OVARIAN CANCER IN FOCUS

Current Developments in the Management of Ovarian Cancer

Section Editor: Robert L. Coleman, MD

Revisiting Immunotherapy in Endometrial Cancer

Ramez N. Eskander, MD
Professor of Obstetrics, Gynecology, and Reproductive Sciences
Division of Gynecologic Oncology
University of California, San Diego
Rebecca and John Moores Cancer Center
San Diego, California

H&O What are the limitations of chemotherapy for endometrial cancer?

RE The management of endometrial cancer has long relied on cytotoxic chemotherapy alone. This approach was principally driven by the fact that we did not understand the molecular underpinnings of the disease and were historically "lumping" all endometrial cancer patients together. Although some patients show meaningful responses to chemotherapy, these responses are usually limited, and disease recurrence is common. For example, the response rates to chemotherapy for patients whose endometrial cancer progressed after prior chemotherapy are approximately 10% to 15%. Even when the agents do work, the responses are limited in duration.

H&O What prompted the recent interest in using immunotherapy in endometrial cancer?

RE The use of immunotherapy reflects an evolution in our understanding of the disease. The molecular characterization of endometrial cancer did not emerge until the pivotal TCGA publication in 2013 revealed that a proportion of patients have tumors that are mismatch repair–deficient (dMMR) or microsatellite instability–high (MSI-H).[1] This understanding helped inform 2 important trials: KEYNOTE-158 and GARNET.[2,3]

KEYNOTE-158 was a large, phase 2 clinical trial looking at the use of pembrolizumab (Keytruda, Merck) in multiple previously treated colorectal and noncolorectal tumors that were dMMR/MSI-H. The largest noncolorectal cancer cohort was the endometrial cancer cohort. Among the 47 patients with endometrial cancer, the objective response rate (ORR) was 57.1% and the median duration of response was not reached. Pembrolizumab produced a dramatic benefit in these patients, highlighting the efficacy of immunotherapy in a dMMR patient population.

The phase 1 GARNET trial was similar, but it looked at dostarlimab (Jemperli, GSK) rather than pembrolizumab. It showed a noteworthy ORR of 43.5%, with the median duration of response not reached. We had very strong responses and when patients responded, the duration of response tended to be very long, particularly in a cohort where cytotoxic chemotherapy historically had limited benefit. The KEYNOTE-158 and GARNET trials led to the US Food and Drug Administration (FDA) approvals of pembrolizumab and dostarlimab, respectively, for advanced or recurrent dMMR/MSI-H endometrial cancer. The results of KEYNOTE-158 also led to the first disease site–agnostic FDA approval for patients with recurrent dMMR/MSI-H cancers. These approvals represented a rapid transformation in the standard of care for biomarker-selected patients who could use immune checkpoint inhibitors. However, this left us with a population of patients who were biomarker-negative or mismatch repair–proficient (pMMR), where we still had to identify effective options.

H&O What are the most important trials of immunotherapy in endometrial cancer that have recently produced results?

RE One of the pivotal trials in the endometrial cancer

space is the KEYNOTE-775 trial, which was led by Dr Vicky Makker.[4] KEYNOTE-775 compared the oral tyrosine kinase inhibitor lenvatinib (Lenvima, Eisai) plus pembrolizumab vs the physician's choice of chemotherapy, which was either weekly paclitaxel or doxorubicin in the recurrent setting. In updated results published in April 2023, the combination of lenvatinib and pembrolizumab vs chemotherapy improved overall survival (OS), progression-free survival (PFS), and ORR in both dMMR and pMMR patients. These results reinforced the clinical benefit of lenvatinib plus pembrolizumab over chemotherapy in the pMMR population.

More recently, we saw the results of the NRG-GY018 and RUBY clinical trials presented at the Society of Gynecologic Oncology 2023 Annual Meeting and published in the *New England Journal of Medicine*.[5,6] Both of these trials looked to expand the incorporation of immunotherapy in the earlier-line treatment setting. Patients were either chemotherapy-naive or had experienced a disease-free interval of 6 to 12 months after chemotherapy and before recurrence. Both trials compared chemotherapy plus immune checkpoint inhibition with immune checkpoint inhibition maintenance vs chemotherapy plus placebo with placebo maintenance in patients with advanced-stage or recurrent disease. NRG-GY018 used the anti–programmed death 1 (anti–PD-1) agent pembrolizumab, whereas RUBY used the anti–PD-1 agent dostarlimab.

Although the studies had differences in eligibility criteria, they both showed that in the dMMR population, the addition of immunotherapy to chemotherapy resulted in a 70% reduction in the risk of disease progression or death. The median PFS was not reached with immunotherapy in either study, whereas the median PFS in the placebo arm of NRG-GY018 was approximately 7.6 months. The control arms of both trials performed remarkably similarly to each other. These data show that chemotherapy plus checkpoint inhibition with maintenance checkpoint inhibition led to a significant improvement in clinical outcomes in the early-line treatment of patients with advanced or recurrent dMMR endometrial cancer. This essentially established this as a new standard-of-care treatment option.

The NRG-GY018 trial independently analyzed the dMMR and pMMR endometrial cancer populations. In the pMMR population, the trial showed a 46% reduction in the risk of disease progression or death in the pembrolizumab group vs the placebo group. The OS data were immature for NRG-GY018. The statistical design was slightly different in the RUBY trial, which analyzed the results for the dMMR population and then the entire population. In RUBY, the intent-to-treat population had a 36% reduction in the risk of disease progression or death compared with the placebo group. Immature OS data also pointed to a benefit with dostarlimab. We look forward to seeing additional data at subsequent congresses that delve deeper into efficacy in specific patient populations.

H&O What other important studies are looking at immunotherapy in endometrial cancer?

RE The phase 3 DUO-E trial is a 3-arm trial looking at first-line immunotherapy with durvalumab (Imfinzi, AstraZeneca) in combination with platinum-based chemotherapy followed by maintenance therapy with durvalumab plus the poly(ADP-ribose) polymerase inhibitor olaparib (Lynparza, AstraZeneca), or maintenance therapy with durvalumab alone for patients with newly diagnosed advanced or recurrent endometrial cancer. Interim results announced in a press release showed a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy alone.[7] The clinical benefit was greater when maintenance treatment consisted of durvalumab/olaparib vs durvalumab alone, which may support the hypothesis that some endometrial cancers are homologous recombination repair deficient. We are now waiting for the full data to be presented at an upcoming meeting.

> The fact that so many trials are being conducted with immunotherapy in different disease settings makes this an incredibly exciting time in endometrial cancer research.

The phase 3 AtTEnd trial is looking at the programmed death ligand 1 (PD-L1) inhibitor atezolizumab (Tecentriq, Genentech) plus chemotherapy vs placebo plus chemotherapy as frontline treatment in patients with advanced or recurrent endometrial carcinoma and dMMR status. In results that were presented at the European Society for Medical Oncology Congress 2023, the use of atezolizumab reduced the risk for disease progression by 64%.[8]

Additional ongoing phase 3 studies that are seeking

to further transform the use of immunotherapy in the endometrial cancer space include the KEYNOTE-B21/GOG-3053/ENGOT-en11 trial (NCT04634877) and the KEYNOTE-C93/GOG-3064/ENGOT-en15 trial (NCT05173987). The KEYNOTE-B21 trial is looking to see whether we can move pembrolizumab into earlier lines of treatment among completely resected endometrial cancer patients. The KEYNOTE-C93 trial is evaluating the safety and efficacy of pembrolizumab vs carboplatin/paclitaxel in patients with dMMR advanced or recurrent disease who have not previously received systemic chemotherapy, essentially trying to move away from cytotoxic chemotherapy altogether.

The phase 3 DOMENICA trial is similar to the KEYNOTE-C93 trial but is looking at dostarlimab rather than pembrolizumab vs carboplatin/paclitaxel as first-line therapy in patients with dMMR advanced or recurrent endometrial cancer (NCT05201547).

Another ongoing phase 3 trial is LEAP-001, which is looking at first-line pembrolizumab plus lenvatinib vs chemotherapy in newly diagnosed advanced or recurrent endometrial cancer (NCT03884101).

The fact that so many trials are being conducted with immunotherapy in different disease settings makes this an incredibly exciting time in endometrial cancer research.

H&O What should be the next step in research?

RE We have numerous questions that need answers. First, how can we further understand the relevance of immunotherapy in the pMMR or biomarker-negative population? There is a clear benefit based on the results of NRG-GY-018 and RUBY, but can this be refined? Are there specific subsets that may exhibit heightened sensitivity to immunotherapy plus chemotherapy? How do we tailor the immunotherapeutic approach to pMMR patients as other drugs become available, such as antibody-drug conjugates and nuclear export inhibitors? Preliminary data from the SIENDO trial that were presented at the 2022 American Society of Clinical Oncology Annual Meeting suggested that maintenance therapy with the XPO1 inhibitor selinexor (Xpovio, Karyopharm) improves PFS in patients with *TP53* wild-type endometrial cancer.[9]

Another question relates to the opportunity for immunotherapy rechallenge following previous immunotherapy. If we begin using immunotherapy in the frontline setting for a large proportion of endometrial cancer patients, what do we do when the cancer recurs? Can we rechallenge with immunotherapy alone or in combination? Is there an immunotherapy-free treatment window that would have clinical relevance? If we stop immunotherapy owing to an adverse event and the patient experiences progression, should we rechallenge with immunotherapy? We still have important questions to answer.

Disclosures

Dr Eskander reports research support (to institution) from AstraZeneca, Eisai, Merck, and Novocure; and consulting and advisory fees from AstraZeneca, Cardiff Oncology, Clovis Oncology, Eisai, Elevar Therapeutics, GSK/Tesaro, ImmunoGen, Seagen, Mersana Therapeutics, Myriad Genetics, Daichi Sankyo, and Gilead.

References

1. Cancer Genome Atlas Research Network; Kandoth C, Schultz N, Cherniack AD, et al. Integrated genomic characterization of endometrial carcinoma. *Nature*. 2013;497(7447):67-73.
2. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. *J Clin Oncol*. 2020;38(1):1-10.
3. Oaknin A, Gilbert L, Tinker AV, et al. Safety and antitumor activity of dostarlimab in patients with advanced or recurrent DNA mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) or proficient/stable (MMRp/MSS) endometrial cancer: interim results from GARNET-a phase I, single-arm study. *J Immunother Cancer*. 2022;10(1):e003777.
4. Makker V, Colombo N, Casado Herráez A, et al. Lenvatinib plus pembrolizumab in previously treated advanced endometrial cancer: updated efficacy and safety from the randomized phase III study 309/KEYNOTE-775. *J Clin Oncol*. 2023;41(16):2904-2910.
5. Eskander RN, Sill MW, Beffa L, et al. Pembrolizumab plus chemotherapy in advanced endometrial cancer. *N Engl J Med*. 2023;388(23):2159-2170.
6. Mirza MR, Chase DM, Slomovitz BM; RUBY Investigators. Dostarlimab for primary advanced or recurrent endometrial cancer. *N Engl J Med*. 2023;388(23):2145-2158.
7. Imfinzi plus Lynparza and Imfinzi alone both significantly improved progression-free survival in advanced endometrial cancer when added to chemotherapy [press release]. AstraZeneca. https://www.astrazeneca.com/media-centre/press-releases/2023/imfinzi-lynparza-prolonged-pfs-in-endometrial-cancer.html#! Posted May 26, 2023. Accessed October 31, 2023.
8. Colombo N, Harano K, Hudson E, et al. Phase III double-blind randomized placebo controlled trial of atezolizumab in combination with carboplatin and paclitaxel in women with advanced/recurrent endometrial carcinoma [ESMO abstract LBA40]. *Ann Onc*. 2023;34(suppl 2).
9. Makker V, Perez-Fidalgo JA, Bergamini A, et al. Randomized phase III study of maintenance selinexor versus placebo in endometrial cancer (ENGOT - EN5/GOG-3055/SIENDO): impact of subgroup analysis and molecular classification [ASCO abstract 5511]. *J Clin Oncol*. 2022;40(16)(suppl).