Endometrial cancer: news from ASCO

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Summary At ASCO 2022 important abstracts were presented. The programmed death1 (PD1) inhibitor dostarlimab was investigated in the phase III GARNET study in advanced or metastatic endometrial cancer after failure of previous platinum-based combination chemotherapy. In the first group of patients with tumors with dMMR (mismatch repair-deficiency) or MSI-H (microsatellite-high; group A), the median progression-free survival (PFS) was significantly higher than in the group with pMMR (mismatch repair-proficiency) or those with MSS (microsatellite-stable) tumors (group B), i.e., 6.0 months in group A and 2.7 months in group B. Overall survival was > 50 months and 17 months, respectively. Immunotherapy-related adverse events were seen in 23% of patients, including grade 3 or 4 events in 8% of women. In all, 9% of patients discontinued treatment due to adverse events. Another important regimen is the combination of lenvatinib and pembrolizumab. In a randomized study of lenvatinib + pembrolizumab versus monotherapy with doxorubicin or paclitaxel in the second-line therapy of metastatic endometrial cancer, the chemotherapy-free regimen was superior. PFS2 was significantly higher in patients in the pMMR group and the all comer group if they received lenvatinib and pembrolizumab, compared to those receiving standard chemotherapy ($p<0.0001$). In conclusion, checkpoint inhibitors ± lenvatinib are now established in the second-line treatment of advanced endometrial cancer. Overall, the inclusion of PD1 or PDL1 inhibitors in systemic treatment regimens offers a significant opportunity for patients whose treatment options in the past only included conventional chemotherapy, radiotherapy or hormonal therapy.

Keywords Endometrial cancer · Checkpoint inhibitors · Lenvatinib · Pembrolizumab · Dostarlimab

At the 2022 annual ASCO Congress in Chicago, some important abstracts on endometrial cancer were presented. The median survival after first-line therapy of metastatic endometrial cancer is usually less than 1 year [2]. In the first line, combination chemotherapy with carboplatin and paclitaxel represent the standard, while in the second line, doxorubicin monotherapy is regarded as the standard cytotoxic regimen.

One study at the ASCO investigated the value of progestin therapy in advanced endometrial cancer. In a single arm multicenter study, 74 patients with advanced or recurrent endometrioid endometrial cancer received progestins [1]. In all, 34 and 39% of patients had grade 1 or 2 tumors, respectively. While 46% of patients had not received any previous systemic therapy, another 46% had received progestins as their second-line treatment. Following gestagen therapy, there was no progression-free survival (PFS) difference between grade 1 or 2 tumors, on the one hand, and grade 3 tumors, on the other, respectively ($p=0.36$). However, there was a significant difference in PFS between patients who had not previously received systemic treatment versus those who had had previous systemic therapy (hazard ratio 1.73; median of 17.9 months versus 6.2 months, respectively; $p=0.04$). However, no such difference was found for overall survival. The authors concluded that there may be a role for progestins in a selected group of patients with endometrial cancer.

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Table 1  Patient and tumor characteristics of the phase III GARNET study investigating dostarlimab in advanced endometrial cancer [2]

| Characteristics                          | dMMR/MSI-H | pMMR/MSS |
|------------------------------------------|------------|----------|
| Patient age, median (range), years       | 65 (39–85) | 66 (30–86) |
| Tumor histology                          |            |          |
| Grade 1 or 2 endometrioid               | 64%        | 23%      |
| Serous                                   | 5%         | 40%      |
| Grade 3 endometrioid                    | 15%        | 9%       |
| Clear cell                               | 1%         | 7%       |
| Squamous                                 | 1%         | 2%       |
| Undifferentiated                         | 3%         | 2%       |
| Other                                    | 12%        | 17%      |
| Number of patients                       | 143        | 156      |
| 1–2 lines of previous therapy            | 87%        | 89%      |
| Previous adjuvant or neoadjuvant therapy | 34%        | 27%      |
| Previous radiotherapy                    | 71%        | 61%      |
| CR and PR (combined)                     | 45.5%      | 15.4%    |
| Time to response, months                 | 2.7        | 2.9      |
| Prolonged response at 12 months          | 93%        | 60%      |
| Prolonged response at 24 months          | 84%        | 44%      |
| Median PFS, months                       | 6.0        | 2.7      |
| PFS at 12 months                         | 46%        | 13%      |
| PFS at 24 months                         | 40%        | 9%       |
| Median overall survival, months          | >50        | 17       |
| Overall survival at 12 months            | 73%        | 61%      |
| Overall survival at 24 months            | 61%        | 38%      |
| dMMR Mismatch repair deficient, pMMR Mismatch repair proficient, MSI-H microsatellite unstable high, MSS Microsatellite stable, CR Complete remission, PR Partial remission |

The programmed death 1 (PD1) inhibitor dostarlimab was investigated in the phase III GARNET study in advanced or metastatic endometrial cancer after failure of previous platinum-based combination chemotherapy [2]. Patients received 500 mg IV dostarlimab once every 3 weeks for 4 cycles, followed by 1000 mg IV every 6 weeks. Two collectives were investigated. The first was the group with dMMR (mismatch repair-deficient) or MSI-H (microsatellite-high) endometrial cancers (group A) and the second comprised patients with pMMR (mismatch repair-proficient) or those with MSS (microsatellite-stable) tumors (group B). Patient and tumor characteristics are given in Table 1.

Dostarlimab caused grade 3 or 4 treatment-related adverse events in 58% of patients. Immunotherapy-related adverse events were seen in 23% of patients, including grade 3 or 4 events in 8% of women. In all, 9% of patients discontinued treatment due to adverse events. No treatment-related mortality was seen. The main side effects were fatigue (18%), diarrhea (15%), nausea (14%) and asthenia (12%). Grade 3 or 4 adverse events were observed in 3.2% of patients: anemia, aspartate transaminase (AST) or aspartate aminotransferase (ALT) elevations, increase of amylase and lipase, diarrhea, fatigue, hyperglycemia and pneumonitis were recorded. No mortality was noted. Dostarlimab has already been licensed in the European Union (EU) in advanced endometrial cancer.

Another important study on targeted therapy in endometrial cancer which had already been licensed in the EU is the combination of the antiangiogenetic drug lenvatinib and pembrolizumab. Progression-free survival 2 (PFS2) was described from the randomized study of lenvatinib + pembrolizumab versus monotherapy with doxorubicin or paclitaxel in the second-line chemotherapy of metastatic endometrial cancer [3]. PFS2 was significantly higher in patients in the pMMR group and the all comers group if they received lenvatinib and pembrolizumab as compared to those receiving standard chemotherapy (p<0.0001).

The KEYNOTE-C93/GOG-3064/ENGOT-en15 study will investigate the use of pembrolizumab monotherapy as first-line treatment in dMMR advanced and recurrent endometrial cancer [4]. This randomized study compares the anti-PD1 activity of pembrolizumab with that of the current standard, a platinum doublet chemotherapy. Results of this study are eagerly awaited. The hypothesis is that a chemotherapy-free regimen of immunotherapy may be as effective as standard chemotherapy in this type of endometrial cancer. This trial seems particularly ambitious since primary study objectives include both PFS and overall survival.

In conclusion, monotherapy with checkpoint inhibitors of either dostarlimab or pembrolizumab (data not shown since there was no presentation at ASCO) is now established in the second-line treatment of advanced dMMR/MSI-high endometrial cancer. Significant benefits exist with regard to PFS and OS (overall survival). On the other hand, combination therapy with pembrolizumab und lenvatinib is now the established standard in patients with pMMR/MSS advanced endometrial cancer but also has been shown to be effective in dMMR/MSI-high disease. Significant PFS benefits have been demonstrated by this combination. However, compared to monotherapy with a checkpoint inhibitor, it exerts more toxicity including mainly hypertension. Overall, the inclusion of PD1 or PD-L1-inhibitors in the systemic treatment regimens of advanced endometrial cancer offers a significant opportunity for patients whose treatment options in the past only included conventional chemotherapy, radiotherapy or hormonal therapy.

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