Immunotherapy in endometrial cancer: who are the most appropriate patients?

Katherine C. Kurnit, Amir A. Jazaeri

In an exciting milestone for endometrial cancer therapeutics, Ott et al. recently published the results from the KEYNOTE-028 study in the Journal of Clinical Oncology (1). This Phase Ib clinical trial was part of a larger set of basket trial expansion cohorts evaluating the safety and preliminary efficacy of pembrolizumab treatment in 20 solid tumor types with PD-L1 positivity. In this study, PD-L1 positivity was defined as staining of the membrane in at least 1% of the tumor and related inflammatory cells, or positive staining noted in the stroma. The authors found that 3 of the 23 patients evaluated for treatment response demonstrated partial responses, and an additional 3 patients had stable disease. All 3 patients with partial responses had durable responses lasting longer than 60 weeks. The other important finding was that of the 75 patients with advanced endometrial cancer who were screened, 36 (48%) had tumors demonstrating PD-L1 positivity.

How to identify likely responders?

While these are exciting findings for a tumor type without many therapeutic options in the recurrent setting, this study had an important fundamental limitation. The question of whether PD-L1 is the best predictive biomarker for pembrolizumab and other anti-PD-L1 therapies has not yet been resolved in any tumor type, including endometrial cancer.

The use of PD-L1 as a biomarker has been studied in the context of multiple checkpoint inhibitors, but most extensively in pembrolizumab. PD-L1 positivity is currently determined using immunohistochemistry. A score is given based upon the percentage of tumor cells and infiltrating immune cells that are positive for PD-L1, relative to the total number of tumor cells present. Although the strategy for scoring tumors has been relatively consistent, there have been significant discrepancies in terms of what cutoff should be used to deem a tumor “positive” (1-7).

KEYNOTE-028 by Ott et al. only included endometrial cancer patients whose tumors had a PD-L1 score of greater than or equal to 1% (1). In KEYNOTE-045, which was a Phase III trial evaluating pembrolizumab as second line therapy in urothelial tumors, the authors evaluated the impact of PD-L1 positivity only as secondary endpoints. Assessing both 1% and 10% as cutoff points, the authors found that the groups with low positivity by either criteria no longer demonstrated a statistically significant improvement in overall survival when receiving pembrolizumab compared with chemotherapy (2). In comparison, KEYNOTE-024 required patients to have tumors demonstrating at least 50% positivity in order to be enrolled in this Phase III trial evaluating pembrolizumab in the up-front setting for non-small cell lung cancer (NSCLC) (3).

These discrepancies have resulted in variations in the PD-L1 levels listed for Food and Drug Administration (FDA) pembrolizumab approvals. In first line therapy for
NSCLC, pembrolizumab is approved for tumors with PD-L1 positivity greater than or equal to 50%. In contrast, pembrolizumab approval for recurrent NSCLC only requires PD-L1 positivity greater than or equal to 1%. Although these labels are simply reflections of the study designs and the companion diagnostics for the trials which led to the drug’s approvals, it does raise the question of whether these different biomarker levels are truly reflective of differences in tumor biology. Although currently there are no good data to answer this question, mechanistically it seems unlikely that the PD-L1 levels required for drug efficacy would be different in the primary versus recurrent settings of the same tumor type. Furthermore, none of the FDA approvals for nivolumab or atezolizumab, nor any of the remaining pembrolizumab approvals, have any mention of PD-L1 at all.

Given the confusing PD-L1 positivity data, immunohistochemistry staining for PD-L1 may not actually be the best predictive biomarker for anti-PD1 and anti-PD-L1 therapy in any tumor type, including endometrial cancer. The authors of KEYNOTE-028 partially address this concern by collecting information on microsatellite instability status and POLE mutation status (1). Unfortunately, only one tumor in the cohort tested positive for high microsatellite instability (MSI-high), and only one tumor was found to have a POLE mutation. Interestingly, the best response in the patient with the MSI-high tumor was progressive disease, while the patient with a POLE mutation (leading to a hypermutated phenotype) achieved a partial response. These small numbers make it nearly impossible to evaluate the impact of these other biomarkers on responses to pembrolizumab in this study.

To underscore this point about alternative biomarkers, a Phase II study by Le et al. published in 2015 showed that tumors with mismatch repair (MMR) deficiency had higher response rates to pembrolizumab than tumors that were MMR proficient (8). A non-colorectal cohort in the study included two patients with endometrial cancer, both of whom demonstrated clinical responses to therapy. A subsequent report by the same group included 86 patients with MMR deficiency, including 15 endometrial cancer patients (9). Eleven of the 14 evaluable endometrial cancer patients had a complete response, partial response, or stable disease. Although the majority of patients enrolled in other pembrolizumab trials evaluating MMR status had colorectal cancer, even non-colorectal tumor types have consistently demonstrated responses to pembrolizumab therapy. What makes this finding even more exciting is that MMR deficiency and microsatellite instability status are already established clinical biomarkers currently in use as standard of care tests for several tumor types, including endometrial cancer. In current clinical practice, these evaluations are mainly being used to help identify endometrial cancer patients with possible Lynch syndrome (hereditary non-polyposis colon cancer).

This histology-independent drug response partnered with an already clinically available biomarker makes the clinical application of checkpoint inhibitor therapy in the setting of MMR deficiency or MSI-high much easier to implement. In fact, the compilation of data from these studies recently resulted in an FDA approval of pembrolizumab in tumors with MMR deficiency or MSI-high in May of 2017. The approval of a therapeutic agent based upon a tumor type-agnostic biomarker is an exciting step for the world of personalized oncology. It is perhaps even more exciting for endometrial cancer, however, as endometrial cancer to date remains without an FDA tumor type-specific approval. Pembrolizumab’s approval changes the options for FDA-approved treatment in endometrial cancer patients, as approximately 25% of endometrial cancers belong to this MSI-high group (10).

Aside from PD-L1 and MMR deficiency/MSI-high, high tumor mutational burden in general has also been studied as a potential biomarker for immunotherapy response in endometrial cancer. Specifically, as alluded by Ott et al., POLE mutation has shown promise as an endometrial cancer biomarker linked with high tumor mutational burden. Not only do these tumors preliminarily appear to have improved responses to immunotherapy treatments (11,12), patients with endometrial cancers harboring POLE mutation may have improved survival outcomes in general (13,14). This latter point is important on its own in terms of prognostic implications, but is also interesting as it may be driven by an upregulation of native immune responses secondary to the high tumor mutational burden (15). Unfortunately, most of these data are from preclinical/translational studies and case reports. Larger clinical trials with prospective evaluation for high tumor mutational burden in endometrial cancer have not yet been completed.

As highlighted by these clinical and preclinical studies, the identification of appropriate predictive biomarkers for checkpoint inhibitors and other immunotherapy agents remains elusive. It will be increasingly important, therefore, that future therapeutic studies include careful biomarker evaluation in clinical trial designs for immunotherapy agents in order to better understand which patients should...
be considered for treatment.

How to improve efficacy?

From a clinical standpoint, MSI-high tumors comprise a minority of unselected newly diagnosed endometrial cancer. As microsatellite instability status has no clear impact on prognosis (10), the vast majority of patients with currently incurable endometrial cancer will, therefore, belong to the microsatellite stable (MSS) group. Although the durations of response were long in the study by Ott et al., the 13% clinical response rate is somewhat disappointing (1), especially considering that all of these patients had already screened positive for PD-L1. This leads us to the broader question of how to develop more effective immunotherapy agents in MSS endometrial cancer patients. Optimal immunotherapy regimens might take the form of a novel single agent, such as a more potent/relevant checkpoint inhibitor (or a costimulatory molecule), or alternatively a combinatorial approach. For example, immunotherapy approaches can be combined with a standard treatment option, such as a cytotoxic chemotherapy or radiation. Such trials are ongoing, including an investigation of the combination of carboplatin, paclitaxel, and pembrolizumab (NCT02549209). Other combination options might include multiple immunotherapy agents, or an immunotherapy agent combined with a targeted agent.

These latter two combinatorial options are exciting prospects, but are also extremely complex undertakings. Lee et al. recently published a Phase I trial which included an investigation of the combination of durvalumab and cediranib in gynecologic and breast cancer patients. The trial included three uterine cancer patients. Although the absolute number of patients was small and specific information for the uterine cancer patients was not available, the data were promising as this combination was associated with a 50% objective response rate (16). Interestingly, there was no association found between PD-L1 positivity or tumor lymphocyte infiltration and response to treatment. While this might simply be another reflection of the yet unclear relationship between checkpoint inhibitors and PD-L1 positivity, this finding might also underscore the complexity of combination therapies. Although the mechanisms of action for cediranib and durvalumab are relatively well understood, far less is known about the mechanism of action when used in combination. The current hypothesis is that hypoxia induced by angiogenesis inhibitors leads to upregulation of PD-L1 expression (16), but these data suggest that this may not be the complete story. Only after clinical trials are completed that include both biomarker data and clinical response data will we more fully understand the complex mechanisms of these novel combination therapies.

From a safety standpoint, the side effects of both immunotherapy agents and targeted agents are also still being discovered. At best, we assume that side effects from combination therapies will reflect a combination of the side effects attributed to each of the single agents. At worst, however, combinations of therapies may potentiate side effects seen with each alone. As much is yet to be discovered in terms of short and long term side effects with these agents, ongoing registries of single agent and combination therapies—including standard of care, on trial, and off-label treatments—will be imperative to the comprehensive understanding of these novel agents.

Finally, from a patient selection standpoint, we again return to the issue of appropriate predictive biomarkers. In order to be a true predictive biomarker, patients must be screened for the relevant biomarker at the start of the trial, and then must undergo stratified randomization so as to address biomarker status. If not done, such as in the cases of the KEYNOTE-028 and KEYNOTE-045 trials, it is impossible to determine whether the biomarker is predictive (i.e., confers a likelihood of having a specific response to treatment), prognostic (i.e., confers a likelihood of having a specific survival outcome), both, or neither.

As we continue to increase our understanding of the mechanisms of action driving immunotherapy treatment in endometrial cancer patients, we will be able to more intelligently identify relevant biomarkers for increasingly complex therapeutic strategies. The challenge for future clinical trials will not only be to identify which single agents and combination strategies are most effective, but to better understand why these strategies are successful. Incorporating biomarker evaluations and translational endpoints into therapeutic trials will be critical to the efficient and effective pursuit of novel immunotherapy agents for endometrial cancer patients.

Conclusions

Although we have not yet identified which biomarkers are best for predicting response to checkpoint inhibitors and other immunotherapy agents, this landmark study by Ott et al. reminds us that we are making progress. Gynecologic cancer researchers and clinicians continue to
employ the lessons learned from research in other cancers. However, it is equally important to acknowledge possible distinct immune targets within the endometrial cancer tumor microenvironment and research in this area is of high priority. It is also important to investigate possible differences between primary and metastatic/recurrent tumors. These studies may ultimately improve the efficiency with which new therapeutic immune-oncology agents are able to reach this important and therapeutically-limited patient population.

Acknowledgements

None.

Footnote

Conflicts of Interest: AA Jazaeri has received research funding from AstraZeneca, Iovance Biotherapeutics, Pfizer, and Bristol Myers Squibb. He has served on Advisory Boards for Genentech-Roche, EMD-Serono. KC Kurnit has no conflicts of interest to declare.

References


Cite this article as: Kurnit KC, Jazaeri AA. Immunotherapy in endometrial cancer: who are the most appropriate patients? Transl Cancer Res 2017;6(Suppl 7):S1132-S1135. doi: 10.21037/tcr.2017.08.26