The PARP inhibitor/Immunotherapy Paradox in Advanced Ovarian Cancer: Positive Endpoints, Perplexing Interpretations

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Unlocking the immune system with antibodies targeting PD-1/L1 and CTLA-4 has opened broad new therapeutic areas in oncology, including the treatment of gynaecological cancers involving the endometrium and cervix[1]. Not unreasonably, researchers hoped that the benefits of immune checkpoint inhibitors would extend to ovarian cancer, a heterogenous group of tumours in which previous studies showed that the presence of infiltrating cytotoxic immune cells in the tumour microenvironment indicated immune recognition and as such, were associated with better outcomes.[2, 3]

Phase I and phase II trials in ovarian cancer soon began with different immune checkpoint inhibitors, both as single agents and in various combinations with chemotherapy, anti-angiogenesis inhibitors, and Poly-(ADP) Ribose Polymerase (PARP) inhibitors[4-6]. Early results from the single-agent trials in patients with recurrent disease demonstrated limited objective responses, despite some patients experiencing prolonged response durations. Nevertheless, industry-sponsored phase III studies soon followed combining immune checkpoint inhibitors with chemotherapy in recurrent and primary disease settings - the results were disappointing[7-9].

During the recruitment of these randomised trials, it became clear that maintenance therapy with PARP inhibitors was having a major impact on improving progression-free survival, particularly in patients with a *BRCA1/2* mutation (*BRCA1/2^{mut})*, but also in those with *BRCA1/2*-wild-type, HRD-test positive tumours[10-13]. The question immediately arose whether immune checkpoint inhibitors could add to the benefits being realised with PARP inhibitors, or more correctly, whether PARP inhibitors might enhance the rather unimpressive results with checkpoint inhibitors alone through several hypothesised mechanisms[14].

In 2018, before formal presentation of the positive results of front-line maintenance therapy with PARP inhibitors, five industry-led trials were initiated. One was abandoned early (NCT03642132) but four completed accrual, amassing 4,675 patients with ovarian cancer (Table). The results of two of these studies are reported in this edition of Annals of Oncology[15, 16]. Although all trials contained a PARP inhibitor (olaparib, niraparib or rucaparib), the designs were different, challenging interpretation and comparability.

For example, two of the trials (DUO-O[16]; KEYLYNK[17]) excluded patients with *BRCA1/2*-mutated tumours, in others, bevacizumab use varied (either mandated [DUO-O] or investigator-chosen [KEYLYNK, FIRST[15]]), and investigational arms included PARP inhibitors with immune checkpoint inhibitors (pembrolizumab), but lacked a PARP inhibitor-only arm in two trials (DUO-O; KEYLYNK)[16, 17]. Experimental regimens varied from concurrent with chemotherapy versus primary post-chemotherapy maintenance (ATHENA-combo)[18] or a combination of both (FIRST, KEYLYNK). The duration of PARP inhibitor therapy was also inconsistent, being up to 2 years in ATHENA-COMBO, DUO-O, and KEYLYNK, but up to 3 years in FIRST.

Further, statistical designs were predicated on different biomarkers - not all of which have been independently validated as predictive; different patient populations were enrolled, including those with very different baseline prognostic characterisitcs, and patients with tumours represented by different genomic signatures were analyzed as nested population cohorts. Nevertheless, with the exception of the ATHENA-combo trial, where the addition of nivolumab to rucaparib as maintenance following the completion of chemotherapy may have been “detrimental”, the other three trials reported a "positive" outcome.

How then should these results be interpreted? The most appropriate and statistically valid interpretation is to follow the primary hypothesis testing procedures. In each trial, eligibility and exclusion criteria defined a population to be evaluated and were sampled to achieve appropriate power to address each hypothesis. Unfortunately, the designs of these trials make it very difficult to know how to apply the data at the patient level. For instance, in DUO-O[16], the experimental arm investigated whether olaparib, added to durvalumab significantly increased PFS compared to an “active” control arm with bevacizumab (modelled after GOG-0218)[19]. The primary outcome results of DUO-O report an improvement in PFS with experimental arm of chemotherapy, bevacizumab and durvalumab induction followed by the triplet of bevacizumab, durvalumab and olaparib maintenance in the non-tBRCA^{mut} HRD-test positive group compared to the chemotherapy and bevacizumab control arm (HR 0.49; 95% confidence interval[CI]

0.34-0.69; P<0.0001). The median PFS was 37.3 versus 23.0 months. However, without an olaparib-only arm in DUO-O, it is not possible to separate the benefit of olaparib from that of combination olaparib/durvalumab, and the lack of improvement with durvalumab alone compared to control [interim analytical endpoint], made the relative benefits of the two modifying drugs unclear. Similarly, in KEYLYNK, the experimental arm with pembrolizumab and olaparib was superior to the control arm (which included bevacizumab maintenance in 45%), but the lack of any benefit of pembrolizumab alone in the PD-L1+ subgroup, and absence of an olaparib monotherapy arm makes interpretation of any added value of pembrolizumab difficult [17]. In FIRST[15], the primary analysis examined the interaction of dostarlimab with niraparib versus niraparib. As with KEYLYNK, the induction treatment (concomitant chemotherapy) included two types of controls – one with bevacizumab and one without, and the experimental arms were similarly doubled up because of this option. FIRST, like the others, demonstrated gains in PFS (in FIRST, there was a 1.4 month increase in the median PFS with the combination [HR: 0.85, 95% CI; 0.73–0.99; P = 0.0351]. Whether this significant difference is clinically meaningful is debatable. OS has reached just 57% maturity but appears at equipoise. In addition, there does not appear to be a subpopulation among those receiving dostarlimab, either by stratified or non-stratified variables, or physician choice, such as bevacizumab, who might have a more prolonged benefit[15] . Although the trial explored the addition of dostarlimab to niraparib maintenance therapy, given as a standard of care, the hypothesis was really testing whether a PARPi in the intention-to-treat population could augment the activity of dostarlimab that, like other immune checkpoint inhibitors, had thus far little evidence of benefit in primary ovarian cancer treatment. None of the exploratory subgroups, such as PD-L1 status or HRR deficiency (whether due to a BRCA mutation or other causes) suggested greater activity with combination therapy.

Finally, trials that report positive outcomes from nested cohort analyses (biomarker positive and intent-to-treat [ITT]) are often incorrectly interpreted as applying to an “all-comer” population, abdicating formal hypothesis testing of the biomarker-negative cohort with inferential interpretation. Dichotomous patient and tumour characteristics, such as surgical timing (primary vs interval) or HRD/PD-L1 testing are patient-specific

and independent; thus, they cannot be experienced at the same time. An intent-to-treat analysis specifically blends these independent prognostic and predictive biomarkers without specifically assuring that the results apply equally – that is, to those with and without the characteristic of interest.

The FIRST and DUO-O trials bring a conclusion to the results of a series of trials combining one or more combinations of anti-VEGF, anti-PARP, and anti PD-1/PD-L1 therapy in the primary management of newly diagnosed advanced stage ovarian cancer. The trials have tried to leverage maximum impact, combining immune checkpoint inhibitors with chemotherapy, bevacizumab and PARPi, all strategies for which there are some clinical data to support this approach[20-22]. In light of the clinical ambiguity of the results, the question arises as to whether the development playbook, which frequently relies on limited phase II investigation, provides sufficient groundwork to proceed to large-scale phase III trials which have consumed a large financial resource, without a more detailed understanding of the immunological drivers (both inhibitory and stimulatory), as well as the degree of non-clonal heterogeneity that is likely to impact on the outcome of immune therapy. The overall message to be taken from these trials is that immune checkpoint inhibitors that 'unlock' the immune system are insufficiently effective in ovarian cancer on their own, and there is no convincing evidence that PARPi (and/or anti-angiogenics) improve their effectiveness.

Thus, the conclusion from the FIRST and DUO-O trials and other similar studies is that future research efforts need to be directed at improving our understanding of the immune microenvironment in individual tumours, and this requires smaller biologically focused studies to enhance or trigger the immune response. More broadly speaking, clinical trial designs need to be orchestrated to provide less ambiguity so that clinical decision-making, at the patient level, can be better informed. Patients present for care with a number of discreet clinical characteristics; better alignment of these factors to those evaluated in a clinical trial provide higher confidence that they may experience the observed outcomes. While no clinical trial can control for every patient characteristic in a randomized way, designs that limit bias that are not, or cannot, be effectively controlled with randomization need to be promoted. Ultimately more

informative modelling with better aligned patient selection will reduce the trial-and-error approach we currently rely on for best practices.

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