



Efficacy and safety updates of poly ADP-ribose polymerase (PARP) inhibitor maintenance in ovarian cancer from ASCO 2020

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Received 11 June 2020

Accepted 15 June 2020

Published Online First

9 July 2020



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To cite: Madariaga A, Bonilla L, McMullen M, et al. *Int J Gynecol Cancer* 2020;**30**:1256–1257.

Poly ADP-ribose polymerase (PARP) inhibitors have transformed the treatment landscape of high-grade ovarian cancer.¹ The presence of homologous recombination deficiencies and particularly alterations in the *BRCA* genes are well described biomarkers of response.² Until the American Society of Clinical Oncology (ASCO) 2020 meeting, maintenance PARP inhibitors in ovarian cancer had demonstrated an improvement in progression-free survival and surrogate endpoints, such as time to subsequent therapy and time to second objective disease progression, with no significant differences in the primary quality of life measures.¹

The gold standard endpoints in phase III clinical trials are overall survival, quality of survival, or both.³ In fact, as clinicians, our goal is that patients live longer and better. The updated analysis of the SOLO2 (NCT01874353) study, assessing maintenance olaparib post-response to platinum-based chemotherapy in women with *BRCA1/2* mutated high-grade serous or endometrioid ovarian cancer, demonstrated unprecedented improvement of overall survival.⁴ Median overall survival increased by nearly 13 months in the olaparib arm compared with placebo in the overall population (olaparib 52 months versus placebo 39 months; HR 0.74 (95% CI 0.54 to 1), $p=0.053$), and by 15 months in the pre-specified germline *BRCA1/2* mutant population as per Myriad test (olaparib 52 months versus placebo 37 months; HR 0.7 (95% CI 0.52 to 0.97), $p=0.03$).⁴ Treatment efficacy and safety did not significantly differ between patients ≥ 65 years old compared with younger patients.⁵

Treatment-related adverse events leading to discontinuation were 17% in the olaparib arm versus 3% in placebo in SOLO2, which reinforces the need for appropriate management of treatment-related toxicity.⁴ The common treatment-related adverse events were as expected;^{1,4} however, at long-term follow-up, 8% (16/195) of patients receiving olaparib and 4% (4/95) receiving placebo developed a myelodysplastic syndrome or acute myeloid leukemia.⁴ This poses an urgent need to better understand the

impact of other potential risk factors of myelodysplastic syndromes or acute myeloid leukemia, such as germline alterations, impact of chemotherapy, and length of exposure to PARP inhibitors. In SOLO2, 38% of patients in the placebo arm and 10% in the olaparib arm received subsequent PARP inhibitors, and whether this affects the risk of development of hematologic malignancies has yet to be reported. A meta-analysis presented at the annual meeting assessed the risk of myelodysplastic syndromes on patients with solid tumors treated with PARP inhibitors.⁶ The study included 14 trials of PARP inhibitors alone or in combination with chemotherapy or bevacizumab, and 5,646 individuals, demonstrating a 3-year cumulative incidence of myelodysplastic syndromes of 2% for PARP inhibitors versus 1.1% for the control arm. Treatment with PARP inhibitors was associated with a risk ratio of 1.60 (95% CI 0.89 to 2.87) of developing myelodysplastic syndromes compared with control.⁶ Overall, the results reinforce the need for careful monitoring. We suggest clinicians should consider maintaining monthly follow-ups that include complete blood count as surveillance on patients receiving long-term PARP inhibitor treatment.

Interestingly, exceptional responders for over 5 years were seen in 22% of women receiving olaparib versus 9% receiving placebo in SOLO2.⁴ A deeper understanding of the characteristics of long-term responders is warranted, including the impact of the type of *BRCA* mutation, other genetic or immune factors, and the evolution of resistance after PARP inhibitor exposure.⁷ Additionally, the role of individual patient factors such as lifestyle, diet, and co-medications should be explored prospectively.⁸

Now that PARP inhibitors are being incorporated as front-line maintenance, the role of 'PARP after PARP' maintenance remains an unanswered question. Several studies are assessing second maintenance treatment with PARP inhibitor monotherapy or combinations. In this setting, learning from the mechanisms of resistance to PARP inhibitors may also help tailor subsequent therapies and their sequence.

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Contributors All authors contributed to writing and reviewing the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests AMO is on the steering committee of GSK, AZ, and Clovis (uncompensated), and is PI on clinical trials for AZ, GSK, and Clovis. SL declares honoraria from Roche, AZ, GSK, and Merck, and is Co-Inv and PI on a number of different clinical trials.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

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