Clinical and Molecular Characteristics of ARIEL3 Patients Who Derived Exceptional Benefit From Rucaparib Maintenance Treatment for High-Grade Ovarian Cancer (HGOC)

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Supplementary Material

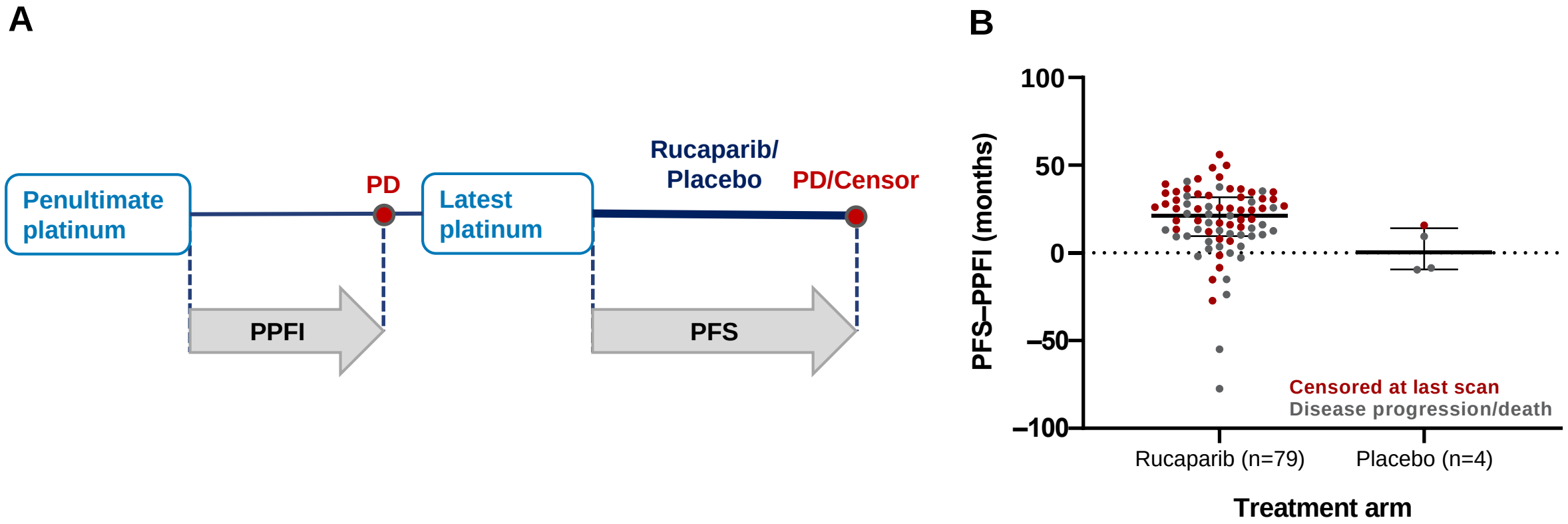
Supplementary Methods

- Archival formalin-fixed paraffin-embedded tumor tissues were centrally analyzed to detect deleterious mutations in HRR genes, including BRCA, and to identify tumors with high genome-wide LOH (≥16%) using Foundation Medicine's T5 NGS assay (Cambridge, MA, USA). Additional BRCA alterations were identified through germline sequencing
- Germline/somatic status for BRCA mutation was established through central germline sequencing using the BRCAnalysis CDx test (Myriad Genetics, Salt Lake City, UT, USA); the germline/somatic status of non-BRCA HRR genes was determined by Color Genomics germline testing (Burlingame, CA, USA)
- Zygosity of non-BRCA HRR genes was established computationally[1]
- Quantification of *BRCA1* methylation levels in archival tumors from ARIEL3 patients was performed by quantitative methylation-sensitive digital droplet polymerase chain reaction (Ambry Genetics, Aliso Viejo, CA, USA) and analyzed as previously described[2]
  - Patient samples were classified as having high or low methylation levels based on a predefined cutoff of 70%[2]

BRCA, *BRCA1* or *BRCA2;* HRR, homologous recombination repair; LOH, loss of heterozygosity.

1. Sun et al. *PLoS Comput Biol.* 2018;14:e1005965. 2. Kondrashova et al. *Nat Commun.* 2018;9:3970.

Supplementary Figure 1. PFS-PPFI in ARIEL3 Patients Who Derived Exceptional Benefit



(A) A schematic showing the definition of PFS and PPFI as used in the current context. (B) A scatterplot showing the difference between the PFS and PPFI of exception benefit patients. A difference greater than 0 indicates the patient derived more durable benefit from maintenance therapy than penultimate platinum. Patients who discontinue drug due to reasons other than disease progression were censored for the PFS analysis. The line shows the median, error bars represent the interquartile range.
PD, progressive disease; PFS, progression-free survival; PPFI, penultimate platinum-free interval.

Supplementary Table 1. Genetic and Epigenetic Alterations in the Placebo Exceptional Benefit and ST Subgroups

Alteration	Exceptional benefit (n=4)	ST subgroup (n=62)	*P* value	Odds ratio (95% CI)
BRCAmut	3 (75.0)	25 (40.3)	0.304	4.4 (0.6–59.0)
BRCAwt + *RAD51C/D*	0	0	NA	NA
BRCAwt + other HRR gene	0	2 (3.2)	>0.99	NA
BRCAwt + LOH-high	0	14 (22.6)	0.571	NA
BRCAwt + LOH-low	1 (25.0)	16 (25.8)	>0.99	1.0 (0.1–6.8)
BRCAwt + high *BRCA1* methylation	0/1	5/29 (17.2)	>0.99	NA

Statistical comparisons based on Fisher's exact test for all cases. Data are n (%) or n/N (%).
BRCA, *BRCA1* or *BRCA2;* HRR, homologous recombination repair; LOH, loss of heterozygosity; mut, mutated; NA, not applicable; ST, short-term; wt, wild type.
Data for the rucaparib arm are available in Table 2 of the poster.

Supplementary Table 2. Frequency and Types of BRCA Mutations in the Placebo Exceptional Benefit and ST Subgroups

	BRCAmut exceptional benefit (n=3)	BRCAmut ST subgroup (n=25)	*P* value	Odds ratio (95% CI)
Gene			>0.99[a]	
BRCA1	2 (66.7)	16 (64.0)		1.1 (0.1–17.9)
BRCA2	1 (33.3)	9 (36.0)		0.9 (0.1–8.5)
Germline/somatic status			0.929[b]	
Germline	2 (66.7)	17 (68.0)		0.9 (0.1–15.2)
Somatic	1 (33.3)	7 (28.0)		1.3 (0.1–12.3)
Unknown	0	1 (4.0)		NA
Mutation type			>0.99[a]	
Short variant	3 (100)	22 (88.0)		NA
Rearrangement/loss	0	3 (12.0)		NA

Data are n (%).
[a]Significance based on Fisher's exact test. [b]Significance based on chi-square test.
BRCA, *BRCA1* or *BRCA2;* mut, mutated; NA, not applicable; ST, short-term.
Data for the rucaparib arm are available in Table 4 of the poster.