TAR-200 for Bacillus Calmette-Guérin–Unresponsive High-Risk Non–Muscle-Invasive Bladder Cancer: Results From the Phase IIb SunRISe-1 Study

Siamak Daneshmand, MD[1]; Michiel S. Van der Heijden, MD, PhD[2]; Joseph M. Jacob, MD[3]; Felix Guerrero-Ramos, MD, PhD[4]; Martin Bögemann, MD[5,6]; Giuseppe Simone, MD, PhD[7]; Christopher M. Pieczonka, MD[8]; Nelson Canales Casco, MD[9]; Daniel Zainfeld, MD[10]; Philipp Spiegelhalder, MD[11]; Evanguelos Xylinas, MD[12]; David Cahn, MD[13]; Yair Lotan, MD[14]; Katie S. Murray, DO[15]; Takashi Kawahara, MD[16]; Katharine Stromberg, PhD[17]; Jason Martin, PhD[18]; Abhijit Shukla, PhD[19]; Christopher J. Cutie, MD[19]; Kristi Bertzos, PhD[20], Shalaka Hampras, PhD, MPH, MBBS[17]; Hussein Sweiti, MD[21]; and Andrea Necchi, MD[22,23]

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ABSTRACT

PURPOSE TAR-200 is a first-in-class intravesical drug-releasing system designed to provide sustained delivery of gemcitabine in the bladder. TAR-200 alone or in combination with cetrelimab (PD-1 inhibitor) could improve outcomes in patients with bacillus Calmette-Guérin (BCG)–unresponsive high-risk non–muscle-invasive bladder cancer (NMIBC) ineligible for or refusing radical cystectomy.

METHODS In this phase IIb parallel cohort study, patients with BCG-unresponsive carcinoma in situ (CIS) with/without papillary disease received TAR-200 monotherapy (Cohort 2 [C2]), TAR-200 plus cetrelimab (C1), or cetrelimab monotherapy (C3). Patients with BCG-unresponsive high-risk papillary disease–only NMIBC received TAR-200 monotherapy (C4). TAR-200 was dosed through month 24 and cetrelimab through month 18. Primary end points were centrally confirmed overall complete response (CR) rate (C1-3) or disease-free survival (DFS) rate (C4) (ClinicalTrials.gov number: NCT04640623).

RESULTS At data cutoff (March 31, 2025), 53, 85, 28, and 52 patients were treated in C1-4, respectively. In C2, CR rate and median duration of response were 82.4% (95% CI, 72.6 to 89.8) and 25.8 months (95% CI, 8.3 to not estimable), respectively. In C4, 6-, 9-, and 12-month DFS rates were 85.3% (95% CI, 71.6 to 92.7), 81.1% (95% CI, 66.7 to 89.7), and 70.2% (95% CI, 51.6 to 82.8), respectively. In C1 and C3, CR rates were 67.9% (95% CI, 53.7 to 80.1) and 46.4% (95% CI, 27.5 to 66.1), respectively. Rates of grade ≥3 treatment-related adverse events (AEs) were 12.9%, 13.5%, 37.7%, and 7.1% in C2, C4, C1, and C3, respectively, and of serious treatment-related AEs, 5.9%, 5.8%, 15.1%, and 3.6%. No treatment-related deaths occurred.

CONCLUSION TAR-200 monotherapy was well tolerated, with a high CR rate, durable responses, and prolonged DFS in patients with BCG-unresponsive high-risk NMIBC. TAR-200 monotherapy offered a more favorable risk-benefit profile versus TAR-200 plus cetrelimab or cetrelimab alone in BCG-unresponsive CIS.

ACCOMPANYING CONTENT

- Appendix
- Data Sharing Statement
- Data Supplement
- Protocol

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INTRODUCTION

Many patients with high-risk non–muscle-invasive bladder cancer (NMIBC) experience disease recurrence (12%-60%) or progression (2%-15%) within 1 year[1-4] after standard-of-care transurethral resection of bladder tumor (TURBT) and intravesical bacillus Calmette-Guérin (BCG) treatment,[5-7] often leading to BCG-unresponsive disease.

The current standard of care for BCG-unresponsive high-risk NMIBC is radical cystectomy,[5-7] which is a life-changing surgery associated with considerable morbidity (50%-70%) and significant impact on quality of life.[8,9] Radical cystectomy is also associated with substantial 90-day mortality risk (approximately 5%), particularly in elderly patients (≤15%).[8-10] Therefore, many patients are unable or unwilling to undergo this procedure, and real-world rates of radical cystectomy for NMIBC are low (<20%).[11] Current US Food and Drug Administration (FDA)–approved treatment options for BCG-unresponsive carcinoma in situ (CIS) include systemic pembrolizumab, intravesical nadofaragene firadenovec, and intravesical nogapendekin alfa inbakicept

CONTEXT

Key Objective

To evaluate the efficacy and safety of TAR-200—an intravesical gemcitabine-releasing system—in patients with bacillus Calmette-Guérin (BCG)–unresponsive high-risk non–muscle-invasive bladder cancer (NMIBC).

Knowledge Generated

TAR-200 monotherapy provided the highest complete response rate of 82.4% to date and durable responses (median duration of response, 25.8 months) in BCG-unresponsive carcinoma in situ (CIS) and showed prolonged disease-free survival in high-risk papillary disease–only NMIBC. TAR-200 monotherapy was well tolerated in both CIS and papillary disease–only NMIBC cohorts.

Relevance *(J.W. Friedberg)*

With caveats of a relatively small sample size and single-arm design, this study demonstrates the efficacy and tolerability of TAR-200 in BCG-refractory high-risk non–muscle-invasive bladder cancer. Longer follow-up of this trial and ongoing randomized trials will define the role of this approach as primary therapy for this disease.*

*Relevance section written by *JCO* Editor-in-Chief Jonathan W. Friedberg, MD.

(NAI) plus BCG.[12-17] However, these treatments are associated with limited complete response (CR) rates and response durability, systemic or immune-related toxicities, frequent urethral catheterizations, reliance on BCG as combination therapy, and limited physician adoption.[12-18] These challenges underscore the persistent need for tolerable, effective, and durable bladder-sparing therapies for this population. Additionally, there are no approved treatments for BCG-unresponsive high-risk papillary disease–only NMIBC.

Intravesical gemcitabine has proven efficacy in NMIBC, but its effect may be limited by short dwell times.[19-22] TAR-200 is a novel intravesical drug-releasing system designed to provide sustained delivery of gemcitabine in the bladder.[19,22,23] In phase I studies, TAR-200 was well tolerated and showed preliminary efficacy in patients with muscle-invasive bladder cancer and intermediate-risk NMIBC,[19,22,23] with detectable levels of gemcitabine in urine 7 days after placement and no detectable gemcitabine in plasma.[19,22] Moreover, in an animal model, gemcitabine metabolites were detected in all layers of bladder tissue 4 days after placement of TAR-200, demonstrating both sustained release and deep penetration of gemcitabine.[24]

Cetrelimab is an anti–PD-1 agent with an efficacy and safety profile consistent with that of approved anti–PD-1 agents.[25,26] The combination of a checkpoint inhibitor with localized TAR-200 therapy may enhance antitumor activity.

SunRISe-1 (ClinicalTrials.gov identifier: NCT04640623) is a phase IIb parallel-cohort study evaluating TAR-200 monotherapy and in combination with cetrelimab in patients with BCG-unresponsive high-risk NMIBC. We report efficacy and safety results from SunRISe-1.

METHODS

Study Oversight

The study protocol was designed by the sponsor, Johnson & Johnson. SunRISe-1 was conducted in accordance with current Good Clinical Practice guidelines of the International Council for Harmonisation, applicable regulatory and country-specific requirements, and principles of the Declaration of Helsinki, and was approved by review boards at all participating institutions. All patients provided written informed consent.

An independent data-monitoring committee was commissioned by the sponsor to review safety and efficacy data and make recommendations regarding study conduct. Data captured by site personnel in case-report forms were transcribed in a sponsor database system. All authors approved the manuscript for submission for publication and confirmed the accuracy and completeness of the data reported. Editorial assistance was provided by a medical writer employed by the sponsor.

Patients

Eligible patients were adults with histologically confirmed diagnosis of BCG-unresponsive CIS with or without papillary disease (high-grade Ta, any T1; Cohorts 1-3) or papillary disease-only NMIBC (high-grade Ta, any T1 and absence of CIS; Cohort 4), within 12 months of last dose of adequate BCG. Adequate BCG is defined as a minimum of five of six full doses of an induction course (adequate induction) plus two of three doses of a maintenance course, or at least two of six full doses of a second induction course. All visible papillary disease was fully resected before enrollment. Eligible

patients had an Eastern Cooperative Oncology Group performance status of 0-2, adequate organ function, and either refused or were ineligible for radical cystectomy.

Study Design and Treatment

Patients were enrolled between March 2021 and April 2024 at 142 sites in 14 countries. Three CIS cohorts were originally designed to enroll 200 patients randomly assigned 2:1:1 to TAR-200 plus cetrelimab (Cohort 1), TAR-200 monotherapy (Cohort 2), or cetrelimab monotherapy (Cohort 3). In June 2023, TAR-200 monotherapy development was prioritized in the CIS population, and enrollment in Cohort 1 and Cohort 3 was closed on the basis of the more favorable risk-benefit profile observed with TAR-200 monotherapy in this setting on the basis of the totality of all available safety and efficacy data. Therefore, the protocol was amended to expand the TAR-200 monotherapy cohort to approximately 80 patients and to add an additional cohort for TAR-200 monotherapy in patients with high-risk papillary disease–only NMIBC (Cohort 4).

Patients received TAR-200,[19,20] administered in a brief office procedure, once every 3 weeks through month 6, then once every 12 weeks through month 24. Cetrelimab dosing was 360 mg intravenously once every 3 weeks through month 18. Patients continued treatment with TAR-200 for up to 2 years and cetrelimab for up to 18 months, or until confirmed high-risk disease persistence, recurrence, or progressive disease on the basis of central urine cytology and/or central biopsy assessment or local biopsy/local imaging. Consistent with FDA guidance, the protocol did not allow continuing treatment for nonresponders[27]; if nonresponse was observed in a patient at any time, the patient discontinued study treatment and entered the follow-up phase.

End Points

The primary end point in Cohorts 1-3 was overall centrally assessed CR rate at any time, on the basis of negative central urine cytology and negative cystoscopy, or negative central urine cytology and positive cystoscopy with benign or low-grade NMIBC on central biopsy. The Cohort 4 primary end point was disease-free survival (DFS). Secondary end points included duration of response (DOR) and overall survival in Cohorts 1-3, change from baseline in patient-reported outcomes in Cohort 2, and safety and tolerability. Incidence and time to cystectomy was an exploratory end point. End points are defined in the Data Supplement (online only).

Assessments

Disease-response assessments included cystoscopy and central urine cytology done every 12 weeks for up to 2 years then every 24 weeks until end of study, local imaging (computed tomography/magnetic resonance imaging) done every 24 weeks until the end of study, and central pathology (bladder biopsy/TURBT) done at weeks 24 and 48 in Cohorts 1-3 or as clinically indicated in cases of positive cystoscopy for Cohorts 1-4. Consistent modality of cystoscopy (eg, white light, fluorescence-guided) was required at screening and throughout the study for an individual patient. Additional assessments are provided in the Data Supplement.

Statistical Analysis

Efficacy and safety analyses involved all enrolled patients who received at least one dose of study treatment. There were no statistical comparisons between cohorts. A Z-test with normal approximation was used to compare the CR rate with the historical CR rate (20%) in Cohorts 1-3.[28] DOR in Cohort 2 and DFS in Cohort 4 were analyzed using the Kaplan-Meier method. Further details, including sample size determination, are provided in the Data Supplement.

RESULTS

TAR-200 Monotherapy in Patients With CIS With or Without Papillary Disease (Cohort 2)

At clinical cutoff (March 31, 2025), 85 patients with BCG-unresponsive CIS were enrolled in the TAR-200 monotherapy cohort (Cohort 2; Fig 1, Data Supplement, Fig S1). Median age was 71 years; most patients were male (80.0%) and White (87.1%; Table 1; representativeness of study population is provided in the Data Supplement, Table S1). One third of patients (32.9%) had concurrent papillary disease (high-grade Ta or T1). Patients had a median of 12 previous BCG doses, and most refused radical cystectomy (96.5%). Most patients (91.8%) had consistent modality of cystoscopy at baseline and after baseline, with white light cystoscopy being the most frequently used modality. Only one patient had blue light cystoscopy at baseline and white light at follow-up.

The centrally confirmed CR rate in Cohort 2 was 82.4% (95% CI, 72.6 to 89.8), with 70 of 85 patients achieving CR (Table 2). Investigator-assessed CR rate was 83.5% (95% CI, 73.9 to 90.7), and the overall concordance between central- and investigator-assessed CR rates was 95.0%. Ninety-six percent of responses were achieved at first disease evaluation (median time to response, 2.8 months). The remaining patients who achieved CR were nonevaluable for disease response at week 12 owing to missing sample or assessment but achieved CR at the next disease evaluation. At 3, 6, and 12 months after treatment initiation, CR rates were 78.8% (95% CI, 68.6 to 86.9), 58.8% (95% CI, 47.6 to 69.4), and 45.9% (95% CI, 35.0 to 57.0), respectively. Subgroup analyses showed consistently high CR rates across all clinically relevant subgroups, including patients with and without concurrent papillary disease (82.1% and 82.5%, respectively; Data Supplement, Fig S2).

After a median follow-up in responders of 20.2 months (range, 5-48), median DOR was 25.8 months (95% CI, 8.3 to not estimable; Fig 2). Among 70 responders, 37 (52.9%) had

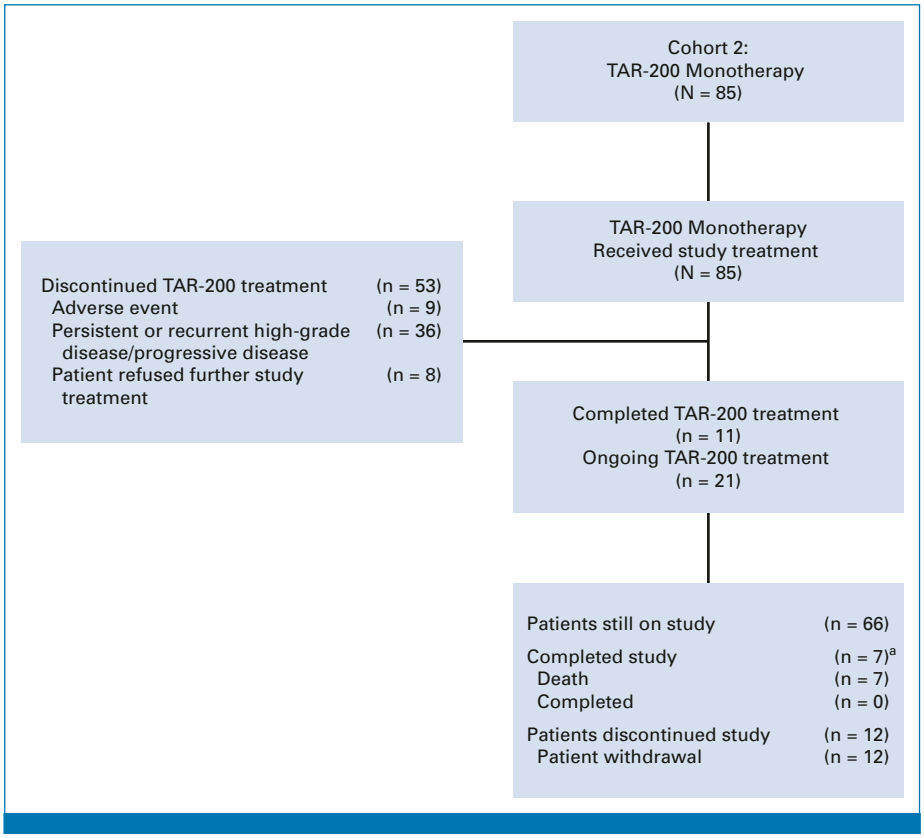

FIG 1. Flow diagram for patient enrollment, treatment, and disposition in Cohort 2: TAR-200 monotherapy in patients with carcinoma in situ with or without papillary disease. [a]Death is counted under study completion.

a DOR of ≥12 months. Thirty-seven responders remained in CR at clinical cutoff, with 11 completing 2 years of treatment. Thirty-three responses were ongoing, with no event as of the clinical cutoff, and four patients were permanently censored because of study discontinuation or receiving subsequent therapy. Among the 33 patients with centrally assessed disease recurrence or progression, three patients died (unrelated to treatment), 23 responders (32.9%) had subsequent high-risk NMIBC recurrence, and four (5.7%) had T2 or higher progression (on the basis of local disease evaluation). Details on recurrence and progression in all patients are provided in Table 2. Moreover, 25 patients received subsequent treatment, including 18 (21.2%) who underwent radical cystectomy. Median time to cystectomy was not estimable. The 12- and 24-month radical cystectomy–free rates were 86.6% (95% CI, 76.6 to 92.6) and 75.5% (95% CI, 63.4 to 84.1), respectively.

Overall survival rates at 6 and 12 months were 98.7% (95% CI, 91.2 to 99.8) and 94.7% (95% CI, 86.5 to 98.0), respectively, with seven deaths (8.2%) occurring on study. No deaths were treatment-related. Details of the deaths are provided in the Data Supplement (Table S2).

Treatment-related adverse events (AEs) of any grade occurred in 71 patients (83.5%; Table 3 and Data Supplement, Table S3). The most frequent treatment-related AEs were low-grade lower urinary tract events, including pollakiuria (43.5%), dysuria (40.0%), micturition urgency (24.7%), and urinary tract infection (UTI; 21.2%). AEs resolved after a median of 3.0 weeks (range, 0.1+ to 150.3+). Grade ≥3 treatment-related AEs occurred in 11 patients (12.9%), with urinary tract pain most frequent (4.7%; Table 3). Treatment-related serious AEs occurred in five patients (5.9%), with cystitis with bladder pain (grade 2), pseudomonal cystitis (grade 3), UTI (grade 3), urosepsis with acute kidney injury (grade 3), and urinary tract pain (grade 3) occurring in one patient each.

Treatment-related AEs leading to TAR-200 interruption occurred in 27 patients (31.8%), with urinary tract pain (5.9%), hematuria (4.7%), and pollakiuria (4.7%) being the most frequent TAR-200–related AEs. Most interruptions were limited to one to two doses, and most patients resumed treatment (Table 3). Three patients (3.5%) discontinued TAR-200 because of treatment-related AEs, including noninfective cystitis (two patients) and pollakiuria and urinary tract disorder (one patient; Table 3).

Mean global health status (75.0 [standard deviation (SD), 16.7]) and physical functioning (86.2 [SD, 17.3]) scores were high at baseline and were maintained during treatment (did not exceed clinically meaningful change threshold of ≥10 points; Data Supplement, Fig S3).[29]

TABLE 1. Demographics and Disease Characteristics at Baseline in Patients With CIS With or Without Papillary Disease Treated With TAR-200 Monotherapy (Cohort 2)

Characteristic	Cohort 2: TAR-200 Monotherapy (N = 85)[a]
Age, years, median (range)	71.0 (40-88)
Sex, No. (%)	
Male	68 (80.0)
Female	17 (20.0)
Race, No. (%)	
White	74 (87.1)
Asian	8 (9.4)
Black or African American	2 (2.4)
Not reported/unknown	1 (1.2)
Geographic region, No. (%)[b]	
America	23 (27.1)
Asia Pacific	10 (11.8)
EMEA	52 (61.2)
Nicotine use, No. (%)	
Current	7 (8.2)
Former	50 (58.8)
Never	28 (32.9)
ECOG performance status, No. (%)	
0	78 (91.8)
1	7 (8.2)
2	0
Tumor stage, No. (%)	
CIS only	57 (67.1)
CIS + Papillary disease	28 (32.9)
CIS + Ta	19 (22.4)
CIS + T1	9 (10.6)
PD-L1 status 1, No. (%)[c]	
CPS ≥10	12 (32.4)
CPS ≤10	25 (67.6)
PD-L1 status 2, No. (%)[c]	
CPS ≥1	23 (62.2)
CPS ≤1	14 (37.8)
Total doses of previous BCG, No., median (range)	12 (7-42)
Time from last BCG to CIS diagnosis, months, median (range)	3.2 (0.1-21.7)[d]
Reason for not undergoing radical cystectomy, No. (%)	
Declined	82 (96.5)
Preservation of bladder	50 (58.8)
Preservation of sexual function	1 (1.2)
Concern about quality of life after procedure	29 (34.1)
Concern about mortality and morbidity risk of procedure	2 (2.4)
Ineligible	3 (3.5)
Age	1 (1.2)
Medical and surgical comorbidities	2 (2.4)

Abbreviations: BCG, bacillus Calmette-Guérin; CIS, carcinoma in situ; CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; EMEA, Europe, Middle East, and Africa.
[a]Patient characteristics are shown for all patients who received at least one dose of study treatment in the full analysis set of TAR-200 monotherapy in CIS with or without papillary disease cohort (N = 85).
[b]America includes Canada and the United States; Asia Pacific includes Australia, Japan, and South Korea; EMEA includes Belgium, France, Germany, Greece, Italy, the Netherlands, Portugal, Russia, and Spain.
[c]Percentages are based on the number of patients with available data (n = 37).
[d]Two patients had >12 months from last BCG dose to CIS diagnosis (protocol deviation); all other patients had ≤12 months from last BCG dose to CIS diagnosis (per protocol).

TAR-200 Monotherapy in Patients With High-Risk Papillary Disease–Only NMIBC (Cohort 4)

Fifty-two patients with BCG-unresponsive high-risk papillary disease–only NMIBC received TAR-200 monotherapy (Cohort 4; Data Supplement, Fig S4). Most were male (71.2%), White (86.5%), and current or former nicotine users (69.2%), with 59.6% having high-grade Ta and 40.4% having T1 disease (Data Supplement, Table S4).

After a median follow-up of 12.8 months (range, 4-17), the median DFS was not estimable. At 6, 9, and 12 months, DFS rates were 85.3% (95% CI, 71.6 to 92.7), 81.1% (95% CI, 66.7 to 89.7), and 70.2 (95% CI, 51.6 to 82.8), respectively (Fig 3). Twelve-month DFS rates were consistent in patients with high-grade Ta and T1 disease (70.0% [95% CI, 44.8 to 85.4] and 72.2% [95% CI, 44.8 to 87.6], respectively). Of 52 patients, 11 had NMIBC recurrence or progression (21.2%), and two (3.8%) died (unrelated to treatment; Data Supplement, Table S2).

Treatment-related AEs occurred in 42 patients (80.8%) and were mostly lower urinary tract symptoms (Data Supplement, Table S5). Grade ≥3 treatment-related AEs occurred in seven patients (13.5%); the most frequent was bladder pain (3.8%). Serious treatment-related AEs occurred in three patients (5.8%), including sepsis, spinal fracture (procedure related), and UTI in one patient each. Four patients (7.7%) discontinued TAR-200 because of treatment-related AEs;

TABLE 2. Efficacy Outcomes of TAR-200 Monotherapy in Patients With CIS With or Without Papillary Disease (Cohort 2)

Outcome	Cohort 2: TAR-200 Monotherapy (N = 85)
Overall CR rate[a]	
Centrally assessed CR rate, % (95% CI)	n = 70 82.4 (72.6 to 89.8)
CR rate, % (95% CI)[b]	
3-month CR rate	78.8 (68.6 to 86.9)
6-month CR rate	58.8 (47.6 to 69.4)
12-month CR rate	45.9 (35.0 to 57.0)
DOR	
DOR of ≥12 months, No. (%)	37 (52.9)
12-month DOR rate, % (95% CI)[b]	56.2 (43.4 to 67.1)
DOR, months, median (95% CI)[b]	25.8 (8.3 to NE)
Follow-up in responders, months, median (range)	20.2 (5-48)
Patients with ongoing response, % (n/N)[a]	47.1 (33/70)[c]

Outcome	Responders	All
Patients with disease persistence (nonresponders only), recurrence, or progression, % (n/N)[d]	42.9 (30/70)	48.2 (41/85)
High-risk NMIBC[e]	32.9 (23/70)	35.2 (30/85)
Positive cytology only	1.4 (1/70)	2.4 (2/85)
CIS and/or Ta only	25.7 (18/70)	27.1 (23/85)
T1 (with or without CIS)	5.7 (4/70)	5.9 (5/85)
T2 or higher progression	5.7 (4/70)	8.2 (7/85)
T2–T4a	2.9 (2/70)	5.9 (5/85)
N1	1.4 (1/70)	1.2 (1/85)
M1a	1.4 (1/70)	1.2 (1/85)
No evidence of disease[f]	4.3 (3/70)	4.7 (4/85)
Patients who underwent cystectomy, % (n/N)	17.1 (12/70)	21.2 (18/85)

Abbreviations: CIS, carcinoma in situ; CR, complete response; DOR, duration of response; M, metastasis; NE, not estimable; NMIBC, non–muscle-invasive bladder cancer; T, tumor; TURBT, transurethral resection of bladder tumor.

[a]Response is based on centrally reviewed urine cytology, local cystoscopy, and central biopsy (if available). A CR is defined as having a negative cystoscopy and negative (including atypical) centrally read urine cytology, or positive cystoscopy with biopsy-proven benign or low-grade NMIBC and negative (including atypical) centrally read cytology at any time point.

[b]Kaplan-Meier estimates.

[c]Thirty-seven of 70 responders (52.9%) were censored, including four (5.7%) who discontinued the study, started subsequent therapy, or missed ≥2 consecutive assessments. Thirty-three (47.1%) patients had an ongoing response with no event at clinical cutoff.

[d]Disease persistence, recurrence, or progression event was based on positive central cytology, high-grade central pathology, or positive imaging. All results are based on highest stage from local TURBT results, investigator-assessed clinical stage, and pathologic stage after cystectomy. Patients who discontinued study before disease evaluation are excluded. Upper tract urothelial carcinoma incident after treatment initiation was not included in assessment of CR; one case was reported in Cohort 2.

[e]Includes patients with high-grade Ta, CIS, or T1 or patients with positive central cytology (n = 5) or high-risk NMIBC from central pathology (n = 2), but no evidence of high-risk NMIBC by investigator. No cases of low-grade Ta recurrence were reported in Cohort 2.

[f]Patients had positive central cytology or high-grade disease by central pathology but no disease on the basis of local assessment.

the most frequent treatment-related AEs leading to TAR-200 discontinuation were micturition urgency in four (7.7%) and dysuria and pollakiuria in two each (3.8%).

TAR-200 Plus Cetrelimab in Patients With CIS With or Without Papillary Disease (Cohort 1)

Baseline characteristics for Cohort 1 (N = 53; Data Supplement, Fig S5) are provided in the Data Supplement (Table S6). Centrally confirmed CR rate in Cohort 1 was 67.9% (95% CI, 53.7 to 80.1). Investigator-assessed CR rate was 83.0% (95% CI, 70.2 to 91.9). In responders, after a median follow-up of 33.4 months (range, 10-47), median DOR was not estimable, 12-month DOR rate was 76.3% (95% CI, 58.1 to 87.4), and 20 patients (55.6%) remained in CR. Twelve-month overall survival rate was 98.0% (95% CI, 86.6 to 99.7). Two deaths occurred in follow-up (both because of progressive disease, unrelated to treatment; Data Supplement, Table S2).

Treatment-related AEs occurred in 49 patients (92.5%); dysuria (30.2%) and pollakiuria (28.3%) were most frequent (Data Supplement, Table S7). Twenty patients (37.7%) experienced grade ≥3 treatment-related AEs. Serious treatment-related AEs were noted in eight patients (15.1%), most commonly UTI (3.8%). Immune-related AEs occurred in 34 patients (64.2%) and included diarrhea (17.0%) and aspartate aminotransferase increased (17.0%). Fourteen (26.4%) and 13 (24.5%) patients discontinued TAR-200 or cetrelimab, respectively, because of treatment-related AEs; most common were bladder pain (11.3%) and pollakiuria (5.7%).

Cetrelimab Monotherapy in Patients With CIS With or Without Papillary Disease (Cohort 3)

Baseline characteristics for Cohort 3 (N = 28; Data Supplement, Fig S6) are provided in the Data Supplement (Table S8). The CR rate was 46.4% (95% CI, 27.5 to 66.1) per central assessment and 50.0% (95% CI, 30.6 to 69.4) per investigator assessment. After a median follow-up in responders of 29.2 months (range, 11-45), median DOR was 8.6 months (95% CI, 2.8 to not estimable); 12-month DOR rate was 38.5% (95% CI, 14.1 to 62.8). Twelve-month overall survival rate was 100% (95% CI, 100 to 100); no deaths occurred (Data Supplement, Table S2).

Fifteen patients (53.6%) had treatment-related AEs, with pruritus (10.7%) being the most frequent (Data Supplement,

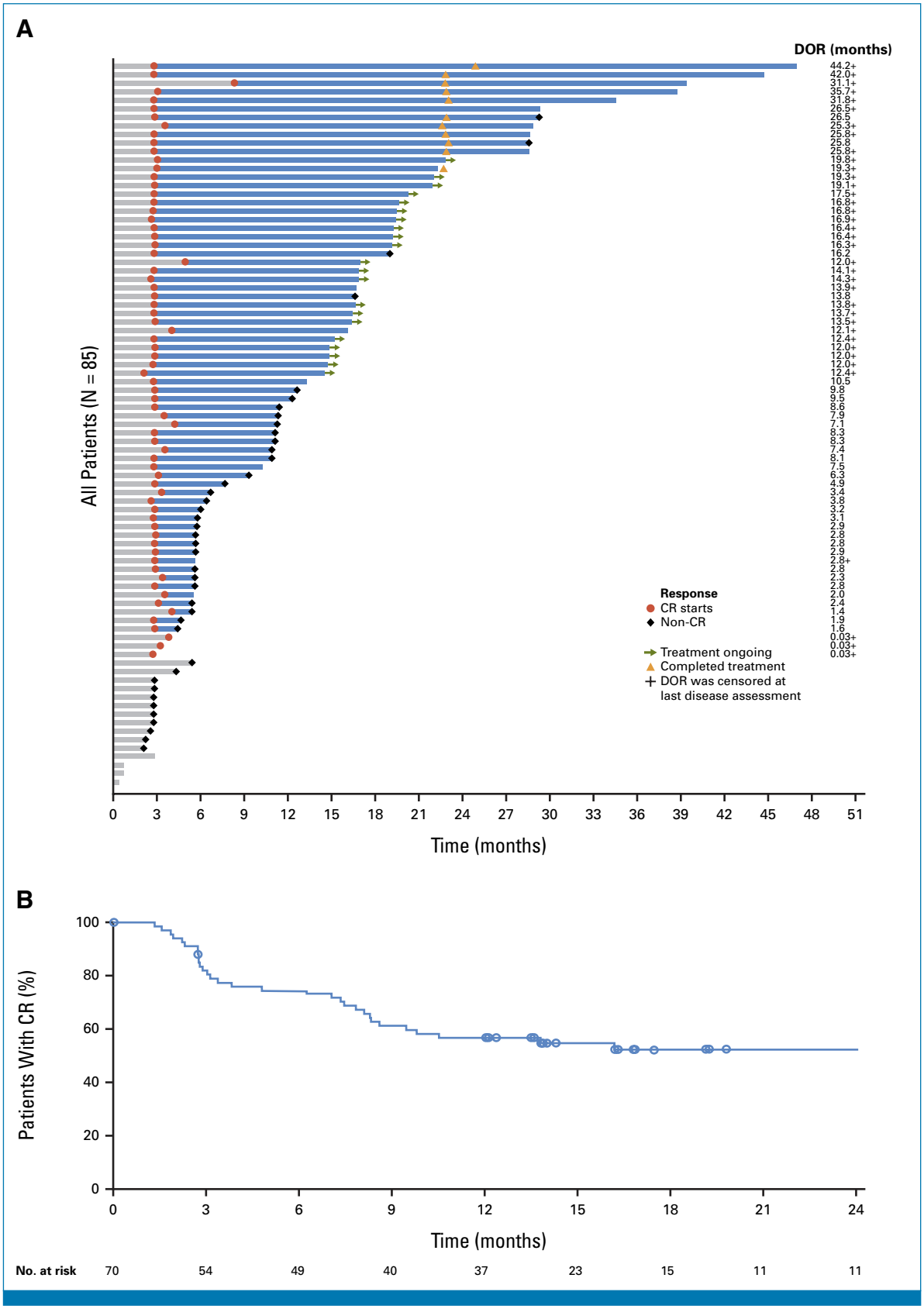

FIG 2. Durability of responses to TAR-200 monotherapy in patients with carcinoma in situ with or without papillary disease (Cohort 2). (A) Time to CR or non-CR in all patients (N = 85), with DOR in individual responders (N = 70). (B) Duration of response (Kaplan-Meier curve). Time points with fewer than 10 patients at risk are excluded from the plot. CR, complete response; DOR, duration of response.

TABLE 3. Treatment-Related AEs (any grade, grade ≥3) and TAR-200 Interruption and Discontinuation Rates in Patients With CIS With or Without Papillary Disease Treated With TAR-200 Monotherapy (Cohort 2)

Patients With ≥1 Event	Cohort 2: TAR-200 Monotherapy (N = 85)[a]	
	Any Grade, No. (%)	Grade ≥3, No. (%)
Treatment-related AEs[b]	71 (83.5)	11 (12.9)[c]
Most frequent treatment-related AEs[d]		
Pollakiuria	37 (43.5)	0
Dysuria	34 (40.0)	0
Micturition urgency	21 (24.7)	0
UTI	18 (21.2)	1 (1.2)
Hematuria	14 (16.5)	0
Urinary tract pain	9 (10.6)	4 (4.7)
Bladder pain	7 (8.2)	2 (2.4)
Bladder spasm	7 (8.2)	0
Noninfective cystitis	6 (7.1)	0
Urinary incontinence	5 (5.9)	0
Nocturia	4 (4.7)	0
Urethral pain	4 (4.7)	0
Urinary retention	4 (4.7)	1 (1.2)
Cystitis	3 (3.5)	1 (1.2)
Lower urinary tract symptoms	3 (3.5)	0
Pelvic pain	3 (3.5)	0
Abdominal pain	2 (2.4)	0
Abdominal pain lower	2 (2.4)	0
Asthenia	2 (2.4)	0
Constipation	2 (2.4)	0
Fatigue	2 (2.4)	0
Penile pain	2 (2.4)	0
Perineal pain	2 (2.4)	0
Urethral injury	2 (2.4)	0
Vulvovaginal pain	2 (2.4)	0
Treatment-related AEs leading to TAR-200 interruption[e]	27 (31.8)[f]	
Treatment-related AEs leading to TAR-200 discontinuation	3 (3.5)[g]	

Abbreviations: AE, adverse event; CIS, carcinoma in situ; UTI, urinary tract infection.

[a]Safety data are shown for all patients who received at least one dose of study drug in the full analysis set of the TAR-200 monotherapy in CIS with or without papillary disease cohort (N = 85).

[b]An AE is categorized as related if the investigator determines that there is a relationship between the AE and study drug/procedure. Patients are counted only once for any given event, regardless of the number of times they actually experienced the event.

[c]In addition to the grade ≥3 treatment-related AEs shown by preferred term in the table, all other grade ≥3 treatment-related AEs were reported in only one patient each and included acute kidney injury, pseudomonal cystitis, and urosepsis. Patients may have had one or more grade ≥3 treatment-related AE.

[d]Treatment-related AEs of any grade by preferred term are listed if they were reported in ≥2% of patients in the TAR-200 monotherapy in CIS with or without papillary disease cohort.

[e]TAR-200 interruption is defined as when a TAR-200 dose is skipped or TAR-200 is removed early.

[f]Most patients had one to two skipped TAR-200 doses, and common reasons for interruption included urinary tract pain (5.9%), pollakiuria (4.7%), and UTI (4.7%).

[g]Treatment-related AEs leading to TAR-200 discontinuation included two patients (2.4%) with noninfective cystitis and one (1.2%) with pollakiuria and with urinary tract disorder. Patients who discontinued may have had one or more treatment-related AE.

Table S9). Two patients (7.1%) experienced grade ≥3 treatment-related AEs; one (3.6%) had a serious treatment-related AE of myopericarditis. Two patients (7.1%) discontinued cetrelimab because of treatment-related AEs, with myopericarditis and neutropenia in one patient each.

DISCUSSION

Although radical cystectomy is the recommended standard of care for BCG-unresponsive high-risk NMIBC, it is not a favored option in this setting, given the risk of morbidity and mortality and the long-term impact on quality of life.[5-7,30] New intravesical treatments for BCG-unresponsive high-risk NMIBC have been developed in recent years[13-16]; however, their adoption as new standard of care has been limited.[18]

In SunRISe-1, TAR-200 monotherapy in patients with CIS with or without papillary disease (Cohort 2) resulted in a CR rate of 82.4%. To our knowledge, TAR-200 monotherapy demonstrated the highest single-agent CR rate reported to date in this setting, with a rapid onset and without continuation of treatment at the first observation of nonresponse.[12,16,17,31,32] Acknowledging the limitations of indirect cross-study comparisons, TAR-200 was associated with a higher CR rate than both conventional gemcitabine instillation and FDA-approved novel agents (pembrolizumab, nadofaragene firadenovec, and NAI + BCG), ranging from 41% to 62%.[15-17,33] Recently, a CR rate of 75% was reported for the investigational agent cretostimogene grenadenorepvec in patients with BCG-unresponsive CIS, although this CR rate included patients with persistent disease who underwent repeat induction treatment, which was not permitted in SunRISe-1.[34] The CR rate with TAR-200 monotherapy was consistent across subgroups, including by age, presence of papillary disease, and PD-L1 status. Although TAR-200 plus cetrelimab (Cohort 1) and cetrelimab alone (Cohort 3) showed efficacy, with CR rates of 67.9% and 46.4%, respectively, TAR-200 monotherapy demonstrated a more favorable risk-benefit profile compared with the combination of TAR-200 plus cetrelimab or cetrelimab monotherapy in this disease setting. Notably, 3-month CR rates of 41% and 43% have been reported for pembrolizumab and atezolizumab, respectively, as monotherapy in patients with BCG-unresponsive CIS.[12,17,31]

Responses with TAR-200 monotherapy in BCG-unresponsive CIS with or without papillary disease were durable, with a

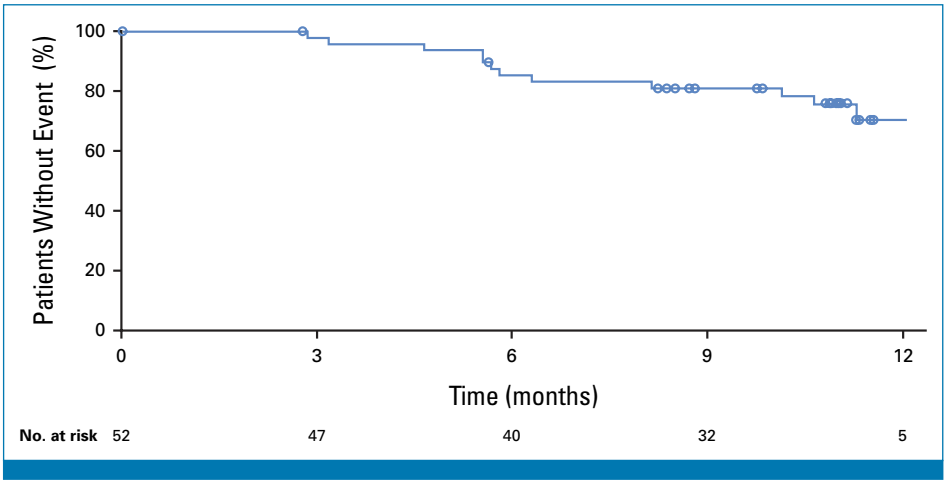

FIG 3. Disease-free survival (Kaplan-Meier curve) in patients with high-risk papillary disease–only non–muscle-invasive bladder cancer treated with TAR-200 monotherapy (Cohort 4). Time points with fewer than five patients at risk are excluded from the plot.

median DOR of 25.8 months and 52.9% of these patients having a DOR of ≥12 months. For context, among patients treated with pembrolizumab, nadofaragene firadenovec, or NAI plus BCG, 46%-58% had a DOR of ≥12 months, with CIs overlapping.[15-17] The high CR rate coupled with the durability of response in SunRISe-1 supports TAR-200 as a promising treatment option in the BCG-unresponsive CIS setting.

Clinical benefit was also observed with TAR-200 monotherapy in high-risk papillary disease–only NMIBC (Cohort 4). TAR-200 showed a 12-month DFS rate of 70.2%, representing, to our knowledge, the highest DFS rate reported in this setting to date, acknowledging the limited follow-up in the present analysis.[13,35,36] These results compare favorably with other novel agents in papillary disease–only NMIBC (12-month DFS, 44% with pembrolizumab, 55% with NAI + BCG; 12-month recurrence-free survival, 44% with nadofaragene firadenovec).[13,14,36]

Patients with BCG-unresponsive CIS have a high risk of progression and limited treatment options, thus guidelines recommend cystectomy.[5-7,37] SunRISe-1 results indicate an overall low risk of progression (8.2%) using a bladder-sparing approach with TAR-200 monotherapy. The rate of radical cystectomy in patients receiving TAR-200 monotherapy was also low, highlighting that TAR-200 treatment allowed most patients to delay or avoid this procedure.

TAR-200 monotherapy was well tolerated in both CIS and papillary disease–only NMIBC cohorts, with a safety profile consistent with that observed in phase I studies.[19,22,23] Overall, most treatment-related AEs were low-grade lower urinary tract symptoms that were managed symptomatically and of short duration (approximately 3 weeks). The frequency of lower urinary tract events (eg, pollakiuria, dysuria, and micturition urgency) with TAR-200 monotherapy was comparable with that with other intravesical treatments.[13,14,28,33] Systemic AEs were rare and unrelated to TAR-200. The safety findings were corroborated with quality-of-life measures of global health status and physical functioning, highlighting the benefit of localized sustained drug delivery through TAR-200 monotherapy. The safety profile in the cetrelimab monotherapy cohort was consistent with that of other anti–PD-(L)1 agents in the BCG-unresponsive CIS setting,[12,17,31] and patients in the TAR-200 plus cetrelimab cohort experienced both lower urinary tract events and systemic and immune-related toxicities, with no new toxicities observed with the combination.

SunRISe-1 has several key strengths, including strict adherence to the FDA guidance on the definition of BCG-unresponsive high-risk NMIBC. The study's single-arm design, with CR rate and DOR as end points, aligns with the FDA recommendations for clinical trials in patients with BCG-unresponsive high-risk NMIBC, given the lack of an established standard-of-care comparator and the presence of active disease at enrollment.[27] The multimodal response assessment on the basis of cystoscopy, urine cytology, biopsy at weeks 24 and 48, and imaging every 24 weeks provides confidence in the rigor of the CR assessment and exceeds the requirements set forth by FDA guidance for industry.[27] The high CR rate was achieved with protocol-mandated stopping of TAR-200 treatment after disease persistence. The high concordance rate between centrally and investigator-assessed response further corroborates the accuracy of the results.

A limitation was the noncomparative cohort design. However, conducting a comparative study in high-risk NMIBC was not feasible or ethical, given the reluctance or inability of patients to undergo radical cystectomy[27,38] and paucity of evidence supporting bladder-sparing treatment options in

this population. The duration of follow-up in the present analysis (median, 20.2 months in Cohort 2 responders) limits the ability to draw firm conclusions regarding long-term efficacy and safety of TAR-200 treatment, although in this disease setting, the majority of recurrence or progression events occur within the first 12 months of treatment.[13,39] Other limitations include the modest cohort sizes and the nonsimultaneous enrollment of cohorts. Potential financial burden and cost-effectiveness of TAR-200 treatment were not investigated in this study.

To our knowledge, the results of SunRISe-1 establish TAR-200 monotherapy as the first intravesical drug-releasing system with demonstrated efficacy and safety in the treatment of localized bladder cancer. TAR-200 monotherapy provides sustained localized delivery of intravesical gemcitabine with a favorable risk-benefit profile, supporting TAR-200 as a novel bladder-sparing treatment option for patients with BCG-unresponsive high-risk NMIBC. TAR-200 represents a substantial shift in the logistics of intravesical treatment administration in the urology clinic setting, as TAR-200 can be administered in a brief office procedure, while other intravesical treatments require 1-2 hours of retention after instillation before first voiding.[15,16,40,41] Furthermore, TAR-200, as both monotherapy and in combination with cetrelimab, is under investigation in other ongoing studies in the SunRISe program (ClinicalTrials.gov identifiers: NCT05714202, NCT04919512, and NCT06211764).

AFFILIATIONS

[1]University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA
[2]Netherlands Cancer Institute, Amsterdam, the Netherlands
[3]Upstate Medical University, Syracuse, NY
[4]Hospital Universitario 12 de Octubre, Madrid, Spain
[5]Münster University Hospital, Münster, Germany
[6]West German Cancer Center, Münster, Germany
[7]'Regina Elena' National Cancer Institute, Rome, Italy
[8]Associated Medical Professionals of New York (an affiliate of US Urology Partners), Syracuse, NY
[9]Hospital de Jerez de la Frontera y Punta Europa, Cádiz, Spain
[10]Urology San Antonio, San Antonio, TX
[11]Urologie Neandertal, Gemeinschaftspraxis für Urologie, Mettmann, Germany
[12]Bichat-Claude Bernard Hospital, Assistance Publique-Hôpitaux de Paris, Université de Paris Cité, Paris, France
[13]Colorado Urology, Lakewood, CO
[14]UT Southwestern Medical Center, Dallas, TX
[15]NYU Langone Health, New York, NY
[16]Yokohama City University Medical Center, Yokohama, Japan
[17]Johnson & Johnson, Raritan, NJ
[18]Johnson & Johnson, High Wycombe, UK
[19]Johnson & Johnson, Lexington, MA
[20]Johnson & Johnson, Horsham, PA
[21]Johnson & Johnson, Spring House, PA
[22]IRCCS San Raffaele Hospital, Milan, Italy
[23]Vita-Salute San Raffaele University, Milan, Italy

CORRESPONDING AUTHOR

Siamak Daneshmand, MD; e-mail: daneshma@med.usc.edu.

PRIOR PRESENTATION

Presented in part at the American Urological Association Annual Meeting in Chicago, IL, April 28-May 1, 2023; the European Society for Medical Oncology Congress in Madrid, Spain, October 20-24, 2023; the American Urological Association Annual Meeting in San Antonio, TX, May 3-6, 2024; and the European Society for Medical Oncology Congress in Barcelona, Spain, September 13-17, 2024.

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AUTHOR CONTRIBUTIONS

Conception and design: Siamak Daneshmand, Katharine Stromberg, Jason Martin, Abhijit Shukla, Christopher J. Cutie, Shalaka Hampras, Hussein Sweiti, Andrea Necchi
Provision of study materials or patients: Siamak Daneshmand, Michiel S. van der Heijden, Joseph M. Jacob, Felix Guerrero-Ramos, Martin Bögemann, Giuseppe Simone, Christopher M. Pieczonka, Nelson Canales Casco, Daniel Zainfeld, Philipp Spiegelhalder, Evanguelos Xylinas, David Cahn, Yair Lotan, Katie S. Murray, Takashi Kawahara, Andrea Necchi
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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TAR-200 for Bacillus Calmette-Guérin–Unresponsive High-Risk Non–Muscle-Invasive Bladder Cancer: Results From the Phase IIb SunRISe-1 Study

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Siamak Daneshmand
Stock and Other Ownership Interests: Taris
Honoraria: Photocure, Ferring, Pacific Edge, Johnson & Johnson, Bristol Myers Squibb, Allergan (I), Bausch and Lomb (I), Pfizer, Protara Therapeutics, CG Oncology, UroGen Pharma, Storz, Sesen Bio, ImmunityBio, enGene, AstraZeneca, Lilly
Consulting or Advisory Role: Photocure, Taris, Ferring, CG Oncology, AstraZeneca, Pfizer, Pacific Edge, Johnson & Johnson/Janssen, enGene, Bristol Myers Squibb/Pfizer, UroGen Pharma, UroToday, ImmunityBio
Research Funding: Photocure
Travel, Accommodations, Expenses: Photocure, Janssen Oncology

Michiel S. Van der Heijden
Consulting or Advisory Role: Astellas Pharma (Inst), AstraZeneca/MedImmune (Inst), Bristol Myers Squibb (Inst), MSD Oncology (Inst), Seagen (Inst), Janssen (Inst), Pfizer (Inst), Daiichi Sankyo (Inst)
Research Funding: Bristol Myers Squibb (Inst), Roche (Inst), AstraZeneca (Inst), Seagen (Inst), 4SC (Inst), MSD Oncology (Inst)
Travel, Accommodations, Expenses: Bristol Myers Squibb (Inst)

Joseph M. Jacob
Consulting or Advisory Role: Janssen, Pfizer, Aura Biosciences

Felix Guerrero-Ramos
Honoraria: AstraZeneca, Janssen, BMS GmbH & Co. KG, Combat Medical, Merck, Pfizer, Nucleix, Roche, Palex, Johnson & Johnson/Janssen, MSD Oncology
Consulting or Advisory Role: AstraZeneca, Pfizer, Janssen Oncology, BMS GmbH & Co. KG, Johnson & Johnson/Janssen, Roche, Nucleix, Merck
Speakers' Bureau: Pfizer, Janssen Oncology, AstraZeneca, Combat Medical, Nucleix, BMS GmbH & Co. KG, Palex
Research Funding: Roche, Combat Medical
Patents, Royalties, Other Intellectual Property: BlaDimiR, miRNA-Based Diagnostic Urine Test
Expert Testimony: Nucleix, Johnson & Johnson/Janssen
Travel, Accommodations, Expenses: Johnson & Johnson/Janssen, AstraZeneca, Janssen Oncology, Ipsen, Combat Medical, Nucleix, Recordati, Pfizer, SALVAT, Italfarmaco, Fidia Farmaceutici S. p. A

Martin Bögemann
Employment: Janssen
Honoraria: Janssen-Cilag, Astellas Pharma, Bayer/Vital, Sanofi/Aventis, MSD, Bristol Myers Squibb, Pfizer, Novartis, Ipsen, EUSA Pharma, Merck, Eisai, Amgen, AstraZeneca, Roche, Advanced Accelerator Applications
Consulting or Advisory Role: Bayer, Janssen-Cilag, Astellas Pharma, AstraZeneca, MSD, Bristol Myers Squibb, Ipsen, Roche, Novartis, Merck, Sanofi, Eisai, Gilead Sciences
Research Funding: Janssen-Cilag, IPSEN (Inst)
Travel, Accommodations, Expenses: Janssen-Cilag, Bayer, Amgen, BMS GmbH & Co. KG

Christopher M. Pieczonka
Employment: Associated Medical Professionals of New York
Leadership: Associated Medical Professionals of New York, US Urology Partners
Stock and Other Ownership Interests: US Urology Partners, ImmunityBio
Honoraria: Janssen, Dendreon, Pfizer/Astellas, Bayer, Sun Pharma, Myovant Sciences, Merck, AstraZeneca, Bristol Myers Squibb, Novartis, ImmunityBio
Consulting or Advisory Role: Pfizer/Astellas, Bayer, Janssen Oncology, Tolmar, Sun Pharma, Dendreon, AstraZeneca, Merck, Bristol Myers Squibb, Novartis, ImmunityBio
Speakers' Bureau: Bayer, Dendreon, Pfizer, Astellas Pharma, Sun Pharma, Myovant Sciences, Janssen Oncology, Astra Zenerca, Merck
Research Funding: Bayer, Pfizer, Astellas Pharma, Merck, AstraZeneca, Advantagene, Dendreon, Janssen Oncology, InVitae, Candel Therapeutics (Inst), CG Oncology (Inst), ImmunityBio (Inst)

Daniel Zainfeld
Consulting or Advisory Role: Johnson and Johnson

Philipp Spiegelhalder
Consulting or Advisory Role: AstraZeneca
Research Funding: Janssen, Pfizer, enGene
Travel, Accommodations, Expenses: Janssen, Astellas Pharma

Evanguelos Xylinas
Employment: W.L. Gore & Associates (I)
Consulting or Advisory Role: Pfizer, Ferring, Boston Scientific
Research Funding: Ferring

David Cahn
Consulting or Advisory Role: Johnson & Johnson/Janssen, Bayer, GlaxoSmithKline, AstraZeneca
Speakers' Bureau: Johnson & Johnson/Janssen
Research Funding: Johnson & Johnson/Janssen (Inst), Merck (Inst), AstraZeneca (Inst), Protara Therapeutics (Inst), Zenith Epigenetics (Inst), Bayer (Inst), CG Oncology (Inst), enGene (Inst)

Yair Lotan
Stock and Other Ownership Interests: Vessi Medical, CAPs medical, Nanorobotics, PHINOMICS, UroViu, Virtuoso Therapeutics, vesica Health, Trigone Pharma
Consulting or Advisory Role: Photocure, pacific edge, Vessi Medical, Merck, AstraZeneca, Nucleix, UroGen Pharma, BMS, FerGene, AbbVie, Cleveland Diagnostics, Nanorobotics, Nanogen Biopharmaceutical, CAPS Medical, Ambu, Seagen, Verity Pharmaceuticals, Virtuoso Surgical, STIMIT, xCures, Aura Biosciences, Convergent Genomics, PHINOMICS, UroViu, Trigone Pharma, NRx pharmaceuticals, ImmunityBio, Janssen
Research Funding: Abbott Molecular (Inst), Pacific Edge (Inst), Cepheid (Inst), GenomeDx (Inst), MDxHealth (Inst), Pacific Edge, Cepheid, Augmenix, BioCancell (Inst), Photocure (Inst), Storz (Inst)

Katie S. Murray
Consulting or Advisory Role: UroGen Pharma
Speakers' Bureau: UroGen Pharma

Katherine Stromberg
Employment: Johnson & Johnson/Janssen
Stock and Other Ownership Interests: Johnson & Johnson/Janssen
Research Funding: Johnson & Johnson/Janssen
Travel, Accommodations, Expenses: Johnson & Johnson/Janssen

Jason Martin
Employment: Johnson and Johnson
Stock and Other Ownership Interests: Johnson and Johnson
Travel, Accommodations, Expenses: Johnson and Johnson

Abhijit Shukla
Employment: Johnson and Johnson
Stock and Other Ownership Interests: Johnson and Johnson

Christopher J. Cutie
Employment: Taris BioMedical, Johnson & Johnson/Janssen
Stock and Other Ownership Interests: Johnson & Johnson/Janssen

Kristi Bertzos
Employment: Johnson & Johnson/Janssen
Stock and Other Ownership Interests: Johnson & Johnson/Janssen
Travel, Accommodations, Expenses: Johnson & Johnson/Janssen

Shalaka Hampras
Employment: Johnson and Johnson
Stock and Other Ownership Interests: Johnson & Johnson/Janssen
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APPENDIX. SUNRISE-1 STUDY INVESTIGATORS

The following investigators screened and enrolled patients in SunRISe-1:

Australia—Manish Patel; Belgium—Thierry Roumeguere, Charles Van Praet, Harm Arentsen, Bart De Troyer, Frederic Baekelandt, Karel Decaestecker; Canada—Girish Kulkarni, Wassim Kassouf, George Vrabec; France—Sabrina Falkowski, Geraldine Pignot, Evanguelos Xylinas, Morgan Roupret, Marc Colombel, Romain Mathieu, Benoit Wolff, Marc-Olivier Timsit, Xavier Artignan, Stephane Droupy, Herve Lang, Mathieu Roumiguie, Frank Bladou, Catherine Becht; Germany—Martin Bögemann, Phillipp Spiegelhalder, Jorg Klier, Tilman Toderhofer, Eva Hellmis; Greece—Petros Sountoulides, Konstantinos Hatzimouratidis; Italy—Giuseppe Simone, Luca Galli, Frederico Deho, Andrea Minervini, Andrea Necchi; Japan—Takashi Kawahara, Shuya Kandori, Masao Tsujihata, Shinji Urakami; South Korea—Taek Won Kang, Ja Hyeon Ku, Kang Su Cho, Wonho Jung, Ho Kyung Seo, Jong Kil Nam; the Netherlands—Diederik Somford, Michiel Van der Heijden; Portugal—Antonio Morais, Vania Grenha, Jorge Rebola, Sandra Custodio; Russia—Vagif Atduev, Denis Kholtdobin; Spain—Jose Luis Alvarez-Ossorio Fernandez, Javier Romero Otero, Felix Guerrero Ramos, Bernardo Herrera Imbroda, Pol Servian Vives, Nelson Canales Casco, Mario Eduardo Alvarez Maestro; United States—David Morris, Siamak Daneshmand, Curtis Dunshee, Daniel Zainfeld, Katie Murray, Laurence Belkoff, Peter Earl Clark, Yair Lotan, Joseph Jacob, David Cahn, Christopher Pieczonka, Amy Luckenbaugh, Marc Pliskin, Jason Hafron, Eugene Cone, Brian Mazzarella, Richard David.