESIs as these events have been observed in patients exposed to PARP inhibitors, including olaparib and niraparib, as well as to cytotoxic chemotherapy (e.g., platinum and anthracyclines) used for the treatment of ovarian cancer. Data are presented for MDS/AML reported in the Clovis-sponsored clinical development program, including 19 Phase 1, 2, and 3 clinical studies of rucaparib alone or in combination with other cancer treatments in multiple solid tumour types as of 10 April 2022.

In approximately 3,025 patients treated with rucaparib (includes patients who received rucaparib in ongoing and completed studies, but excluding investigator-initiated trials), there were 33 patients (1.1%) who developed MDS or AML (including MDS transforming into AML), including during the long-term follow-up. These included:

- Study 10 (n = 2): two patients with MDS;
- ARIEL3 (n = 14): five patients with MDS, including one case of refractory anaemia with excess blasts; five patients with AML, and four patients with MDS transforming into AML;
- ARIEL2 (n = 7): five patients with MDS and two patients with AML;
- ARIEL4 (n = 7): six patients with MDS and one patient with AML;

- ATHENA (n = 3): one patient with MDS and one patient with AML in ATHENA-MONO, and one patient with MDS in ATHENA-COMBO (treatment blinded).

For these 33 patients, the time to onset of the diagnosis of MDS/AML following the first dose of rucaparib ranged from 1.9 months to approximately 71.9 months. Fifteen patients (two patients from Study 10, two patients from ARIEL2, six patients from ARIEL3, three patients from ARIEL4, and two patients from ATHENA-MONO) had an event that occurred during treatment or during the 28-day safety follow up.

Six patients in the placebo group in ARIEL3 developed MDS (n = 5) or AML (n = 1) more than 28 days after discontinuing placebo.

In ATHENA, up to the DCO three events of MDS/AML have been reported, all of them in an arm including rucaparib. Of these three events, one of them occurred in the ATHENA-COMBO and two of them in the ATHENA-MONO. Two events were considered as related by the investigator and one as unrelated.

Pneumonitis

There was one event of pneumonitis (or similar event) reported in the rucaparib group in ATHENA-MONO which was considered as unrelated by the investigator.

Adverse Drug Reactions

Table 41. Changes to the Frequency Categories of Adverse Drug Reactions in the SmPC

MedDRA System Organ Class Preferred Term	Current SmPC N = 937	ATHENA-MONO N = 425		Pooled Ovarian Cancer Safety Population N = 1,594	
Adverse Reaction	Frequency Category[a]	Frequency Category[a]	%[b]	Frequency Category[a]	%[b]
All CTCAEs Grades					
Blood and lymphatic system disorders					
Leukopenia[c]	Common	Very common	12.5	Very common	10.1
Gastrointestinal disorders					
Stomatitis	-	Common	7.5	Common	7.9
Metabolism and nutrition disorders					
Hypercholesterolaemia[c]	Common	Very common	11.1	Very common	10.1
CTCAE Grades 3 and Above					
Blood and lymphatic system disorders					
Neutropenia[c]	Common	Very common	14.6	Very common	10.2
Gastrointestinal disorders					
Stomatitis	-	Uncommon	0.2	Uncommon	0.3
Metabolism and nutrition disorders					
Hypercholesterolaemia[c]	Uncommon	Common	3.1	Common	1.4

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; SmPC = Summary of Product Characteristics.

[a] Frequency categories: very common [≥ 1/10]; common [≥ 1/100 to < 1/10]; uncommon [≥ 1/1,000 to < 1/100]; rare [≥ 1/10,000 to < 1/1,000]; very rare [< 1/10,000], not known [cannot be estimated from the available data]).

All causality.

MedDRA System Organ Class Preferred Term	Current SmPC N = 937	ATHENA-MONO N = 425		Pooled Ovarian Cancer Safety Population N = 1,594	
Adverse Reaction	Frequency Category[a]	Frequency Category[a]	%[b]	Frequency Category[a]	%[b]

Includes laboratory findings.

Laboratory findings

Haematology

Table 42. Maximum Post-baseline Toxicity Grade for Key Hematology Parameters in ATHENA-MONO Safety Population

	Rucaparib (N = 425)					Placebo (N = 110)				
	G1-4	G1	G2	G3	G4	G1-4	G1	G2	G3	G4
Parameter	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Anemia	319 (75.1)	130 (30.6)	90 (21.2)	99 (23.3)	0	49 (44.5)	39 (35.5)	8 (7.3)	2 (1.8)	0
Lymphocyte count decreased	270 (63.5)	170 (40.0)	83 (19.5)	17 (4.0)	0	54 (49.1)	34 (30.9)	18 (16.4)	2 (1.8)	0
Lymphocyte count increased	7 (1.6)	0	7 (1.6)	0	0	6 (5.5)	0	6 (5.5)	0	0
Neutrophil count decreased	226 (53.2)	64 (15.1)	103 (24.2)	46 (10.8)	13 (3.1)	30 (27.3)	14 (12.7)	13 (11.8)	2 (1.8)	1 (0.9)
Platelet count decreased	211 (49.6)	160 (37.6)	29 (6.8)	18 (4.2)	4 (0.9)	19 (17.3)	19 (17.3)	0	0	0
White blood cell decreased	239 (56.2)	75 (17.6)	139 (32.7)	24 (5.6)	1 (0.2)	30 (27.3)	14 (12.7)	15 (13.6)	1 (0.9)	0

Abbreviation: G = Grade.

Clinical chemistry

Table 43. Maximum Post-baseline Toxicity Grade for Key Clinical Chemistry Parameters in ATHENA-MONO Safety Population

	Rucaparib (N = 425)					Placebo (N = 110)				
	G1-4	G1	G2	G3	G4	G1-4	G1	G2	G3	G4
Parameter	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Alanine aminotransferase increased	278 (65.4)	207 (48.7)	50 (11.8)	20 (4.7)	1 (0.2)	16 (14.5)	15 (13.6)	1 (0.9)	0	0
Alkaline phosphatase increased	84 (19.8)	81 (19.1)	3 (0.7)	0	0	7 (6.4)	6 (5.5)	1 (0.9)	0	0
Aspartate aminotransferase increased	327 (76.9)	265 (62.4)	47 (11.1)	15 (3.5)	0	26 (23.6)	25 (22.7)	1 (0.9)	0	0

Table 43. Maximum Post-baseline Toxicity Grade for Key Clinical Chemistry Parameters in ATHENA-MONO Safety Population

	Rucaparib (N = 425)					Placebo (N = 110)				
	G1-4	G1	G2	G3	G4	G1-4	G1	G2	G3	G4
Parameter	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Blood bilirubin increased	91 (21.4)	70 (16.5)	21 (4.9)	0 (0)	0	6 (5.5)	5 (4.5)	1 (0.9)	0	0
Cholesterol high	350 (82.4)	260 (61.2)	73 (17.2)	14 (3.3)	3 (0.7)	92 (83.6)	80 (72.7)	12 (10.9)	0	0
Creatinine increased	190 (44.7)	73 (17.2)	114 (26.8)	3 (0.7)	0	16 (14.5)	12 (10.9)	4 (3.6)	0	0
Hypercalcemia	90 (21.2)	89 (20.9)	1 (0.2)	0	0	16 (14.5)	16 (14.5)	0	0	0
Hyperglycemia	257 (60.5)	177 (41.6)	54 (12.7)	26 (6.1)	0	57 (51.8)	38 (34.5)	15 (13.6)	4 (3.6)	0
Hyperkalemia	49 (11.5)	36 (8.5)	7 (1.6)	3 (0.7)	3 (0.7)	12 (10.9)	8 (7.3)	3 (2.7)	1 (0.9)	0
Hypermagnesemia	3 (0.7)	1 (0.2)	0	2 (0.5)	0	2 (1.8)	0	0	2 (1.8)	0
Hypernatremia	8 (1.9)	8 (1.9)	0	0	0	1 (0.9)	1 (0.9)	0	0	0
Hypoalbuminemia	10 (2.4)	6 (1.4)	4 (0.9)	0	0	3 (2.7)	2 (1.8)	1 (0.9)	0	0
Hypocalcemia	50 (11.8)	33 (7.8)	15 (3.5)	2 (0.5)	0	8 (7.3)	4 (3.6)	3 (2.7)	1 (0.9)	0
Hypoglycemia	91 (21.4)	82 (19.3)	6 (1.4)	2 (0.5)	1 (0.2)	18 (16.4)	18 (16.4)	0	0	0
Hypokalemia	55 (12.9)	0	52 (12.2)	3 (0.7)	0	6 (5.5)	0	5 (4.5)	1 (0.9)	0
Hypomagnesemia	131 (30.8)	121 (28.5)	8 (1.9)	1 (0.2)	1 (0.2)	20 (18.2)	19 (17.3)	1 (0.9)	0	0
Hyponatremia	100 (23.5)	87 (20.5)	0	12 (2.8)	1 (0.2)	14 (12.7)	14 (12.7)	0	0	0
Hypophosphatemia	56 (13.2)	0	50 (11.8)	6 (1.4)	0	5 (4.5)	0	5 (4.5)	0	0

Abbreviation: G = Grade.

- Vital signs

No notable mean changes from baseline in vital signs (diastolic blood pressure, systolic blood pressure, pulse rate, temperature and weight) were observed in ATHENA-MONO, and mean values were comparable between the rucaparib and placebo groups.

Safety in special populations

Analyses have been performed for ATHENA-MONO and the Pooled Ovarian Cancer Safety Population for the following subgroups: age, race, HRD status and renal impairment. Since all patients included in ATHENA-MONO had ovarian cancer, thus were female, no comparison by sex was performed.

Age

In ATHENA-MONO, for the Safety Population, the majority (~63%) of patients were < 65 years old, with ~30% of patients 65 to 74 years old, and ~7% of patients ≥75 years old, with these age groups well-balanced between the rucaparib and placebo groups.

Table 44. Overall Summary of TEAEs by Age: Pooled Ovarian Cancer Safety Population

	< 65 years		65-74 years		≥ 75 years	
	Rucaparib (N = 1,014)	Placebo (N = 184)	Rucaparib (N = 454)	Placebo (N = 97)	Rucaparib (N = 126)	Placebo (N = 18)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with one or more TEAEs	1003 (98.9)	174 (94.6)	448 (98.7)	94 (96.9)	126 (100.0)	16 (88.9)
Patients with one or more treatment-related TEAEs	942 (92.9)	125 (67.9)	433 (95.4)	76 (78.4)	125 (99.2)	14 (77.8)
Patients with one or more TEAEs of Grade 3 or higher	597 (58.9)	35 (19.0)	308 (67.8)	16 (16.5)	92 (73.0)	5 (27.8)
Patients with one or more treatment-related TEAEs of Grade 3 or higher	440 (43.4)	5 (2.7)	244 (53.7)	7 (7.2)	72 (57.1)	2 (11.1)
Patients with one or more TEAEs leading to death	32 (3.2)	0	17 (3.7)	2 (2.1)	6 (4.8)	0
Patients with one or more treatment-related TEAEs leading to death	3 (0.3)	0	3 (0.7)	0	1 (0.8)	0
Patients with one or more serious TEAEs	247 (24.4)	18 (9.8)	138 (30.4)	8 (8.2)	36 (28.6)	1 (5.6)
Patients with one or more serious treatment-related TEAEs	99 (9.8)	2 (1.1)	62 (13.7)	2 (2.1)	12 (9.5)	0

Abbreviation: TEAE = treatment-emergent adverse event.

Table 45. Overall Summary of TEAEs in Patients ⩾ 65 years and < 65 years old: Pooled Ovarian Cancer Safety Population

	< 65 years		≥ 65 years	
	Rucaparib (N = 1,014)	Placebo (N = 184)	Rucaparib (N = 580)	Placebo (N = 115)
	n (%)	n (%)	n (%)	n (%)
Patients with one or more TEAEs	1003 (98.9)	174 (94.6)	574 (99.0)	110 (95.7)
Patients with one or more treatment-related TEAEs	942 (92.9)	125 (67.9)	558 (96.2)	90 (78.3)
Patients with one or more TEAEs of Grade 3 or higher	597 (58.9)	35 (19.0)	400 (69.0)	21 (18.3)
Patients with one or more treatment-related TEAEs of Grade 3 or higher	440 (43.4)	5 (2.7)	316 (54.5)	9 (7.8)
Patients with one or more TEAEs leading to death	32 (3.2)	0	23 (4.0)	2 (1.7)
Patients with one or more treatment-related TEAEs leading to death	3 (0.3)	0	4 (0.7)	0
Patients with one or more serious TEAEs	247 (24.4)	18 (9.8)	174 (30.0)	9 (7.8)
Patients with one or more serious treatment-related TEAEs	99 (9.8)	2 (1.1)	74 (12.8)	2 (1.7)

Abbreviation: TEAE = treatment-emergent adverse event.

Table 46. Overall Summary of TEAEs in Patients ⩾ 75 years and < 75 years old: Pooled Ovarian Cancer Safety Population

	< 75 years		≥ 75 years	
	Rucaparib (N = 1,468)	Placebo (N = 281)	Rucaparib (N = 126)	Placebo (N = 18)
	n (%)	n (%)	n (%)	n (%)
Patients with one or more TEAEs	1,451 (98.8)	268 (95.4)	126 (100.0)	16 (88.9)
Patients with one or more treatment-related TEAEs	1,375 (93.7)	201 (71.5)	125 (99.2)	14 (77.8)
Patients with one or more TEAEs of Grade 3 or higher	905 (61.6)	51 (18.1)	92 (73.0)	5 (27.8)
Patients with one or more treatment-related TEAEs of Grade 3 or higher	684 (46.6)	12 (4.3)	72 (57.1)	2 (11.1)
Patients with one or more TEAEs leading to death	49 (3.3)	2 (0.7)	6 (4.8)	0
Patients with one or more treatment-related TEAEs leading to death	6 (0.4)	0	1 (0.8)	0
Patients with one or more serious TEAEs	385 (26.2)	26 (9.3)	36 (28.6)	1 (5.6)
Patients with one or more serious treatment-related TEAEs	161 (11.0)	4 (1.4)	12 (9.5)	0

Abbreviation: TEAE = treatment-emergent adverse event.

Table 47. Treatment-emergent AEs Reported in ≥ 20% of Overall Rucaparib-treated Patients ⩾ 75 years and < 75 years old: Pooled Ovarian Cancer Safety Population

	< 75 years		≥ 75 years	
System Organ Class	Rucaparib (N = 1,468)	Placebo (N = 281)	Rucaparib (N = 126)	Placebo (N = 18)
Preferred Term	n (%)	n (%)	n (%)	n (%)
TEAEs Reported in ≥ 20% of Patients ≥ 75 Years Old[a]				
Number of Patients With at Least One TEAE	1,451 (98.8)	268 (95.4)	126 (100.0)	16 (88.9)
Combined Preferred Terms				
ALT and AST increased	450 (30.7)	7 (2.5)	40 (31.7)	0
ALT/AST increased	569 (38.8)	15 (5.3)	53 (42.1)	0
Anemia/Hemoglobin decreased	660 (45.0)	17 (6.0)	68 (54.0)	2 (11.1)
Asthenia/Fatigue	959 (65.3)	120 (42.7)	91 (72.2)	6 (33.3)
Asthenia/Fatigue/Lethargy	975 (66.4)	122 (43.4)	95 (75.4)	6 (33.3)
Neutropenia or Neutrophil count decreased	310 (21.1)	15 (5.3)	21 (16.7)	2 (11.1)
Thrombocytopenia or Platelet count decreased	372 (25.3)	6 (2.1)	38 (30.2)	0
Blood and lymphatic system disorders				
Anaemia	641 (43.7)	17 (6.0)	64 (50.8)	2 (11.1)
Gastrointestinal disorders				
Abdominal pain	438 (29.8)	77 (27.4)	30 (23.8)	4 (22.2)
Constipation	434 (29.6)	58 (20.6)	46 (36.5)	3 (16.7)
Diarrhoea	429 (29.2)	62 (22.1)	38 (30.2)	4 (22.2)
Nausea	1002 (68.3)	99 (35.2)	87 (69.0)	4 (22.2)
Vomiting	541 (36.9)	42 (14.9)	41 (32.5)	0
General disorders and administration site conditions				
Asthenia	293 (20.0)	28 (10.0	25 (19.8)	2 (11.1)

System Organ Class Preferred Term	< 75 years		≥ 75 years	
	Rucaparib (N = 1,468) n (%)	Placebo (N = 281) n (%)	Rucaparib (N = 126) n (%)	Placebo (N = 18) n (%)
Fatigue	711 (48.4)	93 (33.1)	70 (55.6)	4 (22.2)
Investigations				
Alanine aminotransferase increased	537 (36.6)	11 (3.9)	45 (35.7)	0
Aspartate aminotransferase increased	482 (32.8)	11 (3.9)	48 (38.1)	0
Blood creatinine increased	235 (16.0)	8 (2.8)	42 (33.3)	1 (5.6)
Metabolism and nutrition disorders				
Decreased appetite	391 (26.6)	39 (13.9)	47 (37.3)	2 (11.1)
Nervous system disorders				
Dysgeusia	360 (24.5)	15 (5.3)	30 (23.8)	2 (11.1)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	229 (15.6)	24 (8.5)	33 (26.2)	2 (11.1)
TEAEs With Incidence < 20% But More Frequent in Patients ≥ 75 Years Old (PT)[b]				
Dizziness	199 (13.6)	22 (7.8)	24 (19.0)	2 (11.1)
Hypertension	97 (6.6)	22 (7.8)	16 (12.7)	2 (11.1)
Hyponatraemia	56 (3.8)	9 (3.2)	9 (7.1)	1 (5.6)
Oedema peripheral	139 (9.5)	24 (8.5)	16 (12.7)	4 (22.2)
Pruritus	163 (11.1)	33 (11.7)	20 (15.9)	0
Pyrexia	174 (11.9)	14 (5.0)	23 (18.3)	1 (5.6)
Urinary tract infection	172 (11.7)	16 (5.7)	21 (16.7)	3 (16.7)
Weight decreased	137 (9.3)	5 (1.8)	17 (13.5)	0

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; PT = preferred term; TEAE = treatment-emergent adverse event.

[e] Frequency ≥ 20% in patients ≥ 75 years old who received rucaparib in the Pooled Ovarian Cancer Safety Population.

[f] Greater than 3% increase in frequency of the TEAE in patients ≥ 75 years old as compared with patients < 75 years old who received rucaparib in the Pooled Ovarian Cancer Safety Population.

Table 48. Summary of TEAEs by Age Groups: <65 years, 65-74 years and ≥ 75 years old (Safety population – ATHENA-MONO)

Table 22.1	< 65 years		65-74 years		≥ 75 years	
	Rucaparib (N = 269)	Placebo (N = 67)	Rucaparib (N = 129)	Placebo (N = 33)	Rucaparib (N = 27)	Placebo (N = 10)
Patients with one or more TEAEs	261 (97.0)	62 (92.5)	123 (95.3)	32 (97.0)	27 (100.0)	8 (80.0)
Patients with one or more TEAEs related to oral study drug	244 (90.7)	45 (67.2)	120 (93.0)	23 (69.7)	27 (100.0)	7 (70.0)
Patients with one or more TEAEs related to IV study drug	146 (54.3)	26 (38.8)	74 (57.4)	21 (63.6)	17 (63.0)	4 (40.0)
Patients with one or more Serious TEAEs	56 (20.8)	5 (7.5)	28 (21.7)	1 (3.0)	6 (22.2)	1 (10.0)
Patients with one or more Serious TEAEs related to oral study drug	22 (8.2)	0	11 (8.5)	1 (3.0)	1 (3.7)	0
Patients with one or more Serious TEAEs related to IV study drug	9 (3.3)	0	2 (1.6)	0	1 (3.7)	0
Patients with one or more TEAEs of grade 3 or higher	148 (55.0)	15 (22.4)	88 (68.2)	6 (18.2)	21 (77.8)	4 (40.0)
Patients with one or more TEAEs related to oral study drug of grade 3 or higher	121 (45.0)	2 (3.0)	67 (51.9)	1 (3.0)	20 (74.1)	2 (20.0)
Patients with one or more TEAEs related to IV study drug of grade 3 or higher	47 (17.5)	2 (3.0)	21 (16.3)	3 (9.1)	4 (14.8)	1 (10.0)
Patients with one or more TEAEs that led to death	1 (0.4)	0	2 (1.6)	0	0	0
Patients with one or more TEAEs related to oral study drug that led to death	0	0	0	0	0	0
Patients with one or more TEAEs related to IV study drug that led to death	0	0	0	0	0	0
Patients with one or more TEAEs that led to oral study drug discontinuation	21 (7.8)	1 (1.5)	24 (18.6)	4 (12.1)	5 (18.5)	1 (10.0)
Patients with one or more TEAEs related to oral study drug that led to oral study drug discontinuation	17 (6.3)	0	19 (14.7)	3 (9.1)	4 (14.8)	1 (10.0)
Patients with one or more TEAEs related to IV study drug that led to oral study drug discontinuation	4 (1.5)	0	1 (0.8)	2 (6.1)	1 (3.7)	0
Patients with one or more TEAEs that led to IV study drug discontinuation	20 (7.4)	2 (3.0)	19 (14.7)	4 (12.1)	3 (11.1)	1 (10.0)
Patients with one or more TEAEs related to oral study drug that led to IV study drug discontinuation	15 (5.6)	1 (1.5)	8 (6.2)	3 (9.1)	2 (7.4)	1 (10.0)
Patients with one or more TEAEs related to IV study drug that led to IV study drug discontinuation	13 (4.8)	2 (3.0)	12 (9.3)	2 (6.1)	2 (7.4)	0
Patients with one or more TEAEs that led to discontinuation of both oral and IV study drug	8 (3.0)	0	7 (5.4)	3 (9.1)	2 (7.4)	1 (10.0)
Patients with one or more TEAEs related to oral study drug that led to discontinuation of both oral and IV study drug	7 (2.6)	0	2 (1.6)	2 (6.1)	1 (3.7)	1 (10.0)
Patients with one or more TEAEs related to IV study drug that led to discontinuation of both oral and IV study drug	3 (1.1)	0	0	1 (3.0)	1 (3.7)	0
Patients with one or more TEAEs that led to dose reduction of oral study drug	118 (43.9)	4 (6.0)	70 (54.3)	4 (12.1)	22 (81.5)	1 (10.0)
Patients with one or more TEAEs related to oral study drug that led to dose reduction of oral study drug	113 (42.0)	4 (6.0)	68 (52.7)	4 (12.1)	22 (81.5)	1 (10.0)
Patients with one or more TEAEs related to IV study drug that led to dose reduction of oral study drug	32 (11.9)	2 (3.0)	14 (10.9)	1 (3.0)	4 (14.8)	0
Patients with one or more TEAEs that led to oral study drug interruption	148 (55.0)	14 (20.9)	89 (69.0)	6 (18.2)	21 (77.8)	2 (20.0)
Patients with one or more TEAEs related to oral study drug that led to oral study drug interruption	126 (46.8)	4 (6.0)	83 (64.3)	5 (15.2)	21 (77.8)	1 (10.0)
Patients with one or more TEAEs related to IV study drug that led to oral study drug interruption	47 (17.5)	4 (6.0)	30 (23.3)	3 (9.1)	8 (29.6)	1 (10.0)
Patients with one or more TEAEs that led to IV study drug interruption	99 (36.8)	5 (7.5)	55 (42.6)	5 (15.2)	14 (51.9)	1 (10.0)
Patients with one or more TEAEs related to oral study drug that led to IV study drug interruption	75 (27.9)	1 (1.5)	45 (34.9)	2 (6.1)	13 (48.1)	0
Patients with one or more TEAEs related to IV study drug that led to IV study drug interruption	51 (19.0)	4 (6.0)	31 (24.0)	4 (12.1)	7 (25.9)	0
Patients with one or more TEAEs that led to both oral and IV study drug interruption	74 (27.5)	3 (4.5)	47 (36.4)	3 (9.1)	12 (44.4)	1 (10.0)
Patients with one or more TEAEs related to oral study drug that led to both oral and IV study drug interruption	65 (24.2)	0	37 (28.7)	2 (6.1)	11 (40.7)	0

Table 22.1	< 65 years		65-74 years		≥ 75 years	
	Rucaparib (N = 269)	Placebo (N = 67)	Rucaparib (N = 129)	Placebo (N = 33)	Rucaparib (N = 27)	Placebo (N = 10)
Patients with one or more TEAEs related to IV study drug that led to both oral and IV study drug interruption	32 (11.9)	2 (3.0)	20 (15.5)	2 (6.1)	7 (25.9)	0
Patients with one or more TEAEs that led to dose reduction or interruption of oral study drug	156 (58.0)	15 (22.4)	91 (70.5)	6 (18.2)	24 (88.9)	3 (30.0)
Patients with one or more TEAEs related to oral study drug that led to dose reduction or interruption of oral study drug	136 (50.6)	5 (7.5)	85 (65.9)	5 (15.2)	24 (88.9)	2 (20.0)
Patients with one or more TEAEs related to IV study drug that led to dose reduction or interruption of oral study drug	49 (18.2)	4 (6.0)	30 (23.3)	3 (9.1)	8 (29.6)	1 (10.0)
Patients with one or more TEAEs that led to interruption, reduction, or discontinuation of oral study drug	165 (61.3)	15 (22.4)	96 (74.4)	6 (18.2)	24 (88.9)	3 (30.0)
Patients with one or more TEAEs related to oral study drug that led to interruption, reduction, or discontinuation of oral study drug	142 (52.8)	5 (7.5)	88 (68.2)	5 (15.2)	24 (88.9)	2 (20.0)
Patients with one or more TEAEs related to IV study drug that led to interruption, reduction, or discontinuation of oral study drug	50 (18.6)	4 (6.0)	31 (24.0)	3 (9.1)	8 (29.6)	1 (10.0)

Data cutoff is 23MAR2022

Table 49. TEAEs Reported in ≥20% of Rucaparib Treated Patients Aged <65 years and ≥65 years (Safety population – ATHENA-MONO)

Table 22.5	< 65 years		≥ 65 years	
System Organ Class Preferred Term	Rucaparib (N = 269)	Placebo (N = 67)	Rucaparib (N = 156)	Placebo (N = 43)
	n (%)	n (%)	n (%)	n (%)
TEAEs reported in ≥ 20% of patients aged ≥ 65 years[a]				
Number of Patients With At Least One TEAE	261 (97.0)	62 (92.5)	150 (96.2)	40 (93.0)
Combined Preferred Terms				
ALT and AST increased	84 (31.2)	4 (6.0)	64 (41.0)	2 (4.7)
ALT/AST increased	107 (39.8)	7 (10.4)	74 (47.4)	2 (4.7)
Anemia/Hemoglobin decreased	110 (40.9)	5 (7.5)	88 (56.4)	5 (11.6)
Asthenia/Fatigue	139 (51.7)	22 (32.8)	98 (62.8)	19 (44.2)
Neutropenia/Neutrophil count decreased	75 (27.9)	4 (6.0)	43 (27.6)	4 (9.3)
Thrombocytopenia/Platelet count decreased	57 (21.2)	0	44 (28.2)	1 (2.3)
Blood and lymphatic system disorders				
Anaemia	108 (40.1)	5 (7.5)	85 (54.5)	5 (11.6)
Gastrointestinal disorders				
Abdominal pain	65 (24.2)	21 (31.3)	41 (26.3)	10 (23.3)
Constipation	49 (18.2)	12 (17.9)	33 (21.2)	5 (11.6)
Diarrhoea	60 (22.3)	13 (19.4)	42 (26.9)	10 (23.3)
Nausea	151 (56.1)	18 (26.9)	88 (56.4)	15 (34.9)
Vomiting	61 (22.7)	9 (13.4)	39 (25.0)	4 (9.3)
General disorders and administration site conditions				
Fatigue	99 (36.8)	13 (19.4)	84 (53.8)	18 (41.9)
Investigations				
Alanine aminotransferase increased	102 (37.9)	5 (7.5)	71 (45.5)	2 (4.7)
Aspartate aminotransferase increased	89 (33.1)	6 (9.0)	67 (42.9)	2 (4.7)
Metabolism and nutrition disorders				

Table 22.5	< 65 years		≥ 65 years	
System Organ Class Preferred Term	Rucaparib (N = 269)	Placebo (N = 67)	Rucaparib (N = 156)	Placebo (N = 43)
Decreased appetite	40 (14.9)	9 (13.4)	36 (23.1)	7 (16.3)
Nervous system disorders				
Dysgeusia	48 (17.8)	4 (6.0)	42 (26.9)	2 (4.7)
TEAEs with incidence < 20% but more frequent in patients aged ≥ 65 years (PT)[b]				
Abdominal distension	23 (8.6)	9 (13.4)	19 (12.2)	5 (11.6)
Abdominal pain lower	5 (1.9)	2 (3.0)	11 (7.1)	3 (7.0)
Back pain	20 (7.4)	5 (7.5)	22 (14.1)	8 (18.6)
Blood cholesterol increased	12 (4.5)	1 (1.5)	13 (8.3)	2 (4.7)
Blood creatinine increased	19 (7.1)	2 (3.0)	28 (17.9)	4 (9.3)
Cough	27 (10.0)	4 (6.0)	25 (16.0)	7 (16.3)
Dizziness	29 (10.8)	5 (7.5)	28 (17.9)	4 (9.3)
Dyspnoea	19 (7.1)	6 (9.0)	26 (16.7)	6 (14.0)
Hypokalaemia	8 (3.0)	1 (1.5)	12 (7.7)	0
Hypomagnesaemia	14 (5.2)	0	16 (10.3)	2 (4.7)
Hyponatraemia	6 (2.2)	2 (3.0)	9 (5.8)	4 (9.3)
Malaise	4 (1.5)	0	8 (5.1)	1 (2.3)
Pain in extremity	19 (7.1)	3 (4.5)	20 (12.8)	4 (9.3)
Pruritus	40 (14.9)	4 (6.0)	29 (18.6)	7 (16.3)
Rhinorrhoea	4 (1.5)	0	7 (4.5)	0
White blood cell count decreased	21 (7.8)	1 (1.5)	17 (10.9)	2 (4.7)

Data cutoff is 23MAR2022

Race

In ATHENA-MONO, for the Safety Population overall, the majority (~77%) of patients were White, ~21% of patients were in the Other race group (~18% were Asian), and < 2% of patients were in the Unknown race subgroup, with these race groups well-balanced between the rucaparib and placebo groups.

Table 50. Overall Summary of TEAEs by Race: Pooled Ovarian Cancer Safety Population

	White		Other[a]		Unknown	
	Rucaparib (N = 1,268)	Placebo (N = 230)	Rucaparib (N = 183)	Placebo (N = 40)	Rucaparib (N = 143)	Placebo (N = 29)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with one or more TEAEs	1,252 (98.7)	219 (95.2)	182 (99.5)	37 (92.5)	143 (100.0)	28 (96.6)
Patients with one or more treatment-related TEAEs	1,188 (93.7)	158 (68.7)	175 (95.6)	30 (75.0)	137 (95.8)	27 (93.1)
Patients with one or more TEAEs of Grade 3 or higher	777 (61.3)	41 (17.8)	126 (68.9)	7 (17.5)	94 (65.7)	8 (27.6)
Patients with one or more treatment-related TEAEs of Grade 3 or higher	580 (45.7)	10 (4.3)	104 (56.8)	2 (5.0)	72 (50.3)	2 (6.9)
Patients with one or more TEAEs leading to death	45 (3.5)	2 (0.9)	2 (1.1)	0	8 (5.6)	0
Patients with one or more treatment-related TEAEs leading to death	6 (0.5)	0	0	0	1 (0.7)	0
Patients with one or more serious TEAEs	325 (25.6)	19 (8.3)	55 (30.1)	3 (7.5)	41 (28.7)	5 (17.2)
Patients with one or more serious treatment-related TEAEs	129 (10.2)	4 (1.7)	22 (12.0)	0	22 (15.4)	0

Abbreviation: TEAE = treatment-emergent adverse event.

g Includes American Indian or Alaska Native, Asian, Black, Native Hawaiian or Other Pacific Islander, Other.

Table 51. Summary of TEAEs by Race Groups: White, Asian and Other (Safety population – ATHENA-MONO)

Table 22.6	White		Asian		Other	
	Rucaparib (N = 326)	Placebo (N = 86)	Rucaparib (N = 80)	Placebo (N = 16)	Rucaparib (N = 19)	Placebo (N = 8)
Patients with one or more TEAEs	313 (96.0)	80 (93.0)	79 (98.8)	15 (93.8)	19 (100.0)	7 (87.5)
Patients with one or more TEAEs related to oral study drug	298 (91.4)	59 (68.6)	78 (97.5)	9 (56.3)	15 (78.9)	7 (87.5)
Patients with one or more TEAEs related to IV study drug	184 (56.4)	43 (50.0)	41 (51.3)	4 (25.0)	12 (63.2)	4 (50.0)
Patients with one or more Serious TEAEs	60 (18.4)	4 (4.7)	25 (31.3)	0	5 (26.3)	3 (37.5)
Patients with one or more Serious TEAEs related to oral study drug	23 (7.1)	1 (1.2)	9 (11.3)	0	2 (10.5)	0
Patients with one or more Serious TEAEs related to IV study drug	9 (2.8)	0	3 (3.8)	0	0	0
Patients with one or more TEAEs of grade 3 or higher	185 (56.7)	19 (22.1)	62 (77.5)	2 (12.5)	10 (52.6)	4 (50.0)
Patients with one or more TEAEs related to oral study drug of grade 3 or higher	144 (44.2)	3 (3.5)	57 (71.3)	0	7 (36.8)	2 (25.0)
Patients with one or more TEAEs related to IV study drug of grade 3 or higher	50 (15.3)	5 (5.8)	20 (25.0)	0	2 (10.5)	1 (12.5)
Patients with one or more TEAEs that led to death	2 (0.6)	0	0	0	1 (5.3)	0
Patients with one or more TEAEs related to oral study drug that led to death	0	0	0	0	0	0
Patients with one or more TEAEs related to IV study drug that led to death	0	0	0	0	0	0
Patients with one or more TEAEs that led to oral study drug discontinuation	37 (11.3)	5 (5.8)	7 (8.8)	0	6 (31.6)	1 (12.5)
Patients with one or more TEAEs related to oral study drug that led to oral study drug discontinuation	32 (9.8)	3 (3.5)	5 (6.3)	0	3 (15.8)	1 (12.5)
Patients with one or more TEAEs related to IV study drug that led to oral study drug discontinuation	6 (1.8)	2 (2.3)	0	0	0	0
Patients with one or more TEAEs that led to IV study drug discontinuation	35 (10.7)	6 (7.0)	4 (5.0)	0	3 (15.8)	1 (12.5)
Patients with one or more TEAEs related to oral study drug that led to IV study drug discontinuation	21 (6.4)	4 (4.7)	2 (2.5)	0	2 (10.5)	1 (12.5)
Patients with one or more TEAEs related to IV study drug that led to IV study drug discontinuation	23 (7.1)	4 (4.7)	2 (2.5)	0	2 (10.5)	0
Patients with one or more TEAEs that led to discontinuation of both oral and IV study drug	15 (4.6)	3 (3.5)	1 (1.3)	0	1 (5.3)	1 (12.5)
Patients with one or more TEAEs related to oral study drug that led to discontinuation of both oral and IV study drug	10 (3.1)	2 (2.3)	0	0	0	1 (12.5)
Patients with one or more TEAEs related to IV study drug that led to discontinuation of both oral and IV study drug	4 (1.2)	1 (1.2)	0	0	0	0
Patients with one or more TEAEs that led to dose reduction of oral study drug	146 (44.8)	5 (5.8)	58 (72.5)	2 (12.5)	6 (31.6)	2 (25.0)
Patients with one or more TEAEs related to oral study drug that led to dose reduction of oral study drug	140 (42.9)	5 (5.8)	57 (71.3)	2 (12.5)	6 (31.6)	2 (25.0)
Patients with one or more TEAEs related to IV study drug that led to dose reduction of oral study drug	35 (10.7)	2 (2.3)	14 (17.5)	0	1 (5.3)	1 (12.5)
Patients with one or more TEAEs that led to oral study drug interruption	191 (58.6)	18 (20.9)	59 (73.8)	2 (12.5)	8 (42.1)	2 (25.0)
Patients with one or more TEAEs related to oral study drug that led to oral study drug interruption	166 (50.9)	8 (9.3)	57 (71.3)	1 (6.3)	7 (36.8)	1 (12.5)
Patients with one or more TEAEs related to IV study drug that led to oral study drug interruption	64 (19.6)	7 (8.1)	20 (25.0)	0	1 (5.3)	1 (12.5)
Patients with one or more TEAEs that led to IV study drug interruption	116 (35.6)	10 (11.6)	45 (56.3)	0	7 (36.8)	1 (12.5)
Patients with one or more TEAEs related to oral study drug that led to IV study drug interruption	88 (27.0)	3 (3.5)	41 (51.3)	0	4 (21.1)	0
Patients with one or more TEAEs related to IV study drug that led to IV study drug interruption	67 (20.6)	8 (9.3)	19 (23.8)	0	3 (15.8)	0
Patients with one or more TEAEs that led to both oral and IV study drug interruption	90 (27.6)	6 (7.0)	39 (48.8)	0	4 (21.1)	1 (12.5)
Patients with one or more TEAEs related to oral study drug that led to both oral and IV study drug interruption	75 (23.0)	2 (2.3)	35 (43.8)	0	3 (15.8)	0

Patients with one or more TEAEs related to IV study drug that led to both oral and IV study drug interruption	46 (14.1)	4 (4.7)	12 (15.0)	0	1 (5.3)	0
Patients with one or more TEAEs that led to dose reduction or interruption of oral study drug	202 (62.0)	18 (20.9)	61 (76.3)	3 (18.8)	8 (42.1)	3 (37.5)
Patients with one or more TEAEs related to oral study drug that led to dose reduction or interruption of oral study drug	179 (54.9)	8 (9.3)	59 (73.8)	2 (12.5)	7 (36.8)	2 (25.0)
Patients with one or more TEAEs related to IV study drug that led to dose reduction or interruption of oral study drug	66 (20.2)	7 (8.1)	20 (25.0)	0	1 (5.3)	1 (12.5)
Patients with one or more TEAEs that led to interruption, reduction, or discontinuation of oral study drug	209 (64.1)	18 (20.9)	65 (81.3)	3 (18.8)	11 (57.9)	3 (37.5)
Patients with one or more TEAEs related to oral study drug that led to interruption, reduction, or discontinuation of oral study drug	184 (56.4)	8 (9.3)	62 (77.5)	2 (12.5)	8 (42.1)	2 (25.0)
Patients with one or more TEAEs related to IV study drug that led to interruption, reduction, or discontinuation of oral study drug	68 (20.9)	7 (8.1)	20 (25.0)	0	1 (5.3)	1 (12.5)

Data cutoff is 23MAR2022

Table 52. TEAEs Reported ≥ 10% of Rucaparib Treated Patients by Race (Safety population – ATHENA-MONO)

Table 22.8	White		Asian		Other	
System Organ Class Preferred Term	**Rucaparib (N = 326)**	**Placebo (N = 86)**	**Rucaparib (N = 80)**	**Placebo (N = 16)**	**Rucaparib (N = 19)**	**Placebo (N = 8)**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
TEAEs reported in ≥ 10% of Rucaparib treated patients[a]						
Number of Patients With At Least One TEAE	313 (96.0)	80 (93.0)	79 (98.8)	15 (93.8)	19 (100.0)	7 (87.5)
Combined Preferred Terms						
ALT and AST increased	105 (32.2)	5 (5.8)	37 (46.3)	1 (6.3)	6 (31.6)	0
ALT/AST increased	129 (39.6)	7 (8.1)	43 (53.8)	2 (12.5)	9 (47.4)	0
Anemia/Hemoglobin decreased	135 (41.4)	9 (10.5)	55 (68.8)	0	8 (42.1)	1 (12.5)
Asthenia/Fatigue	199 (61.0)	32 (37.2)	28 (35.0)	5 (31.3)	10 (52.6)	4 (50.0)
Neutropenia/Neutrophil count decreased	73 (22.4)	7 (8.1)	39 (48.8)	0	6 (31.6)	1 (12.5)
Thrombocytopenia/Platelet count decreased	64 (19.6)	0	32 (40.0)	1 (6.3)	5 (26.3)	0
Blood and lymphatic system disorders						
Anaemia	132 (40.5)	9 (10.5)	55 (68.8)	0	6 (31.6)	1 (12.5)
Neutropenia	52 (16.0)	6 (7.0)	9 (11.3)	0	5 (26.3)	1 (12.5)
Thrombocytopenia	41 (12.6)	0	4 (5.0)	1 (6.3)	5 (26.3)	0
Ear and labyrinth disorders						
Tinnitus	2 (0.6)	2 (2.3)	4 (5.0)	0	2 (10.5)	1 (12.5)
Eye disorders						
Vision blurred	6 (1.8)	1 (1.2)	0	0	2 (10.5)	0
Gastrointestinal disorders						
Abdominal distension	38 (11.7)	11 (12.8)	2 (2.5)	2 (12.5)	2 (10.5)	1 (12.5)
Abdominal pain	89 (27.3)	28 (32.6)	12 (15.0)	1 (6.3)	5 (26.3)	2 (25.0)
Abdominal pain upper	32 (9.8)	7 (8.1)	4 (5.0)	1 (6.3)	2 (10.5)	1 (12.5)
Constipation	65 (19.9)	15 (17.4)	15 (18.8)	2 (12.5)	2 (10.5)	0
Diarrhoea	91 (27.9)	20 (23.3)	5 (6.3)	1 (6.3)	6 (31.6)	2 (25.0)

Dyspepsia	33 (10.1)	3 (3.5)	8 (10.0)	4 (25.0)	0	1 (12.5)
Mouth ulceration	5 (1.5)	0	2 (2.5)	0	2 (10.5)	0
Nausea	179 (54.9)	28 (32.6)	51 (63.8)	3 (18.8)	9 (47.4)	2 (25.0)
Stomatitis	21 (6.4)	3 (3.5)	10 (12.5)	0	1 (5.3)	0
Vomiting	77 (23.6)	11 (12.8)	19 (23.8)	0	4 (21.1)	2 (25.0)
General disorders and administration site conditions						
Asthenia	50 (15.3)	9 (10.5)	8 (10.0)	1 (6.3)	0	0
Fatigue	151 (46.3)	23 (26.7)	22 (27.5)	4 (25.0)	10 (52.6)	4 (50.0)
Malaise	3 (0.9)	1 (1.2)	9 (11.3)	0	0	0
Pyrexia	33 (10.1)	5 (5.8)	10 (12.5)	0	0	1 (12.5)
Infections and infestations						
Nasopharyngitis	15 (4.6)	1 (1.2)	5 (6.3)	1 (6.3)	2 (10.5)	0
Urinary tract infection	34 (10.4)	10 (11.6)	4 (5.0)	0	2 (10.5)	0
Investigations						
Alanine aminotransferase increased	121 (37.1)	5 (5.8)	43 (53.8)	2 (12.5)	9 (47.4)	0
Aspartate aminotransferase increased	113 (34.7)	7 (8.1)	37 (46.3)	1 (6.3)	6 (31.6)	0
Blood alkaline phosphatase increased	32 (9.8)	1 (1.2)	5 (6.3)	0	3 (15.8)	1 (12.5)
Blood creatinine increased	38 (11.7)	6 (7.0)	6 (7.5)	0	3 (15.8)	0
Haemoglobin decreased	6 (1.8)	0	0	0	2 (10.5)	0
Neutrophil count decreased	23 (7.1)	1 (1.2)	32 (40.0)	0	1 (5.3)	0
Platelet count decreased	25 (7.7)	0	30 (37.5)	0	0	0
White blood cell count decreased	19 (5.8)	3 (3.5)	18 (22.5)	0	1 (5.3)	0
Metabolism and nutrition disorders						
Decreased appetite	64 (19.6)	13 (15.1)	9 (11.3)	2 (12.5)	3 (15.8)	1 (12.5)
Hypercholesterolaemia	22 (6.7)	5 (5.8)	1 (1.3)	0	2 (10.5)	1 (12.5)
Hypomagnesaemia	26 (8.0)	1 (1.2)	2 (2.5)	1 (6.3)	2 (10.5)	0
Musculoskeletal and connective tissue disorders						
Arthralgia	67 (20.6)	20 (23.3)	12 (15.0)	3 (18.8)	7 (36.8)	2 (25.0)
Back pain	36 (11.0)	10 (11.6)	4 (5.0)	2 (12.5)	2 (10.5)	1 (12.5)
Myalgia	32 (9.8)	6 (7.0)	17 (21.3)	2 (12.5)	4 (21.1)	2 (25.0)
Joint swelling	3 (0.9)	1 (1.2)	0	0	2 (10.5)	0
Pain in extremity	35 (10.7)	7 (8.1)	4 (5.0)	0	0	0
Nervous system disorders						
Dysgeusia	69 (21.2)	5 (5.8)	15 (18.8)	1 (6.3)	6 (31.6)	0
Dizziness	42 (12.9)	6 (7.0)	12 (15.0)	1 (6.3)	3 (15.8)	2 (25.0)
Headache	64 (19.6)	13 (15.1)	17 (21.3)	1 (6.3)	4 (21.1)	2 (25.0)
Paraesthesia	9 (2.8)	2 (2.3)	2 (2.5)	0	2 (10.5)	1 (12.5)
Taste disorder	21 (6.4)	1 (1.2)	0	0	2 (10.5)	0
Psychiatric disorders						
Insomnia	48 (14.7)	3 (3.5)	10 (12.5)	3 (18.8)	1 (5.3)	2 (25.0)
Respiratory, thoracic and mediastinal disorders						
Cough	44 (13.5)	7 (8.1)	5 (6.3)	2 (12.5)	3 (15.8)	2 (25.0)
Dyspnoea	40 (12.3)	10 (11.6)	2 (2.5)	1 (6.3)	3 (15.8)	1 (12.5)
Oropharyngeal pain	10 (3.1)	3 (3.5)	0	1 (6.3)	2 (10.5)	0
Skin and subcutaneous tissue disorders						
Rash	41 (12.6)	7 (8.1)	15 (18.8)	0	5 (26.3)	1 (12.5)
Pruritus	54 (16.6)	8 (9.3)	12 (15.0)	2 (12.5)	3 (15.8)	1 (12.5)
Vascular disorders						
Hypertension	21 (6.4)	7 (8.1)	3 (3.8)	0	2 (10.5)	1 (12.5)
Hot flush	26 (8.0)	2 (2.3)	2 (2.5)	0	3 (15.8)	1 (12.5)

Data cutoff is 23MAR2022

HRD status

Table 53. Overall Summary of TEAEs by BRCA Mutation Status: Pooled Ovarian Cancer Safety Population

	BRCA		Non-BRCA	
	Rucaparib (N = 677)	**Placebo (N = 98)**	**Rucaparib (N = 917)**	**Placebo (N = 201)**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Patients with one or more TEAEs	671 (99.1)	95 (96.9)	906 (98.8)	189 (94.0)
Patients with one or more treatment-related TEAEs	638 (94.2)	77 (78.6)	862 (94.0)	138 (68.7)

Table 53. Overall Summary of TEAEs by BRCA Mutation Status: Pooled Ovarian Cancer Safety Population

	BRCA		Non-BRCA	
	Rucaparib (N = 677)	Placebo (N = 98)	Rucaparib (N = 917)	Placebo (N = 201)
	n (%)	n (%)	n (%)	n (%)
Patients with one or more TEAEs of Grade 3 or higher	447 (66.0)	17 (17.3)	550 (60.0)	39 (19.4)
Patients with one or more treatment-related TEAEs of Grade 3 or higher	337 (49.8)	5 (5.1)	419 (45.7)	9 (4.5)
Patients with one or more TEAEs leading to death	33 (4.9)	1 (1.0)	22 (2.4)	1 (0.5)
Patients with one or more treatment-related TEAEs leading to death	7 (1.0)	0	0	0
Patients with one or more serious TEAEs	202 (29.8)	13 (13.3)	219 (23.9)	14 (7.0)
Patients with one or more serious treatment-related TEAEs	88 (13.0)	2 (2.0)	85 (9.3)	2 (1.0)

Abbreviations: BRCA = breast cancer gene, type 1 or 2; TEAE = treatment-emergent adverse event.

Table 54. Summary of TEAEs by tBRCA and Non-BRCA (Safety Population – ATHENA-MONO)

Table 22.7	tBRCA		Non-tBRCA	
	Rucaparib (N = 91)	Placebo (N = 23)	Rucaparib (N = 334)	Placebo (N = 87)
Patients with one or more TEAEs	88 (96.7)	22 (95.7)	323 (96.7)	80 (92.0)
Patients with one or more TEAEs related to oral study drug	82 (90.1)	17 (73.9)	309 (92.5)	58 (66.7)
Patients with one or more TEAEs related to IV study drug	52 (57.1)	10 (43.5)	185 (55.4)	41 (47.1)
Patients with one or more Serious TEAEs	26 (28.6)	1 (4.3)	64 (19.2)	6 (6.9)
Patients with one or more Serious TEAEs related to oral study drug	10 (11.0)	0	24 (7.2)	1 (1.1)
Patients with one or more Serious TEAEs related to IV study drug	4 (4.4)	0	8 (2.4)	0
Patients with one or more TEAEs of grade 3 or higher	62 (68.1)	4 (17.4)	195 (58.4)	21 (24.1)
Patients with one or more TEAEs related to oral study drug of grade 3 or higher	49 (53.8)	0	159 (47.6)	5 (5.7)
Patients with one or more TEAEs related to IV study drug of grade 3 or higher	15 (16.5)	0	57 (17.1)	6 (6.9)
Patients with one or more TEAEs that led to death	2 (2.2)	0	1 (0.3)	0
Patients with one or more TEAEs related to oral study drug that led to death	0	0	0	0
Patients with one or more TEAEs related to IV study drug that led to death	0	0	0	0
Patients with one or more TEAEs that led to oral study drug discontinuation	11 (12.1)	0	39 (11.7)	6 (6.9)
Patients with one or more TEAEs related to oral study drug that led to oral study drug discontinuation	8 (8.8)	0	32 (9.6)	4 (4.6)
Patients with one or more TEAEs related to IV study drug that led to oral study drug discontinuation	1 (1.1)	0	5 (1.5)	2 (2.3)
Patients with one or more TEAEs that led to IV study drug discontinuation	9 (9.9)	0	33 (9.9)	7 (8.0)
Patients with one or more TEAEs related to oral study drug that led to IV study drug discontinuation	4 (4.4)	0	21 (6.3)	5 (5.7)
Patients with one or more TEAEs related to IV study drug that led to IV study drug discontinuation	6 (6.6)	0	21 (6.3)	4 (4.6)
Patients with one or more TEAEs that led to discontinuation of both oral and IV study drug	2 (2.2)	0	15 (4.5)	4 (4.6)
Patients with one or more TEAEs related to oral study drug that led to discontinuation of both oral and IV study drug	0	0	10 (3.0)	3 (3.4)

Table 22.7	tBRCA		Non-tBRCA	
	Rucaparib (N = 91)	Placebo (N = 23)	Rucaparib (N = 334)	Placebo (N = 87)
Patients with one or more TEAEs related to IV study drug that led to discontinuation of both oral and IV study drug	0	0	4 (1.2)	1 (1.1)
Patients with one or more TEAEs that led to dose reduction of oral study drug	42 (46.2)	0	168 (50.3)	9 (10.3)
Patients with one or more TEAEs related to oral study drug that led to dose reduction of oral study drug	41 (45.1)	0	162 (48.5)	9 (10.3)
Patients with one or more TEAEs related to IV study drug that led to dose reduction of oral study drug	13 (14.3)	0	37 (11.1)	3 (3.4)
Patients with one or more TEAEs that led to oral study drug interruption	58 (63.7)	2 (8.7)	200 (59.9)	20 (23.0)
Patients with one or more TEAEs related to oral study drug that led to oral study drug interruption	49 (53.8)	0	181 (54.2)	10 (11.5)
Patients with one or more TEAEs related to IV study drug that led to oral study drug interruption	19 (20.9)	0	66 (19.8)	8 (9.2)
Patients with one or more TEAEs that led to IV study drug interruption	38 (41.8)	1 (4.3)	130 (38.9)	10 (11.5)
Patients with one or more TEAEs related to oral study drug that led to IV study drug interruption	28 (30.8)	0	105 (31.4)	3 (3.4)
Patients with one or more TEAEs related to IV study drug that led to IV study drug interruption	22 (24.2)	1 (4.3)	67 (20.1)	7 (8.0)
Patients with one or more TEAEs that led to both oral and IV study drug interruption	27 (29.7)	0	106 (31.7)	7 (8.0)
Patients with one or more TEAEs related to oral study drug that led to both oral and IV study drug interruption	24 (26.4)	0	89 (26.6)	2 (2.3)
Patients with one or more TEAEs related to IV study drug that led to both oral and IV study drug interruption	14 (15.4)	0	45 (13.5)	4 (4.6)
Patients with one or more TEAEs that led to dose reduction or interruption of oral study drug	59 (64.8)	2 (8.7)	212 (63.5)	22 (25.3)
Patients with one or more TEAEs related to oral study drug that led to dose reduction or interruption of oral study drug	50 (54.9)	0	195 (58.4)	12 (13.8)
Patients with one or more TEAEs related to IV study drug that led to dose reduction or interruption of oral study drug	21 (23.1)	0	66 (19.8)	8 (9.2)
Patients with one or more TEAEs that led to interruption, reduction, or discontinuation of oral study drug	64 (70.3)	2 (8.7)	221 (66.2)	22 (25.3)
Patients with one or more TEAEs related to oral study drug that led to interruption, reduction, or discontinuation of oral study drug	53 (58.2)	0	201 (60.2)	12 (13.8)
Patients with one or more TEAEs related to IV study drug that led to interruption, reduction, or discontinuation of oral study drug	22 (24.2)	0	67 (20.1)	8 (9.2)

Data cutoff is 23MAR2022

Renal impairment

Table 55. Overall Summary of TEAEs by Renal Function: Pooled Ovarian Cancer Safety Population

	Mild Impairment		Moderate Impairment		No Impairment	
	Rucaparib (N = 656)	Placebo (N = 123)	Rucaparib (N = 285)	Placebo (N = 43)	Rucaparib (N = 652)	Placebo (N = 133)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with one or more TEAEs	651 (99.2)	116 (94.3)	283 (99.3)	41 (95.3)	642 (98.5)	127 (95.5)
Patients with one or more treatment-related TEAEs	620 (94.5)	87 (70.7)	273 (95.8)	29 (67.4)	606 (92.9)	99 (74.4)
Patients with one or more TEAEs of Grade 3 or higher	418 (63.7)	23 (18.7)	211 (74.0)	9 (20.9)	367 (56.3)	24 (18.0)
Patients with one or more treatment-related TEAEs of Grade 3 or higher	311 (47.4)	8 (6.5)	171 (60.0)	4 (9.3)	273 (41.9)	2 (1.5)
Patients with one or more TEAEs leading to death	21 (3.2)	0	17 (6.0)	0	17 (2.6)	2 (1.5)
Patients with one or more treatment-related TEAEs leading to death	2 (0.3)	0	2 (0.7)	0	3 (0.5)	0
Patients with one or more serious TEAEs	177 (27.0)	10 (8.1)	96 (33.7)	3 (7.0)	148 (22.7)	14 (10.5)
Patients with one or more serious treatment-related TEAEs	65 (9.9)	3 (2.4)	50 (17.5)	1 (2.3)	58 (8.9)	0

Abbreviation: TEAE = treatment-emergent adverse event.

Safety related to drug-drug interactions and other interactions

The MAH has not provided any data on the safety related to drug-drug interactions and other interactions.

Discontinuation due to adverse events

In ATHENA-MONO, the incidences of TEAEs and treatment-related TEAEs that led to discontinuation of oral study drug were low. The most common TEAEs that led to discontinuation of rucaparib included anaemia/haemoglobin decreased, asthenia/fatigue, and nausea. The most common TEAEs leading to discontinuation of placebo were asthenia/fatigue and neuropathy peripheral. The TEAEs were considered related to rucaparib or placebo in most patients experiencing TEAEs that led to discontinuation of oral study drug.

The first TEAE that led to discontinuation occurred earlier for rucaparib compared to placebo in ATHENA-MONO: median time, 2.0 months (95% CI, 1.2-2.8) for rucaparib and 14.1 months (95% CI, 0.9-23.0) for placebo.

Table 56. Treatment-emergent AEs That Led to Study Drug Discontinuation in ⩾ 2% of Overall Rucaparib-treated Patients: Pooled Ovarian Cancer Safety Population

	ATHENA-MONO		Overall	
System Organ Class Preferred Term	Rucaparib (N = 425)	Placebo (N = 110)	Rucaparib (N = 1,594)	Placebo (N = 299)
	n (%)	n (%)	n (%)	n (%)

	ATHENA-MONO		Overall	
System Organ Class Preferred Term	**Rucaparib (N = 425)**	**Placebo (N = 110)**	**Rucaparib (N = 1,594)**	**Placebo (N = 299)**
Number of Patients With At Least One TEAE Leading to Study Drug Discontinuation	**50 (11.8)**	**6 (5.5)**	**269 (16.9)**	**10 (3.3)**
Combined Preferred Terms				
Anemia/Hemoglobin decreased	15 (3.5)	0	38 (2.4)	0
Asthenia/Fatigue	12 (2.8)	3 (2.7)	38 (2.4)	3 (1.0)
Asthenia/Fatigue/Lethargy	12 (2.8)	3 (2.7)	40 (2.5)	3 (1.0)
Blood and lymphatic system disorders				
Anaemia	15 (3.5)	0	38 (2.4)	0
General disorders and administration site conditions				
Fatigue	11 (2.6)	3 (2.7)	32 (2.0)	3 (1.0)

ATHENA-MONO data cutoff date: 23 March 2022

Overall: Incorporates total pooled data with data cutoffs as follows: study 010: complete and closed, ARIEL2: 01Feb2019, ARIEL3: 04Apr2022, ARIEL4: 10Apr2022 and ATHENA: 23Mar2022

Adverse events leading to dose reduction or treatment interruption

Table 57. Treatment-emergent AEs That Led to Dose Reduction of Study Drug in ≥ 2% of Overall Rucaparib-treated Patients: Pooled Ovarian Cancer Safety Population

	ATHENA-MONO		Overall	
System Organ Class	**Rucaparib (N = 425)**	**Placebo (N = 110)**	**Rucaparib (N = 1,594)**	**Placebo (N = 299)**
Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number of Patients With at Least One TEAE Leading to Study Drug Dose Reduction	**210 (49.4)**	**9 (8.2)**	**764 (47.9)**	**17 (5.7)**
Combined Preferred Terms				
ALT and AST increased	14 (3.3)	0	38 (2.4)	0
ALT/AST increased	32 (7.5)	0	101 (6.3)	0
Anemia/Hemoglobin decreased	99 (23.3)	0	284 (17.8)	0
Asthenia/Fatigue	39 (9.2)	6 (5.5)	165 (10.4)	10 (3.3)
Asthenia/Fatigue/Lethargy	40 (9.4)	6 (5.5)	168 (10.5)	10 (3.3)
Neutropenia/Neutrophil count decreased	40 (9.4)	2 (1.8)	92 (5.8)	2 (0.7)
Thrombocytopenia/Platelet count decreased	29 (6.8)	1 (0.9)	123 (7.7)	1 (0.3)
Blood and lymphatic system disorders				
Anaemia	98 (23.1)	0	271 (17.0)	0
Neutropenia	17 (4.0)	2 (1.8)	57 (3.6)	2 (0.7)
Thrombocytopenia	12 (2.8)	1 (0.9)	73 (4.6)	1 (0.3)
Gastrointestinal disorders				
Nausea	30 (7.1)	0	134 (8.4)	1 (0.3)
Vomiting	7 (1.6)	0	45 (2.8)	0
General disorders and administration site conditions				
Asthenia	9 (2.1)	1 (0.9)	42 (2.6)	1 (0.3)
Fatigue	30 (7.1)	5 (4.5)	125 (7.8)	9 (3.0)

System Organ Class Preferred Term	ATHENA-MONO		Overall	
	Rucaparib (N = 425) n (%)	Placebo (N = 110) n (%)	Rucaparib (N = 1,594) n (%)	Placebo (N = 299) n (%)
Investigations				
Alanine aminotransferase increased	29 (6.8)	0	96 (6.0)	0
Aspartate aminotransferase increased	17 (4.0)	0	43 (2.7)	0
Blood creatinine increased	3 (0.7)	0	40 (2.5)	0
Neutrophil count decreased	23 (5.4)	0	35 (2.2)	0
Platelet count decreased	17 (4.0)	0	53 (3.3)	0
Metabolism and nutrition disorders				
Decreased appetite	7 (1.6)	1 (0.9)	33 (2.1)	2 (0.7)

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; TEAE = treatment-emergent adverse event.

Table 58. Treatment-emergent AEs That Led to Study Drug Interruption in ≥ 2% of Overall Rucaparib-treated Patients: Pooled Ovarian Cancer Safety Population

System Organ Class Preferred Term	ATHENA-MONO		Overall	
	Rucaparib (N = 425) n (%)	Placebo (N = 110) n (%)	Rucaparib (N = 1,594) n (%)	Placebo (N = 299) n (%)
Number of Patients With at Least One TEAE Leading to Study Drug Interruption	**258 (60.7)**	**22 (20.0)**	**964 (60.5)**	**41 (13.7)**
Combined Preferred Terms				
ALT and AST increased	29 (6.8)	1 (0.9)	78 (4.9)	1 (0.3)
ALT/AST increased	49 (11.5)	1 (0.9)	139 (8.7)	1 (0.3)
Anemia/Hemoglobin decreased	115 (27.1)	1 (0.9)	325 (20.4)	2 (0.7)
Asthenia/Fatigue	41 (9.6)	4 (3.6)	170 (10.7)	10 (3.3)
Asthenia/Fatigue/Lethargy	42 (9.9)	4 (3.6)	172 (10.8)	10 (3.3)
Leukopenia/White Blood Cell Count decreased	17 (4.0)	0	36 (2.3)	0
Neutropenia/Neutrophil count decreased	63 (14.8)	1 (0.9)	150 (9.4)	2 (0.7)
Thrombocytopenia/Platelet count decreased	45 (10.6)	1 (0.9)	210 (13.2)	1 (0.3)
Blood and lymphatic system disorders				
Anaemia	113 (26.6)	1 (0.9)	312 (19.6)	2 (0.7)
Neutropenia	33 (7.8)	1 (0.9)	93 (5.8)	1 (0.3)
Thrombocytopenia	19 (4.5)	1 (0.9)	129 (8.1)	1 (0.3)
Gastrointestinal disorders				
Abdominal pain	6 (1.4)	0	44 (2.8)	0
Diarrhoea	16 (3.8)	4 (3.6)	51 (3.2)	4 (1.3)
Nausea	38 (8.9)	1 (0.9)	165 (10.4)	3 (1.0)
Vomiting	19 (4.5)	2 (1.8)	138 (8.7)	4 (1.3)
General disorders and administration site conditions				
Asthenia	14 (3.3)	0	49 (3.1)	0
Fatigue	27 (6.4)	4 (3.6)	124 (7.8)	10 (3.3)

Table 58. Treatment-emergent AEs That Led to Study Drug Interruption in ≥ 2% of Overall Rucaparib-treated Patients: Pooled Ovarian Cancer Safety Population

System Organ Class Preferred Term	ATHENA-MONO		Overall	
	Rucaparib (N = 425) n (%)	Placebo (N = 110) n (%)	Rucaparib (N = 1,594) n (%)	Placebo (N = 299) n (%)
Investigations				
Alanine aminotransferase increased	46 (10.8)	1 (0.9)	134 (8.4)	1 (0.3)
Aspartate aminotransferase increased	32 (7.5)	1 (0.9)	83 (5.2)	1 (0.3)
Blood creatinine increased	6 (1.4)	0	45 (2.8)	0
Neutrophil count decreased	30 (7.1)	0	59 (3.7)	1 (0.3)
Platelet count decreased	28 (6.6)	0	89 (5.6)	0
Metabolism and nutrition disorders				
Decreased appetite	7 (1.6)	0	37 (2.3)	2 (0.7)

Source: Table 2.7.4.8.1.1 (t-ae-int-sf), ATHENA-MONO ISS.
Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; TEAE = treatment-emergent adverse event.

Post marketing experience

Rucaparib (Rubraca) is currently marketed in the US, UK, Israel, Switzerland and in selected countries in the EU (Germany, Italy, Spain, France, and the Netherlands). As detailed in the PSUR dated 17 February 2022, with the exception of the EU, UK, Israel and Switzerland exposure data, patient exposure from marketing experience is presented by the number of individual patients exposed to Rubraca since the marketing authorization was granted in the US on 19 December 2016. Commercial exposure to Rubraca in the EU, UK, Israel and Switzerland has been calculated as treatment days. Cumulatively, up to 19 December 2021, 9,043 patients have been exposed worldwide to Rubraca (excluding commercial exposure in the EU, Switzerland, Israel, and the UK). Cumulatively, the total commercial exposure to Rubraca in the EU (Germany, Italy, Spain, France, and the Netherlands), Switzerland, Israel, and the UK was 383,117.5 treatment days.

From US approval on 19 December 2016 to 19 December 2021, there were no safety signals detected from the post-marketing reports. The post-marketing safety data collected from 19 December 2016 to 19 December 2021 are consistent with the known safety profile of rucaparib. Post-marketing safety surveillance is ongoing. Overall, the post-marketing safety data remain consistent with the known safety profile of rucaparib in clinical trials.

2.5.1. Discussion on clinical safety

Introduction

Due to the four-arm study design of ATHENA (see Figure 1 in Monk et al. Int J Gynecol Cancer. 2021), all patients in the rucaparib and placebo groups in addition to oral study treatment also received IV placebo therapy. This could have influenced the safety assessment (of patients and investigators), however, as the same IV placebo therapy was administered in both study arms, the resulting uncertainties remain limited.

The Safety population of ATHENA-MONO included 425 patients in the rucaparib arm and 110 patients in the placebo arm. The Pool includes data from 1,594 patients in the rucaparib arm and 299 patients in the placebo arm.

Patient exposure

At the DCO, 111 patients (101 on rucaparib) had completed treatment with oral study drug, and 64 patients (53 on rucaparib) were still on treatment. Of note, in ATHENA-MONO the maximum duration of patients on rucaparib was capped to 24 months (counting since the start of IV placebo, i.e. cycle 2). At the DCO, safety data from 114 patients (26.8%) on treatment during 12 to < 24 months and from 118 (27.8%) on treatment during ≥ 24 months are available. At this point of the assessment, the number of patients on treatment during a period of time close to 24 months (the maximum duration proposed in the SmPC) is considered sufficient.

Regarding patient demographics, the population of Asian patients in ATHENA-MONO is considerably higher than in the Pool with 18.8% and 14.5% of Asian patients in the rucaparib arm and the placebo arm in ATHENA-MONO, vs. 8.0 and 7.7% respectively in the Pool. BRCA status also differed from ATHENA-MONO to the Pool: 22.4% patients in the rucaparib arm and 21.8% in the placebo arm were BRCA mutated, vs. 42.5% in the rucaparib arm and 32.8% in the placebo arm in the Pool. As mentioned in section 4.4.3 (Discussion on clinical efficacy), a lower than expected proportion of tBRCA patients was enrolled in the study, apparently due to the approval of other PARPi in this setting. This marked difference between ATHENA-MONO and the Pool on BRCA status is not expected to impact the safety results of this study as both arms remained balanced. All the other characteristics were well balanced between arms.

Regarding disease history and prior anticancer therapies, no relevant differences were observed between arms or between ATHENA-MONO and the Pool. All patients had received 4 to 8 cycles of first-line platinum doublet chemotherapy.

Adverse events

In ATHENA-MONO, almost all patients had at least one TEAE: 96.7% in the rucaparib arm and 92.7% in the placebo arm. These percentages are in line with the ones reported for the Pool.

The most frequently reported combined PTs were "asthenia/fatigue/lethargy" (56.0% in the rucaparib arm vs. 37.3% in the placebo arm), "asthenia/fatigue" (55.8% vs. 37.3%), "anaemia/haemoglobin decreased" (46.6% vs. 9.1%) and "ALT/AST increased" (42.6% vs. 8.2%).

By individual PTs the most frequently reported ones in the rucaparib arm were "nausea" (56.2% vs. 30.0%), "anaemia" (45.4% vs. 9.1%), "fatigue" (43.1% vs. 28.2%) and "ALT increased" (40.7% vs. 6.4%).

Overall, the incidence and nature of AE remained broadly similar in comparison with the data from the Pool, although it should be noted that several deviations were observed. Some PTs were reported with a higher frequency in ATHENA-MONO than in the Pool: "neutropenia/neutrophil count decreased" (27.8% in ATHENA-MONO vs. 20.8% in the Pool) and "ALT increased" (40.7% in ATHENA-MONO vs. 36.5% in the Pool). On the other hand, some PTs were reported with a lower frequency in ATHENA-MONO than in the Pool: "asthenia/fatigue" (55.8% in ATHENA-MONO vs. 65.9% in the Pool), "asthenia/fatigue/lethargy" (56.0% in ATHENA-MONO vs. 67.1% in the Pool), "constipation" (19.3% in ATHENA-MONO vs. 30.1% in the Pool), "diarrhoea" (24.0% in ATHENA-MONO vs. 29.3% in the Pool), "nausea" (56.2% in ATHENA-MONO vs. 68.3% in the Pool), "vomiting" (23.5% in ATHENA-MONO vs. 36.5% in the Pool) and "decreased appetite" (17.9% in ATHENA-MONO vs. 27.5% in the Pool).

It seems that there is a tendency towards a lower reporting rate of TEAEs belonging to the SOC "Gastrointestinal disorders", also including the PT "decreased appetite" in ATHENA-MONO compared with the Pool, with differences higher than 10% in some PTs, such as "nausea" and "vomiting". A similar pattern is observed in the placebo arm although differences appear lower in this case. The lower reporting rates in ATHENA-MONO compared with the Pool could be related to the status of the patient population (i.e. a less heavily pre-treated population).

Overall, the same trends observed in the reporting rates of TEAEs are also observed in the reporting rates of treatment-related TEAEs, with no significant differences in terms of incidences.

Regarding Grade 3 (G3) or higher TEAEs, in ATHENA-MONO 60.5% of patients in the rucaparib arm reported an event, vs. 22.7% in the placebo arm. These percentages were similar to the observed in the Pool. There are some PTs that were slightly increased in the rucaparib arm in ATHENA-MONO vs. the Pool: "ALT and AST increased" (4.5% in ATHENA-MONO vs. 2.7% in the Pool), "anaemia/haemoglobin decreased" (28.7% in ATHENA-MONO vs. 25.2% in the Pool), "neutropenia/neutrophil count decreased" (14.6% in ATHENA-MONO vs. 10.4% in the Pool), "anaemia" (28.5% in ATHENA-MONO vs. 24.2% in the Pool) and "neutrophil count decreased" (7.1% in ATHENA-MONO vs. 4% in the Pool). In line with the TEAEs' reporting rates, PTs belonging to the "Gastrointestinal disorders" SOC were reported with a lower frequency in the rucaparib arm in ATHENA-MONO than in the rucaparib arm in the Pool. The same trend is observed in the G3 or higher treatment-related TEAEs.

Overall, it seems that "neutropenia" and "neutrophil count decreased" were more frequently reported in ATHENA-MONO than in the Pool. Those PTs were also increased in terms of G3 or higher TEAEs, dose reductions and dose interruptions. In terms of SAEs the difference between ATHENA-MONO and the Pool is subtle, and in terms of discontinuations there were only 2 patients (0.5%) who discontinued rucaparib due to "neutropenia" or "neutrophil count decreased" in ATHENA-MONO vs. 8 patients (0.5%) in the Pool. Although the rates are slightly increased in ATHENA-MONO compared with the Pool and the reason for this is not fully understood, this finding does not seem to be clinically relevant considering that this AE is already included in section 4.4 and section 4.8 (as "very common"). Additionally, it does not seem that this increase in "neutropenia"/"neutrophil count decreased" translates into a higher rate of infections.

The Pool's safety data were updated with the latest available DCO, and are reflected in the clinical safety tables above.

Serious Adverse Events

In ATHENA-MONO 90 patients (21.2%) in the rucaparib arm reported at least a SAE, vs. 7 patients (6.4%) in the placebo arm. Those percentages are similar to the percentages reported in the Pool: 26.4% in the rucaparib arm vs. 9.0% in the placebo arm. Apart from "anaemia", the only other PT in the rucaparib arm which was reported with a higher frequency than 1% was "neutropenia", which was reported in 1.4% patients, vs. in no patients in the placebo arm. In addition, there were 7 (1.6%) patients that reported an event of intestinal obstruction (including intestinal obstruction and small intestinal obstruction). The absolute absence of patients reporting those events in the placebo arm is a clear indicator of the causal role of rucaparib in its occurrence.

In terms of treatment-related SAEs, there were 34 patients (8.0%) with at least one serious TEAE related to rucaparib. From those patients, 17 patients (4.0%) reported an event of "anaemia". No other PT was reported with an incidence higher than 1%.

Deaths

The percentage of TEAEs that led to death was very low in both arms of ATHENA-MONO: 3 patients (0.7%) in the rucaparib arm vs. 0 patients in the placebo arm. These rates are slightly lower than the rates for the Pool: 3.5% in the rucaparib arm vs. 0.7% in the placebo arm.

It should be noted that after Protocol Amendment 2, events of malignant neoplasm progression were no longer collected as TEAEs in the ATHENA-MONO study. As such, all those deaths have been excluded from the percentages.

In the ATHENA-MONO ITT population the percentage of patients who died in both arms is similar (24.9% and 24.5% in the rucaparib and placebo arm, respectively). Among these patients, the proportion who died due to the disease under study was smaller in the rucaparib arm compared with the placebo arm (84.9% vs. 92.6%), but 4.7% of death in the rucaparib arm were related to SAEs, while there was none in the placebo arm. As such, the potential decrease in the number of deaths due to the disease in the rucaparib arm is counterbalanced by the additional deaths due to SAEs.

It should be noted that 9 patients (8.5%) died due to "unknown causes" in the rucaparib arm compared with 2 patients (7.4%) in the placebo arm. It should be noted that no SAEs were reported in long-term follow-up for these 9 patients.

In ATHENA-MONO there were no deaths considered as TEAEs reported under the PT "MDS/AML", whereas in the Pool there were 5 deaths belonging to this PT. This is not surprising, taking into account that MDS and AML usually occur after a long period of time and the follow-up in ATHENA-MONO up to now is shorter than in the Pool.

None of the deaths in the rucaparib arm of ATHENA-MONO were considered as causally-related to rucaparib. The 3 TEAEs that led to death were as follows:

- There was a TEAE that led to death coded as "multiple organ dysfunction syndrome" associated with "COVID-19 pneumonia". There are no signs suggesting a potential implication of rucaparib in this death.
- There was a TEAE that led to death coded as "myocardial infarction" or "pulmonary embolism". Of note, this patient died 5 days after starting treatment with rucaparib, and had comorbidities. No autopsy was performed, and therefore no official cause of death was known. In absence of further information the potential role of rucaparib in this death remains uncertain, and the treatment can neither be linked with the death, nor potential implication be ruled out. Three deaths (0.2%) due to "pulmonary embolism" and 1 death (0.1%) due to "myocardial infarction" were reported in the rucaparib arm of the Pool. "Pulmonary embolism" is not listed in the SmPC of rucaparib.
- There was a TEAE that led to death coded as "malignant neoplasm progression". There are no signs suggesting a potential implication of rucaparib in this death.

In addition, SAE was recorded by investigator as the primary cause of death for two additional patients, these were not considered as a TEAE due to the time of onset:

- One patient in ATHENA-MONO, experienced an evolution from MDS to AML and died. The patient received treatment for 579 days. The patient was diagnosed with MDS/AML 686 days after the start of the treatment (and 107 days after discontinuation) and died 3 days later. The Investigator reported the G5 AML as related to rucaparib, despite some reserves expressed in the narrative. The MAH considered AML to be more likely related to the platinum-based treatment than to rucaparib, based on genetic features of the disease. However, it is considered that there is not enough evidence to rule out rucaparib potential contribution. MDS/AML is already listed as ADR in the product information.
- One SAE recorded with outcome of death was "Ovarian cancer progression". There are no signs suggesting a potential implication of rucaparib in this death.

Other significant events

Myelodysplastic syndrome (MDS), acute myeloid leukaemia (AML), and pneumonitis have been identified as AESIs for rucaparib.

Up to the DCO, three events of MDS/AML have been reported in ATHENA, all of them in an arm including rucaparib. Of these three events, one of them occurred in the ATHENA-COMBO and two of them in the ATHENA-MONO. In ATHENA-MONO, there was a single event (0.2%) of each of these AEs reported for patients who received rucaparib. Both the case of MDS (observed during treatment) and the case of AML (observed during long-term follow-up and that lead to death -see description above) were assessed by the Investigator as related to rucaparib. This low rate of MDS/AML is consistent with the rate of MDS/AML in the Pool and the rate reported in section 4.8 of the Rubraca SmPC.

Although it is acknowledged that no clear conclusion can be drawn regarding the potential role of rucaparib in the occurrence of MDS/AML, its contribution cannot be discarded either. It is important to note that the implication of the prior platinum-based chemotherapy in the occurrence of these events is well-established and cannot be disregarded, but an imbalance between the rucaparib arm and the placebo arm is also evident.

There was a single event (0.2%) of pneumonitis reported in the rucaparib arm of ATHENA-MONO, which was assessed by the Investigator as not related to rucaparib.

ADRs

Stomatitis is added to the tabulated list of ADRs in section 4.8 of the SmPC. In ATHENA MONO, there were 32 (7.5%) vs. 3 (2.7%) cases of stomatitis in the rucaparib vs. placebo groups, respectively. The median time from the first dose of rucaparib to the start of stomatitis was 75 days (95% CI: 36-169). Thirty one of the 32 rucaparib cases of stomatitis were Grade 1-2 and only a single case (0.2%) was Grade 3. All placebo cases of stomatitis were Grade 1. There were 21 (4.9%) cases of stomatitis that were considered related to rucaparib.

In the Pool, the total number of rucaparib stomatitis cases is 126 (7.9%) vs. 8 (2.7%) placebo cases. Four (0.3%) of these rucaparib stomatitis cases are Grade ≥3.

Of note, stomatitis is (already) included as 'Common' ADR in the SmPC of the other PARP inhibitors olaparib and niraparib, see Lynparza SmPC and Zejula SmPC, respectively.

The updated safety data in patients treated with rucaparib from ATHENA-MONO, and from the Pool, are consistent with the previously submitted ovarian cancer data. The ADR frequency table in section 4.8 of the SmPC is updated based on the latest DCO from the Pool. These proposed changes are acceptable. Stomatitis is added to the product information following a safety signal assessment based on the review of ATHENA-MONO clinical data study and post-marketing cases.

Laboratory findings

Regarding haematology, a significant increase in the incidence of these alterations in the rucaparib arm is observed. However, all these hematologic alterations are well-known ADRs for rucaparib, and are already listed in the SmPC. Of note, the differences between arms are of approximately a 20%, going up to 30% for anaemia and platelet count decreased, the parameter with the least marked difference was "lymphocyte count decreased".

In terms of clinical chemistry parameters, most of them were significantly increased in the rucaparib arm compared with the placebo arm. The two parameters which were most markedly altered in comparison with the placebo arm were "alanine aminotransferase increased" and "aspartate aminotransferase increased". Although these parameters are significantly increased in the rucaparib arm, most of them are of low grade. AST and ALT increases are well-known ADRs for rucaparib, and are already listed in its SmPC.

"Creatinine increased" was also reported with a significantly higher frequency in the rucaparib arm vs. the placebo arm. Most events were low in grade, with a very low percentage of patients reporting a G3 event, and no patients reporting a G4 event.

No other parameters seem to be worrisomely or unexpectedly increased in the rucaparib arm in comparison with the placebo arm, with a very low percentage of patients having reported any G4 event in the rucaparib arm.

Safety in special populations

The MAH has provided safety data in special populations, both in the Pool and in ATHENA-MONO, by age, race, HRD status and HRD BRCA status.

Safety by subgroups in the Pool

By age, it seems that the frequency of patients in the rucaparib arm with one or more G3 or higher TEAEs increases with patients' age (58.9% for < 65 years, 67.8% for 65-74 years, and 73% for ≥ 75 years). However, this trend is not observed in the frequency of patients with one or more TEAEs leading to death or patients with one or more serious TEAEs. For some PT's, an increase of more than 10% was observed between the < 75 years' and ≥ 75 years' patients' subgroups who received rucaparib: "anaemia/haemoglobin decreased", "asthenia/fatigue/lethargy", "blood creatinine increased" and "decreased appetite". Additionally, "hypertension" and "hyponatraemia" were reported with the double frequency in the ≥ 75 years' subgroup. However, the size of the ≥ 75 years' subgroups is, considerably smaller with 126 patients ≥75 years' old who received rucaparib, vs. 1468 patients < 65 years' old.

No relevant differences are observed by race in the Pool. The only difference worth mentioning is the percentage of patients with one or more treatment-related TEAEs of G3 or higher in the rucaparib arm of the "White's subgroup" vs. "Other races" (which includes Asian) vs. "Unknown race": 45.7% vs. 56.8% vs. 50.3%.

By HRD status, no relevant differences were observed among subgroups.

Safety by subgroups in ATHENA-MONO

Regarding safety by age, no particular differences are observed between the results in the Pool and the results in ATHENA-MONO. Overall, it seems that the frequency of TEAEs of grade 3 or higher, discontinuations, dose reductions and interruptions increase as patients are older. The percentage of patients who needed a dose reduction due to TEAEs was notably higher in the subgroup of ≥ 75 years' old patients (43.9% in the < 65 subgroup, 54.3% in the 65-74 subgroup, and 81.5% in the ≥ 75 subgroup). Considering the lower number of patients in the rucaparib ≥ 75 subgroup compared with the other subgroups (27 patients in the ≥ 75 subgroup; 129 patients in the 65-74 subgroup; and 269 patients in the < 65 subgroup); and that the percentage of patients with SAEs and TEAEs that led to death remained similar among subgroups; the differences observed do not seem to be relevant. Some PTs are increased by 10%-15% in the ≥ 65 subgroup vs. the < 65 subgroup, such as "anaemia/haemoglobin decreased" (56.4% vs. 40.9%), "ALT/AST increased" (47.4% vs. 39.8%) and "blood creatinine increased" (17.9% vs. 7.1%). Similar pattern was observed when using the 75 y.o. threshold.

Regarding safety data by race in ATHENA-MONO, the data presented shows a worse toxicity profile in the Asian population compared with White patients, reflected by a higher rate of patients who had SAEs (31.3% Asian vs. 18.4% White), TEAEs of grade 3 or higher (77.5% vs. 56.7%), and who needed dose reductions (72.5% vs. 44.8%) and interruptions (73.8% vs. 58.6%). However, the rate in the discontinuations (8.8% vs. 11.3%) and deaths (0% vs 0.6%) remained similar among subgroups, suggesting that this increased toxicity in Asian patients is clinically manageable with dose reductions or interruptions, with no relevant impact on the rate of discontinuations or deaths. In terms of PTs, this

toxicity appears to be mainly driven by haematological AEs, together with transaminases alterations. This apparent increased toxicity in the Asian population was not observed in prior clinical trials with rucaparib, and as such no mention to it is included in either the EPARs or the SmPC. The MAH provided a thorough review and discussion on the potential worse toxicity of rucaparib in Asian patients, including a review of the safety profile, background characteristics and haematological and ALT/AST/bilirubin parameters. However, it should be noted that the provided review refers only to the ATHENA-MONO results, instead of to the safety Pool, which would have been more relevant in this context. Importantly, it is noted that this increased haematological toxicity has also been observed with other PARPi (i.e., olaparib), as reflected in several of the Lynparza's EPARs (procedures II-20, II-23, II-33, II-35). The reasons for this observed difference remain unclear, although it should be noted that more Asian patients had a history of anaemia and lower blood counts at baseline than Non-Asian patients (28% vs. 15%). Some other background differences between both subgroups were noted, such as Asian patients received study treatment sooner after completion of chemotherapy than non-Asian patients.

Regarding safety by tBRCA and Non-tBRCA, in line with the conclusions drawn for the Pool, the safety profile of rucaparib in the tBRCA patients seems to be worse than in the Non-tBRCA patients. Although the percentage of discontinuations, interruptions and dose reductions remained overall similar between both subgroups, SAEs and TEAEs of grade 3 or higher were more frequent in the tBRCA subgroup than in the Non-tBRCA subgroup. The sample size of the rucaparib tBRCA subgroup is notably smaller than the sample size of the rucaparib Non-tBRCA subgroup (91 patients in the tBRCA subgroup vs. 334 patients in the Non-tBRCA subgroup). As such, drawing conclusions on the impact of the BRCA status in the safety profile of rucaparib is difficult.

No significant differences have been observed in the toxicity profile across the HRD-BRCA subgroups.

Discontinuation due to AEs

Patients who discontinued treatment due to AEs in the rucaparib arm were almost twice as high as patients in the placebo arm: 11.8% vs. 5.5%. However, this percentage was similar to the percentage observed in the rucaparib arm of the Pool: 16.9%. Overall, it does not seem that there is any PT which led to a worryingly higher rate of discontinuations in the ATHENA-MONO's rucaparib arm compared to the Pool's rucaparib arm. Most of these events were considered treatment-related (9.4% rucaparib vs. 3.5% placebo).

Regarding dose reductions, the rates in both the rucaparib arm and the placebo arm remained consistent compared with the rates in the Pool. The most commonly reported PT was "anaemia", with a frequency of 23.1% in the rucaparib arm vs. 0% in the placebo arm. The percentage of patients who had a dose reduction for this reason was slightly higher in ATHENA-MONO than the percentage reported for the Pool (17%). As previously mentioned, "anaemia" is a well-known AE of rucaparib. Apart from "anaemia" (and the combined PT "anaemia/haemoglobin decreased"), there were no relevant differences between the incidences of dose reductions by PTs reported in ATHENA-MONO in comparison with the rates reported for the Pool.

Regarding dose interruptions, the percentages of patients who had a dose interruption in ATHENA-MONO remained similar to the percentages in the Pool. Overall, the incidences by PT in ATHENA-MONO were similar to the incidences in the Pool; although it should be noted that the combined PTs "anaemia/haemoglobin decreased" and "neutropenia/neutrophil count decreased" were reported with a higher frequency in the rucaparib arm in ATHENA-MONO than in the Pool (with a difference higher than 5%).

2.5.2. Conclusions on clinical safety

The safety data does not suggest any relevant change in the safety profile of rucaparib. As already known, rucaparib is associated with a high incidence of some ADR such as "anaemia/haemoglobin decreased", "neutropenia/neutrophil count decreased", "thrombocytopenia/platelet count decreased", "asthenia/fatigue/lethargy", "ALT/AST increased" and "nausea". No relevant differences have been observed in comparison to the safety data already known for rucaparib, apart from some slight deviations in the incidence of some ADRs such as "neutropenia/neutrophil count decreased" which seems to be slightly higher in the ATHENA-MONO study. Stomatitis is added to the product information following a safety signal assessment based on the review of ATHENA-MONO clinical data study and post-marketing cases.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 8.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 8.1 with the following content:

Safety concerns

Table 59 Summary of safety concerns

Summary of safety concerns	
Important identified risks	Myelodysplastic syndrome (MDS/Acute myeloid leukaemia (AML))
Important potential risks	New primary malignancy QTc interval prolongation Embryotoxicity and teratogenicity
Missing information	Safety in patients with severe renal impairment Safety in patients with moderate hepatic impairment

No changes to the list of safety concerns, pharmacovigilance plan and risk minimisation measures were made as a result of the new indication. Routine pharmacovigilance, as well as routine risk minimisation measures remain sufficient to mitigate Rubraca's risk in all approved indications.

Pharmacovigilance plan

Not applicable.

Risk minimisation measures

Table 60 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation activities	Pharmacovigilance activities
Important identified risk 1: Myelodysplastic syndrome (MDS)/Acute myeloid leukaemia (AML)	**Routine risk minimisation measures:** SmPC section: 4.4, 4.8 PL section: 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow up questionnaire **Additional pharmacovigilance activities:** None
Important potential risk 1: New primary malignancy	**Routine risk minimisation measures:** None **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Important potential risk 2: QTc interval prolongation	**Routine risk minimisation measures:** None **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Important potential risk 3: Embryotoxicity and teratogenicity	**Routine risk minimisation measures:** SmPC section: 4.4, 4.6, 5.3 PL section: 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Missing information 1: Safety in patients with severe renal impairment	**Routine risk minimisation measures:** SmPC section: 4.2, 5.2	**Routine pharmacovigilance activities beyond adverse**

	Routine risk minimisation activities recommending specific clinical measures to address the risk: None **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine	**reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Missing information 2: Safety in patients with moderate hepatic impairment	**Routine risk minimisation measures:** SmPC section: 4.2, 5.2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

2.7. Update of the Product information

As a consequence, section 4.1 of the SmPC has been updated to reflect the new indication for rucaparib as monotherapy for the maintenance treatment of adult patients with advanced (FIGO Stages III and IV) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy. Section 4.2 has been updated to reflect the specific duration of treatment cap of 2 years for the new indication. Section 4.4 has been updated with revised frequency of intestinal obstruction. Section 4.8 has been updated with revised frequencies for adverse drug reactions, based on data from 1 594 patients included in clinical trials in ovarian cancer and treated with rucaparib monotherapy. Section 5.1 has been updated with results from study CO-338-087 (ATHENA); this is a Phase III, randomised, double-blind, dual placebo-controlled study of rucaparib as monotherapy and in combination with nivolumab in patients with newly diagnosed EOC, FTC, or PPC who have responded to their first-line treatment (surgery and platinum-based chemotherapy). The Package Leaflet has been updated accordingly.

In addition, the list of local representatives in the PL has been revised.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

It is considered that the submitted type II variation to extend the indication of Rubraca for its use as monotherapy for the maintenance treatment of adult patients with advanced (FIGO Stages III and IV) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy, does not have a relevant impact on the PIL text.

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Rubraca (rucaparib) is included in the

additional monitoring list as New active substance.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication for Rubraca (rucaparib) is "*as monotherapy for the maintenance treatment of adult patients with advanced (FIGO Stages III and IV) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.*"

Ovarian cancer is the eighth most common cancer and the eighth more common cause of cancer death in women. Most patients are diagnosed in an advanced stage, defined by the spread of the disease outside the pelvis (FIGO stage III and IV)[1]. More than 90% of malignant ovarian tumours are of epithelial origin, designated epithelial ovarian cancer (EOC). The most common and most lethal EOC is high-grade serous carcinoma. The 5-year survival rate in advanced ovarian cancer patients decreases from 42% (stage III) to 26% (stage IV)[2].

3.1.2. Available therapies and unmet medical need

Treatment of newly diagnosed ovarian cancer patients includes a combination of surgery and chemotherapy, either primary debulking surgery followed by adjuvant platinum-based chemotherapy (i.e. cisplatin or carboplatin plus a taxane) or neoadjuvant chemotherapy with subsequent interval debulking surgery followed by additional chemotherapy. Primary peritoneal and fallopian tube cancers are treated in the same manner as epithelial ovarian cancer.

However, despite optimal response to the initial treatment, the majority of patients relapse. Thus, maintenance therapy following response to standard treatment provides an opportunity to extend the disease-free interval and avoid recurrence.

Currently approved treatment options in the (first-line) maintenance setting include olaparib either as monotherapy (for BRCA mutated patients) or in combination with bevacizumab (for HRD positive patients) and niraparib (for all comers).[3]

[1] Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-249.

[2] Colombo N, Sessa C, du Bois A, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease†. Ann Oncol. 2019;30(5):672-705.
Torre LA, Trabert B, DeSantis CE, Miller KD, Samimi G, Runowicz CD, Gaudet MM, Jemal A, Siegel RL. Ovarian cancer statistics, 2018. CA Cancer J Clin. 2018 Jul;68(4):284-296.

[3] González-Martín A, Harter P, Leary A, et al., on behalf of the ESMO Guidelines Committee Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up Ann Oncol. 2023;34(10):833-848.

Regarding the unmet medical need, despite the availability of maintenance therapies following standard-of-care treatments for newly diagnosed ovarian cancer, the need for additional therapies is acknowledged in this condition.

3.1.3. Main clinical studies

This application is mainly based on the results of the **Study CO-338-087** (ATHENA), a Phase 3, randomised, double-blind, placebo-controlled, multicenter study in newly diagnosed adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who were in response after having completed first-line platinum-based chemotherapy. The study included 4 treatment arms. As part of this submission, only data for patients who were randomised to rucaparib monotherapy (Arm B) or placebo (Arm D) have been assessed (i.e. **ATHENA-MONO comparison**).

The primary endpoint of the study was PFS by RECIST v1.1. as assessed by the investigator (invPFS). OS and ORR by RECIST v1.1 in patients with measurable disease at baseline were key secondary endpoints. Other secondary endpoints were PFS assessed by BICR and DOR.

The primary and key secondary endpoints were tested using a pre-specified hierarchical step-down procedure in order to preserve the overall type 1 error rate, among the HRD population (patients tBRCA or non-tBRCA LOH-high) first and then the ITT population, using a one-sided alpha of 0.0125.

A total of **538 patients** were randomised 4:1 to receive either rucaparib (n=427) or placebo (n=111). Of these, 234 were HRD positive (185 in the rucaparib arm and 49 in the placebo arm). Randomisation was stratified by HRD status (tBRCA, non-tBRCA LOH-high, non-tBRCA LOH-low, non-tBRCA LOH-unknown), response to first-line platinum (no residual disease, residual disease) and timing of surgery (primary surgery, interval debulking).

The data initially provided were based on a data cut-off (DCO) of 23 March 2022. During the procedure, updated OS data were submitted (DCO 09 March 2023).

3.2. Favourable effects

HRD population (n=234)

At the time of the DCO (23 March 2022), with 43.2% events in the rucaparib arm and 63.3% in the placebo arm, there was a statistically significant improvement in invPFS with rucaparib compared to placebo (log-rank, p = 0.0004). The median invPFS was 28.7 months (95% CI, 23.0-NR) for rucaparib and 11.3 months (95% CI, 9.1-22.1) for placebo. The stratified Cox proportional hazards model showed a statistically significant improvement on invPFS with rucaparib compared to placebo (HR 0.47; 95% CI, 0.31-0.72; p = 0.0005).

ITT population (n=538)

There was a statistically significant improvement in invPFS with rucaparib compared to placebo (log-rank, p < 0.0001). The median invPFS in the ITT Population was 20.2 months (95% CI, 15.2-24.7) for rucaparib and 9.2 months (95% CI, 8.3-12.2) for placebo. The stratified Cox proportional hazards model showed a statistically significant improvement in invPFS with rucaparib compared to placebo (HR 0.52; 95% CI, 0.40-0.68; p < 0.0001). The number of invPFS events at the time of the DCO was 53.9% in the rucaparib arm and 70.3% in the placebo arm.

Sensitivity analyses of invPFS were consistent with the primary analysis for both the HRD and the ITT population.

At the time of analysis OS data were immature in both HRD and ITT population with 15.8% and 24.7% of events respectively. No difference in survival was observed between treatment arms (HRD: HR 0.97; 95% CI: 0.43, 2.19, ITT: HR 0.96; 95% CI: 0.63, 1.47). Results of a second IA based on a data cut-off date of 9 March 2023 were provided during the procedure. At the time of this IA statistical significance was not reached (HRD: HR 0.84; 95% CI: 0.44, 1.58, ITT: HR 0.83; 95% CI 0.58-1.17).

3.3. Uncertainties and limitations about favourable effects

At the time of the final analysis for the primary endpoint, OS data were heavily censored, with only around 16% of events in the HRD population and 25% in the ITT population having occurred. Updated OS data were provided during the procedure, with 35% of events reported (DCO 09 March 2023). Although a detrimental effect on OS seems unlikely, the lack of maturity of OS hampers proper conclusion. Thus, in order to further investigate the efficacy of rucaparib, results from the final OS analysis will be provided by Q2 2027 (see Annex II condition, PAES).

3.4. Unfavourable effects

Overall, the incidence of adverse events was higher in the rucaparib arm as compared to placebo: TEAE (96.7% in the rucaparib arm vs. 92.7% in the placebo arm), patients with one or more TEAEs of G3 or higher (60.5% vs. 22.7%), patients with one or more TEAEs leading to death (0.7% vs. 0%), patients with one or more serious TEAEs (21.2% vs. 6.4%) or patients with one or more TEAEs leading to study drug discontinuation (11.8% vs. 5.5%).

By PTs, the most frequently reported ADRs (≥30%) were "asthenia/fatigue/lethargy" (56.0% in the rucaparib arm vs. 37.3% in the placebo arm), nausea (56.2% vs. 30.0%), "anaemia/haemoglobin decreased" (46.6% vs. 9.1%) and "ALT/AST increased" (42.6% vs. 8.2%).

The most commonly reported Grade ≥3 ADRs (≥10%) were anaemia/haemoglobin decreased (28.7% rucaparib vs. 0 placebo), neutropenia/neutrophil count decreased (14.6% vs. 0.9%) and ALT/AST increased (10.6% vs. 0.9%).

Serious ADRs occurring in ≥1% of patients were anaemia (4%) and neutropenia (1.4%).

Myelodysplastic syndrome (MDS) and AML are considered AESIs of rucaparib and have been observed in patients exposed to other PARP inhibitors. In ATHENA-MONO two events of MDS/AML were reported in the rucaparib arm. This rate of is consistent with the Pool and the section 4.8 of the Rubraca SmPC.

Stomatitis is added as a new Adverse Drug Reaction to the product information following a safety signal assessment based on the review of ATHENA-MONO clinical data study and post-marketing cases. The most common TEAE leading to discontinuation was anaemia (3.5% rucaparib vs. 0 placebo).

3.5. Uncertainties and limitations about unfavourable effects

Not applicable.

3.6. Effects Table

Table 61. Effects Table for Rucaparib in maintenance therapy (1st line) in ovarian cancer (data cut-off: 23 March 2022)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
ITT population; n=538 (427 rucaparib, 111 placebo)						
invPFS	Progression free survival by RECIST as assessed by the investigator	Median (95% CI) months	20.2 (15.2, 24.7)	9.2 (8.3, 12.2)	log-rank, p < 0.0001 HR 0.52 (95% CI, 0.40-0.68); p < 0.0001	CSR. ATHENA-MONO
OS[a]	Overall survival	Median (95% CI), months	NR	46.2	log-rank, p=0.3015 HR 0.83 (95% CI: 0.58, 1.17); p=0.2804	
Unfavourable Effects						
						CSR.
AEs of Grade ≥3	Adverse events of CTCAE Grade ≥3	%	60.5	22.7		Results based in ATHENA-MONO
SAEs	Serious adverse events	%	21.2	6.4		
Deaths	Adverse events leading to death	%	0.7	0		
AEs leading to discontinuation	Adverse events leading to discontinuation of study treatment	%	11.8	5.5		
Nausea	Incidence of nausea	%	56.2	30.0		
Asthenia/ fatigue	Incidence of asthenia/fatigue	%	55.8	37.3		
Anaemia/ haemoglobin decreased	Incidence of anemia/haemoglobin decreased	%	46.6	9.1		
ALT/AST increased	Incidence of ALT/AST increased	%	42.6	8.2		
MDS/AML	Incidence of MDS/AML	%	0.5	0		

Abbreviations: AML= acute myeloid leukemia; CI= confidence interval; HR= hazard ratio; HRD = homologous recombination deficiency; ITT = intent-to-treat; LOH = loss of heterozygosity; MDS= myelodysplastic syndrome; NR=not reached; tBRCA = deleterious tumor mutation in BRCA1 or BRCA2, includes gBRCA and sBRCA.

a. Based on the second interim analysis (data cut-off: 9 March 2023).

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Maintenance treatment with rucaparib in newly diagnosed ovarian cancer patients who have completed first-line platinum-based chemotherapy and are in response has shown a delay in the progression of the disease with a median PFS (as per investigator assessment) of 20.2 months in the rucaparib arm compared with 9.2 months in the placebo arm; HR 0.52 (95% CI, 0.40-0.68). These results, observed in the overall population, were consistent with that observed in the different populations analysed (i.e. HRD, tBRCA, non-tBRCA-LOH-high, non-tBRCA low and the pooled subgroup of non-tBRCA) and most of the subgroups investigated.

The main limitation is the lack of mature OS data, which hampers interpretation of the results. Based on currently available survival data a potential detrimental effect on OS seems unlikely. However, results of the final OS analysis will have to be provided by the MAH as a post-authorisation obligation (PAES - Annex II condition).

In the context of a maintenance treatment, the safety profile is of particular importance. Rucaparib was associated with gastrointestinal adverse reactions (mainly nausea, abdominal pain and diarrhoea), asthenia/fatigue and myelosuppression (neutropenia, anaemia, thrombocytopenia), although overall these adverse reactions were manageable with supportive treatment, and dose interruptions or modifications. Stomatitis is added to the product information as a new ADR.

The safety of rucaparib as observed in ATHENA-MONO is in line with the known toxicity profile of rucaparib as described in section 4.8 of the Rubraca SmPC, and the risks associated with rucaparib treatment are adequately covered by the information in the (updated) SmPC and RMP.

3.7.2. Balance of benefits and risks

The benefits of rucaparib in the indication are considered meaningful with a manageable safety profile.

3.7.3. Additional considerations on the benefit-risk balance

None.

3.8. Conclusions

The overall B/R of Rubraca is positive.

The following measure is considered necessary to address issues related to efficacy:

PAES: In order to further investigate the efficacy of rucaparib monotherapy in 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, the MAH should submit the final analysis of OS of the phase 3, randomized, double-blind, placebo controlled study CO-338-087. With a due date of 30 June 2027.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include 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 for RUBRACA, based on interim results from study CO-338-087 (ATHENA); this is a Phase III, randomised, double-blind, dual placebo controlled study of rucaparib as monotherapy and in combination with nivolumab in patients with newly diagnosed EOC, FTC, or PPC who have responded to their first-line treatment (surgery and platinum-based chemotherapy). As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance, in addition, the list of local representatives has been updated. Version 8.1 of the RMP has also been approved.

The variation leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II and IIIB and to the Risk Management Plan are recommended.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Rubraca is not similar to Zejula within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix 1.

Additional market protection

The request for one year of market protection for a new indication was withdrawn by the MAH during the current procedure.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date

PAES: In order to further investigate the efficacy of rucaparib monotherapy in 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, the MAH should submit the final analysis of OS of the phase 3, randomized, double-blind, placebo controlled study CO-338-087.	30 June 2027

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Rubraca-H-C-004272-II-0036'