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Platinum Priority – Editorial

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Atezolizumab in "Real World" Patients: Do Phase 3b Trials Help Bridge the Gap Between Efficacy and Effectiveness?

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For more than 30 yr, platinum-based chemotherapy was the major treatment option for advanced urothelial cancer (UC). While platinum-based chemotherapy is associated with a relatively high response rate, response durations are generally short and the vast majority of patients experience disease progression. Immune checkpoint blockade (ICB) has changed the landscape of treatment for advanced UC [1]. Since 2016, five anti-PD-1/PD-L1 antibodies have received regulatory authority approval in the platinum-refractory setting; two of these agents have also been approved in the first-line setting for cisplatin-ineligible patients. While trials have established the efficacy of ICB in UC (ie, how these therapies perform in a highly selected clinical trial population), the effectiveness of ICB in UC (ie, how these therapies perform in the more heterogeneous population of patients with UC encountered in the real world) has remained largely unexplored. In this issue of *European Urology*, Sternberg et al. [2] provide data to begin to fill such knowledge gaps as ICB has moved rapidly from clinical trials to routine practice.

Atezolizumab, a humanized monoclonal PD-1 antibody, was initially approved by the US Food and Drug Administration in 2016, and then elsewhere, as monotherapy for patients with UC progressing despite prior platinum-based chemotherapy on the basis of promising safety and activity demonstrated in the IMVigor 210 study [3]. Despite not achieving the protocol-defined primary endpoint, the safety and activity of atezolizumab in the randomized phase 3 IMVigor 211 study were quite similar to those demonstrated in IMVigor 210 in a relatively similar patient population [4]. As is the case with most large phase 2 and 3 clinical trials, however, IMVigor 210 and 211 left gaps in knowledge regarding the balance of activity and safety of atezolizumab in patients ineligible for clinical trial enrollment on the basis of baseline patient- and tumor-specific characteristics. SAUL [2] is a single-arm, open-label, phase 3b study of atezolizumab that begins to expand our understanding of atezolizumab in such patients. Specifically, SAUL included patients with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 2, "well controlled" autoimmune disease, treated asymptomatic brain metastases, severely compromised renal function (creatinine clearance <30 but ≥ 15 ml/min), corticosteroid use at baseline, and nonurothelial histology. Indeed, approximately one-third of patients in the SAUL study would have been excluded from IMVigor 210 and 211, including 10% of enrolled patients with an ECOG PS of 2.

Despite inclusion of a much broader and heterogeneous patient population, atezolizumab reassuringly demonstrated similar activity and safety in the SAUL study as compared with the IMVigor 210 and 211 studies. However, what have we learned about atezolizumab in specific subsets of patients? Among the 101 enrolled patients with a PS of 2, atezolizumab had a very similar safety profile compared to that described in IMVigor 210 and 211, but lower activity and shorter survival were observed compared to patients with a better baseline ECOG PS. Whether the threshold for trying therapies with a better safety profile compared to our historical systemic agents should be lower for patients with poor ECOG PS, despite perhaps a similarly low likelihood of benefit, is a question with many implications that for now is best approached with careful patient–physician discussions and shared decision-making.

Among patients with "well controlled" autoimmune disease (14 psoriasis, 4 rheumatoid arthritis, 3 hypothyroid-

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ism or thyroiditis, and 2 ulcerative colitis), treatment-related adverse events were numerically more common than in the entire study population; grade and the objective response rate were similar. Concomitant corticosteroid use ($n = 40$) was also associated with a higher number of adverse events, although it is notable that the objective response rate was similar to that among patients not receiving corticosteroids at baseline.

The pathogenesis and optimal management of variant UC histologies have attracted increasing attention over the past decade. Observations from molecular profiling efforts indicate that at least some variant histologies probably represent entities of the broad spectrum and heterogeneity of UC rather than distinct disease entities. While SAUL was quite inclusive regarding enrollment of patients with variant UC histology, unfortunately only 18/950 enrolled patients had variant or mixed histologies (8 squamous cell carcinoma, 8 glandular, 7 collecting duct, and 6 neuroendocrine). While responses were seen in this subset of patients, the small sample size limited insights regarding the activity of atezolizumab in specific variant histologies.

The SAUL study has helped to expand the knowledge base regarding the use of atezolizumab for patients with UC and has expanded the generalizability of prior observations. However, major knowledge gaps remain and despite prospective clinical trials representing the gold standard of evidence development to inform treatment decisions in oncology, bridging the gap between the efficacy and effectiveness of novel treatment approaches probably requires collection and synthesis of data derived from diverse sources including those that even more closely reflect the real world (eg, data derived from electronic medical records).

Conflicts of interest: Vaibhav G. Patel has nothing to disclose. Matthew D. Galsky has served on advisory boards for Janssen, Dendreon, Merck, GlaxoSmithKline, Lilly, Astellas, Genentech, Bristol-Myers Squibb, Novartis, Pfizer, EMD Serono, AstraZeneca, Seattle Genetics, Incyte, Aileron Therapeutics, Dracen, and Inovio Pharmaceuticals; has received research funding from Janssen, Dendreon, Novartis, Bristol-Myers Squibb, Merck, AstraZeneca, and Genentech/Roche; and is a cofounder of RAPPTA Therapeutics.

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