21 July 2022
EMA/674344/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure under Article 20 of Regulation (EC) No 726/2004

Invented name: Rubraca

INN: rucaparib

Procedure number: EMEA/H/A-20/1518/C/4272/0033

Note:

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

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1. Information on the procedure

On 27 August 2021, a type II variation application for Rubraca (rucaparib) (EMEA/H/C/004272/II/0029) was submitted to EMA in order to evaluate results from study CO-338-043 (ARIEL4): a phase 3, multicentre, open-label, randomised study evaluating the efficacy and safety of rucaparib versus chemotherapy for the treatment of relapsed ovarian cancer. This study is listed as a specific obligation in Annex II of the product information.

During the assessment of this variation procedure, although a difference in progression free survival (PFS) as assessed by the investigator (invPFS) favouring rucaparib was observed in the final analysis, an interim analysis of overall survival (OS) performed at a 51% data maturity showed a detriment in OS in patients treated with Rubraca compared to patients receiving chemotherapy.

In view of the above, on 22 April 2022, the European Commission (EC) triggered a referral under Article 20 of Regulation (EC) No 726/2004, and requested the CHMP to assess the impact of the above concerns on the benefit-risk balance of Rubraca in the approved "third line or more treatment" indication, i.e.:

- monotherapy treatment of adult patients with platinum sensitive, relapsed or progressive, breast cancer gene (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,

and to issue a recommendation on whether the relevant marketing authorisation(s) should be maintained or amended.

In addition, the EC requested the Agency to give its opinion, as to whether temporary measures were necessary to protect public health.

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 on a direct healthcare professional communication (DHPC) to communicate this temporary restriction to healthcare professionals, together with a communication plan.

2. Scientific discussion

2.1. Introduction

Rucaparib is an inhibitor of poly(ADP-ribose) polymerase (PARP) enzymes, including PARP-1, PARP-2, and PARP-3, which play a role in deoxyribonucleic acid (DNA) repair.

Rucaparib has been shown to have *in vitro* and *in vivo* anti-tumour activity in BRCA mutant cell lines through a mechanism known as synthetic lethality, whereby the loss of two DNA repair pathways is required for cell death. Increased rucaparib-induced cytotoxicity and anti-tumour activity was observed in tumour cell lines with deficiencies in BRCA1/2 and other DNA repair genes. Rucaparib has been shown to decrease tumour growth in mouse xenograft models of human cancer with or without deficiencies in BRCA.

Rubraca (rucaparib) is authorised since 2018 and is indicated:

- as monotherapy for the 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 (so called "3rd line or more treatment" or "treatment" indication);
- as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy (so called "maintenance" indication).

Rubraca was first granted a conditional marketing authorisation (CMA) in the "treatment" indication based on overall response rate (ORR) data from a pooled population from two phase 2 single arm studies, namely study CO-338-010[1] and study CO-338-017[2]. This CMA was subject to confirmation of rucaparib efficacy and safety in study CO-338-043 (ARIEL4): a phase 3, multicentre, open-label, randomized (2:1) study of rucaparib 600 mg BID versus chemotherapy in patients with relapsed, BRCA-mutant, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who received two or more prior lines of chemotherapy. This study is listed as a specific obligation in Annex II of the product information of Rubraca.

In 2019, the indication was extended to add a second indication ("maintenance" indication) based on progression-free survival (PFS) data from study CO-338-014 (ARIEL3)[3].

On 27 August 2021 a type II variation application for Rubraca (EMEA/H/C/004272/II/0029) was submitted to EMA to evaluate results from study CO-338-043 (ARIEL4). During the assessment of this procedure, although a difference in PFS in favour of rucaparib was observed in the final analysis, an interim analysis of OS performed at a 51% data maturity showed nevertheless a detriment in OS.

These OS findings are however not considered relevant for the "maintenance" indication as the pathophysiological characteristics of the tumours of patients receiving rucaparib in this indication are different compared to those of patients in the "treatment" indication. In addition, while the "treatment" indication was based on a pooled population subgroup data from two phase 2 open label studies leading to a conditional marketing authorisation and agreed specific obligations, the "maintenance" indication subsequently approved was based on data from a randomised, double-blind, placebo-controlled phase 3 study (ARIEL3) supporting this indication. During the initial assessment of the "maintenance" indication limited interim OS data were available, but a detrimental effect on OS was considered unlikely. More mature OS data in the maintenance setting have recently become available and do not raise concern on a potential detrimental effect on OS.

In the framework of the present procedure, CHMP considered all available data submitted by the MAH including further results of study CO-338-043 (ARIEL4), including OS data at 70% maturity.

A summary of the most relevant information is included below.

[1] A phase 1/2, open-label, safety, pharmacokinetic, and preliminary efficacy study of oral rucaparib in patients with gBRCA mutation ovarian cancer or other solid tumour
[2] A phase 2, open-label study of rucaparib in patients with platinum-sensitive, relapsed, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer (ARIEL2)
[3] A phase 3 double-blind efficacy study of rucaparib as switch maintenance after platinum in relapsed high grade serous and endometrioid ovarian cancer (ARIEL3), see variation EMEA/H/C/004272/II/0001

2.2. Data on efficacy

During the referral procedure, new data have been submitted using a data cut-off date of 10 April 2022 relating to final analysis of OS data at 70% maturity, second event of progression free survival (PFS2), and the adverse events of special interest (AESIs) of myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) (see safety part further below). Of note, the MAH also claimed in the framework of the procedure that an additional study to confirm the benefit of Rubraca in the "treatment" indication would not be feasible as the use of PARP inhibitors has become uncommon in the later line treatment of BRCA mutation-associated advanced ovarian cancer.

2.2.1. Study design

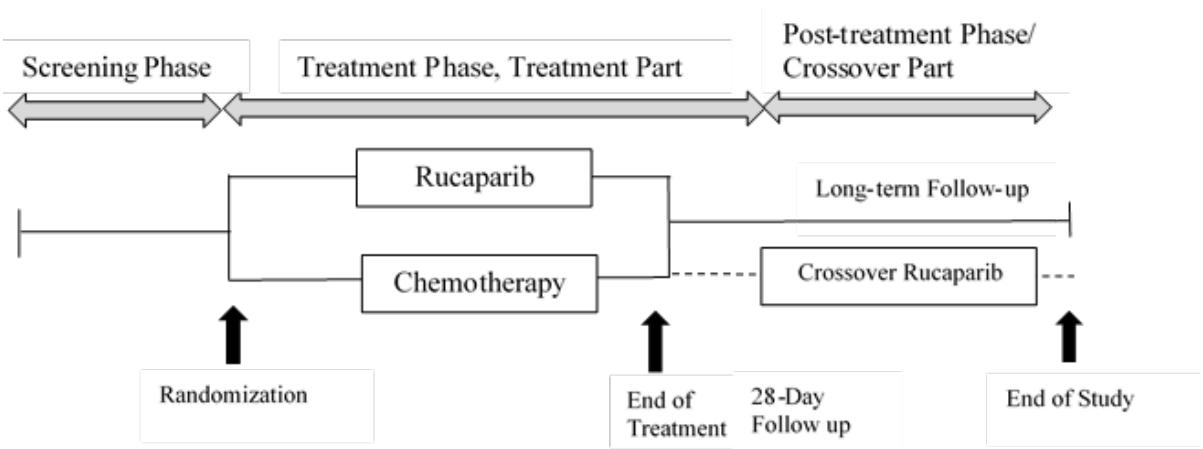
Table 1. Overview of key efficacy data submitted

Study id and design / reference	Key objectives / endpoints	Population	Inclusion/ exclusion criteria	Treatment	Main efficacy results
Therapeutic indication: 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.					
Study CO-338-043 (ARIEL4) Phase 3, open-label, multicentre, randomized, safety and efficacy study	**Primary endpoint:** investigator-assessed progression-free survival (invPFS) by response evaluation criteria in solid tumours (RECIST) version 1.1 **Secondary endpoints:** objective response rate (ORR) by RECIST 1.1, duration of response (DOR), ORR by RECIST 1.1 and cancer antigen-125 (CA-125), patient-reported	N=349 randomized 2:1 to receive rucaparib or chemotherapy Randomisation stratified by progression-free interval (PFI) after the most recent platinum	Patients with confirmed high-grade serous or Grade 2-3 endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer and harbor a deleterious (BRCA 1/2) mutation	Rucaparib 600 mg BID vs. active SoC chemotherapy comparator Chemotherapy treatment was based on randomisation strata Platinum resistant (PFI≥1 to <6 months) and partially platinum-sensitive (PFI≥6 to <12 months): weekly paclitaxel Platinum-sensitive (PFI ≥12 months): platinum monotherapy or platinum-doublet max. 8 cycles	**invPFS** (efficacy population) HR: HR 0.639 (95% CI, 0.489-0.835); p=0.0010. Median invPFS: 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. **ORR:** 40.3% (95% CI 33.6%-47.2%) vs. 32.3% (95% CI 23.1%-42.6%) favouring the rucaparib arm (p=0.1287). **DOR:** 9.4 (95% CI; 7.5-11.1) months for the

	outcomes (PRO). overall survival (OS) (out from the hierarchical testing procedure) **Exploratory endpoint:** progression-free survival on a subsequent line of treatment (PFS2)				rucaparib arm and 7.2 (95% CI; 4.0-11.4) for the chemotherapy arm. **Interim OS:** HR 1.550 (95% CI, 1.085-2.214), p=0.0161 Final OS: HR 1.31 (95% CI, 0.98-1.74), p=0.0704

The study consisted of a screening phase, randomisation (2:1 rucaparib: chemotherapy), treatment part, and post-treatment phase/crossover part. Patients initially randomized to chemotherapy had the option to crossover to rucaparib treatment following progression in the treatment part, with sponsor approval and additional consent (Figure 1).

Figure 1. Simplified schematic of study design for study CO-338-043



2.2.1.1. Inclusion and exclusion criteria

As key inclusion criteria, eligible patients had to have a histologically confirmed diagnosis of high-grade serous or Grade 2 or Grade 3 endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer. Patients with a histology of other than serous or endometrioid were also eligible if they were known to harbour a deleterious germ line or somatic BRCA 1/2 mutation. Patients had to have received ≥2 prior chemotherapy regimens, with at least 1 regimen including a platinum, with a relapse or progressive disease as confirmed by radiologic assessment. Patients had to also have a documented treatment-free interval of ≥6 months following the first chemotherapy regimen received.

In addition, eligible patients had to have a deleterious BRCA 1/2 mutation as confirmed by a central laboratory, and evaluable disease (i.e. at least one target or non-target lesion that can be assessed per response evaluation criteria in solid tumours (RECIST). Patients should also have presented an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 and adequate organ function confirmed by standard laboratory values.

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. In addition, 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 central nervous system (CNS) metastases.

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

- have documented radiological progression per RECIST version 1.1 during or following completion of comparator arm chemotherapy and receive Sponsor approval,
- adequate haematological and biological function, confirmed by standard local laboratory values ≤ 14 days prior to first dose of rucaparib,
- all Grade 3 and 4 hematologic and non-hematologic toxicities (except alopecia, nausea, vomiting, or adequately controlled diarrhoea) improved to baseline or ≤ common terminology criteria for adverse events (CTCAE) Grade 1,
- have an ECOG performance status of 0-1.

2.2.1.2. Treatments

Patients were randomised 2:1 to receive rucaparib or active system organ class (SOC) chemotherapy comparator in the treatment phase. Rucaparib was administered at an initial dose of 600 mg twice daily (BID) in a 28-day treatment cycle. Treatment could be held or reduced in case of toxicity following established criteria.

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.

Patients initially randomized to chemotherapy had 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 had to occur within 8 weeks following radiologic disease progression.

2.2.1.3. Objectives

The primary objective of the study was to determine investigator-assessed progression-free survival (invPFS) by RECIST version 1.1 of rucaparib vs. chemotherapy.

The secondary objectives included progression-free survival (PFS) by blinded independent review, objective response rate (ORR), duration of response (DOR), patient-reported outcomes (PRO) as well as safety objectives.

Multiple exploratory objectives were included in this study, such as progression-free survival on a subsequent line of treatment (PFS2), disease control rate (DCR) and PRO (Euro-Quality of Life 5D (EQ-5D)).

2.2.1.4. Endpoints

The primary endpoint was invPFS. Patients without a documented event of progression (or death) were censored on the date of their last tumour radiologic assessment or date of randomisation if no post-baseline tumour assessments had been performed.

For the Treatment Part, the secondary endpoints part of a hierarchical step-down procedure included ORR by RECIST 1.1, DOR by RECIST 1.1, ORR by RECIST 1.1 and/or cancer antigen-125 (CA-125) response and PRO as assessed by the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire C30 (EORTC QLQ-C30) Global Health Status score.

The stand-alone secondary endpoints for the Treatment Part of the study outside of the step-down procedure were PFS by blinded independent central review (BICR), OS, PRO as assessed by the EORTC QLQ-C30 and quality of life questionnaire ovarian cancer module OV28 (QLQ-OV28).

The exploratory endpoints were PFS2, DCR and PRO (European quality of life 5 dimensions 3 level version (EQ-5D-3L VAS)).

2.2.1.5. Sample size

Approximately 345 patients were planned to be randomised 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.

2.2.1.6. Analysis populations

The Efficacy Population refers to all randomised patients with a deleterious BRCA mutation, excluding those identified to have a BRCA reversion mutation, while the Intent-to-treat (ITT) Population refers to all randomised patients.

2.2.1.7. Statistical methods

All efficacy analyses were performed in both the Efficacy Population and in the ITT Population in this order. When the primary endpoint was statistically significant, the secondary efficacy endpoints were tested in the following order: ORR, DOR, ORR and CA-125 response, PRO as assessed by the EORTC QLQ-C30 Global Health Status score first in the Efficacy Population and then in the ITT Population.

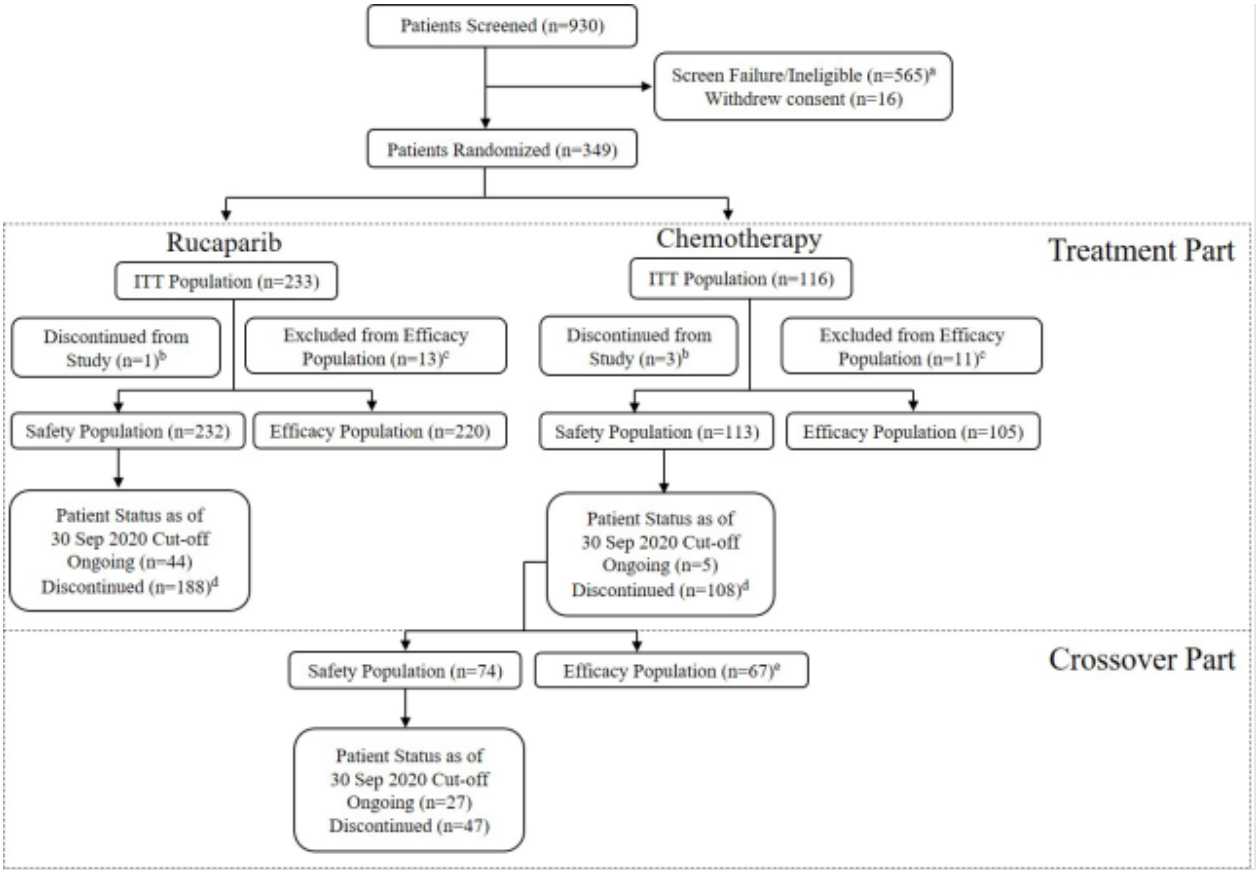
OS was analysed using Cox proportional hazard methodology. The stratified HR from the Cox proportional hazard model is used to estimate the HR between the randomised treatment groups. It was anticipated that the data for OS would be heavily censored at the time of the initial clinical study report (CSR) analysis. In order to adjust for multiple analyses of OS at a later stage, a stopping rule was applied. The Haybittle-Peto stopping rule was applied where an OS result with a p-value < 0.001

could be used to claim superiority of rucaparib compared to chemotherapy. This means that a p-value < 0.05 could be utilised at the final analysis which is projected to be once 70% of death events have been collected (70% maturity of the OS data).

2.2.1.8. Patient disposition

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). A patient disposition flowchart is presented in Figure 2.

Figure 2. Patient disposition flowchart for Study CO-338-043A



2.2.1.9. Patient demographic characteristics

The demographic characteristics of both treatment groups were well balanced. All patients were female with a median age of 58.0 years (range: 38-85 years) and the median body mass index (BMI) was 27.7 kg/m^2. Patients were enrolled from 12 countries with the treatment groups well balanced for each country.

Most 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).

The disease burden was similar between the treatment groups.

Both treatment groups had the same number of prior chemotherapy treatments with a median at 2.0. Enrolled patients had a mean (standard deviation (StD)) progression-free interval (PFI) of 8.3 (9.2) months following the last platinum-containing therapy regimen received.

With regard to the BRCA mutation status, the majority of patients (74.5%) in the ITT Population were identified to have a BRCA1 gene mutation, with a BRCA2 gene mutation identified in 25.2% of patients. Mutated BRCA gene and germ line vs. somatic mutation status were well balanced between the rucaparib and chemotherapy treatment groups.

2.2.1.10. Outcomes and estimation

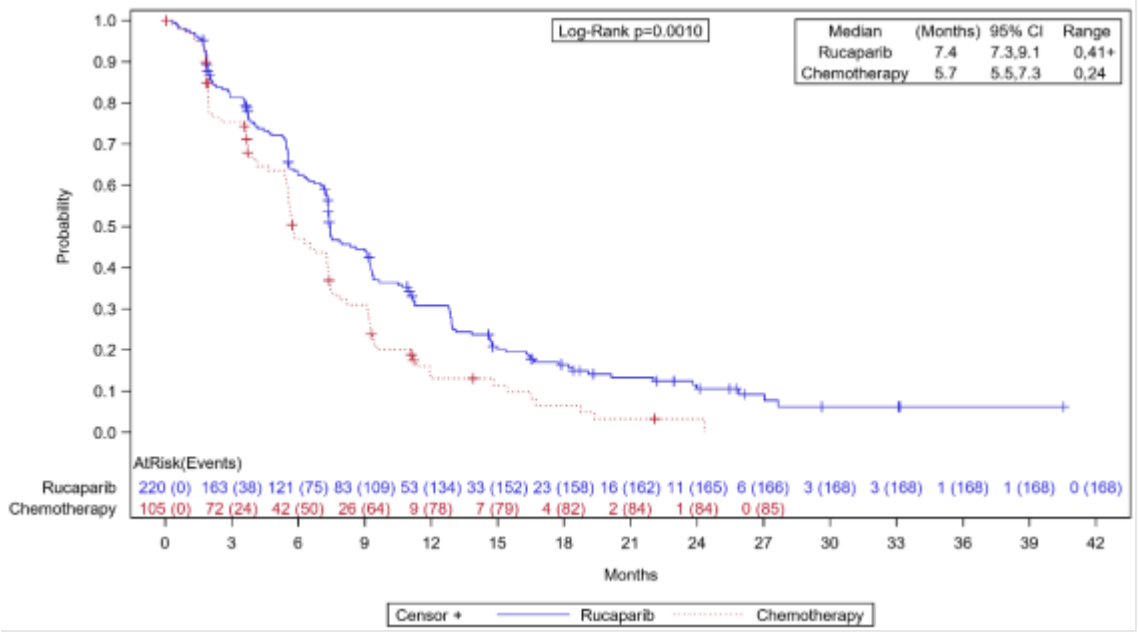
Progression-free survival per investigator (invPFS) (data cut-off date: 30-Sep-2020)

The primary efficacy endpoint was invPFS using RECIST version 1.1 or death due to any cause, using the 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).

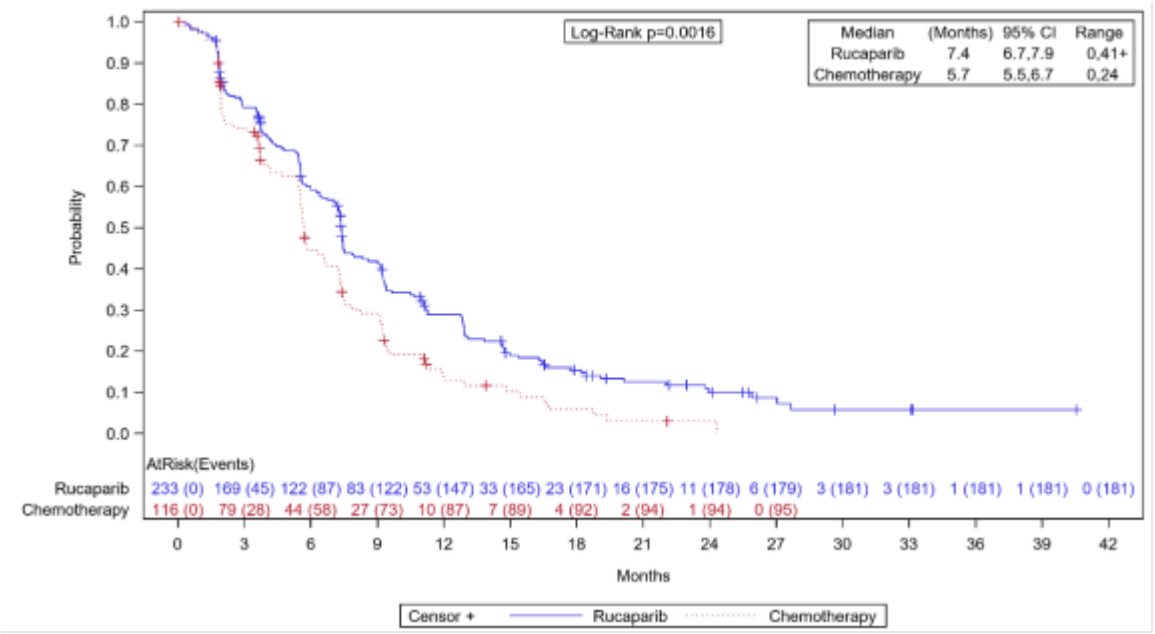
InvPFS was also estimated by the Kaplan-Meier method (Figure 3) and the stratified log-rank test was used to compare invPFS between the rucaparib and chemotherapy treatment groups. The median invPFS was 7.4 months (95% CI, 7.3-9.1) for the rucaparib group compared to 5.7 months (95% CI, 5.5-7.3) for the chemotherapy group.

Figure 3. Progression-free Survival per Investigator – Treatment part (Efficacy Population)



In the ITT Population as part of the 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 4) 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 4. Progression-free Survival per Investigator – Treatment part (ITT Population)



Sensitivity analyses performed were in line with the main analysis results.

Objective response rate (ORR)

The first secondary efficacy endpoint as part of the hierarchal 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).

There was no statistical significance achieved for ORR in the Efficacy Population. Therefore, statistical significance could not be claimed for the subsequent secondary endpoint analyses (ORR, ORR and/or CA-125 response, EORTC QLQ-C30 global health status score).

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

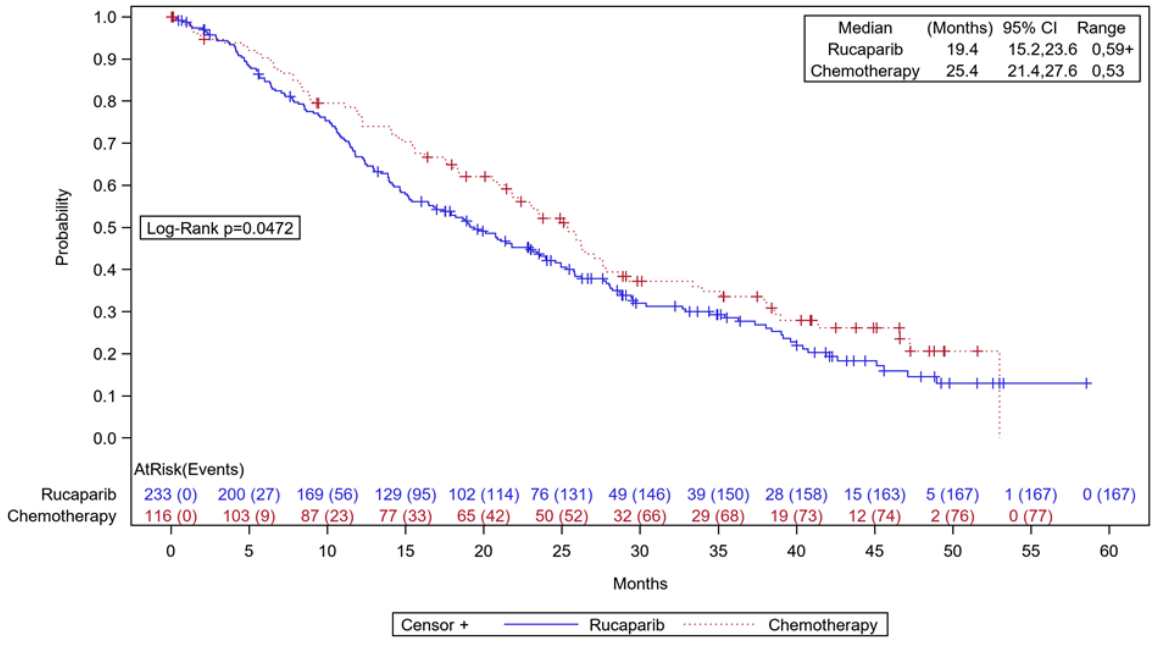
The final OS analysis was set at 70% (244/349) of death events in the ITT Population which was reached in April 2022. The platinum-resistant subgroup was more mature (77.6% [139/179]) than the platinum-sensitive subgroup which had 61.8% (105/170) OS events and was comprised of the partially platinum-sensitive (PPS) (69.8% [67/96]) and the fully platinum-sensitive (FPS) subgroups (51.4% [38/74]) (Table 2).

Table 2. ARIEL4 Final OS (70% maturity) – All Population and Subgroups

Population/ Subgroup	Overall Survival			
	Rucaparib	Chemo	Rucaparib vs Chemo	
			Kaplan-Meier Analysis[a]	Cox Proportional Hazard[b]
	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
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

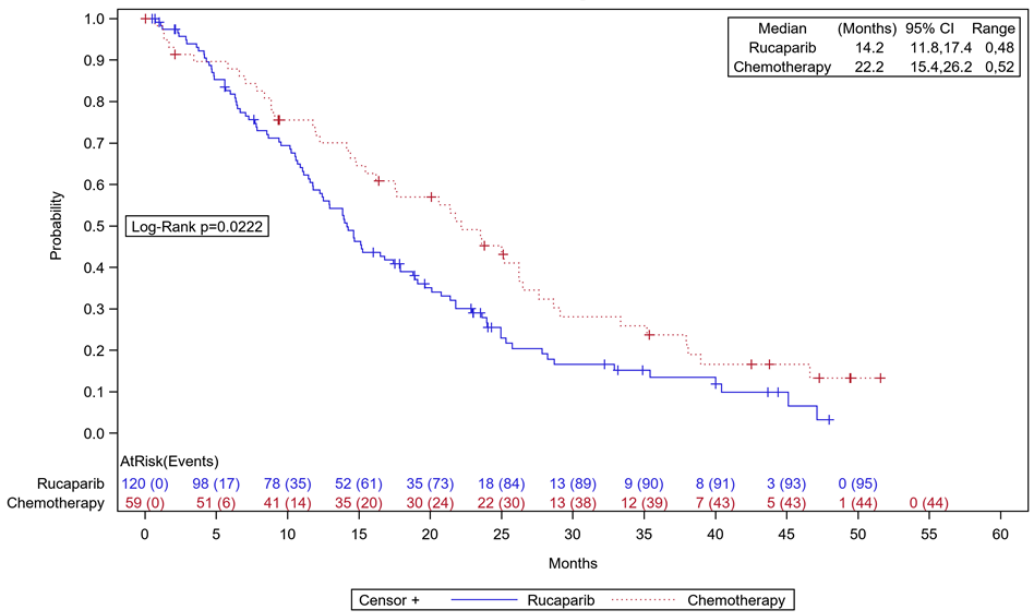
In the ITT population, median OS was 19.4 months in the rucaparib group compared with 25.4 months in the chemotherapy group resulting in a HR of 1.31 [95% CI: 1.00, 1.73] (p=0.0507) (Figure 5). Although not statistically significant, the results from the final OS analysis in this population favour the chemotherapy treatment over rucaparib (Table 2).

Figure 5. ARIEL4 Kaplan-Meier Analysis of OS – ITT Population



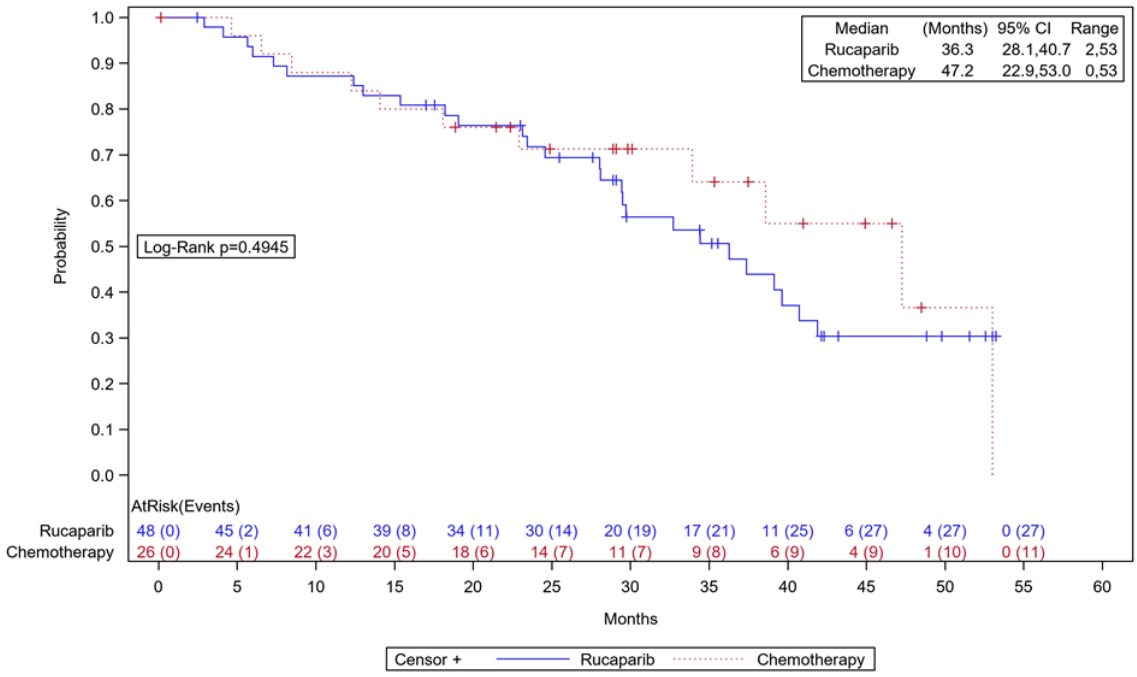
In the platinum-resistant subgroup of the ITT population, median OS was 14.2 months in the rucaparib group compared with 22.2 months in the chemotherapy group (Figure 6) resulting in a HR of 1.51 [95% CI: 1.05, 2.17] (p=0.0251).

Figure 6. ARIEL4 Kaplan-Meier Analysis of OS – Platinum-resistant Subgroup (ITT Population)



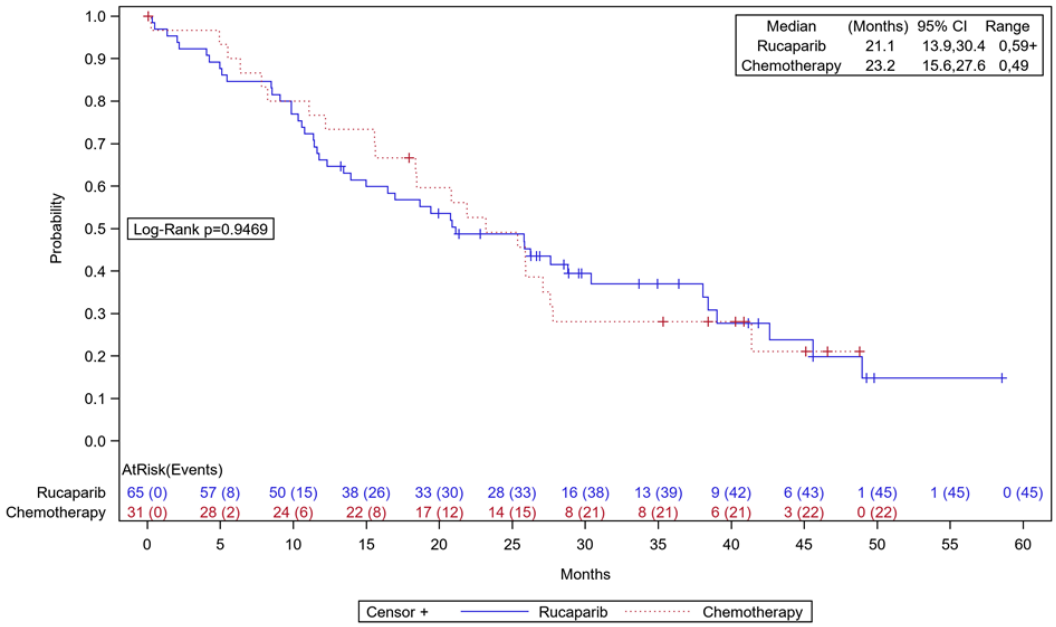
In the fully platinum-sensitive subgroup of the ITT population, median OS was 36.3 months in the rucaparib group compared with 47.2 months in the chemotherapy group (Figure 7) resulting in a HR of 1.24 [95% CI: 0.62, 2.50] (p=0.5405).

Figure 7. ARIEL4 Kaplan-Meier Analysis of OS – Fully Platinum-sensitive Subgroup (ITT Population)



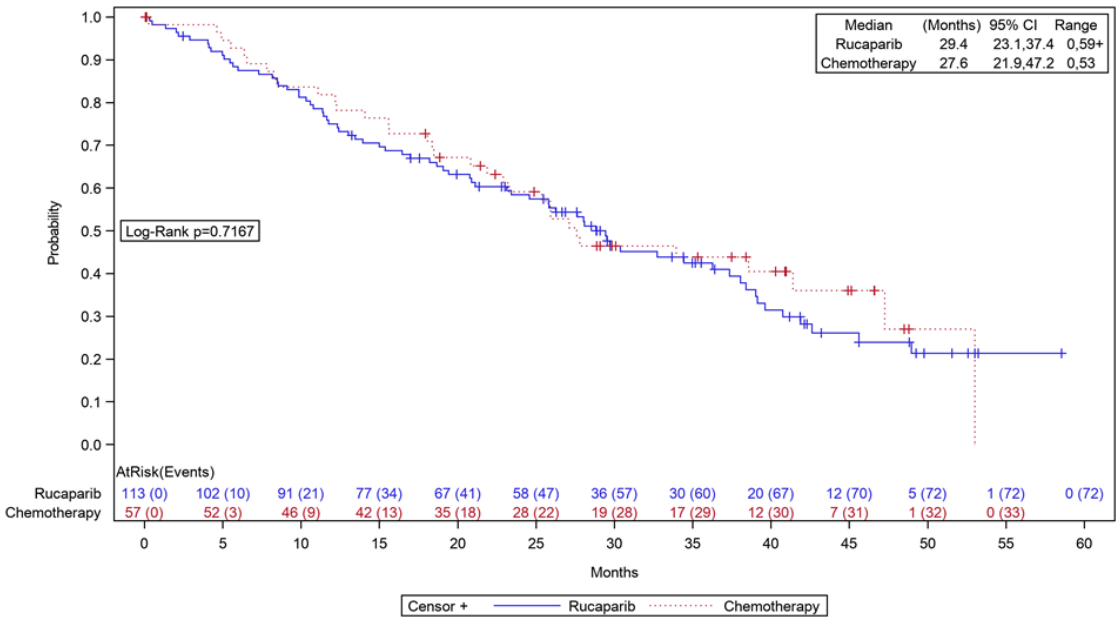
In the partially fully platinum-sensitive subgroup of the ITT population, median OS was 21.1 months in the rucaparib group compared with 23.2 months in the chemotherapy group (Figure 8) resulting in a HR of 0.97 [95% CI: 0.58, 1.62] (p=0.9129).

Figure 8. ARIEL4 Kaplan-Meier Analysis of OS – Partially Platinum-sensitive Subgroup (ITT Population)



In the platinum-sensitive combined (fully and partially) subgroup of the ITT population, median OS was 29.4 months in the rucaparib group compared with 27.8 months in the chemotherapy group (Figure 9) resulting in a HR of 1.07 [95% CI: 0.71, 1.62] (p=0.7167).

Figure 9. ARIEL4 Kaplan-Meier Analysis of OS – Platinum-sensitive Combined (Fully and Partially) Subgroup (ITT Population)



Progression-free survival on a subsequent line of treatment (PFS2) (data cut-off date: 10-Apr-2022)

PFS2 is part of the exploratory efficacy endpoints. At the time of the final analysis, PFS2 data were 80.6% (262/325) and 81.9% (286/349) mature in the Efficacy and ITT Populations respectively (Table 3). There was no significant difference between rucaparib treatment and chemotherapy treatment for PFS2 in either the Efficacy Population or ITT Population.

Table 3. ARIEL4 PFS2 – All Populations and Subgroups

	PFS2			
Population/ Subgroup	**Rucaparib**	**Chemo**	**Rucaparib vs Chemo**	
			Kaplan-Meier Analysis[a]	**Cox Proportional Hazard[b]**
	Event/N (%)	**Event/N (%)**	**Medians Log-rank p-value**	**HR (95% CI) p-value**
Efficacy	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	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	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)	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**	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**	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

Further results for exploratory efficacy endpoints, namely DCR, PRO by EQ-5D and invPFS by randomisation strata are summarised below.

Disease control rate (DCR) (data cut-off date: 30-Sep-2020)

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%). This difference was not statistically significant (p=0.2057). A similar result was seen in the ITT Population, namely 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. This difference was not statistically significant either (p=0.3573).

PRO by EQ-5D (data cut-off date: 30-Sep-2020)

In the Efficacy Population, the EQ-5D-3L VAS scores remained relatively constant or slightly improved over time for both treatment groups.

invPFS by Randomisation strata (data cut-off date: 30-Sep-2020)

For the Efficacy Population, the primary efficacy endpoint of invPFS was analysed by subgroup by randomisation strata, age and race.

A benefit in PFS was observed in the rucaparib treatment arm compared to the chemotherapy treatment arm in all randomisation 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

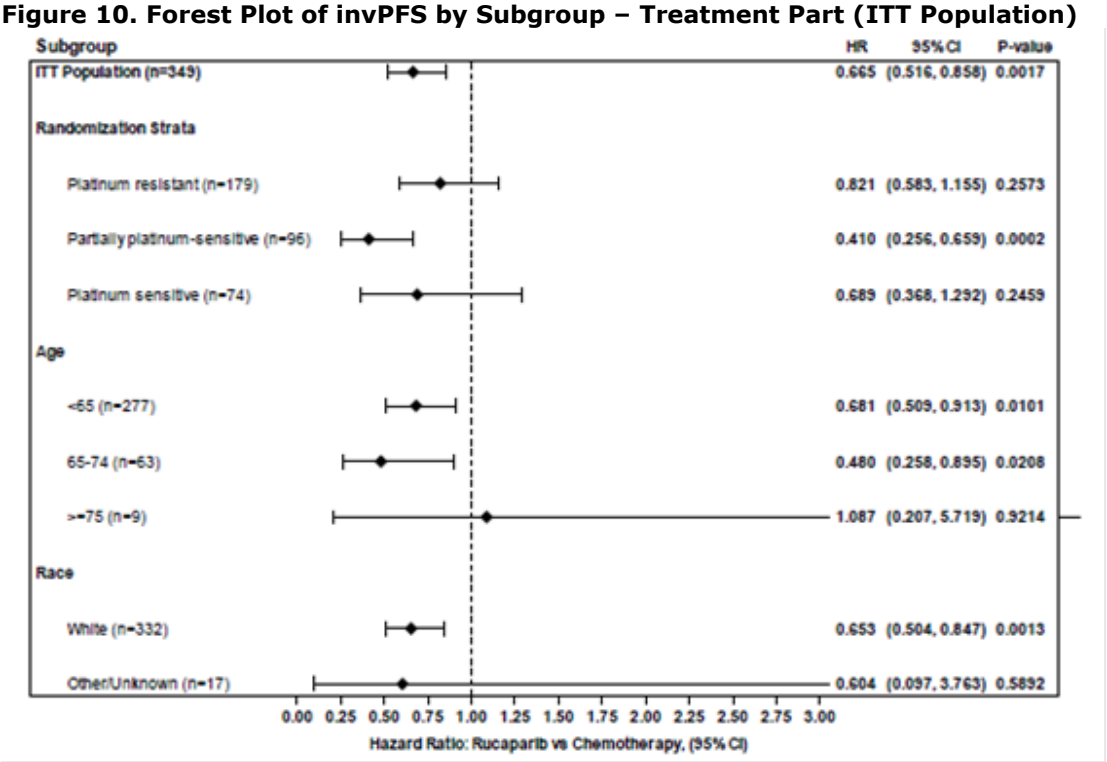
significant increase in median PFS in the rucaparib group of 8.0 months as compared to 5.5 months in the chemotherapy group (Table 4). This platinum status subgroup comprised approximately one-third of the patients in this study.

Table 4. 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)
Stratified Factor Used for Randomization		
Platinum-Resistant	n = 110 6.4 (5.5, 7.4)	n = 51 5.7 (3.7, 7.3)
Partially Platinum-Resistant	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)

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. However, results did not reach statistical significance (Figure 10).

Figure 10. Forest Plot of invPFS by Subgroup – Treatment Part (ITT Population)



Data on crossover of patients from the control arm to rucaparib

Based on the EMA document entitled "Question and answer on adjustment for cross-over in estimating effects in oncology trials (EMA/845963/2018)", the MAH provided results from several sensitivity analyses aiming at disentangling the effect of the crossover from the chemotherapy treatment arm to the rucaparib arm. Although some analyses showed non-negative OS results, concerns were identified with regard to the methods used that did not allow to conclude that a detrimental effect on OS could be ruled out.

2.3. Data on safety

2.3.1.1. Exposure

In study ARIEL4, a total of 349 patients were randomized 2:1 to rucaparib or chemotherapy in the 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 (Table 5).

For the Treatment Part of the Safety Population, the median duration of treatment in the rucaparib group was 7.3 months. The median dose intensity was approximately 0.99, indicating that patients received the intended dose of rucaparib. The median duration of treatment in the chemotherapy group was 3.6 months with a median of 5.0 cycles started (Table 5).

Table 5. 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 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)

Safety data from study ARIEL4 were also integrated with the most recent data-cut offs from studies CO-338-010, CO-338-017, and CO-338-014 (referred to as the "Pooled Ovarian Cancer Safety Population"; N=1,169).

2.3.1.2. Adverse events

In the rucaparib group, the most common treatment-emergent adverse events (TEAEs) in the Treatment Part were combined anemia/hemoglobin decreased, nausea, combined asthenia/fatigue/lethargy, combined alanine aminotransferase (ALT)/aspartate aminotransferase (AST) increased and vomiting. In the chemotherapy group, the most common TEAEs were combined asthenia/fatigue/lethargy, alopecia, combined anemia/hemoglobin decreased, nausea, combined neutropenia/decreased absolute neutrophil count (ANC) and combined neuropathy (Table 6).

Table 6. Treatment-emergent AEs Reported in ≥ 20% of Patients: Study CO-338-043 and Pooled Ovarian Cancer Safety Population

System Organ Class referred 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)**

System Organ Class referred Term	CO-338-043 Treatment Part Safety Population		Pooled Ovarian Cancer Safety Population
	Chemotherapy (N = 113)	Rucaparib (N = 232)	Rucaparib (N = 1,169)
	n (%)		
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)

Grade 3 or higher TEAEs

In the rucaparib group, the most common Grade 3 or higher TEAEs in the Treatment Part were combined anemia/hemoglobin decreased, and combined neutropenia/decreased ANC. In the chemotherapy group, the most common Grade 3 or higher TEAEs were combined neutropenia/decreased ANC (Table 7).

Table 7. 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)

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 (%)		
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)**

Treatment with rucaparib is associated with more severe adverse events (SAEs), 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.

Deaths

Fifteen 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) (Table 8). Following protocol amendment, events related to disease progression were no longer collected.

Table 8. 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)**

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 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)
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)

Serious adverse events (SAEs)

The incidence of SAEs was low in both the rucaparib and chemotherapy groups in the Treatment Part. The most common SAE reported in both treatment groups is myelosuppression from anemia/ hemoglobin decreased (Table 9).

Table 9. 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)**

Discontinuation due to TEAEs

Intestinal obstruction (and death) were the adverse events (AEs) leading most often to study drug discontinuation in the rucaparib treatment group (Table 10).

Table 10. 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)
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)**

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 (%)		
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

3. Benefit-risk balance

Favourable effects

In study ARIEL4, a statistically significant gain in invPFS, the primary endpoint, was reported in the rucaparib treatment group compared with chemotherapy with a reported median invPFS of 7.4 months for the rucaparib group compared to 5.7 months for the chemotherapy group (HR 0.665 [95% CI, 0.516-0.858]; p=0.0017). Results for secondary endpoints such as ORR and DOR were also numerically higher for rucaparib. However, they failed to be statistically significant.

Unfavourable effects

In the ITT population, median OS was 19.4 months in the rucaparib group compared with 25.4 months in the chemotherapy group, resulting in a HR of 1.31 [95% CI: 1.00, 1.73] (p=0.0507).

The observed detrimental effect on OS is 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.

Benefit-risk assessment and discussion

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

All in all, it remains unclear whether the OS detriment is caused by a safety issue, a lack of efficacy or a combination of both. Thus, major concerns remain regarding a potential detrimental effect of rucaparib on OS compared to chemotherapy in the specific patient population covered by the "treatment" indication. Therefore, the benefit-risk balance of Rubraca in that indication can no longer be considered favourable.

As a result, CHMP is of the view that the indication of Rubraca should be 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.

4. Summary of measures

4.1. Amendments to the product information

The CHMP considered that amendments to the SmPC were necessary to reflect the deletion of the treatment indication from section 4.1 and remove the information related to this indication from sections 4.2, 4.4 and 5.1. Annex II was updated to remove the interim measure agreed in April 2022 and prohibiting treating new patients in the treatment indication, since this indication is being removed.

The Package Leaflet was amended accordingly.

4.2. Direct Healthcare Professional Communication and Communication plan

The Committee agreed on the wording of a DHPC to inform healthcare professionals (HCP) that Rubraca (rucaparib) is no longer authorised as monotherapy treatment for 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. Ongoing treatment in this setting should be reconsidered and patients be informed of the latest data and recommendations.

The Committee also agreed on a communication plan.

5. Grounds for Opinion

Whereas,

- CHMP considered the procedure under Article 20 of Regulation (EC) No 726/2004 for Rubraca (rucaparib).
- CHMP reviewed all data made available by the MAH to the Committee from study CO-338-043 (ARIEL4; comparing rucaparib to chemotherapy for treatment of relapsed ovarian cancer) including results from the final analysis of overall survival (OS).
- CHMP considered that it is possible that the OS detriment in the rucaparib group versus the group receiving chemotherapy observed in study ARIEL4 is relevant for the 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 ("treatment" indication).
- It remains unclear whether the OS detriment is caused by a lack of efficacy, a safety issue or a combination of both.

- Since the treatment indication was subject to confirmation of rucaparib efficacy and safety in study CO-338-043 (ARIEL4) and no other available data could alleviate these concerns, CHMP concluded that the benefit of Rubraca (rucaparib) in this indication does not outweigh its risks.
- In view of the above, the Committee concluded that the benefit-risk balance of Rubraca (rucaparib) 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.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisation for Rubraca (rucaparib), subject to changes to the product information as described above.