Immunotherapy in Endometrial Cancer: What Should We Know?

Author: Ada Enesco, EMJ, London, UK

Citation: EMJ Oncol. 2024;12[1]:23-26. https://doi.org/10.33590/emjoncol/ZJLA9296.

IMMUNOTHERAPY with chemotherapy is emerging as a new standard first-line treatment in advanced endometrial cancer (EC). In an insightful session presented at this year's European Society for Medical Oncology (ESMO) Congress, held in Barcelona, Spain from the 13th–17th September, experts in the field discussed what we know, and what we should know, on immunotherapy and EC.

IMMUNOTHERAPY: NEW STANDARD OF CARE IN ADVANCED ENDOMETRIAL CANCER?

EC is the most common gynaecological malignancy globally, with over 400,000 new cases reported in 2020 and mortality rates increasing annually by 1.8% on average. Ana Oaknin, Vall d'Hebron Institute of Oncology, Barcelona, Spain, raised the current challenges in the treatment of EC. While early-stage EC has a favourable prognosis, she stressed that patients diagnosed at an advanced stage (FIGO Stage III/IV) face a much lower 5-year survival rate of around 17%, largely due to limited treatment options for advanced disease.

Traditionally, standard first-line therapy for advanced EC involved either carboplatin and paclitaxel chemotherapy, or hormonotherapy, depending on clinical and histological characteristics. These approaches, however, have had limited effectiveness, with median progression-free survival often under 1 year, particularly with hormonal therapies.

Oaknin stated that major progress has now been made through the Cancer Genome Atlas (TCGA) project, which classified endometrial cancer into four molecular subgroups: *POLE* ultramutated, microsatellite instability-high (MSI-high), copy-number low, and copy-number high. This classification not only provides relevant prognostic information but can also predict responses to different therapies.

EC is the solid tumour with the greatest percentage of MSI-high cases (31%), which are associated with higher rates of mutation, higher neoantigen expression, increased tumour-infiltrating lymphocytes, and higher PD-(L)1 expression. Oaknin explained that this specific microenvironment makes mismatch repair-deficient (dMMR)/MSI-high EC an ideal candidate for immune checkpoint inhibitors (ICI). Recently, dostarlimab and pembrolizumab showed compelling results in patients with dMMR/MSI-high EC after platinum failure,[1,2] leading to the regulatory approval of these two agents. The logical next step, continued Oaknin, is to try to incorporate ICIs into first-line therapy, either with chemotherapy only, or in combination with poly-ADP ribose polymerase (PARP) inhibitors to yield a potential synergistic anti-tumour effect.

"Would the addition of an anti-PD(L)1 antibody to first-line platinum-based chemotherapy sufficiently improve outcomes in advanced dMMR/MSI-high EC to become a new standard of care?" This is the question that currently needs to be addressed, explained Oaknin.

Oaknin highlighted results from four key trials for dMMR EC. RUBY, a Phase III

randomised multicentre study, enrolled patients with advanced/recurrent EC who had not yet undergone therapy for advanced stages.[3] Patients were randomised 1:1 to receive chemotherapy (paclitaxel and carboplatin) + placebo, or chemotherapy + dostarlimab (anti-PD-1 antibody) for a duration of 3 years. Combining dostarlimab with chemotherapy led to a 72% lower risk of progression or death in patients with dMMR EC, and a significant increase in overall survival (OS).[3]

In another important Phase III trial, NRG-GY018, pembrolizumab (anti-PD-1 antibody) + chemotherapy reduced the risk of progression or death by 70% versus placebo + chemotherapy in patients with advanced/recurrent dMMR EC.[4]

In the AtTEnd study, atezolizumab (anti-PD-L1 antibody) + chemotherapy reduced the risk of progression or death by 64% compared to placebo in patients with advanced/recurrent dMMR EC, with a dramatically higher OS also observed in the atezolizumab group.[5]

Finally, the Phase III DUO-E trial demonstrated that durvalumab + chemotherapy followed by maintenance durvalumab with or without PARP inhibitor, olaparib, resulted in significantly lower risk of disease progression or death compared with chemotherapy alone for patients with advanced/recurrent EC.[6] Oaknin stated that all these data highlight the clinical benefit of integrating immunotherapy into first-line chemotherapy.

While dMMR is a known predictor of how certain cancers respond to immunotherapy, there is variability within the dMMR patient population. Oaknin explained that two key mechanisms can lead to MMR deficiency: epigenetic promoter methylation or germline/somatic mutations in mismatch repair genes. These differences could influence how tumours respond to ICIs, and some preliminary findings seem to support this hypothesis. However, results from the NRG-GY018 trial[7] suggested that pembrolizumab provided benefits in both methylated and non-methylated dMMR groups, indicating that dMMR status alone might not fully predict response. Similarly, RUBY trial[3] results showed significant benefit from dostarlimab irrespective of the specific dMMR mechanism.

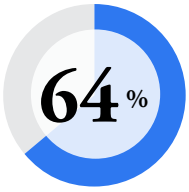
> **ICIs are transforming treatment for advanced/recurrent EC**

Beyond dMMR, other biomarkers such as PD-L1 and tumour mutational burden (TMB) are also investigated for their role in predicting responses to immunotherapy. However, PD-L1 expression remains an ambiguous predictor. Analysis from the NRG-GY018 trial showed that in dMMR subgroups, progression-free survival was similar regardless of whether patients were PD-L1-positive or -negative, indicating that PD-L1 expression alone is not a reliable marker for determining outcomes.[7] In contrast, the DUO-E trial, which used an assay called tandem affinity purification (TAP), found a significant benefit for patients with TAP values ≥1% when given experimental treatments compared to the control arm.[8] However, this effect was not observed in PD-L1-negative patients. This raises the question of how PD-L1 status intersects with other markers like TMB and dMMR in predicting outcomes.

The GARNET trial further explored this interaction by combining multiple biomarkers to predict overall response rates. For dMMR patients who were also PD-L1-positive or had a high TMB, the response rate was significantly higher (60%) compared to dMMR patients without these additional markers.[9] Ongoing trials like KEYNOTE-C93 and DOMENICA now aim to refine these findings to identify which patients may benefit most from immunotherapy, potentially allowing for treatment de-escalation and more personalised approaches.

Oaknin concluded that ICIs are transforming treatment for advanced/recurrent EC. Patients with dMMR/MSI-high tumours obtain a clinically meaningful benefit by combining these ICIs with paclitaxel/carboplatin, and this regimen must be considered a new standard of care, she

Atezolizumab (anti-PD-L1 antibody) + chemotherapy reduced the risk of progression or death by



compared to placebo in patients with advanced/recurrent dMMR EC

stressed. However, work is still needed to identify which patients with dMMR EC might not benefit from these therapies.

OVERCOMING RESISTANCE TO IMMUNO-ONCOLOGY

Frederik Marmé, Heidelberg University, Germany, addressed the key topic of immuno-oncology (IO) resistance, focusing on three different scenarios: primary resistance, acquired resistance, and progression after IO treatment. This classification is crucial because many studies address IO resistance in various diseases, but the setting in which they are conducted must be specified. Furthermore, patterns of resistance might vary between these categories and could respond differently to next-generation immunotherapies. Currently, there is no standardised definition of IO resistance in EC, though definitions exist for other cancers.

For his talk, Marmé focused on ECs with dMMR, a subgroup expected to respond to immunotherapy. He proposed a clinical definition of IO resistance, adapted from that of non-small cell lung cancer. While not intended for routine clinical use, it is important to establish stringent inclusion criteria for clinical trials to ensure data comparability. Marmé distinguished primary resistance, which is non-response to IO therapy from the outset, from acquired resistance, which he defined by three criteria: receiving PD-(L)1 blockade, achieving an objective response such as a complete or partial response, and experiencing disease progression within 6 months of the last PD-(L)1 inhibitor treatment. He added that stable disease does not fall under the definition of acquired resistance, as the focus is on patients who initially respond, but later experience progression.

> **Combining dostarlimab with chemotherapy led to a 72% lower risk of progression or death in patients with dMMR EC, and a significant increase in overall survival**

"When does resistance occur in dMMR EC?" Marmé reviewed data from recent ICI monotherapy trials for dMMR EC, emphasising that, while approximately half

of patients achieve an initial response to IO therapy (50–55% primary resistance), this rate of response diminishes significantly in subsequent courses, with approximately 30% of acquired resistance. Marmé explained that mechanisms of resistance are complex and diverse, but key drivers include low neoantigen presentation, multiple immune checkpoints, neutrophil and T-regulatory cell immunosuppression, and inflammation and immunosuppression.

Because primary resistance is the most common form of IO resistance in dMMR EC, finding new strategies to overcome this initial resistance is crucial. Marmé suggested a role for IO combination, with promising preliminary data on the effectiveness of dual immune checkpoint blockade for advanced EC (anti-TIGIT and anti-PD-L1).[10] However, combination of ICIs with a different class of inhibitors, PARP inhibitors, was not shown to overcome primary resistance.

Finally, Marmé stressed that identifying immune predictors of response to ICIs will be crucial for advancing treatment of dMMR EC. He drew attention to a recent study that conducted an unsupervised hierarchical clustering based on immune markers to identify biomarkers associated with ICI response, such as PD-L1 and HLA-I.[11]

Currently, there are no data indicating the appropriate course of action in case of progression after PD-(L)1 in dMMR EC. However, Marmé pointed out that other IO-sensitive solid tumours, like non-small cell lung cancer, urothelial carcinoma, and melanoma, have been shown to regain some degree of sensitivity to PD-(L)1 blockade after a treatment-free interval of at least 6 months.

Marmé concluded that precise classification of resistance types, alongside novel IO combinations and biomarker discovery, will be pivotal in optimising treatment strategies for dMMR EC.

References

1. O'Malley DM et al. Pembrolizumab in patients with microsatellite instability-high advanced endometrial cancer: results from the KEYNOTE-158 study. J Clin Oncol. 2022;40(7):752-61.
2. Antill Y et al. Clinical activity of durvalumab for patients with advanced mismatch repair-deficient and repair-proficient endometrial cancer. A nonrandomized phase 2 clinical trial. J Immunother Cancer. 2021;9(6):e002255.
3. Tesaro, Inc. A study to evaluate dostarlimab plus carboplatin-paclitaxel versus placebo plus carboplatin-paclitaxel in participants with recurrent or primary advanced endometrial cancer (RUBY). NCT03981796. https://clinicaltrials.gov/study/NCT03981796.
4. National Cancer Institute (NCI). Testing the addition of the immunotherapy drug pembrolizumab to the usual chemotherapy treatment (paclitaxel and carboplatin) in stage III-IV or recurrent endometrial cancer. NCT03914612. https://clinicaltrials.gov/study/NCT03914612.
5. Mario Negri Institute for Pharmacological Research. Atezolizumab trial in endometrial cancer - AtTEnd (AtTEnd). NCT03603184. https://clinicaltrials.gov/study/NCT03603184.
6. AstraZeneca. Durvalumab with or without olaparib as maintenance therapy after first-line treatment of advanced and recurrent endometrial cancer (DUO-E). NCT04269200. https://clinicaltrials.gov/study/NCT04269200.
7. Eskander A et al. Updated response data and analysis of progression free survival by mechanism of mismatch repair loss in endometrial cancer (EC) patients (pts) treated with pembrolizumab plus carboplatin/paclitaxel (CP) as compared to CP plus placebo (PBO) in the NRG GY018 trial. LBA43. ESMO Congress 2023, October 20-24, 2023.
8. Westin SN et al. Durvalumab plus carboplatin/paclitaxel followed by maintenance durvalumab with or without olaparib as first-line treatment for advanced endometrial cancer: the phase III DUO-E trial. J Clin Oncol. 2024;42(3):283-99.
9. Oaknin A et al. Clinical activity and safety of the anti-programmed death 1 monoclonal antibody dostarlimab for patients with recurrent or advanced mismatch repair-deficient endometrial cancer: a nonrandomized phase 1 clinical trial. JAMA Oncol. 2020;6(11):1766-72.
10. Rojas C et al. Vibostolimab coformulated with pembrolizumab (vibo/pembro) for previously treated advanced mismatch repair–deficient (dMMR) endometrial cancer: results from cohort B1 of the phase 2 KEYVIBE-005 study. J Clin Oncol. 2024;42(16):5502.
11. Grau Bejar JF et al. Immune predictors of response to immune checkpoint inhibitors in mismatch repair-deficient endometrial cancer. J Immunother Cancer. 2024;12(7):e009143.