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How to use immune checkpoint inhibitor in ovarian cancer?

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▸ See the article "Early experiences with PD-1 inhibitor treatment of platinum resistant epithelial ovarian cancer" in volume 30, e56.

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Until now, many clinical studies are being conducted and are underway, expecting that the immune checkpoint inhibitor (ICI) could reinvigorate the anti-cancer immune response and have a favorable clinical response to ovarian cancer. However, clinical responses of anti-programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) in ovarian cancer patients have been reported from minimal to moderate (objective response rate: 10%–25%) [1-5]. We read with great interest the recently published article by Normann et al. [6] "Early experiences with PD-1 inhibitor treatment of platinum resistant epithelial ovarian cancer" in the recent edition of *Journal of Gynecologic Oncology*.

Normann et al. [6] reported the toxicity and clinical efficacy of nivolumab monotherapy, a PD-1 inhibitor, on patients with platinum resistant ovarian cancer. Although they showed safety of nivolumab and 44% of disease control rate, none of the enrolled patient reached partial or complete response. These real-world data are somewhat disappointing compared to previous results from clinical trials. As is known, ICIs can not only unleash anti-tumor immunity, but also induce durable cancer regressions. Therefore, we wonder if there were any cases of durable response among 8 patients who showed stable disease. If we can discuss the results of durable response presented in "spider plot" or "waterfall plot", it could be helpful for future research.

Why doesn't anti-PD-1/PD-L1 have shown a good clinical response to ovarian cancer patients? To date, there have been several reports that the tumor-infiltrating lymphocytes (TILs) of ovarian cancer is significant prognostic factors correlated with the patient's survival [7-11]. Furthermore, TILs of ovarian cancer are functionally exhausted and highly express immune checkpoint molecules including PD-1 [12-15]. PD-1 contributes to immunosuppressive tumor microenvironment and consequently poor clinical prognosis, however, on the contrary, can be a target that can reverse tumor-mediated immunosuppression. Although it looks like ovarian cancer will respond well to ICI treatment, the real-world data showed low response.

Previously, Cristesc et al. [16] reported that "tumor mutation burden (TMB)" and a "T cell-inflamed gene expression profile" can independently predict response to PD-1 checkpoint blockade (pembrolizumab). Ovarian cancer was classified as "cold tumor" showing low TMB and low T cell-inflamed gene expression profile [16]. Furthermore, we previously reported that overall expression of PD-L1 in tumor was low and T cells were not infiltrated in most of the tumor tissue of ovarian cancer patients [17].

Thus, anti-PD-1/PD-L1 monotherapy alone does not seem to fully activate the immune response to kill tumor cells. As a result, it is important to find a promising combination of anti-PD-1 and other ICI or treatment modalities that could improve clinical response. Conventional treatment modalities, such as chemotherapy, radiation therapy or other targeted treatments could induce immunogenic cell death of cancer cells. It may eventually turn "cold tumors" into "hot tumors" by increasing antigen release or antigen presentation, inducing cytotoxicity of effector immune subsets, and removing immunosuppression. NRG-GY003 (NCT02498600) already reported that a combination of nivolumab and ipilimumab leads to better response rates in patients with persistent or recurrent ovarian cancer than nivolumab alone. Under these circumstances, various combinational treatment strategies will be tried in the future. Recently, we are trying combination therapy consisted with chemotherapeutic agents, anti-PD-L1, and anti-CTLA-4 in ovarian cancer (NCT03699449, NCT03899610). We hope that an optimal ICI combinational treatment strategy will be established in the near future.

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