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Current Strategies in Non-Muscle Invasive Bladder Cancer (NMIBC)

Alabama Urology Network
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Perdido Beach, AL

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Disclosures

- Consultant to UroGen Pharma Inc.
- NCCN Guideline Member – bladder and penile cancer
- Site PI for multiple ongoing NMIBC studies

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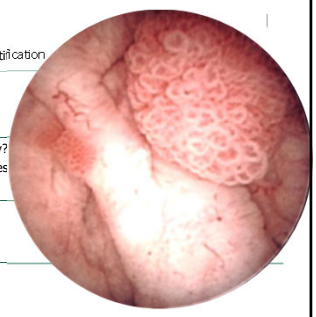
Outline

Introduction	Epidemiology Definitions and Risk Stratification
Guideline Review	AUA/SUO EUA NCCN
BCG Naïve Therapy	Ideal intravesical therapy? BCG History/Controversies Trial Opportunities
BCG Unresponsive Options	Intravesical Chemotherapy Immune checkpoint inhibitors Gene based therapy Targeted therapy
What's on the Horizon?	Clinical Trials



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NMIBC Basics and Epidemiology

- **NMIBC represents 75% of 82,000 new cases of bladder cancer diagnosed in 2023**
- **Males > Females at 3:1**
- **Bladder cancer is the 4th most common malignancy in men**
- **16,700 bladder cancer related deaths in 2023**

NMIBC Prognosis

- **NMIBC cancer specific survival is favorable**
  - **70-85% 10-year cancer specific survival (CSS) for high grade disease**
- **Rate of recurrence and progression are important endpoints**
- **NMIBC is quite <u>heterogenous</u>**
  - **TaLG = 55% recurrence, 6% progression**
  - **T1HG = 45% recurrence, 17% progression to MIBC**
- **<u>Risk Stratification is Critical</u>**

Natural history of NMIBC

Characterized by frequent *recurrence* and possible *progression*.

Recurrence due to local persistence, field effect/stem cells, and implantation.

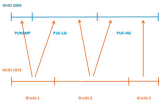
Prognosis dependent on a variety of factors including grade, stage, multifocality, size, prior therapies, etc.

Prognostic calculators can be used to better quantify recurrence risk. (AUA, EORTC[1], CUETO).

HGT1 and BCG-unresponsive HG NMIBC represent significantly "riskier" tumors where cystectomy and clinical trials should be heavily considered.

The regrading scheme by WHO in 2004 makes older data harder to apply to today's scheme and overestimates current risk of HGT1 tumors.

Classification WHO 2004



Classification WHO 1973

Soukup Eur Uro 2017

EORTC risk calculator

Lowest risk scenario		Highest risk scenario	
Number of tumors	Single	Number of tumors	8+
Tumor diameter	< 3 cm	Tumor diameter	> 3 cm
Prior recurrence rate	primary	Prior recurrence rate	> 1 recurrence / year
Stage of the disease	Ta	Stage of the disease	T1
Concomitant CIS	No	Concomitant CIS	Yes
Tumor grade	G1	Tumor grade	G3
Recurrence points	0	Recurrence points	17
Probability of recurrence at 1 year	15 %	Probability of recurrence at 1 year	61 %
Probability of recurrence at 5 years	31 %	Probability of recurrence at 5 years	78 %
Progression points	0	Progression points	23
Probability of progression at 1 year	0.2 %	Probability of progression at 1 year	17 %
Probability of progression at 5 years	0.8 %	Probability of progression at 5 years	45 %

This calculator used pts from 7 different clinical trials investigating intravesical chemo adjuvant therapies.

Thus, this is NOT a natural history risk calculator.

Done before 2004 WHO. Seems to overestimate progression risk for HGT1.

In a pt with prior LG tumor and papillary recurrence, the likelihood of LG again is…90%.

From Sylvester et al, *Eur Urol* 2006

Jad Ferguson, UAB Grand rounds 4/13/21

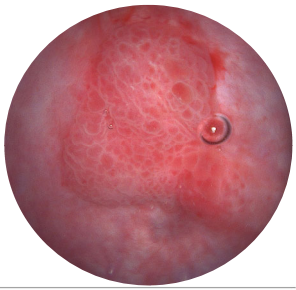
NMIBC Risk Stratification

	AUA/SUO Guidelines	EAU Guidelines
Low Risk	LG solitary Ta ≤ 3 cm	A primary, single, TaT1 LG/G1 tumour < 3 cm in diameter without CIS in a patient ≤ 70 years
	Papillary urothelial neoplasm of low malignant potential (PUNLMP)	A primary Ta LG/G1 tumour without CIS with at most ONE of the additional clinical risk factors
Intermediate Risk	Recurrence within 1-year, low grade Ta Solitary low-grade Ta >3 cm Low grade Ta, multifocal High grade Ta, ≤3 cm Low grade T1	Patients without CIS who are not included in either the low-, high-, or very high-risk groups
High Risk	High grade T1 Any recurrent, high-grade Ta High grade Ta, >3 cm (or multifocal) Any CIS Any BCG failure in high grade case Any variant histology Any lymphovascular invasion (LVI) or prostatic urethral involvement	All T1 HG/G3 without CIS, EXCEPT those included in the very high-risk group All CIS patients, EXCEPT those included in the very high-risk group <u>Stage, grade with additional clinical risk factors:</u> • Ta LG/G2 or T1G1, no CIS with all 3 risk factors • Ta HG/G3 or T1 LG, no CIS with at least 2 risk factors • T1G2 no CIS with at least 1 risk factor
Very High Risk		<u>Stage, grade with additional clinical risk factors:</u> • Ta HG/G3 and CIS with all 3 risk factors • T1G2 and CIS with at least 2 risk factors • T1 HG/G3 and CIS with at least 1 risk factor • T1 HG/G3 no CIS with all 3 risk factors

***EUA Additional clinical risk factors are: age > 70; multiple papillary tumors; and tumor diameter > 3 cm.

Predictors of Recurrence and Progression

- High Grade lesions
- Multifocality
- Large tumor size
- Prior recurrences
- Presences of CIS



Intermediate Risk Heterogeneity

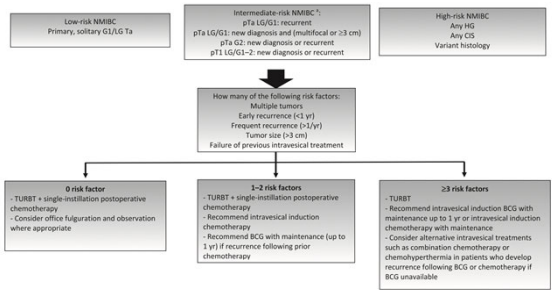
- **Critical for Clinical trial development**
- **Intermediate risk NMIBC cases can be subdivided according to:**
  - **Multiple tumors**
  - **Early recurrence < 1 year**
  - **Frequency of recurrences (>1 per year)**
  - **Tumor size > 3 cm**
  - **Failure of prior intravesical treatments**

	1- year recurrence probability	5-year recurrence probability	1- year progression probability	5-year progression probability
0 risk factors	19.5 %	38.5	0.6	3.4
1-2 risk factors	42.5 %	62	3	11.5
≥ 3 risk factors	61 %	78	5	17

- **Favorable intermediate risk: no risk factors**
- **Unfavorable intermediate risk: ≥ 3 risk factors**
- **Recommend tailoring treatment accordingly**

Tan et al Eur Urol Onc 5 (2022)

Intermediate Risk – Risk adapted approach



Tan et al Eur Urol Onc 5 (2022)

Natural History of T1HG Urothelial Carcinoma

- Recur in up to 50-80%
- Progress in up to 50% at 5 years.
  - Possible overestimate on new data
- Understaging
  - Re-TUR data. (20-40% cT2 on re-resection).
  - 10-15% N+ at cystectomy.
- Risk factors
  - concomitant CIS
  - Residual HGT1 on re-resection
  - Variant histology/LVI
  - Multifocal
  - Refractory tumor at 3-mo surveillance

Disease Specific Survival

T1 HG = cT3b, Gleason 5+5, 12/12 Positive Cores, PSA 75

Based on MSKCC Nomogram

For reference, 5-year CSS = 90%

Ferguson and Kamat. Urol Oncol. 2018 Feb;36(2):39-42.2017 Nov 20.

Herr *J Urol*, 2000
Dutta *J Urol* 2001
Bianco *Urol Oncol* 2004

Defining BCG Failure

Classification	Description
BCG refractory	Persistent high-grade disease at 6 months after adequate induction and maintenance therapy* or any stage/grade progression by 3 months after the first BCG cycle. Example: recurrent high-grade disease at 3 months after initial Ta/T1 high-grade or CIS
BCG relapsing	Recurrent high-grade disease after achieving a disease-free state of ≥ 6 months after adequate* BCG induction and maintenance therapy. Early relapse: <12 months; Intermediate relapse: 12-24 months; late relapse: >24 months
BCG unresponsive	BCG refractory and BCG relapsing disease as described occurring within 6 months of last BCG exposure for patients on maintenance therapy. These patients are at highest risk for recurrence and progression.
BCG intolerant	Disease persistence due to patient intolerance of adequate BCG*
***Adequate BCG induction is defined as when patients have received at least five of six planned induction intravesical treatments and at least two additional doses (as part of maintenance therapy or repeat induction BCG).**	

Kamat et al. 2016 JCO

BCG Unresponsive – HIGHEST risk for recurrence or progression

Must meet at least ONE of the following criteria

1. **Persistent or recurrent carcinoma in situ with or without non–muscle-invasive papillary disease within 12 mo of completion of adequate BCG therapy**
2. **Recurrent high-grade Ta/T1 tumor within 6 mo of completion of adequate BCG therapy**
3. **High-grade T1 disease at the first evaluation following BCG induction**

*Adequate BCG induction is defined as when patients have received at least five of six planned induction intravesical treatments and at least two additional doses (as part of maintenance therapy or repeat induction BCG).

- **HIGHEST risk for recurrence and progression**
- **Clinical trial design considered successful if complete response of 40-50% at 6 months and durable response of 30% at 18 months!**

Jarow JP, Lerner SP, Kluetz PG, Liu K, Sridhara R, Bajorin D, Chang S, Dinney CP, Groshen S, Morton RA, O'Donnell M, Quale DZ, Schoenberg M, Seigne J, Vikram B. 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 Feb;83(2):262-4. doi: 10.1016/j.urology.2013.10.030. Epub 2013 Dec 12. PMID: 24332121.

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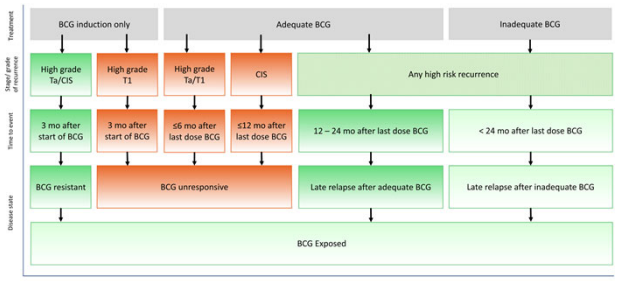
NMIBC Recurrence after BCG Treatment Definitions for Clinical Trial Design



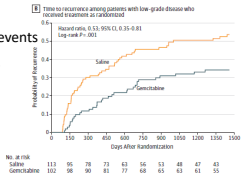
Roumiguié M, Kamat AM, Bivalacqua TJ, Lerner SP, Kassouf W, Böhle A, Brausi M, Buckley R, Persad R, Colombel M, Lamm D, Palou-Redorta J, Solsona M, Brothers K, Steinberg G, Lotan Y, Sylvester R, Alfred Witjes J, Black PC. International Bladder Cancer Group Consensus Statement on Clinical Trial Design for Patients with Bacillus Calmette-Guérin-exposed High-risk Non-muscle-invasive Bladder Cancer. Eur Urol. 2022 Jul;82(1):34-46. doi: 10.1016/j.eururo.2021.12.005. Epub 2021 Dec 23. PMID: 34955291.

NMIBC AUA/SUO Guideline Review

- **TaHG suspected incomplete resection or high-risk, high grade Ta Tumors**
  - **CONSIDER repeat TURBT**
- **T1HG → repeat TURBT within 6 weeks**
- **Known Low risk or Intermediate risk NMIBC → consider single dose postop chemotherapy (no perforation)**
- **Intravesical Therapy**
  - **LOW RISK → NO intravesical therapy**
  - **INTERMEDIATE RISK → Induction BCG + 1 year maintenance**
  - **HIGH RISK → Induction BCG + 3 years maintenance therapy**
    - SWOG 8507 protocol: Maintenance: 3, 6, 12, 18, 24, 30 and 36 months after induction

Primary (BCG Naïve) PostOp Intravesical Therapy

- Postop intravesical therapy for low-risk NMIBC
- Gemcitabine (2 g/100 ml saline)
  - 406 patients randomized control trial
  - 47% risk reduction vs placebo
    - HR 0.54 (95% CI 0.35-0.81), No difference in adverse events
- Absolute risk reduction of recurrence is 14% at 5 yrs
- TURBT alone vs TURBT + intravesical therapy
  - 12 months: 20 vs 10% recurrence
  - 24 months: 25 vs 15% recurrence



- Gem is well tolerated and less expensive than MMC

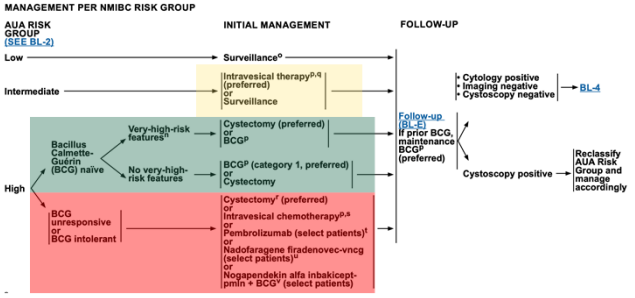
Messing et al. 2018, JAMA

Optimal BCG Induction and Maintenance Schedule (BCG naïve)

- SWOG 8507 maintenance BCG immunomodulation improved magnitude and durability of response based on repeat exposure
- Monthly, quarterly and biannual maintenance schedules are no better that induction BCG alone
- Connaught BCG strain more effective in prolonging time to recurrence than TICE for induction alone
- TICE more effective than Connaught for induction + maintenance
- BCG vs BCG + interferon-alpha – data not robust enough to recommend for induction or maintenance

Akaza et al 1995, Cancer. Badalament et al 1987, JCO. Koga et al. 2010, Int J Urol. Palou et al 2001, J Urol. Sylvester et al. 2010, Eur Urol Duchek et al. 2010, Eur Urol Witjet et al 2017, Uro Onco Shepard et al 2017, Cochrane Syst Rev

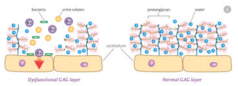
NCCN Guidelines - NMIBC

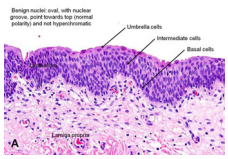


Flaig TW, Spiess PE, Abern M, Agarwal N, Bangs R, Buyyounouski MK, Chan K, Chang SS, Chang P, Friedlander T, Greenberg RE, Guru KA, Herr HW, Hoffman-Censits J, Kaimakliotis H, Kishan AU, Kundu S, Lele SM, Mamtani R, Man OY, Michalski J, Montgomery JS, Parikh M, Patterson A, Peyton CC, Pinnaka SR, Preston MA, Richards K, Sexton WJ, Steffan-Radtke AO, Stewart T, Sundi D, Tollefson M, Tward J, Wright JL, Cassara CJ, Gurski LA. NCCN Guidelines® Insights: Bladder Cancer, Version 3.2024. J Natl Compr Canc Netw. 2024 May;22(4):216-225. doi: 10.6004/jnccn.2024.0024. PMID: 38754471.

Why intravesical therapy?

- **No first-pass metabolism**
  - **Allows for lower dose and direct delivery**
- **Glycosaminoglycan (GAG) layer inhibits absorption to basal layer.**
- **No/minimal systemic absorption.**
  - **Localized side effects. Minimal or NO systemic side effects**
- **Pharmacokinetics are challenging**
  - **Dose kinetics and dwell time**
  - **Urothelial absorption**
  - **Urothelium drug exposure**





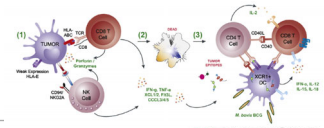
What is the "ideal" intravesical therapy?

- Specific action to cancer cells with few effects on normal cells
- Good bladder penetration without systemic absorption
- Minimal side effects
- Good Efficacy
- Easy to delivery and schedule
- "Cheap"

BCG History and Mechanism

- Attenuated *Mycobacterium bovis*
- Developed as *MTb* vaccine in the early 1900s by Albert Calmette and Camille Guérin at Pasteur Institute in Lille, France.
- BCG first used in cancer therapy as intradermal injection into melanoma with 65% regression. Subsequently tested in multiple tumor types, with bladder cancer emerging as ideal.
- Dose and timing is arbitrary and based on historic trial/error work
- BCG induces an inflammatory response in the innate immune system (NK cells/monocytes)

- "Trained immunity", whereby microscopic tumor cells are non-specifically targeted.
- Cooperation of adaptive immune system and CD4+ Tcells
- No long-lasting tumor specific antigens produced
- Requires repeat exposure



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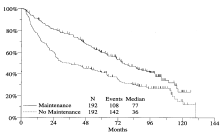
BCG Effectiveness

- BCG induction vs repeat TURBT
- Estimated net benefit 33-40%
- Recurrence common (40% at 2 years)

- **BCG is historically effective that intravesical chemo for preventing recurrence**
- **Several randomized trials**



Median RFS = 6 years for most responders
Historic data.

Reference	% BCG	% Thiotepa	% Doxorubicin	%MitomycinC	pValue
Brosman	0	47	–	–	<0.01
Netto et al	7	43	–	–	<0.01
Martinez - Pineiro et al	13	36	43	–	<0.01
Lamm et al	63	–	83	–	<0.02
DeBruyne et al	30	–	–	25	NS
Juahianen et al	28	–	–	62	<0.01
Rubben et al	35	–	–	35	NS
Wittes	29	–	–	26	NS
Lamm et al	20	–	–	33	<0.01

Lamm et al: J Urol 163: 1124, 2000

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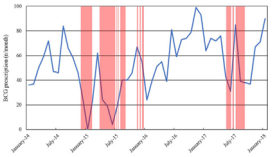
BCG Limitations

- **Only 40% effective at 2-years**
- **Production and availability LIMITATIONS**
  - **Chronic problem**
  - **MERCK is sole US producer of TICE**
  - **Other strains not commercially available**
  - **Follow AUA, NCCN, LUGPA recommendations during BCG shortage**
    - **Prioritization and dose reduction**
- **Tolerance is problematic**



Numbers of Bacillus Calmette–Guerin (BCG) prescriptions per month. The shaded area represents BCG shortages identified through the medical records.

Lee, et al, *Urol Onc* 2020

McElree IM, et al. J. Urology 2022 Sep 1;208(3):589–99

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No BCG . . . What are my non-BCG options?

- Note, most studies in the BCG failure setting, not BCG Naive
- Intravesical chemotherapy – all "off label"
  - Valrubicin
  - Epirubicin
  - Mitomycin
  - Gemcitabine
  - Docetaxel
  - Sequential mitomycin and gemcitabine
  - Sequential gemcitabine and docetaxel
- Referral?
- Clinical Trial ?

Most studies looking at chemotherapy are in the BCG failure, salvage setting

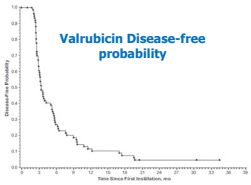
McElree IM, et al. J. Urology 2022 Sep 1;208(3):589–99

Conventional Intravesical Chemotherapy

- Mitomycin
  - Previously most common option. Significant toxicity and less effective that BCG.
  - BCG vs mitomycin prospective comparison reports 19% 3-year disease free survival in 21 patients (Malmstrom et al. 1999, J Urol)
- Valrubicin
  - Only FDA approved drug for BCG-refractory CIS
  - 21% complete response rate at 3 and 6 months
    - —ONLY 9% disease free and 4% response rate
  - NOT effective for T1 disease
  - Rarely used, **NOT recommended**

Steinberg et al 2000, J Urol. Dinney et al 2013, Urol Oncol.

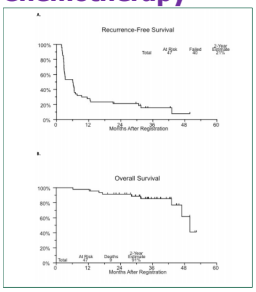
Valrubicin Disease-free probability



Alternative Intravesical Chemotherapy

Gemcitabine

- Phase III study: Gemcitabine vs mitomycin (120 patients)
  - At 36 months: 72 vs 61% recurrence free
- Phase II gemcitabine vs 2nd cycle BCG (80 patients)
  - 2-year recurrence free survival 19%
- Phase II SWOG S0252 study for patient having failed 2 cycles BCG (58 patients)
  - 2-year disease free survival rate of 21% and 36% progression/cystectomy rate



Addeo et al 2010, JCO; Di Lorenzo et al 2010, Cancer; Skinner et al 2013, J Urol.

Alternative Intravesical Chemotherapy

Docetaxel

- Phase I trial 18 patients with BCG failure
  - CR in 56% and 4 year durable response at 22%
- Additional 36 patients
  - Monthly maintenance for 1 year
  - 3 year recurrence free survival 25%
  - 69% of patients avoided cystectomy at 2 years

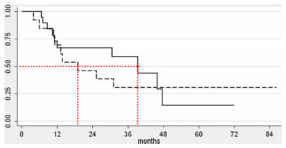


Figure 3. Recurrence-free survival in initial responders with maintenance (solid curve) vs no maintenance (dashed curve). Median recurrence-free survival was 39.3 vs 19.0 months in 19 patients on maintenance vs 13 without maintenance ($p > 0.05$).

Laudano et al 2010, J Urol.; Barlow et al. 2013, J Urol.

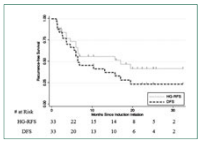
Alternative Intravesical Chemotherapy

Gemcitabine + docetaxel (Iowa)

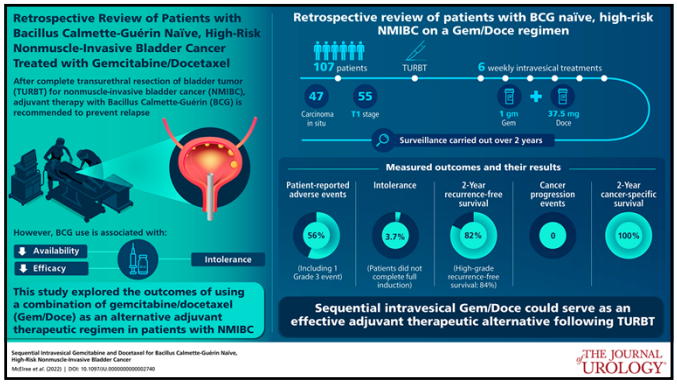
- 45 patients BCG failure patient treated with 1g gemcitabine/50ml saline followed by 37.5mg docetaxel in 50 ml saline.
  - Induction 6 weeks + monthly maintenance
- Median follow up 15 months
- 5 patients unable to tolerate induction
- 28 patients had symptoms and 7 delayed scheduled treatment
- 54% response rate at 1 year
- 34% response rate at 2 years

Gemcitabine + docetaxel (Hopkins)

- 33 patients 2011-2016, BCG unresponsive or intolerant
- 52% recurred with HG disease, 8% with LG disease
- 1-year HG-RFS 56% and 2-year HG-RFS 42%



Velacer et al 2016, Curr Urol Rep; Milbar et al 2017; Bladder Cancer.

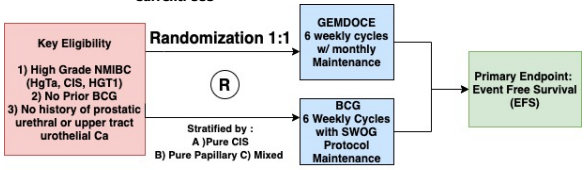


EA8212 BRIDGE: A Phase 3 Trial of BCG Randomized to Intravesical Docetaxel and GEmcitabine for BCG Naïve Non-Muscle Invasive Bladder Cancer – (BRIDGE)

Max Kates – Study Chair
Angie Smith –PRO Co-Chair
Eugene Pietzak –TM Co-Chair
Noah Hahn—ECOG Bladder Chair
Claire Chu–Study Statistician

Objective: To assess whether event-free survival is non-inferior for GemDoce vs. standard BCG for patients with BCG naive high grade NMIBC

EA8212 BRIDGE: N=870
Current: 553



ECOG-ACRIN cancer research group
UAB Department of Urology
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BCG Unresponsive NMIBC

FDA defined BCG unresponsive designation has spurred development of novel bladder sparing therapy

Off Label intravesical chemotherapy:
Single agent: Gemcitabine, taxanes, hyperthermic MMC
Gem/Doce

Recent FDA approval of three drugs:
Pembrolizumab
Nadofaragene firadenovec
Nogapendndekin alfa inbakicept-pmln

Many exciting drugs and trials on the horizon!

CG ONCOLOGY
janssen Oncology
FERRING PHARMACEUTICALS
ADSTILADRIN®
Anktiva® (nogapendekin alfa inbakicept-pmln)
ImmunityBioCARE
UroGen Pharma

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BCG Unresponsive NMIBC – *Single Agent: Gemcitabine*

Presence of CIS tumors	DFS at 12 months	DFS at 24 months
CIS predominant (n=155)	24%	17%
CIS non predominant (n= 273)	67%	37%
No CIS (n=138)	72%	61%
P-values	<0.001	<0.001

DFS: disease free survival; CIS: carcinoma in situ

Li et al. European Urology Aug. 2024

Table adapted from: Abou Chakra M, Packiam VT, O'Donnell MA. Real-world efficacy of adjuvant single-agent intravesical gemcitabine for non-muscle invasive bladder cancer. Expert Opin Pharmacother. 2023;24(18):2081-2091.

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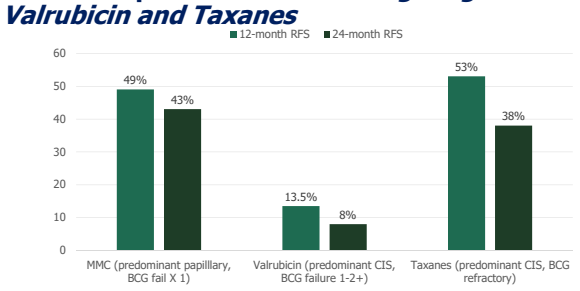
BCG Unresponsive NMIBC – *Single Agent: MMC, Valrubicin and Taxanes*



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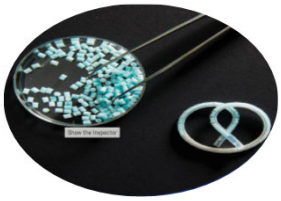
BCG Unresponsive NMIBC – *Single Agent Intravesical Chemo*

- **BOTTOM LINE: Single agent intravesical chemotherapy has limited efficacy in patients with BCG-unresponsive NMIBC, particularly for papillary only disease.**
- **What's next??**
- **SunRise-1 (Janssen)**
- **TAR-200 monotherapy (gemcitabine)**
  - **3 month CR at 73%**
  - **Overall CR at anytime: 83%**



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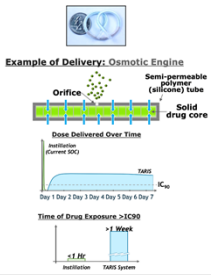
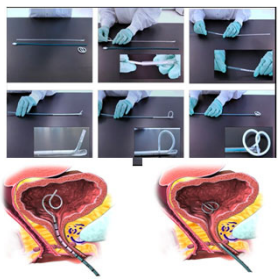
TAR-200 – intravesical gemcitabine osmotic dose release





Images from Janssen TAR-200 Vison Presentation

janssen Oncology

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BCG Unresponsive NMIBC – *Combination Chemotherapy*

- **Intravesical <u>Gemcitabine + Docetaxel</u> (GEM/DOCE)** has emerged as the basic "standard" therapy for patients BCG-U NMIBC ineligible or refusing cystectomy
- **INDUCTION: 6 weeks**
- **MAINTEANCE: monthly for 6 to 24 months**

	12-month RFS	24-month RFS
"any CIS"	56%	40%
Papillary only	61%	50%

<u>ADVANTAGES</u>:

- **EASY (sorta)**
- **Reasonably well tolerated**
- **CHEAP!**
- **Monthly maintenance**

<u>DISADVANTAGES</u>:

- **NO RAMDOMIZED TRIALS**
- **No comparative trials**
- **Can be difficult with hospital/clinic regulations**
- **Reimbursement - ???**

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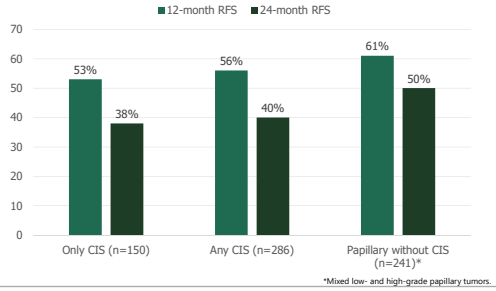
BCG Unresponsive NMIBC – *GEM/DOCE*



*Mixed low- and high-grade papillary tumors.

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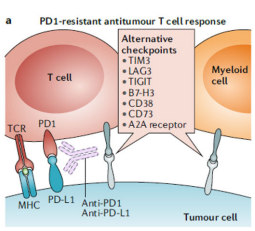
BCG Unresponsive NMIBC – *Immune Checkpoint Inhibitors (ICI)*

- **<u>Pembrolizumab</u> – KEYNOTE-057 trial**
  - first ICI approved by FDA (2020) for BCG-U CIS
  - 3-month CR: 41%, durable response at 16.2 months
  - 18-month CR: 13.5%
  - 3-year cystectomy rate: 49%
  - Toxicity: 13% grade 3-4
    - 11% stopped therapy due to toxicity
- **<u>Atezolizumab</u> – SWOG S1605 stopped due to failure to meet futility**
  - 3-month CR: 43%
  - 12-months CR: 25%
  - 18-month CR: 13.5%



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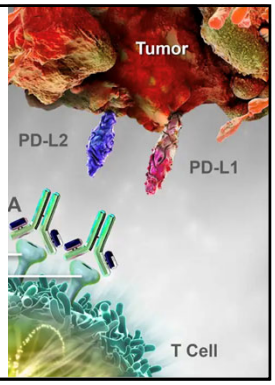
Pembrolizumab (Keytruda)

- PD-1 PD-L1 inhibition
- Only FDA approved mediation for BCG-U NMIBC
- Modest efficacy, significant AEs
- Durability is questionable
- Implications for future combination ICI or ICI + intravesical therapy
- Most appropriate for patients for whom safter alternative treatment options have been exhausted

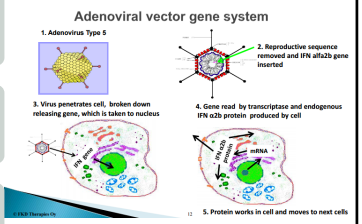


BCG Unresponsive NMIBC – *Gene-based Therapies*

Viral vector intravesical drug delivery

Delivers copy of human gene to urothelial cells

Translational changes to protein expression



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Nadofaragene Firadenovec – Adstiladrin®

- **Replication-deficient recombinant adenovirus vector-based delivery of human IFNα-2b**
- **Single-arm Phase III study, BCG-U NMIBC, N = 157 published 2020**
  - Primary endpoint: CR at any time in CIS +/- Ta/T1 cohort
  - 3-month CR: 53%
  - 12-month high-grade disease free: 46%
  - 12-month CR: 23%
  - 5 year follow up recently published
- **FDA approval for high-risk BCG-unresponsive NMIBC with or without papillary tumors**

Boorjian SA *Lancet Onc* 2020

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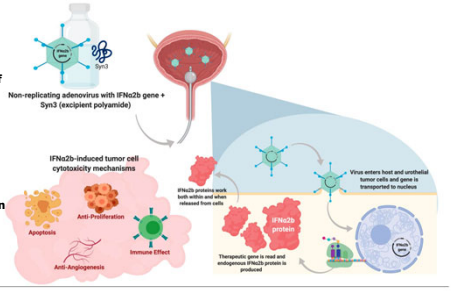
Nadofaragene Firadenovec – Mechanism of Action

- ✓ Intravesical installation of 75 mL at a concentration of 3 x 10^{11} viral particles/mL
- ✓ Quarterly dosing
- ✓ Given in the Urology office
- ✓ No reconstitution of dilution needed



- Narayan and Dinney, *Urol Clin North Am.* 2020;47(1):93-101.

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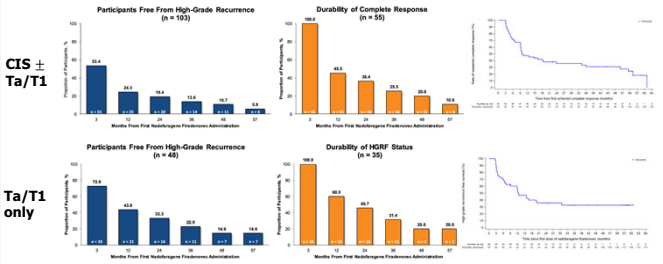
Nadofaragene Firadenovec – Efficacy and Durability



1. Boorjian SA, Alemozaffar M, Konety BR, et al. Intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive non-muscle-invasive bladder cancer: a single-arm, open-label, repeat-dose clinical. Lancet Oncol. 2021;22(1):107-117.
2. Boorjian SA, Narayan VM, Konety BR, et al. Efficacy of intravesical nadofaragene firadenovec for patients with BCG-unresponsive carcinoma in situ of the bladder: 36-month follow-up from a phase 3 trial. Presented at: 26th Annual Meeting of the Society of Urologic Oncology; November 28-December 1, 2023; Washington, DC.

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Nadofaragene Firadenovec – Survival

Cystectomy free survival (CFS) and overall survival (OS)

	Kaplan-Meier Estimate (95% CI)		
	CIS ± Ta/T1 n = 103	HG Ta/T1 n = 48	Total N = 151
CFS rate at month 60[a]	43.2% (32.2-53.7)	58.7% (43.1-71.4)	**48.8%** (40.0-57.1)
OS rate at month 60	76.3% (64.6-84.5)	85.9% (70.9-93.5)	**79.7%** (71.0-86.0)

[a]CFS is the time from the first dose of nadofaragene firadenovec to the first date of cystectomy or death due to any cause.

1. Boorjian SA, Alemozaffar M, Konety BR, et al. Intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive non-muscle-invasive bladder cancer: a single-arm, open-label, repeat-dose clinical. Lancet Oncol. 2021;22(1):107-117.
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Nadofaragene Firadenovec – Adverse Events

	Grade 1 or 2 n (%)	Grade 3 n (%)	Grade 4 or 5 n (%)
Participants with study drug–related AEs	104 (66.2)	6 (3.8)	0
Types of events			
Discharge around the catheter during instillation	39 (24.8)	0	0
Fatigue	31 (19.7)	0	0
Bladder spasm	25 (15.9)	1 (0.6)	0
Micturition urgency	23 (14.6)	2 (1.3)	0
Chills	18 (11.5)	0	0
Dysuria	19 (12.1)	0	0
Pyrexia	16 (10.2)	0	0
Syncope	0	1 (0.6)	0
Hypertension	2 (1.3)	1 (0.6)	0
Urinary incontinence	6 (3.8)	1 (0.6)	0

- **No Grade 4 or 5**
- **2% stopped due to AEs**
- **No new safety signals in the follow up cohort**

1. Boorjian SA, Alemozaffar M, Konety BR, et al. Intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive non-muscle-invasive bladder cancer: a single-arm, open-label, repeat-dose clinical. Lancet Oncol. 2021;22(1):107-117.
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Nadofaragene Firadenovec – Summary

47

Advantages

- At 60 months, bladder preservation achieved in nearly half of all patients and 75% of Ta/TI only
- Well tolerated, minimal side effects
- Convenient dosing pattern

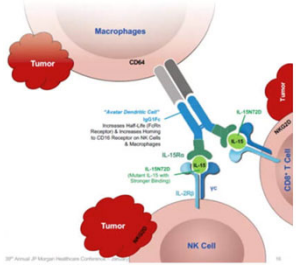
Disadvantages

- Difficulty with production
- New type therapy may pose institutional challenges in adoption
- COST
- **$60,000 PER DOSE!!!!**

1. Boorjian SA, Alemozaffar M, Konety BR, et al. Intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive non-muscle-invasive bladder cancer: a single-arm, open-label, repeat-dose clinical. Lancet Oncol. 2021;22(1):107-117.
2. Boorjian SA, Narayan VM, Konety BR, et al. Efficacy of intravesical nadofaragene firadenovec for patients with BCG-unresponsive carcinoma in situ of the bladder: 36-month follow-up from a phase 3 trial. Presented at: 2005 Annual Meeting of the Society of Urologic Oncology; November 28-December 1, 2023; Washington, DC.

BCG-U NMIBC – *Novel immunotherapy agents*

- **Nogapendekin alfa inbakicept-pmln (NAI or N-803)**
- **Interleukin-15 superagonist – designed to enhance the immune-mediated effects of IL-15 locally and boost response from BCG**
- **Intravesical therapy given with BCG**



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Nogapendkin alfa interleukin-15 – Anktiva®

- **QUILT-3.032 trial – Phase II/III, 77 patients**
  - NAI + BCG for BCG-U NMIBC
  - CR at anytime: 71% (median 26.6 months)
  - CIS +/- Ta/T1 papillary disease
    - Durable response ≥ 12 month: 58%
    - Durable response ≥ 24 months: 40$
  - **Adverse events: Grade 1-2 low, NO grade 4-5**
- **FDA approval for high-risk BCG-unresponsive NMIBC in April 2024**

Chamie & Chang et al NEJM Evid 2022; 2 (1)

Nogapendkin alfa interleukin-15 – Anktiva®

Table 2. Summary of Efficacy in Cohort B.[a]

Response	Value
Median duration of follow-up — mo	20.7
Range of follow-up of all patients — mo	2.9–37.1
Disease-free survival (n=72)	
Median disease-free survival — mo (95% CI)†	19 (bou
Disease-free survival rate — % (95% CI)†	
12 mo	55
18 mo	51
24 mo	48
Progression-free survival rate — % (95% CI)†	
12 mo	97.1 (88.8–99.3)
18 mo	94.8 (84.3–98.3)
24 mo	88.8 (74.1–95.4)
Disease-specific survival — % (95% CI)†	
12 mo	100 (100–100)
24 mo	97.7 (84.6–99.7)
Overall survival — % (95% CI)†	
12 mo	98.6 (90.2–99.8)
18 mo	94.3 (82.9–98.1)
24 mo	91.7 (79.0–96.9)
Cystectomy rate — no. (%)	5 (7)

- 71% CR at 2 years
- 7% cystectomy rate at 2 years
- 100% disease specific survival

Chamie & Chang et al NEJM Evid 2022; 2 (1)

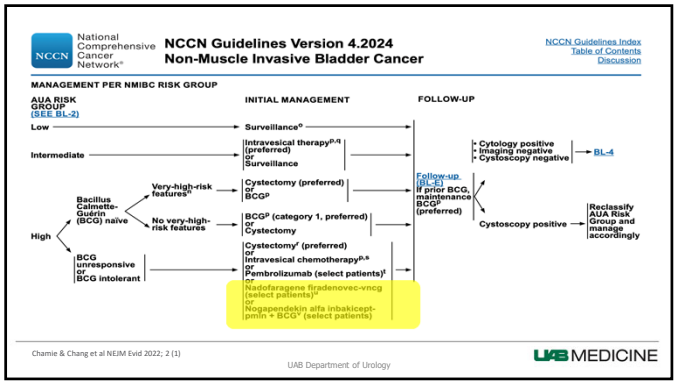
Nogapendkin alfa interleukin-15 – Anktiva®

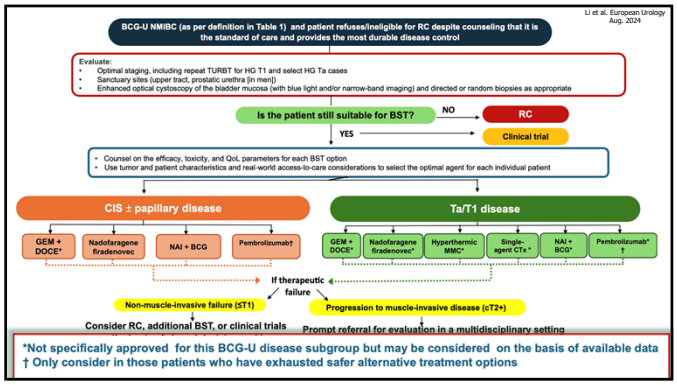
Advantages

- Bladder preservation and response rates are good
- Well tolerated, minimal side effects
- Similar concept to prior combination instillations (INF-α)

Disadvantages

- Requires BCG!
- Data is less mature
- Not as expensive



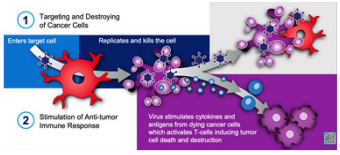


What's next?

- **EG-70 –** nanoparticle formulation of plasmids activating innate and adaptive immune response
- **Targeted Therapy**
  - **Oportuzumab monatox –** monoclonal antibody
  - **Erdafitinib –** selective FGFR inhibitor, only works in tumors expressing FGFR3 mutations.
    - Oral form
    - Intravesical: **TAR-210** – exciting and under investigation
  - **Enfortumab vedotin (EV) –** antibody-drug conjugate targeting Nectin-4
    - Phase 1 investigations of intravesical EV formula ongoing
  - **ABI-009 –** albumin bound rapamycin (m-TOR inhibitor) nanoparticle
- **Photodynamic therapy –** photosensitizing therapy

Cretostimogene Grendaenorepvec

- **Conditionally replicating adenovirus delivery**
- **Oncolytic immunotherapy**
  - Encodes for GM-CSF
  - Insertion of human EE2F-1 promotor
- **Binds to Coxsackie Adenovirus Receptor**
  - Highly immunogenic
- **Viral replication and tumor lysis**



BOND-003 Phase 3 Trial Cretostimogene Monotherapy for BCG-Unresponsive High-Risk NMIBC with CIS[1]

Enrollment Complete (N=116)

Trial Design
- Single-arm, open-label, intravesical administration of cretostimogene monotherapy
- Pathologically confirmed BCG-unresponsive High-Risk NMIBC with CIS +/- TaT1
- Have all TaT1 disease resected prior to treatment
- Mandatory biopsies at 12-month assessment[2]

Dosing Regimen
- **Induction Course:** Weekly x 6
- **Second Induction:** Weekly x 6 for non-responders
- **Maintenance Course:** Weekly x 3 Q3M for Year 1, Weekly x 3 Q6M for Year 2

Endpoints
- CR at any time
- CR at 12-months
- DoR, PFS, RFS

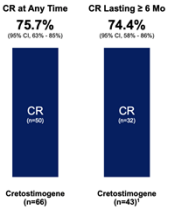
Mark Tyson. Presented at SUO, 12/1/2023 Washington DC

Cretostimogene Grendaenorepvec

FDA Fast Track Designation

First Results From BOND-003: 76% CR at Any Time

74.4% of Responders Maintained Response ≥ 6 Months



Response Evaluation	Cretostimogene Monotherapy %, (n/N)	Confidence Interval (CI)
Complete Response		
Complete Response, Any Time	75.7% (50/66)	95% CI: 63% - 85%
Complete Response, 3 Months	68.2% (45/66)	95% CI: 55% - 79%
Complete Response, 6 Months	63.6% (42/66)	95% CI: 51% - 75%
Duration of Complete Response		
Duration of Response ≥ 3 Months	84.0% (42/50)	95% CI: 70% - 92%
Duration of Response ≥ 6 Months	74.4% (32/43)[1]	95% CI: 58% - 86%

Efficacy data cutoff as of October 5, 2023.

1. Seven patients yet to reach minimum duration of response evaluation and not included in durable CR lasting ≥ 6 months assessment.

Mark Tyson. Presented at SUO, 12/1/2023 Washington DC

TAR–200 – "bladder pretzel"

TAR-200 and Addressing Unmet Needs in Patients With HR NMIBC Unresponsive to BCG Treatment

- SunRISe-1 Is an Ongoing Randomized, Open-Label Phase 2b Study of TAR-200 ± Cetrelimab to Assess Efficacy and Safety in BCG-Unresponsive Patients With NMIBC

- Standard of care for BCG-unresponsive HR NMIBC is radical cystectomy (RC)[1]:
  - RC is a life-changing operation associated with considerable morbidity and impact on quality of life (QoL) and a 90-day mortality risk of up to 8%[2]
  - Many patients are unable or unwilling to undergo RC[1]
- Limited treatment options are available to treat BCG-unresponsive HR NMIBC carcinoma in situ (CIS); 12-month complete response (CR) rates are:
  - 19% with pembrolizumab[3]
  - 15% with atezolizumab[4]
  - 23% with nadofaragene firadenovec[5]

Population:
- Aged ≥18 years
- Histologically confirmed HR NMIBC CIS (with or without papillary disease)
- Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-2
- Persistent or recurrent disease within 12 months of completion of BCG
- Unresponsive to BCG[6,7] and not receiving RC

2:1:1 N=20 Randomization (R) — *Reported here*

- **TAR-200 + cetrelimab[8,9] Cohort 1 (N=55)[7]** — *Cohort 1 was closed*
- **TAR-200 alone[8] Cohort 2 (N=85)** — *Enrollment completed*
- **Cetrelimab[9] alone Cohort 3 (N=28)[7]** — *Cohort 3 was closed*

Cohorts 1-3:
Primary end point
- Overall CR rate

Key secondary end points
- Duration of response
- Overall survival
- Safety
- Tolerability

Population:
- Papillary-only HR NMIBC (no CIS)[8]

- **TAR-200 alone[8] Cohort 4 (N=50)** — *Enrollment was closed*

Cohort 4:
Primary end point
- Disease-free survival (DFS) rate at 12 months

Clinical cutoff date: **January 2,2024**.

Presented at AUA 2023, Chicago, IL

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TAR–200 "bladder pretzel" SunRise-1: BCG-U NMIBC

Characteristics	TAR-200 (N=85)[a]
Age, years, median (range)	71 (40-88)
Sex, male, %	80.0
Race, %	
White	72.9
Asian	9.4
Black or African American	2.4
Not reported/unknown	15.3
Nicotine use, %	
Current	9.4
Former	57.6
Never	32.9

Characteristics	TAR-200 (N=85)[a]
ECOG PS 0, %	91.8
Tumor stage, %	
CIS only	67.1
CIS + papillary disease	32.9
Total doses of prior BCG, n, median (range)	12 (7-42)
Time from last BCG to CIS diagnosis, months, median (range)	3.4 (0-22)[b]
Reason for not receiving RC, %	
Declined	96.5
Ineligible	3.5

Presented at AUA 2023, Chicago, IL

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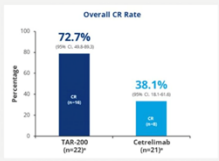
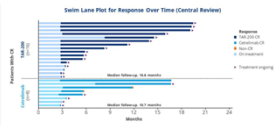
TAR–200 "bladder pretzel" SunRise-1: BCG-U NMIBC

Efficacy of TAR-200 and Cetrelimab Monotherapies: 73% of Evaluable Patients Achieved CR With TAR-200



- CR is based on cystoscopy and centrally assessed urine cytology and biopsy at Weeks 24 and 48



Patients with events, n (%)[a]	TAR-200 (N=23)		Cetrelimab (N=24)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
≥1 AE	21 (91.3)	7 (30.4)	19 (79.2)	2 (8.3)
Micturition urgency	8 (34.8)	0	1 (4.2)	0
Pollakiuria	8 (34.8)	0	0	0
Dysuria	6 (26.1)	0	1 (4.2)	0
Noninfective cystitis	5 (21.7)	1 (4.3)	0	0
Urinary tract infection	5 (21.7)	1 (4.3)	4 (16.7)	0
Pruritus	0	0	5 (20.8)	0
Diarrhea	0	0	5 (20.8)	0

Presented at AUA 2023, Chicago, IL

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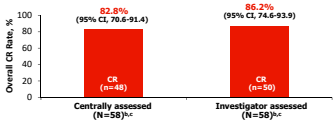
INTRODUCTION | EFFICACY RESULTS (1 OF 2) | EFFICACY RESULTS (2 OF 2) | SAFETY RESULTS | AUTHORS' CONCLUSIONS

TAR-200 Monotherapy: High CR Rate With Rapid Onset and Associated With a Durable Response

CR Rate[a] in Patients With HR NMIBC CIS



Landmark time	Overall CR rate, % (95% CI)
6 months	**75.7** (59.1, 86.3)
12 months	**61.9** (41.4, 77.1)

- 47 of 48 (98%) CRs achieved at the first disease assessment at Week 12

CR rate based on Kaplan-Meier estimate.

Duration of Response (DOR)

- Median follow-up in responders was 29.9 weeks (range, 14-140)
- 48 patients achieved a CR[b,d]
- 41 of 48 (85%) responses were ongoing at clinical cutoff, with 4 of 5 (80%) who completed 2-year treatment remaining in response
- None of the responders progressed to MIBC or metastatic disease
- 1 of 48 (2.1%) responders underwent RC
- Kaplan-Meier estimates for DOR:
  - 6-month DOR rate: 87.0% (95% confidence interval (CI), 69.0-94.9)
  - 12-month DOR rate: 74.6% (95% CI, 49.8-88.4)
  - 18-month DOR rate: 74.6% (95% CI, 49.8-88.4)

CIS, carcinoma in situ; CR, complete response; HR, high-risk; MIBC, muscle-invasive bladder cancer; NMIBC, non–muscle-invasive bladder cancer; RC, radical cystectomy.
[a]Overall CR rate is based on CR at any time. [b]The efficacy analysis was performed on all treated patients who had active disease at baseline and adequate disease assessment postbaseline, or who progressed, died, had been withdrawn from treatment due to the recurrence of high-risk or progressive disease, or discontinued the study. A CR is defined as having a negative cystoscopy and negative (including atypical) centrally read urine cytology or a positive cystoscopy with biopsy-proven benign or low-grade NMIBC and negative (including atypical) centrally read cytology at any time point. [c]2 patients discontinued the study before having a disease evaluation but were included in the denominator of the evaluation of CR rate. [d]Response duration shown for patients with CR (N=48).

TAR–200 "bladder pretzel" SunRise-1: BCG-U NMIBC

- **TAR-200 monotherapy showed a promising overall CR rate of 73% in patients with HR NMIBC unresponsive to BCG**
  - After a median follow-up of 11 months, 15 of 16 responses are ongoing (median DoR was not reached)
  - 6 complete responders maintained their response beyond 12 months
  - None of the complete responders have documented recurrence or progression
- **TAR-200 was well-tolerated**
- TAR-200-related SAEs, grade ≥3 AEs, and discontinuations were infrequent.
- **Cetrelimab monotherapy safety and efficacy profiles were consistent with other anti-PD-L1 treatments in this disease setting**
- **First efficacy and safety data from SunRISe-1 support the ongoing investigation of TAR-200 with or without cetrelimab in patients with BCG-unresponsive HR NMIBC**

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UAB MEDICINE

Bladder Cancer Trials at UAB

- **BCG Naive NMIBC:**
  - **BRIDGE –** phase III, randomized induction **BCG vs GEM/DOCE**
- **BCG-unresponsive NMIBC:**
  - **ALLIANCE A031803 –** phase II intravesical gemcitabine + pembro
- **BCG-U, HR NMIBC BCG naïve or BCG exposed NMIBC**:
  - **enGene Inc**. – Phase I/II, EG-70 nanoparticle DNA plasmid drug. Non-viral gene therapy.
- **MIBC, cis-ineligible or refusing**
  - **SunRise-4 –** Phase III, randomized to cetrelimab vs cetrelimab + TAR-200
  - Enrollment 98% complete

ECOG-ACRIN cancer research group

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

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Thank you!

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