Editorial Commentary

Synergistic clinical efficacy of niraparib in combination with pembrolizumab in patients with recurrent platinum-resistant ovarian carcinoma

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Ovarian cancer is the most common cause of gynecologic cancer death in the United States with 22,530 newly diagnosed cases and 13,980 deaths annually. There has been a miniscule, approximately 2.3% decrease, each year in the death rates from ovarian cancer over the past few decades (1). Although most patients with advanced ovarian cancer respond to initial platinum-based chemotherapy, 70% will relapse and ultimately become resistant, refractory, or unable to receive platinum-based chemotherapy owing to cumulative toxic effects (2,3). This has led to a paradigm shift in the approach to the treatment of ovarian cancer with precision medicine and additional targeted therapies becoming part of the standard treatment regimen.

The incorporation of bevacizumab, an angiogenesis inhibitor, in the treatment of ovarian cancer only provides a modest benefit in progression-free survival (PFS) and it eventually becomes contraindicated in approximately one-third of patients due to the risk of vascular toxic effects and gastrointestinal tract perforation (4-6). Poly (ADP-ribose) polymerase (PARP) inhibitors represent a treatment approach initially believed to work through the concept of synthetic lethality in those tumors with underlying impaired DNA repair via homologous recombination mechanisms such as *BRCA*-mutated tumors. However, only around 20% of patients with ovarian cancer have a *BRCA* mutation and treatment for patients without this mutation remains an unmet need (7). Findings from the European Network of Gynaecological Oncological Trial Groups (ENGOT)-OV16/NOVA trial expanded the use of niraparib to *BRCA* wild-type tumors and homologous recombination deficient (HRD) negative tumors by demonstrating that niraparib treatment significantly improved PFS along a graduated continuum (8). This effect of niraparib is thought to be due to the high exposure of tumors to the drug as a result of its high bioavailability, membrane permeability, lipophilicity, and large volume of distribution (9).

Targeted anti-PD-1 drugs such as pembrolizumab are monoclonal antibodies that block the program cell death receptor 1 (PD-1) expressed on activated T cells. PD-1 is an immune checkpoint receptor, that binds to its ligands (PD-L1 and PD-L2), which are frequently expressed on neoplastic cells allowing them to evade the immune system. Targeted blockade of PD-1 by pembrolizumab promotes T cell-mediated killing (10). Recent preclinical studies demonstrate that PARP inhibitor mediated modulation of the immune response contributes to their therapeutic effects independently of the tumors inherent DNA repair deficiency. In fact, PARP inhibitors were found to promote the accumulation of cytosolic DNA fragments because of unresolved DNA lesions, which then activate the cGAS-STING pathway stimulating the production of type I interferons to induce antitumor immunity independent of

BRCA status. These effects of PARP inhibitors were also thought to enhance immune checkpoint blockade providing the mechanistic rationale for using PARP inhibitors as immunomodulatory agents that can synergistically enhance the therapeutic efficacy of immune checkpoint blockade (11).

PARP monotherapy has previously demonstrated clinical efficacy along a graduated continuum with an overall response rate (ORR) ranging from 25–30% for those with *BRCA*$^{+}$/platinum-resistant disease, 0–14% for those with *BRCA*$^{+}$/platinum refractory disease, 5% for those with *BRCA*$^{-}$/platinum-resistant disease, and 0% for those with *BRCA*$^{-}$/platinum refractory disease (12-18). Whereas, PD-L1 inhibitor monotherapy treatment has an ORR of 4–10% in platinum-resistant ovarian cancer irrespective of PD-L1 expression levels (10,19,20).

The TOPACIO/KEYNOTE-162 (niraparib in combination with pembrolizumab in patients with triple-negative breast cancer or ovarian cancer) trial evaluated the tolerability and efficacy of niraparib in combination with pembrolizumab in 62 patients with platinum-resistant ovarian carcinoma. The patient study population was diverse including those who had mostly *BRCA* wild-type tumors, had previously been treated with bevacizumab and had acquired platinum-resistant or platinum-refractory disease. Response rates and disease stability were similar across all patients regardless of *BRCA* mutation or HRD status with an ORR of 18% (90% CI, 11–29%) and disease control rate of 65% (90% CI, 54–75%). Interestingly, a subgroup analysis of tumor PD-L1 status also did not reveal any specific marker that drove clinical activity from the combination treatment regimen. Additionally, this study demonstrated that combination therapy might be of therapeutic value by providing prolonged periods of stable disease in patients. In fact, nine patients with stable disease received treatment for more than 6 months and two of those nine patients received treatment for longer than 1 year. There were no new safety signals with combination treatment compared to the safety profiles of either drug monotherapy (21).

The true synergistic efficacy and safety of novel combination therapies involving PARP inhibitors and anti-PD-1 drugs for patients with platinum-resistant ovarian cancer will be further elucidated through new clinical trials. For instance, the MOONSTONE trial is a phase 2 open-label, single-arm study that plans to evaluate the efficacy and safety of the combination of niraparib with TSR-042, a humanized monoclonal antibody targeting the PD-1 receptor, in patients with platinum-resistant ovarian cancer (22). Nonetheless, the results already presented by Konstantinopoulos *et al*. demonstrating tolerability and clinical efficacy of niraparib in combination with pembrolizumab in patients with recurrent platinum-resistant ovarian carcinoma regardless of *BRCA* mutation or HRD status are promising. However, these findings warrant further validation beyond this small cohort of patients with a larger trial as the synergistic combination of these targeted agents could present a meaningful treatment option for patients with difficult-to-treat ovarian cancer where there is certainly an unmet need in the contemporary treatment landscape.

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Footnote

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