ARIEL3: Phase 3, Randomised, Double-Blind Study of Rucaparib vs Placebo Following Response to Platinum-Based Chemotherapy for Recurrent Ovarian Carcinoma (OC)

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Abstract ESGO7-1518

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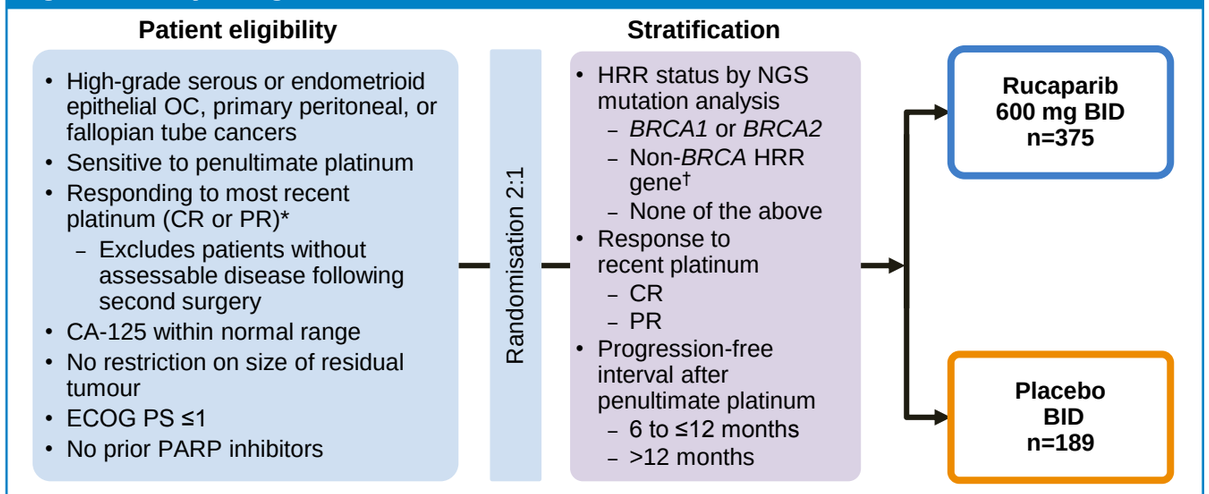
BACKGROUND

- Rucaparib is a potent inhibitor of poly(ADP-ribose) polymerase 1 (PARP1), PARP2, and PARP3[1,2]
- Rucaparib is approved in the United States for the treatment of patients with deleterious *BRCA* mutation (germline and/or somatic) associated advanced OC who have been treated with ≥2 chemotherapy regimens[3,4]
- The ARIEL3 phase 3 trial evaluated rucaparib vs placebo following a response to second-line or later platinum-based chemotherapy in patients with high-grade, recurrent platinum-sensitive OC, including fallopian tube and primary peritoneal carcinomas (**Figure 1**)[5,6]

Figure 1. Study Design

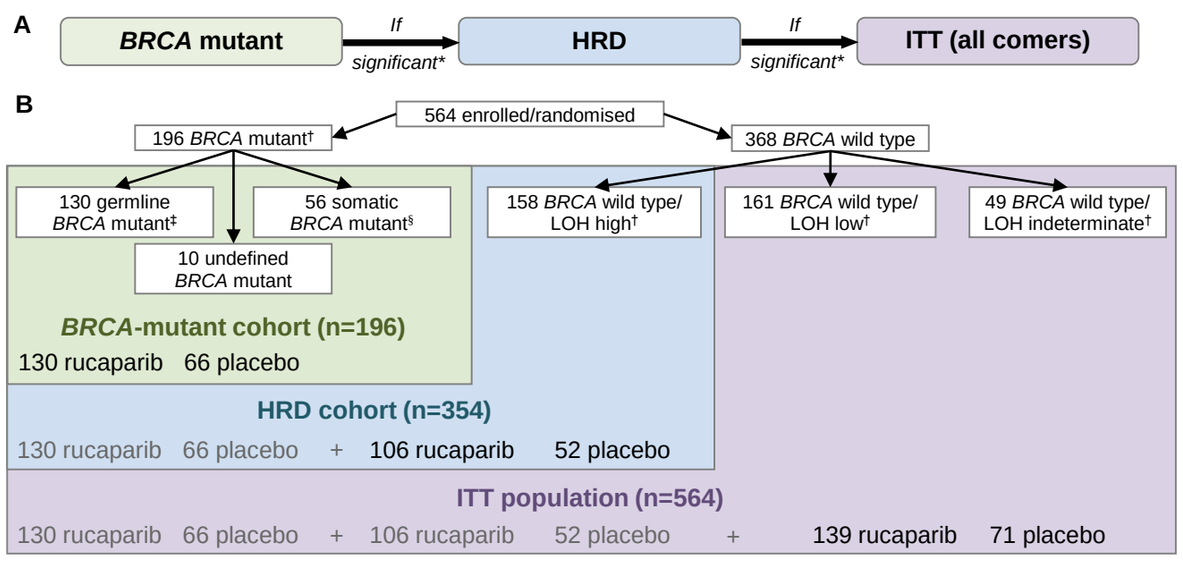


*CR (defined by RECIST) or PR (defined by RECIST and/or a GCIG CA-125 response [CA-125 within normal range]) maintained until entry to ARIEL3 (≤8 weeks of last dose of chemotherapy). †*ATM, ATR, ATRX, BARD1, BLM, BRIP1, CHEK1, CHEK2, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, MRE11A, NBN, PALB2, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RPA1*.
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; 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.

ARIEL3 ENDPOINTS

- Primary endpoint, assessed in a step-down analysis in 3 nested cohorts (**Figure 2**): investigator-assessed progression-free survival (PFS) (per Response Evaluation Criteria In Solid Tumors version 1.1 [RECIST])
- Stand-alone secondary endpoint: blinded independent central review–assessed PFS (per RECIST)
- Select exploratory endpoint: objective response rate (ORR) in patients with measurable disease at baseline

Figure 2. (A) Step-Down Analysis and (B) Analysis Cohorts



Visit cutoff date for all analyses: 15 April 2017.
*Investigator-assessed PFS at a 2-sided 0.05 significance level. †*BRCA* mutation and LOH in tumour samples were measured using Foundation Medicine's T5 NGS assay; LOH high was prespecified as ≥16% genomic LOH. ‡No more than 150 patients with a known deleterious germline *BRCA* mutation were to be enrolled to ensure enough patients with carcinomas associated with a somatic *BRCA* mutation or wild-type *BRCA* were enrolled to determine statistical significance between rucaparib and placebo in the HRD cohort and the ITT population. §Deleterious *BRCA* mutation detected by NGS of tumour tissue but not by central germline blood test.
HRD, homologous recombination deficient; ITT, intent to treat; LOH, loss of heterozygosity; NGS, next-generation sequencing; PFS, progression-free survival.

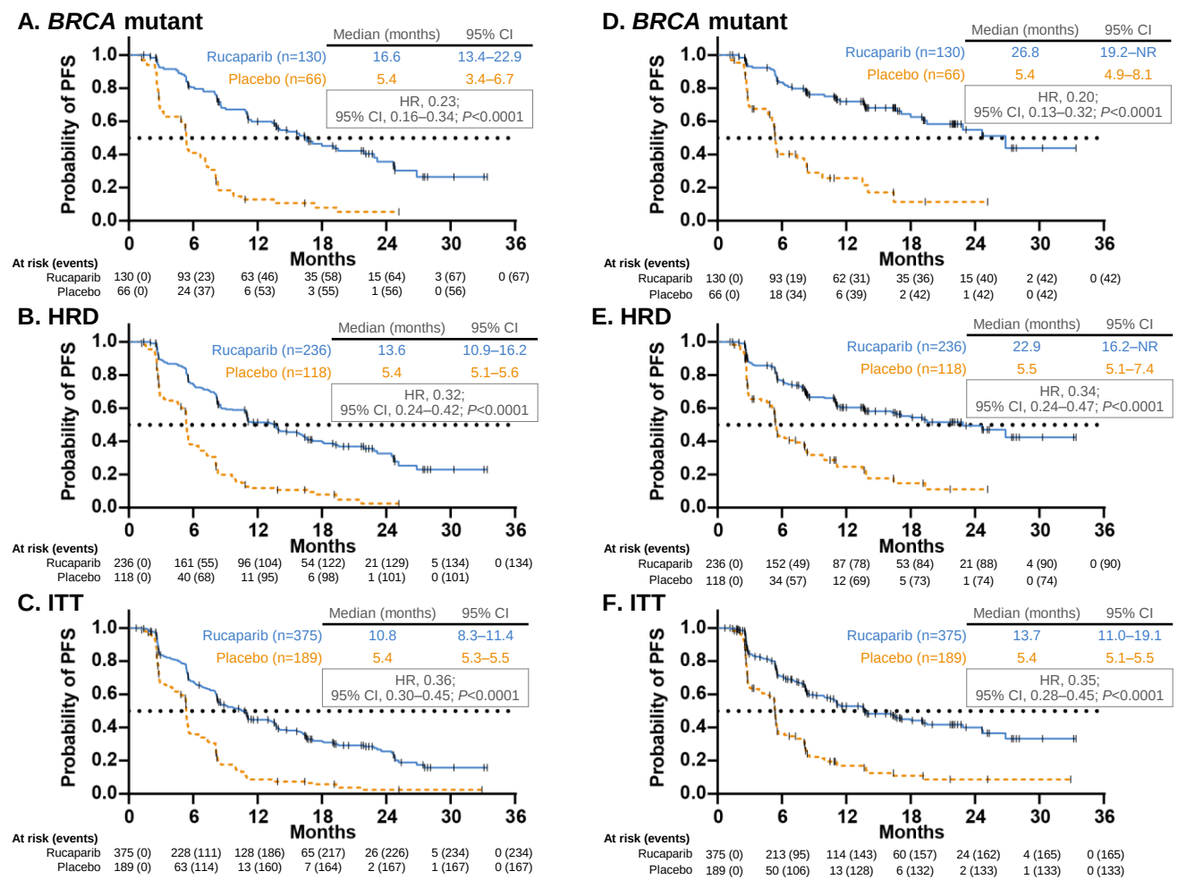
EFFICACY

Table 1. Baseline Demographics

Characteristic	Rucaparib (n=375)	Placebo (n=189)
Age, median years (range)	61.0 (39.0–84.0)	62.0 (36.0–85.0)
Diagnosis, % (n)		
Epithelial ovarian cancer	83.2 (312)	84.1 (159)[a]
Fallopian tube cancer	8.5 (32)	5.3 (10)
Primary peritoneal cancer	8.3 (31)	10.1 (19)
Histology, % (n)		
Serous	95.2 (357)	94.7 (179)
Endometrioid	4.3 (16)	3.7 (7)
Mixed	0.3 (1)	1.6 (3)
Transitional	0.3 (1)	0
***BRCA* and LOH status, % (n)**		
BRCA mutant	34.7 (130)	34.9 (66)
BRCA1	21.3 (80)	19.6 (37)
BRCA2	13.3 (50)	15.3 (29)
Germline	21.9 (82)	25.4 (48)
Somatic	10.7 (40)	8.5 (16)
Undefined[b]	2.1 (8)	1.1 (2)
BRCA wild type	65.3 (245)	65.1 (123)
LOH high	28.3 (106)	27.5 (52)
LOH low	28.5 (107)	28.6 (54)
LOH indeterminate[c]	8.5 (32)	9.0 (17)
ECOG PS 0, % (n)	74.7 (280)	72.0 (136)
No. of prior chemotherapy regimens, median (range)	2 (2–6)	2 (2–6)
No. of platinum-based regimens, median (range)	2 (2–6)	2 (2–5)
≥3, % (n)	37.1 (139)	33.3 (63)
Prior bevacizumab use, % (n)[d]	22.1 (83)	22.8 (43)
Time to progression with penultimate platinum, median months (range)	13.8 (5.8–120.0)	14.6 (6.0–238.5)
6 to ≤12 months, % (n)	40.3 (151)	40.2 (76)
>12 months, % (n)	59.7 (224)	59.8 (113)
Response to last platinum		
CR per RECIST, % (n)	33.6 (126)	33.9 (64)
PR per RECIST or serologic response per GCIG CA-125 criteria, % (n)	66.4 (249)	66.1 (125)
Measurable disease at baseline (per investigator), % (n)	37.6 (141)	34.9 (66)
Bulky disease (any lesion >2 cm) at baseline (per independent radiological review), % (n)	18.9 (71)	15.3 (29)

Visit cutoff date: 15 April 2017.
[a]One (0.5%) patient had a diagnosis of high-grade serous adenocarcinoma that was fallopian and/or ovarian in origin. [b]Tumour sample was *BRCA* mutant by Foundation Medicine's T5 NGS assay, but a blood sample was not available for central germline testing. [c]Tumour sample was not evaluable for percent of genomic LOH due to low tumour content or low aneuploidy. [d]Prior treatment with bevacizumab was permitted as part of penultimate or earlier treatment.
CA-125, cancer antigen 125; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GCIG, Gynecologic Cancer InterGroup; LOH, loss of heterozygosity; NGS, next-generation sequencing; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.
Source: Coleman et al. *Lancet*. 2017 [Epub ahead of print].

Figure 3. (A–C) Investigator-Assessed and (D–F) BICR-Assessed PFS



Visit cutoff date: 15 April 2017.
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficient; ITT, intent to treat; NR, not reached; PFS, progression-free survival.
Source: Coleman et al. *Lancet*. 2017 [Epub ahead of print].

Investigator-Assessed ORR for Patients with Measurable Disease at Baseline

- Among the 207 (36.7%) of 564 patients with measurable disease per investigator at study entry, ORR for the 3 nested cohorts was greater in the rucaparib arm than in the placebo arm (**Table 2**)

Table 2. Objective Response Rate

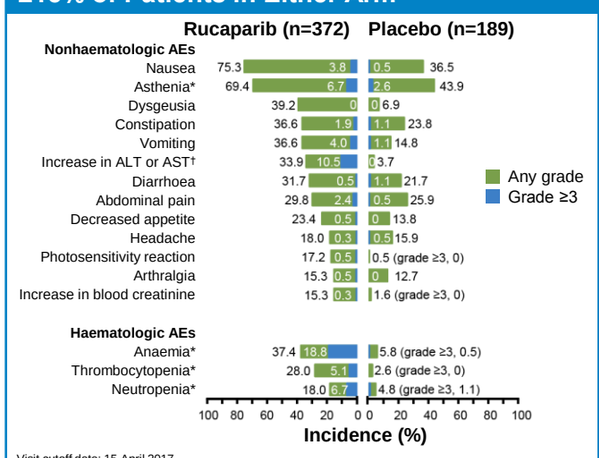
	BRCA mutant, % (n)		HRD, % (n)		ITT, % (n)	
	Rucaparib (n=40)	Placebo (n=23)	Rucaparib (n=85)	Placebo (n=41)	Rucaparib (n=141)	Placebo (n=66)
RECIST ORR	**37.5 (15)***	**8.7 (2)**	**27.1 (23)***	**7.3 (3)**	**18.4 (26)[a]**	**7.6 (5)**
Complete response	17.5 (7)	0	11.8 (10)	0	7.1 (10)	1.5 (1)
Partial response	20.0 (8)	8.7 (2)	15.3 (13)	7.3 (3)	11.3 (16)	6.1 (4)
Stable disease	47.5 (19)	34.8 (8)	50.6 (43)	41.5 (17)	50.4 (71)	43.9 (29)
Progressive disease	12.5 (5)	56.5 (13)	21.2 (18)	51.2 (21)	27.0 (38)	48.5 (32)
Not evaluable	2.5 (1)	0	1.2 (1)	0	4.3 (6)	0

[a]Cochran-Mantel-Haenszel *P*<0.05 vs placebo. HRD, homologous recombination deficient; ITT, intent to treat; ORR, objective response rate.
Source: Coleman et al. *Lancet*. 2017 [Epub ahead of print].

SAFETY

- Median (range) treatment duration was 8.3 (0.1–34.9) months in the rucaparib arm and 5.5 (0.0–35.4) months in the placebo arm
- The most commonly reported treatment-emergent adverse events (TEAEs) are shown in **Figure 4**
  - Alanine aminotransferase and aspartate aminotransferase concentration increases were not associated with abnormal increases in bilirubin or other criteria for drug-induced hepatotoxicity and generally resolved over time (**Figure 5**); no cases met Hy's law criteria for drug-induced liver injury
  - Myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML) was reported in 3 (0.8%) patients in the rucaparib arm and no patients in the placebo arm
- Treatment interruption due to a TEAE: rucaparib arm, 237 (63.7%) patients; placebo arm, 19 (10.1%) patients
- Dose reduction due to a TEAE: rucaparib arm, 203 (54.6%) patients; placebo arm, 8 (4.2%) patients
- Deaths due to an AE:
  - Rucaparib arm: progressive disease (n=2), MDS/AML (n=2), cardiac arrest (n=1), and haematophagic histiocytosis (n=1); deaths due to MDS/AML were considered treatment-related by the investigator
  - Placebo arm: progressive disease (n=1) and pulmonary embolism (n=1)

Figure 4. TEAEs of Any Grade Reported in ≥15% of Patients in Either Arm



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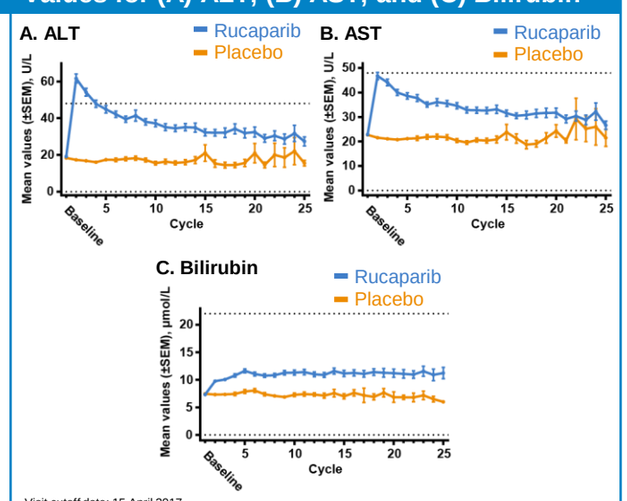
*Combined terms. †Elevations were generally transient, self-limiting, and not associated abnormal increases in bilirubin or other criteria for drug-induced hepatotoxicity.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.
Source: Coleman et al. *Lancet*. 2017 [Epub ahead of print].

Figure 5. Mean Baseline and On-Treatment Values for (A) ALT, (B) AST, and (C) Bilirubin



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ALT, alanine aminotransferase; AST, aspartate aminotransferase; SEM, standard error of the mean.
Source: Coleman et al. *Lancet*. 2017 [Epub ahead of print].

CONCLUSIONS

- Rucaparib maintenance treatment significantly improved PFS vs placebo in the nested *BRCA*-mutant and HRD cohorts and in the overall ITT population
- Several patients with measurable residual disease at baseline had further reduction in tumour burden with rucaparib maintenance treatment
- The most common side effects were gastrointestinal (nausea and vomiting), asthenia, and anaemia, consistent with prior studies of rucaparib
- Rucaparib maintenance treatment could be considered a new standard of care for women with platinum-sensitive OC following a complete or partial response to second-line or later platinum-based chemotherapy

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