Bladder Cancer Research Review™

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Issue 16 - 2025

In this issue:

Abbreviations used in this issue:

ADC = antibody-drug conjugate; **AE** = adverse event; **BCG** = Bacillus Calmette-Guérin; **DFS** = disease-free survival; **EFS** = event-free survival; **HR** = hazard ratio; **MFS** = metastasis-free survival; **(N)MIBC** = (non-) muscle-invasive bladder cancer; **ORR** = objective response rate; **OS** = overall survival; **PFS** = progression-free survival; **T-DXd** = trastuzumab deruxtecan; **TMB** = tumour mutational burden.

Welcome to the latest issue of Bladder Cancer Research Review

We begin with the practice-changing NIAGARA trial, which demonstrated that the addition of perioperative durvalumab to neoadjuvant chemotherapy led to significant and clinically meaningful improvements in EFS and OS among patients with operable MIBC. This is followed by the AMBASSADOR trial which found that after radical cystectomy, patients with high-risk MIBC experienced significantly longer DFS with adjuvant pembrolizumab versus observation. The next paper reports on a phase 2 pilot trial in which tislelizumab plus low-dose nab-paclitaxel showed promising antitumour activity in extensive, very high-risk NMIBC, with a tolerable safety profile. We conclude with a fascinating analysis of the IMvigor210 and IMvigor211 trials, which revealed that patients who received concomitant antihistamines during immunotherapy achieved significantly improved OS, PFS and cancer-specific survival; these findings deserve further investigation in future RCTs.

I hope you find this update in bladder cancer research interesting and informative, and I always look forward to reading your comments.

Warm regards,

Associate Professor Arun Azad
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Perioperative durvalumab with neoadjuvant chemotherapy in operable bladder cancer

Authors: Powles T et al., for the NIAGARA Investigators

Summary: The open-label, phase 3 NIAGARA trial randomised cisplatin-eligible patients with MIBC 1:1 to either durvalumab plus gemcitabine and cisplatin every 3 weeks for 4 cycles, followed by radical cystectomy and adjuvant durvalumab every 4 weeks for 8 cycles (durvalumab arm; n=533) or neoadjuvant gemcitabine and cisplatin followed by radical cystectomy alone (control arm; n=530). At 24 months, patients in the durvalumab arm achieved significantly higher estimated EFS versus controls (67.8% vs. 59.8%; HR 0.68; 95% CI 0.56—0.82; p<0.001), with significantly improved 24-month OS (82.2% vs. 75.2%; HR 0.75; 95% CI 0.59—0.93; p=0.01). Grade 3-4 treatment-related AEs occurred in 40.6% and 40.9% of patients in the durvalumab and control arms, respectively, and 0.6% in each group experienced treatment-related AEs resulting in death. A radical cystectomy was undertaken by 88.0% and 83.2% of patients in the durvalumab and control arms, respectively.

Comment: The NIAGARA trial is a practice-changing study, looking at the benefit of durvalumab for MIBC. In this randomised phase 3 trial of more than 1000 patients, the experimental group was randomised to receive neoadjuvant durvalumab plus cisplatin and gemcitabine every 3 weeks for 4 cycles, followed by radical cystectomy and then durvalumab every 4 weeks for 8 cycles. The control group received neoadjuvant gemcitabine and cisplatin and then radical cystectomy alone. There was a significant improvement in the primary endpoint of event for survival at 24 months, favouring the durvalumab group by nearly 8%. OS also significantly favoured the durvalumab group, with a 7% improvement at 24 months. Treatment-related AEs were similar for the two groups. 88% of patients in the durvalumab group underwent a radical cystectomy. This is truly a practice-changing study and pending approval, and reimbursement will lead to the widespread use of durvalumab in MIBC in patients receiving neoadjuvant cisplatin and gemcitabine. One key question will be whether to re-challenge with immunotherapy in patients who have a relapse post their initial treatment. Also, what do we do in patients who are not suitable or refuse to have cisplatin-based chemotherapy…..?

Reference: N Engl J Med. 2024;391(19):1773-86
Abstract

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Adjuvant pembrolizumab versus observation in muscle-invasive urothelial carcinoma

Authors: Apolo AB et al.

Summary: This phase 3 AMBASSADOR trial explored the role of adjuvant pembrolizumab in patients with high-risk MIBC following radical cystectomy. Eligible patients (n=702) were randomised 1:1 to pembrolizumab every 3 weeks for 1 year (n=354) or observation (n=348). At the time of data cut-off, at a median follow-up of 44.8 months, patients in the pembrolizumab arm achieved significantly longer median DFS versus observation (44.8 vs. 29.6 months; HR 0.73; 95% CI 0.59—0.90; p=0.003). A higher proportion of those treated with pembrolizumab experienced grade ≥3 AEs than those in the observation arm (50.6% vs. 31.6%, respectively).

Comment: The AMMBASADOR trial looked at the efficacy of pembrolizumab in high-risk MIBC after radical cystectomy. In this phase 3 trial of more than 700 patients, the experimental group received pembrolizumab every 3 weeks for 1 year, or observation, after undergoing radical cystectomy. The trial was clearly positive, with more than a doubling of median DFS in the pembrolizumab group. Grade 3 or higher AEs were higher in the pembrolizumab group. In patients who are not suitable or fit for cisplatin-based chemotherapy, or who do not wish to receive it, pembrolizumab would appear to be a viable option; albeit, we await final OS data from this trial.

Reference: N Engl J Med. 2025;392(1):45-55
Abstract

Phase II pilot trial of tislelizumab plus low-dose nab-paclitaxel for extensive very high-risk non-muscle-invasive bladder cancer

Authors: Qie Y et al.

Summary: These researchers explored the safety and efficacy of tislelizumab combined with low-dose nab-paclitaxel in patients with NMIBC and visually incomplete resection and/or high-volume, high-grade T1 tumours who were ineligible for or declined radical cystectomy. Eligible patients (n=63) were administered intravenous tislelizumab and nab-paclitaxel every 3 weeks. At a follow-up of ≈3 months, 62.7% (95% CI 49.1—75.0) of patients achieved a CR (primary endpoint), and the 24-month sustained response rate was 96.3% (95% CI 89.4—100.0). A total of nine patients (14%) experienced grade 3-4 treatment-related AEs, and no fatal events occurred.

Comment: The TRUCE-02 trial was a single-arm, phase 2 trial of 63 patients with high-grade T1 NMIBC who were ineligible for or declined radical cystectomy. The trial looked at the combination of intravenous tislelizumab and nab-paclitaxel every 3 weeks, with the primary endpoint being CR. Thirty-seven of 63 patients (or around 63%) achieved a CR, with a very high 24-month sustained response rate of 96%. Grade 3-4 treatment related AEs only occurred in 14% of patients. This combination looks very promising for high-grade T1 NMIBC. Of course, whether this would be better than BCG is another matter, and a head-to-head trial would be required before this could be considered a standard of care. Likewise, radical cystectomy remains a standard of care for these patients who are fit enough for surgery.

Reference: Clin Cancer Res. 2025;31(5):839-47
Abstract

Trastuzumab deruxtecan with nivolumab in HER2-expressing metastatic breast or urothelial cancer

Authors: Hamilton E et al.

Summary: This paper reports on results from the phase 1b DS8201-A-U105 study, which examined the use of trastuzumab deruxtecan (T-DXd) plus nivolumab in patients with HER2-expressing metastatic breast or urothelial cancer. In part 1, investigators identified T-DXd 5.4mg/kg plus 360mg nivolumab every 3 weeks as the recommended dose for expansion. Part 2 assessed efficacy and safety in patients with HER2-positive metastatic breast cancer (n=32; cohort 1), HER2-low metastatic breast cancer (n=16; cohort 2), HER2-high metastatic urothelial cancer (n=30; cohort 3) and HER2-low metastatic urothelial cancer (n=4; cohort 4). At the time of data cut-off, the confirmed ORRs (primary endpoint) were 65.6% in cohort 1, 50.0% in cohort 2 and 36.7% in cohort 3. Due to the small sample size, ORR could not be assessed in cohort 4. The most common treatment-emergent AE across cohorts 1, 2, 3 and 4 was nausea (55.2%, 62.5%, 73.3%, 75.0%, respectively), and adjudicated drug-related interstitial lung disease/pneumonitis occurred in 20.7% of cohort 1, 0% of cohort 2 and 20.0% of cohort 3, with one death occurring in each of cohorts 1 and 3.

Comment: This phase 1b study investigated the antibody-drug conjugate (ADC), T-DXd, plus nivolumab in patients with HER2-expressing metastatic breast cancer and metastatic urothelial cancer. Four cohorts were recruited in dose expansion: HER2-positive metastatic breast cancer (cohort 1), HER2-low metastatic breast cancer (cohort 2), HER2-high metastatic urothelial cancer (cohort 3) and HER2-low metastatic urothelial cancer (cohort 4). Efficacy was very encouraging, with confirmed ORRs for cohorts 1 to 4 being 65.6%, 50.0%, 36.7%, and not assessed due to small sample size, respectively. Toxicity was a major concern, with drug-related interstitial lung disease/pneumonitis rates of 20% in cohorts 1 and 3, including one death in each of these cohorts. This combination holds promise, but as with many other ADCs, pulmonary toxicity is worrying.

Reference: Clin Cancer Res. 2024;30(24):5548-58
Abstract

Bladder Cancer Research Review™

Independent commentary by Associate Professor Arun Azad

Associate Professor Arun Azad is a medical oncologist and translational researcher based at Peter MacCallum Cancer Centre and University of Melbourne with a subspecialist interest in urological malignancies.

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CI = confidence interval; **HR** = hazard ratio; **mOS** = median overall survival; **mPFS** = median progression-free survival; **OS** = overall survival; **PFS** = progression-free survival; **Q2W** = every 2 weeks; **Q3W** = every 3 weeks; **Q4W** = every 4 weeks; **TGA** = Therapeutic Goods Administration; **TRAE** = treatment-related adverse event.

References: 1. OPDIVO® (nivolumab) approved Product Information (https://rss.medsinfo.com.au/bq/pi.cfm?product=bqpopdiv). **2.** van der Heijden *et al. N Engl J Med* 2023;389:1778–89.

Disitamab vedotin plus toripalimab in patients with locally advanced or metastatic urothelial carcinoma (RC48-C014)

Authors: Zhou L et al.

Summary: These investigators conducted an open-label, phase 1b/2 study of disitamab vedotin plus toripalimab in patients with untreated or chemotherapy-refractory locally advanced/metastatic urothelial cancer. In the dose escalation phase, the recommended phase 2 dose was identified as disitamab vedotin 2.0mg/kg plus toripalimab 3.0mg/kg every 2 weeks (primary endpoint), and no dose-limiting toxicity was observed. In the dose-expansion phase, 35 patients received treatment. At the time of data cut-off, the confirmed ORR was 73.2%, with a median PFS of 9.3 months, and median OS of 33.1 months. Treatment-related AEs most commonly included increased aspartate aminotransferase (65.9%), increased alanine aminotransferase (63.4%) and peripheral sensory neuropathy (63.4%). More than half of all patients (51.2%) experienced grade ≥3 treatment-related AEs (γ-glutamyltransferase increase 12.2%; asthenia 9.8%; alanine aminotransferase increase 7.3%), and there was one death due to pneumonitis.

Comment: Another ADC plus immune checkpoint inhibitor combination. This time, a phase 1b/2 study looking at disitamab vedotin plus toripalimab in patients with locally advanced or metastatic urothelial carcinoma. Efficacy seemed very impressive, with a confirmed ORR of 73.2%, median PFS of 9.3 months, and median OS of 33.1 months. Toxicity was once again a concern, with grade 3 or higher treatment-related AEs in 51%, including one fatal episode of pneumonitis. Nevertheless, this combination looks very promising and is worthy of further investigation.

Reference: Ann Oncol. 2025;36(3):331-9
Abstract

Phase 2 study of preoperative tislelizumab in combination with low-dose nab-paclitaxel in patients with muscle-invasive bladder cancer

Authors: Wu Z et al.

Summary: The efficacy and safety of tislelizumab combined with low-dose nab-paclitaxel in MIBC were examined in the phase 2, single-arm TRUCE-01 trial. Eligible patients (n=62) with T2-4a N0/X M0 MIBC tumours and predominant urothelial histology received intravenous tislelizumab plus nab-paclitaxel before surgical assessment. A clinical CR (primary endpoint) was achieved by 25/48 patients (52%) in the efficacy analysis set, and 6/62 patients (9.7%) in the safety set experienced grade ≥3 treatment-related AEs.

Comment: The TRUCE-01 trial combined tislelizumab with low-dose nab-paclitaxel in patients with MIBC. In this single-arm phase 2 study that included 62 patients, 25 (52%) met the primary endpoint of CR. Treatment also appeared to be well tolerated, with only 9.7% of patients having grade 3 or higher treatment-related AEs. These data certainly support further evaluation, but with the phase 3 NIAGARA trial changing the treatment landscape of MIBC, it is not clear how this combination would be incorporated into routine clinical practice.

Reference: Eur Urol Oncol. 2025;8(1):66-72
Abstract

Nivolumab adjuvant to chemo-radiation in localized muscle-invasive urothelial cancer

Authors: Fortuna GMG et al.

Summary: This article reports on the primary analysis of NEXT, a multicentre, single-arm, phase 2, investigator-initiated trial evaluating the efficacy and tolerability of nivolumab adjuvant to chemo-radiation in patients with localised/locoregional urothelial cancer. Eligible patients (n=28) were administered nivolumab every 4 weeks for up to 12 cycles, adjuvant to chemo-radiation. At 2 years, the failure-free survival rate (primary endpoint) was 33.2% (95% CI 18.5—59.6), and patients with ≤2 high-risk factors achieved significantly longer failure-free survival than those with ≥3 high-risk factors (45.2 vs. 8.2 months; p=0.0024). OS was significantly improved among patients with cfDNA copy number instability scores ≤25 prior to initiating adjuvant nivolumab and at cycle 4, compared to those with scores ≥26 (49.6 vs. 20.5 months; p=0.0024). Treatment-related AEs occurred in 18 patients (64.3%) and three patients experienced grade 3 treatment-related AEs.

Comment: The NEXT trial was a single-arm phase 2 study evaluating adjuvant nivolumab in muscle-invasive urothelial cancer treated with chemo-radiation. Only 33% of patients met the primary endpoint of failure-free survival at 2 years. These results are underwhelming, and it is hard to see this treatment approach moving forwards, to be honest.

Reference: J Immunother Cancer. 2025;13(3):e010572
Abstract

Phase II trial of risk-enabled therapy after neoadjuvant chemotherapy for muscle-invasive bladder cancer (RETAIN 1)

Authors: Geynisman DM et al.

Summary: The phase 2 RETAIN 1 trial aimed to identify patients with MIBC who were suitable for cystectomy-sparing active surveillance, via clinical staging and biomarker selection. Eligible patients with cT2-T3N0M0 MIBC (n=70) received neoadjuvant chemotherapy, after tumour specimens were analysed for *ATM*, *ERCC2*, *FANCC* and *RB1* alterations. Overall, 47% of patients harboured ≥1 mutation, and 36% of these patients achieved cT0 after-neoadjuvant chemotherapy and thus commenced active surveillance. At a follow-up of 40 months, the entire study population achieved a 2-year metastasis-free survival (MFS) rate of 72.9% (active surveillance 2-year MFS 76.0%; remaining patients 71.1%). Among those in the active surveillance group, 48% avoided cystectomy without metastasis, and 68% showed some recurrence. The 2-year OS rate of the entire population was 84.3%; those in the active surveillance group achieved a 2-year OS rate of 84.3%, versus 88.0% in the remaining patients.

Comment: Patients with MIBC who undergo neoadjuvant chemotherapy frequently ask if a radical cystectomy will be required if they achieve an excellent/complete response. The RETAIN 1 trial was a single-arm, phase 2, non-inferiority trial that used a combination of biomarker analysis and clinical staging to identify patients who might be suitable for active surveillance instead of a radical cystectomy. 36% of patients began active surveillance, of whom 48% did not undergo radical cystectomy. However, the study did not meet its primary endpoint with respect to 2-year MFS, and the jury remains out, in my opinion, on whether radical cystectomy can be avoided in this setting.

Reference: J Clin Oncol. 2025;43(9):1113-22
Abstract

Association of tumor mutational burden and PD-L1 with the efficacy of pembrolizumab with or without chemotherapy versus chemotherapy in advanced urothelial carcinoma

Authors: Fléchon A et al.

Summary: Prior data from KEYNOTE-361 showed no PFS or OS benefit with the addition of pembrolizumab to chemotherapy in advanced urothelial carcinoma. The aim of this prespecified exploratory analysis was to examine whether tumour mutational burden (TMB) and PD-L1 combined positive score were associated with outcomes for pembrolizumab monotherapy, pembrolizumab plus chemotherapy, or chemotherapy alone in advanced urothelial carcinoma. TMB and PD-L1 data were available for 82.6% and 100% of all patients, respectively. Continuous TMB had positive associations in the pembrolizumab monotherapy arm with PFS (p<0.001), OS (p=0.007) and ORR (p<0.001), positive associations in the pembrolizumab plus chemotherapy arm with PFS (p=0.007) and OS (p=0.010) and positive associations in the chemotherapy alone arm with OS (p=0.040). The improvements in PFS and OS with the addition of pembrolizumab were greatest for the subgroup of patients with TMB ≥175 mutations/exome and PD-L1 combined positive score ≥10.

Comment: Another trial looking for an elusive biomarker associated with outcomes from immune checkpoint inhibitors; this time the phase 3 KEYNOTE-361 study that did not meet its dual primary endpoints of PFS or OS with first-line pembrolizumab plus chemotherapy versus chemotherapy in advanced urothelial carcinoma. Continuous TMB was positively associated with OS for pembrolizumab monotherapy, pembrolizumab plus chemotherapy and chemotherapy, indicating that it is a prognostic rather than predictive factor. In a subgroup with a very high cut-off of 175 mutations/exome, TMB was associated with better outcomes from pembrolizumab alone or with chemotherapy, versus chemotherapy alone. These results are interesting, but as this was a negative study, it is hard to see the biomarker data having any traction - particularly as TMB was only predictive of benefit from pembrolizumab in the subgroup with a very high score.

Reference: Clin Cancer Res. 2024;30(23):5353-64
Abstract

Concomitant antihistamine administration is associated with improved survival outcomes in patients with locally advanced or metastatic urothelial carcinoma treated with atezolizumab

Authors: Fallara G et al.

Summary: Individual participant data from the IMvigor210 and IMvigor211 trials were evaluated to explore the associations between antihistamine use during immunotherapy and treatment outcomes in patients with metastatic urothelial cancer. The analysis included 896 patients with metastatic urothelial cancer from IMvigor210 (single-arm; second-line atezolizumab) and IMvigor211 (randomised; second-line atezolizumab vs. chemotherapy), of whom 17% were administered concomitant antihistamines. Those who received antihistamines achieved significantly improved OS than those who did not (HR 0.59; 95% CI 0.47—0.74; p<0.001), with significantly longer PFS (HR 0.70; 95% CI 0.57—0.87; p=0.001) and cancer-specific survival (HR 0.58; 95% CI 0.45—0.75; p<0.001). The improvements in OS and cancer-specific survival remained significant after sensitivity analyses to exclude patients who experienced AEs (OS HR 0.71; 95% CI 0.52—0.94; p=0.021; cancer-specific survival HR 0.78; 95% CI 0.59—0.98; p=0.031).

Comment: An intriguing study that looked at the benefit of concomitant antihistamine use in two metastatic urothelial cancer trials: the IMvigor210 (phase 2 single-arm trial on second-line atezolizumab) and IMvigor211 trials (phase 3 randomised trial on second-line atezolizumab vs. chemotherapy). Pre-clinical data suggest that antihistamines may have beneficial effects in combination with immune checkpoint inhibitors through several mechanisms, including reversing macrophage immunosuppression and reactivating cytotoxic T-cells. Patients receiving antihistamines had longer OS (HR 0.59; p<0.001), PFS (HR 0.70; p=0.001) and cancer-specific survival (HR 0.58; p<0.001) compared to those who had not used antihistamine drugs. These are quite remarkable results, and in my opinion, warrant further evaluation in a randomised trial.

Reference: Urol Oncol. 2025;43(3):188.e9-17
Abstract

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