Editorial Commentary

Atezolizumab does not improve progression-free survival in patients with recurrent platinum-sensitive ovarian cancer

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Epithelial ovarian cancer (OC) remains the leading cause of gynecologic cancer-related death among women worldwide (1). The mainstay therapy for newly diagnosed OC patients is a combination of cytoreductive surgery and platinum-taxane based chemotherapy. Targeted therapy, including the antiangiogenic agent bevacizumab and poly-adenosine diphosphate-ribose polymerase (PARP) inhibitors, has been shown to improve progression-free survival (PFS). Nonetheless, over 80% of advanced-stage OC patients recur (2) and the use of immunotherapy has become an area of active research in OC.

In the recent study, ATALANTE/ENGOT-ov29 trial, Kurtz *et al.* report the results of a randomized phase III clinical trial that aimed to evaluate the potential benefits of incorporating the immune checkpoint inhibitor (ICI) atezolizumab for platinum-sensitive recurrent OC (3). The study sought to address whether the addition of atezolizumab to platinum-based chemotherapy and concurrent maintenance bevacizumab would improve PFS and overall survival (OS) in patients with recurrent OC. The coprimary outcomes were PFS in both the intention-to-treat (ITT) and programmed cell death ligand 1 (PD-L1)-positive populations.

The authors reported that among the 614 patients who were randomly assigned to either atezolizumab or placebo the addition of atezolizumab did not significantly improve PFS. Yet, there was a marginally significant improvement in PFS with atezolizumab compared with placebo in the ITT population [hazard ratio (HR), 0.83; 95% confidence interval (CI): 0.69 to 0.99; P=0.041; median PFS 13.5 *vs.* 11.3 months, respectively]. In comparison, in the PD-L1-positive population, that comprised 38% of the entire cohort, the addition of atezolizumab was comparable to placebo (HR, 0.86; 95% CI: 0.63 to 1.16; P=0.30; median 15.2 *vs.* 13.1 months, respectively).

Additional subgroup PFS analyses, including subgroups of patients with both PD-L1-positive and CD8-positive tumors or those with BRCA mutation failed to show significant interaction with atezolizumab treatment. There were no significant differences between the treatment arms in terms of health-related quality of life and grade ≥3 adverse events (AEs). As expected, immune-related AEs were more common with atezolizumab.

A few considerations should be mentioned when interpreting these results:

- First, only 38% of patients were PD-L1-positive compared with the 60% prevalence observed in the IMagyn050 (using the same assay) and 57%

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prevalence in the Javelin Ovarian 200 (using a different assay) (4,5). The authors suggest that this lower prevalence is a result of tumor immunogenicity in platinum-sensitive recurrent OC in contrast to untreated newly diagnosed OC patients that were recruited in the IMagyn050 trial. However, this assertion is called into question considering that the Javelin trial recruited chemo-exposed patients and PD-L1 prevalence was over 50%.

- Second, regardless of PD-L1 and CD-8 status, neither the ATALANTE/ENGOT-ov29 nor the IMagyn050 and Javelin trials demonstrated enhanced PFS justifying the addition of atezolizumab to mainstay treatment. Of importance, a potential benefit from atezolizumab was shown in the IMagyn050 trial for a subgroup of patients with PD-L1-positive high, defined as tumors with ≥5% PD-L1 immune cell expression. However, as only 11% of the population in the ATALANTE/ENGOT-ov29 exhibited PD-L1 expression ≥5% such an analysis would be underpowered for meaningful results. This observation should be considered for future research on ICI in OC.
- Lastly, over 15% of the study participants had a tumor histology other than high grade serous. The authors argue that when the trial was designed, PD-L1 status seemed the most promising marker for ICI response, which ultimately is not the case, and therefore their study population was non-homogenous. It is thus imperative not to generalize the study's conclusions to the much smaller non-HG serous subgroups.

In conclusion, the ATALANTE/ENGOT-ov29 study did not meet its primary PFS objectives, but the preliminary OS results suggest that further analysis with longer follow-up is warranted. The trial has contributed to the ongoing discussion on the role of ICI in OC treatment and the need for better patient selection criteria and biomarkers to identify those who might benefit the most from such therapies.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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