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Safety, Tolerability, and Preliminary Efficacy of TAR-200 in Patients With Muscle-invasive Bladder Cancer Who Refused or Were Unfit for Curative-intent Therapy: A Phase 1 Study

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Study Need and Importance: Standard-of-care treatment for muscle-invasive bladder cancer (MIBC) is platinum-based neoadjuvant chemotherapy followed by radical cystectomy or multimodal treatment combining maximal transurethral resection of bladder tumor with chemo/radiotherapy. However, half of patients with MIBC worldwide may not receive curative-intent therapy. Elderly or frail patients with MIBC are most affected by this unmet need.

TAR-200 is a novel intravesical drug delivery system that provides sustained, local release of gemcitabine into the bladder over a 21-day dosing cycle. This phase 1 study evaluated the safety, tolerability and preliminary efficacy of TAR-200 in patients with MIBC who either refused or were unfit for curative-intent therapy.

What We Found: Overall, 35 patients with MIBC who refused or were unfit for curative-intent therapy received at least 1 dose of TAR-200. Median age was 84 years and 46% had Eastern Cooperative Oncology Group performance status 3-4.

TAR-200 was generally safe and well tolerated. The most common TAR-200–related treatment-emergent adverse events (TEAEs) were dysuria and urinary frequency, generally observed at grades 1-2. Two patients experienced TEAEs leading to removal of TAR-200.

TAR-200 also showed preliminary signs of efficacy, with an overall response rate of 40.0% at 3 months, a median overall survival of 27.3 months, and a progression-free rate at 12 months of 70.5%.

Limitations: Our study is limited by its small sample size, single-arm design, and the absence of complete pathological assessment that would have been provided by radical cystectomy. Additionally, it is a challenge to distinguish whether TAR-200–related TEAEs were attributable to either the drug or the device constituent, as they are integral.

Interpretation for Patient Care: The safety and preliminary efficacy data from this study support the continued development of TAR-200 across the bladder cancer spectrum. Multiple global, randomized, controlled phase 2/3 trials investigating TAR-200 are ongoing.

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Safety, Tolerability, and Preliminary Efficacy of TAR-200 in Patients With Muscle-invasive Bladder Cancer Who Refused or Were Unfit for Curative-intent Therapy: A Phase 1 Study

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Purpose: Half of patients with muscle-invasive bladder cancer worldwide may not receive curative-intent therapy. Elderly or frail patients are most affected by this unmet need. TAR-200 is a novel, intravesical drug delivery system that provides sustained, local release of gemcitabine into the bladder over a 21-day dosing cycle. The phase 1 TAR-200-103 study evaluated the safety, tolerability, and preliminary efficacy of TAR-200 in patients with muscle-invasive bladder cancer who either refused or were unfit for curative-intent therapy.

Materials and Methods: Eligible patients had cT2-cT3bN0M0 urothelial carcinoma of the bladder. TAR-200 was inserted for 4 consecutive 21-day cycles over

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Conflict of Interest: C.J. Cutie and J.C. Maffeo are former employees of TARIS Biomedical and are employees of Janssen Pharmaceuticals. K.A. Keegan, K.A. Stromberg, and B. Raybold are employees of Janssen Pharmaceuticals. A. Chau was a paid consultant for TARIS Biomedical and Janssen Pharmaceuticals. J. Palou has worked as a consultant for Astellas, Janssen Pharmaceuticals, Merck, Ferring, AstraZeneca, Sandoz, and Novartis. R.J. Dickstein was a consultant for Janssen Pharmaceuticals. F. Guerrero-Ramos is an advisor for Pfizer, BMS, AstraZeneca, Janssen, and Combat Medical; and speaker for Astellas Oncology, Janssen, Pfizer, AstraZeneca, Combat Medical, and Nucleix. J.M. Hafron reports personal fees from Amgen, Bayer, and Blue Earth Diagnostics; grants and personal fees from Dendreon Pharmaceuticals, Janssen Biotech, Myriad Genetics, Pfizer, Astellas Pharma, and Merck; and grants from Nucleix and Cellay. K.R. Scarpato has a financial interest and/or other relationship with Photocure and Karl Storz. M.D. Tyson, M.C. Mir, R. Rodriguez, and E.M. Messing have no financial or other conflicts of interest related to this study.

Ethics Statement: The study protocol was approved by an institutional review board or independent ethics committee and was conducted in accordance with the Declaration of Helsinki.

Data Sharing: The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through the Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

This manuscript reports data on the investigational use of a product or device not yet approved by the Food and Drug Administration for any purpose.

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84 days. The primary end points were safety and tolerability at 84 days. Secondary end points included rates of clinical complete response and partial response as determined by cystoscopy, biopsy, and imaging; duration of response; and overall survival.

Results: Median age of the 35 enrolled patients was 84 years, and most were male (24/35, 68.6%). Treatment-emergent adverse events related to TAR-200 occurred in 15 patients. Two patients experienced treatment-emergent adverse events leading to removal of TAR-200. At 3 months, complete response and partial response rates were 31.4% (11/35) and 8.6% (3/35), respectively, yielding an overall response rate of 40.0% (14/35; 95% CI 23.9-57.9). Median overall survival and duration of response were 27.3 months (95% CI 10.1-not estimable) and 14 months (95% CI 10.6-22.7), respectively. Progression-free rate at 12 months was 70.5%.

Conclusions: TAR-200 was generally safe, well tolerated, and had beneficial preliminary efficacy in this elderly and frail cohort with limited treatment options.

Key Words gemcitabine; urinary bladder neoplasms; administration, intravesical

Bladder cancer is frequently a disease of the elderly, with a median age at diagnosis of ~70 years, and represents a substantial public health burden, with approximately 570,000 cases diagnosed annually worldwide.[1,2] Roughly 25% of incident bladder cancer diagnoses are muscle-invasive (MIBC), and approximately 20% of those with high-risk nonmuscle-invasive bladder cancer will progress to MIBC.[3,4] Importantly, patients with MIBC have a relatively poor prognosis, with a 5-year overall survival (OS) of 48%-70% with treatment (5% without), and untreated patients are at high risk for near-term, cancer-specific mortality.[5,6]

Global guidelines recommend platinum-based neoadjuvant chemotherapy, followed by radical cystectomy (RC) with pelvic lymph node dissection, or multimodal treatment that combines maximal transurethral resection of bladder tumor (TURBT) with chemo/radiotherapy as standard-of-care treatments for MIBC.[7] However, RC is associated with high perioperative and postoperative complication rates and a 90-day mortality rate of up to 9%.[8,9] Additionally, chemoradiation represents a significant treatment burden for elderly patients, and is frequently underutilized across many geographies.[10-12] Consequently, while current standard-of-care treatments do confer a considerable survival advantage, they are potentially hindered by significant morbidity, mortality, undesirable effects on quality of life, and inadequate therapeutic efficacy, prompting some patients to decline treatment.[5,13] Accordingly, 25%-57% of patients with MIBC worldwide may not receive any curative-intent therapy, representing a substantial unmet need.[6,10-12] While patients with MIBC may not receive therapy for many reasons, including lack of access, those who are elderly or frail with significant comorbidities may be most affected by this substantial clinical gap.[6,10,14] This suggests a critical need for alternative therapies that are tolerable and effective in an elderly population.

TAR-200 is a novel intravesical drug delivery system that provides continuous, low-dose local delivery of gemcitabine (Figure 1).[15] Gemcitabine has demonstrated efficacy across the bladder cancer disease spectrum and has unique pharmacological properties that result in drug distribution throughout the intravesical urine and, with sustained dosing, into the stromal layers of the bladder wall.[15,16] Preclinical studies conducted on a bioluminescence tumor model in rats demonstrated a reduction in bladder tumor metabolic activity in response to gemcitabine that was perfused (0.3 mL/h) over one or two 5-day treatment cycles, yielding nominal urine concentrations of 0, 20, 40, or 80 μg/mL. This revealed that continuous low-dose intravesical gemcitabine inhibits muscle-invasive bladder tumors in a concentration-dependent manner.[17] Given the impermeability of the bladder, use of TAR-200 results in limited systemic gemcitabine exposure and reduced bladder toxicity due to the delivery of a significantly lower dose compared with standard intravesical gemcitabine instillations.[18,19] In the phase 1 TAR-200-101 study, neoadjuvant TAR-200 was shown to be safe and well tolerated, and demonstrated preliminary antitumor activity in patients with MIBC scheduled for RC.[15] Pharmacokinetic data from the TAR-200-101 study showed that gemcitabine and its metabolite, dFdU (2′,2′-difluorodeoxyuridine), were detected in urine at concentrations of 18.5 μg/mL and 6.7 μg/mL, respectively.[15] However, importantly, gemcitabine was not detected in plasma, while detectable dFdU plasma levels were low (0.1 to 0.3 μg/mL).[15] TAR-200 provides uniform tumor-drug contact, regardless of tumor location within the bladder, as gemcitabine concentrations are maintained over many voiding cycles.

Here we report results of the TAR-200-103 study. TAR-200-103 was a global phase 1 study to evaluate the safety, tolerability, and preliminary efficacy of TAR-200 in patients with MIBC who either refused or were unfit for curative-intent therapy.

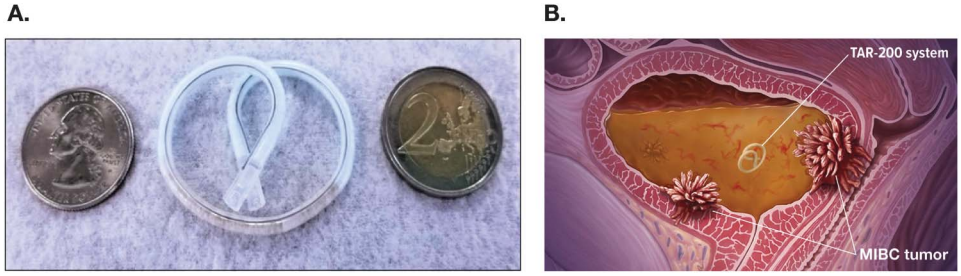

Figure 1. TAR-200 consists of a small, flexible silicone delivery system filled with gemcitabine (A) and is designed to provide controlled release of gemcitabine directly inside the bladder during the indwelling period (B). MIBC indicates muscle-invasive bladder cancer. This figure was published in *Urologic Oncology*, 40, Daneshmand et al, The safety, tolerability, and efficacy of a neoadjuvant gemcitabine intravesical drug delivery system (TAR-200) in muscle-invasive bladder cancer patients: a phase I trial, 344.e1-344.e9, Copyright Elsevier (2022).[15]

MATERIALS AND METHODS

Study Design

TAR-200-103 was a prospective, multicenter, open-label, single-arm, global phase 1 study in which eligible patients received up to 4 consecutive 21-day cycles of TAR-200 during an 84-day induction period within 7 weeks of TURBT (Figure 2). Patients were eligible for 3 optional additional quarterly maintenance cycles starting on day 180, if judged by the investigator to be in their best interest. A final safety follow-up visit occurred after the maintenance period (30 days after last TAR-200 removal). Patients then entered an optional 24-month surveillance period to monitor for recurrence and OS. Here we report an analysis of data up to data cutoff (February 25, 2022).

This study (NCT03404791) was conducted according to the Declaration of Helsinki with the study protocol approved by an institutional review board or independent ethics committee.

Patient Selection

Written informed consent was obtained for each patient. Eligible patients were diagnosed with urothelial MIBC (cT2-cT3bN0M0); those with mixed histology had a documented dominant transitional cell pattern. Micropapillary, sarcomatoid, and adenocarcinoma variants were excluded. Enrolled patients had a life expectancy of $\geq$4 months, had undergone an endoscopic visibly complete resection via TURBT, were deemed unfit for RC by principal investigator assessment (with a mortality risk of RC $\geq$3%, as estimated using the American College of Surgeons' risk calculator [http://riskcalculator.facs.org/RiskCalculator/index.jsp]), and refused or were considered medically ineligible for cisplatin-based chemotherapy or radical radiotherapy ($\geq$50 Gy). Primary exclusion criteria included prior systemic chemotherapy for urothelial carcinoma of the bladder; pelvic radiotherapy <6 months before enrollment; radiation cystitis; other active malignancy within 1 year before enrollment (except prostate cancer); presence of externalized pyeloureteral stent or indwelling urethral catheters; evidence of current bladder perforation; concurrent clinically significant urinary infection; or anatomy that would prevent safe placement, indwelling use, or removal of TAR-200.

TAR-200

The TAR-200 drug delivery system for controlled local release of gemcitabine within the bladder has been described previously.[15] TAR-200 was dosed in 4 consecutive 21-day cycles, with the first TAR-200 inserted on study day 0 and removed on day 21. Another TAR-200 was inserted the same day. Urinalyses and urine cultures were performed at each TAR-200 insertion to rule out urinary tract infection (UTI). This cycle was repeated every 21 days, with the fourth TAR-200 removed on day 84.

Outcomes

The primary end point of the study was safety and tolerability of 4 consecutive 21-day TAR-200 dosing cycles. Safety was assessed via adverse events (AEs), clinical laboratory tests, vital signs, investigational product events (IPEs), and cystoscopy findings. AEs, which include treatment-related, disease-related, and unrelated untoward medical events, were either patient reported or identified during study visits and monthly telephonic interviews, and were recorded from study day 0 through to the final safety follow-up visit, including an evaluation on day 95. IPEs included any observation of TAR-200 not performing as intended. Cystoscopy findings were considered adverse if evidence of urothelial bleeding or bladder

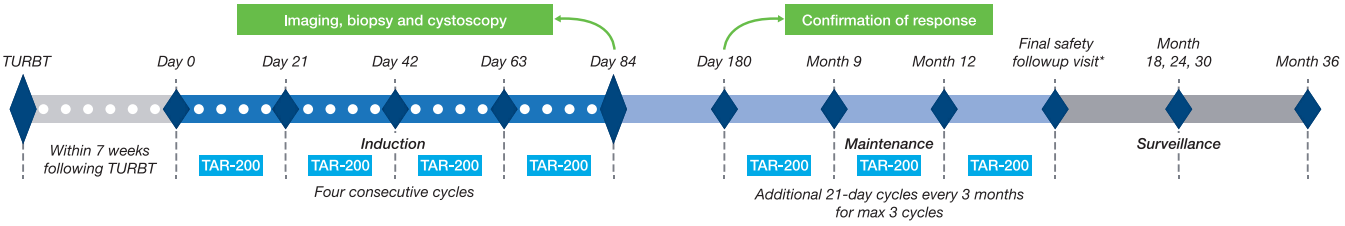

Figure 2. Schema of TAR-200-103 study design. *Thirty days after last TAR-200 removal. TURBT indicates transurethral resection of bladder tumor.

stones were noted. Treatment-emergent adverse events (TEAEs) were defined as any new AE, or worsening of any preexisting AE, that occurred after initiation of the first dose of TAR-200. The TEAE period extended for 30 days after discontinuation of study treatment. AEs were coded using the Medical Dictionary for Regulatory Activities, and their severity was categorized according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. AEs were also assessed as being related to the drug or device constituent or to the insertion/removal procedure by the investigator. Tolerability was defined as not requiring early/unscheduled TAR-200 removal due to meeting any predefined safety criteria (ie, grade $\geq$2 hematuria, aseptic cystitis, severe opportunistic infections, UTI, allergic reaction, signs of systemic gemcitabine toxicity) or any other TAR-200–related TEAEs.

Key secondary and other end points were clinical complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) rates; duration of response (DOR); OS; bladder-related symptom control; time to symptom control intervention; time to progression; and progression-free survival (PFS). Definitions of CR, PR, SD, and PD are presented in supplementary Table 1 (https://www.jurology.com).

The clinical response was evaluated on day 84 (end of induction phase) using cystoscopy for visible lesions, chest/abdominal/pelvic imaging (computerized tomography, magnetic resonance imaging, or positron emission tomography), and pathological staging of mandatory bladder biopsy.

Quarterly efficacy assessments during the maintenance period included cystoscopy, imaging, and additional biopsy, if clinically indicated. Patient-reported urinary symptoms were evaluated at baseline, every 3 weeks during the induction phase, and every month during the maintenance period using the symptom and toxicity grading system by Duchesne et al.[20] Any increase in symptom grade was reviewed by the investigator to determine if reporting as an AE was required.

Statistical Analysis

Safety, tolerability, and early efficacy are descriptively summarized. For continuous variables, descriptive statistics, including the mean, median, minimum, and maximum, were provided. Categorical variables were summarized using frequency counts and percentages. For time-to-event variables, the Kaplan-Meier method was used to calculate the distribution (median and Kaplan-Meier curve). Analyses were performed on all enrolled and treated patients as of the data cutoff date. As this was a phase 1b study, the predetermined sample size of approximately 30 patients per protocol was not based on statistical considerations and there was no hypothesis testing nor P values generated. DOR was defined as the time from first observation of CR or PR to the first observation of PD or death in patients who had a response. Patients who had not progressed or who died were censored at the date of last evaluable disease assessment. The progression-free rate was expressed as the percentage of patients still in response at 6 and 12 months. The time to progression was defined as the time from the date of the first insertion of TAR-200 to the date of the first occurrence of PD or censoring at the time of last evaluable disease assessment. OS was defined as the time from the date of the first insertion of TAR-200 to the date of death, or censoring time at the date that the patient was last known to be alive, and PFS was defined as the time from the date of the first insertion of TAR-200 to the date of the first occurrence of progression of disease or death, or censoring at the date of last evaluable disease assessment. All analyses were performed using SAS statistical software version 9.4.

RESULTS

Patient Disposition and Demographics

Thirty-five patients with MIBC who either refused or were unfit for curative-intent therapy were screened and enrolled (Figure 3). All 35 patients received at least 1 dose of TAR-200; 26 (74.3%) completed the entire 4 dose cycles during the induction period and response assessment on day 84. Twenty-five (71.4%) patients subsequently entered the maintenance period; 18 (51.4%) received at least 1 maintenance dosing cycle, and 12 (34.3%) completed all 3 maintenance dosing cycles. Overall, 8 (22.9%) patients completed all treatments, study assessments, full maintenance period, and the final safety follow-up visit, which occurred 30 days after the last TAR-200 removal. At data cutoff, 4 patients had completed the study by concluding the 24-month surveillance period, with 8 still receiving ongoing surveillance.

Baseline patient characteristics are presented in Table 1. Briefly, most patients were male and White, the median age was 84 years, median body mass index was 27.7 kg/m^2, and the majority of patients had a history of tobacco use.

Safety and Tolerability

Only 2 patients (5.7%; 95% CI 0.7-19.2) were considered not tolerant of TAR-200 (requiring early TAR-200 removal due to TEAEs); 1 patient had TEAEs of nocturia, abdominal pain, UTI, fever, and dysuria (grade 3) that led to study discontinuation and 1 patient had TEAEs of discomfort, dysuria, and urinary frequency, as well as treatment-emergent serious AEs (SAEs) of urosepsis and acute kidney injury. Overall, TAR-200–related TEAEs occurred in 15 patients (42.9%; 95% CI 26.3-60.7), with dysuria (20.0%), urinary frequency (14.3%), nocturia (8.6%), and urethral syndrome (8.6%) the most common (Table 2). Nine (25.7%) patients reported at least 1 procedure-related TEAE (6 urinary placement catheter related, 8 cystoscopy procedure related); the most common were dysuria and UTI (2 patients [5.7%] each). No IPEs were reported during the study. A total of 21 patients (60.0%) had at least 1 SAE; 1 patient experienced SAEs of urosepsis and acute kidney injury that were considered potentially related to TAR-200, and 2 patients had an SAE (1 with event of UTI and 1 with event of pyrexia) considered related to the procedure. Most of the SAEs (88.6%) experienced were considered

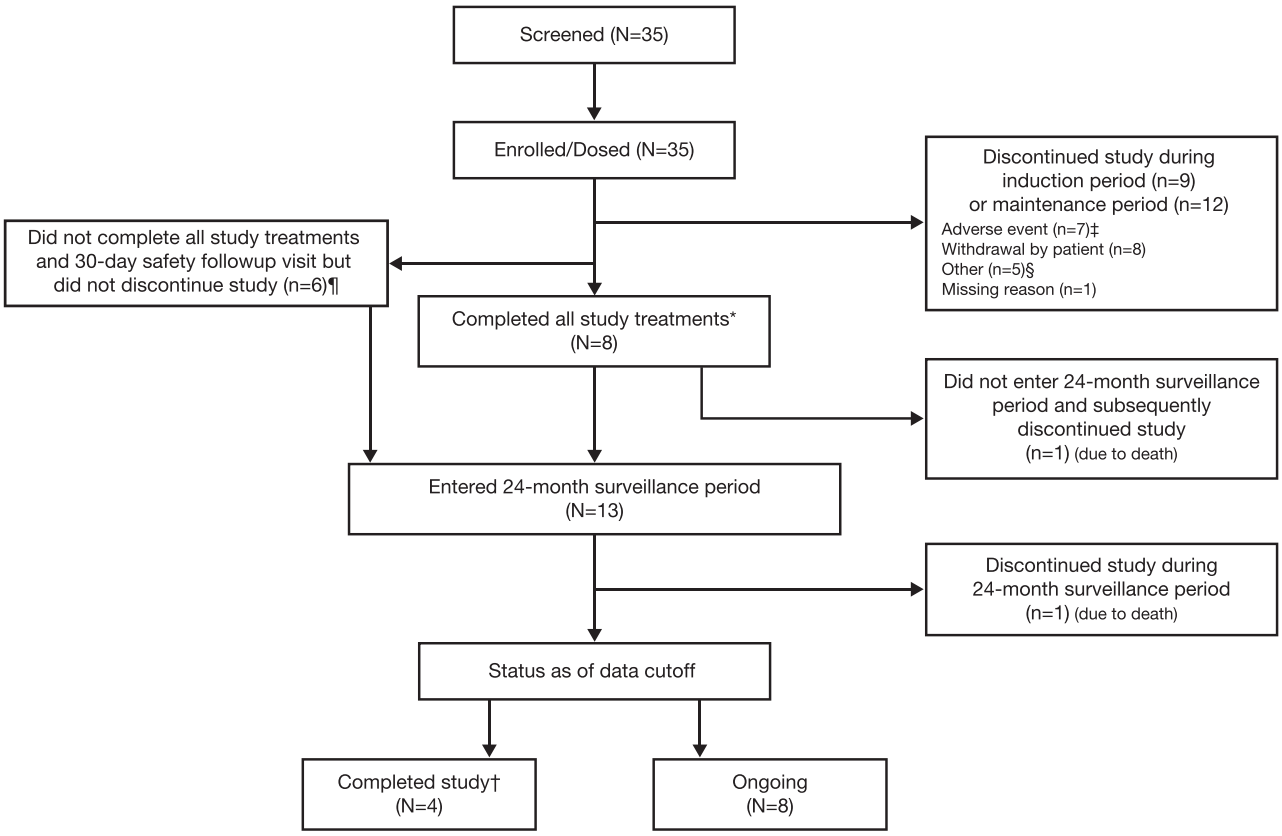

Figure 3. Distribution of enrolled patients. *Number of patients who completed all study treatments includes all patients who completed the 12-month maintenance dosing and 30-day safety follow-up visit. †Number of patients who completed study includes all patients who completed the 24-month surveillance period. ‡Three patients who discontinued the study due to adverse events also had premature permanent TAR-200 removal (due to adverse events not listed in the stopping criteria [n=2] or unspecified/missing reasons [n=1]). §Other reasons included disease progression or recurrence (n=3), death (n=1), and patient under hospice care with catheter in place (n=1). ¶Five patients completed 7 dosing cycles overall, but they did not attend the final safety follow-up visit; 1 patient received 3 dosing cycles; all 6 subsequently entered the surveillance period.

unrelated to TAR-200. None of the TEAEs leading to death in 4 patients (11.4%) were considered related to TAR-200 or the procedure. Causes of death in these 4 patients were cardiac failure, cardiorespiratory arrest, failure to thrive, and acute respiratory failure. None of the TEAEs that led to study discontinuation (17.1%), except for 1 TEAE of urinary incontinence, were considered treatment related. Patients discontinued treatment for a variety of reasons (Table 3). Clot evacuation and blood transfusion were required in 1 patient each. The patient who underwent clot evacuation had a hemostatic TURBT performed after the completion of the fourth dosing cycle during the induction period and thereafter still underwent 2 of the 3 optional quarterly maintenance cycles. The patient who required a blood transfusion had this transfusion after withdrawal from the study and after having undergone completion of all 4 induction dosing cycles and 1 optional quarterly maintenance cycle. As each of these events occurred outside of a dosing period, they were not deemed to be TAR-200–related TEAEs based on time from last TAR-200 exposure. Most patients reported no or minimal change in bladder symptoms. The median time to intervention for symptom palliation was not estimable (NE), while the Kaplan-Meier estimate of the 25th percentile of time to intervention was 3.7 months.

Preliminary Efficacy

Response was assessed in all patients who completed 4 TAR-200 dosing cycles and underwent biopsy/pathology assessment (n=26). Overall, at 3 months, 11 of 35 patients (31.4%) had CR and 3 of 35 patients (8.6%) had PR, yielding an overall response rate of 40.0% (95% CI 23.9-57.9). Six of 35 patients (17.1%) had SD and 6 of 35 (17.1%) had PD. Patients who were not assessed for response (n=9) were assumed to have no response and were included in the denominator of these calculations. The median OS was 27.3 months (95% CI 10.1-NE; Figure 4, A). In patients who were responders (n=14 [CR+PR]; Figure 5), the median DOR was 14.0 months (95% CI 10.6-22.7). Median follow-up duration was 15.7 months for all patients and 37.8 months for survivors.

Table 1. *Demographic and Baseline Characteristics*

Demographic	TAR-200 (N=35)
Age, median (Q1, Q3), y	84 (79, 88)
Sex, No. (%)	
Female	11 (31.4)
Male	24 (68.6)
Race, No. (%)	
White	29 (82.9)
Black or African American	6 (17.1)
Asian	0
Other	0
BMI, median (Q1, Q3), kg/m^2	27.7 (25.4, 31.6)
ECOG performance status, No. (%)	
0-2	19 (54.3)
3-4	16 (45.7)
Smokers (current and former), No. (%)	25 (71.4)
Charlson comorbidity index >2, No. (%)	20 (57.1)
Prior intravesical BCG, No. (%)	6 (17.1)
Clinical staging at diagnosis, No. (%)	
cT2	34 (97.1)
cT3	1 (2.9)

Abbreviations: BCG, bacillus Calmette-Guérin; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; Q, quartile.

The progression-free rate for patients still in response (n=14) was estimated to be 92.3% at 6 months and 70.5% at 12 months. Median time to disease progression was 13.5 months (95% CI 6.2-NE) and median PFS was 9.5 months (95% CI 4.1-15.6; Figure 4, B).

DISCUSSION

The preliminary results of this phase 1 study show that TAR-200 is safe and well tolerated in this elderly patient population (median age 84; Eastern Cooperative Oncology Group performance status 3 to 4, 46%). Fifteen patients experienced TAR-200–related TEAEs. The most common TAR-200–related TEAEs were dysuria and urinary frequency, which are generally observed clinically at grade ≤2. This safety profile is consistent with TEAEs frequently noted after intravesical instillations of gemcitabine and those commonly observed with indwelling urethral catheters and ureteral stents.[21-23] None of the TEAEs leading to death were considered related to TAR-200, only 1 TAR-200–related TEAE led to study discontinuation, and 1 patient reported SAEs that the investigator considered related to the drug delivery system. Placement of TAR-200 into the bladder was successful in all patients. Only 2 patients were considered not tolerant of TAR-200 and no IPEs were reported. Rates of clot evacuation and blood transfusion were considerably lower than in patients who historically received no curative-intent treatment.[24] TEAEs observed in this elderly and frail cohort of patients with MIBC were as expected, with no unanticipated safety issues attributed to treatment with TAR-200.

Table 2. *Summary of Treatment-emergent Adverse Events Considered by the Investigator to Be Related to TAR-200 or to Procedure (Insertion/Removal)*

TEAE by system organ class[a]	TAR-200 related	Procedure related
Any TEAE, No. (%)	15 (42.9)	9 (25.7)
Renal and urinary disorders, No. (%)	14 (40.0)	5 (14.3)
Dysuria	7 (20.0)	2 (5.7)
Urinary frequency	5 (14.3)	1 (2.9)
Nocturia	3 (8.6)	1 (2.9)
Urethral syndrome	3 (8.6)	1 (2.9)
Infections and infestations, No. (%)	1 (2.9)	3 (8.6)
Urinary tract infection	0 (0)	2 (5.7)

Abbreviation: TEAE, treatment-emergent adverse event.
[a] TEAEs by preferred term in ≥5% of patients are listed.

Table 3. *Summary of Reasons for Discontinuation From Study*

Disposition, No. (%)	TAR-200
Patients discontinued from study treatment	27 (77.1)
Primary reason for discontinuation from study treatment	
Adverse event	7 (20.0)
Disease progression/recurrence[a]	5 (14.3)
Withdrawal by patient	6 (17.1)
Early termination was not done	1 (2.9)
No comment	1 (2.9)
None	1 (2.9)
Patient had an SAE but the reason for withdrawal was patient and investigator decision	1 (2.9)
Patient had progressively grown weaker and family believed patient should no longer be in the study	1 (2.9)
Patient experienced treatment failure	1 (2.9)
Other	2 (5.7)
Patient died	1 (2.9)
Patient currently under hospice care and has catheter in place	1 (2.9)
Missing[b]	7 (20.0)

Abbreviation: SAE, serious adverse event.
[a] Discontinuations due to disease progression/recurrence were captured on study as either a "withdrawal by subject" or "other" reason and were combined here for clarity.
[b] Six patients did not complete study treatment but did not discontinue the study and went on to enter the 24-month surveillance period; 1 patient discontinued the study but the reason for discontinuation is missing.

Although this phase 1 study was primarily designed to evaluate the safety and tolerability of this novel intravesical drug delivery system in patients with MIBC, TAR-200 intravesical monotherapy showed preliminary efficacy in this limited cohort with an overall response rate of 40% at 3 months, median OS of 27.3 months, and a progression-free rate of 70.5% at 12 months. The CR rate (31.4%) observed was similar to the CR rate (30%) noted in patients who had undergone maximal TURBT in arm 2 of the prior TAR-200 phase 1 study.[15] The median OS observed with TAR-200 in this study of elderly and frail patients compares favorably with multiple retrospective studies demonstrating that patients with MIBC who did not receive or were ineligible for curative-intent therapy have a median OS of ≤12 months.[12,14,24,25] We interpret this comparison cautiously as our cohort had primarily T2 disease, and the historical data comprised patients with T2 and T3 disease. Figure 5 seems to corroborate these findings, showing that early progression events were associated with survival <12

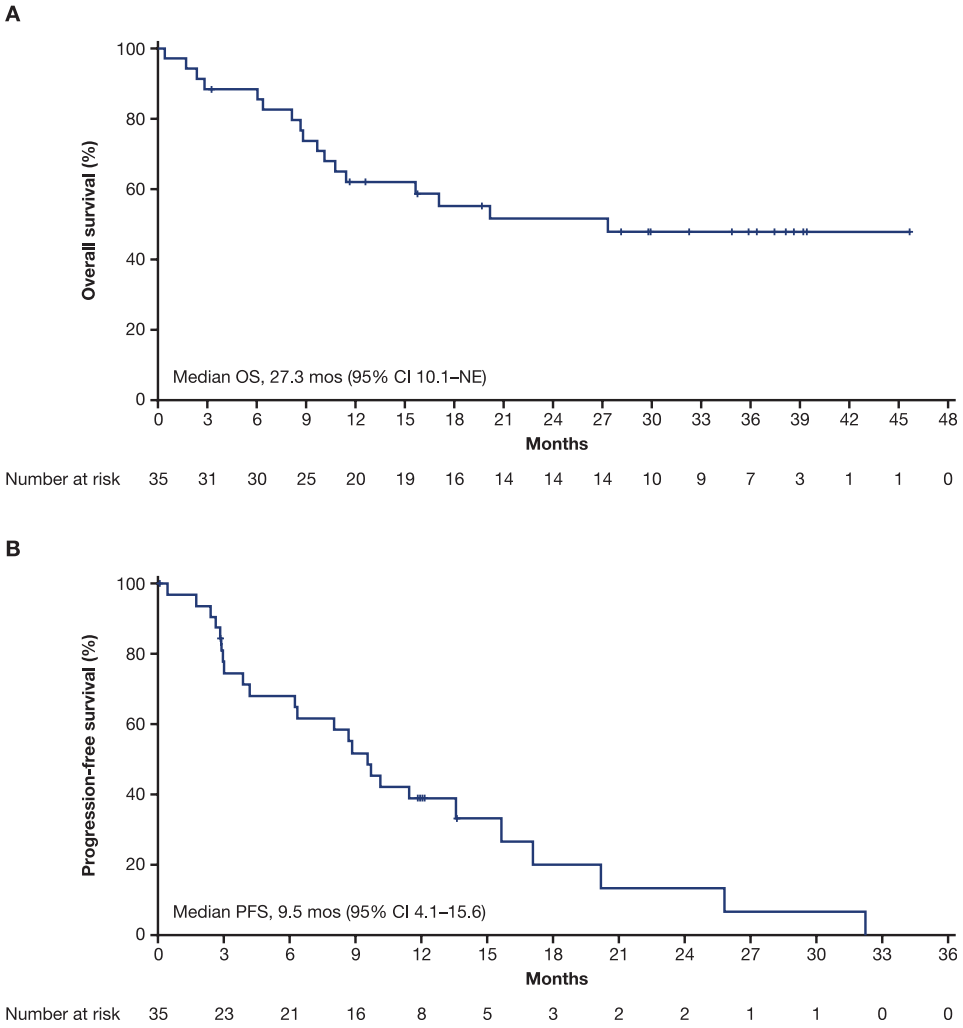

Figure 4. Kaplan-Meier estimates of (A) overall survival (OS) and (B) progression-free survival (PFS). CI indicates confidence interval; NE, not estimable.

months, whereas responders appear to benefit from improved survival. While the possibility exists that the robust CR and PR rates reported here were due to TURBT alone, data demonstrate a response rate attributable to TURBT of up to 15%, suggesting an improvement on those historical CR rates.[26,27] Among patients who responded, those with T2 disease did not progress to T3 disease over 2 years, demonstrating a prolonged response. This prolonged response may suggest that these CR and PR rates are augmented by TAR-200 and are not solely due to TURBT alone. Overall, the observed clinical response to TAR-200 was robust and durable in a cohort with very limited curative-intent treatment options.

Of note, high attrition rates have been observed across many palliative and supportive oncology clinical trials, as reviewed by Hui et al, with 26% attrition rate for reaching the primary end point.[28] Our study results were similar, with 26 patients (74.3%) completing all 4 TAR-200 dosing cycles during the induction period and response assessment, reaching the primary end point of our study; 8 (22.9%) completed the induction period, full optional maintenance period, and final safety follow-up visit. As noted, management of MIBC remains an important global unmet need, especially for elderly patients with multiple comorbidities that may preclude them from curative-intent therapy.[29,30] Therefore, more tolerable and efficacious alternative therapies are needed. This study is limited by its small sample size, single-arm design, and the absence of complete pathological assessment that would have been provided by RC. Additionally, it is a challenge to distinguish whether TAR-200–related TEAEs were attributable to either the drug or the device constituent, as they are integral. The promising preliminary results from this study, in combination with data from the TAR-200-101 study (NCT02722538),[15] lay the foundation for future trials of TAR-200 across the bladder cancer spectrum. TAR-200 combined with the systemic inhibitor of programmed cell

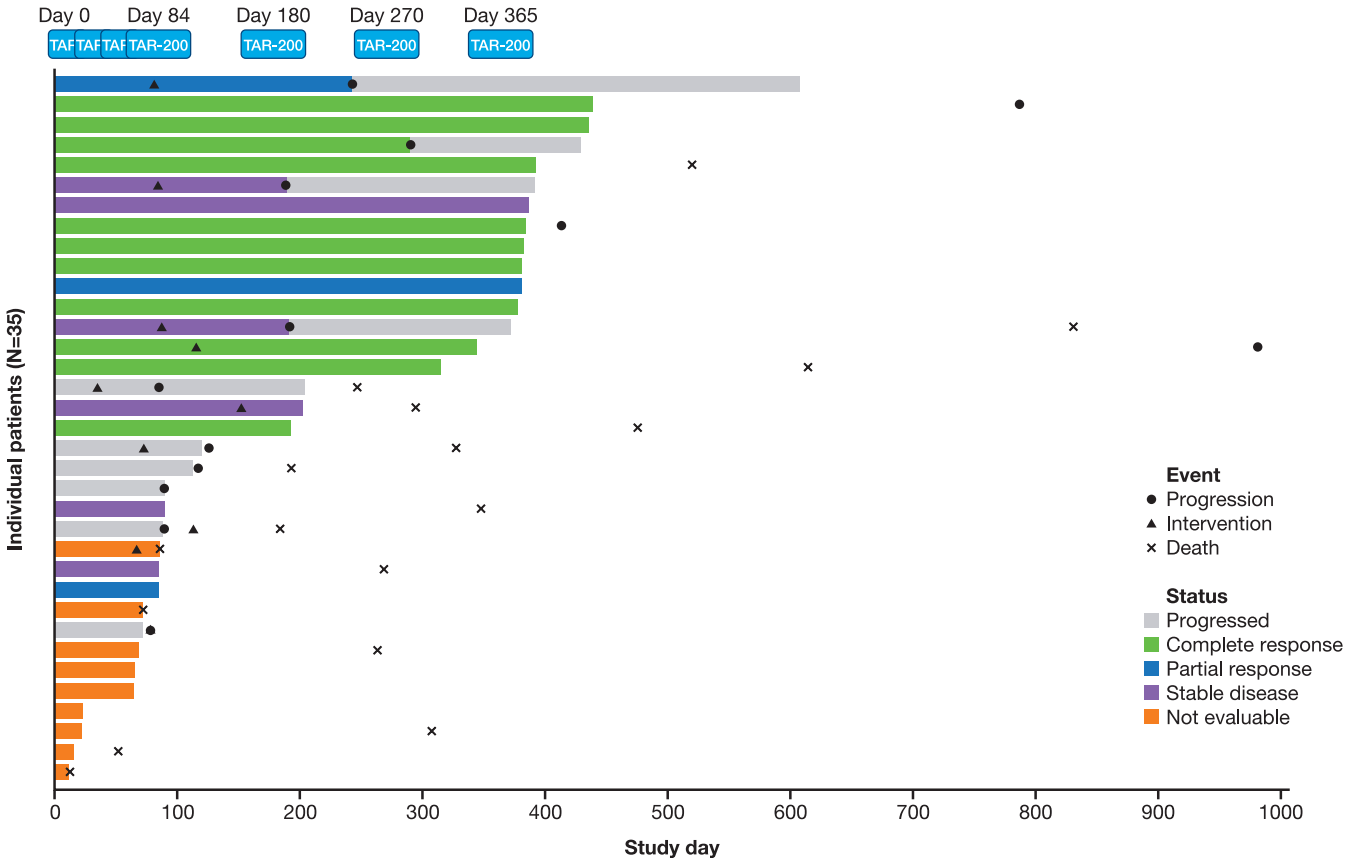

Figure 5. Swimmer plot of tumor responses.

death protein-1 cetrelimab is currently under investigation in the SunRISe clinical trial program (NCT04640623, NCT04658862, NCT04919512).

CONCLUSIONS

TAR-200 was safe and well tolerated in elderly patients with primarily cT2 MIBC who either refused or were unfit for curative-intent therapy. Intravesical TAR-200 monotherapy had promising preliminary effects on patient outcomes, warranting further study as a therapeutic option in this population of patients with predominantly cT2 MIBC.

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EDITORIAL COMMENT

Curative therapies for muscle-invasive bladder cancer (MIBC) are highly morbid with complication rates exceeding 50% after cystectomy[1] and serious potential side effects from chemotherapy and radiation. Elderly and frail patients, who make up a large portion of MIBC patients, are often ineligible for curative approaches and may benefit most from less invasive novel therapies.

Tyson and colleagues investigated the safety, tolerability, and efficacy of TAR-200, a novel intravesical gemcitabine delivery system, in MIBC patients who refused or were unfit for curative-intent therapy.[2] They report high tolerability, with only 2 patients requiring early device removal. Treatment-related adverse events were seen in 40% of patients and overall response rate at 3 months was 40%.

Like any new therapy, the question is whether the benefits of TAR-200 outweigh the risks. The benefit here shows early promise but warrants continued follow-up. In this study, nearly all patients were stage T2, all had complete endoscopic resection prior to treatment, and response rate was assessed at 3 months. Therefore, it is likely that several of the 11 responsive patients would have the same result at 3 months from maximal transurethral resection of bladder tumor alone.

While 60% of patients had 1+ serious adverse events, most were unrelated to treatment and this number is certainly reflective of the frail population. However, the question of whether this patient population has the life expectancy to support encumbering risks related to any therapy at all remains. Treatment-related adverse events were frequent (~40%), with the most common being dysuria and urinary frequency, side effects that heavily impact quality of life but are difficult to attribute to TAR-200 in patients with MIBC.

The authors should be commended for exploring a novel device in a field in dire need of new treatment options. However, it will be imperative to carefully select patients for treatment with TAR-200 to avoid overtreatment.

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REPLY BY AUTHORS

We appreciate the thoughtful and nuanced analysis of our findings by Drs May and Herrel. We agree that TAR-200 is one of many new and exciting technologies in a field with significant unmet needs.

May and Herrel suggest that the number of treatment-related adverse events in our study raises questions about the risk-benefit ratio of TAR-200.[1] We agree that the risk-benefit calculus for TAR-200 remains undefined, but we would emphasize that a majority of these adverse events were mild, consistent with the underlying disease, and not unexpected. Most patients experienced no significant interruption in their daily lives.

The authors also argue that the observed response rates could have been achieved with maximal transurethral resection of bladder tumor alone. Given the single-arm design, we agree that the counterfactual outcome is unknown. However, the 31.4% clinical complete response rate is higher than historical averages, and the robust durability of response suggests that TAR-200 does demonstrate promising antitumor activity. Importantly, many muscle-invasive bladder cancer (MIBC) patients who are managed with transurethral resection of bladder tumor alone often require repeated interventions; no study responders required re-resection during the study period.

Finally, the editorial comment raises concerns about the life expectancy and overtreatment of study participants. While this is a valid concern, MIBC is a life-threatening disease that often requires prompt and aggressive treatment. As noted, a high proportion of patients with MIBC receive no curative-intent treatment and tend to suffer a rapid and symptomatic bladder cancer–related death. We believe that the sustained, low-dose intravesical delivery of gemcitabine via TAR-200 may offer a promising option for elderly and infirm patients living with MIBC.

In conclusion, we acknowledge the limitations of our phase 1 study. Large-scale, randomized, controlled clinical trials are currently underway globally and will be necessary to confirm both the benefits and risks of this innovative and potentially transformative treatment for our bladder cancer patients.

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