Refinement of Prespecified Cutoff for Genomic Loss of Heterozygosity (LOH) in ARIEL2 Part 1: A Phase 2 Study of Rucaparib in Patients with High-Grade Ovarian Carcinoma (HGOC)

Robert L. Coleman,[1] Elizabeth Swisher,[2] Amit Oza,[3] Clare L. Scott,[4] Heidi Giordano,[5] Kevin K. Lin,[5] Gottfried E. Konecny,[6] Anna V. Tinker,[7] David M. O'Malley,[8] Rebecca Kristeleit,[9] Ling Ma,[10] Katherine Bell-McGuinn,[11] James D. Brenton,[12] Janiel M. Cragun,[13] Ana Oaknin,[14] Isabelle Ray-Coquard,[15] Scott H. Kaufmann,[16] Sandra Goble,[5] Lara Maloney,[5] Iain A. McNeish[17]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]University of Washington, Seattle, WA; [3]Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; [4]Royal Melbourne Hospital, Parkville, Victoria, Australia; [5]Clovis Oncology, Inc., Boulder, CO; [6]University of California Los Angeles, Los Angeles, CA; [7]British Columbia Cancer Agency, Vancouver, BC, Canada; [8]The Ohio State University, James Cancer Center, Columbus, OH; [9]University College London, Cancer Institute, London, United Kingdom; [10]Rocky Mountain Cancer Centers, Lakewood, CO; [11]Memorial Sloan Kettering Cancer Center, New York, NY; [12]Cancer Research UK Cambridge Institute, University of Cambridge, Li Ka Shing Centre, Cambridge, United Kingdom; [13]The University of Arizona Cancer Center, Tucson, AZ; [14]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [15]GINECO, Centre Léon Bérard and University Claude Bernard, Lyon, France; [16]Mayo Clinic, Rochester, MN; [17]Institute of Cancer Sciences, University of Glasgow, Glasgow, United Kingdom

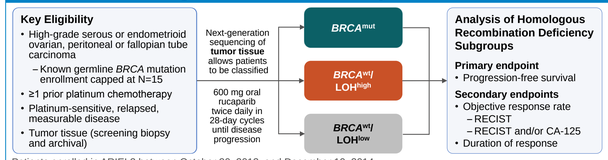
Abstract: 5540
Poster Board: 363

BACKGROUND

- Poly(ADP-ribose) polymerase (PARP) inhibitors have activity in patients with advanced ovarian carcinoma[1-3]
- Mutations in homologous repair genes such as *BRCA1* and *BRCA2* (*BRCA*), along with loss of the wild-type allele, compromise accurate DNA repair, leading to the loss or duplication of chromosomal regions (genomic loss of heterozygosity [LOH])[4-7]
- ARIEL2 (NCT01891344) is the first study to assess the utility of genomic LOH quantified by use of a next-generation sequencing (NGS) assay to predict response to the PARP inhibitor rucaparib

METHODS

Figure 1. ARIEL2 Part 1: Study Schema



Patients enrolled in ARIEL2 between October 30, 2013, and December 19, 2014.
CA-125, cancer antigen 125; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

Tumor Sequencing Assay

- An NGS-based assay (Foundation Medicine, Inc., Cambridge, MA)[8] was used to determine the percentage of genomic LOH and mutations in *BRCA* and other homologous recombination genes in archival tumor tissue and pretreatment biopsies[9,10]
- A prespecified cutoff of ≥14% for LOH^{high} was based on analysis of microarray and survival data for patients in The Cancer Genome Atlas who had ovarian carcinoma and had received platinum-based chemotherapy[11]
  - A planned post hoc analysis using outcome data from ARIEL2 identified a refined genomic LOH cutoff that could differentiate the progression-free survival (PFS) of ARIEL2 patients with *BRCA*^{wt}/LOH^{high} vs *BRCA*^{wt}/LOH^{low} tumors
  - To optimize the genomic LOH cutoff percentage, a range of genomic LOH percentages was tested in a receiver operating characteristic analysis to determine the cutoff that resulted in the largest overall response rate and PFS differences between the *BRCA*^{wt}/LOH^{high} and *BRCA*^{wt}/LOH^{low} subgroups in ARIEL2 Part 1
- Germline mutations were identified in genomic DNA from blood using the BROCA-HR sequencing assay (University of Washington, Seattle, WA)[12]; mutations not detected by BROCA-HR sequencing were classified as somatic

RESULTS

Patient Characteristics

- Enrollment into ARIEL2 Part 1 was initiated on October 30, 2013, and was fully enrolled in 2014
- At the data cutoff date (January 18, 2016), 204 patients were treated with rucaparib (baseline characteristics shown in **Table 1**); 28 patients remained on study

Efficacy

Progression-Free Survival

- Using the prespecified cutoff (≥14%) for tumor genomic LOH^{high}, the risk of disease progression with rucaparib was reduced by 73% in the *BRCA*^{mut} subgroup and by 38% in the *BRCA*^{wt}/LOH^{high} subgroup compared with the *BRCA*^{wt}/LOH^{low} subgroup (**Figure 2A**)
  - More patients in the *BRCA*^{mut} subgroup were progression free at 12 months (50.4%) than in the *BRCA*^{wt}/LOH^{high} (28.0%) and *BRCA*^{wt}/LOH^{low} (9.6%) subgroups
- With the refined cutoff (≥16%) for tumor genomic LOH^{high}, risk of progression for the *BRCA*^{wt}/LOH^{high} subgroup was reduced by 49% (hazard ratio [HR], 0.51; 95% confidence interval [CI], 0.34–0.74; *P*<0.001) (**Figure 2B**)
  - Using the refined cutoff (≥16%), median PFS increased to 7.2 months (95% CI, 5.5–9.6) in the *BRCA*^{wt}/LOH^{high} subgroup compared with a point estimate of 5.7 months (≥14% cutoff)

Table 1. ARIEL2 Part 1: Baseline Demographic and Disease Characteristics by Prespecified HRD Subgroup

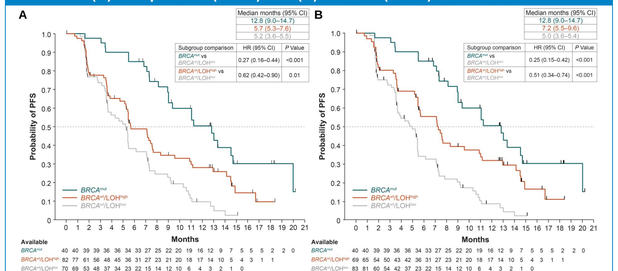
Characteristic	HRD subgroup *BRCA*^{mut} (n=40)	*BRCA*^{wt}/LOH^{high} (n=82)	*BRCA*^{wt}/LOH^{low} (n=70)	Total (N=204)[a]
Median age (range), years	58.5 (33–78)	65.0 (39–83)	65.0 (31–86)	64.5 (31–86)
ECOG PS, n (%)				
0	26 (65.0)	52 (63.4)	46 (65.7)	133 (65.2)
1	14 (35.0)	30 (36.6)	23 (32.9)	70 (34.3)
Pending	0	0	1 (1.4)	1 (0.5)
Diagnosis, n (%)[b]				
Epithelial ovarian cancer	38 (95.0)	68 (82.9)	49 (70.0)	163 (79.9)
Primary peritoneal cancer	1 (2.5)	10 (12.2)	12 (17.1)	24 (11.8)
Fallopian tube cancer	1 (2.5)	4 (4.9)	9 (12.9)	16 (7.8)
Histology, n (%)				
Serous	39 (97.5)	80 (97.6)	66 (94.3)	197 (96.6)
Endometrioid	1 (2.5)	1 (1.2)	2 (2.9)	4 (2.0)
Mixed	0	1 (1.2)	2 (2.9)	3 (1.5)
BRCA mutation type, n (%)				
Germline	20 (50.0)	0	0	20 (9.8)
Somatic	19 (47.5)	0	0	19 (9.3)
Indeterminate	1 (2.5)	0	0	1 (0.5)
BRCA gene mutation, n (%)				
BRCA1	29 (72.5)	0	0	29 (14.2)
BRCA2	11 (27.5)	0	0	11 (5.4)
No. of prior treatment regimens				
Median no. of regimens (range)	2.0 (1–6)	1.0 (1–6)	1.0 (1–3)	1.0 (1–6)
1, n (%)	17 (42.5)	44 (53.7)	47 (67.1)	118 (57.8)
≥2, n (%)	23 (57.5)	38 (46.3)	23 (32.9)	86 (42.2)
Median no. of platinum-based regimens (range)	2.0 (1–5)	1.0 (1–5)	1.0 (1–3)	1.0 (1–5)
1, n (%)	17 (42.5)	45 (54.9)	49 (70.0)	121 (59.3)
≥2, n (%)	23 (57.5)	37 (45.1)	21 (30.0)	83 (40.7)
Progression-free interval following completion of platinum-based chemotherapy, n (%)				
6 to <12 months	23 (57.5)	37 (45.1)	31 (44.3)	96 (47.1)
≥12 months	17 (42.5)	45 (54.9)	39 (55.7)	108 (52.9)

[a]Includes 12 patients (5.9% of total) whose tumor specimens had sufficient nuclei to categorize as *BRCA*^{wt}, but insufficient nuclei to perform genomic LOH analysis.
[b]Diagnosis was unknown for 1 patient (0.5% of total).
ECOG PS, Eastern Cooperative Oncology Group Performance Status; HRD, homologous recombination deficiency.

Response

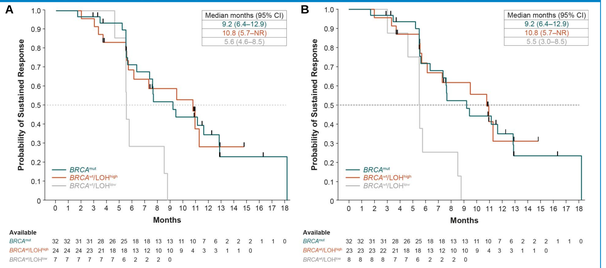
- The confirmed investigator-assessed objective response rate (**Table 2**) (RECIST) was significantly higher (*P*<0.001) in the *BRCA*^{mut} subgroup than in the *BRCA*^{wt}/LOH^{low} subgroup with the prespecified LOH cutoff (≥14%)
- Using the prespecified LOH cutoff (≥14%) and the refined LOH cutoff (≥16%), median duration of confirmed investigator-assessed response was longer in the *BRCA*^{mut} and *BRCA*^{wt}/LOH^{high} subgroups than in the *BRCA*^{wt}/LOH^{low} subgroup (**Figure 3**)

Figure 2. PFS in *BRCA*^{mut}, *BRCA*^{wt}/LOH^{high}, and *BRCA*^{wt}/LOH^{low} Subgroups for (A) Prespecified (≥14%) and (B) Refined (≥16%) LOH Cutoffs



Patients without documented progression were censored as of their last adequate tumor assessment.

Figure 3. Duration of Response* in *BRCA*^{mut}, *BRCA*^{wt}/LOH^{high}, and *BRCA*^{wt}/LOH^{low} Subgroups for (A) Prespecified (≥14%) and (B) Refined (≥16%) LOH Cutoffs



*For patients with responses by RECIST that were confirmed by a second assessment after ≥4 weeks.
Patients with an ongoing response were censored as of their last postbaseline scan. NR, not reached.

Table 2. Objective Response Rates

HRD subgroup	Objective response rate RECIST[a] n (%)	Combined RECIST or CA-125 n (%)
BRCA^{mut} (n=40)	32 (80.0)[b]	34 (85.0)
Germline mutation (n=20)	17 (85.0)	17 (85.0)
Somatic mutation (n=19)	14 (73.7)	16 (84.2)
Indeterminate (n=1)	1 (100.0)	1 (100.0)
BRCA1 mutation (n=29)	23 (79.3)	25 (86.2)
BRCA2 mutation (n=11)	9 (81.8)	9 (81.8)
PFI, ≥6 to <12 months (n=23)	20 (87.0)	20 (87.0)
PFI, ≥12 months (n=17)	12 (70.6)	14 (82.4)
BRCA^{wt}/LOH^{high}		
By prespecified cutoff (≥14%) (n=82)	24 (29.3)[c]	36 (43.9)
By refined cutoff (≥16%) (n=69)	23 (33.3)[d]	34 (49.3)
BRCA^{wt}/LOH^{low}		
By prespecified cutoff (≥14%) (n=70)	7 (10.0)	14 (20.0)
By refined cutoff (≥16%) (n=83)	8 (9.6)	16 (19.3)

[a]Confirmed responses in patients with tumors evaluable according to RECIST. [b]*P*<0.0001, vs *BRCA*^{wt}/LOH^{low} by the prespecified cutoff, and *P*<0.0001, vs *BRCA*^{wt}/LOH^{low} by the refined cutoff. [c]*P*=0.0053, vs *BRCA*^{wt}/LOH^{low} by the prespecified cutoff. [d]*P*=0.0003, vs *BRCA*^{wt}/LOH^{low} by the refined cutoff. PFI, progression-free interval following completion of platinum-based chemotherapy.

Safety

- Median treatment duration was 10.3, 5.5, and 4.8 months for the *BRCA*^{mut} and *BRCA*^{wt}/LOH^{high} and *BRCA*^{wt}/LOH^{low} subgroups using the prespecified cutoff
  - Overall, median treatment duration was 5.7 months (range, 0.1−20.1)
- Treatment-emergent adverse events (AEs) are shown in **Table 3**
  - Nausea (79.9%) and asthenia/fatigue (77.9%) were the most common nonhematologic treatment-emergent AEs
  - Anemia/decreased hemoglobin (36.3%) was the most common hematologic treatment-emergent AE
  - There were no reported cases of myelodysplastic syndrome or acute myeloid leukemia
- Thirty-nine percent of all treated patients required a dose reduction due to adverse events
  - The most common AEs leading to dose reduction were anemia/decreased hemoglobin (15.7%) and nausea (10.8%)
- Nineteen patients (9.3%) discontinued treatment because of an AE; asthenia/fatigue was the most common reason for treatment discontinuation (6 patients; 2.9%)
- Three patients (1.5%) died from disease progression; no treatment-related deaths were reported

Table 3. Treatment-Emergent AEs Reported in ≥20% of Patients (N=204)

Adverse event	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)
Nausea	108 (52.9)	46 (22.5)	9 (4.4)	0	163 (79.9)
Asthenia/fatigue	75 (36.8)	66 (32.4)	18 (8.8)	0	159 (77.9)
Constipation	59 (28.9)	32 (15.7)	3 (1.5)	0	94 (46.1)
Vomiting	61 (29.9)	24 (11.8)	4 (2.0)	0	89 (43.6)
Dysgeusia	64 (31.4)	23 (11.3)	0	0	87 (42.6)
ALT/AST increased[a]	38 (18.6)	23 (11.3)	24 (11.8)	1 (0.5)	86 (42.2)
Decreased appetite	49 (24.0)	31 (15.2)	4 (2.0)	0	84 (41.2)
Anemia/decreased hemoglobin	16 (7.8)	13 (6.4)	43 (21.1)	2 (1.0)	74 (36.3)
Diarrhea	44 (21.6)	17 (8.3)	7 (3.4)	0	68 (33.3)
Abdominal pain	25 (12.3)	31 (15.2)	5 (2.5)	0	61 (29.9)
Dyspnea	33 (16.2)	13 (6.4)	1 (0.5)	0	47 (23.0)
Abdominal distension	29 (14.2)	14 (6.9)	0	0	43 (21.1)

[a]ALT/AST elevations were transient, self-limiting, and not associated with other signs of liver toxicity.
ALT, alanine transaminase; AST, aspartate transaminase.

CONCLUSIONS

- In patients with a germline or somatic *BRCA*^{mut} or *BRCA*^{wt}/LOH^{high} tumor, rucaparib significantly reduced the risk of progression and prolonged duration of response compared with patients with a *BRCA*^{wt}/LOH^{low} tumor
- A planned post hoc analysis of platinum-sensitive patients from ARIEL2 Part 1 identified a refined LOH cutoff (≥16%) that provided further discrimination of PFS, objective response rate, and duration of response in patients with LOH^{high} and LOH^{low} tumors who received a median of 1 prior treatment regimen
- Results from patients enrolled in ARIEL2 Part 1 support the predictive utility of an HRD signature to identify patients with platinum-sensitive HGOC who may benefit from rucaparib treatment
- The NGS-based HRD assay will be prospectively applied to assess the utility of a rucaparib treatment–based LOH^{high} cutoff in predicting response to rucaparib in the phase 3 study ARIEL3 (NCT01968213), which is investigating rucaparib in the maintenance setting in platinum-sensitive HGOC

REFERENCES

1. Drew Y et al. *Br J Cancer.* 2016;114:723-30.
2. McNeish IA et al. *J Clin Oncol.* 2015;33(15 suppl):5508.
3. Kristeleit R et al. *Eur J Cancer.* 2015;51(15 suppl):S531; abstr 2700.
4. Watkins JA et al. *Breast Cancer Res.* 2014;16:211.
5. Pedersen B et al. *Genes Chromosomes Cancer.* 2013;52:794-801.
6. Abkevich V et al. *Br J Cancer.* 2012;107:1776-82.
7. Marquard AM et al. *Biomark Res.* 2015;3:9.
8. Frampton GM et al. *Nat Biotechnol.* 2013;31:1023-31.
9. Lin K et al. *Eur J Cancer.* 2015;51(15 suppl):S531-2; abstr 2701.
10. Sun JX et al. *Cancer Res.* 2014;74(19 suppl):abstr 1893.
11. The Cancer Genome Atlas (TCGA) Research Network. *Nature.* 2011;474:609-15.
12. Walsh T et al. *Proc Natl Acad Sci USA.* 2010;107:12629-33.

ACKNOWLEDGMENTS

The authors would like to acknowledge all patients and their families and caregivers who are participating in the ARIEL2 study, along with the investigators. We also thank Infusion Communications for providing editorial assistance, which was funded by Clovis Oncology, Inc. (Boulder, CO).