NCT04165317

Sasanlimab in combination with Bacillus Calmette-Guérin (BCG) in BCG-naive, high-risk non-muscle-invasive bladder cancer (NMIBC): Patient-reported outcomes (PROs) from CREST

Jens Bedke,[1] Neal D. Shore,[2] Thomas B. Powles,[3] Matthew D. Galsky,[4] Joan Palou Redorta,[5] Daniel Robin Saltzstein,[6] Félix Guerrero-Ramos,[7] Motonobu Nakamura,[8] Tilman Todenhöfer,[9] Raj Satkunasivam,[10] Peter C. Black,[11] Julia Brinkmann,[12] Jane Chang,[13] Anthony Eccleston,[14] Arlene Reisman,[15] Jennifer Vermette,[16] Gary D. Steinberg[17]

[1]Department of Urology & Transplantation Surgery, Eva May-Stihl Cancer Center, Klinikum Stuttgart, Stuttgart, Germany; [2]START Carolinas/Carolina Urologic Research Center, UC Urology Specialists, Myrtle Beach, SC, USA; [3]Barts Experimental Cancer Medicine Centre, Barts Cancer Institute, Queen Mary University of London, London, UK; [4]The Tisch Cancer Institute, Mount Sinai, New York, NY, USA; [5]Department of Urology, Fundació Puigvert, Universitat Autònoma de Barcelona, Barcelona, Spain; [6]Urology San Antonio, San Antonio, TX, USA; [7]Department of Urology, 12 de Octubre Hospital Universitario Madrid, Spain; [8]Department of Urology, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan; [9]Studienpraxis Urologie, Nürtingen, Germany; [10]Department of Urology, Houston Methodist Hospital, Houston, TX, USA; [11]Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada; [12]Pfizer Pharma GmbH, Berlin, Germany; [13]Pfizer Inc, New York, NY, USA; [14]Pfizer Ltd, Tadworth, UK; [15]Pfizer Inc, Pearl River, NY, USA; [16]Pfizer Inc, Cambridge, MA, USA; [17]Department of Urology, Rush University Medical Center, Chicago, IL, USA

Objective

- To evaluate PROs from the CREST study (NCT04165317) to assess the impact of sasanlimab in combination with BCG-I+M on quality of life in patients with high-risk NMIBC

Conclusions

- In both the sasanlimab + BCG-I+M (Arm A) and BCG-I+M (Arm C) arms, PROs across functioning domains and key symptoms measured by the EORTC QLQ-C30 and NMIBC24 questionnaires had no clinically meaningful change from baseline, based on a 10-point threshold
- Between-group differences in within-group change did not meet the threshold of a 5- to 10-point difference to be clinically meaningful
- These PROs can help inform the benefit-risk assessment of sasanlimab in combination with BCG-I+M
- The enhanced efficacy outcomes reported in the primary analysis[1] and these results support that subcutaneous sasanlimab in combination with BCG-I+M has the potential to redefine the treatment paradigm and clinical decision-making for patients with high-risk NMIBC without additional impacts on patient quality of life

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References: **1.** Shore N, *et al. AUA 2025* (Oral). **2.** Holzbeierlein JM, *et al. J Urol.* 2024; 211:533-8. **3.** Gontero P, *et al. Eur Urol.* 2024;86:531-49. **4.** Kamat AM, *et al. J Clin Oncol.* 2016;34(16):1935-1944. **5.** Aguiar-Ibáñez R, *et al. Adv Ther.* 2024;41(12):4396-4417. **6.** Osoba D, *et al. J Clin Oncol.* 1998;16(1):139-144.

Abbreviations: BCG, Bacillus Calmette-Guérin; BL, baseline; C, cycle; CIS, carcinoma in situ; CR, complete response; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; D, day; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; EORTC, European Organization for the Research and Treatment of Cancer; EOT, end of treatment; FU, follow-up; HR, high-risk; I, induction; IC+, PD-L1-positive immune cells; ICP, immune cells present in the tumor area; M, maintenance; NMIBC, non-muscle-invasive bladder cancer; PD-(L)1, PD-1, Programmed cell death-ligand(1; QLQ-C30, Core Quality of Life questionnaire; QLQ-NMIBC24, Non-Muscle-Invasive Bladder Cancer Quality of Life questionnaire; QOL, quality of life; TC, tumor cell; TURBT, transurethral resection of bladder tumor; UC, urothelial carcinoma.

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Contact: Jens Bedke, bedke@live.com

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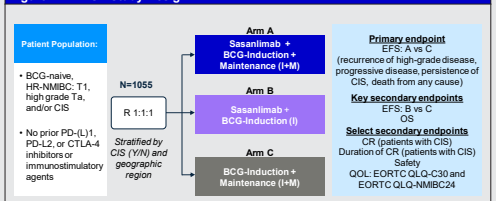
Background

- Standard care for high-risk NMIBC includes TURBT followed by BCG-I+M[2,3]
  - Approximately 40% of patients experience disease recurrence or progression at 24 months, with unfavorable prognosis[4]
  - There is a high unmet need for enhanced treatment options that provide durable disease control by delaying disease recurrence and progression while maintaining quality of life[3]
- In the Phase 3 CREST trial, sasanlimab in combination with BCG-I+M (Arm A) showed a statistically significant prolongation of EFS compared with the standard of care (BCG-I+M; Arm C) in patients with high-risk NMIBC[1]
  - No difference in EFS was observed between sasanlimab in combination with BCG-I (Arm B) and BCG-I+M (Arm C)[1]
- Oncology studies of patient preferences suggest that patients generally prefer the subcutaneous route of administration to other routes[5]
  - In the CREST study, subcutaneous sasanlimab (300 mg) was administered in a 2-mL prefilled syringe every 4 weeks, for up to 25 cycles
- Here, we report PROs for Arm A vs C of the CREST study to assess the impact of sasanlimab in combination with BCG-I+M on quality of life in patients with high-risk NMIBC

Methods

- CREST is a global, phase 3, randomized study (**Figure 1**)

Figure 1. CREST Study Design



Final EFS analysis data cut-off date: Dec 2, 2024

BCG-I+M: BCG induction (6 doses)[a] and maintenance (up to 2 years) therapy
BCG-I: BCG induction (6 doses)[a] only
Sasanlimab: Administered SC for up to 25 four-week cycles

[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. BCG, Bacillus Calmette-Guérin; CIS, carcinoma in situ; CR, complete response; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; EFS, event-free survival; EORTC, European Organization for Research and Treatment of Cancer; HR, high-risk; I, induction; M, maintenance; PD-1, Programmed cell death-1; PD-L1/PD-L2, Programmed cell death-ligand 1/2; QLQ-C30, Core Quality of Life questionnaire; QLQ-NMIBC24, Non-Muscle-Invasive Bladder Cancer Quality of Life questionnaire; QOL, quality of life; R, randomization.

PROs

- PROs were secondary endpoints and not included in the testing hierarchy
- EORTC QLQ-C30 and EORTC QLQ-NMIBC24 questionnaires were conducted at baseline, throughout treatment at select scheduled visits, and during the safety follow-up periods (**Figure 2**)
  - The EORTC QLQ-C30 and NMIBC24 items were scored according to their respective user guides
  - Missing items were handled according to the respective scoring manuals

Figure 2. Schedule of PRO Assessment

BL	C1D1 through C7D1[a]	C10D1	C13D1	C15D1	C19D1	C25D1	EOT	Disease FU[b]
✓	✓	✓	✓	✓	✓	✓	✓	✓

[a]Completed every 4 weeks. [b]Patients with no recurrence of high-grade disease or disease progression before EOT were assessed every 12 weeks for 2 years after randomization and every 24 weeks thereafter until recurrence of high-grade disease or disease progression, consent withdrawal, lost to follow up or death. BL, baseline; C, cycle; D, day; EOT, end of treatment; FU, follow-up.

- Completion rates were calculated as the number of patients who completed all questions divided by the number of patients who were expected to complete the questionnaire at each respective visit
- Plots of mean change from baseline over time for the EORTC QLQ-C30 Global Health Status and NMIBC24 urinary symptoms scores are descriptive
- Longitudinal mixed effect-model analyses were used to assess change from baseline in the EORTC QLQ-C30 and NMIBC24 items
  - All available data for each participant prior to the end of therapy were used in the analyses
  - Data are presented as estimated least square means with 95% CI
  - Random coefficient models were carried out for the EORTC QLQ-C30 and NMIBC24 (all domains, subscales, and symptoms)
  - Model predictors were the corresponding baseline PRO score, treatment, time (treated as a continuous variable), and treatment-by-time interaction; intercept and time were considered as random effects particular to each participant
- A ≥10-point within-group change from baseline has been validated as clinically meaningful for EORTC QLQ-C30[6]
- A between-group estimated mean difference in within-group change of 5 to 10 points is typically considered clinically meaningful
- Data are shown for Arm A and Arm C

Results

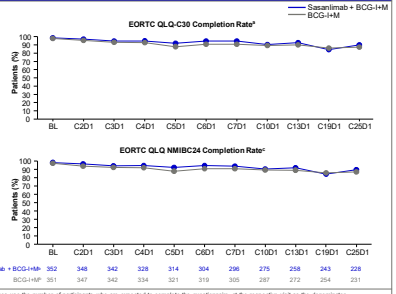
- Baseline demographics and disease characteristics were generally balanced between arms (**Table 1**)
  - The study population for Arms A and C was predominantly male (80.2%) and had an ECOG performance status of 0 (83.8%)
  - UC was reported in 95.4% of patients, 56.6% had T1 tumor as the highest grade, and 25.0% had CIS with or without papillary tumors

Table 1. Baseline Demographics and Disease Characteristics

	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 performance status, n (%)		
0	298 (84.7)	291 (82.9)
1	54 (15.3)	59 (16.8)
2	0	1 (0.3)
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)
Histological classification, n (%)		
UC	339 (96.3)	332 (94.6)
UC with squamous differentiation	6 (1.7)	8 (2.3)
UC with glandular differentiation	2 (0.6)	3 (0.9)
UC with variant histology	4 (1.1)	6 (1.7)
Other	1 (0.3)	2 (0.6)
Presence of CIS at randomization, n (%)	88 (25.0)	88 (25.1)
Worst T stage, n (%)		
CIS	52 (14.8)	50 (14.2)
Ta	96 (27.3)	107 (30.5)
T1	204 (58.0)	194 (55.3)
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)
PD-L1 status		
High[a]	77 (22.6)	73 (21.7)
Low[b]	252 (74.1)	253 (75.1)
Unknown	11 (3.2)	11 (3.3)

[a]PD-L1 status was defined as: High if TC ≥25% or (ICP >1% and IC> ≥25%) or (ICP>1% and IC> ≥10%); [b]PD-L1 status was defined as Low if TC ≥1% and <25% and IC <25% or (ICP<1% and IC< ≥10%) or (ICP<1% and IC< ≥10%) or (ICP<1% and IC<1%). BCG, Bacillus Calmette-Guérin; CIS, carcinoma in situ; ECOG, Eastern Cooperative Oncology Group; I, induction; IC+, PD-L1-positive immune cells; ICP, immune cells present in the tumor area; M, maintenance; TC, tumor cell; UC, urothelial carcinoma.

Figure 3. Completion rates for EORTC QLQ-C30 and EORTC QLQ- NMIBC24



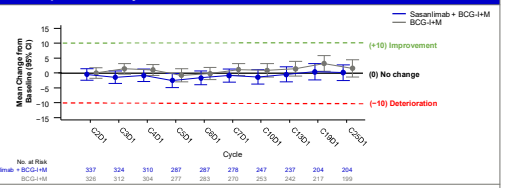
Percentages use the number of participants who are expected to complete the questionnaire at the respective visit as the denominator. [a]All questions answered. [b]Number of participants who are expected to complete the questionnaire at the respective visit. [c]At least 1 question answered. BCG, Bacillus Calmette-Guérin; BL, baseline; C, cycle; D, day; EORTC, European Organization for Research and Treatment of Cancer; I, induction; M, maintenance; QLQ-C30, Core Quality of Life questionnaire; QLQ-NMIBC24, Non-Muscle-Invasive Bladder Cancer Quality of Life questionnaire.

- At data cutoff (Dec 2, 2024), 695 of 703 patients randomized to Arms A (n=348) and C (n=347) had a baseline score and ≥1 post-baseline score
- Completion rates were >84% for all visits through the end-of-treatment visit (Cycle 25) (**Figure 3**)

EORTC QLQ-C30

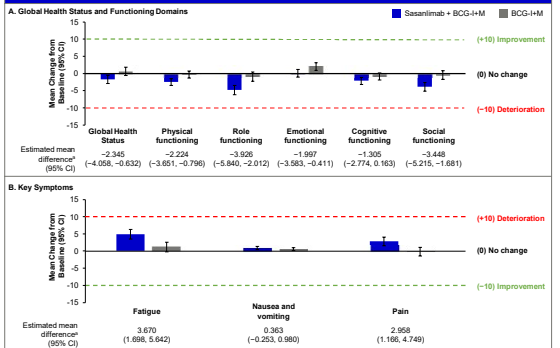
- Baseline Global Health Status scores were numerically similar between arms (mean [SD]: Arm A, 75.1 [17.5] vs Arm C, 75.6 [18.1]; not shown)
- A descriptive summary of mean change from baseline over time for the EORTC QLQ-C30 by visit for each treatment arm is shown for Global Health Status (**Figure 4**)
  - Longitudinal changes for the functioning scales (not shown) had similar findings to the Global Health Status
- In the mixed model analysis, no functioning scale or symptom met the definition of a clinically meaningful change from baseline of ≥10 points for either treatment arm for within-arm comparisons (**Figure 5**)
- No differences met the 5 to 10-point threshold of a clinically meaningful difference between treatment arms (**Figure 5**)

Figure 4. Descriptive Summary of EORTC QLQ-C30: Global Health Status[4]



BCG, Bacillus Calmette-Guérin; C, Cycle; D, Day; EORTC, European Organization for Research and Treatment of Cancer; I, induction; M, maintenance; QLQ-C30, Core Quality of Life questionnaire.

Figure 5. Mixed Model Analysis of EORTC QLQ-C30

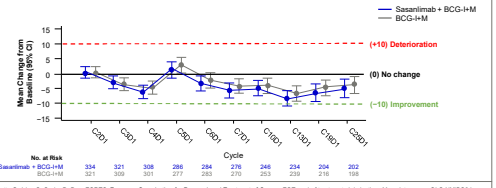


Analysis model included post baseline assessments up to end of treatment, but not including end of treatment. Unscheduled visits were excluded from the analysis. [a]Between-group differences in within-group change. BCG, Bacillus Calmette-Guérin; EORTC, European Organization for Research and Treatment of Cancer; I, induction; M, maintenance; QLQ-C30, Core Quality of Life questionnaire.

EORTC QLQ-NMIBC24

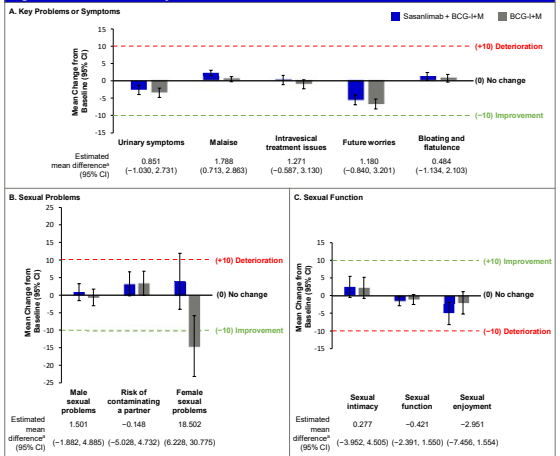
- A descriptive summary of mean change from baseline over time for the EORTC QLQ-NMIBC24 urinary symptoms by visit for each treatment arm is shown (**Figure 6**)
- In the mixed model analysis for estimated mean differences between groups, no symptom met the threshold for a clinically meaningful difference between treatment arms, and no symptom met the definition of a clinically meaningful change from baseline in either treatment arm, except female sexual problems, which was assessed in a small subset of patients (Arm A, n=5; Arm C, n=4) (**Figure 7**)

Figure 6. Descriptive Summary of EORTC QLQ-NMIBC24: Urinary Symptoms



BCG, Bacillus Calmette-Guérin; C, Cycle; D, Day; EORTC, European Organization for Research and Treatment of Cancer; EOT, end of treatment; I, induction; M, maintenance; QLQ-NMIBC24, Non-Muscle-Invasive Bladder Cancer Quality of Life questionnaire.

Figure 7. Mixed Model Analysis of EORTC QLQ-NMIBC24



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