Editorial Commentary

Use of atezolizumab in bacillus Calmette-Guérin-unresponsive high-risk non-muscle-invasive bladder cancer

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Comment on: Black PC, Tangen CM, Singh P, *et al.* Phase 2 Trial of Atezolizumab in Bacillus Calmette-Guérin-unresponsive High-risk Non-muscle-invasive Bladder Cancer: SWOG S1605. Eur Urol 2023;84:536-44.

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Treatment options for patients with high-risk non-muscle invasive bladder cancer (NMIBC) who are unfit or unwilling to undergo radical cystectomy remain limited (1). Due to the lack of treatment options for this group of patients, especially in light of the continued global bacillus Calmette-Guérin (BCG) shortage (2), both the American Urological Association and the Food and Drug Administration (FDA) deemed single-arm phase 2 or 3 trials to be sufficient for approval of alternative treatment options into patient care. As of December 2022, intravesical valrubicin, intravenous pembrolizumab, and intravesical nadofaragene firadenovec remain the only FDA-approved treatments for BCG-unresponsive high-risk NMIBC.

Stimulation of the programmed cell death receptor 1 (PD-1)/PD-ligand 1 (PD-L1) pathway is associated with tumor resistance following BCG treatment. The inhibition of PD-1 or PD-L1 maintains the function of effector T cells that are integral in cancer therapy. In the SWOG S1605 phase 2 clinical trial, Black *et al.* sought to investigate whether systemic atezolizumab (PD-L1 inhibitor) is a treatment option for BCG-unresponsive high-risk NMIBC (3). The study was a single-arm, phase 2 clinical trial that enrolled 178 patients from 68 sites across the US and Canada between February 2017 and July 2019. The investigators stratified the cohort into two groups: those with urothelial carcinoma in situ (CIS) and those with high-grade Ta (non-invasive) or T1 (invasion into lamina propria) without CIS. The co-primary endpoints were complete pathologic response for the CIS group evaluated by obligatory biopsy at 6 months and event-free survival at 18 months in all patients. Atezolizumab was administered every 3 weeks for up to 17 cycles, and complete response was defined as no high-grade urothelial cancer on biopsy and the absence of upper tract recurrence.

Among the CIS group, the authors reported that at 3 and 6 months, 32 patients [43%, 95% confidence interval (CI): 32–55%] and 20 patients (27%, 95% CI: 17–38%) had a complete response, respectively. Whereas, the 18-month event-free survival rate for patients with Ta/T1 disease was 49% (95 CI: 34–57%). The protocol of this phase 2 study included an interim futility analysis that required seven of the first 25 patients with CIS at 6 months to have a complete response to continue accrual. However, the trial was closed as only five patients had complete responses during the interim analysis.

Regarding the safety of atezolizumab, almost all patients (98%) experienced any grade adverse event, but only 14% had grade 3–4 adverse events throughout follow-up.

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Additionally, three other patients died in this study: two from immune-related causes and one from sepsis.

Although atezolizumab demonstrated efficacy in treating BCG-unresponsive high-risk NMIBC, the SWOG S1605 was considered a negative trial based on prespecified thresholds. However, the efficacy and safety profile of SWOG S1605 were comparable to those of KEYNOTE-057, another phase 2 study trial that led to FDA approval of pembrolizumab in the same setting. Pembrolizumab had a 41% complete response rate at the 3-month first evaluable biopsy (4). A unique aspect of the SWOG S1605 trial compared to others was implementing a 6-month mandatory biopsy. As alluded to by the authors, the role of an early mandatory biopsy still needs to be determined. The FDA recommends random biopsies at specific time points (e.g., 6 and 18 months), but does not enforce it (5). Whereas the International Bladder Cancer Group requires biopsy on the basis of visual inspection. Implementing mandatory biopsies could improve the comparability of studies by reducing the reliance on subjective cystoscopic evaluations. It is plausible that the 27% complete response rate seen in the SWOG S1605 would have been higher if a biopsy was left to the discretion of the treating urologist at the time of cystoscopy.

Several other immune checkpoint inhibitors that may show promise in treating BCG-refractory NMIBC are currently being studied (6). Sasanlimab is a subcutaneous PD-1 inhibitor that is currently being investigated in a phase 3 clinical trial (CREST) for high-risk NMIBC (7). Nivolumab is another agent currently being investigated within a phase 2 clinical trial focused on BCG-unresponsive high-risk NMIBC with CIS (with or without a papillary component). However, this study aims to combine nivolumab with either linrodostat mesylate or BCG in this patient population (8). It is worth noting that there are ongoing studies investigating the combination of immune checkpoint inhibitors with BCG for patients with high-risk NMIBC who are BCG-naïve or not BCG-unresponsive. These include KEYNOTE-676 (pembrolizumab), BladderGATE (atezolizumab), and POTOMAC (durvalumab) (9-11).

In addition to immune checkpoint inhibition, studies have used agents with different mechanisms of action, such as viral-based therapy, to treat BCG-refractory disease. For example, nadofaragene firadenovec is a recombinant adenovirus that carries the interferon *alfa-2b* gene that was found to be effective in this setting. In a phase 3 clinical trial that led to FDA approval of nadofaragene firadenovec, the complete response rate was 53% at 3 months, where nearly half of these patients remained disease-free at 1 year (12). CG0070 is another modified adenoviral agent that expresses granulocyte-macrophage colony-stimulating factor inducing malignant urothelial cell lysis (13). In a phase 2 trial, treatment with CG0070 led to a 50% complete response rate at 6 months (14).

While these drugs and others demonstrate potential in treating BCG-refractory NMIBC, investigators and clinicians must weigh this against cost and, more importantly, their safety profile. This is because a significant proportion of patients might experience moderate to severe adverse effects. Ultimately, improving patient care for bladder cancer hinges on adequate trial design and participation. The results from the well-designed study by Black *et al.* add valuable information to the rapidly evolving treatment paradigm of NMIBC and suggest that early mandatory biopsy should be considered in future studies assessing treatment efficacy in patients with CIS.

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