Editorial Commentary

Immune checkpoint inhibitors: here to stay

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Endometrial cancer (EC) incidence is rapidly rising worldwide; the highest rates are found in North America and Western Europe. However, other countries, such as South Africa, Japan, and Brazil, present increasing incidence rates over time. An increase in overweight and a decline in fertility are some factors implicated in this scenario (1). In the United States, uterine corpus cancer is women's fourth most diagnosed cancer, with an incidence of 27 per 100,000 women each year (2). While mortality for most cancers is generally declining, it continues to increase for EC, undoubtedly because of the lack of effective therapeutic options for advanced or recurrent disease (2,3).

Until recently, risk stratification was based on histological type (endometrioid/non-endometrioid), tumor grade, depth of myometrial infiltration, lymphovascular space invasion, and extrauterine extension (4). In 2013, the Cancer Genome Atlas Research Network provided an integrated genomic, transcriptomic, and proteomic characterization of endometrial carcinomas of endometrioid and serous histological types. A combination of somatic mutational burden, somatic copy number alterations, and microsatellite instability (MSI) allowed the division of EC into four distinct prognostic molecular subtypes: DNA polymerase epsilon (POLE) (ultramutated) tumors, tumors with high MSI (MSI-H) (hypermutated), copy-number-low tumors, and copy-number-high tumors (5). The transposition of this classification into daily practice was allowed by the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE), a tool using surrogate clinically-available markers (6). Sequencing of exons 9 to 14 of POLE is used for POLE mutated definition; immunohistochemistry for mismatch repair (MMR) proteins MLH1, MSH2, MSH6, and PMS2 for MSI-H status. The remaining tumors are classified according to p53 protein expression determined by immunohistochemistry as aberrant or normal (6). POLE-mutated tumors are associated with an excellent prognosis, independent of any adverse feature, while the p53 aberrant group has the poorest outcome, even in the early stage. The other two groups have an intermediate prognosis.

MSI-H is a consequence of deficient mismatch repair (dMMR) and corresponds to 25–30% of endometrial cancer (5,6). dMMR can be the consequence of *MLH1* hypermethylation (more common) or mutation in any of the genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*), either germinative (Lynch syndrome) or somatic. Lynch syndrome is found in about 3% of EC. MMR testing is more effective in detecting patients at risk than the clinical criteria based on personal/family history (Amsterdam II revised Bethesda/

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German-DKG criteria) (7).

In our experience, about 30% of dMMR endometrial cancer is present in the advanced stage (8). dMMR/MSI-H status increases immunogenicity and has been associated with response to immune checkpoint inhibitors (ICI) (9). On May 23, 2017, the U.S. Food and Drug Administration (FDA) granted the first tissue/site-agnostic approval to pembrolizumab for patients with unresectable/metastatic, MSI-H/dMMR solid tumors that have progressed after prior treatment (10). Until recently, the preferred first-line therapy for recurrent/advanced disease was carboplatin/paclitaxel based on the phase III trial NRG Oncology/GOG0209, which demonstrated noninferiority of this regimen compared to paclitaxel-doxorubicin-cisplatin, in force until then (11). An essential step with the anti-programmed death-1 (anti-PD-1) therapy with pembrolizumab was the phase II KEYNOTE-158 study (NCT02628067) (12). This study enrolled 233 patients with 27 tumor types, noncolorectal, unresectable/metastatic, dMMR/MSI-H, including 49 endometrial carcinomas previously treated. The results of this study, updated with more patients and longer follow-up, demonstrated durable benefits with an objective response rate of 30.8% (12,13). On February 9, 2023 and March 21, 2022, the FDA approved the two PD-1 inhibitors, respectively dostarlimab and pembrolizumab, for MSI-H/dMMR advanced endometrial carcinoma for patients with disease progression following prior therapy (14,15).

More recently, two independent trials tested the addition of PD-1 inhibitors (dostarlimab and pembrolizumab) to chemotherapy in the first-line treatment of advanced endometrial cancer with similar designs and results (16,17). The phase III randomized trial that used pembrolizumab (NRG-GY018) corresponded to the study of Eskander *et al.* (17). This study enrolled 816 patients, of whom 225 dMMR and 588 proficient in MMR (pMMR), with a median follow-up of 12 and 7.9 months, respectively. The patients were randomly allocated (1:1) to receive paclitaxel-carboplatin in combination with pembrolizumab or placebo for six cycles, followed by pembrolizumab or placebo maintenance every 6 weeks for up to 14 cycles. Among the patients with dMMR tumors, 74% of those treated with pembrolizumab were alive and without progression, compared to 38% in the placebo group [hazard ratio for progression or death 0.30; 95% confidence interval (CI): 0.19–0.48; P<0.001]. Even in the cohort of pMMR tumors, the benefit of pembrolizumab could be demonstrated, resulting in 46% lower unfavorable outcomes. Patients with pMMR tumors presented a median progression-free survival of 13.1 months, compared to 8.7 months in the placebo group (hazard ratio for disease progression or death: 0.54; 95% CI: 0.41–0.71; P<0.001).

Adverse events were seen in at least 15% of all patients. Fatigue, peripheral sensory neuropathy, anemia, and nausea were the most common. The frequencies of adverse events grade 3 or more were higher in patients receiving pembrolizumab than placebo (57.4% *vs.* 45.8%). Events leading to death (grade 5) were seen in seven patients using pembrolizumab and four using a placebo. These events were cardiac arrest, sepsis, and lower gastrointestinal hemorrhage. Except for one patient receiving pembrolizumab in the pMMR cohort with cardiac arrest, the other fatal events were considered probably not related to the medication by the treating physician. Possible immune-related adverse events of any grade were higher in patients using pembrolizumab (34.8% *vs.* 21.6%). The incidence of immune-mediated adverse events was considered similar to those described in previous studies of pembrolizumab monotherapy. In descending order, these events were infusion reaction, hypothyroidism, hyperthyroidism, colitis, pneumonitis, glucose intolerance, acute kidney injury, hepatic failure, myositis, hypophysitis, pancreatitis, and adrenal insufficiency (17).

The study with dostarlimab, the RUBY trial (NCT03981796), randomized (1:1) 494 patients to receive dostarlimab or placebo in combination with carboplatin for six cycles, followed by dostarlimab or placebo every 6 weeks up 3 years or until disease progression. Although with fewer patients, the RUBY trial had longer follow-up than NRG-GY018 (16). At 24 months, in the dMMR cohort, 61% of patients receiving dostarlimab were alive without disease progression compared to 16% in the placebo group. Although the pMMR patients were not under evaluation, they were alive and without progression in 28% and 19%, receiving dostarlimab and placebo, respectively. The incidence of adverse event grade ≥3 was higher among patients using dostarlimab (70.5% *vs.* 59.8%), as well as immune-related events (38.2% and 15.4%).

It is important to mention the different eligibility criteria for dostarlimab and pembrolizumab. The carcinosarcoma (CS) was not included in NRG-GY018, but it was in RUBY, which allowed the FDA to approve dostarlimab, including for CS (15).

These two studies demonstrate that adding either pembrolizumab or dostarlimab to chemotherapy should be the new standard first-line treatment. However, there

is still a long way to go to the standard of care for patients with advanced endometrial cancer. First, we need a longer follow-up to know if the observed benefit persists and for how long. Second, we must determine if chemotherapy is essential for the ICI benefit. The two studies compared the addition of ICI to the standard treatment. Including patients using pembrolizumab or dostarlimab without chemotherapy would be necessary, at least in the dMMR group. Even the increase in adverse events identified in both studies may have been due to the combination of ICI and the chemotherapy regimen. We had an experience with a particular case of stage IV endometrioid carcinoma dMMR treated with first-line pembrolizumab without chemotherapy that achieved a complete response (18). This patient is alive and without disease 63 months after diagnosis. The third point is about biomarkers. There is no doubt that dMMR/MSI-H status is a well-established biomarker for immunotherapy and is essential from the moment of diagnosis. However, how do we identify other patients with potential benefits among pMMR? After all, dMMR/MSI-H is not the only biomarker for immune activation. The studies have proven that the benefit of ICI extends to patients who do not have dMMR, and we need to know who these patients are. Other biomarkers studied, such as intratumoral programmed death ligand-1 (PD-L1) and tumor mutational burden, and others under investigation, such as tumor-infiltrating lymphocytes and *ARID1A* alterations, have not proven useful (19). However, we must insist on the search for robust predictive biomarkers because it is the best way to guarantee safe and effective indications for any drug.

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