Final Overall Survival Results of PRIMA: The Niraparib Conundrum

Akhil Santhosh[1]

[1] Department of Medical Oncology, All India Institute of Medical Sciences, New Delhi, India

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Address for correspondence Akhil Santhosh, MD, DM, BRA, IRCH, Department of Medical Oncology, All India Institute of Medical Sciences, New Delhi 110029, India (e-mail: santhoshakhilps@gmail.com).

The initial progression-free survival (PFS) results of PRIMA were published before, with niraparib substantially prolonging PFS in patients with newly diagnosed advanced ovarian cancer regardless of homologous recombination deficiency (HRD) status.[1] The final overall survival (OS) results were published in the September 2024 edition of *Annals of Oncology* showing no difference in OS between niraparib and placebo.[2] The entire oncology fraternity was inquisitive as to what went wrong with some even questioning the inferiority of niraparib compared with other poly ADP-ribose polymerase (PARP) inhibitors. Nevertheless, given the similarity in PFS across PRIMA, SOLO-1, and PAOLA-1, this seems unlikely. The majority of enrollment in PRIMA and PAOLA-1 was done from Europe and North America with minimal representation of Asians; hence, the difference in ethnicity cannot be accounted for the difference in outcomes. Additionally, there is no significant difference between olaparib, rucaparib, and niraparib in terms of PARP-trapping efficacy in preclinical models.

Regarding disease burden, both the SOLO-1 and PAOLA-1 trials[3] with olaparib and olaparib/bevacizumab, respectively, in an upfront maintenance setting had relatively lower disease burden patients compared with PRIMA, which consisted of higher-risk patients (66.7% patients required neoadjuvant chemotherapy). PRIMA excluded stage III patients who underwent R0 resection in contrast to SOLO-1, which included only *BRCA* mutated disease (favorable subset). The percentage of patients with residual disease postsurgery or no surgery was higher in the niraparib study.[1] Also, the results from all the prespecified subgroups should be interpreted with caution given the small sample size (especially the HRD neg/*BRCA* wild-type subset). PRIMA was not powered to detect an OS benefit in these subgroups. Therefore, the future does not look promising for niraparib, which is a 3-year therapy, in comparison to olaparib (2 years) as maintenance.

Niraparib is also poorly tolerated compared to olaparib with treatment interruptions, dose reductions, and discontinuations occurring in 80.8, 71.7, and16.3%, respectively, for niraparib compared with 52, 28, and 12% patients, respectively, with olaparib in SOLO-1.[4] This issue has been abrogated to an extent with the PRIME trial showing that patients taking an individualized starting dose (patients with $\leq$ 77 kg, platelet count $<$ 150,000 receiving 200 mg once daily [OD], with the remaining receiving 300 mg OD) had better tolerance with an acceptable safety profile.[5] This dosing pattern was followed only for 35% of patients in PRIMA. Access to olaparib in middle- and lower middle-income countries has improved over the past few years with introduction of various patient assistance programs. Clinicians worldwide are more comfortable and adept in prescribing and managing toxicities with olaparib compared to the other drugs in the same category. Unfortunately, the U.S. Food and Drug Administration approval is no longer valid for second-line indications of niraparib in non-BRCA mutated disease.[6] Hence, it is nonfeasible to consider this drug for the contemporary management of advanced ovarian cancer. Results of trials in progress like NIRVANA-1[7] and AGO-OVAR 28[8] for evaluating maintenance therapy with niraparib and bevacizumab combined seem to be favorable and would throw some light on how to better use niraparib in the future.

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Conflict of Interest
None declared.

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