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Expert Opinion

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PRIMA: captivated by the wizard of OS?

Frederik Marmé

Department of Obstetrics and Gynecology, University Hospital Mannheim and Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

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Correspondence to
Frederik Marmé
Department of Obstetrics and Gynecology, University Hospital Mannheim and Medical Faculty Mannheim, Heidelberg University, Theodor-Kutzer-Ufer 1-3, Mannheim 68167, Germany.
Email: Frederik.Marme@umm.de

ORCID iDs
Frederik Marmé
https://orcid.org/0000-0002-6591-3367

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Poly(ADP-ribose) polymerase (PARP) inhibitors have transformed the first-line treatment landscape for advanced high-grade tubo-ovarian cancer. Endorsed by international guidelines, they are now the standard maintenance therapy for patients with *BRCA1/2* mutations or homologous recombination (HR) deficient tumors, either alone or in combination with bevacizumab. In addition, for patients with HR-proficient tumors, they offer an alternative to bevacizumab. PARP inhibitors have also driven the adoption of biomarker testing (*BRCA1/2* and homologous recombination deficiency [HRD]) as a prerequisite to guide first-line systemic therapy decisions [1].

Strong evidence from pivotal phase 3 trials—SOLO-1, PAOLA-1, PRIMA, and ATHENA Mono—has led to the approval of olaparib, niraparib, and rucaparib as monotherapy for first-line maintenance and olaparib also in combination with bevacizumab [2-9].

These studies consistently demonstrate a substantial and persistent progression-free survival (PFS) benefit, ranging from 19% to 29% at 5 years for HR-deficient tumors (18% at 4 years in ATHENA), with hazard ratios between 0.33 in SOLO1 (*BRCA* mutated [*BRCA*mut] tumors only) and 0.51. The Kaplan-Meier curves run flat at this point and indicate a sustained benefit, showing no signs of converging, underscoring the enduring advantage of PARP inhibitors for these patients.

However, the benefit is less sustained in the HRD-negative population, and this discussion centers on data for the HRD-positive patients.

As data matures, attention shifts to overall survival (OS) outcomes. Whilst mature OS data from ATHENA Mono and PRIME is still awaited, PRIMA, the latest study to release final OS data, failed to demonstrate any OS benefit from niraparib in the overall as well as the HR-deficient subpopulation (hazard ratio=1.01; 95% confidence interval [CI]=0.84–1.23; p=0.88 and hazard ratio=0.95; 95% CI=0.70–1.29, respectively) [10]. These findings have sparked debate in the gynecologic oncology community, contrasting with more favorable outcomes reported in SOLO-1 and PAOLA-1 [3,6] and potential explanations are being sought.

SOLO-1, in a prespecified interim analysis at 7 years of median follow-up and a data maturity of 38.1%, has demonstrated a 21.5% difference in OS, a key secondary endpoint, at 7 years in exclusively *BRCA* mutant tumors (hazard ratio=0.55; 95% CI=0.40–0.76; p=0.0004 [not

significant]). The final analysis is pending, and patient selection excluded those with BRCA wildtype tumors [3].

In PAOLA-1 OS was a key secondary endpoint too and as for the primary endpoint, OS was formally assessed in the intention-to-treat (ITT) population, with additional subgroup analysis by BRCA- and HRD-status.

After a median follow-up duration of 61.7 months and a data maturity of 55% the addition of olaparib to bevacizumab did not significantly improve OS (hazard ratio=0.92; 95% CI=0.79–1.12; p=0.41) in the ITT population at the final analysis. Within the HRD-positive subgroup there was a meaningful trend for an improved OS in favor of olaparib with a difference in 5-year OS rates of 17.1% (hazard ratio=0.62; 95% CI=0.45–0.85), however, the analyses by biomarker subgroup are exploratory and no formal statistical testing was performed (**Table 1**) [6].

All of these trials used OS as a secondary endpoint, and none provide unequivocal statistical proof of improved OS with first-line PARP inhibitor maintenance in advanced tubo-ovarian cancer.

While acknowledging the significant limitations of cross-trial comparisons and the lack of statistical evidence for OS benefits across the trials, it is difficult to disregard the clinically meaningful numerical differences in OS rates observed in SOLO-1 and PAOLA-1, particularly within biologically relevant subgroups, which were not evident in PRIMA. Therefore, exploring potential explanations for the presumed discrepancies in OS among these 3 trials is worthwhile.

One possible explanation for PRIMA's failure to show an OS benefit could be statistical chance. The trial was designed with 80% power to detect an OS benefit with a hazard ratio of ≤0.75, indicating a 20% possibility that the reported results are false negatives. While this hypothesis cannot be definitively proven or disproven without replicating the trial, such a replication is unlikely [8].

Another possibility is that Niraparib might be less effective than Olaparib. However, given that the primary endpoint of PFS shows similar outcomes across the studies, this explanation seems less plausible. All trials indicate a significant and sustained PFS benefit at 5 years, observed long after the cessation of maintenance therapy, with Kaplan-Meier curves demonstrating no signs of convergence (**Table 2**) [4,6,10,11].

Table 1. Reported OS data in SOLO1, PAOLA-1 and PRIMA

Trials	Biomarker subgroup	Difference in OS rate	OS hazard ratio (95% confidence interval)	p-value	Comment
SOLO1	*BRCA*mut	@ 5 years: 9.7%	0.55 (0.04–0.76)	0.0004 (NS)	Secondary endpoint
		@ 7 years: 21.5%			Preplanned interim analysis did not reach statistical significance
PAOLA-1	ITT	@ 5 years: 5.8%	0.92 (0.76–1.12)	0.41	Secondary endpoint
	*BRCA*mut	@ 5 years: 19.4%	0.60 (0.39–0.93)	-	Exploratory subgroup analysis
	HR deficient	@ 5 years: 17.2%	0.63 (0.45–0.85)	-	Exploratory subgroup analysis
	HR proficient	@ 5 years: −6.6%	1.19 (0.88–1.63)	-	Exploratory subgroup analysis
PRIMA	ITT	@ 5 years: −2%	1.01 (0.84–1.23)	0.88	Secondary endpoint
	*BRCA*mut	@ 5 years: 0%	0.94 (0.63–1.41)	-	Exploratory subgroup analysis
	HR deficient	@ 5 years: −1%	0.95 (0.70–1.29)	-	In a hierarchical testing strategy formal analysis of the HRD+ subgroup would only have been performed if OS in ITT was significant
	HR proficient	@ 5 years: 2%	0.93 (0.69–1.26)	-	Exploratory subgroup analysis

*BRCA*mut, *BRCA* mutation; HR, homologous recombination; HRD, homologous recombination deficiency; ITT, intention-to-treat; OS, overall survival; NS, not significant.

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Table 2. PFS results for SOLO1, PAOLA-1 and PRIMA by BRCA and HRD status

Study	Biomarker subgroup	Difference in 5-yr PFS rate	Hazard ratio (95% confidence interval)
SOLO1 [4]	BRCA	29%	0.33 (0.25–0.43)
	HRD	-	-
PAOLA-1 [6,11]	BRCA	25%	0.46 (0.32–0.64)
	HRD	27%	0.41 (0.32–0.54)
PRIMA [10]	BRCA	23%	0.43 (0.31–0.59)
	HRD	19%	0.51 (0.40–0.66)

HRD, homologous recombination deficiency; PFS, progression-free survival.

Still, why does a nearly 20% difference in the 5-year PFS rate observed in PRIMA, which seems to persist beyond this period, not translate into an OS benefit in a disease known for its high recurrence rates and regarded widely incurable in case of recurrence? While OS is an endpoint in clinical trials that is easy and objective to measure, it has the drawback of being significantly influenced by subsequent therapies. This is particularly relevant in the context of PRIMA and other first-line PARP inhibitor trials, as the use of PARP inhibitors in later treatment lines had become available during the conduct of the trials and could affect the OS outcomes.

In PRIMA, it was notably observed that 37.8% of patients in the placebo group overall and 48.8% and 57.7% of patients with HRD-positive and *BRCA*-mutant tumors, respectively, received a PARP inhibitor in subsequent treatment lines. Furthermore, the majority of these patients received their PARP inhibitor in the immediate subsequent line, with 46.5% of *BRCA*-mutant patients and 37.3% of HRD-positive patients doing so.

Given that niraparib in platinum-sensitive recurrent high-grade ovarian cancer demonstrated a persistent PFS benefit of 28% over placebo in HRD-positive/BRCA wildtype patients [12], similar to findings with other PARP inhibitors [13-15], the effectiveness of subsequent PARP inhibitor use in PRIMA may have significantly influenced the OS results.

Exploratory analyses of the HRD-positive population in the PRIMA study, using different models to account for subsequent PARP inhibitor use, indicated lower hazard ratios for OS, however all of the 95% CI for these hazard ratios widely cross 1 and results should be interpreted with caution due to the limitations of post-progression data collection and the complexities involved in model fitting and covariate selection.

However, the use of post-study PARP inhibitors in subsequent treatment lines does not adequately explain the apparent differences observed among the 3 trials. The subsequent use of PARP inhibitors was quite similar in SOLO-1 and PAOLA-1. In SOLO-1 (*BRCA*mut only), 44.3% of patients in the control arm received a PARP inhibitor as post-study therapy, with 24.4% receiving it in the immediate subsequent line [3]. Similar patterns were observed in PAOLA-1, where 55% of *BRCA*-mutant patients and 51% of HRD-positive patients in the placebo arm utilized PARP inhibitors in subsequent lines (**Table 3**) [6].

An alternative explanation for the paradox of a persistent 20% PFS difference that does not translate into an OS benefit is that the experimental treatment may negatively impact the efficacy of subsequent treatment lines for patients who progress. This hypothesis is supported by evidence from SOLO-2 and PAOLA-1, which reported that progression during PARP inhibitor maintenance is associated with a significantly reduced effectiveness of subsequent therapies [16,17].

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Table 3. Subsequent PARPi therapy in patients from the placebo arms in SOLO1, PAOLA-1 and PRIMA by BRCA and HRD status and according to treatment line where reported

Study	Biomarker subgroup	Subsequent PARPi use overall	Subsequent PARPi 2nd line
SOLO1	*BRCA*mut	44.3%	24.4%
	HRD+	-	-
PAOLA-1	*BRCA*mut	55.0%	NR
	HRD+	50.8%	NR
PRIMA	*BRCA*mut	57.7%	46.5%
	HRD+	48.8%	37.3%

*BRCA*mut, *BRCA* mutation; HRD+, homologous recombination deficiency-positive; NR, not reported; PARPi, poly(ADP-ribose) polymerase inhibitor.

Treatment durations varied across the trials. In SOLO-1 and PAOLA-1, treatment was limited to 24 months, except for patients with radiographic evidence of disease who continued to benefit. In contrast, the PRIMA trial allowed treatment for 36 months or until progression if patients were deemed to benefit. Consequently, only 25% of patients in SOLO-1 and approximately 35% in PAOLA-1 experienced progression while still on PARP inhibitor maintenance, compared to vast majority in PRIMA. This discrepancy may have adversely affected the post-progression survival of patients in the experimental arm of PRIMA. This observation serves as a warning against extending the duration of first-line PARP inhibitor maintenance therapy beyond 2 years for olaparib and 3 years for niraparib.

In addition to treatment duration, another significant difference between PRIMA and SOLO-1/PAOLA-1 lies in patient selection. In PRIMA, patients were chosen through a unique approach that emphasized selecting those at very high risk of recurrence, including individuals with International Federation of Gynecology and Obstetrics (FIGO) stage IV disease, FIGO stage III patients with gross residual disease after primary debulking, and those who received neoadjuvant chemotherapy when primary debulking surgery was not feasible. Simultaneously, the trial focused on selecting patients who demonstrated the best possible responses to platinum-based therapy, still the best clinical surrogate for PARP inhibitor benefit, requiring at least a partial or complete responses with no measurable lesions larger than 2 cm, a greater than 90% reduction in CA-125 levels, and the ability to objectively assess their response (such as residual disease or neoadjuvant chemotherapy).

This resulted in a study population with a higher proportion of patients having stage IV disease (35.1%), receiving neoadjuvant chemotherapy (66.7%), and exhibiting postoperative visible residual disease (47.5%). In contrast, most stage III patients in SOLO-1 underwent upfront debulking surgery and had no visible residual disease (44% in SOLO-1 compared to 0.4% in PRIMA).

Consequently, in PRIMA, patients in the experimental arm who progressed while on niraparib experienced diminished efficacy with second-line therapy. In contrast, patients in the control arm are likely to have retained some of the exceptional sensitivity to platinum-based therapy and thus PARP inhibitors in the second line. This may have allowed them to partially compensate for their shorter first-line PFS. This contrasts with SOLO-1 and PAOLA-1, where patients were not selected based on these specific criteria, and the treatment durations were shorter.

In conclusion, all these potential explanations remain speculative, and it is impossible to determine which factors, or combinations of factors, may account for the apparent differences in the reported OS data. It is crucial to note that OS was a secondary outcome

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in all these trials, and we are still awaiting the final OS analysis for SOLO-1. The reported OS benefit in the HRD-positive population of PAOLA-1 arises from an exploratory subgroup analysis of a secondary endpoint, which lacks formal statistical testing.

While we await OS data from the PRIME and ATHENA Mono trials, as well as the final OS results from SOLO-1, the recently presented OS data for PRIMA should not prompt any changes in clinical practice. It is essential to emphasize that PARP inhibitors continue to be the standard of care for first-line maintenance therapy in advanced high-grade, HR-deficient tubo-ovarian cancer.

As we consider which PARP inhibitor to use—whether olaparib, olaparib plus bevacizumab, niraparib, or rucaparib—the decision will be individualized. This choice will depend on factors such as each drug's specific approvals, individual contraindications (e.g., related to bevacizumab), safety profiles, potential drug interactions, and which of the trials provided the most compelling data fitting an individual patient.

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