correspondence

SOLO 3 Trial: How Do the Results Fit in With Current Evidence?

TO THE EDITOR:

On the basis of international guidelines and consensus, platinum-sensitive relapsed ovarian cancer (PSROC) is treated with a regimen containing a platinum doublet such as carboplatin-paclitaxel, carboplatin-pegylated doxorubicin, or carboplatin-gemcitabine, with or without concomitant and maintenance bevacizumab or nbsp;maintenance with poly (ADP-ribose) polymerase inhibitors (PARPi's) after response to platinum.[1,2] In a recent article in *Journal of Clinical Oncology*, Penson et al[3] reported the results of the SOLO3 (ClinicalTrials.gov identifier: NCT02282020) trial, a randomized phase III study that compared olaparib with non-platinum chemotherapy (pegylated liposomal doxorubicin, paclitaxel, gemcitabine, or topotecan) in patients with PSROC and a germline *BRCA1/2* mutation. The primary end point was objective response rate (ORR) assessed by blinded independent central review (BICR), and the secondary end point was progression-free survival (PFS). ORR and BICR-assessed PFS were significantly higher with olaparib than with chemotherapy (72.2% *v* 51.4% and 13.4 *v* 9.2 months, respectively). Adverse events (AEs) were consistent with those in the established safety profiles of olaparib.

The results of SOLO3 raised important questions that needed to be answered by the scientific community: Are we ready to change to chemotherapy-free regimens in PSROC? What should be the best treatment sequence for PSROC? Should PARPi's be followed by chemotherapy or the reverse? Can we prevent chemotherapy AEs without compromising overall survival (OS) using non-chemotherapy regimens?

At first glance, cross-trial comparisons showed that olaparib as therapy in SOLO3 demonstrated higher ORR (72% *v* 50%) and PFS (13.4 *v* 8 to 9 months) compared with historical studies of platinum doublets and also showed similar outcomes for platinum doublets with bevacizumab.[4,5] These data are supported by other PARPi's (ie, rucaparib).[6] However, we should keep in mind that in the SOLO3 trial, patients were select by histology and *BRCA* mutation, whereas the other trials included all comers. *BRCA*-mutated patients also have higher response rates to platinum, doxorubicin, and trabectedin. We are facing PARPi's in different scenarios without head-to-head comparisons, so treatment sequence is an important issue. In the SOLO2/ENGOT-Ov21 trial (exclusively for *BRCA* mutation carriers; ClinicalTrials.gov identifier: NCT01874353), patients needed to achieve partial or complete response to platinum re-treatment before they could be randomly re-assigned and receive olaparib as maintenance therapy.[7] Data regarding subsequent therapy in the SOLO3 trial demonstrate that 52% of patients in the experimental arm received some form of chemotherapy, including 36% who received platinum therapy. Although OS was a secondary end point in SOLO3 (and in SOLO2), it will be interesting to compare these data with data from the experimental arm of SOLO2 to evaluate treatment sequencing. A concern related to PARPi treatment is possible impairment of the activity of subsequent retreatment with platinum. So far, data from the SOLO2 study and other phase III studies with PARP in PSROC have shown significant gains in PFS-2 (time for the first and the second subsequent treatment), suggesting that the subsequent treatment is not affected by the use of PARP.[8,9] Another important issue is that, as we are transferring PARPi's from treating recurrence to first-line therapy, we still need to understand how effective PARPi's are after a previous treatment with a PARPi, for example, in progression scenarios during or shortly after PARPi treatment (PARP resistant/refractory disease) or after a long time outside PARP treatment (PARP-sensitive disease). *BRCA* mutation carriers have a better prognosis and are sometimes long-term survivors. AEs such as paresthesia and allergic reactions that result from treatment with platinum doublets can prevent patients from continuing chemotherapy. From this viewpoint, chemotherapy-free regimens seem to be of great value for preventing AEs and also for providing time to recover from previous AEs. In patients without a *BRCA* mutation, the combination of PARP and antiangiogenics has shown impressive results in phase II studies.[10,11] These clinical issues can be addressed only by using randomized controlled trials such as the ongoing NRG Oncology study (ClinicalTrials.gov identifier: NCT02446600) that is evaluating olaparib versus olaparib-cediranib versus standard platinum-based chemotherapy in PSROC.

BRCA carriers derive the most benefit from PARPi's, which highlights the importance of following society guidelines to test every patient who has epithelial ovarian cancer. How can we introduce the results of the SOLO3 trial in our treatment algorithm? Although platinum re-challenge is still the standard of care for PSROC when platinum is not an option because of toxicity from previous chemotherapy or patient preference, the SOLO3 trial has provided important evidence for using olaparib in *BRCA* carriers.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.20.00576.

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DOI: https://doi.org/10.1200/JCO.20.00576; Published at ascopubs.org/journal/jco on June 12, 2020.

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No other potential conflicts of interest were reported.