Editorial Commentary

Balancing risks and benefits in the treatment of patients with Bacillus Calmette-Guerin-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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Balancing risks and benefits are a daily challenge across all of healthcare in order to provide both effective and compassionate patient-centred care. This challenge is perhaps accentuated in the cancer setting and none more so than when managing patients with Bacillus Calmette-Guerin (BCG)-unresponsive non-muscle-invasive bladder cancer (NMIBC), a notoriously complex and heterogenous state of bladder cancer (BC). At this juncture, patients often describe 'standing on a cliff edge' with the most likely subsequent option being radical cystectomy (RC)—whilst cystectomy is effective and durable therapy, it remains life-changing surgery even in the robotic and neobladder era, and may be considered as 'over-treatment' in some cases (1). Cystectomy by whatever approach is also not without morbidity and mortality (2), and so some patients are simply not eligible for this option due to inherent comorbidities effecting overall fitness status; patient choice is limited due to a lack of viable alternative treatments. Hence, there has long been the need for effective bladder-preserving strategies following unsuccessful intravesical BCG treatment, and a plethora of research has been undertaken over the last 15 years with a number of novel agents receiving United States Food and Drug Administration (FDA) approval. We have previously reviewed this exciting and developing landscape whilst also highlighting that a lack of evidence from randomised studies is frequently a stumbling block to approval and subsequent adoption (3).

Black *et al.* discussed the paucity of randomised study data in their article describing the results of the SWOG S1605 study, a single-arm phase 2 trial of intravenous atezolizumab in patients with BCG-unresponsive high-risk NMIBC who were ineligible for or declined RC (4). Atezolizumab is an anti-programmed death-ligand 1 (PD-L1) agent with efficacy in circulating-tumour DNA (ctDNA)-positive muscle-invasive bladder cancer (MIBC) (5) and SWOG S1605 assessed both efficacy and safety of systemic atezolizumab monotherapy. Results showed complete response in 27% of carcinoma in situ (CIS), ±Ta/T1, patients at 6 months (13.5% at 18 months) and an event-free survival (EFS) rate of 49% at 18 months in Ta/T1 only patients. For EFS, an event was defined as the first occurrence of any of the following: biopsy-proven high-grade BC (including persistent CIS at 3 and/or 6 months); high-grade upper tract urothelial carcinoma; high-grade urothelial carcinoma of the prostatic urethra; muscle-invasive disease; clinical evidence of metastatic disease; or death due to any cause. These outcomes did not meet the prespecified thresholds and so SWOG S1605 was considered a negative trial by the investigators.

Regarding treatment-related adverse events (TRAEs), 98% of participants experienced an adverse event of any

grade, of which 86% were treatment-related (5). Grade 3–4 TRAEs were observed in 23 patients (14%). Another three patients (1.8%) died (grade 5) due to immune-related side-effects causing respiratory failure, myositis, and/or sepsis. Other trials of immuno-oncology agents also report high rates of adverse events; however, most are below grade 3 (6,7). Black *et al.* highlighted that the potential disease-free survival benefits of novel agents need to be balanced carefully with the potential risks, including drug toxicity even leading to death.

This study also analysed the efficacy of cystoscopy and cytology compared to biopsy for assessing complete response. Cytology had 48% sensitivity and 95% specificity at 6 months, whilst cystoscopy showed 84% sensitivity with 90% specificity (4). Slightly older trials relied on cystoscopy and cytology which is more likely to miss small volume disease recurrence (8). More recent studies have now been incorporating mandatory 6-month biopsies into their protocols for assessing complete response (5,9), and SWOG S1605 reinforces the potential value of mandatory biopsy in trials where cystoscopic appearances are subjective—a very common occurrence in the management of all BC patients (10).

Analogous to the SWOG S1605 study, there are other immune checkpoint inhibitors that have been investigated (with/without BCG) for high-risk NMIBC (11-13). Akinsola *et al.* commented on the wider treatment options for BCG-unresponsive high-risk NMIBC, mentioning the significant risk profiles for alternative agents (9). And so how do we 'square this circle' in order to better balance risk and benefit for NMIBC patients? Notably, in the setting of adjuvant therapy for patients with operable muscle-invasive bladder cancer (MIBC), the IMvigor010 trial demonstrated a survival benefit for atezolizumab only in patients who were ctDNA-positive, with ctDNA-positivity associated with the Basal-Squamous molecular subtype of MIBC (14). With such findings, and the instigation of molecular subtype-based randomised studies in MIBC (15,16), then molecular subtyping- and ctDNA-based stratification may now need to be considered in the BCG-unresponsive NMIBC setting in order to improve patient selection/stratification and to aid the determination of risk and benefit for individuals. Such NMIBC subtyping approaches are underway (17,18) and sophisticated liquid biopsy assays will become increasingly affordable (19). In parallel, biological readouts of the patient and tumour factors which influence immuno-oncologic toxicity in this population should also be explored. Albeit challenging, leveraging technological advancements to analyse epigenetic modifications induced by immune-mediated mechanisms (or otherwise) is within feasible reach (20). Hence, we encourage the BCG-unresponsive NMIBC trials community to optimally utilise the existing associated biospecimens in order to inform the design and conduct of future trials.

Nevertheless, with such novel therapeutic development and trials activity in this setting, alongside innovations in molecular subtyping and liquid biopsies, we are optimistic that safe and effective 'personalized' bladder-sparing regimens will be derived and implemented for BCG-unresponsive NMIBC patients in the near future.

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