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Sasanlimab in combination with Bacillus Calmette-Guérin (BCG) in BCG-naive, high-risk non-muscle-invasive bladder cancer (HR NMIBC): Exploratory analysis of patients with very HR (VHR) disease from the phase 3 CREST trial

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Objective

- Here we report a summary of the primary analysis of the CREST study, and an exploratory analysis of EFS by disease stage and in patients with VHR disease
  - VHR disease was defined based on modified EAU guidelines as high-grade Ta and CIS with all 3 risk factors (risk factors: age >70 years, multiple papillary tumors, and tumor diameter ≥3 cm), high-grade T1 without CIS with all 3 risk factors, or high-grade T1 and CIS with ≥1 risk factor[1]

Conclusions

- CREST was the first study to show a statistically significant prolongation of EFS with sasanlimab + BCG-I+M compared with BCG-I+M in patients with HR NMIBC
- Prolonged EFS with sasanlimab + BCG-I+M compared with BCG-I+M was observed across disease stage subgroups, with potential enrichment in certain subgroups
- In patients with VHR NMIBC, for whom radical cystectomy is the current standard of care, sasanlimab + BCG-I+M showed prolonged EFS compared with BCG-I+M; however, this exploratory analysis is limited by small sample sizes
- The safety profile for sasanlimab + BCG-I+M was generally consistent with the known safety profile of each individual agent
- Subcutaneous sasanlimab + BCG-I+M has the potential to redefine the treatment paradigm and clinical decision-making for patients with HR NMIBC

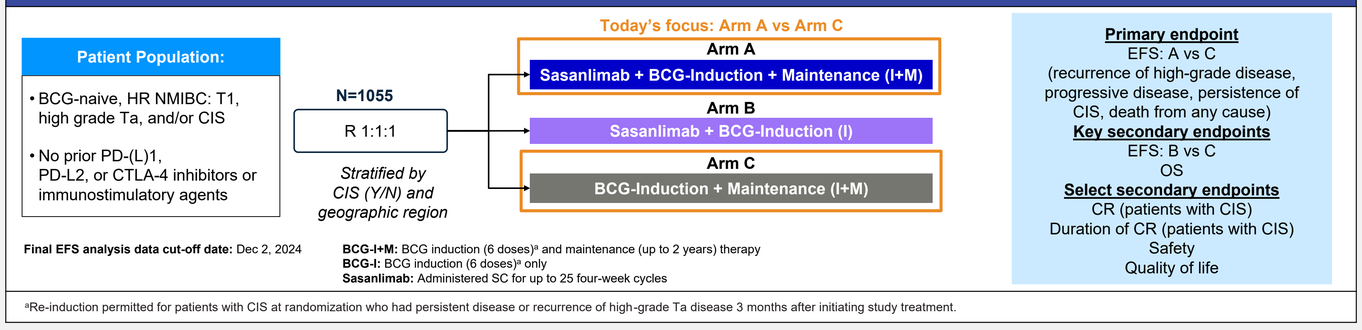
Background

- Standard of care for HR NMIBC is TURBT followed by BCG induction and maintenance[1,2]
  - In HR NMIBC, approximately 30% of patients experience disease recurrence (25%) or progression (5%) at 1 year, with unfavorable prognosis[3]
  - In the subset of patients with VHR NMIBC, the current recommended first-line treatment is radical cystectomy due to the extremely high risk of tumor progression (16% at 1 year and 40% at 5 years);[1] therefore, there is a need for a less invasive treatment for these patients
  - Furthermore, limited treatment options exist to offer durable disease control,[4] most notably for patients with CIS[1]
- Combination of PD-1 inhibitor with BCG is supported by increased PD-L1 expression following treatment with BCG[5-7]
- Sasanlimab is a subcutaneously administered PD-1 inhibitor that showed durable anti-tumor activity and a manageable safety profile in patients with advanced or metastatic solid tumors[8,9]

Materials and Methods

- CREST is a global, phase 3, randomized study (**Figure 1**)
- EFS by disease stage and in patients with VHR disease from the phase 3 CREST study were exploratory analyses

Figure 1. CREST Study Design



[a]Re-induction permitted for patients with CIS at randomization who had persistent disease or recurrence of high-grade Ta disease 3 months after initiating study treatment.

Results

Patients

- Baseline demographics and disease characteristics of the intent-to-treat population were previously reported[10] and are summarized in **Table 1**
- There was a comparable number of patients with VHR disease in both the sasanlimab + BCG-I+M (n=28) and BCG-I+M (n=29) arms

EFS

- The primary endpoint was met by showing a statistically significant prolongation of EFS with sasanlimab + BCG-I+M compared with BCG-I+M in patients with HR NMIBC (stratified hazard ratio (95% CI): 0.68 (0.49-0.94); 1-sided P-value: 0.0095; **Figure 2A**)
  - The risk of experiencing an EFS event was 32% lower with sasanlimab + BCG-I+M than BCG-I+M
  - The rate of events was lower with sasanlimab + BCG-I+M than with BCG-I+M, with a more than 50% reduction in the rate of recurrence of high-grade disease in the sasanlimab + BCG-I+M arm than the BCG-I+M arm (**Figure 2A**)
  - Sasanlimab + BCG-I+M showed prolonged EFS compared with BCG-I+M across subgroups, with potential enrichment in certain subgroups (**Figure 2B**)
  - In patients with VHR disease, the risk of experiencing an EFS event was 66% lower with sasanlimab + BCG-I+M than BCG-I+M (unstratified hazard ratio (95% CI): 0.34 (0.11-1.08); **Figure 2C**)

OS

- At a median overall survival follow-up of 40.9 months, data suggest no meaningful difference between sasanlimab + BCG-I+M and BCG-I+M (**Figure 3**)
- There were a low number of deaths reported at this interim overall survival analysis, which was to be expected for this patient population

CR and duration of CR in patients with CIS who achieved CR

- In the sasanlimab + BCG-I+M arm, 79 of the 88 (89.8%) patients with CIS achieved a CR at any time; and in the BCG-I+M arm, 75 of the 88 (85.2%) patients with CIS achieved a CR at any time
  - The difference in CR rate was 4.4 (95% CI: −5.4 to 14.2; 1-sided P-value [Mantel-Haenzel test]=0.1878)
- In patients with CIS who achieved a CR, the probability of continued CR at 36 months was 92% for sasanlimab + BCG-I+M (**Figure 4**)

Quality of life

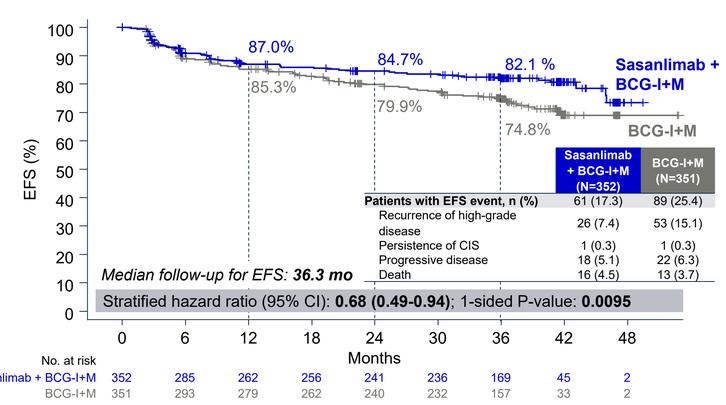
- Completion rates for the EORTC QLQ-C30 questionnaire were >84% for Arms A and C through end of treatment
- Quality of life was maintained with sasanlimab + BCG-I+M (**Figure 5**)

Safety

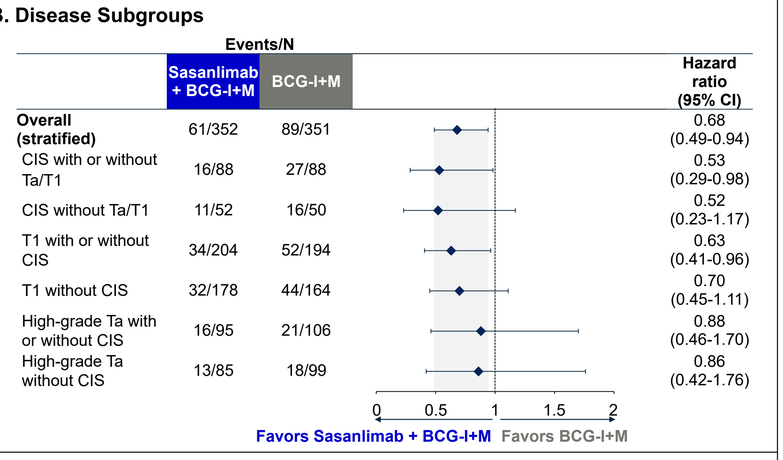
- The median duration of sasanlimab (range) was 80.3 weeks (4.0-103.9) for the sasanlimab + BCG-I+M arm. The median duration of BCG (range) was 98.1 weeks (2.0-125.1) for the sasanlimab + BCG-I+M arm and 98.9 weeks (2.0-110.0) for the BCG-I+M arm
- The observed safety profile was consistent with the known safety profile for each individual agent
- Serious TRAEs were reported in 62 (17.7%) and 5 (1.4%) patients in the sasanlimab + BCG-I+M and BCG-I+M arms, respectively
- There were no TRAEs leading to death in the sasanlimab + BCG-I+M and BCG-I+M arms
- **Figure 6** shows TRAEs that occurred in at least 15% of the patients or grade ≥3 TRAEs that occurred in at least 2% of the patients in the sasanlimab + BCG-I+M and BCG-I+M arms
- The combination with BCG did not substantially impact incidence and severity of irAEs (**Table 2**)
  - There were no irAEs leading to death in the sasanlimab + BCG-I+M arm and 1 in the sasanlimab + BCG-I arm (myocarditis)

Figure 2. EFS: Sasanlimab + BCG-I+M vs BCG-I+M

A. Intent-to-Treat Population



B. Disease Subgroups



C. VHR Disease Subgroup

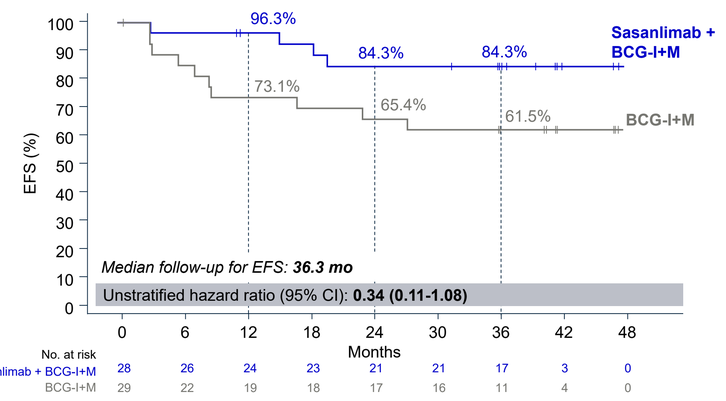


Figure 4. Duration of CR in Patients With CIS Who Achieved CR

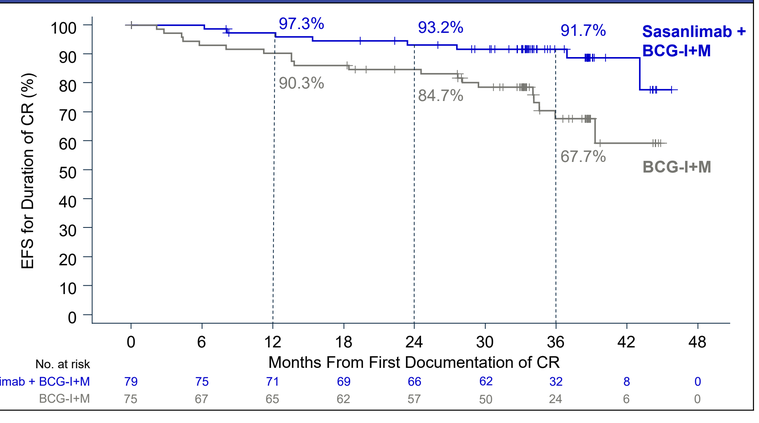


Figure 5. EORTC-QLQ-C30 Global Quality of Life

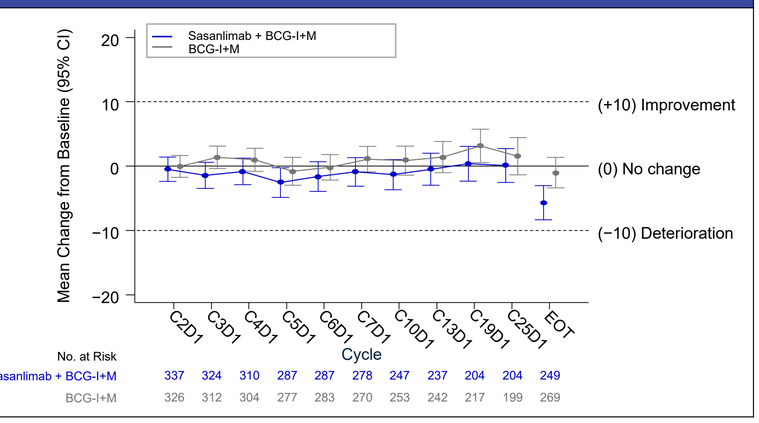


Figure 6. TRAEs for Sasanlimab + BCG-I+M and BCG-I+M

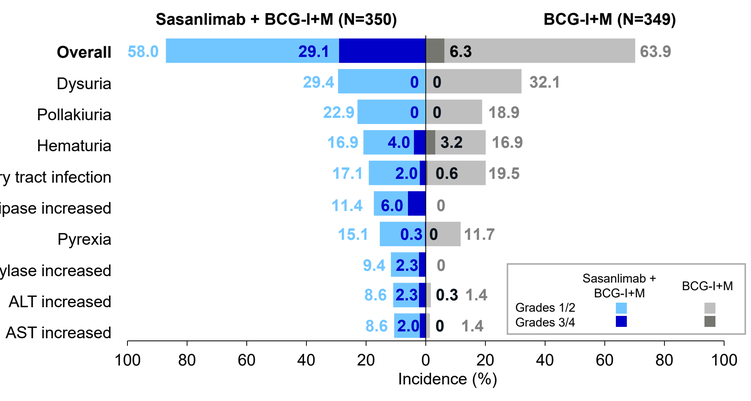


Figure 3. OS: Sasanlimab + BCG-I+M vs BCG-I+M

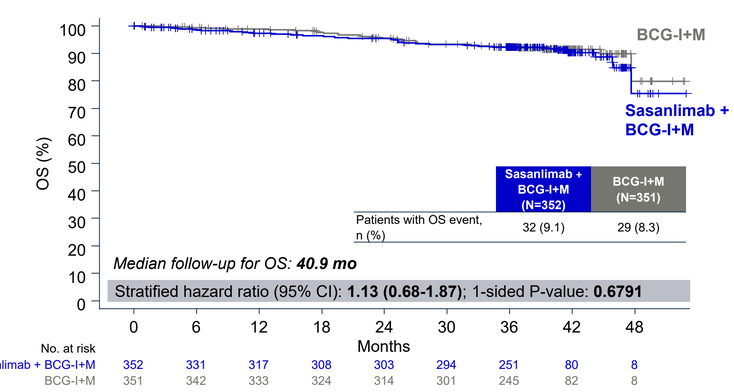


Table 1. Baseline Demographics and Disease Characteristics for Sasanlimab + BCG-I+M vs BCG-I+M

	Sasanlimab + BCG-I+M (N=352)	BCG-I+M (N=351)
Median age, (range) y	67 (31–85)	67 (31–91)
Male, n (%)	280 (79.5)	284 (80.9)
Race, n (%)		
White	225 (63.9)	210 (59.8)
Asian	115 (32.7)	126 (35.9)
ECOG PS, n (%)		
0	298 (84.7)	291 (82.9)
1	54 (15.3)	59 (16.8)
Geographic region, n (%)		
US	49 (13.9)	47 (13.4)
Western Europe or Canada	85 (24.1)	86 (24.5)
Rest of world	218 (61.9)	218 (62.1)
Smoking history, n (%)		
Never smoker	127 (36.1)	126 (35.9)
Current smoker	71 (20.2)	54 (15.4)
Former smoker	154 (43.8)	171 (48.7)
Disease stage, n (%)		
Ta	96 (27.3)	107 (30.5)
T1	204 (58.0)	194 (55.3)
Pure CIS	52 (14.8)	50 (14.2)
CIS ± Ta or T1	88 (25.0)	88 (25.1)

Table 2. irAEs for Sasanlimab + BCG-I+M and Sasanlimab + BCG-I

	Sasanlimab + BCG-I+M (N=350)		Sasanlimab + BCG-I (N=348)	
	Grades 1/2	Grades 3/4	Grades 1/2	Grades 3/4
Any irAE, n (%)	94 (26.9)	55 (15.7)	114 (32.8)	48 (13.8)
Thyroid disorders	60 (17.1)	2 (0.6)	70 (20.1)	1 (0.3)
Rash	36 (10.3)	10 (2.9)	40 (11.5)	8 (2.3)
Hepatitis	3 (0.9)	12 (3.4)	3 (0.9)	11 (3.2)
Pancreatitis	7 (2.0)	7 (2.0)	4 (1.1)	6 (1.7)
Adrenal insufficiency	6 (1.7)	6 (1.7)	7 (2.0)	5 (1.4)
Pneumonitis	6 (1.7)	4 (1.1)	3 (0.9)	1 (0.3)
Colitis	4 (1.1)	5 (1.4)	6 (1.7)	3 (0.9)
Hypophysitis/Hypopituitarism	4 (1.1)	4 (1.1)	6 (1.7)	3 (0.9)
Type 1 diabetes	1 (0.3)	6 (1.7)	0	4 (1.1)
Nephritis and renal dysfunction	2 (0.6)	4 (1.1)	2 (0.6)	7 (2.0)
Myasthenic syndrome/Myasthenia gravis	1 (0.3)	1 (0.3)	0	0
Myocarditis	0	1 (0.3)	1 (0.3)	1 (0.3)
Myositis	0	1 (0.3)	1 (0.3)	1 (0.3)
Uveitis	0	1 (0.3)	0	0
Other irAEs[a]	7 (2.0)	1 (0.3)	12 (3.4)	4 (1.1)

[a]Other irAEs were psoriasis, vitiligo, rheumatoid arthritis, polymyalgia rheumatica, dermatitis psoriasiform, Sjogren's syndrome, immune thrombocytopenia, and pulmonary sarcoidosis.

Abbreviations

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCG, Bacillus Calmette-Guérin; C, cycle; CI, confidence interval; CIS, carcinoma in situ; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; CR, complete response; D, day; EAU, European Association of Urology; EFS, event-free survival; EOT, end of treatment; HR-NMIBC, high-risk non–muscle-invasive bladder cancer; I, induction; irAE, immune-related adverse event; M, maintenance; PD-1, programmed cell death-1; PD-L1/PD-L2, programmed cell death-ligand 1/2; R, randomization; SC, subcutaneous; TRAE, treatment-related adverse event; TURBT, transurethral resection of bladder tumor; VHR, very high risk.

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Disclosures

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