The recent accelerated approval of the anti–programmed cell death ligand-1 (PD-L1) monoclonal antibody atezolizumab for metastatic urothelial bladder cancer (UBC) progressing during or after platinum-based chemotherapy\(^1\) signified a milestone in this disease, for which no new treatments had been approved since 1990.\(^2\) Approval was based on a single-armed, multinational study (IMvigor 210) in which 315 patients with UBC who had archived or fresh tissue available for PD-L1 staining were treated; the data showed an overall response rate (ORR) of 15% with significant durability, and it is noteworthy that the current approval does not require biomarker analysis before treatment. In the article that accompanies this editorial, Massard et al\(^3\) present data from a phase I/II trial of a second anti–PD-L1 monoclonal antibody (durvalumab); these data show that durvalumab also has significant activity in UBC, with an ORR of 31% in a population that was enriched for PD-L1–positive patients. Although the durvalumab trial included fewer patients (61) versus those in the phase II atezolizumab study (315), both studies included analyses of response on the basis of PD-L1 expression on either tumor cells (TCs) or immune cells (ICs), providing a unique opportunity to examine data regarding the potential predictive value of this biomarker.

It is important to recognize at the onset that the two studies used different antibodies for staining; IMvigor used the rabbit monoclonal antibody SP142 (Spring Biosciences, Pleasanton, CA), whereas the durvalumab study used the SP263 antibody (Ventana Medical Systems, Tucson, AZ). This is noteworthy because recent data show that different anti–PD-L1 antibodies may give different results, with a discordance of approximately 25% between the SP142 and the E1L3N antibodies.\(^4\) To date, cross-comparison of the SP142 and SP263 antibodies has not been performed. Studies of atezolizumab have generally found a better correlation between response and staining on ICs, and the IMvigor analysis focused on IC staining. Within the IMvigor study, the ORR was 26% in patients positive for PD-L1 in immune cells (IC2/3), versus approximately 10% in the IC0/1 patients. An ORR of 10% is in the range observed for chemotherapy regimens in this patient population,\(^2\) so, on the basis of its good tolerability profile, atezolizumab is likely to be administered to patients with both PD-L1–positive and PD-L1–negative bladder cancer in its on-label second-line setting.

Similarly, durvalumab responses in UBC correlated with PD-L1 expression on either tumor cells or immune cells. Considering TC only, the ORR was 47% for positive versus 22% for negative staining. IC staining also correlated with ORR, with responses of 57% versus 13%, respectively. The authors of the durvalumab study also explored a novel approach to the PD-L1 biomarker—integrating TC and IC expression to define composite positive and negative categories. In this new definition, PD-L1 positive was

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To contextualize these data, it is important to note that the durvalumab trial was enriched for PD-L1–positive patients; the first 20 patients were enrolled regardless of PD-L1 status, and the next 41 patients were required to have ≥ 5% staining on either TCs or ICs. The small number of patients involved adds further caution to interpreting these results. Indeed, the first data correlating PD-L1 status to response, obtained in a phase Ib study of the anti–programmed death-1 (PD-1) antibody atezolizumab in UBC; phase I data showed response rates often expected to enhance the apparent response rate. Second, as agents are developed from phase I to phase II, response rates often decrease. This phenomenon occurred for atezolizumab in UBC; phase I data showed

designated as ≥ 25% staining in either ICs or TCs, whereas PD-L1 negative specimens were negative (≤ 25%) in both the IC and TC compartments. Using this new composite definition led to a potential improvement in negative predictive value; patients whose samples were negative for PD-L1 in both compartments had an ORR of 0% (0 of 14), and patients positive for PD-L1 in either compartment had an ORR of 46%.

One possible explanation is that PD-L1 expression is not more powerful in terms of predictive value. One possible explanation is that the PD-1/PD-L1 interaction also occurs in the tumor-draining lymph nodes, which are rarely included in PD-L1 expression analyses. A second compelling explanation is intratumoral heterogeneity; tumors generally do not express PD-L1 uniformly throughout their mass. Thus, the incomplete sampling involved in obtaining needle biopsies on the basis of the angle and placement of a biopsy needle could yield positive, intermediate, or negative results from a single tumor sample. Other explanations include discordance between different tumor deposits within a patient (intratumoral heterogeneity), as well as discordance between the primary tumor and metastases, as has been reported for renal cell carcinoma and is likely present in other tumors as well. Finally, PD-L1 expression is controlled to a large degree by the cytokine milieu, meaning that levels can increase and decrease because of dynamic changes in the tumor microenvironment over time. Taken together, these observations make it clear that PD-L1 staining is unlikely to ever achieve perfect positive or negative predictive status and that other measures may add predictive value. In that regard, IMvigor 210 also explored tumor cell subtype, showing that responses were enriched in The Cancer Genome Atlas luminal type II subtype tumors. In addition, response rate in that study also correlated with mutational load. It will be interesting to see if further studies of durvalumab confirm these observations.

In terms of activity, the overall response rate from the durvalumab trial was 31%, and although impressive, those data should also be evaluated in context. As above, patients in this trial were enriched for PD-L1 expression; this enrichment would be expected to enhance the apparent response rate. Second, as agents are developed from phase I to phase II, response rates often decrease. This phenomenon occurred for atezolizumab in UBC; phase I data showed

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Antibodies to PD-1 or PD-L1 are postulated to function by blocking the inhibitory signal transmitted from TCs or ICs to the CD8 T cells that infiltrate a tumor; it might seem somewhat puzzling that PD-L1 expression is generally do not express PD-L1 uniformly throughout their mass.

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an ORR of 26% (17 of 65), with an ORR of 43% in PD-L1–positive patients (13 of 30). In the larger phase II experience, the all-comers’ ORR was 15%, and it was 26% in the PD-L1–positive group. So, it seems likely that larger studies of durvalumab in UBC might similarly show some decrease in response rates. Despite these caveats, the clinical activity of durvalumab in UBC is significant, and this agent is being further evaluated in the ongoing DANUBE trial, in which 525 patients with metastatic UBC will be randomly assigned to either durvalumab, standard platinum-based chemotherapy, or the combination of durvalumab plus the anti–CTLA-4 antibody tremelimumab (NCT02516241). This is a first-line trial, with an expected completion in September 2019.

In summary, UBC, which was previously somewhat neglected in terms of new drug approvals, is emerging as an exciting target for immunotherapy agents. In addition to the trials discussed here, a number of single-agent and combination immunotherapy approaches are under development. At least two strategies are under consideration. In one, combination regimens applicable to large patient pools, regardless of biomarker status, are being investigated. This im-personalized approach has been somewhat successful in melanoma, where the combination of anti–PD-1 (nivolumab) and anti–CTLA-4 (ipilimumab) has impressive activity and is equally active in PD-L1–positive and PD-L1–negative patients. Similar potent combinations could prove effective across the recognized bladder cancer subtypes. More likely, though, the nature of an individual patient’s tumor status will need to be taken into consideration, although the precise nature of which tumor characteristics (PD-L1 status, mutational load, The Cancer Genome Atlas subtype) are most important is not yet clear. Although responses to anti–PD-L1 are generally more prevalent in PD-L1–positive patients, meaningful responses, including complete responses, have been observed in PD-L1–negative patients in a variety of tumor types, including UBC, suggesting that a great deal of work lies ahead for the field.

Key points

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- In addition to the trials discussed here, a number of single-agent and combination immunotherapy approaches are under development.
- At least two strategies are under consideration. In one, combination regimens applicable to large patient pools, regardless of biomarker status, are being investigated.

References