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Immune Checkpoint Inhibitors for High-Risk Nonmuscle-Invasive Bladder Cancer: Lessons Learned From the CREST and POTOMAC Trials

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Bacillus Calmette-Guérin (BCG) was introduced as a treatment for NMIBC almost 50 years ago by Morales et al.[1] Subsequent trials demonstrated that BCG was more effective than intravesical doxorubicin[2] and mitomycin C.[3] Fast-forward to year 2000, Lamm et al[4] showed that BCG induction and maintenance (I + M) for up to 3 years was superior to BCG induction-only for improving recurrence-free, progression-free, and overall survival, establishing BCG as the gold-standard treatment for high-risk NMIBC. Since then, no other treatment has surpassed the effectiveness of BCG I + M.

The CREST trial, published in May 2025, was a phase 3, open-label, randomized controlled trial that included patients with high-risk NMIBC either Ta high-grade, T1, or carcinoma in situ (CIS); eligible patients could have either primary or recurrent disease but had to be BCG-naïve.[5]

This trial enrolled 1055 patients across 3 arms: Arm A = Sasanlimab + BCG I + M, Arm B = Sasanlimab + BCG induction-only, and Arm C = BCG I + M. Patients were stratified based on the presence or absence of CIS and geographic region; each arm included approximately 350 patients.

Sasanlimab (a PD-1/PD-L1 inhibitor) was administered subcutaneously in a 4-weekly fashion for 2 years, BCG I + M followed current recommended protocols, and was planned for 2 years (reinduction was allowed for persistent CIS or high-grade Ta). Follow-up was performed with cystoscopy, cytology, and imaging, as recommended by guidelines.

The primary end point was event-free survival (EFS), defined as high-grade recurrence, disease progression, persistence of CIS, or death from any cause.

Sasanlimab + BCG I + M (Arm A) demonstrated a 32% reduction in the risk of developing an event (stratified HR of 0.68 [95% CI: 0.49-0.94]). This represents an absolute benefit of 7.3% reduction in events at 36 months of follow-up (EFS = 82.1% in Arm A vs 74.8% in Arm C).

Regarding complete response (CR) among patients with CIS, 89.8% of patients in Arm A achieved CR compared with 85.2% in Arm C, yielding an absolute benefit of 4.6% (Table).

Therefore, CREST stands out as the first clinical trial in decades to show a meaningful improvement over BCG.

The POTOMAC trial was published in October 2025[6]; while cross-trial comparison is not ideal, both trials are methodologically almost identical when it comes to inclusion/exclusion criteria, sample size, treatment schedules, and follow-up. While the CREST trial tested Sasanlimab, POTOMAC did the same with Durvalumab another PD-1/PD-L1 inhibitor (administered intravenously).

Durvalumab + BCG I + M (Arm A) demonstrated a 32% reduction in the risk of developing an event (HR 0.68 [95% CI: 0.50-0.93]). This represents an absolute benefit of 4.4% difference in events at 36 months of follow-up against BCG I + M (EFS = 81.8% in Arm A vs 77.4% in Arm C), results that are very similar to those in the CREST trial. CR in CIS was 95% in Arm A and 93% in Arm C (Table).

While the development of more effective treatments for patients with high-risk NMIBC is important, the tolerability of such treatments is key. Discontinuation due to adverse events happened in 26% of patients receiving Sasanlimab and in 16% of patients getting Durvalumab (Table). Prescription of systemic corticosteroids was similar in both trials (20% for Sasanlimab and 16% for Durvalumab).

Another aspect suggesting limited utility is the substantially higher discontinuation rate observed with the addition of immune checkpoint inhibitors (ICI) in these trials. Brausi et al[7] reported that

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Table. *Main Characteristics, Results, and Adverse Events Reported in the CREST and POTOMAC Trials*

	CREST Arm A Sasanlimab + BCG I + M (N = 352)	CREST Arm B Sasanlimab + BCG I (N = 352)	CREST Arm C BCG I + M (N = 351)	POTOMAC Arm A Durvalumab + BCG I + M (n = 339)	POTOMAC Arm B Durvalumab + BCG I (n = 339)	POTOMAC Arm C BCG I + M (N = 340)
T stage[a], No. (%)						
CIS	52 (14.8)	42 (11.9)	50 (14.2)	125 (37)	125 (37)	125 (37)
Ta	96 (27.3)	136 (38.6)	107 (30.5)	112 (33)	114 (34)	99 (29)
T1	204 (58)	174 (49.4)	194 (55.3)	195 (58)	191 (56)	211 (62)
Oncological outcomes, No. (%)						
Recurrence of high-grade disease	26 (7.4)	61 (17.3)	53 (15.1)	53 (15.6)	87 (25.7)	69 (20.3)
Progression to muscle-invasive disease	7 (2)	3 (1)	7 (2)	16 (4.7)	13 (3.8)	15 (4.4)
Deaths reported	32 (9.1)	30 (8.5)	29 (8.3)	14 (4.1)	18 (5.3)	29 (8.5)
Persistence of CIS	1 (0.3)	2 (0.6)	1 (0.3)	1 (0.3)	3 (0.9)	2 (0.6)
Probability of being event-free/disease-free at 36 mo[b]	82.1	71.5	74.8	81.8	69	77.4
Overall survival at 36 mo	92.3	92	92.4	88	NR	85
AEs, No. (%)						
Treatment-related AEs	305 (87.1)	275 (79)	245 (70.2)	298 (89)	269 (80)	245 (72)
Grade 3 or higher AE treatment-related	102 (29.1)	76 (21.8)	22 (6.3)	71 (21)	52 (15)	13 (4)
Treatment-related AE leading to treatment discontinuation, No. (%)						
Sasanlimab	92 (26.3)	58 (16.7)	—	54 (16)	44 (13)	1 (<1)[c]
BCG	59 (16.9)	8 (2.3)	30 (8.6)	55 (16)	15 (4)	55 (16)
Immune-related AEs (Grade 3 or higher), No. (%)	55 (15.7)	49 (14.1)	—	27 (8)	27 (8)	1 (0.3)[c]
Systemic corticosteroid use, No. (%)	69 (19.7)	70 (20.1)	1 (<1)	55 (16)	55 (16)	3 (0.8)

Abbreviations: AE, adverse event; BCG, bacillus Calmette-Guérin; CIS, carcinoma in situ; I, induction; I + M, induction and maintenance; NR, not reported.
Data extracted from the original publication and supplementary files.
[a] Percentages might not sum to 100 because patients may have Ta + CIS or T1 + CIS.
[b] CREST trial used event-free survival and POTOMAC used disease-free survival as primary outcomes; from a practical perspective these 2 can be interpreted as almost identical outcomes.
[c] This patient was recorded as assigned to the comparison group due to a data entry error.

treatment discontinuation with BCG alone was only 7.8% in the first year, whereas in the CREST and POTOMAC trials, it ranged between 16% and 26%, representing more than a 2-fold increase. This higher dropout rate implies that a considerable proportion of patients—up to 1 quarter of those eligible for BCG—may not complete and therefore not benefit from BCG maintenance, ultimately undermining oncologic outcomes in this population.

All things considered, BCG + Sasanlimab or Durvalumab are treatments that carry a 21% to 29% risk of serious (grade 3 or 4) adverse events, yet only offer a 4.4% to 7.3% absolute benefit of avoiding a high-grade recurrence with no benefit on progression to muscle-invasive disease.

To simplify it, we can calculate the number-needed-to-treat (NNT) and number-needed-to-harm (NNH). The NNT represents the number of patients over a given time period that would need to be treated to avoid 1 additional high-grade recurrence, while the NNH represents the number of patients we would need to treat to get 1 additional grade 3 or 4 toxicity.[8]

For Sasanlimab at 36 months, the NNT is 14, while the NNH is 4; for Durvalumab at 36 months the NNT is 23 and the NNH is 6.

POTOMAC reported subgroup analysis for PD-L1 status showing high PD-L1 predicted response to Durvalumab (HR 0.50 [CI: 0.26-0.91]), CREST did not report PD-L1 status in the final publication but was reported as "not predictive of EFS benefit" at the ASCO 2025 meeting presentation.[9]

CIS presence was reported in subgroup analysis of both trials, showing no benefit of adding Durvalumab (HR 1.01 [CI: 0.62-1.64]) but a potential benefit with Sasanlimab (HR 0.53 [CI: 0.29-0.98]).

The observed benefit appears to be driven primarily by the addition of the ICI in combination with BCG maintenance, as reflected by the improved EFS when maintenance was included (HR 0.68) compared with the lack of benefit for induction-only regimens (HR 1.14 and 1.16 in POTOMAC and CREST, respectively). In both trials, the maintenance schedule extended to 2 years, suggesting that 2-years is not inferior to the current standard 3-year BCG maintenance.[10]

The CREST and POTOMAC trials demonstrate that adding ICIs to BCG I + M provides only a modest benefit in recurrence reduction with considerable toxicity. While awaiting the results of emerging alternatives of upcoming trials, a 2-year BCG I + M schedule remains a reasonable go-to choice and may offer comparable efficacy to the traditional 3-year regimen.

Given these considerations, shared decision-making will be key once these drugs reach the market. Whether a patient is willing to assume a 1 in 5 risk of a severe adverse event for an additional 4% to 7% reduction in recurrence risk (with no impact on

progression to muscle-invasive disease) is unknown, but nonetheless, this option should be offered to patients or discussed in a multidisciplinary meeting.

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