Characterization of Patients With Long-term Responses to Rucaparib in Recurrent Ovarian Cancer

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INTRODUCTION

- Cancers that are defective in homologous recombination repair (HRR), such as those with a *BRCA1* or *BRCA2* (*BRCA*) mutation, are sensitive to platinum-based chemotherapies and poly(ADP-ribose) polymerase (PARP) inhibitors[1,2]
- Molecular characterization of patients who derive durable benefit from PARP inhibitor treatment may provide insights into improving outcomes
- Here, we describe long-term responders from Study 10 Part 2 (NCT01482715) and ARIEL2 (NCT01891344), studies of the PARP inhibitor rucaparib for the treatment of patients with recurrent, high-grade ovarian cancer (HGOC)[3-5]

METHODS

- This exploratory post-hoc analysis included patients enrolled in Study 10 (Parts 2A and 2B) and ARIEL2 (Parts 1 and 2). Key patient eligibility criteria for these studies are summarized in **Table 1**
  - Final results from Study 10 (n=54) and ARIEL2 (n=491) were pooled
- Patients were treated with oral rucaparib at a starting dose of 600 mg twice daily until disease progression, unacceptable toxicity, or death
- Platinum status was classified based on time to progression following the most recent platinum-based treatment
- Durations of a best overall response of partial or complete response (confirmed or unconfirmed per Response Evaluation Criteria In Solid Tumors version 1.1 [RECIST]) were used to define long-term and short-term responders
  - Long-term responders were defined as patients with a duration of response (DOR) ≥1 year
  - Short-term responders were defined as patients with a response followed by a short duration to disease progression, resulting in a DOR ≤20 weeks
- Formalin-fixed paraffin-embedded tumor tissues collected before rucaparib treatment were profiled using targeted next-generation sequencing (NGS) to detect deleterious mutations in HRR genes, including *BRCA1* and *BRCA2*
  - In addition, the NGS assay sequences single-nucleotide polymorphisms throughout the genome to identify tumors with high genome-wide loss of heterozygosity (LOH; ≥16%), a genomic scar indicative of homologous recombination deficiency (Foundation Medicine, Cambridge, MA, USA)[5]
- Mutations detected in tumor tissue were identified as germline or somatic by analysis of genomic DNA from blood using the BROCA NGS assay (University of Washington, Seattle, WA, USA)[6]

Table 1. Key Patient Eligibility Criteria

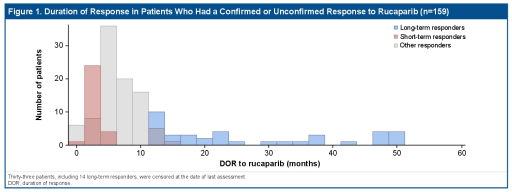
Study 10 Part 2 Phase 2 efficacy and safety study (NCT01482715)[3] (n=54; Part 2A n=42, Part 2B n=12)	ARIEL2 Phase 2 efficacy and safety study (NCT01891344)[4] (n=491; Part 1 n=204, Part 2 n=287)
• HGOC with *BRCA1* or *BRCA2* mutation: – **Part 2A:** Germline only – **Part 2B:** Germline or somatic	• HGOC with or without *BRCA1* or *BRCA2* mutation – Patients with germline *BRCA1* or *BRCA2* mutation capped at 15 in Part 1
• Measurable disease	• Measurable disease
• Number of prior treatment regimens: – **Part 2A:** 2–4 prior chemotherapy regimens – **Part 2B:** 3–4 prior chemotherapy regimens	• Number of prior treatment regimens: – **Part 1:** ≥1 prior platinum-based regimen – **Part 2:** 3–4 prior chemotherapy regimens
• Platinum status: – **Part 2A:** Platinum-sensitive disease – **Part 2B:** Platinum-sensitive, resistant, or refractory disease	• Platinum status: – **Part 1:** Platinum-sensitive disease – **Part 2:** Platinum-sensitive, resistant, or refractory disease
Study completed: primary completion, March 2019	Visit cut-off: February 1, 2019

Platinum-sensitive disease: PFI ≥6 months. Platinum-resistant disease: PFI <6 months. Platinum-refractory disease: best response of progressive disease on last platinum with PFI <2 months. HGOC, high-grade ovarian cancer; PFI, progression-free interval.

RESULTS

- Overall, 29% (159/545) of enrolled patients had a best overall response (confirmed or unconfirmed) of a partial or complete response to rucaparib for ovarian cancer (**Figure 1**), with 25% (138/545) of enrolled patients having a confirmed response
- Thirty-eight patients (28% of patients with confirmed responses) had a long-term confirmed response (DOR ≥1 year), including 16/138 (12%) with a DOR ≥2 years
  - Two patients, originally identified as potential long-term responders, were excluded from the analysis because they had an unconfirmed response or response after the treatment end date
- Twenty-nine patients had a short-term response (DOR ≤20 weeks), including 16 patients with confirmed responses

Figure 1. Duration of Response in Patients Who Had a Confirmed or Unconfirmed Response to Rucaparib (n=159)



Thirty-three patients, including 14 long-term responders, were censored at the date of last assessment.
DOR, duration of response.

- Long- and short-term responders had similar baseline characteristics and prior treatment history (**Table 2**)
  - As expected, based on known prognostics of the disease, there were some trends toward a lower performance status score, a longer progression-free interval, and increased sensitivity to platinum among long-term responders versus short-term responders
  - However, none of the baseline characteristics or the number of prior chemotherapies were significantly different between long- and short-term responders

Table 2. Baseline Patient Characteristics and Prior Chemotherapies in Long- and Short-term Responders to Rucaparib

	Long-term responders (n=38)	Short-term responders (n=29)
Median age (range), years	63 (33–82)	60 (44–83)
Median weight (range), kg	68.7 (47.5–103.3)	76.7 (49.0–106.0)
Median BMI (range), kg/m²	25.9 (18.6–37.5)	29.2 (19.4–39.3)
ECOG PS, n (%)		
0	25 (65.8)	13 (44.8)
1	13 (34.2)	16 (55.2)
Cancer type, n (%)		
Epithelial ovarian carcinoma	33 (86.8)	25 (86.2)
Primary peritoneal carcinoma	3 (7.9)	3 (10.3)
Fallopian tube carcinoma	2 (5.3)	1 (3.4)
Median time since cancer diagnosis (range), months	50.1 (16.3–134.9)	42.1 (12.8–170.1)
Median number of prior chemotherapies (range)	2.5 (1–5)	2 (1–4)
1, n (%)	9 (23.7)	10 (34.5)
2, n (%)	10 (26.3)	5 (17.2)
≥3, n (%)	19 (50.0)	14 (48.3)
Median number of prior platinum-based therapies (range)	2 (1–4)	2 (1–3)
1, n (%)	9 (23.7)	10 (34.5)
2, n (%)	16 (42.1)	8 (27.6)
≥3, n (%)	13 (34.2)	11 (37.9)
Progression-free interval from last platinum-based therapy, n (%)		
>24 months	4 (10.5)	1 (3.4)
>12–24 months	12 (31.6)	5 (17.2)
6–12 months	17 (44.7)	14 (48.3)
>2–<6 months	3 (7.9)	7 (24.1)
≤2 months	2 (5.3)	2 (6.9)
Response to last platinum-based therapy, n (%)		
Sensitive	33 (86.8)	20 (69.0)
Resistant	4 (10.5)	7 (24.1)
Refractory	1 (2.6)	2 (6.9)
BRCA mutation status, n (%)		
Harbor deleterious *BRCA* mutation	27 (71.1)	15 (51.7)
No *BRCA* mutation (*BRCA* wild-type)	11 (28.9)	14 (48.3)
High LOH	9 (23.7)	5 (17.2)
Low LOH	1 (2.6)	6 (20.7)
LOH indeterminate	1 (2.6)	3 (10.3)

BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; LOH, loss of heterozygosity.

- A deleterious *BRCA* mutation was identified in 71% (27/38) of long-term responders and 52% (15/29) of short-term responders
- The distributions of germline versus somatic *BRCA* mutations were similar between long- and short-term responders (**Table 3**)
- A *BRCA* Ashkenazi Jewish founder mutation (*BRCA1* E23fs*17, *BRCA1* Q1756fs*74, or *BRCA2* S1982fs*22) was detected in 30% (8/27) of long-term responders versus 13% (2/15) of short-term responders (P=0.29, Fisher's exact test)
- No significant difference was seen in the fraction of mutations found in *BRCA1* and *BRCA2* genes for long- versus short-term responders (P=0.73, Fisher's exact test)
- Similar distributions of genomic characteristics were also observed when considering just short-term responders with confirmed responses and HGOC associated with a *BRCA* mutation (n=10; 1/10 with a *BRCA* Ashkenazi Jewish founder mutation; 6/10 with *BRCA1* mutations; 4/10 with *BRCA2* mutation; 6/10 with germline mutations)

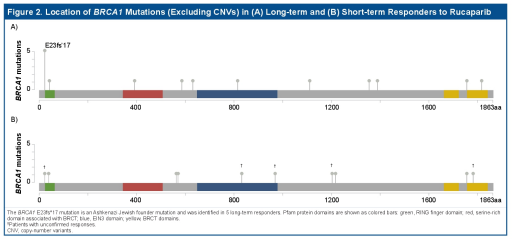
Table 3. Summary of Molecular Characteristics in Long- and Short-term Responders to Rucaparib With Carcinomas Associated With a *BRCA* Mutation

	Long-term responders (n=27)	Short-term responders (n=15)
BRCA mutation origin, n (%)		
Germline	22 (81.5)[a]	10 (66.7)
Somatic	5 (18.5)	5 (33.3)
Presence of *BRCA* founder mutation, n (%)		
Yes	8 (29.6)	2 (13.3)
No	19 (70.4)	13 (86.7)
BRCA gene with mutation, n (%)		
BRCA1	17 (63.0)[a]	11 (73.3)
BRCA2	10 (37.0)	4 (26.7)
BRCA mutation type, n (%)		
Homozygous deletion or rearrangement	4 (14.8)	0
Small insertion/deletion	21 (77.8)	9 (60.0)
Nonsense mutation	1 (3.7)	4 (26.7)
Missense, splice-site mutation	1 (3.7)	2 (13.3)

[a]One long-term responder with a germline *BRCA1* mutation also had a somatic *BRCA2* truncating rearrangement; data did it in the tumor.

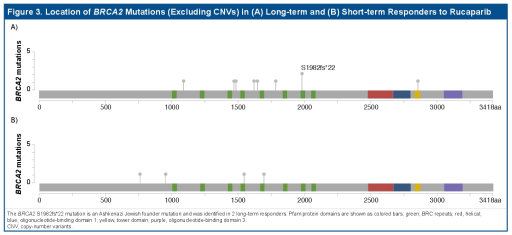
- For *BRCA*-mutated cases, there was no apparent difference in the intragenic location of *BRCA* single nucleotide substitutions or small insertions/deletions for long- versus short-term responders (**Figures 2** and **3**)
- Among patients with HGOC harboring a *BRCA* mutation, a *BRCA* homozygous deletion or truncating/duplication rearrangement was detected in 15% (4/27) of long-term responders versus 0% (0/15) of short-term responders (**Table 3**)
  - Three mutations were detected somatically and 1 mutation was germline

Figure 2. Location of *BRCA1* Mutations (Excluding CNVs) in (A) Long-term and (B) Short-term Responders to Rucaparib



The *BRCA1* E23fs*17 mutation is an Ashkenazi Jewish founder mutation and was identified in 5 long-term responders. Pfam protein domains are shown as colored bars: green, RING finger domain; red, serine-rich domain associated with BRCT blue, BRA1 domain; yellow, BRCT domains.
[a]Patients with unconfirmed responders.
CNV, copy-number variants.

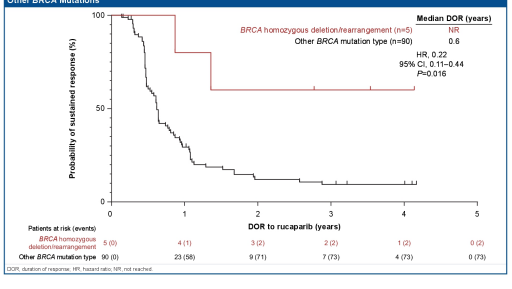
Figure 3. Location of *BRCA2* Mutations (Excluding CNVs) in (A) Long-term and (B) Short-term Responders to Rucaparib



The *BRCA2* S1982fs*22 mutation is an Ashkenazi Jewish founder mutation and was identified in 2 long-term responders. Pfam protein domains are shown as colored bars: green, BRC repeats; red, helical blue, oligonucleotide-binding domain 1; yellow, tower domain; purple, oligonucleotide-binding domain 3.

- An expanded analysis of the 95 patients with a *BRCA* mutation and a confirmed response to rucaparib (regardless of DOR) was performed to further evaluate the impact of homozygous deletions/rearrangements
  - Patients with HGOC harboring a *BRCA* homozygous deletion or rearrangement had significantly longer DOR to rucaparib than patients with other mutation types pooled together (median not reached vs 0.6 years; hazard ratio [HR], 0.22; 95% CI, 0.11–0.44; P=0.016; **Figure 4**)

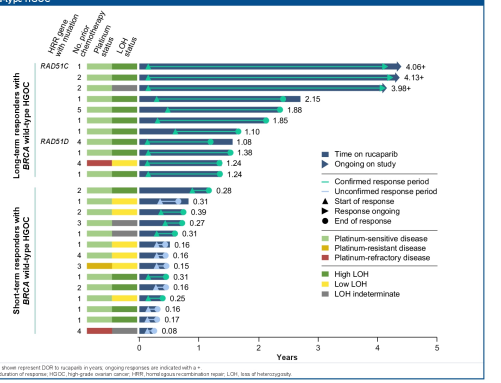
Figure 4. Duration of Response to Rucaparib in Patients With a *BRCA* Homozygous Deletion or Rearrangement Versus Other *BRCA* Mutations



DOR, duration of response; HR, hazard ratio; NR, not reached.

- Among patients with *BRCA* wild-type HGOC, 9 of the 11 (82%) long-term responders had high genome-wide LOH (≥16% LOH); 2 of these patients had a deleterious *RAD51C/D* mutation. In contrast, only 5 of the 14 (36%) short-term responders had high genome-wide LOH, including 2 of the 6 (33%) short-term responders with confirmed responses (**Figure 5**)

Figure 5. Time on Rucaparib and Genomic/Clinical Characteristics of Long- and Short-term Responders With *BRCA* Wild-type HGOC



Values shown represent DOR to rucaparib in years; ongoing responses are indicated with a +.
DOR, duration of response; HGOC, high-grade ovarian cancer; HRR, homologous recombination repair; LOH, loss of heterozygosity.

- Among long-term responders, median treatment duration was 2.5 years (range, 1–5 years) and median dose intensity was 0.82
  - Most long-term responders (28/38; 74%) had ≥1 dose reduction; 18/38 patients (47%) had ≥2 dose reductions
  - The most common treatment-emergent adverse events leading to dose reduction were anemia, asthenia/fatigue, nausea, and neutropenia
- Treatment-emergent adverse event incidence rates were broadly similar for long- and short-term responders
- There were no cases of myelodysplastic syndrome or acute myeloid leukemia among long- or short-term responders

CONCLUSIONS

- Overall, 28% of patients with recurrent HGOC and a confirmed response to rucaparib had a response of at least 1 year, including 12% with a response lasting more than 2 years
- The majority (71%) of long-term responders to rucaparib harbored a deleterious *BRCA* mutation, particularly homozygous deletion or rearrangements which would not be susceptible to somatic reversion mutations
- Most (82%) long-term responders with *BRCA* wild-type ovarian cancer had tumors with high genome-wide LOH, a genomic scar indicative of homologous recombination deficiency
  - In 2 patients with a long-term response, high genome-wide LOH was observed in the context of a deleterious *RAD51C/D* mutation

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