Poster number: F01

Characterisation of Patients (pts) With Long-term Responses to Rucaparib in Recurrent Ovarian Cancer (OC)

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SUMMARY

- **Overall, 28% of patients with recurrent high-grade ovarian cancer and a confirmed response to rucaparib had a response duration of at least 1 year, including 12% with a response duration of more than 2 years**
- **The majority (71%) of long-term responders to rucaparib harboured a deleterious BRCA mutation, with an enrichment of homozygous deletions or rearrangements which would not be susceptible to somatic reversion mutations**
- **Most (82%) long-term responders with BRCA wild-type ovarian cancer had tumours with high genome-wide loss of heterozygosity, a genomic scar indicative of homologous recombination deficiency (Figure 5)**
  - **In 2 patients with a long-term response, high genome-wide loss of heterozygosity was observed in the context of a deleterious *RAD51C/D* mutation**

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 characterisation 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]

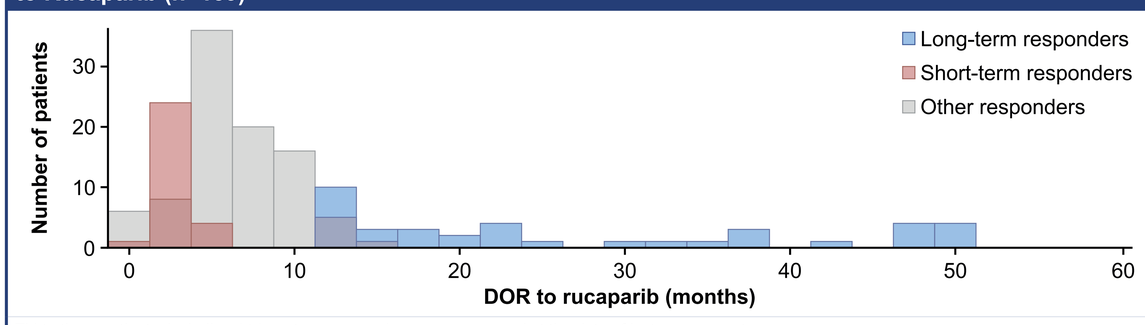
METHODS

- 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 are summarised in **Supplementary 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: Duration of response (DOR) ≥1 year
  - Short-term responders: Response followed by a short duration to disease progression, resulting in a DOR ≤20 weeks
- Formalin-fixed paraffin-embedded tumour tissues collected before rucaparib treatment were profiled using targeted next-generation sequencing (NGS) to detect deleterious mutations in HRR genes, including *BRCA1* and *BRCA2*; deleterious BRCA mutations reported in local BRCA testing results were used for cases without tumour tissue for central NGS
  - For cases with tumour tissue, the NGS assay sequences single-nucleotide polymorphisms throughout the genome to identify tumours with high genome-wide loss of heterozygosity (LOH; ≥16%), a genomic scar indicative of homologous recombination deficiency (Foundation Medicine, Cambridge, USA)[5]
- Mutations detected in tumour tissue were identified as germline or somatic by analysis of genomic DNA from blood using the BROCA NGS assay (University of Washington, Seattle, USA)[6]
  - For Study 10, all local BRCA testing results reported germline BRCA mutations

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
- Long- and short-term responders had similar baseline characteristics and prior treatment history (**Supplementary Tables 2 and 3**)

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.

- 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 1**)
- 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* mutations; 6/10 with germline mutations)

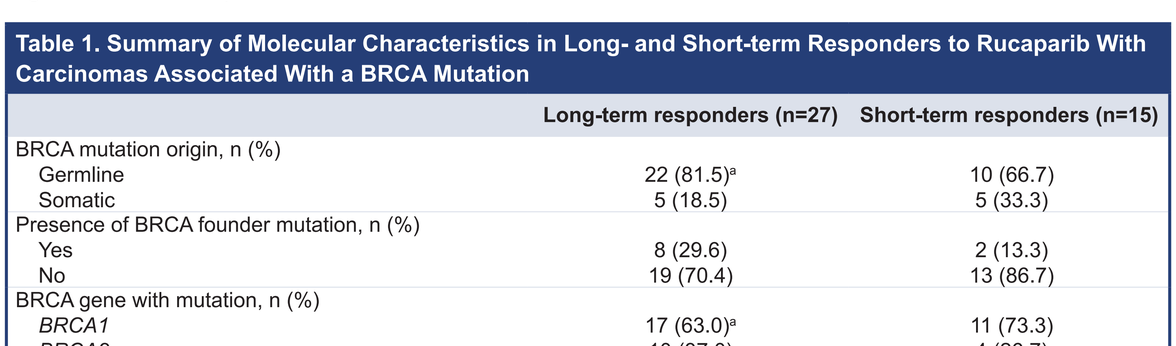
Table 1. Summary of Molecular Characteristics in Long- and Short-term Responders to Rucaparib With Carcinomas Associated With a BRCA Mutation

	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 detected in the tumour.

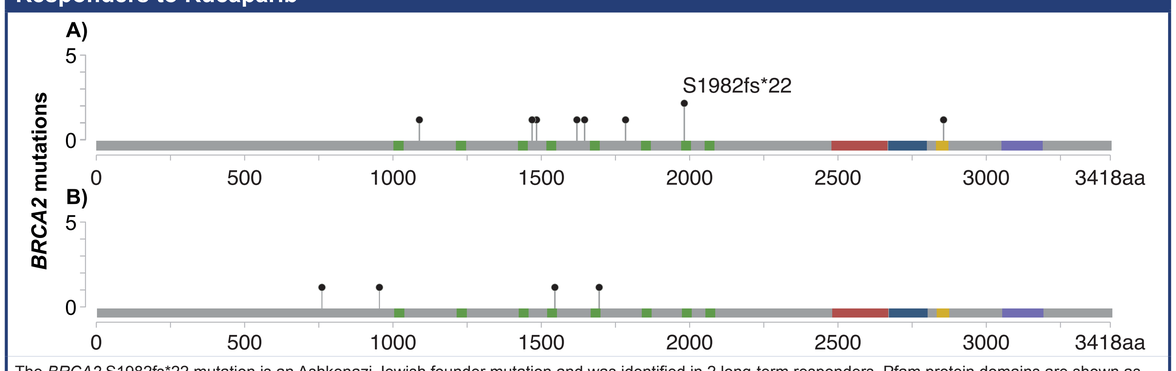
- For BRCA-mutated cases, there was no apparent difference in the intragenic location of BRCA single nucleotide substitutions or small insertions/deletions for long- versus short-term responders (**Figures 2** and **3**)
- Among patients with HGOC harbouring a BRCA mutation, a BRCA homozygous deletion or truncating/duplication rearrangement was detected in 15% (4/27) of long-term responders versus 0% (0/15) of short-term responders (**Table 1**)
  - Three mutations were somatic 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 coloured bars: green, RING finger domain; red, serine-rich domain associated with BRCT; blue, EIN3 domain; yellow, BRCT domains.
†Patients with unconfirmed responses.
CNV, copy-number variants.

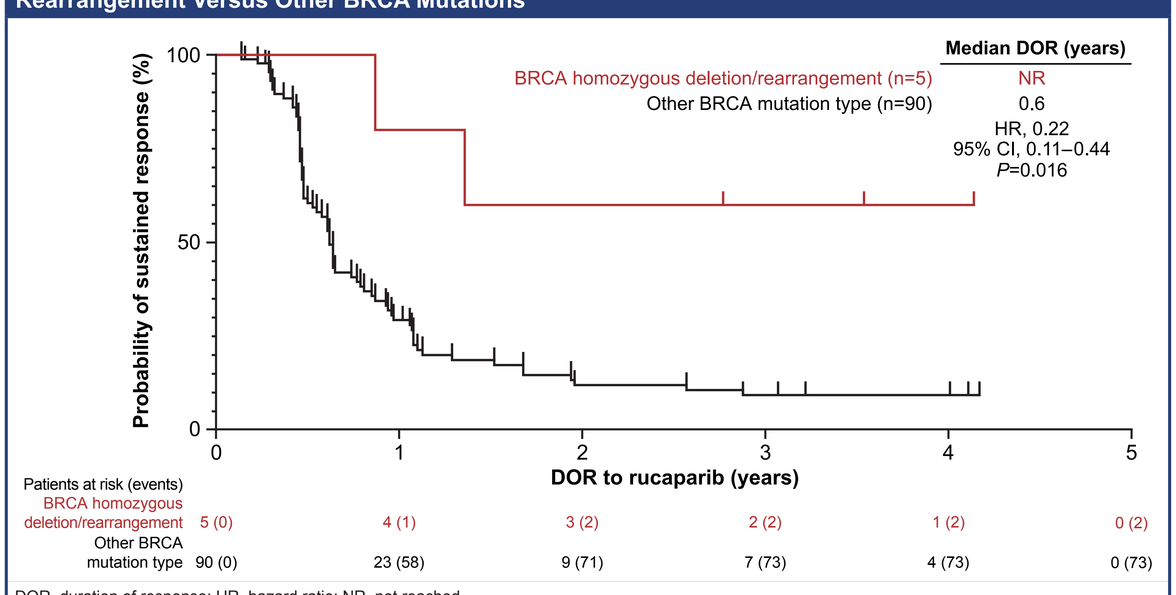
Figure 3. Location of *BRCA2* Mutations (Excluding CNVs) in (A) Long-term and (B) Short-term Responders to Rucaparib



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 coloured bars: green, BRC repeats; red, helical; blue, oligonucleotide-binding domain 1; yellow, tower domain; purple, oligonucleotide-binding domain 3.
CNV, copy-number variants.

- The impact of homozygous deletions/rearrangements was further evaluated in an expanded analysis of the 95 patients with a BRCA mutation and a confirmed response to rucaparib (regardless of DOR)
  - Patients with HGOC harbouring 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**)

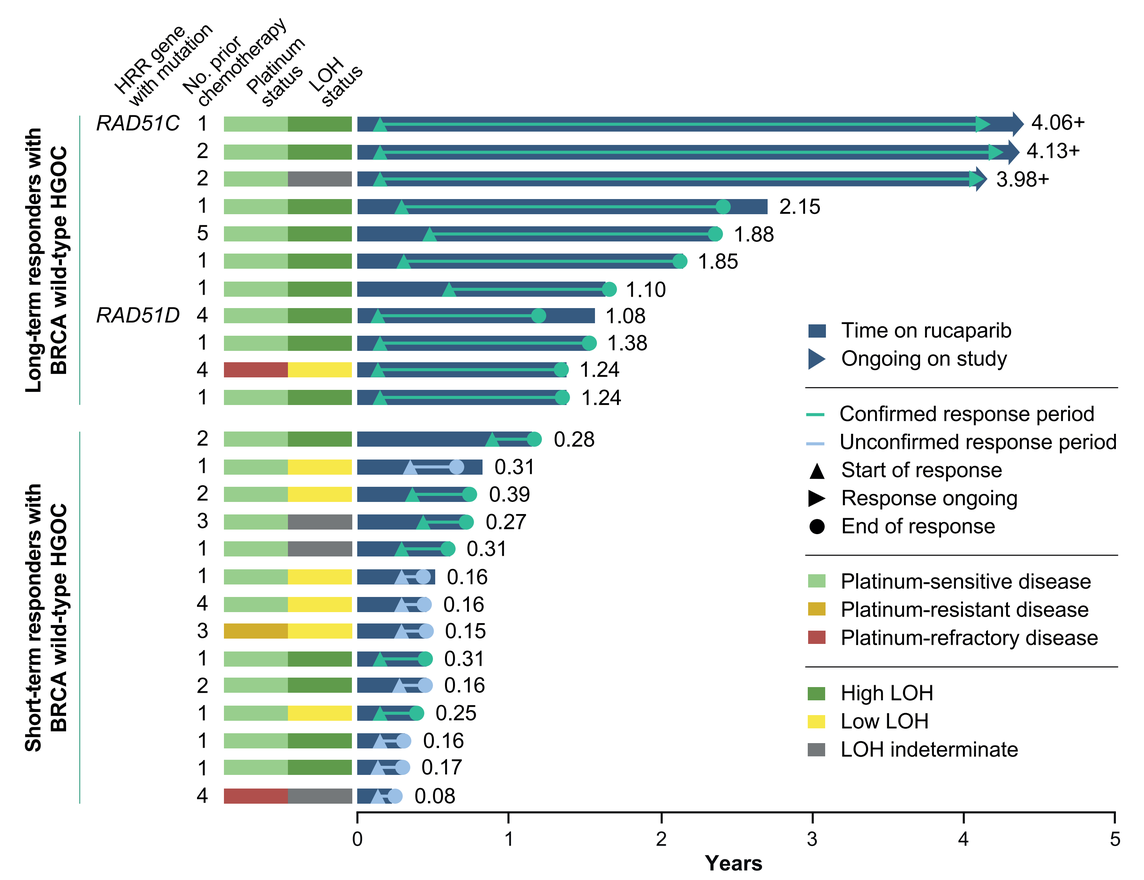
Figure 4. Duration of Response to Rucaparib in Patients With a BRCA Homozygous Deletion or Rearrangement Versus Other BRCA Mutations



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%); 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 anaemia, 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 leukaemia among long- or short-term responders

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Supplementary Material
Also available at: https://clovisoncology.com/files/AIOM2020_Lorusso_Supplement.pdf. Please scan this QR code or visit the website to view additional materials for this poster.

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