ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY DRIVING INNOVATION IN ONCOLOGY

EDITORIAL

Combination with BCG induction and maintenance therapy for high-risk non-muscle invasive bladder cancer

For >50 years, intravesical Bacillus Calmette-Guérin (BCG) has been the standard of care for high-risk non-muscle invasive bladder cancer (HR-NMIBC).[1] Historically, patients with HR-NMIBC treated with BCG have a 50% and 76% chance of disease-free survival at 3 years depending on the amount of maintenance BCG given.[2] Recurrent disease often requires more aggressive treatment, such as bladder instillation of potentially toxic therapies or radical cystectomy.[3] HR-NMIBC disease comprises flat lesions, carcinoma in situ (CIS) and higher-risk papillary disease (T1 and/or grade 3). Although it is accepted that CIS is usually multifocal and associated with worse outcomes compared with papillary-alone HR-NMIBC, in reality, many patients have both CIS and papillary tumors, and there is a biological overlap between disease states.[4] Follow-up and disease detection of HR-NMIBC is not uniformly defined, ranging from office-based cystoscopy and urine cytology to mandatory biopsy at defined endpoints. In clinical trials, event-free survival (EFS) has been used as a primary endpoint, rather than other endpoints, such as time to cystectomy, but it consists of different parameters and varies between trials. It is these inconsistencies in pathology, follow-up, and endpoint assessment that make cross-trial comparison more hazardous than usual.

Immune checkpoint inhibition (ICI) has revolutionized advanced bladder cancer, and the addition of ICI therapy to BCG in HR-MIBC is a legitimate research question.[5,6] Data from three large randomized phase III trials comparing BCG to BCG plus checkpoint immunotherapy in HR-MIBC, with EFS as the primary endpoint, are now available.[7-9] In this issue, Roupret et al. publish ALBAN (GETUG-AFU 37), one of these three trials. ALBAN is a large European randomized trial comparing 255 patients with BCG induction and maintenance (IM) (1 year) and atezolizumab to 262 patients treated with BCG IM (1 year), alone. The trial was well-designed and well-performed, but the primary endpoint was not achieved [hazard ratio (HR) 0.98, 95% confidence interval 0.71-1.36, $P = 0.91$]. Two previous studies with a similar design (ICI+BCG IM versus BCG IM alone) in the same setting (sasanlimab in the CREST trial and durvalumab in the POTOMAC trial) were positive for EFS with an HR of 0.68 for both. Why were the results of ALBAN different than prior reports of anti-programmed cell death protein 1 (PD-1) therapy, such as CREST and POTOMAC?

Firstly, there has been a long debate about whether one ICI therapy is better than another. In urothelial cancer (UC), PD-1- and programmed death-ligand 1- (PD-L1) targeted therapies are thought to have similar outcomes in UC. Although these inconsistent EFS results could come down to luck alone, this seems unlikely, as the ALBAN trial HR looks very different from that of the other two trials; nevertheless, ALBAN is a smaller study with almost 200 fewer patients.

The next consideration is the patient population. Although the trials attempted to enroll similar populations, CREST and POTOMAC had a greater frequency of T1 and CIS patients. T1, the highest risk tumor was found in 58% of CREST, 60% of POTOMAC, but only 39% of ALBAN. Pure CIS was identified in 15% of CREST and 7% of ALBAN; 19% of the patients in ALBAN were nonsmokers, and 36% of the patients in CREST were nonsmokers. In general, CREST may be a higher-risk population that would be anticipated to have a greater number of events.

Although the trials seem roughly similar, there are significant differences in the trials design and conduct that make comparisons challenging. CREST and POTOMAC allowed BCG re-induction with persistent disease in CIS at 3 months whereas ALBAN did not. Persistent CIS was handled differently resulting in more early events. EFS was centrally reviewed in POTOMAC and CREST but not in ALBAN. Low-grade relapse and upper tract recurrence was an event in ALBAN unlike the other two studies. Roughly 20% of events in ALBAN were low-grade, which occurred in both arms, and may have diluted the number of high-grade recurrences. These differences may account for the early drop off in the first 6 months the EFS Kaplin—Meyer curve in ALBAN despite having the lowest cancer risk population. The duration of treatment varied across all three studies. There was only 1 year of both therapies in ALBAN, whereas treatment was 2 years in CREST with 1 year of ICI, and 2 years of BCG IM in POTOMAC. Finally, an unknown role of the BCG strain may impact the outcome of the trials, as 14% received the TICE strain in ALBAN, whereas almost 40% were treated with TICE in CREST. Several small differences in trial design can have a significant overall impact on trial results when combined.

These issues may help explain ALBAN as an outlier, but the difference between the CREST and POTOMAC trials are much more subtle from a design and execution perspective. EFS was defined in similar ways; there was a central pathology review, and the duration of

maintenance BCG was the same period. Indeed, the EFS HR was identical, with similar landmark EFS at 2 years in the two studies. However, there were stark differences in the efficacy of the ICI in the CIS subset, which showed enrichment for EFS with sasanlimab but the opposite with durvalumab. HRs for pure CIS were not given, and the assessment included CIS with papillary histology too, resulting in larger numbers. The difference in response to CIS in CREST may be secondary to the mandated biopsy at 24 weeks that could detect more CIS and identify a greater impact of the sasanlimab. There was a degree of enrichment for both ICI agents in the PD-L1 biomarker-positive, but this appeared modest at best, and the biomarker has performed poorly over time in UC.[10] One might argue that the strain of BCG (TICE versus non-TICE) may play a role, but there was no evidence of this from the results.

Where do we go next with ICI plus BCG IM in HR-NMIBC? There is little data on cystectomy rates or systemic relapse in the three trials, but the risk of life-threatening cancer is low. Most relapses are local rather than muscle invasive or systemic. Few bladder cancer deaths are apparent. There is also well-documented life-changing toxicity with ICI therapy, which is greater than 10%.[9] One could argue that ALBAN is the outlier due to trial design and execution issues, and the other two studies are closer to the real effect of ICI on HR-NMIBC. The inconsistency around the CIS subgroup in these two latter positive trials could be put down to modest numbers and variability in the way it was assessed, with mandatory biopsy within the studies. Further analysis of the pure CIS group would be helpful. The inability to find a subgroup with any consistency means treating only a selected group of patients [different groups for durvalumab (non-CIS) and sasanlimab (CIS)] feels wrong.

A scientific conclusion is that in the two most robust trials, a clear signal for efficacy in NMIBC was seen, underpinning the hypothesis that early ICI therapy is active. From a clinical perspective this may become an option for some patients, but it is unclear who they would be and the treatment is not without significant risks. Treating all HR-NMIBC with ICI and BCG IM feels like a lot of unnecessary overtreatment. Perhaps a biomarker such as urinary tumor DNA or circulating tumor DNA may help identify those at the highest risk in the future.

J. J. Meeks[1] & T. Powles[2]*

[1]*Departments of Urology and Biochemistry, and Molecular Genetics, Northwestern University, Chicago, USA;*
[2]*Barts Cancer Institute Biomedical Research Centre, Queen Mary University of London, London, UK*
(*E-mail: thomas.powles1@nhs.net).

Available online 17 October 2025

https://doi.org/10.1016/j.annonc.2025.10.015
DOI of original article: https://doi.org/10.1016/j.annonc.2025.09.017

FUNDING

None declared.

DISCLOSURE

TP reports grants or contracts from AstraZeneca, Roche, Bristol Myers Squibb (BMS), Exelixis, Ipsen, Merck Sharpe and Dohme (MSD), Novartis, Pfizer, Seattle Genetics, Merck Serono, Astellas, Johnson & Johnson, and Eisai; consulting fees and honoraria from AstraZeneca, BMS, Exelixis, Incyte, Ipsen, MSD, Novartis, Pfizer, Seattle Genetics, Merck Serono, Astellas, Johnson & Johnson, Eisai, Roche, Mashup, and Gilead Sciences; support for attending meetings and (or) travel from Roche, Pfizer, MSD, AstraZeneca, Ipsen, Gilead Sciences, Astellas, and MSD; participation on a data safety monitoring board or advisory board for AstraZeneca, Roche, BMS, Exelixis, Ipsen, MSD, Novartis, Pfizer, Seattle Genetics, Merck Serono, Astellas, Johnson & Johnson, and Eisai; and other financial interests from Novartis, Pfizer, AstraZeneca, Roche/Genentech, Eisai, and Merck. JJM is a consultant for Merck, AstraZeneca, Janssen, BMS, UroGen, Prokarium, Imvax, Pfizer, Seagen/Astellas, Ferring, CG Oncology, Immunity Bio, Protara, Photocure; reports research funding from NIH/NCI, VHA; employment: VHA, Northwestern Medicine; payment for education/talks: MJH, Urology Times, Olympus.

REFERENCES

1. Lobo N, Brooks NA, Zlotta AR, et al. 100 years of Bacillus Calmette-Guérin immunotherapy: from cattle to COVID-19. *Nat Rev Urol*. 2021;18(10):611-622.
2. Lamm DL, Blumenstein BA, Crissman JD, et al. Maintenance Bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. *J Urol*. 2000;163(4):1124-1129.
3. Babjuk M, Burger M, Capoun O, et al. European Association of Urology Guidelines on non-muscle-invasive bladder cancer (Ta, T1, and carcinoma *in situ*). *Eur Urol*. 2022;81(1):75-94.
4. Matulay JT, Li R, Hensley PJ, et al. Contemporary outcomes of patients with nonmuscle-invasive bladder cancer treated with Bacillus Calmette-Guérin: implications for clinical trial design. *J Urol*. 2021;205(6):1612-1621.
5. Powles T, Valderrama BP, Gupta S, et al. Enfortumab vedotin and pembrolizumab in untreated advanced urothelial cancer. *N Engl J Med*. 2024;390(10):875-888.
6. Meeks JJ, Black PC, Galsky M, et al. Checkpoint inhibitors in urothelial carcinoma-future directions and biomarker selection. *Eur Urol*. 2023;84(5):473-483.
7. Roupret M, Bertaut A, Pignot G, et al. ALBAN (GETUG-AFU 37): a phase 3, randomized, open-label, international trial of intravenous atezolizumab and intravesical Bacillus Calmette-Guérin (BCG) versus BCG alone in BCG-naive high-risk, non-muscle invasive bladder cancer (NMIBC). *Ann Oncol*. 2026;37(1):44-52.
8. Shore ND, Powles TB, Bedke J, et al. Sasanlimab plus BCG in BCG-naive, high-risk non-muscle invasive bladder cancer: the randomized phase 3 CREST trial. *Nat Med*. 2025;31(8):2806-2814.
9. De Santis M, Palou Redorta J, Nishiyama H, et al. Durvalumab in combination with BCG for BCG-naive, high-risk, non-muscle-invasive bladder cancer (POTOMAC): final analysis of a randomised, open-label, phase 3 trial. *Lancet*. 2025;406(10516):2221-2234.
10. Powles T, van der Heijden MS, Castellano D, et al. Durvalumab alone and durvalumab plus tremelimumab versus chemotherapy in previously untreated patients with unresectable, locally advanced or metastatic urothelial carcinoma (DANUBE): a randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol*. 2020;21(12):1574-1588.