Poster 3078P

Immune-mediated adverse events (imAEs) associated with sasanlimab in combination with Bacillus Calmette-Guérin (BCG): Phase 3 study (CREST)

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Objective

- To characterize imAEs and their management for sasanlimab in combination with BCG in the CREST study (NCT04165317)

Conclusions

- Sasanlimab in combination with BCG showed a safety profile consistent with both the anti–PD-1/PD-L1 drug class and BCG
  - No increased risk of either imAEs associated with sasanlimab or BCG-related AEs was observed with the combination
- imAEs were mostly grade 1 or 2
- For most imAE categories, median time to first onset was within the first 6 months of treatment initiation, and most resolved within 6 months of onset
- imAEs were effectively managed in line with standard guidelines, including treatment modifications (interruptions and discontinuations) and corticosteroids and/or hormonal therapy[1-4]

General Footnotes

"Other imAEs" by MedDRA Preferred Term included psoriasis, polymyalgia rheumatica, vitiligo, rheumatoid arthritis, dermatitis psoriasiform, Sjogren's syndrome, immune thrombocytopenia, and pulmonary sarcoidosis.

Abbreviations

AE, adverse event; BCG, Bacillus Calmette-Guérin; CI, confidence interval; CIS, carcinoma in situ; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; HR, hazard ratio; I, induction; imAE, immune-mediated adverse event; M, maintenance; MedDRA, Medical Dictionary for Regulatory Activities; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NMIBC, non-muscle invasive bladder cancer; PD-1, programmed cell death-1; PD-L1/PD-L2, programmed cell death-ligand 1/2; R, randomization.

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Disclosures

Jens Bedke reports financial interests from Astellas, AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Eisai, Ipsen, Janssen, Merck Sorono, Merck Sharp & Dohme, Pfizer, Roche, Nektar, Novartis, and Seagen; and membership in the European Association of Urology and the Renal Cell Carcinoma Guidelines Panel (Vice-Chairman).

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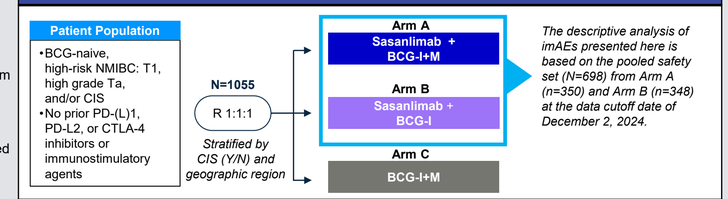
Background

- CREST (NCT04165317) is a global, open-label, phase 3, randomized study that showed a statistically significant prolongation of event-free survival for subcutaneous sasanlimab in combination with BCG-I+M (Arm A) compared with BCG-I+M (Arm C) in patients with high-risk NMIBC (HR, 0.68; 95% CI,0.49-0.94; one-sided P=0.0095)[5]
- The overall safety profile of sasanlimab in combination with BCG has been previously reported and was consistent with the known safety profile for each individual agent[5]
- PD-1/PD-L1 inhibitors, including sasanlimab, are associated with imAEs, which may affect various organ systems[6-8]
- Guidance for monitoring and management of imAEs was included in the CREST protocol[5]
- In current clinical practice, the management of imAEs is outlined in product labels and existing guidelines and involves comprehensive diagnostics and treatments, such as corticosteroids and hormonal therapy[1-4,9-10]

Methods

- Baseline demographics and disease characteristics of the intent-to-treat population have been reported previously[5]
- The safety analysis set comprised all patients who were randomized to a treatment arm and received ≥1 dose of a study drug
- As of the data cutoff date (December 2, 2024), the safety analysis set consisted of 698 patients: 350 patients in the sasanlimab in combination with BCG-I+M arm and 348 patients in the sasanlimab in combination with BCG-I arm (**Figure 1**)
- All analyses are descriptive, and data from both treatment arms containing sasanlimab in combination with BCG are presented as pooled data
- imAEs are presented in categories, which include a cluster of MedDRA Preferred Terms representing similar clinical symptoms or syndromes
- Safety assessments consisted of monitoring and documenting AEs and laboratory abnormalities throughout the treatment and up to 90 days post-final dose (safety assessment period), with clinical and laboratory assessments conducted at least every 4 weeks
- imAEs have been classified as imAEs by the sponsor, and each category has been characterized by maximum severity according to NCI CTCAE version 5.0

Figure 1. CREST Study Design



Treatment schedule
- Sasanlimab was administered subcutaneously for up to 25 four-week cycles
- BCG-I+M consisted of BCG induction (6 doses) and maintenance (up to 2 years) therapy. BCG-I consisted of BCG induction (6 doses) only. Re-induction was permitted for patients with carcinoma in situ at randomization who had persistent disease or recurrence of high-grade Ta disease 3 months after initiating study treatment

Endpoints
- The primary endpoint was investigator-assessed event-free survival for Arms A vs C, defined as time from randomization to recurrence of high-grade disease, progressive disease, persistence of CIS, or death from any cause
- Key secondary endpoints were investigator-assessed event-free survival (Arms B vs C) and overall survival (Arms A vs C; Arms B vs C). Safety was a select secondary endpoint

Results

Exposure

- In the safety analysis set, BCG-I was completed by 96.6%, 96.3%, and 97.4% of patients in Arms A, B, and C, respectively
- The median number (range) of BCG-M doses received was 12 (0-16) for sasanlimab in combination with BCG-I+M arm (Arm A) and 15 (0-18) for the BCG-I+M arm (Arm C)

Frequency and severity of imAEs

- Rates of imAEs were similar between the sasanlimab in combination with BCG-I+M arm (any grade: 42.6%; grade ≥3: 15.7%) and the sasanlimab in combination with BCG-I arm (any grade: 46.8%; grade ≥3: 14.1%)
- imAEs of any grade were reported in 44.7% of patients in the pooled population (**Figure 2**)
- Serious imAEs and imAEs leading to hospitalization occurred in 11.2% and 10.3% of patients, respectively (data not shown)
- The most common any-grade imAEs by category were thyroid disorders (19.1%) and rash (13.5%), and the most common grade ≥3 imAEs by category were hepatitis (3.3%) and rash (2.6%) (**Figure 3**)

Onset of imAEs

- The median time to first onset of any-grade imAEs was 16.1 weeks (**Figure 4**)
  - Median time to first onset was <6 mo for most imAE categories, with all categories having a median time to first onset <1 yr

Dose modification for imAEs

- imAEs led to interruption of sasanlimab in 13.2% of patients and BCG in 2.7% of patients (**Table 1**)
  - The most common reasons for interruption of sasanlimab were thyroid disorder (4.0%), rash (2.9%), and pancreatitis (1.6%); the most common reasons for BCG interruption were colitis (0.7%), pancreatitis (0.4%), and pneumonitis (0.4%)
- Permanent discontinuation of sasanlimab due to imAEs occurred in 16.0% of patients, and permanent discontinuation of BCG occurred in 1.6% of patients (**Table 1**)
  - The most common reasons for discontinuation of sasanlimab were rash (2.9%), hepatitis (2.7%), and adrenal insufficiency (1.6%); the most common reasons for BCG discontinuation were rash (0.6%) and hepatitis (0.3%)

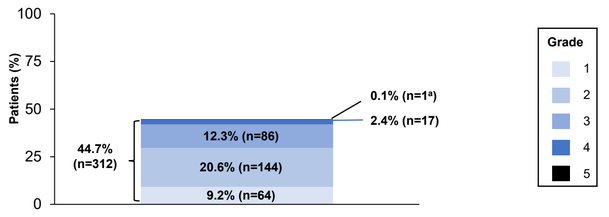
Treatment of imAEs

- Overall, 44.6% of patients with an imAE received corticosteroids, including 24.7% who received ≥40 mg total daily prednisolone dose equivalent (**Figure 5**)
  - A high proportion of patients with adrenal insufficiency (100.0%) and hypophysitis/hypopituitarism (94.1%) received corticosteroids
- Immune suppressants excluding corticosteroids were used in 10 patients (3.2%), including 4 with rash, 2 with hepatitis, 1 with nephritis and renal dysfunction, 1 with myositis, and 2 with other imAEs
- Thyroid replacement therapy was required for 73.7% of patients with an immune-mediated thyroid disorder
- All 11 patients with immune-mediated type 1 diabetes required insulin

Outcomes of imAEs

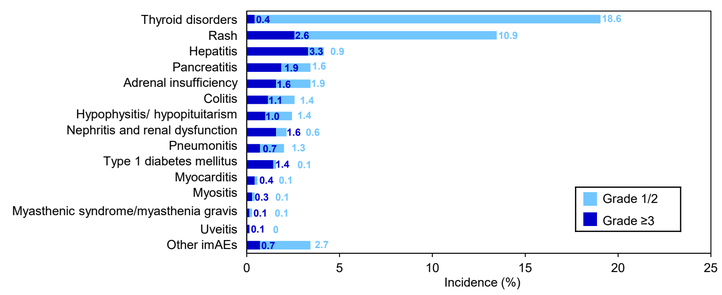
- At the data cutoff date, 17.9% of patients had all imAEs resolved, 26.6% of patients had ≥1 ongoing imAE, and 1 patient (0.1%) had an imAE with a fatal outcome (**Table 1**)
- The overall median time to resolution across all imAEs categories was 18.3 weeks (**Figure 6**)
  - imAE categories with the longest median time to resolution were hypophysitis/hypopituitarism, adrenal insufficiency, and thyroid disorders (**Figure 6**)

Figure 2. Proportion of Patients With imAEs by Highest Grade (Sasanlimab in Combination With BCG—Pooled Data)



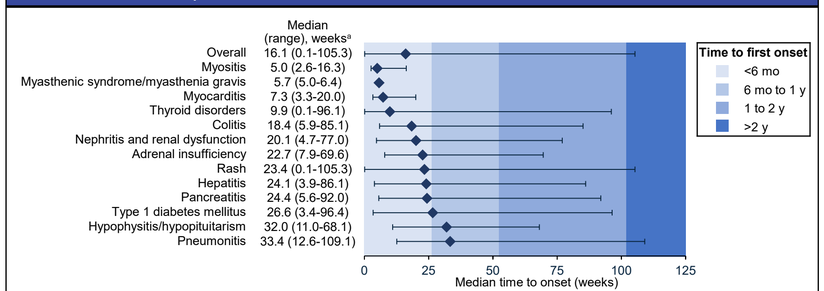
The denominator to calculate percentages is N, the number of participants in the pooled safety analysis set.
[a]Myocarditis in the sasanlimab in combination with BCG-I arm (Arm B).

Figure 3. Incidence and Severity of imAE Categories (Sasanlimab in Combination With BCG—Pooled Data)



The denominator to calculate percentages is N, the number of participants in the pooled safety analysis set.

Figure 4. Median Time to First Onset of imAE (Sasanlimab in Combination With BCG—Pooled Data)



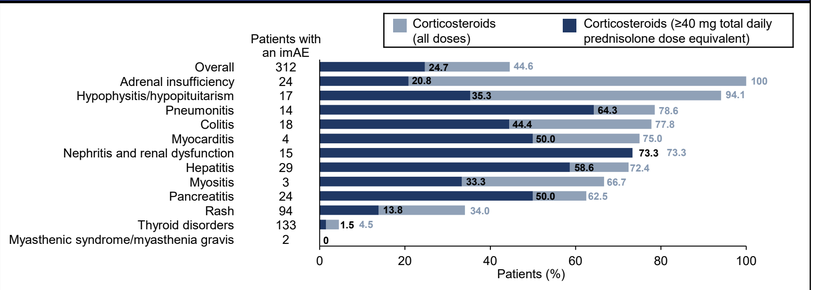
[a]Median onset (range) was 4.1 (4.1-4.1) weeks for uveitis (n=1) and 31.2 (0.1-77.4) weeks for other imAEs (n=24), which are not shown in the figure.

Table 1. Summary of imAE Management and Resolution (Sasanlimab in Combination With BCG—Pooled Data)

Patients, n (%)	Pooled (N=698)
Study drug discontinuation due to an imAE	
imAE leading to sasanlimab discontinuation	112 (16.0)
imAE leading to BCG discontinuation[a]	11 (1.6)
Study drug interruption due to an imAE[a]	
imAE leading to sasanlimab interruption	92 (13.2)
imAE leading to BCG interruption[a]	19 (2.7)
Resolution of imAEs	
All imAEs resolved	125 (17.9)
Any imAEs ongoing	186 (26.6)
imAE with fatal outcome	1 (0.1)[b]

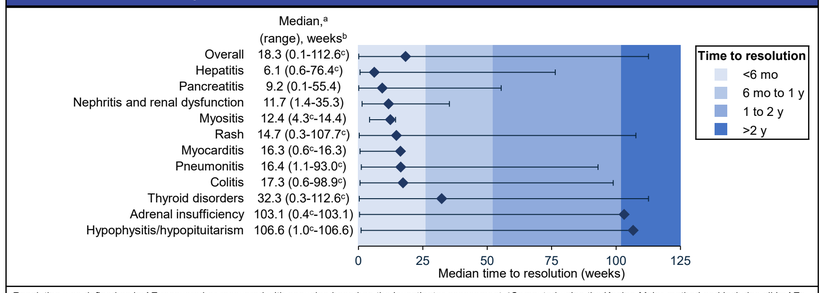
The denominator to calculate percentages is N, the number of participants in the pooled safety analysis set. [a]imAEs leading to discontinuation/interruption of BCG were due to the severity of the imAE and not due to a suspected association with BCG. [b]Myocarditis in the sasanlimab in combination with BCG-I arm (Arm B).

Figure 5. Corticosteroid Use in Patients With an imAE (Sasanlimab in Combination With BCG—Pooled Data)



The denominator to calculate percentages is the number of participants with ≥1 imAE within each cluster.

Figure 6. Median Time to Resolution of all imAEs (Sasanlimab in Combination With BCG—Pooled Data)



Resolution was defined as imAE recovered or recovered with sequelae based on the investigator assessment. [a]Computed using the Kaplan-Meier method and includes all imAEs. [b]Median time to resolution (range) was 10.9 (10.9-10.9) weeks for uveitis (n=1) and 69.3 (1.0-94.3) weeks for other imAEs (n=24), which are not shown in the figure. Myasthenic syndrome/myasthenia gravis and type 1 diabetes not reported due to median time to resolution being not assessable. If multiple imAEs were observed in the same patient, all are included. [c]Indicates the value is censored.