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Review Article

Development of TAR-200: A novel targeted releasing system designed to provide sustained delivery of gemcitabine for patients with bladder cancer

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Abstract

Treatment options for recurrent high-risk non–muscle-invasive bladder cancer (HR NMIBC) and muscle-invasive bladder cancer (MIBC) are limited, highlighting a need for clinically effective, accessible, and better-tolerated alternatives. In this review we examine the clinical development program of TAR-200, a novel targeted releasing system designed to provide sustained intravesical delivery of gemcitabine to address the needs of patients with NMIBC and of those with MIBC. We describe the concept and design of TAR-200 and the clinical development of this gemcitabine intravesical system in the SunRISe portfolio of studies. This includes 3 phase I studies evaluating the safety and initial tumor activity of TAR-200 and 5 phase II/III studies assessing the efficacy and safety of TAR-200, with or without systemic cetrelimab, as a treatment option for patients with HR NMIBC (bacillus Calmette-Guérin naive [papillary and carcinoma in situ] and MIBC (neoadjuvant and patients ineligible for or refusing radical cystectomy). Pharmacokinetics demonstrate intravesical gemcitabine delivery via TAR-200 over a prolonged period without detectable plasma levels. Phase I studies showed that TAR-200 is well tolerated,

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with preliminary antitumor activity in intermediate-risk NMIBC and MIBC. Preliminary data from the phase IIb SunRISe-1 study demonstrate that TAR-200 monotherapy is safe and effective in patients with bacillus Calmette-Guérin–unresponsive high-risk NMIBC. TAR-200 represents an innovative approach to the local treatment of bladder cancer.

Keywords: Bladder cancer; Intravesical chemotherapy; Local disease; Novel therapy

1. Introduction

1.1. Unmet need in bladder cancer

Globally, bladder cancer is the ninth most common cancer, with an estimated 614, 298 new diagnoses and 220, 596 cancer-specific deaths in 2022 [1]. The estimated 1-year prevalence for bladder cancer was 491, 243 in 2022—the seventh highest across cancers worldwide [1]. The burden of bladder cancer is also significant, with 54 disability-adjusted life years lost per 100, 000 individuals, making bladder cancer the fifteenth most burdensome cancer globally in 2019 [2]. Despite this global disease burden, the current standard of care for recurrent high-risk non–muscle-invasive bladder cancer (HR NMIBC) and muscle-invasive bladder cancer (MIBC) offers patients few treatment options. This is due to multiple factors, including varying drug toxicity, quality of life detriments, or inadequate clinical outcomes, thus highlighting a need for clinically effective, accessible, and better-tolerated alternatives. Additionally, bladder cancer is among the most expensive tumors for healthcare systems, as evidenced by the cost of MIBC treatments (e.g., the 5-year median costs for trimodal therapy and radical cystectomy [RC] are approximately US $400, 000 and US $225, 000, respectively) [3,4].

1.2. Contemporary management of HR NMIBC

Treatment options for HR NMIBC include transurethral resection of bladder tumor (TURBT) and subsequent induction and maintenance with intravesical bacillus Calmette-Guérin (BCG), which was approved for bladder cancer by the US Food and Drug Administration (FDA) in the 1990s [5,6]. Compared with BCG as standard induction therapy alone, BCG maintenance therapy was shown to significantly increase recurrence-free survival [7]. Response rates approach 85 % for HR NMIBC [7]; however, more than 50 % of the individuals experience recurrence within 4 years after BCG treatment [8]. Many patients do not complete the maintenance regimen per guideline recommendations due to significant treatment-associated toxicity: approximately two thirds of patients experience local toxicity, and approximately one third suffer systemic toxicity [9,10]. Furthermore, given variable yet substantial challenges with respect to global BCG manufacture shortages, limited supplies for some geographical regions necessitate strategies to provide patients with optimal treatment, including prioritizing high-risk patients for induction or giving split (i.e., 1/3 or 1/2) doses [5]. For patients with disease that recurs following treatment with adequate BCG, RC is the standard of care recommended by the American Urological Association/Society of Urologic Oncology (AUA/SUO) and European Association of Urology (EAU) guidelines [11,12]; however, in the real-world setting, this treatment option is utilized at variable rates owing to patient preference in this older population with a high burden of frailty and comorbidity [13–16].

1.3. Current treatment of MIBC

Treatment options for MIBC include RC with neoadjuvant cisplatin-based therapy for eligible patients [5]. Approximately 50 % of patients are cisplatin ineligible due to age- and/or disease-related comorbidities [5,17,18]. Trimodal therapy, including “maximal” TURBT, radiotherapy, and chemotherapy, is a bladder-sparing option that may be offered to select patients with MIBC, and its use varies by region [5].

1.4. RC in HR NMIBC and MIBC

Although it is a treatment option for patients with recurrent HR NMIBC following adequate BCG exposure and for patients with MIBC [5,12], RC may be associated with significant complication rates, morbidity, hospital readmissions, and perioperative mortality [19]. The weighted overall complication rate for the initial hospitalization is approximately 35 %, with postsurgical rates increasing to 39 % at 30 days and 60 % (ranging to >80 %) at 90 days [14]. Based on recent prospective studies, the 90-day mortality rate from RC ranges between 4.4 % and 6.5 % [20]. In older patients, 90-day mortality rates of 9 % to 15 % have been reported [21,22]. Patients selecting RC also require urinary diversion and thus will often have other comorbidities, which may impact their health-related quality of life and further affect the morbidity and mortality rates among this population [19].

2. Concept and design of TAR-200

A limitation of the current intravesical delivery of liquid-based therapy for the treatment of localized bladder cancer is the inefficiency related to limited drug exposure, sometimes described as the “dwell” or “contact” time of the drug, to the endothelium (i.e., most of the therapeutic drug is evacuated from the bladder within 1 to 2 h post instillation at the time of the patient’s first void). To treat bladder conditions, a drug delivery system must also overcome challenges related to drug dilution due to continuous urine

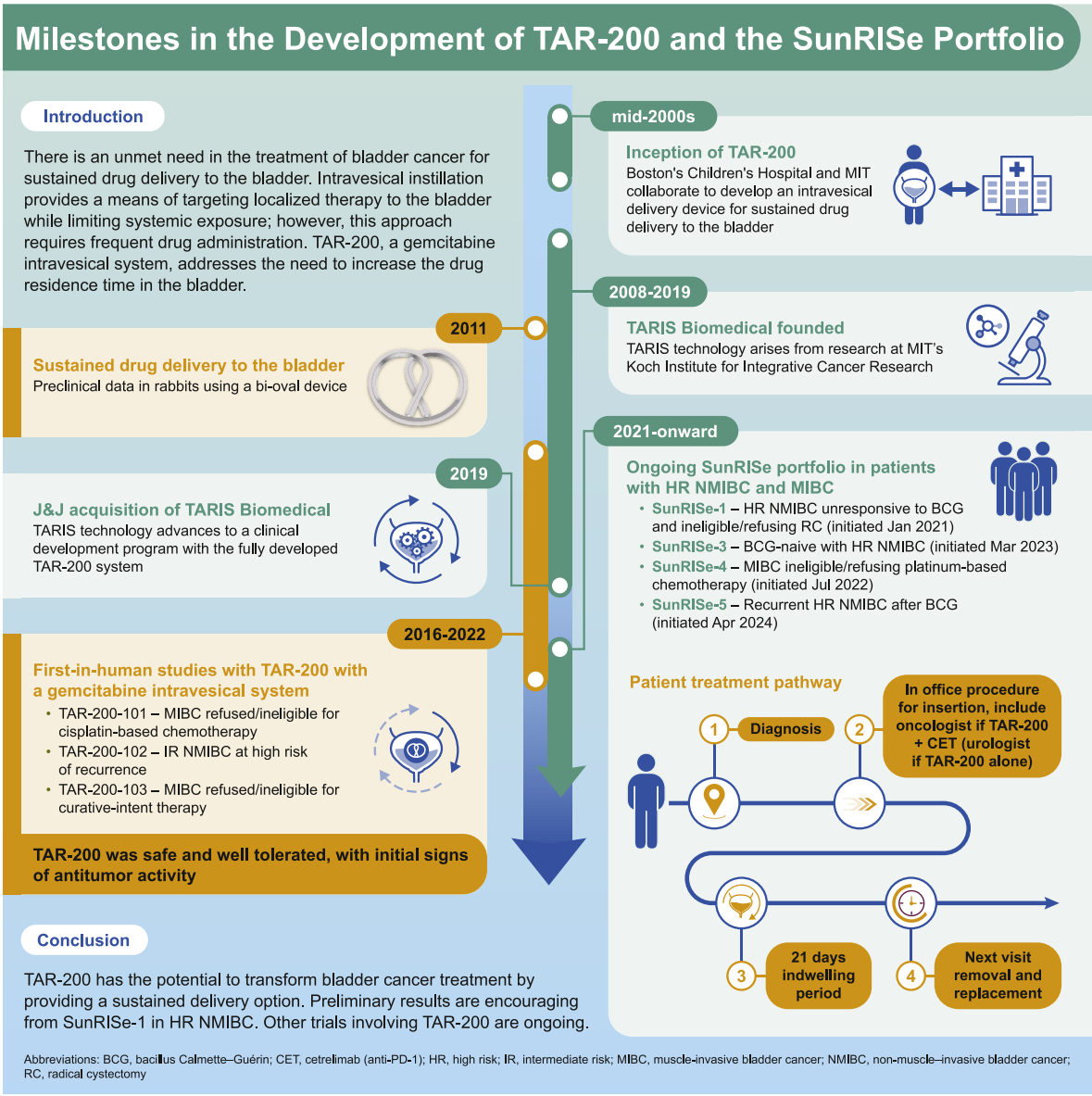

Fig. 1. The development of TAR-200 and the SunRISe program.

formation. Theoretically, repeated instillations could mitigate the progressive dilution of intravesical therapy; however, this presents substantial logistical challenges with respect to patient burden and clinic implementation. Thus, the potential to deliver a therapeutically active dose of medication directly into the patient's bladder in a sustained fashion, while concomitantly avoiding systemic toxicities, would present a highly desirable option for patients with localized disease. The TAR-200 gemcitabine intravesical system was designed to address this critical need for sustained drug delivery within the bladder (Fig. 1).

TAR-200 is a single-compartment, targeted releasing system designed to provide sustained intravesical gemcitabine [23]. TAR-200 elutes a sustained dose of drug to increase the therapeutic window of intravesical exposure and enhance targeted treatment of urothelial carcinoma within the bladder [23]. The goal is to achieve pharmacologically active target dose levels in the affected tissues, which would not be possible with systemic administration given associated toxicities. There is currently no FDA-approved local continuous drug delivery system for the bladder that addresses these constraints. An intravesical releasing system that facilitates prolonged drug-to-urothelial contact times was hypothesized to improve absorption of the administered drug across the urothelium into deeper layers of the bladder as well as to affect tumor tissue.

2.1. Design features of TAR-200

To address the challenge of delivering sustained local therapy within the bladder lumen to treat bladder cancer, also known as intravesical therapy, the TAR-200

gemcitabine intravesical system is composed of a silicone dual lumen tube with gemcitabine placed within the larger lumen, creating a solid drug core (Fig. 2) [23].

The smaller lumen contains a flexible wire that allows for insertion into the urethra and intravesical coiling to enable successful deployment of the drug delivery system and retention within the bladder during the planned indwelling period [23]. TAR-200 is uncurled and loaded into a lubricated urinary placement catheter (UPC), which is then inserted into the bladder lumen through the urethra, after which the product is pushed out of the UPC with a stylet. The system returns to its original bi-oval shape after emerging from the UPC. TAR-200 is designed to resist structural collapse and promote retention within the bladder as it is freely mobile and compressible. The size may be compared to a quarter or €2 coin (Fig. 2) [23]. It is retained within the bladder for an extended period, approximately 3 weeks, and is retrieved via cystoscopy using a grasping forceps [24].

Intravesical gemcitabine instillations have established efficacy and safety in NMIBC and as standard chemotherapy in combination with cisplatin in the treatment of MIBC [25]. As a sustained gemcitabine intravesical system, TAR-200 is loaded with one tenth of the usual intravesical gemcitabine dose (225 vs. 2, 000 mg) [23,26–29], with the goal of optimizing gemcitabine dwell time while minimizing both local and systemic adverse events (AEs) and maximizing efficacy.

Inside the bladder, osmotic pressure regulates gemcitabine release from the TAR-200 internal reservoir, allowing the system to act as an osmotic drug pump (Fig. 2) [23]. Urea serves as an osmotic agent [23]. The system is designed to provide localized, sustained gemcitabine delivery into the bladder over an extended period, while minimizing systemic exposure [23].

2.2. *Pharmacokinetics of gemcitabine delivered via TAR-200*

TAR-200 is designed to allow for sustained release of gemcitabine over an indwelling period of up to 21 days [23,30]. In animal models, TAR-200 delivered gemcitabine into the urine for at least 7 days at concentrations comparable to target levels (Fig. 3A) [26–28,31–33]. TAR-200 maintains the gemcitabine therapeutic dose in urine over time, with no gemcitabine detected in the plasma, and the maximum plasma 2′, 2′-difluorodeoxyuridine (dFdU) concentration at any time point is $\leq 0.35\,\mu$g/ml (Fig. 3B) [23,30].

In preclinical models, gemcitabine penetrated deep into bladder tissue following continuous local exposure (unpublished data, TARIS Biomedical). In a rodent model of MIBC, continuous, low-dose intravesical gemcitabine inhibited tumor growth in a concentration-dependent manner [34]. As gemcitabine is a prodrug, prolonged exposure to a sufficient concentration of gemcitabine may enhance intracellular accumulation of its active tri-phosphorylated metabolite, which impairs DNA synthesis [33]. In addition, preclinical studies provide evidence of gemcitabine augmentation of antitumor T-cell response [34].

3. Phase I studies of TAR-200

Three phase I studies (TAR-200-101, TAR-200-102, TAR-200-103) evaluated the safety and initial antitumor activity of TAR-200 monotherapy in intermediate-risk (IR) NMIBC and MIBC [23,24,30]. Safety and efficacy results are summarized in Supplementary Table 1. Across these studies, TAR-200 was well tolerated, with mostly grade 1 to 2 AEs. TAR-200-101 (NCT02722538) evaluated two 7-day cycles of neoadjuvant TAR-200 in patients with MIBC undergoing RC, including those with a residual tumor of >3 cm after TURBT and those who had undergone maximal TURBT (residual tumor <3 cm) [23]. The most common TAR-200-related AEs were pollakiuria, urinary incontinence, and micturition urgency. Of 20 patients who underwent RC, 10 (50 %) had a pathologic response; 4 (20 %) had a complete response ([CR] T0), and 6 (30 %) had a partial response (<T2, including Ta, T1, and CIS) [23]. TAR-200-102 (NCT02720367) evaluated two 7-day

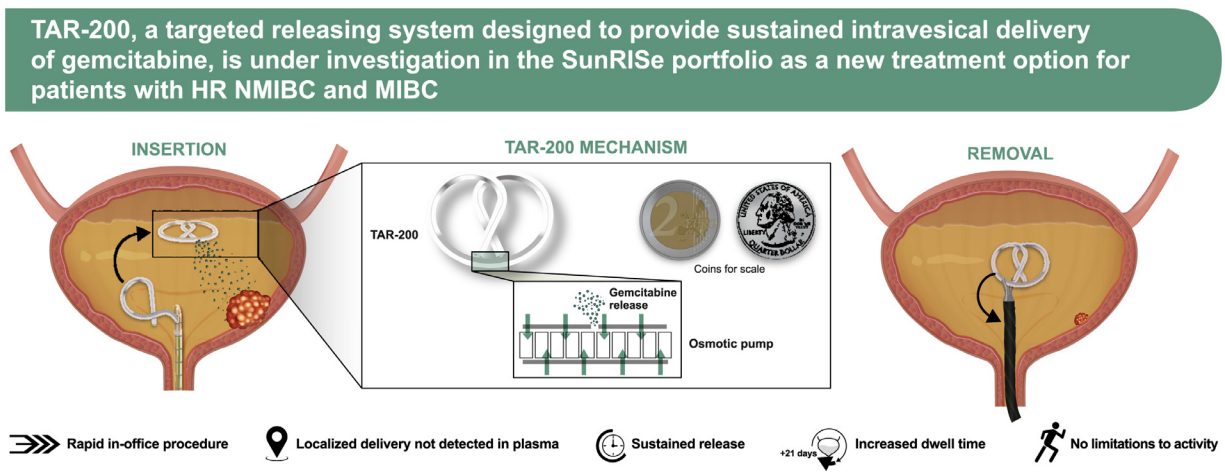

Fig. 2. TAR-200 is a targeted releasing system designed to provide sustained intravesical delivery of gemcitabine.

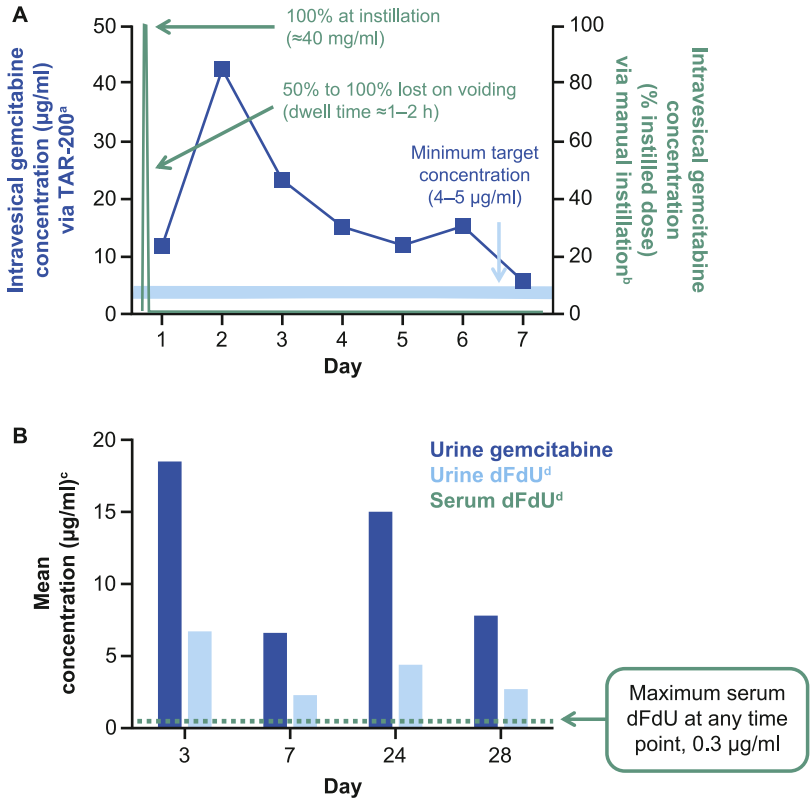

Fig. 3. TAR-200 is designed to provide sustained, local delivery of gemcitabine while limiting systemic toxicity. (A) Gemcitabine dwell time in the bladder over 7 days with TAR-200; TAR-200 delivery (unpublished results, TARIS Biomedical) vs. current intravesical methods [27,28,31]. (B) Maintenance of gemcitabine therapeutic dose in urine over time with no detection in plasma [23].

[a]Estimated clinical concentrations based on miniature pig pharmacokinetics (unpublished results, TARIS Biomedical). Minimum target concentration (4–5 μg/ml) [26,32,33].

[b]Patients received instilled doses of 500 to 2,000 mg in 50 to 100 ml [27], 2,000 mg in 50 ml [28], or 2,000 mg in 50 to 100 ml [31]. Patients received two 7-day dosing cycles of TAR-200, with a 14-day rest period between cycles.

[c]Phase I study in patients with MIBC [23]. Similar findings in phase I study of patients with IR NMIBC [30].

[d]dFdU is an inactive metabolite of gemcitabine.

or two 21-day cycles of TAR-200 in patients with IR NMIBC using a marker lesion/ablation design [30]. The most common TAR-200-related AEs were urgency, dysuria, and hematuria, essentially all consistent with local urinary tract instrumentation. Interval cystoscopy following TAR-200 placement showed recurrent papillary disease and subsequent complete TURBT; 5 of 12 patients (42 %) had a pathologic CR with pathologically confirmed T0 disease [30].

TAR-200-103 (NCT03404791) examined 4 consecutive 21-day cycles of TAR-200 in patients with MIBC who were deemed unfit for RC by investigator assessment, or who refused/were ineligible for curative-intent therapy [24]. The most common TAR-200-related AEs were dysuria, urinary frequency, nocturia, and urethral syndrome. Of 35 patients, 11 had a CR (no evidence of intravesical disease by cystoscopy and biopsy and no evidence of pathologic nodal involvement [>10 mm]), and 3 had a partial response (downstaged intravesical disease [<cT2 and/or decrease in volume on cystoscopy]/no evidence of pathologic nodal involvement [>10 mm]); as such, overall response rate was 40 % [24].

4. Ongoing phase II and III clinical trials of TAR-200

The TAR-200 clinical development program (now referred to as the SunRISe portfolio) is designed to assess intravesical TAR-200 with or without systemic cetrelimab, a programmed cell death protein 1 (PD-1) inhibitor, as a treatment option for patients with bladder cancer, including patients with HR NMIBC (BCG naive [papillary and CIS] and BCG unresponsive [CIS with and without papillary disease]) and MIBC (neoadjuvant setting and patients ineligible for/refusing RC) (Fig. 4, Table). These studies evaluate TAR-200 in patients who are ineligible for or refuse RC and in the neoadjuvant setting prior to RC. The main eligibility criteria for ongoing SunRISe studies are shown in Supplementary Table 2.

4.1. SunRISe-1

Treatment options are limited for patients unresponsive to BCG who are ineligible for or elect not to undergo RC [5,12]. SunRISe-1 (NCT04640623) is an open-label, multicenter, randomized phase IIb study evaluating the efficacy

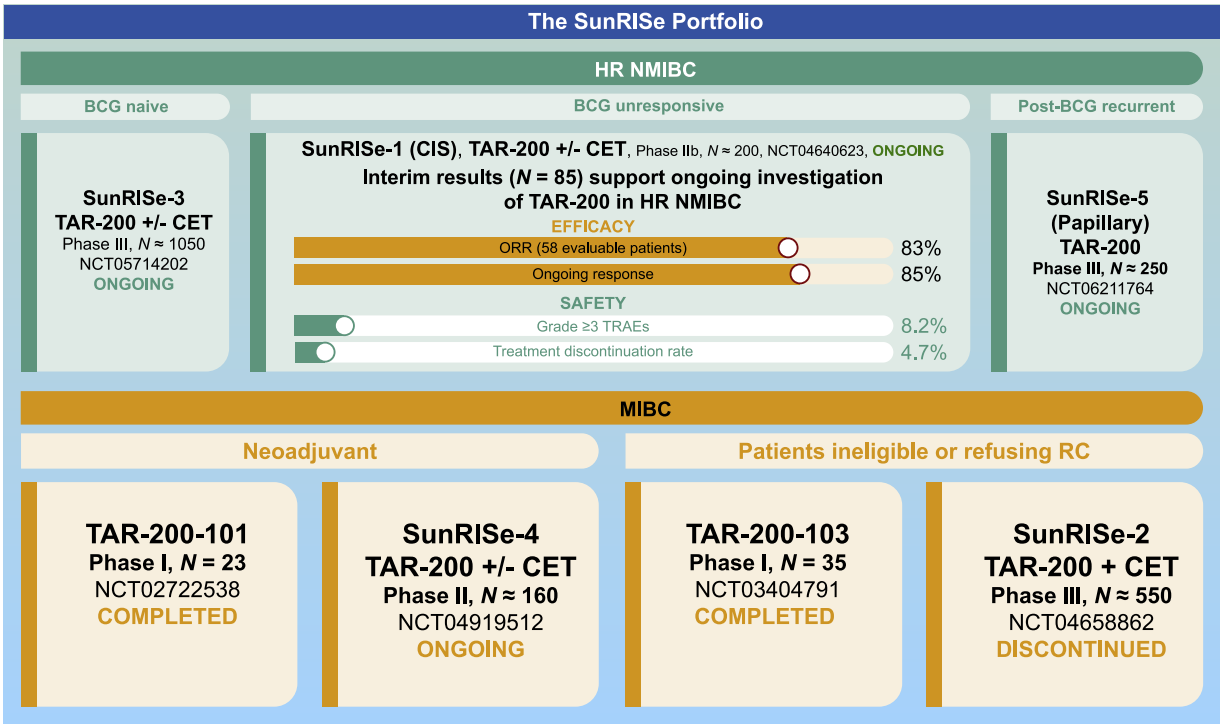

Fig. 4. The SunRISe portfolio.

and safety of TAR-200 monotherapy, TAR-200 plus systemic cetrelimab, and systemic cetrelimab monotherapy in HR NMIBC (Supplementary Fig. 1) [35,36]. The protocol defines eligible patients as those who have histologically confirmed HR NMIBC consisting of CIS ± papillary disease (cohorts 1–3, $n \approx 160$) or papillary disease only (cohort 4, $n \approx 50$), are classified as unresponsive to BCG, and are ineligible for or have elected not to undergo RC (Table). The primary endpoint of cohort 2 is the overall CR rate, defined as the percentage of patients without the presence of high-grade disease at any time point. CR is assessed rigorously based on quarterly cystoscopy and centrally read urine cytology, as well as tissue biopsy at weeks 24 and 48. Key secondary endpoints are the duration of CR at 12 months, overall survival, and safety and tolerability. At an interim analysis (clinical cutoff January 2, 2024), 85 patients in cohort 2 were evaluable for efficacy [37]. The overall CR rate was 83 %, with 41 of 48 responses ongoing (median follow-up of 30 weeks in responders). Most treatment-related AEs (TRAEs) were grade 1 to 2 (pollakiuria, dysuria, micturition urgency, and urinary tract infection were the most frequent). SunRISe-1 was initiated in December 2020, and enrollment is complete.

4.2. SunRISe-2

There are limited bladder-sparing options for patients with MIBC who are ineligible for or refuse RC [5,6]. SunRISe-2 (NCT04658862) is an open-label, multicenter, randomized phase III study evaluating the efficacy and safety of TAR-200 plus cetrelimab vs. chemoradiotherapy in patients with MIBC who are ineligible for or refuse RC (Supplementary Fig. 2) [38,39]. Patients (N ≈ 550) are randomized to intravesical TAR-200 every 3 weeks (21 days indwelling) for the first 18 weeks then, starting on week 24, every 12 weeks through study year 3 plus cetrelimab; or investigator's choice of cisplatin intravenously every week (× 4–6 weeks); or gemcitabine intravenously twice weekly (× 4–6 weeks) as a standard of care along with either conventional radiotherapy of 64 Gy for up to 6.5 weeks or hypofractionated radiotherapy of 55 Gy for up to 4 weeks. The primary endpoint is bladder-intact event-free survival (EFS), defined as MIBC, N+, or M+ disease (as assessed by Response Evaluation Criteria In Solid Tumors [RECIST 1.1]), RC, or any-cause death. Secondary endpoints include metastasis-free survival, overall survival, and overall response rate, as well as safety and tolerability. The SunRISe-2 study opened for enrollment in December 2020. SunRISe-2 was discontinued in October 2024 following a planned interim analysis; patients are in follow-up, and data will be reported at a later date.

4.3. SunRISe-3

Treatment options for patients with HR NMIBC is TURBT followed by intravesical BCG for up to 3 years [5,12]. However, BCG is associated with toxicities [5,40] and supply shortages and, furthermore, not all patients respond, underscoring a need for new treatment options [5]. SunRISe-3 (NCT05714202) is an open-label,

Table
Ongoing phase II and III clinical trials of TAR-200.

Study	Phase	Target population	Cohorts/comparator arms	Primary endpoint	Secondary endpoints
SunRISe-1 (NCT04640623) [35,36]	IIb	Patients with HR NMIBC unresponsive to BCG/ ineligible for or refusing RC ($n \approx 200$)	Cohorts 1-3 (CIS ± papillary disease) Cohort 1: TAR-200 + CET Cohort 2: TAR-200 Cohort 3: CET Cohort 4 (papillary disease only) : TAR-200	Cohorts 1-3: Overall CR Cohort 4: DFS	• DOR • OS • PK • Safety • PROs
SunRISe-3 (NCT05714202) [41,42]	III	Patients with BCG-naive HR NMIBC ($n \approx 1050$)	Group A: TAR-200 + CET Group B: BCG Group C: TAR-200	EFS	• Overall CR • Duration of CR • RFS • TTP • OS • CSS • Safety • PROs
SunRISe-4 (NCT04919512) [43,44]	II	Patients with MIBC ineligible for or refusing platinum-based neoadjuvant CT ($n \approx 160$)	Cohort 1: TAR-200 + CET Cohort 2: CET	pCR	• RFS • Safety
SunRISe-5 (NCT06211764) [45]	III	Patients with HR NMIBC (recurrent, papillary-only) within first year of BCG and ineligible for or refusing RC ($n \approx 250$)	Experimental: TAR-200 Active comparator: CT (mitomycin C or gemcitabine)	DFS	• RFS • TTNI • TTDW • TTP • OS • Safety and tolerability • PROs

BCG = bacillus Calmette-Guérin; BI-EFS = bladder-intact event-free survival; CET = cetrelimab; CIS = carcinoma in situ; CR = complete response; CSS = cancer-specific survival; CT = chemotherapy; DFS = disease-free survival; DOR = duration of response; EFS = event-free survival; HR = high-risk; MFS = metastasis-free survival; MIBC = muscle-invasive bladder cancer; NMIBC = non–muscle-invasive bladder cancer; ORR = overall response rate; OS = overall survival; pCR = pathologic complete response; PK = pharmacokinetics; PRO = patient-reported outcome; RC = radical cystectomy; RFS = recurrence-free survival; RT = radiotherapy; TTDW = time to disease worsening; TTNI = time to next intervention; TTP = time to progression.

multicenter, randomized phase III study designed to assess the efficacy and safety of TAR-200 plus cetrelimab or TAR-200 alone vs. intravesical BCG for patients with BCG-naive HR NMIBC (Supplementary Fig. 3) [41,42]. Eligible patients have HR NMIBC (high-grade Ta, any T1, or CIS) and are BCG naive or had their last BCG exposure more than 3 years prior to randomization. Patients ($N \approx 1050$) are randomized to receive either (1) intravesical TAR-200 (every 3 weeks) plus cetrelimab (group A); (2) intravesical TAR-200 alone (every 3 weeks) (group C); or (3) intravesical BCG (every week for 6 weeks [induction] followed by every week for 3 weeks at weeks 12, 24, 48, 72, and 96 [maintenance]) (group B). The primary endpoint is EFS, defined as the time from randomization to first HR disease recurrence, progression, or any-cause death, whichever occurs first. For patients with CIS, disease persistence is also considered an EFS event. Secondary endpoints are overall CR rate, duration of CR, recurrence-free survival, time to progression, overall survival, cancer-specific survival, safety and tolerability, and patient-reported outcomes. SunRISe-3 opened for enrollment in March 2023, and recruitment is complete.

4.4. SunRISe-4

Treatment options for patients with MIBC is RC preceded by neoadjuvant cisplatin-based systemic chemotherapy [5,6]. SunRISe-4 (NCT04919512) is an open-label, multicenter, randomized phase II study designed to assess the efficacy and safety of TAR-200 plus cetrelimab vs. cetrelimab alone in patients with MIBC scheduled for RC who are ineligible for or refuse neoadjuvant platinum-based chemotherapy (Supplementary Fig. 4) [43,44]. Eligible patients have confirmed cT2-T4a MIBC with absence of nodal or metastatic disease and individual tumor size of ≤3 cm following TURBT. Patients ($N \approx 160$) are randomized to receive TAR-200 plus cetrelimab (cohort 1) or cetrelimab alone (cohort 2). The primary endpoint is the pathologic CR rate. Pathologic CR is defined as no evidence of pathologic intravesical disease and nodal involvement (ypT0N0) at RC. Secondary endpoints are recurrence-free survival per RECIST v1.1 or histologic evidence of nodal or metastatic disease or death due to any cause and evaluation of safety and tolerability. SunRISe-4 opened for enrollment in July 2022.

4.5. SunRISe-5

Therapy options are limited for patients with HR NMIBC whose disease recurs post BCG treatment [5]. SunRISe-5 (NCT06211764) is a randomized, open-label, multicenter phase III study designed to assess the efficacy and safety of TAR-200 vs. investigator's choice of intravesical chemotherapy in patients who received BCG and experienced recurrence of papillary disease–only NMIBC and who are ineligible for or elected not to undergo RC (Supplementary Fig. 5) [45]. Eligible patients are aged ≥18 years with histologically confirmed recurrent, papillary disease–only HR NMIBC (defined as high-grade Ta or any T1, no CIS). Patients ($N \approx 250$) are randomized to receive intravesical TAR-200 every 3 weeks during an induction phase and every 12 weeks during a maintenance phase or investigator's choice of intravesical mitomycin C or intravesical gemcitabine every week during an induction phase and every 4 weeks during a maintenance phase. The primary endpoint is disease-free survival, defined as time from randomization to first recurrence of HR NMIBC (high-grade Ta, any T1, or CIS), progression, or any-cause death, whichever occurs first. Secondary endpoints include recurrence-free survival, time to next intervention, time to disease worsening, time to progression, overall survival, safety and tolerability, and patient-reported health-related quality of life outcomes. Enrollment was initiated in April 2024.

5. Conclusions and future directions

There exists an unmet need for safe and effective bladder-sparing options for patients with HR NMIBC and MIBC. The SunRISe portfolio of studies evaluates TAR-200 as a novel gemcitabine intravesical system in several bladder cancer populations. Preliminary data from SunRISe-1 show that TAR-200 is associated with encouraging responses in patients with BCG-unresponsive CIS and support its continued investigation in HR NMIBC [37]. A targeted intravesical system is also being developed for use with another therapy: TAR-210 is a distinct targeted releasing system designed to provide sustained intravesical delivery of erdafitinib for *FGFR*-altered bladder cancer [46,47]. Phase 1 data have shown preliminary efficacy for TAR-210 in patients with NMIBC, supporting the initiation of the ongoing phase 3 MoonRISe-1 study (NCT06319820) [46,47]. The TAR-200/TAR-210 systems represent innovative approaches to intravesical drug delivery, addressing the need for sustained contact of local therapy with the urothelium, with the potential to transform practice for the treatment of patients with bladder cancer.

Declaration of competing interest

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