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Review

Novel Delivery Mechanisms for Existing Systemic Agents and Emerging Therapies in Bladder Cancer

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Abstract. Systemic agents including immune checkpoint inhibitors, antibody-drug conjugates, and targeted therapies play a critical role in the management of bladder cancer. Novel localized delivery mechanisms for existing systemic agents explore solutions to improve treatment response without compromising safety. Herein, we review the contemporary innovations in modern intravesical agents, hyperthermic drug delivery, reverse-thermal gels, nanocarriers, gene therapy, and subcutaneous therapies.

Keywords: Bladder cancer, urothelial carcinoma, immune checkpoint inhibitors, N-803, TAR-200, CG0070, Nadofaragene firadenovec

INTRODUCTION

The treatment landscape for non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) has evolved at a rapid rate over the past decade. Immune checkpoint inhibitors (ICIs), antibody-drug conjugates (ADCs), and other targeted therapies have been investigated in clinical trials as an option for patients who are ineligible for cisplatin-based chemotherapy and are slowly gaining traction as potential gold standard systemic therapy options for patients with urothelial carcinoma (UC) in the neoadjuvant, adjuvant, and locally advanced/metastatic setting [1]. Alongside the development and application of immunomodulators to UC in later stages of disease progression, new mechanisms to deliver these agents earlier for localized disease are emerging to overcome the challenges in clinical efficacy and compliance. The impetus to apply novel immunotherapeutic agents and delivery mechanisms to bladder cancer management is driven by multiple factors: an international shortage of intravesical bacillus Calmette-Guérin (BCG), [2] challenges with patient compliance and treatment tolerance, a drive to increase efficacy of local therapy to reduce recurrence and progression, and avoidance of the life-altering radical cystectomy and urinary diversion. Herein, we review contemporary and emerging novel delivery mechanisms for existing systemic agents in bladder cancer, including modern intravesical agents, hyperthermic drug delivery, reverse-thermal gels, nanocarriers, gene therapy, and

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subcutaneous therapies. These innovative strategies aim to achieve three goals: 1) effective application of evidence-based systemic immunotherapy options to local treatment 2) improvement of pharmacokinetics and drug exposure to tumor cells, and 3) selective targeting of tumor cells to reduce systemic effects of treatment. However, we caution that to date, these promising intravesical therapies and novel drug delivery mechanisms for BCG-unresponsive NMIBC and MIBC lack substantive late-phase clinical trial data to merit any recommendation over surgical management in patients who are candidates for radical cystectomy.

NOVEL INTRAVESICAL THERAPIES FOR NMIBC

NMIBC, although not immediately life-threatening—with a 5-year relative survival of 96%—has a high rate of recurrence ranging from 31% to 78% [3]. According to National Comprehensive Cancer Network (NCCN) guidelines, intravesical BCG or chemotherapy remains a mainstay for NMIBC depending on risk stratification after initial transurethral resection of the bladder tumor (TURBT) [4]. Intravesical therapy is a relatively noninvasive method to reduce recurrence by enabling direct contact of cytotoxic agents to the entire bladder urothelium for long and repetitive periods of exposure. Although the current standard of care utilizes BCG or traditional chemotherapeutic agents such as Mitomycin C and Gemcitabine for intravesical therapy, [5] there is emerging evidence regarding the intravesical delivery of novel agents for the treatment of NMIBC. Additionally, novel combinations of intravesical chemotherapeutic agents are under investigation for BCG-unresponsive NMIBC, including combination Cabazitaxel, Gemcitabine, and Cisplatin (CGC) that demonstrated an impressive complete response (CR) rate of 89% in a phase I trial [6]. Immune checkpoint inhibitors, antibody-drug conjugates, and various virus-derived therapies have been studied as alternatives to current standard treatments and herein evidence of these agents' applications will be discussed.

Intravesical immune checkpoint inhibitors

Though intravesical BCG can be an effective treatment for NMIBC, between 20–40% of patients fail BCG due to tumor recurrence or progression [7]. Additionally, approximately 20% of patients fail to complete BCG due to local or systemic adverse events (AEs) [7]. The standard definition of BCG failure encompasses four categories: BCG intolerant, BCG refractory, BCG relapse, and BCG-unresponsive [8]. Unlike BCG relapse in which patients achieve a temporary disease-free state, BCG refractory disease refers to persistent high-grade cancer 6 months after initiation of induction BCG, or progressive disease within three months of initiating induction BCG [8]. Because patients who experience BCG relapse within 6 months of their last BCG exposure have similarly poor prognosis as BCG refractory patients, the category "BCG unresponsive" was coined to include both BCG refractory groups and early BCG relapse within 6 months [8]. In patients who are BCG-unresponsive, the recommended salvage treatment is radical cystectomy [9]. However, for patients with comorbidities who are poor surgical candidates, therapeutic options that prioritize bladder-sparing options are a research area of interest. Prior to 2020, the anthracycline-based chemotherapy Valrubicin was the only FDA-approved intravesical agent for BCG-refractory Carcinoma *in Situ* (CIS) based on a phase II trial demonstrating 18% CR at 6 months [10, 11]; however, updated efficacy data suggest that most patients experienced disease recurrence or progression with only 4% disease-free survival (DFS) at two years [11, 12]. The US Food and Drug Administration (FDA) has identified BCG-unresponsive NMIBC as an area of unmet clinical need [13, 14]. Systemic immunotherapy agents have begun to fill this gap.

Currently approved immune checkpoint inhibitors (ICIs) are monoclonal antibodies that target CTLA-4 and the PD-1/PD-L1 axis to boost anti-tumor immune response by augmenting co-inhibitory T-cell signaling and inhibiting tumor growth [15]. Pembrolizumab, a PD-1 inhibitor, was FDA approved in May 2017 to treat patients with locally-advanced or metastatic urothelial carcinoma (la/mUC) who progressed during or after platinum-based therapy or patients who are cisplatin-ineligible [16]. The FDA approval was based on the KEYNOTE-045 trial results that demonstrated higher overall survival (OS) for Pembrolizumab compared with investigator's choice of second-line chemotherapy (10.3 months vs 7.4 months, HR 0.73, 95% CI 0.59–0.91, $p = 0.002$) in patients who progressed on platinum-containing chemotherapy. With increasing interest in systemic Pembrolizumab for la/mUC, efforts concurrently diverted to assessing ICI in earlier stages of disease progression. KEYNOTE-057, a phase II single-arm trial in patients with BCG-unresponsive

NMIBC, demonstrated a 40.6% (95% CI:30.7–51.1) complete response (CR) rate, with a median duration of response of 16.2 months [17]. Based on KEYNOTE-057 results, intravenous Pembrolizumab has been FDA-approved and is supported by NCCN guidelines for the treatment of BCG-unresponsive high-risk NMIBC CIS with or without papillary tumors [4, 18]. Atezolizumab, another ICI (PD-L1 inhibitor) has been studied for this indication in the SWOG S1605 trial, demonstrating a 41.1% CR (95% CI: 29.7%– 53.2%) at 3 months and 20.5% (95% CI: 16.5%–.6%) at 6 months [19]. Additionally, the ongoing POTOMAC trial is examining the clinical utility of intravenous Durvalumab, a PD-L1 inhibitor in combination with BCG compared with BCG alone for the treatment of patients with BCG naïve NMIBC [20]. POTOMAC will evaluate the primary outcome of DFS as well as patient tolerability and quality-of-life assessments as secondary outcome measures [20].

Considering the robust data supporting intravenous ICI in UC, the rationale for novel local drug delivery routes of ICI for NMIBC focuses efforts on reducing toxicity. Although systemic ICIs have demonstrated efficacy in BCG-unresponsive NMIBC, the adverse event (AE) profile gives pause: SWOG S1605 demonstrated an AE rate of 83.6% and grade ≥ 3 AE rate of 12.3%, including one treatment-related death due to myasthenia gravis with respiratory failure and sepsis [19]. Due to this concern for systemic immune-related toxicity in NMIBC, novel mechanisms to promote local delivery of ICI are under investigation. NCT02808143 is a phase I clinical trial assessing the safety and antitumor activity of intravesical pembrolizumab combined with BCG for patients with BCG-unresponsive NMIBC: nine patients were assessed with 6-mo and 1-yr recurrence-free rates of 67% (95% confidence interval [CI]: 42–100%) and 22% (95% CI: 6.5–75%), respectively [21]. Importantly, Pembrolizumab was detected in the urine along with increased CD4 + T-cells, but it was not detected in the blood. However, there was one death from myasthenia gravis potentially attributable to treatment. These findings suggest modest efficacy of intravesical ICI and potentially less systemic toxicities when compared with systemic administration. Although the trial was closed due to the COVID-19 pandemic, these preliminary results are proof of concept that intravesical immune checkpoint inhibition is feasible for eliciting a local immune response [21]. A clinical trial examining intravenous versus intravesical pembrolizumab (NCT031678151) was initiated but terminated in 2020 due to failure to recruit patients within the permitted time frame [22]. Overall, the evidence supporting intravesical ICI is still maturing but represents a promising alternative for BCG-unresponsive NMIBC.

Intravesical antibody-drug conjugates and antibody derivatives

An antibody-drug conjugate (ADC) is a pharmacologic system that delivers chemotherapy to cancer cells by conjugating a cytotoxic agent to monoclonal antibodies specific to tumor antigens [23]. Much of the evidence regarding ADCs in UC investigates its use as a second or third-line therapy for la/mUC in cisplatin-ineligible patients who progressed on ICIs,[24] or as a third-line therapy in patients who had previously received chemotherapy and progressed on ICIs [25] Enfortumab vedotin (EV) is an ADC composed of a monoclonal antibody directed against Nectin-4 (a protein highly expressed in urothelial cancer), conjugated with monomethyl auristatin E (a microtubule-disrupting agent). EV was the first ADC to receive FDA approval for the treatment of la/mUC in patients who have previously received a PD-1/PD-L1 inhibitor and platinum-containing chemotherapy [26]. Intravesical administration of EV is currently under investigation in the phase I clinical trial NCT05014139 to include patients with high-risk BCG-unresponsive disease who are ineligible for or refuse radical cystectomy [27]. This trial is currently still in recruitment for an estimated enrollment of 58 to receive a 6-week induction course of EV followed by once-monthly maintenance administration for 9 doses [27].

Vicinium (Oportuzumab Monatox, VB4-845) is a next-generation recombinant fusion protein which conjugates a Pseudomonas exotoxin to an anti-epithelial cell adhesion molecule (EpCAM) humanized single-chain antibody fragment [28]. Once bound to the EpCAM antigen on the surface of carcinoma cells, Vicinium is internalized through an endocytic pathway, the exotoxin is cleaved off and induces cell death by irreversibly blocking protein synthesis [28]. The use of Vicinium for the treatment of patients with NMIBC who failed BCG therapy has been investigated in phase II and phase III clinical trials [28, 29]. In the phase II study, 45 subjects received induction Vicinium 30 mg over 6 or 12 weeks (cohort 1 or cohort 2, respectively), followed by up to 3 maintenance cycles (3 once-weekly instillations every 3 months). A CR was achieved

by 44% of subjects, and 16% of subjects remained disease-free at 1-year [28]. Interval results from the phase III VISTA clinical trial (NCT02449239) of 134 patients with BCG-unresponsive NMIBC demonstrated CR in 40% at 3 months with 9.4 months median duration of response. It should be noted that these patients received a 12-week course of induction Vicinium (twice weekly for 6 weeks, then weekly for 6 weeks) [29]. Furthermore, intravesical Vicinium in combination with intravenous Durvalumab is under investigation for BCG-unresponsive NMIBC (NCT03258593) with interim analysis of 12 patients suggesting 41% remained disease-free at 3 months and 33% remained disease-free at 6 months [30]. Despite this evidence, the FDA denied approval of Vicinium in this application, citing the study's need for improvements in clinical and statistical data management/analyses and product quality; therefore further development is currently paused [31, 32]. ADCs have demonstrated promising efficacy systemically, but the full scope of its utility in the intravesical setting remains to be seen.

Sacituzumab Govitecan (SG) is an ADC composed of an antibody against trophoblastic cell-surface antigen 2 (Trop-2), a transmembrane glycoprotein highly expressed in UC, conjugated to a topoisomerase inhibitor SN-38 [33]. SG has demonstrated favorable efficacy in the subsequent-line systemic setting for patients with la/mUC who previously received prior platinum-based chemotherapy and ICI, with ORR of 27% in the phase II TROPHY-U-01 trial (cohort-1) [33]. These results led to accelerated FDA approval of SG in 2021 for this third-line indication [34]. Although no trials currently exist to examine intravesical delivery of SG, this is a potential avenue for future clinical trial development.

Gene therapy using viral vectors

Novel gene therapy utilizes viral or plasmid vectors to introduce exogenous DNA into tumor cells to activate an antitumor response. Various viral vectors engineered to specifically target cancer cells have been under investigation for use in bladder cancer. CG0070 is a serotype 5 adenovirus that selectively replicates in retinoblastoma (Rb) pathway-defective bladder tumor cells [35]. The adenovirus additionally causes expression of a cytokine involved in immune activation called granulocyte-macrophage colony-stimulating factor (GM-CSF) [35]. Therefore, CG0070 is postulated to act in two ways: first, by direct tumor lysis in Rb-defective cells, and secondly via immune-mediated killing from GM-CSF production [35]. The use of CG0070 in NMIBC after BCG failure has been under investigation in the BOND/BOND2 clinical trials. In the phase I/II study, 35 patients received intravesical infusions of either a single or multiple doses of CG0070, demonstrating a CR of 48.6% and median 10.4-month duration of CR across all cohorts of varying dose levels. However, multidose cohorts demonstrated higher CR rate of 63.6%. Notably, patients with high phosphorylated Rb immunoreactivity showed higher CR compared with the group with negative Rb phosphorylation status (58% vs. 20%) [36]. Furthermore, exploratory analyses demonstrated even higher 81.8% CR rate in patients with borderline or high Rb phosphorylation who received multidose schedules [36]. Interim results in phase II similarly demonstrated a 47% CR at 6 months for all patients with NMIBC, but also showed particularly strong response (58% CR) and limited progression (29%) in patients with pure CIS with no papillary components [35]. A single arm phase 3 study (NCT04452591) has been launched to confirm the clinical activity of CG0070 in this subset of patients [37]. CG0070 is now generating interest in combination regimens including the phase II CORE-001 trial of intravesical CG0070 in combination with IV Pembrolizumab for BCG-unresponsive CIS with or without concurrent Ta or T1 disease, which has demonstrated a complete response rate of 87.5% at the 3 month time point [38]. So far, data supporting CG0070 suggests that molecular characterization for Rb-defective status may help prognosticate response to therapy.

Nadofaragene firadenovec (rAd-IFNα/Syn3) is another virus-derived agent consisting of rAdIFNα, a non-replicating recombinant adenovirus vector-based gene therapy which delivers a copy of the human interferon alfa-2b gene to urothelial cells as well as Syn3, a polyamide surfactant that enhances the viral transduction of the urothelium. This pharmacologic system results in local rather than systemic interferon alfa-2b production, which induces tumor regression [39]. A phase III clinical trial (NCT02773849) evaluated BCG-unresponsive NMIBC with interim results demonstrating 53.4% CR at 3 months that was maintained at 12 months in 45.5% of those who achieved a complete response [39]. In December 2022, nadofaragene firadenovec was granted FDA approval for high-risk BCG-unresponsive NMIBC with CIS with or without papillary tumors [40]. These results for these novel virus-derived therapies are encouraging but further

investigation is warranted to better predict patients who will respond to therapy.

Other intravesical immunomodulatory agents

Nogapendekin alfa inbakicept (NAI), also known as N-803 or ALT-803, is a potent IL-15 superagonist which has been shown to have anti-tumor activity in bladder cancer models, reducing tumor burden by 35% after a single treatment when used alone and by 46% when used in combination with BCG [41]. IL-15 is a critical factor in the development, proliferation and activation of effector natural killer cells and CD8 + T cells [41]. Though the exact mechanism of BCG is not understood, it's clear BCG induces a pro-inflammatory response. Therefore, the addition of ALT-803 was thought to augment this response and improve BCG efficacy by inducing the production and secretion of IL-1α, IL-1β, and RANTES, which in turn induces the proliferation and activation of NK cells [41]. In a phase I trial of BCG-naïve NMIBC, 9 patients were treated with a combination of BCG and intravesical ALT-803 [42]. 24 months after initiation of treatment, all patients were disease-free and no severe adverse events were reported [42]. Phase II of this trial (NCT02138734) examining BCG-naïve patients is still ongoing [43].

Perhaps the most compelling evidence for N-803 is in the setting of BCG-unresponsive disease: QUILT-3.032, a single arm three-cohort phase II/III trial evaluated the combination of BCG and intravesical N-803 in patients with BCG-unresponsive NMIBC stratified into three cohorts. The multicenter trial included patients with CIS+/- papillary disease treated with N-803 + BCG (Cohort A) or N-803 monotherapy (Cohort C), and BCG-unresponsive high-grade Ta/T1 papillary disease treated with N-803 + BCG (Cohort B) [44]. CR was reached in 71% of cohort A with 26.6 months median duration of response. Importantly, radical cystectomy was avoided in 89.2% at 24 months with disease-specific survival of 100%. In Cohort B of patients with papillary disease, DFS was 55.4% at 12 months with median DFS of 19.3 months. Cohort C was discontinued for futility after enrolling 10 patients, only 2 of whom achieved CR with N-803 monotherapy. In terms of the safety profile, out of 161 patients, the most common low-grade treatment-related AEs were dysuria (30%) and pollakiuria (25%). One patient had a grade 5 AE (cardiac arrest) and only 3/161 experienced grade 3 immune-related TEAEs [44]. Overall, these results suggest that the efficacy and safety profile of combination N-803 + BCG exceeds that of other available intravesical and systemic options for BCG-unresponsive NMIBC [44–46].

NOVEL DRUG DELIVERY MECHANISMS

With the well-established role of intravesical therapies, optimization of drug delivery to improve efficacy represents the next frontier. Intravesical liquid-based agents have variable efficacy due to inability of some patients to tolerate side effects and the inherent discomfort of indwelling therapies. A drug delivery mechanism with improved penetration and sustained release may theoretically reduce the severity of side effects associated with dwell time. Specifically, intravesical administration of chemotherapy or immunotherapy should ideally allow for long duration of contact with bladder urothelium while reducing discomfort. Preliminary results are promising for future applicability of alternative intravesical drug delivery systems including the GemRIS device, reverse-thermal gel formulations, chemohyperthermia, and nanotechnology (Table 1). However, these novel delivery mechanisms require late-phase clinical trial evidence and further maturation of data prior to recommendation for use in lieu of radical cystectomy.

GemRIS TAR-200

The intravesical GemRIS TAR-200, or "pretzel" was developed by Taris Biomedical and achieved Fast Track designation to FDA approval [47]. TAR-200 consists of a silicone tube that releases a dissolvable Gemcitabine tablet over a few weeks. Originally intended to deliver intravesical lidocaine to patients with interstitial cystitis, TAR-200 has since expanded its applicability to NMIBC and MIBC. TAR-200 is currently undergoing evaluation for NMIBC in a clinical trial out of the Netherlands, with interim results suggesting 42% CR and tolerable safety profile (NCT02720367) [48]. For MIBC, the phase Ib clinical trial TAR-200-101 was conducted at multiple sites in Europe and the United States to evaluate its efficacy in the neoadjuvant setting for T2a–T3b, N0–N1, M0 disease in patients who are cisplatin-ineligible or who refuse Cisplatin [49]. Arm 1 of the study includes patients with residual tumor > 3cm after TURBT; Arm 2 includes patients who underwent maximal TURBT with residual tumor < 3cm. Patients received two 7-day dosing cycles of neoadjuvant intravesical TAR-200 with a 14-day rest period

Table 1
Novel drug delivery mechanisms in urothelial carcinoma

Experimental Arm	Clinical Trial	Phase	Number of Patients	Status	Inclusion Criteria	Primary Results
GemRIS (TAR-200)						
Intravesical GemRIS (TAR-200)	(NCT02720367) Van Valenberg et al, 2023 [48]	1b	12	Pending	Low or intermediate risk NMIBC	Primary endpoint: safety (TEAEs) Secondary endpoints: tolerability, pathologic progression Interim results: No serious AEs, 4 of 12 with grade < 2 AEs. CR in 5 of 12 (42%)
Intravesical GemRIS TAR-200 Residual tumor > 3 cm (Arm 1) vs. maximal TURBT (Arm 2)	TAR-200-101 (NCT02722538) Daneshmand et al, 2022 [49]	1	23	Reported	T2a-T3b N0-N1 M0 MIBC, cisplatin-ineligible or cisplatin refusal	10 patients had ≥ 1 TEAEs Most common TEAEs: pollakiuria ($n = 3$), urinary incontinence ($n = 2$). Arm 1:4 of 10 patients with pathologic downstaging; 1 CR, 3 PR. Arm 2:6 of 10 patients with pathologic downstaging; 3 CR, 3 PR.
Intravesical GemRIS (TAR-200)	(NCT03404791) [50]	1	35	Pending	T2a-T3b N0-N1 M0 MIBC, cisplatin-ineligible or cisplatin refusal, unfit for RC	Pending Primary endpoint: Safety (TEAE) Secondary endpoints: CR, PR, pathologic progression, survival, symptom control.
Intravesical GemRIS (TAR-200)+Cetrelimab	SunRISe-2 trial (NCT04658862) [47]	3	550	Pending	cT2-T4a N0 M0 MIBC, ineligible or refuse RC	Pending Primary endpoint: Bladder intact event-free survival (histological MIBC, nodal or metastatic disease, RC, or death) Secondary endpoints: metastasis-free survival, OS, ORR, safety, tolerability.
Reverse thermal gel						
TC-3 hydrogel UGN-101	OLYMPUS (NCT02793128) Kleinmann et al, 2020 [53]	3	74	Reported	Low-grade upper tract UC	59% CR Most common adverse events: ureteric stenosis (44%), urinary tract infection (32%), hematuria (31%), flank pain (30%), nausea (24%)
TC-3 hydrogel	(NCT02307487) [54]	2	14	Pending	Low or high-grade NMIBC	Pending Primary endpoint: safety (TEAE) Secondary endpoints: CR, maximum plasma concentration.

(*Continued*)

Table 1
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Experimental Arm	Clinical Trial	Phase	Number of Patients	Status	Inclusion Criteria	Primary Results
UGN-102 (Mitomycin reverse-thermal gel)	Optima II (NCT03558503) Chevli et al, 2022 [51], Stover et al, 2022 [55]	2b	63	Reported	Low-grade NMIBC at intermediate risk of recurrence	65% CR with durable response 20/22 of those without CR had persistence of worsening of disease 10% discontinued due to adverse event No worsening patient-reported urinary symptoms, bloating/flatulence or malaise at 3 months. Reported mild worsening sexual functioning.
UGN-301 (Zalifrelimab reverse-thermal gel)	(NCT05375903) [56]	1	60	Pending	Recurrent NMIBC with high-grade Ta disease and/or CIS	Pending Primary endpoint: TEAEs, dose-limiting toxicities, CRR, RFS
Chemohyperthermia						
Intravesical chemo-hyperthermia with Mitomycin C vs. BCG	(NCT00384891) Arends et al, 2016 [60]	3	147	Reported	Intermediate- and high-risk NMIBC	81.8% 24 month RFS for chemohyperthermia vs. 64.8% RFS for BCG ($p = 0.02$).
Intravesical chemo-hyperthermia with Mitomycin C vs. conventional Mitomycin C	HIVEC-II (ISRCTN23639415) Tan et al, 2022 [62]	2	259	Reported	Intermediate-risk NMIBC	Disease-free survival, PRS, OS similar between cohorts. Patients undergoing chemohyperthermia less likely to complete treatment.
Nanotechnology						
Intravesical Nab-paclitaxel	McKiernan et al, 2011 [66]	1	18	Reported	High-grade T1, Ta or Tis NMIBC, BCG-refractory	10 (56%) experienced grade I local toxicity, no grade 2-4 toxicities. 5 (28%) no evidence of disease posttreatment.
Intravesical Nab-paclitaxel	McKiernan et al, 2014 [67] Robins et al, 2017 [64]	2	28	Reported	High-grade T1, Ta or Tis NMIBC, BCG-refractory	10 (35.7%) CR, durable at 1 year. RFS of 18% at median 41 months follow-up 9 (32.1%) TEAEs (all grade 1 or 2).
Systemic Nab-paclitaxel	(NCT00683059) Ko et al, 2013 [65]	2	48	Reported	Locally advanced or metastatic UC, failed platinum-based therapy	1 (2.1%) CR,12 (25.5%) PR (OR 27.7%)

Systemic Nab-paclitaxel vs. Paclitaxel	(NCT02033993) Sridhar et al, 2020 [68]	2	199	Reported	Metastatic UC, failed platinum-based therapy	No difference in PFS, OS, or ORR between cohorts Higher grade 3 and 4 AEs with Nab- paclitaxel.
Neoadjuvant Nab-paclitaxel +Nivolumab	NURE-Combo (NCT04876313) [69]	2	29	Pending	T2-T4aN0M0 MIBC	Pending Primary endpoint: complete pathologic response. Secondary endpoints: adverse events, pathologic downgrading, radiologic response, OS, event-free survival.
Perioperative Nab- paclitaxel +Tislelizumab	(NCT05328336) [80]	2	74	Pending	T2-T4a NxM0 MIBC	Pending Primary endpoint: CR. Secondary endpoints: pathologic downgrading, ORR, event-free survival, OS, adverse events.
Subcutaneous Therapies						
Subcutaneous Envafolimab	(NCT02827968) Papadopoulos et al, 2021 [72]	1	28	Reported	Advanced solid tumors, failed established medical therapies	ORR 10.7% Grade 3 AEs in 3 patients, and the most common AEs included fatigue (29%), nausea (18%) diarrhea (14%) and hypothyroidism (14%). No dose-limited toxicities.
Subcutaneous Sasanlimab	CREST (NCT0416531) Shore et al, 2022 [73]	3	110	Pending	High-grade Ta, T1, or CIS NMIBC, refractory to BCG	Pending Primary endpoint: CR and event-free survival. Secondary endpoints: duration of CR (Cohort B1 only), OS, time to RC, safety, health-related quality of life, pharmacokinetic parameters, PD-L1 expression, and incidence of anti-drug antibodies.
Neoadjuvant Subcutaneous Sasan-limab+SBRT	RAD-VACCINE (NCT05241340) Satkunasivam et al, 2022 [74]	2	33	Pending	cT2-T4a N0 M0 MIBC, cisplatin-ineligible	Pending Primary endpoint: pathologic CR. Secondary endpoints: adverse events, major surgical complications, OS, RFS, health-related quality of life.
Suburothelial therapies						
Neoadjuvant sub-urothelial Durvalumab	SUBDUE-1 (ACTRN12620000063910) Moe et al, 2021 [76]	1b	Recruiting	Pending	High risk NMIBC or MIBC without prior chemotherapy or immune checkpoint inhibition	Pending Primary endpoint: safety and tolerability. Secondary endpoints: rates of pT0 status at resection, lymph node status, and change in distribution of tumor-infiltrating lymphocytes and tumor-activated macrophages between pre- and post-injection bladder biopsies.
Phototherapy						
Intravesical photodynamic therapy with TLD-1433	(NCT03053635) Kulkarni et al, 2022 [79]	1b	6	Reported	Resected Ta, T1, or CIS NMIBC, unresponsive to BCG, ineligible or refused RC	6 (100%) had at least 1 grade ≤ 2 AE. Of 3 patients treated at the therapeutic dose, 2 had CR at 180 days, which was durable at 18 months. The 3rd was diagnosed with metastatic disease. Of 3 patients treated at half-dose, all had persistent disease at 3 months.

in between cycles. Pathologic response was based on histopathologic assessment of the radical cystectomy specimen. The most common AEs were pollakiuria and urinary incontinence. Patients with residual tumor demonstrated pathologic downstaging in 4 of 10 cases, and 6 of 10 demonstrated pathologic downstaging among those who underwent maximal TURBT [49]. Currently a separate phase I single-arm clinical trial is under way to investigate safety and tolerability of up to 4 cycles of TAR-200 in patients with muscle-invasive bladder cancer who are either ineligible for cisplatin-based chemotherapy or who refuse cisplatin [50]. Although evolving data on TAR-200 appears promising, some potential issues may need to be addressed for determining optimal patient selection among those with muscle-invasive disease: as intravesical therapy would theoretically not be able to target early micrometastasis outside of the bladder, survival outcomes will require further evaluation and scrutiny in Phase II and III studies of TAR-200 monotherapy in the neoadjuvant setting and for MIBC. Combination therapy with intravesical TAR-200 and systemic ICI may begin to address this issue: TAR-200 in combination with the PD-1 inhibitor Cetrelimab is undergoing phase III evaluation versus chemoradiotherapy for patients with MIBC who are unfit for or refuse radical cystectomy (SunRISe-2, NcT04658862) with results pending [47].

Reverse thermal gel formulations

Chemoablative intravesical gel formulations have been developed, similarly to GemRIS TAR-200, with the strategy to increase drug penetration while reducing patient discomfort. The sustained-release reverse-thermal hydrogel has been developed to improve duration of exposure of urothelium to therapy. Due to its slow-release mechanism, it has been posited as an alternative to repeat transurethral resection of bladder tumor (TURBT) for low-grade intermediate-risk NMIBC [51]. TC-3 hydrogel is a reverse-thermal gel used to deliver mitomycin into the bladder; it is instilled as a liquid and solidifies into slow-dissolving gel form [52]. The TC-3 hydrogel UGN-101 was initially FDA-approved in 2020 for the treatment of low-grade upper tract urothelial carcinoma based on the pivotal phase III OLYMPUS trial demonstrating CR of 58% following 6 weekly instillations [53]. Clinical trials have since transitioned to the evaluation of TC-3 hydrogel for low-grade or high-grade NMIBC prior to TURBT (NCT02307487) in a phase II dose escalation with results pending [54]. study Optima II (OPTimized Instillation of Mitomycin for Bladder Cancer Treatment) is a phase IIb single-arm clinical trial to evaluate a six-treatment induction course of the mitomycin reverse-thermal gel UGN-102 for the treatment of low-grade NMIBC at intermediate risk of recurrence [51, 55]. Of 63 patients who received at least 1 instillation of UGN-102, the complete response (CR) rate was 65% with durable response (95% disease-free at 6 months and 63% remained disease-free at 12 months) [51]. Importantly, of the patients who did not achieve CR, 20/22 demonstrated persistence or worsening disease including CIS and high-grade disease, suggesting these cases were initially understaged [51]. Additionally, it should be noted that majority of patients (90%) completed all 6 induction instillations and only 10% discontinued treatment due to an adverse event [51]. Recently published interim results on patient-reported outcomes suggest that UGN-102 did not cause decrements in patient-reported symptoms at 3 months with the exception of mildly worsened sexual function, which resolved by 6 months [55].

This reverse-thermal gel proprietary formulation has been extended to include other immune checkpoint inhibitors as well, including UGN-301 (Zalifrelimab), an anti-CTLA-4 designed for intravesical administration. UGN-301 is currently undergoing evaluation in a phase I dose escalation study (NCT05375903) for patients with recurrent NMIBC with high-grade Ta disease and/or CIS or recurrent intermediate-risk low-grade Ta disease to include a 6-week induction course followed by an optional maintenance period [56]. Arm B of this trial includes evaluation of UGN-301 with another immunomodulator, the toll-like receptor (TLR)-7 agonist UGN-201 (Imiquimod) that will be administered intravesically as a 6-week induction course and optional maintenance course [56]. TLRs are transmembrane proteins expressed in bladder urothelial cells to activate innate and adaptive immunity, but are decreased in bladder tumors. TLR agonists trigger an antitumor immune response as well as inducing direct cytotoxicity on bladder cancer cell lines [57]. It is hypothesized that combination intravesical UGN-301 and UGN-201 will function synergistically in patients with recurrent NMIBC.

Hyperthermic intravesical chemotherapy

Hyperthermic intravesical chemotherapy, also known as chemohyperthermia, operates within the

premise that higher temperatures may boost drug absorption by improving blood perfusion and cell permeability. Furthermore, the heat induces malignant cell damage and apoptosis of tumor cells [58]. The most well-supported device for chemohyperthermia, the Synergo® system, utilizes radiofrequency microwave energy contained within a catheter to generate heat to 42°Celsius within the bladder. In fact, microwave-induced hyperthermia (Synergo®) is recommended by European Association of Urology (EAU) guidelines as an option for improving efficacy of intravesical chemotherapy based on results of a randomized trial comparing microwave-induced chemohyperthermia+Mitomycin C vs BCG for intermediate- and high-risk NMIBC [59, 60]. Results from 147 patients in the per protocol analyses demonstrated a higher 24 month recurrence-free survival (RFS) of chemohyperthermia compared with BCG (81.8% vs 64.8%, $p = 0.02$), although the CR was similar and the study was underpowered due to early termination [60].

Despite early promise of microwave-induced hyperthermia, other heat-generating mechanisms, including conductive heat, require additional evidence [59, 61]. A phase II randomized controlled trial of adjuvant intravesical chemohyperthermia with Mitomycin C vs conventional Mitomycin C alone for intermediate-risk NMIBC (HIVEC-II) did not yield a significant oncologic benefit compared with the standard of care [62]. Additionally, patients in the chemohyperthermia arm who utilized the Combat Bladder Recirculation System involving an aluminum heat exchanger, were less likely to complete their course of treatment [62]. The EAU thereby states that other non-microwave technologies for hyperthermic intravesical chemotherapy are lacking convincing efficacy data [59]. However, although prospective data is currently insufficient to support HIVEC for intermediate risk disease, some limited retrospective data have suggested a potential role for the COMBAT system for BCG-unresponsive disease [63]. We do address that one potential advantage of chemohyperthermia is the ability to apply hyperthermic intravesical technology to various intravesical agents. This leaves the avenue open for future intravesical hyperthermic interventions.

Nanotechnology

Nanocarriers are miniscule materials between 1–200 nm that are used to transport drugs into various organs [61]. Albumin-bound nanoparticles, when combined with established systemic chemotherapeutic agents, may increase drug solubility by interacting with albumin receptors to facilitate transport across tumor epithelial cells [61, 64]. Nab-Paclitaxel is a modified taxane that has been evaluated for systemic intravenous therapy in the adjuvant [62] and second-line treatment of metastatic urothelial carcinoma [65] as well as for intravesical therapy for NMIBC [66, 67]. However, its potential application as monotherapy in the second-line metastatic setting has fallen out of favor after the phase III randomized Canadian trial of intravenous nab-paclitaxel vs Paclitaxel demonstrated similar efficacy but worse AEs (66% grade 3 or 4 AEs with nab-Paclitaxel compared with 46% with paclitaxel) [68]. Nevertheless, interest persists regarding synergistic efficacy of systemic nab-paclitaxel, with current clinical trials of combination anti-PD1 and intravenous nab-Paclitaxel in the neoadjuvant setting for muscle-invasive UC actively recruiting (NCT04876313 [69] and NCT05328336). In the NMIBC space, phase I and II single-center trials have assessed a 6-weekly induction course of intravesical nab-Paclitaxel followed by monthly maintenance for 6 months in patients with recurrent NMIBC (Tis, T1 and Ta) who failed at least one course of BCG [64, 66, 67]. In the phase II single-arm trial, CR rate was 35.7% that remained durable at 1 year [67]. However, long-term follow-up results of the phase II trial were published separately and demonstrated a lower RFS of 18% at median 41 months of follow-up [64]. As of 2022, intravesical nab-Paclitaxel has not proceeded to phase III trials.

SUBCUTANEOUS THERAPIES IN UROTHELIAL CARCINOMA

The inconvenience of intravenous ICI infusions may present a barrier to compliance in patients requiring checkpoint inhibitors for urothelial carcinoma, especially in the locally advanced or metastatic disease setting that may require long-term therapy. The rationale driving the development of subcutaneous forms of ICI is to achieve similar tissue penetration and drug stability while decreasing the required frequency of administration. Envafolimab is a novel recombinant protein consisting of a humanized PD-L1 antibody and human IgG1 Fc fragment with a unique structure with a lower molecular weight and improved structural stability compared to traditional PD-1/PD-L1 inhibitors, making it optimal for subcutaneous injection [70, 71]. Subcutaneous

Envafolimab has been investigated in a phase I trial in 28 patients with previously treated advanced solid tumors including 1 patient with bladder cancer (NCT02827968): extended drug dosing was administered to 10 patients during a dose-exploration period (300mg Envafolimab once every 4 weeks) and demonstrated a similar pharmacokinetic profile compared with other antibodies [72]. Objective response rate (ORR) was 10.7%—similar to that of other traditional PD-1/PD-L1 inhibitors. Grade 3 AEs occurred in 3 patients, and the most common AEs included fatigue (29%), nausea (18%) diarrhea (14%) and hypothyroidism (14%) [72]. Furthermore, no dose-limiting toxicities or injection-site reactions were reported in the initial phase I study [72].

To date, the majority of existing evidence for subcutaneous PD-L1 therapies are basket trials evaluating various advanced solid tumors, particularly focusing on microsatellite-instability-high or mismatch repair deficient tumors. One exception to this is the subcutaneous humanized anti-PD1 IgG monoclonal antibody Sasanlimab, which has been specifically investigated for bladder UC in the NMIBC space [73] as well as in the neoadjuvant setting for MIBC [74]. CREST (NCT0416531), a phase III clinical trial of subcutaneous anti-PD-1 Sasanlimab in combination with alternative BCG regimens that has been evaluated specifically as monotherapy for BCG-unresponsive high-risk NMIBC. Cohort B1 of CREST plans to enroll 110 patients to assess CR of Sasanlimab monotherapy for persistent or recurrent CIS with or without concomitant high-grade Ta/T1 disease within 12 months of completing BCG, while cohort B2 aims to assess event-free survival of Sasanlimab in patients with recurrent high-grade Ta/T1 disease within 6 months of BCG completion [73]. For patients with MIBC, neoadjuvant subcutaneous Sasanlimab in combination with stereotactic body radiation therapy (SBRT) is currently undergoing phase II evaluation as an "*in situ* vaccination" strategy prior to radical cystectomy [74]. This single-arm trial intends to enroll 33 cisplatin-ineligible patients with cT2–4a, cN0, cM0 disease and includes two subcutaneous injection doses of Sasanlimab followed by three doses of stereotactic body radiotherapy (SBRT) prior to radical cystectomy (RAD VACCINE MIBC) [75].

The novel concept of intralesional sub-urothelial injection of ICI is also under exploration in early-phase trials. The drug would be injected under cystoscopic vision directly into the sub-urothelial layer of visible tumor in a procedure similar to intravesical Botulinum injections for refractory overactive bladder. The most notable trial in this space is SUBDUE-1, a phase Ib open label Australian study to assess sub-urothelial Durvalumab in high-risk NMIBC or MIBC who are scheduled for radical cystectomy [76, 77]. One rationale discussed by investigators for exploring sub-urothelial injection of Durvalumab rather than intravesical instillation is based on the hypothesis that the large size of antibody-based ICI may theoretically be a barrier to passive urothelial absorption [76]. Another advantage of intralesional injection is the avoidance of dilution effect in intravesical instillations, allowing administration of high local drug concentrations. However, there are anticipated limitations of this the intralesional injection approach as well: because this administration route only treats visible tumors, this increases the chance of leaving CIS and subtle tumors untreated.

PHOTODYNAMIC THERAPY

Intravesical photodynamic therapy (PDT) with a novel ruthenium-based photosensitizer TLD-1433 has recently emerged as a novel delivery mechanism for patients with NMIBC after BCG failure. The rationale behind TLD-1433 is that light activation induces the generation of cytotoxic singlet oxygen and radical oxygen species that are selective for bladder tumor cells and induces downstream antitumor immune signaling. This may be activated with a diffused laser light created by a novel device. Historically, photodynamic therapy using an intravenous injection of a porfimer sodium photosensitizer followed by intravesical application of red light has demonstrated efficacy in bladder CIS with 58% CR at 3 months [78]. However, this has not translated to widespread clinical practice because the intravenous administration of porfimer sodium is associated with morbidity including skin photosensitivity and significant bladder contracture rate. Intravesical administration of the TLD-1433 photosensitizer may reduce systemic effects. A recently published phase 1b single-arm clinical trial has investigated intravesical photodynamic therapy with TLD-1433 in patients with BCG-unresponsive disease [79]. Results demonstrated no serious AEs, with the most common grade < 2 AE of lower urinary tract symptoms. Two of three patients treated with a therapeutic dose (0.7 mg/cm2) demonstrated durable CR with no evidence of disease at 18 months, and the

third was diagnosed with metastatic disease within 6 months, suggesting the possible initial understaging and presence of early micrometastasis. Three patients were treated with a half dose 0.35 mg/cm^2 and all demonstrated persistent disease at 3 months [79]. Initial results of this novel intravesical approach to PDT is favorable, but requires additional validation before proceeding to late-phase trials and widespread adoption.

CONCLUSION

While the armamentarium for the treatment of localized bladder cancer is rapidly expanding with novel drug delivery mechanisms, it is the access to exciting new systemic agents that makes the treatment landscape for bladder cancer so exciting. During this critical period, future steps must focus on identifying optimal and synergistic combinations to augment treatment response without compromising safety.

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JHZ: conception, performance, interpretation, writing of article, this author has access to data.

SLS: writing of article, this author has access to data, this author has access to data.

KC: conception, interpretation, writing of article, this author has access to data.

CONFLICTS OF INTEREST

JHZ: JJ Zhang has no conflict of interest to report.

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