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Making urothelial carcinomas less immune to immunotherapy

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Metastatic urothelial carcinoma is associated with a poor prognosis, with a median overall survival of 15 months and 5-year survival rates of about 5%.[1, 2] Cisplatin-based chemotherapy is effective in the first-line metastatic setting, but responses are not long lasting. Additionally, second-line single agent chemotherapy has resulted in meager response rates.[3–6] However, through the recognition of the importance of the role of T-cell inhibitory pathways in regulating the immune response to tumors, promising cancer immunotherapies have now emerged. The development of novel monoclonal antibodies targeting immune checkpoints, such as cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and programmed death-1 (PD-1), have resulted in improved outcomes in a wide range of malignancies.[7–13] Recently, atezolizumab, a programmed death-ligand 1 (PD-L1) inhibitor, was granted regulatory approval for the treatment of locally advanced or metastatic urothelial carcinoma that has progressed on or following platinum-based chemotherapy. The success of atezolizumab has now ushered in a new era in the development of therapeutic agents for the management of urothelial carcinoma, focused on building on the early promise of immune-oncology agents.

It should not come as a surprise that patients with urothelial carcinoma respond to immune checkpoint inhibitors. Intravesicular Bacillus Calmette-Guerin (BCG) works, at least in part, for the treatment of non-muscle invasive bladder cancer (NMIBC) through local immune cell recruitment and stimulation.[14] BCG has been shown to reduce recurrence, delay progression, and improve survival in patients with NMIBC.[15] As a result, BCG was FDA-approved in 1990 for the treatment of NMIBC, representing one of the earliest cancer immunotherapies. More recently, Alexandrov et al. demonstrated that urothelial carcinoma had one of the highest somatic mutational burdens when compared with a variety of other malignancies, only superseded by melanoma and non-small cell lung cancer (NSCLC).[16] Increasing evidence suggests that the mechanism for the clinical responses to immune checkpoint inhibitors in malignancies with high mutational burden is through the production of a variety of tumor-specific neoantigens capable of eliciting a T-cell response.[8]

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As outlined in the accompanying review by Zibelman, Ramamurthy, and Plimack, several studies have now shown meaningful durable responses with limited toxicity to immune checkpoint inhibitors in patients with metastatic urothelial carcinoma.[17] These studies have been compelling enough to encourage development of the many checkpoint inhibitors in earlier disease settings, and this will be discussed by the accompanying review by Singh and Black.[18] Nonetheless, it is important to point out that, at best, objective response rates (ORR) are in the 30% range. Therefore, the majority of patients are not having radiographic evidence of response from immune checkpoint inhibition and the development of predictive biomarkers to identify likely responders and non-responders is critical. Sweis and Galsky will thoroughly discuss this issue in their accompanying review, but below we touch base on some of the key issues.[19]

To date, the expression of PD-L1, based on immunohistochemistry (IHC), in tumor or tumor infiltrating immune cells has been the most widely studied predictive biomarker of response with conflicting results. In early phase trials, ORRs to atezolizumab were assessed based on PD-L1 expression on IHC of tumor infiltrating immune cells using the Ventana SP142 assay. Patients with ≥ 5% infiltrating immune cells based on IHC staining were scored an IHC 2/3, those with < 5% infiltrating immune cells were scored an IHC 0/1. In the Phase I study, ORRs to atezolizumab were 43.3% and 11.4% in the IHC 2/3 and IHC 0/1 groups, respectively.[20] In cohort 2 of the IMvigor210 Phase II study, where patients had received previous platinum-based chemotherapy, the ORR to atezolizumab was 28% in patients with IHC 2/3 as opposed to 10% in those with IHC 0/1.[21] However, in the cisplatin-ineligible cohort (cohort 1) of the study, the ORR was only slightly higher in the IHC 2/3 patient compared to IHC 0/1 at 28% and 22%, respectively.[22] In the KEYNOTE-012 study, patients with ≥ 1% PD-L1 staining on tumor cells, had a 33% ORR in contrast to only 9% in < 1% PD-L1 staining patients treated with pembrolizumab using the 22C3 antibody on IHC.[23] Yet, the CheckMate 032 study did not demonstrate significant difference in ORR (24.0% vs. 26.2%) to nivolumab in PD-L1(+) and PD-L1(−) metastatic urothelial cancer patients.[24] For this study, PD-L1(+) was defined as ≥1% PD-L1 expression on tumor cells using the Dako PD-L1 antibody. Taken together, these studies suggest that while there may be some association with PD-L1+ staining and response, the results have been inconsistent. Currently, the Ventana SP 142 assay is approved for PD-L1 testing on tumor-infiltrating immune cells, but is not required prior to treatment with atezolizumab.

However, further investigation is necessary to identify the best assay, appropriate cut-off value to define PD-L1 positivity, and which cells (tumor vs. immune infiltrating or both) are most consistently associated with response. It may be that PD-L1 staining may not ever be a reliable predictive biomarker, as expression of PD-L1 has been shown to be dynamic and heterogeneous, resulting in potential for sampling error.[25–27] Another important point is that the negative predictive value of these assays may be low, as there were a significant proportion of patients in these studies that had responses to treatment and did not stain positive for PD-L1 in the tumor. Furthermore, these responses are frequently durable with limited toxicity in contrast to cytotoxic chemotherapy where responses are often brief and with substantial toxicity. Therefore, it is only logical that all eligible patients be treated with immune checkpoint inhibitors irrespective of PD-L1 staining status until these assays are improved or better predictive biomarkers are identified.

With the limitations of PD-L1 staining in predicting response, alternative potential biomarkers are currently under investigation. High mutational burden has been found to be associated with response to immune checkpoint blockade in melanoma and NSCLC.[8, 28] In advanced urothelial carcinoma, Rosenberg et al. examined the impact of mutational load on response to atezolizumab using the FoundationOne panel of 315 cancer genes. The authors found that the median mutation load was significantly higher in responders compared to non-responders, 12.4 versus 6.4 per megabase, respectively.[29] Additionally, when mutational load was split into quartiles, there was an association with overall survival in both cohorts of the IMvigor210 study.[30] Mutational load has some encouraging early data as a potential predictive biomarker, however, these results require validation, and there remain many unanswered questions. For example, there remain many patients with a high mutational load that don't respond and visa versa. Some cancers, like clear cell renal cell carcinoma have a very low mutational load and yet still respond to PD-1 inhibition.[11] One likely answer is that there are specific, recurrent genomic alterations that associate with response to immune-oncology agents, and this has been demonstrated in non-small lung cancer.[8] High mutational load may be an imperfect marker that just increases the likelihood that a patient has the right set of mutations and neoantigens that can confer response to immune-oncology agents.

Another potential predictive biomarker of response to immune checkpoint blockade is based on The Cancer Genome Atlas (TCGA) classification of tumor subtypes. In cohort 2 of the IMvigor 210 study, objective response rates to atezolizumab were highest in the luminal II subtype (34%), with the other subtypes having a combined response rate of 14%.[29] Of note, PD-L1 staining in tumor infiltrating immune cells and tumor cells was highest in the basal subtype, again indicating that PD-L1 may not be an effective predictive biomarker. Interestingly, luminal II and basal subtypes have high T-effector gene expression, however, the basal tumors also have high stromal gene expression as opposed to low stromal gene expression seen in the luminal II subtype.[30] Therefore, it is possible that the immune response is inhibited in the basal subtype as a result of the high stromal gene expression in the tumor microenvironment, and thus, may represent a potential target for combination therapy in the future.[30] Additionally, luminal I (papillary) subtypes have both low T-effector and stromal gene expression, but have been shown to be enriched for fibroblast growth factor receptor 3 (FGFR3) alterations.[31] Accordingly, patients with a luminal I subtype should be considered for clinical trials utilizing FGFR inhibitors. Research is also underway investigating the role of peripheral blood and tumor T-cell clonality as a response biomarker.[32] Ultimately, stratification of potential responders and non-responders will likely require a combination of these strategies or the development of novel biomarkers.

Moving forward, approaches combining immune checkpoint inhibitors with other treatment modalities will likely improve the response rates seen with immune checkpoint inhibitors alone. Indeed, in metastatic melanoma, patients treated with the combination of nivolumab and ipilimumab had a better ORR and progression free survival than ipilimumab alone, albeit at the expense of more grade 3/4 toxicity.[33] In preclinical models, other immune checkpoints, such as T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) and lymphocyte-activation gene 3 (LAG3), have been shown to have anti-tumor activity.[34–37] Monoclonal antibodies against TIM-3 and LAG3 are in early clinical development as monotherapy or in combination with PD-1 inhibitors (NCT03608268, NCT01968109, and

NCT02460224). An alternative approach would be to educate quiescent T-cells by inducing tumor cell death through treatment with chemotherapy or radiation therapy resulting in the release of tumor antigens for T-cell activation and migration to tumors, followed by treatment with immune checkpoint inhibitors. Similarly, vaccines carrying tumor-specific antigens can also be used to “prime” T-cells prior to administration of immune checkpoint inhibitors, with potential to increase ORR. Many of these approaches are discussed in great detail in the accompanying review by Park and Hahn.[38]

Finally, adoptive T-cell therapies, such as chimeric antigen receptor-modified T-cells (CAR-Ts) or tumor infiltrating lymphocyte (TIL) therapy, may provide durable responses in patients with urothelial carcinoma. Chimeric antigen receptors (CARs) are comprised of a single-chain antibody specific for a tumor antigen fused with intracellular signaling sequences. CD19+ CAR-Ts have been shown to have exceptional responses in patients with B-cell malignancies.[39, 40] Currently, a receptor tyrosine kinase-like orphan receptor 1 (ROR1) CAR-T cell trial is opening at our institution and will enroll patients with not only hematologic malignancies, but also patients with NSCLC and triple negative breast cancer (NCT02706392). This is also a particularly interesting target for patients with urothelial carcinoma, as ROR1 has been shown to be expressed on 43% of urothelial cancers.[41] With TIL therapy, patient tumor samples are harvested, dissected into small fragments, with subsequent proliferation of TILs in the presence of IL-2 in the laboratory. The TILs with the highest tumor recognition are then isolated and further expanded for subsequent infusion back to the patient after lymphodepleting chemotherapy.[42] TILs have been most studied and successful in metastatic melanoma, demonstrating response rates of 56% and a complete response in about 20% of patients.[43] Early studies of TIL therapy in urothelial cancer are currently underway at our institution.

In all, the FDA-approval of atezolizumab provides advanced urothelial carcinoma patients a new treatment option and the possibility of long-term durable, responses. Nonetheless, a minority of patients will respond to monotherapy with immune checkpoint inhibitors. Going forward, research efforts should focus on identification of predictive biomarkers of response to immune-oncology agents. Moreover, investigation of novel therapeutic strategies and combinations to build on the early success with checkpoint blockade is essential.

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