Subgroup Analysis of Rucaparib in Platinum-Sensitive Recurrent Ovarian Carcinoma: Effect of Prior Chemotherapy Regimens in ARIEL3

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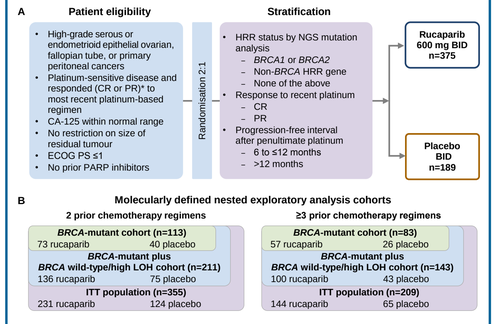
INTRODUCTION

- In the phase 3 ARIEL3 (NCT01968213) study (**Figure 1A**), rucaparib maintenance treatment significantly improved progression-free survival (PFS) vs placebo in all primary analysis groups of patients with recurrent ovarian cancer following response to platinum-based chemotherapy[1]
- Based on results from ARIEL3, rucaparib was approved in April 2018 by the U.S. Food and Drug Administration for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy[1,2]
  - An application to expand the European Medicines Agency's authorisation for rucaparib to include maintenance treatment has been submitted[3]
- In the setting of recurrent ovarian cancer, median PFS and median overall survival decrease with increasing lines of chemotherapy[4,5]
- Here we present an exploratory subgroup analysis investigating the effect of the number of prior chemotherapy regimens on select primary and secondary endpoints in ARIEL3

METHODS

Figure 1. (A) ARIEL3 Study Design and (B) Exploratory Analysis Cohorts



*CR (defined by RECIST) or PR (defined by RECIST and/or a GCIG CA-125 response [CA-125 within normal range]) maintained until entry to ARIEL3 (≤8 weeks of last dose of chemotherapy).
BID, twice daily; CA-125, cancer antigen 125; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GCIG, Gynecologic Cancer InterGroup; HRR, homologous recombination repair; ITT, intent to treat; LOH, loss of heterozygosity; NGS, next-generation sequencing; PARP, poly(ADP-ribose) polymerase; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

Exploratory Subgroup Analysis

- In ARIEL3, all patients received ≥2 prior platinum-based regimens in accordance with the protocol
  - The regimen immediately prior to enrolment in ARIEL3 must have been platinum based
  - Up to 1 nonplatinum chemotherapy regimen was permitted
  - Neoadjuvant and adjuvant treatment administered both before and after debulking surgery were considered 1 treatment regimen
- Investigator-assessed and blinded independent central review (BICR)-assessed PFS were evaluated for patients who received either 2 or ≥3 prior chemotherapy regimens in 3 molecularly defined nested cohorts (**Figure 1B**)

RESULTS

- For this analysis, visit cutoff dates for efficacy and safety were 15 April 2017 and 15 August 2017, respectively

Patient Demographics

- The majority of patients (62.9%) received 2 prior chemotherapy regimens (**Table 1**)

Table 1. Baseline Demographics

	2 prior chemotherapy regimens		≥3 prior chemotherapy regimens	
Characteristic	**Rucaparib (n=231)**	**Placebo (n=124)**	**Rucaparib (n=144)**	**Placebo (n=65)**
Age, median (range), y	61 (39–84)	61 (36–85)	61 (42–83)	63 (41–78)
Diagnosis, n (%)				
Epithelial ovarian cancer	186 (80.5)	103 (83.1)[a]	126 (87.5)	56 (86.2)
Fallopian tube cancer	21 (9.1)	6 (4.8)[a]	11 (7.6)	4 (6.2)
Primary peritoneal cancer	24 (10.4)	14 (11.3)	7 (4.9)	5 (7.7)
Histology, n (%)				
Serous	223 (96.5)	119 (96.0)	134 (93.1)	60 (92.3)
Endometrioid	6 (2.6)	3 (2.4)	10 (6.9)	4 (6.2)
Mixed or translational	2 (0.9)	2 (1.6)	0	1 (1.5)
***BRCA* and LOH status, n (%)**				
BRCA mutant	73 (31.6)	40 (32.3)	57 (39.6)	26 (40.0)
BRCA wild type	158 (68.4)	84 (67.7)	87 (60.4)	39 (60.0)
LOH high	63 (27.3)	35 (28.2)	43 (29.9)	17 (26.2)
LOH low	73 (31.6)	39 (31.5)	34 (23.6)	15 (23.1)
LOH indeterminate[b]	22 (9.5)	10 (8.1)	10 (6.9)	7 (10.8)
ECOG PS 0, n (%)	168 (72.7)	88 (71.0)	112 (77.8)	48 (73.8)
No. of prior chemotherapy regimens, median (range)	2 (2–2)	2 (2–2)	3 (3–6)	3 (3–6)
Prior chemotherapies, n (%)[c]				
Carboplatin	231 (100)	124 (100)	144 (100)	65 (100)
Paclitaxel	228 (98.7)	121 (97.6)	143 (99.3)	63 (96.9)
Doxorubicin	105 (45.5)	41 (33.1)	107 (74.3)	51 (78.5)
Gemcitabine	59 (25.5)	33 (26.6)	88 (61.1)	41 (63.1)
Cisplatin	51 (22.1)	27 (21.8)	52 (36.1)	13 (20.0)
No. of platinum-based regimens, median (range)	2 (2–2)	2 (2–2)	3 (2–6)	3 (2–5)
2, n (%)	231 (100)	124 (100)	5 (3.5)	2 (3.1)
3, n (%)	0	0	109 (75.7)	47 (72.3)
≥4, n (%)	0	0	30 (20.8)	16 (24.6)
Previous bevacizumab use, n (%)[d]	52 (22.5)	23 (18.5)	31 (21.5)	20 (30.8)
Time to progression with penultimate platinum, median (range), mo	16.0 (6.1–120.0)	18.0 (6.0–238.5)	10.8 (5.8–81.3)	11.5 (6.4–58.0)
6 to ≤12 mo, n (%)	71 (30.7)	40 (32.3)	80 (55.6)	36 (55.4)
Response to last platinum, n (%)				
CR per RECIST	76 (32.9)	42 (33.9)	50 (34.7)	22 (33.8)
PR per RECIST or serologic response per GCIG CA-125 criteria	155 (67.1)	82 (66.1)	94 (65.3)	43 (66.2)

[a]One (0.8%) patient had a diagnosis of high-grade serous adenocarcinoma that was fallopian tube and/or ovarian in origin. [b]Tumour sample was not evaluable for percentage of genomic LOH due to low tumour content or low aneuploidy. [c]Chemotherapies received by >20% of patients in any subgroup (excluding bevacizumab). [d]Prior bevacizumab was allowed, with the exception of bevacizumab maintenance after the most recent platinum.
CA-125, cancer antigen 125; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GCIG, Gynecologic Cancer InterGroup; LOH, loss of heterozygosity; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

Efficacy

- For patients who received either 2 or ≥3 prior chemotherapy regimens, investigator-assessed PFS (primary endpoint; **Figure 2**) and BICR-assessed PFS (secondary endpoint; **Figure 3**) were improved with rucaparib vs placebo across all 3 molecularly defined nested cohorts
  - Treatment-by-prior chemotherapy regimen subgroup interaction tests were nonsignificant for all populations, indicating that there was a similar treatment effect across prior chemotherapy subgroups
- In both subgroups, a greater proportion of rucaparib-treated patients than placebo-treated patients were progression free at 18 and 24 months (**Table 2**)
- Among rucaparib-treated patients with measurable disease at baseline, objective responses were observed in 16.3% of patients who received 2 prior chemotherapies and 21.8% of patients who received ≥3 prior chemotherapies (**Table 3**)

Table 2. Percentage of Patients in the ITT Population Who Were Progression Free at 18 and 24 Months

	2 prior chemotherapy regimens, %		≥3 prior chemotherapy regimens, %	
Characteristic	**Rucaparib (n=231)**	**Placebo (n=124)**	**Rucaparib (n=144)**	**Placebo (n=65)**
Investigator-assessed PFS				
At 18 mo	33.3	6.7	29.8	3.7
At 24 mo	26.9	3.0	23.2	3.7
BICR-assessed PFS				
At 18 mo	49.0	11.3	38.8	10.4
At 24 mo	44.7	9.0	31.7	10.4

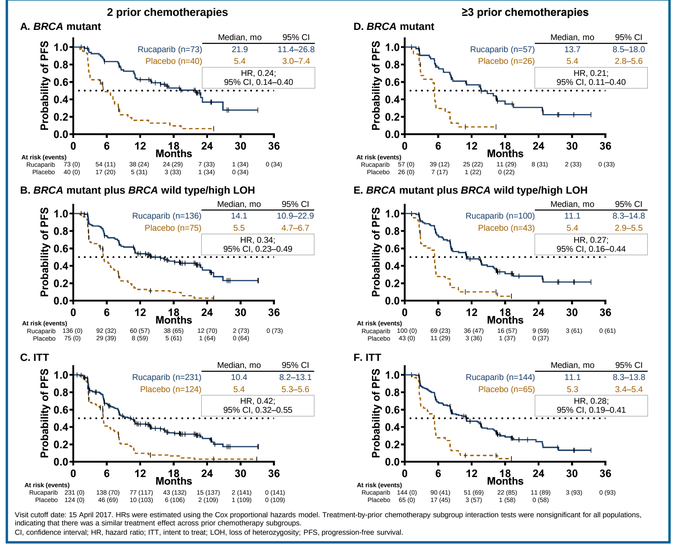
BICR, blinded independent central review; ITT, intent to treat; PFS, progression-free survival.

Table 3. Investigator-Assessed ORR for Patients in the ITT Population with Measurable Disease at Baseline

	2 prior chemotherapy regimens		≥3 prior chemotherapy regimens	
Characteristic	**Rucaparib (n=86)**	**Placebo (n=49)**	**Rucaparib (n=55)**	**Placebo (n=17)**
RECIST ORR, n (%) [95% CI]	14 (16.3) [9.2–25.8]	5 (10.2) [3.4–22.2]	12 (21.8) [11.8–35.0]	0 [0.0–19.5]
Complete response	7 (8.1)	1 (2.0)	3 (5.5)	0
Partial response	7 (8.1)	4 (8.2)	9 (16.4)	0
Stable disease	42 (48.8)	22 (44.9)	29 (52.7)	7 (41.2)
Progressive disease	26 (30.2)	22 (44.9)	12 (21.8)	10 (58.8)
Not evaluable	4 (4.7)	0	2 (3.6)	0

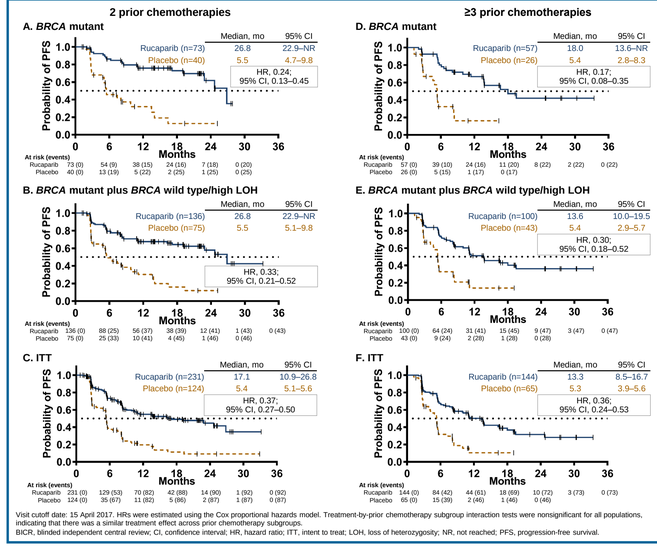
CI, confidence interval; ITT, intent to treat; ORR, objective response rate; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

Figure 2. Investigator-Assessed PFS



Visit cutoff date: 15 April 2017. HRs were estimated using the Cox proportional hazards model. Treatment-by-prior chemotherapy subgroup interaction tests were nonsignificant for all populations, indicating that there was a similar treatment effect across prior chemotherapy subgroups.
CI, confidence interval; HR, hazard ratio; ITT, intent to treat; LOH, loss of heterozygosity; PFS, progression-free survival.

Figure 3. BICR-Assessed PFS

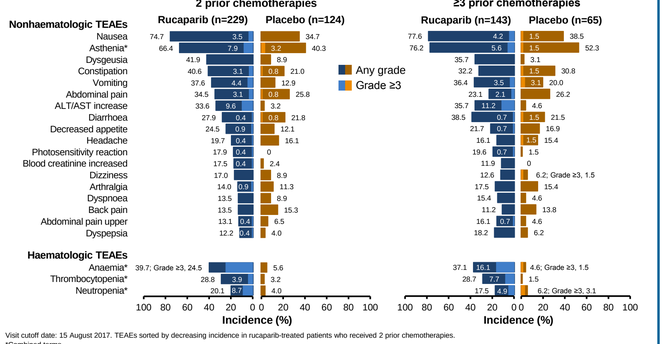


Visit cutoff date: 15 April 2017. HRs were estimated using the Cox proportional hazards model. Treatment-by-prior chemotherapy subgroup interaction tests were nonsignificant for all populations, indicating that there was a similar treatment effect across prior chemotherapy subgroups.
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; ITT, intent to treat; LOH, loss of heterozygosity; NR, not reached; PFS, progression-free survival.

Safety

- In the rucaparib arm, the most common grade ≥3 treatment-emergent adverse event in patients who received either 2 or ≥3 prior chemotherapy regimens was anaemia (24.5% and 16.1%, respectively; **Figure 4**)

Figure 4. Most Common (≥15%) TEAEs of Any Grade in Patients in Either Subgroup



Visit cutoff date: 15 August 2017. TEAEs sorted by decreasing incidence in rucaparib-treated patients who received 2 prior chemotherapies.
*Combined terms.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Patients who received either 2 or ≥3 prior chemotherapy regimens had improved PFS with rucaparib maintenance treatment vs placebo
  - For both subgroups, an improvement in PFS was observed in all cohorts, including the intent-to-treat (ITT) population
- In both subgroups, several patients with measurable disease at baseline had further reduction in tumour burden with rucaparib maintenance treatment
- The safety profile in rucaparib-treated patients who received either 2 or ≥3 prior chemotherapy regimens was consistent with that of the ITT population reported previously[1]

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