Current Urology Reports (2019) 20: 84
https://doi.org/10.1007/s11934-019-0952-y

UROTHELIAL CANCER (S DANESHMAND, SECTION EDITOR)

Current Clinical Trials in Non-muscle-Invasive Bladder Cancer: Heightened Need in an Era of Chronic BCG Shortage

Vignesh T. Packiam[1] · Ryan P. Werntz[2] · Gary D. Steinberg[3]

Published online: 28 November 2019

Abstract

Purpose of Review BCG is the gold standard agent used in high-risk non-muscle-invasive bladder cancer (NMIBC) that is amenable to bladder sparing management. However, recent BCG shortages appear to be a chronic problem. There are limited effective intravesical options in lieu of BCG or in patients in whom BCG is not effective. This review aims to highlight emerging bladder sparing therapies and trials for NMIBC.

Recent Findings Patients with high-risk NMIBC who do not respond to BCG are at increased risk for progression and death from bladder cancer. There are a variety of clinical trials exploring different therapeutic approaches including checkpoint inhibition, novel chemotherapy and drug delivery, viral and gene therapy, vaccines, and targeted therapy.

Summary In the era of limited supply of BCG, there is a need for both effective first-line alternatives as and options for patients who do not respond to BCG. Fortunately, there are a variety of active trials and mechanisms exploring these areas aggressively.

Keywords Non-muscle-invasive bladder cancer · BCG-unresponsive · Urothelial carcinoma · Clinical trials · Immunotherapy · Chemotherapy

Introduction

There are an estimated 549,393 new cases of bladder cancer diagnosed per year worldwide, with an estimated 81,190 new diagnoses in the USA in 2019 [1, 2]. Non-muscle-invasive bladder cancer (NMIBC) accounts for approximately 75% of bladder cancer diagnoses [3]. NMIBC is a heterogenous category including both low- and high-grade disease, and tumor stages of carcinoma in situ (CIS), papillary tumor (Ta), and tumor invasive to the lamina propria (T1) [4]. Disease progression and mortality have wide variability across tumor grade, stage, and other risk factors, which has been the attention of publications that attempt to risk stratify disease [5, 6].

The initial management of NMIBC is well documented in guidelines including those put forth by the American Urology Association (AUA), European Association of Urology (EAU), and National Comprehensive Cancer Network (NCCN) [7–9]. The first step in management is local tumor staging by performing a high-quality transurethral resection of bladder tumor (TURBT) [7–9]. TURBT is a critically important procedure as it yields staging, therapeutic, and prognostic benefits [10].

In patients with high-risk NMIBC (CIS, high-grade Ta, or high-grade T1 bladder cancer), the two aims of management are to limit bladder cancer–specific morbidity and mortality, and to maintain quality of life (QOL). In addition, the key component in managing high-risk NMIBC is to intervene before the patient progresses to muscle-invasive disease. Progression to muscle-invasive bladder cancer (MIBC) during management of NMIBC has been shown to raise the risk of disease-specific mortality [11].

This article is part of the Topical Collection on *Urothelial Cancer*

✉ Vignesh T. Packiam
packiam.vignesh@mayo.edu

Ryan P. Werntz
rywerntz@gmail.com

Gary D. Steinberg
Gary.Steinberg@nyulangone.org

[1] Department of Urology, Mayo Clinic, 200 1st St. SW, Gonda Building 7, South Rochester, MN 55905, USA

[2] Prisma Health-Upstate, Section of Urology, Department of Surgery, University of South Carolina-Greenville, 11 Park Creek Drive, Greenville, SC 29605, USA

[3] Department of Urology, NYU Langone Health, NYU Urology Associates, New York University, 222 E 41ST ST, 12TH Floor, New York, NY 10017, USA

Intravesical bacillus Calmette-Guérin (BCG) is utilized in the adjuvant setting following TURBT for intermediate and high-risk NMIBC to improve disease-specific mortality and allow for bladder preservation, with response noted in approximately 50% of patients [12–14]. At this time, multiple daughter strains have been obtained during the process of serial passages that include Tice, Connaught, and Tokyo [15].

There are several contemporary problems with the use of BCG. First, recurrence rates for patients who receive BCG range as high as 80%, and up to 45% of patients, can develop MIBC within 5 years [16]. For patients who progress or harbor persistent high-risk disease, there are no definitive intravesical salvage therapies. The only FDA-approved salvage therapy for patients who fail BCG is valrubicin, with a 2-year efficacy of only 8% [17, 18]. Recently, the availability of BCG, particularly in the USA, has become a major issue requiring physicians to ration and in some cases, use alternative medications [19••, 20]. The three predominant strains all have unique impediments to availability; Sanofi announced shortages of the Connaught strain since 2012 with permanent closure of production in 2017, Merck announced shortages of the Tice strain in 2014 with diminishing supplies over time, and the Tokyo strain is not approved for use in the USA [19••].

Given the aforementioned needs, there has been a resurgence of interest in novel intravesical therapies [21]. This review will outline currently accruing and yet to be published clinical trials for various NMIBC disease states. Each section will be organized as follows: background information, previously published data, and ongoing or unpublished clinical trials for the spectrum of BCG-Naïve, BCG-exposed, and BCG-unresponsive NMIBC (Table 1).

Definitions for BCG-Exposure and Unresponsiveness

Risk groups for NMIBC have large amounts of variability and portend specific management options and prognosis. The receipt of BCG can also be used to classify patients. Patients with high-risk NMIBC who have not yet received BCG are BCG-naïve. BCG-unresponsive is a definition that refers to those the highest risk of progression after receipt of adequate BCG: (1) no response to BCG treatment and with new or recurrent high-grade Ta/T1 or CIS, (2) recurrence at or around 6 months after BCG initiation, or (3) relapse within 6 months of last BCG treatment despite an initial complete response [22]. In our manuscript, we will refer to patients who are not strictly BCG-naïve or BCG-unresponsive as "BCG-exposed."

In order to contextualize historic trials, it is important to understand the classic terminology "BCG failure," or NMIBC which recurs or progresses within 6 months of BCG therapy [23], and other various subgroups including BCG-refractory, failure to achieve disease-free status by 6 months after induction BCG with maintenance or re-treatment; BCG-persistent, recurrent or persistent lower stage/grade tumor at 3 months with complete response at 6 months; BCG-relapsing, recurrence of disease by 6 months after disease-free status was achieved; and BCG intolerant, disease recurrence after an inadequate treatment course was applied due to serious adverse effects or symptomatic intolerance [24].

Given the unmet need for effective bladder sparing treatments, the FDA has set a threshold for NMIBC trials, particularly for BCG-unresponsive disease, which includes both the allowance of open-label and non-randomized trial design, and an informal criteria of early complete response rate of 50% with a long-term complete response rate of about 30% at 1 year [22, 25].

BCG-Augmented Immunotherapy

There are trials evaluating immunomodulators that can potentially augment the innate immune response activity of BCG. IFN was studied in monotherapy trials in the 1990s that demonstrated durable complete response rates between 8 and 22% [26, 27]. IFN was subsequently studied in combination trials with BCG and showed up to 45% durable complete response rates in select NMIBC populations [28, 29]. Mycobacterial cell wall nucleic acid complex (MCNA) is originally derived from emulsified Mycobacterial cell walls, and contains both cell wall and DNA [30]. MCNA was shown to have 2-year complete response rates between 19 and 46% across patients with a range of prior BCG-exposures [31, 32]. This agent was ultimately denied FDA approval in 2016 [33].

A more recent BCG-augmenting agent is ALT-803, which is an IL-15 super-agonist with both immune and adaptive immune response stimulation. The IL-15 cytokine is a predominantly a natural killer (NK) cell agonist although it also stimulates effector T cells. There is currently a Phase Ib/II randomized trial comparing ALT-803 with BCG versus BCG alone in patients with high-risk BCG-naïve NMIBC (NCT02138734). There is also a single-arm Phase II trial assessing ALT-803 with BCG in the BCG-unresponsive setting (NCT03022825; QUILT-3.032). Preliminary data from these trials are promising, and a trial of ALT-803 alone seems warranted.

VPM1002BC is a genetically modified strain of BCG (*Mycobacterium bovis*) with insertion of a gene from Listeria (*listeriolysin*), with the aim of increased immune response. Phase I results confirmed safety, and a Phase I/II study of 39 patients with prior BCG-exposure is underway (NCT02371447).

Checkpoint Inhibition

Checkpoint inhibition has shown success in the metastatic setting for bladder cancer, as well as recent promise in the

Table 1 Ongoing or unpublished clinical trials for patients with non-metastatic NMIBC

Treatment agent (control)	Phase	BCG-Status (risk)*	Title [trial IDs]	Accrual target	Completion date
BCG-augmented immunotherapy					
ALT-803 plus BCG (BCG)	I/II	N (H)	A Study of Intravesical BCG in Combination With ALT-803 in Patients With Non-Muscle Invasive Bladder Cancer [NCT02138734]	596	October 2021
ALT-803 plus BCG	II	U	QUILT-3.032: A Multicenter Clinical Trial of Intravesical Bacillus Calmette-Guerin (BCG) in Combination With ALT-803 in Patients With BCG Unresponsive High Grade Non-Muscle Invasive Bladder Cancer [NCT03022825]	160	September 2020
VPM1002BC	I/II	E	A Phase I/II Open Label Clinical Trial Assessing Safety and Efficacy of Intravesical Instillation of VPM1002BC in Patients With Recurrent Non-muscle Invasive Bladder Cancer After Standard BCG Therapy [NCT02371447]	39	December 2022
Checkpoint inhibition					
Pembrolizumab	II	N (H)	Phase II Study of Pembrolizumab (MK-3475) as First-Line Therapy for High Risk T1 Non-Muscle-Invasive Bladder Cancer [NCT03504163]	37	April 2020
Pembrolizumab + BCG (BCG)	III	E (H)	Efficacy and Safety of Pembrolizumab (MK-3475) in Combination With Bacillus Calmette-Guerin (BCG) in High-Risk Non-Muscle Invasive Bladder Cancer (HR NMIBC) [NCT03711032; KEYNOTE-676]	550	November 2024
Intravesical pembrolizumab (intravenous)	I/II	N (I)	Pembrolizumab in Intermediate Risk Recurrent Non-muscle Invasive Bladder Cancer (NMIBC) (PemBla) [NCT03167151]	36	August 2021
Intravesical pembrolizumab	I	N (H), U	A Phase 1 Dose-Escalation Study of Intravesical MK-3475 and Bacillus Calmette-Guerin (BCG) in Subjects With High Risk and BCG-Refractory Non-Muscle-Invasive Bladder Cancer [NCT02808143]	27	February 2020
Pembrolizumab	II	U	A Phase II Clinical Trial to Study the Efficacy and Safety of Pembrolizumab (MK-3475) in Subjects With High Risk Non-muscle Invasive Bladder Cancer (NMIBC) Unresponsive to Bacillus Calmette-Guerin (BCG) Therapy [NCT02625961; KEYNOTE-057]	260	July 2023
Durvalumab with BCG (BCG)	III	N (H)	Assessment of Efficacy and Safety of Durvalumab Plus BCG Compared to the Standard Therapy With BCG in Non-muscle Invasive Bladder Cancer [NCT03528694;POTOMAC]	975	November 2024
Durvalumab	II	U	Intravesical Administration of Durvalumab (MEDI4736) to Patients With High-risk, Non-muscle-invasive Bladder Cancer (NMIBC). A Phase II Study With Correlative [NCT03759496]	39	December 2021
Durvalumab ± 18-Gy XRT (BCG)	I/II	U	PhAse 1/2 StuDy of Modern ImmunotherApy in BCG-RelaPsing UroThelial Carcinoma of the BLADDER–[NCT03317158; ADAPT-BLADDER; HCRN GU16-243]	186	September 2021
Durvalumab with vicinium–oportuzumab Monatox–VB4-845	I	U	A Phase I Single-Arm Study of the Combination of Durvalumab (MEDI4736) and Vicinium (Oportuzumab Monatox, VB4-845) in Subjects With High-Grade Non-Muscle-Invasive Bladder Cancer Previously Treated With BCG [NCT03258593]	40	December 2022
Atezolizumab with BCG (BCG)	III	N (H)	An Open Label, Randomized, Phase III Trial, Evaluating Efficacy of Atezolizumab in Addition to One Year BCG (Bacillus CaLmette-Guerin) Bladder Instillation in BCG-naive Patients With High-risk Non-muscle Invasive Bladder cANcer [NCT03799835; ALBAN]	614	February 2028
Atezolizumab with BCG (BCG)	Ib/II	N/U	A Phase Ib/II, Open-Label Study of the Safety and Pharmacology of Atezolizumab Administered With or Without Bacille Calmette-Guérin in Patients With High-Risk Non−Muscle-Invasive Bladder Cancer [NCT02792192]	24	March 2020
Atezolizumab	II	U	Phase II Trial of Atezolizumab in BCG-Unresponsive Non-Muscle Invasive Bladder Cancer [NCT02844816]	202	April 2021
Avelumab + 60-66-Gy XRT	II	U	Bladder PREserVation by RadioTherapy and Immunotherapy in BCG Unresponsive Non-muscle Invasive Bladder Cancer [NCT03950362]	67	June 2024
Avelumab with BCG	Ib	U	Phase Ib Study of Avelumab Plus Bacille Calmette-Guerin (BCG) in Patients With Non-muscle Invasive Bladder Cancer (ABC Trial) [NCT03892642]	27	October 2025
Nivolumab ± BMS-986205 ± BCG	II	U	A Phase 2, Randomized, Open-label Study of Nivolumab or Nivolumab/BMS-986205 Alone or Combined With Intravesical BCG in Participants With BCG-Unresponsive, High-Risk, Non-Muscle Invasive Bladder Cancer [NCT03519256; CheckMate 9UT]	436	June 2023
Chemotherapy					
Neoadjuvant mitomycin C (TURBT alone)	II	N (L/I/H)	The Effectiveness and Safety of Neoadjuvant Intravesical Mitomycin-C Instillation in Non-muscle Invasive Bladder Cancer Patients: Prospective, Randomized, Phase II Study [NCT03058757]	78	December 2022
Neoadjuvant mitomycin C (adjuvant)	II	N (L/I/H)	Neoadjuvant Short-term Intensive Chemoresection Versus Standard Adjuvant Intravesical Instillations in NMIBC (NICSA) [NCT03348969]	120	October 2020
Mitomycin C with BCG (BCG)	III	N (H)	Adding Mitomycin C to Bacillus of Calmette-Guerin (BCG) as Adjuvant Intravesical Therapy for High-risk, Non-Muscle-invasive Bladder Cancer: a Randomised Phase 3 Trial [NCT02948543]	500	December 2020
Mitomycin C with BCG (BCG)	III	N (H)	The Effects of Sequential Mitomycin and Bacillus Calmette-Guérin Treatment Versus Bacillus Calmette-Guérin Monotherapy in Patients With High Risk Non-Muscle Invasive Bladder Cancer	140	January 2021

Table 1 (continued)

Treatment agent (control)	Phase	BCG-Status (risk)*	Title [trial IDs]	Accrual target	Completion date
Docetaxel-PM (mitomycin C)	III	E (H)	A Phase III Study to Evaluate the Efficacy and Safety Of Intravesical Nanoxel®M (Docetaxel-PM) In Bacillius Calmette-Guerin Refractory Non-Muscle Invasive Bladder Cancer [NCT02982395]	88	June 2021
Apaziquone (placebo)	III	N (L/I)	A Randomized, Single-Dose, Double-Blind, Placebo-CONtrolled Phase 3 Study of Qapzola™ (Apaziquone) as a Chemotherapy Adjuvant to TransUrEthral Resection of Bladder Tumors in Patients With Low-To-Intermediate-Risk NMIBC [NCT03224182;CONQUER]	500	December 2022
Apaziquone 1 dose (apaziquone 2 doses, placebo)	III	N (L/I)	A Multicenter, Multi-Arm, Randomized, Multi-Dose, Placebo-Controlled, Double-Blind, Phase 3 Study of Intravesical Apaziquone (EOquin®) as a Surgical Adjuvant in the Immediate Postoperative Period in Patients Undergoing TURBT [NCT02563561]	1869	March 2021
Cabazitaxel, gemcitabine, cisplatin-CGC	I	U	A Phase I Trial for the Use of Intravesical Cabazitaxel, Gemcitabine, and Cisplatin (CGC) in the Treatment of BCG-Refractory Non-muscle Invasive Urothelial Carcinoma of the Bladder Cancer [NCT02202772]	19	December 2020
Novel chemotherapy drug delivery					
GemRIS 225 mg-gemcitabine	I	N	A Phase 1b, Multicenter, Open Label Study Evaluating Safety, Tolerability and Preliminary Efficacy of GemRIS 225 mg in Subjects With Non-Muscle-Invasive Urothelial Carcinoma of the Bladder [NCT02720367]	12	January 2020
TC-3 hydrogel with mitomycin C	II	N	Evaluating the Effect of Pre-TURBT Intravesical Instillation of Mitomycin C (MMC) Mixed With TC-3 Gel in Patients With Non Muscle Invasive Bladder Cancer (NMIBC) [NCT01803295]	80	June 2017
UGN-102 hydrogel with mitomycin C	IIb	N (I)	A Phase 2b, Single-Arm, Multicenter Trial to Evaluate the Efficacy and Safety of UGN-102 as Primary Chemoablative Therapy in Patients With Low Grade (LG) Non-Muscle-Invasive Bladder Cancer (NMIBC) at Intermediate Risk of Recurrence [NCT03558503]	60	September 2020
EMDA-mitomycin C with BCG (BCG)	III	N (H)	Intravesical Instillation Therapy With Bacillus Calmette-Guérin (BCG) and Sequential BCG and Electromotive Mitomycin-C (EMDA-MCC) in Patients With High-risk Non-muscle-invasive Bladder Carcinoma [NCT03664869]	300	November 2025
NanoDoce	I/II	U	Phase 1/2 Trial Evaluating the Safety and Tolerability of NanoDoce® Injection and Intravesical Instillation in Subjects With Urothelial Carcinoma [NCT03636256]	75	November 2020
Synergo–RITE + mitomycin C	III	U	A Multicenter, Single-Arm Study Evaluating the Efficacy of Synergo® Radiofrequency-Induced Thermochemotherapy Effect (RITE) With Mitomycin C (Synergo® RITE + MMC) in CIS Non-Muscle Invasive Bladder Cancer (NMIBC) Bacillus Calmette-Guérin (BCG)-Unresponsive Patients With or Without Papillary NMIBC (RITE-USA) [NCT03335059]	106	March 2025
Viral/gene therapy					
Instiladrin-rAd-IFN/Syn3	III	U	A Phase III, Open Label Study to Evaluate the Safety and Efficacy of INSTILADRIN® (rAd-IFN)/Syn3) Administered Intravesically to Patients With High Grade, BCG Unresponsive Non-Muscle Invasive Bladder Cancer (NMIBC) [NCT02773849]	150	June 2022
CG0070	II	U	An Open Label, Single Arm, Phase II, Multicenter Study of the Safety and Efficacy of CG0070 Oncolytic Vector Regimen in Patients With Non-Muscle Invasive Bladder Carcinoma Who Have Failed BCG Therapy and Refused Cystectomy [NCT02365818; BOND2]	67	February 2019
BC-819	II	U	Codex: Study of Inodiftagene Vixteplasmid (BC-819) in Unresponsive NMIBC [NCT03719300]	140	November 2021
Vaccines					
Ty21a–typhoid vaccine	I	N (L/I)	Intravesical Ty21a for the Treatment of Patients With Non-muscle-invasive Bladder Cancer (NMIBC) [NCT03421236]	25	March 2021
RUTIVAC-1 (placebo)	I	N (H)	A Randomized, Double-Blind, Placebo-Controlled Phase I Trial to Evaluate the Immunomodulatory Effect of RUTI® in Individuals With High-Risk Non-Muscle-Invasive Bladder Cancer (NMIBC) Treated With Intravesical Bacillus Calmette-Guerin [NCT03191578]	40	March 2024
TICE BCG (Tokyo-172 BCG, Tokyo172-BCG with priming)	III	N (H)	S1602, A Phase III Randomized Trial to Evaluate the Influence of BCG Strain Differences and T Cell Priming With Intradermal BCG Before Intravesical Therapy for BCG-Naive High-Grade Non-muscle Invasive Bladder Cancer [NCT03091660; S1602]	969	February 2025
HS-410–vesigenurtacel-L with BCG (BCG)	I/II	N (I/H)	A Phase 1/2, Placebo-Controlled, Randomized Study to Evaluate the Safety, Immune Response and Clinical Activity of HS-410 in Patients With Non-Muscle Invasive Bladder Cancer Who Have Undergone Transurethral Resection of Bladder Tumor (TURBT) [NCT02010203]	104	April 2018
PANVAC with BCG (BCG)	II	E (H)	A Randomized, Prospective, Phase II Study to Determine the Efficacy of Bacillus Calmette-Guerin (BCG) Given in Combination With PANVAC Versus BCG Given Alone in Adults With High Grade Non-Muscle Invasive Bladder Cancer (NMIBC) Who Failed at Least 1 Induction Course of BCG [NCT02015104]	32	February 2020

non-metastatic MIBC setting [34]. There has been a surge of

Table 1 (continued)

Treatment agent (control)	Phase	BCG-Status (risk)*	Title [trial IDs]	Accrual target	Completion date
Targeted therapy/toxins/photodynamic therapy					
Rapamycin with BCG	I	N	A Randomized Study of Rapamycin Combined With Intravesical BCG in Patients With Non-muscle Invasive Bladder Cancer [NCT02753309]	33	September 2021
Tamoxifen citrate	II	N (L/I)	Phase II Trial of Estrogen Receptor Targeted Treatment of Non-Muscle Invasive Bladder Cancer With Tamoxifen [NCT02197897]	19	July 2018
Metformin	II	N (L/I)	Phase II Study of Oral Metformin for Intravesical Treatment of Non-muscle-invasive Bladder Cancer (TROJAN) [NCT03379909]	49	October 2025
Pemigatinib–FGFR1,2,3 inhibitor	II	N (I)	Phase 2 Window of Opportunity Study of Pemigatinib in Non-muscle Invasive Bladder Cancer Patients With Recurrent Low- or Intermediate-Risk Tumors [NCT03914794]	43	May 2023
Sunitinib with BCG	II	N (H)	A Phase II Study of Intravesical Bacillus Calmette-Guerin Followed by Sunitinib for the Treatment of High Risk Non-muscle Invasive Lower Urinary Tract Urothelial Carcinoma [NCT00794950]	36	August 2019
Lenalidomide with BCG (BCG)	II	N (H)	Immune Modulation by Addition of Oral Lenalidomide to Intravesical BCG (Bacille Calmette-Guerrin) for Therapy of Non-muscle-invasive Transitional Cell Bladder Cancer [NCT01373294]	17	December 2018
APL-1202-methionine aminopeptidase II type inhibitor	Ib	E (I/H)	Study of APL-1202 in Non-Muscle Invasive Bladder Cancer Patients Who Are Resistant to One Induction Course of BCG Treatment (NMIBC) [NCT03672240]	NR	October 2019
BGJ398	I	E (H)	Pilot Study of BGJ398 in Non-Muscle-Invasive Urothelial Carcinoma of the Bladder [NCT02657486]	NR	January 2020
Vicinium	III	U	Open-Label, Multicenter, Ph 3 Study to Evaluate the Efficacy and Tolerability of Intravesical Vicinium™ in Subjects With Non Muscle-Invasive Carcinoma in Situ and/or High-Grade Papillary Disease of the Bladder Treated With BCG [NCT02449239]	134	December 2021
ABI-009	I/II	U	A Combined Phase 1 and Phase 2 Study of Albumin-bound Rapamycin Nanoparticles (Nab-rapamycin, ABI-009) in the Treatment of BCG Refractory or Recurrent Nonmuscle Invasive Transitional Cell Bladder Cancer [NCT02009332]	40	December 2020
TLD-1433	II	U	Intravesical Photodynamic Therapy (PDT) in BCG Refractory/Intolerant Non-Muscle Invasive Bladder Cancer (NMIBC) Patients [NCT03945162]	125	May 2022
Radiation					
XRT + fluorouracil + mitomycin C	II	N/E (H)	A Phase II Protocol for Patients With Stage T1 Bladder Cancer to Evaluate Selective Bladder Preserving Treatment by Radiation Therapy Concurrent With Radiosensitizing Chemotherapy Following a Thorough Transurethral Surgical Re-Staging [NCT00981656; RTOG0926]	37	October 2023

*BCG-status/risk: *N* BCG-naïve, *E* BCG-exposed (not including BCG-unresponsive), *U* BCG-unresponsive, *L* low-risk, *I* intermediate risk, *H* high risk. *NR* not reported

interest in using checkpoint inhibitors earlier in the disease course for NMIBC. There are currently trials assessing pembrolizumab, durvalumab, atezolizumab, avelumab, and nivolumab across a variety of NMIBC disease risk states and BCG-exposure settings.

Pembrolizumab (MK-3475) is a programmed cell death protein 1 (PD-1) inhibitor that is investigated as a single agent in a phase II trial for high-risk T1 NMIBC (NCT03504163), as well as in a large randomized combination trial with BCG for patients with persistent disease following an induction course of BCG, aiming to enroll 550 patients (NCT03711032; KEYNOTE-676). This agent is typically administered via intravenous transfusion, but intravesical pembrolizumab is being explored in both a single-arm trial (NCT02808143) and a randomized marker lesion trial versus intravenous pembrolizumab (NCT03167151). There are important practice pattern implications in the ability of checkpoint inhibitors to be delivered via intravesical route. KEYNOTE-057 is a trial assessing pembrolizumab for patients with BCG-unresponsive NMIBC, and aims to enroll 260 patients. Interim results from this study demonstrated 3-month complete response of 38%, with approximately 50% durability of response at 12 months, although formal 12-month complete response data is pending [35•].

Durvalumab is a PD-L1 inhibitor that is being assessed in the large POTOMAC study, a three-arm Phase III trial aiming to accrue 975 BCG-naïve high-risk patients comparing durvalumab with induction BCG alone, durvalumab with induction and maintenance BCG, and induction and maintenance BCG alone. Durvalumab is also being assessed in patients with BCG-unresponsive bladder cancer in combination with radiation and BCG in the ADAPT-BLADDER trial, as well as in combination with vicinium (oportuzumab monatox) (NCT03258593).

Atezolizumab is a PD-L1 inhibitor that is being evaluated in several studies. The ALBAN trial is a Phase III trial assessing 614 BCG-naïve patients comparing a year of BCG alone versus Atezolizumab with BCG. There is also a Phase II trial of 202 BCG-unresponsive patients that will assess 6-month complete response and 18-month event-free survival after 1 year of atezolizumab (NCT02844816). Avelumab is a PD-L1 inhibitor being assessed for patients with BCG-unresponsive disease in a combination trial with 60-–66-Gy radiation (NCT03950362) and with BCG (NCT03892642). Nivolumab is a PD-1 inhibitor that is evaluated in the CheckMate 9UT trial which is a Phase II study aiming to accrue 436 patients with BCG-unresponsive NMIBC. Another agent evaluated in this trial is BMS-986205, which inhibits indoleamine 2,3-dioxygenase 1 (IDO1). Four arms of this trial compare nivolumab alone, nivolumab with BCG, nivolumab with BMS-986205, and BMS-896205 with BCG.

Chemotherapy

Intravesical chemotherapy for BCG-naïve patients, including thiotepa, adriamycin, and mitomycin c have been used and studied in the past [36]. Mitomycin C is currently utilized as a first-line treatment if BCG is not available, although studies have generally shown higher risk of recurrence with mitomycin C [37, 38]. Salvage intravesical chemotherapy for patients with prior BCG-exposure has also been investigated and shown suboptimal results [21, 39]. Gemcitabine is relatively well studied, demonstrating 21% 2-year complete response in the Phase II SWOG S0353 trial [40].

Mitomycin C with or without BCG is currently being studied, predominately in patients with BCG-naïve disease. The largest of such trials is a randomized Phase III trial that aims to accrue 500 patients with high-risk NMIBC to either 1 year of BCG or 1 year of BCG with mitomycin C (NCT02948543). The trial expects to complete in December 2020 and has a primary endpoint of disease-free survival. Another Phase III trial is accruing patients with high-risk BCG-refractory NMIBC and compares Nanoxel®M, a nanoparticle formulation of docetaxel, versus mitomycin C (NCT02982395).

Apaziquone is a synthetic alkylating agent that has been assessed in both the BCG-naïve and BCG-unresponsive settings, although predominantly as an immediate post-operative intravesical chemotherapy agent following TURBT [41, 42]. There are two large Phase III trials planned for this agent. The first is the CONQUER trial that is assessing the impact of immediate post-operative instillation of apaziquone versus placebo following TURBT of low- to intermediate-risk NMIBC. The second is a multi-arm randomized trial comparing one dose of apaziquone versus two doses of apaziquone versus placebo following TURBT (NCT02563561). However, it should be noted that the FDA has previously rejected this apaziquone as an immediate post-operative intravesical chemotherapy agent following TURBT after analysis of over 2800 trial patients failed to show benefit of the agent.

Combination of chemotherapy agents has been previously assessed, the most well studied of which is sequential intravesical gemcitabine and docetaxel [43–45]. This regimen has been shown to confer approximately 30–40% disease-free survival at 2 years [43, 45]. A small study assessed gemcitabine and mitomycin C with promising results in 10 BCG-refractory patients [46]. A Phase I trial is current aiming to accrue 19 patients with BCG-unresponsive NMIBC and receive intravesical cabazitaxel, gemcitabine, and cisplatin (CGC) (NCT02202772).

Novel Chemotherapy Drug Delivery

The goal of novel intravesical delivery systems is to improve the absorption of intravesical chemotherapies relative to

traditional intravesical drug instillation techniques. The simplest of these techniques is to change the penetration characteristics of the chemotherapeutic agent. Paclitaxel has been modified as conjugated paclitaxel-hyaluronic acid and assessed in a Phase I study of 16 patients, showing promising early results [47]. Another formulation of paclitaxel is nanoparticle albumin-bound (nab-)paclitaxel, which was assessed in a Phase II study and showed 36% complete response at 1 year [48]. The NanoDoce trial is a unique Phase I/II study that evaluates the safety and efficacy of both intravesical instillation and peritumoral injection of NanoDoce, which is a submicron particle docetaxel suspension (NCT03636256).

TC-3 hydrogel is drug delivery vehicle for mitomycin C. TC-3 mixed with mitomycin C is instilled in a liquid state into the bladder, where it solidifies and forms a drug reservoir inside the bladder, and dissolves over time with urinary contact. There have been a series of completed but unpublished studies of mitomycin C in TC-3 Gel for patients prior to TURBT, and after TURBT of both NMIBC and MIBC (NCT01803295, NCT02307487, NCT02891460, NCT01648010). The largest of these trials was a Phase II trial that accrued 80 patients with instillation prior to TURBT (NCT01803295). A similar hydrogel system is UGN-102, which is currently accruing to a Phase II trial.

The GemRIS system is modified from the previously studied Lidocaine Releasing Intravesical System (LiRIS) for interstitial cystitis that deploys into a "pretzel" shape in the bladder after cystoscopic placement and allows for slow release of intravesical gemcitabine. This is currently being evaluated in BCG-naïve patients in a Phase Ib study (NCT02720367).

Thermo-chemotherapy is based on the concept of suboptimal bladder wall penetration from traditional intravesical chemotherapy instillation techniques. Addition of heat may allow for increased drug penetration, which has been tested for Mitomycin C administered at 42 °C [49]. This study demonstrated up to 61% response rates. A current single-arm trial is utilizing the Synergo system to deliver mitomycin C in patients with BCG-unresponsive NMIBC. The COMBAT-BRS® system is another mitomycin C hyperthermic delivery system that has demonstrated efficacy and is currently being evaluated in European trials [50]. Finally, electromotive therapy is being studied in a high-risk BCG-naïve population (NCT03664869).

Viral and Gene Therapy

The use of oncolytic viruses to deliver genes facilitating cell destruction was first explored with the vaccinia virus, a derivative of the smallpox vaccine [51]. There is currently an ongoing trial studying use of an attenuated measles virus (MV-NIS) in patients with who are undergoing urothelial carcinoma but are ineligible or do not desire neoadjuvant chemotherapy (NCT03171493). There are currently three trials actively assessing oncolytic viral agents for NMIBC.

CG0070 is a replication selective serotype-5 oncolytic adenovirus that functions by preferential replication in RB pathway defective cells. The adenovirus inserts a gene that results in production of GM-CSF, and cell killing occurs both by direct cytotoxicity and immune mediated killing. A Phase I study showed that clinical response was increased in patients with RB pathway defective compared with wild-type RB patients (58% versus 20%) [52]. The Phase II BONDII study demonstrated an interim overall 47% complete response rate at 6 months in 45 patients with BCG-unresponsive NMIBC [53]. The primary outcome of 18-month complete response in the full 67 patient cohort was presented at the 2018 AUA, showing 21% complete response, but these results have not been formally published (NCT02365818).

INSTILADRIN (nanofaragene firadenovec) is a replication-deficient adenovirus-based gene transfer vector that encodes for IFNα-2b. Syn3 is a novel surfactant that improves adenoviral transduction into tumor cells. Phase I results of 17 patients with BCG-unresponsive NMIBC showed no dose-limiting toxicity, evidence of clinical response, and elevated urinary IFNα levels [18]. A Phase II study randomized 43 patients to two doses of INSTILADRIN and showed that 35% of patients were free of high-grade disease at 12 months [54]. Results are awaited from a single-arm Phase III study of 150 patients with BCG-unresponsive NMIBC that completed accrual in June 2018 (NCT02773849).

BC-819 (inodiftagene vixteplasmid) is a tumor-selective recombinant double-stranded DNA plasmid resulting in production of the bacterial diphtheria toxin. Tumor selectivity is secondary to use of the H19 gene which is upregulated in bladder tumors. Results from an early trial in patients with intermediate-risk NMIBC and prior BCG-exposure demonstrated promising complete response rates [55]. This is currently being investigated in a Phase II study of patients with BCG-unresponsive NMIBC (NCT03719300).

Finally, intravesical Coxsackievirus A21 (CVA21) showed promising clinical activity in ta study of 15 patients who were administered the oncolytic adenovirus and underwent radical cystectomy (CAVATEK trial), and a larger trial of this agent is currently being designed [56].

Vaccines

Vaccine therapy is appealing because vaccines can theoretically confer lifelong cancer immunity. Vaccines are being evaluated in numerous trials. One vaccine therapy that was recently reported includes injections of a subunit cancer vaccine (recMAGE-A3 protein+AS15) alone or in two combinations of intravesical BCG-instillations, and demonstrated

increased serum vaccine–specific T cells without significant increase in adverse events versus BCG alone [53].

SWOG S1602 is a study that predominantly compares strains of BCG, but also has an intradermal priming component with BCG vaccination. This is a large Phase III study aiming to accrue 969 patients with BCG-naïve high-risk NMIBC and compares intravesical TICE BCG, intravesical Tokyo-172 BCG, and intravesical Tokyo-172 BCG with intradermal priming with BCG (NCT03091660). The trial is important since it will simultaneously evaluate for potential use of the Tokyo strain as well as evaluate the efficacy of intradermal priming.

HS-410 (Vesigenurtacel-L) is an intradermal vaccine comprised of a cancer cell line with increased expression of bladder tumor antigens that was transfected with a heat shock protein (hsp90B1) and neoantigen (gp96-Ig). Preliminary data suggests no significant difference in recurrences for HS-410 versus placebo, although increased immune response to tumor-associated peptides was observed in patients exposed to the vaccine (NCT02010203) [57].

PANVAC is a recombinant poxviral vector vaccine that contains genes for human CEA, MUC-1, and T cell co-stimulatory molecules (B7, ICAM, LFA-3). CEA is a cell surface glycoprotein and MUC-1 is a glycosylated transmembrane protein that are overexpressed in > 75% of bladder tumors. Preliminary results for 16 patients showed that the vaccine resulted in increased immunologic response, although the final results of the Phase II study in patients with high-grade NMIBC exposed to prior BCG are still pending (NCT02015104).

Two active vaccine trials for BCG-naïve disease are investigating Ty21a, a component of the typhoid vaccine, in 25 patients (NCT03421236) and RUTIVAC-1 in 40 patients (NCT03191578).

Targeted Therapy/Toxins/Photodynamic Therapy

There has been a surge of trials for targeted therapies and toxins. In patients with BCG-naïve NMIBC, a variety of agents are being explored, including rapamycin (NCT02753309), tamoxifen (NCT02197897), metformin (NCT03379909), pemagitinib, an FGFR 1, 2, 3 inhibitor (NCT03914794), sunitinib (NCT00794950), and lenalidomide (NCT01373294). A Phase II study was performed and published for imiquimod (TMX-101), a TLR-7 agonist that is typically used for skin malignancies, showing that the agent was safe and well tolerated in 12 patients with CIS with and without BCG-exposure [58]. Other currently pending Phase I trials for patients with history of BCG-exposure include APL-1202, a methionine aminopeptidase II inhibitor (NCT03672240), and BGJ398, an oral FGFR kinase inhibitor (NCT02657486).

A Phase I/II trial of ABI-009, an albumin-bound rapamycin nanoparticle agent (Nab-rapamycin), is currently ongoing for BCG-unresponsive patients (NCT02009332). One of the most heavily studied targeted therapies for BCG-unresponsive NMIBC is vicinium (oportuzumab monatox, VB4-845). This agent is a recombinant fusion protein with an antiEpCAM antibody linked to the Pseudomonas exotoxin. The desired mechanism is selective internalization by tumor cells and subsequent cell death. A phase II study demonstrated excellent tolerability but low complete response [59]. There is a current Phase III trial assessing 134 patients with BCG-unresponsive NMIBC that reported interim results of 42% complete response at 3 months (NCT02449239). Another intriguing trial is evaluating combination of this agent with the immune checkpoint inhibitor durvalumab in patients with BCG-unresponsive disease (NCT03258593).

Photodynamic therapy has been assessed in several older studies of both 5-aminolevulinic acid and hexaminolevulinic acid [60, 61]. These agents are precursors of protoporphyrin that are preferentially absorbed by tumor cells, and targets for subsequent cytotoxic radiation to a specific wavelength of light. More recently, a Phase Ib study of TLD-1433, another photodynamic compound, was completed (NCT03053635), and a Phase II study aiming to accrue 125 BCG-unresponsive patients is ongoing (NCT03945162).

Radiation

Radiation alone for NMIBC has not been associated with promising results [62]. However, there is renewed interest in combining radiation with other therapies, to cause synergistic effect. There are several ongoing trials combining radiation with chemotherapy or with checkpoint inhibition. The Phase II RTOG 0926 trial combines radiation with fluorouracil and mitomycin C following thorough transurethral resection, and aims to accrue 37 patients with high-grade BCG-ineligible or BCG-refractory NMIBC. The trial aims to evaluate 3-year cystectomy free survival as its primary endpoint. The ADAPT-BLADDER trial is a multi-arm multi-stage study that assesses combinations of durvalumab, BCG, and 18-Gy external beam radiation to the bladder, and aims to accrue 186 patients. Finally, there is a trial evaluating the combination of Avelumab and 60–66-Gy radiation (NCT03950362).

Discussion

NMIBC is a heterogenous condition that is currently the focus of over 50 active and registered clinical trials. This clinical trial landscape has previously been limited by heterogeneous disease states and inclusion criteria, accrual issues, and inconsistent endpoints [63••]. In 2016 a consensus statement

addressed some of these problems and posited consistent guidelines in trial design [63••]. Given the explosion of studies in this space, it is important to have a comprehensive understanding of currently available trials. Our review focused on high-risk NMIBC, but there are important developments being made for low-risk disease as well.

It is becoming increasingly apparent that the decreased availability of BCG will be a chronic problem for urologists, and thus, novel agents for high-risk BCG-naïve disease are needed. It is encouraging to see new trials, particularly with checkpoint inhibitors, moving into this space. In the meantime, the SWOG S1602 trial is very important since it will potentially allow for an additional BCG strain (Tokyo) to be utilized in the USA. While awaiting these data, many institutions are using reduced dose BCG with shortened maintenance regiments, as recommended by a recent Society of Urologic Oncology advisory. In lieu of BCG, chemotherapy is used either as a single agent or combination regimens.

Regarding patients with prior BCG-exposure of BCG-unresponsive NMIBC, using standardized inclusion criteria and the BCG-unresponsive designation will improve interpretation of results from trials in this setting. Checkpoint inhibition in isolation or in combination with other agents offers a possibility for higher response rates than previously seen. It will be important to assess predictive biomarkers and correlative studies to facilitate targeted use of these agents with proper patient selection. A final critically important principle is that radical cystectomy should be used aggressively in patients with BCG-unresponsive disease who are fit and agreeable to surgery, as well as in patients who are not responding to salvage treatments.

Conclusion

Intravesical BCG remains the mainstay of management of intermediate and high-risk NMIBC. However, BCG shortages that appear to be permanent are speeding up the development of novel agents in this setting. Furthermore, for patients in whom BCG is not effective, there is myriad of new trials assessing promising salvage therapies.

Compliance with ethical standards

Conflict of Interest Vignesh T. Packiam received honorarium from Cold Genesys.

Ryan P. Werntz has no disclosures.

Gary D. Steinberg is a scientific advisor/consultant for the following companies: Heat Biologics, Cold Genesys, Photo-Cure, Merck, Roche/Genentech, CiClomed, Taris Biomedical, MDxHealth, Fidia Farmaceuticals, Urogen, Ferring, Aduro, Boston Scientific, BMS, Astra Zeneca, Pfizer, Janssen, Epivax Oncology, Natera, FKD, EnGene Bio, SesenBio. He is a member of the Clinical Trial Protocol Committee for the following companies: Merck, BMS, Janssen, Cold Genesys. He has equity stock/options for Epivax Oncology and Urogen.

Human and Animal Rights All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424. https://doi.org/10.3322/caac.21492.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69:7–34. https://doi.org/10.3322/caac.21551.
3. Kamat AM, Hahn NM, Efstathiou JA, Lerner SP, Malmström P-U, Choi W, et al. Bladder cancer. Lancet Lond Engl. 2016;388:2796–810. https://doi.org/10.1016/S0140-6736(16)30512-8.
4. Amin MB, American Joint Committee on Cancer, American Cancer Society, editors. AJCC cancer staging manual. Eight edition / editor-in-chief, Mahul B. Amin, MD, FCAP ; editors, Stephen B. Edge, MD, FACS [and 16 others] ; Donna M. Gress, RHIT, CTR-Technical editor ; Laura R. Meyer, CAPM-Managing editor. Chicago IL: American Joint Committee on Cancer, Springer; 2017.
5. Kamat AM, Witjes JA, Brausi M, Soloway M, Lamm D, Persad R, et al. Defining and treating the spectrum of intermediate risk nonmuscle invasive bladder cancer. J Urol. 2014;192:305–15. https://doi.org/10.1016/j.juro.2014.02.2573.
6. Rieken M, Shariat SF, Kluth L, Crivelli JJ, Abufaraj M, Foerster B, et al. Comparison of the EORTC tables and the EAU categories for risk stratification of patients with nonmuscle-invasive bladder cancer. Urol Oncol Semin Orig Investig. 2018;36:8.e17–24. https://doi.org/10.1016/j.urolonc.2017.08.027.
7. Chang SS, Boorjian SA, Chou R, Clark PE, Daneshmand S, Konety BR, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO Guideline. J Urol. 2016;196:1021–9. https://doi.org/10.1016/j.juro.2016.06.049.
8. Babjuk M, Burger M, Zigeuner R, Shariat SF, van Rhijn BWG, Compérat E, et al. EAU Guidelines on non–muscle-invasive urothelial carcinoma of the bladder: update 2013. Eur Urol. 2013;64:639–53. https://doi.org/10.1016/j.eururo.2013.06.003.
9. Flaig TW, Spiess PE, Agarwal N, Bangs R, Boorjian SA, Buyyounouski MK, et al. NCCN guidelines insights: bladder cancer, Version 5.2018. J Natl Compr Cancer Netw JNCCN. 2018;16:1041–53. https://doi.org/10.6004/jnccn.2018.0072.
10. Richards KA, Smith ND, Steinberg GD. The importance of transurethral resection of bladder tumor in the management of nonmuscle invasive bladder cancer: a systematic review of novel technologies. J Urol. 2014;191:1655–64. https://doi.org/10.1016/j.juro.2014.01.087.
11. Pietzak EJ, Zabor EC, Bagrodia A, Armenia J, Hu W, Zehir A, et al. Genomic differences between "primary" and "secondary" muscle-invasive bladder cancer as a basis for disparate outcomes to cisplatin-based neoadjuvant chemotherapy. Eur Urol. 2019;75:231–9. https://doi.org/10.1016/j.eururo.2018.09.002.
12. Sylvester RJ, van der MEIJDEN AP, Lamm DL. Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with

superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. J Urol. 2002;168:1964–70.
13. Schrier BP, Hollander MP, van Rhijn BWG, Kiemeney LALM, Alfred WJ. Prognosis of muscle-invasive bladder cancer: difference between primary and progressive tumours and implications for therapy. Eur Urol. 2004;45:292–6. https://doi.org/10.1016/j.eururo.2003.10.006.
14. Witjes JA. Management of BCG failures in superficial bladder cancer: a review. Eur Urol. 2006;49:790–7. https://doi.org/10.1016/j.eururo.2006.01.017.
15. Behr MA, Small PM. A historical and molecular phylogeny of BCG strains. Vaccine. 1999;17:915–22.
16. van Rhijn BWG, Burger M, Lotan Y, Solsona E, Stief CG, Sylvester RJ, et al. Recurrence and progression of disease in non-muscle-invasive bladder cancer: from epidemiology to treatment strategy. Eur Urol. 2009;56:430–42. https://doi.org/10.1016/j.eururo.2009.06.028.
17. Steinberg G, Bahnson R, Brosman S, Middleton R, Wajsman Z, Wehle M. Efficacy and safety of valrubicin for the treatment of Bacillus Calmette-Guerin refractory carcinoma in situ of the bladder. The Valrubicin Study Group. J Urol. 2000;163:761–7.
18. Dinney CPN, Greenberg RE, Steinberg GD. Intravesical valrubicin in patients with bladder carcinoma in situ and contraindication to or failure after bacillus Calmette-Guérin. Urol Oncol. 2013;31:1635–42. https://doi.org/10.1016/j.urolonc.2012.04.010.
19.•• Messing EM. The BCG Shortage. Bladder Cancer Amst Neth. 2017;3:227–8. https://doi.org/10.3233/BLC-179018 **An editorial explaining the current status of the BCG shortage.**
20. Davies BJ, Hwang TJ, Kesselheim AS. Ensuring access to injectable generic drugs - the case of intravesical BCG for bladder cancer. N Engl J Med. 2017;376:1401–3. https://doi.org/10.1056/NEJMp1615697.
21. Patel SG, Cohen A, Weiner AB, Steinberg GD. Intravesical therapy for bladder cancer. Expert Opin Pharmacother. 2015;16:889–901. https://doi.org/10.1517/14656566.2015.1024656.
22. Lerner SP, Dinney C, Kamat A, Bivalacqua TJ, Nielsen M, O'Donnell M, et al. Clarification of bladder cancer disease states following treatment of patients with intravesical BCG. Bladder Cancer. 2015;1:29–30. https://doi.org/10.3233/BLC-159002.
23. Yates DR, Brausi MA, Catto JWF, Dalbagni G, Rouprêt M, Shariat SF, et al. Treatment options available for bacillus Calmette-Guérin failure in non–muscle-invasive bladder cancer. Eur Urol. 2012;62:1088–96. https://doi.org/10.1016/j.eururo.2012.08.055.
24. O'Donnell MA, Boehle A. Treatment options for BCG failures. World J Urol. 2006;24:481–7. https://doi.org/10.1007/s00345-006-0112-0.
25. Jarow JP, Lerner SP, Kluetz PG, Liu K, Sridhara R, Bajorin D, et al. Clinical trial design for the development of new therapies for nonmuscle-invasive bladder cancer: report of a Food and Drug Administration and American Urological Association public workshop. Urology. 2014;83:262–4. https://doi.org/10.1016/j.urology.2013.10.030.
26. Glashan RW. A randomized controlled study of intravesical alpha-2b-interferon in carcinoma in situ of the bladder. J Urol. 1990;144:658–61.
27. Hudson MA, Ratliff TL. Failure of intravesical interferon-alfa-2b for the treatment of patients with superficial bladder cancer previously failing intravesical BCG Therapy. Urol Oncol Semin Orig Investig. 1995;1:115–8. https://doi.org/10.1016/1078-1439(95)00039-K.
28. Joudi FN, Smith BJ, O'Donnell MA. Final results from a national multicenter phase II trial of combination bacillus Calmette-Guérin plus interferon α-2B for reducing recurrence of superficial bladder cancer☆. Urol Oncol Semin Orig Investig. 2006;24:344–8. https://doi.org/10.1016/j.urolonc.2005.11.026.
29. Gallagher BL, Joudi FN, Maymí JL, O'Donnell MA. Impact of previous Bacille Calmette-Guérin failure pattern on subsequent response to Bacille Calmette-Guérin plus interferon intravesical therapy. Urology. 2008;71:297–301. https://doi.org/10.1016/j.urology.2007.09.050.
30. Filion MC, Lepicier P, Morales A, Phillips NC. Mycobacterium phlei cell wall complex directly induces apoptosis in human bladder cancer cells. Br J Cancer. 1999;79:229.
31. Morales A, Phadke K, Steinhoff G. Intravesical mycobacterial cell wall-DNA complex in the treatment of carcinoma in situ of the bladder after standard intravesical therapy has failed. J Urol. 2009;181:1040–5. https://doi.org/10.1016/j.juro.2008.11.019.
32. Morales A, Herr H, Steinberg G, Given R, Cohen Z, Amrhein J, et al. Efficacy and Safety of MCNA in patients with nonmuscle invasive bladder cancer at high risk for recurrence and progression after failed treatment with bacillus Calmette-Guérin. J Urol. 2015;193:1135–43. https://doi.org/10.1016/j.juro.2014.09.109.
33. INDICATIONS N. New drug approvals Adzenys XR-ODT for ADHD. n.d.
34. Necchi A, Anichini A, Raggi D, Briganti A, Massa S, Lucianò R, et al. Pembrolizumab as neoadjuvant therapy before radical cystectomy in patients with muscle-invasive urothelial bladder carcinoma (PURE-01): An Open-Label, Single-Arm, Phase II Study. J Clin Oncol. 2018;36:3353–60. https://doi.org/10.1200/JCO.18.01148.
35.• Balar AV, Kulkarni GS, Uchio EM, Boormans J, Mourey L, Krieger LEM, et al. Keynote 057: Phase II trial of Pembrolizumab (pembro) for patients (pts) with high-risk (HR) nonmuscle invasive bladder cancer (NMIBC) unresponsive to bacillus calmette-guérin (BCG). J Clin Oncol. 2019;37:350. https://doi.org/10.1200/JCO.2019.37.7_suppl.350. **One of the earliest reported checkpoint inhibitor trials for NMIBC.**
36. Mostafid AH, Palou Redorta J, Sylvester R, Witjes JA. Therapeutic options in high-risk non-muscle-invasive bladder cancer during the current worldwide shortage of bacille Calmette-Guérin. Eur Urol. 2015;67:359–60. https://doi.org/10.1016/j.eururo.2014.11.031.
37. BöHle A, Jocham D, Bock PR. Intravesical Bacillus Calmette-Guerin versus mitomycin c for superficial bladder cancer: a formal meta-analysis of comparative studies on recurrence and toxicity. J Urol. 2003;169:90–5. https://doi.org/10.1016/S0022-5347(05)64043-8.
38. Shelley MD, Wilt TJ, Court J, Coles B, Kynaston H, Mason MD. Intravesical bacillus Calmette-Guerin is superior to mitomycin C in reducing tumour recurrence in high-risk superficial bladder cancer: a meta-analysis of randomized trials. BJU Int. 2004;93:485–90. https://doi.org/10.1111/j.1464-410X.2003.04655.x.
39. Steinberg RL, Thomas LJ, Nepple KG. Intravesical and alternative bladder-preservation therapies in the management of non–muscle-invasive bladder cancer unresponsive to bacillus Calmette-Guérin. Urol Oncol Semin Orig Investig. 2016. https://doi.org/10.1016/j.urolonc.2015.12.004.
40. Skinner EC, Goldman B, Sakr WA, Petrylak DP, Lenz H-J, Lee CT, et al. SWOG S0353: Phase II trial of intravesical gemcitabine in patients with nonmuscle invasive bladder cancer and recurrence after 2 prior courses of intravesical bacillus Calmette-Guérin. J Urol. 2013;190:1200–4. https://doi.org/10.1016/j.juro.2013.04.031.
41. Karsh L, Shore N, Soloway M, Bhat G, Reddy G, Leu S-Y, et al. Double-blind, randomized, placebo-controlled studies evaluating apaziquone (E09, Qapzola™) intravesical instillation post transurethral resection of bladder tumors for the treatment of low-risk non-muscle invasive bladder cancer. Bladder Cancer Amst Neth. 2018;4:293–301. https://doi.org/10.3233/BLC-180166.
42. Jain A, Phillips RM, Scally AJ, Lenaz G, Beer M, Puri R. Response of multiple recurrent TaT1 bladder cancer to intravesical apaziquone (EO9): comparative analysis of tumor recurrence rates. Urology. 2009;73:1083–6. https://doi.org/10.1016/j.urology.2007.12.062.

43. Milbar N, Kates M, Chappidi MR, Pederzoli F, Yoshida T, Sankin A, et al. Oncological outcomes of sequential intravesical gemcitabine and docetaxel in patients with non-muscle invasive bladder cancer. Bladder Cancer Amst Neth. 2017;3:293–303. https://doi.org/10.3233/BLC-170126.
44. Velaer KN, Steinberg RL, Thomas LJ, O'Donnell MA, Nepple KG. Experience with sequential intravesical gemcitabine and docetaxel as salvage therapy for non-muscle invasive bladder cancer. Curr Urol Rep. 2016;17. https://doi.org/10.1007/s11934-016-0594-2.
45. Steinberg RL, Thomas LJ, O'Donnell MA, Nepple KG. Sequential intravesical gemcitabine and docetaxel for the salvage treatment of non-muscle invasive bladder cancer. Bladder Cancer Amst Neth. 2015;1:65–72. https://doi.org/10.3233/BLC-150008.
46. Breyer BN, Whitson JM, Carroll PR, Konety BR. Sequential intravesical gemcitabine and mitomycin C chemotherapy regimen in patients with non-muscle invasive bladder cancer. Urol Oncol. 2010;28:510–4. https://doi.org/10.1016/j.urolonc.2008.11.019.
47. Bassi PF, Volpe A, D'Agostino D, Palermo G, Renier D, Franchini S, et al. Paclitaxel-hyaluronic acid for intravesical therapy of bacillus Calmette-Guérin refractory carcinoma in situ of the bladder: results of a phase I study. J Urol. 2011;185:445–9. https://doi.org/10.1016/j.juro.2010.09.073.
48. McKiernan JM, Holder DD, Ghandour RA, Barlow LJ, Ahn JJ, Kates M, et al. Phase II trial of intravesical nanoparticle albumin bound paclitaxel for the treatment of nonmuscle invasive urothelial carcinoma of the bladder after bacillus Calmette-Guérin treatment failure. J Urol. 2014;192:1633–8. https://doi.org/10.1016/j.juro.2014.06.084.
49. Nativ O, Witjes JA, Hendricksen K, Cohen M, Kedar D, Sidi A, et al. Combined thermo-chemotherapy for recurrent bladder cancer after Bacillus Calmette-Guerin. J Urol. 2009;182:1313–7. https://doi.org/10.1016/j.juro.2009.06.017.
50. Sousa A, Inman BA, Piñeiro I, Monserrat V, Pérez A, Aparici V, et al. A clinical trial of neoadjuvant hyperthermic intravesical chemotherapy (HIVEC) for treating intermediate and high-risk non-muscle invasive bladder cancer. Int J Hyperth. 2014;30:166–70. https://doi.org/10.3109/02656736.2014.900194.
51. Gomella LG, Mastrangelo MJ, McCue PA, Maguire HCJR, Mulholland SG, Lattime EC. Phase i study of intravesical vaccinia virus as a vector for gene therapy of bladder cancer. J Urol. 2001;166:1291–5.
52. Burke JM, Lamm DL, Meng MV, Nemunaitis JJ, Stephenson JJ, Arseneau JC, et al. A first in human phase 1 study of CG0070, a GM-CSF expressing oncolytic adenovirus, for the treatment of nonmuscle invasive bladder cancer. J Urol. 2012;188:2391–7. https://doi.org/10.1016/j.juro.2012.07.097.
53. Packiam VT, Lamm DL, Barocas DA, Trainer A, Fand B, Davis RL, et al. An open label, single-arm, phase II multicenter study of the safety and efficacy of CG0070 oncolytic vector regimen in patients with BCG-unresponsive non-muscle-invasive bladder cancer: Interim results. Urol Oncol. 2018;36:440–7. https://doi.org/10.1016/j.urolonc.2017.07.005.
54. Shore ND, Boorjian SA, Canter DJ, Ogan K, Karsh LI, Downs TM, et al. Intravesical rAd-IFNα/Syn3 for patients with high-grade, Bacillus Calmette-Guerin-refractory or relapsed non-muscle-invasive bladder cancer: a phase ii randomized study. J Clin Oncol Off J Am Soc Clin Oncol. 2017;35:3410–6. https://doi.org/10.1200/JCO.2017.72.3064.
55. Gofrit ON, Benjamin S, Halachmi S, Leibovitch I, Dotan Z, Lamm DL, et al. DNA based therapy with diphtheria toxin-A BC-819: a phase 2b marker lesion trial in patients with intermediate risk nonmuscle invasive bladder cancer. J Urol. 2014;191:1697–702. https://doi.org/10.1016/j.juro.2013.12.011.
56. Annels NE, Mansfield D, Arif M, Ballesteros-Merino C, Simpson GR, Denyer M, et al. Viral targeting of non-muscle invasive bladder cancer and priming of anti-tumour immunity following intravesical Coxsackievirus A21. Clin Cancer Res. 2019. https://doi.org/10.1158/1078-0432.CCR-18-4022.
57. Steinberg GD, Shore ND, Karsh LI, Bailen JL, Bivalacqua TJ, Chamie K, et al. Immune response results of vesigenurtacel-l (HS-410) in combination with BCG from a randomized phase II trial in patients with non-muscle invasive bladder cancer (NMIBC). J Clin Oncol. 2017;35:319. https://doi.org/10.1200/JCO.2017.35.6_suppl.319.
58. Donin NM, Chamie K, Lenis AT, Pantuck AJ, Reddy M, Kivlin D, et al. A phase 2 study of TMX-101, intravesical imiquimod, for the treatment of carcinoma in situ bladder cancer. Urol Oncol. 2017;35:39.e1–7. https://doi.org/10.1016/j.urolonc.2016.09.006.
59. Kowalski M, Guindon J, Brazas L, Moore C, Entwistle J, Cizeau J, et al. A phase II study of oportuzumab monatox: an immunotoxin therapy for patients with noninvasive urothelial carcinoma in situ previously treated with bacillus Calmette-Guérin. J Urol. 2012;188:1712–8. https://doi.org/10.1016/j.juro.2012.07.020.
60. Uchibayashi T, Koshida K, Kunimi K, Hisazumi H. Whole bladder wall photodynamic therapy for refractory carcinoma in situ of the bladder. Br J Cancer. 1995;71:625–8. https://doi.org/10.1038/bjc.1995.122.
61. Nseyo UO, Dougherty TJ, Boyle DG, Potter WR, Wolf R, Huben R, et al. Whole bladder photodynamic therapy for transitional cell carcinoma of bladder. Urology. 1985;26:274–80.
62. Raby SEM, Choudhury A. Radiotherapy for high-grade T1 bladder cancer. Eur Urol Focus. 2018;4:506–8. https://doi.org/10.1016/j.euf.2018.07.017.
63.•• Kamat AM, Sylvester RJ, Bohle A, Palou J, Lamm DL, Brausi M, et al. Definitions, end points, and clinical trial designs for non-muscle-invasive bladder cancer: Recommendations From the International Bladder Cancer Group. J Clin Oncol. 2016. https://doi.org/10.1200/JCO.2015.64.4070. **An important paper highlighting standardized trial methodology in this space.**