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Exploratory Analysis of Percentage of Genomic Loss of Heterozygosity (LOH) in Patients with Platinum-Sensitive Recurrent Ovarian Carcinoma in ARIEL3

Abstract 5545

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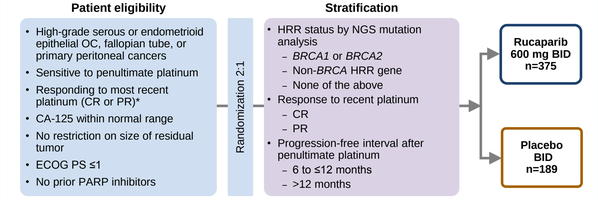
INTRODUCTION

- ARIEL3 (NCT01968213) was a phase 3 study of rucaparib (600 mg twice daily) vs placebo following response to platinum-based chemotherapy for recurrent ovarian carcinoma (**Figure 1**)
  - Rucaparib significantly improved progression-free survival (PFS) vs placebo in all randomized patients, including patients with *BRCA*-mutant, *BRCA* wild-type/high-LOH (prespecified as ≥16% genomic LOH), or *BRCA* wild-type/low-LOH (<16% genomic LOH) recurrent ovarian carcinoma[1]
- Based on ARIEL3 results,[1] rucaparib was approved in April 2018 by the U.S. Food and Drug Administration (FDA) 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]
- ARIEL3 was the first trial to prospectively test the genomic LOH cutoff discriminator that was optimized as a predictive biomarker for sensitivity to rucaparib treatment based on results from Part 1 of the ARIEL2 phase 2 study (NCT01891344)[3,4]
  - Genomic LOH is a type of genomic scar associated with homologous recombination deficiency (HRD) and is characterized by the loss of 1 copy of a gene or chromosomal region in a diploid cell[5]
- Here we present an exploratory analysis that evaluated the predictive utility of the prespecified cutoff (16%) and a range of different cutoffs for percentage of genomic LOH in *BRCA* wild-type recurrent ovarian carcinomas in ARIEL3

METHODS

ARIEL3 Study Design

Figure 1. ARIEL3 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).
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.

Exploratory Analysis of Different Cutoffs for Percentage of Genomic LOH

- Genomic LOH of archival tumor tissue DNA was centrally assessed as follows:
  - DNA extracted from archival tumor tissue underwent whole-genome shotgun library construction and hybridization-based capture, followed by sequencing using the Foundation Medicine next-generation sequencing (NGS)-based T5 clinical trial assay (Cambridge, MA)
  - Sequence data were analyzed to detect base substitutions, insertions/deletions, copy number alterations (CNAs), and genomic rearrangements
  - A genome-wide LOH profile based on single nucleotide polymorphisms is measured as part of the CNA pipeline and summarized as the percentage of the tumor genome displaying LOH (scored from 0% to 100%)
- Treatment effect for investigator-assessed PFS was analyzed in patients with *BRCA* wild-type recurrent ovarian carcinoma for the prespecified cutoff (16%) and across a range of different cutoffs for percentage of LOH (5%–30%)
- Hazard ratios (HRs) were estimated using a stratified Cox proportional hazards model
- The interaction between treatment with rucaparib and LOH was evaluated using the Cox proportional hazards model for the prespecified cutoff (16%)
- Prognostic and predictive utility of percentage of LOH was assessed by comparing investigator-assessed PFS between and within the treatment arms

RESULTS

Patient Demographics

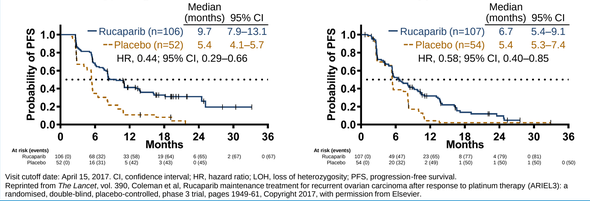
Table 1. Baseline Demographics (All Randomized Patients)

Characteristic	Rucaparib (n=375)	Placebo (n=189)
Age, median (range), years	61 (39–84)	62 (36–85)
Diagnosis, n (%)		
Epithelial ovarian cancer	312 (83.2)	159 (84.1)[a]
Fallopian tube cancer	32 (8.5)	10 (5.3)
Primary peritoneal cancer	31 (8.3)	19 (10.1)
***BRCA* and LOH status, n (%)**		
BRCA mutant	130 (34.7)	66 (34.9)
BRCA1	80 (21.3)	37 (19.6)
BRCA2	50 (13.3)	29 (15.3)
Germline	82 (21.9)	48 (25.4)
Somatic	40 (10.7)	16 (8.5)
Unknown[b]	8 (2.1)	2 (1.1)
BRCA wild type	245 (65.3)	123 (65.1)
Genomic LOH ≥16%[c]	106 (28.3)	52 (27.5)
Genomic LOH <16%	107 (28.5)	54 (28.6)
Genomic LOH indeterminate[d]	32 (8.5)	17 (9.0)

Visit cutoff date: April 15, 2017. [a]Additionally, 1 (0.5%) patient had a diagnosis of high-grade serous adenocarcinoma that was fallopian and/or ovarian in origin. [b]Tumor sample was *BRCA* mutant by Foundation Medicine's T5 NGS assay, but a blood sample was not available for central germline testing. [c]For ARIEL3, high LOH was prespecified as ≥16% genomic LOH. [d]Tumor sample was not evaluable for percentage of genomic LOH due to low tumor content or low aneuploidy.
LOH, loss of heterozygosity; NGS, next-generation sequencing.

- Of the 368 patients with *BRCA* wild-type associated recurrent ovarian carcinoma, LOH was evaluable for 319 (rucaparib, n=213; placebo, n=106; **Table 1**)
- Using the prespecified cutoff of 16% for percentage of genomic LOH, rucaparib significantly improved investigator-assessed PFS vs placebo for patients with high-LOH recurrent ovarian carcinoma (*P*<0.0001; **Figure 2A**) and patients with low-LOH recurrent ovarian carcinoma (*P*=0.0049; **Figure 2B**)
  - The treatment-by-LOH subgroup interaction was nonsignificant (*P*=0.4106) using the prespecified cutoff of 16%

Figure 2. Investigator-Assessed PFS in Patients with a *BRCA* Wild-Type Carcinoma with (A) High LOH or (B) Low LOH Using the 16% Prespecified Cutoff

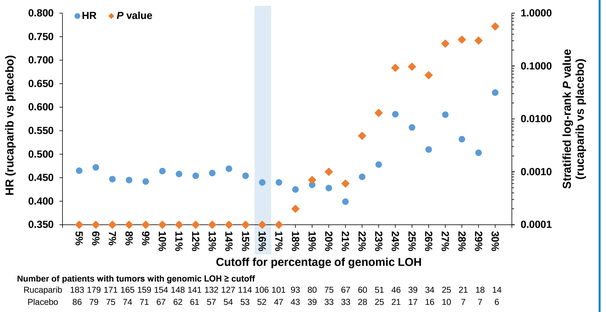


Visit cutoff date: April 15, 2017. CI, confidence interval; HR, hazard ratio; LOH, loss of heterozygosity; PFS, progression-free survival.
Reprinted from *The Lancet*, vol. 390, Coleman et al, Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial, pages 1949-61, Copyright 2017, with permission from Elsevier.

Evaluation of Percentage of Genomic LOH

- Rucaparib significantly improved (*P*<0.02) investigator-assessed PFS vs placebo between the 5% and 23% cutoffs for percentage of genomic LOH (**Figure 3**)
  - Using the prespecified LOH cutoff (16%), the HR (rucaparib vs placebo) was 0.44 (95% confidence interval [CI], 0.29–0.66; *P*<0.0001) for patients with high-LOH recurrent ovarian carcinoma

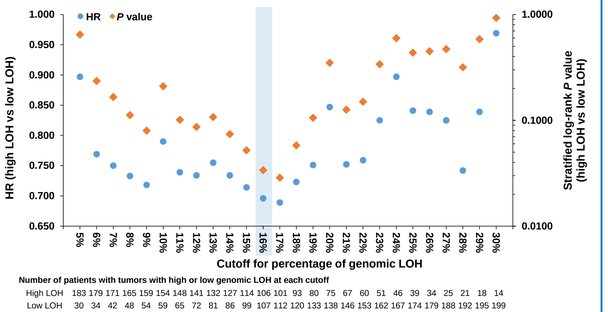
Figure 3. Investigator-Assessed PFS Using Different Cutoffs for Percentage of Genomic LOH



Visit cutoff date: April 15, 2017. Shaded blue bar indicates the prespecified cutoff of 16% used for ARIEL3 primary analysis.
HR, hazard ratio; LOH, loss of heterozygosity; PFS, progression-free survival.

- To further assess the percentage of genomic LOH cutoff, we compared patients with high- vs low-LOH recurrent ovarian carcinoma within the rucaparib arm (**Figure 4**)
  - There was a significant benefit for investigator-assessed PFS at the prespecified cutoff of 16% (HR, 0.70; 95% CI, 0.50–0.97; *P*=0.0338)
  - A significant benefit for investigator-assessed PFS was also observed using a cutoff of 17% (HR, 0.69; 95% CI, 0.49–0.96; *P*=0.0287)
- In the placebo arm, no significant benefit was observed for investigator-assessed PFS in patients with high- vs low-LOH recurrent ovarian carcinoma at any cutoff tested

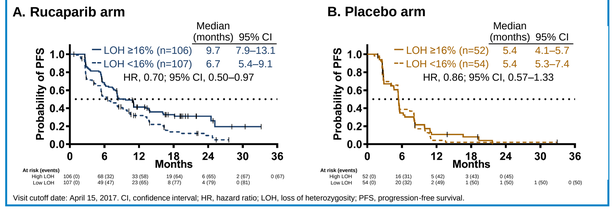
Figure 4. Comparison of Investigator-Assessed PFS for Patients with a High-LOH vs Low-LOH Tumor in the Rucaparib Arm



Visit cutoff date: April 15, 2017. Shaded blue bar indicates the prespecified cutoff of 16% used for ARIEL3 primary analysis.
HR, hazard ratio; LOH, loss of heterozygosity; PFS, progression-free survival.

- In the rucaparib arm, at the prespecified cutoff of 16%, patients with a *BRCA* wild-type/high-LOH carcinoma had significantly longer investigator-assessed PFS than patients with a *BRCA* wild-type/low-LOH carcinoma (*P*=0.0338; **Figure 5A**); no significant difference was observed in the placebo arm (*P*=0.5132; **Figure 5B**)

Figure 5. Investigator-Assessed PFS (LOH ≥16% vs LOH <16%) in Patients with a *BRCA* Wild-Type Carcinoma in the (A) Rucaparib and (B) Placebo Arms



Visit cutoff date: April 15, 2017. CI, confidence interval; HR, hazard ratio; LOH, loss of heterozygosity; PFS, progression-free survival.

Confirmation of HRD status using the FoundationFocus™ CDx $_{BRCA\ LOH}$ test

- Detection of *BRCA* mutations and assessment of the percentage of genomic LOH were analytically validated using the NGS-based FoundationFocus CDx $_{BRCA\ LOH}$ test[6]
- Tumor tissue samples were initially sequenced using the T5 clinical trial assay (N=564), and subsequently 518 samples were available for sequencing using the FoundationFocus CDx $_{BRCA\ LOH}$ test
- Of the samples evaluated with both tests, HRD-positive status (as defined by the presence of a deleterious *BRCA* mutation or high genomic LOH) was confirmed by the CDx test for 94% (313/332) of HRD-positive patients determined by the clinical trial assay, and of these, tumor *BRCA* mutation status was confirmed by the CDx test for 99% (177/178) of patients with a *BRCA*-mutant tumor as determined by the clinical trial assay

CONCLUSIONS

- Rucaparib improved investigator-assessed PFS vs placebo across a wide range of cutoffs tested for percentage of genomic LOH, including the prespecified cutoff of 16% for high LOH
- The observance of significant differences between patients with high- vs low-LOH recurrent ovarian carcinoma in the rucaparib arm, but not the placebo arm, suggests that genomic LOH is a predictive, but likely not a prognostic, biomarker
- Although rucaparib provides benefit irrespective of tumor HRD status, and tumor molecular testing is not required for use, based on the potential predictive utility of the genomic LOH biomarker, on April 6, 2018, the FDA approved the FoundationFocus CDx $_{BRCA\ LOH}$ assay as a complementary diagnostic test for rucaparib

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