

Bladder Cancer Research Review™

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Issue 15 - 2024

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Abbreviations used in this issue:

ADC = antibody-drug conjugate; AE = adverse event;
BCG = Bacillus Calmette-Guérin; CR = complete response;
ctDNA = circulating tumour DNA; DCR = disease control rate;
DFS = disease-free survival; HR = hazard ratio;
(N)MIBC = (non-)muscle-invasive bladder cancer; OR = odds ratio;
ORR = objective response rate; OS = overall survival;
PFS = progression-free survival; RFS = recurrence-free survival;
TURBT = transurethral resection of bladder tumour.

Welcome to the latest issue of Bladder Cancer Research Review

We begin with an exploratory analysis of the KEYNOTE-361 trial, which suggests that baseline ctDNA is indicative of response and survival among patients with metastatic urothelial cancer treated with pembrolizumab. This is followed by the SWOG S1011 trial, which found that compared to standard lymphadenectomy, extended lymphadenectomy did not lead to improved survival among patients with MIBC undergoing radical cystectomy, and that it was in fact associated with higher morbidity and mortality. The next paper reports on KEYNOTE-057, a single-arm, phase 2 study in which pembrolizumab showed encouraging efficacy among patients with BCG-unresponsive, high-risk NMIBC who were ineligible for or declined radical cystectomy, with a manageable toxicity profile. We conclude with a phase 1b trial which found that nivolumab without and with lirilumab before radical cystectomy was feasible and well tolerated in patients with MIBC who were unable to receive cisplatin-based chemotherapy, with lower pathologic response rates than other neoadjuvant immunotherapy trials and promising survival rates.

I hope you find these and the other articles in this review interesting and informative, and I always look forward to reading your feedback.

Warm regards,

Associate Professor Arun Azad

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Pembrolizumab for advanced urothelial carcinoma: exploratory ctDNA biomarker analyses of the KEYNOTE-361 phase 3 trial

Authors: Powles T et al.

Summary: The phase 3 KEYNOTE-361 trial compared pembrolizumab with and without chemotherapy, versus chemotherapy alone, in patients with metastatic urothelial cancer; however, the efficacy thresholds in the trial did not reach statistical significance. In order to determine possible biomarkers of response, this retrospective analysis examined the relationships between clinical outcomes and pre- and post-treatment ctDNA between patients treated with pembrolizumab (n=130) or chemotherapy (n=130). Among those who received pembrolizumab, baseline ctDNA was associated with best overall response (p=0.009), PFS (p<0.001) and OS (p<0.001), whereas no associations were observed among patients treated with chemotherapy.

Comment: ctDNA has shown promise as a biomarker in early-stage urothelial cancer, but its utility in metastatic disease remains unclear. In this study, a retrospective analysis was conducted in a subset of patients enrolled in the phase 3 KEYNOTE-361 study to correlate pre- and post-treatment ctDNA levels with clinical outcomes on pembrolizumab (± chemotherapy) versus chemotherapy. Interestingly, baseline ctDNA was associated with outcomes including best overall response, PFS and OS in patients treated with pembrolizumab, but not chemotherapy. These intriguing results suggest that ctDNA may be both a prognostic and predictive biomarker in metastatic urothelial cancer, but they require further validation.

Reference: *Nat Med.* 2024;30(9):2508-16

[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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Standard or extended lymphadenectomy for muscle-invasive bladder cancer

Authors: Lerner SP et al., for the SWOG S1011 Trial Investigators

Summary: These investigators randomly assigned 592 eligible patients undergoing radical cystectomy with localised muscle-invasive bladder cancer (MIBC; T2-T4a; N0, N1 or N2) to undergo bilateral standard lymphadenectomy (dissection of lymph nodes on both sides of the pelvis; n=292) or extended lymphadenectomy (including removal of common iliac, presciatic and presacral nodes; n=300). The study was carried out across 27 sites in Canada and the US, and 57% of patients had received neoadjuvant chemotherapy. At a median follow-up of 6.1 years, extended lymphadenectomy did not lead to improved DFS compared to standard lymphadenectomy (primary outcome; 5-year DFS 56% vs. 60%, respectively; HR 1.10; 95% CI 0.86—1.40; p=0.45) or OS (5-year OS 59% vs. 63%; HR 1.13; 95% CI 0.88—1.45). There was a higher rate of grade 3-5 AEs among patients in the extended lymphadenectomy arm (54% vs. 44%), and higher rate of death within 90 days of surgery (7% vs. 2%).

Comment: A point of contention in the surgical management of many localised and locally advanced cancers is whether to perform an extended lymphadenectomy versus a standard lymphadenectomy. Typically, extended lymphadenectomy has not shown superior oncological outcomes in most, if not all cancers, with an increase in morbidity. In this study, patients with MIBC undergoing cystectomy were randomised to extended lymphadenectomy versus standard lymphadenectomy. No improvement in OS was seen with extended lymphadenectomy, which also led to higher perioperative morbidity and mortality. In my opinion, these are practice-shaping results and should mean that patients undergoing cystectomy for MIBC undergo a standard lymphadenectomy.

Reference: *N Engl J Med* 2024;391:1206-16

[Abstract](#)

Pembrolizumab monotherapy for high-risk non-muscle-invasive bladder cancer without carcinoma in situ and unresponsive to BCG (KEYNOTE-057)

Authors: Necchi A et al.

Summary: KEYNOTE-057 is a single-arm, multicentre, phase 2 trial which assessed the activity and safety of pembrolizumab monotherapy in patients with BCG-unresponsive, high-risk non-muscle-invasive bladder cancer (NMIBC) who were ineligible for or declined radical cystectomy. Previous results from cohort A (patients with carcinoma in situ, with or without papillary tumours) showed a 3-month CR rate of 41%, with 46% of responders maintaining a response for ≥ 12 months. This paper reports on cohort B, in which 132 patients with papillary tumours (high-grade Ta or any-grade T1) without carcinoma in situ were administered pembrolizumab 200mg intravenously every 3 weeks, for up to 35 cycles. At a median follow-up of 45.4 months, patients had received a median of 10 cycles of pembrolizumab, and five patients (4%) remained on treatment. The 12-month DFS rate (primary endpoint) was 43.5% (95% CI 34.9—51.9). It was commented that pembrolizumab monotherapy showed manageable toxicity; 14% of patients experienced grade 3 or 4 treatment-related AEs, with serious treatment-related AEs occurring in 13%. There were no treatment-related deaths.

Comment: Optimising outcomes in BCG-unresponsive NMIBC remains a huge challenge. KEYNOTE-057 was a multicentre, phase 2, single-arm trial evaluating 2 years of pembrolizumab for BCG-unresponsive, high-risk NMIBC with papillary tumours (high-grade Ta or any-grade T1) without carcinoma in situ. In 132 patients, the 12-month DFS was 43.5% and treatment appeared to be well tolerated, with 14% experiencing grade 3 or 4 treatment-related AEs and no treatment-related deaths. Overall, these are very promising results, but they need validation in a randomised trial.

Reference: *Lancet Oncol.* 2024;25(6):720-30

[Abstract](#)

Impact of pathologic re-review on grade, clinical stage, and risk stratification for patients with non-musical invasive bladder cancer

Authors: Campbell RA et al.

Summary: This study was conducted at the Cleveland Clinic in the US, whereby pathologic re-reviews of TURBT specimens are frequently carried out. The aim of this study was to evaluate how often a pathologic re-review of specimens initially assessed at other institutions altered the grade, stage and risk stratification of NMIBC. Researchers identified a total of 173 eligible patients who underwent TURBT between 2021-22. Overall, re-review of TURBT pathology by a dedicated genitourinary pathologist resulted in a change in grade and/or stage in 21% of patients with NMIBC. Among those with $< cT2$ disease (n=113; 12 benign, 10 Tis, 46 Ta, 45 T1), 10% of patients were upgraded and 7% were downgraded, while clinical stage was increased in 5% and decreased in 5%. Among patients with $cT2$ disease (n=60), no cases were upstaged and 5% were downstaged, while risk stratification was increased in 13% and decreased in 8%. Of note, four cases which were initially classified as high-grade urothelial carcinoma were reclassified as benign disease.

Comment: An interesting, albeit single-centre retrospective study examining the impact of pathological re-review in NMIBC. Getting pathological staging as accurate as possible is essential in NMIBC, and can have implications for the use of intra-vesical therapy such as BCG and the need for cystectomy. The authors found that review by a dedicated genitourinary pathologist led to a change in risk stratification in more than 20% of cases. Intriguingly, four patients were re-classified from high-grade urothelial cancer to benign disease on re-review. These four patients, in particular, show the potential benefit of having a pathologist with sub-specialist interest and expertise reviewing cases of NMIBC. Should a dedicated tumour stream pathologist review all cases as part of standard-of-care management?

Reference: *Urol Oncol.* 2024;42(11):372.e21-7

[Abstract](#)

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1L, first line; BSC, best supportive care; CI, confidence interval; HR, hazard ratio; mOS, median overall survival; UC, urothelial carcinoma.

References: 1. Powles T, *et al.* *J Clin Oncol.* 2023;41(19):3486-3492. 2. BAVENCIO® Approved Product Information. 3. Powles T, *et al.* *NEJM.* 2020;383(13):1218-1230. 4. Sridhar SS, *et al.* Avelumab first-line (1L) maintenance for advanced urothelial carcinoma (UC): Long-term follow-up from the JAVELIN Bladder 100 trial in subgroups defined by 1L chemotherapy regimen and analysis of overall survival (OS) from start of 1L chemotherapy. Abstract No. 508. Presented at the 2023 ASCO Genitourinary Cancers Symposium, February 16–18, 2023; San Francisco, CA, USA. 5. Powles T, *et al.* *J Clin Oncol.* 2023;41(19):3486-3492. Supplementary appendix.



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Whole-genome mutational analysis for tumor-informed detection of circulating tumor DNA in patients with urothelial carcinoma

Authors: Nordentoft I et al.

Summary: These investigators explored the clinical utility of a whole-genome sequencing approach for ultrasensitive ctDNA detection in patients with urothelial carcinoma. A total of 916 longitudinally collected plasma samples were collected from 112 patients with localised MIBC who had received neoadjuvant chemotherapy prior to radical cystectomy. After radical cystectomy, the ctDNA analysis was able to detect recurrence with a sensitivity of 91% and specificity of 92%, and the assay was able to identify recurrence at a median of 131 days earlier than radiographic imaging.

Comment: There is an increasing recognition that bespoke tumour-informed ctDNA assays can be highly effective for detection of minimal residual disease in many malignancies. In this study, the authors analysed 916 longitudinally collected plasma samples from 112 patients with MIBC undergoing neoadjuvant chemotherapy. Using whole genome sequencing, the ctDNA assay was 91% sensitive and 92% specific for disease recurrence. Importantly, ctDNA detected recurrences at a median of 131 days before radiographic imaging. These results illustrate the major clinical impact ctDNA analysis could have in disease monitoring in MIBC. Evaluation in prospective trials is paramount and warranted.

Reference: *Eur Urol.* 2024;86(4):301-11

[Abstract](#)

Dual mTOR1/2 inhibitor sapanisertib (FTH-003/TAK-228) in combination with weekly paclitaxel in patients with previously treated metastatic urothelial carcinoma

Authors: Bellmunt J et al.

Summary: This open-label, phase 2 study assessed the safety and efficacy of sapanisertib plus paclitaxel in patients with metastatic urothelial cancer who had received prior platinum therapy. A total of 22 patients were recruited, however, due to the COVID-19 pandemic and slow accrual, the trial was closed early. The ORR (primary endpoint) was 18.2% (n=4), with a DCR of 50%, median PFS of 3.4 months (95% CI 1.8—6.1) and median OS of 6.1 months (95% CI 1.8—13.4). Grade 3-4 AEs occurred in 86% of patients, yet there were no discontinuations due to AEs. Researchers also examined the association of response with *NFE2L2* alterations, and found no such alterations among responders.

Comment: The PI3K/AKT/mTOR pathway has been one of the best characterised and studied oncogenic signalling pathways, and is implicated in a wide array of cancers. Unfortunately, with the notable exception of ER-positive breast cancer, therapeutic modulation of this pathway has proven fruitless. In this phase 2 single-arm study, patients with refractory metastatic urothelial cancer were treated with sapanisertib (a highly selective mTOR1 and mTOR2 inhibitor) and paclitaxel. The study failed to meet its primary endpoint, with an ORR of just 18.2%. Although the authors state that sapanisertib could be evaluated with immunotherapy and/or ADCs, in my opinion, this trial should close the door on further clinical development of sapanisertib in metastatic urothelial cancer.

Reference: *Glin Genitourin Cancer.* 2024;22(5):102123

[Abstract](#)

Oncolytic adenoviral therapy plus pembrolizumab in BCG-unresponsive non-muscle-invasive bladder cancer: the phase 2 CORE-001 trial

Authors: Li R et al.

Summary: The phase 2 CORE-001 trial explored the efficacy of intravesical cretostimogene (serotype-5 oncolytic adenovirus) plus systemic pembrolizumab in 35 patients with BCG-unresponsive NMIBC with carcinoma in situ. At 12 months, the CR rate (primary endpoint) was 57.1% (n=20), and 82.9% of these patients (n=29) had achieved a CR at 3 months. At a median follow-up of 26.5 months, the CR rate was 51.4% (n=18), and the median duration of response had not been reached. None of the patients in the trial progressed to MIBC. Grade 3 treatment-related AEs occurred in 14.3% of patients, and no novel or unexpected toxicity signals were observed.

Comment: This phase 2 trial evaluated intravesical cretostimogene grenadenorepvec (which is much easier to refer to as an oncolytic adenovirus) with intravenous pembrolizumab in BCG-unresponsive NMIBC. The CR rate at 12 months was an impressive 57.1%, meeting the primary endpoint. Even more impressively in my opinion, was that the CR rate at 24 months was 51.4%, indicating durable responses with this combination. Impressively, grade 3 treatment-related AEs only occurred in 14.3% of patients. The combination of intravesical cretostimogene grenadenorepvec and intravenous pembrolizumab looks like a winner following BCG in NMIBC, and I look forward to seeing outcomes from a future phase 3 trial.

Reference: *Nat Med.* 2024;30(8):2216-23

[Abstract](#)

Longitudinal tumor-informed circulating tumor DNA status predicts disease upstaging and poor prognosis for patients undergoing radical cystectomy

Authors: Ben-David R et al.

Summary: The objective of this study was to determine the prognostic utility of ctDNA status before radical cystectomy for outcomes in patients with bladder cancer. The study population included 112 patients who underwent radical cystectomy between 2021-23, with a median follow-up of 8 months. Before radical cystectomy, 53% of patients had detectable ctDNA. Patients with detectable ctDNA had poorer RFS ($p < 0.0001$), and poorer outcomes overall, regardless of disease stage ($< cT2$ vs. $\geq cT2$) or whether they had received neoadjuvant therapy. Those with detectable ctDNA prior to cystectomy had higher likelihoods of nodal disease (OR 5.4; 95% CI 1.9—18.2; $p = 0.003$) and locally advanced disease (OR 3.6; 95% CI 1.5—9.0; $p = 0.005$), and a higher risk of disease recurrence (HR 4.5; 95% CI 1.0—19.0; $p = 0.04$).

Comment: Yet another ctDNA study in bladder cancer patients. This study looked at serial ctDNA samples collected both before and after radical cystectomy for bladder cancer. Importantly, 53% of patients had detectable ctDNA before radical cystectomy, indicating just how insensitive imaging modalities are for bladder cancer. Detection of ctDNA before radical cystectomy was an independent poor prognostic factor and was associated with a higher risk of lymph node disease. Altogether, these are potentially highly important results and need evaluation in prospective trials.

Reference: *Eur Urol Oncol.* 2024;7(5):1105-12

[Abstract](#)

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A phase 2 study of sitravatinib in combination with nivolumab in patients with advanced or metastatic urothelial carcinoma

Authors: Msaouel P et al.

Summary: This open-label, phase 2 study assessed the safety and efficacy of sitravatinib plus nivolumab in patients with advanced/metastatic urothelial carcinoma. The study population included 244 patients across eight cohorts, depending on prior treatment with checkpoint inhibitor therapy, platinum-based chemotherapy or ADC. In the cohort of patients treated with prior platinum-based therapy, checkpoint inhibitor-naïve patients (n=53) achieved an ORR of 32.1% and PFS of 3.9 months, checkpoint inhibitor-refractory patients (n=67) showed an ORR of 14.9% and PFS of 3.9 months, and those who were refractory to both checkpoint inhibitors and ADCs (n=56) had an ORR of 5.4% with a PFS of 3.7 months. Grade 3 treatment-related AEs occurred in 51.2% of patients overall across all eight cohorts, with grade 4 AEs occurring in 3.3%; 6.1% of patients discontinued treatment due to AEs. There was one treatment-related death (cardiac failure).

Comment: This phase 2 study in advanced and pre-treated urothelial cancer evaluated sitravatinib (a multitargeted receptor tyrosine kinase inhibitor of TYRO3, AXL and MERTK [TAM] receptors and VEGFR2), with nivolumab. Although there has been a lot of interest in targeting the TAM receptors to enhance the efficacy of immune checkpoint inhibitors, this study was negative and did not meet the pre-specified threshold for ORR (the primary endpoint). Treatment was generally deliverable, with only 6.1% of patients discontinuing sitravatinib/nivolumab due to treatment-related AEs. In my opinion, it is hard to see sitravatinib moving forward in advanced urothelial cancer.

Reference: *Eur Urol Oncol.* 2024;7(4):933-43

[Abstract](#)

PrECOG PrE0807: a phase 1b feasibility trial of neoadjuvant nivolumab without and with lirilumab in patients with muscle-invasive bladder cancer ineligible for or refusing cisplatin-based neoadjuvant chemotherapy

Authors: Grivas P et al.

Summary: In this phase 1b trial, researchers evaluated the safety and feasibility of neoadjuvant nivolumab alone, or in combination with lirilumab, in patients with localised MIBC (cT2-4a; N0-1M0) who were ineligible for or refused cisplatin-based neoadjuvant chemotherapy. Evaluable patients were administered two doses of nivolumab alone (n=13), or two doses of nivolumab plus lirilumab (n=30). The median time between the last dose and radical cystectomy was 4 weeks. The rates of grade 3 treatment-related AEs were 0% in the nivolumab monotherapy arm and 7% with nivolumab plus lirilumab; all of these AEs resolved, and no grade 4 or 5 treatment-related AEs were reported. The ypT0N0 rates were 17% in the nivolumab monotherapy arm and 21% in the combination arm, while the <ypT2N0 rates were 25% and 32%, respectively. The 2-year RFS rates were 73% with nivolumab and 71% with nivolumab plus lirilumab, and the 2-year OS rates were 82% and 89%, respectively. Patients who received nivolumab plus lirilumab showed significant increases in CD8+ T-cell density between TURBT and radical cystectomy.

Comment: This phase 1b trial investigated neoadjuvant nivolumab with and without lirilumab (a monoclonal antibody targeting KIR2DL1/2/3 that inhibits natural killer [NK] cell function) in patients with MIBC who refused or were ineligible for cisplatin-based neoadjuvant. The results look promising, with a 2-year RFS rate of 73% for cohort 1 (two doses of nivolumab) and 71% for cohort 2 (two doses of nivolumab + lirilumab). A key question of course, is how much impact lirilumab had, given the very similar RFS of cohorts 1 and 2. Treatment was better tolerated than I had anticipated, with a 0% rate of grade 3 treatment-related AEs in the nivolumab monotherapy arm. Overall, this combination looks highly encouraging, and it supports further clinical trials.

Reference: *Eur Urol Oncol.* 2024;7(4):914-22

[Abstract](#)



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