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Evaluation of Rucaparib in Platinum-Sensitive Recurrent Ovarian Carcinoma (rOC) in Patients With or Without Residual Bulky Disease at Baseline in the ARIEL3 Study

Abstract 5537

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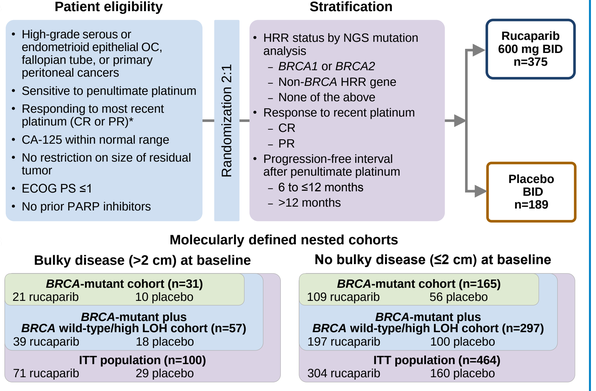
INTRODUCTION

- ARIEL3 is a phase 3 study of rucaparib 600 mg twice daily (BID) vs placebo following response to platinum-based chemotherapy for rOC (**Figure 1A**)
- Based on results from ARIEL3,[1] 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]
- Previous studies have shown that for patients with ovarian cancer, the size of residual disease is a prognostic factor for outcomes following treatment; a smaller tumor size at the start of treatment is correlated with longer progression-free survival (PFS) and longer overall survival[3-5]
- Here we present an exploratory subgroup analysis comparing the outcomes of patients with and those without bulky residual disease (defined in ARIEL3 as any tumor >2 cm per blinded independent central review [BICR]) at baseline in ARIEL3

METHODS

ARIEL3 Study Design

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; OC, ovarian carcinoma; PARP, poly(ADP-ribose) polymerase; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

Exploratory Subgroup Analysis

- All baseline scans for patients in the intent-to-treat (ITT) population were evaluated by BICR in order to assess if patients had bulky residual disease (defined as any tumor >2 cm) or no bulky residual disease (defined as no disease or all tumors ≤2 cm)
- Investigator-assessed and BICR-assessed PFS were evaluated for patients with or without bulky disease in 3 molecularly defined nested cohorts (**Figure 1B**)

RESULTS

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

Patient Demographics

- In ARIEL3, 100 patients (18%) had bulky disease as assessed by BICR at baseline (rucaparib arm, 71; placebo arm, 29) (**Table 1**)

Table 1. Baseline Demographics

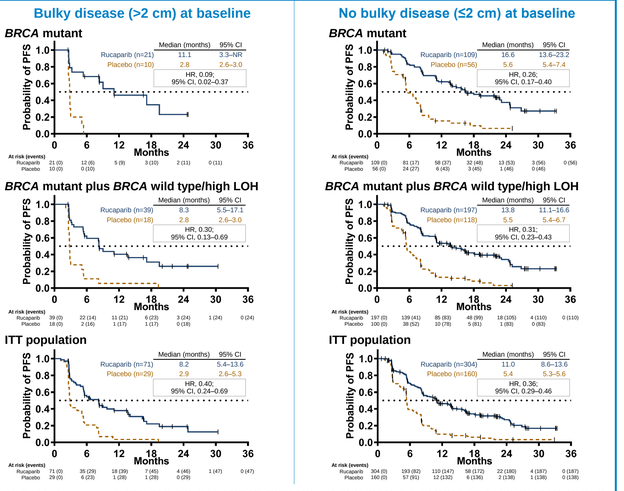
Characteristic	Bulky disease at baseline (BICR assessed)[a]		No bulky disease at baseline (BICR assessed)[b]	
	Rucaparib (n=71)	Placebo (n=29)	Rucaparib (n=304)	Placebo (n=160)
Age, median (range), y	61 (44–84)	65 (41–84)	61 (39–83)	62 (36–85)
Diagnosis, n (%)				
Epithelial ovarian cancer	62 (87.3)	25 (86.2)	250 (82.2)	134 (83.8)[c]
Fallopian tube cancer	4 (5.6)	1 (3.4)	28 (9.2)	9 (5.6)
Primary peritoneal cancer	5 (7.0)	3 (10.3)	26 (8.6)	16 (10.0)
Histology, n (%)				
Serous	67 (94.4)	27 (93.1)	290 (95.4)	152 (95.0)
Endometrioid	3 (4.2)	2 (6.9)	13 (4.3)	5 (3.1)
Mixed or translational	1 (1.4)	0	1 (0.3)	3 (1.9)
***BRCA* and LOH status, n (%)**				
BRCA mutant	21 (29.6)	10 (34.5)	109 (35.9)	56 (35.0)
BRCA wild type	50 (70.4)	19 (65.5)	195 (64.1)	104 (65.0)
LOH high	18 (25.4)	8 (27.6)	88 (28.9)	44 (27.5)
LOH low	27 (38.0)	9 (31.0)	80 (26.3)	45 (28.1)
LOH indeterminate[d]	5 (7.0)	2 (6.9)	27 (8.9)	15 (9.4)
ECOG PS 0, n (%)	47 (66.2)	22 (75.9)	233 (76.6)	114 (71.3)
No. of prior chemotherapy regimens, median (range)	2 (2–5)	2 (2–6)	2 (2–6)	2 (2–5)
No. of platinum-based regimens, median (range)	2 (2–5)	2 (2–4)	2 (2–6)	2 (2–5)
≥3, n (%)	27 (38.0)	12 (41.4)	112 (36.8)	51 (31.9)
Time to progression with penultimate platinum, median (range), mo	11.3 (6.2–115.4)	14.4 (6.5–71.6)	14.8 (5.8–120.0)	14.8 (6.0–238.5)
6 to ≤12 mo, n (%)	38 (53.5)	9 (31.0)	113 (37.2)	67 (41.9)
Response to last platinum (investigator assessed), n (%)				
CR per RECIST	18 (25.4)	3 (10.3)	108 (35.5)	61 (38.1)
PR per RECIST or serologic response per GCIG CA-125 criteria	53 (74.6)	26 (89.7)	196 (64.5)	99 (61.9)

Visit cutoff date: April 15, 2017. [a]Bulky residual disease was defined as any tumor >2 cm per BICR. [b]No bulky residual disease was defined as no disease or all tumors ≤2 cm per BICR. [c]One (0.6%) patient had a diagnosis of high-grade serous adenocarcinoma that was fallopian and/or ovarian in origin. [d]Tumor sample was not evaluable for percentage of genomic LOH due to low tumor content or low aneuploidy.
BICR, blinded independent central review; 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 with or without bulky residual disease at baseline, 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
  - Within each cohort, results were similar between patients with and those without bulky disease
  - *P* values for treatment-by-bulky disease subgroup interaction were significant for investigator-assessed PFS in the *BRCA*-mutant cohort (*P*=0.0108) and nonsignificant for all other analyses
    - Patients with *BRCA*-mutant tumors are predicted to receive the greatest benefit from rucaparib

Figure 2. Investigator-Assessed PFS

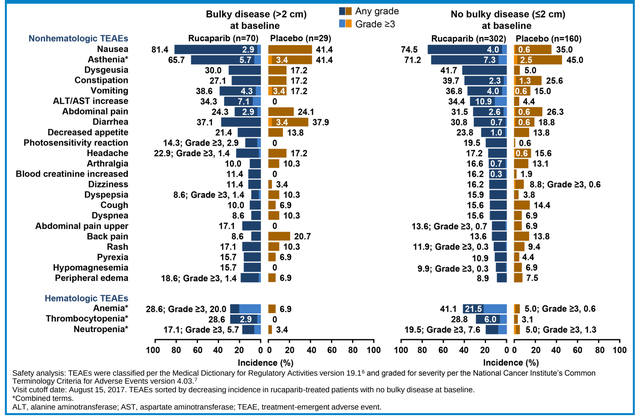


Visit cutoff date: April 15, 2017. HRs were estimated using the Cox proportional hazards model; *P* values for treatment-by-bulky disease subgroup interaction were significant for the *BRCA*-mutant cohort (*P*=0.0108) and nonsignificant for all other analyses. CI, confidence interval; HR, hazard ratio; ITT, intent to treat; LOH, loss of heterozygosity; NR, not reached; PFS, progression-free survival.

Safety

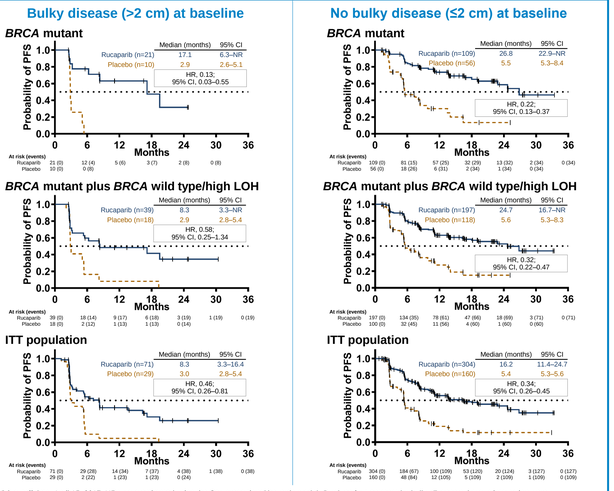
- In the rucaparib arm, the most common grade ≥3 treatment-emergent adverse events in patients with and patients without bulky disease was anemia (20.0% and 21.5%, respectively; **Figure 4**)

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



Safety analysis; TEAEs were classified per the Medical Dictionary for Regulatory Activities version 19.1[6] and graded for severity per the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.03.[7]
Visit cutoff date: August 15, 2017. TEAEs sorted by decreasing incidence in rucaparib-treated patients with no bulky disease at baseline.
*Combined terms.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

Figure 3. BICR-Assessed PFS



Visit cutoff date: April 15, 2017. HRs were estimated using the Cox proportional hazards model; *P* values for treatment-by-bulky disease subgroup interaction were nonsignificant for all analyses. 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.

CONCLUSIONS

- Maintenance treatment with rucaparib improved PFS for both patients with and patients without bulky residual disease at baseline in all 3 molecularly defined nested cohorts
- The safety profile was similar between rucaparib-treated patients with and those without bulky residual disease at baseline and was consistent with the safety profile in the ITT population reported previously[1]

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