Title: Patient-Reported Outcomes of Maintenance Rucaparib in Patients With Recurrent Ovarian Carcinoma in ARIEL3, a Phase III, Randomized, Placebo-Controlled Trial

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Running Head: NFOSI-18 Outcomes of Rucaparib

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Abstract (264/275 words)

Purpose: To compare NFOSI-18 Disease Related Symptoms – Physical (DRS-P), Total score, and side effect bother between maintenance rucaparib (600 mg twice daily) vs. placebo in the phase III ARIEL3 trial.

Methods: ARIEL3 (NCT01968213) included patients with ovarian carcinoma who responded to second-line or later platinum-based chemotherapy. The NFOSI-18 DRS-P and Total scales were secondary endpoints. The NFOSI-18 contains a side effect impact item (GP5): "I am bothered by side effects of treatment." We compared treatment arms on change from baseline of DRS-P and Total scores using mixed models with repeated measures (MRMM). Time to first and confirmed deterioration of NFOSI-18 DRS-P and Total scales were analyzed using Cox regression. We also calculated the proportion of patients reporting moderate to high side effect bother on GP5.

Results: In the intention-to-treat (ITT) cohort, mean change from baseline favored the placebo. Compared to placebo, rucaparib was associated with higher risk of deterioration [e.g., 4-point deteriorator definition hazard ratio (HR): 1.85; 95% CI: 1.46, 2.36; median time to first deterioration on DRS-P: 1.9 vs. 7.0 months]. Confirmed deterioration results resembled those for first deterioration. Proportions of patients reporting moderate/high side effect bother on GP5 fluctuated around 20% across treatment cycles. Results in BRCA mutant and homologous recombination deficient cohorts were generally similar to those from the ITT cohort.

Conclusion: This placebo-controlled study in the maintenance therapy setting provides a unique view of the impact of PARP inhibition on the patient-reported outcomes that are commonly used in ovarian cancer clinical trials. Information regarding the adverse side effect impact of PARP inhibitors should be weighed against their clinical benefit.

Introduction

In 2020, over 300,000 new cases of primary ovarian, fallopian tube, and primary peritoneal cancers were recorded globally and over 200,000 died of the disease.[1] Though many patients respond to first line treatment, which often includes surgery and platinum-based chemotherapy, relapses are common.[2] Poly (ADP-ribose) polymerase (PARP) enzyme inhibitors represent an important second-line, maintenance therapy among patients who respond to platinum. Recent trials of PARP inhibitors have demonstrated their efficacy in ovarian cancer, extending PFS for patients in comparison to placebo.[3] Based on this evidence, several PARP inhibitors were approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in ovarian cancer as a maintenance therapy for patients with platinum-sensitive relapsed disease, including rucaparib, which is approved for second-line maintenance. Based on the progression-free survival (PFS) results from the ATHENA-MONO trial,[4] a supplemental New Drug Application has been submitted for rucaparib as first-line maintenance in newly-diagnosed, advanced ovarian cancer, regardless of biomarker status.

In the ARIEL3 trial (NCT01968213), rucaparib demonstrated 11.2 months PFS benefit (at the median) in the BRCA mutant cohort, 8.2 months in the homologous recombination deficiency (HRD) cohort, and 5.4 months in the overall intention to treat (ITT) cohort.[5] Rucaparib's quality-adjusted PFS benefit and quality-adjusted time without symptoms or toxicity (TWiST) estimates were also superior to placebo in ARIEL3 (e.g., quality-adjusted PFS difference between rucaparib and placebo for BRCA mutant patients was 9.4 months vs. non-quality adjusted PFS of 11.2 months).[6] The analysis of the National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy Ovarian Cancer Symptom Index - 18 Item Version (NFOSI-18), used for a secondary endpoint in ARIEL3, has not yet been presented and

can add useful additional insight on the patient experience with rucaparib. Though initial analyses were conducted for time to deterioration on the NFOSI-18's Disease-Related Symptoms – Physical (DRS-P) scale, these were not carried out on all study cohorts due to the pre-specified hierarchical analysis plan, nor were they carried out for the NFOSI-18 Total score, which includes additional aspects of health-related quality of life (HRQoL). Finally, the NFOSI-18 includes the FACT GP5 item ("I am bothered by side effects of treatment"), creating an opportunity to capture a more direct patient report of tolerability of rucaparib. The GP5 item has recently been identified as among the most promising approaches for patient-reported tolerability assessment in cancer trials.[7] The objectives of this study were to conduct a post-hoc comparison of the following between patients randomized to receive rucaparib and placebo in ARIEL3: 1) change in the NFOSI-18 DRS-P and Total scores; 2) time to first and confirmed deterioration on NFOSI-18 DRS-P and Total scales; 3) responses to the GP5 item.

Methods

Participants and Data

The ARIEL3 trial (NCT01968213) is a randomized, double-blind, placebo-controlled, phase 3 trial designed to assess the efficacy and safety of rucaparib in comparison to placebo after response to second-line or later platinum based chemotherapy in patients with high-grade, platinum-sensitive ovarian carcinoma.[5] Details of the trial design and analytical plan have been previously reported.[5,8] Briefly, patients were randomized 2:1 to receive rucaparib at 600 mg twice daily or placebo. Patients were eligible if they: 1) were aged $\geq$18 years; 2) had platinum-sensitive, high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube carcinoma; 3) had received at least two previous platinum-based chemotherapy regimens (later amended to require that most recent platinum-based regimen was to be administered as a

chemotherapy doublet for at least 4 cycles); 4) achieved complete or partial response to last platinum-based therapy; 5) had an ECOG performance status rating of 0 or 1; and 6) had adequate organ function. Individuals were excluded if they had symptomatic or untreated central nervous system metastases, received anticancer therapy 14 days or fewer before starting the study, or received previous treatment with a PARP inhibitor. As this was a maintenance trial, the duration of follow-up varied by patient. Patient reported outcome measures, including the NFOSI-18, were assessed at multiple time points, including a pre-randomization time point (1 to 28 days before randomization), day 1 of treatment cycles 1 through to end of treatment (EOT; maximum cycle is 39), at the time of treatment discontinuation, and 28 days post- treatment discontinuation.

NFOSI-18

The NFOSI-18 is an ovarian cancer-specific symptom index comprised of 18 items that can be summed into a Total score ranging from 0-72 [9,10] In addition, a 9-item subscale assesses physical symptoms, the NFOSI-18 Disease-Related Symptoms – Physical (DRS-P; score range 0-36). Scores are created using a prorated sum wherein scores are calculated for patients with at least 50% of completed items on the DRS-P. Higher scores indicate better HRQoL or lower symptom burden. An item in the NFOSI-18 [“I am bothered by side effects of treatment” (GP5)] was used to capture patient-reported impact of side effects. This item has demonstrated association with adverse event severity and duration, and it has predicted early treatment discontinuation.[11,12]

Patient Characteristics

Demographic and clinical characteristics of the patients included age, ECOG Performance Status Rating (PSR), number of prior therapies, and tumor response to last platinum therapy, categorized by Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST) criteria, and serologic response per Gynecologic Cancer InterGroup (GCIG) cancer antigen 125 (GCIG CA-125) criteria.

Statistical Analyses

As with the primary efficacy analyses of ARIEL3,[5] analyses were conducted on 3 study cohorts, including: 1) a *BRCA* mutant subset; 2) an HRD carcinoma (BRCA mutation plus BRCA wild type/high loss of heterozygosity [LOH]) subset; and 3) the ITT cohort, which included all randomized patients. Baseline was defined as either randomization date or, where no NFOSI assessment was made at randomization, cycle 1, day 1. Per trial protocol, cycle 1, day 1 NFOSI-18 scores were obtained prior to dosing and other study procedures. Missing baseline scores were imputed with any available score prior to cycle 2, day 1. All analyses were conducted separately for these cohorts. We summarized key patient demographic and clinical characteristics using means and standard deviations for continuous variables and frequencies and proportions for categorical variables.

We used mixed-model repeated measures (MMRM) analysis to compare change from baseline in NFOSI-18 DRS-P and Total scores. Each MMRM model included the change from baseline on each NFOSI score as the dependent variable and the following fixed effects as independent variables: study arm (rucaparib vs. placebo), timepoint (cycle), the baseline NFOSI score, the interaction between study arm and timepoint, and the interaction between the baseline NFOSI score and timepoint. A random intercept was included, as well as the timepoint as a repeated factor. An autoregressive covariance matrix was used. Least squares means for change

from baseline to each post-baseline timepoint with at least 10 patients with NFOSI data in each study arm were calculated. The MMRM models assumed missing data were missing at random. We compared trends of patients reporting high side effect bother between the treatment arms across all cycles. To do so, we calculated the proportion of patients reporting moderate/high side effect bother ("Very much," "Quite a bit," or "Somewhat") at each cycle stratified by study arm. This dichotomy of the GP5 item has been used in previous research.[11] We visualized these results using bar charts.

We conducted time to first deterioration and time to confirmed deterioration analyses. Time to first deterioration was defined as the time from baseline to the date of a reduction in the NFOSI-18 score equal to or exceeding individual-patient level change thresholds calculated using the reliable change index (RCI) and likely change (index). Details of this method are given in the Supplemental Materials. For the DRS-P, the RCI generated a deteriorator definition of 7 points and the LCI generated a deteriorator definition of 3 points. In addition, we included a deteriorator definition of 4 points for the DRS-P since it was pre-specified in the trial protocol. For the Total, the RCI generated a deteriorator definition of 10 points and the LCI generated a deteriorator definition of 4 points. In addition, we included a deteriorator definition of 8 points for the Total since it was pre-specified in the trial protocol. Confirmed deterioration was defined as a second deterioration event following first deterioration in the next consecutive assessment timepoint, or a first deterioration followed by dropout. Patients without baseline or post-baseline NFOSI scores were censored at baseline. Progression and death were not counted as deterioration. Log-rank tests were used to test whether the survival curves were significantly different between arms. Next, we derived hazard ratios for differences in time to deterioration of each deteriorator definition specified above between arms using simple Cox regression models.

Results

In the ITT cohort of ARIEL3, 564 patients were randomized to treatment: 375 to rucaparib and 189 to placebo. The maximum number of cycles at which NFOSI-18 was completed was 39. Demographic and clinical characteristics of the NFOSI sample are given in Table 1. At baseline, the mean NFOSI-18 DRS-P and Total scores were similar across study arms and reflected moderate symptom burden and HRQoL impairment. (Table 1)

Table 1. Baseline Patient and Disease Characteristics among Intention to Treat Population

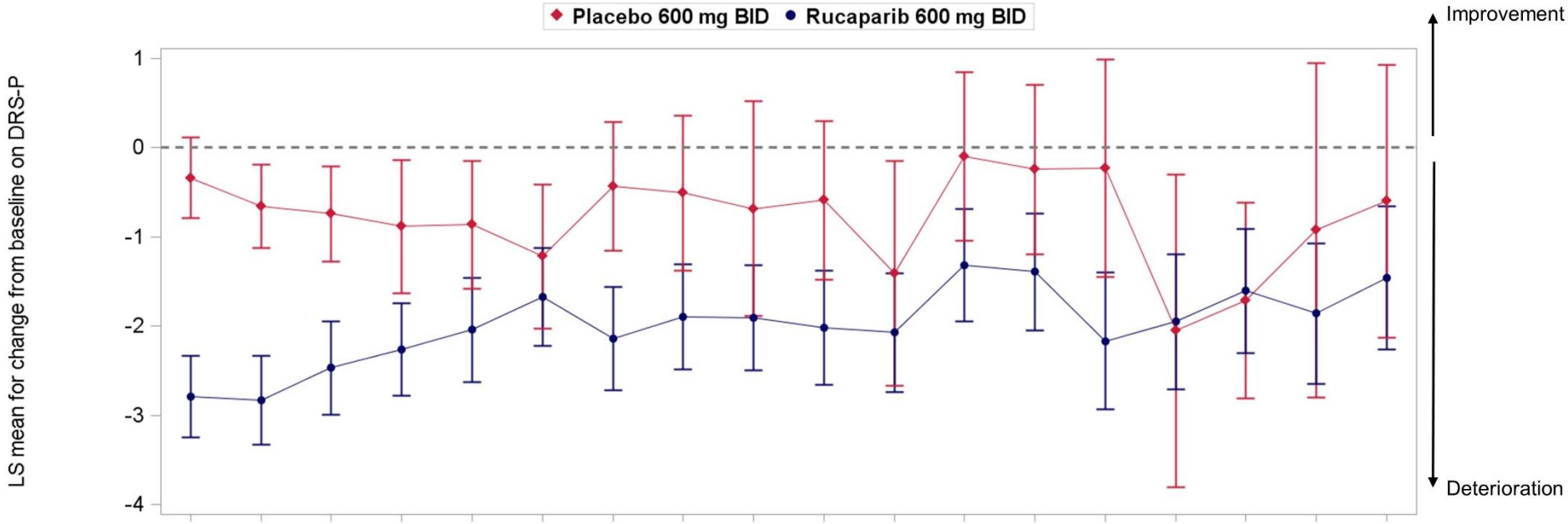
Characteristic	Rucaparib (N=375)	Placebo (N=189)
Age (years), median (IQR)	61 (53-67)	62 (53-68)
ECOG Performance Stats, n (%)		
0	280 (75%)	136 (72%)
1	95 (25%)	53 (28%)
Diagnosis, n (%)		
Epithelial ovarian cancer	312 (83%)	159 (84%)
Fallopian tube cancer	32 (9%)	10 (5%)
Primary Peritoneal Cancer	31 (8%)	19 (10%)
Other	0 (0%)	1 (<1%)
Study Cohort		
BRCA Mutant	130 (35%)	66 (35%)
HRD	245 (65%)	123 (65%)
Number of Prior Therapies, n (%)		
2	229 (61%)	122 (65%)
≥3	146 (39%)	67 (35%)
Response to Last Platinum, n (%)		
Complete response per RECIST	126 (34%)	64 (34%)
Partial response per RECIST/ Serologic Response per Gynecologic Cancer InterGroup Cancer Antigen 125	249 (66%)	125 (66%)
Platinum-Free Months, n (%)		
6-12 Months	151 (40%)	76 (41%)
>12 Months	224 (60%)	113 (60%)
NFOSI-18 DRS-P score (mean, SD)	29.3 (4.4)	29.2 (4.7)
NFOSI-18 Total score (mean, SD)	58.4 (8.1)	57.9 (8.2)

NFOSI-18 data were available for at least 10 patients in each arm up to cycle 19. In the ITT cohort, least squares mean change from baseline favored the placebo for most cycles from 2 to 19 on both the DRS-P and Total scales. For both scales, change from baseline was typically

approximately 1 point in either direction for placebo patients, but was higher magnitude and negative for rucaparib, indicating deterioration. Statistically significant differences between arms were observed at several cycles. There was a consistent trend of significant differences between arms in cycles 1-6 and intermittently afterward. [Figures 1 (DRS-P) and 2 (Total)] Similar results were observed in the BRCA mutant and HRD cohorts (Figures S1-S4).

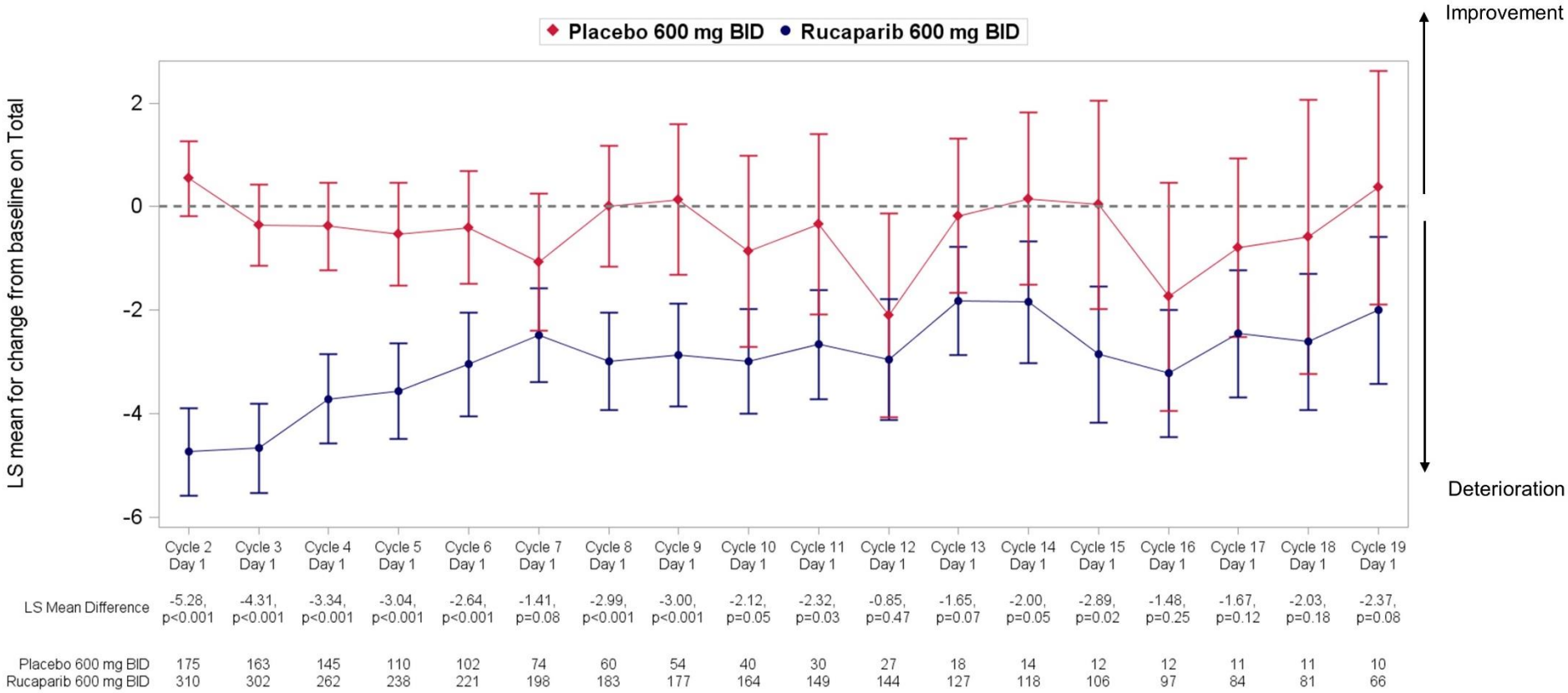
Kaplan Meier curves for time to first deterioration stratified by treatment arm in the ITT cohort are presented in Figures 3 (4-point deterioration on DRS-P), S5-S6 (7 and 3 points on DRS-P, respectively), 4 (8-point deterioration on Total), and S7-S8 (10 and 4 points on Total, respectively). Overall, for each DRS-P deteriorator definition in the ITT cohort, patients receiving rucaparib had a higher risk of deterioration than those receiving the placebo. Time to first deterioration analyses among the BRCA mutant and HRD cohorts are shown in Tables S9-S20. Results of these analyses largely resembled those from the ITT cohort with a few notable exceptions. For the 4- and 3-point deteriorator definitions on the DRS-P, study arms did not differ for the BRCA mutant cohort. In addition, for the 4-point deteriorator definition on the NFOSI-18 Total, study arms did not differ for the BRCA mutant cohort. Results of time to confirmed deterioration analyses followed a similar pattern, though median times to confirmed deteriorator tended to be longer for both arms (where estimable), and differences between treatment arms were smaller than those observed for time to first deterioration, with a few exceptions (Figures S21-S38). For the 7-point confirmed deterioration definition on the DRS-P, there were no differences between arms in any cohort. On the other hand, in the BRCA mutant cohort, the difference between arms for the 3-point confirmed deterioration definition was significant.

Figure 1. Mixed Model Repeated Measures Analysis of Change from Baseline in NFOSI-18 DRS-P Score



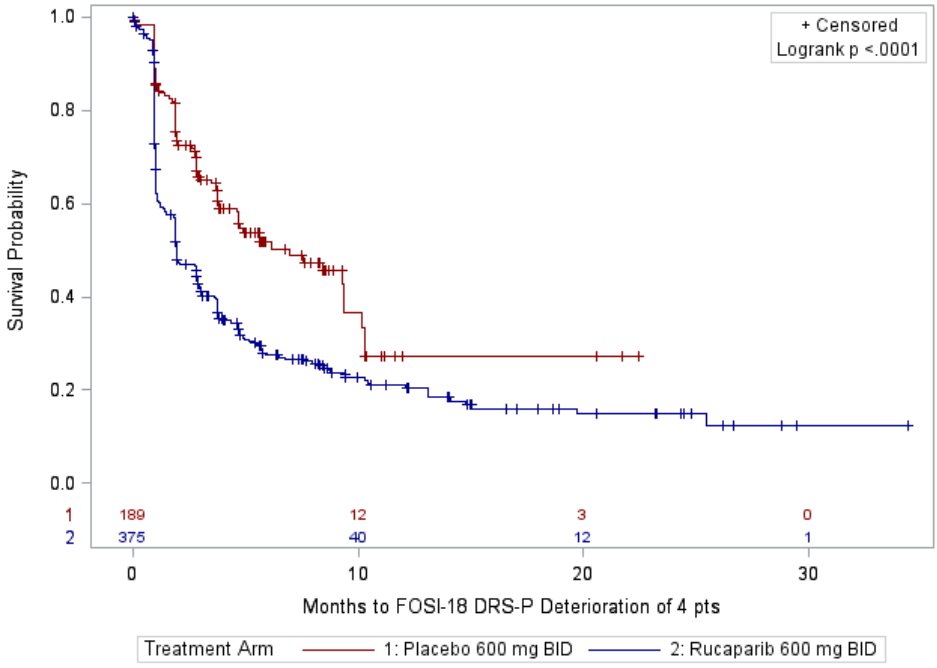
	Cycle 2 Day 1	Cycle 3 Day 1	Cycle 4 Day 1	Cycle 5 Day 1	Cycle 6 Day 1	Cycle 7 Day 1	Cycle 8 Day 1	Cycle 9 Day 1	Cycle 10 Day 1	Cycle 11 Day 1	Cycle 12 Day 1	Cycle 13 Day 1	Cycle 14 Day 1	Cycle 15 Day 1	Cycle 16 Day 1	Cycle 17 Day 1	Cycle 18 Day 1	Cycle 19 Day 1
LS Mean Difference	-2.45, p<0.001	-2.18, p<0.001	-1.73, p<0.001	-1.38, p=0.003	-1.18, p=0.01	-0.46, p=0.36	-1.71, p<0.001	-1.39, p=0.01	-1.22, p=0.07	-1.43, p=0.01	-0.66, p=0.36	-1.22, p=0.04	-1.15, p=0.05	-1.94, p=0.009	0.10, p=0.92	0.11, p=0.87	-0.93, p=0.37	-0.86, p=0.33
Placebo 600 mg BID	175	163	145	110	102	74	60	54	40	30	27	18	14	12	12	11	11	10
Rucaparib 600 mg BID	310	302	262	238	221	198	183	177	164	149	144	127	118	106	97	84	81	66

Figure 2. Mixed Model Repeated Measures Analysis of Change from Baseline in NFOSI-18 Total Score in the Intention to Treat Cohort



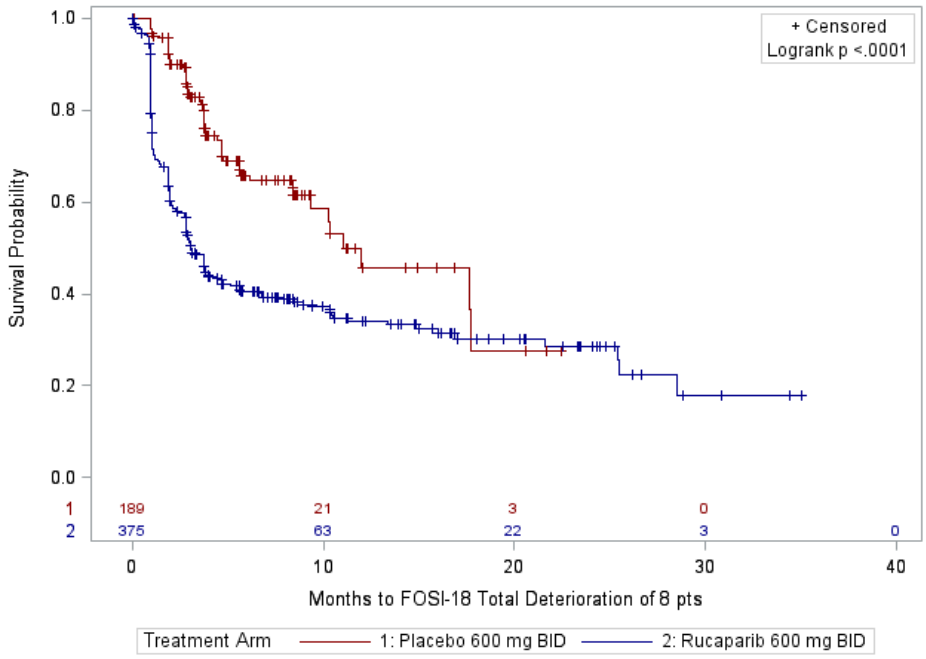
	Cycle 2 Day 1	Cycle 3 Day 1	Cycle 4 Day 1	Cycle 5 Day 1	Cycle 6 Day 1	Cycle 7 Day 1	Cycle 8 Day 1	Cycle 9 Day 1	Cycle 10 Day 1	Cycle 11 Day 1	Cycle 12 Day 1	Cycle 13 Day 1	Cycle 14 Day 1	Cycle 15 Day 1	Cycle 16 Day 1	Cycle 17 Day 1	Cycle 18 Day 1	Cycle 19 Day 1
LS Mean Difference	-5.28, p<0.001	-4.31, p<0.001	-3.34, p<0.001	-3.04, p<0.001	-2.64, p<0.001	-1.41, p=0.08	-2.99, p<0.001	-3.00, p<0.001	-2.12, p=0.05	-2.32, p=0.03	-0.85, p=0.47	-1.65, p=0.07	-2.00, p=0.05	-2.89, p=0.02	-1.48, p=0.25	-1.67, p=0.12	-2.03, p=0.18	-2.37, p=0.08
Placebo 600 mg BID	175	163	145	110	102	74	60	54	40	30	27	18	14	12	12	11	11	10
Rucaparib 600 mg BID	310	302	262	238	221	198	183	177	164	149	144	127	118	106	97	84	81	66

Figure 3. Kaplan Meier Curves for Time to First Deterioration of 4 points on NFOSI-18 DRS-P Stratified by Treatment Arm in the Intention to Treat Cohort



Hazard ratio: 1.85 (95% confidence interval: 1.46, 2.36). Median time to first deterioration: rucaparib = 1.9 months (95% CI: 1.9, 2.8); placebo = 7.0 months (95% CI: 4.7, 9.4).

Figure 4. Kaplan Meier Curves for Time to First Deterioration of 8 points on NFOSI-18 Total Stratified by Treatment Arm in the Intention to Treat Cohort

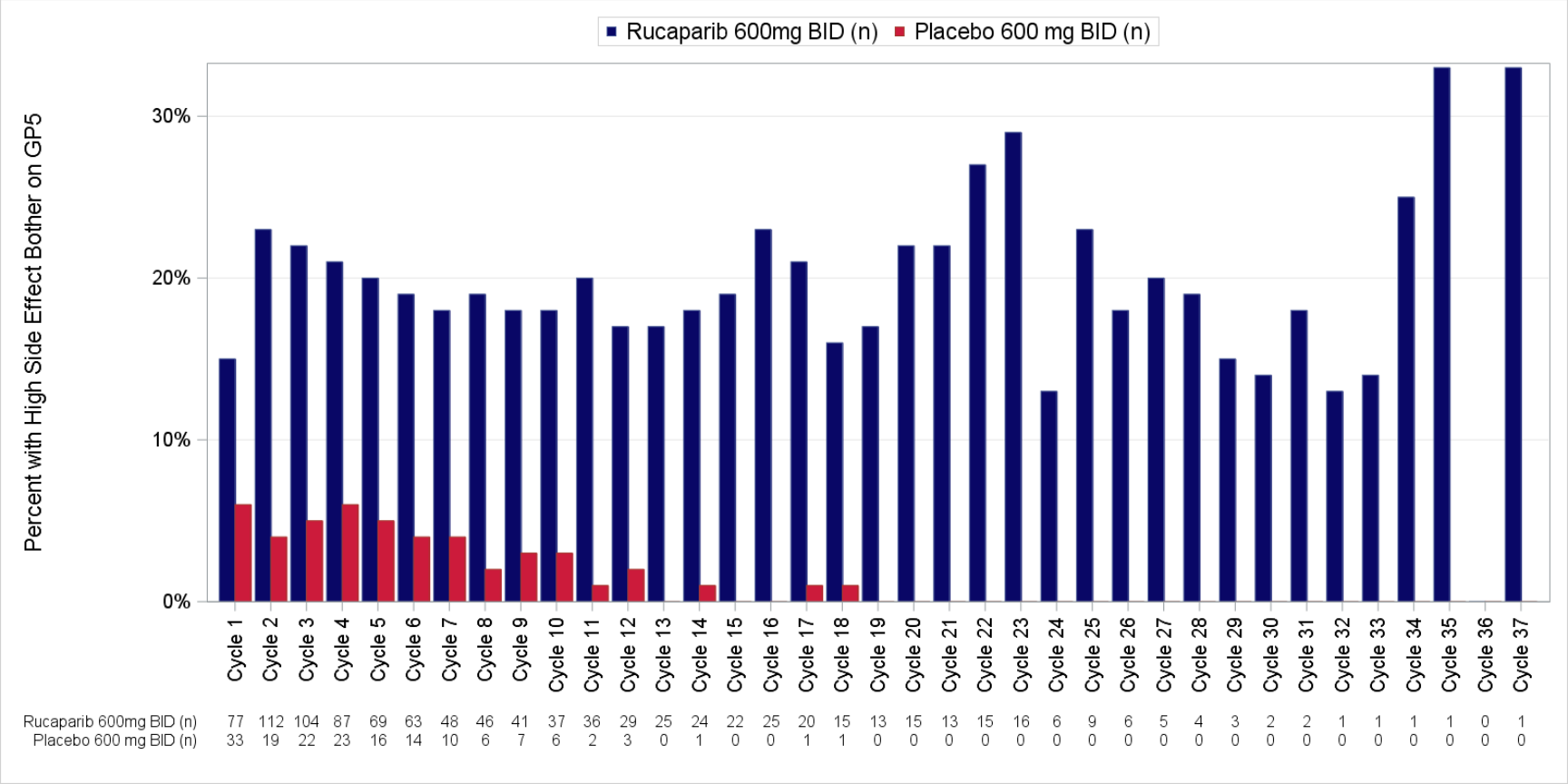


Hazard ratio: 2.31 (95% confidence interval: 1.73, 3.09). Median time to first deterioration: rucaparib = 3.1 months (95% CI: 2.8, 3.8); placebo = 11.0 months (95% CI: 9.4, 17.7).

Side Effect Bother

Figure 5 shows the proportions of patients reporting moderate/high side effect bother on GP5 at each cycle by study arm. Relatively low proportions of patients reported clinically-significant bother in either arm. As expected, the proportions were very low in the placebo arm. In the rucaparib arm, the proportion of patients reporting moderate/high side effect bother between cycles 2 and 21 was approximately 20% (+/- 1-3%). This proportion increased to 27 and 29% in cycles 22 and 23, respectively, and declined thereafter. Notably, 15% and 6% of patients in the rucaparib and placebo arms, respectively, reported moderate/high side effect bother at cycle 1. Similar results were observed in the BRCA mutant cohort (Figure S39) and HRD cohort (Figure S40).

Figure 5. Percentages of Patients Reporting High Side Effect Bother on GP5 Item Stratified by Treatment Arm in Intention to Treat Cohort



High side effect bother was defined as a response of “Very much,” “Quite a bit,” or “Somewhat” to the GP5 item (“I am bothered by side effects of treatment”).

Discussion

PARP inhibitors, including rucaparib, have demonstrated significant clinical benefit in comparison to placebos in the setting of maintenance therapy for ovarian cancer, offering for the first time an effective treatment option for this clinical population. Yet, the known treatment benefits of PARP inhibitors must be evaluated alongside their side effects, which affect patients' HRQoL and have implications for treatment decisions. Using data from the ARIEL3 trial, we found that patients' experience on rucaparib as measured by the NFOSI DRS-P and Total scores, were routinely worse in comparison to placebo. In addition, higher proportions of rucaparib patients reported high/moderate side effect bother on FACT item GP5. These results highlight the importance of the patient experience with treatment and provide a unique opportunity to understand the impact of PARP inhibition using patient-reported outcome measures that are commonly used in ovarian cancer clinical trials. It is critical to highlight the large PFS benefit associated with rucaparib when interpreting the NFOSI-18 results. Though, like many active treatments in oncology, rucaparib was associated with an HRQoL deficit due to side effects, the PFS benefit will likely drive decisions to adopt PARP inhibitor therapy. Nonetheless, information regarding the side effect impact of PARP inhibitors may be useful to clinicians and their patients who are embarking on treatment.

Two previous studies have examined HRQoL in ARIEL3 using quality-adjusted PFS and Q-TWiST approachs.[6,13] While helpful for quantifying trade-offs between PFS and HRQoL, both of

these approaches summarize the patient's experience in terms of HRQoL at a very high level and employ only the EQ-5D-3L. The current study expands on these previous investigations with the NFOSI-18, which contains a rich set of questions on ovarian cancer specific symptoms and functional concerns. In addition, previous analyses have yielded mixed results around the impact of other PARP inhibitors on HRQoL. For example, in the SOLO2 trial, mean changes on FACT – Ovarian Trial Outcome Index over the first 12 months of the study were similar (difference = 0.03, p=0.98).[14] Similarly, in the ENGOT-OV16/NOVA trial, changes in score of the 8 item version of the FOSI (FOSI-8) from baseline to cycles 2-14 were very similar between patients randomized to receive niraparib and placebo (all differences < 2 points and 95% confidence intervals included 0).[15] Critically, the FOSI-8 does not include questions on a few symptomatic side effects that are captured in the NFOSI-18 and that are very relevant to experience with rucaparib, including constipation, sleep disturbance, and skin problems. Moreover, the NFOSI-18 includes the GP5 item, which captures overall side effect bother. For this reason, the NFOSI-18 is better positioned to capture the side effect experience of PARP inhibitors. In addition, both the SOLO2 and ENGOT-OV16/NOVA analyses included patients who remained in the trial after multiple cycles and, therefore, were more likely to have stable or improved FOSI scores relative to those who discontinued study treatment. In our analysis, we addressed this potential bias with time to deterioration analyses. Additional analyses of ENGOT-OV16/NOVA and SOLO2 trials

to include time to deterioration analyses would help make comparisons of PARP inhibitors in ovarian cancer more easily comparable.[16]

We point out that interpretation of the TTD analyses comparing the rucaparib and placebo arms must take into consideration that after a very short period of follow-up, typically far shorter than the median TTD regardless of deteriorator threshold, the number of patients at risk tends to be small and reflects only those patients whose disease has not progressed despite not being on treatment. This likely contributes to the precision of effects for the between arm TTD comparisons. Further, we note that, in many cases, the median TTD for patients on placebo was somewhat close to the median PFS in the ITT population for this arm (5.4 months), giving rise to the plausible hypothesis that deterioration among these patients reflects symptoms of disease. This hypothesis could be tested in future studies.

Our analyses further articulated the impact of treatment intolerance by examining patient-reported side effect bother on the GP5 item ("I am bothered by side effects of treatment"). Recent interest in patient-centeredness has led to the addition of patient report to standard, clinician-reported adverse events in cancer trials.[17,18] The GP5 item is among the leading options for capturing overall side effect impact.[11,12,19-21] In the current study, GP5 responses indicated a consistent pattern of high side effect bother among a small but appreciable proportion of patients assigned to receive rucaparib throughout the trial, showing that more patients on rucaparib

experienced bothersome side effects than would be indicated only by the standard common terminology criteria for adverse events (CTCAE). Toxicities associated with rucaparib in ovarian cancer are known, and the need to manage these toxicities has been emphasized in previous research,[22] with multiple promising approaches described.[23] The results of our GP5 analyses reinforce the need for close monitoring of AEs among patients on rucaparib and indicate potential benefit of toxicity management. Doing so may help more patients benefit from the PFS offered by rucaparib and reduce the number of patients discontinuing treatment completely due to toxicity, which has exceeded 15% across trials.[8]

This study has important limitations to consider when interpreting our results. As a secondary, post-hoc analysis, the study design did not account for the statistical power needed to detect effects. In addition, since our statistical tests were exploratory, we did not adjust for multiple comparisons. Next, it is possible that dose modifications made in response to toxicity are associated with HRQoL, but this analysis is beyond the scope of the current study and will be investigated in future analyses. Finally, since the ARIEL3 trial compared maintenance rucaparib to a placebo, results PROs asking about treatment toxicities are somewhat more difficult to interpret than comparison to an active control. Despite these limitations, we consider our results to be robust.

In conclusion, in a post-hoc analysis of the NFOSI-18 DRS-P and Total scales in the ARIEL3 trial, we found that patients randomized to receive rucaparib had decreased HRQoL in comparison to the placebo. These differences were observed for the ITT cohort, as well as the BRCA mutant and HRD cohorts. It is important to consider these results along with the impressive PFS benefit observed for rucaparib in the same trial, as well as the poor prognosis associated with ovarian cancer. Though rucaparib is still an excellent treatment choice for many patients, having information available about potential impacts on quality of life is critical to enhance patient-centered care.

Author Contributions

- John Devin Peipert: Conceptualization, formal analysis, roles/writing - original draft, project administration, writing - review & editing
- Sandra Goble: Data curation, methodology, project administration, writing - review & editing
- Jeff Isaacson: Investigation, methodology, writing - review & editing
- Xiaodan Tang: Formal analysis, writing - review & editing
- Katrine Wallace: Writing - review & editing
- Robert L. Coleman: Investigation, methodology, writing - review & editing
- Jonathan A. Ledermann: Investigation, methodology, writing - review & editing
- David Cella: Funding acquisition, conceptualization, investigation, methodology, roles/writing - original draft, supervision

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