Results from the Phase 3 Study ARIEL3: Mutations in Non-*BRCA* Homologous Recombination Repair Genes Confer Sensitivity to Maintenance Treatment with the PARP Inhibitor Rucaparib in Patients with Recurrent Platinum-Sensitive High-Grade Ovarian Carcinoma

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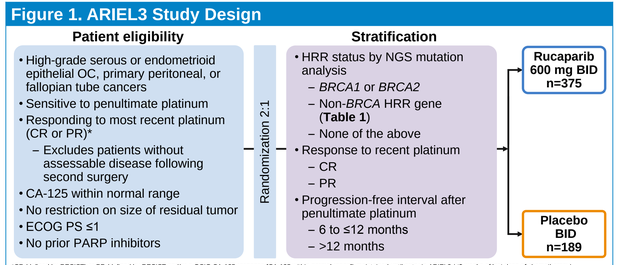
Abstract LB-A12

BACKGROUND

- High-grade ovarian carcinoma (HGOC) with a deleterious mutation in *BRCA1/2* or other core homologous recombination repair (HRR) gene is sensitive to treatment with poly(ADP-ribose) polymerase (PARP) inhibitors[1]
- Rucaparib is a PARP inhibitor that has received accelerated approval in the United States for the treatment of patients with deleterious *BRCA1/2* mutation (germline and/or somatic) associated advanced OC who have been treated with ≥2 chemotherapies[2]
- In a randomized, double-blind, placebo-controlled, phase 3 study (ARIEL3, NCT01968213, **Figure 1**), rucaparib significantly improved progression-free survival (PFS) in patients with platinum-sensitive HGOC who had achieved a response to platinum-based chemotherapy[3]
- To study whether deleterious mutations from specific HRR genes confer sensitivity to rucaparib in the maintenance setting, we performed next-generation sequencing (NGS) on carcinomas from the ARIEL3 study

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 in 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.

METHODS

- Archival OC specimens were required for the 564 patients randomized in ARIEL3 and were sequenced using Foundation Medicine's NGS assay to identify deleterious mutations in a prespecified list of HRR genes (*BRCA1/2* and 28 non-*BRCA* HRR genes, **Table 1**); germline mutations were confirmed by sequencing of blood using the Color Genomics assay
- Foundation Medicine's NGS assay also determines the percentage of tumor genome with loss of heterozygosity (genomic LOH), which is a type of genomic scar characteristic of HRR deficiency
- The primary endpoint was investigator-assessed PFS per Response Evaluation Criteria In Solid Tumors version 1.1
  - A planned, exploratory analysis of the primary endpoint was conducted for the subgroup of patients with a non-*BRCA* HRR gene mutation
  - A planned, exploratory analysis of confirmed response was conducted for the subgroup of patients with measurable disease at study entry

Table 1. Prespecified List of HRR Genes used for Stratification in ARIEL3

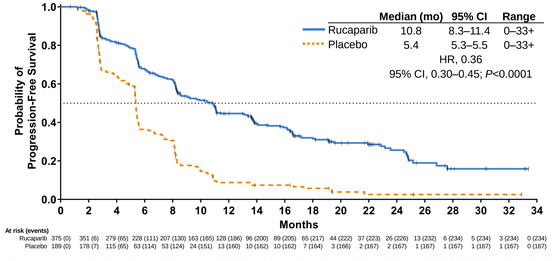
BRCA Genes	Non-*BRCA* HRR Genes						
BRCA1	*ATM*	*BLM*	*FANCA*	*FANCF*	*FANCM*	*RAD50*	*RAD51D*
BRCA2	*ATR*	*BRIP1*	*FANCC*	*FANCG*	*MRE11A*	*RAD51*	*RAD52*
	ATRX	*CHEK1*	*FANCD2*	*FANCI*	*NBN*	*RAD51B*	*RAD54L*
	BARD1	*CHEK2*	*FANCE*	*FANCL*	*PALB2*	*RAD51C*	*RPA1*

HRR, homologous recombination repair.

RESULTS

- In all randomized patients (N=564; **Figure 2**) and in the subset of patients with OC harboring a deleterious mutation in *BRCA1/2* (n=196**; Figure 3**), investigator-assessed PFS was significantly longer with rucaparib than with placebo[3]
- A deleterious mutation in a non-*BRCA* HRR gene was detected in carcinomas from 7.6% (43/564) of patients. In these patients, investigator-assessed PFS was also significantly longer with rucaparib than with placebo (**Figure 4**)
- Among the 28 patients in the rucaparib group with a non-*BRCA* HRR gene mutation, the most common gene mutations were *RAD51C* (n=6), *RAD51D* (n=4), and *RAD54L* (n=3) (**Table 2**)
  - All 10 *RAD51C/D* mutations were homozygous within the carcinoma, indicating loss of all alleles
  - Additionally, all *RAD51C/D*-mutant carcinomas exhibited high genomic LOH, which is a type of genomic scar characteristic of HRR deficiency
  - At the visit cutoff date (Apr 15, 2017), only 2 of 10 patients with a *RAD51C/D* mutation in the rucaparib group had disease progression; 7 had a PFS duration of ≥1 year (median PFS, 16.4 months; range, 5.4+ to 30.4+ months)
  - Three of the patients with a *RAD51C/D* mutation had measurable disease at baseline, and all 3 achieved a confirmed response (1 complete response and 2 partial responses)
- Among the 15 patients in the placebo group with a non-*BRCA* HRR gene mutation, the most common gene mutations were *BRIP1* (n=5) and *RAD51C* (n=2); 1 patient had a *RAD51D* mutation
  - The 3 patients with a *RAD51C/D* mutation in the placebo group had a median PFS of 5.4 months (range, 3.9–5.5 months)
- In the safety population (n=561; rucaparib n=372, placebo n=189), grade ≥3 adverse events (AEs) were reported in 209 (56.2%) patients in the rucaparib group and in 28 (14.8%) patients in the placebo group. AEs led to a dose reduction and/or treatment interruption in 70.7% of patients in the rucaparib group and 10.6% of patients in the placebo group and to treatment discontinuation (excluding disease progression) in 13.4% and 1.6% of patients, respectively[3]
  - Similar safety results were observed in the subgroup of patients with a carcinoma harboring a mutation in a non-*BRCA* HRR gene

Figure 2. Investigator-Assessed PFS in All Randomized Patients



Visit cutoff date: Apr 15, 2017. CI, confidence interval; HR, hazard ratio; PFS, progression-free survival. Reprinted from *The Lancet*, 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 [Epub ahead of print]. Copyright 2017, with permission from Elsevier.

Figure 3. Investigator-Assessed PFS in Patients with Carcinomas Harboring a Mutation in *BRCA1/2*

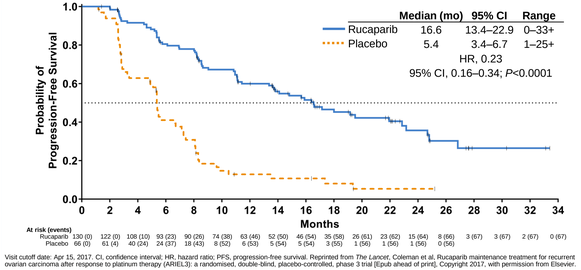


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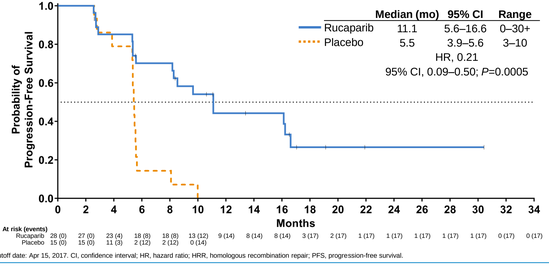
Figure 4. Investigator-Assessed PFS in Patients with Carcinomas Harboring a Mutation in a Non-*BRCA* HRR Gene



Visit cutoff date: Apr 15, 2017. CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; PFS, progression-free survival.

Table 2. Rucaparib-Treated Patients with Carcinomas Harboring a Mutation in a Non-*BRCA* HRR Gene

Patient no.	HRR gene	Mutation protein effect	Germline/ somatic status	Mutation zygosity in tumor[a]	Genomic LOH status	PFS, mo
1	*ATM*	D479fs*7	Germline	Heterozygous	LOH low	5.6
2	*ATM*	E347*	NE	Indeterminate	Indeterminate	0.0+
3	*ATR*	A1266fs*8	NA	Heterozygous	LOH low	2.7
4	*ATR*	splice site 1170+1G>T	NA	Indeterminate	LOH low	11.1+
5	*BARD1*	Q564*	Germline	Homozygous	LOH high	9.7
6	*CHEK2*	splice site 684-1G>A	Somatic	Homozygous	LOH high	8.5
7	*CHEK2*	Homozygous deletion	Somatic	Homozygous	LOH high	8.2
8	*FANCD2*	W1450*	NA	Heterozygous	LOH low	2.6
9	*FANCD2*	splice site 1413+1G>T	NA	Indeterminate	LOH low	5.4
10	*FANCI*	I425fs*2	NA	Indeterminate	LOH low	10.6+
11	*FANCL*	T367fs*12+	NA	Indeterminate	LOH high	8.3
12	*FANCL*	T367fs*12+	NA	Indeterminate	LOH high	11.1
13	*FANCM*	L691fs*5	NA	Indeterminate	LOH low	2.9
14	*RAD50*	S181fs*1	NA	Heterozygous	LOH low	16.6
15	*RAD50*	Q833fs*11	NA	Indeterminate	Indeterminate	5.3
16	*RAD51C*	splice site 706-2A>G	NE	Homozygous	LOH high	17.1+
17	*RAD51C*	R193*	Germline	Homozygous	LOH high	19.1+
18	*RAD51C*	E218fs*33	NE	Homozygous	LOH high	16.2
19	*RAD51C*	splice site 572-1G>A	Somatic	Homozygous	LOH high	13.4+
20	*RAD51C*	splice site 706-2A>G	Germline	Homozygous	LOH high	30.4+
21	*RAD51C*	Y75fs*1	Germline	Homozygous	LOH high	8.4+
22	*RAD51D*	R74*	Somatic	Homozygous	LOH high	16.5+
23	*RAD51D*	R120*	Germline	Homozygous	LOH high	21.9+
24	*RAD51D*	T97fs*118	Somatic	Homozygous	LOH high	5.6+
25	*RAD51D*	Q56fs*7	Germline	Homozygous	LOH high	5.4
26	*RAD54L*	H676fs*19	NA	Heterozygous	LOH high	2.7
27	*RAD54L*	E601*	NA	Heterozygous	LOH high	16.1
28	*RAD54L*	C457fs*2	NA	Indeterminate	Indeterminate	11.1

[a]Based on Foundation Medicine sequencing results, in which a tumor is classified as homozygous if all copies in the tumor carry the mutant allele and heterozygous if both the wild-type and mutant allele are present. +, PFS data censored; HRR, homologous recombination repair; LOH, loss of heterozygosity; NA, not available due to gene not included in Color Genomics assay; NE, not evaluable due to lack of blood sample; PFS, progression-free survival.

CONCLUSIONS

- In ARIEL3, rucaparib maintenance treatment significantly improved PFS in patients with platinum-sensitive OC who had achieved a response to platinum-based chemotherapy
- The subset of patients with carcinomas harboring a deleterious mutation in a non-*BRCA* HRR gene also had significantly longer PFS with rucaparib than with placebo
- In particular, *RAD51C/D*-mutant carcinomas were inactivated at all alleles, exhibited high genomic LOH, and were associated with rucaparib sensitivity, confirming the findings from the ARIEL2 study (NCT01891344)[1,4]

REFERENCES

1. Swisher et al. *Lancet Oncol.* 2017;18:75-87.
2. Oza et al. *Gynecol Oncol.* 2017 [Epub ahead of print].
3. Coleman et al. *Lancet.* 2017 [Epub ahead of print].
4. Kondrashova et al. *Cancer Discov.* 2017;7:984-98.

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