Bladder Cancer Research Review™

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Abbreviations used in this issue:

AE = adverse event; **BCG** = bacillus Calmette-Guérin; **DMFS** = distant metastasis-free survival; **HR** = hazard ratio; **(N)MIBC** = (non-)muscle-invasive bladder cancer; **OS** = overall survival; **(p)CR** = (pathologic) complete response; **PFS** = progression-free survival; **RFS** = recurrence-free survival; **TURBT** = trans urethral resection of bladder tumour.

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Welcome to the latest issue of Bladder Cancer Research Review

We begin with CheckMate 901 which was recently presented at ESMO 2023 and demonstrated that nivolumab + cisplatin/gemcitabine led to substantially better outcomes versus cisplatin/gemcitabine alone in patients with treatment-naïve, advanced urothelial carcinoma. This is followed by the phase 3 THOR trial, which found that patients with metastatic urothelial carcinoma and *FGFR* alterations experienced significantly longer OS with erdafitinib than with chemotherapy. The next paper reports on the phase 2 THOR-2 trial that showed a significant RFS benefit with erdafitinib versus intravesical chemotherapy in papillary-only, *FGFR*-altered, BCG-treated, high-risk NMIBC. We conclude with a sobering 20-year chart review which highlights the poor long-term survival outcomes for patients with plasmacytoid variant bladder cancer, while also identifying potential opportunities for intervention.

We trust you find these updates in bladder cancer of value for your clinical practice and the lives of your patients, and we welcome your feedback.

Warm regards,

Associate Professor Ben Tran
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Nivolumab plus gemcitabine–cisplatin in advanced urothelial carcinoma

Authors: van der Heijden MS et al; for the CheckMate 901 Trial Investigators

Summary: CheckMate 901 was an open-label, phase 3 trial which randomised 608 eligible patients with treatment-naïve, unresectable/metastatic urothelial carcinoma to either intravenous nivolumab + cisplatin/gemcitabine (cis/gem) 3-weekly for 6 cycles, before nivolumab 4-weekly for 2 years (n=304), or to cis/gem alone 3-weekly for 6 cycles (n=304). At a follow-up of 33.6 months, patients in the nivolumab-combination arm had significantly longer OS than cis/gem alone (21.7 vs. 18.9 months, respectively; HR 0.78; p=0.02), as well as improved median PFS (7.9 vs. 7.6 months; HR 0.72; p=0.001), 12-month PFS (34.2% vs. 21.8%), overall objective response (57.6% vs. 43.1%), complete response (21.7% vs. 11.8%) and duration of complete response (37.1 vs. 13.2 months). A higher rate of grade ≥3 AEs occurred in the nivolumab-combination arm (61.8% vs. 51.7%).

Comment: I don't know if ESMO got the right order of presentations. EV302 (manuscript pending) was presented and showed that pembrolizumab/enfortumab vedotin (pembro/EV) significantly and substantially improved survival beyond that of cisplatin/gemcitabine (cis/gem) as first-line treatment for advanced urothelial carcinoma - and received a standing ovation. The presentation immediately following this was CheckMate 901, presented by Michiel van der Heijden. In this study, cis/gem with nivolumab significantly improved survival compared to cis/gem alone, but less substantially than the pembro/EV combo. On its own, these data from CheckMate 901 are amazing. The addition of nivolumab to cis/gem is able to achieve a survival advantage but there are caveats: only those fit for cisplatin were included, as this was the backbone for the experimental arm and the control arm; additionally, maintenance avelumab was received by only ≈10% of the control arm. Is cis/gem + nivolumab truly better than the current standard of care of platinum/gem + maintenance avelumab? We don't know the answer to this question. If available and reimbursed, in the absence of pembro/EV, would I offer my patients who were cisplatin-eligible the combination of cis/gem + nivolumab instead of platinum/gem + maintenance avelumab? I would probably say yes!

Reference: N Engl J Med. 2023;389(19):1778-89

Abstract

Erdafitinib or chemotherapy in advanced or metastatic urothelial carcinoma

Authors: Loriot Y et al; for the THOR Cohort 1 Investigators

Summary: In THOR, the global, phase 3 trial, 266 eligible patients with metastatic urothelial carcinoma and *FGFR3/2* alterations who had progressed after anti-PD-1/anti-PD-L1 treatments were randomised to either erdafitinib (n=136; *FGFR*-inhibitor) or investigator's choice of docetaxel or vinflunine chemotherapy (n=130). At a median follow-up of 15.9 months, patients administered erdafitinib demonstrated significantly longer OS than chemotherapy (12.1 vs. 7.8 months; respectively; HR 0.64; p=0.005), as well as longer median PFS (5.6 vs. 2.7 months; HR 0.58; p<0.001). Comparable rates of grade 3/4 AEs occurred in the two treatment arms, however, treament-related AEs which led to death occurred less frequently with erdafitinib (0.7% vs. 5.4% of patients).

Comment: I was lucky enough to be an author of this practice-changing paper. *FGFR3* alterations occur in ≈20% of advanced urothelial cancer. *FGFR*-inhibitors have shown activity in this patient population. Cohort 1 of the THOR study compared erdafitinib as an *FGFR*-inhibitor to third-line chemotherapy (docetaxel or vinflunine) in advanced urothelial cancer. Pleasingly, erdafitinib improved survival. Erdafitinib is a daily tablet and generally tolerable. It is a great option for our patients. In the modern era, where molecular profiling is more and more accessible, finding these patients shouldn't be too difficult - and we're still hoping for approval and reimbursement of erdafitinib along with the companion diagnostic test to identify these patients. If your patient had an *FGFR3* mutation and needed third-line treatment, would you choose enfortumab vedotin (current standard of care in Australia) or erdafitinib? Even for the convenience of a tablet you can take at home versus intravenous infusions weekly for 3 out of every 4 weeks, I think erdafitinib is an attractive option.

Reference: N Engl J Med. 2023;389(21):1961-71

Abstract

Erdafitinib in BCG-treated high-risk non-muscle-invasive bladder cancer

Authors: Catto JWF et al; for the THOR-2 Cohort 1 Investigators

Summary: The phase 2 THOR-2 trial randomly assigned 73 patients with recurrent, BCG-treated, papillary-only, high-risk NMIBC harbouring *FGFR3/2* alterations, who were ineligible for/refused radical cystectomy, to either erdafitinib (n=49) or intravesical chemotherapy (n=24; mitomycin C/gemcitabine). Due to slow accrual, study enrolment was discontinued. At a median follow-up of 13.4 months, median RFS was prolonged with erdafitinib versus chemotherapy (not reached vs. 11.6 months, respectively; HR 0.28; p=0.0008). No novel safety signals were reported. However, it was noted that treatment discontinuation due to AEs occurred more frequently with erdafitinib than with chemotherapy (29% vs. 0%).

Comment: Those of you who know me know that I have a long-standing interest in *FGFR* as a target. I worked on several phase 1 studies of *FGFR*-inhibitors and was lucky enough to be involved with erdafitinib in these later-phase studies. While I am sure I wasn't the only one with the idea, I'll take credit for it anyway; back in 2010 when erdafitinib was only just entering the clinic, I had a discussion with the head of early drug development at J & J and suggested that we needed to get erdafitinib into NMIBC patients. I spoke to him about investigating how it could be given intravesically instead of systemically… that led to the development of TAR-210, a pretzel containing erdafitinib! But this paper here is the precursor to that. Again, I'm lucky enough to be an author of THOR-2 which investigated erdafitinib systemic treatment (tablets) for NMIBC with *FGFR3* alterations, comparing it to standard of care mitomycin C or gemcitabine. *FGFR3* alterations are much more common in NMIBC; and in this setting, in this small study that was closed early due to accrual issues through COVID-19, erdafitinib demonstrated improved RFS - this is great news. But what we did find was that NMIBC patients tolerated erdafitinib less well than advanced urothelial cancer patients. I guess there might be less at stake for NMIBC patients, and hence the willingness to tolerate toxicities is lower?

Reference: Ann Oncol. Published online 5 October, 2023
Abstract

Erdafitinib versus pembrolizumab in pretreated patients with advanced or metastatic urothelial cancer with select *FGFR* alterations

Authors: Siefker-Radtke AO et al; for the THOR Cohort 2 Investigators

Summary: This paper presented findings from cohort 2 of the phase 3 THOR trial, in which anti–PD-(L)1-naïve patients with unresectable, advanced/metastatic urothelial cancer and select *FGFR* alterations were randomly assigned to either erdafitinib 8mg once daily with pharmacodynamically-guided up-titration to 9mg (n=175) or pembrolizumab 200mg every 3 weeks (n=176). There was no difference in median OS (primary endpoint) between patients administered erdafitinib and pembrolizumab (10.9 vs. 11.1 months, respectively; HR 1.18; p=0.18). With regard to the secondary endpoints, the respective objective response rates were 40.0% and 21.6%, and median PFS 4.4 and 2.7 months. Patients in the erdafitinib arm had a markedly shorter duration of response than pembrolizumab (4.3 vs. 14.4 months). Investigators noted that the outcomes observed with pembrolizumab in this population were comparable to those seen in *FGFR*-unselected patients. No novel safety signals were reported for either agent.

Comment: As an *FGFR* aficionado, results from cohort 2 of the THOR study were very disappointing. This cohort compared erdafitinib to pembrolizumab, essentially as a second-line treatment for advanced urothelial cancer patients. Again, this was only in patients with selected *FGFR* alterations. The theory was that patients with *FGFR* alterations were less likely to respond to pembrolizumab, and hence erdafitinib would win out here. These assumptions were wrong. Despite having lower PD-L1 expression, as expected, these patients still responded well to pembrolizumab. Hence, erdafitinib was no better than pembrolizumab in this setting. I am hoping this does not dampen enthusiasm for erdafitinib as a great option for patients in the third-line setting.

Reference: Ann Oncol. Published online 11 October, 2023
Abstract

Efficacy and safety of bladder preservation therapy in combination with atezolizumab and radiation therapy (BPT-ART) for invasive bladder cancer

Authors: Kimura T et al; on behalf of the BPT-ART Investigators Group

Summary: This interim analysis of a multicentre, open-label, prospective phase 2 trial from Japan examined the safety and pathologic complete response (pCR) rates (key secondary endpoint) of radiation therapy + atezolizumab as a bladder-preserving therapy for patients with high-risk MIBC. Patients received radiation therapy (41.4Gy to the small pelvic field; 16.2Gy to the whole bladder) + intravenous atezolizumab (1200mg 3-weekly). Following 24 weeks of treatment, investigators examined response by TURBT and PD-L1 expression. Data from 45 patients were reported. The rates of T2, T1 and T3 disease were 73.3%, 15.6% and 11.1%, respectively; 88.9% of tumours were without concurrent carcinoma in situ, 77.8% were solitary and 57.8% were <3cm. A total of 38 patients achieved a pCR, and the overall pCR rate was 84.4%. Older patients achieved particularly high pCR rates (90.9%), as did those with high-PD-L1-expressing tumours (95.8%). Data regarding PFS, the primary endpoint, are still to come.

Comment: Radiation and checkpoint inhibitors were all the rage a few years ago. The PACIFIC study in lung cancer showed that the combination of radiotherapy and durvalumab improved survival. The thinking was that we could replicate this in another smoking-related cancer, namely bladder cancer. This study examined MIBC patients who were not fit for cystectomy and were administered radiotherapy with atezolizumab for 24 weeks. There was high pCR at repeat TURBT at the end of treatment, and treatment was well-tolerated. Recurrence rates were not reported.

Reference: Int J Radiat Oncol Biol Phys. 2023;117(3):644-51
Abstract

Pembrolizumab with chemoradiation as treatment for muscle-invasive bladder cancer

Authors: Weickhardt A et al.

Summary: The feasibility and safety of pembrolizumab + chemoradiation for MIBC were evaluated in the single-arm, phase 2, PCR-MIB clinical trial (ANZUP 1502). A total of 28 eligible patients were administered whole bladder radiotherapy followed by cisplatin and pembrolizumab. Follow-up took place at a median of 31 months. Within 12 weeks of treatment, six patients experienced grade >3 non-urinary AEs; three of whom undertook a dose reduction of cisplatin. At 24 weeks, the overall CR rate was 88%. Non-metastatic progression occurred in three patients, and eight developed metastatic disease. At 2 years, the DMFS is 78%, loco-regional PFS 87% and median OS 39 months (95% CI 17.1—not evaluable).

Comment: This is an ANZUP study led by Andrew Weickhardt looking at a similar question to the atezolizumab/radiotherapy study. Again enrolling MIBC patients, standard radiotherapy was given with chemotherapy as well as pembrolizumab for 21 weeks. This is different to the Japanese study which did not include chemotherapy. A similar CR rate was reported as in the Japanese study. However, DMFS was also reported here, recorded as 78% at 2 years. This is certainly an interesting combination, and we await the later-phase studies for robust long-term survival data.

Reference: Eur Urol Oncol. Published online 6 October, 2023
Abstract

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Underutilization of intravesical chemotherapy and immunotherapy for high grade non-muscle invasive bladder cancer in California between 2006–2018

Authors: Noel ODV et al.

Summary: This analysis of California Cancer Registry data examined the effects of race, age and socioeconomic status on treatment disparities among patients with high-grade NMIBC after initial TURBT. Among a total of 19,237 patients identified between 2006-18, the rates of BCG therapy following TURBT were comparable between all ethnic groups (28%-32%), however, a greater proportion of patients in the highest neighbourhood socioeconomic quintile received BCG therapy than those in the lowest two quintiles (37% vs. 23%-26%). Similarly, intravesical therapy was 45% less likely to be administered to patients in the lowest socioeconomic quintile than those in the highest quintile (OR 0.55). Socioeconomic status, ethnicity, age, marital status and insurance type all influenced the administration of intravesical therapies. Compared to patients who had private insurance, BCG after TURBT was less likely to be given to those with Medicare (OR 0.76) or other insurance (OR 0.70).

Comment: This is certainly disappointing. In California, this study demonstrated that intravesical treatment for NMIBC was significantly lower in those of lower socioeconomic status. Hopefully this is not the case in Australia.

Reference: Urol Oncol. 2023;41(10):431.e7-14
Abstract

Conditional survival following radical cystectomy for urothelial carcinoma of the bladder

Authors: Moreno MF et al.

Summary: These investigators utilised retrospective data from the US National Cancer Database to determine the 2- and 5-year conditional OS of patients with urothelial bladder cancer after radical cystectomy. Between 2006-15, a total of 15,594 patients were followed for a median of 27.8 months. Throughout the first 36 months of follow-up, the overall 2- and 5-year conditional OS improved, before plateauing. Over time, patients experienced greater gains in conditional OS with higher pT and pN stage; the greatest increases were seen among patients with pTany N1-3 disease (5-year conditional OS 23% at baseline, 58% at 36 months, 71% at 60 months). Between baseline and 36 and 60 months, the hazard ratios for all-cause mortality decreased in magnitude according to pT and pN stage.

Comment: Conditional survival is something that we need data for. Often as clinicians, we are asked to complete insurance paperwork detailing the likelihood of recurrence across X number of years following definitive treatment. The data presented here do not have cancer-specific survival data, and so are not as valuable but it would be good to have data that tell us what the risk of dying from bladder cancer is if you are disease-free at 3 and 5 years following definitive treatment.

Reference: Urol Oncol. 2023;41(10):432.e11-20
Abstract

European Association of Urology guidelines on muscle-invasive and metastatic bladder cancer

Authors: Witjes JA et al.

Summary: The updated 2023 European Association of Urology guidelines were summarised in this review published by European Urology. Consensus statements and recommendations were formed from data across various databases. It was recommended that physicians discuss risk factors for bladder cancer, and that pathologists provide detailed descriptions for tumours and lymph nodes, including histological subtypes. It is crucial to determine the presence/absence of urothelial carcinoma in the prostatic urethra. When determining disease stage, MRI is preferable to CT – particularly when differentiating T1 and T2 disease; this may inform a switch in approach for patients who are at risk of developing an invasive tumour. The value of added fluorodeoxyglucose positron emission tomography/CT is still not clear; CT or MRI imaging should be used for the upper urinary tract, lymph nodes and metastasis. A multidisciplinary team is essential for the management of comorbid and frail patients. The key prognostic variable continues to be post-operative histology, although circulating tumour DNA seems to be a promising predictive marker.

Cisplatin-based treatments remain at the forefront for neoadjuvant systemic therapy. Oncological outcomes are not shown to be compromised with sexual organ-preserving cystectomy. Comparable outcomes are observed with both open and robotic cystectomy, and (extended) lymph node dissection should accompany both of these. Substantial morbidity and risk of mortality remain with radical cystectomy, however hospitals with higher volumes of procedures yield lower rates. Trimodal therapy/chemoradiation has similar outcomes to radical cystectomy when patients are selected appropriately. It is highly recommended that patients with high-risk disease who did not undergo neoadjuvant therapy receive adjuvant chemotherapy following surgery to improve overall and disease-specific survival. As OS data are not yet mature, there is a tentative recommendation for adjuvant nivolumab. Questionnaires at baseline and following treatment should be used to assess health-related quality of life. Surveillance for recurrence is essential; patients with symptomatic recurrences generally have poorer outcomes than those whose recurrences are identified on follow-up.

Comment: In medical oncology, guidelines are much more utilised in North America and Europe than here, where much of our practice is based upon reimbursement (for systemic treatment). However, for our urology and radiation oncology colleagues, perhaps guidelines play a larger role. It is always great to have these guidelines published. I recommend that trainees review this paper to get a great summary of modern treatments for metastatic and MIBC.

Reference: Eur Urol. Published online 17 October, 2023
Abstract

Bladder Cancer Research Review™

Independent commentary by Associate Professor Ben Tran

Ben is a medical oncologist in Melbourne, Australia with appointments at Peter MacCallum Centre and Walter and Eliza Hall Institute. He is actively involved in clinical trials and translational research, with special interests in genitourinary cancers, drug development and real-world evidence. Ben is currently the chair of the Phase 1 group within Cancer Trials Australia (CTA), and is also the Chair of the germ cell subcommittee within the Australian and New Zealand Urological and Prostate Cancer Trials (ANZUP) Group.

Long-term oncological outcomes in patients diagnosed with non-metastatic plasmacytoid variant of bladder cancer

Authors: Sood A et al.

Summary: A 20-year retrospective chart review was conducted at the University of Texas MD Anderson Cancer Centre to determine the disease recurrence and metastasis patterns in patients with plasmacytoid variants of bladder cancer. A total of 56 patients with non-metastatic disease were treated with curative intent between 1998-2018. At presentation, 39.3% had stage ≤cT2N0 disease, 26.8% cT3N0, 23.2% cT4N0 and 10.7% ≥cN1. Chemotherapy was administered to 87.5% of patients, and surgery was unable to be performed in 75%. At the time of surgery, 52.4% of eligible patients had pN+ disease, while only four (7.2%) had pT0. At a follow-up of 36 months, 22.2% of patients were free of metastatic disease and 28.4% remained alive. In patients with localised/locally advanced disease, successful completion of surgery was associated with significantly improved 36-month metastasis-free survival (32.4% vs. 0%; p<0.001), however this was not the case among patients with regionally advanced disease (12.5% vs. 10%; p=0.49). Overall, metastasis occurred at a median of 6.5 months after the end of primary treatment occurred, primarily in the peritoneum (76.1%); the risk of death for these patients was significantly decreased with salvage immunotherapy (HR 0.11; p=0.001). Investigators noted that research into hyperthermic intraperitoneal chemotherapy/immunotherapy for this high-risk population is warranted.

Comment: Plasmacytoid variants are rare, but definitely bad news. This chart review of 56 patients is probably the largest dataset reported. Anecdotally, my experience is that these are rapid-growing and can invade the peritoneum. These data show that surgery following chemotherapy did not improve metastasis-free survival for regionally advanced disease (T4 or N1); but in earlier stages of disease, surgery did improve metastasis-free survival. The data also showed a high rate of peritoneal spread; this can be difficult to appreciate on CT imaging. I wonder whether MRI might be useful to determine whether there is local peritoneal spread in patients with plasmacytoid variants; although, if waiting for an MRI were to result in lengthy delays, this might not be a good idea.

Reference: J Urol. Published online 3 November, 2023
Abstract