Taylor & Francis
Taylor & Francis Group

Future Oncology

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ifon20

CREST: phase III study of sasanlimab and Bacillus Calmette-Guérin for patients with Bacillus Calmette-Guérin-naïve high-risk non-muscle-invasive bladder cancer

Gary D Steinberg, Neal D Shore, Joan Palou Redorta, Matthew D Galsky, Jens Bedke, Ja Hyeon Ku, Michal Kretkowski, Hailong Hu, Konstantin Penkov, Jennifer J Vermette, Jamal C Tarazi, Alison E Randall, Kristen J Pierce, Daniel Saltzstein & Thomas B Powles

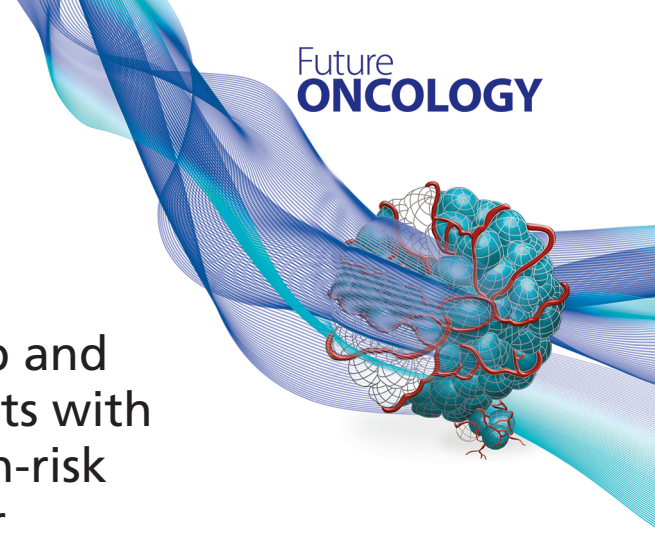
To cite this article: Gary D Steinberg, Neal D Shore, Joan Palou Redorta, Matthew D Galsky, Jens Bedke, Ja Hyeon Ku, Michal Kretkowski, Hailong Hu, Konstantin Penkov, Jennifer J Vermette, Jamal C Tarazi, Alison E Randall, Kristen J Pierce, Daniel Saltzstein & Thomas B Powles (2024) CREST: phase III study of sasanlimab and Bacillus Calmette-Guérin for patients with Bacillus Calmette-Guérin-naïve high-risk non-muscle-invasive bladder cancer, Future Oncology, 20:14, 891-901, DOI: 10.2217/fon-2023-0271

To link to this article: https://doi.org/10.2217/fon-2023-0271

Clinical Trial Protocol

For reprint orders, please contact: reprints@futuremedicine.com

Future ONCOLOGY



CREST: phase III study of sasanlimab and Bacillus Calmette-Guérin for patients with Bacillus Calmette-Guérin-naïve high-risk non-muscle-invasive bladder cancer

Gary D Steinberg*[,1], Neal D Shore[2], Joan Palou Redorta[3], Matthew D Galsky[4], Jens Bedke[5], Ja Hyeon Ku[6], Michal Kretkowski[7], Hailong Hu[8], Konstantin Penkov[9], Jennifer J Vermette[10], Jamal C Tarazi[11], Alison E Randall[12], Kristen J Pierce[13], Daniel Saltzstein[14] & Thomas B Powles[15]

[1]Department of Urology, Rush University Medical Center, Chicago, IL, USA
[2]Carolina Urologic Research Center, Grand Strand Urology, 823 82nd Parkway, Myrtle Beach, SC 29572, USA
[3]Department of Urology, Fundació Puigvert, Universitat Autònoma de Barcelona, C. de Cartagena 340-350, 08025 Barcelona, Spain
[4]The Tisch Cancer Institute, Mount Sinai, 1190 One Gustave L. Levy Place, New York, NY 10029, USA
[5]Department of Urology, Eberhard Karls University Tübingen, Geschwister-Scholl-Platz, 72074 Tübingen, Germany
[6]Department of Urology, Seoul National University Hospital, 101 Daehak-ro Jongno-gu, Seoul 03080, Republic of Korea
[7]Clinical Research Center, Spolka z Ograniczona, Feliksa Nowowiejskiego 5, 61-731 Poznań, Poland
[8]Institute of Urology, Second Hospital of Tianjin Medical University, 23 Pingjiang Road, Hexi District, Tianjin 300211, China
[9]Private Medical Institution Euromedservice, Suvorovskiy Prospekt, 60, St Petersburg, Russia
[10]Pfizer Oncology, Pfizer, 1 Portland Street, Cambridge, MA 02139, USA
[11]Pfizer Oncology, Pfizer, 10646 Science Center Drive, San Diego, CA 92121, USA
[12]Pfizer Oncology, Pfizer, 235 East 42nd Street, New York, NY 10017, USA
[13]Pfizer Oncology, Pfizer, 280 Shennecossett Road, Groton, CT 06340, USA
[14]Division of Urology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78229, USA
[15]Barts Experimental Cancer Medicine Centre, Barts Cancer Institute, Queen Mary University of London, Charterhouse Square, London EC1M 5PZ, UK
*Author for correspondence: Tel.: +1 646 825 6300; Gary.Steinberg@nyulangone.org

Bacillus Calmette-Guérin (BCG) is the standard of care for patients with high-risk non-muscle-invasive bladder cancer (NMIBC) after transurethral resection of bladder tumor (TURBT). BCG in combination with programmed cell death-1 (PD-1) inhibitors may yield greater anti-tumor activity compared with either agent alone. CREST is a phase III study evaluating the efficacy and safety of the subcutaneous PD-1 inhibitor sasanlimab in combination with BCG for patients with BCG-naive high-risk NMIBC. Eligible participants are randomized to receive sasanlimab plus BCG (induction ± maintenance) or BCG alone for up to 25 cycles within 12 weeks of TURBT. The primary outcome is event-free survival. Secondary outcomes include additional efficacy end points and safety. The target sample size is around 1000 participants.

Plain language summary: Non-muscle-invasive bladder cancer (NMIBC) is the most common type of bladder cancer. Most people have surgery to remove the cancer cells while leaving the rest of the bladder intact. This is called transurethral resection of a bladder tumor (TURBT). For people with high-risk NMIBC, a medicine called Bacillus Calmette-Guérin (BCG) is placed directly inside the bladder after TURBT. A 'high risk' classification means that the cancer is more likely to spread or come back after treatment. Some people's cancer does not respond to BCG or returns after BCG treatment. Researchers are currently looking at whether BCG combined with other immunotherapies may prevent cancer growth more than BCG on its own. Immunotherapy helps the immune system recognize and kill cancer cells. Sasanlimab is an immunotherapy medicine that is not yet approved to treat people with NMIBC. It is given as an injection under the skin. In this CREST study, researchers are looking at how safe and effective sasanlimab plus BCG is for people with high-risk NMIBC. Around 1000 people are taking part in CREST. They must have had TURBT 12 weeks or less before joining the study. Researchers want to know how long people live without

Taylor & Francis
Taylor & Francis Group

certain events occurring, such as bladder cancer cells returning. A plain language summary of this article can be found as Supplementary Material.

Clinical Trial Registration: NCT04165317; 2019-003375-19 (EudraCT) (ClinicalTrials.gov)

Tweetable abstract: CREST is a phase III study evaluating the subcutaneous PD-1 inhibitor sasanlimab in combination with BCG versus current standard-of-care BCG monotherapy for patients with high-risk non-muscle-invasive bladder cancer (NMIBC).

First draft submitted: 30 March 2023; Accepted for publication: 1 December 2023; Published online: 8 January 2024

Keywords: Bacillus Calmette-Guérin • BCG • bladder cancer • immune checkpoint inhibitor • immunotherapy • NMIBC • non-muscle-invasive bladder cancer • PD-1 • PD-L1 • sasanlimab

Combination of sasanlimab and alternative BCG Regimens to Evaluate outcomes with Subcutaneous anti-PD-1 Treatment (CREST; ClinicalTrials.gov: NCT04165317; EudraCT: 2019-003375-19) is a phase III study evaluating the efficacy and safety of sasanlimab in combination with Bacillus Calmette-Guérin (BCG) versus BCG monotherapy for patients with BCG-naive high-risk non-muscle-invasive bladder cancer (NMIBC). CREST is sponsored by Pfizer (NY, USA).

Background & rationale

Bladder cancer is the tenth most commonly diagnosed cancer worldwide, with an estimated 573,278 new cases and 212,536 cancer-related deaths in 2020 [1]. Countries with the highest rates of bladder cancer are largely found in East Asia, as well as Southern and Western Europe [1]. Around 90% of cases in the USA are in people aged 55 years or older, with diagnosis four-times more common in males versus females [2]. While diagnosis is more common in men, women tend to present with advanced disease [3,4]. NMIBC is a heterogenous disease affecting around 75% of people diagnosed with bladder cancer [5]. NMIBC comprises noninvasive papillary carcinomas (Ta), submucosal invasive tumors (T1), and carcinoma *in situ* (CIS) [6]. Patients can be stratified into low-, intermediate- and high-risk groups for progression to muscle-invasive or advanced bladder cancer; in CREST, high-risk NMIBC is defined as the presence of CIS and/or high-grade Ta or T1 disease [7]. Treatment considerations include the European Organisation for Research and Treatment of Cancer (EORTC) risk table scores of recurrence and progression [8].

BCG is a live, attenuated vaccine form of *Mycobacterium bovis* that attaches to the urothelium via fibronectin and is subsequently internalized by bladder cancer cells. Upregulated expression of major histocompatibility class II and intracellular adhesion molecule-1 on bladder cancer cells is seen, followed by immune cell recruitment and infiltration to the tumor microenvironment via cytokine and chemokine release. This results in immune-mediated cytotoxicity of bladder cancer cells [9,10]. For patients with high-risk NMIBC, the current standard of care is transurethral resection of bladder tumor followed by intravesical BCG instillation at least 2 weeks after the last TURBT, according to the Southwest Oncology Group protocol [8,11,12]. The standard schedule for BCG is induction (once weekly for 6 weeks) followed by maintenance for 1 to 3 years [8,11,12]. The optimal duration of BCG maintenance therapy has been investigated in the EORTC genito-urinary study, where full-dose BCG maintenance for 3 years was associated with a reduction in recurrence in high-risk patients as compared with 1 year of BCG maintenance; however, there were no differences in progression or survival [13]. While around 70% of patients may achieve complete response (CR) [14], disease recurrence or progression is likely to occur in approximately 40% of high-risk patients [15,16]. Subsequent treatment options are limited for these patients, who may require radical cystectomy [17,18]. However, radical cystectomy may impact patient's health-related quality of life, in particular their body image and sexual function [19,20]. Given limited further treatment options for these patients and challenges associated with BCG treatment, such as supply shortages [21], alternative and enhanced treatments are needed to improve outcomes [16].

In recent years, several new treatment options have been investigated for patients with NMIBC, including immune checkpoint inhibitors of programmed cell death-1 (PD-1) and programmed cell death-ligand 1 (PD-L1) [18]. PD-1 is an inhibitory receptor expressed on the extracellular surface of T cells and is involved in regulating T cell-mediated immune responses [22]. Research has shown that PD-L1 is widely expressed by cancer cells [23], with overexpression accelerating tumor progression (Figure 1) [24]. One of the pro-oncogenic functions of PD-L1 is strong immunosuppression; by binding PD-1, it induces tumor tolerance and T cell exhaustion [22,24]. Increased

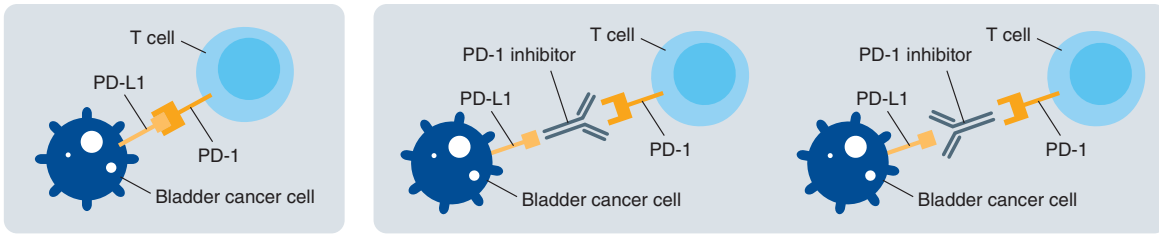


Figure 1. Mechanism of action of PD-(L)1 inhibitors.
PD-1: Programmed cell death-1; PD-L1: Programmed cell death-ligand 1.

PD-L1 expression has been observed in bladder cancer cells in response to BCG treatment in both *in vitro* and *in vivo* preclinical models [25]. Moreover, PD-L1 expression has been poised as a predictive factor of response to BCG therapy for patients with high-risk NMIBC. Evidence indicates that higher PD-L1 expression may facilitate localized progression of NMIBC and BCG treatment failure by neutralizing T cells [26,27].

Preclinical and clinical data indicate that PD-(L)1 inhibitors are active against several types of cancer, including bladder cancer [28]. The first results for PD-(L)1 inhibitors in NMIBC were reported for patients with NMIBC in the BCG-unresponsive setting [29]; however, several PD-(L)1 inhibitors are also being studied in phase III clinical trials of patients with BCG-naive high-risk NMIBC [30]. Ongoing phase III trials in this population of patients include ALBAN (atezolizumab; NCT03799835), POTOMAC (durvalumab; NCT03528694), KEYNOTE-676 (pembrolizumab; NCT03711032) and CREST (sasanlimab; NCT04165317). These PD-(L)1 inhibitors are being tested in combination with either a full course of BCG (induction followed by maintenance of different durations), or BCG (induction only) monotherapy, and are being compared with standard-of-care BCG without a PD-(L)1 inhibitor [30]. Clinical trials of BCG in combination with PD-(L)1 inhibitors have shown higher inhibition of tumor growth and longer survival times versus either treatment alone [28,31]. For patients with recurrent or persistent NMIBC, PD-(L)1 inhibitors in combination with BCG appear safe and have been shown to exert an anti-tumor effect [32], prompting further clinical investigation of this approach to treating patients with BCG-naive high-risk NMIBC.

Sasanlimab (PF-06801591) is a humanized immunoglobulin G4 monoclonal antibody that selectively binds PD-1 and prevents the interaction between PD-1 and PD-L1/PD-L2 expressed by cancer cells [33]. In a phase I trial, sasanlimab was administered as a subcutaneous (SC) injection, at 300 mg every 4 weeks, to patients with advanced solid tumors [34]. Among patients with urothelial carcinoma (n = 38), 21.1% had a partial response (median duration, 183.0 days) and 31.6% had stable disease (median duration, 118.5 days) [35]. The SC administration route and monthly dosing of sasanlimab are likely to offer great convenience for patients while maintaining a safety and efficacy profile aligned to other PD-(L)1 inhibitors administered intravenously. In addition, SC administration and monthly dosing may also reduce the burden on the healthcare system by limiting the need for a clinic chair or bed space [34]. Based on preclinical and clinical data, sasanlimab in combination with BCG (induction with or without maintenance period) for patients with BCG-naive high-risk NMIBC may provide a greater benefit with longer event-free survival (EFS) versus BCG monotherapy. The combination may also reduce the rate of subsequent radical cystectomy compared with BCG monotherapy.

Objectives

The primary objective of CREST is to demonstrate that sasanlimab in combination with BCG (induction with or without maintenance period) is superior to BCG monotherapy (induction and maintenance period) in prolonging EFS for patients with high-risk NMIBC.

The key secondary objective of CREST is to demonstrate that sasanlimab in combination with BCG (induction with or without maintenance period) is superior to BCG monotherapy (induction and maintenance period) in prolonging overall survival for patients with high-risk NMIBC.

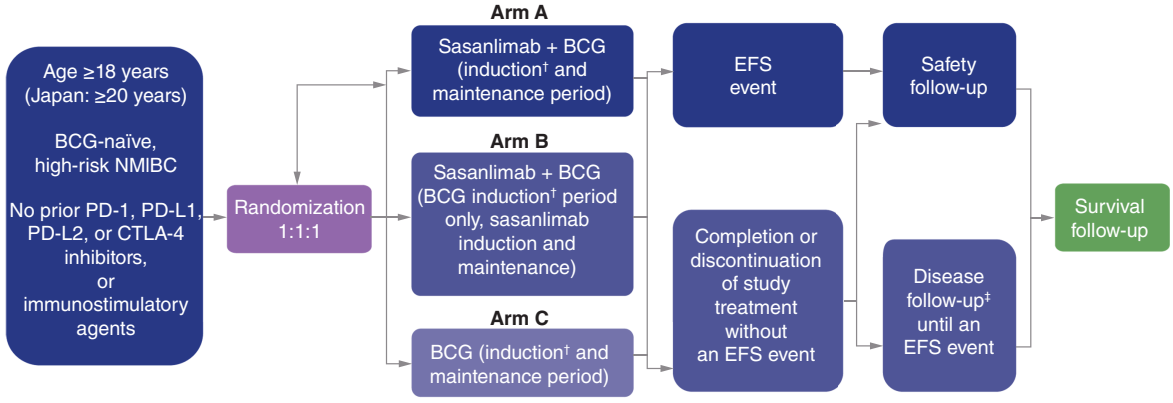


Figure 2. Study design. CREST is a phase III study evaluating the efficacy and safety of sasanlimab in combination with BCG versus BCG monotherapy for patients with BCG-naive high-risk NMIBC. EFS is defined as the time from randomization to date of the first EFS event.
†Re-induction is permitted for participants with CIS at randomization who have persistent disease at 3 months after initiating study treatment, or participants who have recurrence of high-grade Ta disease at 3 months after initiating study treatment (TURBT is required before re-induction).
‡Only participants who complete treatment with no evidence of disease progression or recurrence proceed to disease follow-up.
BCG: Bacillus Calmette-Guérin; CIS: Carcinoma *in situ*; CTLA-4: Cytotoxic T lymphocyte-associated antigen 4; EFS: Event-free survival; NMIBC: Non-muscle-invasive bladder cancer; PD-1: Programmed cell death-1; PD-L1/PD-L2: Programmed cell death-ligand 1/2; Ta: Stage of bladder cancer defined as a non-invasive papillary carcinoma; TURBT: Transurethral resection of bladder tumor.

Box 1. Key inclusion and exclusion criteria.

Key inclusion criteria
- Age ≥18 years (≥20 years in Japan)
- Histologically confirmed high-risk non-muscle-invasive TCC of the bladder urothelium (T1 tumor, high-grade Ta tumor, and/or CIS)
- Complete resection of all Ta/T1 papillary disease, with the most recent TURBT ≤12 weeks prior to randomization†

Key exclusion criteria
- Evidence of muscle-invasive, locally advanced, or metastatic urothelial cancer or concurrent extravesical, non-muscle-invasive TCC of the bladder urothelium
- Intravesical BCG treatment ≤2 years prior to randomization; prior intravesical chemotherapy is permitted

†A second TURBT is required if indicated according to the current locally applicable guidelines.
BCG: Bacillus Calmette-Guérin; CIS: Carcinoma *in situ*; T1: Stage of bladder cancer defined as a submucosal invasive tumor; Ta: Stage of bladder cancer defined as a noninvasive papillary carcinoma; TCC: Transitional cell carcinoma; TURBT: Transurethral resection of bladder tumor.

Trial design

CREST is a phase III, randomized, multicenter, multinational, open-label study for patients with BCG-naive high-risk NMIBC. The study design is shown in Figure 2. The SPIRIT 2013 statement was used as a guide in developing this clinical trial protocol manuscript [36].

Methods: participants, interventions & outcomes

Patients with histologically confirmed BCG-naive high-risk NMIBC are eligible to take part in CREST. Other key inclusion and exclusion criteria are shown in Box 1. PD-L1 expression level at randomization is not a criterion for participation in CREST. The target sample size is approximately 1000 participants with BCG-naive high-risk NMIBC from centers in Asia, Australia, Europe and North America (Figure 3). The target sample size of this study was determined through comprehensive power analysis to ensure that the study is sufficiently powered to test the superiority of the combinations to BCG. The first participant was enrolled in December 2019. Follow-up is planned for 5 years after the last participant is randomized to treatment. The estimated study completion date is December 2027.

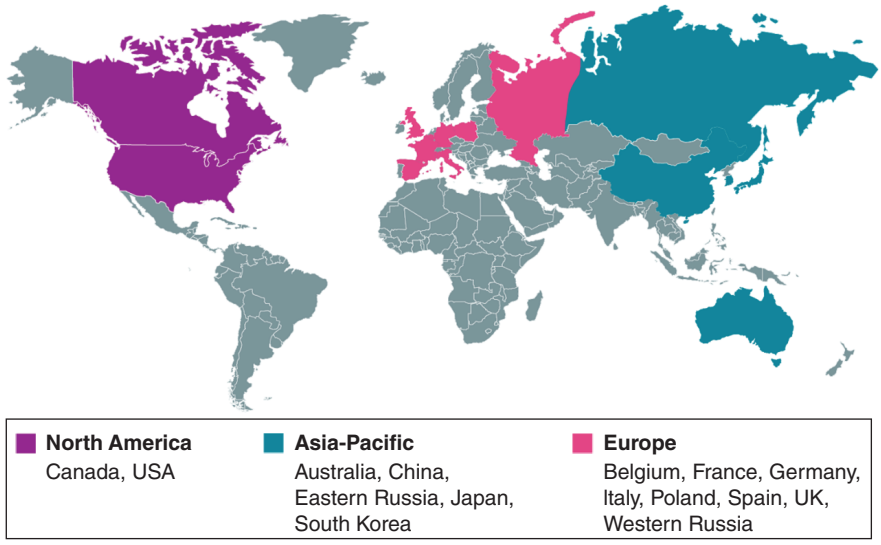


Figure 3. Study sites. CREST's target sample size is approximately 1000 patients across centers in Asia, Australia, Europe and North America.

Box 2. Study end points.

End points

Primary

- Event-free survival[†]

Secondary

- Overall survival
- CR in participants with CIS at randomization[†]
- Duration of CR for participants with CIS at randomization[†]
- Time to recurrence of low-grade disease[†]
- Time to cystectomy
- Disease-specific survival[†]
- Incidence and severity of AEs and laboratory abnormalities[‡]
- HRQoL[§]
- Ctrough for sasanlimab[¶]
- ADA and NAb to sasanlimab[¶]
- Tumor sample biomarker status based on PD-L1 expression (high or low)

[†]As assessed by the investigator.
[‡]Severity graded according to NCI CTCAE version 5.0.
[§]Measured by EORTC QLQ-C30, EORTC QLQ-NMIBC24, and PTAB.
[¶]When in combination with BCG (induction and maintenance period) and BCG (induction only) in Arms A and B, respectively.
ADA: Anti-drug antibody; AE: Adverse event; BCG: Bacillus Calmette-Guérin; CIS: Carcinoma *in situ*; CR: Complete response; Ctrough: Trough plasma concentration; EORTC: European Organisation for Research and Treatment of Cancer; HRQoL: Health-related quality of life; NAb: Neutralizing antibody; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; PD-L1: Programmed cell death-ligand 1; PTAB: Patient treatment administration burden; QLQ-C30: Core quality-of-life questionnaire; QLQ-NMIBC24: Quality-of-life questionnaire for patients with non-muscle-invasive bladder cancer.

Participants are receiving either sasanlimab plus BCG (induction and maintenance period) or sasanlimab plus BCG (induction period only) or BCG (induction and maintenance period). Concomitant treatment considered necessary for participants' well-being may be given at the discretion of the treating physician.

The primary end point is EFS, as assessed by the investigator. Primary and secondary end points are listed in Box 2. EFS is defined as the time from randomization to date of the first EFS event.

Methods: assignment of interventions

Within approximately 28 days of screening, patients are randomly assigned to sasanlimab plus BCG (induction and maintenance period) or sasanlimab plus BCG (induction period only) or BCG (induction and maintenance

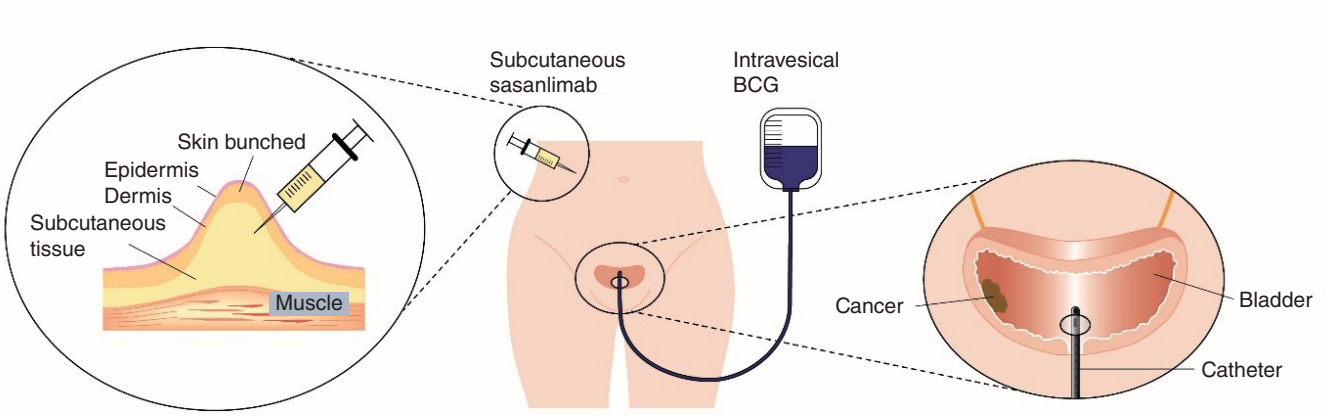


Figure 4. Route of administration of sasanlimab and BCG. Sasanlimab is administered by subcutaneous injection into the adipose tissue layer below the epidermis and dermis. BCG is administered by intravesical instillation directly into the bladder via a urinary catheter.
BCG: Bacillus Calmette-Guérin.

period) with a 1:1:1 allocation stratified by presence of CIS (yes vs no) and geography (USA vs Western Europe and Canada vs rest of world) using Interactive Response Technology (central Interactive Web Response system).

Participants receive sasanlimab via SC injection in combination with BCG via intravesical instillation (Figure 4). For the induction period, one dose of BCG is administered weekly (QW) for 6 consecutive weeks. Following the first induction period, participants with CIS at randomization who have persistent disease and participants with recurrence of high-grade Ta disease may receive re-induction with one dose of BCG QW for up to 6 consecutive weeks. In the event of significant toxicity, dosing may be skipped (sasanlimab or BCG) or delayed (BCG). No dose reductions are permitted. Sasanlimab is provided centrally by the sponsor (manufactured by Pfizer). BCG is sourced centrally or locally by the sponsor or sourced locally by investigational centers.

Methods: data collection, management & analysis

Disease status is assessed by cystoscopy and urine cytology. If cystoscopy or urine cytology findings are positive and indicate the presence of malignant or suspicious cells, biopsy and imaging are used. Patient-reported outcomes (PROs) include satisfaction with treatment and impact on health-related quality of life and are collected electronically. Safety assessments include incidence, causality, severity (graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0), outcomes of adverse events and changes in laboratory values.

Time-to-event efficacy end points (EFS, overall survival, time to recurrence of low-grade disease, time to cystectomy and disease-specific survival) are analyzed for all randomized participants. Treatment effects are estimated using a Cox's Proportional Hazards model stratified by randomization strata to calculate the hazard ratios between each experimental and control arm. Kaplan–Meier estimates for time-to-event efficacy end points are presented by treatment arm, together with a summary of associated statistics including median values with two-sided 95% CIs. CR rates for participants with CIS at randomization are calculated alongside the two-sided 95% CI using the Clopper-Pearson method for each treatment arm, with duration of CR summarized by treatment arm using the Kaplan–Meier method; the median duration and 95% CI are provided for each treatment arm, as well as duration of CR rates at different time points. Safety end points are summarized descriptively. Blood samples for pharmacokinetic analyses are collected at regular intervals throughout the study and assayed using a validated analytical method. Pharmacokinetic parameters, immunogenicity and PROs are summarized descriptively unless otherwise stated.

Participants' personal data are stored securely at individual study sites; only authorized study staff have access. All participants are assigned a single numerical identification code to maintain participant confidentiality. Records or datasets transferred to the sponsor contain participants' numerical identification code only.

Methods: monitoring

Safety is assessed throughout the study. All participants enter the safety follow-up period at the end of treatment; visits occur 30, 60 and 90 days after the end of treatment. Concurrent to the safety follow-up, participants without an EFS event before the end of treatment are followed through the disease follow-up period until recurrence of high-grade disease, progression of disease, persistence of CIS, withdrawal of consent for further study participation, loss to follow-up, or death. Participants with an EFS event before the end of treatment are followed up for survival until withdrawal of consent, loss to follow-up, death, study termination, or the end of the study.

CREST uses an external data monitoring committee (EDMC) and a steering committee. The EDMC is responsible for ongoing monitoring of the safety of participants as well as reviewing the interim analyses for EFS. The steering committee includes leading experts in oncology and provides advice on the study protocol as needed. Compliance with the protocol is assessed by drug accountability form/record; any deviation from the prescribed dosage regimen is reported in the electronic case report form.

Ethics & dissemination

The study is approved by institutional review boards and independent ethics committees at each center and is being conducted in accordance with local legal and regulatory requirements, as well as the general principles set forth in the Council for International Organizations of Medical Sciences International Ethical Guidelines, International Council for Harmonisation Good Clinical Practice Guidelines and Declaration of Helsinki.

Investigators or their representatives explain the nature of the study to participants and answer any questions associated with the informed consent document, which contains a separate section addressing the use of remaining mandatory samples for optional exploratory research. All participants provide written informed consent; a separate signature is required to document agreement to allow remaining specimens to be used for exploratory research.

Any amendments to the protocol require institutional review board and independent ethics committee approval before changes are implemented to the study design, except for changes necessary to eliminate an immediate hazard to participants.

The results of CREST will be publicly disclosed in accordance with applicable laws and regulations; results may also be published or presented at scientific meetings and in peer-reviewed journals.

Conclusion

The combination of PD-(L)1 inhibitors and BCG may increase anti-tumor effects compared with either agent alone for patients with high-risk NMIBC. CREST aims to evaluate the efficacy and safety of the SC PD-1 inhibitor sasanlimab in combination with BCG (induction with or without maintenance period) for participants with BCG-naive high-risk NMIBC. SC sasanlimab in combination with BCG in this population of patients may provide a greater benefit with longer EFS versus BCG monotherapy.

Supplementary data

A plain language summary of publication and video accompanies this paper. To view or download this in your browser please click here: www.futuremedicine.com/doi/suppl/10.2217/fon-2023-0271

Author contributions

GD Steinberg, ND Shore, J Palou Redorta, M Galsky, J Bedke, JJ Vermette, JC Tarazi, AE Randall, KJ Pierce, and TB Powles contributed to conceptualization. GD Steinberg, ND Shore, J Palou Redorta, M Galsky, J Bedke, JH Ku, M Kretkowski, H Hu, K Penkov, D Saltzstein, and TB Powles are contributing to the acquisition of data for the work. JJ Vermette, JC Tarazi, AE Randall, and KJ Pierce are contributing to analysis and interpretation of data for the work. All authors reviewed and revised the manuscript. All authors approved the final manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Acknowledgments

The authors thank the patients and their families/caregivers who are participating in this study. The authors also thank the investigators, research nurses, study coordinators, and operations staff who are contributing to this study.

Financial disclosure

CREST is sponsored by Pfizer. GD Steinberg reports advisory/consultancy roles for Heat Biologics, CG Oncology, PhotoCure, Merck, Roche/Genentech, Ciclomed, Taris Biomedical (now Janssen), MDxHealth, Fidia Farmaceutici, UroGen, Ferring, Aduro, Boston Scientific, Bristol Myers Squibb, AstraZeneca, Pfizer, Janssen, Epivax Therapeutics, Natera, FKD, EnGene Bio, Sesen Bio, BioCanCell (now Archiano), Nucleix, Ipsen, Combat Medical, Astellas, FerGene, Dendreon, AbbVie, Seagen, Verity Pharmaceuticals, Regeneron, STIMIT, Vyriad, Protara, xCures, Nonagen, Nanology, and Imvax; clinical trial protocol committee membership for Bristol Myers Squibb, CG Oncology, Fidia, Janssen, Merck, Pfizer, PhotoCure, Protara, and Seagen; stock/shares in CG Oncology, EnGene Bio, EpiVax Therapeutics, and UroGen. ND Shore reports consultancy and speaker's bureau for Bayer, Janssen, Dendreon, Tolmar, Ferring, Medivation/Astellas, Amgen, Pfizer, AstraZeneca, Myovant Sciences, Astellas Pharma, AbbVie, Merck, BMS, Sanofi, Boston Scientific, Clovis Oncology, Exact Imaging, FerGene, Foundation Medicine, CG Oncology, InVitae, MDxHealth, Myriad Genetics, Nymox, Propella Therapeutics, Genzyme, Sanofi, and Sesen Bio; grant or research support from AbbVie, Amgen, Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb/Pfizer, Boston Scientific, Clovis Oncology, Dendreon, Exact Imaging, Ferring, Foundation Medicine, InVitae, Janssen, MDxHealth, Merck, Myovant Sciences, Myriad Genetics, Nymox, Pfizer, Sanofi, Sesen Bio, and Tolmar; and employment by GenesisCare. JP Redorta reports advisory/consultancy roles for Arquer Diagnostics, Biotech, BTA Pharmaceuticals, Combat, Genomic Expression, and Olympus; steering committee membership for AstraZeneca, Bristol Myers Squibb, Janssen, and Pfizer; and grant or research support from Arquer Diagnostics, Biotech, BTA Pharmaceuticals, Cepheid, TARIS Biomedical, and Nucleix. M Galsky reports research funding from AstraZeneca, Bristol Myers Squibb, Dendreon, Genentech, Merck, and Novartis; advisory/consultancy roles for Alligator, AstraZeneca, Basilea, Bristol Myers Squibb, Curis, Dragonfly, EMD Serono, Fujifilm, Genentech, GlaxoSmithKline, Janssen, Merck, Numab, Pfizer, Rappta Therapeutics, Seagen, Silverback, and UroGen. J Bedke reports institutional research funding from AstraZeneca, Astellas, Bristol Myers Squibb, Eisai, Ipsen, Merck Sharp & Dohme, Novartis, Nektar, Pfizer, Roche, and Seattle Genetics; honoraria for speaker, consultancy, or advisory role from: AstraZeneca, Astellas, Bristol Myers Squibb, Eisai, EUSA Pharma, Ipsen, Merck Sharp & Dohme, Merck Serono, Novartis, Pfizer, and Roche on a personal basis. JH Ku, M Kretkowski, and H Hu have nothing to disclose. K Penkov reports honoraria from AstraZeneca, Merck Sharp & Dohme, Nektar, Pfizer, Regeneron Pharmaceuticals, and Roche; consultancy or advisory role for Nektar. JJ Vermette, JC Tarazi, AE Randall, and KJ Pierce report employment by Pfizer and stock/shares in Pfizer. D Saltzstein reports consultancy for UroGen. TB Powles reports consultancy for Astellas, AstraZeneca, Bristol Myers Squibb, Eisai, Exelixis, Incyte, Ipsen, Johnson & Johnson, Merck, Merck Serono, Merck Sharp & Dohme, Novartis, Pfizer, Roche, and Seattle Genetics. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Competing interests disclosure

The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Writing disclosure

Medical writing support was provided by S Stones and H Javaid of Engage Scientific Solutions and was funded by Pfizer.

Ethical disclosure

The study is approved by institutional review boards and independent ethics committees at each center and is being conducted in accordance with local legal and regulatory requirements, as well as the general principles set forth in the Council for International Organizations of Medical Sciences International Ethical Guidelines, International Council for Harmonisation Good Clinical Practice Guidelines, and Declaration of Helsinki. All participants provide written informed consent.

Executive summary

Non-muscle-invasive bladder cancer

- Bacillus Calmette-Guérin (BCG) therapy is the standard of care for patients with high-risk non-muscle-invasive bladder cancer (NMIBC) after transurethral resection of bladder tumor.
- Disease recurrence or progression is common and subsequent treatment options are limited (e.g., cystectomy).
- New treatment options to improve outcomes for patients with high-risk NMIBC are urgently required.

Programmed cell death-1 (PD-1) inhibitors plus BCG

- Preclinical and clinical data suggest that combining BCG with immune checkpoint inhibitors, including PD-1 and programmed cell death-ligand 1 (PD-L1) inhibitors, yields greater anti-tumor activity compared with either agent alone.
- Sasanlimab is a PD-1 inhibitor that selectively binds PD-1 on T cells; this prevents interaction between PD-1 and PD-L1/PD-L2 on tumor cells, allowing T cells to be activated.
- In a phase I study, sasanlimab administered subcutaneously at 300 mg every 4 weeks had an acceptable safety profile and demonstrated clinical activity for patients with advanced solid tumors, including patients with urothelial carcinoma.
- Treatment enhancement with PD-(L)1 inhibitors may optimize outcomes, including avoiding the need for radical cystectomy.

CREST study design

- CREST is a phase III study evaluating the efficacy and safety of sasanlimab in combination with BCG (induction with or without maintenance period) for participants with BCG-naive high-risk NMIBC; CREST is sponsored by Pfizer (NY, USA).

CREST study end points

- The primary end point is event-free survival.
- The secondary end points include overall survival, complete response (CR), duration of CR, time to recurrence of low-grade disease, time to cystectomy, disease-specific survival, safety, health-related quality of life, pharmacokinetics and immunogenicity.

References

Papers of special note have been highlighted as: • of interest •• of significant interest

1. International Agency for Research on Cancer (IARC). *Bladder* (2020). Available at: https://gco.iarc.fr/today/data/factsheets/cancers/30-Bladder-fact-sheet.pdf (Accessed: 10 January 2023).
2. Saginala K, Barsouk A, Aluru JS, Rawla P, Padala SA, Barsouk A. Epidemiology of bladder cancer. *Med. Sci. (Basel)* 8(1), 15 (2020).
3. Bilski K, Zapała Ł, Skrzypczyk MA, Oszczudłowski M, Dobruch J. Review on gender differences in non-muscle invasive bladder cancer. *Transl. Androl. Urol.* 8(1), 12–20 (2019).

• **This systematic review sought to identify the role of gender on outcomes of patients with non-muscle invasive bladder cancer; however, no clear conclusions were made and prospective trials were recommended.**

4. Palou J, Sylvester RJ, Faba OR *et al.* Female gender and carcinoma *in situ* in the prostatic urethra are prognostic factors for recurrence, progression, and disease-specific mortality in T1G3 bladder cancer patients treated with bacillus Calmette-Guérin. *Eur. Urol.* 62(1), 118–125 (2012).

• **This paper showed that female gender or the presence of carcinoma *in situ* in the prostatic urethra was associated with increased risk of disease recurrence, progression and death related to bladder cancer.**

5. Han MA, Maisch P, Jung JH *et al.* Intravesical gemcitabine for non-muscle invasive bladder cancer. *Cochrane Database Syst. Rev.* 6(6), CD009294 (2021).

• **This paper showed that intravesical gemcitabine was associated with reduced disease recurrence and prolonged progression-free survival compared with mitomycin in patients with non-muscle-invasive bladder cancer (NMIBC). Compared with Bacillus Calmette-Guérin (BCG), gemcitabine had similar effects on patients with high-risk disease who had previously failed BCG.**

6. Kamat AM, Shore N, Hahn N *et al.* KEYNOTE-676: Phase III study of BCG and pembrolizumab for persistent/recurrent high-risk NMIBC. *Future Oncology* 16(10), 507–516 (2020).

• **This paper presents the rationale, design and outcomes to be analyzed for the phase III KEYNOTE-676 trial. This trial investigated the safety and efficacy of pembrolizumab combined with BCG for the treatment of patients with reccurent or persistent high-risk NMIBC who had received BCG during the induction phase of treatment.**

7. Williams SB, Howard LE, Foster ML *et al.* Estimated Costs and Long-term Outcomes of Patients With High-Risk Non-Muscle-Invasive Bladder Cancer Treated With Bacillus Calmette-Guérin in the Veterans Affairs Health System. *JAMA Network Open* 4(3), e213800–e213800 (2021).

•• **This paper found that patients with NMIBC and carcinoma in situ that had received BCG had an increased risk of disease progression and reduced disease-free survival compared with patients without carcinoma in situ. Furthermore, disease progression was assocuated with significant increases in treatment- and disease-related costs.**

8. Babjuk M, Böhle A, Burger M *et al.* EAU Guidelines on Non-Muscle-invasive Urothelial Carcinoma of the Bladder: update 2016. *Eur. Urol.* 71(3), 447–461 (2017).

•• **This paper presents the current guidelines for the management of NMIBC as determined by the European Association of Urology.**

9. Redelman-Sidi G, Glickman MS, Bochner BH. The mechanism of action of BCG therapy for bladder cancer–a current perspective. *Nature Reviews Urology* 11(3), 153–162 (2014).

10. Han J, Gu X, Li Y, Wu Q. Mechanisms of BCG in the treatment of bladder cancer-current understanding and the prospect. *Biomedicine & Pharmacotherapy* 129, 110393 (2020).

11. Chang SS, Boorjian SA, Chou R *et al.* Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline. *J. Urol.* 196(4), 1021–1029 (2016).

• **This paper presents the 2016 American Urological Association/Society for Urologic Oncology guidelines on NMIBC.**

12. 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.* 81(1), 75–94 (2022).

• **This paper presents the 2021 European Association of Urology guidelines on NMIBC, based on the literature up to 2020.**

13. Oddens J, Brausi M, Sylvester R *et al.* Final results of an EORTC-GU cancers group randomized study of maintenance bacillus Calmette-Guérin in intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary bladder: one-third dose versus full dose and 1 year versus 3 years of maintenance. *Eur. Urol.* 63(3), 462–472 (2013).

14. Shore ND, Palou Redorta J, Robert G *et al.* Non-muscle-invasive bladder cancer: an overview of potential new treatment options. *Urol. Oncol.* 39(10), 642–663 (2021).

• **This paper provided an overview of potential new treatment options for patients with NMIBC.**

15. Gual Frau J, Palou J, Rodríguez O, Parada R, Breda A, Villavicencio H. Failure of Bacillus Calmette-Guérin therapy in non-muscle-invasive bladder cancer: definition and treatment options. *Arch. Esp. Urol.* 69(7), 423–433 (2016).

16. Cambier S, Sylvester RJ, Collette L *et al.* EORTC Nomograms and Risk Groups for Predicting Recurrence, Progression, and Disease-specific and Overall Survival in Non-Muscle-invasive Stage Ta-T1 Urothelial Bladder Cancer Patients Treated with 1–3 Years of Maintenance Bacillus Calmette-Guérin. *Eur. Urol.* 69(1), 60–69 (2016).

17. Spiess PE, Agarwal N, Bangs R *et al.* Bladder Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network J. Natl Compr. Canc. Netw.* 15(10), 1240–1267 (2017).

18. Audisio A, Buttigliero C, Delcuratolo MD *et al.* New Perspectives in the Medical Treatment of Non-Muscle-Invasive Bladder Cancer: Immune Checkpoint Inhibitors and Beyond. *Cells* 11(3), 357 (2022).

19. Choi H, Park JY, Bae JH, Tae BS. Health-related quality of life after radical cystectomy. *Transl. Androl. Urol.* 9(6), 2997–3006 (2020).

20. Clements MB, Atkinson TM, Dalbagni GM *et al.* Health-related Quality of Life for Patients Undergoing Radical Cystectomy: Results of a Large Prospective Cohort. *Eur. Urol.* 81(3), 294–304 (2022).

21. Lobo N, Bree KK, Hensley PJ *et al.* Reduced-dose bacillus Calmette-Guérin (BCG) in an era of BCG shortage: real-world experience from a tertiary cancer centre. *BJU International* 130(3), 323–330 (2022).

22. Shiravand Y, Khodadadi F, Kashani SMA *et al.* Immune Checkpoint Inhibitors in Cancer Therapy. *Current Oncology* 29(5), 3044–3060 (2022).

23. Bellmunt J, Mullane SA, Werner L *et al.* Association of PD-L1 expression on tumor-infiltrating mononuclear cells and overall survival in patients with urothelial carcinoma. *Ann. Oncol.* 26(4), 812–817 (2015).

24. Escors D, Gato-Cañas M, Zuazo M *et al.* The intracellular signalosome of PD-L1 in cancer cells. *Signal Transduction and Targeted Therapy* 3(1), 26 (2018).

25. Hashizume A, Umemoto S, Yokose T *et al.* Enhanced expression of PD-L1 in non-muscle-invasive bladder cancer after treatment with Bacillus Calmette-Guerin. *Oncotarget* 9(75), 34066–34078 (2018).

• **This paper showed that PD-L1 expression (which may contribute to immune escape) was enhanced on tumor tissue after BCG treatment in BCG-resistant patients with NMIBC.**

26. Roumiguie M, Comperat E, Neuzillet Y *et al.* PD-L1/PD-1 expression as a predictor of response to BCG in patients with high-risk non-muscle invasive bladder cancer. *J. Clin. Oncol.* 37(Suppl. 15), 4550–4550 (2019).

27. Inman BA, Sebo TJ, Frigola X *et al.* PD-L1 (B7-H1) expression by urothelial carcinoma of the bladder and BCG-induced granulomata: associations with localized stage progression. *Cancer* 109(8), 1499–1505 (2007).

28. Wang Y, Liu J, Yang X *et al.* Bacillus Calmette-Guérin and anti-PD-L1 combination therapy boosts immune response against bladder cancer. *Onco. Targets Ther.* 11, 2891–2899 (2018).

• **This paper suggested that the combination of BCG immunotherapy with PD-L1 inhibitors may improve treatment outcomes for patients with NMIBC.**

29. Balar AV, Kamat AM, Kulkarni GS *et al.* Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, Phase II study. *The Lancet Oncology* 22(7), 919–930 (2021).

30. García-Perdomo HA, Sánchez AL, Spiess PE. Immune checkpoints inhibitors in the management of high-risk non-muscle-invasive bladder cancer. A scoping review. *Urol. Oncol.* 40(9), 409.e401–409.e408 (2022).

31. Hahn N, O'Donnell M, Efstathiou J *et al.* Phase 1 trial of durvalumab in combination with BCG or external beam radiation in BCG-unresponsive non-muscle invasive bladder cancer patients. Presented at: *21st Annual Meeting of the Society of Urologic Oncology.* Virtual Meeting (3–5 December 2020).

32. Alanee S, Sana S, El-Zawahry A *et al.* Phase I trial of intravesical Bacillus Calmette-Guérin combined with intravenous pembrolizumab in recurrent or persistent high-grade non-muscle-invasive bladder cancer after previous Bacillus Calmette-Guérin treatment. *World J. Urol.* 39(10), 3807–3813 (2021).

33. Al-Khami AA, Youssef S, Abdiche Y *et al.* Pharmacologic properties and preclinical activity of sasanlimab, a high-affinity engineered anti-human PD-1 antibody. *Mol. Cancer Ther.* 19(10), 2105–2116 (2020).

34. Johnson ML, Braiteh F, Grilley-Olson JE *et al.* Assessment of Subcutaneous vs Intravenous Administration of Anti-PD-1 Antibody PF-06801591 in Patients With Advanced Solid Tumors: A Phase 1 Dose-Escalation Trial. *JAMA Oncol.* 5(7), 999–1007 (2019).

35. Cho BC, Penkov K, Bondarenko I *et al.* 1055P Updated results of subcutaneous (SC) anti-programmed cell death 1 (PD-1) receptor antibody PF-06801591 for locally advanced or metastatic non-small cell lung cancer (NSCLC) or urothelial carcinoma (UC). *Ann. Oncol.* 31(Suppl. 4), S721 (2020).

- **Showed the longer-term safety profile of sasanlimab in patients with non-small-cell lung cancer and urothelial carcinoma was consistent with previous reports. Durable antitumor activity was also demonstrated.**

36. Chan A-W, Tetzlaff JM, Altman DG *et al.* SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann. Intern. Med.* 158(3), 200–207 (2013).