14 November 2022
EMA/883431/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rubraca

International non-proprietary name: rucaparib

Procedure No. EMEA/H/C/004272/II/0029

Note

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

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Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	13 Sep 2021	13 Sep 2021	☐
☐	CHMP Rapporteur Assessment Report	12 Oct 2021	01 Nov 2021	☐
☐	PRAC Rapporteur Assessment Report	15 Oct 2021	14 Oct 2021	☐
☐	PRAC members comments	20 Oct 2021	20 Oct 2021	☐
☐	Updated PRAC Rapporteur Assessment Report	21 Oct 2021	22 Oct 2021	☐
☐	PRAC endorsed relevant sections of the assessment report	28 Oct 2021	28 Oct 2021	☐
☐	CHMP members comments	29 Oct 2021	5 Nov 2021	☐
☐	Updated CHMP Rapporteur Assessment Report	04 Nov 2021	5 Nov 2021	☐
☐	RSI	11 Nov 2021	11 Nov 2021	☐
☐	Re-start of procedure	24 Jan 2022		☐
☐	CHMP Rapporteur Assessment Report	28 Feb 2022	12 Mar 2021	☐
☐	CHMP members comments	14 Mar 2022	17 Mar 2021	☐
☐	Updated CHMP Rapporteur Assessment Report	17 Mar 2022	19 Mar 2021	☐
☐	RSI	24 Mar 2022	24 Mar 2022	☐
☐	Submission Deadline	20 May 2022	20 May 2022	☐
☐	Re-start of procedure	23 May 2022	23 May 2022	☐
☐	CHMP Rapporteurs Assessment Report	27 Jun 2022	06 Jul 2022	☐
☐	CHMP members comments	11 Jul 2022	12 Jul 2022	☐
☐	Updated CHMP Rapporteur Assessment Report	14 Jul 2022	16 Jul 2022	☐
☐	Request for supplementary information	21 Jul 2022	21 Jul 2022	☐
☐	Submission Deadline	16 Aug 2022	16 Aug 2022	☐
☐	Re-start of procedure	17 Aug 2022	17 Aug 2022	☐
☐	CHMP Rapporteur Assessment Report	31 Aug 2022	01 Sep 2022	☐
☐	Comments from CHMP	05 Sep 2022	06 Sep 2022	☐
☐	Updated CHMP Assessment Report	08 Sep 2022	09 Sep 2022	☐
☒	Opinion	15 Sep 2022	15 Sep 2022	☐

List of abreviations

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 leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BER	base excision repair
BICR	blinded independent committee review
BID	twice a day
BRCA	breast cancer gene, includes BRCA1 and BRCA2
BRCA1	breast cancer gene 1
BRCA2	breast cancer gene 2
CA-125	cancer antigen-125
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CMA	Conditional Marketing Authorization
CR	complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DOR	duration of response
EC	European Commission
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EOC	epithelial ovarian cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30

EORTC QLQ-OV28	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Ovarian Cancer Module OV28
EQ-5D	Euro-Quality of Life 5D
EU	European Union
FDA	Food and Drug Administration
FTC	fallopian tube cancer
gBRCA	germline BRCA
HR	hazard ratio
HRD	homologous recombination deficiency
HRR	homologous recombination repair
invPFS	investigator-assessed progression-free survival
ISS	Integrated Summary of Safety
ITT	intent-to-treat
LS	least squares
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival
PARP	poly (ADP-ribose) polymerase
PFI	progression-free interval
PFS	progression-free survival
PFS2	progression-free survival on a subsequent line of treatment
PLD	pegylated liposomal doxorubicin
PPC	primary peritoneal cancer
PR	partial response
PRO	patient-reported outcomes
PSUR	Periodic Safety Update Report
PT	Preferred Term
QTc	heart rate corrected QT interval
QTcB	QT interval corrected by Bazett’s formula
QTcF	QT interval corrected using Fridericia's formula

REC	Recommendation
RECIST	Response Evaluation Criteria in Solid Tumors
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
sBRCA	somatic BRCA
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SmPC	Summary of Product Characteristics
SOB	Specific Obligation
SOC	System Organ Class
StD	standard deviation
T2V	Type II Variation
tBRCA	tumor tissue mutation in BRCA1 or BRCA2, includes gBRCA and sBRCA
TEAE(s)	treatment-emergent adverse event(s)
UK	United Kingdom
ULN	upper limit of normal
US	United States

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Clovis Oncology Ireland Limited submitted to the European Medicines Agency on 27 August 2021 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II and IIIB

Update of sections 4.4, 4.8 and 5.1 of the Summary of Product Characteristics (SmPC) based on final results from study CO-338-043 (ARIEL4); this is a phase 3, multicentre, open-label, randomised study evaluating the efficacy and safety of rucaparib versus chemotherapy for treatment of relapsed ovarian cancer listed as a specific obligation in the Annex II; the Package Leaflet (PL) is updated accordingly. The Risk Management Plan (RMP) version 6.1 has also been submitted. With this variation application, the MAH requests for the Rubraca marketing authorisation to no longer be subject to specific obligations. The SmPC, Annex II and PL are updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes and bring the PI in line with the latest QRD template version 10.2 Rev.1.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the RMP.

2. Overall conclusion and impact on the benefit/risk balance

Background

On 24 May 2018, Rubraca obtained a conditional marketing authorisation (CMA) for the monotherapy treatment of adult patients with platinum sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian cancer (EOC), fallopian tube cancer (FTC), or primary peritoneal cancer (PPC), who have been treated with 2 or more prior lines of platinum based chemotherapy, and who are unable to tolerate further platinum based chemotherapy. This authorisation was based on pooled population subgroup data from two Phase 2 open label studies (Study CO 338 010 [Study 10] and Study CO 338 017 [ARIEL2]), which included adult patients with ovarian cancer who received 2 or more previous lines of chemotherapy and whose tumours had a deleterious mutation (germ line or somatic) in BRCA1 or BRCA2.

Submission of results from study CO-338-043 (ARIEL 4) was imposed as a specific obligation (SOB) during the initial CMA assessment to further confirm the safety and efficacy of rucaparib in the treatment of platinum sensitive, relapsed or progressive, BRCA mutated (germline and/ or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, as included in Annex II.

Through the current application, the MAH submitted the (initial) Clinical Study Report (CSR) of ARIEL 4 including the primary analysis to fulfil the outstanding SOB and requested conversion from CMA to a Marketing Authorisation not subject to SOBs, based on the confirmation of rucaparib efficacy and safety in the comparative, randomized, Phase 3 Study CO-338-043 (ARIEL 4).

Initially, no request was made by the MAH to update the current indication wording on the basis of the results from study CO-338-043.

In view of the reported results from the ARIEL4 study (see details below), the European Commission (EC) initiated on 22 April 2022 in parallel to this variation EMEA/H/C/004272/II/0029, a procedure under Article 20 of Regulation (EC) No 726/2004 (EMEA/H/A-20/1518/C/4272/0033) and requested the CHMP to assess all the concerns and their impact on the B/R balance of Rubraca (rucaparib) in the "treatment" indication (i.e. "*as monotherapy treatment of adult patients with platinum sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum based chemotherapy, and who are unable to tolerate further platinum based chemotherapy*").

At the April 2022 CHMP plenary meeting, based on the available data, the Committee agreed as a temporary measure that no new treatment with Rubraca should be initiated in adult patients with platinum sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum-based chemotherapy, and who are unable to tolerate further platinum-based chemotherapy. CHMP also agreed to communicate this temporary restriction to healthcare professionals through a direct healthcare professional communication (DHPC), together with a communication plan. The content of the letter was published on the EMA website on 06 May 2022.

On 9 June 2022 the MAH sent a notification to request the removal of the "treatment" indication (as defined above) from the Product Information. This (voluntary) request followed the MAH's decision to no longer market Rubraca in the third line treatment indication justified on the basis that "most ovarian cancer patients that receive a PARP inhibitor do so earlier as a maintenance therapy after first or second-line chemotherapy". The request to remove the treatment indication was acknowledged and considered necessary following confirmation, in the context of the above-mentioned procedure under Article 20 of Regulation (EC) No 726/2004, that the benefit/risk of Rubraca in the "treatment" indication was no longer considered favourable.

More concretely, on 21 July 2022 the CHMP adopted an opinion pursuant to Article 20 of Regulation (EC) No 726/2004 recommending the variation to the terms of the marketing authorisation for Rubraca. The Committee concluded that the benefit-risk balance of Rubraca in the treatment indication is negative. Therefore, this product should only be used 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. Reference is made to procedure EMEA/H/A-20/1518/C/4272/0033 for further details. A further DHPC was agreed by CHMP and sent to relevant healthcare professionals. The content of the letter was published on the EMA website on 8 August 2022.

Study CO-338-043 (ARIEL 4)

Study ARIEL 4 showed a benefit for rucaparib, compared with standard chemotherapy, in terms of progression free survival (PFS), as assessed by the investigator in the Efficacy Population (all randomized excluding patients with a BRCA reversion mutation). A hazard ratio (HR) of 0.639 [95% confidence interval (CI): 0.489, 0.835]; p=0.0010 was reported with a median invPFS of 7.4 months (95% CI: 7.3, 9.1) for the rucaparib group compared to 5.7 months (95% CI: 5.5, 7.3) for the chemotherapy group. Results for the secondary endpoints objective response rate (ORR) by RECIST 1.1, duration of response (DOR), ORR by RECIST 1.1 and/or cancer antigen-125 (CA-125) response and patient reported outcome (PRO) (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C-30 (EORTC QLQ-C30) Global Health Status score) were also numerically higher for rucaparib but failed to be statistically significant based on the planned hierarchical step-down testing procedure. Other ('stand-alone') secondary endpoints were overall survival (OS) and PFS as assessed by a blinded independent committee review (BICR) (though the latter has not been tested).

The initially available OS data (based on an interim analysis (IA)) clearly favoured the chemotherapy treatment over rucaparib (HR=1.55; 95% CI: 1.085, 2.214).

During the procedure, results from the final OS analysis (DCO 10 April 2022) were provided. OS results in the ITT population of Study ARIEL 4 were consistent with the IA and although not statistically significant, clearly favoured the chemotherapy treatment over rucaparib (HR=1.31; 95% CI: 1.00, 1.73; p=0.0507).

The observed detrimental effect on OS was driven by results in the platinum resistant subgroup in which the worst results were observed (HR 1.51; [95% CI: 1.05, 2.17]; p=0.0251) representing 51% of the patient population. The HR for OS in the other subgroups of fully platinum sensitive and partially platinum sensitive were 1.24 [95% CI: 0.62, 2.50] (p=0.5405) and 0.97 [95% CI: 0.58, 1.62] (p=0.9129), respectively, which are not considered reassuring.

For PFS2 in all populations, no difference was observed between the rucaparib and chemotherapy arms.

In terms of safety, rucaparib treatment was associated with more SAEs compared to chemotherapy, such as Grade 3 or higher AEs, serious AEs, AEs leading to death, and AEs leading to study drug interruptions or study drug dose reduction compared to the chemotherapy control arm.

The most common AEs in the rucaparib group were combined anaemia/haemoglobin decreased, nausea, combined asthenia/fatigue/lethargy, combined alanine aminotransferase (ALT)/aspartate aminotransferase (AST) increased, and vomiting. The most common Grade 3 or higher TEAEs in the rucaparib group were combined anaemia/haemoglobin decreased and combined neutropaenia/decreased ANC. SAEs in the rucaparib group were mostly caused by myelosuppression from anaemia/decreased haemoglobin. Intestinal obstruction and death were observed at a higher frequency in the rucaparib group compared to the chemotherapy group and were most often leading to study drug discontinuation with rucaparib treatment. Several concerns were also related to the timing of deaths due to progression, AEs or other causes, which could not be alleviated by the MAH during the procedure.

Results from study ARIEL4 were expected to confirm the efficacy (and safety) of rucaparib evidenced in a pooled analyses from two single arm trials (Study CO 338 010 and Study CO 338 017) that supported the initial conditional authorisation of Rubraca (rucaparib) in the "treatment" indication.

Despite a statistically significant gain in terms of invPFS reported in the study, a detrimental effect of rucaparib on OS compared with the chemotherapy control was observed within the interim and final data analyses of the study.

The subgroup of platinum sensitive patients of the study, particularly those partially sensitive, represented the most relevant population to confirm the benefit-risk balance of rucaparib in the approved "treatment" indication. However, and albeit the limitations to extract from the study definitive conclusions from subgroups' data in the platinum sensitive populations, results on OS were not considered reassuring as explained above.

The MAH claimed the findings were the result of the crossover of patients from the control arm to rucaparib following disease progression, which was allowed for all patients irrespective of their platinum-sensitivity status. In this context, the MAH provided results from several sensitivity analyses. However, despite non-negative OS results were observed in some of these analyses, concerns remain in terms of the methods used in said analyses, which relied on strong assumptions, and which did not allow to rule out a detrimental effect on OS.

Further, convincing evidence to support that the detrimental effect on OS could be specifically considered related to platinum resistant disease is not available. Hence, it is not possible to exclude a detrimental effect in other subgroups including platinum sensitive patients.

The detriment in OS could also not be fully explained as PFS2 curves overlap and timing of deaths, either due to underlying disease, adverse events or other causes is unknown.

Moreover, the subgroup of study patients with platinum-sensitive disease included in the study was not identical to the approved "treatment" indication (platinum-sensitive patients who are unable to tolerate further platinum-based therapy) since part of the patients in the study received platinum therapy either as control or subsequent therapy. This hampered interpretation of the OS results of the study by subsequent platinum therapy in all platinum-sensitivity subgroups. Importantly, additional data provided during the procedure did not alleviate the concern that the OS detriment may also be applicable for the "treatment" indication as approved for Rubraca.

Regarding safety aspects, uncertainties remained in connection with the timing of deaths due to progression, AEs or other causes. It was thus unclear how far AEs or related aspects (e.g. discontinuations, treatment interruptions) contributed to the observed OS detriment.

In light of the above, further data/analyses, including OS data from the ongoing ARIEL 3 study in the maintenance setting, were also requested. The submitted results from the ARIEL 3 study did not raise concern on a potential detrimental effect on OS and therefore the "maintenance" indication (i.e. "*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"*) was not subject to further questions in the context of this procedure. A CSR addendum of ARIEL 3 will be provided in 3Q 2022 (see Annex II condition, PAES).

All in all, it remained unclear whether the OS detriment observed in ARIEL 4 was caused by a safety issue, a lack of efficacy or a combination of both. Thus, major concerns remained regarding a potential detrimental effect of rucaparib on OS compared to chemotherapy in the specific patient population covered by the "treatment" indication.

Furthermore, the MAH did not provide the requested data and/or further arguments aimed at trying to address the above mentioned outstanding uncertainties and therefore the SOB could not be considered fullfiled.

Therefore, it was concluded as part of procedure EMEA/H/A-20/1518/C/4272/0033 that the benefit/risk of Rubraca in the 'treatment' indication can no longer be considered favourable. The indication of Rubraca was restricted to the maintenance treatment as monotherapy for 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 and that the product information should be amended accordingly.

As a result of the removal of the 'treatment' indication implemented as part of EMEA/H/A-20/1518/C/4272/0033, and considering the 'maintenance' indication is not subject to any specific obligation, the CHMP is of the view that there are no remaining grounds for the marketing authorisation to remain conditional. Therefore, the CHMP recommends the granting of a marketing authorisation no longer subject to specific obligations in accordance with Article 14-a(8) of Regulation (EC) No 726/2004 and the deletion of the specific obligation from Annex II can be agreed. The product information and risk management have been updated accordingly.

The CHMP recommends that the MAH provides the final CSR for study ARIEL 4 (CO-338-043) including final PFS2 and OS analyses as well as safety data.

Sections 4.4 and 4.8 of SmPC have been adequately updated to reflect safety data from study ARIEL 4 and from the updated Pooled Ovarian Cancer Safety Population (N=1169). Of note, intestinal obstruction has been included as a new ADR in section 4.8 of the SmPC and a warning has been added to section 4.4 of the SmPC.

The MAH submitted an updated RMP version 6.2 with changes to the safety concerns and removal of the "treatment" indication, which is considered acceptable (see section 9).

The benefit/risk of Rubraca remains positive in the maintenance indication.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II and IIIB

Update of sections 4.4 and 4.8 of the SmPC based on safety data from study CO-338-043 (ARIEL 4); this is a phase 3, multicentre, open-label, randomised study evaluating the efficacy and safety of rucaparib versus chemotherapy for treatment of relapsed ovarian cancer listed as a specific obligation in the Annex II; the Package Leaflet is updated accordingly. The RMP version 6.2 is acceptable.

Update of Annex II to remove the specific obligation. The SmPC and Package leaflet are amended accordingly to reflect the conversion from a conditional marketing authorisation to a marketing authorisation no longer subject to specific obligations as recommended by the CHMP as a result of this variation and further to the removal of the indication for monotherapy treatment of adult patients with platinum sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum based chemotherapy, and who are unable to tolerate further platinum based chemotherapy (EMEA/H/A-20/1518/C/4272/0033). In addition, the MAH took the opportunity to make minor editorial changes and bring the PI in line with the latest QRD template version 10.2 Rev.1.

☒is recommended for approval

The CHMP, having considered the application as set out in the appended assessment report and having reviewed the data submitted by the marketing authorisation holder including the evidence concerning compliance with specific obligations, is of the opinion that the risk-benefit balance of the above mentioned medicinal product remains favourable, and that comprehensive data supports a favourable benefit-risk balance of the above mentioned medicinal product for the remaining therapeutic indication (i.e. "*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)*. Therefore, pursuant to Article 14-a(8) of Regulation (EC) No 726/2004, the CHMP recommends by consensus the granting of a marketing authorisation in accordance with Article 14(1) of Regulation (EC) No 726/2004 for Rubraca.

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.

As a result of this variation, it is recommended that the following obligation is deleted from the Annex II to the Opinion:

Description	Due date
In order to further confirm the safety and efficacy of rucaparib in the treatment of platinum sensitive, relapsed or progressive, BRCA mutated (germline and/ or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, the MAH should submit the results of study CO-338-043 (ARIEL4), a phase 3, multicentre, open-label, randomised study evaluating the efficacy and safety of rucaparib versus chemotherapy for treatment of relapsed ovarian cancer.	Due date: Q2 2023

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Rubraca-H-C-4272-II-0029'.

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

Rucaparib (CO-338) is a small molecule inhibitor of poly (adenosine diphosphate [ADP] ribose) polymerase (PARP) being developed for the treatment of cancer associated with homologous recombination deficiency (HRD). Rucaparib has been shown to inhibit PARP-1, PARP 2, and PARP-3 and has demonstrated activity in cells, animal models, and patients with a breast cancer gene BRCA1 or BRCA2 mutation in nonclinical and clinical studies.

On 24 May 2018, a CMA was granted for the monotherapy treatment of adult patients with platinum sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian cancer (EOC), fallopian tube cancer (FTC), or primary peritoneal cancer (PPC), who have been treated with 2 or more prior lines of platinum based chemotherapy, and who are unable to tolerate further platinum based chemotherapy. This authorisation was based on pooled population subgroup data from 2 Phase 2 open label studies (Study CO 338 010 [Study 10] and Study CO 338 017 [ARIEL2]), which included adult patients with ovarian cancer who received 2 or more previous lines of chemotherapy and whose tumours had a deleterious mutation (germ line or somatic) in BRCA1 or BRCA2.

The initial CMA was granted subject to a Specific Obligation (SOB) (also referred below as SOB001), pursuant to Article 14(7) of Regulation (EC) No 726/2004: "*In order to further confirm the safety and efficacy of rucaparib in the treatment of platinum sensitive, relapsed or progressive, BRCA mutated (germ line and/ or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, the MAH should submit the results of study CO 338-043 (ARIEL4), a phase 3, multicentre, open label, randomised study evaluating the efficacy and safety of rucaparib versus chemotherapy for treatment of relapsed ovarian cancer*", with due date Q2 2023, as included in Annex II.

On 23 January 2019, the indication was subsequently extended, via variation procedure EMEA/H/C/004272/II/0001, to include maintenance treatment of adult patients with platinum sensitive relapsed high-grade EOC, FTC, or PPC who are in complete or partial response to platinum-based chemotherapy. This approval was based on data from the randomized, double-blind, placebo-controlled Phase 3 study, Study CO 338-014 (ARIEL3).

Through this application, the MAH initially requested conversion from a CMA to a Full Marketing Authorization not subject to SOBs, based on the confirmation of rucaparib efficacy and safety in the comparative, randomized, Phase 3 Study CO-338-043 (ARIEL 4) without a modification of the existing indications. However during the procedure and following the triggering of an Article 20 referral (EMEA/H/A-20/1518/C/4272/0033), the MAH requested to remove the indication for Rubraca as *monotherapy treatment of adult patients with platinum sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum based chemotherapy, and who are unable to tolerate further platinum based chemotherapy (see section 2 above).*

In addition, safety data provided within this submission include results from patients treated with rucaparib in Study CO-338-043 (N=232) and the updated Pooled Ovarian Cancer Safety Population (N=1169) which integrates the last data-cuts from Studies CO-338-010, CO-338-017 and CO-338-014 (Table 1).

Table 1. Summary of Visit Cut-offs for Ovarian Cancer Studies (CO-338-043, CO-338-014, CO-338-017 and CO-338-010)

Study	N	Visit Cut-off
CO-338-043 (ARIEL4)		
Rucaparib	232	30 September 2020
Chemotherapy	113	
CO-338-014 (ARIEL3)		
Rucaparib	372	31 December 2019
Placebo	189	
CO-338-017 (ARIEL2)		
Part 1	204	01 February 2019
Part 2	287	
CO-338-010 (Study 10)		
Part 1	5	27 March 2019 (Study completed)
Part 2A	42	
Part 2B	12	
Part 3	15[a]	
Total number of patients with ovarian cancer treated with rucaparib	1,169	

[a] Patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer.

6. Clinical Efficacy aspects

6.1. Methods – analysis of data submitted

Study CO-338-043 (ARIEL 4) is an ongoing phase 3, multicenter, randomized study of rucaparib versus chemotherapy in patients with relapsed, BRCA-mutant, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer (table 2).

Table 2. Description of Clinical Efficacy Study CO-338-043

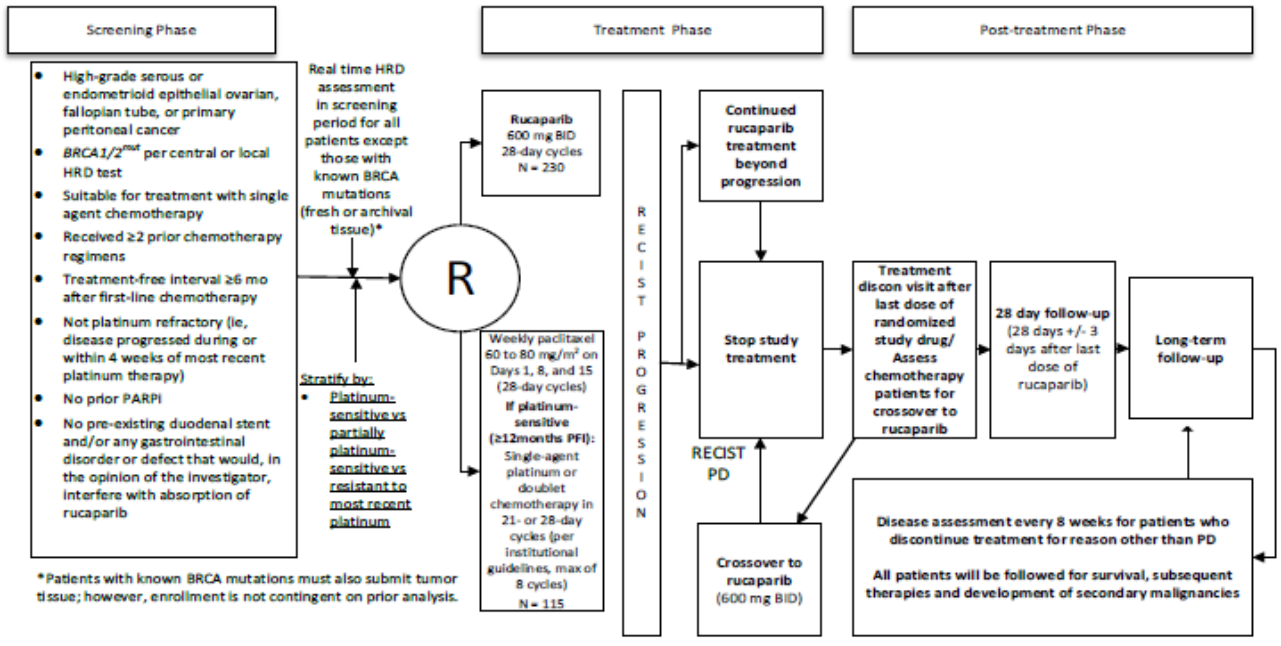
Number of Study Centers (Location)	First Patient Entered/Last Patient Completed Total Enrollment/ Enrollment Goal	Design Control Type	Primary Objective	Treatment	Patient Population
Study CO-338-043					
64 sites (Brazil, Canada, the Czech Republic, Hungary, Israel, Italy, Poland, Russia, Spain, Ukraine, UK, US)	01 March 2017 Ongoing, last patient enrolled on 24 September 2020. Total: 345 planned; 349 were randomized 2:1 to receive treatment with rucaparib or chemotherapy.	Phase 3, open-label, multicenter, randomized, safety and efficacy study.	To determine investigator-assessed progression-free survival by RECIST version 1.1 for rucaparib versus chemotherapy.	Rucaparib 600 mg BID Active standard-of-care chemotherapy comparator. Treatments were based on randomization strata (PFI after the most recent platinum). Platinum resistant (PFI ≥ 1 to < 6 months) and partially platinum-sensitive (PFI ≥ 6 to < 12 months) subgroups: weekly paclitaxel. Platinum-sensitive (PFI ≥ 12 months) subgroup: either monotherapy platinum (cisplatin, or carboplatin) or doublet platinum (carboplatin + paclitaxel, carboplatin + gemcitabine, or cisplatin + gemcitabine). Maximum of 8 cycles.	Patients with confirmed high-grade serous or Grade 2 or Grade 3 endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer and harbor a deleterious BRCA1/2 mutation. Patients with a histology other than serous or endometrioid known to harbor a deleterious BRCA1/2 mutation were also eligible.

Abbreviations: BID = twice a day; BRCA1 = breast cancer gene 1; BRCA2 = breast cancer gene 2; PFI = progression-free interval; RECIST = Response Evaluation Criteria in Solid Tumors; UK = United Kingdom; US = United States.

Patients were stratified based on the time to progression following the last dose of platinum containing therapy: platinum-resistant (PF I ≥1 to <6 months); partially platinum sensitive (PFI ≥6 to <12 months); and platinum-sensitive (PFI ≥12 months).

The study consisted of a Screening Phase, Randomization (2:1 rucaparib: chemotherapy), Treatment Part, and Post-treatment Phase/Cross-over Part. Patients initially randomized to chemotherapy had the option to cross over to rucaparib treatment following progression in the Treatment Part, with sponsor approval and additional consent (Figure 1).

Figure 1. Study CO-338-043 schema



Abbreviations: BID = twice a day; BRCA = breast cancer gene; HRD = homologous recombination deficiency; PARPi = poly(ADP-ribose) polymerase inhibitor; PD = progressive disease; PFI = progression-free interval; R = randomization; RECIST = Response Evaluation Criteria in Solid Tumors.

- **Study participants**

Inclusion criteria: eligible patients should have a histologically confirmed diagnosis of high-grade serous or Grade 2 or Grade 3 endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer.

1. If mixed histology, > 50% of the primary tumour must be confirmed to be high-grade serous or endometrioid upon review by local pathology
2. Patients with a histology of other than serous or endometrioid are also eligible if they are known to harbor a deleterious germ line or somatic BRCA 1/2 mutation

Patients must have received ≥2 prior chemotherapy regimens, with at least 1 regimen including a platinum, and have relapsed or progressive disease as confirmed by radiologic assessment:

- Had documented treatment-free interval of ≥6 months following the **first** chemotherapy regimen received
- Hormonal agents (e.g., tamoxifen, letrozole, etc.), anti-angiogenic agents (e.g., bevacizumab, pazopanib, cediranib, etc.), and other non-chemotherapy agents will **not** be counted as a chemotherapy regimen for the purpose of determining patient eligibility
- Agents administered in the maintenance setting will not be counted as a separate regimen

Eligible patients should have a deleterious BRCA 1/2 mutation as confirmed by a central laboratory and had evaluable disease (i.e. at least one target or non-target lesion that can be assessed per RECIST v. 1.1. Patients should also present an ECOG performance status of 0-1 and adequate organ function confirmed by the following laboratory values:

- Bone marrow function
    - ANC ≥ 2 x 10^9/L
    - Platelets > 100 x 10^9/L
    - Haemoglobin > 10 g/dL
- Hepatic function
    - AST and ALT ≤ 3 x ULN; if liver metastases, then ≤ 5 x ULN
    - Bilirubin ≤ 1.5 x ULN; < 2 x ULN if hyperbilirubinemia is due to Gilbert's syndrome
    - Serum albumin ≥ 30 g/L (3.0 g/dL)
- Renal function
    - Serum creatinine ≤ 1.5 x ULN or estimated glomerular filtration rate (GFR) ≥ 45 mL/min using the Cockcroft-Gault formula

Regarding main **exclusion criteria**, enrolled patients could not have received prior treatment with any PARP inhibitor, regardless of duration or prior treatment with single-agent paclitaxel or nab-paclitaxel. Patients should not have platinum refractory disease, as defined by disease progressed by radiologic assessment during or within 4 weeks after completing treatment with **most recent** platinum-based therapy or, also, symptomatic and/or untreated CNS metastases. The rest of exclusion criteria were the usual for this kind of trials and disease.

To be eligible for participation in the **crossover** part of the study, patients must fulfill the following **criteria** and initiate treatment with rucaparib ≤ 8 weeks after radiologic disease progression:

1. Have documented radiological progression per RECIST Version 1.1 during or following completion of comparator arm chemotherapy and receive Sponsor approval
2. Adequate haematological and biological function, confirmed by the following local laboratory values ≤ 14 days prior to first dose of rucaparib:
    a. Bone marrow function
        i. ANC ≥ 1.5 x 10^9/L
        ii. Platelets > 100 x 10^9/L
        iii. Haemoglobin > 10 g/dL
    b. Hepatic function
        i. AST and ALT ≤ 3 × ULN; if liver metastases, then ≤ 5 × ULN
        ii. Bilirubin ≤ 1.5 x ULN; < 2 x ULN if hyperbilirubinemia is due to Gilbert's syndrome
        iii. Serum albumin ≥ 30 g/L (3.0 g/dL)
    c. Renal function
        i. Serum creatinine ≤ 1.5 x ULN or estimated GFR ≥ 45 mL/min using the Cockcroft-Gault formula
3. All Grade 3 and 4 hematologic and non-hematologic toxicities (except alopecia, nausea, vomiting, or adequately controlled diarrhoea) improved to baseline or ≤ CTCAE Grade 1
4. Have an ECOG performance status of 0-1

- **Treatments**

Following confirmation of eligibility in the Screening Phase, patients were randomized 2:1 to receive rucaparib or active standard-of-care chemotherapy comparator in the Treatment Phase.

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 monotherapy rucaparib in patients with advanced solid tumours. This dosage is the currently approved dosage for marketing authorization in the US and EU for the treatment and maintenance treatment of ovarian cancer. Patients could take rucaparib with or without food. Each dose was to be taken with at least 240 mL of water. Tablets were to be swallowed whole without crushing or chewing. Each treatment cycle is 28 days. Treatment with rucaparib should be held or reduced in case of toxicity (Table 3), following established criteria and recording each modification.

Table 3. Rucaparib Dose Reduction Steps

Starting Dose	600 mg BID
Dose Level – 1	500 mg BID
Dose Level – 2	400 mg BID
Dose Level - 3[a]	300 mg BID

Abbreviation: BID = twice a day.

[a] Consult with Sponsor's medical monitor before reducing to dose level 3. Further dose reduction may be possible, but requires consultation with the Sponsor's medical monitor.

In the control arm, patients could receive different **Chemotherapy** regimens grouped by platinum-sensitivity:

- **Platinum-resistant** and **partially platinum-sensitive** patients received weekly paclitaxel, at a starting dose of 60-80 mg/m^2 (per institution protocols), administered on Days 1, 8 and 15 of a 28-day cycle, up to 8 cycles.
- **Platinum-sensitive** patients received, by investigator choice, platinum (carboplatin or cisplatin) monotherapy or platinum-based doublet (carboplatin and paclitaxel, carboplatin and gemcitabine, or cisplatin and gemcitabine), up to 8 cycles. Dosing should follow local guidelines.

Patients initially randomized to chemotherapy have the option to **cross over to rucaparib** treatment upon radiologic disease progression with Sponsor (or designee) approval of the radiology report confirming disease progression, signed consent for crossover, and meeting eligibility for the crossover. Initiation of treatment with rucaparib should occur within 8 weeks following radiologic disease progression.

- **Objectives**

The **primary objective** of this study is:

- To determine investigator-assessed progression-free survival (invPFS) by RECIST version 1.1 of rucaparib vs. chemotherapy

The **secondary objectives** of this study are:

- To evaluate PFS by RECIST Version 1.1, as assessed by BICR (bicrPFS)
- To compare efficacy of rucaparib versus chemotherapy as measured by ORR using RECIST Version 1.1 by investigator assessment
- To compare efficacy of rucaparib versus chemotherapy as measured by DOR by investigator assessment
- To compare efficacy of rucaparib versus chemotherapy as measured by ORR using RECIST Version 1.1 by investigator assessment and Gynecologic Cancer InterGroup (GCIG) cancer antigen-125 (CA-125) response criteria
- To evaluate patient-reported outcomes (PRO) for rucaparib versus chemotherapy as assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 and ovarian cancer module QLQ-OV28
- To evaluate the safety and tolerability of rucaparib versus chemotherapy

Exploratory objectives in this study are:

- To evaluate the second event of PFS, in subsequent line of treatment (PFS2), both by investigator assessment
- To evaluate disease control rate (RECIST Version 1.1 CR, PR, and prolonged SD ≥12 weeks, by investigator assessment)
- To evaluate PRO utilizing the Euro-Quality of Life 5D (EQ-5D)
- To assess molecular changes in tumour samples over time in matched pairs
- To assess circulating cell-free tumour DNA (ctDNA) as a molecular marker of efficacy
- To evaluate the impact of gene expression molecular subgroups on PFS and OS
- To assess efficacy in BRCA-mutation subgroups (i.e., germ line/somatic and BRCA1/BRCA2)
- To characterize steady-state trough concentrations of rucaparib
- To explore the relationship between rucaparib exposure and responses (safety and efficacy)

- **Outcomes/Endpoints**

Primary endpoint: **invPFS** (i.e. investigator assessed progression free survival) for the Treatment Part, was defined as the time (months) from randomization to disease progression +1 day, as determined by RECIST v1.1 criteria or death due to any cause, whichever occurred first. Patients without a documented event of progression (or death) were censored on the date of their last tumour radiologic assessment or date of randomization if no post-baseline tumour assessments had been performed.

Secondary endpoints for the Treatment Part were part of the hierarchical step-down procedure included:

- **ORR** by RECIST 1.1: assessed by investigator and analyzed in the subgroup of patients who were response evaluable at baseline for both the Efficacy Population and the ITT Population. The ORR was defined as proportion of patients with a confirmed CR or PR by RECIST v1.1. The confirmed response was defined as a CR or PR on subsequent tumour assessment at least 28 days after first response documentation.
- **DOR** by RECIST 1.1: was measured from the date of the first response until the first date that PD was documented. Any patients with an ongoing response were censored at the date of the last post-baseline scan.
- **ORR** by RECIST 1.1 and/or **CA-125 response**. Patients evaluable for CA-125 response must have had a baseline CA-125 value at least twice the upper limit of normal (ULN; i.e., ≥ 70 IU/mL) and at least 2 post baseline values. The endpoint of CA-125 response rate was defined as a 50% reduction from baseline. The response needed to be confirmed in a subsequent sample collected ≥21 days after the prior sample. The value of this confirmatory sample must have been ≤ 110% of the prior sample. The date when the first sample with a 50% decrease from baseline was observed was considered the date of the CA-125 response. In patients who had measurable disease by RECIST v1.1, the date of response was the date of the earlier of the two events.
- **PRO** as assessed by the EORTC QLQ-C30 Global Health Status score: change from baseline during the first 6 treatment cycles.

Stand-alone secondary endpoints for the Treatment Part of the study outside of the step-down procedure were as follows:

- **PFS** by BICR

- Interim **OS:** the time to OS was calculated in months as the time from randomization to date of death due to any cause. Patients who were still alive were censored on the date of their last available visit or last date known to be alive.
- **PRO** as assessed by the EORTC QLQ-C30 and QLQ-OV28

Exploratory endpoints:

- **PFS2** was defined as the time from randomization to the second event of disease progression as assessed by the investigator, or death due to any cause. This second event of PFS could be a documented event per RECIST v1.1 or could be an event of symptomatic progression. Patients without a second event of progression (or death) were censored on the last date the patient was known to be alive, study visit, or on the date of randomization if no post-baseline visits had been performed.
- **DCR**: defined as RECIST v1.1 evaluation of CR, PR, or SD ≥ 12 weeks and SD ≥ 24 weeks as assessed by the investigator.
- **PRO** as assessed by the EQ-5D-3L Visual Analogue Scale (VAS)

- **Sample size**

Approximately 345 patients were planned to be randomized 2:1 to receive either rucaparib or chemotherapy. The median PFS was assumed to be 12 months for rucaparib and 8 months for the comparator. Assuming an accrual over about 3 years, a dropout rate of 2%, a hazard ratio (HR) of 0.65, and at least 275 events, a sample size of 345 patients (230 patients randomized to rucaparib and 115 patients randomized to chemotherapy) would yield at least 80% power at a two-sided 0.05 significance level.

- **Analysis populations**

The following analysis populations are defined for the treatment part of the study:

- **Efficacy population**: all randomized patients with a deleterious BRCA mutation, excluding those identified to have a BRCA reversion mutation
- **ITT population**: all randomized patients
- **Safety population**: patients who received, at least, one dose of protocol-specified treatment

The crossover part will only be summarized for the Safety population, which is defined as all patients who crossed over to rucaparib treatment and received, at least, one dose of rucaparib.

- **Statistical methods**

All efficacy analyses will be performed both in the Efficacy Population and in the ITT Population. The primary endpoint and key secondary endpoints will be tested using a hierarchical step-down procedure starting with the primary efficacy endpoint in the Efficacy Population then testing the primary endpoint for the ITT Population.

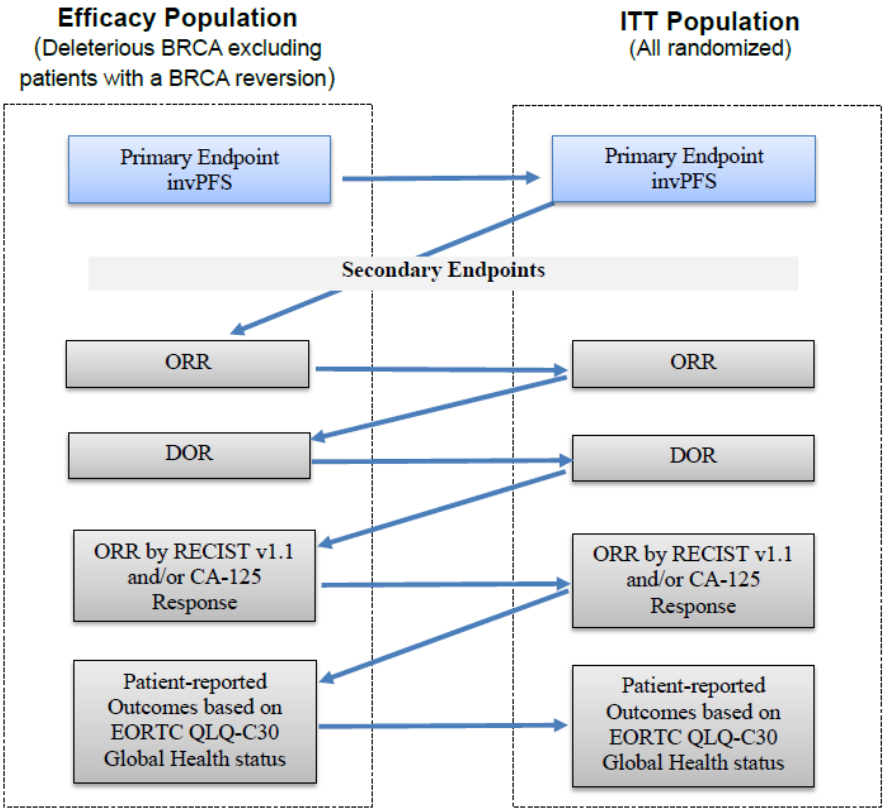
The **primary endpoint** of invPFS was analyzed using the stratified Cox proportional hazard methodology. The stratified HR from the Cox proportional hazards model was used to estimate the HR between the randomized treatment groups. **Subgroup analyses** were also conducted for the primary endpoint in the Treatment Part using age group (< 65, 65-74, ≥ 75), race (White, non-White), and randomization strata (platinum-resistant, partially platinum-sensitive, platinum-sensitive). In addition, subgroups based on BRCA mutation status (germ line or somatic BRCA), mutated gene (BRCA1, BRCA2), and detection of a BRCA reversion are presented as part of exploratory endpoint. **Sensitivity analyses** for the primary endpoint were performed to evaluate the impact of censored patients. A sensitivity analysis of invPFS was

performed using the randomization strata of platinum status (platinum-resistant, partially platinum-sensitive, platinum-sensitive) based on the prior anticancer data reported.

If the primary endpoint is statistically significant, then the **secondary efficacy endpoints** will be tested in the order specified below where for each endpoint, first in the Efficacy Population, and then in the ITT Population (Figure 2). In order to preserve the overall interim error rate, statistical significance will only be declared for the secondary endpoints, listed below, if the primary endpoint and previous secondary endpoints are also statistically significant:

- ORR
- DOR
- ORR and CA-125 response
- PRO as assessed by the EORTC QLQ-C30 Global Health Status score

Figure 2. Ordered Step-down Procedure



ORR by RECIST Version 1.1 as assessed by the investigator: The proportion of responders will be analyzed using a stratified Cochran-Mantel-Haenszel (CMH) test. Duration of response will be summarized and analyzed using the same methodology as described for the primary endpoint. Regarding ORR and CA-125 response, the proportion of responders will be analyzed using a stratified chi-square test. For PRO scores, at a given visit, the change from baseline will be compared between the randomized treatment groups using an ANCOVA using the treatment and stratification variable as a categorical factor and baseline measurement for the parameter as a continuous covariate.

OS will be analyzed using Cox proportional hazard methodology. The stratified hazard ratio from the Cox proportional hazards model will be used to estimate the HR between the randomized treatment groups. It was anticipated that the data for OS would be heavily censored at the time of the initial CSR analysis. In order to adjust for multiple analyses of OS at a later stage, a stopping rule will be applied. The Haybittle-

Peto stopping rule will be applied where an OS result with a p-value < 0.001 can be used to claim superiority of rucaparib compared to chemotherapy. This means that a p-value < 0.05 can be utilized at the final analysis which is projected to be once 70% of the death events have been collected.

No formal interim efficacy analyses were planned but ongoing review of data was performed by the IDMC.

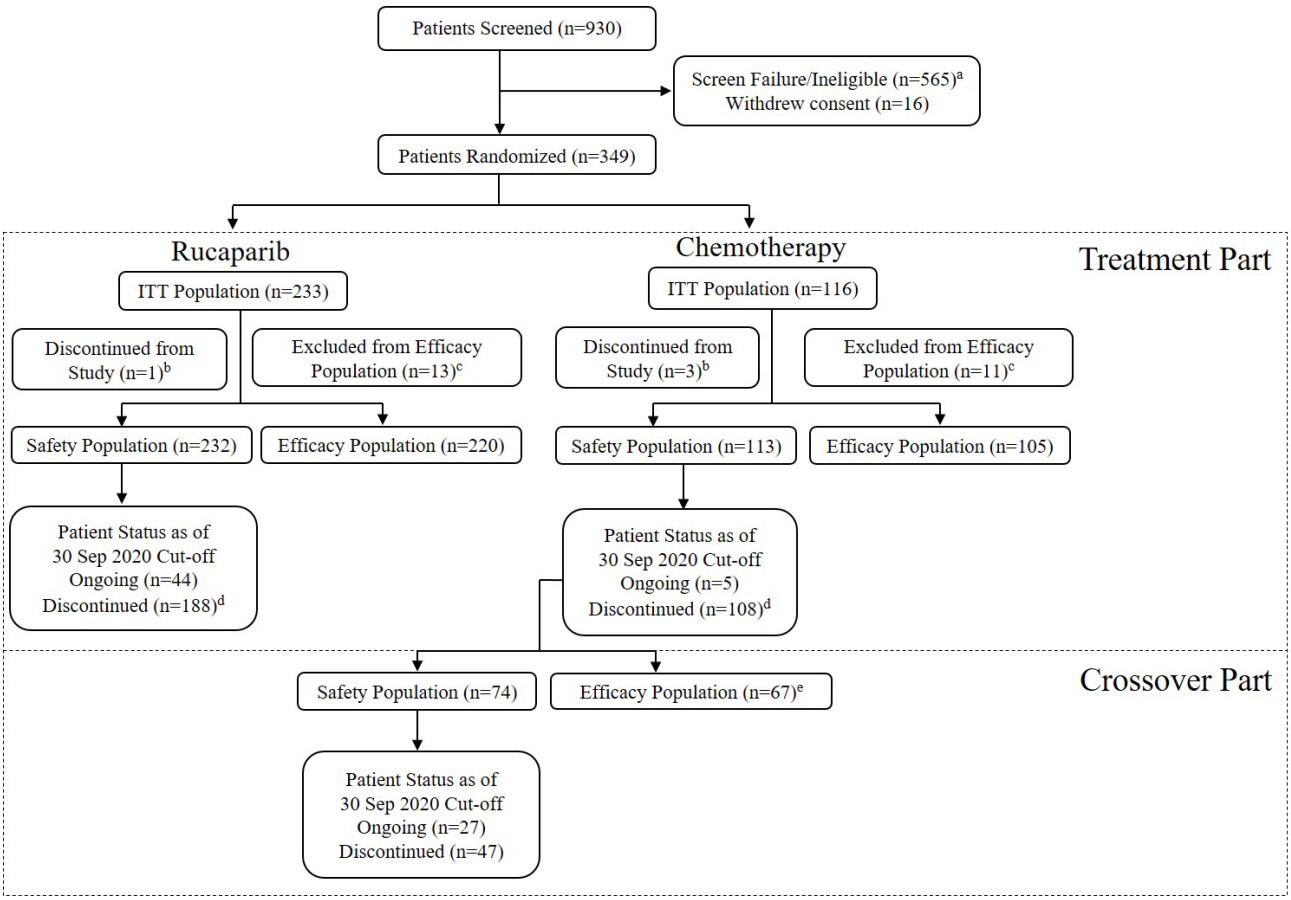
6.2. Results

- **Participant flow**

A total of 930 patients were screened. Of them, 349 were randomized. Of the patients who failed screening, the majority (464 patients) were ineligible due to lack of a deleterious BRCA mutation. First patient was enrolled on 1 March 2017 and last one on 24 September 2020.

Up to the visit cut-off date (30-Sep-2020), the 349 eligible patients were randomized 2:1 to receive rucaparib (N=233) or chemotherapy (N=116). Four patients were randomized and discontinued prior to receiving any study drug (1 patient randomized to the rucaparib group, 3 patients to the chemotherapy group); therefore, the Safety Population consisted of 345 patients, 232 of whom initiated treatment with 600 mg BID of rucaparib and 113 of whom initiated chemotherapy treatment. A flow diagram illustrating this is presented in Figure 3.

Figure 3. Patient disposition flowchart for Study CO-338-043A



Sources: Table 14.1.1.1, Table 14.1.1.2, Table 14.1.4.3.1, Listing 16.2.1, Listing 16.2.4.1.4, Listing 16.2.3, Study CO-338-043 CSR.
Abbreviations: AE = adverse event; CSR = clinical study report; ECOG = Eastern Cooperative Oncology Group; BRCA = breast cancer gene; ITT = intent-to-treat; RECIST = Response Evaluation Criteria in Solid Tumors.

[a] Reasons for screen failure/ineligible: ECOG performance status > 1 (12 patients); no BRCA mutation (464 patients); no RECIST evaluable lesions (10 patients); platinum-refractory disease (8 patients); prior hypersensitivity (6 patients); other reason (65 patients).

[b] Four enrolled patients withdrew from the study prior to receiving study drug: 1 patient randomized to rucaparib due to "other" (worsening of clinical symptoms), 3 patients randomized to chemotherapy (withdrew consent).

[c] In the ITT Population, 24 patients were excluded from the Efficacy Population: 13 patients randomized to rucaparib who had a BRCA reversion mutation; 11 patients randomized to chemotherapy who had a BRCA reversion mutation (10 patients) and non-BRCA status (1 patient).

[d] Discontinuation from study drug in the ITT Population (n): in the rucaparib group (188 patients) due to AEs (22), clinical progression (14), investigator decision (3), withdrawal of consent (8), progressive disease (133), protocol noncompliance (1), unknown/lost to follow-up (1), and other (6); in chemotherapy group (108 patients) due to AEs (14), clinical progression (3), investigator decision (2), withdrawal of consent (4), progressive disease (62), unknown/lost to follow-up (2), and treatment completed (21).

[e] Seven patients were excluded from the efficacy analysis in the Cross-over Part: BRCA reversion mutation (6 patients), non-BRCA (1 patient).

For the ITT population, end-of-study status included 2.1% and 3.4% of patients lost to follow-up, 2.6% and 1.7% of patients withdrawing consent, 54.1% and 44.0% patient deaths, and 18.9% and 4.3% of patients ongoing with treatment in the rucaparib and chemotherapy groups, respectively. As of the visit cut-off date, there were 51 patients (21.9%) in the rucaparib group and 24 patients (20.7%) in the chemotherapy group who were ongoing in long-term follow-up (alive) and continue to be followed for OS (Table 4).

Table 4. Summary of patient disposition (ITT population)

	Rucaparib	Chemotherapy
	n (%)	
Patient Population	N = 233	N = 116
Intent-to-Treat Population	233 (100.0%)	116 (100.0%)
Safety Population	232 (99.6%)	113 (97.4%)
Efficacy Population	220 (94.4%)	105 (90.5%)
TREATMENT PART	N = 233	N = 116
End-of-Treatment Status		
Ongoing	44 (18.9%)	5 (4.3%)
Discontinued	188 (80.7%)	108 (93.1%)
Primary Reason for Discontinuation of Study Drug[a]		
Adverse Event(s)	22 (11.7%)	14 (13.0%)
Clinical Progression	14 (7.4%)	3 (2.8%)
Investigator Decision	3 (1.6%)	2 (1.9%)
Withdrew Consent	8 (4.3%)	4 (3.7%)
Pregnancy	0 (0%)	0 (0%)
Progressive disease by RECIST v1.1	133 (70.7%)	62 (57.4%)
Protocol Noncompliance	1 (0.5%)	0 (0%)
Unknown / Lost to Follow-up	1 (0.5%)	2 (1.9%)
Other	6 (3.2%)	0 (0%)
Treatment completed	Not Applicable	21 (19.4%)
COVID	0 (0%)	0 (0%)

CROSSOVER PART		N = 74
Patients entering Crossover Part		
Safety Population		74 (100.0%)
Efficacy Population		67 (90.5%)
End-of-Treatment Status		
Ongoing		27 (36.5%)
Discontinued		47 (63.5%)
Primary Reason for Discontinuation of Study Drug [a]		
Adverse Event(s)		3 (6.4%)
Clinical Progression		2 (4.3%)

	Rucaparib	Chemotherapy
	n (%)	
Investigator Decision		0 (0%)
Withdrew Consent		0 (0%)
Pregnancy		0 (0%)
Progressive disease by RECIST v1.1		41 (87.2%)
Protocol Noncompliance		0 (0%)
Unknown / Lost to Follow-up		1 (2.1%)
Other		0 (0%)
COVID		0 (0%)
END-OF-STUDY STATUS	N = 233	N = 116
Not treated	1 (0.4%)	3 (2.6%)
Lost to follow-up	5 (2.1%)	4 (3.4%)
Withdrew consent	6 (2.6%)	2 (1.7%)
Death	126 (54.1%)	51 (44.0%)
Patients ongoing in Treatment Part	44 (18.9%)	5 (4.3%)
Patients ongoing in Crossover Part	Not Applicable	27 (23.3%)
Patients ongoing in long-term follow-up (alive)	51 (21.9%)	24 (20.7%)

Source: Table 14.1.1.1.
Abbreviations: BRCA = breast cancer gene 1 or 2; ITT = intent-to-treat; RECIST = Response Evaluation Criteria in Solid Tumors.
[a] Percentages based on the number of patients who discontinued study drug.

- **Conduct of the Study**

Original protocol is dated on 15-Jun-2016. A first amendment to the original protocol was issued on 11-Jan-2018. In this updated version, PFS by RECIST v1.1 as assessed by Independent Radiology Review (irrPFS) was included as the key secondary endpoint, first to be tested, followed by OS and, then, the rest of endpoints presented in this report.

By Amendment 2, dated 23-Oct-2020, irrPFS and OS were removed from the hierarchical step down testing procedure and they are included as stand-alone secondary endpoints, in the current protocol version.

In addition, Amendment 2 re-defined the population of analyses and established Efficacy Population (excluding patients with a BRCA reversion mutation) as the primary efficacy analysis population and ITT Population to be tested, for each endpoint, if the first one was statistically significant. An extract of the Summary of Changes provided by the MAH is included as figure 4.

Figure 4. Summary of Changes, Clinical Protocol CO-338-043, Amendment 2 (23 October 2020)

Statistical Methods Efficacy Analysis	The primary endpoint of invPFS will be analyzed using the stratified Cox proportional hazard methodology. The stratified hazard ratio from the Cox proportional hazards model will be used to estimate the HR between the randomized treatment groups. If the primary endpoint is statistically significant, then the secondary efficacy endpoints will be tested in the order they are presented. In order to preserve the overall Type 1 error rate, statistical significance will only be declared for secondary endpoints if the primary endpoint and previous secondary endpoints are also statistically significant. Additional supportive efficacy analyses include: 1. invPFS; 2. OS; 3. ORR by RECIST Version 1.1; 4. DOR by RECIST Version 1.1 5. ORR by RECIST Version 1.1 and CA 125 response; and 6. PRO as assessed by the EORTC QLQ C30 and QLQ OV28	The primary endpoint of invPFS will be analyzed using the stratified Cox proportional hazard methodology. The stratified hazard ratio from the Cox proportional hazards model will be used to estimate the HR between the randomized treatment groups. **All efficacy analyses will be performed for the Efficacy Population and the ITT Population. The Efficacy Population consists of all randomized patients with a deleterious BRCA mutation, excluding those with a BRCA reversion mutation, and the ITT Population consists of all randomized patients.** ~~If the primary endpoint is statistically significant, then the secondary efficacy endpoints will be tested in the order they are presented.~~ In order to preserve the overall Type 1 error rate, **the primary endpoint will first be tested in the Efficacy Population. If the primary endpoint in the Efficacy Population is statistically significant, then the primary endpoint in the ITT Population will be tested. If the primary endpoint is significant for both populations, then the first secondary efficacy endpoints will be tested, first in the Efficacy Population and then in the ITT Population in the order specified below for each endpoint.** Sstatistical significance will only be declared for secondary endpoints if the primary endpoint and previous secondary endpoints are also statistically significant. ~~Additional supportive efficacy analyses include~~**The key secondary endpoints and the testing order are listed below**: ~~invPFS;~~ ~~OS;~~ 1. ORR by RECIST Version 1.1; 2. DOR by RECIST Version 1.1 3. ORR by RECIST Version 1.1 and CA 125 response; and	To summarize updates to Statistical Methods detailed in Section 11

Regarding protocol deviations, up to the data cut-off date, a total of 30 patients (30 of 349 [8.6%]) had major protocol deviations (Table 5). Of the 7 inclusion/exclusion criteria violations, 5 were in patients randomized to the chemotherapy group. The 13 violations for initiating treatment more than 3 days after randomization ranged from 4 to 10 days post-randomization, with 10 of the violations occurring in patients randomized to the rucaparib group.

Table 5. Major protocol deviations for Study CO-338-043

Deviation	Description	Number of Deviations Reported	Number (%) of Patients (N=349)
Inclusion or exclusion criteria deviations	Exclusion criterion 3 not met: Prior treatment with single-agent paclitaxel for platinum-resistant disease.	1	7 (2.0)

Deviation	Description	Number of Deviations Reported	Number (%) of Patients (N=349)
	Exclusion criterion 4 not met: Prior known hypersensitivity to paclitaxel, or prior known hypersensitivity to platinum.	2[a]	
	Exclusion criterion 6 not met: Symptomatic and/or untreated CNS metastases.	1	
	Exclusion criterion 8 not met: Known HIV or AIDS-related illness, or history of chronic hepatitis B or C.	1	
	Exclusion criterion 15 not met: Hospitalization for bowel obstruction within 3 months prior to randomization.	1	
	Inclusion criterion 5 not met: Have a deleterious BRCA1 or BRCA2 mutation as confirmed by the central laboratory.	1	
3+ days randomization to treatment		13	13 (3.7)
Failure to reduce study drug dose		5	5 (1.4)
IP overdose/misuse		3	3 (0.9)
Treatment assignment[b]		1	1 (0.3)
Efficacy – no disease progression before starting Crossover		1	1 (0.3)

Source: Listing 16.2.2.1, Listing 16.2.2.2.

Abbreviations: AIDS = acquired immunodeficiency syndrome; BRCA = breast cancer gene 1 or 2; CNS = central nervous system; HIV = human immunodeficiency virus; IP = investigational product.

[a] Both patients were randomized and treated under the original protocol version that did not include desensitization as part of the exclusion criteria.

[b] Patient last platinum-containing chemotherapy stop date was less than 1 year, however the patient was stratified as platinum-sensitive.

No patients were excluded from analyses in the ITT Population because of a protocol deviation. One patient was excluded from Efficacy Population due to non-BRCA status; this patient was randomized based on a local laboratory result, and subsequent verification of the laboratory data indicated that the BRCA mutation was not deleterious (and this was confirmed by central laboratory testing). Overall, these deviations did not seem to have an impact on the study results.

- **Baseline data**

Demographic data for the ITT population are summarized in Table 6. The demographic characteristics of both treatment groups were well balanced. All patients were female. The overall median age was 58.0 years (range: 38-85 years), with the majority in each treatment group younger than 65 years (81.1% rucaparib; 75.9% chemotherapy), and the median BMI was 27.7 kg/m^2 overall. Nearly all patients in either treatment group were White (94.0% rucaparib; 97.4% chemotherapy), reflective of the countries of recruitment. Patients were enrolled from 12 countries, with treatment groups well balanced for each

country. The majority of patients were from central or eastern Europe. In accordance with the study inclusion criteria, all patients had an ECOG performance status of 0 (56.4% total) or 1 (43.6%) at baseline, and 80.2% overall had never smoked.

Table 6. Patient demographics – Treatment Part (ITT Population)

	Rucaparib (n = 233)	Chemotherapy (n = 116)	Total (N = 349)
Age (yr)			
n	233	116	349
Mean (StD)	57.4 (8.87)	58.6 (8.53)	57.8 (8.77)
Median	58.0	58.5	58.0
Min, Max	38, 81	38, 85	38, 85
Age Group, n (%)			
< 65 yr	189 (81.1)	88 (75.9)	277 (79.4)
65-74 yr	37 (15.9)	26 (22.4)	63 (18.1)
≥ 75-85 yr	7 (3.0)	2 (1.7)	9 (2.6)
Gender, n (%)			
Female	233 (100)	116 (100)	349 (100)
Race, n (%)			
American Indian or Alaska Native	1 (0.4)	0	1 (0.3)
Asian	3 (1.3)	0	3 (0.9)
Black or African American	4 (1.7)	2 (1.7)	6 (1.7)
Native Hawaiian or Other Pacific Islander	0	0	0
White	219 (94.0)	113 (97.4)	332 (95.1)
Multiple	1 (0.4)	0	1 (0.3)
Not Reported	5 (2.1)	1 (0.9)	6 (1.7)
Race Group, n (%)			
White	219 (94.0)	113 (97.4)	332 (95.1)
Other	9 (3.9)	2 (1.7)	11 (3.2)
Unknown	5 (2.1)	1 (0.9)	6 (1.7)
Ethnicity, n (%)			
Hispanic or Latino	34 (14.6)	11 (9.5)	45 (12.9)
Not Hispanic or Latino	194 (83.3)	103 (88.8)	297 (85.1)
Not Reported	3 (1.3)	1 (0.9)	4 (1.1)
Unknown	2 (0.9)	1 (0.9)	3 (0.9)
Country, n (%)			
Brazil	34 (14.6)	9 (7.8)	43 (12.3)
Canada	5 (2.1)	2 (1.7)	7 (2.0)
Czech Republic	15 (6.4)	10 (8.6)	25 (7.2)
Hungary	6 (2.6)	6 (5.2)	12 (3.4)
Israel	7 (3.0)	1 (0.9)	8 (2.3)
Italy	27 (11.6)	17 (14.7)	44 (12.6)
Poland	8 (3.4)	3 (2.6)	11 (3.2)
Russian Federation	73 (31.3)	40 (34.5)	113 (32.4)
Spain	6 (2.6)	4 (3.4)	10 (2.9)
Ukraine	33 (14.2)	8 (6.9)	41 (11.7)
United Kingdom	19 (8.2)	13 (11.2)	32 (9.2)
United States	0	3 (2.6)	3 (0.9)

	Rucaparib (n = 233)	Chemotherapy (n = 116)	Total (N = 349)
Height (cm)			
n	233	115	348
Mean (StD)	160.97 (6.476)	161.02 (7.175)	160.99 (6.705)
Median	161.00	160.80	161.00
Min, Max	143.0, 178.0	140.0, 181.0	140.0, 181.0
Weight (kg)			
n	233	116	349
Mean (StD)	73.58 (15.583)	73.63 (16.584)	73.60 (15.899)
Median	72.00	73.00	72.30
Min, Max	37.0, 125.0	42.0, 139.0	37.0, 139.0
BMI (kg/m^2)			
n	233	115	348
Mean (StD)	28.47 (6.152)	28.31 (5.971)	28.41 (6.085)
Median	27.69	27.64	27.67
Min, Max	15.4, 50.3	18.2, 47.0	15.4, 50.3
ECOG PS at Baseline, n (%)			
0	125 (53.6)	72 (62.1)	197 (56.4)
1	108 (46.4)	44 (37.9)	152 (43.6)
Smoking Status, n (%)			
Current Smoker	11 (4.7)	8 (6.9)	19 (5.4)
Former Smoker	36 (15.5)	14 (12.1)	50 (14.3)
Never Smoked	186 (79.8)	94 (81.0)	280 (80.2)

Source: Table 14.1.3.1.2.
Abbreviations: BMI = body mass index; BRCA = breast cancer gene 1 or 2; ECOG PS = Eastern Cooperative Oncology Group; max = maximum; min = minimum; StD = standard deviation.

Regarding **disease characteristics**, a summary of disease burden for the ITT Population is presented in Table 7. Disease burden was considered similar between treatment groups. Most patients had measurable disease at baseline per the investigator (96.1% rucaparib, 91.4% chemotherapy), with a mean (± StD) of 2 target lesions (± 1) in the rucaparib group and 2 (± 1) in the chemotherapy group. The mean (StD) sum of the diameters of target lesions was also similar: rucaparib, 65.9 mm (± 48.96); chemotherapy, 74.2 mm (± 48.32).

Table 7. Disease burden at baseline – Treatment part (ITT Population)

	Rucaparib (n = 233)	Chemotherapy (n = 116)	Total (N = 349)
Measurable Disease per Investigator, n (%)			
Yes	224 (96.1)	106 (91.4)	330 (94.6)
No	9 (3.9)	10 (8.6)	19 (5.4)
Number of Target Lesions per Investigator			
n	233	116	349
Mean (StD)	2.2 (1.29)	2.4 (1.41)	2.3 (1.33)
Median	2.0	2.0	2.0
Min, Max	0, 5	0, 5	0, 5
Number of Target Lesions per Investigator, n (%)			
0	9 (3.9)	10 (8.6)	19 (5.4)
1	68 (29.2)	19 (16.4)	87 (24.9)
2	75 (32.2)	37 (31.9)	112 (32.1)
3	35 (15.0)	23 (19.8)	58 (16.6)
4	30 (12.9)	15 (12.9)	45 (12.9)
5	16 (6.9)	12 (10.3)	28 (8.0)
Sum of the Diameters of Target Lesions per Investigator (mm)			
n	224	106	330
Mean (StD)	65.9 (48.96)	74.2 (48.32)	68.6 (48.84)
Median	55.0	62.2	57.0
Min, Max	10, 300	11, 257	10, 300

Source: Table 14.1.4.4.2.
Abbreviations: ITT = intent to treat; max = maximum; min = minimum; StD = standard deviation.

Nearly all patients had epithelial ovarian cancer (94.4% rucaparib; 95.7% chemotherapy), with the remainder approximately evenly split between fallopian tube and primary peritoneal cancer, and most patients had serous histology (89.3% rucaparib; 90.5% chemotherapy) (table 8).

In accordance with the study inclusion criteria, the histology was high-grade in all patients, and the majority of patients had been initially diagnosed with extensive disease with International Federation of Gynecology and Obstetrics (FIGO) Stage IIIC (58.4% rucaparib; 62.9% chemotherapy) and FIGO Stage IV (15.0% rucaparib; 10.3% chemotherapy). The median time since cancer diagnosis was 43.1 months in the overall population, which was similar for both treatment groups, with the majority of patients having been diagnosed > 24 months prior to enrolment (88.4% rucaparib; 87.1% chemotherapy).

Table 8. Cancer history – Treatment part (ITT Population)

	Rucaparib (n = 233)	Chemotherapy (n = 116)	Total (N = 349)
Time Since Cancer Diagnosis (months)			
n	232	113	345
Mean (StD)	52.52 (32.031)	50.62 (25.243)	51.89 (29.954)
Median	42.55	44.40	43.10
Min, Max	13.0, 185.2	14.0, 139.7	13.0, 185.2
Time Since Cancer Diagnosis Group, n (%)			
0-12 months	0	0	0
> 12-24 months	26 (11.2)	12 (10.3)	38 (10.9)
> 24 months	206 (88.4)	101 (87.1)	307 (88.0)
Missing[a]	1 (0.4)	3 (2.6)	4 (1.1)
Type of Ovarian Cancer, n (%)			
Epithelial Ovarian Cancer	220 (94.4)	111 (95.7)	331 (94.8)
Fallopian Tube Cancer	7 (3.0)	3 (2.6)	10 (2.9)
Primary Peritoneal Cancer	6 (2.6)	2 (1.7)	8 (2.3)
Other	0	0	0
Histological Classification, n (%)			
Serous	208 (89.3)	105 (90.5)	313 (89.7)
Endometrioid	18 (7.7)	6 (5.2)	24 (6.9)
Mixed	2 (0.9)	2 (1.7)	4 (1.1)
Other	5 (2.1)	3 (2.6)	8 (2.3)
Histological Grade, n (%)			
High Grade	233 (100.0)	116 (100.0)	349 (100.0)
Low Grade	0	0	0
FIGO Stage at Diagnosis, n (%)			
FIGO Stage IA	2 (0.9)	1 (0.9)	3 (0.9)
FIGO Stage IB	1 (0.4)	0	1 (0.3)
FIGO Stage IC	6 (2.6)	0	6 (1.7)
FIGO Stage IIA	4 (1.7)	5 (4.3)	9 (2.6)
FIGO Stage IIB	8 (3.4)	3 (2.6)	11 (3.2)
FIGO Stage IIC	5 (2.1)	3 (2.6)	8 (2.3)
FIGO Stage IIIA	15 (6.4)	5 (4.3)	20 (5.7)
FIGO Stage IIIB	14 (6.0)	12 (10.3)	26 (7.4)
FIGO Stage IIIC	136 (58.4)	73 (62.9)	209 (59.9)
FIGO Stage IV	35 (15.0)	12 (10.3)	47 (13.5)
Other	2 (0.9)	1 (0.9)	3 (0.9)
Missing	5 (2.1)	1 (0.9)	6 (1.7)

Source: Table 14.1.4.1.2.
Abbreviations: FIGO = International Federation of Gynecology and Obstetrics; ITT = intent to treat; max = maximum; min = minimum; StD = standard deviation.
[a] The "Missing" designation relates to lack of dosing date, not missing diagnosis date, as these 4 patients were randomized but discontinued prior to receiving any study drug.

Both treatment groups had the same number of prior chemotherapy treatments: median 2.0, range 2-9 rucaparib, 2-6 chemotherapy. As specified in Inclusion Criterion 4, all patients received ≥ 2 prior chemotherapy regimens, with most having received 2 (57.9% overall) or 3 regimens (24.6% overall). All patients also had at least 1 prior platinum-containing chemotherapy regimen, with a median or 2 prior platinum regimens in both treatment groups (range 1-6 rucaparib; 1-5 chemotherapy). The majority of patients had 2 (65.9%) or 3 (21.8%) prior platinum regimens with 0 (77.7% or 1 (19.5%) intervening non-platinum chemotherapy regimens.

Enrolled patients had a mean (StD) PFI of 8.3 (9.2) months following the last platinum-containing therapy regimen received. The 2:1 randomization of rucaparib and chemotherapy was stratified by PFI; however, there were no design restrictions on how many patients could enrol from each PFI stratum group. t (Table 9).

Table 9. Prior anticancer treatment – Treatment part (ITT Population)

	Rucaparib (n = 233)	Chemotherapy (n = 116)	Total (N = 349)
Number of Prior Therapy Regimens			
n	233	116	349
Mean (StD)	2.8 (1.26)	2.8 (1.07)	2.8 (1.20)
Median	2.0	2.0	2.0
Min, Max	2, 9	2, 6	2, 9
Number of Prior Therapy Regimens Group, n (%)			
2	126 (54.1)	65 (56.0)	191 (54.7)
3	62 (26.6)	30 (25.9)	92 (26.4)
4	25 (10.7)	10 (8.6)	35 (10.0)
5	9 (3.9)	7 (6.0)	16 (4.6)
> 5	11 (4.7)	4 (3.4)	15 (4.3)
Number of Prior Chemotherapy Regimens			
n	233	116	349
Mean (StD)	2.8 (1.24)	2.7 (1.04)	2.7 (1.18)
Median	2.0	2.0	2.0
Min, Max	2, 9	2, 6	2, 9
Number of Prior Chemotherapy Regimens Group, n (%)			
2	134 (57.5)	68 (58.6)	202 (57.9)
3	58 (24.9)	28 (24.1)	86 (24.6)
4	23 (9.9)	11 (9.5)	34 (9.7)
5	7 (3.0)	5 (4.3)	12 (3.4)
> 5	11 (4.7)	4 (3.4)	15 (4.3)
Number of Prior Platinum Regimens			
n	233	116	349
Mean (StD)	2.3 (0.83)	2.3 (0.71)	2.3 (0.79)
Median	2.0	2.0	2.0
Min, Max	1, 6	1, 5	1, 6
Number of Prior Platinum Regimens Group, n (%)			
1	12 (5.2)	6 (5.2)	18 (5.2)
2	156 (67.0)	74 (63.8)	230 (65.9)
3	48 (20.6)	28 (24.1)	76 (21.8)
4	11 (4.7)	7 (6.0)	18 (5.2)
5	2 (0.9)	1 (0.9)	3 (0.9)
> 5	4 (1.7)	0	4 (1.1)
Number of Intervening Non-platinum Chemotherapy Regimens Prior to Randomization			
n	233	116	349
Mean (StD)	0.3 (0.55)	0.3 (0.61)	0.3 (0.57)
Median	0.0	0.0	0.0

	Rucaparib (n = 233)	Chemotherapy (n = 116)	Total (N = 349)
Min, Max	0, 4	0, 4	0, 4
Number of Intervening Non-platinum Chemotherapy Regimens Prior to Randomization Group, n (%)			
0	179 (76.8)	92 (79.3)	271 (77.7)
1	49 (21.0)	19 (16.4)	68 (19.5)
2	3 (1.3)	4 (3.4)	7 (2.0)
≥ 3	2 (0.9)	1 (0.9)	3 (0.9)
Progression-free Interval After Last Dose of Prior Platinum Regimen (months)			
n	233	116	349
Mean (StD)	7.92 (8.111)	9.05 (11.118)	8.30 (9.219)
Median	5.56	5.77	5.65
Min, Max	1.1, 67.4	1.0, 90.1	1.0, 90.1
Progression-free Interval After Last Dose of Prior Platinum Regimen Group, n (%)			
< 1 months	0	0	0
1 to < 6 months	123 (52.8)	59 (50.9)	182 (52.1)
6 to < 12 months	66 (28.3)	32 (27.6)	98 (28.1)
≥ 12 months	44 (18.9)	25 (21.6)	69 (19.8)
Randomization Stratification: Platinum Status, n (%)			
Platinum-resistant	120 (51.5)	59 (50.9)	179 (51.3)
Partially platinum-sensitive	65 (27.9)	31 (26.7)	96 (27.5)
Platinum-sensitive	48 (20.6)	26 (22.4)	74 (21.2)
Platinum Status Based on Prior Platinum Regimens Recorded on CRF, n (%)			
Platinum-resistant	123 (52.8)	59 (50.9)	182 (52.1)
Partially platinum-sensitive	66 (28.3)	32 (27.6)	98 (28.1)
Platinum-sensitive	44 (18.9)	25 (21.6)	69 (19.8)

Source: Table 14.1.4.1.2.
Abbreviations: CRF = case report form; ITT = intent to treat; max = maximum; min = minimum; StD = standard deviation.

A summary of **BRCA mutation status** (local and central laboratory testing) is presented for the ITT population in Table 10. The majority (74.5%) of patients in the ITT Population were identified to have a BRCA1 gene mutation, with a BRCA2 gene mutation identified in 25.2% of patients. One patient randomized to the chemotherapy group had non-BRCA status (0.3%) due to an error in the interpretation of the local result; this patient was included in all efficacy analyses for ITT population and all safety analyses but was excluded from the Efficacy Population.

The majority of patients had germ line BRCA mutation status, identified in 84.0% and 84.6% of patients in the ITT Population and Efficacy Population, respectively. A somatic BRCA mutation was seen in 15.5% and 15.1% of patients in the ITT Population and Efficacy Population, respectively. Mutated BRCA gene and germ line vs. somatic mutation status were well balanced between the rucaparib and chemotherapy treatment groups. In addition, a BRCA reversion mutation was identified in 6.6% (23 patients) of patient samples. These 23 patients, along with the 1 patient with non-BRCA status, were excluded from the Efficacy Population.

Table 10. Baseline BRCA status and type (ITT Population)

	Rucaparib (n = 233)	Chemotherapy (n = 116)	Total (N = 349)
	n (%)		
Mutated Gene (Combined Local and Central Laboratory BRCA Mutation Results)*			
BRCA1	181 (77.7)	79 (68.1)	260 (74.5)
BRCA2	52 (22.3)	36 (31.0)	88 (25.2)
Non-BRCA	0	1 (0.9)	1 (0.9)
BRCA Germline/Somatic Mutation Status			
Germline	198 (85.0)	95 (81.9)	293 (84.0)
Somatic	35 (15.0)	19 (16.4)	54 (15.5)
Not available	0	2 (1.7)	2 (0.6)
Patients With a BRCA Reversion Mutation			
Reversion	13 (5.6)	10 (8.6)	23 (6.6)

Source: Table 14.1.4.3.1.
Abbreviations: BRCA = breast cancer gene 1 or 2; ITT = intent-to-treat.
* Central result was used if there was a discrepancy between local and central testing results.

- **Outcomes and estimation**

Primary efficacy endpoint

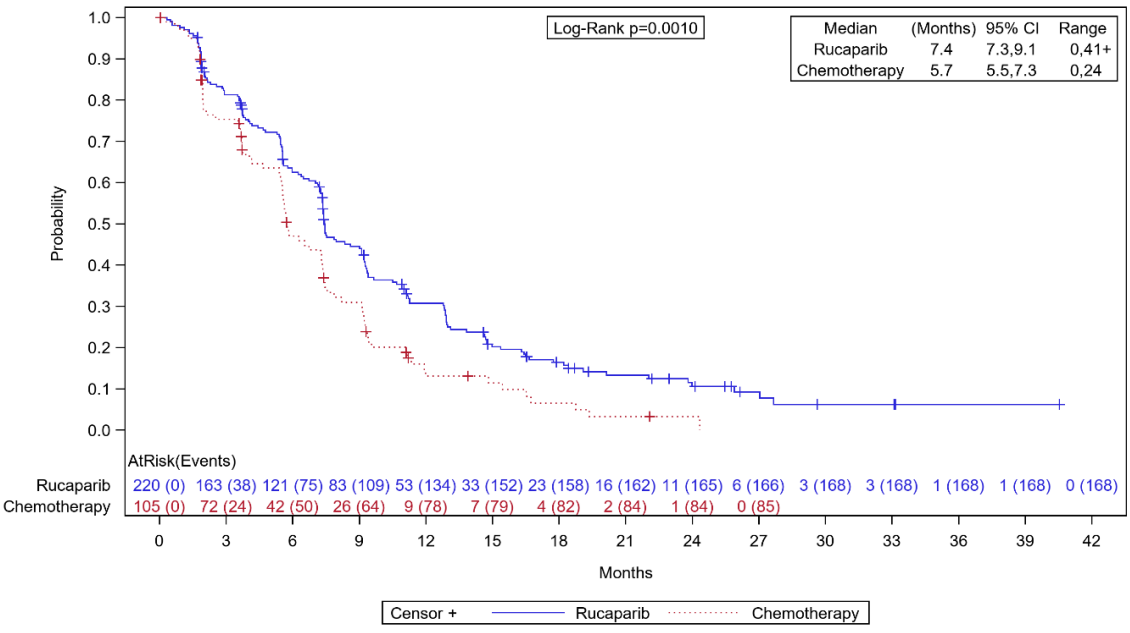
invPFS

The primary efficacy endpoint was invPFS using RECIST version 1.1 or death due to any cause, with a hierarchical step-down analysis from the Efficacy Population (if significant) to the ITT Population.

In the **Efficacy Population**, the stratified Cox proportional hazard methodology showed a statistically significant improvement in invPFS with rucaparib treatment compared with chemotherapy (HR 0.639 [95% CI, 0.489-0.835]; p=0.0010).

Investigator-assessed PFS was also estimated by the Kaplan-Meier method (figure 5) and the stratified log-rank test was used to compare invPFS between the rucaparib and chemotherapy treatment groups. The median invPFS was 7.4 months (95% CI, 7.3-9.1) for the rucaparib group compared to 5.7 months (95% CI, 5.5-7.3) for the chemotherapy group.

Figure 5. Progression-free Survival – Treatment part (Efficacy Population)



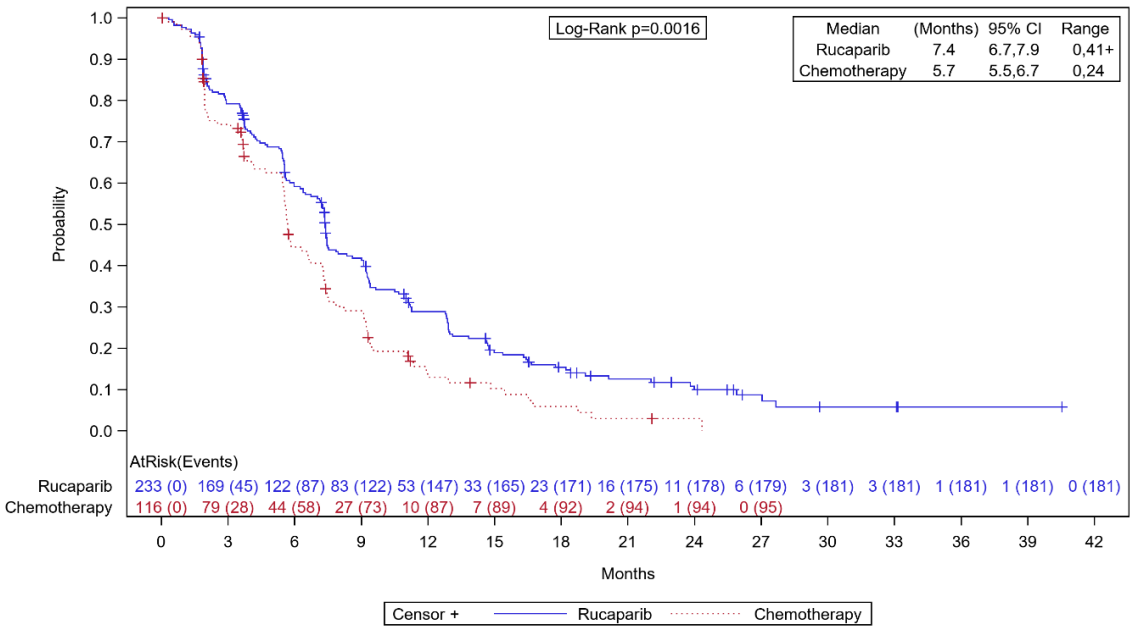
Source: Figure 14.2.1.1.1.

Abbreviation: CI = confidence interval.

[a] Note: Log-rank analysis was performed by randomization strata for the progression-free interval after most recent platinum-containing therapy (ie, platinum-resistant, partially platinum-sensitive, or platinum-sensitive).

In the **ITT Population** (second step of the multiplicity procedure), similar results were reported, with a statistically significant improvement in invPFS in the rucaparib treatment group compared with chemotherapy. A stratified Cox proportional hazard model showed a statistically significant improvement in invPFS with rucaparib treatment compared with chemotherapy (HR 0.665 [95% CI, 0.516-0.858]; p=0.0017). Results from the stratified log-rank analysis of invPFS (figure 6) were consistent with the stratified Cox proportional methodology, showing a statistically significant difference in invPFS with rucaparib treatment over chemotherapy (stratified log-rank, p=0.0016) for the ITT Population. The median invPFS was 7.4 months (95% CI, 6.7-7.9) for the rucaparib group and 5.7 months (95% CI, 5.5-6.7) for the chemotherapy group.

Figure 6. Progression-free Survival per Investigator – Treatment part (ITT Population)



Source: Figure 14.2.1.1.2, Study CO-338-043 CSR.

Abbreviations: CI = confidence interval; CSR = clinical study report; ITT = intent-to-treat.

[a] Log-rank analysis was performed by randomization strata for the progression-free interval after most recent platinum-containing therapy (ie, platinum-resistant, partially platinum-sensitive, or platinum-sensitive).

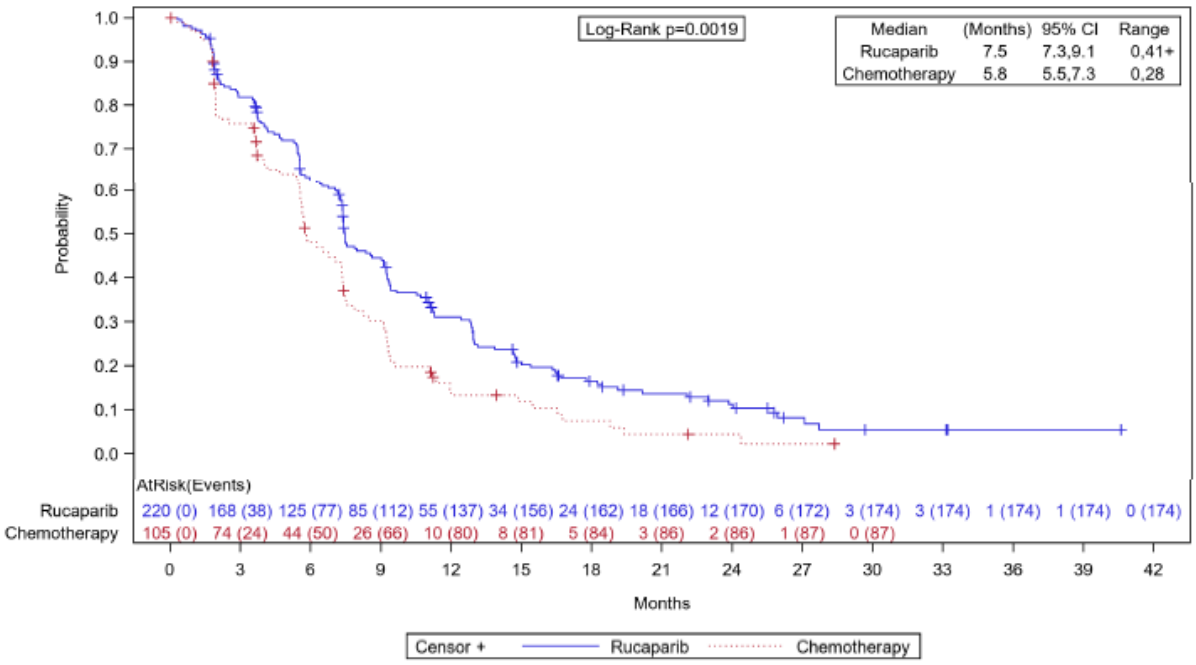
Sensitivity analyses

Prespecified sensitivity analyses for the primary endpoint of invPFS were performed to evaluate the impact of censored patients, on both the ITT Population and the Efficacy Population.

- In the first sensitivity analysis, all scans were included for assessment of PFS, regardless of whether they were taken, including after the start of subsequent anticancer therapy. The results were similar to the primary efficacy analysis described above for the respective populations, indicating that the censoring rules implemented for the primary analysis had minimal impact on the evaluation of invPFS. For the Efficacy Population, the median invPFS was 7.4 months (95% CI, 7.3-9.1) for the rucaparib group and 5.8 months (95% CI, 5.5-7.3) for the chemotherapy group; p = 0.0019. For the ITT Population, the median invPFS was 7.4 months (95% CI, 6.7-8.0) for the rucaparib group and 5.7 months (95% CI, 5.5-7.3) for the chemotherapy group, p=0.0029. Consistent with the primary efficacy analysis of these populations, the stratified Cox proportional hazard model showed a

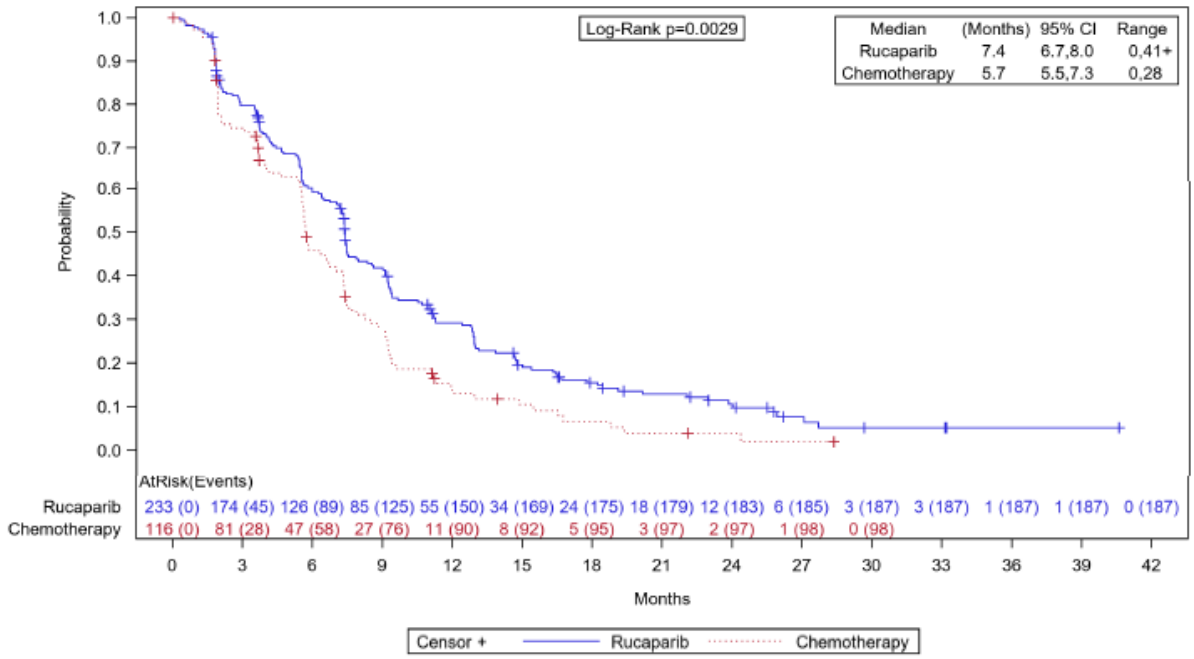
statistically significant improvement in invPFS with rucaparib treatment compared with chemotherapy in both the Efficacy (figure 7) and ITT (figure 8) Populations: HR 0.660 (95% CI, 0.507-0.858), p=0.0020 and HR 0.685 (95% CI, 0.553-0.880), p=0.0031.

Figure 7. Sensitivity analysis of primary efficacy endpoint: PFS including all scans, treatment part – Efficacy Population



Log-rank analysis performed by randomization strata for the progression free interval after most recent platinum containing therapy (i.e., platinum resistant, partially platinum sensitive, or platinum sensitive).
Data cutoff is 30Sep2020.

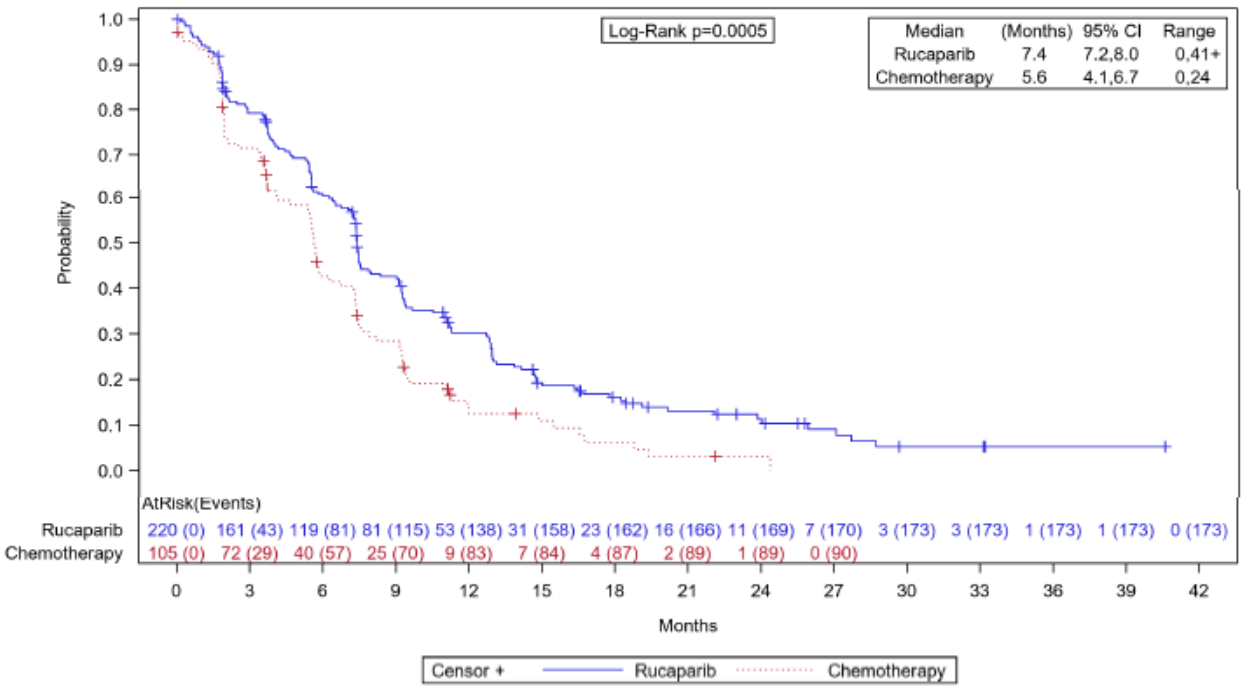
Figure 8. Sensitivity analysis of primary efficacy endpoint: PFS including all scans, treatment part – ITT Population



Log-rank analysis performed by randomization strata for the progression free interval after most recent platinum containing therapy (i.e., platinum resistant, partially platinum sensitive, or platinum sensitive).
Data cutoff is 30Sep2020.

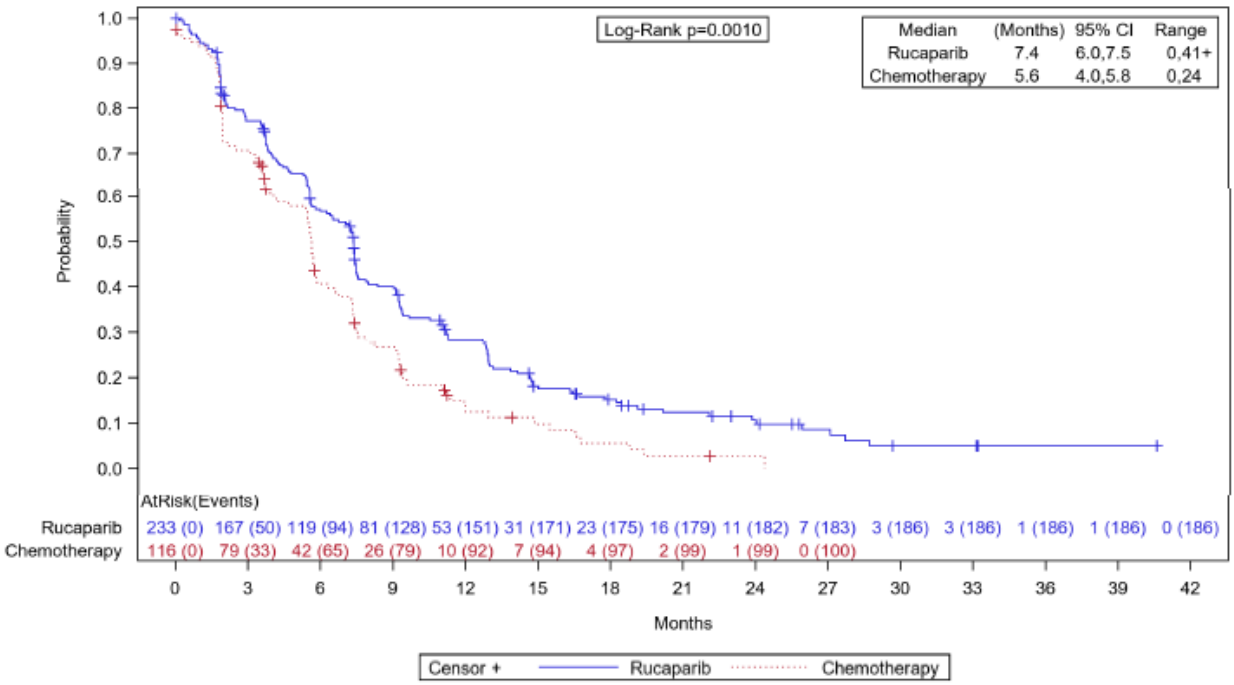
- The second sensitivity analysis included patients who discontinued treatment in the randomized Treatment Part due to clinical progression or withdrew consent (considered as events of invPFS on the date of the last dose of study drug). The results were similar to the primary efficacy analysis described above for these analysis populations, indicating that the inclusion of clinical progression or withdrew consent as an event of disease progression did not impact the evaluation of invPFS. For the Efficacy Population, the median invPFS was 7.4 months (95% CI, 7.2-8.0) for the rucaparib group and 5.6 months (95% CI, 4.1-6.7) for the chemotherapy group, log-rank p=0.0005. For the ITT Population, the median invPFS was 7.4 months (95% CI, 6.0-7.5) for the rucaparib group and 5.6 months (95% CI, 4.0-5.8) for the chemotherapy group, log-rank p=0.0010. Consistent with the primary analysis of these population, the stratified Cox proportional hazard model showed a statistically significant improvement in invPFS with rucaparib treatment compared to chemotherapy in both the Efficacy (figure 9) and ITT (figure 10) Populations, respectively: HR 0.633 (95% CI, 0.487-0.822); p=0.0006 and HR 0.660 (95% CI, 0.515-0.847); p=0.0011.

Figure 9. Sensitivity analysis of primary endpoint: PFS including clinical progression and withdrew consent, treatment part – Efficacy Population



Log-rank analysis performed by randomization strata for the progression free interval after most recent platinum containing therapy (i.e., platinum resistant, partially platinum sensitive, or platinum sensitive).
Data cutoff is 30Sep2020.

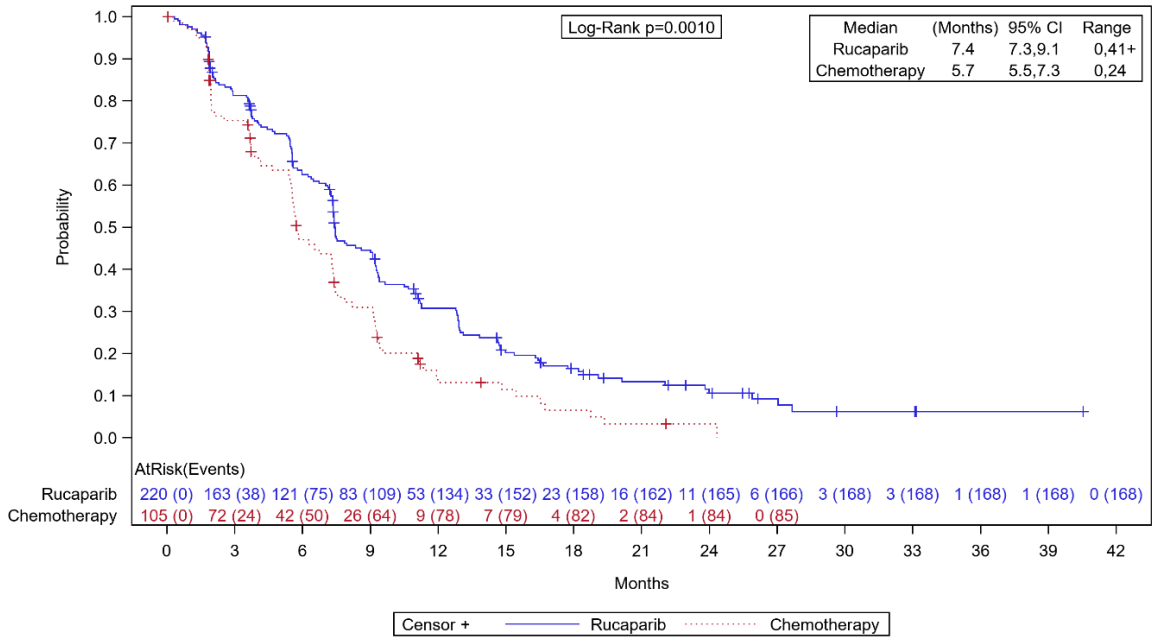
Figure 10. Sensitivity analysis of primary endpoint: PFS including clinical progression and withdrew consent, treatment part – ITT Population



Log-rank analysis performed by randomization strata for the progression free interval after most recent platinum containing therapy (i.e., platinum resistant, partially platinum sensitive, or platinum sensitive).
Data cutoff is 30Sep2020.

- A third sensitivity analysis of invPFS was performed using the final data entered into eCRF for PFI strata, as some patients were allocated incorrectly by the site at the time of randomization. There were 14 patients who were allocated incorrectly, 1 patient in the chemotherapy group and 13 patients in the rucaparib group, as follows: 3 patients (all rucaparib) who were partially platinum-sensitive on the CRF but randomized to platinum-resistant; 5 patients (1 chemotherapy and 4 rucaparib) who were partially platinum-sensitive but randomized to fully platinum-sensitive; and 6 patients (all rucaparib) who were platinum-resistant but randomized to partially platinum-sensitive. As shown in figure 11, invPFS using actual strata data were consistent with the initial analysis, showing a significant benefit with rucaparib treatment compared to chemotherapy (log-rank, p=0.0010). Analysis using the stratified Cox proportional hazard model also showed consistent benefit of rucaparib for PFS compared to chemotherapy (HR 0.642, 95% CI 0.491, 0.838), p=0.0011, when actual strata allocation was used.

Figure 11. Sensitivity analysis of invPFS using actual stratification – Treatment part (Efficacy Population)



Source: Figure 14.2.1.4.1.

Abbreviation: CI = confidence interval; invPFS = investigator-assessed progression-free survival.

[a] Note: Log-rank analysis was performed by actual strata for the progression-free interval after most recent platinum-containing therapy (ie, platinum-resistant, partially platinum-sensitive, or platinum-sensitive).

Secondary efficacy endpoints

ORR

The first secondary endpoint as part of the step-down multiple comparison procedure was ORR for the Efficacy Population in the Treatment Part in the subgroup of patients who were response evaluable at baseline (i.e., had measurable target lesions). ORR was defined as the proportion of patients with a confirmed CR or PR by RECIST v1.1. The response rates between treatment groups were compared using the stratified CMH test, and are summarized for the Efficacy Population in the Treatment Part is shown in Table 11. A higher confirmed response rate was observed in the rucaparib group (40.3%, 95% CI 33.6%-47.2%) as compared to the chemotherapy group (32.3%, 95% CI 23.1%-42.6%), however this difference was not statistically significant (p=0.1287). There were 4.7% of patients in the rucaparib group who achieved a CR compared to 2.1% in the chemotherapy group.

Table 11. ORR – Treatment part (Efficacy Population with measurable disease at baseline)

	Rucaparib (N=211)	Chemotherapy (N=96)	P-value[a]
Confirmed Response Rate			
n (%)	85 (40.3)	31 (32.3)	0.1287
95% CI, %	33.6 - 47.2	23.1 - 42.6	
Best Overall Confirmed Response, n (%)			
CR	10 (4.7)	2 (2.1)	
PR	75 (35.5)	29 (30.2)	
SD	77 (36.5)	38 (39.6)	
Discontinued or PD	65	36	
Ongoing with a single response	1	0	
Ongoing without a response	11	2	
PD	25 (11.8)	15 (15.6)	
NE	24 (11.4)	12 (12.5)	

Source: Table 14.2.2.1.1.
Abbreviations: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] The stratified CMH test was used to test the difference in proportions between treatment adjusting for the randomization strata for the PFI after most recent platinum-containing therapy (ie, platinum resistant, partially platinum-sensitive, or platinum sensitive).

Per the ordered step-down procedure, because statistical significance was not achieved for ORR in the Efficacy Population, statistical significance could not be claimed for the subsequent secondary endpoint analyses but they are displayed for descriptive purposes.

The next step of the multiplicity procedure was ORR as assessed in the ITT Population for patients with measurable disease at baseline (Treatment Part), as summarized in Table 12. Similar results were observed, with a confirmed response rate in the rucaparib treatment group of 37.9% (95% CI, 31.6%-44.7%) compared to 30.2% (95% CI, 21.7%-39.9%) in the chemotherapy group.

Table 12. ORR – Treatment part (ITT Population with measurable disease at baseline)

	Rucaparib (N=224)	Chemotherapy (N=106)	P-value[a]
Confirmed Response Rate			
n (%)	85 (37.9)	32 (30.2)	0.1250
95% CI, %	31.6 - 44.7	21.7 - 39.9	
Best Overall Confirmed Response, n (%)			
CR	10 (4.5)	2 (1.9)	
PR	75 (33.5)	30 (28.3)	
SD	83 (37.1)	43 (40.6)	
Discontinued or PD	71	41	
Ongoing with a single response	1	0	
Ongoing without a response	11	2	
PD	31 (13.8)	19 (17.9)	
NE	25 / 224 (11.2)	12 (11.3)	

Source: Table 14.2.2.1.2.

Abbreviations: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CR = complete response; ITT = intent-to-treat; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] The stratified CMH test was used to test the difference in proportions between treatment adjusting for the randomization strata for the progression-free interval after most recent platinum-containing therapy (ie, platinum resistant, partially platinum-sensitive, or platinum sensitive).

DOR

The next step of the multiplicity procedure was DOR as assessed by investigator, analyzed sequentially in the Efficacy and ITT Populations in the subgroup of patients who had a confirmed response (CR or PR) by RECIST v1.1. DOR was measured from the date of the first response until the date that progressive disease was documented. Similar results were seen for both populations, showing a longer duration of response in the rucaparib group compared to the chemotherapy group. For the Efficacy Population, the DOR was 9.4 months (95% CI, 7.5-11.1) for the rucaparib group, compared to 7.2 months (95% CI, 4.0-11.4) in the chemotherapy group. For the ITT Population, DOR was 9.4 months (95% CI, 7.5-11.1) for the rucaparib group, compared to 7.2 months (95% CI, 3.9-9.4) in the chemotherapy group.

ORR and/or CA-125 response

The next step of the multiplicity procedure was ORR by RECIST v1.1 as assessed by investigator and/or CA-125 response, analyzed sequentially in the Efficacy and ITT Populations in the subgroup of patients who were response evaluable at baseline (i.e., had measurable target lesions) or CA-125 response evaluable. The endpoint of CA-125 response rate was defined as a 50% reduction from baseline. The response needed to be confirmed in a subsequent sample collected ≥ 21 days after the prior sample with the confirmatory sample ≤110% of the prior sample.

The proportion of patients with a confirmed RECIST v1.1 response and/or CA-125 response are summarized for the Efficacy Population in Table 13, followed by the ITT Population in Table 14 for the Treatment Part. For the Efficacy Population, 50.7% of patients in the rucaparib group (95% CI 43.8%-57.5%) had a confirmed response by either measure compared to 43.6% of patients in the chemotherapy group (95% CI 33.7%-53.8%). For the ITT Population, 47.8% of patients in the rucaparib group (95% CI 41.2% - 54.5%) had a confirmed response by either measure compared to 40.5% of patients in the chemotherapy group (95% CI 31.3%-50.3%).

Table 13. ORR and/or CA-125 response – Treatment part (Efficacy Population)

	Rucaparib (N=220)	Chemotherapy (N=105)	P-value[a]
Number of Patients With Measurable Disease at Baseline and/or CA-125 Response Evaluable[b,c]	217	101	
Confirmed Response Rate by either RECIST v1.1 and/or CA-125 Response, n (%)[d]	110 (50.7)	44 (43.6)	0.1602
95% CI, %	43.8 - 57.5	33.7 - 53.8	

Source: Table 14.2.2.3.1 and Table 14.2.2.1.1.

Abbreviation: CA-125 = cancer antigen-125; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; RECIST = Response Evaluation Criteria in Solid Tumors; v = version.

[a] The stratified CMH test was used to test the difference in proportions between treatment adjusting for the randomization strata for the PFI after most recent platinum-containing therapy (ie, platinum resistant, partially platinum-sensitive, or platinum sensitive).

[b] The date when the first sample with a 50% decrease from baseline is observed is the date of the CA-125 response.

[c] There were 131 and 56 CA-125 response-evaluable patients and 211 and 96 RECIST response-evaluable patients in the rucaparib and chemotherapy groups, respectively.

[d] In patients who have measurable disease by RECIST v1.1, the date of response is the earlier of the dates of RECIST or CA-125 response.

Table 14. ORR and/or CA-125 response – Treatment part (ITT Population)

	Rucaparib (N=233)	Chemotherapy (N=116)	P-value[a]
Number of Patients With Measurable Disease at Baseline and/or CA-125 Response Evaluable[b,c]	230	111	
Confirmed Response Rate by either RECIST v1.1 and/or CA-125 Response, n (%)[d]	110 (47.8)	45 (40.5)	0.1407

	Rucaparib (N=233)	Chemotherapy (N=116)	P-value[a]
95% CI, %	41.2 - 54.5	31.3 - 50.3	

Source: Table 14.2.2.3.2 and Table 14.2.2.1.2.

Abbreviation: CA-125 = cancer antigen-125; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = intent-to-treat; RECIST = Response Evaluation Criteria in Solid Tumors; v = version.

[a] The stratified CMH test was used to test the difference in proportions between treatment adjusting for the randomization strata for the PFI after most recent platinum-containing therapy (ie, platinum resistant, partially platinum-sensitive, or platinum sensitive).

[b] The date when the first sample with a 50% decrease from baseline is observed is the date of the CA-125 response.

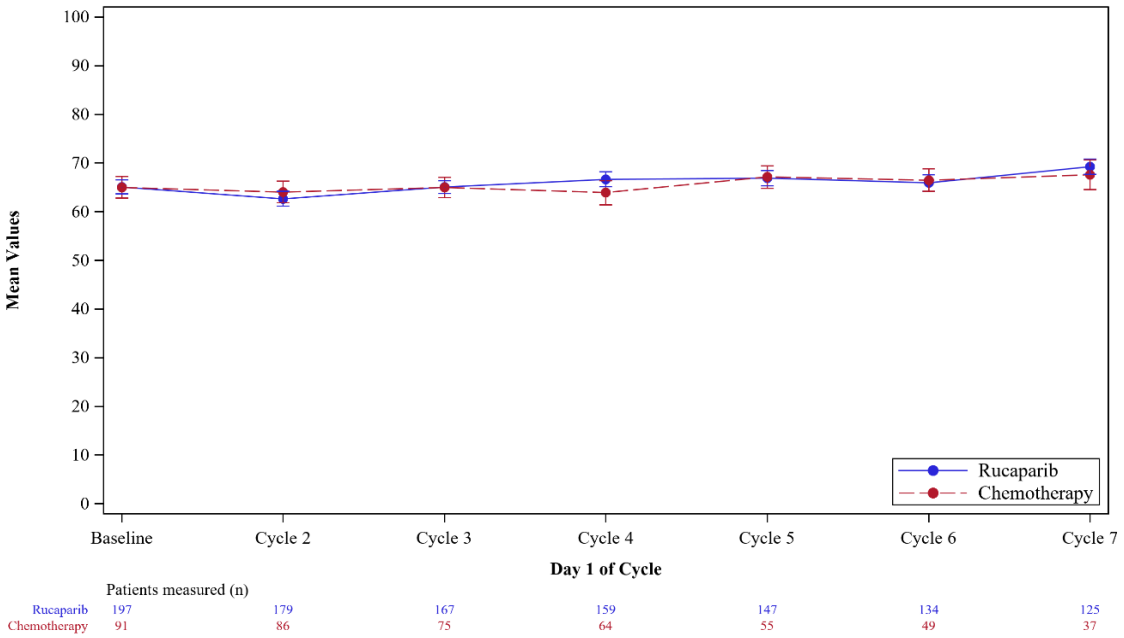
[c] There were 140 and 62 CA-125 response-evaluable patients and 224 and 106 RECIST response-evaluable patients in the rucaparib and chemotherapy groups, respectively.

[d] In patients who have measurable disease by RECIST v1.1, the date of response is the earlier of the dates of RECIST or CA-125 response.

PRO by EORTC QLQ-C30 Global Health Status

The last step-down analysis performed was PRO as measured by European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 Global Health Status Score, which integrates functional and symptom scoring results. Changes from baseline of this score over the first 6 cycles in the treatment part were analyzed. Results for the Efficacy Population and ITT Population are shown in Figure 12 and Figure 13, respectively and show no difference in QOL as assessed by EORTC QLQ-C30 Global health status score between treatment groups. Overall, Global Health Status per the EORTC QLQ-C30 instrument appears similar in patients in the rucaparib group as compared to patients in the chemotherapy group.

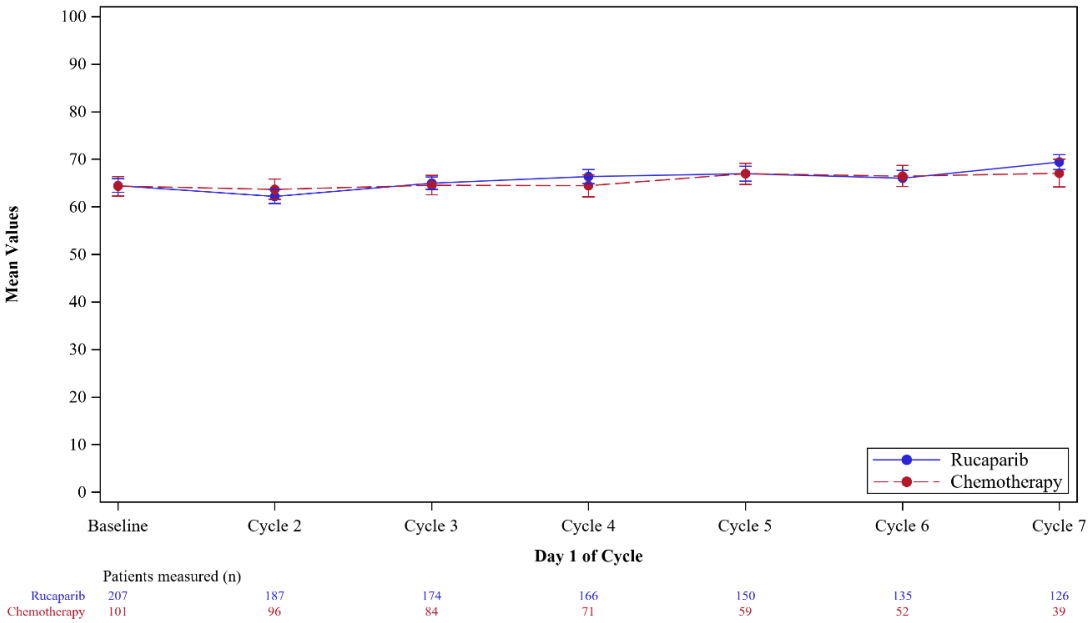
Figure 12. Mean values (±SE) for EORTC QLQ-C30 Global Health Status score for the first 6 cycles – Treatment part (Efficacy Population)



Source: Figure 14.2.2.4.1.1.

Abbreviation: EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; SE = standard error.

Figure 13. Mean values (±SE) for EORTC QLQ-C30 Global Health Status score for the first 6 cycles – Treatment part (ITT Population)



Source: Figure 14.2.2.4.1.2.

Abbreviations: EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; ITT = intent-to-treat; SE = standard error.

PFS by BICR

The PFS by BICR was included as a secondary endpoint outside of the step-down procedure in the SAP. According to the MAH, as this analysis was not required, by the SAP, at the time of the primary efficacy analysis, it was not performed.

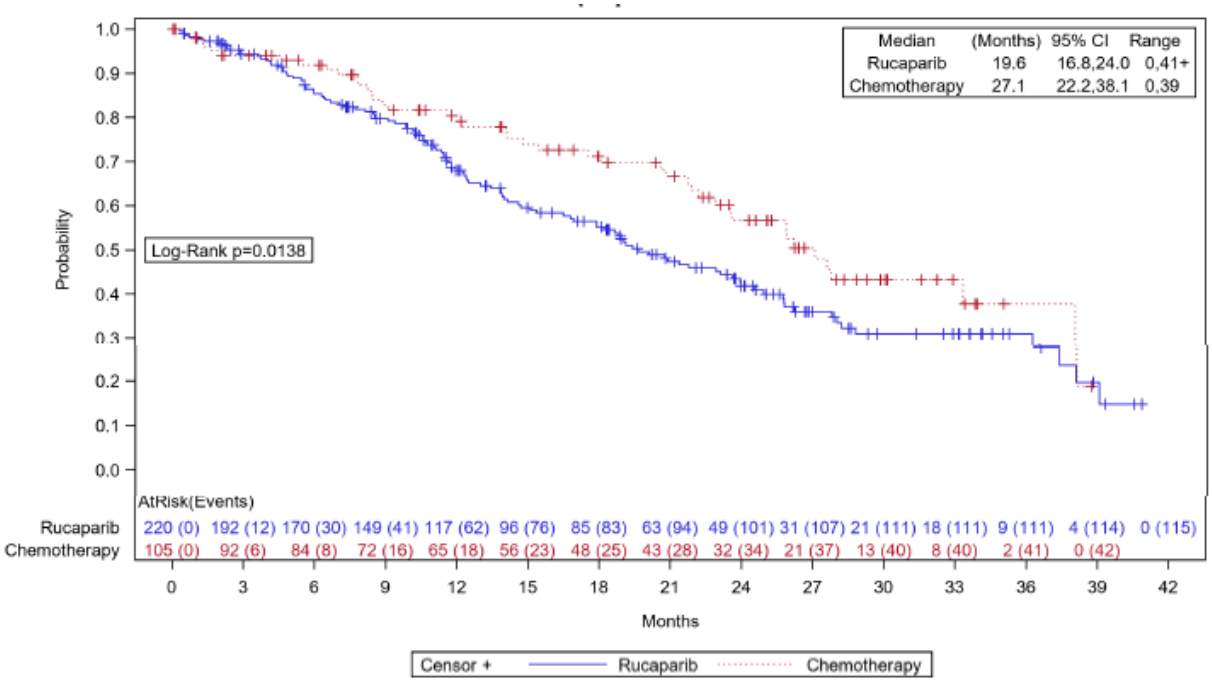
Interim OS

At the time of visit cut-off, OS data were at 51% maturity (51% of events), with the final readout for OS planned per the SAP when 70% maturity has been reached. Thus, the interim analysis submitted is considered exploratory, with the final OS analysis to be submitted when complete, in an addendum to the CSR.

Patients who were still alive at the time of this IA were censored on the date of their last available visit or last date known to be alive. The preliminary, exploratory interim OS analyses were performed for the Efficacy Population and ITT Population for patients randomized to the Treatment Part.

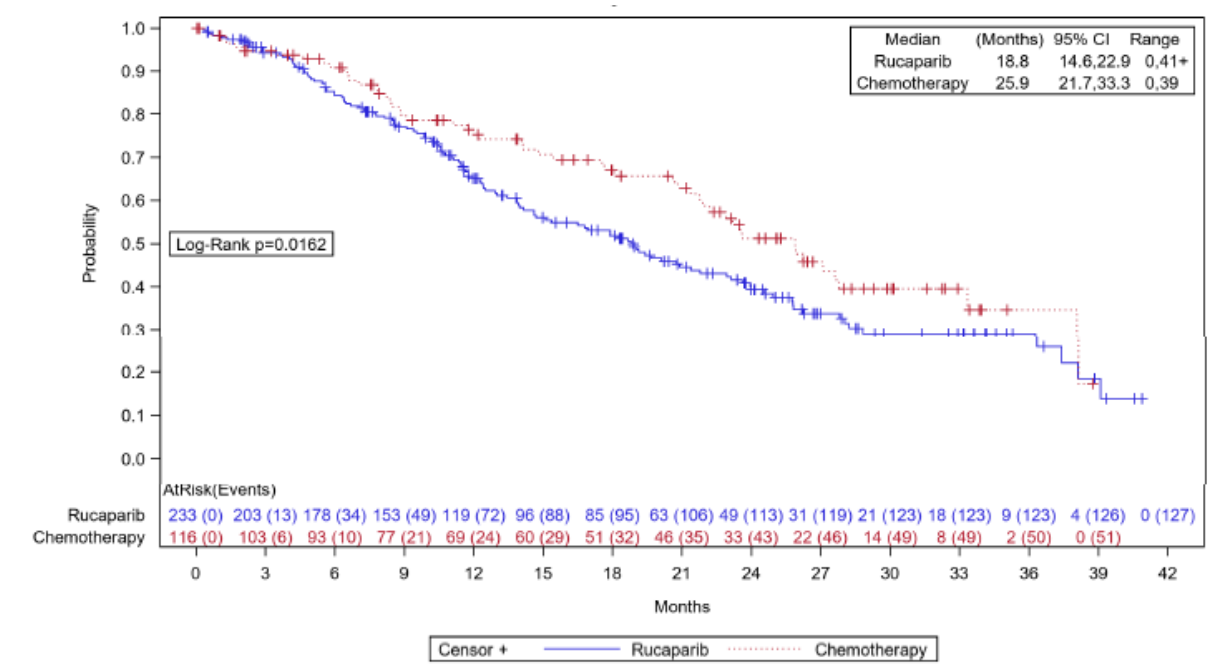
For patients treated with rucaparib in the Efficacy Population, the median OS was 19.6 months (95% CI, 16.8-24.0) in the rucaparib group compared to 27.1 months (95% CI, 22.2-38.1) in the chemotherapy group; stratified log-rank, p=0.0138 (figure 14). Similar results were seen for the ITT Population, where the median OS was 18.8 months (95% CI, 14.6-22.9) for the rucaparib group compared to 25.9 months (95% CI, 21.7-33.3) for chemotherapy group stratified log-rank p=0.0162 (figure 15). Results using the stratified Cox proportional hazard model are as follows: HR 1.550 (95% CI, 1.085-2.214), p=0.0161 for the Efficacy Population and HR 1.484 (95% CI, 1.069-2.061), p=0.0185 for the ITT Population.

Figure 14. Interim OS – Treatment part (Efficacy Population)



Log-rank analysis performed by randomization strata for the progression free interval after most recent platinum containing therapy (i.e., platinum resistant, partially platinum sensitive, or platinum sensitive).
Data cutoff is 30Sep2020.

Figure 15. Interim OS – Treatment part (ITT Population)



Log-rank analysis performed by randomization strata for the progression free interval after most recent platinum containing therapy (i.e., platinum resistant, partially platinum sensitive, or platinum sensitive).
Data cutoff is 30Sep2020.

Final OS (data cut-off: 10-Apr-2022)

At the time of the final OS analysis, 70% (244/349) of death events had occurred in the ITT Population. The platinum-resistant subgroup was more mature (77.6% [139/179]) than the platinum-sensitive subgroup, which had 61.8% (105/170) OS events and was comprised of the PPS (69.8% [67/96]) and the FPS subgroups (51.4% [38/74]).

The hazard ratio (HR) for OS between rucaparib and chemotherapy patients in the ITT Population of ARIEL4 was 1.31 (95% confidence interval [CI], 1.00-1.73; p = 0.0507) (Table 15).

Table 15. ARIEL4 Final OS (70% maturity) – All Population and Subgroups

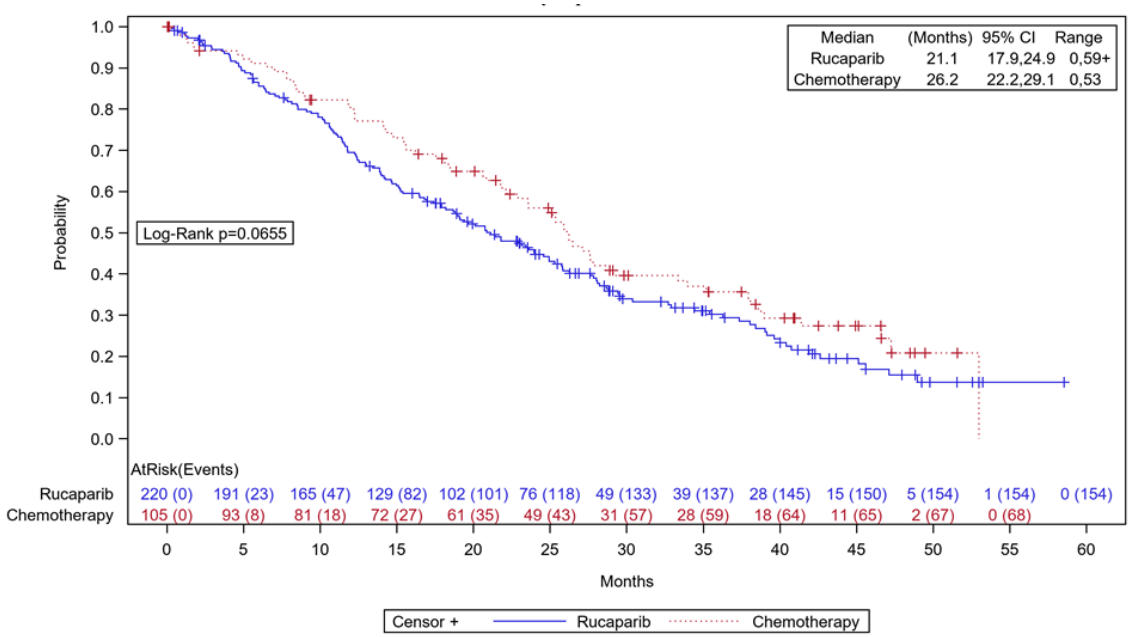
Population/ Subgroup	Overall Survival			
			Rucaparib vs Chemo	
	Rucaparib Event/N (%)	Chemo Event/N (%)	Kaplan-Meier Analysis[a] Medians Log-rank p-value	Cox Proportional Hazard[b] HR (95% CI) p-value
Efficacy	154/220 (70.0)	68/105 (64.8)	21.1 vs 26.2 p = 0.0655	1.31 (0.98, 1.74) p = 0.0704
ITT	167/233 (71.7)	77/116 (66.4)	19.4 vs 25.4 p = 0.0472	1.31 (1.00, 1.73) p = 0.0507
Platinum-resistant	95/120 (79.2)	44/59 (74.6)	14.2 vs 22.2 p = 0.0222	1.51 (1.05, 2.17) p = 0.0251
Platinum-sensitive (Fully + Partially)	72/113 (63.7)	33/57 (57.9)	29.4 vs 27.6 p = 0.7167	1.07 (0.71, 1.62) p = 0.7455
- Fully Platinum-sensitive	27/48 (56.3)	11/26 (42.3)	36.3 vs 47.2 p = 0.4945	1.24 (0.62, 2.50) p = 0.5405
- Partially Platinum-sensitive	45/65 (69.2)	22/31 (71.0)	21.1 vs 23.2 p = 0.9469	0.97 (0.58, 1.62) p = 0.9129

Abbreviations: chemo = chemotherapy; CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; OS = overall survival; PFS2 = second event of progression-free survival.

[a] Log-rank analysis performed by randomization strata of platinum status for ITT and Efficacy Populations.

[b] Cox proportional hazard method performed by randomization strata of platinum status for ITT and Efficacy Populations.

Figure 15. ARIEL4 Kaplan-Meier Analysis of OS – Efficacy Population

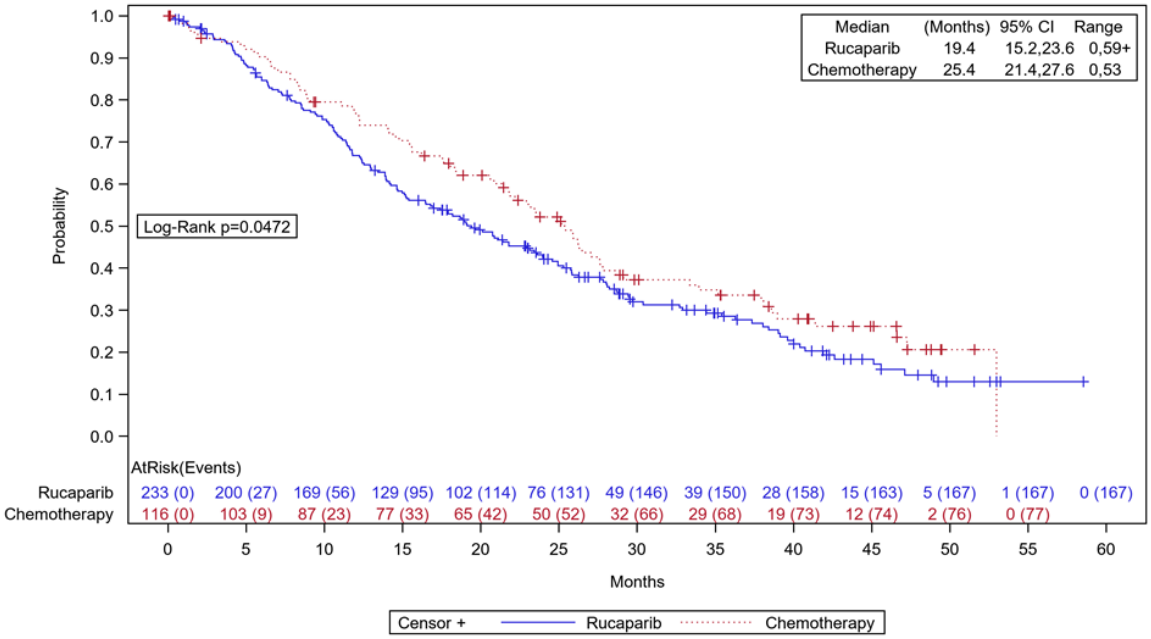


Source: Figure 14.2.3.4.1.

Abbreviations: CI = confidence interval; OS = overall survival.

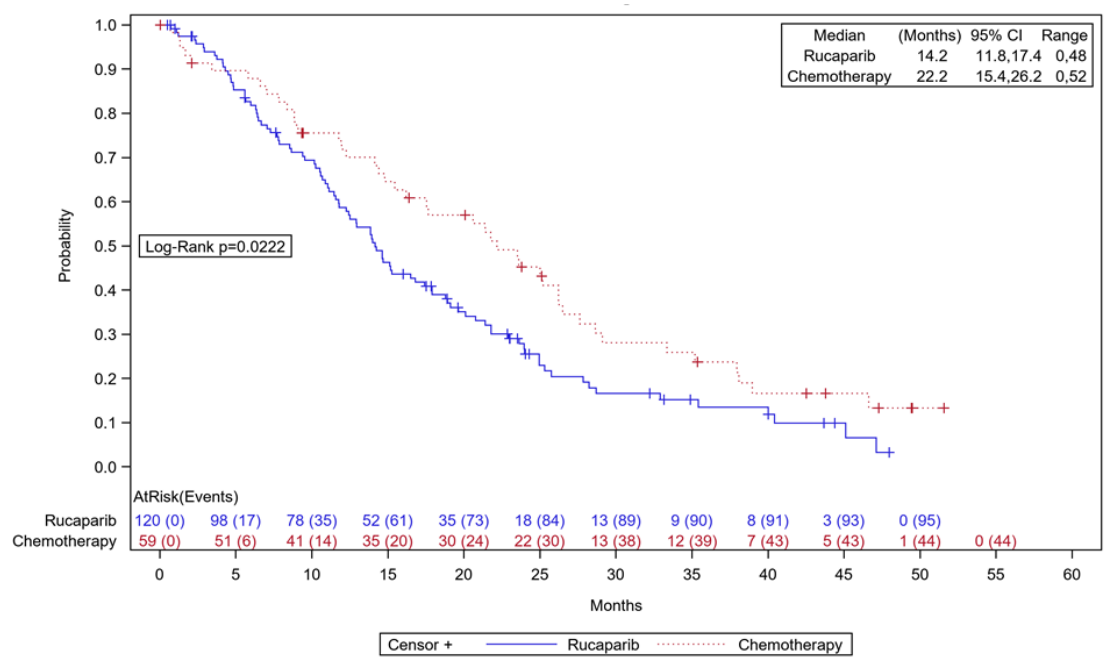
Note: Log-rank analysis performed by randomization strata of platinum status.

Figure 16. ARIEL4 Kaplan-Meier Analysis of OS – ITT Population



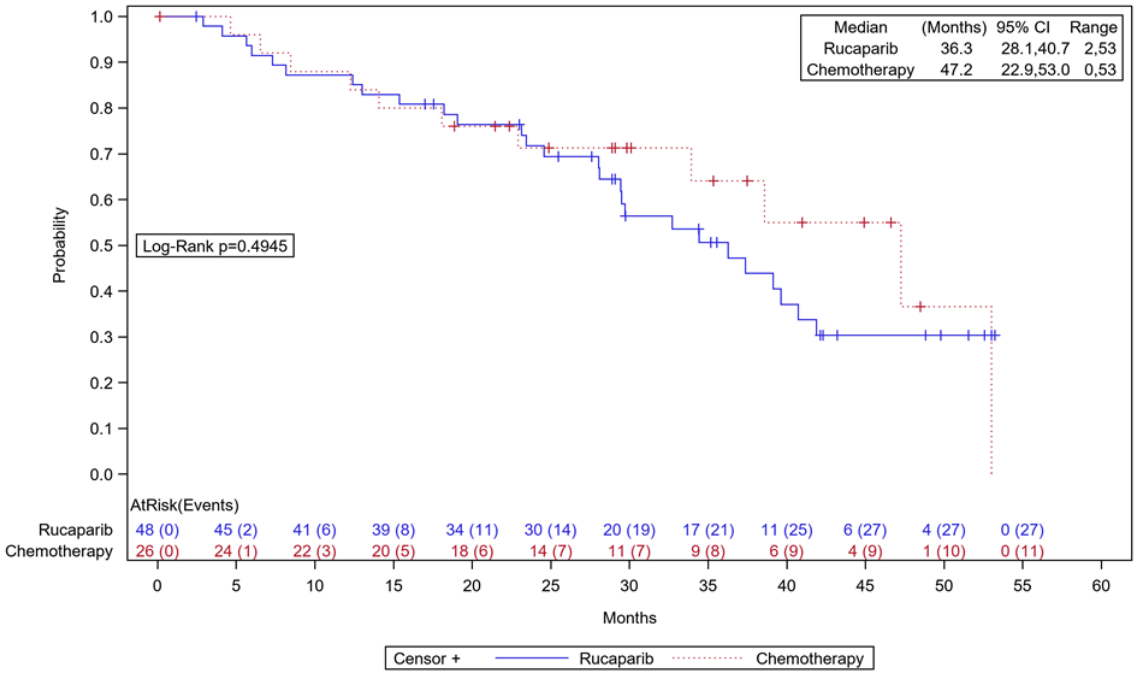
Source: Figure 14.2.3.4.2.
Abbreviations: CI = confidence interval; ITT = intent-to-treat; OS = overall survival.
Note: Log-rank analysis performed by randomization strata of platinum status.

Figure 17. ARIEL4 Kaplan-Meier Analysis of OS – Platinum-resistant Subgroup (ITT Population)



Source: Figure 14.2.3.4.8.
Abbreviations: CI = confidence interval; ITT = intent-to-treat; OS = overall survival.
Note: Log-rank analysis performed by randomization strata of platinum status.

Figure 18. ARIEL4 Kaplan-Meier Analysis of OS – Fully Platinum-sensitive Subgroup (ITT Population)

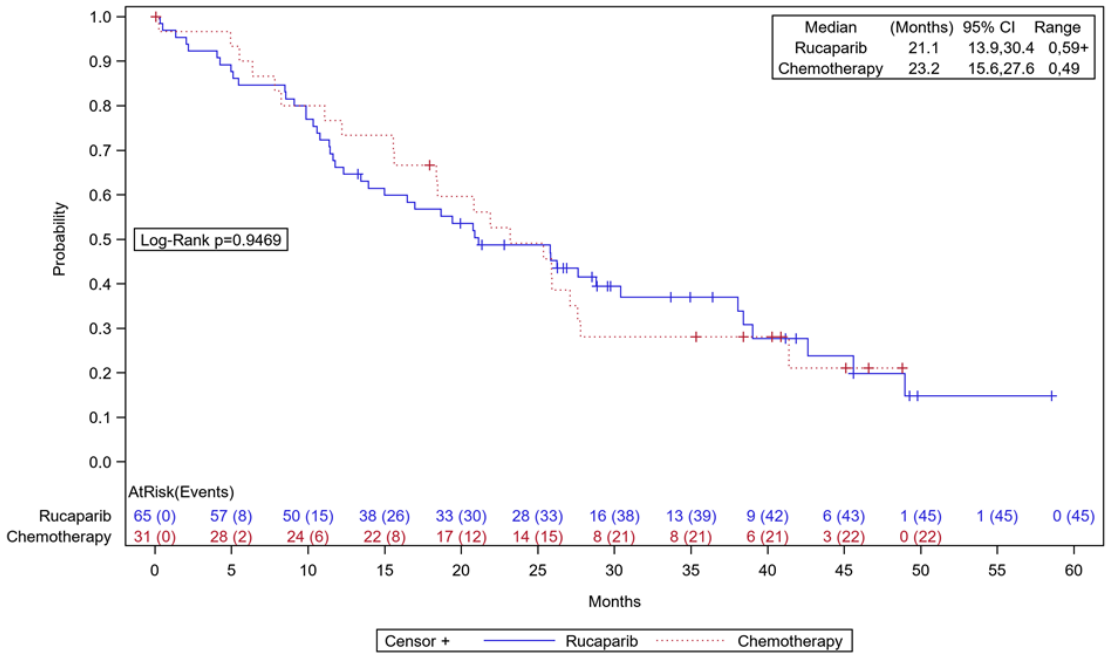


Source: Figure 14.2.3.4.10.

Abbreviations: CI = confidence interval; ITT = intent-to-treat; OS = overall survival.

Note: Log-rank analysis performed by randomization strata of platinum status.

Figure 19. ARIEL4 Kaplan-Meier Analysis of OS – Partially Platinum-sensitive Subgroup (ITT Population)

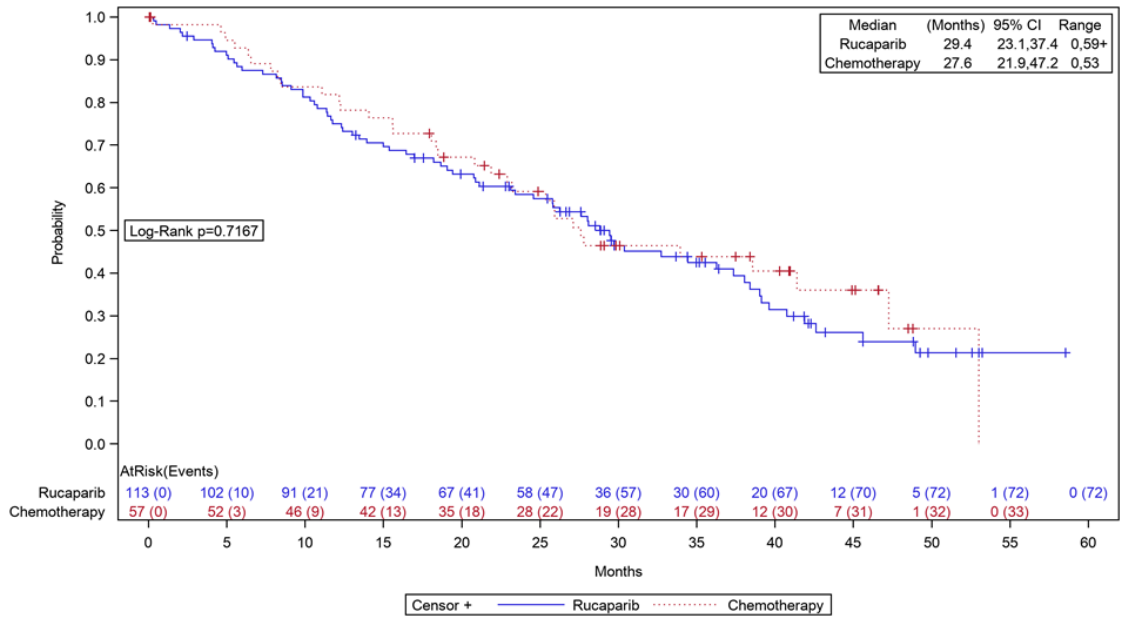


Source: Figure 14.2.3.4.9.

Abbreviations: CI = confidence interval; ITT = intent-to-treat; OS = overall survival.

Note: Log-rank analysis performed by randomization strata of platinum status.

Figure 20. ARIEL4 Kaplan-Meier Analysis of OS – Platinum-sensitive Combined (Fully and Partially) Subgroup (ITT Population)



Source: Figure 14.2.3.4.11.
Abbreviations: CI = confidence interval; ITT = intent-to-treat; OS = overall survival.
Note: Log-rank analysis performed by randomization strata of platinum status.

Exploratory efficacy endpoints

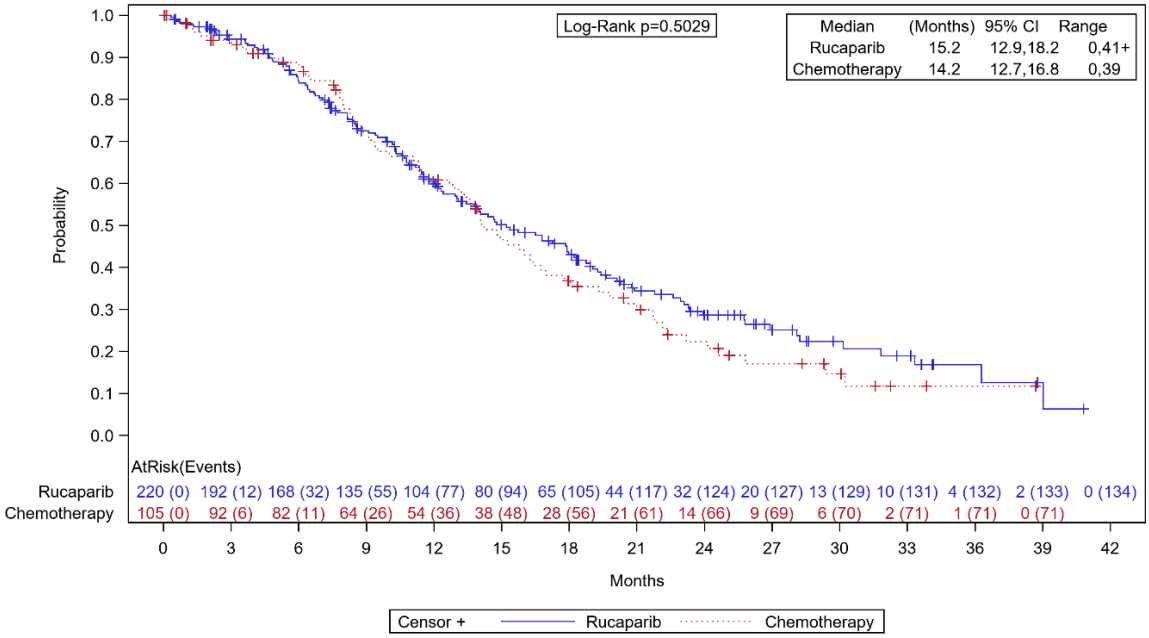
PFS2

At the time of the visit cut-off for this report, the PFS2 data had reached 60.9% maturity in the rucaparib group (134 of 220 patients with an event) and 67.6% maturity in the chemotherapy group (71 of 105 patients with an event). A final PFS2 analysis will be conducted when final OS data are available.

Of note, the second event of progression could be due to progression per RECIST v1.1 or symptomatic progression.

In the Efficacy Population (Figure 18), the median PFS2 was 15.2 months (95% CI, 12.9-18.2) for the rucaparib group compared to 14.2 months (95% CI, 12.7-16.8) for the chemotherapy group, stratified log rank, p=0.5029. Similarly, no difference was seen in the ITT Population (Figure 19) for PFS2 between treatment groups, with a median PFS2 of 14.4 months (95% CI, 12.0-17.2) for the rucaparib group compared to 14.0 months (95% CI, 11.3-16.0) for the chemotherapy group, stratified log rank, p=0.5887. There was no significant reduction in the risk of a second event of progression or death in the rucaparib group compared to the chemotherapy group in either the Efficacy Population (HR 0.903 [95% CI, 0.676-1.207]; p = 0.4897) or the ITT Population (HR 0.925 [95% CI, 0.703-1.216]; p = 0.5761).

Figure 18. Analysis of Second Event of Progression-free Survival per Investigator – Treatment part (Efficacy Population)

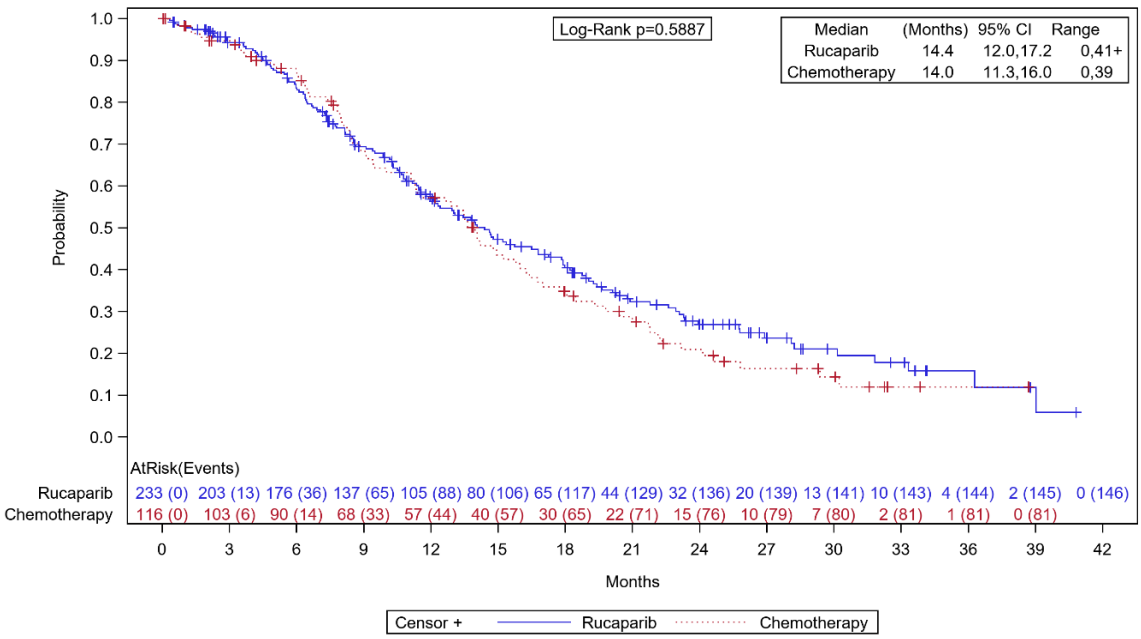


Source: Figure 14.2.3.1.1.

Abbreviation: CI = confidence interval.

Note: Log-rank analysis was performed by randomization strata for the progression-free interval after most recent platinum-containing therapy (ie, platinum-resistant, partially platinum-sensitive, or platinum-sensitive).

Figure 19. Analysis of Second Event of Progression-free Survival per Investigator – Treatment part (ITT Population)



Source: Figure 14.2.3.1.2.

Abbreviation: CI = confidence interval; ITT = intent-to-treat.

Note: Log-rank analysis was performed by randomization strata for the progression-free interval after most recent platinum-containing therapy (ie, platinum-resistant, partially platinum-sensitive, or platinum-sensitive).

Updated PFS2 data (data cut-off: 10 Apr 2022)

At the time of final analysis, the PFS2 data were 80.6 % (262/325) and 81.9% (286/349) mature in the Efficacy and ITT Populations, respectively. Similar to the interim PFS2 results, there was no significant

difference between rucaparib treatment and chemotherapy treatment for PFS2 in either the Efficacy Population or ITT Population in the final analysis.

Table 16. ARIEL4 Final OS and PFS2 – All Populations and Subgroups

Population/ Subgroup	Overall Survival				PFS2			
			Rucaparib vs Chemo				Rucaparib vs Chemo	
	Rucaparib Event/N (%)	Chemo Event/N (%)	Kaplan-Meier Analysis[a] Medians Log-rank p-value	Cox Proportional Hazard[b] HR (95% CI) p-value	Rucaparib Event/N (%)	Chemo Event/N (%)	Kaplan-Meier Analysis[a] Medians Log-rank p-value	Cox Proportional Hazard[b] HR (95% CI) p-value
Efficacy	154/220 (70.0)	68/105 (64.8)	21.1 vs 26.2 p = 0.0655	1.31 (0.98, 1.74) p = 0.0704	171/220 (77.7)	91/105 (86.7)	15.5 vs 14.1 p = 0.1904	0.84 (0.65, 1.09) p = 0.1848
ITT	167/233 (71.7)	77/116 (66.4)	19.4 vs 25.4 p = 0.0472	1.31 (1.00, 1.73) p = 0.0507	184/233 (79.0)	102/116 (87.9)	14.7 vs 13.6 p = 0.2332	0.86 (0.67, 1.10) p = 0.2273
Platinum-resistant	95/120 (79.2)	44/59 (74.6)	14.2 vs 22.2 p = 0.0222	1.51 (1.05, 2.17) p = 0.0251	101/120 (84.2)	55/59 (93.2)	11.8 vs 11.5 p = 0.8658	0.97 (0.70, 1.34) p = 0.8450
Platinum-sensitive (Fully + Partially)	72/113 (63.7)	33/57 (57.9)	29.4 vs 27.6 p = 0.7167	1.07 (0.71, 1.62) p = 0.7455	83/113 (73.5)	47/57 (82.5)	19.4 vs 14.2 p = 0.1034	0.74 (0.51, 1.06) p = 0.0996
- Fully Platinum-sensitive	27/48 (56.3)	11/26 (42.3)	36.3 vs 47.2 p = 0.4945	1.24 (0.62, 2.50) p = 0.5405	32/48 (66.7)	18/26 (69.2)	26.9 vs 24.4 p = 0.7187	0.89 (0.49, 1.60) p = 0.6861
- Partially Platinum-sensitive	45/65 (69.2)	22/31 (71.0)	21.1 vs 23.2 p = 0.9469	0.97 (0.58, 1.62) p = 0.9129	51/65 (78.5)	29/31 (93.5)	16.5 vs 13.3 p = 0.0695	0.65 (0.41, 1.03) p = 0.0669

Sources: Tables 14.2.3.1.1, 14.2.3.1.2, 14.2.3.1.3, 14.2.3.4.1, 14.2.3.4.2, 14.2.3.4.5, 14.2.3.4.7, and 14.2.3.99.2; Figures 14.2.3.1.1, 14.2.3.1.2, 14.2.3.1.6, 14.2.3.1.7, 14.2.3.1.8, 14.2.3.4.1, 14.2.3.4.2, 14.2.3.4.8, 14.2.3.4.9, 14.2.3.4.10, 14.2.3.4.11, and 14.2.3.5.1.

Abbreviations: chemo = chemotherapy; CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; OS = overall survival; PFS2 = second event of progression-free survival.

[a] Log-rank analysis performed by randomization strata of platinum status for ITT and Efficacy Populations.

[b] Cox proportional hazard method performed by randomization strata of platinum status for ITT and Efficacy Populations.

DCR

For the Efficacy Population, DCR was 66.4% in the rucaparib group (n=211; 95% CI, 59.5%- 72.7%) compared to 59.4% in the chemotherapy group (n = 96; 95% CI, 48.9%-69.3%), though this difference was not statistically significant (p=0.2057). A similar result was seen in the ITT Population: 63.4% (95% CI, 56.7%-69.7%) in the rucaparib group compared to 58.5% (95% CI, 48.5%-68.0%) in the chemotherapy group, p=0.3573.

PRO by EQ-5D

In the Efficacy Population, the EQ-5D-3L VAS scores remained relatively constant or slightly improved over time for both treatment groups. At baseline, the mean VAS score (± StD) was 68.9 (18.41) in the rucaparib group (n=204) and 67.7 (20.09) in the chemotherapy group (n=95). The mean VAS score for last value on treatment prior to the cut-off was 63.9 (20.75) in the rucaparib group and 65.7 (18.87), with the difference from chemotherapy in the rucaparib group (LS ± SE) being -2.1 (2.23, 95% CI, -6.5 to 2.3, p=0.3576).

Efficacy in BRCA mutation groups

The primary endpoint was further analyzed in relation to BRCA status as an exploratory endpoint using treatment-by-BRCA mutation type variable in the model (with treatment and BRCA mutation type as interaction terms).

As seen by the stratified Cox proportional hazard model (Table 15), the treatment effects across subgroups by gene (BRCA1, BRCA2) or mutation type were similar and not significant compared to the effect of study treatment on PFS. In contrast, a difference in treatment effect was seen for the BRCA reversion mutation. While the BRCA reversion mutation itself did not predict PFS (p=0.5123), it did affect

PFS in the context of response to study treatment between those with versus without BRCA reversion (p=0.0097).

Table 15. InvPFS by BRCA mutation type with treatment and BRCA mutation type as interaction terms – Treatment part (Efficacy and ITT Populations)

	P-value
Gene: BRCA1, BRCA2	
Efficacy Population	
Treatment	0.0104
BRCA1 vs BRCA2	0.7302
Treatment-by-BRCA1/2 Interaction	0.3952
ITT Population	
Treatment	0.0100
BRCA1 vs BRCA2	0.5569
Treatment-by-BRCA1/2 Interaction	0.6752

	P-value
Mutation Type: Germline, Somatic	
Efficacy Population	
Treatment	0.0009
Germline vs Somatic	0.4221
Treatment-by-Germline/Somatic Interaction	0.9986
ITT Population	
Treatment	0.0013
Germline vs Somatic	0.2802
Treatment-by-Germline/Somatic Interaction	0.8327
BRCA Reversion: Yes, No	
ITT Population	
Treatment	0.0010
BRCA Reversion (Yes vs No)	0.5123
Treatment-by-BRCA Reversion (Yes/No)	0.0097

Source: Table 14.2.3.5.1.
Abbreviations: BRCA = breast cancer gene 1 or 2; invPFS = investigator-assessed progression-free survival; ITT = intent-to-treat.
Note: The stratified Cox proportional hazard model was adjusted for the randomization strata for the progression-free interval after most recent platinum-containing therapy (ie, platinum-resistant, partially platinum-sensitive, or platinum-sensitive). It also includes a factor for treatment, BRCA mutation subgroup, and treatment-by-mutation subgroup.

- **Efficacy during the crossover part**

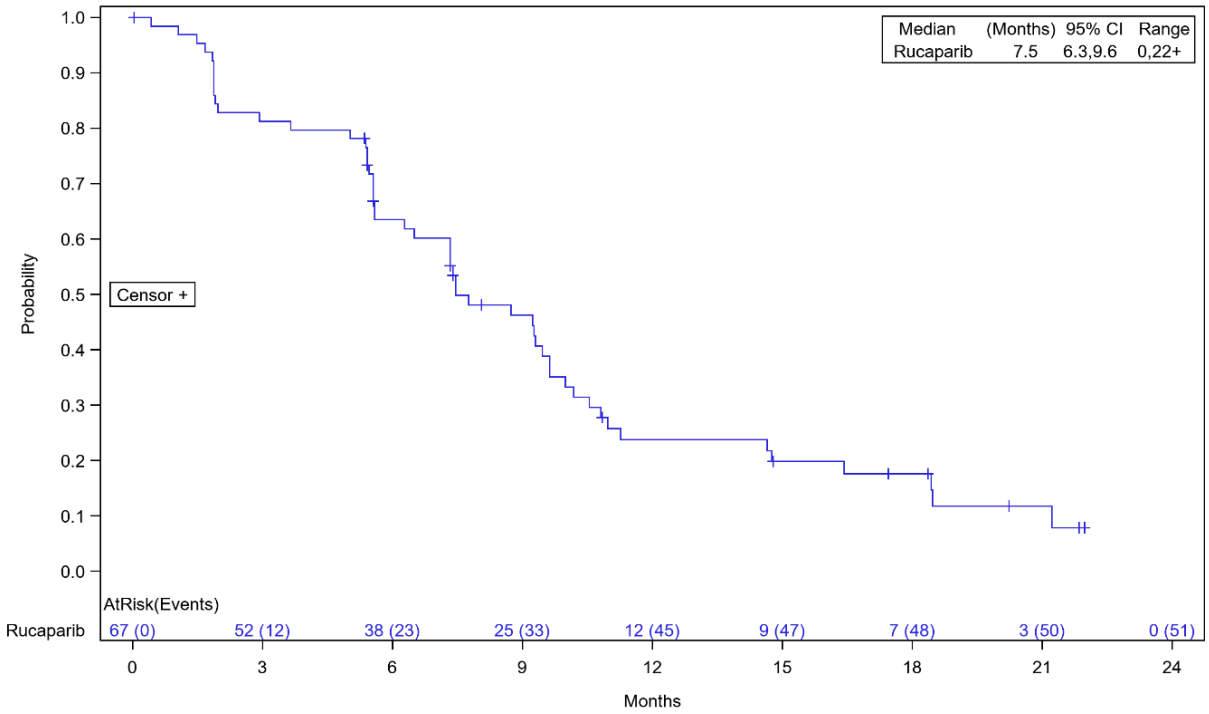
As explained above, patients in the chemotherapy arm who had evidence of disease progression were allowed to cross over to receive treatment with rucaparib in the Crossover Part of the study. Patients were re-baselined and assessed for invPFS, ORR, DCR and CA-125 response prior to starting rucaparib in the crossover part.

A total of 74/116 (64%) patients randomized to chemotherapy opted to cross over and receive rucaparib as of the visit cut-off date (30-Sept-2020). Of these patients, 67 were included in the efficacy analysis: the 7 patients excluded included 6 patients with a BRCA reversion mutation and 1 patient with non-BRCA status.

InvPFS (Crossover Part)

As shown in Figure 20 for the Efficacy Population, results were similar to those for the rucaparib group in the Treatment Part: the median invPFS was 7.5 months (95% CI, 5.6-9.5) for the Safety Population and 7.5 months (95% CI, 6.3-9.6) for the Efficacy Population in the Crossover Part, compared to 7.4 months (95% CI, 7.3-9.1) and 7.4 months (95% CI, 6.7-7.9) for the rucaparib group in the Efficacy and ITT Populations, respectively, in the Treatment Part.

Figure 20. PFS – Crossover Part (Efficacy Population)



Source: Figure 14.2.1.1.4.
Abbreviation: CI = confidence interval.

ORR (Crossover Part)

ORR was analyzed in the crossover part for patients with measurable disease at baseline. Results for the Efficacy Population are shown on table 16. A confirmed response of CR or PR was observed in 35.9% of patients in the Efficacy Population.

Table 16. ORR by RECIST v.1.1 – Crossover Part (Efficacy Population with Measurable Disease at Crossover Baseline)

	Rucaparib (N=64)
Confirmed Response Rate	
n (%)	23 (35.9)
95% CI	24.3% - 48.9%
Best Overall Confirmed Response, n (%)	
CR	2 (3.1)
PR	21 (32.8)
SD	25 (39.1)
Discontinued or PD	17
Ongoing with a single response	2
Ongoing without a response	6

	Rucaparib (N=64)
PD	10 (15.6)
NE	6 (9.4)

Source: Table 14.2.2.1.4.
Abbreviations: CI = confidence interval; CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; v = version.

DCR (Crossover Part)

DCR for the Efficacy Population in the Crossover Part was 73.4% (95% CI, 60.9%-83.7%). Of note, DCR for the Efficacy Population in the Treatment Part was 66.4% for the rucaparib arm.

ORR and/or CA-125 response (Crossover Part)

ORR by RECIST v1.1 and/or CA-125 was analyzed for patients treated with rucaparib in the Crossover Part, for those patients with measurable disease and/or CA-125 response evaluable at crossover baseline. Results are summarized in Table 17 (Efficacy Population).

Table 17. ORR by RECIST v1.1 and/or CA-125 – Crossover Part (Efficacy Population with Measurable Disease at Crossover Baseline and/or CA-125 Response Evaluable)

	Rucaparib (N=67)
Number of Patients with Measurable Disease at Crossover Baseline and/or CA-125 Response Evaluable at Crossover Baseline[a]	67
Confirmed Response Rate by either RECIST v1.1 and/or CA-125 Response, n (%)	36 (53.7)
95% CI	41.1% - 66.0%

Source: Table 14.2.2.3.4 and Table 14.2.2.1.4.
Abbreviations: CA-125 = cancer antigen-125; CI = confidence interval; RECIST = Response Evaluation Criteria in Solid Tumors; v = version.
[a] There were 43 CA-125 response-evaluable patients and 64 RECIST response-evaluable patients at crossover baseline in the Efficacy Population.

- **Subgroups analyses**

The primary efficacy endpoint of invPFS was analyzed by subgroup by randomization strata, age and race, for the Efficacy Population, as follows:

- By age (<65, 65-74; ≥75 years)
- By race (white, other race; unknown)
- Stratification factor used for randomization (platinum-resistant, partially platinum-sensitive, platinum-sensitive

invPFS by Age

In the Efficacy Population, patients in the <65 years (N=259) and 65-74 years (N=58) age groups showed a benefit from treatment with rucaparib compared to chemotherapy: stratified log-rank p=0.0144, median PFS of 7.4 (95% CI; 7.2, 5.8) months for rucaparib arm (N=181), 5.8 (95% CI; 5.5, 7.4) months for chemotherapy arm (N=78); and log-rank p=0.0048, median PFS of 10.5 (95% CI; 6.4, 14.6) months for rucaparib (N=33) and 4.1 (95% CI; 1.9, 7.6) months for chemotherapy arm (N=25), respectively. Nearly all of the patients in this study were in these age groups (97.5% in the Efficacy Population). For the remaining 8 patients 75 years or older (2.5%), median PFS was higher in the chemotherapy group (7.4 vs. 13.9 months), though this result was not statistically significant (log-rank p=0.9182). This subgroup was too small to reach any conclusion.

invPFS by Race

In the Efficacy Population, patients in the White race subgroup (N=308) showed a significant benefit with rucaparib treatment compared to chemotherapy (log-rank p=0.0007), with most patients in this study of White race (94.8% in the Efficacy Population). In non-White patients (Other Race) in the Efficacy Population, benefit was seen with rucaparib, though patient numbers were small, and the results are not significant (log-rank p=0.8084).

invPFS by Randomization Strata

As shown in Table 18, a benefit in PFS was seen in the Efficacy Population with rucaparib treatment as compared to chemotherapy in all of the randomization strata subgroups (platinum-sensitive, partially platinum-sensitive, and platinum-resistant). Patients in the partially platinum-sensitive subgroup (PFI ≥6 months to <12 months after last dose of platinum-based chemotherapy) (log-rank p=0.0002) had a statistically significant increase in median PFS in the rucaparib group of 8.0 months as compared to 5.5 months in the chemotherapy group (Figure 21). This platinum status subgroup comprised approximately one-third of the patients in this study.

Table 18. Median invPFS by Subgroup (Efficacy Population)

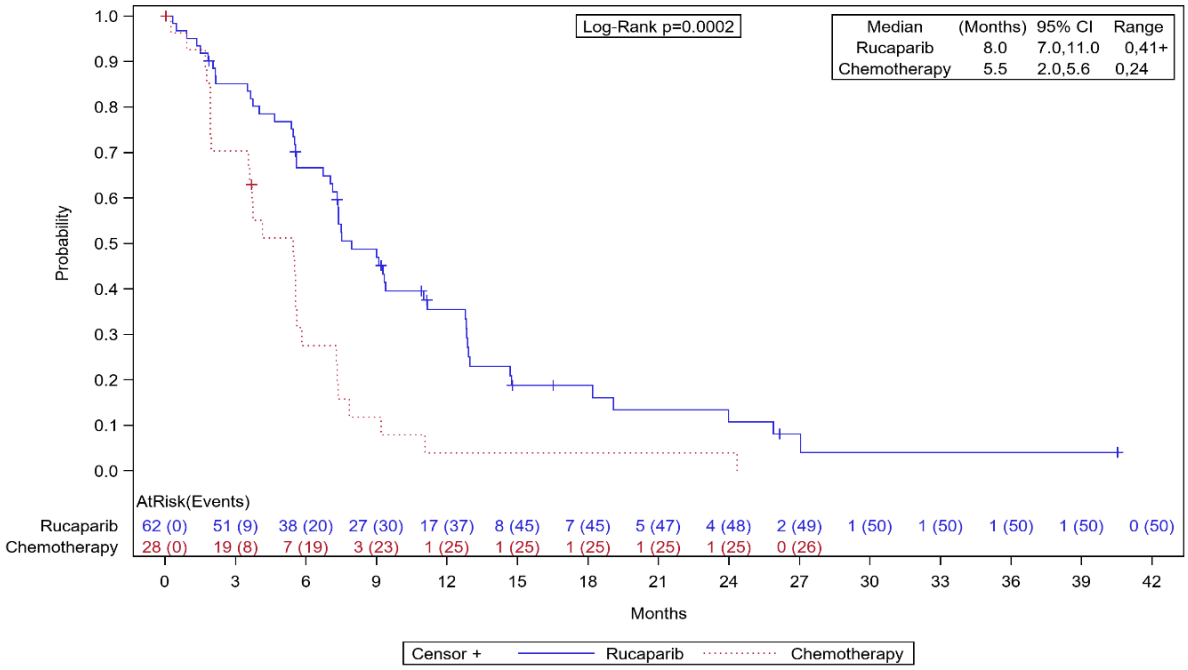
Population/ Subgroup	Rucaparib median PFS (95%CI), months	Chemotherapy median PFS (95%CI), months
Efficacy Population	N=220 7.4 (7.3, 9.1)	N=105 5.7 (5.5, 7.3)
Age		
< 65 yr	n = 181 7.4 (7.2, 8.6)	n = 78 5.8 (5.5, 7.4)
65-74 yr	n = 33 10.5 (6.4, 14.6)	n = 25 4.1 (1.9, 7.6)
≥ 75 yr	n = 6 7.4 (2.0, 27.7)	n = 2 13.9 (11.2, 16.7)
Race		
White	n = 206 7.4 (7.3, 9.2)	n = 102 5.7 (5.5, 7.3)
Other Race	n = 9 7.5 (0.9, 16.5)	n = 2 4.1 (NA, NA)
Unknown	n = 5 10.1 (2.9, 25.9)	n = 1 7.3 (NA, NA)
Stratification Factor Used for Randomization		
Platinum-Resistant	n = 110 6.4 (5.5, 7.4)	n = 51 5.7 (3.7, 7.3)
Partially Platinum-sensitive	n = 62 8.0 (7.0, 11.0)	n = 28 5.5 (2.0, 5.6)
Platinum-Sensitive	n = 48 12.9 (9.2, 14.8)	n = 26 9.6 (7.5, 15.4)

Source: Figure 14.2.1.1.8 (< 65 years old); Figure 14.2.1.1.9 (65-74 years old); Figure 14.2.1.1.10 (≥ 75 years old); Figure 14.2.1.1.11 (White race); Figure 14.2.1.1.12 (non-White race); Figure 14.2.1.1.13 (Unknown race); Figure 14.2.1.1.5 (Platinum-Resistant Strata); Figure 14.2.1.1.6 (Partially Platinum-Sensitive Strata); Figure 14.2.1.1.7 (Platinum-Sensitive Strata).

Abbreviations: CI = confidence interval; NA = not available; PFS = progression-free survival; yr = year.

As shown in table 18, patients in the platinum-resistant and platinum-sensitive randomization strata also showed a trend toward longer PFS with rucaparib treatment compared to chemotherapy, but results did not reach statistical significance.

Figure 21. Subgroup analysis of invPFS by Randomization Strata – Treatment part (Partially Platinum-Sensitive Efficacy Population)

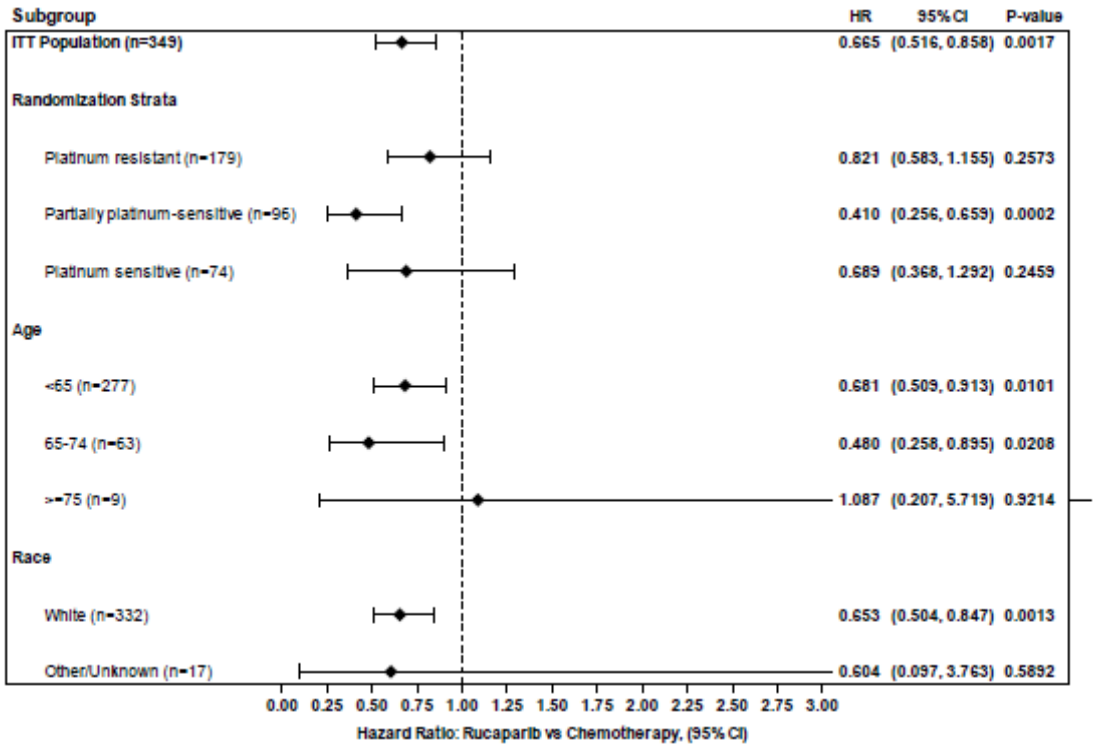


Source: Figure 14.2.1.1.6.

Abbreviation: CI = confidence interval; invPFS = investigator-assessed progression-free survival.

The Cox proportional hazard model showed similar results, with a significant benefit in PFS with rucaparib treatment compared with chemotherapy treatment in the partially platinum-sensitive subgroup (ITT Population): HR 0.410 (95% CI, 0.256-0.659; p=0.0002). There was a similar trend toward longer PFS with rucaparib treatment compared to chemotherapy in the platinum-resistant and platinum-sensitive subgroups, but results did not reach statistical significance (Figure 22).

Figure 22. Forest Plot of invPFS by Subgroup – Treatment Part (ITT Population)



Source: Table 14.2.1.1.2 (ITT), Table 14.2.1.1.3 (All Populations, Strata), Table 14.2.1.1.4 All Populations, Age), Table 14.2.1.1.5 (All Populations, Race).

Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat.

The stratified Cox proportional hazard model was adjusted for the randomization strata for the PFI after the most recent platinum-containing therapy (ie, platinum-resistant, partially platinum-sensitive, or platinum-sensitive).

The median time of invPFS for the ITT Population, within each of the randomization strata groups are described in Figures 23, 24 and 25.

Figure 23. Subgroup analysis of invPFS in ITT Population by randomization strata – Platinum Resistant

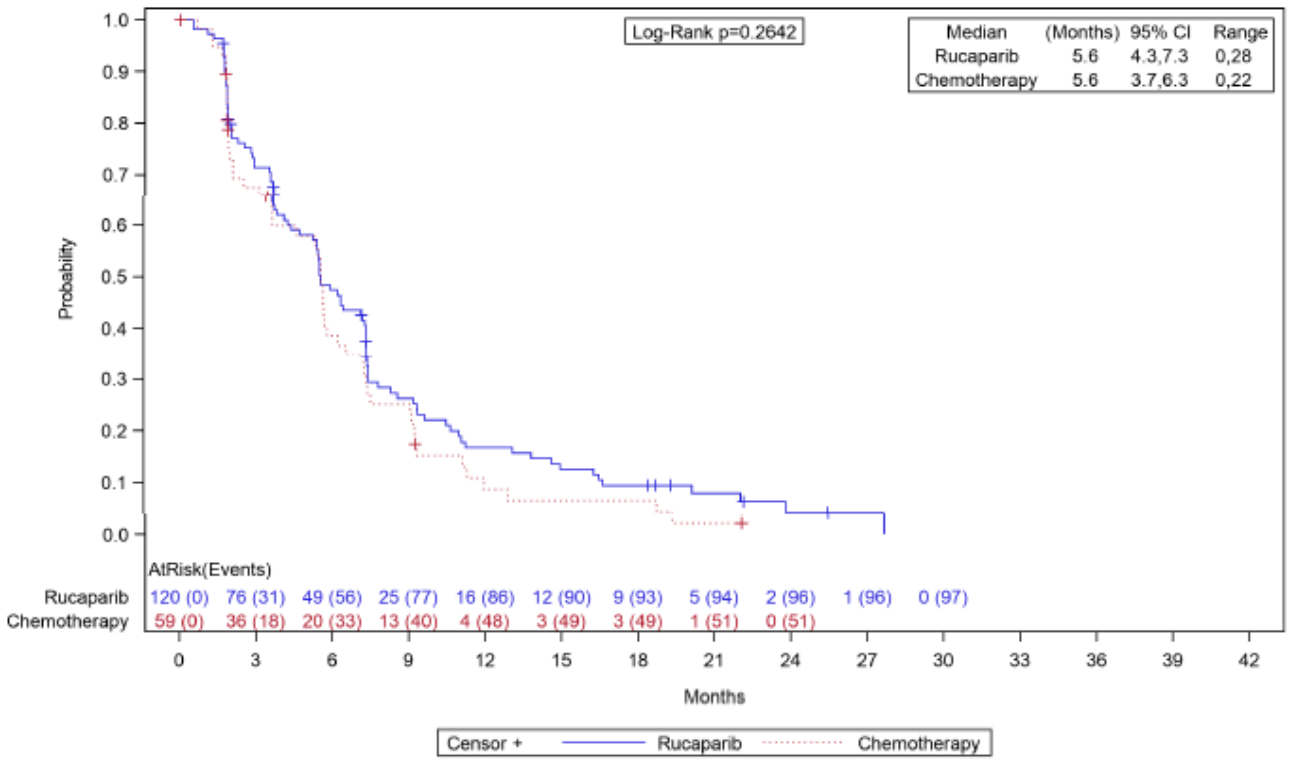


Figure 24. Subgroup analysis of invPFS in ITT Population by randomization strata – Partially Platinum Sensitive

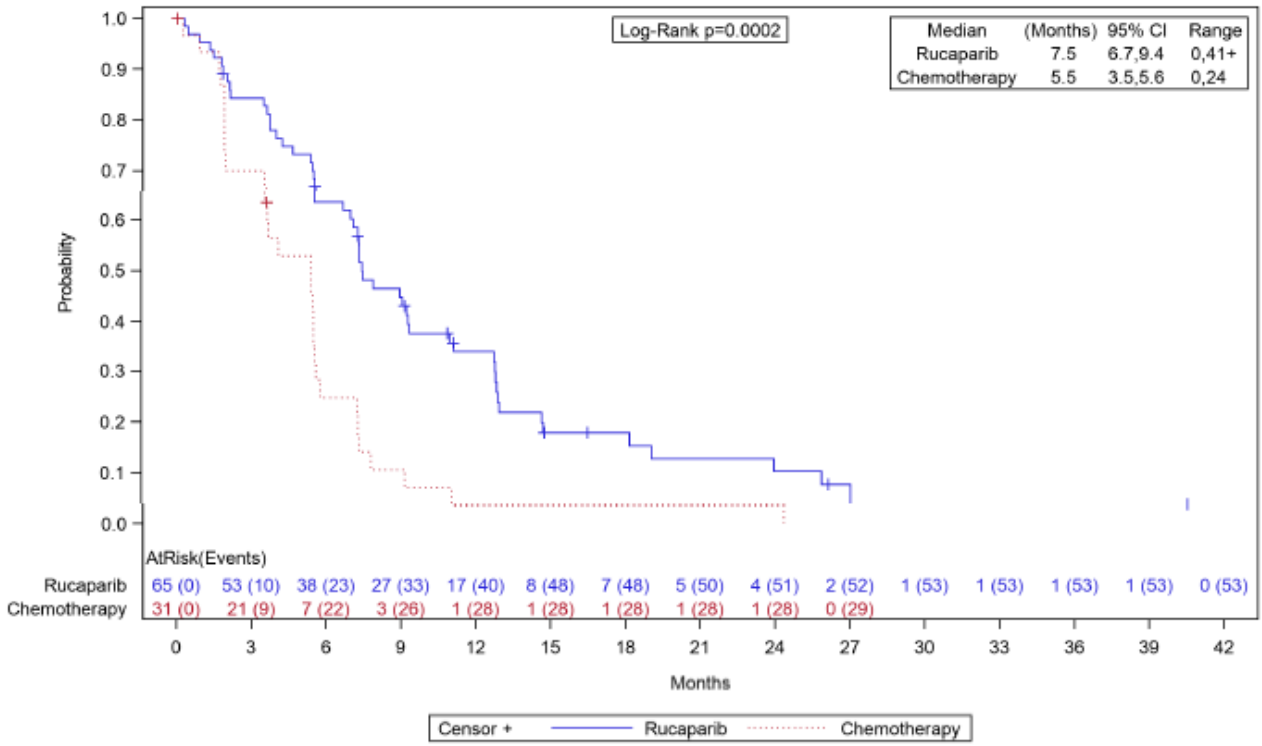
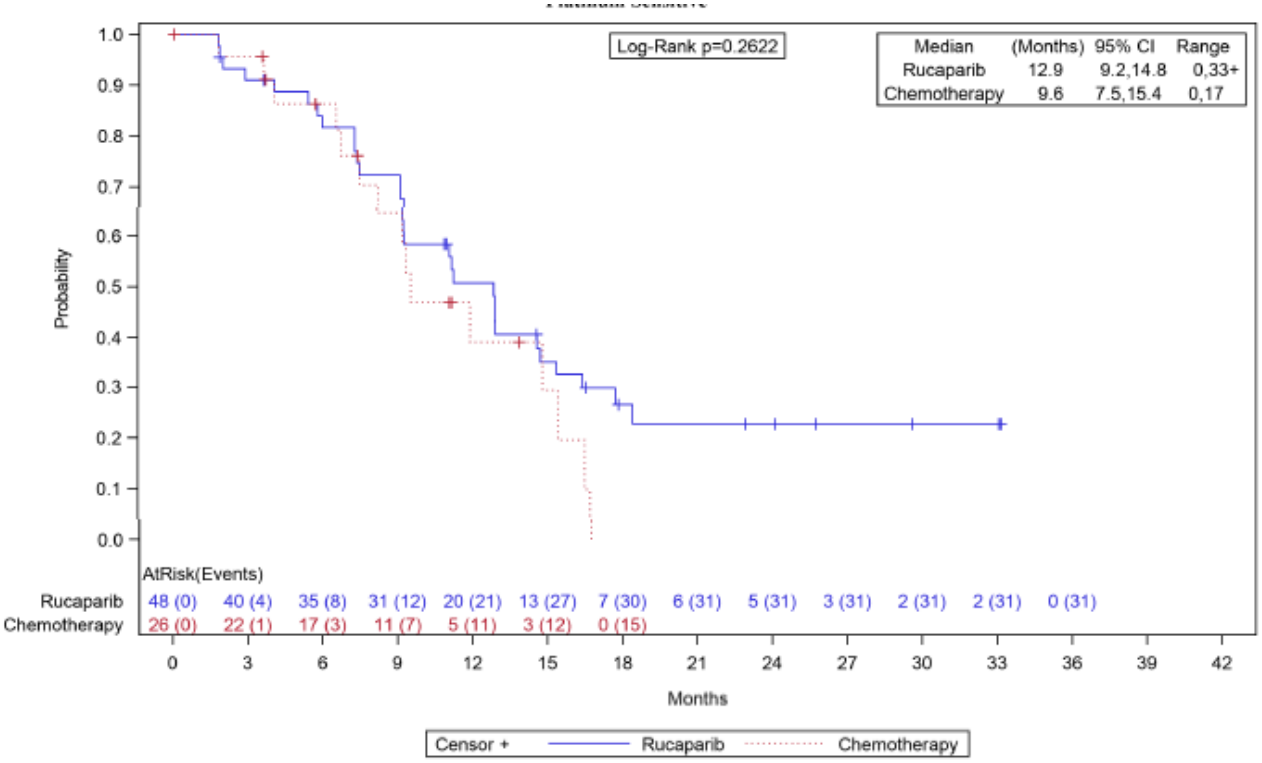
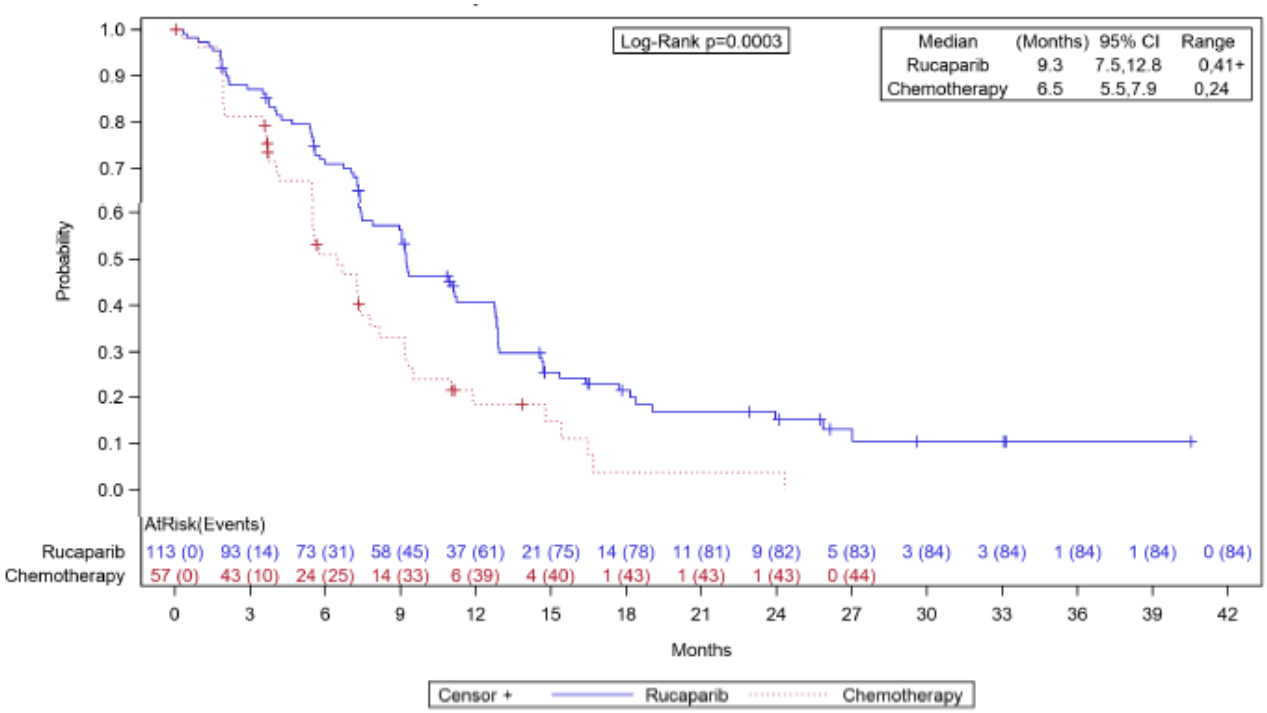


Figure 25. Subgroup analysis of invPFS in ITT Population by randomization strata – Platinum Sensitive



To better match the population included in the CMA, invPFS in patients from both the partially platinum sensitive and platinum sensitive subgroups is presented in Figure 26 below:

Figure 26. Subgroup analysis of invPFS in ITT Population by randomization strata – Partially Platinum Sensitive and Platinum Sensitive



Log-rank analysis performed by randomization strata for the progression free interval after most recent platinum containing therapy (i.e., platinum resistant, partially platinum sensitive, or platinum sensitive).
Data cutoff is 30Sep2020.

The Cox proportional hazard model of subgroup analysis of invPFS by randomization strata in the ITT Population for Partially Platinum Sensitive and Platinum Sensitive resulted in a estimated HR of 0.502 (95% CI; 0.343, 0.733), p-value=0.0004.

ORR by Platinum Sensitivity Status

An additional analysis was performed for ORR by platinum sensitivity status comparing rucaparib to the chemotherapy group, although it was not prespecified in the SAP.

Similar results were seen in both the Efficacy and ITT Populations in the 3 platinum sensitivity subgroups (table 19). Partially platinum-sensitive patients showed a statistically significant improvement in ORR when treated with rucaparib compared to chemotherapy (Treatment Part with measurable disease at baseline): 53.3% in the rucaparib group compared to 20.0% in the chemotherapy group in the Efficacy Population (p=0.0050); 50.8% vs. 21.4% in the ITT Population (p=0.0091). The ORR was comparable for rucaparib and chemotherapy in both the platinum-sensitive and platinum-resistant subgroups, though results did not reach statistical significance. Over half of platinum-sensitive patients achieved a confirmed response following treatment with either rucaparib or chemotherapy, and approximately one-quarter of patients in the platinum-resistant subgroup achieved a confirmed response to either treatment.

Table 19. ORR by Platinum Sensitivity Subgroup – Treatment Part (Efficacy and ITT Populations with Measurable Disease at Baseline)

Confirmed Response Rate	Rucaparib	Chemotherapy	P-value[a]	Rucaparib	Chemotherapy	P-value[a]
	Efficacy Population			ITT Population		
Partially Platinum-sensitive	N = 60	N = 25		N = 63	N = 28	
n (%)	32 (53.3)	5 (20.0)	0.0050	32 (50.8)	6 (21.4)	0.0091
95% CI, %	40.0 - 66.3	6.8 – 40.7		37.9 - 63.6	8.3 – 41.0	
Platinum-Sensitive	N = 44	N = 23		N = 44	N = 23	
n (%)	28 (63.6)	13 (56.5)	0.5733	28 (63.6)	13 (56.5)	0.5733
95% CI, %	47.8 - 77.6	34.5 - 76.8		47.8 - 77.6	34.5 - 76.8	
Platinum-Resistant	N = 107	N = 48		N = 117	N = 55	
n (%)	25 (23.4)	13 (27.1)	0.6199	25 (21.4)	13 (23.6)	0.7387
95% CI, %	15.7 - 32.5	15.3 - 41.8		14.3 - 29.9	13.2 - 37.0	

Source: Table 14.2.2.1.5 (platinum-resistant; Efficacy), Table 14.2.2.1.6 (partially platinum-sensitive; Efficacy), Table 14.2.2.1.7 (platinum-sensitive; Efficacy), Table 14.2.2.1.8 (platinum-resistant; ITT), Table 14.2.2.1.9 (partially platinum-sensitive; ITT), Table 14.2.2.1.10 (platinum-sensitive; ITT).
Abbreviations: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = intent-to-treat.
[a] The stratified CMH test was used to test the difference in proportions between treatments.

Subgroup Analysis by BRCA Mutation

The invPFS was further explored based on mutated BRCA gene and mutation status, as follows:

1. Mutated gene: BRCA1, BRCA2
2. Mutation status: germ line, somatic
3. BRCA reversion mutation

The invPFS was estimated by the Kaplan-Meier method; the median invPFS and stratified log-rank p-value are presented for the BRCA gene (BRCA1 or BRCA2), BRCA mutation status (germ line or somatic), and BRCA reversion mutation subgroups in Table 20.

In the Efficacy Population, rucaparib prolonged invPFS compared to chemotherapy in the BRCA1, BRCA2, germ line, and somatic mutation subgroups, each subgroup reaching statistical significance except for the somatic mutation subgroup: log-rank p=0.0129 (BRCA1), log-rank p = 0.0152 (BRCA2), log-rank p=0.0005 (germ line), log-rank p=0.2857 (somatic). In contrast, in the ITT Population, patients in the BRCA reversion subgroup, treatment with chemotherapy showed increased benefit compared to rucaparib (log-rank p=0.0301).

Table 20. Subgroup Analysis of invPFS by BRCA Mutation - Treatment Part

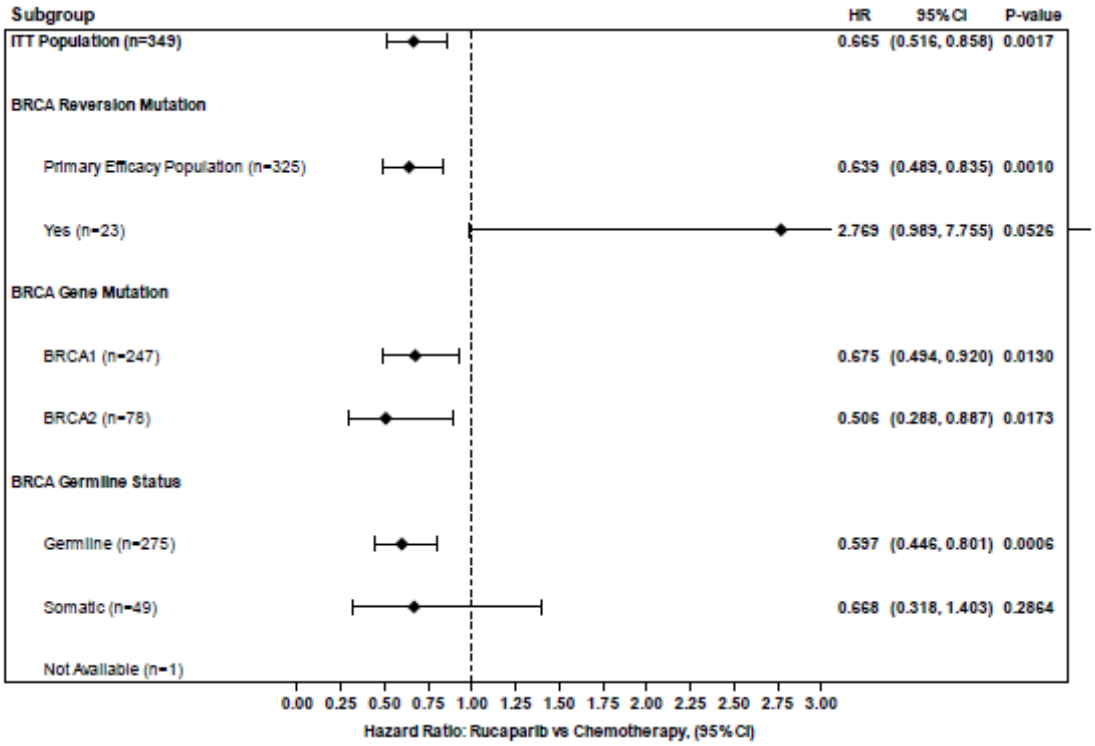
	Rucaparib median PFS (95%CI), months	Chemotherapy median PFS (95%CI), months
ITT Population	n = 233 7.4 (6.7, 7.9)	n =116 5.7 (5.5, 6.7)
BRCA Reversion - ITT	n = 13 2.9 (1.8, 4.2)	n = 10 5.5 (1.9 6.6)
Mutated Gene – Efficacy Population		
BRCA1	n = 173 7.4 (7.2, 9.1)	n = 74 5.7 (4.7, 7.4)
BRCA2	n = 47 8.3 (6.5, 16.3)	n = 31 5.6 (4.1, 7.9)
Mutation Status – Efficacy Population		
Germline	n = 187 7.4 (7.3, 9.2)	n = 88 5.7 (4.1, 7.3)
Somatic	n = 33 7.5 (5.6, 11.2)	n = 16 7.3 (1.8, 9.3)

Source: Figure 14.2.1.1.16 (BRCA1); Figure 14.2.1.1.17 (BRCA2); Figure 14.2.1.1.18 (Germline); Figure 14.2.1.1.19 (Somatic); Figure 14.2.1.1.14 (BRCA Reversion).

Abbreviations: BRCA = breast cancer gene 1 or 2; CI = confidence interval; invPFS = investigator-assessed progression-free survival; ITT = intent-to-treat.

Consistent results were seen for the invPFS analyses using the Cox proportional hazard model, presented for each BRCA gene (BRCA1, BRCA2), BRCA reversion (yes [ITT Population], no), and mutation status (germ line, somatic) subgroup in a Forest Plot in Figure 27.

Figure 27. Forest Plot of invPFS by BRCA Gene and Mutation Status – Treatment Part (ITT Population)



Source: Table 14.2.1.1.2 (ITT), Table 14.2.1.1.8 (All Populations; BRCA1,2), Table 14.2.1.1.9 (All Populations; Germline, Somatic), and Table 14.2.1.1.6 (ITT Population with BRCA Reversion; BRCA Reversion).

Abbreviations: BRCA = breast cancer gene 1 or 2; CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat.

- **Analyses performed across studies**

As introduced at the beginning of this report, the efficacy of rucaparib was initially investigated in 106 patients based on a pooled efficacy population from 2 multicenter, single-arm, open-label clinical studies, Studies CO-338-010 and and CO-338-017, in patients with advanced BRCA-mutant EOC, FTC or PPC who had progressed after 2 or more prior chemotherapies (the primary efficacy population). As a result of this assessment, a CMA was granted in 2018 and the already ongoing Study CO-338-043 (ARIEL 4) was selected to provide confirmation of the positive benefit-risk of rucaparib in this setting.

The baseline characteristics of the patient population included in ARIEL 4 are considered comparable to those from the pooled efficacy population assessed in the initial application. The median age of rucaparib-treated patients in Study CO-338-043 was 58 years (range, 38-81) versus 59 years (range, 33-84) in Studies CO-338-010 and CO-338-017. The majority of patients were White (94% versus 78%), and had an ECOG performance status of 0 (54% versus 61%) or 1 (46% versus 39%). The median time since cancer diagnosis was 43 months (range, 13-185) in rucaparib-treated patients in Study CO-338-043 versus 52 months (range, 6-197) in Studies CO-338-010 and CO-338-017; 42.5% (versus 61.8%) had received 3 or more prior lines of chemotherapy, and 57.5% (versus 38.7%) had received 2 prior lines of chemotherapy. The median PFI was 5.6 months (range, 1.1-67.4) versus 7.9 months (range, -0.7-116.4).

Study CO-338-043 included a similar proportion of rucaparib-treated patients in the randomization stratum of platinum-sensitive (PFI >12 months) compared with the pooled efficacy population of Studies CO-338-010 and CO-338-017 with PFI >12 months (20.6% versus 22.6%). While there were fewer patients in the randomization stratum of partially platinum-sensitive (PFI ≥6 -12 months) in Study CO-338-043 than patients with PFI ≥6 -12 months in Studies CO-338-010 and CO-338-017 (27.9% versus 51.9%), and a higher proportion of patients in the randomization stratum of platinum-resistant (PFI ≥1 to <6 months) in Study CO-338-043 than patients with PFI <6 months in Studies CO-338-010 and CO-338-017 (51.5% versus 25.5%), the proportion of patients from the combined randomization strata of platinum-sensitive (PFI >12 months) and partially platinum-sensitive (PFI ≥6-12 months) represented half of the patients in Study CO-338-043, and matches the population in the approved treatment indication.

The primary efficacy endpoint of Studies CO-338-010 and CO-338-017 was ORR as assessed by the investigator according to RECIST version 1.1. An analysis of PFS was also performed although comparison of the results is difficult to interpret due to the single-arm design of these studies. A tabular comparison of efficacy data is displayed below (Table 21):

Table 21. Comparison of Efficacy Data by Platinum-free Interval in Pooled Efficacy Population (Studies CO-338-010 and CO-338-017) versus Study CO 338-043

	Pooled Efficacy Population, Studies CO-338-010 and CO-338-017			ITT Population Rucaparib-Treated, Study CO-338-043		
	Platinum-sensitive (PFI > 12 months)	Partially Platinum-sensitive (PFI ≥ 6 to 12 months)	Platinum-resistant (PFI > 2 to < 6 months)	Platinum-sensitive (PFI > 12 months)	Partially Platinum-sensitive (PFI ≥ 6 to 12 months)	Platinum-resistant (PFI > 1 to < 6 months)
invPFS						
Patients, n	24	55	20	48	65	120
PFS events, n (%)	18	42	16	31	53	97
PFS, median in months[a] (95% CI)	12.8 (10.5-22.8)[b]	9.2 (6.9-12.5)[c]	9.3 (7.2-11.0)[d]	12.9 (9.2-14.8)	7.5 (6.7-9.4)	5.6 (4.3-7.3)
ORR						
Patients, n	24	55	20	44	63	117
n (%)	17 (70.8)	34 (61.8)	7 (35.0)	28 (63.6)	32 (50.8)	25 (21.4)
95% CI, %	48.9-87.4	47.7-74.6	15.4-59.2	47.8-77.6	37.9-63.6	14.3-29.9
DOR						
Median (months)[a] (95% CI)	12.6 (7.6-23.3)[e]	8.9 (5.6-12.9)[f]	6.4 (3.7-not achieved)[g]	10.8 (7.4-16.6)	9.2 (5.6-11.1)	9.4 (5.6-18.5)

Sources: Figure 2.7.3.1.1, Figure 2.7.3.1.2, Figure 2.7.3.1.3, Figure 2.7.3.2.1, Figure 2.7.3.2.2, Figure 2.7.3.2.3, CO-338-043 Efficacy Supporting Data; Table 2.34.1, Table 2.35.1, Figure 2.12.2, Figure 2.7.3.7 Day 120 ISE; Table 14.2.2.1.8, Table 14.2.2.1.9 and Table 14.2.2.1.10, CO-338-043 CSR.

Abbreviations: CI = confidence interval; CSR = clinical study report; DOR = duration of response; invPFS = investigator-assessed progression-free survival; ISE = integrated summary of efficacy; ITT = intent-to-treat; ORR = objective response rate; PFI = progression-free interval; PFS = progression-free survival; SmPC = Summary of Product Characteristics.

[a] Months were calculated as number of days divided by 30.4375.

[b] Median PFS - Days (95% CI): 391 (319-693) (Figure 2.12.2, Day 120 ISE).

[c] Median PFS - Days (95% CI): 279 (210-381) (Figure 2.12.2, Day 120 ISE).

[d] Median PFS - Days (95% CI): 282 (218-335) (SmPC, Section 5.1).[4]

[e] Median DOR - Days (95% CI): 382.5 (232-709) (Figure 2.7.3.7, Day 120 ISE).

[f] Median DOR - Days (95% CI): 270 (169-392) (Figure 2.7.3.7, Day 120 ISE).

[g] Median DOR - Days (95% CI): 196 (113-not achieved) (SmPC, Section 5.1).[4]

In order to compare more directly against data supporting the currently approved treatment indication, ORR, DOR, and PFS in Study CO-338-043 were analyzed for the platinum-sensitive (PFI ≥6 months) patients in the ITT population in Table 22, combining the patients from randomization strata: platinum-sensitive (PFI >12 months) and partially platinum-sensitive (PFI ≥6-12 months). In the platinum-sensitive (PFI ≥ 6 months) population in Study CO-338-043, the ORR by investigator review was 56.1% (95% CI, 46.1-65.7) versus 64.6% (95% CI, 53.0-75.0) in the platinum-sensitive pooled efficacy population from Studies CO-338-010 and CO-338-017 (SmPC, Section 5.1), with a median DOR of 9.4 months (95% CI, 7.4-11.1) versus 9.7 months (95% CI, 7.4-12.9; SmPC, Section 5.1).

Table 22. Comparison of Efficacy Data in Rucaparib-Treated Platinum-Sensitive Patients (PFI ≥6 months) in Pooled Efficacy Population (CO-338-010 and CO-338-017) versus CO-338-043

Efficacy Analysis	Platinum-sensitive (PFI ≥ 6 months) Subgroup	
	Studies CO-338-010 and CO-338-017	Study CO-338-043[d]
	N = 79	N = 107
Median PFS (95% CI, [months])[a]	10.9 (8.4-12.8)[b]	9.3 (7.5-12.8)
ORR N (%) (95% CI)	51 (64.6) (53.0-75.0)	60 (56.1) (46.1-65.7)
CR	10.1%	5.6%
PR	54.4%	50.5%
Median DOR (95% CI [months])	9.7 (7.4-12.9)[c]	9.4 (7.4-11.1)

Sources: Figure 2.7.3.1.4, Figure 2.7.3.2.7, Table 2.7.3.3.1, CO-338-043 Efficacy Supporting Data; SmPC, Section 5.1.[4]

Abbreviations: CI = confidence interval; CR = complete response; DOR = duration of response; ORR = objective response rate; PFI = progression-free interval; PFS = progression-free survival; PR = partial response; SmPC = Summary of Product Characteristics.

[a] Investigator-assessed PFS.

[b] Median PFS Days (95% CI): 332 (255-391) (SmPC, Section 5.1).[4]

[c] Median DOR - Days (95% CI): 294 (224-393) (SmPC, Section 5.1).[4]

[d] The platinum-sensitive (PFI ≥ 6 months) population in Study CO-338-043 includes patients stratified as partially platinum-sensitive (PFI ≥ 6 -12 months) and platinum-sensitive (PFI > 12 months).

According to the MAH, the results from Study CO-338-043 in the platinum-sensitive (PFI ≥6 months) population were consistent with, and provide confirmation of the pooled efficacy data from Studies CO-338-010 and CO-338-017, that formed the basis of the conditional approval in platinum-sensitive patients with a BRCA mutation (germline or somatic) who have received ≥2 prior chemotherapy regimens.

6.3. Discussion

Submission of results from study CO-338-043 (ARIEL 4) was imposed as a specific obligation (SOB) during the initial CMA assessment because, as a randomized trial in a similar setting, it was likely to provide comprehensive clinical data to further confirm the safety and efficacy of rucaparib in the treatment of platinum sensitive, relapsed or progressive, BRCA mutated (germ line and/ or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer (as included in Annex II). As explained in the EPAR, clinical evidence at the time of granting the CMA was limited, but an unmet medical need was established in patients who could not further tolerate platinum treatment, also taking into account that an oral treatment could improve patient's convenience.

The initial conditional authorisation was based on pooled population subgroup (n=106) data from two Phase 2 open label studies (Study CO 338 010 [Study 10] and Study CO 338 017 [ARIEL2]), which included adult patients with ovarian cancer who received 2 or more previous lines of chemotherapy and whose tumours had a deleterious mutation (germline or somatic) in BRCA1 or BRCA2.

Study CO-338-043 is an ongoing phase 3, open-label, multicenter, randomized study of rucaparib versus chemotherapy in patients with relapsed, BRCA-mutant, high-grade epithelial serous or Grade 2 or 3 endometrioid ovarian, fallopian tube, or primary peritoneal cancer.

Design and conduct of the trial

This is an open-label study, as the investigational treatment (rucaparib) and the comparator (chemotherapy) differ in their route of administration, thus lack of blinding of the study is acknowledged. The study is comprised by three phases: screening and randomization, treatment and post-treatment/crossover phase, where patients initially randomized to chemotherapy had the option to cross over to rucaparib treatment following progression.

Overall, inclusion and exclusion criteria appear acceptable. Patients should have received two or more prior chemotherapy regimens, including a platinum in at least one of them; and have relapsed or progressive disease confirmed by radiologic assessment. Patients should have a deleterious BRCA 1/2 mutation as confirmed by the central lab, although subjects could be enrolled based on local lab assessment provided there was tumour tissue available for the central confirmation. Patients who had received any previous PARP inhibitor and/or single-agent paclitaxel or nab-paclitaxel were excluded. As opposed to the initial application pooled efficacy population, platinum resistant patients (disease progression had occurred between 4 weeks and 6 months after previous platinum treatment) could be recruited and not only platinum sensitive patients (i.e. fully platinum sensitive and partially platinum sensitive patients).

Randomization (2:1) was stratified based on the time to progression following the last dose of platinum containing therapy: platinum-resistant (PFI ≥1 to <6 months); partially platinum sensitive (PFI ≥6 to <12 months); and platinum-sensitive (PFI ≥12 months). At the time of the CMA, the MAH was recommended (REC 8) to amend the protocol to ensure that, at least, 270 partially platinum-sensitive patients were enrolled in this study to confirm the positive benefit-risk of rucaparib in this population. During annual renewal procedure EMEA/H/C/004272/R/0016, the MAH alleged that, due to the increasing

availability of PARP inhibitors, recruitment had slowed down and that amendment to the protocol would prevent them from fulfilling SOB001 on the due date. This was accepted by the CHMP albeit it was made clear that the study was not powered to detect the treatment effect individually for each subgroup.

Patients in the rucaparib arm received the 600 mg BID currently approved dosage in 28-days cycles. In the control arm, patients could receive weekly paclitaxel (platinum-resistant and partially platinum-sensitive) or, by investigator choice, platinum monotherapy or doublet (platinum-sensitive), up to 8 cycles. The comparator seems appropriate although other options for platinum-resistant subjects could have been explored such as PLD, gemcitabine or topotecan, but none of them have shown superiority. Platinum-based doublets could have been a treatment option for partially platinum sensitive patients but, as the approved indication for rucaparib is restricted to patients who are not further candidates to receive platinum treatment, weekly paclitaxel seems to be an adequate comparator for this subgroup in Study CO-338-043. This said, the fact that patients with fully platinum sensitive disease were randomized to received platinum therapy renders the subgroup of study patients with platinum-sensitive disease included in ARIEL4 not identical to the approved indication with platinum-sensitive patients who are unable to tolerate further platinum-based therapy; see further comments below.

The study design was subject to different changes. A first amendment to the original protocol was issued on 11-Jan-2018, with around 100 subjects enrolled, where PFS by RECIST v1.1 as assessed by Independent Radiology Review (irrPFS) was included as the key secondary endpoint, first to be tested, followed by OS and, then, the rest of secondary endpoints. By Amendment 2, dated 23-Oct-2020, irrPFS and OS were removed from the hierarchical step down testing procedure and were defined as stand-alone secondary endpoints. This protocol update was performed after the data cut-off (i.e. 30-Sep-2020), with enrolment complete, which called into question the integrity of the study, particularly in the context of an open-label trial, since it could not be ruled out that the changes were data-driven. Upon request, the MAH provided an outline of the events/changes that occurred after the needed number of events for the main endpoint analysis was reached. In this description it was highlighted that the Sponsor was only unblinded in December 2020 so that they did not have access to individual results and treatment allocation data at the time when Amendment 2 was being prepared. The only SAP version for this study (dated 28-Oct-2020) was also finalized after the database lock, at the same time that Amendment 2. Amendment 2 re-defined the primary analysis population and established the Efficacy Population (excluding patients with a BRCA reversion mutation) as the primary efficacy analysis population and the ITT Population as the one to be tested, for each endpoint, if the first one was statistically significant; as part of an step-down testing procedure. The included changes were supported by available literature that identified reversion mutations as an important mechanism of acquired resistance to PARP inhibitors and even to platinum agents (as DNA-damaging chemotherapy) as these mutations seemed to partly restore wild-type gene function. In any case, no relevant efficacy differences have been identified between the 'efficacy' and 'ITT' population, probably due to the fact that they only differ in 23 subjects and in fact the original protocol already stated that these patients would be excluded from the main efficacy analyses.

The fact that no (secondary) analysis of PFS by blinded independent committee review (BICR; IRR as referred by the MAH) was submitted constitute a limitation, see below. For pathologies like ovarian cancer with frequent non-target lesions and diffuse intraperitoneal spread patterns, centralized independent confirmation of PFS is of particular relevance, moreover in the context of an open label study. At the very least irrPFS results from an 'audit' sample to assess/confirm concordance would have been expected. The primary efficacy endpoint is PFS by RECIST v.1.1 as assessed by the investigator. The secondary endpoints ORR, DOR, ORR and/or CA-125 response and PRO were part of a hierarchical step-down testing procedure, in order to preserve the overall Type 1 error rate. PFS as assessed by a BICR and OS are defined as stand-alone secondary efficacy endpoints in the current version of the protocol. According to the SAP (latest version), PFS by BICR was not required to be performed at the time of the initial CSR, therefore it was not tested and its results are not available.

Efficacy data and additional analyses

Up to the visit cut-off date (30-Sep-2020), 349 patients were randomized (ITT Population) to receive rucaparib (N=233) or chemotherapy (N=116). For the Efficacy Population, 220 and 105 subjects remained in the rucaparib and chemotherapy treatment arms, respectively. At the DCO, 188 (80.7%) subjects from rucaparib arm and 108 (93.1%) subjects from chemotherapy arm had discontinued treatment, most of them (70.7% vs. 54.4%) due to disease progression by RECIST v.1.1. Also, 7.4% patients in the rucaparib arm and 2.8% in the chemotherapy arm discontinued treatment due to clinical progression. The fact that around 30% more patients discontinued due to radiological disease progression in the rucaparib arm as compared to the chemotherapy arm could be due to certain number of subjects in the chemotherapy arm who may have progressed after receiving the maximum number of treatment cycles, while rucaparib is given until progression.

Regarding baseline characteristics, in general, they seemed to be well balanced between both treatment arms except for ECOG performance status and age groups, i.e. slightly younger patients were included in the rucaparib arm and patients in chemotherapy arm had a relatively better ECOG PS. These differences are however not expected to have a relevant impact on the reported results. Most patients had measurable disease at baseline per the investigator (96.1% rucaparib, 91.4% chemotherapy), for whom ORR and DOR have been tested. Nearly all patients had epithelial ovarian cancer (94.4% rucaparib; 95.7% chemotherapy), with the remainder approximately evenly split between fallopian tube and primary peritoneal cancer, and most patients had serous histology (89.3% rucaparib; 90.5% chemotherapy).

As already said, randomization was stratified by PFI; however, there were no restrictions on how many patients could be enrolled in each PFI stratum. For the ITT Population, 20.6% of rucaparib patients and 22.4% of chemotherapy patients were in the platinum-sensitive stratum; 27.9% of rucaparib patients and 26.7% of chemotherapy patients were in the partially platinum-sensitive stratum, and 51.5% of rucaparib patients and 50.9% of chemotherapy patients were included in the platinum-resistant randomization stratum. Regarding BRCA mutation status, 74.5% of patients in the ITT Population presented BRCA1 gene mutation while BRCA2 mutation was identified in 25.2% of patients. Eighty four percent of patients in the ITT Population had germline BRCA mutation.

The study met its **primary endpoint**. A statistically significant improvement in **invPFS** was reported with rucaparib treatment compared with chemotherapy (HR 0.639 [95% CI, 0.489-0.835]; p=0.0010) in the Efficacy Population. The estimated median invPFS was 7.4 months (95% CI, 7.3-9.1) for the rucaparib group compared to 5.7 months (95% CI, 5.5-7.3) for the chemotherapy group. Comparable results were seen in the ITT Population, with a point estimate HR of 0.665 (95% CI, 0.516-0.858), p=0.0017. Prespecified sensitivity analyses for the primary endpoint were performed to evaluate the impact of censored patients and results confirmed what had been observed for the primary analysis.

Regarding **secondary endpoints**, a higher confirmed **ORR**, as assessed by the investigator, was observed in the rucaparib group (40.3%, 95% CI 33.6%-47.2%) as compared to the chemotherapy group (32.3%, 95% CI 23.1%-42.6%), however this difference was not statistically significant (p=0.1287) so, per the ordered step-down procedure, statistical significance cannot be claimed for the subsequent endpoints and they are considered descriptive. For ORR in the ITT Population, similar results were observed, with an ORR in the rucaparib treatment group of 37.9% (95% CI, 31.6%-44.7%) compared to 30.2% (95% CI, 21.7%-39.9%) in the chemotherapy group. Focusing on DOR, similar results were seen for both populations, with a longer duration of response reported in the rucaparib group compared to the chemotherapy group: 9.4 vs. 7.2 months for the rucaparib and chemotherapy arms, respectively, in the Efficacy Population. The proportion of patients with a confirmed RECIST v1.1 response and/or CA-125 response were also higher for the rucaparib arm (50.7% vs. 43.6%) in the Efficacy Population.

Out of the hierarchical step-down testing procedure, **PFS by BICR** was not tested (see comments above). Since scans were collected for review, the MAH was requested to provide the results of the analysis of PFS by BICR for both the Efficacy and ITT Populations, bearing in mind the open-label nature of the study and the particular nature of the disease. It is acknowledged that some discrepancies between investigator and BICR-assessed PFS have been reported in the literature in trials where PARP inhibitors are used, but, as stated above, at the very least an audit sample to confirm the concordance between both PFS assessments would have been expected. Results from this analysis were expected to be provided at the time of the final OS analysis, which was projected to occur later this year. However, in view that the MAH had requested to remove the 'treatment' indication (see additional information below), no further efficacy data from the ARIEL4 study was formally requested.

At the time of the data cut-off, an IA of OS was performed, when 51% of the planned events had occurred. The final OS analysis was planned, per the SAP, when 70% maturity would have been reached, i.e. 245 events of death are needed within the 349 randomized patients.

Regarding **OS** results, at the time of the IA, in the Efficacy Population, the median OS was 19.6 months (95% CI, 16.8-24.0) in the rucaparib group compared to 27.1 months (95% CI, 22.2-38.1) in the chemotherapy group, with a HR of 1.55 (95% CI, 1.085-2.214), p=0.0161. Similar results were observed for the ITT Population (median OS was 18.8 months for the rucaparib group vs. 25.9 months for the chemotherapy group; HR 1.484 [95% CI, 1.069-2.061]). While statistical significance was not reached, a clear benefit seems to be observed with chemotherapy over rucaparib. The MAH argues that at the time of the IA OS data were still immature, but this analysis was performed with a 51% of data maturity when the final OS analysis was planned with 70% of events, so data do not seem so immature. It appears thus unlikely that these results may change with longer follow up. The MAH initially provided a *post-hoc* OS analysis excluding patients who crossed over to rucaparib (not included in this report). However, the reported OS results are not likely to be explained only by cross-over since cross-over would rather be expected to lead to a convergence of the OS results in the two groups. Further, the presented analyses of patients not crossing over likely represents a removal of the subset of patients in the control arm that are most fit and have the best prognosis which hampers interpretation. It was considered during the first round of this procedure that conducting additional analyses using alternative methods could be helpful to adjust for this crossover even if they are not devoid of limitations as they rely on underlying (strong) assumptions and would only be considered as supportive. Reference was made to the following EMA guidance: "Question and answer on adjustment for cross-over in estimating effects in oncology trials (EMA/845963/2018)". No analyses according to this guideline were however submitted by the MAH. Instead, the MAH considered that as a result of the cross-over, three distinct non-crossing survival curves can be observed and that employing a time-adjusted Cox Proportional Hazards model is appropriate to further explore the confounding OS results. This method has been applied for the ITT, the Efficacy Population and the platinum status subgroups. There are 2 factors which assess the treatment effect in this model: the Z fixed factor for the randomisation to the control arm and the time-dependent X factor for the exposure to rucaparib at any time. This approach has several methodological concerns and would need to be supplemented with a series of analysis with and without the fixed Z factor and the use of covariates, in particular including those measuring the patient status and the severity of the disease at crossover. This will give a range of scenarios, which could be helpful for the understanding of the crossover on the OS. Bearing in mind all the above, the MAH was referred again to the above mentioned EMA guidance and was asked to provide further analyses. Additional analyses were submitted. However, even though some of the sensitivity analyses displayed non-negative OS results with regards to the effect of rucaparib over the chemotherapy arm, there were several concerns in terms of the methods used (relying on strong assumptions) that do not allow to conclude that a detrimental effect on OS can be ruled-out. In addition, as the number of patients in the control arm is small, it was considered that baseline covariates might have impacted the results and the MAH was asked to perform a multi-variate analysis modelling the impact of different baseline/prognostic factors on OS. Results from the full model

are however not interpretable due to its complexity and the inclusion of too many variables so it only can be seen as an hypothesis generating analysis. To better clarify the weight of possible imbalances in the baseline demographics and disease characteristics in these unexpected OS results, the MAH was requested to provide tabular summaries of these baseline demographics and disease characteristics at the time of randomization for three different subgroups of patients: patients randomized to rucaparib, patients randomized to chemotherapy who crossed over to rucaparib after progression, and patients from the chemotherapy arm who did not cross over. These data were provided and no relevant differences were identified between groups that could justify the observed findings in OS. In addition, further information on patients who crossed-over to the rucaparib arm was also requested. According to the MAH, the reasons why eligible patients did not cross over to rucaparib were not collected. However, since there were only 13 (14%) patients who did not cross-over, the influence of bias due to these patients not switching at progression is expected to be limited.

PFS2 results have also been provided as an exploratory endpoint. Up to the data cut-off date (30 Sept 2020), a total of 200 (57.3%) patients received subsequent anti-cancer treatment, 115 (49.4%) in the rucaparib arm and 85 (73.3%) in the placebo arm. No statistically significant differences were observed in either the Efficacy population (HR 0.903 [95% CI, 0.676-1.207]) and the ITT Population (HR 0.925 [95% CI, 0.703-1.216]). PFS2 data by stratification subgroups were also provided.

As already outlined, **subgroup analyses** by stratification strata are especially relevant in the context of the purpose of this procedure: confirming rucaparib efficacy for 3L treatment of platinum-sensitive patients who are unable to tolerate further platinum based chemotherapy. During the CMA assessment, efficacy of rucaparib was established in a pooled population of 106 BRCA mutated patients who had receive ≥2 previous treatment lines where almost 74% of subjects had a PFI ≥6 months (considered as platinum-sensitive). For this reason, in Study CO-338-043, the main efficacy endpoints analyses in the platinum-sensitive (PFI ≥12 months, n=74, 48 vs. 26) and partially platinum-sensitive (PFI ≥6 to <12 months, n=96, 65 vs. 31) strata have been further discussed along this report. In both subgroups, an improvement in invPFS, was observed with rucaparib over chemotherapy, i.e. HR of 0.69 (95% CI: 0.37, 1.29) and HR of 0.41 (95% CI: 0.26, 0.66), respectively. An estimated HR for both subgroups combined is also reported, i.e. HR of 0.502 (95% CI: 0.343, 0.733). Also, additional post-hoc analyses were performed for ORR by platinum sensitivity status confirming the beneficial effect of rucaparib in both the Efficacy and ITT Population with measurable disease.

Additional analyses of the OS interim results by platinum sensitivity subgroup were provided for both the ITT and the Efficacy Population. The reported HRs for the Efficacy Population were 1.124 (95% CI: 0.438, 2.884) for the platinum-sensitive (PFI > 12 months) group, 1.258 (95% CI: 0.645, 2.454) for the partially platinum-sensitive (PFI ≥ 6 to 12 months) group, and 1.789 (95% CI: 1.120, 2.858) for the platinum-resistant (PFI >1 to <6 months) group.

During the procedure, updated OS and PFS2 data were provided. Results from the final OS analysis (DCO 10 April 2022) in the ITT population of study ARIEL4, were consistent with the IA and athough not statistically significant, clearly favoured the chemotherapy treatment over rucaparib (HR=1.31; 95% CI: 1.00, 1.73; p=0.0507). It is acknowledged that the detrimental effect on OS observed in the ARIEL4 study is driven (mostly) by the platinum resistant subgroup where the worst results are observed (HR=1.51; 95% CI: 1.05, 2.17) and which, represented 51% of the patient population. It is also agreed that in the context of the approved 'treatment' indication (i.e. platinum sensitive, relapsed or progressive, BRCA mutated patients who are unable to tolerate further platinum-based chemotherapy), the subgroup of platinum sensitive patients (particularly those partially sensitive), represent the most relevant population to confirm efficacy of rucaparib. However, and albeit the limitations to extract definitive conclusions from subgroups' data, in the platinum sensitive populations, either pooled or separate, OS results are also not reassuring (HR for the fully + partially, fully, and partially platinum sensitive subgroups are, respectively, 1.07 [95% CI: 0.71, 1.62], 1.24 [95% CI: 0.62, 2.50] and 0.97 [95% CI:

0.58, 1.62]. Of note, a worse effect in the fully-sensitive subgroup is not to be compensated by a better effect in the partially-sensitive, also due to difficulties in pooling to subgroups with in principle different prognosis. In addition, as mentioned above, the subgroup of study patients with platinum-sensitive disease included in ARIEL4 is not identical to the approved indication with platinum-sensitive patients who are unable to tolerate further platinum-based therapy. This is also supported by the information on subsequent therapies provided by the MAH. For those patients who were randomised to the rucaparib arm and who progressed, nearly all received a subsequent chemotherapy regimen, with the majority receiving platinum-based treatment and a smaller percentage receiving non-platinum chemotherapy treatment. Platinum-based regimens were the most frequent first subsequent therapies in patients who were partially platinum-sensitive or platinum-sensitive at baseline initially randomised to rucaparib. Interestingly, despite these patients being platinum-resistant, 38.2% patients received platinum-based chemotherapy as monotherapy or in combination therap. This constitutes an additional uncertainty that relates to the representativeness of the ARIEL4 study for the treatment indication population.

In **summary**, the PFS results observed in study CO-338-043 can be considered as overall consistent with those reported in the pooled efficacy population from Studies CO-338-010 and CO-338-017A, which were the basis of the initial conditional approval. However, important uncertainties still remain regarding a potential detrimental effect on OS when rucaparib is used over chemotherapy in the specific patient population covered by the indication. To address these outstanding uncertainties further information / discussion would be needed, which was requested during the Article 20 referral procedure. However the MAH did not provide responses to the adopted list of issues for the referral, following their (voluntary) request to remove the "treatment" indication from the product information. Therefore, no further questions to the MAH were posed in the context of this procedure.

7. Clinical Safety aspects

In fulfillment of SOB001, the CSR for Study CO-338-043 (ARIEL4) has been completed and submitted. Study CO-338-043 (ARIEL4) is an ongoing Phase 3, multicenter, randomized study evaluating rucaparib versus chemotherapy for the treatment of patients with relapsed, high-grade epithelial serous or Grade 2 or 3 endometrioid ovarian, FTC, or PPC.

7.1. Methods – analysis of data submitted

In **Study CO-338-043**, a total of 349 patients were randomized 2:1 to rucaparib or chemotherapy (ie, Intent-to-treat [ITT] population). The Safety Population included **345 patients** who received at least 1 dose of study treatment (600 mg twice a day [BID] rucaparib [232 patients] or chemotherapy [113 patients]), as there were 4 patients who were randomized but never dosed.

Safety data from Study CO-338-043 are presented in the SCS as stand-alone data, and safety data from Study CO-338-043 have also been integrated with the most recent data-cuts from Studies CO-338-010, CO-338-017, and CO-338-014 (referred to as the "**Pooled Ovarian Cancer Safety Population**"; **N=1,169**).

Table 23: Clinical Studies of Rucaparib Referenced in the Summary of Clinical Safety

Study No.	Description	Formulations and Doses Evaluated	Study Status (as of 04 June 2021)
CO-338-043 (ARIEL4)	A Phase 3, randomized study evaluating rucaparib versus chemotherapy as treatment for patients with relapsed high-grade ovarian cancer associated with a deleterious BRCA1/2 mutation and who have received at least 2 prior chemotherapy regimens	2:1 randomization 600 mg BID PO OR Chemotherapy: paclitaxel 60-80 mg/m^2 (Day 1,8,15), single-agent (cisplatin or carboplatin), or doublet (carboplatin/paclitaxel, carboplatin/gemcitabine, cisplatin/gemcitabine) in 28-day cycles IV.	Enrolment completed; Study ongoing; **Final CSR completed**[a]
CO-338-014 (ARIEL3)	A Phase 3, randomized, double-blind study of oral rucaparib monotherapy versus placebo as switch maintenance treatment in patients with platinum-sensitive, relapsed, high-grade ovarian cancer who achieved a response to platinum-based chemotherapy	2:1 randomization 600 mg BID PO OR Placebo BID PO	Enrolment completed; Study completed; **Interim CSR completed**[b]
CO-338-010	A Phase 1/2 open-label, safety, PK, and preliminary efficacy study of oral rucaparib monotherapy in advanced gBRCA mutant ovarian cancer and solid tumors	Phase 1 (Part 1) 40-500 mg QD PO 240-840 mg BID PO Phase 2 (Part 2, Part 3) 600 mg BID PO	All Parts: Enrolment completed; Study completed; **Final CSR completed**
CO-338-017 (ARIEL2)	A Phase 2 open-label study of oral rucaparib monotherapy in relapsed, high-grade ovarian cancer	Part 1 and Part 2 600 mg BID PO	Enrolment completed; Study completed[c]; **Final CSR completed**

Abbreviations: BID = twice a day; BRCA = breast cancer gene; CSR = clinical study report; gBRCA = germline breast cancer gene; IV = intravenous; PK = pharmacokinetic; PO = orally; QD = once a day.

[a] An addendum to the Final CO-338-043 CSR will be prepared to summarize final overall survival and long-term follow-up data when complete.

[b] Final overall survival and long-term follow-up data (with a visit cut-off date of 31 December 2019) will be submitted in the Final CO-338-014 CSR.

[c] A final CSR was written for Study CO-338-017 as all endpoints had been met, with no safety signals observed. At the time of the final data cut, 14 of 491 patients remained on treatment as of the visit cut-off date of 01 February 2019. Through global protocol amendment 6.0 (dated 17 July 2019) and UK-specific protocol amendment 6.1 (dated 26 August 2019), study assessments have been reduced to standard of care; safety monitoring continues with data collection limited to SAEs. An addendum to the Final CO-338-017 CSR will be prepared after all patients are discontinued or transferred from the study to summarize data collected after the visit cut-off date.

7.2. Results

Patient exposure

Table 24: Exposure – Treatment Part (Safety Population) in Study CO-338-043

	Rucaparib (N = 232)	Chemotherapy (N = 113)
Duration of Treatment (months)		
n	232	113
Mean (StD)	9.0 (8.18)	4.4 (3.70)
Median	7.3	3.6
Min, Max	0, 41	0, 25
Duration of Treatment (months, by category), n (%)		
0 to < 6 months	107 (46.1)	90 (79.6)
6 to < 12 months	62 (26.7)	19 (16.8)
12 to < 24 months	44 (19.0)	3 (2.7)
≥ 24 months	19 (8.2)	1 (0.9)
Dose Reductions[a], n (%)		
At least 1 Dose Reduction	80 (34.5)	15 (13.3)
Reduced due to adverse event[a]	78 (97.5)	12 (80.0)
Noncompliance resulting in a dose reduction (rucaparib) or other reason (chemotherapy)[a]	2 (2.5)	3 (20.0)
Only 1 Dose Reduction[a]	50 (62.5)	
≥ 2 Dose Reductions[a]	30 (37.5)	
Dose Reduced to 500 mg BID[a]	78 (97.5)	
Reduced due to adverse event[b]	77 (98.7)	

	Rucaparib (N = 232)	Chemotherapy (N = 113)
Reduced due to noncompliance[b]	1 (1.3)	
Dose Reduced to 400 mg BID[a]	31 (38.8)	
Reduced due to adverse event[b]	28 (90.3)	
Reduced due to noncompliance[b]	3 (9.7)	
Dose Reduced to 300 mg BID[a]	11 (13.8)	
Reduced due to adverse event[b]	9 (81.8)	
Reduced due to noncompliance[b]	2 (18.2)	
Rucaparib Dose Intensity[c]		
n	232	
Mean (StD)	0.91 (0.140)	
Median	0.99	
Min, Max	0.4, 1.0	
Number of Chemotherapy Cycles Started		
n		113
Mean (StD)		5.3 (3.46)
Median		5.0
Min, Max		1, 21
Type of Chemotherapy, n (%)		
Monotherapy Platinum		9 (8.0)
Paclitaxel		88 (77.9)
Platinum-based Doublet		16 (14.2)

Source: Table 14.1.2.1.1, Study CO-338-043 CSR.

Abbreviations: BID = twice a day; CSR = clinical study report; Max = maximum; Min = minimum; StD = standard deviation.

[a] The denominator is the number of patients with at least 1 dose reduction.

[b] The denominator is the number of patients with at least 1 dose reduction at that dose level of rucaparib.

[c] Dose intensity is defined as the actual dose received divided by the first dose (ie, 600 mg).

The median duration of rucaparib exposure was 7.4 months for the ovarian cancer patients with BRCA mutations from the pooled Safety Population for Studies CO-338-010 and CO-338-017 (N = 143) in the initial Marketing Authorization Application (MAA). Within the maintenance setting in Study CO-338-014, the median duration of rucaparib exposure was 11.6 months for the tBRCA (includes germline BRCA [gBRCA] and somatic BRCA [sBRCA] mutations) Safety Population (N = 129).

Adverse events

Table 25: Overall Summary of TEAEs: Study CO-338-043, and Pooled Ovarian Cancer Safety Population

	CO-338-043 Treatment Part Safety Population		Pooled Ovarian Cancer Safety Population
	Chemotherapy (N = 113)	Rucaparib (N = 232)	Rucaparib (N = 1,169)
	n (%)		
Patients with 1 or more TEAE	106 (93.8)	222 (95.7)	1,159 (99.1)
Patients with 1 or more treatment-related TEAE	98 (86.7)	206 (88.8)	1,105 (94.5)
Patients with 1 or more serious TEAE	13 (11.5)	62 (26.7)	327 (28.0)
Patients with 1 or more serious treatment-related TEAE	6 (5.3)	32 (13.8)	138 (11.8)
Patients with 1 or more TEAE of Grade 3 or higher	43 (38.1)	136 (58.6)	727 (62.2)
Patients with 1 or more treatment-related TEAE of Grade 3 or higher	32 (28.3)	98 (42.2)	540 (46.2)
Patients with 1 or more TEAE leading to death	3 (2.7)	15 (6.5)	50 (4.3)
Patients with 1 or more treatment-related TEAE leading to death	0	3 (1.3)	7 (0.6)
Patients with 1 or more TEAE leading to study drug discontinuation	15 (13.3)	20 (8.6)	209 (17.9)
Patients with 1 or more treatment-related TEAE leading to study drug discontinuation	10 (8.8)	10 (4.3)	120 (10.3)
Patients with 1 or more TEAE leading to study drug interruption	43 (38.1)	111 (47.8)	699 (59.8)
Patients with 1 or more treatment-related TEAE leading to study drug interruption	31 (27.4)	94 (40.5)	589 (50.4)
Patients with 1 or more TEAE leading to study drug dose reduction	12 (10.6)	78 (33.6)	547 (46.8)
Patients with 1 or more treatment-related TEAE leading to study drug dose reduction	12 (10.6)	76 (32.8)	529 (45.3)
Patients with 1 or more TEAE leading to study drug dose reduction or interruption	50 (44.2)	115 (49.6)	757 (64.8)
Patients with 1 or more treatment-related TEAE leading to study drug dose reduction or interruption	40 (35.4)	98 (42.2)	668 (57.1)

Abbreviations: CSR = clinical study report; ISS = integrated summary of safety; TEAE = treatment-emergent adverse event.

Common adverse events

Table 26: Treatment-emergent AEs Reported in ≥ 20% of Patients: Study CO-338-043, and Pooled Ovarian Cancer Safety Population

System Organ Class Preferred Term	CO-338-043 Treatment Part Safety Population		Pooled Ovarian Cancer Safety Population
	Chemotherapy (N = 113)	Rucaparib (N = 232)	Rucaparib (N = 1,169)
	n (%)		
Number of Patients With At Least 1 TEAE	**106 (93.8)**	**222 (95.7)**	**1,159 (99.1)**
Combined Preferred Terms			
Combined Abdominal Pain	25 (22.1)	74 (31.9)	474 (40.5)
Combined ALT/AST Increased	13 (11.5)	80 (34.5)	437 (37.4)
Combined Anemia/Hemoglobin Decreased	36 (31.9)	125 (53.9)	522 (44.7)
Combined Asthenia/Fatigue/Lethargy	51 (45.1)	115 (49.6)	823 (70.4)
Combined Neuropathy	35 (31.0)	7 (3.0)	69 (5.9)
Combined Neutropenia/Decreased ANC	32 (28.3)	52 (22.4)	210 (18.0)
Combined Thrombocytopenia/Decreased Platelets	13 (11.5)	54 (23.3)	304 (26.0)
Blood and lymphatic system disorders	**50 (44.2)**	**143 (61.6)**	**601 (51.4)**
Anaemia	35 (31.0)	123 (53.0)	504 (43.1)
Neutropenia	28 (24.8)	47 (20.3)	145 (12.4)
Gastrointestinal disorders	**75 (66.4)**	**168 (72.4)**	**1,040 (89.0)**
Abdominal pain	18 (15.9)	54 (23.3)	359 (30.7)
Constipation	19 (16.8)	37 (15.9)	391 (33.4)
Diarrhoea	24 (21.2)	47 (20.3)	360 (30.8)
Nausea	36 (31.9)	124 (53.4)	845 (72.3)
Vomiting	19 (16.8)	79 (34.1)	478 (40.9)
General disorders and administration site conditions	**57 (50.4)**	**134 (57.8)**	**905 (77.4)**
Asthenia	24 (21.2)	64 (27.6)	257 (22.0)
Fatigue	28 (24.8)	55 (23.7)	593 (50.7)
Infections and infestations	**27 (23.9)**	**73 (31.5)**	**490 (41.9)**
Investigations	**35 (31.0)**	**129 (55.6)**	**705 (60.3)**
Alanine aminotransferase increased	12 (10.6)	74 (31.9)	404 (34.6)
Aspartate aminotransferase increased	8 (7.1)	72 (31.0)	371 (31.7)
Metabolism and nutrition disorders	**52 (46.0)**	**88 (37.9)**	**588 (50.3)**
Decreased appetite	20 (17.7)	44 (19.0)	358 (30.6)
Musculoskeletal and connective tissue disorders	**26 (23.0)**	**49 (21.1)**	**447 (38.2)**
Nervous system disorders	**54 (47.8)**	**80 (34.5)**	**674 (57.7)**
Dysgeusia	8 (7.1)	39 (16.8)	391 (33.4)

Psychiatric disorders	**12 (10.6)**	**30 (12.9)**	**260 (22.2)**
Respiratory, thoracic and mediastinal disorders	**27 (23.9)**	**54 (23.3)**	**435 (37.2)**
Skin and subcutaneous tissue disorders	**49 (43.4)**	**53 (22.8)**	**486 (41.6)**
Alopecia	38 (33.6)	12 (5.2)	87 (7.4)

Sources: Table 14.3.1.1.2.1 and Table 14.3.1.1.1.3, Study CO-338-043 CSR; Table 14.3.1.1.2.6, Table 2.7.4.1.1, and Table 2.7.4.13.1, A4 T2V ISS.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CSR = clinical study report; ISS = integrated summary of safety; TEAE = treatment-emergent adverse event.

Treatment-related TEAEs

Table 27: Treatment-related TEAEs Reported in ≥ 20% of Patients: Study CO-338-043, and Pooled Ovarian Cancer Safety Population

System Organ Class Preferred Term	CO-338-043 Treatment Part Safety Population		Pooled Ovarian Cancer Safety Population
	Chemotherapy (N = 113)	Rucaparib (N = 232)	Rucaparib (N = 1,169)
	n (%)		
Number of Patients With At Least 1 Treatment-related TEAE	**98 (86.7)**	**206 (88.8)**	**1,105 (94.5)**
Combined Preferred Terms			
Combined ALT/AST Increased	12 (10.6)	77 (33.2)	411 (35.2)
Combined Anemia/Hemoglobin Decreased	32 (28.3)	105 (45.3)	465 (39.8)
Combined Asthenia/Fatigue/Lethargy[a]	NA	NA	717 (61.3)
Combined Asthenia/Fatigue	41 (36.3)	85 (36.6)	700 (59.9)
Combined Neuropathy	35 (31.0)	4 (1.7)	25 (2.1)
Combined Neutropenia/Decreased ANC	32 (28.3)	46 (19.8)	189 (16.2)
Combined Thrombocytopenia/Decreased Platelets	13 (11.5)	44 (19.0)	280 (24.0)
Blood and lymphatic system disorders	**47 (41.6)**	**123 (53.0)**	**536 (45.9)**
Anaemia	32 (28.3)	104 (44.8)	450 (38.5)
Neutropenia	28 (24.8)	42 (18.1)	130 (11.1)
Gastrointestinal disorders	**56 (49.6)**	**140 (60.3)**	**905 (77.4)**
Nausea	33 (29.2)	116 (50.0)	765 (65.4)
Vomiting	15 (13.3)	54 (23.3)	336 (28.7)
General disorders and administration site conditions	**44 (38.9)**	**94 (40.5)**	**741 (63.4)**
Asthenia	18 (15.9)	47 (20.3)	215 (18.4)
Fatigue	25 (22.1)	41 (17.7)	516 (44.1)
Investigations	**31 (27.4)**	**110 (47.4)**	**622 (53.2)**
Alanine aminotransferase increased	11 (9.7)	72 (31.0)	377 (32.2)
Aspartate aminotransferase increased	8 (7.1)	70 (30.2)	351 (30.0)

Metabolism and nutrition disorders	**31 (27.4)**	**65 (28.0)**	**418 (35.8)**
Decreased appetite	19 (16.8)	37 (15.9)	285 (24.4)
Nervous system disorders	**49 (43.4)**	**57 (24.6)**	**503 (43.0)**
Dysgeusia	8 (7.1)	39 (16.8)	370 (31.7)
Skin and subcutaneous tissue disorders	**46 (40.7)**	**35 (15.1)**	**339 (29.0)**
Alopecia	38 (33.6)	8 (3.4)	53 (4.5)

Sources: Table 14.3.1.1.4.1, and Table 14.3.1.1.1.3, Study CO-338-043 CSR; Table 2.7.4.1.2, and Table 2.7.4.13.2, A4 T2V ISS.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CSR = clinical study report; ISS = integrated summary of safety; NA = not analyzed; SmPC = Summary of Product Characteristics; TEAE = treatment-emergent adverse event.

[a] Combined events of asthenia/fatigue/lethargy were summarized for the Pooled Ovarian Cancer Safety Population to support the summary presented in the Rubraca SmPC; however, this combined group of terms was not analyzed for the individual treatment groups from Study CO-338-043.

Grade 3 or Higher TEAEs

The majority of patients in either treatment group experienced Grade 2 or Grade 3 TEAEs, and Grade 2 or Grade 3 treatment-related TEAEs. In the rucaparib group, a higher incidence of Grade 3 TEAEs (all causality and treatment-related) was reported as compared to the chemotherapy group.

Table 28: Summary of TEAEs and Treatment-related TEAEs by Grade – Treatment Part (Safety Population)

	Rucaparib (N=232)	**Chemotherapy (N=113)**
NCI-CTCAE Grade	**n (%)**	
Patients With at Least One TEAE		
Overall	222 (95.7)	106 (93.8)
1	12 (5.2)	11 (9.7)
2	74 (31.9)	52 (46.0)
3	104 (44.8)	33 (29.2)
4	17 (7.3)	7 (6.2)
5	15 (6.5)	3 (2.7)
Patients With at Least One Treatment-related TEAE		
Overall	206 (88.8)	98 (86.7)
1	32 (13.8)	14 (12.4)
2	76 (32.8)	52 (46.0)
3	82 (35.3)	27 (23.9)
4	13 (5.6)	5 (4.4)
5	3 (1.3)	0 (0)

Source: Table 14.3.1.1.10.1 (TEAEs by grade); Table 14.3.1.1.11.1 (Treatment-related TEAEs by grade).

Abbreviations: NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; TEAE = treatment-emergent adverse event.

Table 29: Grade 3 or Higher TEAEs Reported in ≥ 2% of Patients: Study CO-338-043, and Pooled Ovarian Cancer Safety Population

System Organ Class Preferred Term	CO-338-043 Treatment Part Safety Population		Pooled Ovarian Cancer Safety Population
	Chemotherapy (N = 113)	Rucaparib (N = 232)	Rucaparib (N = 1,169)
	n (%)		
Number of Patients With At Least 1 Grade 3 or Higher TEAE	**43 (38.1)**	**136 (58.6)**	**727 (62.2)**
Combined Preferred Terms			
Combined Abdominal Pain	0	9 (3.9)	49 (4.2)
Combined ALT/AST Increased	0	18 (7.8)	118 (10.1)
Combined Anemia/Hemoglobin Decreased	6 (5.3)	52 (22.4)	272 (23.3)
Combined Asthenia/Fatigue/Lethargy	3 (2.7)	19 (8.2)	116 (9.9)
Combined Leukopenia/White Blood Cell Count Decreased	3 (2.7)	5 (2.2)	21 (1.8)
Combined Neutropenia/Decreased ANC	17 (15.0)	24 (10.3)	101 (8.6)
Combined Thrombocytopenia/Decreased Platelets	0	19 (8.2)	77 (6.6)
Blood and lymphatic system disorders	**22 (19.5)**	**73 (31.5)**	**332 (28.4)**
Anaemia	6 (5.3)	51 (22.0)	258 (22.1)
Leukopenia	3 (2.7)	5 (2.2)	10 (0.9)
Neutropenia	15 (13.3)	21 (9.1)	70 (6.0)
Thrombocytopenia	0	15 (6.5)	54 (4.6)
Gastrointestinal disorders	**4 (3.5)**	**34 (14.7)**	**196 (16.8)**
Abdominal pain	0	9 (3.9)	43 (3.7)
Ascites	1 (0.9)	6 (2.6)	19 (1.6)
Intestinal obstruction	0	8 (3.4)	21 (1.8)
Nausea	0	6 (2.6)	49 (4.2)
Small intestinal obstruction	0	2 (0.9)	27 (2.3)
Vomiting	0	11 (4.7)	52 (4.4)
General disorders and administration site conditions	**3 (2.7)**	**24 (10.3)**	**138 (11.8)**
Asthenia	0	8 (3.4)	46 (3.9)
Fatigue	3 (2.7)	11 (4.7)	71 (6.1)
Infections and infestations	**3 (2.7)**	**15 (6.5)**	**69 (5.9)**
Investigations	**7 (6.2)**	**36 (15.5)**	**234 (20.0)**
Alanine aminotransferase increased	0	18 (7.8)	112 (9.6)
Aspartate aminotransferase increased	0	2 (0.9)	29 (2.5)
Blood creatinine increased	0	5 (2.2)	8 (0.7)
Neutrophil count decreased	3 (2.7)	3 (1.3)	32 (2.7)
Platelet count decreased	0	4 (1.7%)	23 (2.0)
Metabolism and nutrition disorders	**9 (8.0)**	**12 (5.2)**	**95 (8.1)**
Hyperglycaemia	3 (2.7)	2 (0.9)	4 (0.3)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**3 (2.7)**	**9 (3.9)**	**61 (5.2)**
Malignant neoplasm progression	3 (2.7)	8 (3.4)	42 (3.6)
Nervous system disorders	**2 (1.8)**	**2 (0.9)**	**28 (2.4)**
Renal and urinary disorders	**1 (0.9)**	**6 (2.6)**	**31 (2.7)**
Respiratory, thoracic and mediastinal disorders	**4 (3.5)**	**8 (3.4)**	**32 (2.7)**
Skin and subcutaneous tissue disorders	**3 (2.7)**	**1 (0.4)**	**8 (0.7)**
Vascular disorders	**1 (0.9)**	**5 (2.2)**	**36 (3.1)**

Sources: Table 14.3.1.1.8.1, Study CO-338-043 CSR; Table 14.3.1.1.8.4 and Table 2.7.4.2.1, A4 T2V ISS.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CSR = clinical study report; ISS = integrated summary of safety; TEAE = treatment-emergent adverse event.

Table 30: Incidence Per 100 Patient-years of Treatment for Grade 3 or Higher TEAEs Reported in ≥ 2% of Patients in Any Group -Treatment Part (Safety Population) in Study CO-338-043

System Organ Class Preferred Term	Chemotherapy (N=113)	Rucaparib (N=232)
	n	
Number of Grade 3 or Higher TEAEs per 100 Patient-years of Treatment	**103.3**	**78.0**
Combined Preferred Terms		
Combined ALT/AST Increased	0	10.3
Combined Anemia/Hemoglobin Decreased	14.4	29.8
Combined Asthenia/Fatigue	7.2	10.9
Combined Neutropenia/Decreased ANC	40.8	13.8
Combined Thrombocytopenia/Decreased Platelets	0	10.9
Blood and lymphatic system disorders	**52.9**	**41.9**
Anaemia	14.4	29.3
Leukopenia	7.2	2.9
Neutropenia	36.0	12.0
Thrombocytopenia	0	8.6
Gastrointestinal disorders	**9.6**	**19.5**
Abdominal pain	0	5.2
Ascites	2.4	3.4
Intestinal obstruction	0	4.6
Nausea	0	3.4
Vomiting	0	6.3
General disorders and administration site conditions	**7.2**	**13.8**
Asthenia	0	4.6
Fatigue	7.2	6.3
Infections and infestations	**7.2**	**8.6**
Investigations	**16.8**	**20.7**
Alanine aminotransferase increased	0	10.3
Blood creatinine increased	0	2.9
Neutrophil count decreased	7.2	1.7
Metabolism and nutrition disorders	**21.6**	**6.9**
Hyperglycaemia	7.2	1.1
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**7.2**	**5.2**
Malignant neoplasm progression	7.2	4.6
Renal and urinary disorders	**2.4**	**3.4**
Respiratory, thoracic and mediastinal disorders	**9.6**	**4.6**
Skin and subcutaneous tissue disorders	**7.2**	**0.6**
Vascular disorders	**2.4**	**2.9**

Sources: Table 14.3.1.1.8.3 and Table 14.3.1.1.8.1, Study CO-338-043 CSR.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CSR = clinical study report; TEAE = treatment-emergent adverse event.

In Study CO-338-043, commonly experienced **Grade 3 or higher treatment-related TEAEs** in the rucaparib group included combined anemia/hemoglobin decreased and combined neutropenia/decreased ANC. In the chemotherapy group, commonly experienced Grade 3 or higher treatment-related TEAEs

included combined neutropenia/decreased ANC. The observations were consistent with all causality Grade 3 or higher TEAEs in both groups.

The incidences of treatment-related Grade 3 or higher TEAEs in patients treated with rucaparib in the Pooled Ovarian Cancer Safety Population were similar to those presented for all causality. Grade 3 or higher TEAEs were typically considered by the investigator to be related to rucaparib, with combined anemia/hemoglobin decreased and combined ALT/AST increased being most common.

Table 31: Grade 3 or Higher Treatment-related TEAEs Reported in ≥ 2% of Patients: Study CO-338-043, and Pooled Ovarian Cancer Safety Population

System Organ Class Preferred Term	CO-338-043 Treatment Part Safety Population		Pooled Ovarian Cancer Safety Population
	Chemotherapy (N = 113)	Rucaparib (N = 232)	Rucaparib (N = 1,169)
	n (%)		
Number of Patients With At Least 1 Grade 3 or Higher Treatment-related TEAE	**32 (28.3)**	**98 (42.2)**	**540 (46.2)**
Combined Preferred Terms			
Combined ALT/AST Increased	0	18 (7.8)	108 (9.2)
Combined Anemia/Hemoglobin Decreased	6 (5.3)	44 (19.0)	247 (21.1)
Combined Asthenia/Fatigue/Lethargy[a]	NA	NA	85 (7.3)
Combined Asthenia/Fatigue	2 (1.8)	7 (3.0)	83 (7.1)
Combined Neutropenia/Decreased ANC	16 (14.2)	21 (9.1)	87 (7.4)
Combined Thrombocytopenia/Decreased Platelets	0	14 (6.0)	65 (5.6)
Blood and lymphatic system disorders	**21 (18.6)**	**62 (26.7)**	**297 (25.4)**
Anaemia	6 (5.3)	44 (19.0)	236 (20.2)
Neutropenia	15 (13.3)	18 (7.8)	59 (5.0)
Thrombocytopenia	0	12 (5.2)	46 (3.9)
Gastrointestinal disorders	**0**	**8 (3.4)**	**79 (6.8)**
Nausea	0	1 (0.4)	37 (3.2)
Vomiting	0	3 (1.3)	28 (2.4)
General disorders and administration site conditions	**3 (2.7)**	**8 (3.4)**	**89 (7.6)**
Asthenia	0	4 (1.7)	32 (2.7)
Fatigue	2 (1.8)	3 (1.3)	52 (4.4)
Investigations	**4 (3.5)**	**27 (11.6)**	**196 (16.8)**
Alanine aminotransferase increased	0	18 (7.8)	106 (9.1)
Aspartate aminotransferase increased	0	2 (0.9)	23 (2.0)
Neutrophil count decreased	2 (1.8)	3 (1.3)	29 (2.5)
Metabolism and nutrition disorders	**3 (2.7)**	**7 (3.0)**	**45 (3.8)**
Skin and subcutaneous tissue disorders	**3 (2.7)**	**1 (0.4)**	**7 (0.6)**

Sources: Table 14.3.1.1.9.1, Study CO-338-043 CSR; Table 2.7.4.2.2, A4 T2V ISS.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CSR = clinical study report; ISS = integrated summary of safety; NA = not analyzed; SmPC = Summary of Product Characteristics; TEAE = treatment-emergent adverse event.

[a] Combined events of asthenia/fatigue/lethargy were summarized for the Pooled Ovarian Cancer Safety Population to support the summary presented in the Rubraca SmPC; however, this combined group of terms was not analyzed for the individual treatment groups from Study CO-338-043.

Deaths, Serious Adverse Events, and Other Significant Adverse Events

Deaths

In Study CO-338-043, 15 patients (6.5%) in the rucaparib group and 3 patients (2.7%) in the chemotherapy group had at least 1 TEAE with a fatal outcome. Many of the TEAEs reported with an outcome of death were malignant neoplasm progression (5 patients in the rucaparib group and 2 patients in the chemotherapy group). Upon implementation of Protocol Amendment 2, such events were no longer collected. There were no treatment-related TEAEs with an outcome of death in the chemotherapy group. Three patients in the rucaparib group experienced treatment-related TEAEs with an outcome of death (MDS, Cardiac disorder, and Death Not Otherwise Specified).

Table 32: Treatment-emergent AEs With an Outcome of Death – Study CO-338-043, and Pooled Ovarian Cancer Safety Population

System Organ Class Preferred Term	CO-338-043 Treatment Part Safety Population		Pooled Ovarian Cancer Safety Population
	Chemotherapy (N = 113)	Rucaparib (N = 232)	Rucaparib (N = 1,169)
	n (%)		
Number of Patients With At Least 1 TEAE Leading to Death	**3 (2.7)**	**15 (6.5)**	**50 (4.3)**
Combined Preferred Terms			
Combined Neutropenia/Decreased ANC	0	1 (0.4)	1 (0.1)
Combined Thrombocytopenia/Decreased Platelets	0	1 (0.4)	1 (0.1)
Blood and lymphatic system disorders	**0**	**1 (0.4)**	**2 (0.2)**
Histiocytosis haematophagic	0	0	1 (0.1)
Neutropenia	0	1 (0.4)	1 (0.1)
Thrombocytopenia	0	1 (0.4)	1 (0.1)
Cardiac disorders	**0**	**1 (0.4)**	**2 (0.2)**
Cardiac arrest	0	0	1 (0.1)
Cardiac disorder	0	1 (0.4)	1 (0.1)
Gastrointestinal disorders	**0**	**1 (0.4)**	**2 (0.2)**
Intestinal obstruction	0	0	1 (0.1)
Large intestine perforation	0	1 (0.4)	1 (0.1)
General disorders and administration site conditions	**0**	**3 (1.3)**	**7 (0.6)**
Death	0	3 (1.3)	3 (0.3)
General physical health deterioration	0	0	4 (0.3)
Infections and infestations	**0**	**2 (0.9)**	**4 (0.3)**
Pneumonia	0	1 (0.4)	1 (0.1)
Sepsis	0	0	1 (0.1)
Septic shock	0	1 (0.4)	2 (0.2)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**2 (1.8)**	**6 (2.6)**	**30 (2.6)**
Acute myeloid leukaemia	0	0	1 (0.1)
B-cell type acute leukaemia	0	0	1 (0.1)
B-cell unclassifiable lymphoma high grade	0	0	1 (0.1)

System Organ Class Preferred Term	CO-338-043 Treatment Part Safety Population		Pooled Ovarian Cancer Safety Population
	Chemotherapy (N = 113)	Rucaparib (N = 232)	Rucaparib (N = 1,169)
	n (%)		
Malignant neoplasm progression	2 (1.8)	5 (2.2)	22 (1.9)
Metastatic neoplasm	0	0	1 (0.1)
Myelodysplastic syndrome	0	1 (0.4)	3 (0.3)
Neoplasm malignant	0	0	1 (0.1)
Nervous system disorders	**0**	**0**	**1 (0.1)**
Cerebrovascular accident	0	0	1 (0.1)
Respiratory, thoracic and mediastinal disorders	**1 (0.9)**	**1 (0.4)**	**2 (0.2)**
Pulmonary embolism	1 (0.9)	1 (0.4)	2 (0.2)

Sources: Table 14.3.1.1.12.1.1, Study CO-338-043 CSR; Table 2.7.4.10.1, A4 T2V ISS.

Abbreviations: ANC = absolute neutrophil count; CSR = clinical study report; ISS = integrated summary of safety; TEAE = treatment-emergent adverse event.

Deaths – Crossover Part

Two patients (2.7%) had at least 1 TEAE with a fatal outcome, including 1 patient with malignant neoplasm progression and 1 patient with acute respiratory failure, neither of which were considered treatment-related.

Serious adverse events

Serious TEAEs occurred in 26.7% of patients in the rucaparib group and 11.5% of patients in the chemotherapy group in the Treatment Part of Study CO-338-043. The most frequently reported SAEs were combined anemia/hemoglobin decreased in both the rucaparib and chemotherapy groups. These SAEs were also the most frequently experienced treatment-related SAEs, with every incidence considered related to the study treatment administered. The numbers of treatment-emergent SAEs adjusted to 100 patient-years exposure were similar between rucaparib (35.6 events) and chemotherapy (31.2 events).

Table 33: Treatment-emergent SAEs Reported in ≥ 2% of Patients: Study CO-338-043, and Pooled Ovarian Cancer Safety Population

System Organ Class Preferred Term	CO-338-043 Treatment Part Safety Population		Pooled Ovarian Cancer Safety Population
	Chemotherapy (N = 113)	Rucaparib (N = 232)	Rucaparib (N = 1,169)
	n (%)		
Number of Patients With At Least 1 Serious TEAE	**13 (11.5)**	**62 (26.7)**	**327 (28.0)**
Combined Preferred Terms			
Combined Anemia/Hemoglobin Decreased	2 (1.8)	19 (8.2)	64 (5.5)
Combined Thrombocytopenia/Decreased Platelets	1 (0.9)	7 (3.0)	17 (1.5)
Blood and lymphatic system disorders	**3 (2.7)**	**22 (9.5)**	**87 (7.4)**
Anaemia	2 (1.8)	19 (8.2)	63 (5.4)
Thrombocytopenia	1 (0.9)	5 (2.2)	12 (1.0)
Gastrointestinal disorders	**4 (3.5)**	**16 (6.9)**	**114 (9.8)**
Intestinal obstruction	0	5 (2.2)	17 (1.5)
Small intestinal obstruction	0	1 (0.4)	28 (2.4)
General disorders and administration site conditions	**0**	**6 (2.6)**	**36 (3.1)**
Infections and infestations	**3 (2.7)**	**12 (5.2)**	**57 (4.9)**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**2 (1.8)**	**7 (3.0)**	**57 (4.9)**
Malignant neoplasm progression	2 (1.8)	5 (2.2)	35 (3.0)
Respiratory, thoracic and mediastinal disorders	**1 (0.9)**	**5 (2.2)**	**26 (2.2)**

Sources: Table 14.3.1.1.6.1, Study CO-338-043 CSR; Table 2.7.4.7.1, A4 T2V ISS.

Abbreviations: CSR = clinical study report; ISS = integrated summary of safety; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Table 34: Incidence Per 100 Patient-Years of Treatment for Treatmentemergent SAEs Reported in ≥ 2% of Patients in Any Group -Treatment Part (Safety Population) in Study CO-338-043

System Organ Class Preferred Term	Chemotherapy (N = 113)	Rucaparib (N = 232)
	n	
Number of Serious TEAEs Per 100 Patient-years of Treatment	**31.2**	**35.6**
Combined Preferred Terms		
Combined Anemia/Hemoglobin Decreased	4.8	10.9
Combined Thrombocytopenia/Decreased Platelets	2.4	4.0
Blood and lymphatic system disorders	**7.2**	**12.6**
Anaemia	4.8	10.9
Thrombocytopenia	2.4	2.9
Gastrointestinal disorders	**9.6**	**9.2**
Intestinal obstruction	0	2.9
Small intestinal obstruction	0	0.6
General disorders and administration site conditions	**0**	**3.4**
Infections and infestations	**7.2**	**6.9**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**4.8**	**4.0**
Malignant neoplasm progression	4.8	2.9
Respiratory, thoracic and mediastinal disorders	**2.4**	**2.9**

Sources: Table 14.3.1.1.6.1 and Table 14.3.1.1.6.3, Study CO-338-043 CSR.

Abbreviations: CSR = clinical study report; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Serious Adverse Events – Crossover Part

Table 35: Treatment-emergent SAEs Reported in ≥ 2% of Patients - Crossover Part (Safety Population)

System Organ Class Preferred Term	Rucaparib (N=74) n (%)
Number of Patients With At Least One Serious TEAE	**17 (23.0)**
Combined Preferred Terms	
Combined Anemia/Hemoglobin decreased	4 (5.4)
Blood and lymphatic system disorders	**5 (6.8)**
Anaemia	4 (5.4)
Gastrointestinal disorders	**5 (6.8)**
Intestinal obstruction	4 (5.4)
Infections and infestations	**3 (4.1)**

Source: Table 14.3.1.1.6.2.

Abbreviations: SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Adverse Events of Special Interest (AESIs)

Myelodysplastic syndrome and acute myeloid leukemia (MDS/AML) and pneumonitis have been identified as AESIs.

- *Myelodysplastic Syndrome and Acute Myeloid Leukemia*

Myelodysplastic syndrome and AML are considered AESIs and are listed as a potential risk in the EU-RMP. Data are presented for AESIs reported in the Clovis-sponsored clinical development program, including 15 Phase 1, 2, and 3 clinical studies of rucaparib alone or in combination with other cancer treatments in multiple solid tumor types as of 19 December 2020.

In approximately 2,972 patients treated with rucaparib (includes patients who received rucaparib in ongoing and completed studies, but excluding investigator-initiated trials), there were 27 patients (0.91%) who developed MDS or AML (including MDS transforming into AML), including during the long-term follow-up. These included:

- Study CO-338-043 (n = 5; 2.2% [N = 232]): 4 patients with MDS and 1 patient with AML;
- Study CO-338-010 (n = 2; 2.7% [N = 74]): 2 patients with MDS;
- Study CO-338-017 (n = 6; 1.2% [N = 491]): 4 patients with MDS and 2 patients with AML;
- Study CO-338-014 (n = 14; 3.8% [N = 372]): 6 patients with MDS, including refractory anemia with excess blasts; 5 patients with AML, and 3 patients with MDS transforming into AML.

For these 27 patients, the duration of rucaparib treatment prior to the diagnosis of MDS/AML ranged from < 2 months to > 4 years. Thirteen patients (2 patients from Study CO-338-010, 2 patients from Study CO-338-017, 6 patients from Study CO-338-014, and 3 patients from Study CO-338-043) had an event that occurred during treatment or during the 28-day safety follow-up.

- *Pneumonitis*

Pneumonitis and associated events, including interstitial lung disease, pulmonary fibrosis, acute interstitial pneumonitis, alveolitis necrotizing, alveolitis, hypersensitivity pneumonitis, and organizing pneumonia, were collected as TEAEs through the 30 September 2020 visit cutoff of this report, being added as AESIs in Amendment 2 of the protocol, dated 23 October 2020. None of these events were collected in the scope of AESI collection. However, 1 patient in the chemotherapy group reported a TEAE of pneumonitis 54 days after starting study drug. The TEAE was not related to chemotherapy and was not serious. The patient recovered from this TEAE and continued the study. There were no other AEs of pneumonitis or associated events reported in the study.

Laboratory findings

Haematology

Based on laboratory data, myelosuppression (anemia, decreased white blood cell count, decreased lymphocytes and decreased neutrophils) was observed during treatment with rucaparib or chemotherapy in the Treatment Part of Study CO-338-043.

Most of the worst grade on-treatment and shifts from baseline for hematology parameters during the Treatment Part were Grade 1 or 2, with low incidences observed for Grade 3 or 4. Patients who received rucaparib more frequently experienced shifts to Grade 3 and Grade 4 anemia and platelet count decreased as compared with chemotherapy, and patients who received chemotherapy more frequently experienced shifts to Grade 3 and Grade 4 neutrophil count decreased and lymphocyte count decreased. Laboratory observations were consistent with the TEAE reporting of Grade 3 and Grade 4 events of myelosuppression.

Table 36: Shift in Key Hematology Parameters – Treatment Part (Safety Population) in Study CO-338-043

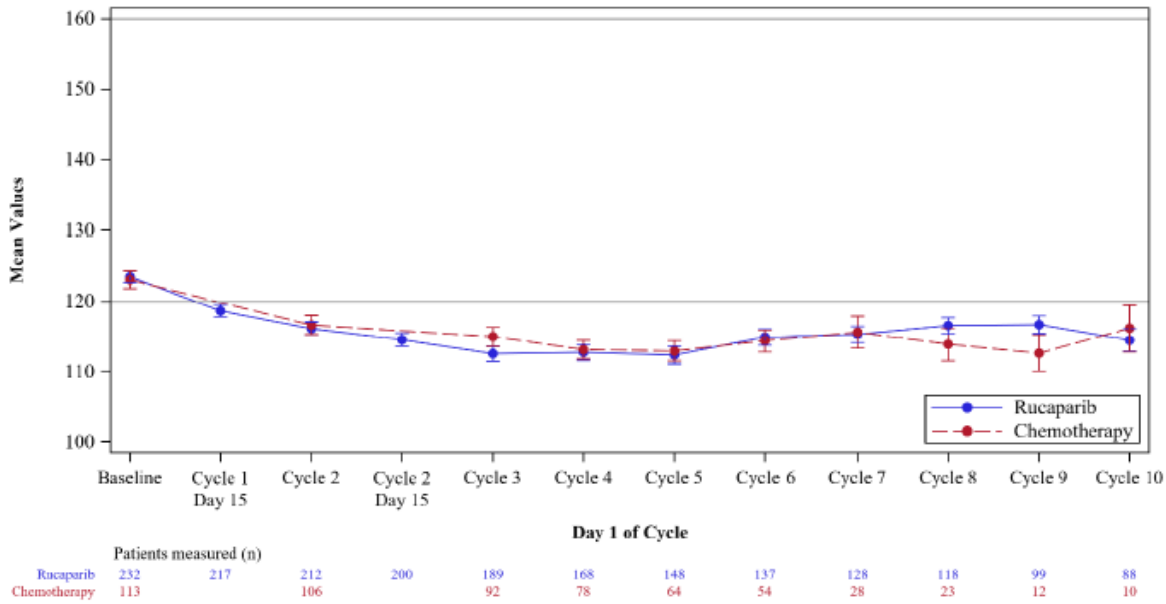
	Rucaparib (N = 232)		Chemotherapy (N = 113)	
	Shift From Baseline in CTCAE Grade[a]			
	G1-4	G3-4	G1-4	G3-4
	n/N (%)		n/N (%)	
Anemia	173 / 224 (77.2)	48 / 224 (21.4)	76 / 111 (68.5)	3 / 111 (2.7)
Lymphocyte count decreased	108 / 207 (52.2)	14 / 207 (6.8)	55 / 105 (52.4)	11 / 105 (10.5)
Lymphocyte count increased	2 / 207 (1.0)	0 / 207	3 / 105 (2.9)	0 / 105
Neutrophil count decreased	129 / 220 (58.6)	23 / 220 (10.5)	73 / 108 (67.6)	17 / 108 (15.7)
Platelet count decreased	85 / 224 (37.9)	19 / 224 (8.5)	17 / 111 (15.3)	0 / 111
White blood cell decreased	133 / 224 (59.4)	10 / 224 (4.5)	76 / 111 (68.5)	8 / 111 (7.2)

Source: Table 14.3.4.1.1.1, Study CO-338-043 CSR.

Abbreviations: CSR = clinical study report; CTCAE = Common Terminology Criteria for Adverse Events; G = grade.

[a] Shifts are based on worst grade experienced on treatment and patients who had at least a 1 grade shift from baseline.

Figure 28: Hemoglobin (g/L): Mean (± SE) Values by Cycle at Baseline and On-treatment – Treatment Part (Safety Population)

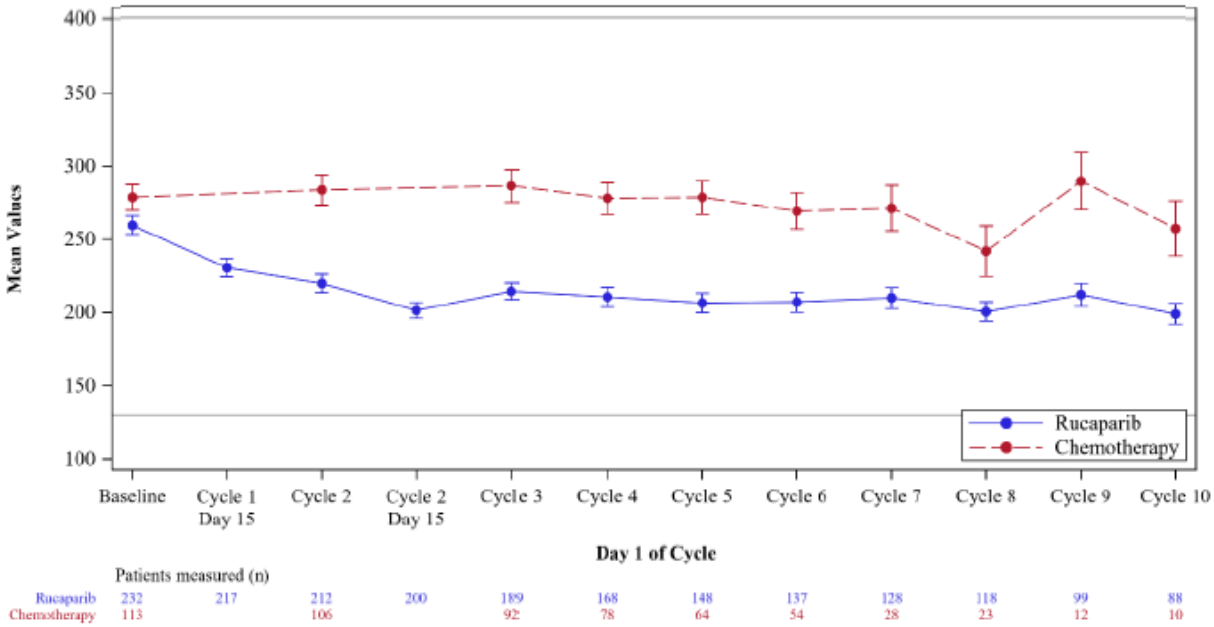


Abbreviations: SE = standard error.

Notes: The normal range is 120 to 160 g/L. The upper horizontal line represents the upper limit of normal, and the lower horizontal line represents the lower limit of normal.

The on-treatment period is defined as the time from first dose of study drug to 28 days after the last dose of study drug in the Treatment Part and prior to start of rucaparib in the Crossover Part.

Figure 29: Platelets (x 109/L): Mean (± SE) Values by Cycle at Baseline and On-Treatment – Treatment Part (Safety Population)

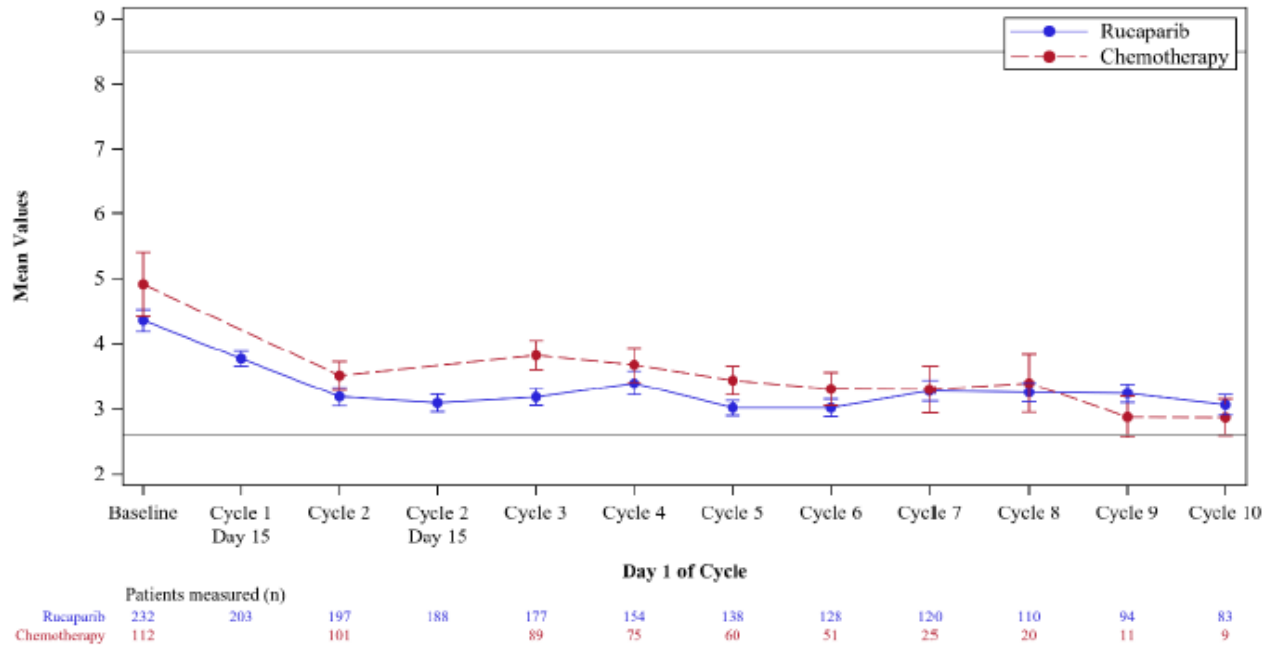


Abbreviations: SE = standard error.

Notes: The normal range is 130 to 400 (10^9)/L. The upper horizontal line represents the upper limit of normal, and the lower horizontal line represents the lower limit of normal.

The on-treatment period is defined as the time from first dose of study drug to 28 days after the last dose of study drug in the Treatment Part and prior to start of rucaparib in the Crossover Part.

Figure 30: Neutrophils (x 109/L): Mean (± SE) Values by Cycle at Baseline and On-Treatment - Treatment Part (Safety Population)



Abbreviations: SE = standard error.

Notes: The normal range is 2.6 to 8.5 (10^9)/L. The upper horizontal line represents the upper limit of normal, and the lower horizontal line represents the lower limit of normal

The on-treatment period is defined as the time from first dose of study drug to 28 days after the last dose of study drug in the Treatment Part and prior to start of rucaparib in the Crossover Part.

Clinical chemistry

In Study CO-338-043, the most common clinical chemistry abnormalities for patients in the rucaparib group were increases in cholesterol, increases in ALT/AST, hyperglycemia, hypophosphatemia, and hypertriglyceridemia.

Most of the worst grade on-treatment and shifts from baseline for clinical chemistry parameters were Grade 1 or 2, with low incidences observed for Grade 3 or 4. The highest incidences of worst grade on-treatment were for ALT increased in the rucaparib group and for hyperglycemia in the chemotherapy group. In the rucaparib group, the incidences of shifts to Grade 3 or Grade 4 were highest with ALT increased, hypophosphatemia, hypokalemia, and creatinine increased; in the chemotherapy group, these shifts were highest with hypertriglyceridemia, hyperglycemia, and hyponatremia.

Table 37: Shift in Key Clinical Chemistry Parameters – Treatment Part, (Safety Population) in Study CO-338-043

	Rucaparib (N = 232)		Chemotherapy (N = 113)	
	Shift From Baseline in CTCAE Grade[a]			
	G1-4	G3-4	G1-4	G3-4
	n/N (%)		n/N (%)	
Alanine aminotransferase increased[b]	184 / 224 (82.1)	27 / 224 (12.1)	58 / 111 (52.3)	1 / 111 (0.9)
Alkaline phosphatase increased[b]	82 / 224 (36.6)	1 / 224 (0.4)	15 / 111 (13.5)	0 / 111
Aspartate aminotransferase increased[b]	85 / 224 (37.9)	0 / 224	14 / 111 (12.6)	0 / 111
Blood bilirubin increased[b]	86 / 224 (38.4)	2 / 224 (0.9)	15 / 111 (13.5)	1 / 111 (0.9)
Cholesterol high	85 / 224 (37.9)	3 / 224 (1.3)	46 / 111 (41.4)	2 / 111 (1.8)
Creatinine increased	86 / 224 (38.4)	8 / 224 (3.6)	15 / 111 (13.5)	1 / 111 (0.9)
Hypercalcemia	80 / 223 (35.9)	1 / 223 (0.4)	31 / 111 (27.9)	3 / 111 (2.7)
Hyperglycemia[c]	90 / 224 (40.2)	4 / 224 (1.8)	58 / 110 (52.7)	5 / 110 (4.5)
Hyperkalemia	41 / 224 (18.3)	2 / 224 (0.9)	25 / 110 (22.7)	0 / 110 (0)
Hypernatremia	43 / 224 (19.2)	1 / 224 (0.4)	23 / 110 (20.9)	2 / 110 (1.8)
Hypertriglyceridemia	105 / 223 (47.1)	3 / 223 (1.3)	56 / 111 (50.5)	6 / 111 (5.4)
Hypoalbuminemia	21 / 224 (9.4)	1 / 224 (0.4)	16 / 111 (14.4)	2 / 111 (1.8)
Hypocalcemia	49 / 223 (22.0)	6 / 223 (2.7)	28 / 111 (25.2)	2 / 111 (1.8)
Hypoglycemia	2 / 224 (0.9)	0 / 224	3 / 110 (2.7)	0 / 110 (0)
Hypokalemia	44 / 224 (19.6)	10 / 224 (4.5)	15 / 110 (13.6)	3 / 110 (2.7)
Hyponatremia[c]	69 / 224 (30.8)	6 / 224 (2.7)	33 / 110 (30.0)	5 / 110 (4.5)
Hypophosphatemia[c]	140 / 223 (62.8)	13 / 223 (5.8)	53 / 111 (47.7)	2 / 111 (1.8)

Sources: Table 14.3.4.1.2.1 and Table 14.3.4.1.7.1, Study CO-338-043 CSR.

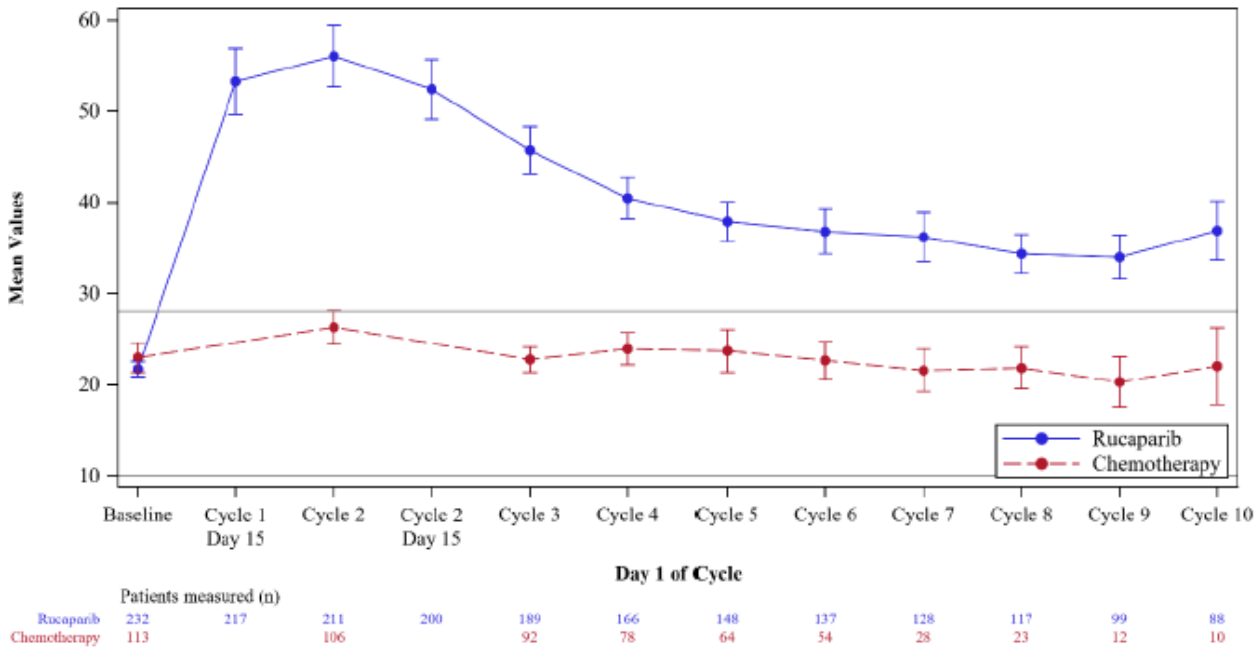
Abbreviations: CSR = clinical study report; CTCAE = Common Terminology Criteria for Adverse Events; G = grade.

[a] Shifts are based on worst grade experienced on treatment and patients who had at least a 1 grade shift from baseline.

[b] In CTCAE v5.0, a shift to worst grade experienced on-treatment for alanine aminotransferase increased, alkaline phosphatase increased, aspartate aminotransferase increased, and blood bilirubin increased is the same as the worst toxicity grade experienced on-treatment.

[c] Labs were graded using CTCAE v5.0 except for hyperglycemia, hyponatremia, and hypophosphatemia, which used CTCAE v4.03.

Figure 31: ALT (U/L): Mean (± SE) Values by Cycle at Baseline and On-Treatment – Treatment Part (Safety Population)

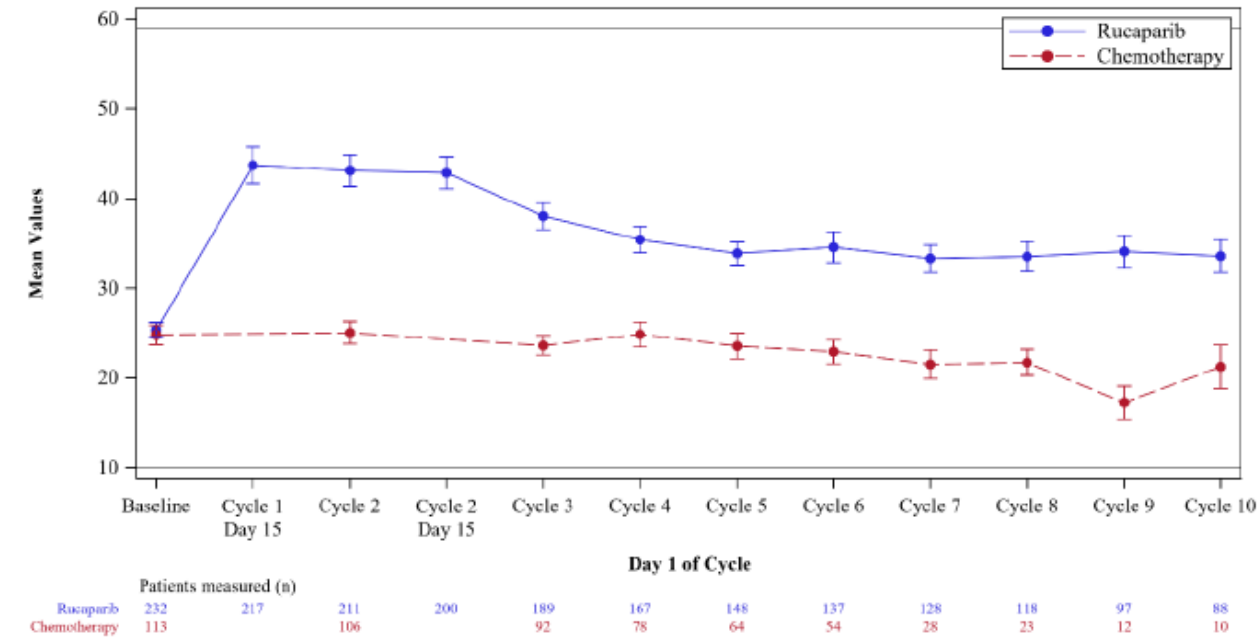


Abbreviations: ALT = alanine aminotransferase; SE = standard error.

Notes: The normal range is 10 to 28 U/L. The upper horizontal line represents the upper limit of normal, and the lower horizontal line represents the lower limit of normal.

The on-treatment period is defined as the time from first dose of study drug to 28 days after the last dose of study drug in the Treatment Part and prior to start of rucaparib in the Crossover Part.

Figure 32: AST (U/L): Mean (± SE) Values by Cycle at Baseline and On-Treatment – Treatment Part (Safety Population)

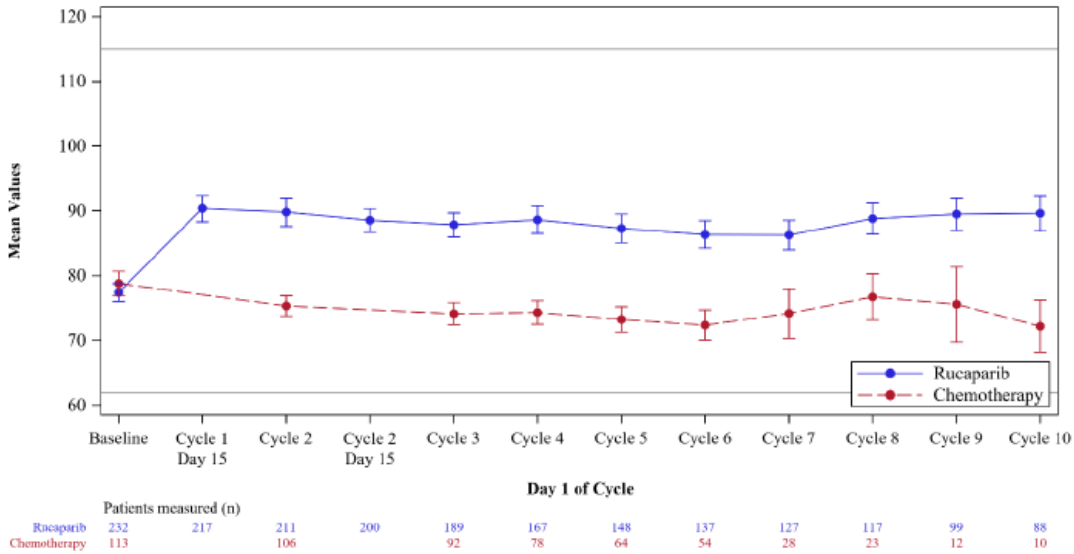


Abbreviations: AST = aspartate aminotransferase; SE = standard error.

Notes: The normal range is 10 to 59 U/L. The upper horizontal line represents the upper limit of normal, and the lower horizontal line represents the lower limit of normal.

The on-treatment period is defined as the time from first dose of study drug to 28 days after the last dose of study drug in the Treatment Part and prior to start of rucaparib in the Crossover Part.

Figure 33: Creatinine (µmol/L): Mean (± SE) Values by Cycle at Baseline and On-Treatment – Treatment Part (Safety Population)



Source: Figure 14.4.4.1.3.2.2.

Abbreviations: SE = standard error.

Notes: The normal range is 61.9 to 115 µmol/L. The upper horizontal line represents the upper limit of normal, and the lower horizontal line represents the lower limit of normal.

The on-treatment period is defined as the time from first dose of study drug to 28 days after the last dose of study drug in the Treatment Part and prior to start of rucaparib in the Crossover Part.

Electrocardiograms

In the rucaparib and chemotherapy groups across time points, the percent of patient with QTcB and QTcF values ≥ 450 msec was typically < 20% of patients and QTcB and QTcF ≥ 481 msec or ≥ 501 msec occurred in few patients. The ranges in proportion of patients with change from baseline in QTcB and QTcF > 30 msec and > 60 msec through Cycle 6 of treatment in rucaparib and chemotherapy groups are in the table below.

Table 38: Change from Baseline in QTcF and QTcB Values On-treatment Through Cycle 6 of Treatment With Rucaparib or Chemotherapy – Treatment Part (Safety Population)

ECG Parameter	Rucaparib (N=232)	Chemotherapy (N=113)
	Range of Patients With Change from Baseline	
	n/total (%)	
QTcF		
Change from baseline > 30 msec	26 / 199 (13.1) - 22 / 129 (17.1)	3 / 72 (4.2) - 7 / 50 (14.0)
Change from baseline > 60 msec	3 / 199 (1.5) - 7 / 129 (5.4)	1 / 100 (1.0) - 3 / 61 (4.9)
QTcB		
Change from baseline > 30 msec	21 / 159 (13.2) - 26 / 129 (20.2)	9 / 100 (9.0) - 7 / 50 (14.0)
Change from baseline > 60 msec	3 / 139 (2.2) - 7 / 129 (5.4)	1 / 72 (1.4) - 4 / 61 (6.6)

Source: Table 14.3.6.1.1.1.1 and Table 14.3.6.1.1.2.1.

Abbreviations: ECG = electrocardiogram; QT = time from the beginning of the Q wave to the end of the T wave; QTcB = QT interval was corrected by Bazett's method; QTcF = QT interval was corrected by Fridericia's method.

Table 39: Summary of QTcF Values On Treatment - Treatment Part (Safety Population)

	Rucaparib		Chemotherapy	
	Baseline (N = 232)	Longest Value On Treatment (N = 214)	Baseline (N = 113)	Longest Value On Treatment (N = 110)
QTcF values, n (%)[a]				
≥ 450 msec	9 (3.9%)	66 (30.8%)	5 (4.4%)	26 (23.6%)
≥ 481 msec	3 (1.3%)	18 (8.4%)	2 (1.8%)	8 (7.3%)
≥ 501 msec	1 (0.4%)	11 (5.1%)	2 (1.8%)	6 (5.5%)
Change from baseline > 30 msec	-	100 (46.7%)	-	31 (28.2%)
Change from baseline > 60 msec	-	31 (14.5%)	-	10 (9.1%)

Source: Table 15.2

Abbreviation: QTcF = QT interval corrected using Fridericia's method.

[a] Categories are not mutually exclusive: ≥ 450 msec category includes patients in both ≥ 481 msec and ≥ 501 msec categories and the ≥ 481 msec category includes patients in the ≥ 501 msec category. Similarly, the category "Change from baseline > 30 msec" includes patients with "Change from baseline > 60 msec".

Table 40: Summary of QTcB Values On Treatment - Treatment Part (Safety Population)

	Rucaparib		Chemotherapy	
	Baseline (N = 232)	Longest Value On Treatment (N = 214)	Baseline (N = 113)	Longest Value On Treatment (N = 110)
QTcB values, n (%)[a]				
≥ 450 msec	24 (10.3)	115 (53.7)	14 (12.4)	48 (43.6)
≥ 481 msec	5 (2.2)	35 (16.4)	3 (2.7)	18 (16.4)
≥ 501 msec	3 (1.3)	23 (10.7)	2 (1.8)	8 (7.3)
Change from baseline > 30 msec	-	105 (49.1)	-	38 (34.5)
Change from baseline > 60 msec	-	39 (18.2)	-	16 (14.5)

Source: Table 15.1

Abbreviation: QTcB = QT interval corrected using Bazett's method.

[a] Categories are not mutually exclusive: ≥ 450 msec category includes patients in both ≥ 481 msec and ≥ 501 msec categories and the ≥ 481 msec category includes patients in the ≥ 501 msec category. Similarly, the category "Change from baseline > 30 msec" includes patients with "Change from baseline > 60 msec".

Safety in special populations

Age

In Study CO-338-043, for the Treatment Part, Safety Population, the rucaparib group comprised 81.0% (188/232) patients who were < 65 years old, 15.9% (37/232) patients who were 65 to 74 years old, and 3.0% (7/232) patients who were ≥ 75 years old. The chemotherapy group comprised 76.1% (86/113) patients who were < 65 years old, 22.1% (25/113) patients who were 65 to 74 years old, and 1.8% (2/113) patients who were ≥ 75 years old.

Table 41: Summary of TEAEs in Patients Aged ≥ 75 years – Pooled Ovarian Cancer Safety Population

System Organ Class Preferred Term	Pooled Ovarian Cancer Safety Population	
	Rucaparib	
	Age Group (years)	
	< 75 N = 1,070	≥ 75 N = 99
	n (%)	
Patients with 1 or more TEAE	1,060 (99.1)	99 (100)
Patients with 1 or more treatment-related TEAE	1,007 (94.1)	98 (99.0)
TEAEs reported in ≥ 20% of patients aged ≥ 75 years (SOC or PT)[a]		
Combined Preferred Terms		
Combined Abdominal Pain	442 (41.3)	32 (32.3)
Combined ALT/AST Increased	396 (37.0)	41 (41.4)
Combined Anemia/Hemoglobin Decreased	473 (44.2)	49 (49.5)
Combined Asthenia/Fatigue/Lethargy	747 (69.8)	76 (76.8)
Combined Thrombocytopenia/Decreased Platelets	276 (25.8)	28 (28.3)
Blood and lymphatic system disorders	**548 (51.2)**	**53 (53.5)**
Anaemia	457 (42.7)	47 (47.5)
Gastrointestinal disorders	**952 (89.0)**	**88 (88.9)**
Abdominal pain	333 (31.1)	26 (26.3)
Constipation	352 (32.9)	39 (39.4)
Diarrhoea	328 (30.7)	32 (32.3)
Nausea	770 (72.0)	75 (75.8)
Vomiting	443 (41.4)	35 (35.4)
General disorders and administration site conditions	**825 (77.1)**	**80 (80.8)**
Asthenia	236 (22.1)	21 (21.2)
Fatigue	538 (50.3)	55 (55.6)
Infections and infestations	**451 (42.1)**	**39 (39.4)**
Investigations	**640 (59.8)**	**65 (65.7)**
Alanine aminotransferase increased	370 (34.6)	34 (34.3)
Aspartate aminotransferase increased	335 (31.3)	36 (36.4)
Blood creatinine increased	190 (17.8)	33 (33.3)
Metabolism and nutrition disorders	**526 (49.2)**	**62 (62.6)**
Decreased appetite	318 (29.7)	40 (40.4)
Musculoskeletal and connective tissue disorders	**411 (38.4)**	**36 (36.4)**
Nervous system disorders	**613 (57.3)**	**61 (61.6)**
Dysgeusia	361 (33.7)	30 (30.3)
Psychiatric disorders	**240 (22.4)**	**20 (20.2)**

System Organ Class Preferred Term	Pooled Ovarian Cancer Safety Population	
	Rucaparib	
	Age Group (years)	
	< 75 N = 1,070	≥ 75 N = 99
	n (%)	
Respiratory, thoracic and mediastinal disorders	**398 (37.2)**	**37 (37.4)**
Dyspnoea	191 (17.9)	22 (22.2)
Skin and subcutaneous tissue disorders	**439 (41.0)**	**47 (47.5)**
Vascular disorders	**197 (18.4)**	**20 (20.2)**
TEAEs with incidence < 20% but more frequent in patients aged ≥ 75 years (PT)[b]		
Dizziness	143 (13.4)	19 (19.2)
Hypertension	73 (6.8)	13 (13.1)
Lethargy	27 (2.5)	6 (6.1)
Oedema peripheral	107 (10.0)	14 (14.1)
Pruritus	92 (8.6)	14 (14.1)
Pyrexia	131 (12.2)	19 (19.2)
Urinary tract infection	130 (12.1)	18 (18.2)
Weight decreased	120 (11.2)	16 (16.2)

Sources: Table 2.7.4.5.1.1, Table 2.7.4.5.2.1, Table 2.7.4.5.1.2, and Table 2.7.4.5.2.2, A4 T2V ISS.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CSR = clinical study report; ISS = integrated summary of safety; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

[a] Frequency ≥ 20% in patients who received rucaparib in the Pooled Ovarian Cancer Safety Population.

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

Platinum status

Table 42: Summary of TEAEs by Platinum Status – Treatment Part (Safety Population) in Study CO-338-043

	Rucaparib			Chemotherapy		
	Platinum-Sensitive (N = 48)	Partially Platinum-Sensitive (N = 65)	Platinum-Resistant (N = 119)	Platinum-Sensitive (N = 25)	Partially Platinum-Sensitive (N = 30)	Platinum-Resistant (N = 58)
	n (%)			n (%)		
Patients with 1 or more TEAE	47 (97.9)	63 (96.9)	112 (94.1)	23 (92.0)	30 (100.0)	53 (91.4)
Patients with 1 or more treatment-related TEAE	47 (97.9)	56 (86.2)	103 (86.6)	23 (92.0)	29 (96.7)	46 (79.3)
Patients with 1 or more serious TEAE	13 (27.1)	22 (33.8)	27 (22.7)	3 (12.0)	2 (6.7)	8 (13.8)
Patients with 1 or more serious treatment-related TEAE	9 (18.8)	9 (13.8)	14 (11.8)	2 (8.0)	1 (3.3)	3 (5.2)
Patients with 1 or more TEAE of Grade 3 or higher	26 (54.2)	45 (69.2)	65 (54.6)	13 (52.0)	9 (30.0)	21 (36.2)
Patients with 1 or more treatment-related TEAE of Grade 3 or higher	24 (50.0)	32 (49.2)	42 (35.3)	11 (44.0)	5 (16.7)	16 (27.6)
Patients with 1 or more TEAE leading to death	0	8 (12.3)	7 (5.9)	0	1 (3.3)	2 (3.4)
Patients with 1 or more treatment-related TEAE leading to death	0	2 (3.1)	1 (0.8)	0	0	0
Patients with 1 or more TEAE leading to study drug discontinuation	3 (6.3)	9 (13.8)	8 (6.7)	3 (12.0)	2 (6.7)	10 (17.2)
Patients with 1 or more treatment-related TEAE leading to study drug discontinuation	3 (6.3)	4 (6.2)	3 (2.5)	3 (12.0)	1 (3.3)	6 (10.3)
Patients with 1 or more TEAE leading to dose reduction or interruption	24 (50.0)	39 (60.0)	52 (43.7)	17 (68.0)	9 (30.0)	24 (41.4)
Patients with 1 or more treatment-related TEAE leading to dose reduction or interruption	20 (41.7)	34 (52.3)	44 (37.0)	15 (60.0)	6 (20.0)	19 (32.8)

Sources: Table 14.3.1.1.1.1.17, Table 14.3.1.1.1.1.18 and Table 14.3.1.1.1.1.19, A4 T2V ISS.

Abbreviations: ISS = integrated summary of safety; TEAE = treatment-emergent adverse event.

Table 43: Treatment-emergent AEs Reported in ≥ 20% of Patients in Any Group by Platinum Status – Treatment Part (Safety Population) in Study CO-338-043

	Rucaparib			Chemotherapy		
	Platinum-Sensitive (N = 48)	Partially Platinum-Sensitive (N = 65)	Platinum-Resistant (N = 119)	Platinum-Sensitive (N = 25)	Partially Platinum-Sensitive (N = 30)	Platinum-Resistant (N = 58)
	n (%)			n (%)		
Number of Patients With At Least 1 TEAE	**47 (97.9)**	**63 (96.9)**	**112 (94.1)**	**23 (92.0)**	**30 (100.0)**	**53 (91.4)**
Combined Preferred Terms						
Combined ALT/AST Increased	22 (45.8)	21 (32.3)	37 (31.1)	3 (12.0)	3 (10.0)	7 (12.1)
Combined Anemia/Hemoglobin Decreased	28 (58.3)	41 (63.1)	56 (47.1)	5 (20.0)	8 (26.7)	23 (39.7)
Combined Asthenia/Fatigue	27 (56.3)	28 (43.1)	60 (50.4)	16 (64.0)	11 (36.7)	23 (39.7)
Combined Neuropathy	2 (4.2)	1 (1.5)	4 (3.4)	8 (32.0)	10 (33.3)	17 (29.3)
Combined Neutropenia/Decreased ANC	9 (18.8)	20 (30.8)	23 (19.3)	11 (44.0)	4 (13.3)	17 (29.3)
Combined Thrombocytopenia/Decreased Platelets	7 (14.6)	20 (30.8)	27 (22.7)	6 (24.0)	1 (3.3)	6 (10.3)
Blood and lymphatic system disorders	**29 (60.4)**	**47 (72.3)**	**67 (56.3)**	**10 (40.0)**	**11 (36.7)**	**29 (50.0)**
Anaemia	27 (56.3)	40 (61.5)	56 (47.1)	5 (20.0)	8 (26.7)	22 (37.9)
Leukopenia	5 (10.4)	6 (9.2)	10 (8.4)	5 (20.0)	1 (3.3)	12 (20.7)
Neutropenia	8 (16.7)	17 (26.2)	22 (18.5)	10 (40.0)	4 (13.3)	14 (24.1)
Thrombocytopenia	4 (8.3)	18 (27.7)	24 (20.2)	6 (24.0)	1 (3.3)	6 (10.3)
Gastrointestinal disorders	**41 (85.4)**	**47 (72.3)**	**80 (67.2)**	**20 (80.0)**	**24 (80.0)**	**31 (53.4)**
Abdominal pain	8 (16.7)	18 (27.7)	28 (23.5)	3 (12.0)	5 (16.7)	10 (17.2)
Constipation	13 (27.1)	10 (15.4)	14 (11.8)	5 (20.0)	7 (23.3)	7 (12.1)
Diarrhoea	14 (29.2)	6 (9.2)	27 (22.7)	5 (20.0)	7 (23.3)	12 (20.7)
Nausea	29 (60.4)	33 (50.8)	62 (52.1)	17 (68.0)	7 (23.3)	12 (20.7)
Vomiting	15 (31.3)	22 (33.8)	42 (35.3)	8 (32.0)	4 (13.3)	7 (12.1)
General disorders and administration site conditions	**30 (62.5)**	**34 (52.3)**	**70 (58.8)**	**17 (68.0)**	**13 (43.3)**	**27 (46.6)**

	Rucaparib			Chemotherapy		
	Platinum-Sensitive (N = 48)	Partially Platinum-Sensitive (N = 65)	Platinum-Resistant (N = 119)	Platinum-Sensitive (N = 25)	Partially Platinum-Sensitive (N = 30)	Platinum-Resistant (N = 58)
	n (%)			n (%)		
Asthenia	14 (29.2)	18 (27.7)	32 (26.9)	8 (32.0)	3 (10.0)	13 (22.4)
Fatigue	15 (31.3)	11 (16.9)	29 (24.4)	9 (36.0)	9 (30.0)	10 (17.2)
Infections and infestations	**20 (41.7)**	**20 (30.8)**	**33 (27.7)**	**5 (20.0)**	**8 (26.7)**	**14 (24.1)**
Investigations	**33 (68.8)**	**35 (53.8)**	**61 (51.3)**	**8 (32.0)**	**5 (16.7)**	**22 (37.9)**
Alanine aminotransferase increased	22 (45.8)	21 (32.3)	31 (26.1)	3 (12.0)	2 (6.7)	7 (12.1)
Aspartate aminotransferase increased	19 (39.6)	19 (29.2)	34 (28.6)	2 (8.0)	3 (10.0)	3 (5.2)
Metabolism and nutrition disorders	**18 (37.5)**	**24 (36.9)**	**46 (38.7)**	**14 (56.0)**	**12 (40.0)**	**26 (44.8)**
Decreased appetite	8 (16.7)	10 (15.4)	26 (21.8)	8 (32.0)	5 (16.7)	7 (12.1)
Musculoskeletal and connective tissue disorders	**16 (33.3)**	**11 (16.9)**	**22 (18.5)**	**6 (24.0)**	**10 (33.3)**	**10 (17.2)**
Nervous system disorders	**22 (45.8)**	**24 (36.9)**	**34 (28.6)**	**12 (48.0)**	**14 (46.7)**	**28 (48.3)**
Dysgeusia	16 (33.3)	9 (13.8)	14 (11.8)	3 (12.0)	3 (10.0)	2 (3.4)
Neuropathy peripheral	1 (2.1)	0	1 (0.8)	2 (8.0)	8 (26.7)	6 (10.3)
Respiratory, thoracic and mediastinal disorders	**16 (33.3)**	**15 (23.1)**	**23 (19.3)**	**6 (24.0)**	**9 (30.0)**	**12 (20.7)**
Skin and subcutaneous tissue disorders	**21 (43.8)**	**16 (24.6)**	**16 (13.4)**	**9 (36.0)**	**18 (60.0)**	**22 (37.9)**
Alopecia	9 (18.8)	2 (3.1)	1 (0.8)	7 (28.0)	15 (50.0)	16 (27.6)
Vascular disorders	**3 (6.3)**	**11 (16.9)**	**12 (10.1)**	**5 (20.0)**	**4 (13.3)**	**6 (10.3)**

Sources: Table 14.3.1.1.2.1.17, Table 14.3.1.1.2.1.18, Table 14.3.1.1.2.1.19, Table 14.3.1.1.1.1.21, Table 14.3.1.1.1.1.22, Table 14.3.1.1.1.1.23, A4 T2V ISS.

Abbreviations: ALT = alanine aminotransferase increased; ANC = absolute neutrophil count; AST = aspartate aminotransferase increased; ISS = integrated summary of safety; TEAE = treatment-emergent adverse event.

Renal impairment

In Study CO-338-043, for the Treatment Part, Safety Population, the rucaparib group included 40.1% (93/232) patients with no renal impairment, 41.8% (97/232) patients with mild renal impairment, and 18.1% (42/232 patients) with moderate renal impairment. The chemotherapy group included 33.6% (38/113) patients with no renal impairment, 44.2% (50/113) patients with mild renal impairment, and 22.1% (25/113) patients with moderate renal impairment.

Table 44: Summary of TEAEs by Renal Function – Treatment Part (Safety Population) in Study CO-338-043

	Rucaparib			Chemotherapy		
	No Renal Impairment[a] (N = 93)	Mild Renal Impairment[b] (N = 97)	Moderate Renal Impairment[c] (N = 42)	No Renal Impairment[a] (N = 38)	Mild Renal Impairment[b] (N = 50)	Moderate Renal Impairment[c] (N = 25)
	n (%)			n (%)		
Patients with 1 or more TEAE	90 (96.8)	90 (92.8)	42 (100)	33 (86.8)	48 (96.0)	25 (100)
Patients with 1 or more treatment-related TEAE	84 (90.3)	83 (85.6)	39 (92.9)	29 (76.3)	46 (92.0)	23 (92.0)
Patients with 1 or more serious TEAE	23 (24.7)	25 (25.8)	14 (33.3)	5 (13.2)	4 (8.0)	4 (16.0)
Patients with 1 or more serious treatment-related TEAE	12 (12.9)	12 (12.4)	8 (19.0)	2 (5.3)	2 (4.0)	2 (8.0)
Patients with 1 or more TEAE of Grade 3 or higher	51 (54.8)	59 (60.8)	26 (61.9)	15 (39.5)	20 (40.0)	8 (32.0)
Patients with 1 or more treatment-related TEAE of Grade 3 or higher	35 (37.6)	41 (42.3)	22 (52.4)	9 (23.7)	16 (32.0)	7 (28.0)
Patients with 1 or more TEAE leading to death	3 (3.2)	7 (7.2)	5 (11.9)	0	2 (4.0)	1 (4.0)
Patients with 1 or more treatment-related TEAE leading to death	1 (1.1)	1 (1.0)	1 (2.4)	0	0	0
Patients with 1 or more TEAE leading to study drug discontinuation	3 (3.2)	10 (10.3)	7 (16.7)	5 (13.2)	6 (12.0)	4 (16.0)
Patients with 1 or more treatment-related TEAE leading to study drug discontinuation	2 (2.2)	4 (4.1)	4 (9.5)	3 (7.9)	4 (8.0)	3 (12.0)
Patients with 1 or more TEAE leading to dose reduction or interruption	44 (47.3)	47 (48.5)	24 (57.1)	17 (44.7)	24 (48.0)	9 (36.0)
Patients with 1 or more treatment-related TEAE leading to dose reduction or interruption	38 (40.9)	39 (40.2)	21 (50.0)	13 (34.2)	20 (40.0)	7 (28.0)

Sources: Table 14.3.1.1.1.1.14, Table 14.3.1.1.1.1.15 and Table 14.3.1.1.1.1.16, A4 T2V ISS.

Abbreviations: CLcr = creatinine clearance; EMA = European Medicines Agency; ISS = integrated summary of safety; TEAE = treatment-emergent adverse event.

[a] Patients with no renal impairment had CLcr ≥ 90 mL/min according to EMA guideline

[b] Patients with mild renal impairment had CLcr ≥ 60 mL/min to < 90 mL/min according to EMA guideline.

[c] Patients with moderate renal impairment had CLcr ≥ 30 mL/min to < 60 mL/min according to EMA guideline.

Table 45: Grade 3 or Higher TEAEs Reported in ≥ 5% of Rucaparib-treated Patients by Renal Function – Study CO-338-043, and Pooled Ovarian Cancer Safety Population

	CO-338-043 Treatment Part Safety Population			Pooled Ovarian Cancer Safety Population		
	Rucaparib			Rucaparib		
	No Renal Impairment[a] (N = 93)	Mild Renal Impairment[b] (N = 97)	Moderate Renal Impairment[c] (N = 42)	No Renal Impairment[a] (N = 439)	Mild Renal Impairment[b] (N = 495)	Moderate Renal Impairment[c] (N = 234)
	n (%)			n (%)		
Number of Patients With At Least 1 Grade 3 or Higher TEAE	**51 (54.8)**	**59 (60.8)**	**26 (61.9)**	**244 (55.6)**	**312 (63.0)**	**170 (72.6)**
Combined Preferred Terms						
Combined ALT/AST Increased	4 (4.3)	12 (12.4)	2 (4.8)	30 (6.8)	60 (12.1)	28 (12.0)
Combined Anemia/Hemoglobin Decreased	21 (22.6)	18 (18.6)	13 (31.0)	92 (21.0)	106 (21.4)	73 (31.2)
Combined Asthenia/Fatigue/Lethargy[d]	NA	NA	NA	37 (8.4)	48 (9.7)	31 (13.2)
Combined Asthenia/Fatigue	7 (7.5)	10 (10.3)	2 (4.8)	36 (8.2)	47 (9.5)	31 (13.2)
Combined Neutropenia/Decreased ANC	5 (5.4)	13 (13.4)	6 (14.3)	30 (6.8)	44 (8.9)	27 (11.5)
Combined Thrombocytopenia/Decreased Platelets	8 (8.6)	9 (9.3)	2 (4.8)	23 (5.2)	30 (6.1)	24 (10.3)
Blood and lymphatic system disorders	**28 (30.1)**	**29 (29.9)**	**16 (38.1)**	**115 (26.2)**	**134 (27.1)**	**82 (35.0)**

	CO-338-043 Treatment Part Safety Population			Pooled Ovarian Cancer Safety Population		
	Rucaparib			Rucaparib		
	No Renal Impairment[a] (N = 93)	Mild Renal Impairment[b] (N = 97)	Moderate Renal Impairment[c] (N = 42)	No Renal Impairment[a] (N = 439)	Mild Renal Impairment[b] (N = 495)	Moderate Renal Impairment[c] (N = 234)
	n (%)			n (%)		
Anaemia	21 (22.6)	17 (17.5)	13 (31.0)	90 (20.5)	102 (20.6)	65 (27.8)
Neutropenia	4 (4.3)	11 (11.3)	6 (14.3)	24 (5.5)	29 (5.9)	17 (7.3)
Thrombocytopenia	8 (8.6)	6 (6.2)	1 (2.4)	18 (4.1)	23 (4.6)	13 (5.6)
Gastrointestinal disorders	**11 (11.8)**	**17 (17.5)**	**6 (14.3)**	**66 (15.0)**	**77 (15.6)**	**53 (22.6)**
Abdominal pain	2 (2.2)	6 (6.2)	1 (2.4)	16 (3.6)	18 (3.6)	9 (3.8)
Nausea	3 (3.2)	3 (3.1)	0	22 (5.0)	15 (3.0)	12 (5.1)
Vomiting	5 (5.4)	3 (3.1)	3 (7.1)	21 (4.8)	15 (3.0)	16 (6.8)
General disorders and administration site conditions	**9 (9.7)**	**12 (12.4)**	**3 (7.1)**	**44 (10.0)**	**56 (11.3)**	**38 (16.2)**
Fatigue	4 (4.3)	6 (6.2)	1 (2.4)	17 (3.9)	30 (6.1)	24 (10.3)
Infections and infestations	**8 (8.6)**	**5 (5.2)**	**2 (4.8)**	**17 (3.9)**	**29 (5.9)**	**23 (9.8)**
Investigations	**10 (10.8)**	**18 (18.6)**	**8 (19.0)**	**62 (14.1)**	**110 (22.2)**	**62 (26.5)**
Alanine aminotransferase increased	4 (4.3)	12 (12.4)	2 (4.8)	29 (6.6)	56 (11.3)	27 (11.5)
Blood creatinine increased	2 (2.2)	0	3 (7.1)	3 (0.7)	1 (0.2)	4 (1.7)
Metabolism and nutrition disorders	**7 (7.5)**	**1 (1.0)**	**4 (9.5)**	**32 (7.3)**	**32 (6.5)**	**31 (13.2)**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**3 (3.2)**	**3 (3.1)**	**3 (7.1)**	**27 (6.2)**	**24 (4.8)**	**10 (4.3)**
Malignant neoplasm progression	3 (3.2)	2 (2.1)	3 (7.1)	17 (3.9)	17 (3.4)	8 (3.4)
Renal and urinary disorders	**2 (2.2)**	**2 (2.1)**	**2 (4.8)**	**9 (2.1)**	**10 (2.0)**	**12 (5.1)**
Respiratory, thoracic and mediastinal disorders	**2 (2.2)**	**3 (3.1)**	**3 (7.1)**	**8 (1.8)**	**15 (3.0)**	**9 (3.8)**

Abbreviations: ALT = alanine aminotransferase increased; ANC = absolute neutrophil count; AST = aspartate aminotransferase increased; CLcr = creatinine clearance; EMA = European Medicines Agency; ISS = integrated summary of safety; NA = not analyzed; SmPC = Summary of Product Characteristics; TEAE = treatment-emergent adverse event.

[a] Patients with no renal impairment had CLcr ≥ 90 mL/min according to EMA guideline

[b] Patients with mild renal impairment had CLcr ≥ 60 mL/min to < 90 mL/min according to EMA guideline.

[c] Patients with moderate renal impairment had CLcr ≥ 30 mL/min to < 60 mL/min according to EMA guideline.

[d] Combined events of asthenia/fatigue/lethargy were summarized for the Pooled Ovarian Cancer Safety Population to support the summary presented in the Rubraca SmPC; however, this combined group of terms was not analyzed for the individual treatment groups from Study CO-338-043.

Discontinuation due to TEAEs

Table 46: Treatment-emergent AEs That Led to Study Drug Discontinuation in ≥ 2 Patients: Study CO-338-043, and Pooled Ovarian Cancer Safety Population

System Organ Class Preferred Term	CO-338-043 Treatment Part Safety Population		Pooled Ovarian Cancer Safety Population
	Chemotherapy (N = 113)	Rucaparib (N = 232)	Rucaparib (N = 1,169)
	n (%)		
Number of Patients With At Least 1 TEAE Leading to Study Drug Discontinuation	**15 (13.3)**	**20 (8.6)**	**209 (17.9)**
Combined Preferred Terms			
Combined Abdominal Pain[a]	NA	NA	7 (0.6)
Combined ALT/AST Increased	0	0	2 (0.2)
Combined Anemia/Hemoglobin Decreased	1 (0.9)	1 (0.4)	20 (1.7)
Combined Asthenia/Fatigue/Lethargy[a]	NA	NA	28 (2.4)
Combined Asthenia/Fatigue	0	2 (0.9)	27 (2.3)
Combined Leukopenia/White Blood Cell Count Decreased[a]	NA	NA	2 (0.2)
Combined Neutropenia/Decreased ANC	0	0	5 (0.4)

System Organ Class Preferred Term	CO-338-043 Treatment Part Safety Population		Pooled Ovarian Cancer Safety Population
	Chemotherapy (N = 113)	Rucaparib (N = 232)	Rucaparib (N = 1,169)
	n (%)		
Combined Thrombocytopenia/Decreased Platelets	0	1 (0.4)	20 (1.7)
Blood and lymphatic system disorders	**1 (0.9)**	**1 (0.4)**	**37 (3.2)**
Anaemia	1 (0.9)	1 (0.4)	20 (1.7)
Febrile neutropenia	0	0	4 (0.3)
Neutropenia	0	0	2 (0.2)
Thrombocytopenia	0	0	14 (1.2)
Cardiac disorders	**0**	**1 (0.4)**	**6 (0.5)**
Gastrointestinal disorders	**1 (0.9)**	**6 (2.6)**	**67 (5.7)**
Abdominal pain	0	0	6 (0.5)
Ascites	1 (0.9)	0	5 (0.4)
Diarrhoea	0	0	2 (0.2)
Intestinal obstruction	0	3 (1.3)	7 (0.6)
Large intestinal obstruction	0	0	2 (0.2)
Nausea	0	0	21 (1.8)
Small intestinal obstruction	0	0	11 (0.9)
Vomiting	0	1 (0.4)	15 (1.3)
General disorders and administration site conditions	**2 (1.8)**	**5 (2.2)**	**35 (3.0)**
Asthenia	0	1 (0.4)	7 (0.6)
Death	0	3 (1.3)	3 (0.3)
Fatigue	0	1 (0.4)	21 (1.8)
General physical health deterioration	0	0	3 (0.3)
Immune system disorders	**2 (1.8)**	**0**	**1 (0.1)**
Infections and infestations	**0**	**2 (0.9)**	**6 (0.5)**
Sepsis	0	0	3 (0.3)
Investigations	**0**	**3 (1.3)**	**21 (1.8)**
Alanine aminotransferase increased	0	0	2 (0.2)
Aspartate aminotransferase increased	0	0	2 (0.2)
Blood creatinine increased	0	1 (0.4)	3 (0.3)
Neutrophil count decreased	0	0	3 (0.3)
Platelet count decreased	0	1 (0.4)	6 (0.5)

System Organ Class Preferred Term	CO-338-043 Treatment Part Safety Population		Pooled Ovarian Cancer Safety Population
	Chemotherapy (N = 113)	Rucaparib (N = 232)	Rucaparib (N = 1,169)
	n (%)		
Weight decreased	0	0	3 (0.3)
Metabolism and nutrition disorders	**0**	**0**	**5 (0.4)**
Decreased appetite	0	0	4 (0.3)
Musculoskeletal and connective tissue disorders	**0**	**0**	**6 (0.5)**
Back pain	0	0	2 (0.2)
Pain in extremity	0	0	2 (0.2)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**1 (0.9)**	**2 (0.9)**	**41 (3.5)**
Acute myeloid leukaemia	0	0	2 (0.2)
Malignant neoplasm progression	1 (0.9)	1 (0.4)	28 (2.4)
Myelodysplastic syndrome	0	1 (0.4)	7 (0.6)
Nervous system disorders	**2 (1.8)**	**0**	**9 (0.8)**
Seizure	1 (0.9)	0	2 (0.2)
Renal and urinary disorders	**0**	**1 (0.4)**	**7 (0.6)**
Acute kidney injury	0	0	2 (0.2)
Hydronephrosis	0	0	2 (0.2)
Renal failure	0	1 (0.4)	2 (0.2)
Respiratory, thoracic and mediastinal disorders	**1 (0.9)**	**0**	**6 (0.5)**
Dyspnoea	0	0	3 (0.3)
Skin and subcutaneous tissue disorders	**2 (1.8)**	**0**	**5 (0.4)**
Nail disorder	2 (1.8)	0	0
Pruritus	0	0	2 (0.2)
Vascular disorders	**2 (1.8)**	**0**	**1 (0.1)**
Deep vein thrombosis	2 (1.8)	0	0

Sources: Table 14.3.1.1.13.1.1.1, Study CO-338-043 CSR; Table 2.7.4.4.1, A4 T2V ISS.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CSR = clinical study report; ISS = integrated summary of safety; NA = not analyzed; SmPC = Summary of Product Characteristics; TEAE = treatment-emergent adverse event.

[a] Events of combined abdominal pain, combined asthenia/fatigue/lethargy, and combined leukopenia/white blood cell count decreased were summarized for the Pooled Ovarian Cancer Safety Population to support the summary presented in the Rubraca SmPC; however, these combined groups of terms were not analyzed for the individual treatment groups from Study CO-338-043.

Adverse events leading to dose reduction or treatment interruption

Table 47: Treatment-emergent AEs That Led to Dose Reduction of Study Drug in ≥ 2% of Patients in Any Group in Study CO-338-043, and Pooled Ovarian Cancer Safety Population

System Organ Class Preferred Term	CO-338-043 Treatment Part Safety Population		Pooled Ovarian Cancer Safety Population
	Chemotherapy (N = 113)	Rucaparib (N = 232)	Rucaparib (N = 1,169)
	n (%)		
Number of Patients With At Least 1 TEAE Leading to Study Drug Dose Reduction	**12 (10.6)**	**78 (33.6)**	**547 (46.8)**
Combined Preferred Terms			
Combined ALT/AST Increased	0	7 (3.0)	69 (5.9)
Combined Anemia/Hemoglobin Decreased	1 (0.9)	33 (14.2)	180 (15.4)
Combined Asthenia/Fatigue	0	10 (4.3)	125 (10.7)
Combined Asthenia/Fatigue/Lethargy[a]	NA	NA	127 (10.9)
Combined Neuropathy	6 (5.3)	0	2 (0.2)
Combined Neutropenia/Decreased ANC	3 (2.7)	13 (5.6)	50 (4.3)
Combined Thrombocytopenia/Decreased Platelets	0	15 (6.5)	93 (8.0)
Blood and lymphatic system disorders	**4 (3.5)**	**51 (22.0)**	**233 (19.9)**
Anaemia	1 (0.9)	33 (14.2)	168 (14.4)
Neutropenia	3 (2.7)	13 (5.6)	39 (3.3)
Thrombocytopenia	0	13 (5.6)	60 (5.1)
Gastrointestinal disorders	**0**	**9 (3.9)**	**137 (11.7)**
Nausea	0	8 (3.4)	105 (9.0)
Vomiting	0	2 (0.9)	39 (3.3)
General disorders and administration site conditions	**2 (1.8)**	**10 (4.3)**	**128 (10.9)**
Asthenia	0	7 (3.0)	33 (2.8)
Fatigue	0	4 (1.7)	94 (8.0)
Investigations	**0**	**18 (7.8)**	**176 (15.1)**
Alanine aminotransferase increased	0	7 (3.0)	67 (5.7)
Aspartate aminotransferase increased	0	3 (1.3)	26 (2.2)
Blood creatinine increased	0	5 (2.2)	37 (3.2)
Platelet count decreased	0	2 (0.9)	36 (3.1)
Metabolism and nutrition disorders	**0**	**7 (3.0)**	**49 (4.2)**
Decreased appetite	0	3 (1.3)	26 (2.2)
Nervous system disorders	**7 (6.2)**	**1 (0.4)**	**34 (2.9)**

Sources: Table 14.3.1.1.14.1.1.1 and Table 14.3.1.1.1.3, Study CO-338-043 CSR; Table 2.7.4.12.1, and Table 2.7.4.13.2, A4 T2V ISS.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CSR = clinical study report; ISS = integrated summary of safety; NA = not analyzed; SmPC = Summary of Product Characteristics; TEAE = treatment-emergent adverse event.

[a] Combined events of asthenia/fatigue/lethargy were summarized for the Pooled Ovarian Cancer Safety Population to support the summary presented in the Rubraca SmPC; however, this combined group of terms was not analyzed for the individual treatment groups from Study CO-338-043.

Table 48: Treatment-emergent AEs That Led to Study Drug Interruption Reported in ≥ 2% of Patients in Any Group in Study CO-338-043, and Pooled Ovarian Cancer Safety Population

System Organ Class Preferred Term	CO-338-043 Treatment Part Safety Population		Pooled Ovarian Cancer Safety Population
	Chemotherapy (N = 113)	Rucaparib (N = 232)	Rucaparib (N = 1,169)
	n (%)		
Number of Patients With At Least 1 TEAE Leading to Study Drug Interruption	**43 (38.1)**	**111 (47.8)**	**699 (59.8)**
Combined Preferred Terms			
Combined ALT/AST Increased	1 (0.9)	12 (5.2)	91 (7.8)
Combined Abdominal Pain[a]	NA	NA	48 (4.1)
Combined Anemia/Hemoglobin Decreased	9 (8.0)	42 (18.1)	199 (17.0)
Combined Asthenia/Fatigue	3 (2.7)	14 (6.0)	128 (10.9)
Combined Asthenia/Fatigue/Lethargy[a]	NA	NA	129 (11.0)
Combined Neutropenia/Decreased ANC	16 (14.2)	25 (10.8)	86 (7.4)
Combined Thrombocytopenia/Decreased Platelets	3 (2.7)	29 (12.5)	161 (13.8)
Blood and lymphatic system disorders	**22 (19.5)**	**67 (28.9)**	**290 (24.8)**
Anaemia	9 (8.0)	42 (18.1)	188 (16.1)
Leukopenia	5 (4.4)	5 (2.2)	8 (0.7)
Neutropenia	14 (12.4)	22 (9.5)	60 (5.1)
Thrombocytopenia	3 (2.7)	24 (10.3)	107 (9.2)
Gastrointestinal disorders	**6 (5.3)**	**28 (12.1)**	**257 (22.0)**
Abdominal pain	0	3 (1.3)	38 (3.3)
Diarrhoea	0	5 (2.2)	35 (3.0)
Intestinal obstruction	0	5 (2.2)	14 (1.2)
Nausea	5 (4.4)	11 (4.7)	124 (10.6)
Vomiting	3 (2.7)	15 (6.5)	117 (10.0)
General disorders and administration site conditions	**6 (5.3)**	**18 (7.8)**	**158 (13.5)**
Asthenia	2 (1.8)	8 (3.4)	35 (3.0)
Fatigue	1 (0.9)	6 (2.6)	96 (8.2)
Infections and infestations	**4 (3.5)**	**14 (6.0)**	**70 (6.0)**
Investigations	**6 (5.3)**	**31 (13.4)**	**229 (19.6)**
Alanine aminotransferase increased	1 (0.9)	12 (5.2)	89 (7.6)
Aspartate aminotransferase increased	0	8 (3.4)	51 (4.4)
Blood creatinine increased	0	7 (3.0)	41 (3.5)
Neutrophil count decreased	4 (3.5)	3 (1.3)	28 (2.4)
Platelet count decreased	0	6 (2.6)	60 (5.1)
Metabolism and nutrition disorders	**3 (2.7)**	**9 (3.9)**	**65 (5.6)**
Decreased appetite	1 (0.9)	3 (1.3)	29 (2.5)
Nervous system disorders	**3 (2.7)**	**1 (0.4)**	**35 (3.0)**
Respiratory, thoracic and mediastinal disorders	**4 (3.5)**	**4 (1.7)**	**29 (2.5)**

Sources: Table 14.3.1.1.15.1.1.1, Study CO-338-043 CSR; Table 2.7.4.11.1, A4 T2V ISS.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CSR = clinical study report; ISS = integrated summary of safety; NA = not analyzed; SmPC = Summary of Product Characteristics; TEAE = treatment-emergent adverse event.

[a] Events of combined abdominal pain and combined asthenia/fatigue/lethargy were summarized for the Pooled Ovarian Cancer Safety Population to support the summary presented in the Rubraca SmPC; however, these combined groups of terms were not analyzed for the individual treatment groups from Study CO-338-043.

Adverse drug reactions

Safety data reviewed for identification of ADRs presented in Section 4.8 of the current SmPC included safety data from Studies CO-338-010 and CO-338-017, and the placebo-controlled Study CO-338-014. These data represented 937 patients with ovarian cancer who received rucaparib as monotherapy in these studies in the treatment and maintenance treatment settings.

The updated safety data in patients treated with rucaparib from Study CO-338-043 (N = 232), and from the Pooled Ovarian Cancer Safety Population (N = 1,169), are consistent with the previously submitted ovarian cancer data. Hence only modest changes to some of the ADR frequency categories are proposed in Section 4.8 of the SmPC, while no ADRs are proposed by the MAH for addition or removal from the tabulated list of adverse reactions in the SmPC.

The proposed changes to the frequency categories of some ADRs in the tabulated list of adverse reactions in the SmPC are summarized in the table below.

Table 49: Proposed Changes to the Frequency Categories of Adverse Drug Reactions in the SmPC

MedDRA System Organ Class Preferred Term	**Current SmPC**	**Study CO-338-043**		**Pooled Ovarian Cancer Safety Population**	
Adverse Reaction	**Frequency Category[a]**	**Frequency Category[a]**	**%**	**Frequency Category[a]**	**%**
All CTCAEs Grades (all causality)					
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)					
Myelodysplastic syndrome	Common	Uncommon	0.4	Uncommon[b]	[b]
Acute myeloid leukaemia	Common	-	0	Uncommon[b]	[b]
Respiratory, thoracic and mediastinal disorders					
Dyspnoea	Common	Very common	10.8	Very common	18.2
Skin and subcutaneous tissue disorders					
Rash	Very common	Common	5.2	Common	9.6
CTCAE Grades 3 and Above (all causality)					
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)					
Myelodysplastic syndrome	Common	Uncommon	0.4	Uncommon[b]	[b]
Acute myeloid leukaemia	Common	-	0	Uncommon[b]	[b]
Blood and lymphatic system disorders					
Lymphopenia (incl. lab values)	Uncommon	Uncommon	0.4	Common	1.2

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; incl. = including; lab = laboratory; 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])

[b] MDS/AML frequency is based on an overall total patient population of 2,972 who have received 1 dose of oral rucaparib. The incidence (all CTCAE grades and CTCAE Grade 3 and above) of MDS/AML during therapy in patients who received rucaparib in Study CO-338-043 and Study CO-338-014 was 1.3% and 1.6%, respectively.

Post marketing experience

Rucaparib (Rubraca) is currently marketed in the US, United Kingdom (UK), Israel, and in selected countries in the EU (Germany, Italy, Spain, France, Netherlands). As detailed in the current Periodic Safety Update Report (PSUR) dated 16 February 2021, 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, whereas commercial exposure to Rubraca in the EU and UK has been calculated as treatment days. Cumulatively, to 19 December 2020, 7,509 patients have been

exposed worldwide to Rubraca (excluding commercial exposure in the EU and UK). Cumulatively, the total commercial exposure to Rubraca in the EU (Germany, Italy, Spain, France) and the UK was 139,365 treatment days.

According to the MAH, from US approval on 19 December 2016 to 19 December 2020, there were no safety signals detected from the post-marketing reports. The post-marketing safety data collected from 19 December 2016 to 19 December 2020 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.

7.3. Discussion

Through the current variation application, the MAH is providing results of **study CO-338-043 (ARIEL4)** to fulfil the SOB 001.

The safety dataset is comprised by **345 patients** who received at least one dose of study treatment (232 rucaparib and 113 chemotherapy). In addition, pooled safety data from studies CO-338-010 (a phase 1/2 open label study; n=74), study CO-338-017 (a phase 2, open-label study; n=491) and study CO-338-014 (a phase 3, randomised study of rucaparib versus placebo; n= 561) with study ARIEL4 have been provided (referred to as the "pooled ovarian safety population"), based on a total of 1,169 patients treated with rucaparib.

Safety data of studies CO-338-014, CO-338-010 and CO-338-017 were submitted during the initial CMA application with the 15 April 2017 visit cut-off date. During a subsequent procedure updated safety data were provided (data cut-off of 31 Dec 2017). The current safety data of these 3 studies are based, on a data cut-off of 31 Dec 2019, 1 Feb 2019 and 27 March 2019, respectively. Results of study ARIEL4 presented below are based on a data cut-off of 30 Sep 2020.

In the ARIEL4 study, the median duration of rucaparib exposure was of 7.3 months (range: 0, 41), compared with the 3.6 months (range: 0, 25) of chemotherapy. Moreover, in the rucaparib arm 27.2% of patients received treatment for ≥12 months compared with 3.5% in the chemotherapy arm. Due to differences in treatment exposure, which may have impacted the results, safety data adjusted by treatment exposure (i.e., incidence per 100 patient-years of treatment), have also been provided.

The majority of patients in the chemotherapy arm received paclitaxel (78%) followed by platinum-based doublet (14%) and platinum monotherapy (8%). The median number of cycles of chemotherapy was of 5 (range: 1, 21). As per protocol, patients in the chemotherapy arm, can receive up to 8 cycles However, the restriction to a maximum of 8 cycles applied only to platinum-containing regimens. Patients receiving weekly paclitaxel could continue treatment until disease progression or other reason for discontinuation. Patients treated with rucaparib had a median age of 59 (range: 38, 85) years, with only 7 (3%) patients being 75 years or older. The majority of patients were white (94%) and had a good performance status (ECOG 0 or 1). Patients with ECOG≥2 were excluded from the study. The proportion of patients with ECOG 1 was higher in the rucaparib arm (46% vs. 39%). Patients had received a median of 2 prior therapies (range: 2, 9).

The **most commonly reported** (≥30%) treatment-emergent adverse events (TEAEs) in the rucaparib arm were: combined anaemia/haemoglobin decreased (53.9% rucaparib vs. 31.9% chemotherapy), nausea (53.4% vs. 31.9%), combined asthenia/fatigue/lethargy (49.6% vs. 45.1%), combined ALT/AST increased (34.5% vs. 11.5%), vomiting (34.1% vs. 16.8%) and combined abdominal pain (31.9% vs. 22.1%). After adjusting for treatment exposure, the only TEAE with a higher incidence in the rucaparib arm was combined ALT/AST increased (45.9 TEAEs per 100 patient-years of treatment).

There were a total of 12 (5.2%) patients in the rucaparib arm while only 1 (0.9%) in the chemotherapy arm that reported an event of intestinal obstruction. Of the events reported in the rucaparib arm, 5

patients reported a SAE of intestinal obstruction (see below). The MAH was requested to provide further information on all the events of intestinal obstruction reported in the ARIEL4 study (as well as the pooled population) and discuss to what extent there was any relationship with rucaparib treatment. According to the MAH the events of intestinal obstruction reported in patients treated with rucaparib appear to be primarily related to the underlying disease rather than rucaparib treatment. The majority of events were not considered related to rucaparib by the investigator. In addition, the MAH stated that no differences were observed between treatment arms in the ARIEL3 study (3.2% rucaparib vs. 3.2% placebo), suggesting that these events were not related to study treatment. Regarding study ARIEL4, the MAH argues that differences observed between treatment arms may be due to the longer treatment exposure in the rucaparib arm. Thus, the MAH was requested to provide exposure-adjusted incidences of these events and the narratives of all patients that reported an event of intestinal obstruction. The submitted results still showed higher incidence in the rucaparib arm although the imbalances seemed to be smaller (8.0 events per 100 patient-years of treatment for rucaparib vs. 4.8 events per 100 patient-years for chemotherapy). For related AEs, the numbers were 0.6 events per 100 patient-years of treatment for rucaparib vs. 0 events per 100 patient-years for chemotherapy. After the review of the narratives, it is difficult to exclude a potential relationship with rucaparib. In this context, even if it is agreed that the underlying disease may have played a role, based on the exposure-adjusted rates and previous observations of intestinal obstruction, including serious events (Rubraca EPARs EMA/CHMP/238139/2018, EMA/902679/2019), the MAH included information on this AE in the SmPC (sections 4.4 and 4.8).

TEAEs of **Grade ≥3** were reported in 58.6% of patients in the rucaparib arm and 38.1% in the chemotherapy arm. After adjusting for treatment exposure, the incidence per 100 patient-years of TEAEs of Grade≥3 was lower in the rucaparib arm (78 vs. 103.3). The most commonly reported (≥10%) TEAEs of Grade≥3 were combined anaemia/haemoglobin decreased (22.4% rucaparib vs. 5.3% chemotherapy) and combined neutropenia/decreased ANC (10.3% vs. 15.1%).

Treatment-emergent **serious adverse events (TESAEs)** occurred in 26.7% of patients treated with rucaparib and 11.5% of patients treated with chemotherapy. TESAEs adjusted to 100 patient-years exposure were similar between treatment arms (35.6% rucaparib vs. 31.2% chemotherapy). TESAEs most frequently reported were combined anaemia/haemoglobin decreased (19 [8.2%] rucaparib vs. 2 [1.8%]), combined thrombocytopenia/decreased platelets (7 [3.0%] vs. 1 [0.9%]), intestinal obstruction (6 [2.6%], including one case of small intestinal obstruction) and malignant neoplasm progression (5 [2.2%] vs. 1 [0.9%]). In addition, 4 cases were reported among patients who crossed-over to rucaparib treatment. Some of these events appears to be related to the underlying disease, but in some others, contribution of rucaparib cannot be ruled out. See further discussion above.

Regarding **TEAEs with a fatal outcome**, there were 15 patients (6.5%) in the rucaparib arm and 3 (2.7%) in the chemotherapy arm. Five of these events in the rucaparib arm and 2 in the chemotherapy arm were due to malignant neoplasm progression. According to the MAH, with amendment 2 of the protocol, disease progression was no longer collected as TEAE. In the rucaparib arm, there were 3 deaths that were considered treatment-related (MDS, cardiac failure and death not otherwise specified).

Myelodysplastic syndrome and acute myeloid leukaemia (MDS/AML) are considered adverse events of special interest (**AESIs**) of rucaparib. Among a total of 2,972 patients treated with rucaparib in clinical trials, 27 patients (0.91%) had reported an event of MDS or AML. In study ARIEL4, five patients reported an event of MDS/AML (4 MDS and 1 AML) in the rucaparib arm, one of them fatal. Most of these events (all except one) were considered treatment-related by the investigator. MDS/AML is currently included in section 4.4 and 4.8 of the SmPC and it is considered an important potential risk of rucaparib. These events have also been reported with other PARP inhibitors such as olaparib and niraparib. During the procedure, updated safety data regarding MDS/AML were provided. Based on a later DCO (10 April 2022), 2 additional cases of MDS were reported in patients randomized to rucaparib. As a result of the new data provided the SmPC was updated to reflect these new cases of MDS/AML.

Pneumonitis was included as AESI with Amendment 2 of the protocol. According to the MAH, only one event of pneumonitis was reported in the chemotherapy arm. No further events were reported in the study in either treatment arm.

Changes from baseline in **laboratory results** were consistent with the reported TEAEs, being the most common anaemia and abnormal liver function tests. Further, hypophosphatemia and hyperglycaemia were also frequently reported. Most of the reported elevations were of Grade 1 or Grade 2.

The number of patients with QTc values ≥481 msec or ≥501 msec, and change from baseline of >60 msec were comparable between treatment arms. However, there was a higher number of patients with a QTc value ≥450 msec and change from baseline of >30 msec in the rucaparib arm. Nevertheless, an increase in TEAEs was not observed.

Safety data by age, race, BRCA mutated gene and BRCA mutation status (germline and somatic) have been provided. Overall, some differences in the reported AE rates were found but the subgroups sample size and the lack of stratification prevent any definitive conclusion about them.

In patients with moderate renal impairment (classified per the EMA guideline) rucaparib treatment resulted in an increased incidence of TESAEs, Grade ≥3 TEAEs, TEAEs leading to death, TEAEs leading to study drug discontinuation and dose reduction/interruption compared to patients with normal renal function. In patients with mild renal impairment a higher incidence of Grade ≥3 TEAEs and TEAEs leading to study drug discontinuation was also observed. However, these results are in line with prior data submitted. As recommended in the SmPC, no starting dose adjustment is required in patients with mild or moderate renal impairment. Further recommendations are currently included regarding use of rucaparib in patients with severe renal impairment (see section 4.2).

Safety data by platinum status showed a higher rate of TESAEs, TEAEs of Grade≥3, TEAEs leading to death, TEAEs leading to study drug discontinuation and TEAEs leading to dose reduction/interruption in the partially platinum-sensitive group (n=65). Among the most commonly reported TEAEs in patients treated with rucaparib, combined anaemia/haemoglobin decreased and combined neutropenia/decreased ANC had a higher incidence in this subgroup of patients. Other common TEAEs were more frequently reported in the subgroup of platinum-sensitive compared with the overall population (combined AST/ALT increased, gastrointestinal disorders, dysgeusia and alopecia). Overall, when comparing the platinum-sensitive and partially platinum-sensitive population (the population most similar to the one covered by the CMA) versus the platinum resistant subjects, no clinically relevant imbalances were identified for deaths, SAEs and TEAEs leading to discontinuation or dose modifications.

Discontinuation due to TEAEs was low in the rucaparib arm (20 [8.6%] rucaparib vs. 15 [13.3%] chemotherapy).

In **conclusion**, the safety profile of rucaparib in study ARIEL4 appears to be in line with its already known safety profile based on previous clinical trials. Moreover, most TEAEs were less frequently reported than in the pooled population, except for combined anaemia/haemoglobin decreased (53.9% vs. 44.7%).

The MAH has proposed to add a new post-authorisation measure (recommendation) to its Letter of Recommendation to submit and addendum to the CSR of ARIEL4 study. Even if the the 'treatment' indication is removed from the PI (EMEA/H/A-20/1518/C/4272/0033), updated safety from the ARIEL4 study should be provided with the final CSR in order to update the PI. The MAH proposed that section 4.8 of the SmPC will include safety data from a pooled analysis of studies where ovarian cancer patients received rucaparib monotherapy at the same posology, and therefore including also the ARIEL4 study (even if the treatment indication is no longer be approved). This is endorsed. In addition, potential cases of secondary MDS/AML are expected to be presented at the time of this final analysis.

7.4. PSUR cycle

Considering the marketing authorisation will no longer be subject to specific obligations, the CHMP is of the opinion that the already existing entry in the EURD list for rucaparib needs to be amended as follows: the PSUR cycle for the medicinal product should follow a yearly cycle from 20 December 2022. The next two PSURs will cover a period of 6 months (20 December 2021-19 June 2022 and 20 June 2022 - 19 December 2022 respectively). The following PSUR will then cover the period from 20 December 2022 to 19 December 2023 to maintain alignment with the IBD.

7.5. Direct Healthcare Professional Communication

In view of the reported results from the ARIEL4 study DHPC were agreed by CHMP and sent to relevant healthcare professionals. The content of the letters was published on the EMA website on 06 May 2022 and 8 August 2022.

8. PRAC advice

During the assessment of the current variation application, in view of the results from the ARIEL4 study and the potential detrimental effect in OS observed with rucaparib over chemotherapy, PRAC advice was requested.

The PRAC advice was adopted on 7 April 2022. The PRAC shared the concern of the CHMP, namely that the data from the OS interim analysis in the ARIEL4 study suggestive of a detrimental effect, were worrisome and that these data should be made available to health care professionals in a timely manner and recommended that this should be communicated by dissemination of a DHPC. PRAC recommended, as a first step, dissemination of a DHPC, to inform health care professionals of the OS data from the confirmatory ARIEL4 study. Subject to the CHMP assessment of the MAH's responses to the list of outstanding issues, the PRAC noted that further regulatory actions may be warranted.

A DHPC was adopted by CHMP on 22 April 2022 and dissemination of the DHPC to relevant healthcare professionals started on 5 May 2022 (see section 7.5).

The CHMP adopted an opinion pursuant to Article 20 of Regulation (EC) No 726/2004 on 21 July 2022 recommending the variation to the terms of the marketing authorisation for Rubraca (rucaparib). A second DHPC was sent to relevant healthcare professionals on 8 August 2022 (see section 7.5).

9. Risk management plan

The MAH submitted an updated RMP version 6.2 with the submission of study CO-338-043 (ARIEL4) CSR in fulfilment of Specific Obligation (SOB001) and removal of the treatment indication.

The significant changes in the RMP are summarised below:

Part II: Module SI – Epidemiology of the indication

Removal of the ovarian cancer treatment indication.

Part II: Module SIII - Clinical trial exposure

Exposure in Study CO-338-043 (ARIEL4) was included according to the DLP of 30 Sep 2020.

Part II: Module SIV - Populations not studied in clinical trials

This section was aligned with the changes in the safety specifications and the data from Study CO-338-043 (ARIEL4).

Part II: Module SV - Post-authorisation experience

This section was updated to align with the Periodic Safety Update Report (PSUR)#5 (DLP 19 Dec 2020).

Part II: Module SVII.2 New safety concerns and reclassification with a submission of an updated RMP

This section was aligned with the changes in the safety specifications.

Risk	Reclassification	Rationale
Important Identified Risks		
Myelosuppression	Removed	Data from ARIEL4 do not provide any new information, and the risk is well characterised and appropriately managed. There are no outstanding pharmacovigilance activities or additional risk minimisation measures. The measures to avoid the risk are adequately described in the product information. Section 4.2 of the SmPC gives the following advice: Adverse reactions may be managed through dose interruptions and/or dose reductions for moderate to severe reactions (i.e. CTCAE Grade 3 or 4) such as neutropenia, anaemia and thrombocytopenia. Section 4.4 of the SmPC gives the following advice: During treatment with rucaparib, events of myelosuppression (anaemia, neutropenia, thrombocytopenia) may be observed and are typically first observed after 8-10 weeks of treatment with rucaparib. These reactions are manageable with routine medical treatment and/ or dose adjustment for more severe cases. Complete blood count testing prior to starting treatment with Rubraca, and monthly thereafter, is advised. Patients should not start Rubraca treatment until they have recovered from haematological toxicities caused by previous chemotherapy (≤ CTCAE Grade 1). Supportive care and institutional guidelines should be implemented for the management of low blood counts for the treatment of anaemia, and neutropenia. Rubraca should be interrupted or dose reduced and blood counts monitored weekly until recovery. If the levels have not recovered to CTCAE grade 1 or better after 4 weeks, the patient should be referred to a haematologist for further investigations. The Patient Leaflet section 2 gives the following information: Your doctor or nurse will perform blood tests to check your blood cell-counts: ▪ before treatment with Rubraca ▪ every month during treatment with Rubraca This is because Rubraca can cause low blood counts of red blood-cells, white blood-cells, or platelets. The signs and symptoms of low blood cell counts include fever, infection, bruising or bleeding. Your doctor may also do weekly tests, if you have low blood cell counts for a long time. They may stop treatment with Rubraca until your blood cell counts improve. The Patient Leaflet section 4 gives the following instructions/information: Tell your doctor straight away if you notice any of the following side effects – you may need urgent medical treatment: Very common (may affect more than 1 in 10 people): ▪ being short of breath, feeling tired, having pale skin, or fast heart beat - these may be signs of a low red blood cell count (anaemia) ▪ bleeding or bruising for longer than usual if you hurt yourself - these may be signs of a low blood platelet count (thrombocytopenia) ▪ fever or infection – these may be signs of a low white blood cell count (neutropenia)
Nausea and vomiting	Removed	Data from ARIEL4 do not provide any new information, and the risk is well characterised and appropriately managed. There are no outstanding pharmacovigilance activities or additional risk minimisation measures. The measures to avoid the risk are adequately described in the product information. Section 4.2 of the SmPC gives the following advice: Other moderate to severe non-haematological adverse reactions such as nausea and vomiting, can be managed through dose interruption and/or

		reductions, if not adequately controlled by appropriate symptomatic management. Section 4.4 of the SmPC gives the following advice: GI toxicities (nausea and vomiting) are frequently reported with rucaparib, are generally low grade (CTCAE Grade 1 or 2), and may be managed with dose reduction or interruption. Antiemetics, such as 5-hydroxytryptamine 3 (5-HT_3) antagonists, dexamethasone, aprepitant and fosaprepitant, can be used as treatment for nausea/vomiting and may also be considered for prophylactic (i.e., preventative) use prior to starting Rubraca. It is important to proactively manage these events to avoid prolonged or more severe events of nausea/vomiting which have the potential to lead to complications such as dehydration or hospitalisation. The Patient Leaflet section 2 gives the following instructions/information: Symptoms you should be aware of: Talk to your doctor if you feel sick (nauseous), have been sick (vomiting) or you have had diarrhoea. These may be signs and symptoms that Rubraca is affecting your stomach. The Patient Leaflet section 4 gives the following information: Very common (may affect more than 1 in 10 people): ▪ feeling sick (nausea) ▪ being sick (vomiting)
Missing Information		
Use in patients for longer than 18 months	Removed	There is no indication from clinical trials (including the data from ARIEL4) and post-marketing experience that the safety profile with long-term use (i.e., longer than 18 months) is different from short-term use. In addition, there are no outstanding pharmacovigilance and risk minimisation measures activities to address this missing information.
Efficacy and safety of rucaparib in patients previously treated with olaparib or another PARP inhibitor	Removed	Based on the PSUR#5 assessment report (EMEA/H/C/PSUSA/00010694/202012), the PRAC considered that the missing information can be removed from the list of safety concerns. There was a total of 108 post-marketing reports where the patient had prior treatment with olaparib or niraparib. The reported events appear to be in line with the known safety profile of PARP inhibitors and does not give raise to concern. Furthermore, efficacy data are not expected from post-marketing reports and the RMP does not include any post-marketing efficacy study to specifically address this issue.

Assessor's comment:

The proposal of the MAH to remove important identified risks 'Myelosuppression' and 'Nausea and vomiting' and missing information 'Use in patients for longer than 18 months' and 'Efficacy and safety of rucaparib in patients previously treated with olaparib or another PARP inhibitor' is supported.

Both important identified risks (myelosuppression, nausea and vomiting) are well characterised and described in the SmPC. No new information was identified in ARIEL4 study. There are no additional pharmacovigilance activities ongoing or planned to further evaluate these risks.

The MAH also proposes to remove missing information 'Use in patients for longer than 18 months' and 'Efficacy and safety of rucaparib in patients previously treated with olaparib or another PARP inhibitor'. The data from ARIEL4 confirmed that the safety of rucaparib with long-term use is comparable to that one with short-term use.

Following assessment of the PSUR#5 it was stated that prior treatment with other PARP inhibitors (olaparib and niraparib) has had no impact on safety of rucaparib and it was recommended to remove these safety concerns from missing information.

Part II: Module SVII.3.1 Presentation of important identified risks and important potential risks and **Module SVII.3.2 Presentation of the missing information**

The characterisation of risks was updated to align with the DLP of 19 Dec 2020.

Safety specification

The important identified risks of 'Myelosuppression' and 'Nausea and vomiting' were removed. The missing information of 'Use in patients for longer than 18 months' and 'Efficacy and safety of rucaparib in patients previously treated with olaparib or another PARP inhibitor' was removed.

Pharmacovigilance plan

Study CO-338-043 (ARIEL4) was removed.

Plans for post-authorisation efficacy studies

Study CO-338-043 (ARIEL4) was removed.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk minimisation measures for the important identified risks of 'Myelosuppression' and 'Nausea and vomiting' and the missing information of 'Use in patients for longer than 18 months' and 'Efficacy and safety of rucaparib in patients previously treated with olaparib or another PARP inhibitor' were removed.

9.1. Overall conclusion on the RMP

The changes to the RMP and the changes to the conditions and obligations of the MA are acceptable.

10. Changes to the Product Information

As a result of this variation, sections 4.4 and 4.8 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly.

Changes are made to the Opinion Annex II conditions as detailed in the recommendations section above.

In addition, the MAH took the opportunity to make minor editorial changes and bring the PI in line with the latest QRD template version 10.2 Rev.1.

Please refer to Attachment 1 which includes all changes to the Product Information.

11. Request for supplementary information

11.1. Major objections

Clinical aspects

1. A HR of 1.55 (95% CI: 1.085, 2.214) for OS has been reported in the context of an IA performed with a 51% of data maturity (the final OS analysis seems to be planned with 70% of events). The provided explanation of the MAH that these results can be explained by the immaturity of the results and cross over are not convincing. Therefore, it should be further elucidated whether the reported OS data might reflect a detrimental effect of rucaparib. Updated OS data, further OS analyses and safety information should be submitted and discussed. At least the following is expected for both the efficacy population and the ITT population:

    a. OS data by i) platinum sensitivity and ii) BRCA mutational status.

    b. As the number of patients in the control arm is small, it may be that baseline covariates might impact the result. Therefore, the MAH should perform a multi-variate analysis modelling the impact of different baseline/prognostic factors on OS.

c. A comprehensive presentation on the reasons for death should be provided to elucidate whether there is an imbalance in death due to adverse events.

d. Potential cases of secondary MDS/AML are expected to be presented.

11.2. Other concerns

Clinical aspects

Clinical efficacy

2. The integrity of Study CO-338-043 (ARIEL 4) can be questioned due to the very late protocol amendment performed at the same time of the data cut-off date, which modified the populations of analysis and removed PFS as assessed by BICR and OS from the step-down testing procedure. Therefore, the MAH is requested to provide further explanations/clarifications on how the integrity of the trial was maintained, including descriptions of who had access to what data at each point in the decision making process for the amendments as well as provide further justification for the amendments performed in the protocol and SAP.
3. As mentioned, PFS as assessed by BICR was changed from (key) secondary endpoint, to be tested as part of a step-down procedure, to a 'stand-alone' secondary endpoint. However, no analysis of irrPFS has been conducted/submitted by the MAH. No justification as to why data from this analysis should not be needed has been provided either. The MAH is requested to submit this (secondary) analysis for both the Efficacy and ITT Populations.
4. The MAH should provide previous versions of the SAP (if any) with tracked changes and justify the rationale behind relevant changes.
5. The fact that around 30% more patients discontinued due to radiological disease progression in the rucaparib arm as compared to the chemotherapy arm (i.e. 70.7% vs. 54.4%) is striking and deserves further discussion by the MAH.
6. The MAH should clarify if the reported OS interim analysis was pre-specified in the study protocol and SAP.
7. The MAH is requested to clarify the number of OS events needed for the final analysis and estimation of when it will be available.
8. Performing additional analyses using alternative relevant methods might be helpful to adjust for the reported crossover even if results from these analyses would be considered as supportive (bearing in mind their limitations as they mostly rely on underlying (strong) assumptions). Reference is made to EMA guidance: "Question and answer on adjustment for cross-over in estimating effects in oncology trials (EMA/845963/2018)". Results should be provided for both the efficacy population and the ITT population. Subgroup analyses according to stratification data should also be provided.
9. The MAH should submit and discuss OS and PFS2 results by stratification subgroups (i.e. by platinum sensitivity).
10. The MAH should provide tabular information about subsequent anti-cancer therapies.
11. The MAH is requested to submit final analysis for OS and PFS2 when available (REC already proposed).

Clinical safety

12. As per protocol, patients in the chemotherapy arm, can receive up to 8 cycles. However, it seems that some patients received more than 8 cycles (median 5; range: 1, 21). The MAH should clarify the number of patients that received more than 8 cycles (if any). Further, the exact number of patients that completed 8 cycles should be provided.

13. There were a total of 12 (5.2%) patients in the rucaparib arm while only 1 (0.9%) in the chemotherapy arm that reported an event of intestinal obstruction. Of these, 6 events in the rucaparib arm were considered as serious. In addition, 4 serious adverse events were reported among patients who crossed-over to rucaparib treatment The MAH is requested to provide further information on all the events of intestinal obstruction reported in the ARIEL4 study (as well as the pooled population) and discuss to what extent these events may be related to rucaparib treatment.

14. The incidence of MDS/AML has been established based on a total of 2,972 patients treated with rucaparib in clinical trials. The MAH should specify to which studies (including a brief description) these patients come from.

15. According to the MAH, the percentage of patients with QTcB and QTcF values ≥ 450 msec was typically < 20% and QTcB and QTcF ≥ 481 msec or ≥ 501 msec occurred in few patients in the rucaparib and chemotherapy groups across time points. In order to have a better comparison, a table summarising all events of QTcF and QTcB values ≥450 msec, QTcB values ≥481 msec and QTcB values ≥501 msec reported during the study in both the rucaparib and chemotherapy arms should be provided.

16. Safety data by age, race, BRCA mutated gene and BRCA mutation status (germline and somatic) have been provided. For a proper assessment the MAH is requested to provide comparative data (in the same table) for all these subgroups. The same data currently provided are requested.

17. Comparative data by platinum status of most frequent TESAEs, deaths and TEAEs leading to discontinuation and dose reduction/interruption should be provided.

12. Assessment of the responses to the request for supplementary information

12.1. Major objections

Clinical aspects

Question 1

A HR of 1.55 (95% CI: 1.085, 2.214) for OS has been reported in the context of an IA performed with a 51% of data maturity (the final OS analysis seems to be planned with 70% of events). The provided explanation of the MAH that these results can be explained by the immaturity of the results and cross over are not convincing. Therefore, it should be further elucidated whether the reported OS data might reflect a detrimental effect of rucaparib. Updated OS data, further OS analyses and safety information should be submitted and discussed. At least the following is expected for both the efficacy population and the ITT population:

a) OS data by i) platinum sensitivity and ii) BRCA mutational status.

b) As the number of patients in the control arm is small, it may be that baseline covariates might impact the result. Therefore, the MAH should perform a multi-variate analysis modelling the impact of different baseline/prognostic factors on OS.

c) A comprehensive presentation on the reasons for death should be provided to elucidate whether there is an imbalance in death due to adverse events.

d) Potential cases of secondary MDS/AML are expected to be presented.

Summary of the MAH's response

The responses to this question utilized the data cut-off of 30 September 2020. The pre-specified required maturity for final overall survival (OS) is at least 70% and the current OS maturity is 69%. Clovis anticipates that the final OS data will be available in May 2022 (with final clinical study report [CSR] submitted in Q4 2022). The preference is to run this analysis again at the time of final OS instead of conducting another interim OS analysis.

a) The OS data by i) platinum sensitivity and ii) breast cancer gene (BRCA) mutational status are presented below.

The interim OS data by platinum sensitivity are summarized in Table 1 for both the intent-to-treat (ITT) and Efficacy Populations. These data were also presented and discussed in response to Question 9 and KM curves of the different subgroups are included in that question.

Table 1. Study CO-338-043 Interim OS by Platinum Status – Treatment Part, ITT Population and Efficacy Population

	Platinum-sensitive (PFI > 12 months)		Partially Platinum-sensitive (PFI ≥ 6 to 12 months)		Platinum-resistant (PFI > 1 to < 6 months)	
ITT Population						
	Rucaparib N = 48	Chemotherapy N = 26	Rucaparib N = 65	Chemotherapy N = 31	Rucaparib N = 120	Chemotherapy N = 59
events, n (%)	15 (31.3)	6 (23.1)	34 (52.3)	15 (48.4)	78 (65)	30 (50.8)
median in months (95% CI)	36.3 (24.6, 37.4)	NA (18.1, NA)	20.9 (11.8, 38.0)	25.9 (20.8, 27.8)	13.9 (11.5, 16.5)	21.7 (14.8, 33.3)
HR, (95% CI)	1.124 (0.438, 2.884) p-value = 0.8080		1.141 (0.618, 2.107) p-value = 0.6738		1.724 (1.128, 2.635) p-value = 0.0119	
Efficacy Population						
	Rucaparib N = 48	Chemotherapy N = 26	Rucaparib N = 62	Chemotherapy N = 28	Rucaparib N = 110	Chemotherapy N = 51
events, n (%)	15 (31.3)	6 (23.1)	32 (51.6)	12 (42.9)	68 (61.8)	24 (47.1)
median in months (95% CI)	36.3 (24.6, 37.4)	NA (18.1, NA)	25.8 (12.3, 38.0)	27.1 (21.9, NA)	14.6 (11.8, 18.8)	23.5 (15.4, 38.1)
HR, (95% CI)	1.124 (0.438, 2.884) p-value = 0.8080		1.258 (0.645, 2.454) p-value = 0.5013		1.789 (1.120, 2.858) p-value = 0.0149	

Sources: Figure 9.2.1, Figure 9.2.2, Figure 9.2.3, Figure 9.2.4, Figure 9.2.5, Figure 9.2.6, and Table 10.2.7.
Abbreviations: CI = confidence interval; HR = hazard ratio (from Cox proportional hazard model); ITT = intent-to-treat; NA = not achieved; OS = overall survival; PFI = platinum-free interval.

The interim OS by mutational status is summarized by BRCA-mutated gene in Table 2 and by BRCA mutation type in Table 3 for the ITT and Efficacy Populations.

Table 2. Study CO-338-043 (ARIEL4) Interim OS by BRCA1 vs BRCA2 – Treatment Part, ITT Population and Efficacy Population

	BRCA Mutation			
	BRCA1		BRCA2	
ITT Population				
	Rucaparib N = 181	Chemotherapy N = 79	Rucaparib N = 52	Chemotherapy N = 36
Events, n (%)	101 (55.8)	35 (44.3)	26 (50.0)	16 (44.4)
Median in months (95% CI)	17.9 (13.9, 20.9)	23.2 (18.1, 38.1)	23.6 (12.9, 28.2)	27.1 (20.8, NA)
HR, 95% CI	1.407 (0.952, 2.080) p-value = 0.0866		1.492 (0.794, 2.804) p-value = 0.2141	
Efficacy Population				
	Rucaparib N = 173	Chemotherapy N = 74	Rucaparib N = 47	Chemotherapy N = 31
Events, n (%)	93 (53.8)	30 (40.5)	22 (46.8)	12 (38.7)
Median in months (95% CI)	18.9 (14.6, 23.1)	25.9 (20.6, 38.1)	25.8 (17.9, 28.8)	27.6 (21.9, NA)
HR, 95% CI	1.469 (0.967, 2.233) p-value = 0.0718		1.539 (0.754, 3.143) p-value = 0.2365	

Sources: Figure 1.1.1, Figure 1.1.2, Figure 1.1.5, Figure 1.1.6 and Table 1.1.9.

Abbreviations: BRCA = breast cancer gene; CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; NA = not achieved; OS = overall survival;

Table 3. Study CO-338-043 (ARIEL4) Interim OS by Germline vs Somatic BRCA Mutation Type – Treatment Part, ITT Population and Efficacy Population

	BRCA Mutation Type			
	Germline		Somatic	
ITT population				
	Rucaparib N = 198	Chemotherapy N = 95	Rucaparib N = 35	Chemotherapy N = 19
Events, n (%)	107 (54.0)	42 (44.2)	20 (57.1)	9 (47.4)
Median in months (95% CI)	19.1 (14.6, 23.1)	23.6 (20.8, 27.6)	14.7 (7.8, 38.0)	33.3 (6.6, 33.3)
HR, 95% CI	1.375 (0.960, 1.969) p-value = 0.0826		2.011 (0.857, 4.720) p-value = 0.1084	
Efficacy Population				
	Rucaparib N = 187	Chemotherapy N = 88	Rucaparib N = 33	Chemotherapy N = 16
Events, n (%)	97 (51.9)	35 (39.8)	18 (54.5)	7 (43.8)
Median in months (95% CI)	20.8 (17.9, 24.6)	25.9 (21.7, 38.1)	16.8 (11.4, 38.0)	33.3 (8.4, 33.3)
HR, 95% CI	1.447 (0.980, 2.135) p-value = 0.0629		2.182 (0.846, 5.626) p-value = 0.1064	

Sources: Figure 1.1.3, Figure 1.1.4, Figure 1.1.7, Figure 1.1.8 and Table 1.1.9.

Abbreviations: BRCA = breast cancer gene; CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; NA = not achieved; OS = overall survival;

There was no difference observed for interim OS between patients treated with either rucaparib or chemotherapy who were platinum-sensitive or partially platinum-sensitive at study entry in either the ITT or Efficacy Populations. The patients in the ITT Population who were platinum-resistant and treated with chemotherapy appeared to have a longer OS (21.7 months) as compared to platinum-resistant patients treated with rucaparib (13.9 months), with similar results in the Efficacy Population. However, 39 of 59 patients (66%) in the platinum-resistant group (ITT Population) crossed over to receive rucaparib in the open-label Crossover Part of Study CO-338-043, thus appropriate analyses adjusting for confounding effects due to crossover are necessary to interpret the interim OS data.

b) As the number of patients in the control arm is small, it may be that baseline covariates might impact the result. Therefore, the Marketing Authorization Holder (MAH) should perform a multi-variate analysis modelling the impact of different baseline/prognostic factors on OS.

A stepwise Cox proportional multi-variate analysis of OS was evaluated with common demographic and baseline variables and also the randomized treatment allocation, a factor for crossover (Yes/No), and randomization strata of platinum status. The significance level used for the stepwise analysis was p = 0.20. The full model with all the potential demographics and baseline predictors and reduced model after stepwise prediction are presented in Table 4.

Table 4. Study CO-338-043 (ARIEL4) Predictors of Interim OS

Factor	Coefficient Estimate	Adjusted HR	95% CI	P-value
Full Model (all variables at once)				
Randomized Treatment (Rucaparib vs. Chemotherapy)	-0.78134	0.458	(0.281, 0.745)	0.0017
Randomization Strata: Platinum Status				0.0031
Platinum-sensitive vs. Platinum-resistant	-0.95736	0.384	(0.220, 0.669)	
Partially Platinum-sensitive vs. Platinum-resistant	-0.28758	0.750	(0.516, 1.091)	
Patient crossed over (Yes vs. No)	-1.58819	0.204	(0.113, 0.369)	< 0.0001
Number of prior chemotherapy regimens	0.20473	1.227	(1.035, 1.455)	0.0186
Number of prior platinum-based chemotherapy regimens	-0.09218	0.912	(0.671, 1.240)	0.5564
Measurable Disease at Baseline (Yes vs. No)	-0.60323	0.547	(0.273, 1.096)	0.0890
Age (in years)	-0.00565	0.994	(0.977, 1.012)	0.5375
Race: White vs. All others	0.21131	1.235	(0.574, 2.657)	0.5886
BMI at baseline	-0.03289	0.968	(0.943, 0.993)	0.0126
Ovarian Cancer Type:				0.5223
PPC vs. EOC	0.50153	1.651	(0.683, 3.993)	
FTC vs. EOC	0.12190	1.130	(0.525, 2.429)	
Time Since Diagnosis (in months)	-0.01283	0.987	(0.979, 0.996)	0.0042
ECOG PS at baseline (1 vs. 0)	0.19240	1.212	(0.888, 1.655)	0.2260
BRCA Mutation Type:				0.8178
Germline vs. Somatic	-0.10137	0.904	(0.598, 1.365)	
Not Available vs. Somatic	-0.68717	0.503	(0.028, 9.062)	
Reduced Model (after stepwise selection)				
Randomized Treatment (Rucaparib vs. Chemotherapy)	-0.82950	0.436	(0.273, 0.697)	0.0005
Randomization Strata: Platinum Status				< 0.0001
Platinum-sensitive vs. Platinum-resistant	-1.38107	0.251	(0.155, 0.408)	
Partially Platinum-sensitive vs. Platinum-resistant	-0.46485	0.628	(0.446, 0.885)	
Patient crossed over (Yes vs. No)	-1.67581	0.187	(0.105, 0.333)	< 0.0001
Measurable Disease at Baseline (Yes vs. No)	-0.62152	0.537	(0.274, 1.053)	0.0703
BMI at baseline	-0.03294	0.968	(0.943, 0.992)	0.0110
ECOG PS at baseline (1 vs. 0)	0.28563	1.331	(0.982, 1.803)	0.0655

Sources: Table 1.3.1 and Table 1.3.2.
Abbreviations: HR = hazard ratio; BMI = body mass index; BRCA = breast cancer gene; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; EOC = epithelial ovarian cancer; OS = overall survival; FTC = fallopian tube cancer; PPC = primary peritoneal cancer; vs. = versus.

The variables found to be significant predictors in the model were stratification group by Platinum status, Patient crossed over (Yes/No), Randomized treatment (rucaparib vs chemotherapy), body mass index (BMI), Measurable disease, and Eastern Cooperative Oncology Group Performance Status (ECOG PS) at baseline. Platinum status is a well-known prognostic factor of OS in ovarian cancer. The crossover and randomized treatment variables are consistent with the discussion around apparent confounding of OS results due to chemotherapy patients crossing over to receive

rucaparib. The crossover patients are likely to be associated with longer survival, since by design these patients are alive to enroll into the Crossover Part of Study CO-338-043.

c) A comprehensive presentation on the reasons for death should be provided to elucidate whether there is an imbalance in death due to adverse events.

In the Study CO-338-043 clinical study report (CSR), all treatment-emergent adverse events (TEAEs) leading to death during the Treatment Part were discussed. Fifteen patients (6.5%) in the rucaparib group and 3 patients (2.7%) in the chemotherapy group had at least 1 TEAE with an outcome of death. The most frequently reported TEAE with an outcome of death was malignant neoplasm progression (5 patients in the rucaparib group and 2 patients in the chemotherapy group). Upon implementation of Protocol Amendment 2, such events were no longer collected in EDC. Overall, only 3 patients (1.3%) in the rucaparib group had a treatment-related TEAE with an outcome of death compared with no patients in the chemotherapy group. These included events of Myelodysplastic syndromes (MDS), Cardiac disorder, and Death, not otherwise specified (NOS). The higher incidence of TEAEs with an outcome of death observed in the rucaparib group is likely due to these patients receiving treatment for a longer period, leading to events associated with disease progression.

In addition to the TEAEs with an outcome of death, the primary reason for death was captured in the database for every OS event during the survival follow up. Table 5 summarizes the primary reasons for death for all patients who died in the OS analysis in the ITT Population, excluding those patients already described above who had a TEAE with an outcome of death during the Treatment Part of the study.

Table 5. Study CO-338-043 (ARIEL4) Primary Reason of Death – Treatment Part, ITT Population Excluding Those Patients With TEAE Leading to Death

	Rucaparib (N = 218)	Chemotherapy (N = 113)
Survival Status		
Died	112 (51.4%)	48 (42.5%)
Alive	106 (48.6%)	65 (57.5%)
Primary Cause of Death[a]		
Disease Under Study	101 (90.2%)	46 (95.8%)
Other (further broken out below)	11 (9.8%)	2 (4.2%)
Unknown	4 (3.6%)	1 (2.1%)
Total body failure	2 (1.8%)	1 (2.1%)
Cardiac arrest	1 (0.9%)	0 (0.0%)
COVID-19	1 (0.9%)	0 (0.0%)
Sepsis	1 (0.9%)	0 (0.0%)
Stroke	1 (0.9%)	0 (0.0%)
Surgical complications	1 (0.9%)	0 (0.0%)

Source: Table 1.2.2.

Abbreviations: ITT = intent-to-treat; TEAE = treatment-emergent adverse event.

[a] Denominator includes patients that died.

There is no aparent imbalance between treatment arms in the proportion of patients who experienced a treatment-related TEAE that resulted in death.

d) Potential cases of secondary MDS/acute myeloid leukemia (AML) are expected to be presented.

In the Study CO-338-043 CSR, MDS/AML were identified as adverse events of special interest (AESIs). As of the visit cut-off for this report, 4 cases of MDS and 1 case of AML were reported for patients who received rucaparib in the Treatment Part of the study. A summary of the patients with MDS/AML is provided in Section 12.3.1.13 of the CSR.

One patient who received rucaparib died during the Treatment Part of the study as a result of MDS. Two additional patients who were diagnosed with MDS (one while on treatment and the other during long-term follow up) died as a result of disease progression (disease under study). The remaining two patients were alive as of the CSR visit cut-off date (30 September 2020).

Assessment of the MAH's response

Due to the unexpected results obtained in the OS IA of study CO-338-043, the MAH was asked to provide updated OS data and supportive OS analyses to exclude a detrimental effect of rucaparib in patients' survival. However, the MAH has chosen to wait until the final OS analysis, anticipated to take place in May 2022, where the requested analyses will be performed, instead of conducting another IA. For this reason, all the requested analyses have been presented based on the already reported OS IA, with a data cut-off date of 30 September 2020.

a) OS results by platinum sensitivity status have been provided for the ITT and the Efficacy Population. Reported HR for the Efficacy Population were 1.124 (95% CI: 0.438, 2.884) for the platinum-sensitive (PFI > 12 months) group, 1.258 (95% CI: 0.645, 2.454) for the partially platinum-sensitive (PFI ≥ 6 to 12 months) group, and 1.789 (95% CI: 1.120, 2.858) for the platinum- resistant (PFI > 1 to <6 months) group. For the ITT Population, in which only number of subjects included in the partially platinum-sensitive and platinum-resistant group have changed, the estimated HR were 1.141 (95% CI: 0.618, 2.107) and 1.724 (95% CI: 1.128, 2.635) in the mentioned groups, respectively. Interim OS results by BRCA mutation were similar for both BRCA 1 and BRCA 2 mutation and for the Efficacy and ITT Population. In the Efficacy Population, HR (95% CI) were 1.469 (0.967, 2.233) for BRCA 1 and 1.539 (0.754, 3.143) for BRCA 2. Consistent results were reported in the ITT Population. For the BRCA mutation type (germline vs. somatic), estimated HR for the Efficacy Population was 1.447 (95%CI: 0.980, 2.135) in the group with germline BRCA mutation and 2.182 (95% CI: 0.846, 5.626) for the somatic BRCA mutation subgroup. Similar results were observed in the ITT Population. Focusing on median OS in all these groups of subjects, all the results favoured the chemotherapy arm, particularly in the subgroup of platinum-resistant patients but, again, due to the relatively high percentage of patients who crossed-over to rucaparib, interpretation of these results is difficult and additional sensitivity analyses are deemed necessary, see question 8.

b) A stepwise Cox proportional multi-variate analysis of OS was performed with demographic and baseline variables, the randomized treatment allocation, a factor for crossover and randomization strata of platinum sensitivity status. Of note, the significance level used was p=0.20. In this model, significant interaction was found for platinum status, patient crossed over (Yes/No), randomized treatment, BMI, measurable disease, and ECOG PS at baseline. The full model is not interpretable for the complexity and for the inclusion of too many variables, even those that are too far from the statistical significance level. The interpretation of the proposed reduced model which includes a patient crossover factor as a baseline variable is really difficult. In fact, crossover is not a baseline variable, actually it occurred always after randomisation. Thus, unfortunately, nothing beyond hypothesis generating can be concluded from this analysis. To better clarify the weight of possible imbalances in the baseline demographics and disease characteristics in these unexpected OS results, the MAH is requested to provide tabular summaries of these baseline demographics and disease characteristics at the time of randomization for three different subgroups of patients: patients randomized to rucaparib, patients randomized to chemotherapy who crossed over to rucaparib after

progression, and patients from the chemotherapy arm who did not cross over. Data for these 3 subgroups should be included in the same table to facilitate assessment.

c) A tabular summary of primary reasons for death for the ITT Population excluding patients with a reported TEAE leading to death has been provided. A higher proportion of subjects in the rucaparib arm died due to other reasons, different from disease under study (9.8% vs. 4.2%). It is understood that these deaths were not reported as TEAEs because they occurred more than 28 days after last treatment dose. In this summary, there were 4 (3.6%) deaths and 1 (2.1%) death in the rucaparib and placebo arms, respectively, that were recorded as due to "unknown" reasons and 2 (1.8%) deaths and 1 (2.1%) death, respectively, due to "total body failure" which seem to be confusing terms. Other deaths attributed to more concrete reasons were reported in a higher frequency in the rucaparib arm. The rationale given by the MAH for these higher incidences to be related to longer study treatment duration in the rucaparib arm seems plausible.

d) As the analyses have been performed with the Sept-2020 data cut-off, no updated information has been provided regarding MDS/AML

Conclusion

Data requested have been provided, when available, and discussed. The MAH was also asked to conduct a multi-variate analysis modelling the impact of different baseline/prognostic factors on OS. This analysis has been presented but as discussed above it is difficult to interpret. Overall the HR of 1.55 (95% CI: 1.085, 2.214) for OS reported in the context of an IA performed with a 51% of data maturity in study CO-338-043 is still not fully clarified, see also questions below, and remains of concern. With this in mind and while recognizing that i) the reported invPFS results in study CO-338-043 are to be regarded as the key data for confirmation of the positive benefit/risk of rucaparib in the initial (conditionally granted) indication (so that the agreed SOB at that time could be considered as fulfilled) and ii) that taking into account the design of the trial it appears likely that the OS results will in the end remain inconclusive, some further analyses are still requested in order to get further clarification of the unexpected OS results reported in study CO-338-043 before a final decision for this procedure is drawn. These are requested as other concerns, see questions below.

Issue partly solved. Additional OCs are posed.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

12.2. Other concerns

Clinical aspects

Clinical efficacy

Question 2

The integrity of Study CO-338-043 (ARIEL 4) can be questioned due to the very late protocol amendment performed at the same time of the data cut-off date, which modified the populations of analysis and removed PFS as assessed by BICR and OS from the step-down testing procedure. Therefore, the MAH is requested to provide further explanations/clarifications on how the integrity of the trial was maintained, including descriptions of who had access to what data at each point in the decision making process for the

amendments as well as provide further justification for the amendments performed in the protocol and SAP.

Summary of the MAH's response

Amendment 2 of the Study CO-338-043 (ARIEL4) protocol was initiated prior to the data cut-off date and was finalized prior to the Clovis team having access to aggregate data and performing the blind break. The integrity of Study CO-338-043 was maintained by following a blinding plan and relying on an Independent Data Monitoring Committee (IDMC) to monitor progression-free survival (PFS) event maturity and by prohibiting Clovis access to aggregate data by treatment assignment until the blind break was performed by Clovis on 15 December 2020, as specified in the blinding plan.

The Clovis Biostatistics group did not have access to treatment assignments throughout the study until blind break. To monitor and review study data, the Clovis Clinical Operations and Clinical Development staff had access to individual patient data but not to any aggregate study results by treatment arm.

To monitor the study, the IDMC had access to the complete set of unblinded aggregate study data throughout the conduct of Study CO-338-043. An independent biostatistician at AXIO Research (Seattle, Washington, US), contracted for independent statistical support of the IDMC, was responsible for compiling the data and generating the necessary tables, listings, and figures for the IDMC review. In addition, Clovis contracted with EMB Statistical Solutions, LLC (Overland Park, Kansas US), an independent statistical vendor for Study CO-338-043, to produce the statistical package and tables, listings, and figures (TLFs) for the clinical study report (CSR). EMB Statistical Solutions received all clinical study data including the various vendor data for Study CO-338-043. Data sets and TLFs were not shared with Clovis until the official release of treatment codes on 15 December 2020.

In August 2020, the ARIEL4 IDMC communicated that the required number of PFS events (n = 275) were projected to be achieved by September 2020 in the intent-to-treat (ITT) population. The IDMC also acknowledged that both the protocol and the Statistical Analysis Plan (SAP) excluded patients with a breast cancer gene (BRCA) reversion mutation from the primary analysis but questioned the value of delaying the readout until the BRCA reversion mutation data were available. After receiving the communication from the IDMC, Clovis made a decision to expedite the BRCA reversion mutation testing and in parallel to amend the Study CO-338-043 protocol (ie, prepare Amendment 2) to include a hierarchical step-down procedure to adjust for the multiple testing of primary endpoints and key secondary endpoints starting with the Efficacy population (which excluded patients with BRCA reversion mutations) and followed by the ITT Population. The original protocol for Study CO-338-043 and Amendment 1 had not pre-specified this multiplicity adjustment, thus Amendment 2 was finalized prior to release of treatment codes and aggregate study results.

The sequence of events that occurred after the notification from the IDMC in August 2020 and the specifics of who had access to which data at different timepoints is summarized in Table 1.

Table 1. Timeline of Events and Access to Study CO-338-043 (ARIEL4) Data

Date	Event	Access to Data
18 August 2020	The IDMC communicated to Clovis that the required number of PFS events (n = 275) were expected to be achieved by September 2020 in the ITT population. BRCA reversion mutation testing had not been completed, thus data were not available. The IDMC also acknowledged that both the protocol and the SAP prespecified that patients with a BRCA reversion mutation were to be excluded from the primary analysis but questioned the value of delaying the read-out until the BRCA reversion mutation data were available.	**IDMC and EMB**: Complete set of unblinded aggregate study data excluding BRCA reversion mutation status data **Clovis**: No access to aggregate data by treatment arm or BRCA reversion mutation status
18 August 2020 to 23 October 2020	The Clovis team initiated BRCA reversion mutation testing of tumor samples and Amendment 2 of the ARIEL4 protocol.	**Clovis**: No access to aggregate data by treatment arm or BRCA reversion mutation status
23 October 2020	ARIEL4 Amendment 2 finalized	**Clovis**: No access to aggregate data by treatment arm or BRCA reversion mutation status
28 October 2020	ARIEL4 SAP version 1 finalized	**Clovis**: No access to aggregate data by treatment arm or BRCA reversion mutation status
11 December 2020	BRCA reversion mutation data available.	**Clovis:** No access to aggregate data by treatment arm. The Clovis in-house Translational Group performed a QC of BRCA reversion and central BRCA testing and provided it to the independent statistical vendor (EMB Statistical Solutions)
15 December 2020	Per the ARIEL4 blinding plan, the VP of Biostatistics and Chief Medical Officer requested the randomization schedule from the IWRS vendor, Endnote as specified in the blind break procedures in the blinding plan. A blind break was performed by Clovis applying a 30 September 2020 data cutoff.	**Clovis**: Complete set of unblinded aggregate study data including BRCA reversion mutation status data

Abbreviations: BRCA = breast cancer gene; EMB = EMB Statistical Solutions; IDMC = Independent Data Monitoring Committee; ITT = intent-to-treat; IWRS = interactive web-based response system; PFS = progression-free survival; QC = quality check; SAP = statistical analysis plan; VP = Vice President

Assessment of the MAH's response

The MAH has provided a tabular timeline of the events related to the dabase lock and the treatment unblinding for the sponsor. According to them, no access to any aggregate study results by treatment arm took place before the blind break, performed on 15 December 2020. The IDMC communicated to the sponsor that the required events for the primary endpoint analysis were expected to be reached in September. At this time, the IDMC noted that the protocol stated that patients with a BRCA reversion mutation were to be excluded from the efficacy analyses but, apparently, the reversion mutation tumour

samples testing had not been done. From that date in August to October, the samples testing was performed, at the same time that Amendment 2 was being prepared. This amendment 2 was finalized on the 23 October 2020 and also the SAP was dated on the 28 October. Finally, the BRCA reversion mutation data was available on the 11 December and the unblinding took place on the 15 December, applying the already mentioned 30 September 2020 data cut-off.

It is acknowledged that the original protocol already stated that subjects with a BRCA reversion mutation should be excluded from the main efficacy analyses, therefore the changes applied in Amendment 2 regarding the analyses populations (Efficacy and ITT) and the hierarchical testing methodology seem to be justified. In the same way, it is not understood why the reversion mutation samples testing had not been performed before if this information was needed for the efficacy analyses and this caused a delay in the read-out of the results. Furthermore, the rationale behind removing OS from the step-down testing procedure based on the expected immaturity of the OS data at the time of the primary endpoint analysis can be followed but this could have also been anticipated at the time of the Amendment 1 avoiding this late modification of the study main endpoints.

In conclusion, the timeline of events and access to data is acknowlegded but it does not exclude the possibility that the late protocol amendment and SAP could have been data-driven. However, it seems highly unlikely that the study results could have been different without the applied changes.

Conclusion

Issue not further pursued.

Question 3

As mentioned, PFS as assessed by BICR was changed from (key) secondary endpoint, to be tested as part of a step-down procedure, to a 'stand-alone' secondary endpoint. However, no analysis of irrPFS has been conducted/submitted by the MAH. No justification as to why data from this analysis should not be needed has been provided either. The MAH is requested to submit this (secondary) analysis for both the Efficacy and ITT Populations.

Summary of the MAH's response

Investigator-assessed PFS (invPFS) was selected by the MAH as the primary efficacy endpoint to allow real-time evaluation and determination of disease progression in Study CO-338-043 (ARIEL4). The lack of a delay in evaluation of disease progression not only alleviated the potential of informative censoring bias, but it also allowed investigators to make timely, medically-informed decisions regarding the best clinical course for their patients. In this way, the MAH considered that the determination of invPFS rather than BICR PFS allowed a more reliable assessment of benefit/risk.

The MAH decided not to analyze the secondary endpoint of BICR PFS following a review of study publications while Study CO-338-043 was ongoing. Recent data in ovarian cancer trials demonstrated different results between the duration of local investigator- and BICR-assessed median progression-free survival (mPFS). When local investigator review alone indicated disease progression, generally, no further assessments were carried out and patients were censored in the BICR analysis, thus leading to informative censoring. As a result of this informative censoring, BICR may be less reliable and have the tendency to exaggerate the mPFS, whereas investigator-assessed PFS provides a more conservative approach.

As noted by the CHMP, the existing body of efficacy data from Study CO-338-043 are consistent with the data obtained from the pooled Efficacy Population from Study CO-338-010 and Study CO-338-017. Based on the considerations above, the MAH does not consider the absence of BICR PFS as a limitation in confirming these data. The MAH therefore maintains its decision to have not performed BICR PFS analyses at the time of the blind break and preparation of the CSR.

Assessment of the MAH's response

The MAH has not performed the requested PFS by BICR analysis for the same reasons that were already specified in the initial submission: high differences between PFS by investigator and BICR have been reported in previous ovarian cancer trials with PARP inhibitors. The solution, though, cannot be not performing such analysis but trying to identify the reasons behind the observed differences. The analysis of this endpoint was included in all versions of the protocol although its timing was not specified. As mentioned in the initial report, this analysis is considered of particular relevance for this pathology, even more in the context of an open-label design and, at least, results from an 'audit' sample to assess/confirm concordance would have been expected, therefore the justification provided by the MAH is not valid and the results should be provided at the time of the OS final analysis.

Conclusion

Issue not solved. PFS by BICR analysis results are expected to be provided at the time of the final OS analysis, which is projected to occur later this year (REC).

Question 4

The MAH should provide previous versions of the SAP (if any) with tracked changes and justify the rationale behind relevant changes.

Summary of the MAH's response

The Statistical Analysis Plan (SAP) v1.0 signed and dated on 28 October 2020 was submitted as part of the Study CO-338-043 (ARIEL4) Clinical Study Report (CSR). This is the first and only version of the SAP. The SAP aligned with Section 11 Planned Statistical Methods in the effective ARIEL4 protocol Amendment 2 (dated 23 October 2020), and elaborated on the already-specific details of the planned statistical methods written in protocol Section 11. According to the MAH, they worked closely with an independent data monitoring committee (IDMC) and remained blinded to aggregate output results until 15 December 2020 (Section 6.5 of the Study CO-338-043 CSR). Thus, Clovis finalized and signed the SAP on 28 October 2020 prior to Clovis being unblinded to study results on 15 December 2020.

Assessment of the MAH's response

The MAH has confirmed that the submitted SAP v1.0 is the first and only version, which was signed, along with Amendment 2, after the data cut-off date but before the data unblinding for the sponsor.

Conclusion

Issue not further pursued.

Question 5

The fact that around 30% more patients discontinued due to radiological disease progression in the rucaparib arm as compared to the chemotherapy arm (i.e. 70.7% vs. 54.4%) is striking and deserves further discussion by the MAH.

Summary of the MAH's response

The discrepancy between the percentage of patients who discontinued treatment due to radiologic disease progression in the rucaparib arm as compared to the chemotherapy arm is largely due to the fact that rucaparib was allowed to be administered until disease progression, whereas chemotherapy was often administered for a set number of cycles. The platinum-based regimens were capped at 8 cycles maximum. Patients receiving weekly paclitaxel could continue treatment until disease progression or other reason for discontinuation. However, some patients received weekly paclitaxel treatment cycles for a set number of cycles according to institutional or local guidelines, consistent with data indicating that discontinuation of study drug was due to completion of treatment. To also note, more patients receiving

platinum-based regimens and weekly paclitaxel treatment discontinued treatment due to an adverse event than patients receiving rucaparib.

Twenty-one (19.4%) patients randomized to chemotherapy discontinued treatment with a primary reason of having completed their maximum allowed number of treatment cycles. Details regarding 12 patients in the chemotherapy arm who received >8 cycles of treatment (all with weekly paclitaxel) are provided in the response to question 12.

Most patients in the chemotherapy arm did not experience disease progression while receiving treatment, ie, who had stable disease or better upon treatment discontinuation. Patients in the chemotherapy arm were not allowed to cross over to open-label rucaparib until they had a disease progression event. The number of patients with progression-free survival (PFS) events is balanced in the study and present in a high proportion in both treatment arms; PFS events are 81.9% (95/116) for chemotherapy and 77.7% (181/233) for rucaparib in the ITT population.

Assessment of the MAH's response

According to the MAH, the observed imbalance between treatment arms for patients who discontinued treatment due to disease progression was due to the fact that patients in the chemotherapy arm could only receive a limited number of treatment cycles (except for patients receiving weekly paclitaxel) and this was not the case for the rucaparib arm where the treatment was to continue until disease progression. There were 21 (19.4%) subjects from the chemotherapy arm who discotinued treatment due to "treatment completed" which means they had already received eight cycles but had not progressed on it. Considering the response to this question and to question 12, there must be some patients who did not receive the maximun allowed number of cycles but that were considered not candidates to receive more than 4 or 6 cycles which is compatible with current clinical practice in these heavily treated patients. This could explain the observed imbalance.

Conclusion

Issue solved.

Question 6

The MAH should clarify if the reported OS interim analysis was pre-specified in the study protocol and SAP.

Summary of the MAH's response

The reported overall survival (OS) interim analysis was prespecified prior to the blind break that occurred on 15 December 2020. It is described in the Statistical Analysis Plan (SAP), Section 10.3.2 Interim Overall Survival, and includes a prespecified stopping rule and the adjustment for the final OS analysis.

It was anticipated that the data for OS would be heavily censored at the time of the initial CSR analysis. In order to adjust for multiple analyses of OS at a later stage, a stopping rule will be applied. The Haybittle-Peto stopping rule will be applied where an interim OS result with a p-value <0.001 can be used to claim superiority of rucaparib compared to chemotherapy. This means that a p-value very close to 0.05 can be utilized at the final analysis which is projected to be once at least 70% of the death events have been collected.

Assessment of the MAH's response

According to the MAH, the reported OS IA was established in the SAP v1.0 although there is not a specific reference to the fact that this was an interim analysis, except for the section title. The previous protocol version stated that "if the primary endpoint is statistically significant, then OS will be tested" but OS was considered a key secondary endpoint at that time. The SAP v1.0 anticipates that OS data would be

heavily censored at the time of the initial CSR analysis and establishes a stopping rule to claim superiority an to adjust for multiple analyses of OS at a later stage. This can be interpreted as defining this initial OS analysis (CSR) as an interim analysis with a prespecified p-value <0.001 to claim superiority of rucaparib versus chemotherapy. However, the fact that the SAP and protocol version were finalized after the data cut-off date raise concern, as already pointed out in this report.

Conclusion

Issue not further pursued.

Question 7

The MAH is requested to clarify the number of OS events needed for the final analysis and estimation of when it will be available.

Summary of the MAH's response

The final overall survival (OS) will be evaluated when at least 70% of the events have been collected, which was prespecified in the Statistical Analysis Plan (SAP) Section 10.3.2 Interim Overall Survival. Thus, the number of events needed are 245 deaths within the 349 randomized patients in Study CO-338-043 (ARIEL4). Clovis is utilizing an independent statistical vendor (AXIO Research [Seattle, Washington, US]) to maintain the overall blind of death data and also estimate when final OS events will be reached. The current OS maturity is 69% and the current projected estimate for collecting at least 70% of OS events is approximately May 2022.

Assessment of the MAH's response

The MAH has provided the requested information. The final OS analysis will be performed when 245 deaths are reported which is expected to occur in May 2022, approximately.

Conclusion

Issue solved.

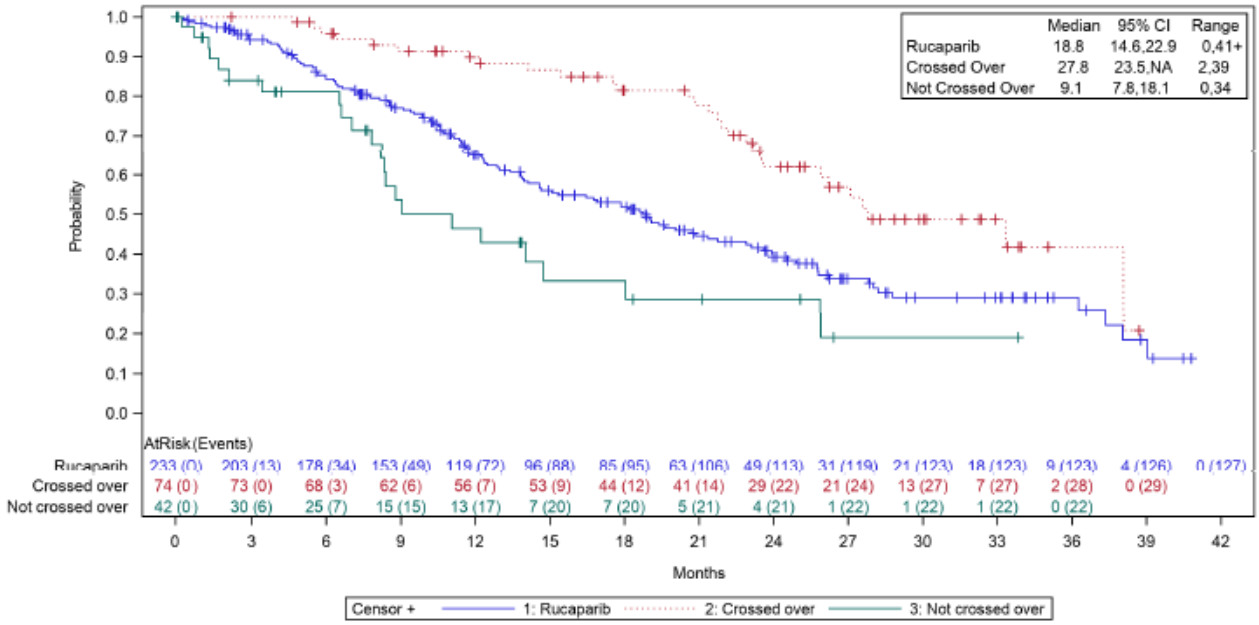
Question 8

Performing additional analyses using alternative relevant methods might be helpful to adjust for the reported crossover even if results from these analyses would be considered as supportive (bearing in mind their limitations as they mostly rely on underlying (strong) assumptions). Reference is made to EMA guidance: "Question and answer on adjustment for cross-over in estimating effects in oncology trials (EMA/845963/2018)". Results should be provided for both the efficacy population and the ITT population. Subgroup analyses according to stratification data should also be provided.

Summary of the MAH's response

As suggested in the EMA guidance EMA/845963/2018, exploration of statistical models that adjust for crossover should be used. As can be seen in the Kaplan-Meier survival plot in Figure 1, these groups produce 3 distinct non-crossing survival curves, which suggests that employing a time-adjusted Cox Proportional Hazards model may be an appropriate and useful way to further explore the confounding OS results.

Figure 1. Exploratory Endpoint: Interim OS – Treatment Part, ITT Population



Logrank Analysis Performed by randomization strata for the progression free interval after most recent platinum containing therapy (i.e., platinum resistant, partially platinum sensitive, or platinum sensitive).
Data cutoff is 30Sep2020

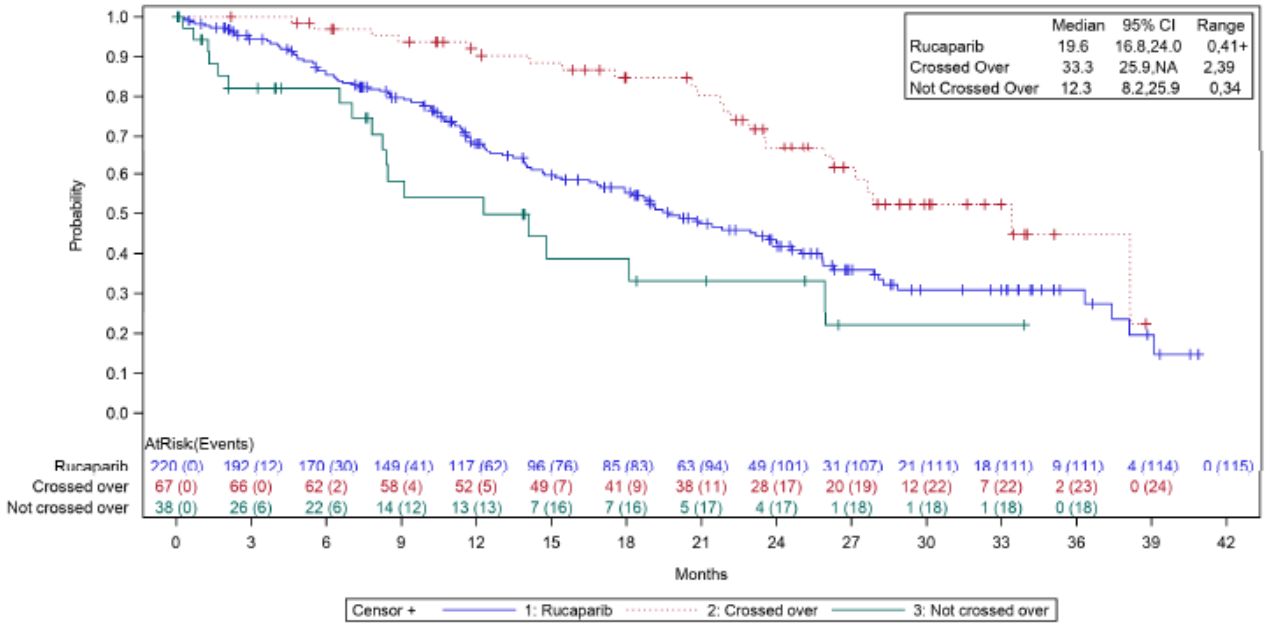
Table 2. Parameter Estimates from Cox Model Including a Time-Dependent Covariate for Initiating Rucaparib (ITT Population)

ITT Population	HR	Lower Limit	Upper Limit	P-Value
Partially platinum-sensitive	2.107	1.257	3.531	0.0047
Platinum resistant	3.346	2.081	5.379	<.0001
Baseline Chemotherapy, Z=1	0.578	0.380	0.877	0.0101
Began Rucaparib at time t; X(t)=1	0.688	0.380	1.245	0.2163

Table 3. Sensitivity/Resistance Subgroup Analysis: Parameter Estimates from Cox Model Including a Time-Dependent Covariate for Initiating Rucaparib (ITT Population)

Subgroup	Parameter	HR	Lower Limit	Upper Limit	P-Value
Platinum resistant	Baseline Chemotherapy, Z=1	0.435	0.249	0.759	0.0034
	Began Rucaparib at time t; X(t)=1	0.507	0.235	1.093	0.0830
Partially platinum-sensitive	Baseline Chemotherapy, Z=1	0.907	0.448	1.836	0.7864
	Began Rucaparib at time t; X(t)=1	1.192	0.350	4.064	0.7792
Platinum-sensitive	Baseline Chemotherapy, Z=1	0.708	0.150	3.342	0.6625
	Began Rucaparib at time t; X(t)=1	0.752	0.118	4.809	0.7637

Figure 2. Exploratory Endpoint: Interim OS – Treatment Part, Efficacy Population



Logrank Analysis Performed by randomization strata for the progression free interval after most recent platinum containing therapy (i.e., platinum resistant, partially platinum sensitive, or platinum sensitive).
Data cutoff is 30Sep2020

Proportional Hazards model that adjusts for randomization strata (Platinum sensitivity status as (1) "Platinum-resistant", (2) "Platinum-sensitive", or (3) "Partially platinum-sensitive") and a time-adjusted parameterization of the treatment effect as defined below:

1. Defined crossover patients as patients who progressed under chemotherapy and subsequently crossed over to rucaparib. Note, this means that only patients assigned to chemotherapy are eligible to be crossover patients, as per the protocol. Crossover patients spend *Tchemo* months on chemotherapy (time from study enrollment to crossover), followed by *Tparp* time on rucaparib (time from crossover to death/censoring).

2. Included a time-varying covariate *X(t)* in the Cox Proportional Hazards model, defined as:

   X(t)=0 if patient has not received rucaparib at time t

   X(t)=1 if patient is receiving rucaparib at time t

Note that $X(t \leq T_{chemo})=0$ and $X(t>T_{chemo})=1$ for crossover patients. *X* reduces to a constant for non-crossover patients: for all t, *X(t)*=0 for non-crossover chemotherapy patients and *X(t)*=1 for patients receiving rucaparib.

This parameterization of the treatment effect allows information to be shared between patients who received rucaparib, regardless of initial treatment assignment. If we allow the baseline treatment assignment to be parameterized such that rucaparib is the reference group (meaning that the baseline treatment assignment effect *Z* is such that *Z*=0 if baseline treatment assignment is rucaparib, and *Z*=1 if chemotherapy), then the "overall" rucaparib effect on overall survival can be estimated by the covariate associated with *X(t).* Similarly, the "overall" chemotherapy effect can be estimated by the covariate associated with *Z*.

Note, that a patient assigned to chemotherapy will have their hazard ratio (HR) changed according to the coefficient associated with *Z*=1. Similarly, a patient assigned to rucaparib will have their HR changed according to the coefficient associated with *X(t)*=1. Finally, a crossover patient will have their HR changed by the coefficient associated with *Z*=1 for $t \leq T_{chemo}$, and then their hazard will be changed by an additional amount according to the coefficient associated with *X*(*t*)=1.

Because of this, to directly compare chemotherapy to rucaparib, a custom hypothesis test must be performed comparing Z=1 vs. X(t)=1. This is because we need to compare "being on chemotherapy" (equivalently [Z=1] + [X(t)=0] = [Z=1]) vs. "being on rucaparib" (equivalently [Z=0] + [X(t)=1] = [X(t)=1]).

The results of the parametrization of the time-adjusted Cox Proportional Hazards model described above for the ITT population (N=349) are presented in Table 4.

Table 4. Cox Proportional Hazards Model Adjusted for Platinum Status in Study CO-338-043 – ITT Population

ITT Population	HR	Lower Limit	Upper Limit	P-Value
Partially platinum-sensitive	2.107	1.257	3.531	0.0047
Platinum-resistant	3.346	2.081	5.379	< 0.0001
Randomized to Chemotherapy, $Z = 1$ at baseline[a]	0.578	0.380	0.877	0.0101
Began Rucaparib at any time t; $X(t) = 1$[b]	0.688	0.380	1.245	0.2163

Source: Table 8.2.1

Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat.

[a] Randomized to chemotherapy at baseline is equivalent to $Z = 1$.

[b] Began rucaparib at any time t is equivalent to $X(t) = 1$, and includes subjects randomized to rucaparib at baseline.

Note, that randomized treatment assignment of chemotherapy is associated with a statistically significant decrease in hazard. Beginning rucaparib at time t (including subjects who started rucaparib at baseline when t = 0), is also associated with a decrease in hazard. Thus, crossover patients benefit from both the decrease attributed to (1) being randomized to chemotherapy assignment as well as then (2) subsequently receiving rucaparib. As expected, the covariate for platinum status is also statistically significant for overall survival.

Using the same model, similar results are seen in the Efficacy Population (N=325) presented in Table 5.

Table 5. Cox Proportional Hazards Model Adjusted for Platinum Status in Study CO-338-043 – Efficacy Population

Efficacy Population	HR	Lower Limit	Upper Limit	P-Value
Partially platinum-sensitive	1.940	1.147	3.282	0.0134
Platinum resistant	3.082	1.904	4.989	< 0.0001
Randomized to Chemotherapy, $Z = 1$ at baseline[a]	0.554	0.352	0.873	0.0109
Began Rucaparib at any time t; $X(t) = 1$[b]	0.684	0.356	1.313	0.2536

Source: Table 8.2.2.

Abbreviations: CI = confidence interval; HR = hazard ratio.

[a] Randomized to chemotherapy at baseline is equivalent to $Z = 1$.

[b] Began rucaparib at any time t is equivalent to $X(t) = 1$, and includes subjects randomized to rucaparib at baseline.

Exploring OS in subgroups based on platinum status was performed using the same time-adjusted Cox Proportional Hazards model within each subgroup but without the stratification factor in the model. The results for this model are presented in Table 4. Note that the platinum-resistant subgroup (N=179) seems

to have a strong effect for decreasing the hazard for both chemotherapy and rucaparib (p-values <0.01 and <0.10 respectively), but the other subgroups (N=96 partially platinum-sensitive and N=74 platinum-sensitive) do not seem to have any notable effect.

Table 6. Cox Proportional Hazards Model Analysis for Stratification Factor of Platinum Status Subgroups in Study CO-338-043 – ITT Population

Subgroup	Parameter	HR	Lower Limit	Upper Limit	P-Value
Platinum-resistant	Randomized to Chemotherapy, $Z = 1$ at baseline[a]	0.435	0.249	0.759	0.0034
	Began Rucaparib at any time t; $X(t) = 1$[b]	0.507	0.235	1.093	0.0830
Partially platinum-sensitive	Randomized to Chemotherapy, $Z = 1$ at baseline[a]	0.907	0.448	1.836	0.7864
	Began Rucaparib at any time t; $X(t) = 1$[b]	1.192	0.350	4.064	0.7792
Platinum-sensitive	Randomized to Chemotherapy, $Z = 1$ at baseline[a]	0.708	0.150	3.342	0.6625
	Began Rucaparib at any time t; $X(t) = 1$[b]	0.752	0.118	4.809	0.7637

Source: Table 8.2.3.

Abbreviations: HR = hazard ratio; ITT = intent-to-treat.

[a] Randomized to chemotherapy at baseline is equivalent to $Z = 1$.

[b] Began rucaparib at any time t is equivalent to $X(t) = 1$, and includes subjects randomized to rucaparib at baseline.

Using the time-adjusted Cox Proportional Hazards model described above for the ITT and Efficacy Population and Platinum status subgroups a direct comparison of chemotherapy vs. rucaparib (eg, Z=1 vs. $X(t)$=1) was performed using a CONTRAST statement in SAS. The models for all the populations and subgroups yielded a non-significant treatment difference (HR<1 is in favor of chemotherapy, HR>1 is in favor of rucaparib) as displayed in Table 7. These results show that there is not a statistically significant difference in OS when comparing chemotherapy directly to rucaparib for any subgroup. Because of this, and in addition to the large increase in OS seen in patients receiving both rucaparib and chemotherapy, it is possible that there is an additive benefit from both treatments, especially among platinum-resistant patients.

On the other hand, it is important to recall that a key limitation of this modelling approach is that it is a post-hoc analysis of OS among patients who had the potential to crossover. Any such analysis will be inherently biased by the fact that for a patient to crossover they must have survived long enough/been "healthy enough" to do so.

Table 7. Cox Proportional Hazards Model Directly Comparing Rucaparib vs Chemotherapy Treatment Groups for OS in ITT and Efficacy Populations and by Platinum Status Subgroups in Study CO-338-043

Group	HR	Lower Limit	Upper Limit	P-Value
ITT Population	0.8401	0.5269	1.3395	0.4643
Efficacy Population	0.8103	0.4855	1.3523	0.4208
Platinum-resistant	0.8580	0.4777	1.5409	0.6081
Partial platinum-sensitive	0.7611	0.2592	2.2350	0.6195
Platinum-sensitive	0.9408	0.3005	2.9458	0.9165

Source: Table 8.2.4.

Abbreviations: HR = hazard ratio; ITT = intent-to-treat; OS = overall survival.

In conclusion, OS is highly confounded due to high proportion of patients who crossed over by first being treated with chemotherapy and then subsequently received rucaparib in open-label crossover portion of the trial. When modeled with a time-dependent Cox Proportional Hazards model, the variable of beginning rucaparib did not reach statistical significance, but the HR was <1 (favourable) for the ITT population and the Efficacy population.

The pre-specified required maturity for final OS is at least 70% and the current OS maturity is 69%. Further exploratory analyses will be provided when the final OS will be reported in Q4 2022 (see response to question 11). The above analyses support that being treated with rucaparib at any timepoint is a good alternative option for these patients.

Assessment of the MAH's response

The MAH was requested to provide additional supportive analyses to adjust for the reported crossover in the study. Using available EMA guidance was suggested in this respect, and it was therefore expected that the MAH would have submitted results from analysis(es) proposed in such document. Instead of that, the MAH considers that as a result of the cross-over, three distinct non-crossing survival curves can be observed and that employing a time-adjusted Cox Proportional Hazards model is appropiate to further explore the confounding OS results. This method has been applied for the ITT, the Efficacy Population and the platinum status subgroups.There are 2 factors which assess the treatment effect in this model: the Z fixed factor for the randomisation to the control arm and the time-dependent X factor for the exposure to Rucaparib at any time. This approach has several methodological concerns.

First, the two treatment factors are being influenced by each other. While this model might be used as one of among a list of analyses, it is difficult to determine which one could be considered more appropriate post-hoc. The objective in that analysis should likely be the effect of the exposure to rucaparib (the X factor) at any time without the effect of the randomisation. It might be argued that this imply losing the randomised therapeutical strategy, but in fact this is also lost in the presented model by using the time-dependent (post-randomisation) factor. This means that any of the analyses including post-baseline variables is subject to potential confounders and biases, such as the patient status at the moment of the decision to crossover or not. This analysis should be considered as in the context of observational methods rather a sensitivity analysis of a randomised experiment, and as so, the addition of more covariates, some of them time-dependent, would be needed. The analysis provided should be supplemented with a series of analysis with and without the fixed Z factor and the use of covariates, in particular including those measuring the patient status and the severity of the disease at crossover.

In essence this will give a range of scenarios, which apparently will be helpful for the understanding of the crossover on the OS. However, the Applicant is referred again to the EMA guidance "Question and answer on adjustment for cross-over in estimating effects in oncology trials (EMA/845963/2018)". In this sense, they are strongly requested to provide the analysis censoring the data at crossover and at least 1 or 2 (preferable all 3) of the proposed methods for handling crossover.

Conclusion

Issue not solved.

Question 9

The MAH should submit and discuss OS and PFS2 results by stratification subgroups (i.e. by platinum sensitivity).

Summary of the MAH's response

At the time of visit cutoff for Study CO-338-043 (ARIEL4), overall survival (OS) data were at 51% maturity (51% of events), with the final readout for OS planned per the Statistical Analysis Plan (SAP), Section 10.3.2, when 70% maturity has been reached. The following presentation of the OS and, in the subsequent line of treatment, the second event of progression-free survival (PFS2) results by stratification subgroups therefore remains interim and immature and will be updated at the time of final OS analysis. The interim results for OS and PFS2 by each subgroup based on the randomization stratification variable of platinum status (ie, platinum-resistant, partially platinum-sensitive, platinum-sensitive) are summarized for the intent-to-treat (ITT) Population in Table 8. Similarly, OS and PFS2 are summarized by platinum status for the Efficacy Population in Table 9.

Table 8. Study CO-338-043 Interim OS and PFS2 by Platinum Status – Treatment Part, ITT Population

	Platinum-sensitive (PFI > 12 months)		Partially Platinum-sensitive (PFI ≥ 6 to 12 months)		Platinum-resistant (PFI > 1 to < 6 months)	
	Rucaparib N = 48	Chemotherapy N = 26	Rucaparib N = 65	Chemotherapy N = 31	Rucaparib N = 120	Chemotherapy N = 59
Interim OS						
events, n (%)	15 (31.3)	6 (23.1)	34 (52.3)	15 (48.4)	78 (65.0)	30 (50.8)
median in months (95% CI)	36.3 (24.6, 37.4)	NA (18.1, NA)	20.9 (11.8, 38.0)	25.9 (20.8, 27.8)	13.9 (11.5, 16.5)	21.7 (14.8, 33.3)
HR, (95% CI)	1.124 (0.438, 2.884) p-value = 0.8080		1.141 (0.618, 2.107) p-value = 0.6738		1.724 (1.128, 2.635) p-value = 0.0119	
Interim PFS2						
events, n (%)	22 (45.8)	10 (38.5)	40 (61.5)	23 (74.2)	84 (70.0)	48 (81.4)
median in months (95% CI)	23.1 (18.2, 36.3)	19.3 (14.1, NA)	15.7 (11.2, 23.3)	13.5 (8.2, 14.9)	10.9 (8.5, 13.1)	11.3 (8.8, 15.2)

	Platinum-sensitive (PFI > 12 months)		Partially Platinum-sensitive (PFI ≥ 6 to 12 months)		Platinum-resistant (PFI > 1 to < 6 months)	
	Rucaparib N = 48	Chemotherapy N = 26	Rucaparib N = 65	Chemotherapy N = 31	Rucaparib N = 120	Chemotherapy N = 59
HR, (95% CI)	0.995 (0.472, 2.100) p-value = 0.9900		0.685 (0.407, 1.153) p-value = 0.1544		1.029 (0.721, 1.468) p-value = 0.8763	

Sources: Figure 9.1.1, Figure 9.1.2, Figure 9.1.3, Table 10.1.7, Figure 9.2.1, Figure 9.2.2, Figure 9.2.3, and Table 10.2.7.

Abbreviations: CI = confidence interval; HR = hazard ratio (from Cox proportional hazard model); ITT = intent-to-treat; NA = not achieved; OS = overall survival; PFI = platinum-free interval; PFS = progression-free survival; PFS2 = the second event of PFS, in subsequent line of treatment.

Table 9. Study CO-338-043 Interim OS and PFS2 by Platinum Status – Treatment Part, Efficacy Population

	Platinum-sensitive (PFI > 12 months)		Partially Platinum-sensitive (PFI ≥ 6 to 12 months)		Platinum-resistant (PFI > 1 to < 6 months)	
	Rucaparib N = 48	Chemotherapy N = 26	Rucaparib N = 62	Chemotherapy N = 28	Rucaparib N = 110	Chemotherapy N = 51
Interim OS						
events, n (%)	15 (31.3)	6 (23.1)	32 (51.6)	12 (42.9)	68 (61.8)	24 (47.1)
median in months (95% CI)	36.3 (24.6, 37.4)	NA (18.1, NA)	25.8 (12.3, 38.0)	27.1 (21.9, NA)	14.6 (11.8, 18.8)	23.5 (15.4, 38.1)
HR, (95% CI)	1.124 (0.438, 2.884) p-value = 0.8080		1.258 (0.645, 2.454) p-value = 0.5013		1.789 (1.120, 2.858) p-value = 0.0149	
Interim PFS2						
events, n (%)	22 (45.8)	10 (38.5)	38 (61.3)	20 (71.4)	74 (67.3)	41 (80.4)
median in months (95% CI)	23.1 (18.2, 36.3)	19.3 (14.1, NA)	15.7 (11.4, 23.3)	13.6 (8.2, 17.0)	12.0 (9.5, 13.9)	12.7 (9.1, 15.8)
HR, (95% CI)	0.995 (0.472, 2.100) p-value = 0.9900		0.691 (0.399, 1.197) p-value = 0.1876		0.983 (0.671, 1.441) p-value = 0.9301	

Sources: Figure 9.1.4, Figure 9.1.5, Figure 9.1.6, Table 10.1.7, Figure 9.2.4, Figure 9.2.5, Figure 9.2.6, and Table 10.2.7.

Abbreviations: CI = confidence interval; HR = hazard ratio (from Cox proportional hazard model); NA = not achieved; OS = overall survival; PFI = platinum-free interval; PFS = progression-free survival; PFS2 = the second event of PFS, in subsequent line of treatment.

The distribution of patients who crossed over from the chemotherapy arm to rucaparib treatment in the open-label phase (N=74) is displayed by platinum status at the time of randomization in Table 10 below.

Table 10. Study CO-338-043 Proportion of Patients by Strata of Platinum Status at Time of Randomization - Patients Who Crossed Over to Rucaparib in the Crossover Part

Platinum Status Group	Overall N = 74
Platinum-sensitive	10 (13.5%)
Partially platinum-sensitive	25 (33.8%)
Platinum-resistant	39 (52.7%)

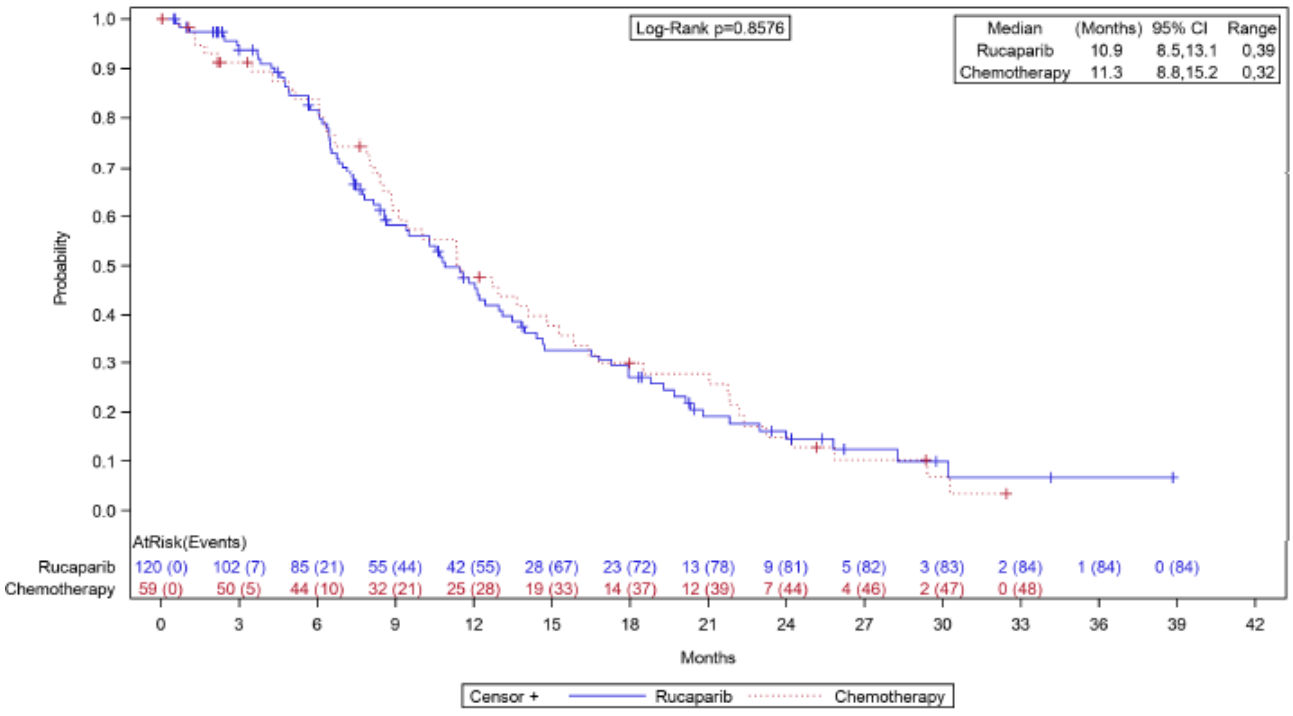
Sources: Table 9.3.1

In conclusion, this interim OS analysis showed no difference between patients treated with either rucaparib or chemotherapy who were platinum-sensitive or partially platinum-sensitive at study entry in

either the ITT or Efficacy Populations. This confirms that rucaparib can offer an effective, alternative nonplatinum-based treatment option for ovarian cancer patients with platinum-sensitive disease. The patients in the ITT Population who were platinum resistant and treated with chemotherapy appeared to have a longer OS (21.7 months) as compared to platinum-resistant patients treated with rucaparib (13.9 months), with similar results observed in an analysis of the Efficacy Population. Given, however, that 39/59 (66%) patients in the platinum-resistant group (ITT Population), initially treated with chemotherapy, crossed over to receive rucaparib in the open-label Crossover Part of Study CO-338-043, appropriate analyses adjusting for confounding effects due to crossover are needed. Please see response to question 8 for further details on the adjustment of the treatment effect for the Crossover Part.

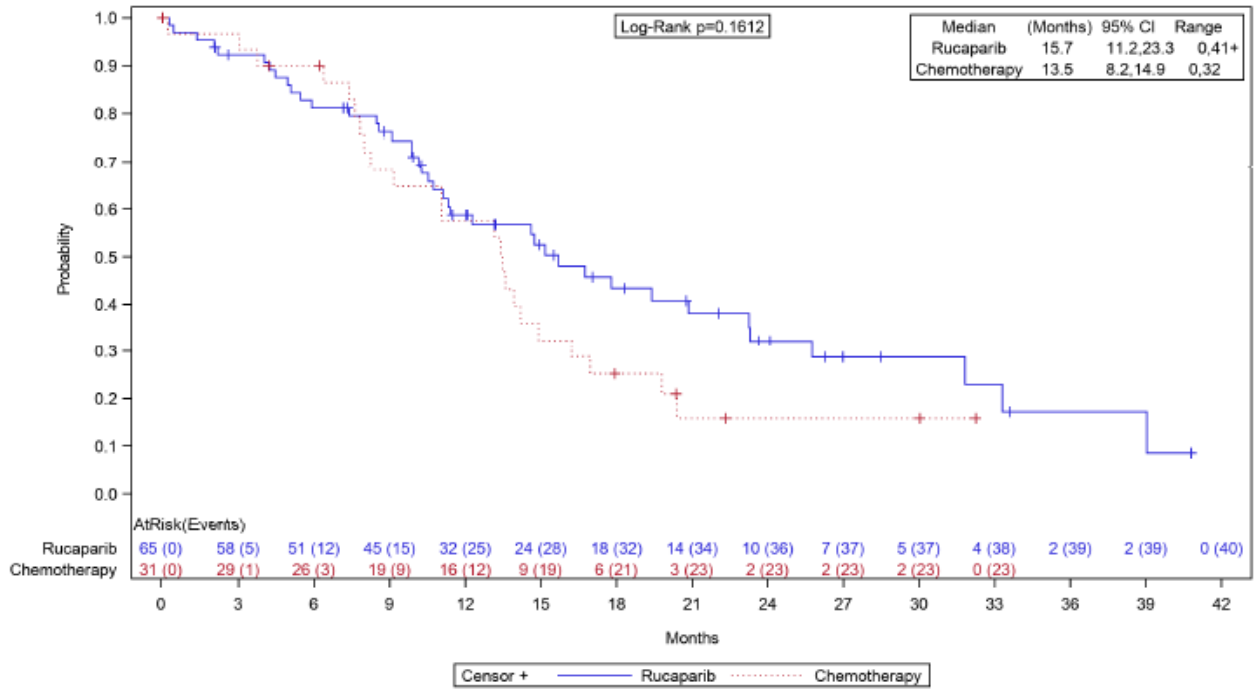
The interim PFS2 did not show any difference between patients initially randomized to rucaparib or chemotherapy in the treatment phase who were platinum-sensitive, partially platinum-sensitive, or platinum-resistant at study entry in either the ITT or Efficacy Populations. The PFS2 analyses can be seen as a simplistic approach to evaluate the time to relapse for two different sequences of treatments (patients treated with rucaparib followed by chemotherapy vs patients initially randomized to chemotherapy followed by PARP-inhibitor due to crossover) and the overall results indicate that there seems to be no difference in efficacy.

Figure 3. Subgroup analysis of Exploratory Endpoint of PFS2 – ITT Population who are Platinum resistant



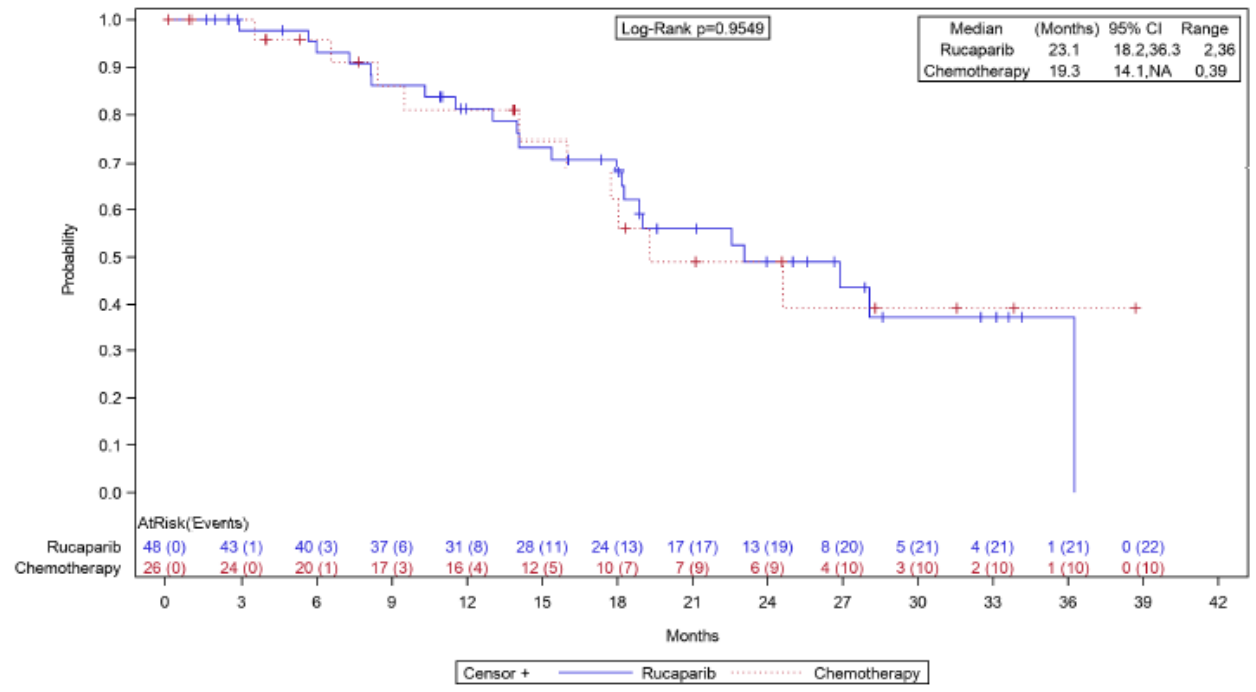
Data cutoff is 30Sep2020

Figure 4. Subgroup analysis of Exploratory Endpoint of PFS2- ITT Population who are Partially platinum-sensitive



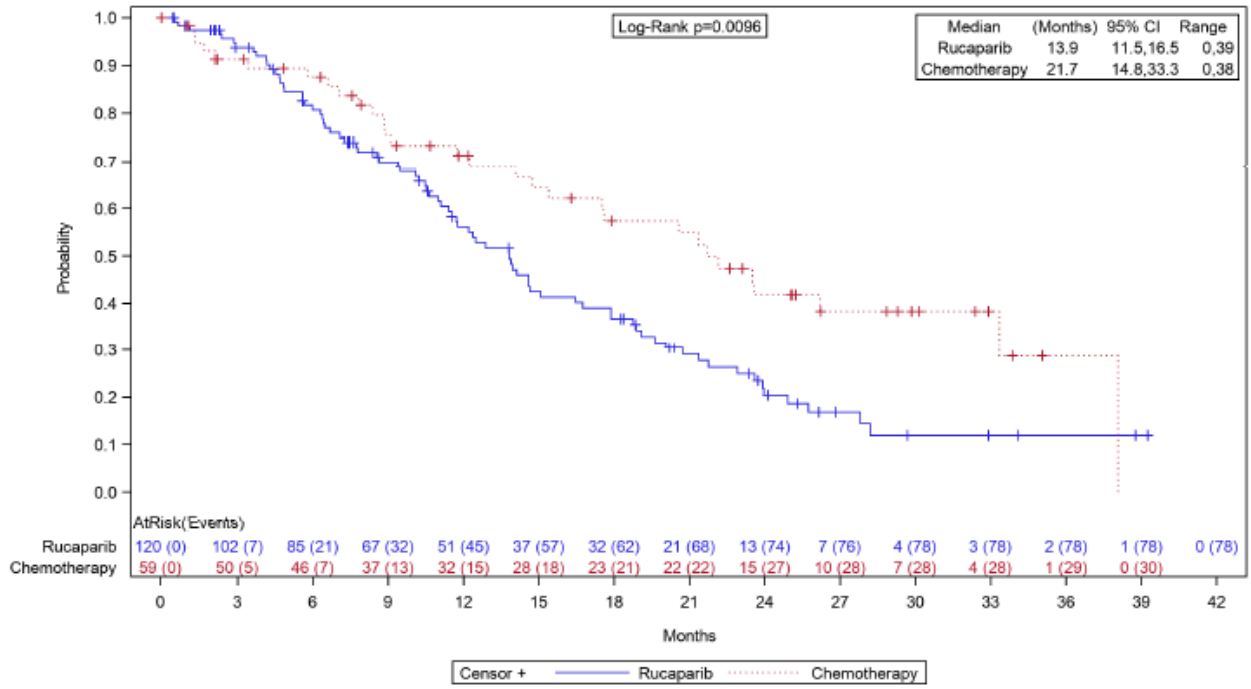
Data cutoff is 30Sep2020

Figure 5. Subgroup analysis of Exploratory Endpoint of PFS2- ITT Population who are Platinum sensitive



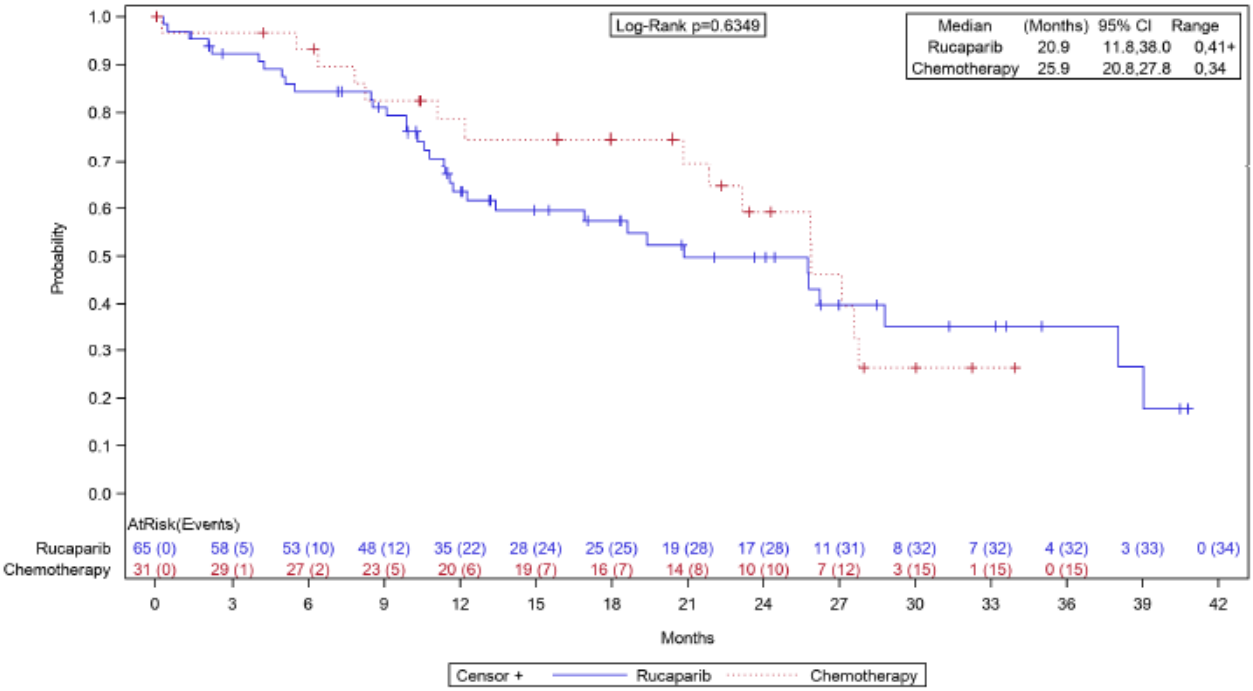
Data cutoff is 30Sep2020

Figure 6. Subgroup analysis of Exploratory Endpoint of Interim OS – ITT Population who are Platinum resistant



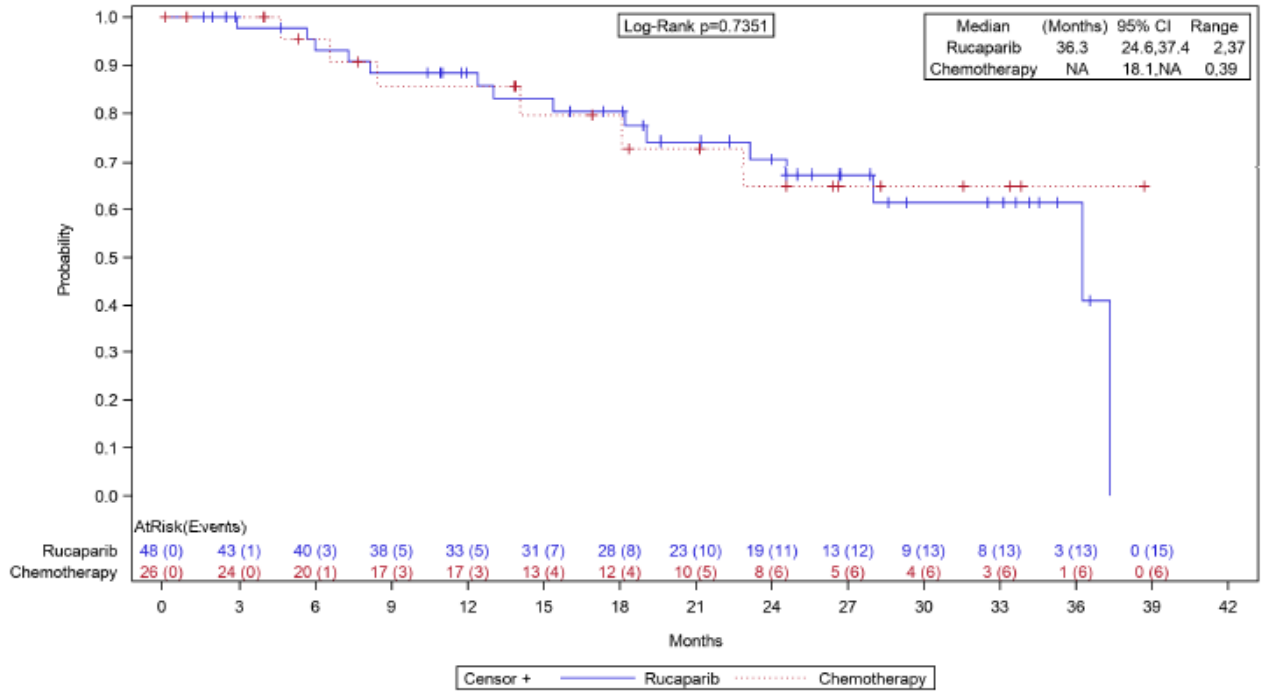
Data cutoff is 30Sep2020

Figure 7. Subgroup analysis of Interim OS – ITT Population who are Partially platinum-sensitive



Data cutoff is 30Sep2020

Figure 8. Subgroup analysis of Interim OS – ITT Population who are Platinum sensitive



Data cutoff is 30Sep2020

Assessment of the MAH's response

It is acknowledged that the reported OS results remain immature but, considering that the presented OS analysis has been performed with the 51% of events (final OS analysis planned at 70% of events), some information can be extracted. For the ITT and Efficacy Population, OS results by platinum status have already be included in the response to the MO (question 1). PFS2 results, for the ITT Population, favoured the rucaparib arm for the partially platinum-sensitive subgroup (HR = 0.685 [95% CI: 0.407, 1.153] p=0.1544); which is the subgroup of most interest in the context of the confirmation exercise for the results on which the initial conditional approval for rucaparib was based. For the platinum-sensitive subgroup the reported HR for PFS2 was of 0.995 ([95% CI: 0.472, 2.100] p=0.990) and for the platinum-resistant subgroup, the estimated HR was 1.029 ([95% CI: 0.721, 1.468]), p=0.8763 and the median PFS2 in this subgroup was 10.9 (8.5, 13.1) months for the rucaparib arm and 11.3 (8.8, 15.2) months for the chemotherapy treatment arm. Consistent results were found for the Efficacy Population except for the fact that, in the platinum-resistant subgroup, the HR was below 1 (HR= 0.983 [95% CI: 0.671, 1.441] p=0.9301). Also, the median PFS2 for this subgroup were similar between arms. From the 74 subjects from the placebo arm who crossed over to receive rucaparib, the highest proportion (52.7%) of subjects correspond to the platinum-resistant subgroup, which is to be expected, the same for the shorter PFS2 , as their response to further treatments is supposed to be more limited. Overall, the results for the exploratory endpoint of PFS2 are consistent with the already commented OS findings.

Conclusion

The requested data has been provided and therefore the issue is considered solved.

Question 10

The MAH should provide tabular information about subsequent anti-cancer therapies.

Summary of the MAH's response

At the time of the clinical study report (CSR) visit cut-off (30 September 2020), a total of 57.3% (200/349) patients had reported at least one regimen of subsequent anti-cancer treatment (SAT). The breakdown of reasons for those patients without SAT data recorded are found in Table 11.The presented data is reflective of the state of the data collection at the time of the CSR visit cut-off date.

Table 11. Summary of Patients With and Without Subsequent Anti-cancer Treatment (Visit cut-off 30-Sept-2020)

	Rucaparib (N = 233)	Chemotherapy (N = 116)	Total (N = 349)
Subsequent anti-cancer treatment reported	115 (49.4%)	85 (73.3%)	200 (57.3%)
No subsequent anti-cancer treatment reported	118 (50.6%)	31 (26.7%)	149 (42.7%)
Reason:			
Died	57 (48.3%)	15 (48.4%)	72 (48.3%)
Withdrew Consent	4 (3.4%)	1 (3.2%)	5 (3.4%)
Lost to Follow Up	1 (0.8%)	1 (3.2%)	2 (1.3%)
Ongoing in randomized portion	44 (37.3%)	5 (16.1%)	49 (32.9%)
Discontinued from randomized portion and no subsequent therapy reported	12 (10.2%)	9 (29.0%)	21 (14.1%)

Source: Table 10.1.1

For those patients with SAT, the first and second SAT regimens are broadly summarized by the following 7 categories:

- Poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP)-inhibitor or PARP-inhibitor combination (treatment with either single-agent rucaparib, niraparib or olaparib, or rucaparib plus nivolumab and ipilumumab)
- Platinum combination chemotherapy (at least one agent was carboplatin, cisplatin, or oxaliplatin plus a non-platinum chemotherapy agent), and with or without bevacizumab or hormonal therapies
- Platinum monotherapy (single-agent platinum; includes switch between carboplatin and cisplatin for tolerability reasons)
- Non-platinum combination chemotherapy, with or without bevacizumab or hormonal therapies (eg. doxorubicin plus gemcitabine, paclitaxel plus bevacizumab, liposomal doxorubicin plus trabectedin, cyclophosphamide, methotrexate plus anastrozole)
- Hormonal therapy (eg, single agent tamoxifen, anastrozole)
- Immunotherapy (eg, avelumab, atezolizumab)
- Investigational or Unknown anti-cancer treatments

The first and second regimens are summarized in Table 2. Upon confirmation of disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, patients who had been randomized to the chemotherapy arm could crossover to receive rucaparib under open-label treatment. Given that all patients enrolled into Study SO-338-043 (ARIEL4) had a deleterious breast cancer gene (BRCA) mutation, it is not unexpected that 91.7% (78/85) of patients in the chemotherapy arm received

subsequent treatment with a PARP-inhibitor upon disease progression, the vast majority receiving rucaparib treatment.

For those patients who were randomized to the rucaparib arm in the Treatment Part of the Study CO-338-043, and whose disease progressed, nearly all of these patients received a subsequent chemotherapy regimen, with the majority receiving platinum-based treatment (56.5%; 65/115 patients) and a slightly smaller percentage receiving non-platinum chemotherapy treatment (37.4%; 43/115 patients). Platinum-based regimens were the most frequent first SATs in patients who were partially platinum-sensitive or platinum-sensitive at baseline initially randomized to rucaparib. Of 120 patients who were considered platinum-resistant at baseline and were randomized to the rucaparib arm, 45.8% (55/120) patients had received a first SAT at the time of data cut-off. Interestingly, despite these patients being platinum-resistant, 21/55 (38.2%) patients received platinum-based chemotherapy as monotherapy or in combination therapy, while 31/55 (56.4%) patients received a nonplatinum-based chemotherapy regimen and 2 (3.6%) patients received hormonal therapy.

At the time of the CSR visit cut-off date, 89 patients had received a second SAT regimen. Of 51 patients originally randomized to the rucaparib arm, and who already received one subsequent chemotherapy regimen, the majority of these patients 62.7% (32/51) received further chemotherapy, with a shift to nonplatinum-based regimens either as monotherapy or as combination. For the chemotherapy arm, in which the majority of patients received rucaparib as their first SAT regimen, nearly 90% of those patients who continued to a second SAT regimen (n = 38) received chemotherapy as their next treatment regimen.

Table 12. Summary of First and Second Subsequent Anti-cancer Treatments (Visit cut-off 30-Sept-2020)

	Rucaparib (N = 233)	Chemotherapy (N = 116)	Total (N = 349)
Patients with at least 1 SAT, n (%)[a]	**115 (49.4%)**	**85 (73.3%)**	**200 (57.3%)**
PARP Inhibitor	0 (0%)	78 (91.8%)	78 (39.0%)
Platinum-combination chemotherapy[b]	53 (46.1%)	2 (2.4%)	55 (27.5%)
Platinum monotherapy	12 (10.4%)	0 (0%)	12 (6.0%)
Non-platinum combination chemotherapy[b]	6 (5.2%)	0 (0%)	6 (3.0%)
Non-platinum monotherapy	37 (32.2%)	3 (3.5%)	40 (20.0%)
Hormonal therapy	4 (3.5%)	1 (1.2%)	5 (2.5%)
Immunotherapy	0 (0%)	1 (1.2%)	1 (0.5%)
Investigational treatment/Unknown	3 (2.6%)	0 (0%)	3 (0.5%)
Patients with at least 2 SATs, n (%)[a]	**51 (21.9%)**	**38 (32.8%)**	**89 (25.5%)**
PARP Inhibitor	2 (3.9%)	1 (2.6%)	3 (3.4%)
Platinum combination chemotherapy[b]	7 (13.7%)	17 (44.7%)	24 (27.0%)
Platinum monotherapy	6 (11.8%)	3 (7.9%)	9 (10.1%)
Non-platinum combination chemotherapy[b]	8 (15.7%)	2 (5.2%)	10 (11.2%)
Non-platinum monotherapy	24 (47.1%)	12 (31.6%)	36 (40.4%)
Hormonal therapy	3 (5.9%)	2 (5.3%)	5 (5.6%)
Immunotherapy	1 (2.0%)	1 (2.6%)	2 (2.2%)

Source: Table 10.2.1 and Table 10.3.1

Abbreviation: SAT = subsequent anti-cancer treatment.

[a] Denominator includes patients that have at least one subsequent therapy for ovarian cancer data entered by visit cut-off date.

[b] Includes chemotherapy combinations with bevacizumab or hormonal therapy.

Assessment of the MAH's response

Up to the data cut-off date (30 Sept 2020), a total of 200 (57.3%) patients received, at least, one subsequent anti-cancer treatment, 115 (49.4%) in the rucaparib arm and 85 (73.3%) in the placebo arm, which is supposed to include the 74 patients in the chemotherapy arm who crossed-over to received rucaparib after progression. The most common subsequent therapy received in the rucaparib arm was a platinum-based combination while in the chemotherapy arm, most patients received a PARP inhibitor. There were 37 (32.2%) patients in the rucaparib arm who received non-platinum monotherapy, which could correlate to the number of platinum-resistant subjects who received later therapy, although according to the MAH there were 21 patients considered platinum-resistant that received platinum chemotherapy as subsequent therapy.

In addition to these data, there were a total of 89 (25.5%) subjects who received two or more subsequent anti-cancer therapy. In this later stage, the type of therapy received was more varied, as can be found in clinical practice. It does not seem that rucaparib treatment prevent patients from receiving posterior anti-cancer treatments.

Conclusion

Issue solved.

Question 11
The MAH is requested to submit final analysis for OS and PFS2 when available (REC already proposed).

Summary of the MAH's response
As acknowledged by the CHMP, an updated Letter of Recommendation was included with the initial variation package reflecting the MAH's commitment to submit an addendum to the Study CO-338-043 clinical study report (CSR), incorporating overall survival (OS) and second event of progression-free survival (PFS2) final analyses, when available. The MAH estimates it will be able to submit the final analyses of OS and PFS2 as a CSR addendum in Q4 2022 via the appropriate regulatory procedure.

Assessment of the MAH's response

The MAH has provided an updated Letter of Recommendation including the MAH's commitment to submit an addendum to the Study CO-338-043 clinical study report (CSR), incorporating overall survival (OS) and second event of progression-free survival (PFS2) final analyses, with an estimated date of Q4 2022.

Conclusion

Issue solved.

Clinical safety

Question 12
As per protocol, patients in the chemotherapy arm, can receive up to 8 cycles. However, it seems that some patients received more than 8 cycles (median 5; range: 1, 21). The MAH should clarify the number of patients that received more than 8 cycles (if any). Further, the exact number of patients that completed 8 cycles should be provided.

Summary of the MAH's response
The median number of treatment cycles received in the chemotherapy arm was 5 cycles (range: 1, 21). Per protocol, the restriction to a maximum of 8 cycles applied only to platinum-containing regimens to be consistent with standard of care and limit cumulative platinum toxicity. Patients receiving weekly paclitaxel could continue treatment until disease progression or other reason for discontinuation. For some patients, the maximum number of cycles of weekly paclitaxel treatment cycles was determined by institutional or local guidelines, consistent with data indicating that discontinuation of study drug was due to completion of treatment. All patients who received more than 8 cycles of chemotherapy on the study were receiving weekly paclitaxel.

Of the 88 patients who received weekly paclitaxel, the median number of cycles received was 5 (range: 1, 21). Twelve (13.6%) patients received > 8 cycles with 3 patients each receiving 9 and 10 cycles respectively, and single patients each receiving 11, 12, 14, 15, 20 and 21 cycles respectively.

Of the 25 patients who received platinum monotherapy or doublet therapy, only 3 (12%) received the maximum 8 cycles. Of 9 patients receiving platinum monotherapy, the median number of cycles received was 6 (range: 4, 8). Of 16 patients receiving platinum doublet, the median number of cycles received was 5 (range: 2, 8).

Table 13. Summary of Number of Cycles for Those Randomized and Treated in the Chemotherapy Arm.

	Paclitaxel (N=88)	Monotherapy Platinum (N=9)	Platinum Doublet (N=16)
Number of Cycles Started			
N	88	9	16
Mean (SD)	5.4 (3.81)	5.8 (1.20)	4.9 (1.93)
Standard Error	0.41	0.40	0.48
Median	5.0	6.0	5.0
Q1, Q3	2.5,7.0	6.0,6.0	3.5,6.0
Min, Max	1,21	4,8	2,8
Number of Cycles Started (cat)			
1	8 (9%)	0 (0%)	0 (0%)
2	14 (16%)	0 (0%)	3 (19%)
3	10 (11%)	0 (0%)	1 (6%)
4	10 (11%)	2 (22%)	2 (13%)
5	6 (7%)	0 (0%)	3 (19%)
6	16 (18%)	6 (67%)	5 (31%)
7	4 (5%)	0 (0%)	0 (0%)
8	8 (9%)	1 (11%)	2 (13%)
9	3 (3%)	0 (0%)	0 (0%)
10	3 (3%)	0 (0%)	0 (0%)
11	1 (1%)	0 (0%)	0 (0%)
12	1 (1%)	0 (0%)	0 (0%)

	Paclitaxel (N=88)	Monotherapy Platinum (N=9)	Platinum Doublet (N=16)
14	1 (1%)	0 (0%)	0 (0%)
15	1 (1%)	0 (0%)	0 (0%)
20	1 (1%)	0 (0%)	0 (0%)
21	1 (1%)	0 (0%)	0 (0%)
Chemotherapy Agent Name			
Carboplatin	0 (0%)	5 (56%)	0 (0%)
Carboplatin, Gemcitabine	0 (0%)	0 (0%)	4 (25%)
Carboplatin, Paclitaxel	0 (0%)	0 (0%)	7 (44%)
Cisplatin	0 (0%)	4 (44%)	0 (0%)
Cisplatin, Gemcitabine	0 (0%)	0 (0%)	5 (31%)
Paclitaxel	88 (100%)	0 (0%)	0 (0%)

Data cutoff is 30Sep2020

Assessment of the MAH's response

According to the MAH, the restriction to a maximum of 8 cycles applied only to platinum-containing regimens and all patients that received more than 8 cycles of chemotherapy were receiving weekly paclitaxel. The median number of cycles in patients that received platinum monotherapy (n=9) and platinum doublet (n=16) was, respectively, 6 (range: 4, 8) and 5 (range: 2, 8). Among the 88 patients that received weekly paclitaxel, there were 12 (13.6%) patients that received >8 cycles.

Conclusion

Issue solved.

Question 13

There were a total of 12 (5.2%) patients in the rucaparib arm while only 1 (0.9%) in the chemotherapy arm that reported an event of intestinal obstruction. Of these, 6 events in the rucaparib arm were

considered as serious. In addition, 4 serious adverse events were reported among patients who crossed-over to rucaparib treatment The MAH is requested to provide further information on all the events of intestinal obstruction reported in the ARIEL4 study (as well as the pooled population) and discuss to what extent these events may be related to rucaparib treatment.

Summary of the MAH's response

Overall, the incidence of intestinal obstruction (preferred terms [PTs]: intestinal obstruction, small intestinal obstruction, large intestinal obstruction) in patients who received rucaparib in the Treatment Part of the ARIEL4 study (12 of 232 patients [5.2%]; Table 1) was similar to the incidence observed in the pooled population of patients with ovarian cancer from Study CO-338-010, Study CO-338-017 (ARIEL2), and Study CO-338-014 (ARIEL3) (52 of 937 patients [5.5%]; Table 2). The incidence of events of intestinal obstruction assessed as treatment-related was also similar in patients who received rucaparib in the Treatment Part of ARIEL4 (1 of 232 patients [0.4%]) and in the pooled population (1 of 937 patients [0.1%]).

In addition, a comparison of the rucaparib and placebo treatment groups in ARIEL3 showed a similar incidence of events of intestinal obstruction between groups (rucaparib: 12 of 372 patients [3.2%]; placebo: 6 of 189 patients [3.2%]) (Table 2). This suggests that intestinal obstruction is not a treatment-related event.

In ARIEL4, 14 events of intestinal obstruction were reported in 12 patients receiving rucaparib during the Treatment Part, of which only one event was considered related to rucaparib by the investigator. Six of the events were considered to be serious, and eight events were nonserious. Of the 14 events, 12 events resolved, one event was resolving, and the one remaining event was ongoing at the time of the data cut on 30 September 2020. No fatal cases of intestinal obstruction were reported. In the majority of cases (11 of 12 patients [91.7%]), patients received treatment with concomitant medication, supportive therapy or procedural intervention. Treatment with rucaparib was interrupted following five events and withdrawn permanently after three events. For one event, dosing with rucaparib was maintained, and action taken with rucaparib was not applicable for four events, as treatment had already stopped.

Time to onset of the events was variable from 7 to 499 days (mean = 132.1 days; median = 83.0 days). Prior abdominal surgery was noted in all 12 patients, primarily hysterectomy, oophorectomy, and omentectomy (related to the underlying disease of ovarian cancer). Overall, 5 patients experienced disease progression prior to or around the time of the event of intestinal obstruction. Three patients experienced disease progression after the onset of intestinal obstruction (22, 96, and 433 days after onset). No relevant tumor response data were available for 3 patients (as patients were withdrawn from the study prior to the first Investigator Objective Tumor Assessment), and one patient had stable disease.

In addition, 7 patients who had originally received chemotherapy in ARIEL4 and had crossed over to treatment with rucaparib (ie, Crossover Part of the study) experienced an event of intestinal obstruction (Table 1). Nine events were reported, none of which were considered to be related to rucaparib by the investigator. Four events were considered to be serious, and five were nonserious. All events resolved with or without sequelae. All patients received treatment with concomitant medication or procedural intervention. Treatment with rucaparib was interrupted following four events and was permanently withdrawn after one event. Dosing with rucaparib was maintained after one event, and action taken with rucaparib was not applicable for the remaining three events.

Time to onset of intestinal obstruction varied between 6 and 294 days (mean = 76.4 days; median = 29.0 days). Prior abdominal surgery indicative of underlying ovarian cancer was noted in all patients. Four patients experienced disease progression prior to the onset of the intestinal obstruction. Three patients experienced disease progression after the onset of the event (95, 163 and 200 days after onset).

In the Treatment Part of ARIEL4, one patient (0.9%) experienced an event of intestinal obstruction following treatment with chemotherapy compared with the 12 patients (5.2%) who received rucaparib. However, the mean duration of treatment for patients receiving rucaparib was more than double that for patients receiving chemotherapy during the Treatment Part of the study (9.0 months vs. 4.4 months, respectively). As intestinal obstruction is most frequently associated with disease progression, the longer treatment duration in the rucaparib group may explain the disparity in the incidence of events, as more patients will have experienced worsening of their underlying disease while receiving extended daily therapy. In addition, patients who received platinum monotherapy or doublet therapy within the chemotherapy treatment group could only receive a maximum of 8 cycles (per protocol), meaning that treatment may have been completed before disease progression, and the possible associated risk of intestinal obstruction, was observed.

Pooled Population (Study CO-338-010, ARIEL2, and ARIEL3) Intestinal Obstruction Events

In the pooled population of patients with ovarian cancer, a total of 78 events were reported in 52 patients, of which only one event was considered to be related to administration of rucaparib by the investigator. Fifty-six of the events were considered to be serious, and 22 were nonserious. Of the 78 events of intestinal obstruction, 64 events (82.1%) resolved, seven events (9.0%) resolved with sequelae, six events were ongoing (7.7%), and one event was fatal. With the exception of 1 patient, all were treated with concomitant medication or procedural intervention or were hospitalized. Treatment with rucaparib was interrupted for 30 events (38.5%) and discontinued for 17 events (21.8%). Treatment with rucaparib was maintained for 13 events (16.7%), and action taken with rucaparib was not applicable for 18 events (23.1%) as dosing had already stopped.

Time to onset of the first event of intestinal obstruction was variable in the pooled population (3 to 983 days; mean, 143.3 days; median, 99.0 days). Prior abdominal surgery was recorded for all 52 patients, reflecting the underlying disease of ovarian cancer. Overall, 17 patients (32.7%) experienced disease progression prior to or around the same time as the event. Fifteen patients (28.8%) experienced disease progression after the onset of intestinal obstruction. Ten patients (19.2%) did not experience disease progression (ie, had a complete or partial response or stable disease), and 10 patients (19.2%) had tumor data that was either unevaluable or not available.

In conclusion, global prevalence of malignant bowel obstruction is estimated at 3% to 15% of cancer patients. Intestinal obstruction is even more common in ovarian cancer patients, with rates between 20% and 50% reported in the literature and these rates may be understimated due to difficulties in collection data from patients with late-stage disease when intestinal obstruction associated with disease progression may occur. Disease progression is a strong link to intestinal obstruction with cancer recurrence responsible for approximately 60% of intestinal obstruction cases in ovarian cancer patients. In addition, prior surgery is attributed as the cause of intestinal obstruction in a substantial proportion of cases, with estimates varying from 12% to 71% of cases.

Overall, 71 of 1,169 patients (6.1%) experienced a total of 101 events of intestinal obstruction following treatment with rucaparib in ARIEL4 (including crossover patients), Study CO-338-010, ARIEL2, and ARIEL3. Only 2 of 101 events (2.0%) were considered related to administration of rucaparib by the investigator. All but one of the patients had undergone prior abdominal surgery (70 of 71 patients [98.6%]), which is strongly associated with the subsequent occurrence of intestinal obstruction. In addition, of the patients with available tumor data regarding disease progression, intestinal obstruction was noted for 26 of 49 patients (53.1%) prior to or around the same time as disease progression. Again, this shows a clear link to progression of the underlying disease rather than a treatment-related event, as observed.

A comparison of the rucaparib and placebo treatment groups in ARIEL3 shows a similar incidence of events of intestinal obstruction between groups (rucaparib: 12 of 372 patients [3.2%]; placebo: 6 of 189 patients [3.2%]). This suggests again that intestinal obstruction is not a treatment-related event.

Review of the data from the ARIEL4 study and the pooled ovarian cancer population indicates that the occurrence of intestinal obstruction appears to be primarily related to the underlying disease rather than to administration of rucaparib. This conclusion is in line with the review of events of intestinal obstruction performed at the request of the Pharmacovigilance Risk Assessment Committee (PRAC) and presented in the rucaparib Periodic Safety Update Report (PSUR) 2 (covering 20 September 2018 to 19 June 2019). The PRAC Rapporteur concluded: *"It is agreed that there remains insufficient evidence to consider intestinal obstruction as an identified or potential risk for patients receiving rucaparib. The MAH should continue to monitor this topic through routine pharmacovigilance."*

Assessment of the MAH's response

According to the MAH the events of intestinal obstruction reported in patients treated with rucaparib appear to be primarily related to the underlying disease rather than rucaparib treatment. The majority of events were not considered related to rucaparib by the investigator. In addition, the MAH stated that no differences were observed between treatment arms in the ARIEL3 study (3.2% rucaparib vs. 3.2% placebo), suggesting that these events were not related to study treatment.

Regarding study ARIEL4, the MAH argues that differences observed between treatment arms may be due to the longer treatment exposure in the rucaparib arm. Even if MAH's justification can be acknowledged, in order to further rule out a causal relationship with rucaparib, the MAH is requested to provide safety data of intestinal obstruction adjusted by treatment exposure. In addition, the narratives of all patients that reported an event of intestinal obstruction in the study ARIEL4 should also be submitted.

Conclusion

Issue not solved.

Question 14

The incidence of MDS/AML has been established based on a total of 2,972 patients treated with rucaparib in clinical trials. The MAH should specify to which studies (including a brief description) these patients come from.

Summary of the MAH's response

Table 14 presents the numbers of patients exposed to oral rucaparib in each Clovis-sponsored clinical trial to five a total of 2.972 patients. The numbers of patients experiencing an event of myelodysplastic syndromes/ acute myeloid leukemia (MDS/AML) are also presented by study.

Table 14. Summary of Patients Reporting MDS/AML in Clinical Studies of Oral Rucaparib

Study Number/ Study ID	EudraCT Number	Brief Description of Study Design and Population	Number of Patients Receiving Oral Rucaparib	Number of Patients Reporting MDS/AML
A4991014	2009-013879-22	Phase 1 dose-escalation, safety, PK and pharmacodynamic study of rucaparib in combination with several chemotherapeutic regimens in patients with advanced solid tumors	33	0
CO-338-010/ Study 10	2011-004250-26	Phase 1/2 open-label, dose-escalation study of oral rucaparib in solid tumors and germline breast cancer gene (gBRCA) mutation ovarian cancer • Phase 1 (Part 1): Patients with advanced sold tumor • Phase 2 (Part 2A): Patients with platinum-sensitive, relapsed, ovarian cancer associated with a gBRCA mutation • Phase 2 (Part 2B): Patients with relapsed, ovarian cancer with a gBRCA or somatic breast cancer gene (sBRCA) mutation who received ≥3 prior chemotherapy regimens • Phase 2 (Part 3): Patients with advanced solid tumor with evidence of a gBRCA or sBRCA mutation	136	2 [2 on treatment]
CO-338-014/ ARIEL3	2013-000518-39	Phase 3 double-blind, randomized, placebo-controlled study of rucaparib as switch maintenance following platinum-based chemotherapy in platinum-sensitive, relapsed, high-grade epithelial ovarian cancer	372	14 [6 on treatment] [8 in LTFU]
CO-338-017/ ARIEL2	2013-000517-20	Phase 2 open-label study of rucaparib in the treatment of relapsed, high-grade ovarian cancer • Part 1: Patients with platinum-sensitive ovarian cancer who have received ≥ 1 platinum regimen • Part 2: Advanced ovarian cancer patients who have received ≥ 3 prior chemotherapy regimens	491	6 [2 on treatment] [4 in LTFU]

Study Number/ Study ID	EudraCT Number	Brief Description of Study Design and Population	Number of Patients Receiving Oral Rucaparib	Number of Patients Reporting MDS/AML
CO-338-043/ ARIEL4	2016-000816-14	Phase 3 study of rucaparib versus chemotherapy in relapsed, BRCA-mutant, ovarian cancer	232 (+76 in crossover)	5 [3 on treatment] [2 in LTFU]
CO-338-052/ TRITON2	2016-003162-13	Phase 2 open-label rucaparib study in metastatic castration-resistant prostate cancer (mCRPC) and mutation in BRCA1/2, ataxia telangiectasia-mutated serine/threonine kinase (ATM), or other homologous recombination gene	277	0
CO-338-063/ TRITON3	2016-003163-20	Phase 3 study of rucaparib versus physician's choice of therapy and mCRPC and deleterious mutation in BRCA1/2 or ATM genes	205* (+ 42 in crossover)	0
CO-338-078/ Hepatic Impairment	2017001877-17	Phase 1 open-label study of rucaparib in patients with advanced solid tumor and either moderate hepatic impairment or normal hepatic function	16	0
CO-338-081/ RUCA-J	N/A	Phase 1 open-label study of rucaparib in Japanese patients with previously-treated solid tumor	29	0
CO-338-085/ ATLAS	2017-004166-10	Phase 2 open-label study of rucaparib in patients with locally advanced or metastatic urothelial carcinoma	97	0
CO-338-087/ ATHENA	2017-004557-17	Phase 3 double-blind, randomized study of rucaparib with nivolumab, rucaparib with placebo, placebo with nivolumab, or placebo (randomization 4:4:1:1) as maintenance treatment following response to front-line platinum-based chemotherapy	866*	0
CO-338-095/ DDI2	2018-000884-98	Phase 1 open-label, DDI study to determine the effect of rucaparib on the PK of oral rosuvastatin (Arm A) and oral contraceptives (ethinylestradiol and levonorgestrel) (Arm B) in patients with advanced solid tumors	36	0

Study Number/ Study ID	EudraCT Number	Brief Description of Study Design and Population	Number of Patients Receiving Oral Rucaparib	Number of Patients Reporting MDS/AML
CO-338-098/ SEASTAR	2018-003758-39	Phase 1b/2 open-label, parallel-arm study of safety, PK, and efficacy of oral rucaparib with other anticancer agents in patients with a solid tumor • Phase 1b: Open-label, dose escalation • Phase 2: Open-label dose expansion	22	0
CO-338-100/ LODESTAR	2019-002142-20	Phase 2 open-label, multicenter, study of rucaparib as treatment for solid tumors associated with deleterious mutation in an HRR gene	34	0
CO-338-107/ RAMP	N/A	Phase 1b open-label, parallel-arm study of safety, PK, and efficacy of rucaparib in combination with other anticancer agents in mCRPC	8	0
TOTAL			**2,972**	**27**

Abbreviations: AML = acute myeloid leukemia; ATM = ataxia telangiectasia mutate-serine/threonine kinase; BRCA = breast cancer gene; DDI = drug-drug interaction; EudraCT = European Union Drug Regulating Authorities Clinical Trials database; gBRCA = germline BRCA; HRR = homologous recombination repair; ID = identifier; LTFU = long-term follow up; mCRPC = metastatic castration-resistant prostate cancer; MDS = myelodysplastic syndromes; N/A = not applicable; PK = pharmacokinetics; sBRCA = somatic BRCA.

* Estimated, study ongoing and blinded.

Assessment of the MAH's response

The MAH has provided the requested information. Potential cases of secondary MDS/AML are expected to be presented at the time of when the addendum to the CSR with OS and PFS2 final analyses would be submitted.

Conclusion

Issue solved.

Question 15

According to the MAH, the percentage of patients with QTcB and QTcF values ≥450 msec was typically <20% and QTcB and QTcF ≥481 msec or ≥501 msec occurred in few patients in the rucaparib and chemotherapy groups across time points. In order to have a better comparison, a table summarising all events of QTcF and QTcB values ≥450 msec, QTcB values ≥481 msec and QTcB values ≥501 msec reported during the study in both the rucaparib and chemotherapy arms should be provided.

Summary of the MAH's response

Table 15 y table 16, respectively, summarize the numbers of patients in which longest QT interval corrected using Fridericia's method (QTcF) and QT interval corrected using Bazett's method (QTcB) values of ≥ 450 msec, ≥ 481 msec and ≥501 msec were reported during the treatment part of the study as compared to baseline values in both the rucaparib and chemotherapy arms. The longest change from baseline values >30 and >60 msec is also provided.

There was no study entry exclusion criterion for QT interval. With regard to QTcF, 9 (3.9%) patients in the rucaparib arm and 5 (4.4%) patients in the chemotherapy arm had baseline values of 450 msec or greater. For QTcB, 24 (10.3%) patients in the rucaparib arm and 14 (12.4%) patients in the chemotherapy arm had baseline values of 450 msec or greater.

The frequency of QTc values 481 msec, ≥501 msec, and change from baseline of >60 msec) are comparable across treatment arms. In the categories of ≥450 msec and change from baseline of >30 msec, there is a trend to a numerically higher frequency in the rucaparib -treated patients.

In terms of treatment-emergent adverse events (TEAEs), no cardiac or other clinical events indicative of, or potentially related to, QT prolongation disorders have been reported. One patient in the rucaparib arm, with known cardiac risk factors, had a fatal event of cardiac disorder considered unrelated to study drug (see response to question 17). CTCAE Grade 1/2 Electrocardiogram QT prolonged was reported in 5 (2.2%) and 6 (5.3%) patients in the rucaparib and chemotherapy treatment arms, of which 4 (1.7%) and

6 (5.3%) respectively were considered related to study treatment. Given the very low incidence of TEAEs, the trend to a numerically higher frequency of QTc values between 450 to 480 msec and change from baseline of >30 msec, are not considered clinically significant.

Table 15. Summary of QTcF Values On Treatment - Treatment Part (Safety Population)

	Rucaparib		Chemotherapy	
	Baseline (N = 232)	Longest Value On Treatment (N = 214)	Baseline (N = 113)	Longest Value On Treatment (N = 110)
QTcF values, n (%)[a]				
≥ 450 msec	9 (3.9%)	66 (30.8%)	5 (4.4%)	26 (23.6%)
≥ 481 msec	3 (1.3%)	18 (8.4%)	2 (1.8%)	8 (7.3%)
≥ 501 msec	1 (0.4%)	11 (5.1%)	2 (1.8%)	6 (5.5%)
Change from baseline > 30 msec	-	100 (46.7%)	-	31 (28.2%)
Change from baseline > 60 msec	-	31 (14.5%)	-	10 (9.1%)

Source: Table 15.2

Abbreviation: QTcF = QT interval corrected using Fridericia's method.

[a] Categories are not mutually exclusive: ≥ 450 msec category includes patients in both ≥ 481 msec and ≥ 501 msec categories and the ≥ 481 msec category includes patients in the ≥ 501 msec category. Similarly, the category "Change from baseline > 30 msec" includes patients with "Change from baseline > 60 msec".

Table 16. Summary of QTcB Values On Treatment - Treatment Part (Safety Population)

	Rucaparib		Chemotherapy	
	Baseline (N = 232)	Longest Value On Treatment (N = 214)	Baseline (N = 113)	Longest Value On Treatment (N = 110)
QTcB values, n (%)[a]				
≥ 450 msec	24 (10.3)	115 (53.7)	14 (12.4)	48 (43.6)
≥ 481 msec	5 (2.2)	35 (16.4)	3 (2.7)	18 (16.4)
≥ 501 msec	3 (1.3)	23 (10.7)	2 (1.8)	8 (7.3)
Change from baseline > 30 msec	-	105 (49.1)	-	38 (34.5)
Change from baseline > 60 msec	-	39 (18.2)	-	16 (14.5)

Source: Table 15.1

Abbreviation: QTcB = QT interval corrected using Bazett's method.

[a] Categories are not mutually exclusive: ≥ 450 msec category includes patients in both ≥ 481 msec and ≥ 501 msec categories and the ≥ 481 msec category includes patients in the ≥ 501 msec category. Similarly, the category "Change from baseline > 30 msec" includes patients with "Change from baseline > 60 msec".

Assessment of the MAH's response

The information requested has been provided. The number of patients with QTc values ≥481 msec or ≥501 msec, and change from baseline of >60 msec were comparable between treatment arms. However, there was a higher number of patients with a QTc value ≥450 msec and change from baseline of >30 msec in the rucaparib arm. Nevertheless, an increase in TEAEs has not been observed.

Conclusion

Issue solved.

Question 16

Safety data by age, race, BRCA mutated gene and BRCA mutation status (germline and somatic) have been provided. For a proper assessment the MAH is requested to provide comparative data (in the same table) for all these subgroups. The same data currently provided are requested.

Summary of the MAH's response

Age

Summaries of the incidence of treatment-emergent adverse events (TEAEs), Grade 3 or higher TEAEs, and treatment-emergent serious adverse events (TESAEs), by system organ class (SOC) and preferred term (PT), are presented in Table 17, Table 18, and Table 19, respectively, for patients in the rucaparib and chemotherapy treatment groups by age subgroups of patients <65 years old, 65 to 74 years old, and ≥75 years old in the Treatment Part, Safety Population.

There were no notable differences in the incidence of TEAEs (Table 17), Grade 3 or higher TEAEs (Table 18) or TESAEs (Table 19) between patients <65 years old, 65 to 74 years old, or ≥75 years old in either rucaparib or chemotherapy treatment groups. Some numerical differences were observed between rucaparib and chemotherapy treatment groups across the 3 age subgroups; however, the relatively small number of patients 65 to 74 years old and too few patients ≥75 years old in either treatment group considerably limited the interpretation of results in comparison with other age subgroups and overall patients.

Events in the age subgroups <65 years old, 65 to 74 years old, or ≥75 years old subgroups appeared consistent with the overall safety population summarized in Section 12 of the Study CO-338-043 CSR, and primarily consisted of myelosuppression, asthenia/fatigue, alanine aminotransferase (ALT)/aspartate aminotransferase (AST) increased, nausea, and vomiting in both treatment groups. Alopecia was also commonly observed in patients in the chemotherapy group across age subgroups.

Table 17. TEAEs Reported in ≥20% of Patients in Any Group by Age and Treatment Group – Treatment Part (Safety Population) in Study CO-338-043

System Organ Class Preferred Term[a]	Age Group (year)					
	< 65		65-74		≥ 75	
	Rucaparib (N = 188)	Chemotherapy (N = 86)	Rucaparib (N = 37)	Chemotherapy (N = 25)	Rucaparib (N = 7)	Chemotherapy (N = 2)
	n (%)		n (%)		n (%)	
Number of Patients With At Least 1 TEAE	**179 (95.2)**	**79 (91.9)**	**36 (97.3)**	**25 (100.0)**	**7 (100.0)**	**2 (100.0)**
Combined Preferred Terms						
Combined ALT/AST Increased	61 (32.4)	12 (14.0)	16 (43.2)	1 (4.0)	3 (42.9)	0
Combined Anemia/Hemoglobin decreased	97 (51.6)	27 (31.4)	24 (64.9)	7 (28.0)	4 (57.1)	2 (100.0)
Combined Asthenia/Fatigue	93 (49.5)	34 (39.5)	18 (48.6)	16 (64.0)	4 (57.1)	0
Combined Neutropenia/Decreased ANC	44 (23.4)	26 (30.2)	5 (13.5)	4 (16.0)	3 (42.9)	2 (100.0)
Combined Thrombocytopenia/Decreased platelets	41 (21.8)	10 (11.6)	12 (32.4)	2 (8.0)	1 (14.3)	1 (50.0)
Blood and lymphatic system disorders	**113 (60.1)**	**37 (43.0)**	**26 (70.3)**	**11 (44.0)**	**4 (57.1)**	**2 (100.0)**
Anaemia	95 (50.5)	26 (30.2)	24 (64.9)	7 (28.0)	4 (57.1)	2 (100.0)
Leukopenia	19 (10.1)	13 (15.1)	1 (2.7)	3 (12.0)	1 (14.3)	2 (100.0)
Neutropenia	39 (20.7)	22 (25.6)	5 (13.5)	4 (16.0)	3 (42.9)	2 (100.0)
Thrombocytopenia	38 (20.2)	10 (11.6)	7 (18.9)	2 (8.0)	1 (14.3)	1 (50.0)
Cardiac disorders	**20 (10.6)**	**11 (12.8)**	**3 (8.1)**	**2 (8.0)**	**2 (28.6)**	**0**
Sinus tachycardia	5 (2.7)	6 (7.0)	0	0	2 (28.6)	0
Gastrointestinal disorders	**134 (71.3)**	**53 (61.6)**	**28 (75.7)**	**20 (80.0)**	**6 (85.7)**	**2 (100.0)**
Abdominal pain	43 (22.9)	16 (18.6)	11 (29.7)	2 (8.0)	0	0
Constipation	28 (14.9)	15 (17.4)	7 (18.9)	4 (16.0)	2 (28.6)	0
Diarrhoea	35 (18.6)	15 (17.4)	11 (29.7)	8 (32.0)	1 (14.3)	1 (50.0)
Dyspepsia	15 (8.0)	3 (3.5)	1 (2.7)	4 (16.0)	3 (42.9)	0

System Organ Class Preferred Term[a]	Age Group (year)					
	< 65		65-74		≥ 75	
	Rucaparib (N = 188)	Chemotherapy (N = 86)	Rucaparib (N = 37)	Chemotherapy (N = 25)	Rucaparib (N = 7)	Chemotherapy (N = 2)
	n (%)		n (%)		n (%)	
Nausea	100 (53.2)	26 (30.2)	20 (54.1)	9 (36.0)	4 (57.1)	1 (50.0)
Vomiting	60 (31.9)	17 (19.8)	14 (37.8)	2 (8.0)	5 (71.4)	0
General disorders and administration site conditions	**109 (58.0)**	**39 (45.3)**	**21 (56.8)**	**18 (72.0)**	**4 (57.1)**	**0**
Asthenia	51 (27.1)	17 (19.8)	11 (29.7)	7 (28.0)	2 (28.6)	0
Fatigue	45 (23.9)	18 (20.9)	8 (21.6)	10 (40.0)	2 (28.6)	0
Infections and infestations	**56 (29.8)**	**21 (24.4)**	**16 (43.2)**	**6 (24.0)**	**1 (14.3)**	**0**
Investigations	**100 (53.2)**	**31 (36.0)**	**25 (67.6)**	**4 (16.0)**	**4 (57.1)**	**0**
Alanine aminotransferase increased	59 (31.4)	11 (12.8)	13 (35.1)	1 (4.0)	2 (28.6)	0
Aspartate aminotransferase increased	54 (28.7)	7 (8.1)	15 (40.5)	1 (4.0)	3 (42.9)	0
Blood creatinine increased	25 (13.3)	7 (8.1)	5 (13.5)	2 (8.0)	3 (42.9)	0
Creatinine renal clearance decreased	6 (3.2)	2 (2.3)	2 (5.4)	1 (4.0)	2 (28.6)	0
Electrocardiogram repolarization abnormality	1 (0.5)	3 (3.5)	0	1 (4.0)	2 (28.6)	0
Low density lipoprotein increased	0	0	0	1 (4.0)	2 (28.6)	0
Metabolism and nutrition disorders	**71 (37.8)**	**39 (45.3)**	**13 (35.1)**	**13 (52.0)**	**4 (57.1)**	**0**
Decreased appetite	31 (16.5)	14 (16.3)	11 (29.7)	6 (24.0)	2 (28.6)	0
Musculoskeletal and connective tissue disorders	**39 (20.7)**	**19 (22.1)**	**9 (24.3)**	**5 (20.0)**	**1 (14.3)**	**2 (100.0)**
Arthralgia	12 (6.4)	4 (4.7)	2 (5.4)	3 (12.0)	0	2 (100.0)

System Organ Class Preferred Term[a]	Age Group (year)					
	< 65		65-74		≥ 75	
	Rucaparib (N = 188)	Chemotherapy (N = 86)	Rucaparib (N = 37)	Chemotherapy (N = 25)	Rucaparib (N = 7)	Chemotherapy (N = 2)
	n (%)		n (%)		n (%)	
Nervous system disorders	**65 (34.6)**	**40 (46.5)**	**14 (37.8)**	**13 (52.0)**	**1 (14.3)**	**1 (50.0)**
Dysgeusia	34 (18.1)	2 (2.3)	5 (13.5)	6 (24.0)	0	0
Neuropathy peripheral	1 (0.5)	10 (11.6)	1 (2.7)	5 (20.0)	0	1 (50.0)
Psychiatric disorders	**23 (12.2)**	**10 (11.6)**	**4 (10.8)**	**2 (8.0)**	**3 (42.9)**	**0**
Insomnia	15 (8.0)	6 (7.0)	2 (5.4)	1 (4.0)	2 (28.6)	0
Respiratory, thoracic and mediastinal disorders	**44 (23.4)**	**19 (22.1)**	**8 (21.6)**	**8 (32.0)**	**2 (28.6)**	**0**
Dyspnoea	20 (10.6)	6 (7.0)	3 (8.1)	3 (12.0)	2 (28.6)	0
Skin and subcutaneous tissue disorders	**38 (20.2)**	**34 (39.5)**	**13 (35.1)**	**15 (60.0)**	**2 (28.6)**	**0**
Alopecia	6 (3.2)	26 (30.2)	5 (13.5)	12 (48.0)	1 (14.3)	0

Source: Table 16.1.1.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; TEAE = treatment-emergent adverse event.

[a] A patient is counted only once for a TEAE preferred term if that patient experiences the same TEAE preferred term multiple times.

Table 18. Grade 3 or Higher TEAEs Reported in ≥2% of Patients in Any Group by Age and Treatment Group– Treatment Part (Safety Population) in Study CO-338-043

System Organ Class Preferred Term[a]	Age Group (year)					
	< 65		65-74		≥ 75	
	Rucaparib (N = 188)	Chemotherapy (N = 86)	Rucaparib (N = 37)	Chemotherapy (N = 25)	Rucaparib (N = 7)	Chemotherapy (N = 2)
	n (%)		n (%)		n (%)	
Number of Patients With At Least 1 Grade 3 or Higher TEAE	**109 (58.0)**	**33 (38.4)**	**23 (62.2)**	**10 (40.0)**	**4 (57.1)**	**0**
Combined Preferred Terms						
Combined ALT/AST Increased	15 (8.0)	0	3 (8.1)	0	0	0
Combined Anemia/Hemoglobin decreased	41 (21.8)	3 (3.5)	8 (21.6)	3 (12.0)	3 (42.9)	0
Combined Asthenia/Fatigue	17 (9.0)	2 (2.3)	2 (5.4)	1 (4.0)	0	0
Combined Neutropenia/Decreased ANC	22 (11.7)	15 (17.4)	2 (5.4)	2 (8.0)	0	0
Combined Thrombocytopenia/Decreased platelets	15 (8.0)	0	4 (10.8)	0	0	0
Blood and lymphatic system disorders	**59 (31.4)**	**17 (19.8)**	**11 (29.7)**	**5 (20.0)**	**3 (42.9)**	**0**
Anaemia	40 (21.3)	3 (3.5)	8 (21.6)	3 (12.0)	3 (42.9)	0
Febrile neutropenia	0	0	0	0	1 (14.3)	0
Leukopenia	5 (2.7)	3 (3.5)	0	0	0	0
Neutropenia	19 (10.1)	13 (15.1)	2 (5.4)	2 (8.0)	0	0
Thrombocytopenia	14 (7.4)	0	1 (2.7)	0	0	0
Cardiac disorders	**2 (1.1)**	**0**	**1 (2.7)**	**0**	**0**	**0**
Cardiac disorder	0	0	1 (2.7)	0	0	0
Ear and labyrinth disorders	**0**	**0**	**0**	**1 (4.0)**	**0**	**0**
Hypoacusis	0	0	0	1 (4.0)	0	0
Eye disorders	**0**	**0**	**1 (2.7)**	**0**	**0**	**0**
Cataract	0	0	1 (2.7)	0	0	0

System Organ Class Preferred Term[a]	Age Group (year)					
	< 65		65-74		≥ 75	
	Rucaparib (N = 188)	Chemotherapy (N = 86)	Rucaparib (N = 37)	Chemotherapy (N = 25)	Rucaparib (N = 7)	Chemotherapy (N = 2)
	n (%)		n (%)		n (%)	
Gastrointestinal disorders	**30 (16.0)**	**1 (1.2)**	**2 (5.4)**	**3 (12.0)**	**2 (28.6)**	**0**
Abdominal pain	9 (4.8)	0	0	0	0	0
Ascites	5 (2.7)	1 (1.2)	1 (2.7)	0	0	0
Diarrhoea	3 (1.6)	0	0	1 (4.0)	1 (14.3)	0
Dyspepsia	0	0	0	0	1 (14.3)	0
Gastrointestinal haemorrhage	0	0	0	1 (4.0)	0	0
Intestinal obstruction	7 (3.7)	0	0	0	1 (14.3)	0
Large intestine perforation	0	0	1 (2.7)	0	0	0
Nausea	6 (3.2)	0	0	0	0	0
Subileus	0	0	0	1 (4.0)	0	0
Vomiting	11 (5.9)	0	0	0	0	0
General disorders and administration site conditions	**22 (11.7)**	**2 (2.3)**	**2 (5.4)**	**1 (4.0)**	**0**	**0**
Asthenia	8 (4.3)	0	0	0	0	0
Fatigue	9 (4.8)	2 (2.3)	2 (5.4)	1 (4.0)	0	0

System Organ Class Preferred Term[a]	Age Group (year)					
	< 65		65-74		≥ 75	
	Rucaparib (N = 188)	Chemotherapy (N = 86)	Rucaparib (N = 37)	Chemotherapy (N = 25)	Rucaparib (N = 7)	Chemotherapy (N = 2)
	n (%)		n (%)		n (%)	
Immune system disorders	**0**	**0**	**1 (2.7)**	**1 (4.0)**	**0**	**0**
Anaphylactic reaction	0	0	0	1 (4.0)	0	0
Drug hypersensitivity	0	0	1 (2.7)	0	0	0
Infections and infestations	**11 (5.9)**	**2 (2.3)**	**4 (10.8)**	**1 (4.0)**	**0**	**0**
Colonic abscess	0	0	1 (2.7)	0	0	0
Cytomegalovirus colitis	0	0	1 (2.7)	0	0	0
Intervertebral discitis	0	0	0	1 (4.0)	0	0
Osteomyelitis	0	0	0	1 (4.0)	0	0
Pneumonia	3 (1.6)	0	1 (2.7)	0	0	0
Urinary tract infection	0	0	1 (2.7)	0	0	0
Injury, poisoning and procedural complications	**2 (1.1)**	**0**	**0**	**1 (4.0)**	**0**	**0**
Infusion related reaction	0	0	0	1 (4.0)	0	0
Investigations	**28 (14.9)**	**7 (8.1)**	**8 (21.6)**	**0**	**0**	**0**
Alanine aminotransferase increased	15 (8.0)	0	3 (8.1)	0	0	0
Aspartate aminotransferase increased	1 (0.5)	0	1 (2.7)	0	0	0
Blood alkaline phosphatase increased	2 (1.1)	0	1 (2.7)	0	0	0
Blood bilirubin increased	2 (1.1)	0	1 (2.7)	0	0	0
Blood creatinine increased	5 (2.7)	0	0	0	0	0

System Organ Class Preferred Term[a]	Age Group (year)					
	< 65		65-74		≥ 75	
	Rucaparib (N = 188)	Chemotherapy (N = 86)	Rucaparib (N = 37)	Chemotherapy (N = 25)	Rucaparib (N = 7)	Chemotherapy (N = 2)
	n (%)		n (%)		n (%)	
Neutrophil count decreased	3 (1.6)	3 (3.5)	0	0	0	0
Platelet count decreased	1 (0.5)	0	3 (8.1)	0	0	0
Metabolism and nutrition disorders	**12 (6.4)**	**9 (10.5)**	**0**	**0**	**0**	**0**
Hyperglycaemia	2 (1.1)	3 (3.5)	0	0	0	0
Hypertriglyceridaemia	2 (1.1)	2 (2.3)	0	0	0	0
Hypoalbuminaemia	0	2 (2.3)	0	0	0	0
Hyponatraemia	1 (0.5)	2 (2.3)	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**6 (3.2)**	**3 (3.5)**	**3 (8.1)**	**0**	**0**	**0**
Malignant neoplasm progression	6 (3.2)	3 (3.5)	2 (5.4)	0	0	0
Myelodysplastic syndrome	0	0	1 (2.7)	0	0	0
Nervous system disorders	**2 (1.1)**	**1 (1.2)**	**0**	**1 (4.0)**	**0**	**0**
Seizure	0	1 (1.2)	0	1 (4.0)	0	0
Renal and urinary disorders	**4 (2.1)**	**1 (1.2)**	**2 (5.4)**	**0**	**0**	**0**
Chronic kidney disease	1 (0.5)	0	1 (2.7)	0	0	0
Hydronephrosis	0	1 (1.2)	1 (2.7)	0	0	0
Respiratory, thoracic and mediastinal disorders	**6 (3.2)**	**3 (3.5)**	**1 (2.7)**	**1 (4.0)**	**1 (14.3)**	**0**
Dyspnoea	2 (1.1)	2 (2.3)	0	0	1 (14.3)	0
Pleural effusion	0	0	1 (2.7)	0	0	0
Pulmonary embolism	1 (0.5)	1 (1.2)	0	1 (4.0)	0	0
Skin and subcutaneous tissue disorders	**1 (0.5)**	**3 (3.5)**	**0**	**0**	**0**	**0**
Nail disorder	0	2 (2.3)	0	0	0	0
Vascular disorders	**4 (2.1)**	**1 (1.2)**	**0**	**0**	**1 (14.3)**	**0**
Hypotension	0	0	0	0	1 (14.3)	0

Source: Table 16.1.2.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; TEAE = treatment-emergent adverse event.

[a] A patient is counted only once for a TEAE preferred term if that patient experiences the same TEAE preferred term multiple times.

Table 19. Treatment-emergent SAEs Reported in ≥2% of Patients in Any Group by Age and Treatment Group– Treatment Part (Safety Population) in Study CO-338-043

System Organ Class Preferred Term[a]	Age Group (year)					
	< 65		65-74		≥ 75	
	Rucaparib (N = 188)	Chemotherapy (N = 86)	Rucaparib (N = 37)	Chemotherapy (N = 25)	Rucaparib (N = 7)	Chemotherapy (N = 2)
	n (%)		n (%)		n (%)	
Number of Patients With At Least 1 Serious TEAE	**46 (24.5)**	**9 (10.5)**	**14 (37.8)**	**4 (16.0)**	**2 (28.6)**	**0**
Combined Preferred Terms						
Combined Anemia/Hemoglobin decreased	16 (8.5)	1 (1.2)	3 (8.1)	1 (4.0)	0	0
Combined Neutropenia/Decreased ANC	4 (2.1)	0	0	0	0	0
Combined Thrombocytopenia/Decreased platelets	5 (2.7)	1 (1.2)	2 (5.4)	0	0	0
Blood and lymphatic system disorders	**18 (9.6)**	**2 (2.3)**	**3 (8.1)**	**1 (4.0)**	**1 (14.3)**	**0**
Anaemia	16 (8.5)	1 (1.2)	3 (8.1)	1 (4.0)	0	0
Febrile neutropenia	0	0	0	0	1 (14.3)	0
Neutropenia	4 (2.1)	0	0	0	0	0
Thrombocytopenia	5 (2.7)	1 (1.2)	0	0	0	0
Cardiac disorders	**1 (0.5)**	**0**	**1 (2.7)**	**0**	**0**	**0**
Cardiac disorder	0	0	1 (2.7)	0	0	0
Gastrointestinal disorders	**14 (7.4)**	**2 (2.3)**	**1 (2.7)**	**2 (8.0)**	**1 (14.3)**	**0**
Gastrointestinal haemorrhage	0	0	0	1 (4.0)	0	0
Intestinal obstruction	4 (2.1)	0	0	0	1 (14.3)	0
Large intestine perforation	0	0	1 (2.7)	0	0	0
Subileus	1 (0.5)	0	0	1 (4.0)	0	0

System Organ Class Preferred Term[a]	Age Group (year)					
	< 65		65-74		≥ 75	
	Rucaparib (N = 188)	Chemotherapy (N = 86)	Rucaparib (N = 37)	Chemotherapy (N = 25)	Rucaparib (N = 7)	Chemotherapy (N = 2)
	n (%)		n (%)		n (%)	
General disorders and administration site conditions	**6 (3.2)**	**0**	**0**	**0**	**0**	**0**
Immune system disorders	**0**	**0**	**0**	**1 (4.0)**	**0**	**0**
Drug hypersensitivity	0	0	0	1 (4.0)	0	0
Infections and infestations	**8 (4.3)**	**2 (2.3)**	**4 (10.8)**	**1 (4.0)**	**0**	**0**
Colonic abscess	0	0	1 (2.7)	0	0	0
Cytomegalovirus colitis	0	0	1 (2.7)	0	0	0
Osteomyelitis	0	0	0	1 (4.0)	0	0
Pneumonia	3 (1.6)	0	1 (2.7)	0	0	0
Upper respiratory tract infection	1 (0.5)	1 (1.2)	1 (2.7)	0	0	0
Injury, poisoning and procedural complications	**2 (1.1)**	**0**	**1 (2.7)**	**1 (4.0)**	**0**	**0**
Infusion related reaction	0	0	0	1 (4.0)	0	0
Post procedural fever	0	0	1 (2.7)	0	0	0
Investigations	**1 (0.5)**	**0**	**2 (5.4)**	**0**	**0**	**0**
Platelet count decreased	0	0	2 (5.4)	0	0	0
Metabolism and nutrition disorders	**4 (2.1)**	**1 (1.2)**	**0**	**0**	**0**	**0**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**3 (1.6)**	**2 (2.3)**	**4 (10.8)**	**0**	**0**	**0**
Intraductal proliferative breast lesion	0	0	1 (2.7)	0	0	0
Malignant neoplasm progression	3 (1.6)	2 (2.3)	2 (5.4)	0	0	0
Myelodysplastic syndrome	0	0	1 (2.7)	0	0	0

System Organ Class Preferred Term[a]	Age Group (year)					
	< 65		65-74		≥ 75	
	Rucaparib (N = 188)	Chemotherapy (N = 86)	Rucaparib (N = 37)	Chemotherapy (N = 25)	Rucaparib (N = 7)	Chemotherapy (N = 2)
	n (%)		n (%)		n (%)	
Nervous system disorders	**2 (1.1)**	**2 (2.3)**	**1 (2.7)**	**0**	**0**	**0**
Depressed level of consciousness	0	0	1 (2.7)	0	0	0
Reproductive system and breast disorders	**0**	**0**	**1 (2.7)**	**0**	**0**	**0**
Fibrocystic breast disease	0	0	1 (2.7)	0	0	0
Respiratory, thoracic and mediastinal disorders	**4 (2.1)**	**0**	**1 (2.7)**	**1 (4.0)**	**0**	**0**
Pleural effusion	0	0	1 (2.7)	0	0	0
Pulmonary embolism	1 (0.5)	0	0	1 (4.0)	0	0
Skin and subcutaneous tissue disorders	**0**	**0**	**0**	**1 (4.0)**	**0**	**0**
Rash	0	0	0	1 (4.0)	0	0
Vascular disorders	**1 (0.5)**	**1 (1.2)**	**2 (5.4)**	**0**	**0**	**0**
Deep vein thrombosis	1 (0.5)	1 (1.2)	2 (5.4)	0	0	0

Source: Table 16.1.3.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] A patient is counted only once for a TEAE preferred term if that patient experiences the same TEAE preferred term multiple times.

Race

For the Treatment Part, Safety Population, the majority of patients were White in both the rucaparib group (94.0% of patients, 218/232) and chemotherapy group (97.3% of patients, 110/113). Thus, the incidence of TEAEs for the White race subgroup was similar to overall Treatment Part, Safety Population, limiting the interpretation of race subgroup data.

Summaries of the incidence of TEAEs, Grade 3 or higher TEAEs, and TESAEs, by SOC and PT, are presented in Table 20, Table 21, and Table 22, respectively, for patients in the rucaparib and chemotherapy treatment groups by White, Other, and Unknown race subgroups in the Treatment Part, Safety Population.

Table 20. TEAEs Reported in ≥20% of Patients in Any Group by Race and Treatment Group – Treatment Part (Safety Population) in Study CO-338-043

System Organ Class Preferred Term[a]	Race Subgroup					
	White		Other		Unknown	
	Rucaparib (N = 218)	Chemotherapy (N = 110)	Rucaparib (N = 9)	Chemotherapy (N = 2)	Rucaparib (N = 5)	Chemotherapy (N = 1)
	n (%)		n (%)		n (%)	
Number of Patients With At Least 1 TEAE	**208 (95.4)**	**103 (93.6)**	**9 (100.0)**	**2 (100.0)**	**5 (100.0)**	**1 (100.0)**
Combined Preferred Terms						
Combined ALT/AST Increased	73 (33.5)	13 (11.8)	4 (44.4)	0	3 (60.0)	0
Combined Anemia/Hemoglobin decreased	119 (54.6)	35 (31.8)	4 (44.4)	1 (50.0)	2 (40.0)	0
Combined Asthenia/Fatigue	105 (48.2)	48 (43.6)	7 (77.8)	2 (100.0)	3 (60.0)	0
Combined Neutropenia/Decreased ANC	47 (21.6)	32 (29.1)	3 (33.3)	0	2 (40.0)	0
Combined Thrombocytopenia/Decreased platelets	51 (23.4)	13 (11.8)	2 (22.2)	0	1 (20.0)	0
Blood and lymphatic system disorders	**135 (61.9)**	**49 (44.5)**	**5 (55.6)**	**1 (50.0)**	**3 (60.0)**	**0**
Anaemia	117 (53.7)	34 (30.9)	4 (44.4)	1 (50.0)	2 (40.0)	0
Leukopenia	19 (8.7)	18 (16.4)	1 (11.1)	0	1 (20.0)	0
Neutropenia	43 (19.7)	28 (25.5)	3 (33.3)	0	1 (20.0)	0
Thrombocytopenia	43 (19.7)	13 (11.8)	2 (22.2)	0	1 (20.0)	0
Cardiac disorders	**24 (11.0)**	**12 (10.9)**	**1 (11.1)**	**1 (50.0)**	**0**	**0**
Atrial fibrillation	1 (0.5)	0	0	1 (50.0)	0	0
Gastrointestinal disorders	**155 (71.1)**	**72 (65.5)**	**9 (100.0)**	**2 (100.0)**	**4 (80.0)**	**1 (100.0)**
Abdominal distension	12 (5.5)	4 (3.6)	2 (22.2)	0	0	0
Abdominal pain	48 (22.0)	18 (16.4)	6 (66.7)	0	0	0
Constipation	32 (14.7)	19 (17.3)	3 (33.3)	0	2 (40.0)	0
Diarrhoea	41 (18.8)	23 (20.9)	5 (55.6)	1 (50.0)	1 (20.0)	0

System Organ Class Preferred Term[a]	Race Subgroup					
	White		Other		Unknown	
	Rucaparib (N = 218)	Chemotherapy (N = 110)	Rucaparib (N = 9)	Chemotherapy (N = 2)	Rucaparib (N = 5)	Chemotherapy (N = 1)
	n (%)		n (%)		n (%)	
Dry mouth	6 (2.8)	2 (1.8)	0	1 (50.0)	0	0
Dyspepsia	17 (7.8)	7 (6.4)	1 (11.1)	0	1 (20.0)	0
Dysphagia	0	0	0	0	1 (20.0)	0
Gastritis	0	0	0	0	1 (20.0)	1 (100.0)
Haemorrhoids	1 (0.5)	0	0	0	1 (20.0)	0
Intestinal obstruction	7 (3.2)	0	3 (33.3)	0	0	0
Nausea	112 (51.4)	34 (30.9)	9 (100.0)	2 (100.0)	3 (60.0)	0
Odynophagia	1 (0.5)	0	0	0	1 (20.0)	0
Stomatitis	10 (4.6)	7 (6.4)	0	0	1 (20.0)	0
Vomiting	73 (33.5)	19 (17.3)	5 (55.6)	0	1 (20.0)	0
General disorders and administration site conditions	**122 (56.0)**	**54 (49.1)**	**8 (88.9)**	**2 (100.0)**	**4 (80.0)**	**1 (100.0)**
Asthenia	59 (27.1)	23 (20.9)	4 (44.4)	1 (50.0)	1 (20.0)	0
Fatigue	50 (22.9)	27 (24.5)	3 (33.3)	1 (50.0)	2 (40.0)	0
Mucosal inflammation	4 (1.8)	0	2 (22.2)	1 (50.0)	0	0
Non-cardiac chest pain	0	1 (0.9)	0	1 (50.0)	1 (20.0)	0
Oedema peripheral	11 (5.0)	7 (6.4)	0	0	1 (20.0)	1 (100.0)
Pyrexia	17 (7.8)	7 (6.4)	4 (44.4)	0	2 (40.0)	0
Temperature intolerance	0	0	0	0	1 (20.0)	0
Vessel puncture site bruise	0	0	0	0	1 (20.0)	0

System Organ Class Preferred Term[a]	Race Subgroup					
	White		Other		Unknown	
	Rucaparib (N = 218)	Chemotherapy (N = 110)	Rucaparib (N = 9)	Chemotherapy (N = 2)	Rucaparib (N = 5)	Chemotherapy (N = 1)
	n (%)		n (%)		n (%)	
Immune system disorders	**2 (0.9)**	**8 (7.3)**	**0**	**1 (50.0)**	**0**	**0**
Drug hypersensitivity	1 (0.5)	4 (3.6)	0	1 (50.0)	0	0
Infections and infestations	**65 (29.8)**	**27 (24.5)**	**5 (55.6)**	**0**	**3 (60.0)**	**0**
Lower respiratory tract infection	1 (0.5)	2 (1.8)	0	0	1 (20.0)	0
Neutropenic sepsis	0	0	0	0	1 (20.0)	0
Pneumonia	9 (4.1)	0	0	0	1 (20.0)	0
Upper respiratory tract infection	6 (2.8)	3 (2.7)	1 (11.1)	0	1 (20.0)	0
Urinary tract infection	14 (6.4)	5 (4.5)	2 (22.2)	0	0	0
Investigations	**121 (55.5)**	**35 (31.8)**	**5 (55.6)**	**0**	**3 (60.0)**	**0**
Alanine aminotransferase increased	67 (30.7)	12 (10.9)	4 (44.4)	0	3 (60.0)	0
Aspartate aminotransferase increased	66 (30.3)	8 (7.3)	3 (33.3)	0	3 (60.0)	0
Blood alkaline phosphatase increased	14 (6.4)	3 (2.7)	2 (22.2)	0	0	0
Neutrophil count decreased	4 (1.8)	7 (6.4)	0	0	1 (20.0)	0
Metabolism and nutrition disorders	**79 (36.2)**	**50 (45.5)**	**6 (66.7)**	**2 (100.0)**	**3 (60.0)**	**0**
Decreased appetite	40 (18.3)	19 (17.3)	2 (22.2)	1 (50.0)	2 (40.0)	0
Dehydration	7 (3.2)	2 (1.8)	2 (22.2)	0	0	0
Hypercholesterolaemia	7 (3.2)	5 (4.5)	1 (11.1)	0	1 (20.0)	0
Hyperglycaemia	14 (6.4)	14 (12.7)	1 (11.1)	1 (50.0)	1 (20.0)	0
Hypokalaemia	8 (3.7)	3 (2.7)	2 (22.2)	1 (50.0)	0	0

System Organ Class Preferred Term[a]	Race Subgroup					
	White		Other		Unknown	
	Rucaparib (N = 218)	Chemotherapy (N = 110)	Rucaparib (N = 9)	Chemotherapy (N = 2)	Rucaparib (N = 5)	Chemotherapy (N = 1)
	n (%)		n (%)		n (%)	
Hypomagnesaemia	12 (5.5)	2 (1.8)	2 (22.2)	0	0	0
Hyponatraemia	5 (2.3)	3 (2.7)	3 (33.3)	0	0	0
Musculoskeletal and connective tissue disorder	**43 (19.7)**	**26 (23.6)**	**3 (33.3)**	**0**	**3 (60.0)**	**0**
Arthralgia	11 (5.0)	9 (8.2)	2 (22.2)	0	1 (20.0)	0
Back pain	10 (4.6)	5 (4.5)	2 (22.2)	0	0	0
Muscle spasms	2 (0.9)	0	2 (22.2)	0	2 (40.0)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**10 (4.6)**	**3 (2.7)**	**0**	**0**	**1 (20.0)**	**0**
Malignant melanoma	0	0	0	0	1 (20.0)	0
Myelodysplastic syndrome	0	0	0	0	1 (20.0)	0
Nervous system disorders	**74 (33.9)**	**52 (47.3)**	**5 (55.6)**	**1 (50.0)**	**1 (20.0)**	**1 (100.0)**
Dysgeusia	36 (16.5)	8 (7.3)	2 (22.2)	0	1 (20.0)	0
Headache	15 (6.9)	5 (4.5)	1 (11.1)	1 (50.0)	1 (20.0)	0
Paraesthesia	4 (1.8)	10 (9.1)	0	0	0	1 (100.0)
Peripheral sensory neuropathy	3 (1.4)	4 (3.6)	1 (11.1)	1 (50.0)	0	0
Psychiatric disorders	**28 (12.8)**	**12 (10.9)**	**1 (11.1)**	**0**	**1 (20.0)**	**0**
Insomnia	17 (7.8)	7 (6.4)	1 (11.1)	0	1 (20.0)	0
Restlessness	0	0	0	0	1 (20.0)	0
Renal and urinary disorders	**22 (10.1)**	**11 (10.0)**	**1 (11.1)**	**1 (50.0)**	**0**	**0**
Urine odour abnormal	1 (0.5)	0	0	1 (50.0)	0	0

System Organ Class Preferred Term[a]	Race Subgroup					
	White		Other		Unknown	
	Rucaparib (N = 218)	Chemotherapy (N = 110)	Rucaparib (N = 9)	Chemotherapy (N = 2)	Rucaparib (N = 5)	Chemotherapy (N = 1)
	n (%)		n (%)		n (%)	
Respiratory, thoracic and mediastinal disorders	**46 (21.1)**	**26 (23.6)**	**5 (55.6)**	**1 (50.0)**	**3 (60.0)**	**0**
Cough	17 (7.8)	9 (8.2)	0	0	2 (40.0)	0
Dyspnoea	23 (10.6)	8 (7.3)	2 (22.2)	1 (50.0)	0	0
Nasal congestion	2 (0.9)	1 (0.9)	0	0	1 (20.0)	0
Pulmonary oedema	0	0	0	0	1 (20.0)	0
Skin and subcutaneous tissue disorders	**50 (22.9)**	**46 (41.8)**	**2 (22.2)**	**2 (100.0)**	**1 (20.0)**	**1 (100.0)**
Alopecia	12 (5.5)	37 (33.6)	0	1 (50.0)	0	0
Nail disorder	0	4 (3.6)	0	0	0	1 (100.0)
Photosensitivity reaction	9 (4.1)	0	0	0	1 (20.0)	0
Pruritis	8 (3.7)	2 (1.8)	1 (11.1)	1 (50.0)	0	0
Rash	10 (4.6)	3 (2.7)	2 (22.2)	1 (50.0)	0	0
Rash pruritic	1 (0.5)	0	0	1 (50.0)	0	0
Skin toxicity	1 (0.5)	0	0	0	0	1 (100.0)

Source: Table 16.2.1.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; TEAE = treatment-emergent adverse event.

[a] A patient is counted only once for a TEAE preferred term if that patient experiences the same TEAE preferred term multiple times.

Table 21. Grade 3 or Higher TEAEs Reported in ≥2% of Patients in Any Group by Race and Treatment Group– Treatment Part (Safety Population) in Study CO-338-043

System Organ Class Preferred Term[a]	Race Subgroup					
	White		Other		Unknown	
	Rucaparib (N = 218)	Chemotherapy (N = 110)	Rucaparib (N = 9)	Rucaparib (N = 2)	Chemotherapy (N = 5)	Rucaparib (N = 1)
	n (%)		n (%)		n (%)	
Number of Patients With At Least 1 Grade 3 or Higher TEAE	**127 (58.3)**	**42 (38.2)**	**5 (55.6)**	**1 (50.0)**	**4 (80.0)**	**0**
Combined Preferred Terms						
Combined ALT/AST Increased	15 (6.9)	0	1 (11.1)	0	2 (40.0)	0
Combined Anemia/Hemoglobin decreased	49 (22.5)	5 (4.5)	2 (22.2)	1 (50.0)	1 (20.0)	0
Combined Asthenia/Fatigue	18 (8.3)	3 (2.7)	1 (11.1)	0	0	0
Combined Neutropenia/Decreased ANC	23 (10.6)	17 (15.5)	0	0	1 (20.0)	0
Combined Thrombocytopenia/Decreased platelets	17 (7.8)	0	1 (11.1)	0	1 (20.0)	0
Blood and lymphatic system disorders	**68 (31.2)**	**21 (19.1)**	**3 (33.3)**	**1 (50.0)**	**2 (40.0)**	**0**
Anaemia	48 (22.0)	5 (4.5)	2 (22.2)	1 (50.0)	1 (20.0)	0
Leukopenia	5 (2.3)	3 (2.7)	0	0	0	0
Neutropenia	21 (9.6)	15 (13.6)	0	0	0	0
Thrombocytopenia	13 (6.0)	0	1 (11.1)	0	1 (20.0)	0
Gastrointestinal disorders	**30 (13.8)**	**4 (3.6)**	**4 (44.4)**	**0**	**0**	**0**
Abdominal pain	7 (3.2)	0	2 (22.2)	0	0	0
Ascites	6 (2.8)	1 (0.9)	0	0	0	0
Constipation	0	0	1 (11.1)	0	0	0
Intestinal obstruction	7 (3.2)	0	1 (11.1)	0	0	0
Nausea	4 (1.8)	0	2 (22.2)	0	0	0
Pancreatitis	0	0	1 (11.1)	0	0	0

System Organ Class Preferred Term[a]	Race Subgroup					
	White		Other		Unknown	
	Rucaparib (N = 218)	Chemotherapy (N = 110)	Rucaparib (N = 9)	Rucaparib (N = 2)	Chemotherapy (N = 5)	Rucaparib (N = 1)
	n (%)		n (%)		n (%)	
Small intestinal obstruction	1 (0.5)	0	1 (11.1)	0	0	0
Vomiting	7 (3.2)	0	4 (44.4)	0	0	0
General disorders and administration site conditions	**22 (10.1)**	**3 (2.7)**	**2 (22.2)**	**0**	**0**	**0**
Asthenia	7 (3.2)	0	1 (11.1)	0	0	0
Fatigue	11 (5.0)	3 (2.7)	0	0	0	0
Pyrexia	0	0	1 (11.1)	0	0	0
Infections and infestations	**13 (6.0)**	**3 (2.7)**	**0**	**0**	**2 (40.0)**	**0**
Lower respiratory tract infection	0	0	0	0	1 (20.0)	0
Neutropenic sepsis	0	0	0	0	1 (20.0)	0
Pneumonia	3 (1.4)	0	0	0	1 (20.0)	0
Investigations	**33 (15.1)**	**7 (6.4)**	**1 (11.1)**	**0**	**2 (40.0)**	**0**
Alanine aminotransferase increased	15 (6.9)	0	1 (11.1)	0	2 (40.0)	0
Blood alkaline phosphatase increased	2 (0.9)	0	1 (11.1)	0	0	0
Blood creatinine increased	5 (2.3)	0	0	0	0	0
Neutrophil count decreased	2 (0.9)	3 (2.7)	0	0	1 (20.0)	0
Metabolism and nutrition disorders	**11 (5.0)**	**8 (7.3)**	**1 (11.1)**	**1 (50.0)**	**0**	**0**
Hyperglycaemia	2 (0.9)	2 (1.8)	0	1 (50.0)	0	0
Hypomagnesaemia	0	0	1 (11.1)	0	0	0
Hyponatraemia	0	2 (1.8)	1 (11.1)	0	0	0

System Organ Class Preferred Term[a]	Race Subgroup					
	White		Other		Unknown	
	Rucaparib (N = 218)	Chemotherapy (N = 110)	Rucaparib (N = 9)	Rucaparib (N = 2)	Chemotherapy (N = 5)	Rucaparib (N = 1)
	n (%)		n (%)		n (%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**8 (3.7)**	**3 (2.7)**	**0**	**0**	**1 (20.0)**	**0**
Malignant neoplasm progression	8 (3.7)	3 (2.7)	0	0	0	0
Myelodysplastic syndrome	0	0	0	0	1 (20.0)	0
Psychiatric disorders	**0**	**1 (0.9)**	**1 (11.1)**	**0**	**0**	**0**
Anxiety	0	1 (0.9)	1 (11.1)	0	0	0
Insomnia	0	0	1 (11.1)	0	0	0
Renal and urinary disorders	**5 (2.3)**	**1 (0.9)**	**1 (11.1)**	**0**	**0**	**0**
Acute kidney injury	0	0	1 (11.1)	0	0	0
Respiratory, thoracic and mediastinal disorders	**7 (3.2)**	**4 (3.6)**	**0**	**0**	**1 (20.0)**	**0**
Pulmonary oedema	0	0	0	0	1 (20.0)	0
Skin and subcutaneous tissue disorders	**1 (0.5)**	**3 (2.7)**	**0**	**0**	**0**	**0**
Vascular disorders	**5 (2.3)**	**1 (0.9)**	**0**	**0**	**0**	**0**

Source: Table 16.2.2.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; TEAE = treatment-emergent adverse event.

[a] A patient is counted only once for a TEAE preferred term if that patient experiences the same TEAE preferred term multiple times.

Table 22. Treatment-emergent SAEs Reported in ≥2% of Patients in Any Group by Race and Treatment Group – Treatment Part (Safety Population) in Study CO-338-043

System Organ Class Preferred Term[a]	Race Subgroup					
	White		Other		Unknown	
	Rucaparib (N = 218)	Chemotherapy (N = 110)	Rucaparib (N = 9)	Chemotherapy (N = 2)	Rucaparib (N = 5)	Chemotherapy (N = 1)
	n (%)		n (%)		n (%)	
Number of Patients With At Least 1 Serious TEAE	**57 (26.1)**	**12 (10.9)**	**3 (33.3)**	**1 (50.0)**	**2 (40.0)**	**0**
Combined Preferred Terms						
Combined ALT/AST Increased	0	0	1 (11.1)	0	0	0
Combined Anemia/Hemoglobin decreased	19 (8.7)	2 (1.8)	0	0	0	0
Combined Neutropenia/Decreased ANC	3 (1.4)	0	1 (11.1)	0	0	0
Combined Thrombocytopenia/Decreased platelets	6 (2.8)	1 (0.9)	1 (11.1)	0	0	0
Blood and lymphatic system disorders	**21 (9.6)**	**3 (2.7)**	**1 (11.1)**	**0**	**0**	**0**
Anaemia	19 (8.7)	2 (1.8)	0	0	0	0
Neutropenia	3 (1.4)	0	1 (11.1)	0	0	0
Thrombocytopenia	4 (1.8)	1 (0.9)	1 (11.1)	0	0	0
Gastrointestinal disorders	**15 (6.9)**	**4 (3.6)**	**1 (11.1)**	**0**	**0**	**0**
Abdominal pain	0	0	1 (11.1)	0	0	0
Constipation	0	0	1 (11.1)	0	0	0
Intestinal obstruction	5 (2.3)	0	0	0	0	0
Pancreatitis	0	0	1 (11.1)	0	0	0
Small intestinal obstruction	0	0	1 (11.1)	0	0	0
General disorders and administration site conditions	**5 (2.3)**	**0**	**1 (11.1)**	**0**	**0**	**0**
Pyrexia	0	0	1 (11.1)	0	0	0

System Organ Class Preferred Term[a]	Race Subgroup					
	White		Other		Unknown	
	Rucaparib (N = 218)	Chemotherapy (N = 110)	Rucaparib (N = 9)	Chemotherapy (N = 2)	Rucaparib (N = 5)	Chemotherapy (N = 1)
	n (%)		n (%)		n (%)	
Immune system disorders	**0**	**0**	**0**	**1 (50.0)**	**0**	**0**
Drug hypersensitivity	0	0	0	1 (50.0)	0	0
Infections and infestations	**10 (4.6)**	**3 (2.7)**	**0**	**0**	**2 (40.0)**	**0**
Lower respiratory tract infection	0	0	0	0	1 (20.0)	0
Neutropenic sepsis	0	0	0	0	1 (20.0)	0
Pneumonia	3 (1.4)	0	0	0	1 (20.0)	0
Investigations	**2 (0.9)**	**0**	**1 (11.1)**	**0**	**0**	**0**
Alanine aminotransferase increased	0	0	1 (11.1)	0	0	0
Blood alkaline phosphatase increased	0	0	1 (11.1)	0	0	0
Blood creatinine increased	0	0	1 (11.1)	0	0	0
Metabolism and nutrition disorders	**3 (1.4)**	**1 (0.9)**	**1 (11.1)**	**0**	**0**	**0**
Hypomagnesaemia	0	0	1 (11.1)	0	0	0
Hyponatraemia	0	1 (0.9)	1 (11.1)	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**6 (2.8)**	**2 (1.8)**	**0**	**0**	**1 (20.0)**	**0**
Malignant neoplasm progression	5 (2.3)	2 (1.8)	0	0	0	0
Myelodysplastic syndrome	0	0	0	0	1 (20.0)	0
Renal and urinary disorders	**1 (0.5)**	**0**	**1 (11.1)**	**0**	**0**	**0**
Acute kidney injury	0	0	1 (11.1)	0	0	0

System Organ Class Preferred Term[a]	Race Subgroup					
	White		Other		Unknown	
	Rucaparib (N = 218)	Chemotherapy (N = 110)	Rucaparib (N = 9)	Chemotherapy (N = 2)	Rucaparib (N = 5)	Chemotherapy (N = 1)
	n (%)		n (%)		n (%)	
Respiratory, thoracic and mediastinal disorders	**4 (1.8)**	**1 (0.9)**	**0**	**0**	**1 (20.0)**	**0**
Pulmonary oedema	0	0	0	0	1 (20.0)	0
Skin and subcutaneous tissue disorders	**0**	**0**	**0**	**1 (50.0)**	**0**	**0**
Rash	0	0	0	1 (50.0)	0	0

Source: Table 16.2.3.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] A patient is counted only once for a TEAE preferred term if that patient experiences the same TEAE preferred term multiple times.

BRCA Mutated Gene

The majority of patients in the rucaparib group had a BRCA1 gene mutation (78.0% of patients, 181/232) as compared to a BRCA2 gene mutation (22.0% of patients, 51/232). Similarly, the majority of patients in the chemotherapy group had a BRCA1 gene mutation (67.9% of patients, 76/112) as compared to a BRCA2 gene mutation (32.1% of patients, 36/112).

Some numerical differences were observed in comparison of incidence of TEAEs (Table 23), Grade 3 or higher TEAEs (Table 24), or SAEs (Table 25) between patients with a BRCA1 or BRCA2 gene mutation in rucaparib or chemotherapy groups; however, the small size of the BRCA2 gene mutation subgroup made it difficult to interpret differences observed between the BRCA2 and BRCA1 gene mutation subgroups.

Events in BRCA1 and BRCA2 gene mutation subgroups appeared consistent with the overall safety population, primarily consisting of myelosuppression, asthenia/fatigue, ALT/AST increased, nausea, and vomiting in both treatment groups. Alopecia was also commonly observed in patients in the chemotherapy group in BRCA1 and BRCA2 subgroups.

Table 23. TEAEs Reported in ≥20% of Patients in Any Group by BRCA Mutated Gene and Treatment Group – Treatment Part (Safety Population) in Study CO-338-043

System Organ Class Preferred Term[a]	BRCA Mutated Gene			
	BRCA1		BRCA2	
	Rucaparib (N = 181)	Chemotherapy (N = 76)	Rucaparib (N = 51)	Chemotherapy (N = 36)
	n (%)		n (%)	
Number of Patients With At Least 1 TEAE	**173 (95.6)**	**69 (90.8)**	**49 (96.1)**	**36 (100.0)**
Combined Preferred Terms				
Combined ALT/AST increased	60 (33.1)	7 (9.2)	20 (39.2)	6 (16.7)
Combined Anemia/Hemoglobin decreased	96 (53.0)	22 (28.9)	29 (56.9)	13 (36.1)
Combined Asthenia/Fatigue	92 (50.8)	30 (39.5)	23 (45.1)	20 (55.6)
Combined Neutropenia/Decreased ANC	39 (21.5)	25 (32.9)	13 (25.5)	6 (16.7)
Combined Thrombocytopenia/Decreased platelets	41 (22.7)	10 (13.2)	13 (25.5)	3 (8.3)
Blood and lymphatic system disorders	**110 (60.8)**	**34 (44.7)**	**33 (64.7)**	**15 (41.7)**
Anaemia	94 (51.9)	21 (27.6)	29 (56.9)	13 (36.1)
Neutropenia	36 (19.9)	22 (28.9)	11 (21.6)	5 (13.9)
Cardiac disorders	**19 (10.5)**	**5 (6.6)**	**6 (11.8)**	**8 (22.2)**
Gastrointestinal disorders	**131 (72.4)**	**47 (61.8)**	**37 (72.5)**	**27 (75.0)**
Abdominal pain	43 (23.8)	15 (19.7)	11 (21.6)	3 (8.3)
Constipation	26 (14.4)	11 (14.5)	11 (21.6)	8 (22.2)
Diarrhoea	33 (18.2)	12 (15.8)	14 (27.5)	11 (30.6)
Nausea	96 (53.0)	24 (31.6)	28 (54.9)	12 (33.3)
Vomiting	60 (33.1)	14 (18.4)	19 (37.3)	5 (13.9)
General disorders and administration site conditions	**103 (56.9)**	**34 (44.7)**	**31 (60.8)**	**23 (63.9)**
Asthenia	53 (29.3)	17 (22.4)	11 (21.6)	7 (19.4)
Fatigue	41 (22.7)	14 (18.4)	14 (27.5)	14 (38.9)
Infections and infestations	**53 (29.3)**	**16 (21.1)**	**20 (39.2)**	**11 (30.6)**
Investigations	**95 (52.5)**	**26 (34.2)**	**34 (66.7)**	**9 (25.0)**
Alanine aminotransferase increased	56 (30.9)	7 (9.2)	18 (35.3)	5 (13.9)
Aspartate aminotransferase increased	54 (29.8)	4 (5.3)	18 (35.3)	4 (11.1)
Blood creatinine increased	21 (11.6)	7 (9.2)	12 (23.5)	2 (5.6)
Metabolism and nutrition disorders	**67 (37.0)**	**33 (43.4)**	**21 (41.2)**	**19 (52.8)**
Decreased appetite	32 (17.7)	12 (15.8)	12 (23.5)	8 (22.2)

System Organ Class Preferred Term[a]	BRCA Mutated Gene			
	BRCA1		BRCA2	
	Rucaparib (N = 181)	Chemotherapy (N = 76)	Rucaparib (N = 51)	Chemotherapy (N = 36)
	n (%)		n (%)	
Musculoskeletal and connective tissue disorders	**35 (19.3)**	**18 (23.7)**	**14 (27.5)**	**8 (22.2)**
Nervous system disorders	**60 (33.1)**	**32 (42.1)**	**20 (39.2)**	**22 (61.1)**
Psychiatric disorders	**19 (10.5)**	**9 (11.8)**	**11 (21.6)**	**3 (8.3)**
Respiratory, thoracic and mediastinal disorders	**42 (23.2)**	**14 (18.4)**	**12 (23.5)**	**13 (36.1)**
Skin and subcutaneous tissue disorders	**39 (21.5)**	**27 (35.5)**	**14 (27.5)**	**22 (61.1)**
Alopecia	7 (3.9)	22 (28.9)	5 (9.8)	16 (44.4)

Source: Table 16.3.1.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BRCA = breast cancer gene; TEAE = treatment-emergent adverse event.

[a] A patient is counted only once for a TEAE preferred term if that patient experiences the same TEAE preferred term multiple times.

Table 24. Grade 3 or Higher TEAEs Reported in ≥2% of Patients in Any Group by BRCA Mutated Gene and Treatment Group – Treatment Part (Safety Population) in Study CO-338-043

System Organ Class Preferred Term[a]	BRCA Mutated Gene			
	BRCA1		BRCA2	
	Rucaparib (N = 181)	Chemotherapy (N = 76)	Rucaparib (N = 51)	Chemotherapy (N = 36)
	n (%)		n (%)	
Number of Patients With At Least 1 Grade 3 or Higher TEAE	**103 (56.9)**	**32 (42.1)**	**33 (64.7)**	**10 (27.8)**
Combined Preferred Terms				
Combined ALT/AST increased	14 (7.7)	0	4 (7.8)	0
Combined Anemia/Hemoglobin decreased	39 (21.5)	5 (6.6)	13 (25.5)	1 (2.8)
Combined Asthenia/Fatigue	17 (9.4)	2 (2.6)	2 (3.9)	1 (2.8)
Combined Neutropenia/Decreased ANC	16 (8.8)	14 (18.4)	8 (15.7)	2 (5.6)
Combined Thrombocytopenia/Decreased platelets	13 (7.2)	0	6 (11.8)	0
Blood and lymphatic system disorders	**53 (29.3)**	**17 (22.4)**	**20 (39.2)**	**4 (11.1)**
Anaemia	38 (21.0)	5 (6.6)	13 (25.5)	1 (2.8)
Febrile neutropenia	0	0	1 (2.0)	0
Leukopenia	4 (2.2)	3 (3.9)	1 (2.0)	0
Lymphopenia	1 (0.6)	0	0	1 (2.8)
Neutropenia	15 (8.3)	12 (15.8)	6 (11.8)	2 (5.6)
Thrombocytopenia	11 (6.1)	0	4 (7.8)	0
Ear and labyrinth disorders	**0**	**0**	**0**	**1 (2.8)**
Hypoacusis	0	0	0	1 (2.8)
Gastrointestinal disorders	**27 (14.9)**	**1 (1.3)**	**7 (13.7)**	**3 (8.3)**
Abdominal pain	8 (4.4)	0	1 (2.0)	0
Ascites	6 (3.3)	1 (1.3)	0	0
Diarrhoea	3 (1.7)	0	1 (2.0)	1 (2.8)
Dyspepsia	0	0	1 (2.0)	0
Enterocolitis	0	0	1 (2.0)	0
Gastrointestinal haemorrhage	0	0	0	1 (2.8)
Haematemesis	0	0	1 (2.0)	0
Intestinal obstruction	4 (2.2)	0	4 (7.8)	0
Nausea	5 (2.8)	0	1 (2.0)	0
Small intestinal obstruction	1 (0.6)	0	1 (2.0)	0

System Organ Class Preferred Term[a]	BRCA Mutated Gene			
	BRCA1		BRCA2	
	Rucaparib (N = 181)	Chemotherapy (N = 76)	Rucaparib (N = 51)	Chemotherapy (N = 36)
	n (%)		n (%)	
Subileus	0	0	0	1 (2.8)
Vomiting	9 (5.0)	0	2 (3.9)	0
General disorders and administration site conditions	**21 (11.6)**	**2 (2.6)**	**3 (5.9)**	**1 (2.8)**
Asthenia	7 (3.9)	0	1 (2.0)	0
Death[b]	2 (1.1)	0	1 (2.0)	0
Fatigue	10 (5.5)	2 (2.6)	1 (2.0)	1 (2.8)
Immune system disorders	**0**	**1 (1.3)**	**1 (2.0)**	**0**
Drug hypersensitivity	0	0	1 (2.0)	0
Infections and infestations	**11 (6.1)**	**2 (2.6)**	**4 (7.8)**	**1 (2.8)**
Intervertebral discitis	0	0	0	1 (2.8)
Lower respiratory tract infection	0	0	1 (2.0)	0
Neutropenic sepsis	0	0	1 (2.0)	0
Osteomyelitis	0	0	0	1 (2.8)
Pneumonia	2 (1.1)	0	2 (3.9)	0
Urinary tract infection	0	0	1 (2.0)	0
Injury, poisoning and procedural complications	**0**	**0**	**2 (3.9)**	**1 (2.8)**
Allergic transfusion reaction	0	0	1 (2.0)	0
Infusion related reaction	0	0	0	1 (2.8)
Seroma	0	0	1 (2.0)	0
Investigations	**23 (12.7)**	**6 (7.9)**	**13 (25.5)**	**1 (2.8)**
Alanine aminotransferase increased	14 (7.7)	0	4 (7.8)	0
Blood alkaline phosphatase increased	1 (0.6)	0	2 (3.9)	0
Blood bilirubin increased	2 (1.1)	0	1 (2.0)	0
Blood creatinine increased	3 (1.7)	0	2 (3.9)	0
Glomerular filtration rate decreased	0	0	2 (3.9)	0
Lymphocyte count decreased	0	0	0	1 (2.8)
Neutrophil count decreased	1 (0.6)	3 (3.9)	2 (3.9)	0
Platelet count decreased	2 (1.1)	0	2 (3.9)	0
Transaminases increased	0	1 (1.3)	1 (2.0)	0

System Organ Class Preferred Term[a]	BRCA Mutated Gene			
	BRCA1		BRCA2	
	Rucaparib (N = 181)	Chemotherapy (N = 76)	Rucaparib (N = 51)	Chemotherapy (N = 36)
	n (%)		n (%)	
Metabolism and nutrition disorders	**11 (6.1)**	**8 (10.5)**	**1 (2.0)**	**1 (2.8)**
Decreased appetite	1 (0.6)	0	1 (2.0)	0
Hyperglycaemia	2 (1.1)	3 (3.9)	0	0
Hypertriglyceridaemia	2 (1.1)	1 (1.3)	0	1 (2.8)
Hypoalbuminaemia	0	2 (2.6)	0	0
Hyponatraemia	1 (0.6)	2 (2.6)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**5 (2.8)**	**3 (3.9)**	**4 (7.8)**	**0**
Malignant neoplasm progression	5 (2.8)	3 (3.9)	3 (5.9)	0
Myelodysplastic syndrome	0	0	1 (2.0)	0
Nervous system disorders	**2 (1.1)**	**1 (1.3)**	**0**	**1 (2.8)**
Seizure	0	1 (1.3)	0	1 (2.8)
Renal and urinary disorders	**6 (3.3)**	**1 (1.3)**	**0**	**0**
Respiratory, thoracic and mediastinal disorders	**7 (3.9)**	**3 (3.9)**	**1 (2.0)**	**1 (2.8)**
Dyspnoea	3 (1.7)	2 (2.6)	0	0
Pulmonary embolism	1 (0.6)	1 (1.3)	0	1 (2.8)
Pulmonary oedema	0	0	1 (2.0)	0
Skin and subcutaneous tissue disorders	**1 (0.6)**	**2 (2.6)**	**0**	**1 (2.8)**
Nail disorder	0	1 (1.3)	0	1 (2.8)
Vascular disorders	**3 (1.7)**	**1 (1.3)**	**2 (3.9)**	**0**
Hypertensive crisis	1 (0.6)	0	1 (2.0)	0
Hypotension	0	0	1 (2.0)	0

Source: Table 16.3.2.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BRCA = breast cancer gene; TEAE = treatment-emergent adverse event.

[a] A patient is counted only once for a TEAE preferred term if that patient experiences the same TEAE preferred term multiple times.

[b] The causes of death for the 3 TEAEs of "Death" were unknown.

Table 25. Treatment-emergent SAEs Reported in ≥2% of Patients in Any Group by BRCA Mutated Gene and Treatment Group – Treatment Part (Safety Population) in Study CO-338-043

System Organ Class Preferred Term[a]	BRCA Mutated Gene			
	BRCA1		BRCA2	
	Rucaparib (N = 181)	Chemotherapy (N = 76)	Rucaparib (N = 51)	Chemotherapy (N = 36)
	n (%)		n (%)	
Number of Patients With At Least 1 Serious TEAE	**48 (26.5)**	**9 (11.8)**	**14 (27.5)**	**4 (11.1)**
Combined Preferred Terms				
Combined Anemia/Hemoglobin decreased	15 (8.3)	2 (2.6)	4 (7.8)	0
Combined Neutropenia/Decreased ANC	3 (1.7)	0	1 (2.0)	0
Combined Thrombocytopenia/Decreased platelets	5 (2.8)	1 (1.3)	2 (3.9)	0
Blood and lymphatic system disorders	**17 (9.4)**	**3 (3.9)**	**5 (9.8)**	**0**
Anaemia	15 (8.3)	2 (2.6)	4 (7.8)	0
Febrile neutropenia	0	0	1 (2.0)	0
Leukopenia	0	0	1 (2.0)	0
Neutropenia	3 (1.7)	0	1 (2.0)	0
Thrombocytopenia	4 (2.2)	1 (1.3)	1 (2.0)	0
Gastrointestinal disorders	**13 (7.2)**	**2 (2.6)**	**3 (5.9)**	**2 (5.6)**
Gastrointestinal haemorrhage	0	0	0	1 (2.8)
Haematemesis	0	0	1 (2.0)	0
Intestinal obstruction	3 (1.7)	0	2 (3.9)	0
Subileus	1 (0.6)	0	0	1 (2.8)
Vomiting	2 (1.1)	1 (1.3)	1 (2.0)	0
General disorders and administration site conditions	**5 (2.8)**	**0**	**1 (2.0)**	**0**
Death[b]	2 (1.1)	0	1 (2.0)	0
Immune system disorders	**0**	**0**	**0**	**1 (2.8)**
Drug hypersensitivity	0	0	0	1 (2.8)
Infections and infestations	**8 (4.4)**	**2 (2.6)**	**4 (7.8)**	**1 (2.8)**
Lower respiratory tract infection	0	0	1 (2.0)	0
Neutropenic sepsis	0	0	1 (2.0)	0
Osteomyelitis	0	0	0	1 (2.8)
Pneumonia	2 (1.1)	0	2 (3.9)	0
Urinary tract infection	1 (0.6)	1 (1.3)	1 (2.0)	0

System Organ Class Preferred Term[a]	BRCA Mutated Gene			
	BRCA1		BRCA2	
	Rucaparib (N = 181)	Chemotherapy (N = 76)	Rucaparib (N = 51)	Chemotherapy (N = 36)
	n (%)		n (%)	
Injury, poisoning and procedural complications	**1 (0.6)**	**0**	**2 (3.9)**	**1 (2.8)**
Infusion related reaction	0	0	0	1 (2.8)
Radious fracture	0	0	1 (2.0)	0
Seroma	0	0	1 (2.0)	0
Tibia fracture	0	0	1 (2.0)	0
Investigations	**2 (1.1)**	**0**	**1 (2.0)**	**0**
Platelet count decreased	1 (0.6)	0	1 (2.0)	0
Metabolism and nutrition disorders	**4 (2.2)**	**1 (1.3)**	**0**	**0**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**3 (1.7)**	**2 (2.6)**	**4 (7.8)**	**0**
Intraductal proliferative breast lesion	0	0	1 (2.0)	0
Malignant neoplasm progression	3 (1.7)	2 (2.6)	2 (3.9)	0
Myelodysplastic syndrome	0	0	1 (2.0)	0
Nervous system disorders	**2 (1.1)**	**1 (1.3)**	**1 (2.0)**	**1 (2.8)**
Depressed level of consciousness	0	0	1 (2.0)	0
Transient ischaemic attack	0	0	0	1 (2.8)
Respiratory, thoracic and mediastinal disorders	**4 (2.2)**	**0**	**1 (2.0)**	**1 (2.8)**
Pulmonary embolism	1 (0.6)	0	0	1 (2.8)
Pulmonary oedema	0	0	1 (2.0)	0
Skin and subcutaneous tissue disorders	**0**	**0**	**0**	**1 (2.8)**
Rash	0	0	0	1 (2.8)
Vascular disorders	**2 (1.1)**	**1 (1.3)**	**1 (2.0)**	**0**
Deep vein thrombosis	2 (1.1)	1 (1.3)	1 (2.0)	0

Source: Table 16.3.3.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BRCA = breast cancer gene; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] A patient is counted only once for a TEAE preferred term if that patient experiences the same TEAE preferred term multiple times.

[b] The causes of death for the 3 TEAEs of "Death" were unknown.

BRCA Mutation Status

In the rucaparib group, 84.9% of patients (197/232) had a germline BRCA mutation and 15.1% of patients (35/232) had a somatic BRCA mutation. In the chemotherapy group, 82.9% of patients (92/111) had a germline BRCA mutation and 17.1% of patients (19/111) had a somatic BRCA mutation. Overall,

the small number of patients in either treatment group with a somatic BRCA mutation limited the interpretability of comparisons by BRCA mutation status.

Some numerical differences were observed in comparison of incidence of TEAEs (Table 26), Grade 3 or higher TEAEs (Table 27), or SAEs (Table 28) between patients with a germline BRCA or somatic BRCA mutation in rucaparib or chemotherapy groups; however, the small size of the somatic BRCA mutation subgroup made it difficult to interpret differences observed between the somatic and germline BRCA mutation subgroups.

As observed in other subgroup analyses, events in germline BRCA and somatic BRCA subgroups appeared consistent with the overall safety population, primarily consisting of myelosuppression, asthenia/fatigue, ALT/AST increased, nausea, and vomiting in both treatment groups. Alopecia was also commonly observed in patients in the chemotherapy group in germline BRCA and somatic BRCA subgroups.

Table 26. TEAEs Reported in ≥20% of Patients in Any Group by BRCA Mutation Status and Treatment Group – Treatment Part (Safety Population) in Study CO-338-043

System Organ Class Preferred Term[a]	BRCA Mutation Status			
	Germline		Somatic	
	Rucaparib (N = 197)	Chemotherapy (N = 92)	Rucaparib (N = 35)	Chemotherapy (N = 19)
	n (%)		n (%)	
Number of Patients With At Least 1 TEAE	**189 (95.9)**	**86 (93.5)**	**33 (94.3)**	**18 (94.7)**
Combined Preferred Terms				
Combined ALT/AST increased	67 (34.0)	10 (10.9)	13 (37.1)	3 (15.8)
Combined Anemia/Hemoglobin decreased	109 (55.3)	29 (31.5)	16 (45.7)	5 (26.3)
Combined Asthenia/Fatigue	99 (50.3)	38 (41.3)	16 (45.7)	11 (57.9)
Combined Neutropenia/Decreased ANC	42 (21.3)	26 (28.3)	10 (28.6)	4 (21.1)
Combined Thrombocytopenia/Decreased platelets	49 (24.9)	11 (12.0)	5 (14.3)	2 (10.5)
Blood and lymphatic system disorders	**124 (62.9)**	**41 (44.6)**	**19 (54.3)**	**7 (36.8)**
Anaemia	107 (54.3)	28 (30.4)	16 (45.7)	5 (26.3)
Neutropenia	39 (19.8)	22 (23.9)	8 (22.9)	4 (21.1)
Thrombocytopenia	42 (21.3)	11 (12.0)	4 (11.4)	2 (10.5)
Gastrointestinal disorders	**142 (72.1)**	**61 (66.3)**	**26 (74.3)**	**12 (63.2)**
Abdominal pain	48 (24.4)	18 (19.6)	6 (17.1)	0
Diarrhoea	43 (21.8)	18 (19.6)	4 (11.4)	4 (21.1)
Nausea	105 (53.3)	28 (30.4)	19 (54.3)	7 (36.8)
Vomiting	65 (33.0)	15 (16.3)	14 (40.0)	4 (21.1)
General disorders and administration site conditions	**116 (58.9)**	**45 (48.9)**	**18 (51.4)**	**11 (57.9)**
Asthenia	55 (27.9)	15 (16.3)	9 (25.7)	8 (42.1)
Fatigue	48 (24.4)	24 (26.1)	7 (20.0)	4 (21.1)
Infections and infestations	**56 (28.4)**	**22 (23.9)**	**17 (48.6)**	**5 (26.3)**
Investigations	**110 (55.8)**	**28 (30.4)**	**19 (54.3)**	**6 (31.6)**
Alanine aminotransferase increased	63 (32.0)	9 (9.8)	11 (31.4)	3 (15.8)
Aspartate aminotransferase increased	61 (31.0)	7 (7.6)	11 (31.4)	1 (5.3)
Metabolism and nutrition disorders	**69 (35.0)**	**44 (47.8)**	**19 (54.3)**	**7 (36.8)**
Decreased appetite	34 (17.3)	15 (16.3)	10 (28.6)	4 (21.1)

System Organ Class Preferred Term[a]	BRCA Mutation Status			
	Germline		Somatic	
	Rucaparib (N = 197)	Chemotherapy (N = 92)	Rucaparib (N = 35)	Chemotherapy (N = 19)
	n (%)		n (%)	
Musculoskeletal and connective tissue disorders	**42 (21.3)**	**20 (21.7)**	**7 (20.0)**	**6 (31.6)**
Nervous system disorders	**66 (33.5)**	**43 (46.7)**	**14 (40.0)**	**10 (52.6)**
Dysgeusia	32 (16.2)	5 (5.4)	7 (20.0)	3 (15.8)
Psychiatric disorders	**25 (12.7)**	**6 (6.5)**	**5 (14.3)**	**6 (31.6)**
Respiratory, thoracic and mediastinal disorders	**45 (22.8)**	**21 (22.8)**	**9 (25.7)**	**6 (31.6)**
Skin and subcutaneous tissue disorders	**43 (21.8)**	**40 (43.5)**	**10 (28.6)**	**8 (42.1)**
Alopecia	9 (4.6)	30 (32.6)	3 (8.6)	7 (36.8)

Source: Table 16.4.1.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BRCA = breast cancer gene; TEAE = treatment-emergent adverse event.

[a] A patient is counted only once for a TEAE preferred term if that patient experiences the same TEAE preferred term multiple times.

Table 27. Grade 3 or Higher TEAEs Reported in ≥2% of Patients in Any Group by BRCA Mutation Status and Treatment Group – Treatment Part (Safety Population) in Study CO-338-043

System Organ Class Preferred Term[a]	BRCA Mutation Status			
	Germline		Somatic	
	Rucaparib (N = 197)	Chemotherapy (N = 92)	Rucaparib (N = 35)	Chemotherapy (N = 19)
	n (%)		n (%)	
Number of Patients With At Least 1 Grade 3 or Higher TEAE	**116 (58.9)**	**34 (37.0)**	**20 (57.1)**	**7 (36.8)**
Combined Preferred Terms				
Combined ALT/AST increased	16 (8.1)	0	2 (5.7)	0
Combined Anemia/Hemoglobin decreased	49 (24.9)	5 (5.4)	3 (8.6)	1 (5.3)
Combined Asthenia/Fatigue	15 (7.6)	2 (2.2)	4 (11.4)	1 (5.3)
Combined Neutropenia/Decreased ANC	22 (11.2)	12 (13.0)	2 (5.7)	3 (15.8)
Combined Thrombocytopenia/Decreased platelets	19 (9.6)	0	0	0
Blood and lymphatic system disorders	**69 (35.0)**	**15 (16.3)**	**4 (11.4)**	**5 (26.3)**
Anaemia	48 (24.4)	5 (5.4)	3 (8.6)	1 (5.3)
Leukopenia	5 (2.5)	3 (3.3)	0	0
Lymphopenia	1 (0.5)	0	0	1 (5.3)
Neutropenia	20 (10.2)	10 (10.9)	1 (2.9)	3 (15.8)
Thrombocytopenia	15 (7.6)	0	0	0
Eye disorders	**0**	**0**	**1 (2.9)**	**0**
Cataract	0	0	1 (2.9)	0
Gastrointestinal disorders	**30 (15.2)**	**3 (3.3)**	**4 (11.4)**	**1 (5.3)**
Abdominal pain	8 (4.1)	0	1 (2.9)	0
Ascites	6 (3.0)	1 (1.1)	0	0
Diarrhoea	3 (1.5)	1 (1.1)	1 (2.9)	0
Intestinal obstruction	8 (4.1)	0	0	0
Large intestine perforation	0	0	1 (2.9)	0
Nausea	6 (3.0)	0	0	0
Subileus	0	0	0	1 (5.3)
Vomiting	10 (5.1)	0	1 (2.9)	0

System Organ Class Preferred Term[a]	BRCA Mutation Status			
	Germline		Somatic	
	Rucaparib (N = 197)	Chemotherapy (N = 92)	Rucaparib (N = 35)	Chemotherapy (N = 19)
	n (%)		n (%)	
General disorders and administration site conditions	**19 (9.6)**	**2 (2.2)**	**5 (14.3)**	**1 (5.3)**
Asthenia	6 (3.0)	0	2 (5.7)	0
Death[b]	2 (1.0)	0	1 (2.9)	0
Fatigue	9 (4.6)	2 (2.2)	2 (5.7)	1 (5.3)
Infections and infestations	**10 (5.1)**	**3 (3.3)**	**5 (14.3)**	**0**
Colonic abscess	0	0	1 (2.9)	0
Cytomegalovirus colitis	0	0	1 (2.9)	0
Lower respiratory tract infection	0	0	1 (2.9)	0
Neutropenic sepsis	0	0	1 (2.9)	0
Pneumonia	3 (1.5)	0	1 (2.9)	0
Systemic infection	0	0	1 (2.9)	0
Investigations	**33 (16.8)**	**5 (5.4)**	**3 (8.6)**	**1 (5.3)**
Alanine aminotransferase increased	16 (8.1)	0	2 (5.7)	0
Blood creatinine increased	5 (2.5)	0	0	0
Glomerular filtration rate decreased	1 (0.5)	0	1 (2.9)	0
Neutrophil count decreased	2 (1.0)	2 (2.2)	1 (2.9)	1 (5.3)
Platelet count decreased	4 (2.0)	0	0	0
Metabolism and nutrition disorders	**8 (4.1)**	**9 (9.8)**	**4 (11.4)**	**0**
Dehydration	1 (0.5)	0	1 (2.9)	0
Hypercholesterolaemia	1 (0.5)	0	1 (2.9)	0
Hyperglycaemia	1 (0.5)	3 (3.3)	1 (2.9)	0
Hyperkalaemia	0	0	1 (2.9)	0
Hypertriglyceridaemia	1 (0.5)	2 (2.2)	1 (2.9)	0
Hypoalbuminaemia	0	2 (2.2)	0	0
Hyponatraemia	1 (0.5)	2 (2.2)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**7 (3.6)**	**3 (3.3)**	**2 (5.7)**	**0**
Malignant neoplasm progression	6 (3.0)	3 (3.3)	2 (5.7)	0
Nervous system disorders	**2 (1.0)**	**1 (1.1)**	**0**	**1 (5.3)**
Seizure	0	1 (1.1)	0	1 (5.3)

System Organ Class Preferred Term[a]	BRCA Mutation Status			
	Germline		Somatic	
	Rucaparib (N = 197)	Chemotherapy (N = 92)	Rucaparib (N = 35)	Chemotherapy (N = 19)
	n (%)		n (%)	
Psychiatric disorders	**1 (0.5)**	**0**	**0**	**1 (5.3)**
Anxiety	1 (0.5)	0	0	1 (5.3)
Mental disorder	0	0	0	1 (5.3)
Renal and urinary disorders	**3 (1.5)**	**1 (1.1)**	**3 (8.6)**	**0**
Hydronephrosis	0	1 (1.1)	1 (2.9)	0
Renal failure	0	0	1 (2.9)	0
Renal impairment	0	0	1 (2.9)	0
Respiratory, thoracic and mediastinal disorders	**6 (3.0)**	**3 (3.3)**	**2 (5.7)**	**1 (5.3)**
Dyspnoea	2 (1.0)	2 (2.2)	1 (2.9)	0
Pulmonary embolism	1 (0.5)	1 (1.1)	0	1 (5.3)
Pulmonary oedema	0	0	1 (2.9)	0
Skin and subcutaneous tissue disorders	**1 (0.5)**	**3 (3.3)**	**0**	**0**
Nail disorder	0	2 (2.2)	0	0
Vascular disorders	**4 (2.0)**	**1 (1.1)**	**1 (2.9)**	**0**
Hypertension	1 (0.5)	1 (1.1)	1 (2.9)	0

Source: Table 16.4.2.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BRCA = breast cancer gene; TEAE = treatment-emergent adverse event.

[a] A patient is counted only once for a TEAE preferred term if that patient experiences the same TEAE preferred term multiple times.

[b] The causes of death for the 3 TEAEs of "Death" were unknown.

Table 28. Treatment-emergent SAEs Reported in ≥2% of Patients in Any Group by BRCA Mutation Status and Treatment Group – Treatment Part (Safety Population) in Study CO-338-043

System Organ Class Preferred Term[a]	BRCA Mutation Status			
	Germline		Somatic	
	Rucaparib (N = 197)	Chemotherapy (N = 92)	Rucaparib (N = 35)	Chemotherapy (N = 19)
	n (%)		n (%)	
Number of Patients With At Least 1 Serious TEAE	**52 (26.4)**	**9 (9.8)**	**10 (28.6)**	**4 (21.1)**
Combined Preferred Terms				
Combined Anemia/Hemoglobin decreased	18 (9.1)	1 (1.1)	1 (2.9)	1 (5.3)
Combined Neutropenia/Decreased ANC	4 (2.0)	0	0	0
Combined Thrombocytopenia/Decreased platelets	7 (3.6)	1 (1.1)	0	0
Blood and lymphatic system disorders	**21 (10.7)**	**2 (2.2)**	**1 (2.9)**	**1 (5.3)**
Anaemia	18 (9.1)	1 (1.1)	1 (2.9)	1 (5.3)
Neutropenia	4 (2.0)	0	0	0
Thrombocytopenia	5 (2.5)	1 (1.1)	0	0
Gastrointestinal disorders	**13 (6.6)**	**3 (3.3)**	**3 (8.6)**	**1 (5.3)**
Intestinal obstruction	5 (2.5)	0	0	0
Large intestine perforation	0	0	1 (2.9)	0
Subileus	0	0	1 (2.9)	1 (5.3)
Vomiting	2 (1.0)	1 (1.1)	1 (2.9)	0
General disorders and administration site conditions	**5 (2.5)**	**0**	**1 (2.9)**	**0**
Death[b]	2 (1.0)	0	1 (2.9)	0
Infections and infestations	**8 (4.1)**	**2 (2.2)**	**4 (11.4)**	**1 (5.3)**
Colonic abscess	0	0	1 (2.9)	0
Cytomegalovirus colitis	0	0	1 (2.9)	0
Lower respiratory tract infection	0	0	1 (2.9)	0
Neutropenic sepsis	0	0	1 (2.9)	0
Pneumonia	3 (1.5)	0	1 (2.9)	0
Urinary tract infection	2 (1.0)	0	0	1 (5.3)
Metabolism and nutrition disorders	**3 (1.5)**	**1 (1.1)**	**1 (2.9)**	**0**
Dehydration	1 (0.5)	0	1 (2.9)	0

System Organ Class Preferred Term[a]	BRCA Mutation Status			
	Germline		Somatic	
	Rucaparib (N = 197)	Chemotherapy (N = 92)	Rucaparib (N = 35)	Chemotherapy (N = 19)
	n (%)		n (%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**6 (3.0)**	**2 (2.2)**	**1 (2.9)**	**0**
Malignant neoplasm progression	4 (2.0)	2 (2.2)	1 (2.9)	0
Nervous system disorders	**3 (1.5)**	**1 (1.1)**	**0**	**1 (5.3)**
Seizure	0	0	0	1 (5.3)
Renal and urinary disorders	**1 (0.5)**	**0**	**1 (2.9)**	**0**
Renal failure	0	0	1 (2.9)	0
Respiratory, thoracic and mediastinal disorders	**4 (2.0)**	**0**	**1 (2.9)**	**1 (5.3)**
Pulmonary embolism	1 (0.5)	0	0	1 (5.3)
Pulmonary oedema	0	0	1 (2.9)	0

Source: Table 16.4.3.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BRCA = breast cancer gene; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] A patient is counted only once for a TEAE preferred term if that patient experiences the same TEAE preferred term multiple times.

[b] The causes of death for the 3 TEAEs of "Death" were unknown.

Assessment of the MAH's response

The MAH has provided the requested tabular summaries of common AEs, Grade 3-4 AEs and SAEs by age, race, BRCA mutated gene and BRCA mutation status. In relation to age, apparent higher AEs incidences were observed for the 65-74 years subgroup, which is somehow expected, although these higher rates of AEs are not evenly reported for all SOC and PTs. In addition, the number of patients included in the older subgroups (65-74 and ≥75) is lower than the <65 years group so any difference in the number of patients who reported a PT in this smaller subgroup would have a remarkable impact on the observed AEs incidences. Regarding race, as most subjects were white (95%), it is imposible to identify a trend in the other subgroups (other and unknown) toxicities. For BRCA mutated gene (BRCA 1 vs. BRCA2) and BRCA mutation status (germline vs. somatic), once again we have unbalanced subgroups considering the number of subjects in each one of them. Higher incidences of AEs, by SOC, appear to be associated to BRCA2 mutated gene, in comparison with BRCA1 but no differences were identified between germline and somatic BRCA mutations. Overall, some differences in the reported AE rates were found but the subgroups sample size and the lack of stratification prevent any definitive conclusion about them.

Conclusion

Issue solved.

Question 17

Comparative data by platinum status of most frequent SAEs, deaths and TEAEs leading to discontinuation and dose reduction/interruption should be provided.

Summary of the MAH's response

Treatment-emergent adverse events (TEAEs) from Study CO-338-043 are summarized by platinum status at study entry and treatment group in the following tables for the Treatment Part of the study.

Table 29 provides the incidence of TEAEs with an outcome of death by platinum-status subgroup. Many TEAEs with an outcome of death were single incidences, not appearing to be associated with treatment or platinum-status. Three TEAEs with an outcome of death (ie, Cardiac disorder, Death Not Otherwise Specified [NOS], and Myelodysplastic syndromes [MDS]) were assessed as treatment-related by the investigator; however, the events of Cardiac disorder and Death NOS were assessed by the Sponsor as unlikely related to rucaparib. Narratives of TEAEs with an outcome of death have been provided.

Malignant neoplasm progression was the most common TEAE with an outcome of death, which was reported in patients who were platinum-resistant in either treatment group or partially platinum-sensitive in the rucaparib group. These cases were likely the result of the natural course of underlying disease and unrelated to study drug. No TEAEs with an outcome of death were reported for patients in the platinum-sensitive subgroup.

All events of disease progression with a fatal outcome within the safety reporting period were recorded as treatment-emergent serious adverse events (TESAEs), since the study had been fully enrolled (ie, by 24 September 2020) and the visit cut-off had occurred (ie, on 30 September 2020) prior to the implementation of Protocol Amendment 2 (dated 23 October 2020) in which events of disease progression were no longer collected as TEAEs.

Table 29. Incidence of TEAEs With an Outcome of Death by Platinum Status and Treatment Group – Treatment Part (Safety Population) in Study CO-338-043

System Organ Class Preferred Term[a]	Platinum-resistant		Partially Platinum-sensitive		Platinum-sensitive	
	Rucaparib (N = 119)	Chemotherapy (N = 58)	Rucaparib (N = 65)	Chemotherapy (N = 30)	Rucaparib (N = 48)	Chemotherapy (N = 25)
	n (%)		n (%)		n (%)	
Number of Patients With At Least 1 TEAE Leading to Death	**7 (5.9)**	**2 (3.4)**	**8 (12.3)**	**1 (3.3)**	**0**	**0**
Combined Preferred Terms						
Combined Neutropenia/Decreased ANC	0	0	1 (1.5)	0	0	0
Combined Thrombocytopenia/Decreased platelets	0	0	1 (1.5)	0	0	0
Blood and lymphatic system disorders	**0**	**0**	**1 (1.5)**	**0**	**0**	**0**
Neutropenia	0	0	1 (1.5)	0	0	0
Thrombocytopenia	0	0	1 (1.5)	0	0	0
Cardiac disorders	**1 (0.8)**	**0**	**0**	**0**	**0**	**0**
Cardiac disorder	1 (0.8)	0	0	0	0	0
Gastrointestinal disorders	**1 (0.8)**	**0**	**0**	**0**	**0**	**0**
Large intestine perforation	1 (0.8)	0	0	0	0	0
General disorders and administration site conditions	**1 (0.8)**	**0**	**2 (3.1)**	**0**	**0**	**0**
Death[b]	1 (0.8)	0	2 (3.1)	0	0	0
Infections and infestations	**2 (1.7)**	**0**	**0**	**0**	**0**	**0**
Pneumonia	1 (0.8)	0	0	0	0	0
Septic shock	1 (0.8)	0	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2 (1.7)**	**0**	**4 (6.2)**	**0**	**0**	**0**
Malignant neoplasm progression	2 (1.7)	2 (3.4)	3 (4.6)	0	0	0
Myelodysplastic syndromes	0	0	1 (1.5)	0	0	0
Respiratory, thoracic and mediastinal disorders	**0**	**0**	**1 (1.5)**	**1 (3.3)**	**0**	**0**
Pulmonary embolism	0	0	1 (1.5)	1 (3.3)	0	0

Source: Table 17.1.2.

Abbreviations: ANC = absolute neutrophil count; incl = including; TEAE = treatment-emergent adverse event.

[a] A patient is counted only once for a TEAE preferred term if that patient experiences the same TEAE preferred term multiple times.

[b] The causes of death for the 3 TEAEs of "Death" were unknown.

Table 30 summarizes the incidence of TESAEs by platinum-status subgroup. There were no notable differences in the incidence of TESAEs in patients treated with rucaparib or chemotherapy across the platinum-resistant, partially platinum-sensitive, and platinum-sensitive subgroups. Anemia/hemoglobin decreased was the most common TESAE in patients treated with rucaparib; the incidence of anemia/hemoglobin decreased in the rucaparib arm was comparable across the 3 platinum-status subgroups.

A higher incidence of SAEs was reported in patients who received rucaparib as compared to chemotherapy in any platinum-status subgroup, likely the result of longer time on treatment with rucaparib. The incidence of TESAEs was comparable between rucaparib and chemotherapy groups when adjusted for time on treatment.

Table 30. Incidence of Serious TEAEs Reported in ≥2% by Platinum Status and Treatment Group – Treatment Part (Safety Population) in Study CO-338-043

System Organ Class Preferred Term[a]	Platinum-resistant		Partially Platinum-sensitive		Platinum-sensitive	
	Rucaparib (N = 119)	Chemotherapy (N = 58)	Rucaparib (N = 65)	Chemotherapy (N = 30)	Rucaparib (N = 48)	Chemotherapy (N = 25)
	n (%)		n (%)		n (%)	
Number of Patients With At Least 1 Serious TEAE	**27 (22.7)**	**8 (13.8)**	**22 (33.8)**	**2 (6.7)**	**13 (27.1)**	**3 (12.0)**
Combined Preferred Terms						
Combined Anemia/Hemoglobin decreased	7 (5.9)	2 (3.4)	6 (9.2)	0	6 (12.5)	0
Combined Neutropenia/Decreased ANC	3 (2.5)	0	1 (1.5)	0	0	0
Combined Thrombocytopenia/Decreased platelets	3 (2.5)	0	2 (3.1)	0	2 (4.2)	1 (4.0)
Blood and lymphatic system disorders	**9 (7.6)**	**2 (3.4)**	**7 (10.8)**	**0**	**6 (12.5)**	**1 (4.0)**
Anaemia	7 (5.9)	2 (3.4)	6 (9.2)	0	6 (12.5)	0
Neutropenia	3 (2.5)	0	1 (1.5)	0	0	0
Thrombocytopenia	3 (2.5)	0	2 (3.1)	0	0	1 (4.0)
Gastrointestinal disorders	**7 (5.9)**	**2 (3.4)**	**5 (7.7)**	**1 (3.3)**	**4 (8.3)**	**1 (4.0)**
Ascites	0	0	2 (3.1)	0	0	0
Dolichocolon acquired	0	0	0	0	1 (2.1)	0
Gastrointestinal haemorrhage	0	0	0	0	0	1 (4.0)
Intestinal obstruction	1 (0.8)	0	1 (1.5)	0	3 (6.3)	0
Megacolon	0	0	0	0	1 (2.1)	0
Subileus	1 (0.8)	0	0	1 (3.3)	0	0
General disorders and administration site conditions	**2 (1.7)**	**0**	**4 (6.2)**	**0**	**0**	**0**
Death[b]	1 (0.8)	0	2 (3.1)	0	0	0

System Organ Class Preferred Term[a]	Platinum-resistant		Partially Platinum-sensitive		Platinum-sensitive	
	Rucaparib (N = 119)	Chemotherapy (N = 58)	Rucaparib (N = 65)	Chemotherapy (N = 30)	Rucaparib (N = 48)	Chemotherapy (N = 25)
	n (%)		n (%)		n (%)	
Infections and infestations	**7 (5.9)**	**1 (1.7)**	**2 (3.1)**	**0**	**3 (6.3)**	**2 (8.0)**
Abdominal infection	0	0	0	0	1 (2.1)	0
Cytomegalovirus colitis	0	0	0	0	1 (2.1)	0
Device related infection	0	0	0	0	0	1 (4.0)
Lower respiratory tract infection	0	0	0	0	1 (2.1)	0
Neutropenic sepsis	0	0	0	0	1 (2.1)	0
Osteomyelitis	0	0	0	0	0	1 (4.0)
Pneumonia	2 (1.7)	0	2 (3.1)	0	0	0
Injury, poisoning and procedural complications	**1 (0.8)**	**0**	**1 (1.5)**	**0**	**1 (2.1)**	**1 (4.0)**
Infusion related reaction	0	0	0	0	0	1 (4.0)
Post procedural fever	0	0	0	0	1 (2.1)	0
Investigations	**1 (0.8)**	**0**	**0**	**0**	**2 (4.2)**	**0**
Platelet count decreased	0	0	0	0	2 (4.2)	0
Metabolism and nutrition disorders	**3 (2.5)**	**1 (1.7)**	**1 (1.5)**	**0**	**0**	**0**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**3 (2.5)**	**2 (3.4)**	**4 (6.2)**	**0**	**0**	**0**
Malignant neoplasm progression	2 (1.7)	2 (3.4)	3 (4.6)	0	0	0
Nervous system disorders	**0**	**2 (3.4)**	**3 (4.6)**	**0**	**0**	**0**
Respiratory, thoracic and mediastinal disorders	**2 (1.7)**	**0**	**2 (3.1)**	**1 (3.3)**	**1 (2.1)**	**0**
Pulmonary embolism	0	0	1 (1.5)	1 (3.3)	0	0
Pulmonary oedema	0	0	0	0	1 (2.1)	0
Skin and subcutaneous tissue disorders	**0**	**0**	**0**	**1 (3.3)**	**0**	**0**
Rash	0	0	0	1 (3.3)	0	0
Vascular disorders	**1 (0.8)**	**1 (1.7)**	**2 (3.1)**	**0**	**0**	**0**
Deep vein thrombosis	1 (0.8)	1 (1.7)	2 (3.1)	0	0	0

Source: Table 17.1.1.
Abbreviations: ANC = absolute neutrophil count; incl = including; TEAE = treatment-emergent adverse event.
[a] A patient is counted only once for a TEAE preferred term if that patient experiences the same TEAE preferred term multiple times.
[b] The causes of death for the 3 TEAEs of "Death" were unknown.

Table 31 summarizes the incidence of TEAEs that led to study drug discontinuation by platinum-status subgroup. The incidence of TEAEs that led to discontinuation of study drug was generally low. There were no notable differences in the incidence of TEAEs that led to study drug discontinuation in patients treated with rucaparib or chemotherapy across the platinum-status subgroups or treatment groups.

Table 31. TEAEs That Led to Study Drug Discontinuation in ≥2% of Patients by Platinum Status and Treatment Group – Treatment Part (Safety Population) in Study CO-338-043

System Organ Class Preferred Term[a]	Platinum-resistant		Partially Platinum-sensitive		Platinum-sensitive	
	Rucaparib (N = 119)	Chemotherapy (N = 58)	Rucaparib (N = 65)	Chemotherapy (N = 30)	Rucaparib (N = 48)	Chemotherapy (N = 25)
	n (%)		n (%)		n (%)	
Number of Patients With At Least 1 TEAE Leading to Study Drug Discontinuation	**8 (6.7)**	**10 (17.2)**	**9 (13.8)**	**2 (6.7)**	**3 (6.3)**	**3 (12.0)**
Combined Preferred Terms						
Combined Thrombocytopenia/Decreased platelets	0	0	0	0	1 (2.1)	0
Gastrointestinal disorders	**3 (2.5)**	**1 (1.7)**	**2 (3.1)**	**0**	**1 (2.1)**	**0**
Intestinal obstruction	1 (0.8)	0	1 (1.5)	0	1 (2.1)	0
General disorders and administration site conditions	**2 (1.7)**	**2 (3.4)**	**3 (4.6)**	**0**	**0**	**0**
Death[b]	1 (0.8)	0	2 (3.1)	0	0	0
Immune system disorders	**0**	**0**	**0**	**1 (3.3)**	**0**	**1 (4.0)**
Drug hypersensitivity	0	0	0	1 (3.3)	0	0
Hypersensitivity	0	0	0	0	0	1 (4.0)
Infections and infestations	**0**	**0**	**1 (1.5)**	**0**	**1 (2.1)**	**0**
Neutropenic sepsis	0	0	0	0	1 (2.1)	0
Injury, poisoning and procedural complications	**0**	**0**	**0**	**0**	**0**	**1 (4.0)**
Infusion related reaction	0	0	0	0	0	1 (4.0)
Investigations	**1 (0.8)**	**0**	**1 (1.5)**	**0**	**1 (2.1)**	**0**
Platelet count decreased	0	0	0	0	1 (2.1)	0
Nervous system disorders	**0**	**2 (3.4)**	**0**	**0**	**0**	**0**
Respiratory, thoracic and mediastinal disorders	**0**	**0**	**0**	**1 (3.3)**	**0**	**0**
Pulmonary embolism	0	0	0	1 (3.3)	0	0
[illegible]	[illegible]		[illegible]		[illegible]	
Skin and subcutaneous tissue disorders	**0**	**2 (3.4)**	**0**	**0**	**0**	**0**
Nail disorder	0	2 (3.4)	0	0	0	0
Vascular disorders	**0**	**1 (1.7)**	**0**	**0**	**0**	**1 (4.0)**
Deep vein thrombosis	0	1 (1.7)	0	0	0	1 (4.0)

Source: Table 17.1.3.
Abbreviations: TEAE = treatment-emergent adverse event.
[a] A patient is counted only once for a TEAE preferred term if that patient experiences the same TEAE preferred term multiple times.
[b] The causes of death for the 3 TEAEs of "Death" were unknown.

Table 32 summarizes the incidence of TEAEs that led to study drug interruption or dose reduction by platinum-status subgroup. Events of myelosuppression, including anemia/hemoglobin decreased, thrombocytopenia/decreased platelets, and neutropenia/decreased absolute neutrophil count (ANC) were more common in rucaparib or chemotherapy groups across the platinum-status subgroups; however, there were no notable differences across platinum-status subgroups in either treatment group. It seemed that dose reductions or study drug interruptions appeared to contribute to the managemente of these TEAEs across all platinum-status subgroups regardless of treatment.

Table 32. TEAEs That Led to Study Drug Interruption or Dose Reduction in ≥2% of Patients by Platinum Status and Treatment Group – Treatment Part (Safety Population) in Study CO-338-043

System Organ Class Preferred Term[a]	Platinum-resistant		Partially Platinum-sensitive		Platinum-sensitive	
	Rucaparib (N = 119)	Chemotherapy (N = 58)	Rucaparib (N = 65)	Chemotherapy (N = 30)	Rucaparib (N = 48)	Chemotherapy (N = 25)
	n (%)		n (%)		n (%)	
Number of Patients With At Least 1 TEAE Leading to Study Drug Interruption or Dose Reduction	**52 (43.7)**	**24 (41.4)**	**39 (60.0)**	**9 (30.0)**	**24 (50.0)**	**17 (68.0)**
Combined Preferred Terms						
Combined ALT/AST increased	4 (3.4)	0	7 (10.8)	0	3 (6.3)	1 (4.0)
Combined Anemia/Hemoglobin decreased	20 (16.8)	6 (10.3)	15 (23.1)	1 (3.3)	10 (20.8)	2 (8.0)
Combined Asthenia/Fatigue	9 (7.6)	3 (5.2)	7 (10.8)	0	1 (2.1)	0
Combined Neutropenia/Decreased ANC	11 (9.2)	8 (13.8)	10 (15.4)	2 (6.7)	6 (12.5)	8 (32.0)
Combined Thrombocytopenia/Decreased platelets	16 (13.4)	1 (1.7)	10 (15.4)	0	5 (10.4)	2 (8.0)
Blood and lymphatic system disorders	**32 (26.9)**	**12 (20.7)**	**25 (38.5)**	**3 (10.0)**	**13 (27.1)**	**8 (32.0)**
Anaemia	20 (16.8)	6 (10.3)	15 (23.1)	1 (3.3)	10 (20.8)	2 (8.0)
Leukopenia	2 (1.7)	3 (5.2)	3 (4.6)	0	1 (2.1)	2 (8.0)
Neutropenia	11 (9.2)	7 (12.1)	8 (12.3)	2 (6.7)	5 (10.4)	7 (28.0)
Thrombocytopenia	14 (11.8)	1 (1.7)	10 (15.4)	0	2 (4.2)	2 (8.0)
Ear and labyrinth disorders	**0**	**0**	**0**	**0**	**0**	**1 (4.0)**
Tinnitus	0	0	0	0	0	1 (4.0)
Gastrointestinal disorders	**17 (14.3)**	**3 (5.2)**	**8 (12.3)**	**0**	**7 (14.6)**	**3 (12.0)**
Abdominal pain	1 (0.8)	0	2 (3.1)	0	0	0
Abdominal pain upper	0	0	0	0	0	1 (4.0)
Diarrhoea	4 (3.4)	0	1 (1.5)	0	0	0
Dolichocolon acquired	0	0	0	0	1 (2.1)	0
Duodenitis	0	0	0	0	0	1 (4.0)

System Organ Class Preferred Term[a]	Platinum-resistant		Partially Platinum-sensitive		Platinum-sensitive	
	Rucaparib (N = 119)	Chemotherapy (N = 58)	Rucaparib (N = 65)	Chemotherapy (N = 30)	Rucaparib (N = 48)	Chemotherapy (N = 25)
	n (%)		n (%)		n (%)	
Dyspepsia	1 (0.8)	0	0	0	1 (2.1)	0
Intestinal obstruction	2 (1.7)	0	1 (1.5)	0	2 (4.2)	0
Megacolon	0	0	0	0	1 (2.1)	0
Nausea	8 (6.7)	3 (5.2)	6 (9.2)	0	3 (6.3)	2 (8.0)
Pancreatitis chronic	0	0	0	0	0	1 (4.0)
Vomiting	7 (5.9)	2 (3.4)	4 (6.2)	0	4 (8.3)	1 (4.0)
General disorders and administration site conditions	**11 (9.2)**	**4 (6.9)**	**8 (12.3)**	**3 (10.0)**	**2 (4.2)**	**1 (4.0)**
Asthenia	6 (5.0)	2 (3.4)	4 (6.2)	0	1 (2.1)	0
Fatigue	4 (3.4)	1 (1.7)	3 (4.6)	0	0	0
Inflammation	1 (0.8)	0	0	1 (3.3)	0	0
Influenza like illness	0	0	0	0	1 (2.1)	0
Non-cardiac chest pain	0	0	0	1 (3.3)	0	0
Peripheral swelling	0	0	0	1 (3.3)	0	0
Pyrexia	1 (0.8)	1 (1.7)	2 (3.1)	0	0	1 (4.0)
Immune system disorders	**0**	**0**	**1 (1.5)**	**1 (3.3)**	**0**	**1 (4.0)**
Anaphylactic reaction	0	0	0	0	0	1 (4.0)
Drug hypersensitivity	0	0	0	1 (3.3)	0	0
Infections and infestations	**5 (4.2)**	**3 (5.2)**	**3 (4.6)**	**0**	**6 (12.5)**	**1 (4.0)**
Abdominal infection	0	0	0	0	1 (2.1)	0
Anal abscess	0	0	0	0	1 (2.1)	0

System Organ Class Preferred Term[a]	Platinum-resistant		Partially Platinum-sensitive		Platinum-sensitive	
	Rucaparib (N = 119)	Chemotherapy (N = 58)	Rucaparib (N = 65)	Chemotherapy (N = 30)	Rucaparib (N = 48)	Chemotherapy (N = 25)
	n (%)		n (%)		n (%)	
Bronchitis	0	0	0	0	1 (2.1)	0
Cytomegalovirus colitis	0	0	0	0	1 (2.1)	0
Gastroenteritis	0	0	0	0	2 (4.2)	0
Influenza	0	0	0	0	1 (2.1)	0
Lower respiratory tract infection	0	0	0	0	1 (2.1)	0
Neutropenic sepsis	0	0	0	0	1 (2.1)	0
Pneumonia	2 (1.7)	0	2 (3.1)	0	0	0
Upper respiratory tract infection	0	1 (1.7)	0	0	0	1 (4.0)
Injury, poisoning and procedural complications	**0**	**0**	**0**	**0**	**0**	**1 (4.0)**
Infusion related reaction	0	0	0	0	0	1 (4.0)
Investigations	**12 (10.1)**	**3 (5.2)**	**14 (21.5)**	**1 (3.3)**	**9 (18.8)**	**2 (8.0)**
Alanine aminotransferase increased	4 (3.4)	0	7 (10.8)	0	3 (6.3)	1 (4.0)
Aspartate aminotransferase increased	2 (1.7)	0	5 (7.7)	0	2 (4.2)	0
Blood bilirubin increased	0	0	0	0	2 (4.2)	0
Blood creatinine increased	4 (3.4)	0	3 (4.6)	0	1 (2.1)	0
Blood pressure increased	0	0	0	1 (3.3)	0	0
Blood triglycerides increased	0	0	0	1 (3.3)	0	0
Gamma-glutamyltransferase increased	1 (0.8)	0	0	0	1 (2.1)	0

System Organ Class Preferred Term[a]	Platinum-resistant		Partially Platinum-sensitive		Platinum-sensitive	
	Rucaparib (N = 119)	Chemotherapy (N = 58)	Rucaparib (N = 65)	Chemotherapy (N = 30)	Rucaparib (N = 48)	Chemotherapy (N = 25)
	n (%)		n (%)		n (%)	
Neutrophil count decreased	0	3 (5.2)	2 (3.1)	0	1 (2.1)	1 (4.0)
Platelet count decreased	3 (2.5)	0	0	0	3 (6.3)	0
Transaminases increased	0	0	0	0	2 (4.2)	0
Metabolism and nutrition disorders	**7 (5.9)**	**1 (1.7)**	**5 (7.7)**	**0**	**1 (2.1)**	**2 (8.0)**
Decreased appetite	4 (3.4)	0	2 (3.1)	0	0	1 (4.0)
Dehydration	3 (2.5)	0	0	0	0	0
Hypertriglyceridaemia	0	0	0	0	1 (2.1)	0
Hypoalbuminaemia	0	0	0	0	0	1 (4.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**3 (2.5)**	**0**	**0**	**0**	**0**	**0**
Nervous system disorders	**1 (0.8)**	**4 (6.9)**	**1 (1.5)**	**4 (13.3)**	**0**	**2 (8.0)**
Neuropathy peripheral	0	0	0	1 (3.3)	0	0
Neurotoxicity	0	1 (1.7)	0	0	0	1 (4.0)
Paraesthesia	0	1 (1.7)	0	1 (3.3)	0	0
Peripheral sensory neuropathy	0	0	0	1 (3.3)	0	0
Polyneuropathy	0	1 (1.7)	0	0	0	1 (4.0)
Seizure	0	0	0	1 (3.3)	0	0
Renal and urinary disorders	**1 (0.8)**	**0**	**2 (3.1)**	**0**	**0**	**0**
Respiratory, thoracic and mediastinal disorders	**2 (1.7)**	**3 (5.2)**	**2 (3.1)**	**0**	**1 (2.1)**	**1 (4.0)**
Cough	0	1 (1.7)	1 (1.5)	0	0	1 (4.0)
Pulmonary oedema	0	0	0	0	1 (2.1)	0

System Organ Class Preferred Term[a]	Platinum-resistant		Partially Platinum-sensitive		Platinum-sensitive	
	Rucaparib (N = 119)	Chemotherapy (N = 58)	Rucaparib (N = 65)	Chemotherapy (N = 30)	Rucaparib (N = 48)	Chemotherapy (N = 25)
	n (%)		n (%)		n (%)	
Skin and subcutaneous tissue disorders	**0**	**1 (1.7)**	**1 (1.5)**	**3 (10.0)**	**1 (2.1)**	**0**
Nail disorder	0	0	0	1 (3.3)	0	0
Onycholysis	0	0	0	1 (3.3)	0	0
Rash	0	0	0	1 (3.3)	1 (2.1)	0

Source: Table 17.1.4.
Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; incl = including; TEAE = treatment-emergent adverse event.
[a] A patient is counted only once for a TEAE preferred term if that patient experiences the same TEAE preferred term multiple times.

Assessment of the MAH's response

The MAH was requested to provide comparative safety data by platinum status to better assess the safety profile of rucaparib in a similar patient population to the one covered by the CMA. When comparing the platinum-sensitive and partially platinum-sensitive population versus the platinum resistant subjects, no relevant imbalances have been identified for deaths, SAEs and TEAEs leading to discontinuation or dose modifications. The safety profile of rucaparib in a similar population than the one covered by the therapeutic indication approved by the CMA seem comparable to the overall population included in this study.

Conclusion

Issue solved.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

13. 2nd Request for supplementary information

Major objections

1. The MAH is requested to justify a positive benefit/risk balance in the approved indication in patients with platinum sensitive, relapsed or progressive, BRCA mutated high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, based on data from the ARIEL 4 study. To this end, the following should be provided:

   a) To help contextualising the worrisome OS findings resulting from the OS IA in study ARIEL 4, the MAH is asked to discuss available evidence for the impact on OS of the platinum chemotherapy in the control arm, compared to no treatment.

   b) It is noted that ARIEL 3 study in the maintenance setting is ongoing with a due submission date of the CSR of December 2022. An OS snapshot at full maturity (70% of events) is already expected in May 2022. The MAH is requested to submit those top-line results as soon as available and work actively to deliver a report containing (final) OS results. Any information/report submitted is expected to include OS results for both the ITT population as well as restricted to BRCA mutated patients.

Other concerns

Clinical efficacy

2. In view of the reported OS results in study ARIEL 4 the MAH is asked to discuss:

   a) whether these results have been communicated to other regulatory agencies or in any other forum

   b) whether consideration has already been given to the need to inform healthcare professionals about these worrisome findings, both in relation to the initiation of new treatments, management of patients currently treated with rucaparib and potentially also ongoing clinical trials. In this context, the MAH should submit what they would consider an appropriate communication to HCPs in the format of a DHPC.

3. To clarify the weight of possible imbalances in the baseline demographics and disease characteristics in the (unexpected) reported OS results, the MAH is requested to provide tabular summaries of these baseline demographics and disease characteristics at the time of randomization for three different subgroups of patients: patients randomized to rucaparib, patients randomized to chemotherapy who crossed over to rucaparib after progression and patients from the chemotherapy arm who did not cross over. Data for these 3 subgroups should be included in the same tables for a better comparison.
4. The MAH is requested to provide further information on patients who crossed-over to the rucaparib arm. In this regard, information on who did cross over (and who did not) among patients with disease progression and for which reasons should be submitted.
5. Regarding the supportive analyses adjusting for cross-over, the MAH is referred again to the EMA guidance "Question and answer on adjustment for cross-over in estimating effects in oncology trials (EMA/845963/2018)" and should provide the analysis censoring the data at crossover (method 1 of the guideline) and at least one or two of the proposed methods for handling crossover.
6. The MAH is requested to submit the final analysis for OS and updated PFS2 results when available (REC already proposed). This report should include OS results by platinum sensitivity randomization status. In addition, potential cases of secondary MDS/AML are expected to be presented at the time of this final analysis.

Clinical safety

7. Regarding study ARIEL4, the MAH is requested to provide: i) safety data of intestinal obstruction adjusted by treatment exposure; ii) the narratives of all patients that reported an event of intestinal obstruction during the study.

14. Assessment of the responses to the 2nd request for supplementary information

14.1. Major objections

Question 1

The MAH is requested to justify a positive benefit/risk balance in the approved indication in patients with platinum sensitive, relapsed or progressive, BRCA mutated high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, based on data from the ARIEL 4 study. To this end, the following should be provided:

a) To help contextualising the worrisome OS findings resulting from the OS IA in study ARIEL-4, the MAH is asked to discuss available evidence for the impact on OS of the platinum chemotherapy in the control arm, compared to no treatment.

b) It is noted that ARIEL-3 study in the maintenance setting is ongoing with a due submission date of the CSR of December 2022. An OS snapshot at full maturity (70% of events) is already expected in May 2022. The MAH is requested to submit those top-line results as soon as available and work actively to deliver a report containing (final) OS results. Any information/report submitted is expected to include OS results for both the ITT population as well as restricted to BRCA mutated patients.

Summary of the MAH's response to question 1a)

ARIEL4 evaluated the efficacy and safety of rucaparib versus active, standard-of-care chemotherapy comparators in a very heterogenous ovarian cancer patient population. Patients received ≥ 2 prior lines of chemotherapy had fully platinum-sensitive (FPS), partially platinum-sensitive (PPS), or platinum-resistant disease, and had evidence of a BRCA mutation. Of the patients randomized, 51% had platinum-resistant

disease and 28% had PPS disease; these patients were randomized to receive rucaparib or paclitaxel monotherapy. The remaining 21% of patients had FPS disease and were randomized to receive either rucaparib or investigator-selected platinum monotherapy or platinum doublet, combined with paclitaxel or with gemcitabine.

In support of this response, the MAH is now presenting the top-line final overall survival (OS) and second event of progression-free survival (PFS2) analyses using a data cut-off of 10 April 2022 as shown in Table 1 for the intent-to-treat (ITT) and Efficacy Populations, and also for the platinum-status subgroups. The Kaplan-Meier curves for the Efficacy Population, ITT Population, and the platinum subgroups are presented in Figure 1 to Figure 12 below.

At the time of the final OS analysis, 70% (244/349) of death events had occurred in the ITT Population. The platinum-resistant subgroup was more mature (77.6% [139/179]) than the platinum-sensitive subgroup, which had 61.8% (105/170) OS events and was comprised of the PPS (69.8% [67/96]) and the FPS subgroups (51.4% [38/74]).

The hazard ratio (HR) for OS between rucaparib and chemotherapy patients in the ITT Population of ARIEL4 was 1.31 (95% confidence interval [CI], 1.00-1.73; p = 0.0507) (Table 1). This analysis was heavily confounded by crossover to rucaparib of patients who were initially randomized to be treated with chemotherapy (69% [80/116] patients) and also by the different outcomes in the platinum subgroups.

Outcomes in the Fully Platinum-sensitive Subgroup

At the time of the final OS analysis (cut-off date of 10 April 2022), 51% of death events had occurred in the FPS subgroup. The median OS in the rucaparib arm was 36.3 months versus 47.2 months for the comparator arm (HR 1.24 [95% CI, 0.62-2.50]) (Table 1). The Kaplan-Meier curves are superimposed until the 25-30 month timepoint (Figure 5). At this time, when the curves separated, only 11 patients in the chemotherapy arm remained at risk.

Of these 11 patients, 8 patients (73%) were treated with rucaparib in the Crossover Part; therefore, the data at later timepoints could change and should be interpreted with caution. In the rucaparib arm, 13% of patients (6/48) were still receiving rucaparib treatment. In the comparator arm, 54% of patients (14/26) had progressed and crossed over to receive rucaparib. Table 2 summarizes OS outcomes from Phase 3 randomized clinical trials evaluating platinum-containing regimens in patients with platinum-sensitive, recurrent ovarian cancer. The reported median OS ranges from 17.3 to 33 months. It should be noted that the trials with the longest reported median OS enrolled a majority of second-line patients, whereas ARIEL4 included only patients in third or later-line treatment.

Outcomes in the Partially Platinum-sensitive Subgroup

At the time of the final OS analysis, 70% of death events had occurred in the PPS subgroup.

The median OS in the rucaparib arm was 21.1 months and 23.2 months for the comparator arm (HR 0.97 [95% CI, 0.58-1.62]) (Table 1). In the rucaparib arm, 6.2% (4/65) were still receiving rucaparib treatment. In the comparator arm, 81% (25/31) had progressed and crossed over to receive rucaparib.

Discussion of Outcomes in Platinum-sensitive Subgroups of ARIEL4

At the time of the final OS analysis, the platinum-sensitive subgroups (FPS and PPS combined), 62% of death events had occurred. In the platinum-sensitive population (FPS and PPS), there was no significant difference in OS between patients randomized to the rucaparib versus chemotherapy arm. The median OS was 29.4 months in the rucaparib arm vs 27.6 months in the chemotherapy arm (HR 1.07 [95% CI, 0.71-1.62]; p = 0.7455) (Table 1).

The MAH claims that this result is also consistent with the results from the randomized Phase 3 trial SOLO3, which compared the PARP inhibitor (PARPi) olaparib with chemotherapy in patients with platinum-

sensitive disease, but which did not include a platinum comparator (HR 1.07 [95% CI, 0.76-1.49]). In the SOLO3 trial, a high proportion of patients randomized to comparator also received PARPi as a subsequent line of therapy. The median OS in patients randomized to rucaparib within the platinum-sensitive subgroups of ARIEL4 was also consistent with reported median OS in Phase 3 trials that evaluated platinum-based or paclitaxel treatment in the recurrent setting (Table 2).

Discussion of Outcomes in Platinum-resistant Subgroup of ARIEL4

The difference in OS is driven by the result in platinum-resistant patients, the subgroup whose population is not within the current approved treatment indication for Rubraca.

Although the median OS estimates in the platinum-resistant subgroup are longer in patients randomized to weekly paclitaxel versus rucaparib (22.2 vs 14.2 months), the OS in platinum-resistant patients receiving paclitaxel in ARIEL4 is considerably longer than outcomes reported for paclitaxel in trials of women with platinum resistant ovarian cancer (13.2 to 15.5 months), while the outcomes in the patients randomized to rucaparib are within the range expected with standard-of-care in this setting.

Table 1. ARIEL4 Final OS and PFS2 – All Populations and Subgroups

Population/ Subgroup	Overall Survival				PFS2			
			Rucaparib vs Chemo				Rucaparib vs Chemo	
	Rucaparib	Chemo	Kaplan-Meier Analysis[a]	Cox Proportional Hazard[b]	Rucaparib	Chemo	Kaplan-Meier Analysis[a]	Cox Proportional Hazard[b]
	Event/N (%)	Event/N (%)	Medians Log-rank p-value	HR (95% CI) p-value	Event/N (%)	Event/N (%)	Medians Log-rank p-value	HR (95% CI) p-value
Efficacy	154/220 (70.0)	68/105 (64.8)	21.1 vs 26.2 p = 0.0655	1.31 (0.98, 1.74) p = 0.0704	171/220 (77.7)	91/105 (86.7)	15.5 vs 14.1 p = 0.1904	0.84 (0.65, 1.09) p = 0.1848
ITT	167/233 (71.7)	77/116 (66.4)	19.4 vs 25.4 p = 0.0472	1.31 (1.00, 1.73) p = 0.0507	184/233 (79.0)	102/116 (87.9)	14.7 vs 13.6 p = 0.2332	0.86 (0.67, 1.10) p = 0.2273
Platinum-resistant	95/120 (79.2)	44/59 (74.6)	14.2 vs 22.2 p = 0.0222	1.51 (1.05, 2.17) p = 0.0251	101/120 (84.2)	55/59 (93.2)	11.8 vs 11.5 p = 0.8658	0.97 (0.70, 1.34) p = 0.8450
Platinum-sensitive (Fully + Partially)	72/113 (63.7)	33/57 (57.9)	29.4 vs 27.6 p = 0.7167	1.07 (0.71, 1.62) p = 0.7455	83/113 (73.5)	47/57 (82.5)	19.4 vs 14.2 p = 0.1034	0.74 (0.51, 1.06) p = 0.0996
- Fully Platinum-sensitive	27/48 (56.3)	11/26 (42.3)	36.3 vs 47.2 p = 0.4945	1.24 (0.62, 2.50) p = 0.5405	32/48 (66.7)	18/26 (69.2)	26.9 vs 24.4 p = 0.7187	0.89 (0.49, 1.60) p = 0.6861
- Partially Platinum-sensitive	45/65 (69.2)	22/31 (71.0)	21.1 vs 23.2 p = 0.9469	0.97 (0.58, 1.62) p = 0.9129	51/65 (78.5)	29/31 (93.5)	16.5 vs 13.3 p = 0.0695	0.65 (0.41, 1.03) p = 0.0669

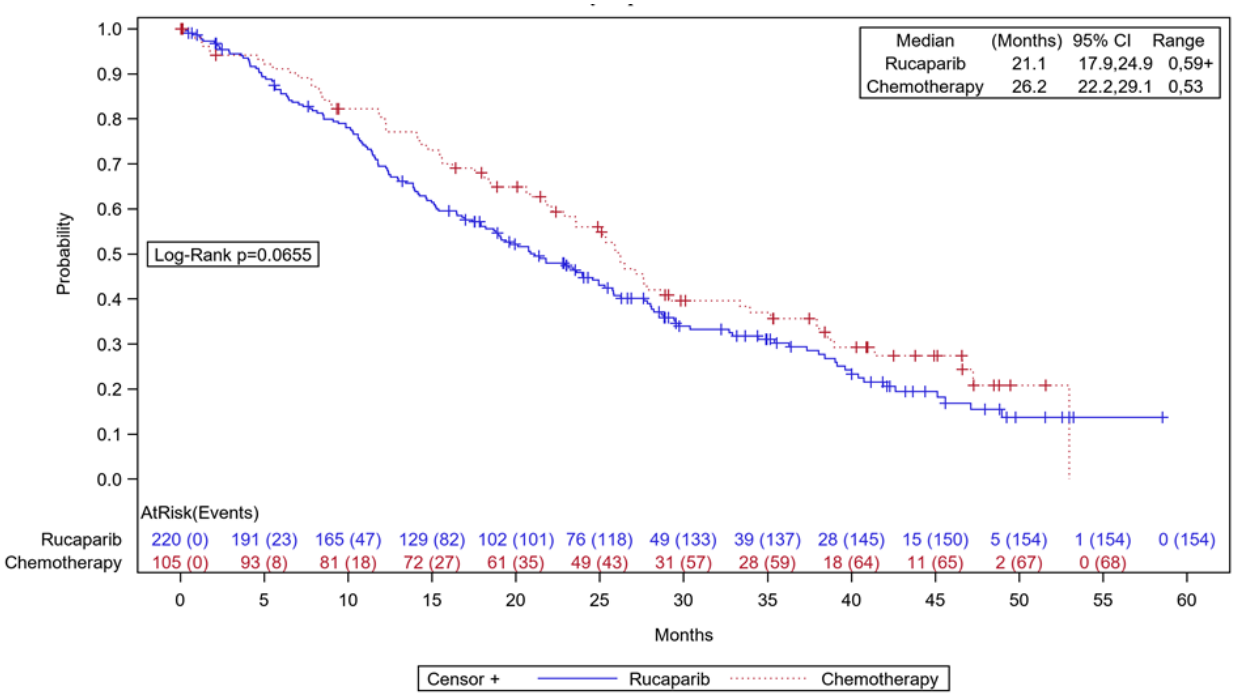
Sources: Tables 14.2.3.1.1, 14.2.3.1.2, 14.2.3.1.3, 14.2.3.4.1, 14.2.3.4.2, 14.2.3.4.5, 14.2.3.4.7, and 14.2.3.99.2; Figures 14.2.3.1.1, 14.2.3.1.2, 14.2.3.1.6, 14.2.3.1.7, 14.2.3.1.8, 14.2.3.4.1, 14.2.3.4.2, 14.2.3.4.8, 14.2.3.4.9, 14.2.3.4.10, 14.2.3.4.11, and 14.2.3.5.1.

Abbreviations: chemo = chemotherapy; CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; OS = overall survival; PFS2 = second event of progression-free survival.

[a] Log-rank analysis performed by randomization strata of platinum status for ITT and Efficacy Populations.

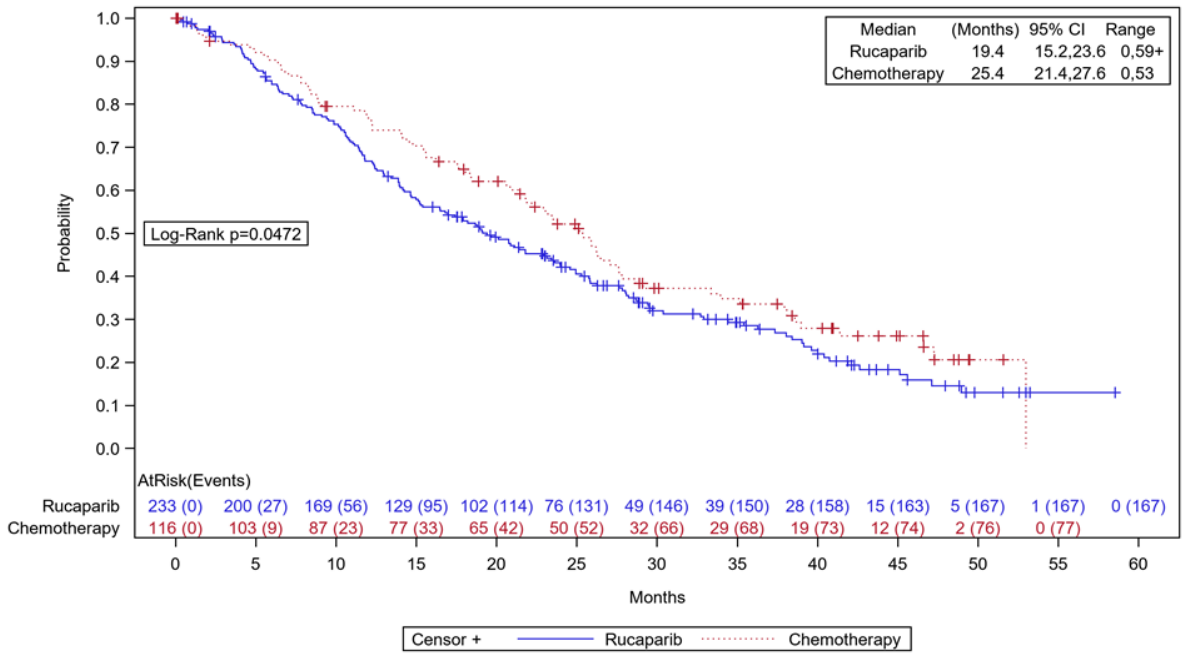
[b] Cox proportional hazard method performed by randomization strata of platinum status for ITT and Efficacy Populations.

Figure 1. ARIEL4 Kaplan-Meier Analysis of OS – Efficacy Population



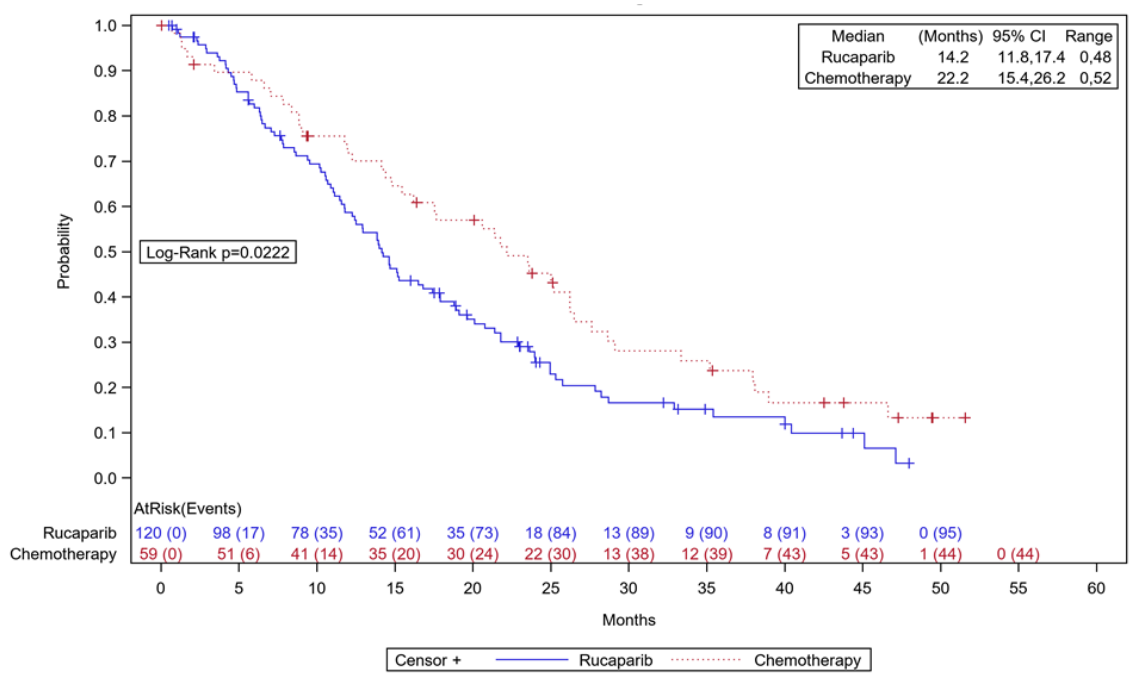
Source: Figure 14.2.3.4.1.
Abbreviations: CI = confidence interval; OS = overall survival.
Note: Log-rank analysis performed by randomization strata of platinum status.

Figure 2. ARIEL4 Kaplan-Meier Analysis of OS – ITT Population



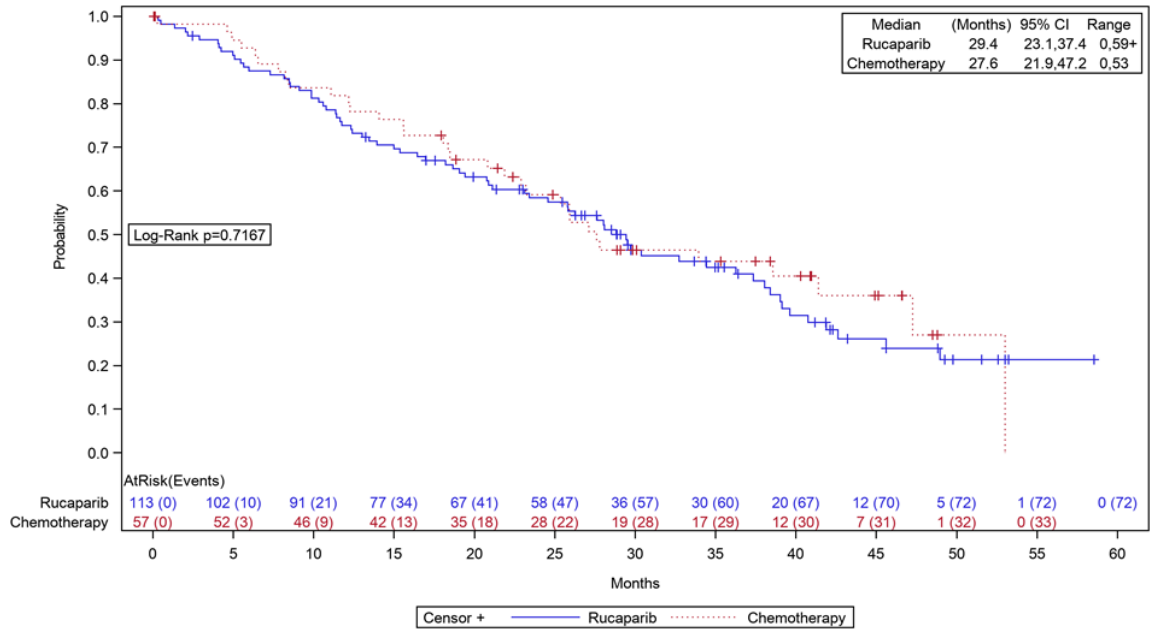
Source: Figure 14.2.3.4.2.
Abbreviations: CI = confidence interval; ITT = intent-to-treat; OS = overall survival.
Note: Log-rank analysis performed by randomization strata of platinum status.

Figure 3. ARIEL4 Kaplan-Meier Analysis of OS – Platinum-resistant Subgroup (ITT Population)



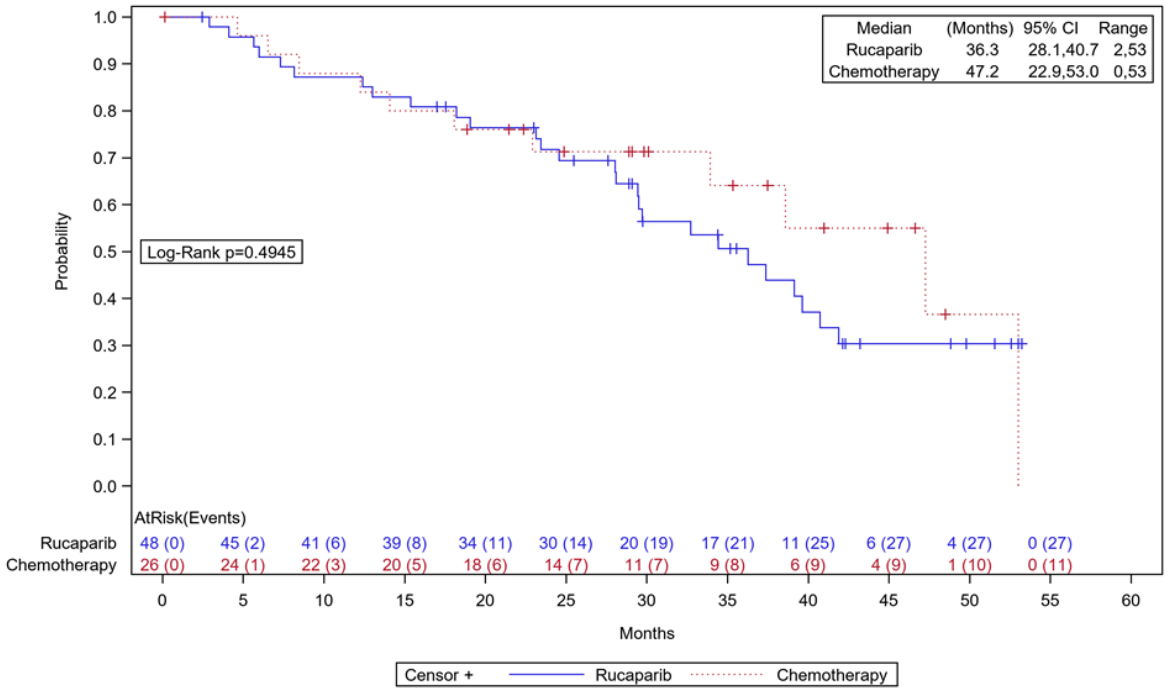
Source: Figure 14.2.3.4.8.
Abbreviations: CI = confidence interval; ITT = intent-to-treat; OS = overall survival.
Note: Log-rank analysis performed by randomization strata of platinum status.

Figure 4. ARIEL4 Kaplan-Meier Analysis of OS – Platinum-sensitive Combined (Fully and Partially) Subgroup (ITT Population)



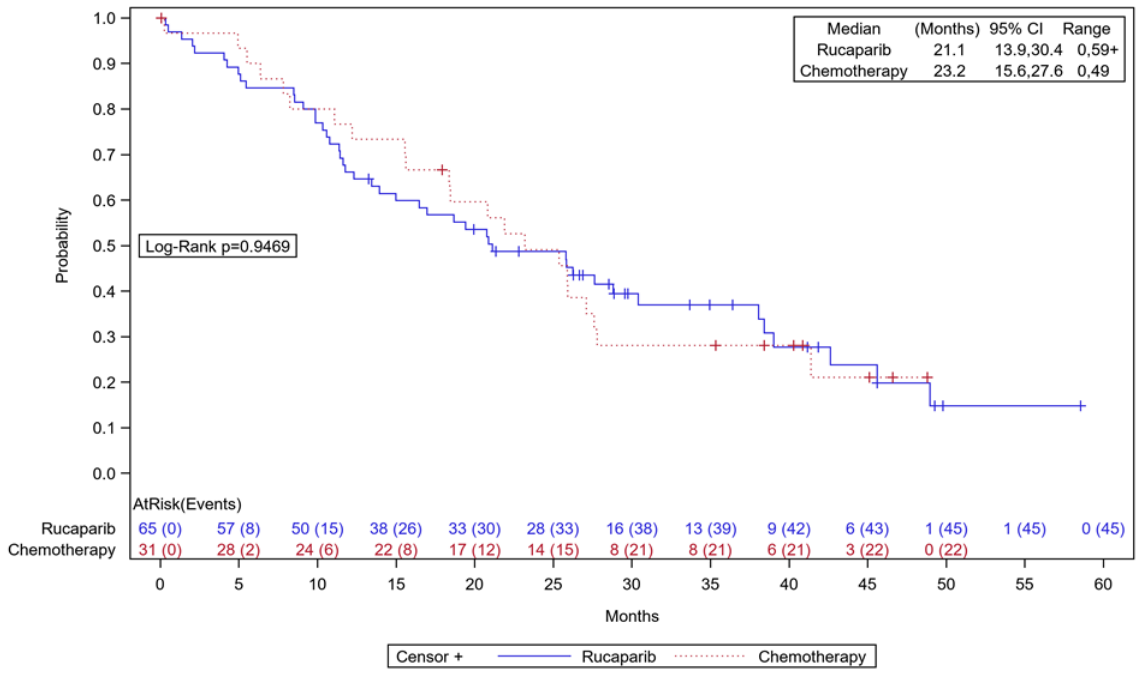
Source: Figure 14.2.3.4.11.
Abbreviations: CI = confidence interval; ITT = intent-to-treat; OS = overall survival.
Note: Log-rank analysis performed by randomization strata of platinum status.

Figure 5. ARIEL4 Kaplan-Meier Analysis of OS – Fully Platinum-sensitive Subgroup (ITT Population)



Source: Figure 14.2.3.4.10.
Abbreviations: CI = confidence interval; ITT = intent-to-treat; OS = overall survival.
Note: Log-rank analysis performed by randomization strata of platinum status.

Figure 6. ARIEL4 Kaplan-Meier Analysis of OS – Partially Platinum-sensitive Subgroup (ITT Population)



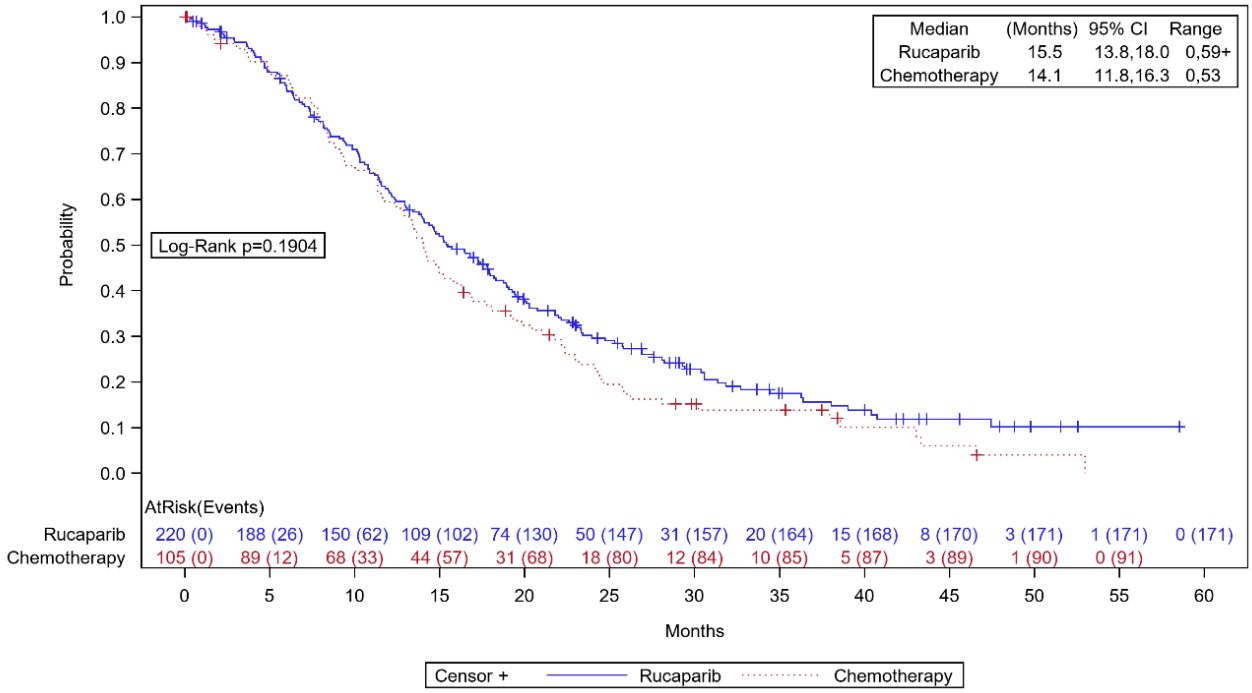
Source: Figure 14.2.3.4.9.
Abbreviations: CI = confidence interval; ITT = intent-to-treat; OS = overall survival.
Note: Log-rank analysis performed by randomization strata of platinum status.

Supportive Analysis: Second Event of Progression-free Survival (PFS2)

PFS2 is the time from randomization until progression on the line of therapy after the first trial therapy. It is accepted as a valid measure of long-term benefit in ovarian cancer and other solid tumors.

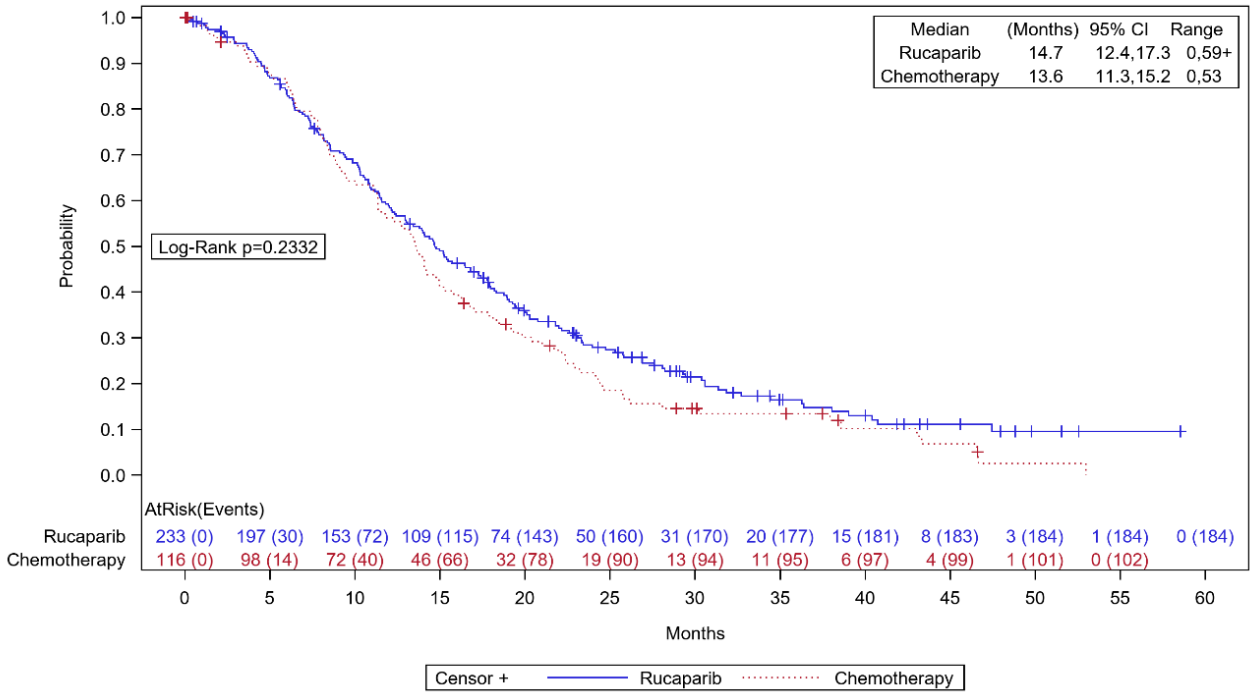
At the time of final analysis, the PFS2 data were 80.6 % (262/325) and 81.9% (286/349) mature in the Efficacy and ITT Populations, respectively. Similar to the interim PFS2 results, there was no significant difference between rucaparib treatment and chemotherapy treatment for PFS2 in either the Efficacy Population or ITT Population in the final analysis.

Figure 7. ARIEL4 Kaplan-Meier Analysis of PFS2 – Efficacy Population



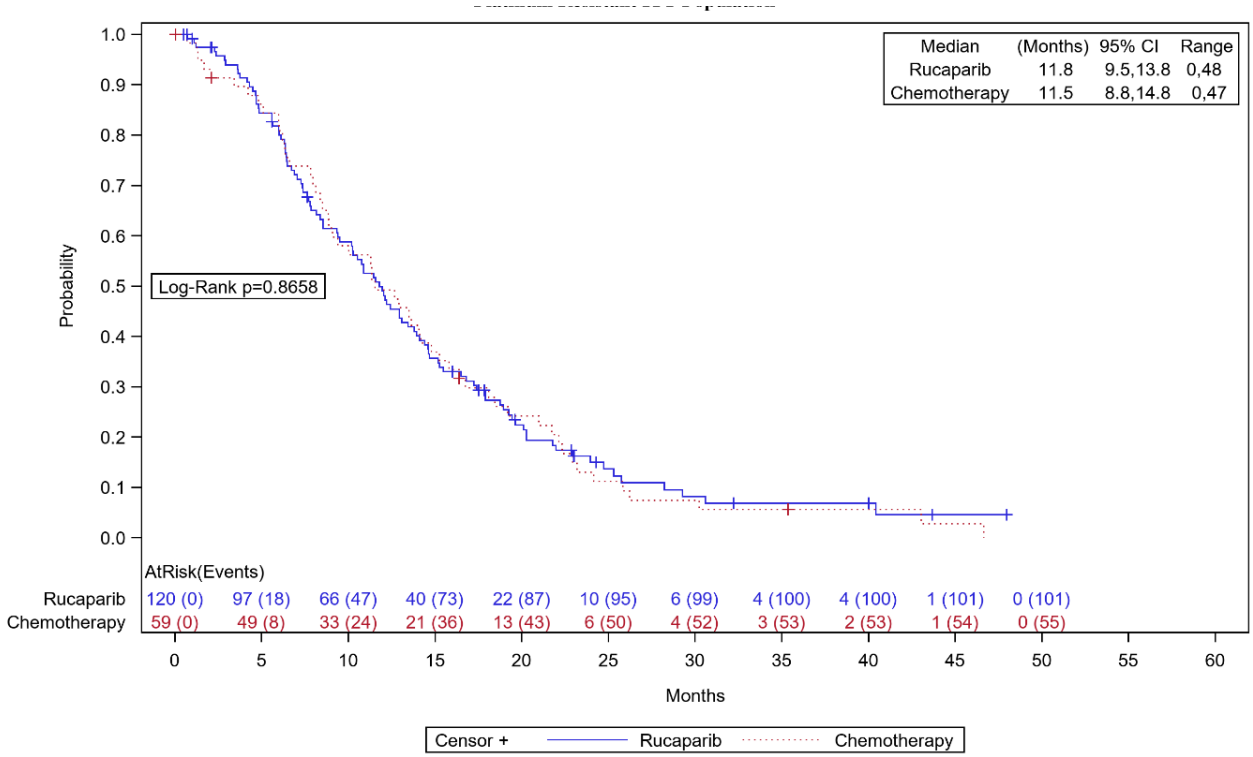
Source: Figure 14.2.3.1.1.
Abbreviations: CI = confidence interval; PFS2 = second event of progression-free survival.
Note: Log-rank analysis performed by randomization strata of platinum status.

Figure 8. ARIEL4 Kaplan-Meier Analysis of PFS2 – ITT Population



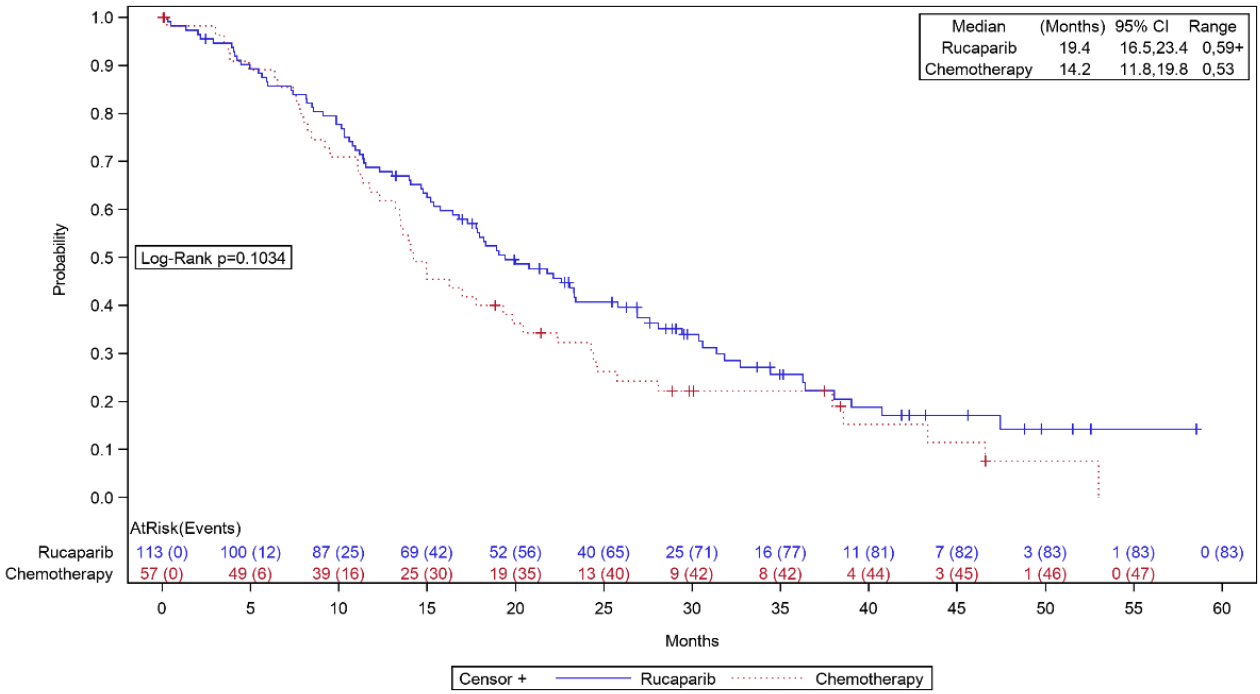
Source: Figure 14.2.3.1.2.
Abbreviations: CI = confidence interval; ITT = intent-to-treat; PFS2 = second event of progression-free survival.
Note: Log-rank analysis performed by randomization strata of platinum status.

Figure 9. ARIEL4 Kaplan-Meier Analysis of PFS2 –Platinum-resistant Subgroup (ITT Population)



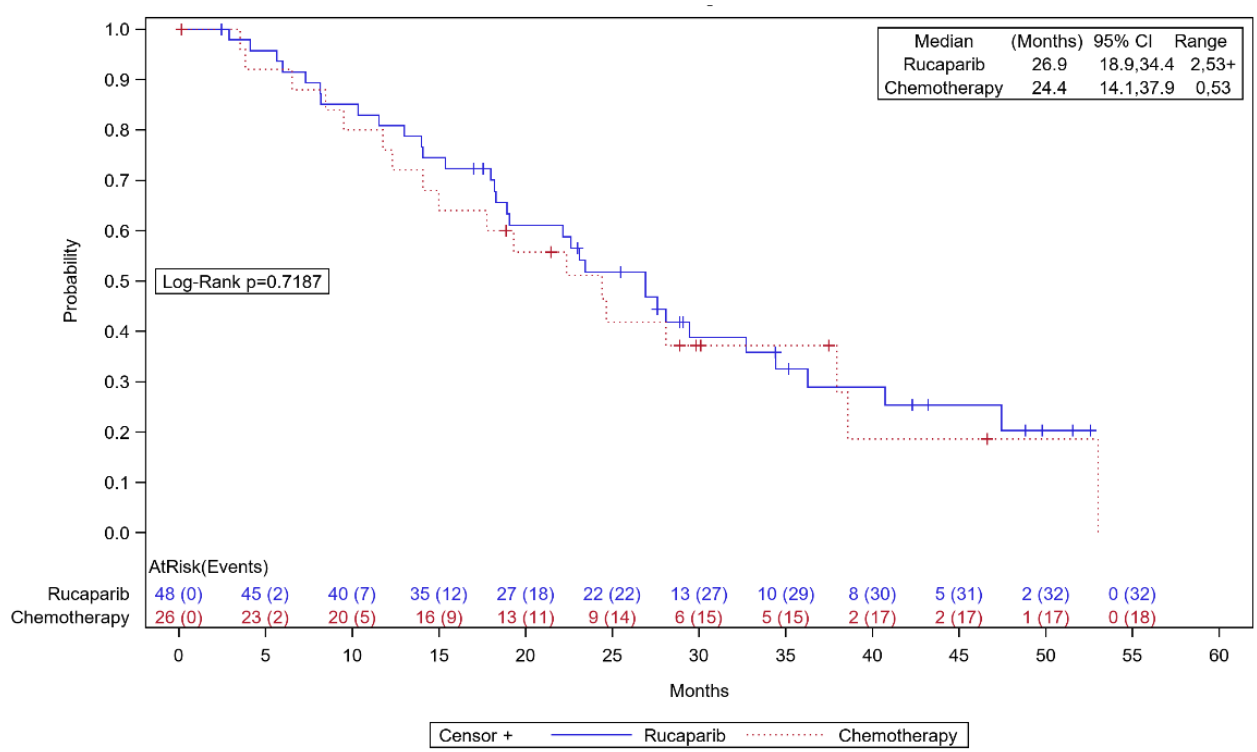
Source: Figure 14.2.3.1.6.
Abbreviations: CI = confidence interval; ITT = intent-to-treat; PFS2 = second event of progression-free survival.
Note: Log-rank analysis performed by randomization strata of platinum status.

Figure 10. ARIEL4 Kaplan-Meier Analysis of PFS2 – Platinum-sensitive Combined (Fully and Partially) Subgroup (ITT Population)



Source: Figure 14.2.3.5.1.
Abbreviations: CI = confidence interval; ITT = intent-to-treat; PFS2 = second event of progression-free survival.
Note: Log-rank analysis performed by randomization strata of platinum status.

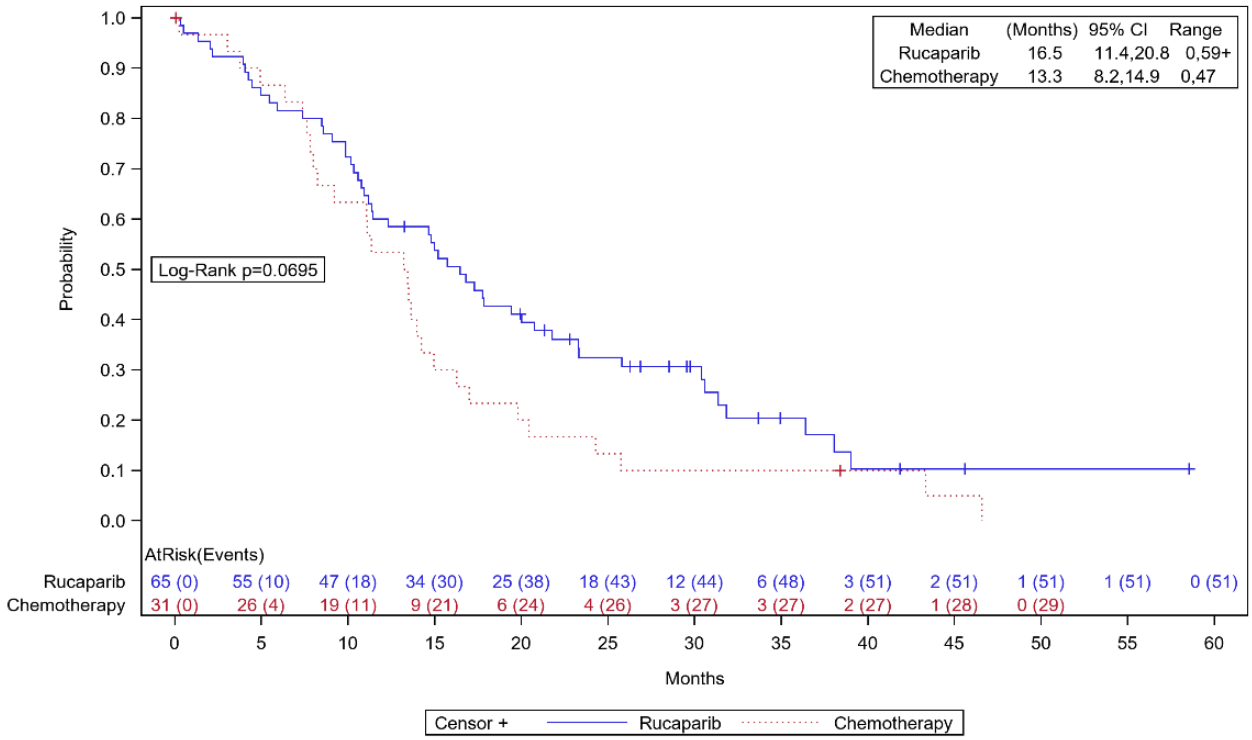
Figure 11. ARIEL4 Kaplan-Meier Analysis of PFS2 – Fully Platinum-sensitive Subgroup (ITT Population)



Source: Figure 14.2.3.1.8.
Abbreviations: CI = confidence interval; ITT = intent-to-treat; PFS2 = second event of progression-free survival.

Note: Log-rank analysis performed by randomization strata of platinum status.

Figure 12. ARIEL4 Kaplan-Meier Analysis of PFS2 – Partially Platinum-sensitive Subgroup (ITT Population)



Source: Figure 14.2.3.1.7.
Abbreviations: CI = confidence interval; ITT = intent-to-treat; PFS2 = second event of progression-free survival.
Note: Log-rank analysis performed by randomization strata of platinum status.

Table 2. Phase 3 Trials Evaluating Paclitaxel or Platinum in Relapsed Ovarian Cancer Patients

Ovarian Cancer Patient Population	Treatments	N	PFS			OS			Author	Year
			Median (months)[a]	HR	p-value	Median (months)[a]	HR	p-value		
Plat-sens, ≤ 2 prior regimens	Carboplatin + PLD	467	11.3	0.823	0.005	30.7	0.99	0.94	Pujade-Lauraine[7]	2010
	Carboplatin + paclitaxel	509	9.4			33.0			Wagner[8]	2012
Plat-sens, 95% received 1 or 2 prior regimens	Paclitaxel + platinum-based chemotherapy	392	12	0.76	0.0004	29	0.82	0.02	Parmar[9]	2003
	Platinum monotherapy (carboplatin or cisplatin)	410	9			24				
Plat-sens, 1 prior platinum	Carboplatin + gemcitabine	178	8.6	0.72	0.0031	18.0	0.96	0.7349	Pfisterer[10]	2006
	Carboplatin	178	5.8			17.3				
Plat-res ± plat-sens, (≤ 12 mo PFI), ≤3 prior chemotherapy regimens	Paclitaxel + trebananib	461	7.2	0.66	< 0.0001	19.0	0.86	0.19	Monk[11]	2014
	Paclitaxel + placebo	458	5.4			17.3				
Plat-res ± plat-sens, ≥ 1 prior plat regimen	Topotecan	112	5.3	0.58	0.0021	14.0	1.21	0.5153	ten Bokkel et al[12]	1997
	Paclitaxel	114	3.2			9.9				
Plat-res ± plat-sens, ≥ 1 prior plat regimen	PLD	107	5	NR	NR	10.5	NR	NR	O'Byrne et al[13]	2002
	Paclitaxel	107	5.2			12.9				
Plat-res ± plat-sens, ≥ 1 prior plat regimen ≤ 12 mo PFI)	Paclitaxel	106	6	1.00	0.96	14	1.17	0.33	Buda et al[14]	2004
	Paclitaxel + epidoxorubicin	106	6			12				
Plat-res, 1 prior regimen	Weekly paclitaxel	30	7	NR	NR	15.5	NR	NR	Osman[3]	2016
	Three weekly paclitaxel	25	4.5			12.5				
Plat-res ≤ 2 prior regimens	Chemotherapy + bevacizumab	179	6.7	0.48	< 0.001	16.6	0.85	< 0.174	Pujade-Lauraine[2]	2014
	Chemotherapy	182	3.4			13.3				
	Paclitaxel + bevacizumab	60	9.2	0.47	NR	22.4	0.64	NR	Bevacizumab SmPC[4] & USPI[5]	Current version
	Paclitaxel	55	3.9		NR	13.2		NR		
	Topotecan + bevacizumab	57	6.2	0.28	NR	13.8	1.07	NR		
	Topotecan	63	2.1		NR	13.3		NR		
	PLD + bevacizumab	62	5.1	0.53	NR	13.7	0.91	NR		
	PLD	64	3.5		NR	14.1		NR		

Abbreviations: HR = hazard ratio; mo = month(s); NR = not reported; OS = overall survival; PFI = progression-free interval; PFS = progression-free survival; plat = platinum; plat-res = platinum-resistant; plat-sens = platinum-sensitive; PLD = pegylated liposomal doxorubicin; SmPC = Summary of Product Characteristics; USPI = United States Prescribing Information.

[a] Where applicable, PFS and OS reported out in weeks were converted to months using the following formula: month = weeks/4.34812.

Conclusion

ARIEL4 included a broad spectrum of ovarian cancer patients with platinum sensitive or platinum resistant disease. Within the platinum sensitive group, those with PPS disease were randomized to rucaparib or paclitaxel, and those with FPS disease were randomized to rucaparib or a platinum regimen.

Although the HR has improved in the final OS analysis from the interim analysis, in the overall trial population, the HR continues to favor the group originally randomized to chemotherapy with many also crossing over to receive rucaparib. However, the results between the platinum subgroups differ markedly. When considering the EMA approved indication, this is important, because the approved indication only applies to patients with platinum-sensitive disease who can no longer tolerate further platinum.

In the analysis of all platinum-sensitive patients in ARIEL4, PFS2 favors rucaparib, and the median OS is longer for rucaparib as compared to chemotherapy (29.4 months vs 27.6 months; HR 1.07 [95% CI, 0.71-1.62]; p = 0.746). These results are strikingly similar to those reported for another PARPi in the SOLO3 randomized Phase 3 trial which evaluated olaparib vs chemotherapy in platinum-sensitive patients harboring a BRCA mutation but which did not include platinum as a comparator (HR 1.07 [95% CI, 0.76-1.49]; p = 0.714).

As in ARIEL4, the primary endpoint in SOLO3 was PFS. Taken together, the results from ARIEL4 and SOLO3 suggest a beneficial effect of PARPi treatment with no decrement in OS in the overall platinum-sensitive population.

As part of the CMA approval, the CHMP agreed (as per Rapporteurs Day 180 Joint [4th RSI] CHMP and PRAC Response Assessment Report) that within ARIEL4, the PPS subgroup is directly relevant to the approved indication. In this subgroup, the comparator chemotherapy was non-platinum (ie, weekly paclitaxel), representing an active standard of care that is routinely used in platinum-sensitive patients who are unable to tolerate further chemotherapy.

Importantly, in that PPS subgroup, without making any adjustments for the confounding effects of the high rate of crossover, all efficacy endpoints (including the primary endpoint of PFS, the longer-term benefit endpoint of PFS2, and the OS endpoint) support a positive benefit:risk of rucaparib for monotherapy treatment of adult patients with platinum-sensitive, relapsed or progressive, BRCA-mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum based chemotherapy, and who are unable to tolerate further platinum based chemotherapy.

This response provides a summary of the top-line final OS dataset. Further analyses are ongoing. These include additional statistical modeling using EMA-recommended methodology to account for the effects of crossover, and a detailed analysis of treatments received after rucaparib, to understand the potential effects of treatment sequencing when PARPi are integrated into the ovarian cancer treatment paradigm.

Summary of the MAH's response to question 1b)

The **ARIEL3** OS data have reached sufficient maturity and the MAH is therefore providing the topline OS results in response to this question.

Topline analyses using a data cut-off of 04 April 2022 showed no difference in OS between rucaparib and placebo in the intent-to-treat (ITT) Population (72.7% maturity; HR 0.995, 95% CI, 0.809-1.223, p = 0.9621) or the homologous recombination deficiency (HRD) Population (68.9% maturity; HR 1.005, 95% CI, 0.766-1.320, p = 0.9693) (Table 3). A non-statistically significant trend towards improvement was observed in the tBRCA Population (66.3% maturity: HR 0.832, 95% CI, 0.581-1.192, p = 0.3162) (Table 3). Kaplan-Meier analyses of OS between rucaparib and placebo patients are presented for the tBRCA Population in Figure 13, for the HRD Population in Figure 14 and in the ITT Population in Figure 15.

A confounding factor with respect to the above results is that the patients who are still alive have been treated with multiple subsequent regimens of anticancer treatment following the randomized treatment received in ARIEL3. A summary of the overall number of lines of subsequent anticancer treatments and the time from randomization to start of subsequent line of anticancer treatment for the analysis populations are presented in Table 4 and Table 5, respectively. The median number of subsequent treatment regimens was 3 (range 1-10). Overall, of the patients in the ITT Population who went on to receive subsequent treatment, 30% (138/461) received a PARP inhibitor (Table 4).

In ARIEL3, 89% (168/189) of patients randomized to placebo received at least one subsequent anticancer regimen and out of the patients that received subsequent therapy, 46% of patients (77/168) received subsequent treatment with a PARP inhibitor, including 72% of patients (43/60) and 59% of patients (62/105) in the tBRCA and HRD populations, respectively (Table 6). The frequency of subsequent PARPi usage was higher than reported in trials of other PARP inhibitors, and likely resulted from the widespread availability of marketed PARPi at the time ARIEL3 participants were candidates for subsequent treatment lines. The majority of patients received a single subsequent treatment containing a PARP inhibitor, but 5% (8/168) of patients in the ITT Population received 2 or 3 subsequent regimens containing a PARP inhibitor; this was more frequent in the tBRCA population (10% [6/60]) (Table 6).

To understand the time that subsequent PARP inhibitor therapies were received, analyses were performed to evaluate the median time to first subsequent PARP inhibitor therapy relative to randomization date into placebo treatment on study, as well as the median duration of subsequent PARP inhibitor therapy given to these placebo patients. In the 77 patients randomized to placebo who received treatment with subsequent PARP inhibitors, the median time to first subsequent PARP inhibitor treatment was 14.1months (95% CI, 11.6, 16.7) in the tBRCA Population, 15.8 months (95% CI 13.4, 20.8) in the HRD Population, and 16.8 months (95% CI, 14.1, 21.0) in the ITT Population (Table 7).

The median duration of first PARPi usage was similar across the populations and ranged from 11.5 months (95% CI, 8.6, 16.5) in the ITT Population to 13.8 months (95% CI, 8.6, 16.9) in the tBRCA

Population (Table 8). The duration of PARPi usage is longer than the duration of placebo usage in the ARIEL3 trial (median duration of 5.5 months in the ITT Population) and suggests that the patients experienced beneficial effects of the PARPi when given in a subsequent line of therapy.

In placebo patients in the ITT Population treated with subsequent lines of treatment, the subsequent PARPi therapy was primarily administered with the first (23.8% [40/168] of patients), second (21.6% [29/134] of patients), and third (16.5% [16/97] of patients) subsequent treatments, with more limited usage in the fourth (7.4% [5/68] of patients) and fifth (4.3% [2/46] of patients) subsequent treatments (Table 9).

Conclusion

The results provide additional confirmation of the positive benefit:risk of rucaparib in recurrent ovarian cancer even with the high proportion of patients in the ARIEL3 placebo arm who went on to receive a PARPi as a subsequent treatment with a beneficial outcome. An ARIEL3 CSR Addendum, which will include OS and updated safety will be provided to the EMA in 3Q2022.

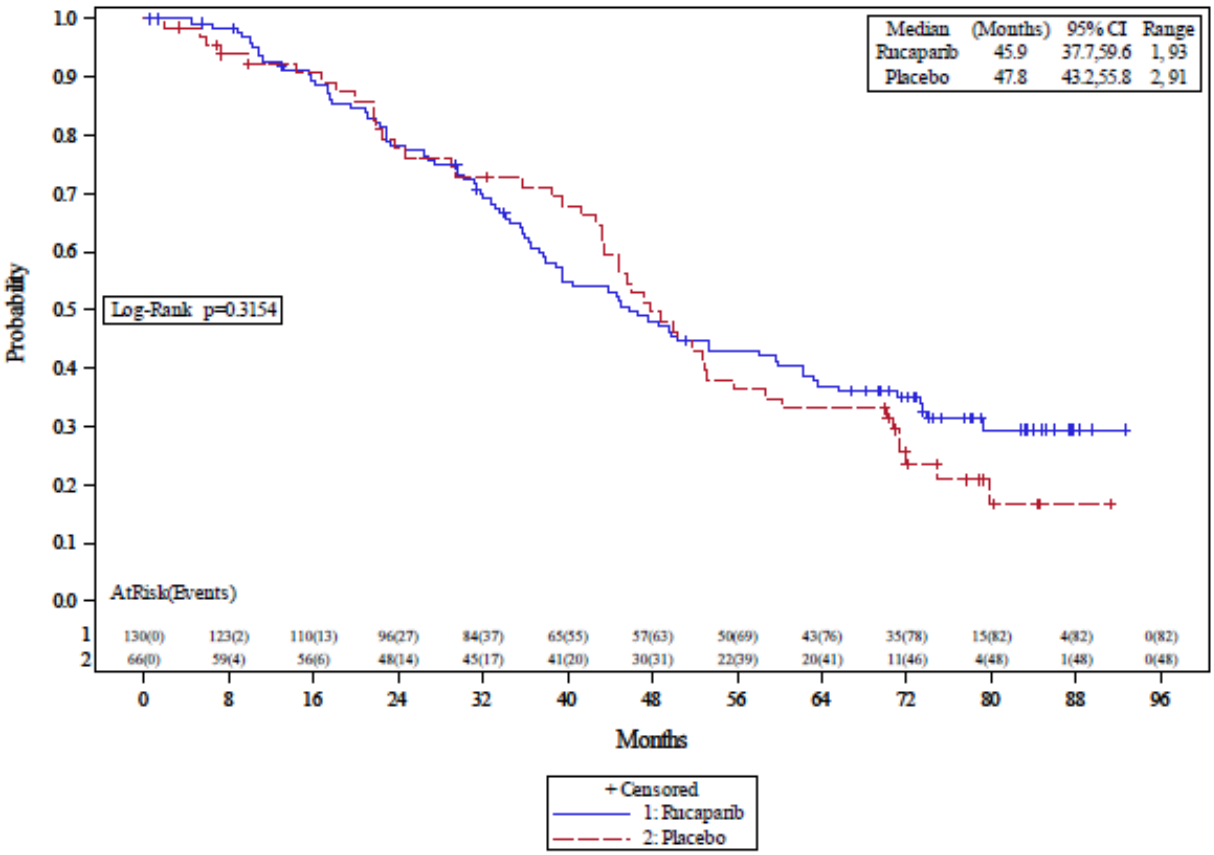
Table 3. ARIEL3 Overall Survival – All Populations

Analysis	Hazard Ratio	95% Confidence Interval	P-value
tBRCA Population[a]: Rucaparib vs Placebo	0.832	0.581, 1.192	0.3162
HRD Population[b]: Rucaparib vs Placebo	1.005	0.766, 1.320	0.9693
ITT Population[b]: Rucaparib vs Placebo	0.995	0.809, 1.223	0.9621

Source: Table 14.2.1.2.11 ARIEL3 topline output.

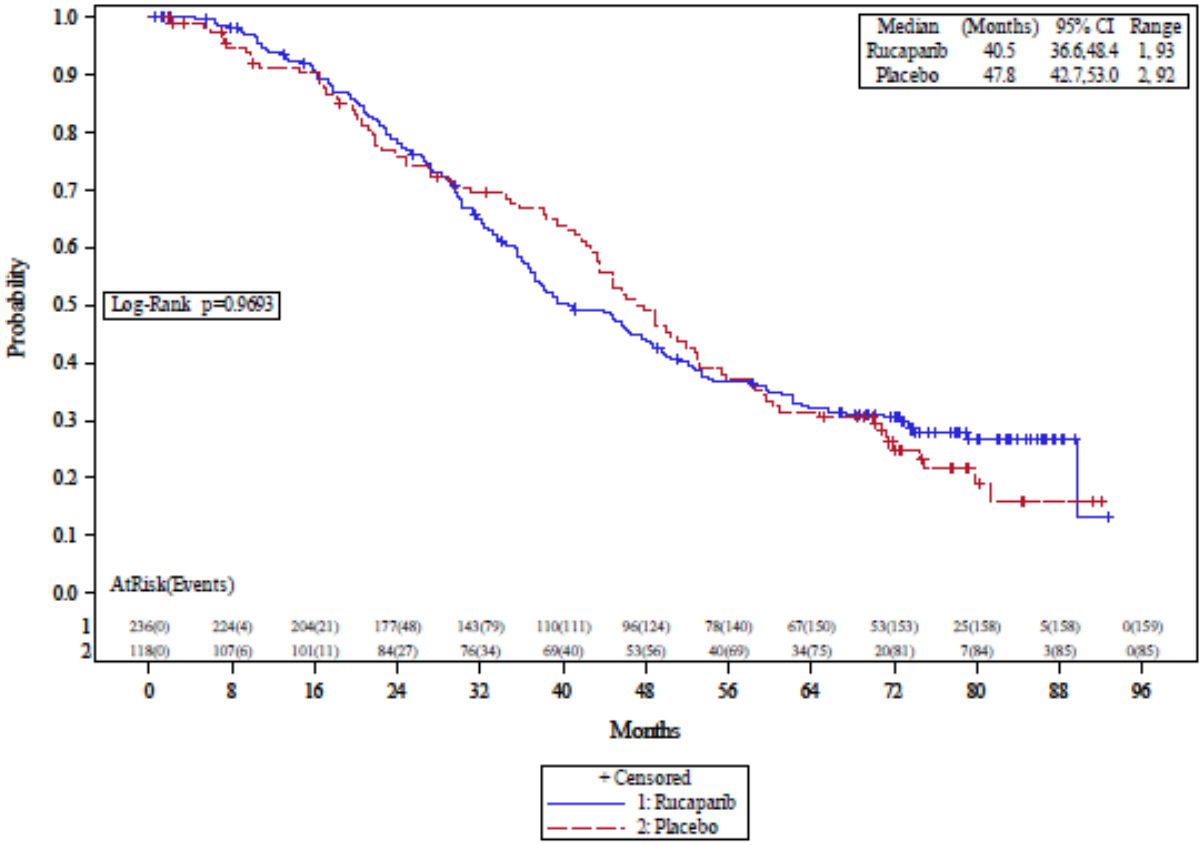
Abbreviations: BRCA1 = BRCA1 DNA repair associated; BRCA2 = BRCA2 DNA repair associated; CTA = clinical trial assay; DNA = deoxyribonucleic acid; gBRCA = germline BRCA; HRD = homologous recombination deficiency; ITT = intent-to-treat; PFI = progression-free interval; sBRCA = somatic BRCA; tBRCA = tumor tissue mutation in BRCA1 or BRCA2, includes gBRCA and sBRCA.
a For tBRCA Population, the analysis is performed by randomization strata of best response and penultimate platinum PFI.
b For the HRD Population and ITT Population, analysis is performed by randomization strata of HRD classification by the CTA, best response, and penultimate PFI.

Figure 13. ARIEL3 Kaplan-Meier Analysis of Exploratory Endpoint: Overall Survival – tBRCA Population



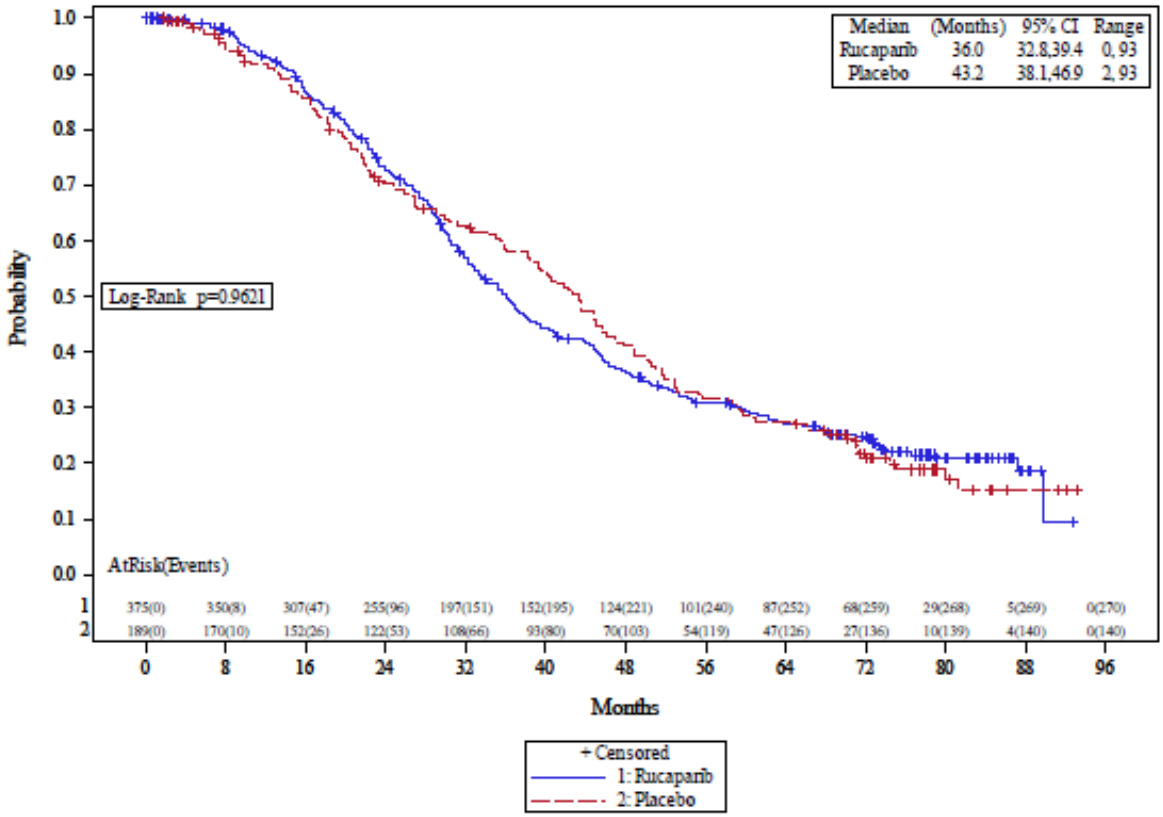
Source: Figure 14.2.6.1 in ARIEL3 topline output.
Abbreviations: CI = confidence interval; BRCA1 = BRCA1 DNA repair associated; BRCA2 = BRCA2 DNA repair associated; DNA = deoxyribonucleic acid; gBRCA = germline BRCA; sBRCA = somatic BRCA; tBRCA = tumor tissue mutation in BRCA1 or BRCA2, includes gBRCA and sBRCA.
Note: Log-rank analysis performed by randomization strata for best response and penultimate platinum progression-free interval.

Figure 14. ARIEL3 Kaplan-Meier Analysis of Exploratory Endpoint: Overall Survival – HRD Population



Source: Figure 14.2.6.2 in ARIEL3 topline output.
Abbreviations: CI = confidence interval; BRCA1 = BRCA1 DNA repair associated; BRCA2 = BRCA2 DNA repair associated; CTA = clinical trial assay; DNA = deoxyribonucleic acid; gBRCA = germline BRCA; HRD = homologous recombination deficiency; sBRCA = somatic BRCA; tBRCA = tumor tissue mutation in BRCA1 or BRCA2, includes gBRCA and sBRCA.
Note: Log-rank analysis performed by randomization strata for HRD classification by CTA, best response, and penultimate platinum progression-free interval.

Figure 15. ARIEL3 Kaplan-Meier Analysis of Exploratory Endpoint: Overall Survival – ITT Population



Source: Figure 14.2.6.3 in ARIEL3 topline output.
Abbreviations: CI = confidence interval; BRCA1 = BRCA1 DNA repair associated; BRCA2 = BRCA2 DNA repair associated; CTA = clinical trial assay; DNA = deoxyribonucleic acid; gBRCA = germline BRCA; HRD = homologous recombination deficiency; sBRCA = somatic BRCA; tBRCA = tumor tissue mutation in BRCA1 or BRCA2, includes gBRCA and sBRCA.
Note: Log-rank analysis performed by randomization strata for HRD classification by CTA, best response, and penultimate platinum progression-free interval

Table 4. Summary of Subsequent Treatment

	tBRCA		HRD		ITT	
	Rucaparib (n=130)	Placebo (n=66)	Rucaparib (n=236)	Placebo (n=118)	Rucaparib (n=375)	Placebo (n=189)
Median PFS (months)	16.6	5.4	13.6	5.4	10.8	5.4
Continuing on randomized treatment (April 2022)	7	0	14	0	15	0
Started at least 1 subsequent line	94/123 (76.4%)	60 (90.9%)	180/222 (81.1%)	105 (89.0%)	293/360 (81.4%)	168 (88.9%)
Number of lines[a]						
1	21 (22.3%)	14 (23.3%)	36 (20.0%)	20 (19.0%)	56 (19.1%)	34 (20.2%)
2	29 (30.9%)	10 (16.7%)	47 (26.1%)	20 (19.0%)	76 (25.9%)	37 (22.0%)
3	17 (18.1%)	8 (13.3%)	34 (18.9%)	18 (17.1%)	60 (20.5%)	29 (17.3%)
4	13 (13.8%)	7 (11.7%)	31 (17.2%)	14 (13.3%)	44 (15.0%)	22 (13.1%)
> 4	14 (14.9%)	21 (35.0%)	32 (17.8%)	33 (31.4%)	57 (19.5%)	46 (27.4%)
Median (Range)	2 (1,8)	3 (1,8)	3 (1,8)	3 (1,8)	3 (1,10)	3 (1,8)
Started at least one subsequent PARP inhibitor	32 (34.0%)	43 (71.7%)	49 (27.2%)	62 (59.0%)	61 (20.8%)	77 (45.8%)

Sources: Table 1.1.1 (t-sat-ovr-tbrca), 1.1.2 (t-sat-ovr-hrd)., and 1.1.3 (t-sat-ovr-itt), Tables 1.1.1 (t-sat-parpany-itt), 1.1.2 (t-sat-parp-any-hrd), and 1.1.3 (t-sat-parp-any-tbrca), and Figures 14.2.1.1.1, 14.2.1.1.2, and 14.2.1.1.3.
Abbreviations: BRCA = breast cancer gene; HRD = homologous recombination deficiency; ITT = intent-to-treat; PFS = progression-free survival; tBRCA = tumor tissue mutation in BRCA1 or BRCA2, incudes gBRCA and sBRCA.
a Denominator includes patients with at least one regimen of subsequent therapy for ovarian cancer entered by data cutoff that was 04 April 2022.

Table 5. Summary of Time to Start of each Subsequent Treatment

	tBRCA		HRD		ITT	
	Rucaparib (n=130)	Placebo (n=66)	Rucaparib (n=236)	Placebo (n=118)	Rucaparib (n=375)	Placebo (n=189)
Time to start of each subsequent line, Median in months (95% CI) [a]						
First	18.7 (15.9, 24.3)	7.2 (5.5, 9.1)	15.9 (12.4, 18.0)	7.4 (6.5, 9.1)	12.3 (11.0, 15.0)	7.2 (6.4, 8.6)
Second	28.7 (23.8, 34.2)	19.4 (16.7, 24.8)	24.8 (22.2, 27.9)	19.4 (16.7, 22.2)	21.5 (19.0, 23.9)	17.7 (15.7, 19.5)
Third	37.3 (32.0, 45.0)	30.4 (24.7, 36.4)	32.8 (27.7, 36.8)	29.3 (24.8, 35.5)	27.7 (25.4, 30.3)	26.4 (23.6, 29.6)
Fourth	40.5 (33.6, 50.4)	38.0 (26.5, 48.5)	36.0 (32.9, 41.2)	38.0 (31.1, 45.1)	32.0 (29.6, 34.8)	32.6 (27.9, 36.4)

Sources: Figures 1.3.1, 1.3.2, 1.3.3, 1.4.1, 1.4.2, 1.4.3, 1.5.1, 1.5.2, 1.5.3, 1.6.1, 1.6.2, and 1.6.3.
Abbreviations: BRCA = breast cancer gene; CI = confidence interval; HRD = homologous recombination deficiency; ITT = intent-to-treat; tBRCA = tumor tissue mutation in BRCA1 or BRCA2, incudes gBRCA and sBRCA.
a Kaplan-Meier Methodology used with an event at the start of each treatment and patients without starting respective treatment is censored at last visit.

Table 6. Subsequent PARP Inhibitor Treatment in Patients Randomized to Placebo in ARIEL3 by HRD Subgroup

	ARIEL3 Placebo		
	t-BRCA n = 66	HRD n = 118	ITT n = 189
Number of Patients With At Least One Subsequent Therapy for Ovarian Cancer	60 (90.9%)	105 (89.0%)	168 (88.9%)
Total Number of Patients Who Received 1 or More Subsequent PARP Inhibitor Containing Regimen(s)	43 (72%)	62 (59%)	77 (46%)
Number of Patients Who Received 2 Subsequent PARP Inhibitor Containing Regimens	3 (5%)	4 (4%)	5 (3%)
Number of Patients Who Received 3 Subsequent PARP Inhibitor Containing Regimens	3 (5%)	3 (3%)	3 (2%)

Sources: Tables 1.1.1, 1.1.2, 1.1.3.
Abbreviations: BRCA = breast cancer gene; HRD = homologous recombination deficiency; ITT = intent to treat; tBRCA = tumor tissue mutation in BRCA1 or BRCA2, incudes gBRCA and sBRCA.

Table 7. Summary of Median time in Months to First Subsequent PARP Inhibitor Use from Date of Randomization to Placebo

	Placebo
tBRCA Population	
Number of Patients with Subsequent PARPi	43
Time to Start of First PARP Inhibitor, Median (95% CI)	14.1 (11.6, 16.7)
HRD Population	
Number of Patients with Subsequent PARP Inhibitor	62
Time to Start of First PARP Inhibitor, Median (95% CI)	15.8 (13.4, 20.8)
ITT Population	
Number of Patients	77
Time to Start of First PARP Inhibitor, Median (95% CI)	16.8 (14.1, 21.0)

Source: Table 1.3.1.
Abbreviations: BRCA = breast cancer gene; CI = confidence interval; HRD = homologous recombination deficiency; ITT = intent to treat; PARPi = PARP inhibitor; tBRCA = tumor tissue mutation in BRCA1 or BRCA2, incudes gBRCA and sBRCA.

Table 8. Summary of PARP Inhibitor Duration in Months During Subsequent Anticancer Regimen - Patients Randomized to Placebo

	Placebo
tBRCA Population	
Number of Patients with Subsequent PARP Inhibitor	43
First subsequent PARPi duration, Median (95% CI)	13.8 (8.6, 16.9)
Total PARP Inhibitor duration (if > 1 regimen received), Median (95% CI)	16.6 (11.1, 20.3)
HRD Population	
Number of Patients with Subsequent PARP Inhibitor	62
First subsequent PARPi duration, Median (95% CI)	12.9 (8.6, 16.9)
Total PARP Inhibitor duration (if > 1 regimen received), Median (95% CI)	16.5 (9.5, 20.3)
ITT Population	
Number of Patients with Subsequent PARP Inhibitor	77
First subsequent PARPi duration, Median (95% CI)	11.5 (8.6, 16.5)
Total PARP Inhibitor duration (if > 1 regimen received), Median (95% CI)	15.9 (9.0, 19.3)

Sources: Table 1.4.1.
Abbreviations: BRCA = breast cancer gene; CI = confidence interval; HRD = homologous recombination deficiency; ITT = intent to treat; PARPi = PARP inhibitor; tBRCA = tumor tissue mutation in BRCA1 or BRCA2, incudes gBRCA and sBRCA.

Table 9. PARP Inhibitor Usage by Timing of Subsequent Treatment -

Patients Randomized to Placebo

	Placebo[a]
tBRCA Population, with subsequent treatment	
First Subsequent Treatment	25/60 (41.7%)
Second Subsequent Treatment	19/46 (41.3%)
Third Subsequent Treatment	9/36 (25.0%)
Fourth Subsequent Treatment	2/28 (7.1%)
Fifth Subsequent Treatment	1/21 (4.8%)
HRD Population, with subsequent treatment	
First Subsequent Treatment	35/105 (33.3%)
Second Subsequent Treatment	24/85 (28.2%)
Third Subsequent Treatment	13/65 (20.0%)
Fourth Subsequent Treatment	3/47 (6.4%)
Fifth Subsequent Treatment	2/33 (6.1%)
ITT Population, with subsequent treatment	
First Subsequent Treatment	40/168 (23.8%)
Second Subsequent Treatment	29/134 (21.6%)
Third Subsequent Treatment	16/97 (16.5%)
Fourth Subsequent Treatment	5/68 (7.4%)
Fifth Subsequent Treatment	2/46 (4.3%)

Sources: Table 1.2.1.
Abbreviations: BRCA = breast cancer gene; HRD = homologous recombination deficiency; ITT = intent to treat; tBRCA = tumor tissue mutation in BRCA1 or BRCA2, incudes gBRCA and sBRCA.
a Denominator is the number of patients who started each subsequent treatment.

Assessment of the MAH's response

a. The final OS analysis from study ARIEL4 (DCO 10 April 2022) showed results consistent with the IA. In the ITT population a detrimental effect in OS is observed with rucaparib over chemotherapy, although

with a lower HR (HR 1.31; 95% CI: 1.00, 1.73). Similar results were observed in the efficacy population (HR 1.31; 95% CI: 0.98, 1.74). Study ARIEL4 included a heterogeneous patient population, i.e. not only platinum sensitive patients (i.e. fully platinum sensitive and partially platinum sensitive patients), but also platinum resistant patients, all of them BRCA mutated. Further, the comparator arm could be paclitaxel (for those resistant and partially platinum sensitive) or platinum therapy (for the subgroup of fully platinum sensitive patients). The MAH argues that the (detrimental) effect is driven by the results in platinum-resistant patients and the fact that results in patients receiving paclitaxel in the ARIEL4 study are longer than those reported in other trials in patients with platinum-resistant ovarian cancer. The latter is however difficult to ascertain and may be due to differences in baseline characteristics of the patient population. Further, according to the summary of results from available trials in this treatment setting submitted by the MAH (see table 2 above that provides OS outcomes from phase 3 randomised clinical trials evaluating platinum-containing regimens in patients with platinum-sensitive, recurrent ovarian cancer), the impact of platinum based chemotherapy on OS is not really known / established. In addition, the argumentation by the MAH that the observed detrimental effect could be explained by crossover is not supported (see question 5).

The MAH asserts that in the subgroup of partially-platinum sensitive (PPS) patients (n=96), which represents approximately 28% of the patient population both PFS (HR 0.41; 95% CI: 0.256, 0.659), primary endpoint, and PFS2 (HR 0.65; 95% CI: 0.41, 1.03) favoured the rucaparib arm, with no detrimental effect in OS (HR 0.97; 95% CI: 0.58, 1.62). With regards to the (post-hoc) 'pooled' subgroup of platinum-sensitive patients the MAH states that no significant differences were observed (HR 1.07; 95% CI: 0.71, 1.62), but without a detriment in OS, showing therefore the beneficial effect. Further, the MAH also argues that these results are in line with those of the SOLO3 trial, a Phase 3 study of olaparib versus non-platinum chemotherapy in a similar patient population of platinum sensitive patients.

It is acknowledged that the effect might partially be driven by the subgroup of platinum-resistant patients, which represents 51% of the patient population, where the reported detrimental effect appears clearer (HR 1.51; 95% CI: 1.05, 2.17) and that in the context of the approved indication (i.e. platinum sensitive, relapsed or progressive, BRCA mutated patients who are unable to tolerate further platinum-based chemotherapy), the subgroup of patients platinum sensitive (particularly those partially sensitive), represent the most relevant population to confirm the B/R balance of rucaparib in the treatment indication. However, and albeit the limitations to extract definitive conclusions from subgroups' data, in the platinum sensitive populations, either pooled or separate, OS results are also not reassuring, particularly in fully platinum sensitive patients. Importantly, no specific discussion has been provided by the MAH for the results observed in platinum resistant patients. This is considered a limitation since in the absence of further justification why the detrimental effect on OS should be understood as related/linked (specifically) to platinum resistant disease it is difficult to disregard such findings when considering the results reported in other subgroups, as discussed above.

b. The MAH has provided topline results of more mature OS analysis from the ARIEL3 study, a Phase 3, double-blind study of rucaparib versus placebo in patients with advanced platinum-sensitive high-grade serous ovarian cancer who had received 2 or more previous platinum-based chemotherapy and which was the basis for the approval or rucaparib in the 'maintenance treatment' indication (EMEA/H/C/004272/II/0001).

At the DCO (04 April 2022), no statistically significant differences were observed in OS between rucaparib and placebo, neither in the ITT population (**HR 0.995; 95% CI, 0.809-1.223**; **median OS 36 months rucaparib vs 43.2 placebo**) nor in the homologous recombination deficiency (HRD) population (HR 1.005, 95% CI, 0.766-1.320). Data maturity was, respectively, of 72.7% and 68.9%. In the tBRCA population a trend in favour of rucaparib was observed, but statistically significance was not reached (HR 0.832; 95% CI, 0.581-1.192). According to the MAH, these results may be affected by subsequent treatments received and in particular subsequent treatment with PARP inhibitors. Of note, in the ITT

population the proportion of patients that received subsequent treatment was higher in the placebo arm compared with the rucaparib arm (88.9% vs 78.1%). Of these, 45.8% and 20.8%, respectively, received treatment with a PARPi, being olaparib the most commonly used in both treatment arms (28.6% vs. 14.3%).

These results do not indicate so far a negative impact on OS. Nevertheless a CSR Addendum of the study is expected to be provided in 3Q2022.

Conclusion

Having all considered, the positive B/R balance of rucaparib in the 'treatment' indication cannot be considered confirmed based on the results from the ARIEL4 study. Important uncertainties still remain regarding a potential detrimental effect on OS when rucaparib is used over chemotherapy in the specific patient population covered by the indication.

In view of the reported results from the ARIEL4 study on 22 April 2022 the EC initiated a procedure under Article 20 of Regulation (EC) No 726/2004 and requested the CHMP to assess all the concerns and their impact on the B/R balance of rucaparib in the 'treatment' indication.

On 9 June 2022 the MAH sent a notification to request the removal of the "treatment" indication (i.e. monotherapy treatment of adult patients with platinum sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum based chemotherapy, and who are unable to tolerate further platinum based chemotherapy") from the product information. This (voluntary) request followed the MAH's decision to no longer market Rubraca in the third line treatment indication as "*most ovarian cancer patients that receive a PARP inhibitor do so earlier as a maintenance therapy after first or second-line chemotherapy*".

As stated above, in view of the remaining unresolved uncertainties regarding the observed OS detriment in the ARIEL4 study, it is currently not possible to confirm the positive B/R of rucaparib in the third line treatment indication (see EMEA/H/A-20/1518/C/4272/0033).

Considering the outcome of procedure EMEA/H/A-20/1518/C/4272/0033, this **issue** is **not further pursued**.

14.2. Other concerns

Clinical efficacy

Question 2

In view of the reported OS results in study ARIEL-4 the MAH is asked to discuss:

a) whether these results have been communicated to other regulatory agencies or in any other forum

b) whether consideration has already been given to the need to inform healthcare professionals about these worrisome findings, both in relation to the initiation of new treatments, management of patients currently treated with rucaparib and potentially also ongoing clinical trials. In this context, the MAH should submit what they would consider an appropriate communication to HCPs in the format of a DHPC.

Summary of the MAH's response

a) Interim OS data and associated datasets were included in the Global ARIEL4 Clinical Study Report (CSR) which was submitted to the US Food and Drug Administration (FDA) (15 September 2021) and the EMA (current variation submitted on 27 August 2021).

As previously stated, at the time of the CSR visit cut-off, overall survival (OS) data were at 51% maturity, with the final readout for OS planned per the SAP when 70% maturity has been reached. Thus, the interim analysis presented in the report was considered exploratory, with the final OS analysis to be submitted when final, in an addendum to the CSR.

The benefit-risk was continuously monitored in the ARIEL4 trial by an Independent Data Monitoring Committee (IDMC), which reviewed safety and efficacy data, including OS data, for both treatment arms. The IDMC did not require any actions regarding study conduct; it recommended that the study continue following each meeting. Overall, rucaparib has been extensively investigated in clinical trials and has demonstrated a consistent profile of safety and efficacy across numerous studies.

b) As the EMA is aware, as a result of the Clarification Meeting held between EMA and Clovis on 01 April 2022:

A Cover Letter, an initial draft of a Communication Plan, and an initial draft of a Dear Healthcare Professional Communication (DHPC) were provided to the EMA on 06 April 2022. The communication plan and DHPC were subsequently agreed with the agency on 22 April 2022 and published by the EMA on 26 April 2022. In accordance with the agreed timetable, the DHCP has been translated, agreed upon, and distributed in line with the timelines and national requirements of each Member State.

As per the draft Communication Plan provided to the EMA on 06 April 2022, a Dear Investigator Letter (DIL) was provided to investigators involved in the ARIEL4 study (and by extension, those investigators involved in the ARIEL2 study). This ARIEL4 DIL was sent to the EMA, via email as per request, on 21 April 2022. A communication has been sent to members of Independent Data Monitoring Committees (IDMC)/Data Monitoring Committees (DMC) for the ongoing clinical studies, where those committees are in place, informing them of the communications with the EMA and the agreed-upon EMA DHCP and FDA DHCP. Further communication with those studies' investigators and other investigators for Clovis sponsored or non-sponsored studies where rucaparib is an investigational medicinal product (IMP), is ongoing to determine recommendations for those ongoing trials. In addition, Clovis is in the process of communicating the ARIEL4 OS dataset to all principal investigators of investigator initiated trials of rucaparib across all indications.

On 06 April 2022, the US FDA informed Clovis that they have met with EMA regarding the interim OS data for ARIEL4 and requested a copy of the EU DHPC. On 08 April 2022, Clovis provided a copy of the documentation sent to EMA on 06-07 April 2022 (cover letter, draft communication plan, initial draft DHPC, and statement from the Co-lead investigators). Clovis has subsequently agreed with the FDA on the final content of a DHCP letter for the US on 11 May 2022. The US version of the DHCP is broadly similar to the EMA-agreed version with the exception that final OS data for the ARIEL4 trial is included.

Assessment of the MAH's response

In view of the reported results from the ARIEL4 study on 22 April 2022 the EC initiated a procedure under Article 20 of Regulation (EC) No 726/2004 and requested the CHMP to assess all the concerns and their impact on the B/R balance of rucaparib in the 'treatment' indication. This procedure is still ongoing. Further, a DHPC was published on the EMA website on 06 May 2022.

Of note, the indication of rucaparib 'for the treatment of adult patients with a deleterious BRCA mutation (germline and/or somatic)-associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more chemotherapies', which is different from the one approved in the EU, has been removed in the US.

Conclusion

Issue solved.

Question 3

To clarify the weight of possible imbalances in the baseline demographics and disease characteristics in the (unexpected) reported OS results, the MAH is requested to provide tabular summaries of these baseline demographics and disease characteristics at the time of randomization for three different subgroups of patients: patients randomized to rucaparib, patients randomized to chemotherapy who crossed over to rucaparib after progression and patients from the chemotherapy arm who did not cross over. Data for these 3 subgroups should be included in the same tables for a better comparison.

Summary of the MAH's response

The MAH has provided tabular summaries of the baseline demographics (Table 1), disease characteristics (Table 2), and cancer history and prior anticancer treatment (Table 3) at the time of randomization based on the final OS data cut of 10 April 2022. Of the total of 349 patients in the intent-to-treat (ITT) Population, there were 233, 80, and 36 patients for the following 3 different subgroups of patients in the ITT Population:

- Group 1: patients randomized to rucaparib (N=233)
- Group 2: patients randomized to chemotherapy who crossed over to rucaparib after disease progression (N=80)
- Group 3: patients from the chemotherapy arm who did not crossover (N=36)

Apparently, the different subgroups were well balanced for baseline demographic characteristics, cancer history, prior anticancer treatment, and disease characteristics. There was a slight tendency for the crossover patients to have had a better Eastern Cooperative Oncology Group performance status (ECOG PS) at baseline (ECOG PS of 0 in 67.5% of patients in Group 2 as compared to 53.6% and 50.0% of patients in Groups 1 and 3, respectively; Table 1).

Patients in the chemotherapy arm who did not cross over (Group 3), surprisingly, may be less heavily pre-treated population (≥ 3 prior chemotherapy regimens: 33.3% in Group 3 as compared to 42.5% and 45.0% in Groups 1 and 2, respectively) and more platinum-sensitive (progression-free interval [PFI] ≥ 12 months: 33.3% in Group 3 as compared to 20.6.0% and 17.5% in Groups 1 and 2, respectively; Table 3).

According to the MAH, although the group of patients randomized to chemotherapy who did not cross over to receive rucaparib appeared to have worse OS outcomes than both the group randomized to rucaparib and the crossover group, there is no evidence to suggest that the non-crossover patients represented a group with a significantly worse prognosis at the start of the trial.

Table 1. Patient Demographics – Treatment Part (ITT Population)

	Group 1 Rucaparib Patients (N = 233)	Group 2 Chemotherapy Crossover Patients (N = 80)	Group 3 Chemotherapy Non-crossover Patients (N = 36)	Total (N = 349)
Age (yr)				
N	233	80	36	349
Mean (StD)	57.4 (8.87)	58.8 (8.81)	58.0 (7.95)	57.8 (8.77)
Median	58.0	58.5	58.5	58.0
Min, Max	38, 81	42, 85	38, 70	38, 85
Age Group, n (%)				
≤ 50 yr	60 (25.8)	13 (16.3)	6 (16.7)	79 (22.6)
51-60 yr	89 (38.2)	36 (45.0)	17 (47.2)	142 (40.7)
61-70 yr	68 (29.2)	23 (28.8)	13 (36.1)	104 (29.8)
71-80 yr	14 (6.0)	7 (8.8)	0	21 (6.0)
81-90 yr	2 (0.9)	1 (1.3)	0	3 (0.9)
Age Group, n (%)				
< 65 yr	189 (81.1)	59 (73.8)	29 (80.6)	277 (79.4)
65-74 yr	37 (15.9)	19 (23.8)	7 (19.4)	63 (18.1)
≥ 75 yr	7 (3.0)	2 (2.5)	0	9 (2.6)
Gender, n (%)				
Female	233 (100)	80 (100)	36 (100)	349 (100)
Race, n (%)				
American Indian or Alaska Native	1 (0.4)	0	0	1 (0.3)
Asian	3 (1.3)	0	0	3 (0.9)
Black or African American	4 (1.7)	1 (1.3)	1 (2.8)	6 (1.7)
Native Hawaiian or Other Pacific Islander	0	0	0	0
White	219 (94.0)	78 (97.5)	35 (97.2)	332 (95.1)
Multiple	1 (0.4)	0	0	1 (0.3)
Not Reported	5 (2.1)	1 (1.3)	0	6 (1.7)
Race Group, n (%)				
White	219 (94.0)	78 (97.5)	35 (97.2)	332 (95.1)
Other	9 (3.9)	1 (1.3)	1 (2.8)	11 (3.2)
Unknown	5 (2.1)	1 (1.3)	0	6 (1.7)
Ethnicity, n (%)				
Hispanic or Latino	34 (14.6)	7 (8.8)	4 (11.1)	45 (12.9)
Not Hispanic or Latino	194 (83.3)	72 (90.0)	31 (86.1)	297 (85.1)
Not Reported	3 (1.3)	1 (1.3)	0	4 (1.1)
Unknown	2 (0.9)	0	1 (2.8)	3 (0.9)
Country, n (%)				
Brazil	34 (14.6)	7 (8.8)	2 (5.6)	43 (12.3)
Canada	5 (2.1)	2 (2.5)	0	7 (2.0)

	Group 1 Rucaparib Patients (N = 233)	Group 2 Chemotherapy Crossover Patients (N = 80)	Group 3 Chemotherapy Non-crossover Patients (N = 36)	Total (N = 349)
Czech Republic	15 (6.4)	8 (10.0)	2 (5.6)	25 (7.2)
Hungary	6 (2.6)	3 (3.8)	3 (8.3)	12 (3.4)
Israel	7 (3.0)	1 (1.3)	0	8 (2.3)
Italy	27 (11.6)	12 (15.0)	5 (13.9)	44 (12.6)
Poland	8 (3.4)	2 (2.5)	1 (2.8)	11 (3.2)
Russian Federation	73 (31.3)	30 (37.5)	10 (27.8)	113 (32.4)
Spain	6 (2.6)	4 (5.0)	0	10 (2.9)
Ukraine	33 (14.2)	3 (3.8)	5 (13.9)	41 (11.7)
United Kingdom	19 (8.2)	6 (7.5)	7 (19.4)	32 (9.2)
United States	0	2 (2.5)	1 (2.8)	3 (0.9)
Height (cm)				
N	233	80	36	348
Mean (StD)	160.97 (6.476)	161.09 (7.529)	160.84 (6.391)	160.99 (6.705)
Median	161.00	161.50	160.00	161.00
Min, Max	143.0, 178.0	140.0, 181.0	150.0, 174.0	140.0, 181.0
Height Group, n (%)				
≤ 75 cm	0	0	0	0
> 75-100 cm	0	0	0	0
> 100-125 cm	0	0	0	0
> 125-150 cm	15 (6.4)	5 (6.3)	2 (5.6)	22 (6.3)
> 150-175 cm	216 (92.7)	71 (88.8)	33 (91.7)	320 (91.7)
> 175 cm	2 (0.9)	4 (5.0)	0	6 (1.7)
Missing	0	0	1 (2.8)	1 (0.3)
Weight (kg)				
N	233	80	36	349
Mean (StD)	73.58 (15.583)	74.79 (17.206)	71.06 (15.020)	73.60 (15.899)
Median	72.00	74.00	70.00	72.30
Min, Max	37.0, 125.0	46.0, 139.0	42.0, 98.0	37.0, 139.0
Weight Group, n (%)				
≤ 50 kg	8 (3.4)	3 (3.8)	3 (8.3)	14 (4.0)
> 50-75 kg	132 (56.7)	39 (48.8)	20 (55.6)	191 (54.7)
> 75-100 kg	80 (34.3)	34 (42.5)	13 (36.1)	127 (36.4)
> 100-125 kg	13 (5.6)	3 (3.8)	0	16 (4.6)
> 125-150 kg	0	1 (1.3)	0	1 (0.3)
> 150 kg	0	0	0	0
BMI (kg/m^2)				
N	233	80	36	348
Mean (StD)	28.47 (6.152)	28.74 (5.919)	27.32 (6.060)	28.41 (6.085)
Median	27.69	27.91	27.55	27.67

	Group 1 Rucaparib Patients (N = 233)	Group 2 Chemotherapy Crossover Patients (N = 80)	Group 3 Chemotherapy Non-crossover Patients (N = 36)	Total (N = 349)
Min, Max	15.4, 50.3	18.8, 47.0	18.2, 39.3	15.4, 50.3
ECOG PS at Baseline, n (%)				
0	125 (53.6)	54 (67.5)	18 (50.0)	197 (56.4)
1	108 (46.4)	26 (32.5)	18 (50.0)	152 (43.6)
Smoking Status, n (%)				
Current Smoker	11 (4.7)	7 (8.8)	1 (2.4)	19 (5.4)
Former Smoker	36 (15.5)	9 (11.3)	5 (13.9)	50 (14.3)
Never Smoked	186 (79.8)	64 (80.0)	30 (83.3)	280 (80.2)

Source: Table Q1a.1.1.
Abbreviations: BMI = body mass index; BRCA = breast cancer gene 1 or 2; ECOG PS = Eastern Cooperative Oncology Group performance status; max = maximum; min = minimum; StD = standard deviation.

Table 2. Disease Characteristics at Baseline – Treatment Part (ITT Population)

	Group 1 Rucaparib Patients (N = 233)	Group 2 Chemotherapy Crossover Patients (N = 80)	Group 3 Chemotherapy Non-crossover Patients (N = 36)	Total (N = 349)
Measurable Disease per Investigator, n (%)				
Yes	225 (96.6)	73 (91.3)	33 (91.7)	331 (94.8)
No	8 (3.4)	7 (8.8)	3 (8.3)	18 (5.2)
Number of Target Lesions per Investigator				
N	233	80	36	349
Mean (StD)	2.2 (1.29)	2.4 (1.44)	2.5 (1.36)	2.3 (1.33)
Median	2.0	2.0	3.0	2.0
Min, Max	0, 5	0, 5	0, 5	0, 5
Number of Target Lesions per Investigator, n (%)				
0	9 (3.9)	7 (8.8)	3 (8.3)	18 (5.2)
1	68 (29.2)	14 (17.5)	5 (13.9)	88 (25.2)
2	75 (32.2)	29 (36.3)	9 (25.0)	113 (32.4)
3	35 (15.0)	11 (13.8)	11 (30.6)	57 (16.3)
4	30 (12.9)	10 (12.5)	5 (13.9)	45 (12.9)
5	16 (6.9)	9 (11.3)	3 (8.3)	28 (8.0)
Sum of the Diameters of Target Lesions per Investigator (mm)				
N	224	73	33	330
Mean (StD)	65.7 (48.97)	73.3 (49.91)	75.8 (45.59)	68.4 (48.88)
Median	54.9	62.3	60.0	57.0
Min, Max	10, 300	15, 257	11, 176	10, 300

Source: Table Q1a.2.1.
Abbreviations: ITT = intent to treat; max = maximum; min = minimum; StD = standard deviation.

Table 3. Cancer History and Prior Anti-cancer Treatment – Treatment Part (ITT Population)

	Group 1 Rucaparib Patients (N = 233)	Group 2 Chemotherapy Crossover Patients (N = 80)	Group 3 Chemotherapy Non-crossover Patients (N = 36)	Total (N = 349)
Time Since Cancer Diagnosis (months)				
N	232	80	36	345
Mean (StD)	52.52 (32.031)	52.09 (26.491)	47.04 (21.881)	51.90 (29.953)
Median	42.55	49.85	40.00	43.10
Min, Max	13.0, 185.2	14.0, 139.7	20.0, 94.9	13.0, 185.2
Time Since Cancer Diagnosis Group, n (%)				
0-12 months	0	0	0	0
> 12-24 months	26 (11.2)	7 (8.8)	5 (13.9)	38 (10.9)
> 24 months	206 (88.4)	73 (91.3)	28 (77.8)	307 (88.0)
Missing[a]	1 (0.4)	0	3 (8.3)	4 (1.1)
Type of Ovarian Cancer, n (%)				
Epithelial Ovarian Cancer	220 (94.4)	78 (97.5)	33 (91.7)	331 (94.8)
Fallopian Tube Cancer	7 (3.0)	1 (1.3)	2 (5.6)	10 (2.9)
Primary Peritoneal Cancer	6 (2.6)	1 (1.3)	1 (2.8)	8 (2.3)
Other	0	0	0	0
Histological Classification, n (%)				
Serous	208 (89.3)	73 (91.3)	32 (88.9)	313 (89.7)
Endometrioid	18 (7.7)	4 (5.0)	2 (5.6)	24 (6.9)
Mixed	2 (0.9)	1 (1.3)	1 (2.8)	4 (1.1)
Other	5 (2.1)	2 (2.5)	1 (2.8)	8 (2.3)
Histological Grade, n (%)				
High Grade	233 (100)	80 (100)	36 (100)	349 (100)
Low Grade	0	0	0	0
FIGO Stage at Diagnosis, n (%)				
FIGO Stage IA	2 (0.9)	0	1 (2.8)	3 (0.9)
FIGO Stage IB	1 (0.4)	0	0	1 (0.3)
FIGO Stage IC	6 (2.6)	0	0	6 (1.7)
FIGO Stage IIA	4 (1.7)	4 (5.0)	1 (2.8)	9 (2.6)
FIGO Stage IIB	8 (3.4)	0	3 (8.3)	11 (3.2)
FIGO Stage IIC	5 (2.1)	2 (2.5)	1 (2.8)	8 (2.3)
FIGO Stage IIIA	15 (6.4)	4 (5.0)	1 (2.8)	20 (5.7)
FIGO Stage IIIB	14 (6.0)	9 (11.3)	3 (8.3)	26 (7.4)
FIGO Stage IIIC	136 (58.4)	52 (65.0)	21 (58.3)	209 (59.9)
FIGO Stage IV	35 (15.0)	7 (8.8)	5 (13.9)	47 (13.5)
Other	2 (0.9)	1 (1.3)	0	3 (0.9)
Missing	5 (2.1)	1 (1.3)	0	6 (1.7)

	Group 1 Rucaparib Patients (N = 233)	Group 2 Chemotherapy Crossover Patients (N = 80)	Group 3 Chemotherapy Non-crossover Patients (N = 36)	Total (N = 349)
Number of Prior Therapy Regimens				
N	233	80	36	349
Mean (StD)	2.8 (1.26)	2.8 (1.14)	2.6 (0.96)	2.8 (1.20)
Median	2.0	2.0	2.0	2.0
Min, Max	2, 9	2, 7	2, 5	2, 9
Number of Prior Therapy Regimens Group, n (%)				
2	127 (54.5)	44 (55.0)	22 (61.1)	193 (55.3)
3	61 (26.2)	21 (26.3)	8 (22.2)	90 (25.8)
4	26 (11.2)	8 (10.0)	3 (8.3)	37 (10.6)
5	8 (3.4)	3 (3.8)	3 (8.3)	14 (4.0)
> 5	11 (4.7)	4 (5.0)	0	15 (4.3)
Number of Prior Chemotherapy Regimens				
N	233	80	36	349
Mean (StD)	2.8 (1.24)	2.8 (1.12)	2.6 (0.94)	2.7 (1.18)
Median	2.0	2.0	2.0	2.0
Min, Max	2, 9	2, 7	2, 5	2, 9
Number of Prior Chemotherapy Regimens Group, n (%)				
2	134 (57.5)	44 (55.0)	24 (66.7)	202 (57.9)
3	59 (24.3)	21 (26.3)	7 (19.4)	87 (24.9)
4	22 (9.4)	9 (11.3)	2 (5.6)	33 (9.5)
5	7 (3.0)	2 (2.5)	3 (8.3)	12 (3.4)
> 5	11 (4.7)	4 (5.0)	0	15 (4.3)
Number of Prior Platinum Regimens				
N	233	80	36	349
Mean (StD)	2.3 (0.83)	2.4 (0.72)	2.3 (0.74)	2.3 (0.79)
Median	2.0	2.0	2.0	2.0
Min, Max	1, 6	1, 5	1, 4	1, 6
Number of Prior Platinum Regimens Group, n (%)				
1	12 (5.2)	4 (5.0)	2 (5.6)	18 (5.2)
2	156 (67.0)	48 (60.0)	26 (72.2)	230 (65.9)
3	48 (20.6)	23 (28.8)	4 (11.1)	75 (21.5)
4	11 (4.7)	4 (5.0)	4 (11.1)	19 (5.4)
5	2 (0.9)	1 (1.3)	0	3 (0.9)
> 5	4 (1.7)	0	0	4 (1.1)

	Group 1 Rucaparib Patients (N = 233)	Group 2 Chemotherapy Crossover Patients (N = 80)	Group 3 Chemotherapy Non-crossover Patients (N = 36)	Total (N = 349)
Progression-free Interval After Last Dose of Prior Platinum Regimen (months)				
N	233	80	36	349
Mean (StD)	7.92 (8.112)	9.31 (11.669)	9.13 (10.185)	8.36 (9.252)
Median	5.56	5.93	5.84	5.72
Min, Max	1.1, 67.4	1.0, 90.1	1.0, 50.6	1.0, 90.1
Progression-free Interval After Last Dose of Prior Platinum Regimen Group, n (%)				
< 1 months	0	0	0	0
1 to < 6 months	123 (52.8)	40 (50.0)	18 (50.0)	181 (52.9)
6 to < 12 months	66 (28.3)	25 (31.3)	7 (19.4)	98 (28.1)
≥ 12 months	44 (18.9)	15 (18.8)	11 (30.6)	70 (20.1)
Number of Intervening Non-platinum Chemotherapy Regimens Prior to Randomization				
N	233	80	36	349
Mean (StD)	0.3 (0.55)	0.3 (0.65)	0.2 (0.42)	0.3 (0.56)
Median	0.0	0.0	0.0	0.0
Min, Max	0, 4	0, 4	0, 1	0, 4
Randomization Stratification: Platinum Status, n (%)				
Platinum-resistant	120 (51.5)	41 (51.3)	18 (50.0)	179 (51.3)
Partially platinum-sensitive	65 (27.9)	25 (31.3)	6 (16.7)	96 (27.5)
Platinum-sensitive	48 (20.6)	14 (17.5)	12 (33.3)	74 (21.2)

Source: Table Q1a..3.1.

Abbreviations: CRF = case report form; FIGO = International Federation of Gynecology and Obstetrics; ITT = intent to treat; max = maximum; min = minimum; StD = standard deviation.

[a] The "Missing" designation relates to lack of dosing date, not missing diagnosis date, as these 4 patients were randomized but discontinued prior to receiving any study drug.

Assessment of the MAH's response

As requested, the MAH has provided demographics and baseline disease characteristics separately for patients randomized to rucaparib (n=233), patients randomized to chemotherapy who crossed over to rucaparib upon disease progression (n=80) and those who did not cross over (n=36). The aim of this request was to check whether patient's demographics or (baseline) disease characteristics would indicate that patients who crossed over had a better prognosis that could have led to a prolonged survival (even) when receiving chemotherapy as upfront treatment in this trial, and better than in patients originally randomized to rucaparib. Overall, no relevant differences have been identified between groups, at least, not to the extent that could justify the observed findings. The group of patients who did not cross over is small (n=36) and therefore interpretation is difficult. According to the MAH, ECOG PS was slightly better for patients who crossed over and they also seemed to be less heavily pretreated. This last reasoning is however not agreed as, although there were fewer patients who had 3 and 4 previous lines in the group of patients who did not cross over, there were also more patients who had received 5 previous lines in this group.

The submitted data do not help justifying the observed differences in OS.

Conclusion

Issue solved.

Question 4

The MAH is requested to provide further information on patients who crossed-over to the rucaparib arm. In this regard, information on who did cross over (and who did not) among patients with disease progression and for which reasons should be submitted.

Summary of the MAH's response

The ARIEL4 Protocol specified that patients could cross over from chemotherapy to rucaparib after it was confirmed that the criteria for radiologic disease progression were met either during treatment or at some point following discontinuation of chemotherapy.

At the time the dataset was analysed for the primary endpoint of PFS, 80% of patients (93/116) in the chemotherapy arm had experienced disease progression. Of these, 80 patients crossed over and 13 patients did not. Reasons that eligible patients did not cross over to rucaparib were not collected in the database. In addition, as chemotherapy was typically administered with a set maximum number of cycles (platinum-based chemotherapy was capped at 8 cycles per protocol and paclitaxel was per institutional guidelines), with progression events occurring at various timepoints during or beyond the safety follow-up phase of the trial, it is not possible to analyze safety, laboratory, or Quality-of-Life status at the time of progression uniformly. Therefore, in order to understand potential factors that may have influenced patient/investigator decision management after chemotherapy progression, subsequent treatments have been analysed in the group eligible for crossover who did not cross over.

Of the 13 eligible patients who did not cross over, 2 withdrew consent, 4 had no subsequent therapy reported and died 3 to 6 months after progression, and 7 received subsequent treatment, including subsequent treatment with a PARP inhibitor (PARPi) in 3 of these 7 patients. The subsequent treatment for these 7 patients was as follows:

- PLD
- Gemcitabine
- Paclitaxel + cisplatin + bevacizumab
- Rucaparib – Doxorubicin + carboplatin (2 regimens)

- Avelumab – PLD (2 regimens)
- Carboplatin + paclitaxel + niraparib maintenance – Carboplatin + gemcitabine – Carboplatin + PLD (3 regimens)
- Ipilimumab + nivolumab – Rucaparib – Paclitaxel (3 regimens)

More than 50% of patients who progressed on chemotherapy but who did not cross over to rucaparib received subsequent treatment(s). Many of the patients who progressed but did not cross over to rucaparib went on to receive 1 or more chemotherapy-based regimens, suggesting that suboptimal activity of subsequent regimens, rather than patient-related factors contributed to the inferior OS in these patients as compared to eligible patients who crossed over.

Assessment of the MAH's response

The study protocol specified that patients could cross over from chemotherapy to rucaparib after radiologic disease progression was confirmed. At time of the primary PFS analysis, 80% (93/116) of patients in the chemotherapy arm had disease progression. Of these, 80 patients (86%) crossed over and 13 (14%) did not. Therefore, the influence of bias due to 13 patients not switching at progression is limited.

According to the MAH, the reasons why eligible patients did not cross over to rucaparib were not collected in the database so this question cannot be answered. Instead, the MAH has provided information about subsequent therapies for the 13 patients who did not cross over to rucaparib upon progression. Four patients did not receive subsequent therapy and died within 6 months. Two patients withdrew consent so no data are available for them. The remaining seven patients received various therapies that included not only standard chemotherapy regimens recommended in this setting but also anti PD-(L)1 monoclonal antibodies and PARP inhibitors, including rucaparib and also niraparib (given to one patient as maintenance following response to platinum-based chemotherapy).

Half of the patients who were eligible to cross over to rucaparib but did not choose this option received subsequent therapy that impacted their survival after study treatment. The impact of results in these very few patients in the context of the reported results in the overall population randomized to chemotherapy is expected to be very low.

Conclusion

Issue considered resolved.

Question 5

Regarding the supportive analyses adjusting for cross-over, the MAH is referred again to the EMA guidance "Question and answer on adjustment for cross-over in estimating effects in oncology trials (EMA/845963/2018)" and should provide the analysis censoring the data at crossover (method 1 of the guideline) and at least one or two of the proposed methods for handling crossover.

Summary of the MAH's response

The ARIEL4 design allowed for patients randomized to chemotherapy to cross over upon radiologic disease progression to receive rucaparib as part of the clinical trial. Patients randomized to rucaparib did not have an option to cross over to chemotherapy within the trial and received their next line of treatment outside of the trial as standard of care. In total, 69% of the patients randomized to chemotherapy crossed over and received rucaparib. In total, 90% of patients enrolled in ARIEL4, 313 out

of 349, patients received treatment with rucaparib (233 patients initially randomized and 80 patients crossing over after completing chemotherapy) during the clinical trial. When interpreting the final OS results it is important to account for the crossover.

The MAH has performed conventional adjustments described in method 1 of the guideline "Question and answer on adjustment for cross-over in estimating effects in oncology trials (EMA/845963/2018)" for crossover on the final OS dataset (visit cutoff 10 April 2022). In addition, the MAH has performed the more complex adjustment models (time-varying covariate adjustment and the Two-stage Estimation (TSE) model, which is one of the proposed methods in the guidance) for the final OS and are presenting them below.

Conventional methods adjusting Final OS for crossover

The first analysis excludes the patients who crossed over from chemotherapy to rucaparib. In the second analysis, the data are censored at crossover (method 1 of the guideline EMA/845963/2018). When excluding patients who crossover over, the OS is significantly improved in favour of those randomized to rucaparib. The analysis where the data was censored at crossover, showed no difference or determinant between the 2 randomized arms by this method.

Table 1. ARIEL4 Final OS – Adjusting for Crossover in ITT Population

Population/ Subgroup	Rucaparib	Chemotherapy	Rucaparib vs Chemotherapy	
			Kaplan-Meier Analysis[a]	Cox Proportional Hazard[b]
	Event/N (%)	Event/N (%)	Median (Months) Log-rank p-value	HR (95% CI) p-value
Exclude Patients who crossed over	167/233 (71.7%)	26/36 (72.2%)	19.4 vs 9.1 p < 0.0001	0.42 (0.28, 0.65) p < 0.0001
Censored at crossover (method 1 of guidelines)[c]	167/233 (71.7%)	26/116 (22.4%)	19.4 vs 26.2 p = 0.7441	1.06 (0.69, 1.63) p = 0.7949

Sources: Table 14.2.3.4.4, Table 14.2.3.4.6, Figure 14.2.3.4.4, and Figure 14.2.3.4.12.

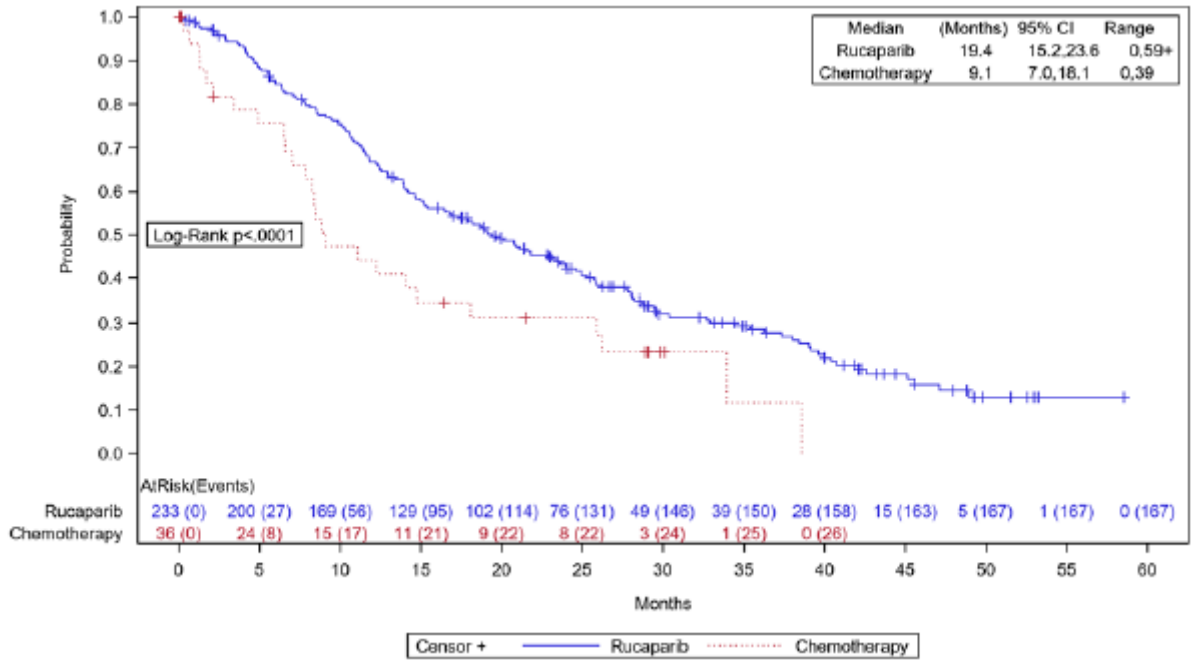
Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; OS = overall survival.

[a] Log-rank analysis performed by randomization strata of platinum status for ITT and Efficacy Populations.

[b] Cox proportional hazard method performed by randomization strata of platinum status for ITT and Efficacy Populations.

[c] European Medicines Agency. Question and answer on adjustment for cross-over in estimating effects in oncology trials 13 December 2018. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/question-answer-adjustment-cross-over-estimating-effects-oncology-trials_en.pdf.

Figure 1. ARIEL4 Kaplan-Meier Analysis of Final OS – Excluding Patients Who Crossed Over to Rucaparib (ITT Population)

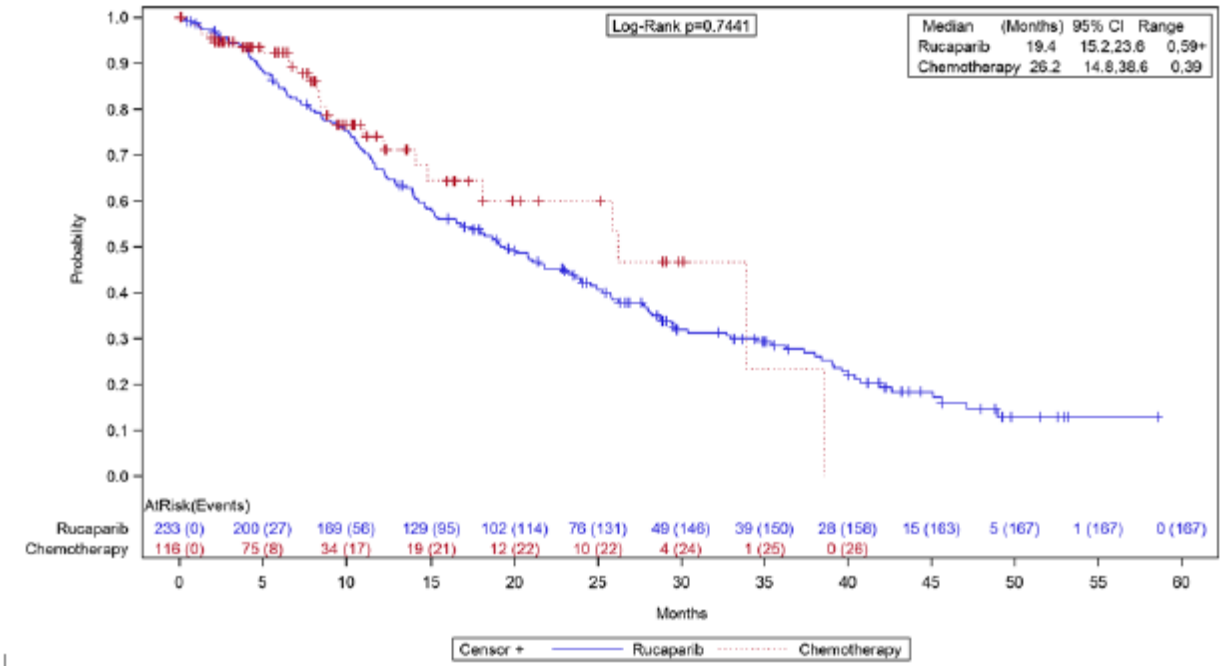


Source: Figure 14.2.3.4.4.

Abbreviations: CI = confidence interval; ITT = intent-to-treat; OS = overall survival.

Note: Log-rank analysis performed by randomization strata of platinum status.

Figure 2. ARIEL4 Kaplan-Meier Analysis of Final OS – Censoring Data at Time of Crossing Over to Rucaparib (ITT Population)



Source: Figure 14.2.3.4.12.

Abbreviations: CI = confidence interval; ITT = intent-to-treat; OS = overall survival.

Note: Log-rank analysis performed by randomization strata of platinum status.

Complex Adjustment Models per The EMA Guidelines

As an initial proposal to adjust for crossover, the MAH used a Cox proportional hazards model with time-dependent treatment effect covariate for adjusting for the effect of treatment crossover and to isolate the overall effect of rucaparib on OS. This analysis demonstrated no difference between the randomized treatment groups in OS when adjusting for starting rucaparib either at randomization or in crossover (hazard ratio [HR] = 0.912, [95% CI, 0.593-1.402]; p = 0.673). The MAH acknowledges that this method is more relevant to an observational study in which all patients received rucaparib, however, the majority (90%) of patients did receive rucaparib in this study. It is also acknowledged that, if additional time dependent covariates were available, it would be helpful to also include them in this modelling to help assess the robustness of the model.

The MAH did review the methods in the guidelines (EMA/845963/2018) and believes that out of the 3 models proposed, the Two-stage Estimation (TSE) model is the most appropriate for the ARIEL4 dataset.1 The TSE model for the final OS is presented in this report. The reasons for lack of suitability of the other 2 models (Inverse Probability of Censoring Weighting [IPCW] and Rank Preserving Structural Failure Time [RPSFT]) are discussed below.

Inverse Probability of Censoring Weighting

The IPCW is a method that employs 2 steps. The first step involves estimating the probability of a patient switching treatments. The second step incorporates the inverse of these predicted probabilities as weights, in a weighted Cox proportional hazards analysis. The MAH decided to not pursue the IPCW method due to not having any time-dependent (changing) covariates (eg, longitudinal analysis of circulating tumour DNA [ctDNA] or other marker). It is recommended in the literature to use what are called "stabilized" weights for this model. These weights require the use of both "baseline" covariates and time dependent (changing) covariates. The lack of time-dependent covariates in this study would mean that only unstabilized weights could be used and thus this method cannot be implemented as recommended.

Rank Preserving Structural Failure Time

The second method of RPSFT assumes what is referred to as the "common treatment effect," which requires that control group patients who switch to the experimental treatment during the trial receive the same treatment effect compared to patients who were originally randomized to the experimental group. The authors state that the common treatment effect assumption can be problematic, because it would seem possible that after having received one treatment until progression, and then deciding to switch to the experimental treatment, the prognosis would not be the same as if they were originally randomized to the experimental treatment. Thus, this model requires that the treatment effect received by patients who decide to cross over to experimental treatment must be the same as that received by patients initially randomized to the experimental group". In addition, the RPSFT counterfactual survival model assumes that patients are either 'on' treatment or 'off' treatment. In situations where the comparator treatment is active, rather than placebo, this is problematic as two treatment effects exist.3 Lastly, parameter estimation with the RPSFT model is difficult when the mean time on experimental therapy is similar between the 2 randomized arms, as it is in the ARIEL4 study. The mean duration of treatment was approximately 9 months for both the patients randomized to rucaparib and in the group of patients that crossed over to rucaparib. Due to these limitations, the MAH decided not to pursue this method in this response, either.

Two-stage Estimation Model

The last method in the guidance, the TSE method, is presented below. With this method, as described in the EMA/845963/2018, the first stage involves using only the control group patients to estimate the treatment effect received by patients who switched compared to patients who did not switch. Then, in the second stage, the treatment effect estimate is used as an "acceleration factor" for the patients who

switched to obtain counterfactual event times in the absence of crossover. During the first stage, a "secondary baseline" is identified, and a parametric accelerated failure time model is fit to the post-progression control group data to obtain the treatment effect estimate. In order to fully characterize the utility of this adjustment method a range of acceleration factors were estimated. Note that at the end of the first stage, the counterfactual times for subjects may be re-censored. However, Latimer et. Al. suggest that, while both re-censoring and not re-censoring may result in bias, a TSE without re-censoring performs adequately with minimal bias and what bias it has tends to be in favor of the control group; therefore, it is a more conservative approach. In light of this, no re-censoring was performed (meaning the original death/censoring variables are used for the counterfactual survival times in chemotherapy patients who crossed over).

The first approach was to directly follow the description of the TSE method in Latimer et al. In the first stage of the analysis, only the post-progression control group data are used. These data are treated as an "observational study", and thus we are only considering patients in the control group (regardless of crossover) who experienced disease progression at some time T_0, which becomes the new "secondary baseline". Then, a parametric Accelerated Failure Time (AFT) model using the Weibull distribution is fit to the post-progression data, with terms for (1) randomization stratification at baseline; (2) the time to disease progression from the randomization baseline; and (3) an indicator for treatment switching.

The SAS procedure PROC LIFEREG estimates the coefficient associated with treatment switching as β =0.9614 (95% CI, 0.5017-1.42). Note that PROC LIFEREG models the log-time, meaning that the difference in post-progression survival time TT between patients who switched vs those who did not is as follows:

$$\log(T|switch) = \beta \log(T|no\ switch)$$
$$(T|switch) = e^{\beta}(T|no\ switch)$$

To determine the counterfactual post-progression survival time $\hat{T}$ for patients who crossed over, we solve for $(T|no\ switch)$:

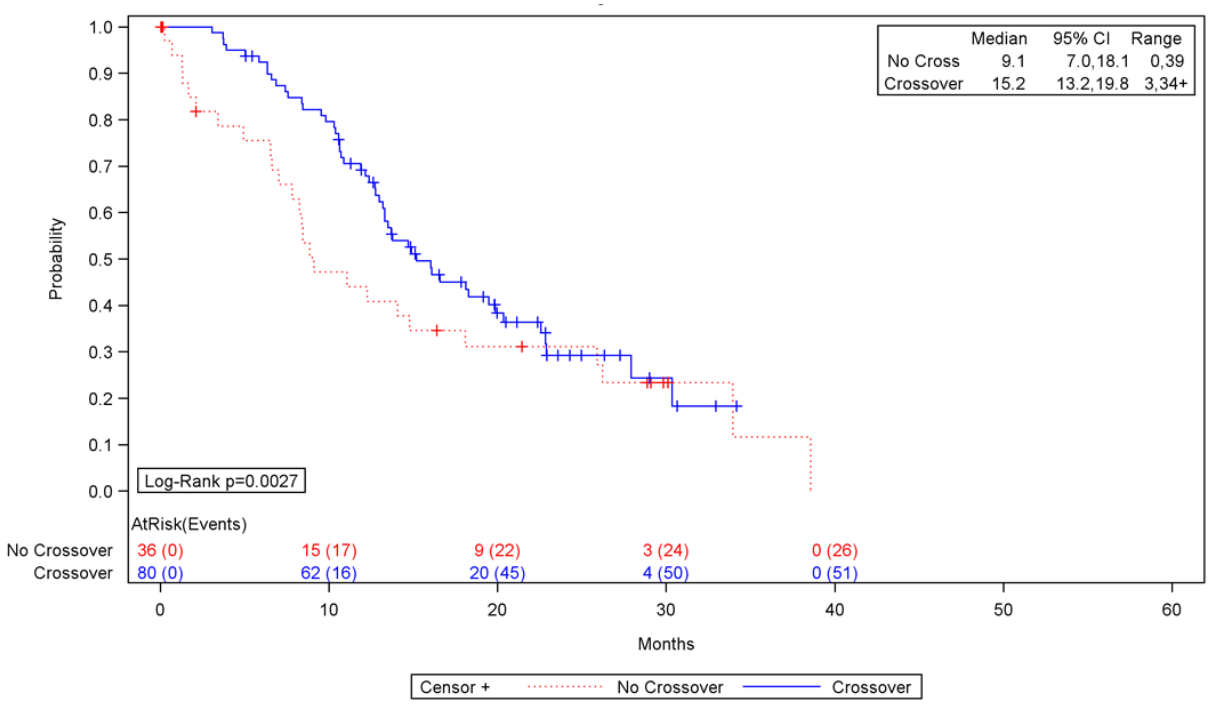
$$\hat{T} = e^{-\beta}(T|switch)$$

Which means the "aceleration factor" is $e^{-0.9614} \approx 0.382$. This means that, had the crossover patients not switched to rucaparib, we expect their survival time after switching treatments would have been roughly 38% of what was observed. Thus, the counterfactual OS time U (from the randomization baseline) for patients who crossed over at time T_{off} ("off" as in time spent "off rucaparib"; similarly, T_{on} represents the observed time "on" rucaparib after crossing over) is estimated as:

$$U = T_{off} + e^{-\beta}T_{on} = T_{off} + \hat{T}$$

Figure 3 shows a Kaplan-Meier plot of the counterfactual survival times of only the chemotherapy patients (crossover vs. non-crossover). The median OS in chemotherapy patients who cross over is now adjusted to 15.2 vs. 9.1 months in those who did not cross over. While the acceleration factor has resulted in bringing the estimates of the groups closer by reducing the survival time in the patients who crossover, the stratified log-rank test is still statistically significant (p = 0.0027) so the adjustment is conservative in that it does not completely bring the 2 groups together.

Figure 3. Kaplan-Meier Estimates Using Counterfactual Survival Times from TSE, AFT Model Approach (Chemotherapy Patients: Crossover vs Non-crossover) – Final OS Analysis (ITT Population)

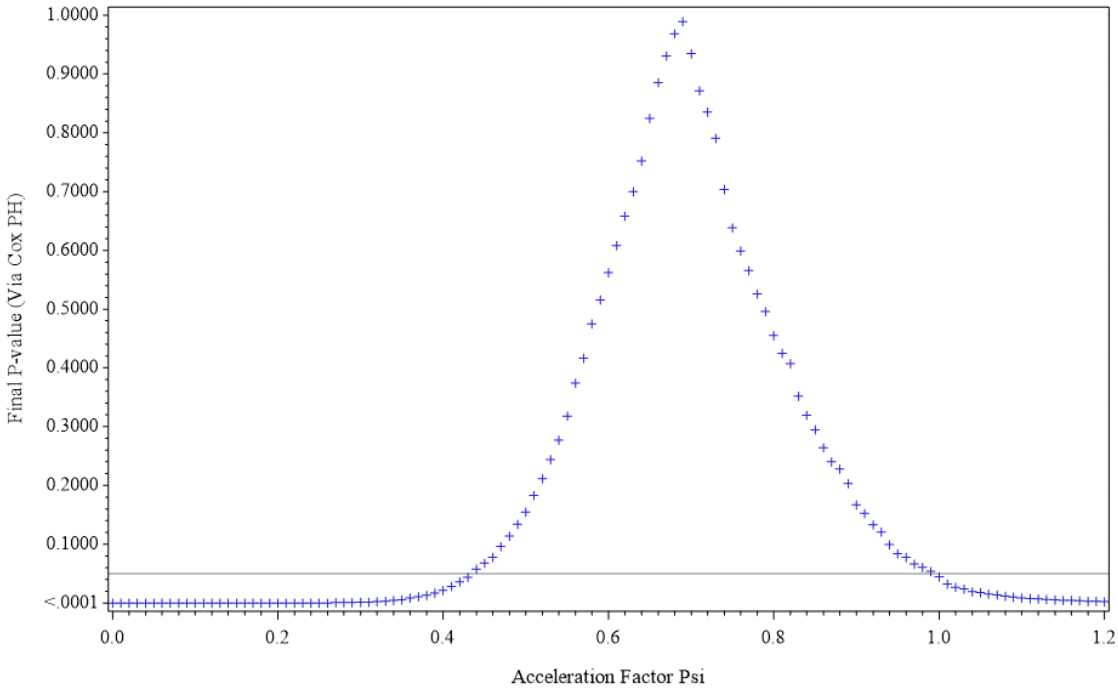


Source: Figure 5.1.3.

Abbreviations: AFT = Accelerated Failure Time; CI = confidence interval; ITT = intent-to-treat; OS = overall survival; TSE = Two-stage Estimation.

As a sensitivity analysis, the MAH explored the "tipping-points", which were values of the acceleration factor $e^{-\beta}$ that would result in statistically significant differences in the HR, both (1) in favour of rucaparib (HR significantly < 1), and (2) in favour of chemotherapy (HR significantly > 1). Testing values of $\psi \in [0,2]$ and comparing them to the final p-value (as determined by a stratified log-rank test comparing treatment arms) gave the following results, displayed in Figure 4.

Figure 4. Tipping Point Analysis of Acceleration Factor from TSE, AFT Model Approach – Final OS Analysis (ITT Population)



Source: Figure 5.1.5.

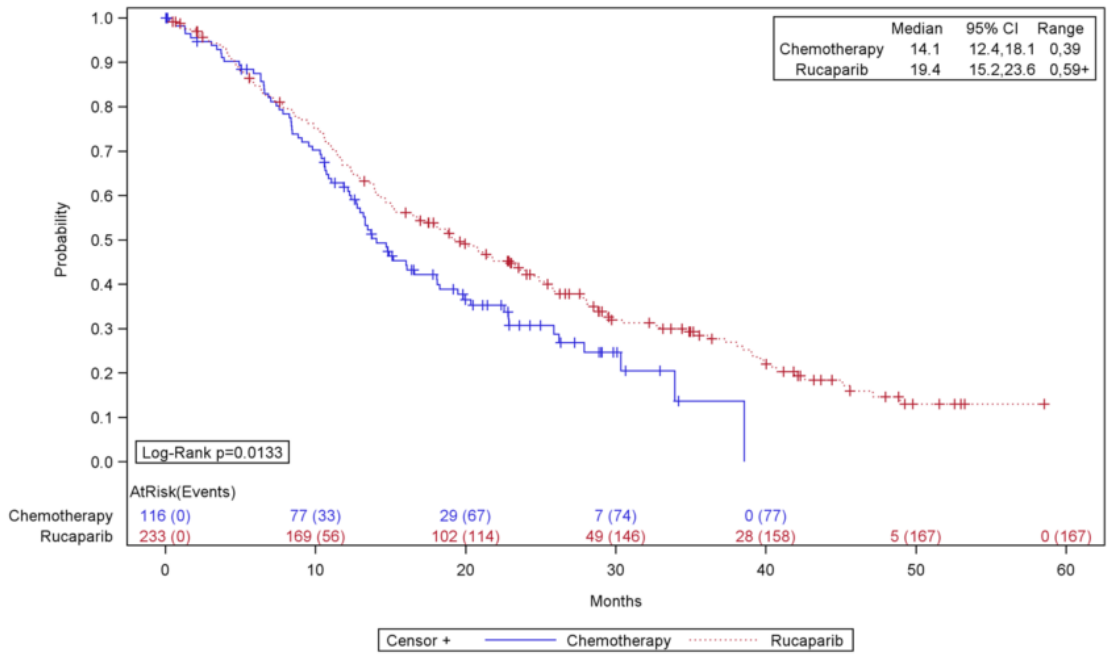
Abbreviations: AFT = Accelerated Failure Time; ITT = intent-to-treat; OS = overall survival; PH = proportional hazards; TSE = Two-stage Estimation.

As can be seen in the graph above, the x-axis is the value of acceleration factor ψ, and the y-axis is the resultant p-value for the HR via the TSE. A horizontal reference line at 0.05 is included and shows that the largest value of $e^{-\beta}$ that results in a significantly small HR (in favour of rucaparib) is roughly $e^{-\beta}$ = 0.435, which is slightly larger than the value of 0.382 that was estimated by the two-stage model. In the other direction, the smallest value of $e^{-\beta}$ that results in a significantly large HR (in favour of chemotherapy) is roughly $e^{-\beta}$ = 0.995. Note that $e^{-\beta}$ = 1 is equivalent to the naïve ITT analysis that uses the observed death or censoring time for crossover patients and ignores treatment switching, and this just happens to coincide directly with what the tipping point analysis shows as the point where a statistical difference in OS in favour of chemotherapy occurs. Thus, even a very small adjustment for crossover, eg, $e^{-\beta}$ < 0.995, results in a non-statistically significant difference between rucaparib and adjusted chemotherapy OS times.

Proceeding to the second stage of the TSE method using the estimated acceleration factor of 0.382, the OS time for all crossover patients (who are henceforth treated as adjusted chemotherapy patients) was replaced by their counterfactual survival time U. Then, all patients were modelled using typical survival methods and compared using both Kaplan-Meier estimates and Cox proportional hazards model.

First, using a Kaplan-Meier approach (Figure 5) comparing rucaparib vs adjusted chemotherapy, which suggested improved OS for rucaparib patients (stratified log-rank p = 0.0133 in favor of rucaparib).

Figure 5. Kaplan-Meier Estimates Using Counterfactual Survival Times – Final OS Analysis (ITT Population)



Source: Figure 5.1.4.

Abbreviations: BID = twice a day; CI = confidence interval; ITT = intent-to-treat; OS = overall survival.

Lastly, using a stratified Cox proportional hazards model, incorporating randomization strata of platinum status, yielded similar OS results (see Table 2).

Table 2. Cox Proportional Model Using Counterfactual Survival Times – Final OS (ITT Population)

Parameter	Hazard Ratio	p-value
Randomized Treatment (Rucaparib vs Chemotherapy)	0.697	0.0117
Randomization Strata (Partially Platinum-sensitive vs Platinum-sensitive)	2.005	0.0007
Randomization Strata (Platinum-resistant vs Platinum-Sensitive)	3.061	< 0.0001

Abbreviations: ITT = intent-to-treat; OS = overall survival.

An HR >1 is an increase in hazard, meaning worse survival. Similarly, an HR <1 is an improvement in survival. Thus, we see that the HR of OS comparing rucaparib vs adjusted chemotherapy is estimated to be significantly less than 1 (in favor of rucaparib). The randomization stratum (partially platinum-sensitive, platinum-sensitive, or platinum-resistant) is, as expected, found to be a significant predictor of OS and thus used as a stratification factor in the design of the study (as seen by p-values < 0.05 in Table 2). The platinum-sensitive group is the reference group, so hazard ratios greater than 1 in Table 2, mean there is an increase in hazard (and thus a decrease in survival) for that group relative to the platinum-sensitive reference group (in other words, the survival is best in the platinum-sensitive group, as would be expected).

Conclusion

In conclusion, when interpreting final OS, it is important to account for the fact that this study had a high proportion of crossover. In total, 90% of the patients enrolled in ARIEL4 received treatment with rucaparib, with 69% of the patients in the chemotherapy control group crossing over to receive rucaparib. The median OS in patients randomized to rucaparib within the platinum subgroups of ARIEL4 seems consistent with reported median OS in Phase 3 trials that evaluated platinum-based or paclitaxel treatment in the recurrent setting.

The analysis of final OS for the ITT population by initial randomization groups shows a difference in OS in favour of chemotherapy when no adjustment is made to account for the patients that crossed over to rucaparib. Three additional models that account for the effect of crossover have been presented. The first is a simple model (method 1 of the guideline EMA/845963/2018) where data are censored at crossover, which resulted in no difference in OS (HR = 1.06, p = 0.7949). The second model is a Cox proportional hazards model with a time-dependent covariate for the start of rucaparib, which also resulted in no difference in OS (HR = 0.912, p = 0.673). Finally, the MAH used a TSE model to adjust for crossover, which resulted in an estimate of OS (HR = 0.697, p = 0.0117) that was significantly better in the rucaparib arm versus chemotherapy. Therefore, the MAH concludes that any type of analysis adjusting for crossover on final OS supports that there is no detriment in OS associated with rucaparib treatment.

Assessment of the MAH's response

As a consequence of major concerns due to the detrimental effect on the OS endpoint observed in some analyses, the Applicant was requested to provide a number of sensitivity analyses oriented at disentangling the effect of the crossover from the chemotherapy arm to the rucaparib arm. Analyses for both the interim and final data results stages have been reported.

The MAH has presented three sensitivity analyses partially following the "*Question and answer on adjustment for cross-over in estimating effects in oncology trials*" document (EMA/845963/2018). From

the 3 recommended complex statistical methods, the MAH has presented the analysis following the two-stage method and has provided some arguments to discard the Inverse Probability of Censoring Weighting (IPCW) and the Rank Preserving Structural Failure Time models (RPSFT) approaches.

The MAH has provided results from 5 different strategies: (1) excluding of patients who crossed over, (2) censoring patients at crossover, (3) and adaptation of the time-varying analyses for the treatment effect, and the (4) two-stage method and finally (5) a tipping-point sensitivity analysis. The following table (prepared by the assessors) shows some of the most relevant analyses results, which includes the standard analysis ignoring crossover plus the first 4 of the 5 methods listed above.

Of note, conventional methods adjusting for cross-over were performed on updated data, the more complex methods were based on the interim OS data of September 2020 and the MAH proposed to update them later using the final OS data.

Approach	Analysis	Population Set	Estimation	HR [95%CI]	p-value
Ignoring cross over	IA	Efficacy	HR for rucaparib	1.55 [1.09 - 2.21]	0.016
		ITT	HR for rucaparib	1.48 [1.07 - 2.06]	0.019
	Final	Efficacy	HR for rucaparib	1.30 [0.98 - 1.74]	0.070
		ITT	HR for rucaparib	1.31 [1.00 - 1.73]	0.051
Excluding cross over	IA	Efficacy	HR for rucaparib	0.45 [0.27 - 0.74]	0.002
		ITT	HR for rucaparib	0.43 [0.27 - 0.69]	<0.001
	Final	ITT	HR for rucaparib	0.42 [0.28 - 0.65]	<0.001
Censoring at cross over	Final	ITT	HR for rucaparib	1.06 [0.69 - 1.63]	0.079
Time-varying	Final	Efficacy	Baseline Chemotherapy, Z=1	0.55 [0.35 - 0.87]	0.011
			Began rucaparib at time t; X(t)=1	0.68 [0.36 - 1.31]	0.254
		ITT	Baseline chemotherapy, Z=1	0.58 [0.38 - 0.88]	0.010
			Began rucaparib at time t; X(t)=1	0.69 [0.38 - 1.25]	0.216
Two-Stage	IA	ITT	HR for rucaparib	0.96 [NA]	0.813
	Final	ITT	HR for rucaparib	0.67 [NA]	0.021

Overall, the uncertainties triggered by the standard analyses approach, considering all data and ignoring crossover, remain and cannot be considered ruled out by the results of the provided analyses. In fact, this standard analysis resembles what it might be expected as a result of the decision to treat, following the intention-to-treat principle as well as the treatment policy strategy for handling intercurrent events. This said, it is acknowledged that the HR from these analyses, which varied between 1.30 to 1.55 (some even statistically significant), does not reflect exclusively the direct treatment effect but a mixture of effects, including the 'contamination' by the crossed-over treatment and the potential additional confounding by the differential patients' characteristics of the crossed-over patients. In this scenario, and in the absence of a direct randomised comparison for assessing the effect of the cross over, all analyses are considered of interest for assessing this effect.

Notably, the MAH has declined to conduct two of the analyses recommended in the EMA Q&A document referred above (EMA/845963/2018), despite requested. For the IPCW, it was argued that "*the lack of time-dependent covariates in this study would mean that only unstabilized weights could be used and*

thus this method cannot be implemented as recommended". While it is acknowledged that not all interesting time-dependent covariates might be available, variables reflecting the patient status which include covariates such as ECOG, progression, laboratory data other than circulating tumour DNA [ctDNA], might have been used for the analysis. In any case, the reasoning is not considered sufficient to preclude the conduction of this IPCW analysis. For the RPSFT, the MAH has declined to conduct this analysis arguing that the non-testable assumption of the "common treatment effect" is a major and absolute limitation. The "common treatment effect" means that the treatment effect would not depend on whether it was received after randomisation or later at the point of crossover. Again, while it may be a limitation, the argumentation on why this analysis is not worth run, is not considered sufficient at all. It is highlighted that a very strong detrimental effect for OS was found in the standard analysis and that any analysis would be helpful to better understand the results.

The exclusion of patients who crossed-over leads to statistically significant protective HR, varying from 0.42 to 0.45. However, this analysis is considered as the most biased approach and therefore not even considered in the EMA referred Q&A document to adjust for cross-over. Thus, the reported HR cannot be considered as positive or even reassuring result from a regulatory point of view.

Censoring patients at crossover is one of the 4 approaches of the referred EMA Q&A document, but it is clearly stated in that document that "*censoring is often anti-conservative and cannot be recommended*". Therefore, it is only considered as one of the additional analyses. Of note, the HR is still above one (1.06) and taken into account also the wideness of the 95%CI, it is concluded that the major concern on OS still remains.

The MAH provided also results from time-varying analyses to assess the treatment effect along the trial follow-up. There are 2 factors which assess the treatment effect in this model: a "Z" fixed factor for the randomisation to the control arm and the time-dependent "X" factor for the exposure to rucaparib at any time. It was already stated in previous rounds of assessment that this approach had several methodological concerns. First, the two treatment factors are being influenced by each other. While this model might be used as one of among a list of analyses, it is difficult to determine which one could be considered more appropriate post-hoc. Actually, the objective in that analysis should had been the effect of the exposure to rucaparib (the X factor) at any time without the effect of the randomisation to avoid estimating a mixture of effects when assessing the rucaparib potential benefit/harm. This analysis has not been conducted and the interpretation of the results made by the MAH cannot be endorsed, at least without the above referred time-dependent analysis requested. Also, this observational analysis on the randomised trial would have needed (reasonable and scientifically justified) lagged windows of effect and the use of time-dependent covariates at different time points (with at least the patient severity status at crossover).

The MAH has provided results using the two-stage estimation (TSE) model, which is only of the 3 complex statistical methods referred in the EMA Q&A document, despite it has been previously recommended to conduct and submit the results from all those analyses. It is noted that not only the 2 discarded strategies but also the TSE method has underlying assumptions. In fact, the MAH has used a parametric accelerated failure time model based on the Weibull distribution, which *per se* is just one among a number of alternatives, and where different settings for parameters may be used for fitting the final model. In essence, the acceleration factor, which is the key in the TSE model, might be different in different scenarios which have not been shown or discussed. Also, there is a more than notable change in the risk estimates between the IA (HR: 0.96) and the final analyses (HR: 0.67 and statistically significant). Overall, the TSE method as the only conducted analysis among the regulatory recommended methods is considered to show very unstable results and they do not help to mitigate the uncertainties regarding the potential detrimental effect on OS.

As per the "tipping-points" analysis, the MAH provided a series of values of the acceleration factor. The interpretation of this analysis should be assessed together with the TSE, and the results cannot be considered sufficiently robust and compelling given the limitations discussed above.

Finally, it is noted that since there is no single best universal method, the lack of analysis using the IPCW and the RPST strategies is regretted. The EMA Q&A document to adjust for crossover states:

"Given that the underlying assumptions of the adjustment methods for cross-over described above can in principle not be proven to be true, a positive result from an analysis adjusted for cross-over cannot be used to rescue a trial that is negative as per other evidence, or to ascertain that a treatment confers an OS advantage when this is not apparent in an analysis that does not (strongly) depend on unverifiable assumptions, such as an 'ITT-analysis' that uses the observed OS outcome for each patient. For these reasons, these analyses may only be useful for regulatory purposes as supportive or sensitivity analyses with (as outlined above) a clearly demonstrated robustness against deviations from the underlying assumptions."

In summary, even though some of the sensitivity analyses have displayed non-negative OS results with regards to the effect of rucaparib over the chemotherapy arm, several concerns that have been previously described do not allow such a conclusion from a regulatory perspective. For this reason and taking into account all the above discussion, it cannot be considered that a detrimental effect on OS can be ruled-out and this uncertainty cannot be considered resolved. Further, in view that the MAH has requested to remove the third line treatment indication from the product information (see question 1), this issue will no longer be pursued.

Conclusion

Issue not further pursued.

Question 6

The MAH is requested to submit the final analysis for OS and updated PFS2 results when available (REC already proposed). This report should include OS results by platinum sensitivity randomization status. In addition, potential cases of secondary MDS/AML are expected to be presented at the time of this final analysis.

Summary of the MAH's response

Final analysis for Top-line OS and PFS2 results

Top-line final OS and second event of progression-free survival (PFS2) analyses using a data cut-off of 10 April 2022 are shown in Table 1 for the ITT and Efficacy Populations, and also for the platinum status subgroups. The Kaplan-Meier curves for the Efficacy, ITT, and the platinum subgroups are presented in Figure 1 to Figure 11 below.

Overall Survival

At the time of the final OS analysis, 70% (244/349) of death events had occurred in the ITT Population. The platinum-resistant subgroup was more mature (77.5% [139/179]) than the platinum-sensitive subgroup which had 61.8% (105/170) OS events and was comprised of the PPS (69.8% [67/96]) and the FPS subgroups (51.4% [38/74]).

The HR for OS between rucaparib and chemotherapy patients in the ITT Population of ARIEL4 was 1.31 (95% CI, 1.00-1.73; p = 0.0507). This analysis was heavily confounded by crossover to rucaparib of patients who were initially randomized treated with chemotherapy, (69% [80/116] patients) and also by the different outcomes in the platinum subgroups.

In the platinum-sensitive population (FPS and PPS), there was no significant difference in OS between patients randomized to the rucaparib versus chemotherapy. The median OS was 29.4 months in the rucaparib arm vs. 27.6 months in the chemotherapy arm (HR 1.07 [95% CI, 0.71-1.62]; p = 0.7455). This result is also consistent with the results from the randomized Phase 3 trial SOLO3, which compared the PARPi olaparib with chemotherapy in patients with platinum-sensitive disease, but which did not include a platinum comparator (HR 1.07 [95% CI, 0.76-1.49]). In the SOLO3 trial, a high proportion of patients randomized to comparator also received PARPi as a subsequent line of therapy.

The difference in OS seems to be driven by the result in platinum-resistant patients. The subgroup whose population is not within the current approved treatment indication for Rubraca. Although the median OS estimates in the platinum-resistant subgroup are longer in patients randomized to weekly paclitaxel versus rucaparib (22.2 vs 14.2 months), the OS in platinum-resistant patients receiving paclitaxel in ARIEL4 is considerably longer than outcomes reported for paclitaxel in trials of women with platinum resistant ovarian cancer (13.2 to 15.5 months) while the outcomes in the patients randomized to rucaparib are within the range expected with standard of care in this setting.

Table 1. ARIEL4 Final OS and PFS2 – All Population and Subgroups

Population/ Subgroup	Overall Survival				PFS2			
			Rucaparib vs Chemo				Rucaparib vs Chemo	
	Rucaparib Event/N (%)	Chemo Event/N (%)	Kaplan-Meier Analysis[a] Medians Log-rank p-value	Cox Proportional Hazard[b] HR (95% CI) p-value	Rucaparib Event/N (%)	Chemo Event/N (%)	Kaplan-Meier Analysis[a] Medians Log-rank p-value	Cox Proportional Hazard[b] HR (95% CI) p-value
Efficacy	154/220 (70.0)	68/105 (64.8)	21.1 vs 26.2 p = 0.0655	1.31 (0.98, 1.74) p = 0.0704	171/220 (77.7)	91/105 (86.7)	15.5 vs 14.1 p = 0.1904	0.84 (0.65, 1.09) p = 0.1848
ITT	167/233 (71.7)	77/116 (66.4)	19.4 vs 25.4 p = 0.0472	1.31 (1.00, 1.73) p = 0.0507	184/233 (79.0)	102/116 (87.9)	14.7 vs 13.6 p = 0.2332	0.86 (0.67, 1.10) p = 0.2273
Platinum Resistant	95/120 (79.2)	44/59 (74.6)	14.2 vs 22.2 p = 0.0222	1.51 (1.05, 2.17) p = 0.0251	101/120 (84.2)	55/59 (93.2)	11.8 vs 11.5 p = 0.8658	0.97 (0.70, 1.34) p = 0.8450
Platinum Sensitive (Fully + Partially)	72/113 (63.7)	33/57 (57.9)	29.4 vs 27.6 p = 0.7167	1.07 (0.71, 1.62) p = 0.7455	83/113 (73.5)	47/57 (82.5)	19.4 vs 14.2 p = 0.1034	0.74 (0.51, 1.06) p = 0.0996
- Fully Platinum Sensitive	27/48 (56.3)	11/26 (42.3)	36.3 vs 47.2 p = 0.4945	1.24 (0.62, 2.50) p = 0.5405	32/48 (66.7)	18/26 (69.2)	26.9 vs 24.4 p = 0.7187	0.89 (0.49, 1.60) p = 0.6861
- Partially Platinum Sensitive	45/65 (69.2)	22/31 (71.0)	21.1 vs 23.2 p = 0.9469	0.97 (0.58, 1.62) p = 0.9129	51/65 (78.5)	29/31 (93.5)	16.5 vs 13.3 p = 0.0695	0.65 (0.41, 1.03) p = 0.0669

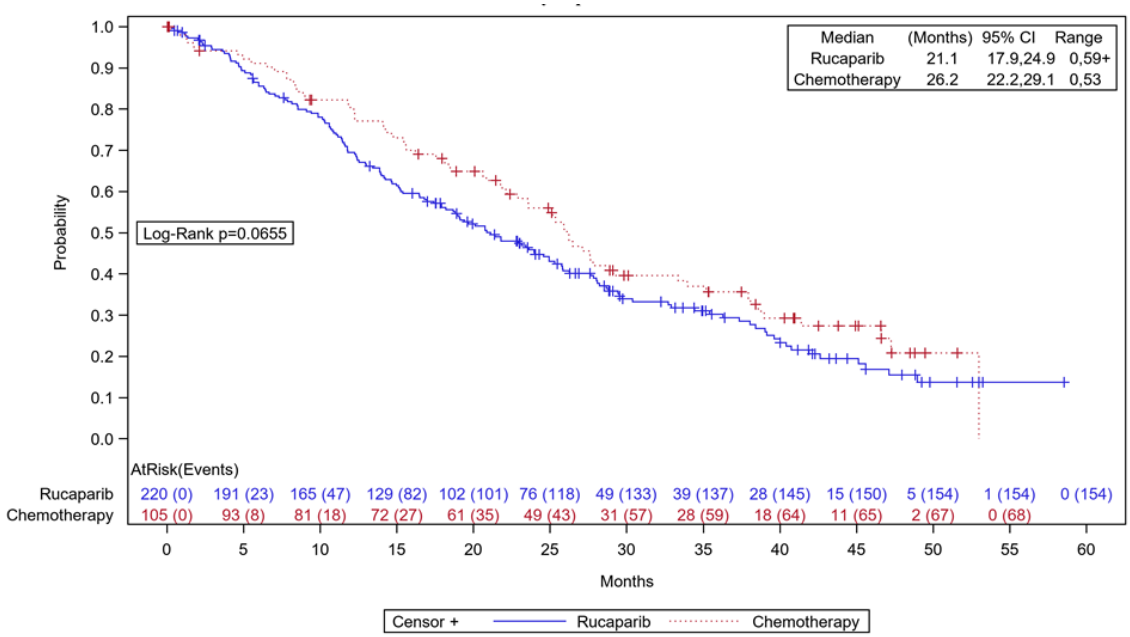
Sources: Tables 14.2.3.1.1, 14.2.3.1.2, 14.2.3.1.3, 14.2.3.4.1, 14.2.3.4.2, 14.2.3.4.5, 14.2.3.4.7, and 14.2.3.99.2; Figures 14.2.3.1.1, 14.2.3.1.2, 14.2.3.1.6, 14.2.3.1.7, 14.2.3.1.8, 14.2.3.4.1, 14.2.3.4.2, 14.2.3.4.8, 14.2.3.4.9, 14.2.3.4.10, 14.2.3.4.11, and 14.2.3.5.1.

Abbreviations: chemo = chemotherapy; CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; OS = overall survival; PFS2 = second event of progression-free survival.

[a] Log-rank analysis performed by randomization strata of platinum status for ITT and Efficacy Populations.

[b] Cox proportional hazard method performed by randomization strata of platinum status for ITT and Efficacy Populations.

Figure 1. ARIEL4 Kaplan-Meier Analysis of OS – Efficacy Population

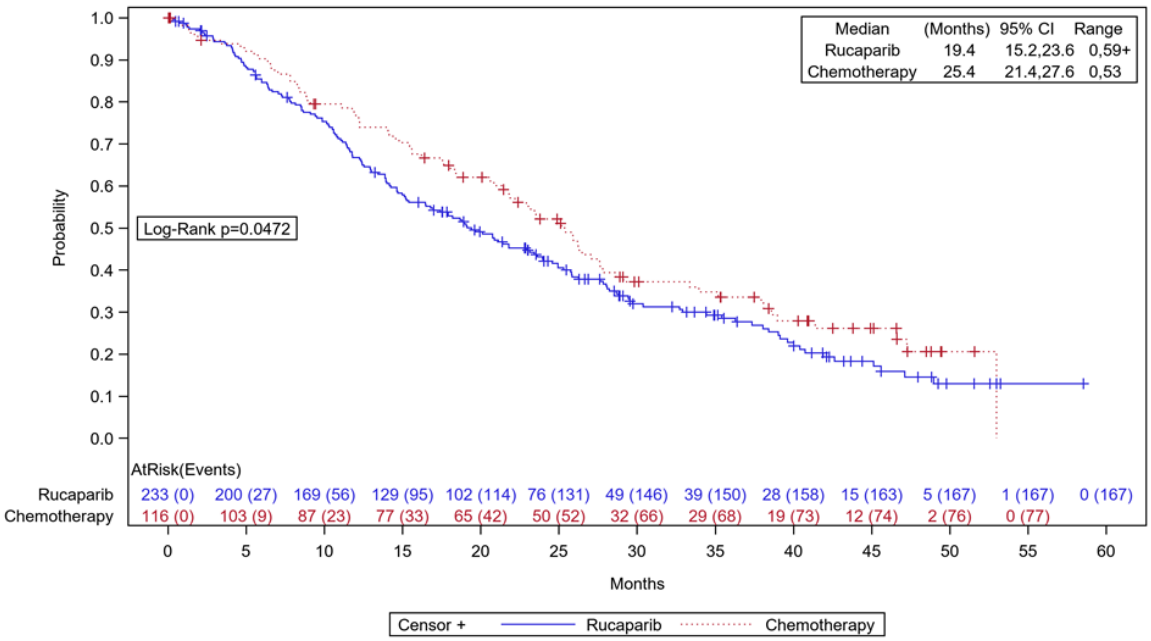


Source: Figure 14.2.3.4.1.

Abbreviations: CI = confidence interval; OS = overall survival.

Note: Log-rank analysis performed by randomization strata of platinum status.

Figure 2. ARIEL4 Kaplan-Meier Analysis of OS – ITT Population

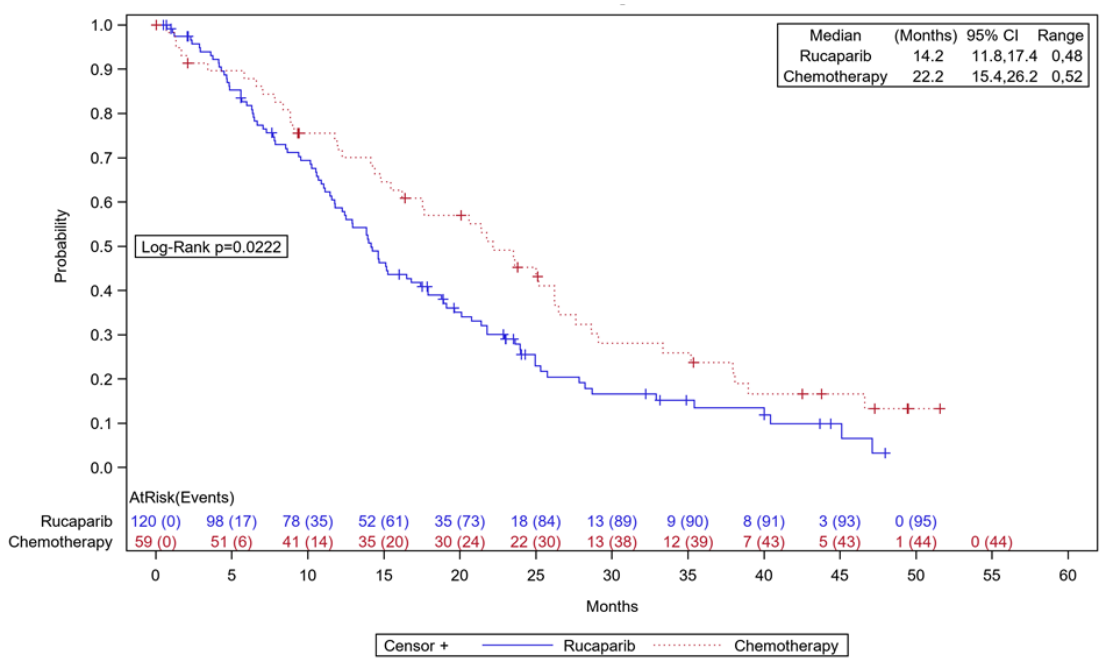


Source: Figure 14.2.3.4.2.

Abbreviations: CI = confidence interval; ITT = intent-to-treat; OS = overall survival.

Note: Log-rank analysis performed by randomization strata of platinum status.

Figure 3. ARIEL4 Kaplan-Meier Analysis of OS – Platinum-resistant Subgroup (ITT Population)

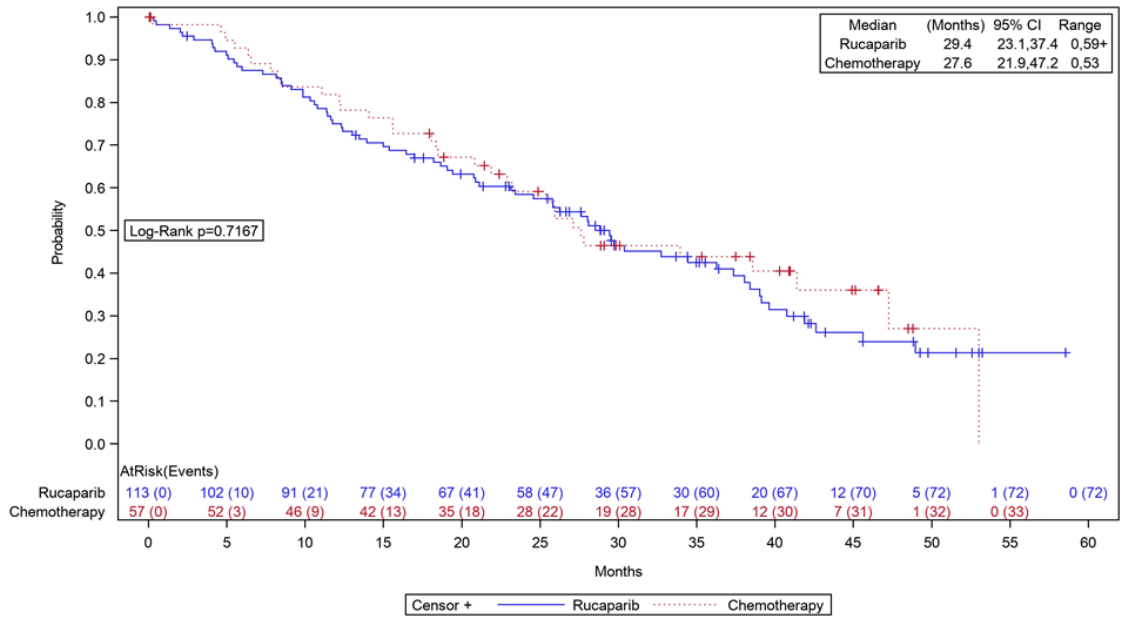


Source: Figure 14.2.3.4.8.

Abbreviations: CI = confidence interval; ITT = intent-to-treat; OS = overall survival.

Note: Log-rank analysis performed by randomization strata of platinum status.

Figure 4. ARIEL4 Kaplan-Meier Analysis of OS – Platinum-sensitive Combined (Fully and Partially) Subgroup (ITT Population)

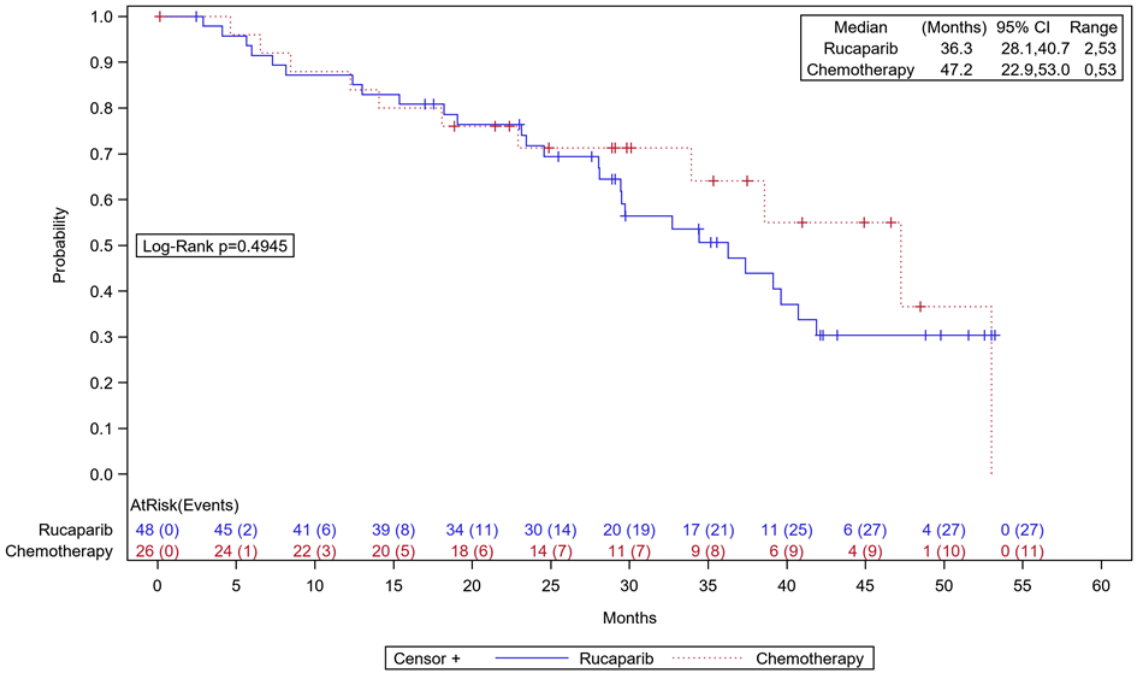


Source: Figure 14.2.3.4.11.

Abbreviations: CI = confidence interval; ITT = intent-to-treat; OS = overall survival.

Note: Log-rank analysis performed by randomization strata of platinum status.

Figure 5. ARIEL4 Kaplan-Meier Analysis of OS – Fully Platinum-sensitive Subgroup (ITT Population)

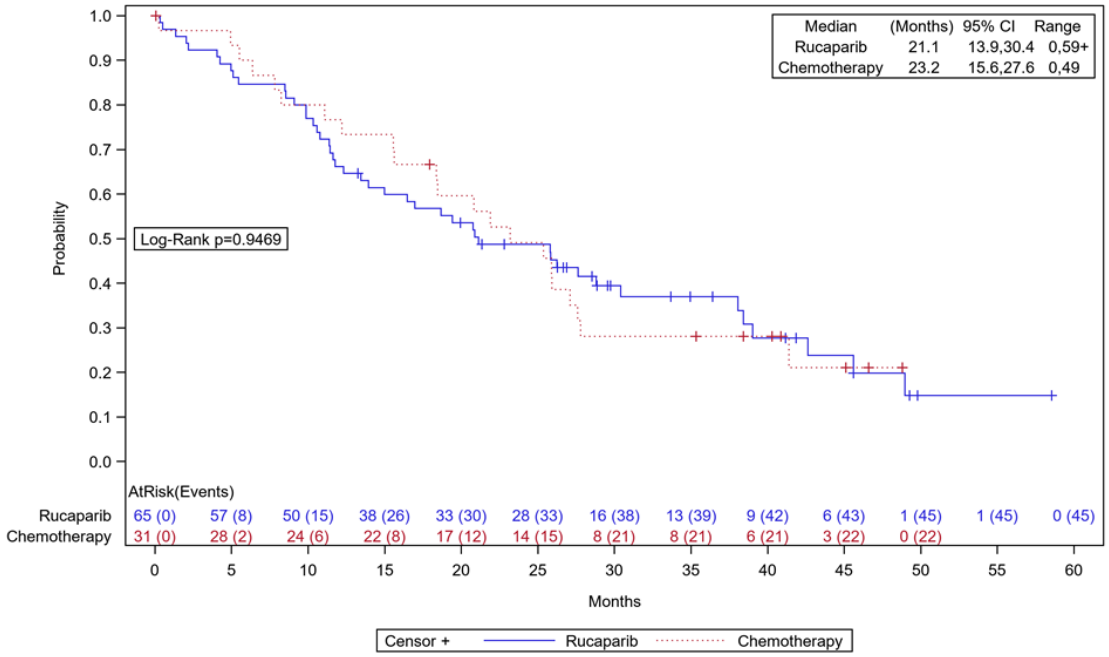


Source: Figure 14.2.3.4.10.

Abbreviations: CI = confidence interval; ITT = intent-to-treat; OS = overall survival.

Note: Log-rank analysis performed by randomization strata of platinum status.

Figure 6. ARIEL4 Kaplan-Meier Analysis of OS – Partially Platinum-sensitive Subgroup (ITT Population)



Source: Figure 14.2.3.4.9.

Abbreviations: CI = confidence interval; ITT = intent-to-treat; OS = overall survival.

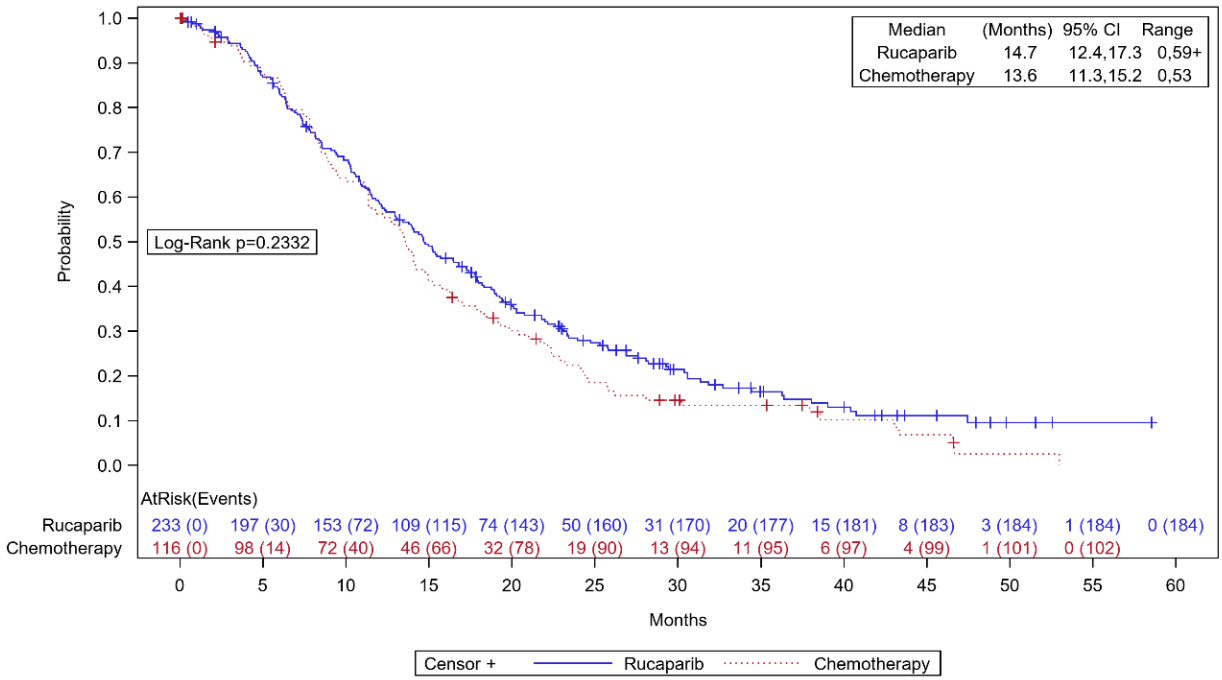
Note: Log-rank analysis performed by randomization strata of platinum status.

Supportive analysis: Second Event of Progression-free Survival

PFS2 is the time from randomization until progression on the line of therapy after the first trial therapy.

At the time of final analysis, the PFS2 data were 80.6 % (262/325 and 81.9% (286/349) mature) in the Efficacy and ITT Populations, respectively. Similar to the interim PFS2 results, there was no significant difference between rucaparib treatment and chemotherapy treatment for PFS2 in either the Efficacy Population or ITT Population in the final analysis.

Figure 7. ARIEL4 Kaplan-Meier Analysis of PFS2 – ITT Population

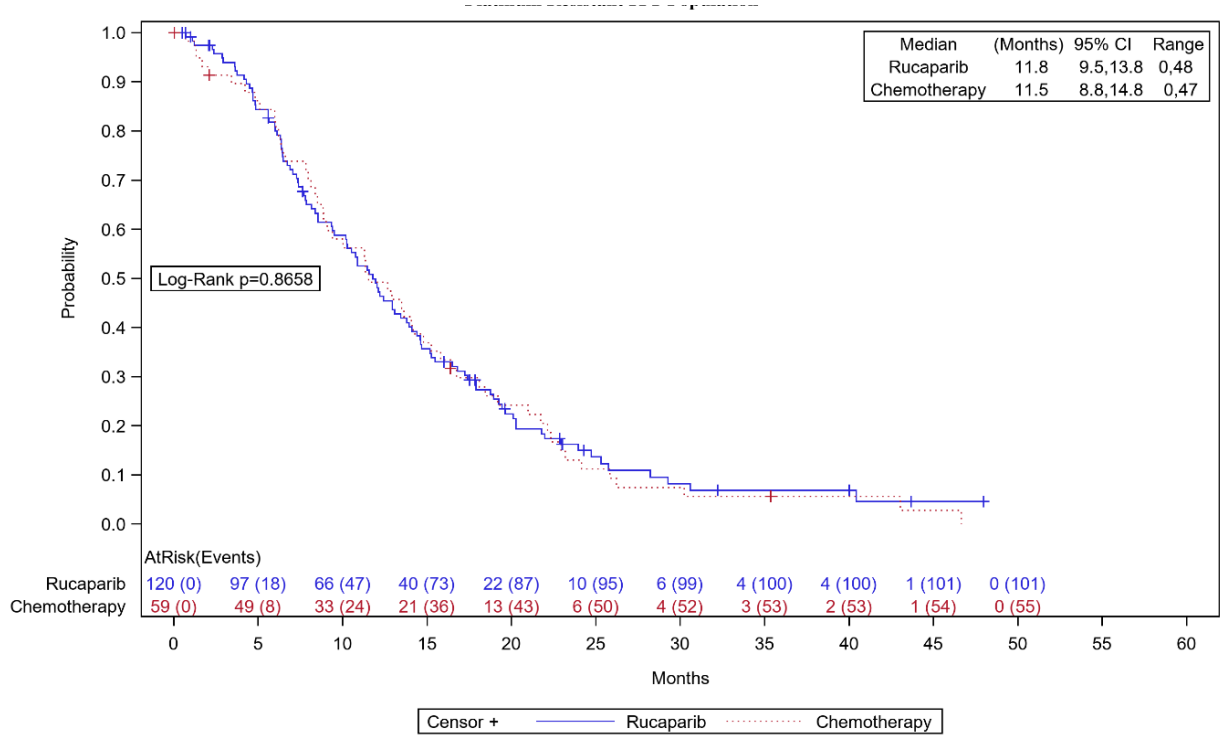


Source: Figure 14.2.3.1.2.

Abbreviations: CI = confidence interval; ITT = intent-to-treat; PFS2 = second event of progression-free survival.

Note: Log-rank analysis performed by randomization strata of platinum status.

Figure 8. ARIEL4 Kaplan-Meier Analysis of PFS2 – Platinum-resistant Subgroup (ITT Population)

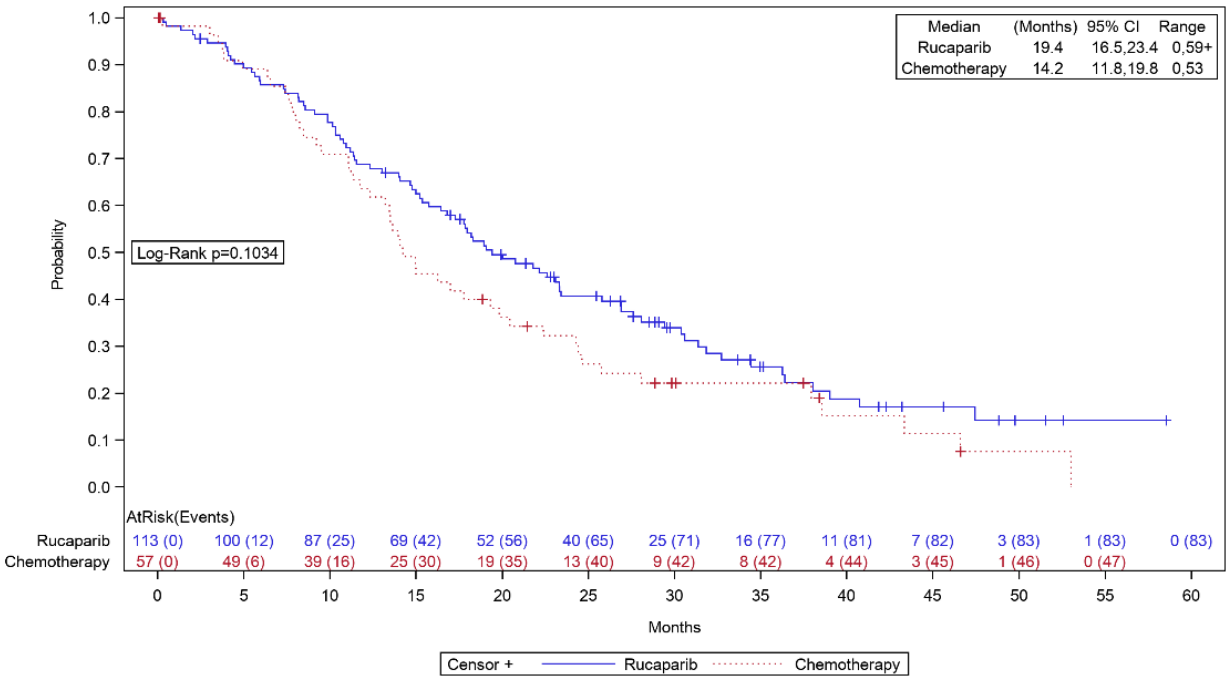


Source: Figure 14.2.3.1.6.

Abbreviations: CI = confidence interval; ITT = intent-to-treat; PFS2 = second event of progression-free survival.

Note: Log-rank analysis performed by randomization strata of platinum status.

Figure 9. ARIEL4 Kaplan-Meier Analysis of PFS2 – Platinum-sensitive Combined (Fully and Partially) Subgroup (ITT Population)

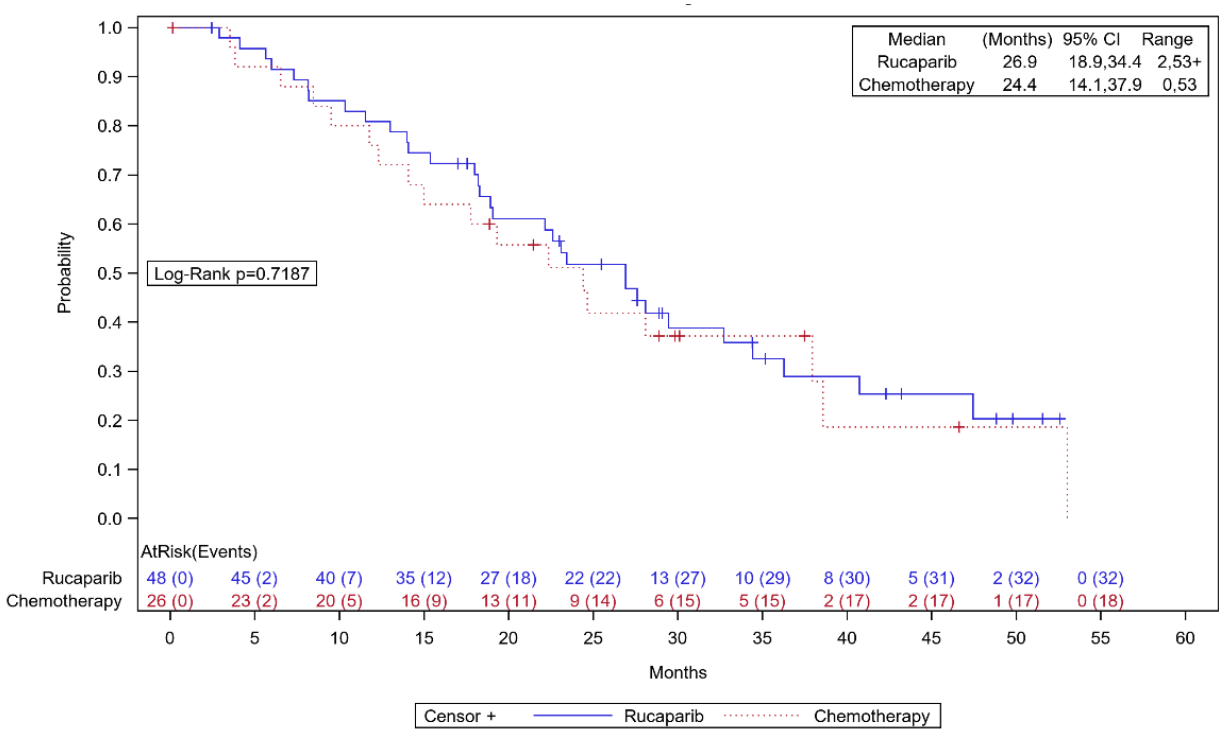


Source: Figure 14.2.3.5.1.

Abbreviations: CI = confidence interval; ITT = intent-to-treat; PFS2 = second event of progression-free survival.

Note: Log-rank analysis performed by randomization strata of platinum status.

Figure 10. ARIEL4 Kaplan-Meier Analysis of PFS2 – Fully Platinum-sensitive Subgroup (ITT Population)

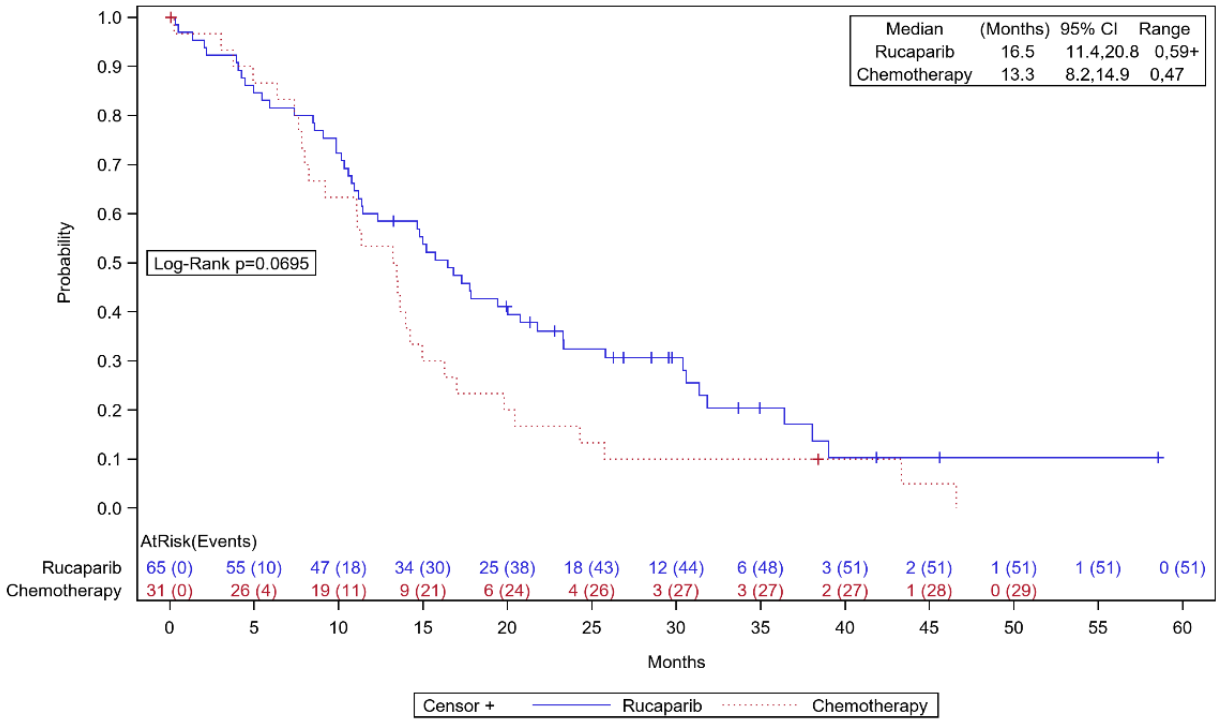


Source: Figure 14.2.3.1.8.

Abbreviations: CI = confidence interval; ITT = intent-to-treat; PFS2 = second event of progression-free survival.

Note: Log-rank analysis performed by randomization strata of platinum status.

Figure 11. ARIEL4 Kaplan-Meier Analysis of PFS2 – Partially Platinum-sensitive Subgroup (ITT Population)



Source: Figure 14.2.3.1.7.

Abbreviations: CI = confidence interval; ITT = intent-to-treat; PFS2 = second event of progression-free survival.

Note: Log-rank analysis performed by randomization strata of platinum status.

Conclusion: ***Final ARIEL4 Overall Survival***

ARIEL4 included a broad spectrum of ovarian cancer patients with platinum sensitive or platinum resistant disease. Within the platinum sensitive group, those with PPS disease were randomized to rucaparib or paclitaxel, and those with FPS disease were randomized to rucaparib or a platinum regimen.

Although the HR has improved in the final OS analysis, in the overall trial population, the HR continues to favour chemotherapy. However, the results between the subgroups based on platinum subgroups differ markedly. When considering the EMA approved indication, this is important, because the approved indication only applies to patients with platinum-sensitive disease who can no longer tolerate further platinum.

In the OS analysis of all platinum sensitive patients in ARIEL4, PFS2 favours rucaparib, the median OS is longer for rucaparib as compared to chemotherapy (29.4 months vs. 27.6 months) with a HR of 1.07 (95% CI 0.71-1.62; p = 0.746). These results are similar those reported for another PARPi in the SOLO3 randomized Phase 3 trial which evaluated olaparib versus chemotherapy in platinum-sensitive patients harbouring a BRCA mutation but which did not include platinum as a comparator (HR 1.07 [95% CI, 0.76-1.49]; p = 0.714).6 As in ARIEL4, the primary endpoint in SOLO3 was PFS. Taken together, the results from ARIEL4 and SOLO3 suggest a beneficial effect of PARPi treatment with no decrement in OS in the overall platinum-sensitive population.

The PPS subgroup is most relevant to the approved indication. In that subgroup, without making any adjustments for the confounding effects of the high rate of crossover, all efficacy endpoints, including the primary endpoint of PFS, the longer-term benefit endpoint of PFS2 and the OS endpoint support a positive benefit:risk of rucaparib for monotherapy treatment of adult patients with platinum sensitive, relapsed or progressive, BRCA-mutated (germline and/or somatic), high-grade epithelial ovarian,

fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum based chemotherapy, and who are unable to tolerate further platinum based chemotherapy.

An ARIEL 4 CSR addendum, which will include these analyses together with final OS, PFS2, and updated safety will be provided to the EMA in 3Q 2022.

MDS/AML Incidence in Final ARIEL4 Analysis

Between the visit cut-off for the initial ARIEL4 CSR of 30 September 2020 and the visit cut-off for the final OS analysis (10 April 2022), 2 additional cases of MDS were reported in patients who were randomized to the rucaparib arm. In total, 7 cases of MDS/AML (MDS = 6 cases, AML = 1 case) were reported for patients randomized to the rucaparib arm of ARIEL4. No cases have been reported in patients who crossed over to rucaparib from the chemotherapy arm. Of the 7 cases of MDS/AML, 3 cases of MDS were treatment emergent and the other 4 cases of MDS/AML (MDS = 3, AML = 1) occurred during long term follow up.

A Table summarizing the survival status for the 7 patients with reported cases of MDS/AML was provided.

As mentioned, an ARIEL4 CSR Addendum, which will include updated safety will be provided to the EMA in 3Q 2022.

Assessment of the MAH's response

The MAH has provided top-line results from the final analysis of OS and exploratory data for PFS2. A CSR addendum will be submitted later this year. Regarding OS, the platinum-resistant subgroup was more mature (77.5%) than the platinum-sensitive subgroup (61.8%). Data maturity was about 81% for the final PFS2 analysis.

The results from the final **OS** analysis (DCO 10-Apr-2022) have shown a HR of 1.31 (95% CI: 1.00, 1.73; p = 0.0507) in the ITT population. This is slightly better than the one reported at the time of the OS interim analysis and not statistically significant. By randomization subgroups (platinum sensitivity status), the worst results are again reported for the platinum-resistant population with a HR of 1.51 (95% CI: 1.05, 2.17) p = 0.0251. In platinum sensitive patients (fully and partially) a HR for OS of 1.07 (95% CI: 0.71, 1.62; p = 0.7455) is reported (pooled data) while separate results show better results in the partially platinum sensitive subgroup with a HR of 0.97 (95% CI: 0.58, 1.62; p = 0.9129) while the HR is of 1.24 (95% CI: 0.62, 2.50; p = 0.5405) in the fully platinum-sensitive population. The KM curves have been included and are quite similar to the ones available at the time of the interim OS analysis.

PFS2 results by subgroups and for the Efficacy and ITT Populations have also been provided. These are considered as supportive analyses considering that final results for OS are available. All estimated HRs favour rucaparib but the 95% confidence intervals include the unity in all cases. Again, the worst results are observed in the platinum resistant subgroup, in line with the reported OS data.

Of note, the MAH has sent a notification to request the removal of the "treatment" indication from the PI. In view of the remaining unresolved uncertainties regarding the observed OS detriment in the ARIEL4 study, it is currently not possible to confirm the positive B/R of rucaparib in the third line treatment indication and the proposal from the MAH to remove the indication is acknowledged and considered necessary, see also question 1.

Regarding **MDS/AML** incidence, based on the latest cut-off (10 April 2022), 2 additional cases of MDS have been reported in patients randomized to rucaparib. In the overall study, 7 cases of MDS/AML have been notified. One patient died due to MDS. Although their causal relationship with rucaparib can be questioned as development of such pathologies is a known risk of platinum-based chemotherapy, it

cannot be excluded. MDS/AML is already included in the SmPC and the new reported cases of MDS/AML were incorporated in a revised PI provided after circulation of the preliminary assessment report. Further information about cases of MDS/AML is expected at the time when the final CSR will be submitted (see below).

Since the 'treatment' indication is removed, no further efficacy data from the ARIEL4 study are formally required. However, the MAH should provide updated safety from the ARIEL4 study with the final CSR in order to update the PI (**REC**). The MAH proposed that section 4.8 of the SmPC will include safety data from a pooled analysis of studies where ovarian cancer patients received rucaparib monotherapy at the same posology, and therefore including also the ARIEL4 study (even if the treatment indication will no longer be approved).

Conclusion

Issue solved.

Clinical safety

Question 7

Regarding study ARIEL4, the MAH is requested to provide: i) safety data of intestinal obstruction adjusted by treatment exposure; ii) the narratives of all patients that reported an event of intestinal obstruction during the study.

Summary of the MAH's response

Table 1 presents a summary of TEAEs of intestinal obstruction (MedDRA preferred terms [PTs]: intestinal obstruction, large intestinal obstruction, and small intestinal obstruction) occurring during the Treatment Part of ARIEL4 as incidence per 100 patient-years to account for and normalize differing duration of exposure to the study drug between rucaparib and chemotherapy groups.

Table 1. Summary of TEAEs of Combined Intestinal Obstruction[a] per 100 Patient-years of Treatment – Treatment Part (Safety Population)

	Rucaparib (N=232)	Chemotherapy (N=113)
Number of TEAEs per 100 patient-years of treatment	8.0	4.8
Number of treatment-related TEAEs per 100 patient-years of treatment	0.6	0.0
Number of serious TEAEs per 100 patient-years of treatment	3.4	2.4
Number of serious treatment-related TEAEs per 100 patient-years of treatment	0.6	0.0
Number of TEAEs of Grade 3 or higher per 100 patient-years of treatment	5.7	0.0
Number of treatment-related TEAEs of Grade 3 or higher per 100 patient-years of treatment	0.6	0.0
Number of TEAEs leading to death per 100 patient-years of treatment	0.0	0.0
Number of TEAEs leading to study drug discontinuation per 100 patient-years of treatment	1.7	0.0
Number of treatment-related TEAEs leading to study drug discontinuation per 100 patient-years of treatment	0.6	0.0
Number of TEAEs leading to dose reduction or interruption per 100 patient-years of treatment	3.4	2.4
Number of treatment-related TEAEs leading to dose reduction or interruption per 100 patient-years of treatment	0.0	0.0

Source: Table 7.1.2.

Abbreviations: PT = preferred term; TEAE = treatment-emergent adverse event.

[a] Combined Intestinal Obstruction includes PTs of Intestinal obstruction, Large intestinal obstruction, and Small intestinal obstruction.

Taking duration of treatment into account, the number of TEAEs of intestinal obstruction is more comparable between treatment groups (8.0 events per 100 patient-years of treatment for rucaparib vs 4.8 events per 100 patient-years for chemotherapy). In particular, when related TEAEs are considered, the numbers are very similar (0.6 events per 100 patient-years of treatment for rucaparib vs 0 events per 100 patient-years for chemotherapy). In addition, the numbers of TEAEs leading to study drug discontinuation or dose reduction or interruption are comparable between treatment groups. Overall, these numbers do not indicate a safety concern regarding intestinal obstruction following administration of rucaparib.

Narratives for patients who received rucaparib during the Treatment Part of the study, patients who received chemotherapy during the Treatment Part of the study, and patients who received chemotherapy during the Treatment Part of the study then crossed over to receive rucaparib have been provided.

Assessment of the MAH's response

Intestinal obstruction is a common complication of advanced gynaecological tumours, where peritoneal disease is often present. In study ARIEL4, a higher incidence of intestinal obstructions was reported with rucaparib, compared to chemotherapy. As longer treatment duration with rucaparib could have played a role in these reported results, the MAH was request to provide exposure-adjusted incidences of these events. The submitted results still show higher incidence in the rucaparib arm but the imbalances seem to be smaller (8.0 events per 100 patient-years of treatment for rucaparib vs. 4.8 events per 100 patient-years for chemotherapy). For related AEs, the numbers were 0.6 events per 100 patient-years of treatment for rucaparib vs. 0 events per 100 patient-years for chemotherapy.

Narratives for the patients reporting TEAEs of intestinal obstruction in both treatment arms have been provided. All patients, similarly to the overall included population in this study, presented metastatic cancer, after several treatment lines and some of them had already suffered an episode of intestinal obstruction during previous chemotherapy treatment regimens. Some of the patients were on progressive disease at the time of the event but others were in response. Most of the cases were considered not related to treatment by the investigators but related to the disease under investigation. It is difficult to exclude any possibility of relation between rucaparib and cases of intestinal obstruction but, although it is agreed that the underlying disease may have played a relevant role based on the exposure-adjusted rates and previous observations of intestinal obstruction, including serious events (Rubraca EPARs EMA/CHMP/238139/2018, EMA/902679/2019), information on this AE should be included in the SmPC sections 4.4 and 4.8. The MAH has added intestinal obstruction in sections 4.4. and 4.8 of the SmPC in a revised PI provided after circulation of the preliminary assessment report. However the text proposed in section 4.4 is not considered informative and is therefore not agreed. Even if a reference to that reports could be confounded by the underlying disease may be kept, a description of the reported events (seriousness, fatal cases) should also be included together with guidance how to proceed in case of a suspected event. The MAH is requested to make a proposal.

Conclusion

Issue not solved.

15. 3rd Request for supplementary information

15.1. Other concerns

Product information

1. Intestinal obstruction has been included as ADR in the SmPC (sections 4.4 and 4.8). However the text proposed in section 4.4 is not considered informative and is therefore not agreed. Even if a reference to that reports could be confounded by the underlying disease may be kept, a description of the reported events (seriousness, fatal cases) should also be included together with guidance how to proceed in case of a suspected event. The MAH is requested to make a proposal.

Letter of recommendations

2. The following recommendation "to provide the Study CO-338-043 final PFS2 and OS analyses as a CSR Addendum" should be amended to "The MAH will provide the final CSR for study CO-338-043 (ARIEL4)." The MAH should provide an updated letter of recommendations.

16. Assessment of the responses to the 3rd request for supplementary information

Product information

Question 1

Intestinal obstruction has been included as ADR in the SmPC (sections 4.4 and 4.8). However the text proposed in section 4.4 is not considered informative and is therefore not agreed. Even if a reference to that reports could be confounded by the underlying disease may be kept, a description of the reported events (seriousness, fatal cases) should also be included together with guidance how to proceed in case of a suspected event. The MAH is requested to make a proposal.

Summary of the MAH's response

An initial proposal for information to be included in section 4.4 was made by the MAH that was not agreed as it was considered not informative. It was noted that a description of the reported events (seriousness, fatal cases) should be included together with guidance how to proceed in case of a suspected event. The MAH has made the following proposal:

"Intestinal obstruction

Intestinal obstruction has been observed in patients treated with rucaparib; 4.5% of ovarian cancer patients experienced a serious event of intestinal obstruction, with a fatal outcome of less than 0.1%. Reports are confounded as underlying disease may play a role in the development of intestinal obstruction in patients with ovarian cancer. In the event of suspected intestinal obstruction, perform a prompt diagnostic evaluation and treat appropriately."

Assessment of the MAH's response

The proposal made by the MAH is not entirely agreed. The following text is proposed (**new text added**; ~~**text deleted**~~):

"Intestinal obstruction

Cases of ~~**I**~~intestinal obstruction **have** ~~**has**~~ been observed in **ovarian cancer** patients treated with rucaparib **in clinical trials**; 4.5% of ~~**ovarian cancer**~~ patients experienced a serious event of intestinal obstruction, with a fatal outcome of less than 0.1%. ~~**Reports are confounded as**~~ **The** underlying disease may play a role in the development of intestinal obstruction in patients with ovarian cancer. In the event of suspected intestinal obstruction, ~~**perform**~~ a prompt diagnostic evaluation **should be conducted** and **the patient should** be treat**ed** appropriately."

Conclusion

The MAH submitted an updated PI on 7th September. The above proposed changes were implemented. Issue solved.

Letter of recommendations

Question 2

The following recommendation "to provide the Study CO-338-043 final PFS2 and OS analyses as a CSR Addendum" should be amended to "The MAH will provide the final CSR for study CO-338-043 (ARIEL4)." The MAH should provide an updated letter of recommendations.

Summary of the MAH's response

The MAH has provided an updated letter of recommendations.

Assessment of the MAH's response

The MAH has submitted an updated letter of recommendations that has been updated as follows.

~~10.~~11. The MAH commits to provide the Study CO-338-043 CSR Addendum containing final PFS2~~, and~~ OS analyses and safety. ~~as a CSR Addendum~~.	EMEA/H/C/004272/II/0029

The MAH should update the letter as requested. Inclusion of a specific reference to PFS2, OS and safety data can be agreed, i.e. "The MAH commits to provide the final CSR for study CO-338-043 including final PFS2 and OS analyses as well as safety data."

Conclusion

The MAH provided an updated letter of recommendations on 7th September. The above proposed changes were implemented. Issue solved.