Highlights in Gynecological Cancer from ESMO 2021

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Immune checkpoint inhibition in mismatch repair-proficient patients with previously treated advanced endometrial cancer

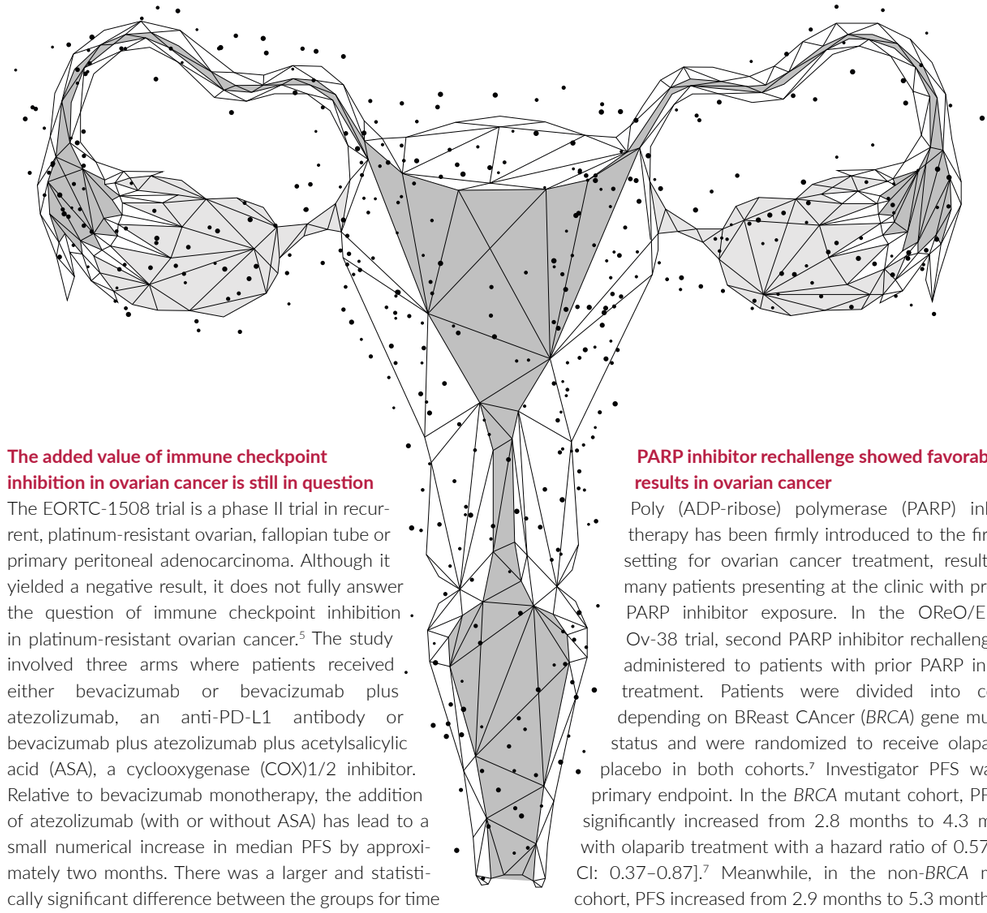
The phase III KEYNOTE 775 trial reported groundbreaking evidence illustrating the efficacy and safety of lenvatinib plus pembrolizumab, an immune checkpoint inhibitor (ICI), versus treatment of physician's choice in patients with previously treated, advanced endometrial cancer patients proficient for mismatch repair (MMR).[1] Patients were randomized 1:1 to receive either lenvatinib plus pembrolizumab or chemotherapy (doxorubicin or paclitaxel). Randomization was stratified by MMR status (proficient versus deficient). A subgroup analysis, which compared prior therapies, suggested that the benefit of immune checkpoint inhibition was more pronounced the earlier the treatment lines were. Given that MMR deficient patients have many efficient options with single-agent immune checkpoint inhibition, it is promising to have data showing a clear increase in response rate for similar treatment in MMR proficient endometrial cancer patients. In conclusion, lenvatinib plus pembrolizumab provided meaningful efficacy improvements in this patient population across all histologies (including difficult to treat histologies). However, as these were post-hoc analyses, the results should be interpreted with caution.

Pembrolizumab combination regimen shows efficacy in the first-line treatment of cervical cancer

The practice-changing KEYNOTE-826 trial involved patients with persistent, recurrent and metastatic cervical cancer, with no prior systemic chemotherapy except chemoradiation. Patients were randomly assigned 1:1 to either pembrolizumab plus paclitaxel plus cisplatin (or carboplatin) and bevacizumab treatment group or paclitaxel plus cisplatin and bevacizumab group (alone or combined with placebo).[2] Overall survival (OS) and progression-free survival (PFS) were the co-primary endpoints of the trial. The Gynecologic Oncology Group (GOG) 240 backbone was a standard maintained during the trial, with the only restriction being the toxicity of bevacizumab.[3] Patients with a programmed death-ligand 1 (PD-L1) combined positive score (CPS) ≥1 reported a hazard ratio of 0.62 [95% CI: 0.50–0.77]. Furthermore, 12-month progression-free rates increased from 34–45% while remaining in a stable delta. This data suggests that there is a substantial fraction of long-term responders to the treatment, although it is too early to judge. In the all-comer population, there was a 24-month OS rate of 50% [95% CI: 43.8–56.6] versus 40% [95% CI: 3.0–46.6] between the pembrolizumab group and the placebo group, respectively; this is regarded as practice-changing data. Between subgroups, there is an equally distributed clinical effect, except for patients lacking PD-L1 expression who did not experience any therapeutic benefit. An increase in response rates by 15–18% is an important result given how debilitating the disease can be. With respect to safety, there was a large variation in general adverse events (AE) reported while immune-mediated AEs were experienced primarily within the pembrolizumab group. In summary, pembrolizumab plus chemotherapy with or without bevacizumab, maybe a new standard of care for women with persistent, recurrent, or metastatic cervical cancer.

Cemiplimab significantly improves survival outcomes for patients with recurrent/metastatic cervical cancer

EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9 is an open-label, randomized, multi-center, phase III trial of cemiplimab, anti- PD-1 versus investigator's choice chemotherapy in patients with recurrent or metastatic cervical carcinoma who have progressed after first-line platinum-based treatment.[4] This study reported an improved median OS in the cemiplimab group versus chemotherapy group (12.0 months vs 8.5 months; HR: 0.69; [95% CI: 0.56–0.84]; p=0.00011).[4] There was a significant beneficial effect of cemiplimab in this study, which may become a new treatment option for patients without prior immune checkpoint inhibition therapy.



The added value of immune checkpoint inhibition in ovarian cancer is still in question

The EORTC-1508 trial is a phase II trial in recurrent, platinum-resistant ovarian, fallopian tube or primary peritoneal adenocarcinoma. Although it yielded a negative result, it does not fully answer the question of immune checkpoint inhibition in platinum-resistant ovarian cancer.[5] The study involved three arms where patients received either bevacizumab or bevacizumab plus atezolizumab, an anti-PD-L1 antibody or bevacizumab plus atezolizumab plus acetylsalicylic acid (ASA), a cyclooxygenase (COX)1/2 inhibitor. Relative to bevacizumab monotherapy, the addition of atezolizumab (with or without ASA) has lead to a small numerical increase in median PFS by approximately two months. There was a larger and statistically significant difference between the groups for time to first subsequent therapy, but this may have been impacted by treatment cross-over, putting more pressure on patients not receiving atezolizumab. While this trial may not have a clinical impact, further research is warranted and patients should be encouraged for treatment within the ongoing AGO-OVAR 2.29 trial. As already shown, in the phase III PENELOPE trial overall response rates are generally low in this population of 24–30%.[6] Although platinum-resistant ovarian cancer is not fully understood, particularly the immune phenotype, it is important to proceed with ICI trials.

PARP inhibitor rechallenge showed favorable results in ovarian cancer

Poly (ADP-ribose) polymerase (PARP) inhibitor therapy has been firmly introduced to the first-line setting for ovarian cancer treatment, resulting in many patients presenting at the clinic with previous PARP inhibitor exposure. In the OReO/ENGOT Ov-38 trial, second PARP inhibitor rechallenge was administered to patients with prior PARP inhibitor treatment. Patients were divided into cohorts depending on BReast CAncer (*BRCA*) gene mutation status and were randomized to receive olaparib or placebo in both cohorts.[7] Investigator PFS was the primary endpoint. In the *BRCA* mutant cohort, PFS was significantly increased from 2.8 months to 4.3 months with olaparib treatment with a hazard ratio of 0.57 [95% CI: 0.37–0.87].[7] Meanwhile, in the non-*BRCA* mutant cohort, PFS increased from 2.9 months to 5.3 months (HR: 0.52 [95% CI: 0.26–0.71]; p=0.0023) which was also a significant result. The data suggest that PARP inhibitor exposure for a duration of more than 12–18 months predicts a beneficial response from second line of PARP inhibition. Regarding safety, there was a low rate of new primary malignancy and no occurrences of myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML). In summary, both cohorts benefited from maintenance olaparib rechallenge and safety is not an issue. The duration of previous PARP exposure needs to be taken into consideration when prescribing PARP rechallenge therapy.

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