THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

INTERNATIONAL BLADDER CANCER GROUP

High Risk NMIBC: State of the Art

Ashish M. Kamat, MD, MBBS

Professor of Urologic Oncology
Wayne B. Duddlesten Professor of Cancer Research
Director, Bladder Cancer Research
President, International Bladder Cancer Group (IBCG)

Definition of High Risk

INTERNATIONAL BLADDER CANCER GROUP

sitc Society for Immunotherapy of Cancer

International Bladder Cancer Group Risk Categories

Risk Category	Tumor Characteristics	Outcomes
Low Risk	Ta **low grade (LG):** Solitary, primary, ≤3 cm	Low risk of recurrence/progression
Intermediate Risk	Anything that falls between low risk and high risk	Recurrence is main concern
High Risk	Any **HG** (Ta, T1, CIS) Any **T1**	Progression is main concern

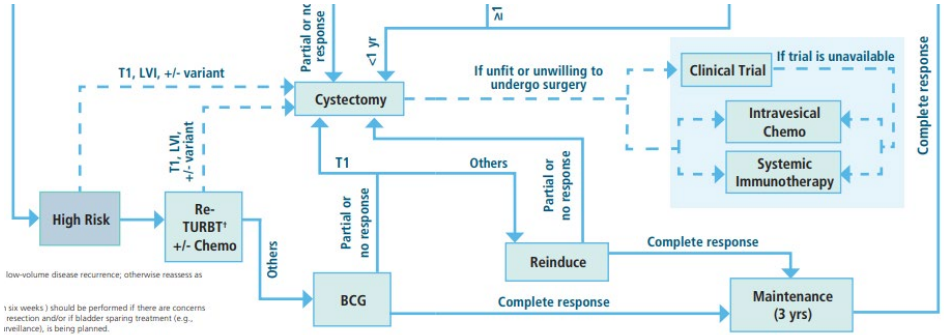
High Risk: 30% progression, ~75% recurrence
Low Risk: < 5% progression, ~45% recurrence

Journal of Clinical Oncology® An American Society of Clinical Oncology Journal

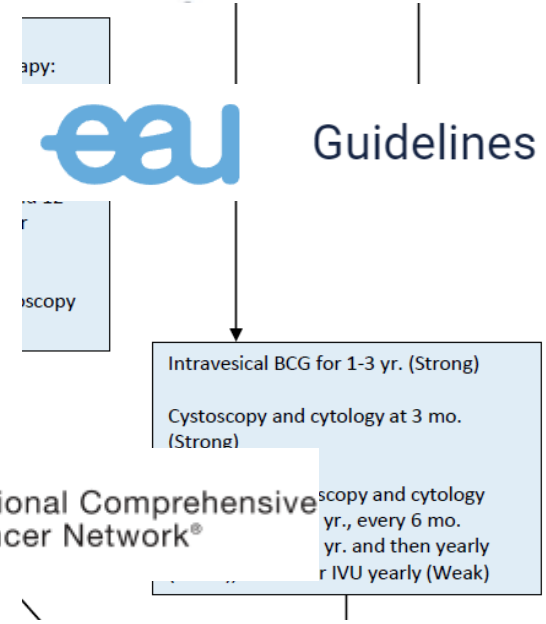
What is the Standard of Care for High Risk NMIBC?

American Urological Association

sitc Society for Immunotherapy of Cancer



eau Guidelines

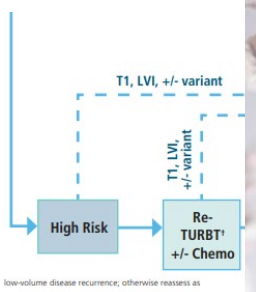


INTERNATIONAL BLADDER CANCER GROUP

NCCN National Comprehensive Cancer Network®

American Urological Asso

sitc Society for Immunotherapy of Cancer



eau

al BCG for 1-3 yr. (Strong)

y and cytology at 3 mo.

scopy and cytology
yr., every 6 mo.
yr. and then yearly
r IVU yearly (Weak)

INTERNATIONAL BLADDER CANCER GROUP

NCCN National Comprehensive Cancer Network®

EUROPEAN UROLOGY 65 (2014) 267–269

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Opinion

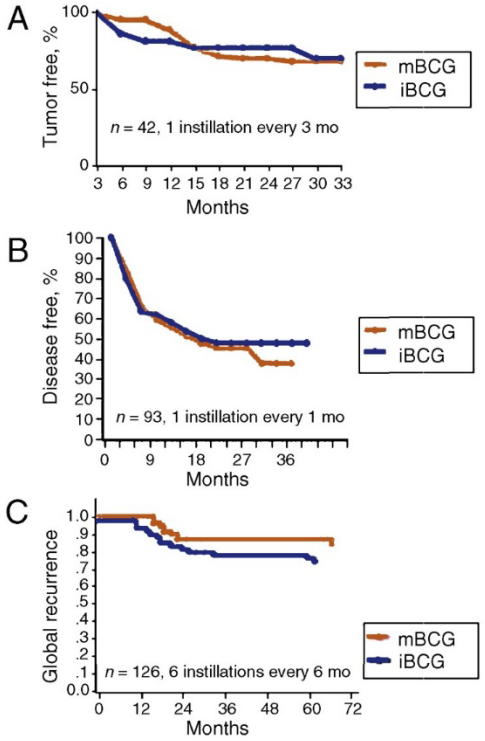
Myths and Mysteries Surrounding Bacillus Calmette-Guérin Therapy for Bladder Cancer

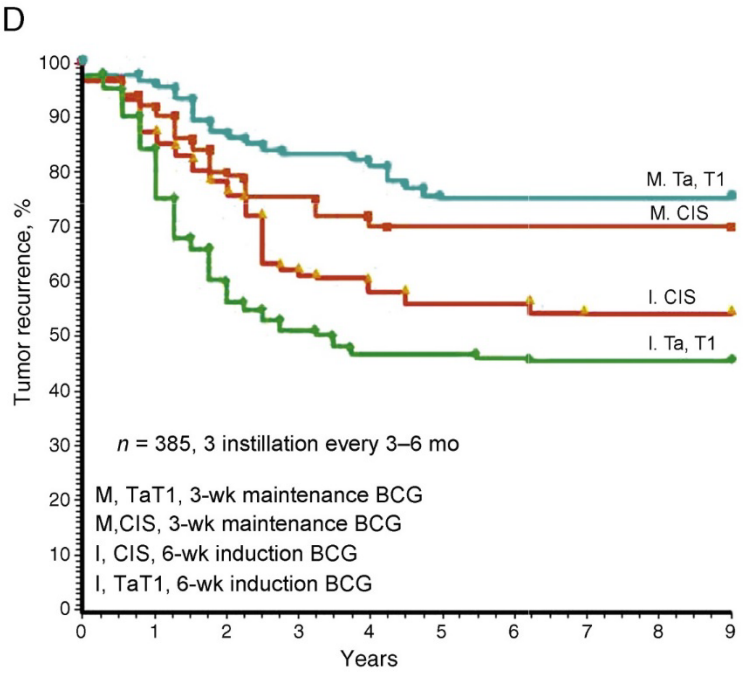
Ashish M. Kamat *, *Sima Porten*

Department of Urology, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

BCG Maintenance: Not Created Equal

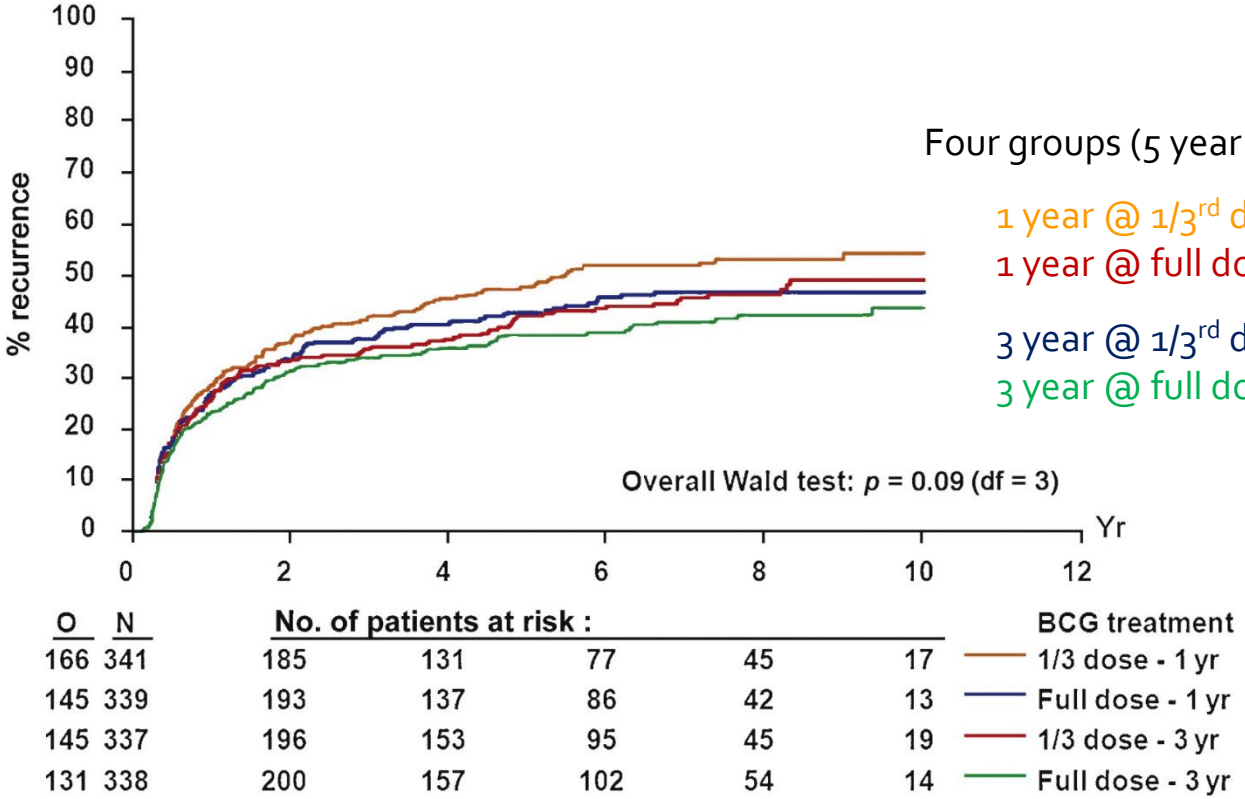
Only SWOG protocol shows clear benefit





Kamat & Porten, Eur Urol, 2014

EORTC30962 – Full Dose vs Low Dose, 1 yr vs 3 yr



Four groups (5 year Disease Free Rates)

1 year @ 1/3rd dose: 54.5%

1 year @ full dose: 58.8%

3 year @ 1/3rd dose: 62.6%

3 year @ full dose: 64.2%

Oddens et al, Eur Urol, 2013

Contemporary Outcomes of Patients with Nonmuscle-Invasive Bladder Cancer Treated with bacillus Calmette-Guérin: Implications for Clinical Trial Design

Justin T. Matulay, Ro
H. Barton Grossman, Ne
…l. Kamat §,‡

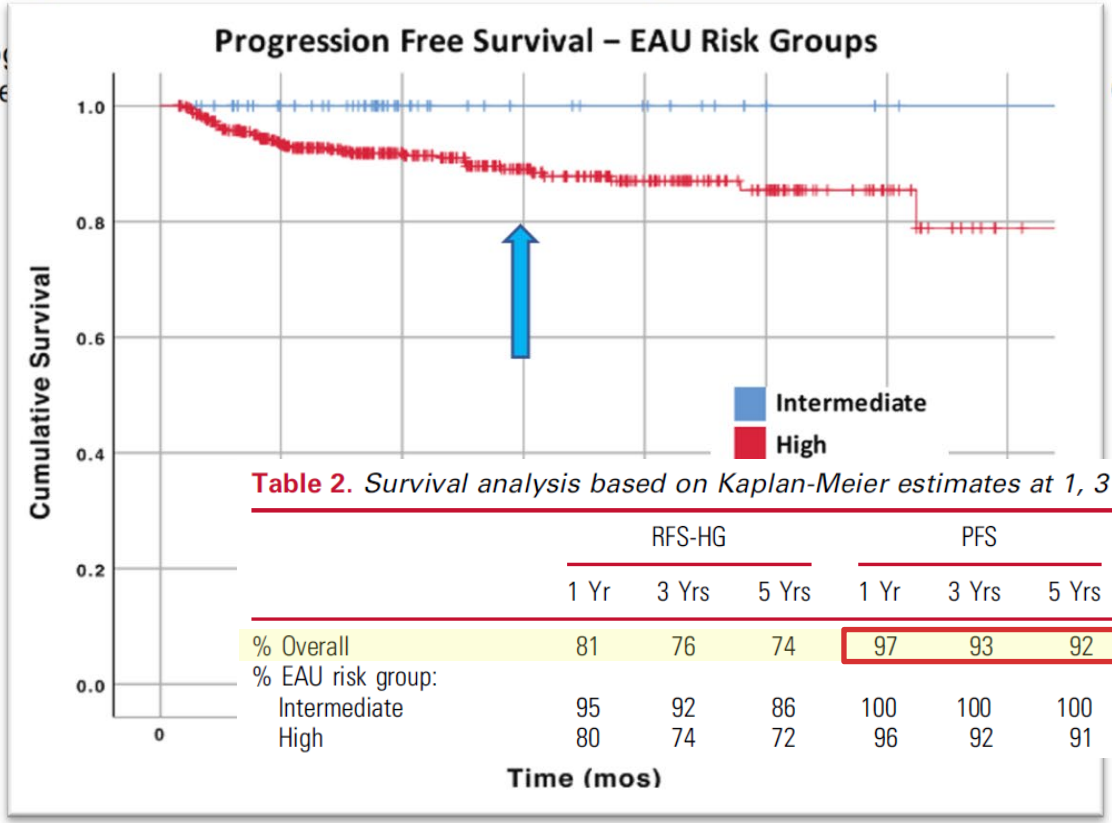
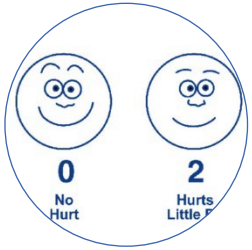


Table 2. *Survival analysis based on Kaplan-Meier estimates at 1, 3 and 5-year time points*

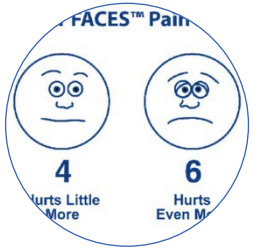
	RFS-HG			PFS			CFS		
	1 Yr	3 Yrs	5 Yrs	1 Yr	3 Yrs	5 Yrs	1 Yr	3 Yrs	5 Yrs
% Overall	81	76	74	97	93	92	95	89	86
% EAU risk group:									
Intermediate	95	92	86	100	100	100	98	96	90
High	80	74	72	96	92	91	95	88	86

Matulay…Kamat, *J Urol*, 2021



BCG Naïve

- (+very late relapse)

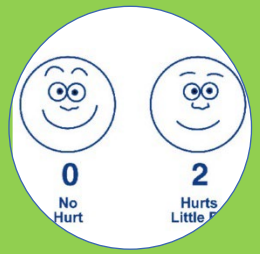


BCG Exposed

- Induction only (Ta, CIS)
- Late Relapse

BCG Unresponsive

- Refractory
- Early Relapse



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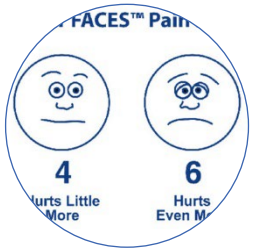

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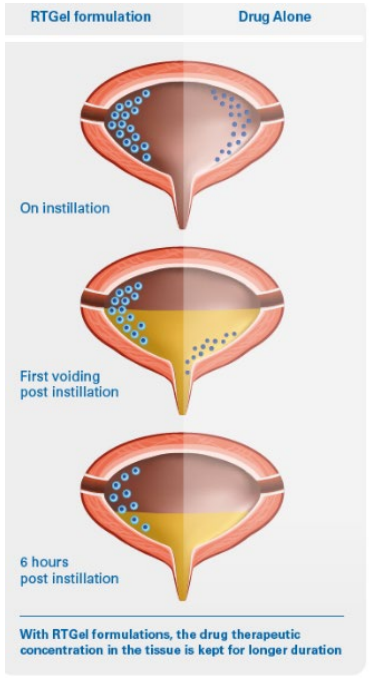
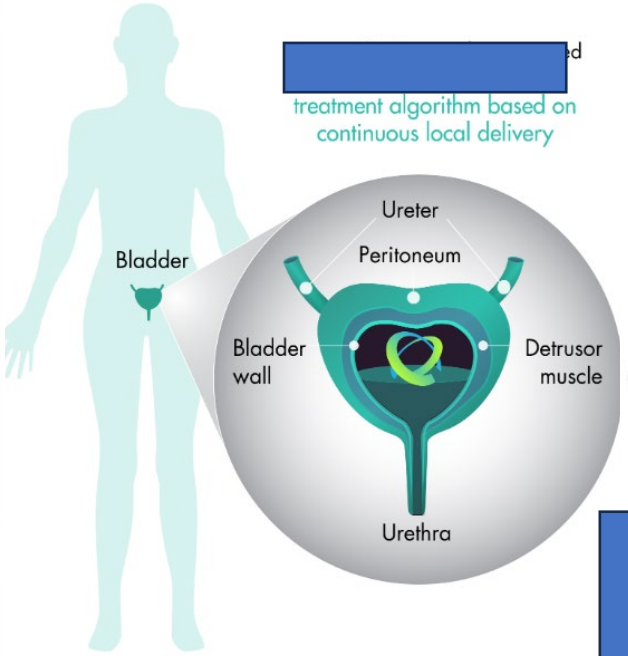
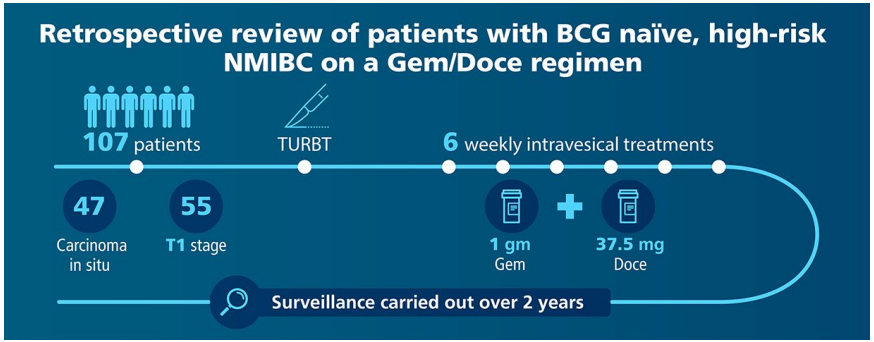
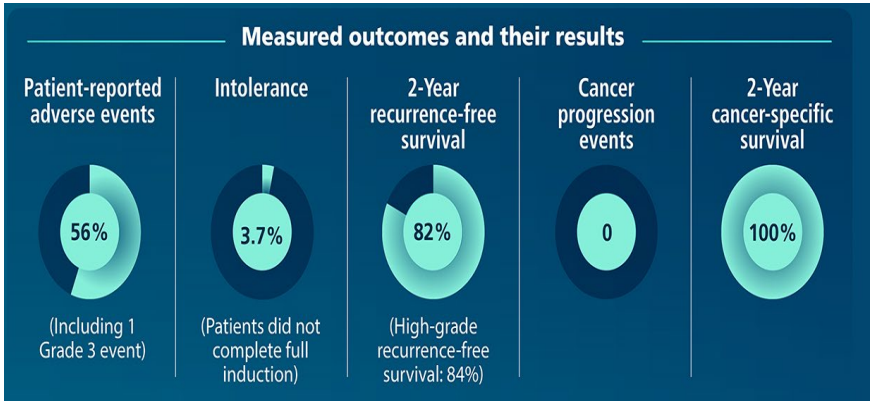

RTGel formulation
Drug Alone
On instillation
First voiding post instillation
6 hours post instillation
With RTGel formulations, the drug therapeutic concentration in the tissue is kept for longer duration

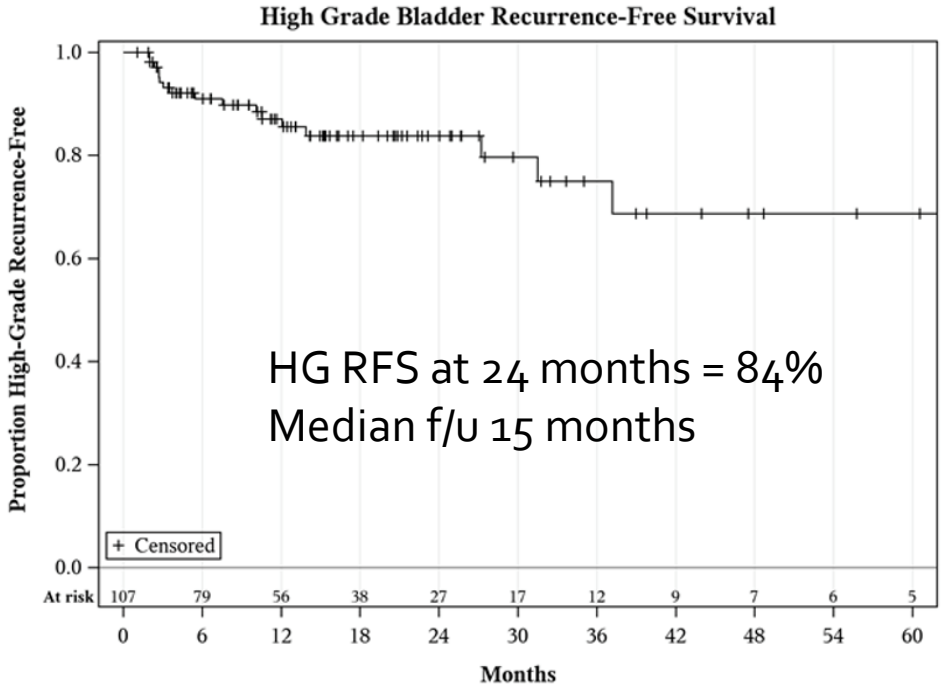

treatment algorithm based on continuous local delivery
Bladder
Ureter
Peritoneum
Bladder wall
Detrusor muscle
Urethra


HIVEC

Sequential Intravesical Gemcitabine and Docetaxel for BCG Naïve High Risk Bladder Cancer

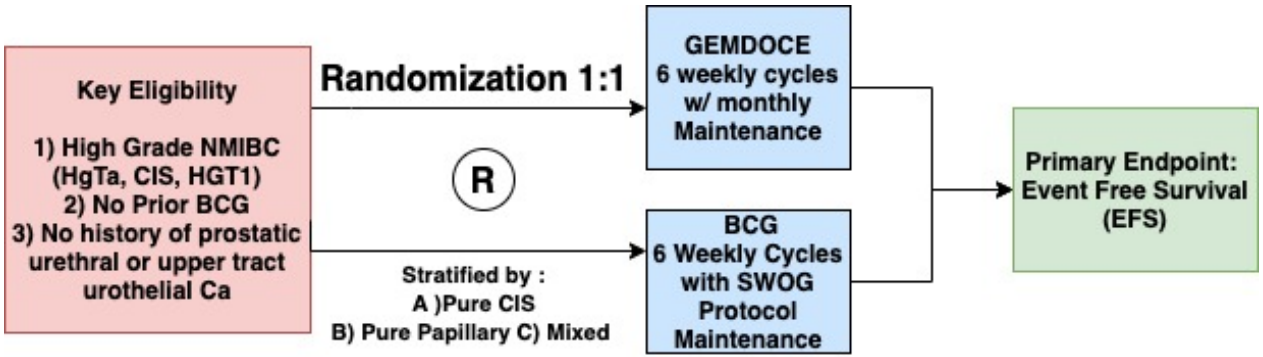






McElree et al, J Urol, 2022

BRIDGE: A Randomized Phase III Trial of Intravesical BCG veRsus Intravesical Docetaxel and GEmcitabine in BCG Naïve NMIBC



Non-Inferiority Design w/ Primary Endpoint: Event Free Survival (EFS)

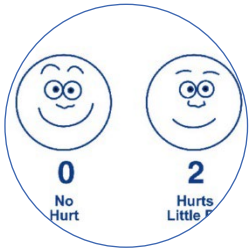
Gemcitabine 2g in sodium chloride 0.9 % 102.6 mL
Docetaxel 40g in sodium chloride 0.9 % 54 mL
BCG 50 mg in sodium chloride 0.9 % 50 ml

SWOG Protocol BCG Maintenance: 3 weekly instillations 3,6,12,18,24,30,36 months after initial induction course

EFS: Defined as the time from randomization to high grade recurrence in the bladder (CIS, HgTa, HGT1 or HGT2), progression of disease, or death, whichever occurs first.

ECOG-ACRIN cancer research group

PI: Max Kates & Angie Smith



BCG Naïve

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- Early Relapse

Anti PD1/PDL-1 Studies

POTOMAC

High risk NMIBC:
1. Any HG
2. Any T1
3. Low grade Ta if >3cm + recurrent + multifocal

No prior BCG therapy

RANDOMIZE

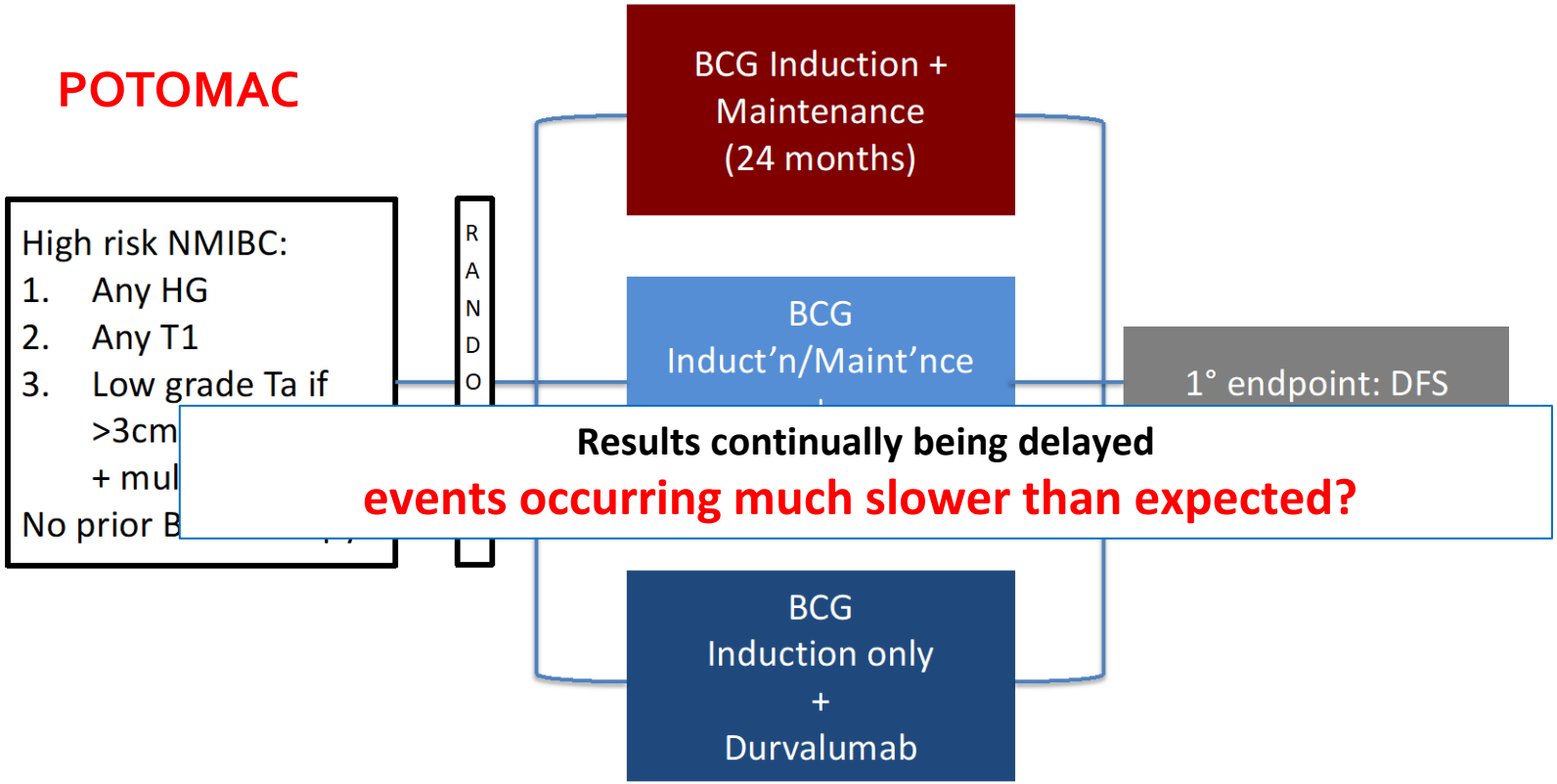
- BCG Induction + Maintenance (24 months)
- BCG Induct'n/Maint'nce + Durvalumab
- BCG Induction only + Durvalumab

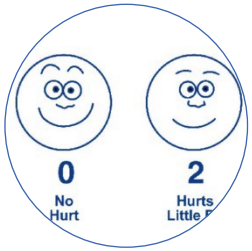
→ 1° endpoint: DFS

Similar Trials:

- **ALBAN** - atezolizumab
- **CREST** - sasanlimab (subq)
- **KN676** – pembrolizumab* (also in BCG exposed)

Anti PD1/PDL-1 Studies





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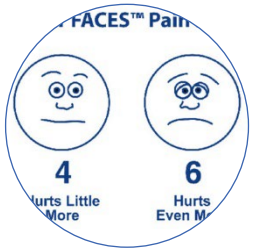

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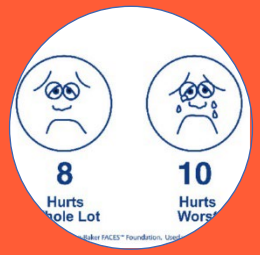


BCG Unresponsive

- Refractory
- Early Relapse

JOURNAL OF CLINICAL ONCOLOGY REVIEW ARTICLE

Definitions, End Points, and Clinical Trial Designs for Non–Muscle-Invasive Bladder Cancer: Recommendations From the International Bladder Cancer Group

Ashish M. Kamat, Richard J. Sylvester, Andreas Böhle, Joan Palou, Donald L. Lamm, Maurizio Brausi, Mark Soloway, Raj Persad, Roger Buckley, Marc Colombel, and J. Alfred Witjes

Bladder Cancer 1 (2015) 29–30
DOI 10.3233/BLC-159002
IOS Press

Short Communication

Clarification of Bladder Cancer Dise States Following Treatment of Patien with Intravesical BCG

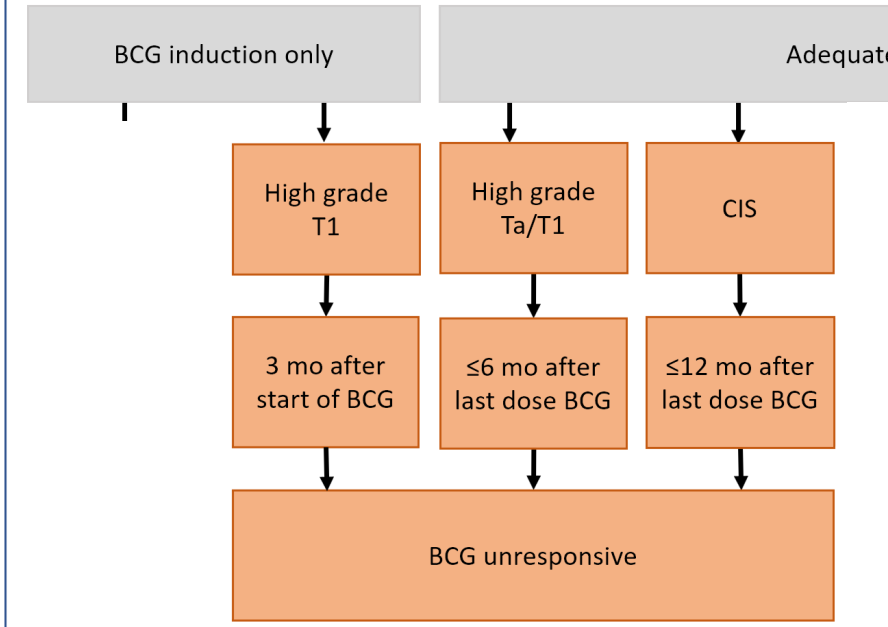
GU ASCO Panel: Lerner, Dinney, Kamat, Bivalacqua, Nielsen, O'Donnell, Schoenberg, Steinberg

BCG-Unresponsive Nonmuscle Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment

Guidance for Industry

FDA APPROVED

NMIBC recurrence after BCG treatment



Adequate BCG therapy defined as:

at least 5 of 6 doses of iBCG

+ at least 2 additional doses of mBCG

Kamat et al, JCO, 2016; Lerner et al, Bladder Cancer, 2016; FDA Document, 2018

Roumiguié M, Eur Uro 2021, IBCG Consensus Statement, 2021

AUA Guidelines

Role of Cystectomy in NMIBC

29. In a high-risk patient with persistent or recurrent disease within one year following treatment with two induction cycles of BCG or BCG maintenance, a clinician should offer radical cystectomy. (Moderate Recommendation; Evidence Strength: Grade C)

https://www.auanet.org/education/guidelines/non-muscle-invasive-bladder-cancer.cfm

Options for Patients with NMIBC

INTRAVESICAL CHEMOTHERAPY

ENHANCED DRUG DELIVERY

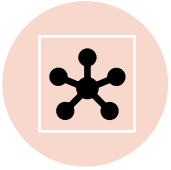
VACCINES

GENE THERAPY

IMMUNOTHERAPY

TARGETED THERAPY

RADIATION



OTHER

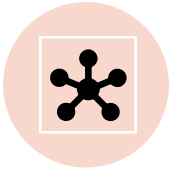
Options for Patients with NMIBC

Systemic

IMMUNOTHERAPY

TARGETED THERAPY

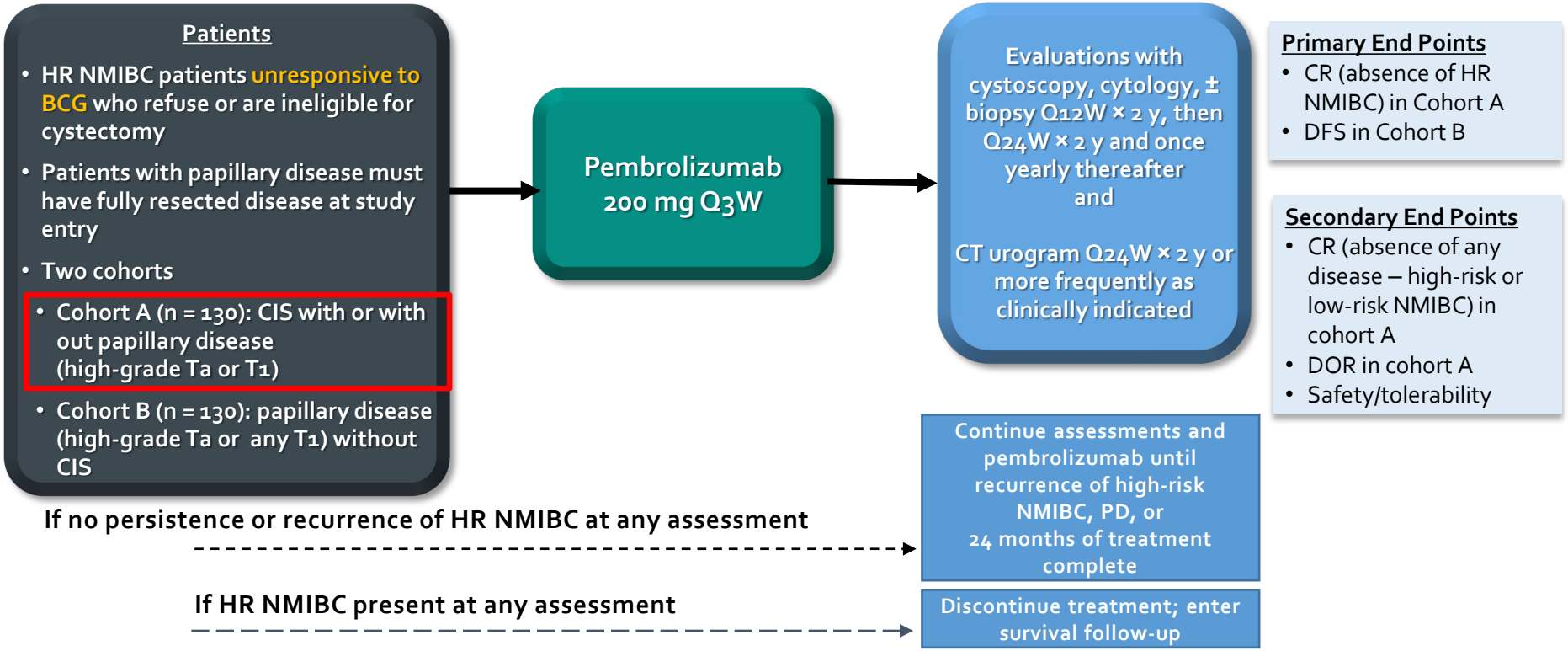
RADIATION



OTHER

* (PDT IS INTRAVESICAL)

Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG



Lancet Oncology, May 25, 2021

Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre,

Characteristic	N=96
Median age, years (range)	73 (44-92)
<65	30 (31.3)
≥65 to <75	24 (25.0)
≥75 to <85	33 (34.4)
≥85	9 (9.3)
Male, n (%)	81 (84.4)
Female, n (%)	15 (15.6)
Race, n (%)	
White	64 (66.7)
Asian	26 (27.1)
Missing	6 (6.3)
ECOG PS, n (%)	
0	70 (72.9)
1	26 (27.1)

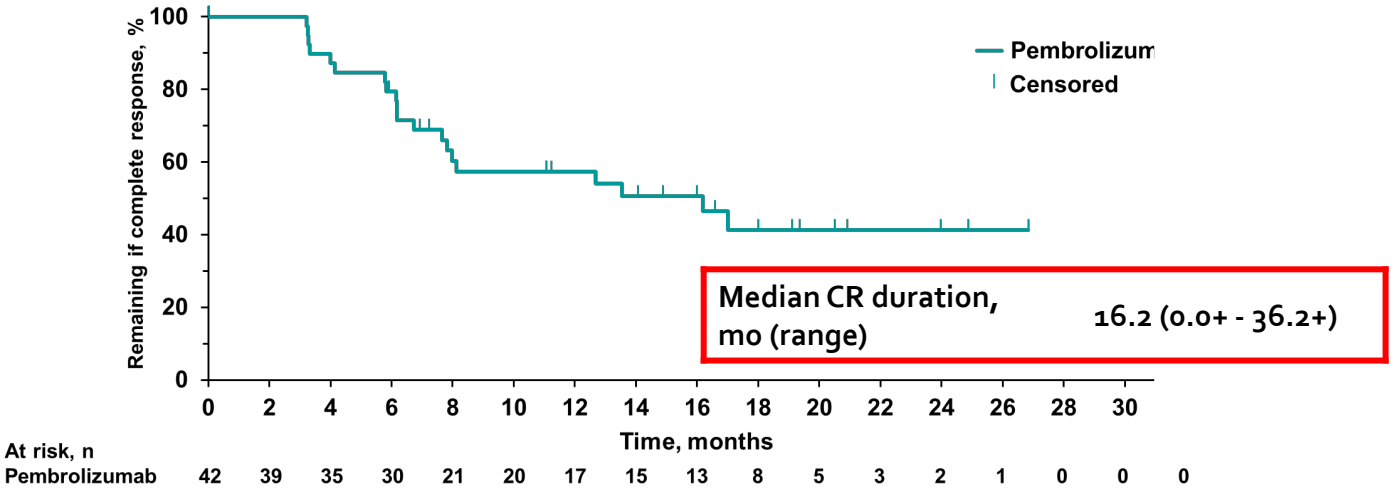
Characteristic	N=97
Median prior BCG instillations, n (range)	12.0 (7.0-45.0)
Tumor pattern at study entry, n (%)	
CIS with T1	12 (12.5)
CIS with high-grade Ta	24 (25.0)
CIS alone	60 (62.5)
PD-L1 status, n (%)	
CPS ≥10	35 (36.5)
CPS <10	56 (58.3)
Not evaluable	5 (5.2)
Reason prior cystectomy not performed, n (%)	
Declined	91 (94.8)
Ineligible	5 (5.2)

Lancet Oncology, May 25, 2021

Pembrolizumab for **BCG Unresponsive** CIS

FDA APPROVED

Best response	N=96 n (%)	95% CI
CR	39 (40.6)	30.7, 51.1

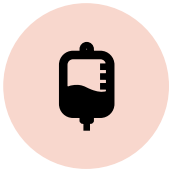


CR, complete response. [a]1 month = 30.4367 days. [b]Month 0 = time point when initial CR was achieved.

Balar, Kamat et al, Lancet Oncology, 2021

Options for Patients with NMIBC

Intravesical



INTRAVESICAL CHEMOTHERAPY

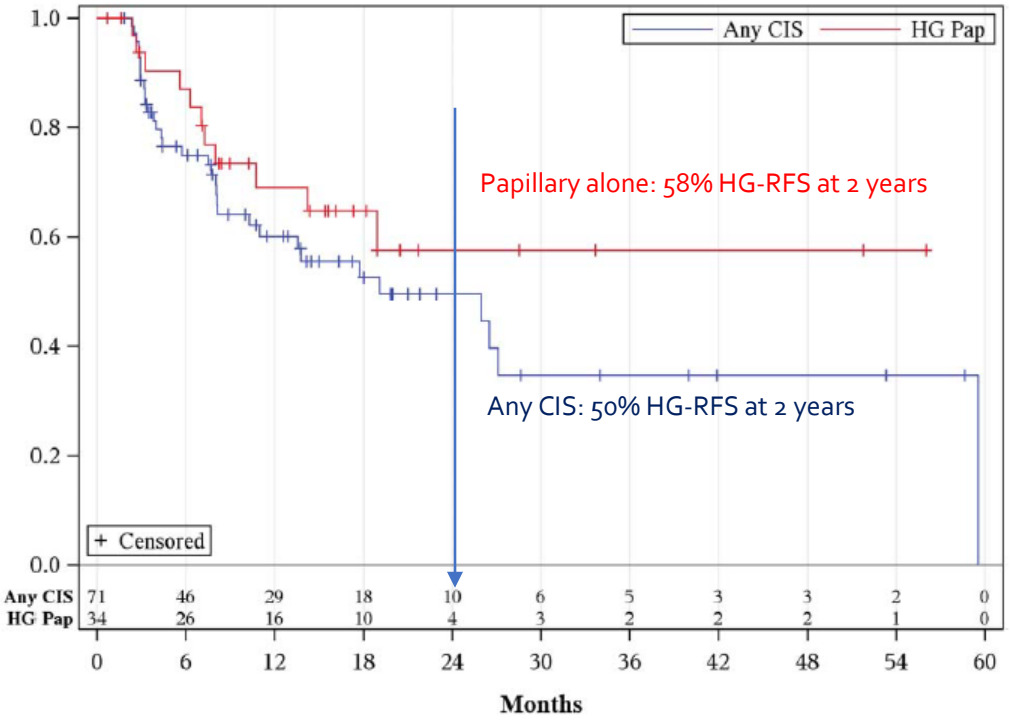
ENHANCED DRUG DELIVERY

VACCINES (BCG ++)

GENE THERAPY

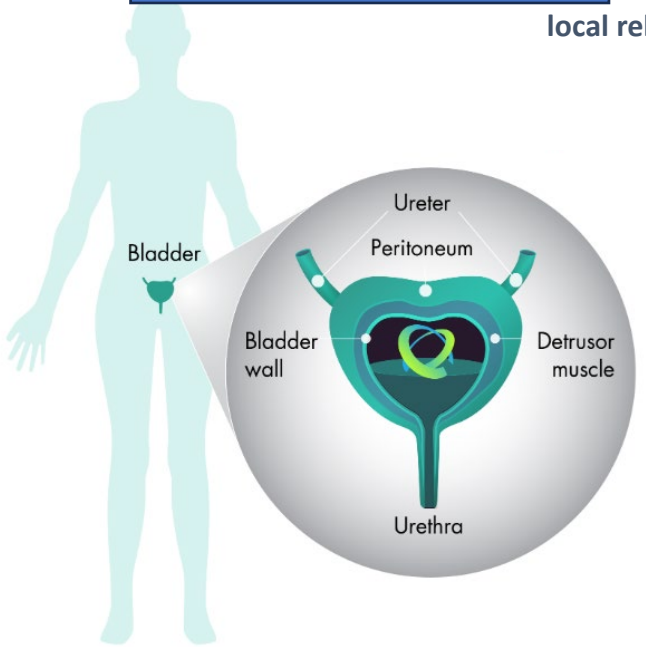
Multi-Institution Evaluation of Sequential Gemcitabine and Docetaxel as Rescue Therapy for Nonmuscle Invasive Bladder Cancer

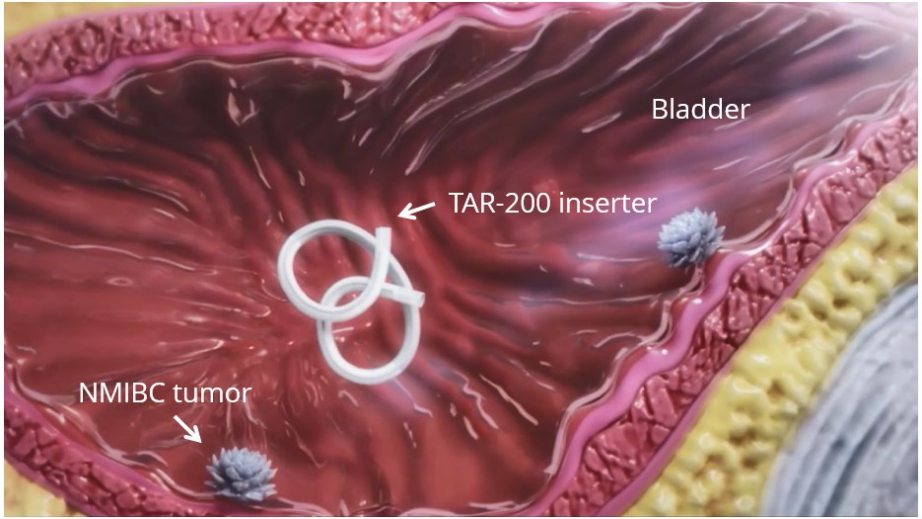
High grade bladder recurrence-free survival for BCG unresponsive cases



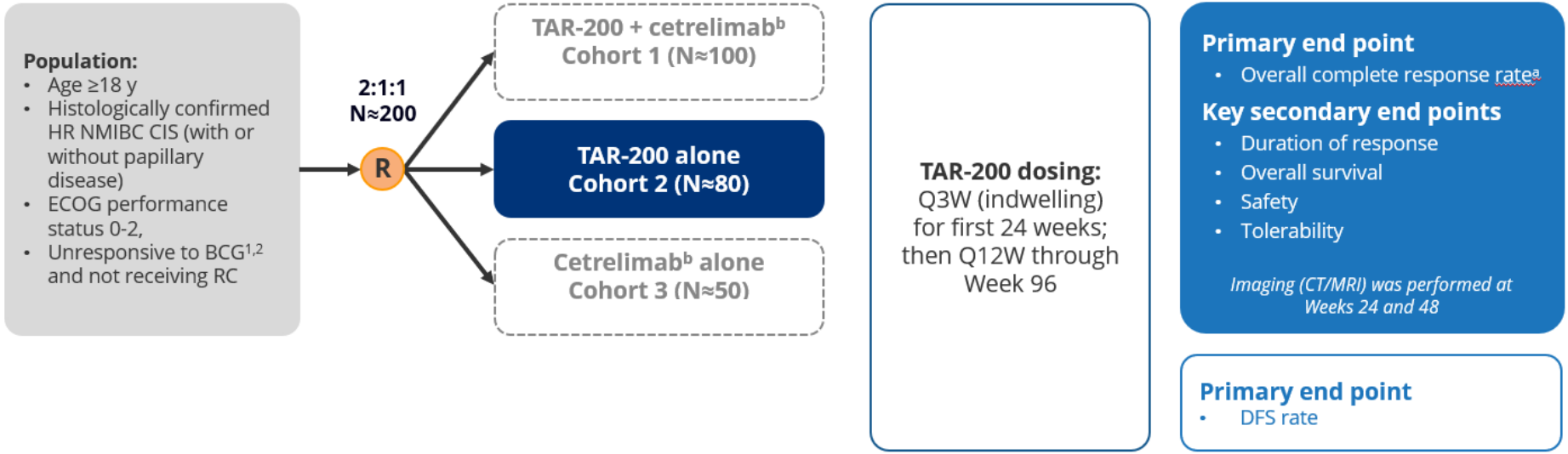
Steinberg, Kamat, O'Donnell et al, J Urol, May 2020

a novel drug delivery system for sustained, local release of gemcitabine in the bladder





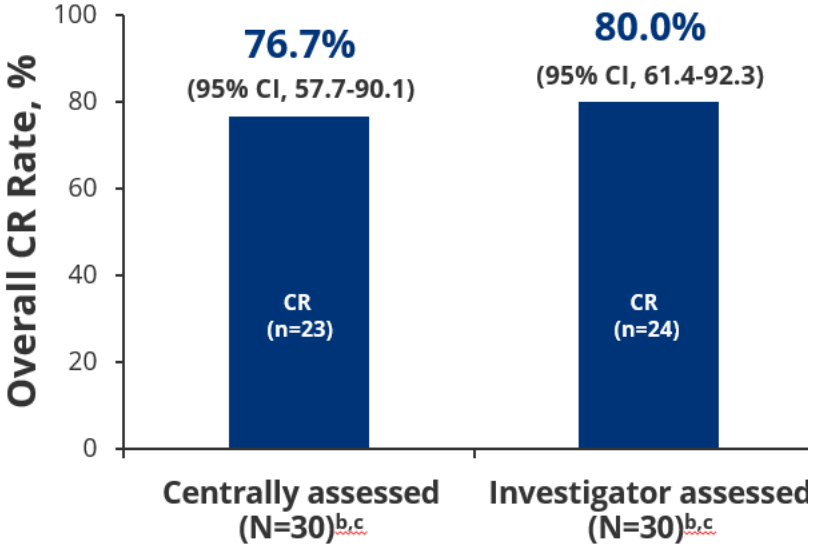
SunRISe-1 is an Ongoing Phase 2b Randomized, Open-label Study



- Complete response is determined by cystoscopy, central cytology, and central pathology at Weeks 24 and 48
- Here we report updated results from the **TAR-200 monotherapy cohort (Cohort 2)** of SunRISe-1

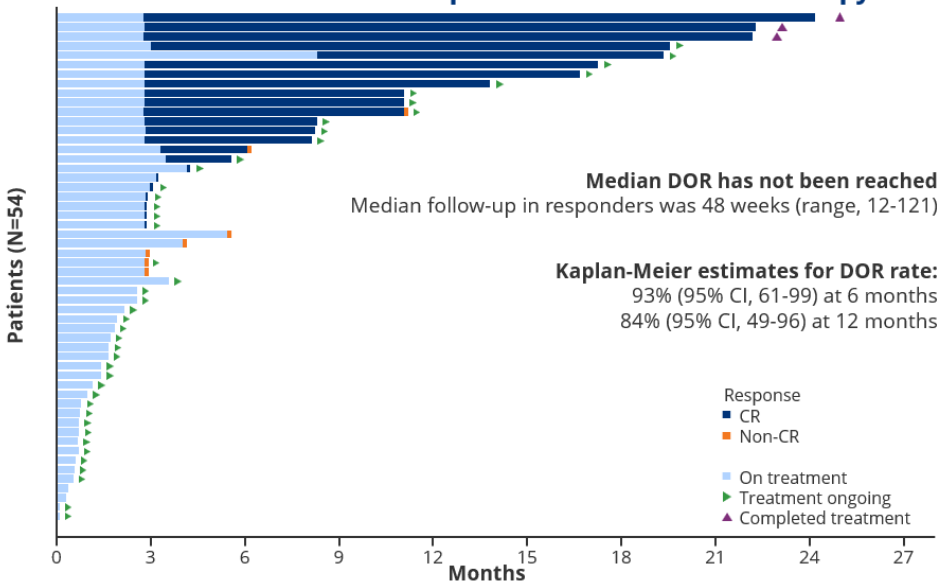
Presented at the 2023 ESMO Congress; October 20-24, 2023; Madrid, Spain.

CR Rate in Patients With HR NMIBC CIS (Cohort 2)



- CR is based on cystoscopy and centrally assessed urine cytology and biopsy at Weeks 24 and 48[b,c]

Treatment Duration and Response to TAR-200 Monotherapy



Necchi et al, ESMO23

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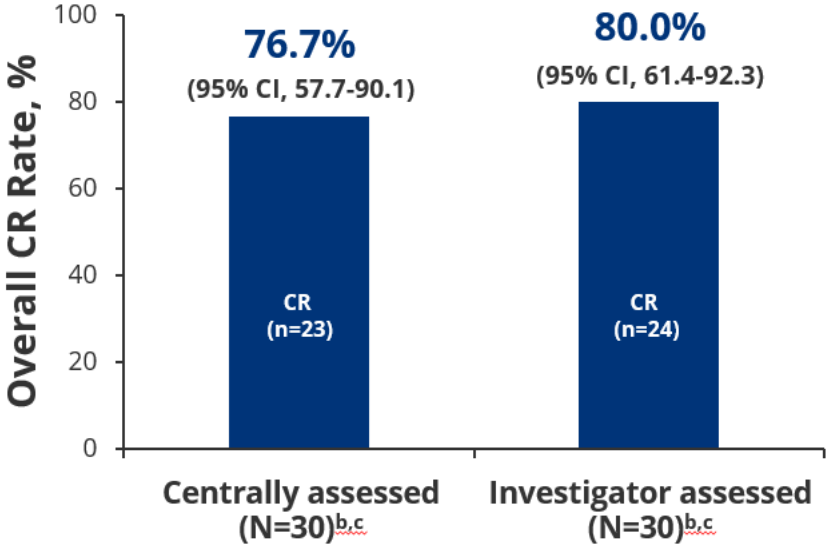

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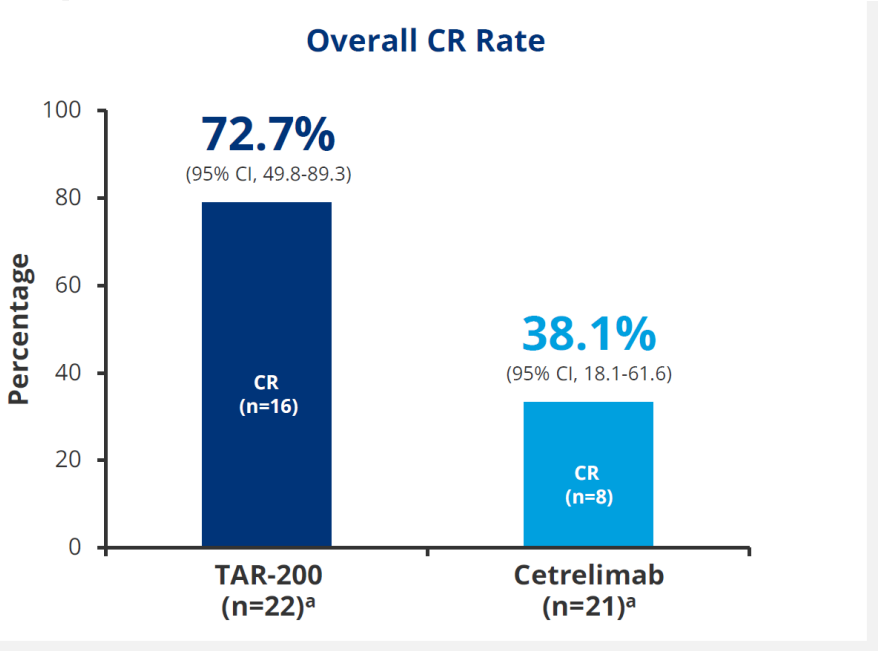
Data from AUA23



Necchi et al, ESMO23

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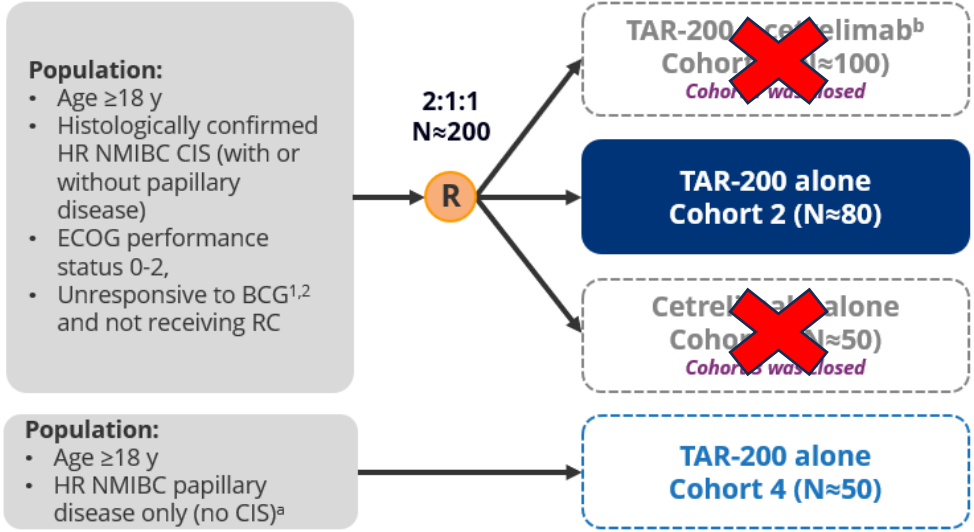


TAR-200 dosing:
Q3W (indwelling) for first 24 weeks; then Q12W through Week 96

Primary end point
- Overall complete response rate[a]

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

Imaging (CT/MRI) was performed at Weeks 24 and 48

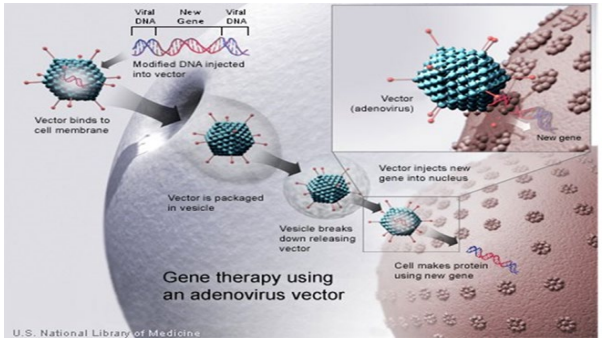
Primary end point
- DFS rate

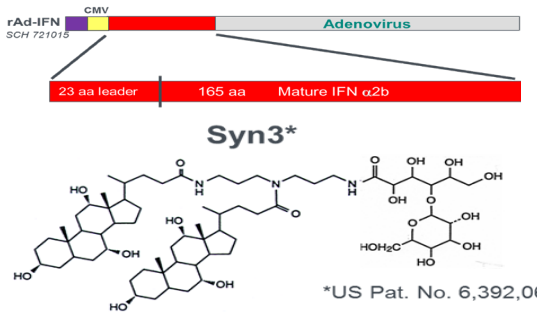
NCT04640623

- Complete response is determined by cystoscopy, central cytology, and central pathology at Weeks 24 and 48
- Here we report updated results from the **TAR-200 monotherapy cohort (Cohort 2)** of SunRISe-1

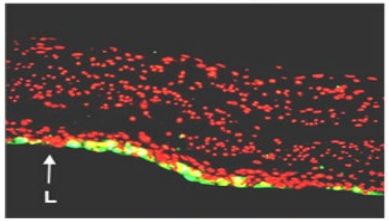
Presented at the 2023 ESMO Congress; October 20-24, 2023; Madrid, Spain.

(nadofaragene firadenovec)



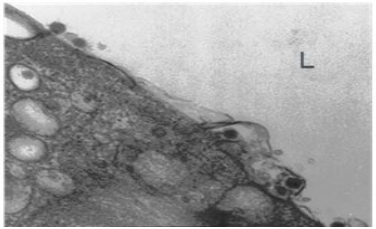


rAd-IFN in Syn3



L – Lumen of bladder

Adenovirus particles on bladder epithelium and within vesicles using Syn3



Protein active in transfected cells

Released into microenvironment

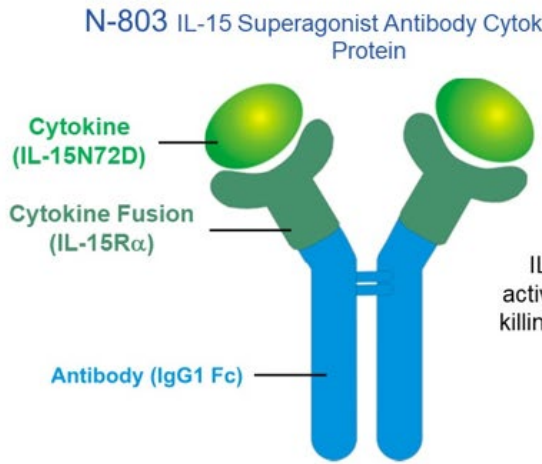
Nadofaragene Firadenovec: Phase 3, Multi-Center, Open-Label Study

	Carcinoma in situ cohort (n=103)	High-grade Ta or T1 cohort (n=48)	All patients (n=151)
Patients with complete response at month 3*	55 (53·4%; 43·3–63·3)	35 (72·9%; 58·2–84·7)	90 (59·6%; 51·3–67·5)
Duration of complete response† or high-grade recurrence-free survival‡, months	9·69 (9·17–NE)	12·35 (6·67–NE)	7·31 (5·68–11·93)
Patients who were free from high-grade recurrence			
Month 6	42 (40·8%; 31·2–50·9)	30 (62·5%; 47·4–76·0)	72 (47·7%; 39·5–56·0)
Month 9	36 (35·0%; 25·8–45·0)	28 (58·3%; 43·2–72·4)	64 (42·4%; 34·4–50·7)
Month 12	25 (24·3%; 16·4–33·7)	21 (43·8%; 29·5–58·8)	46 (30·5%; 23·2–38·5)

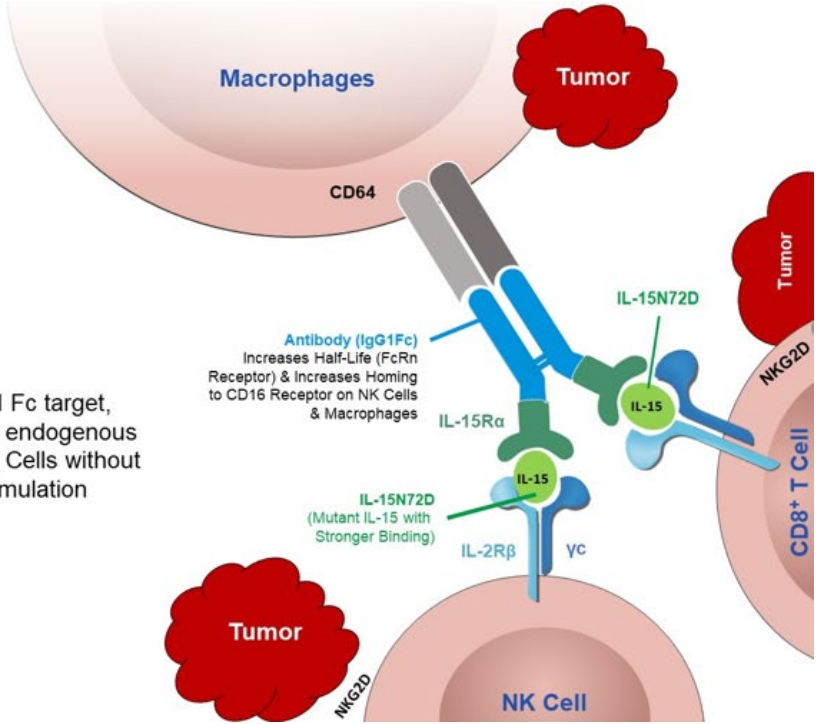
Median duration of HG-RFS was 12.35 months (95% CI: 6.67, NE) in patients with papillary disease
Progression to ≥ MIBC in 8 (5.3%) patients

Boorjan SA, Lancet Oncology, 2021

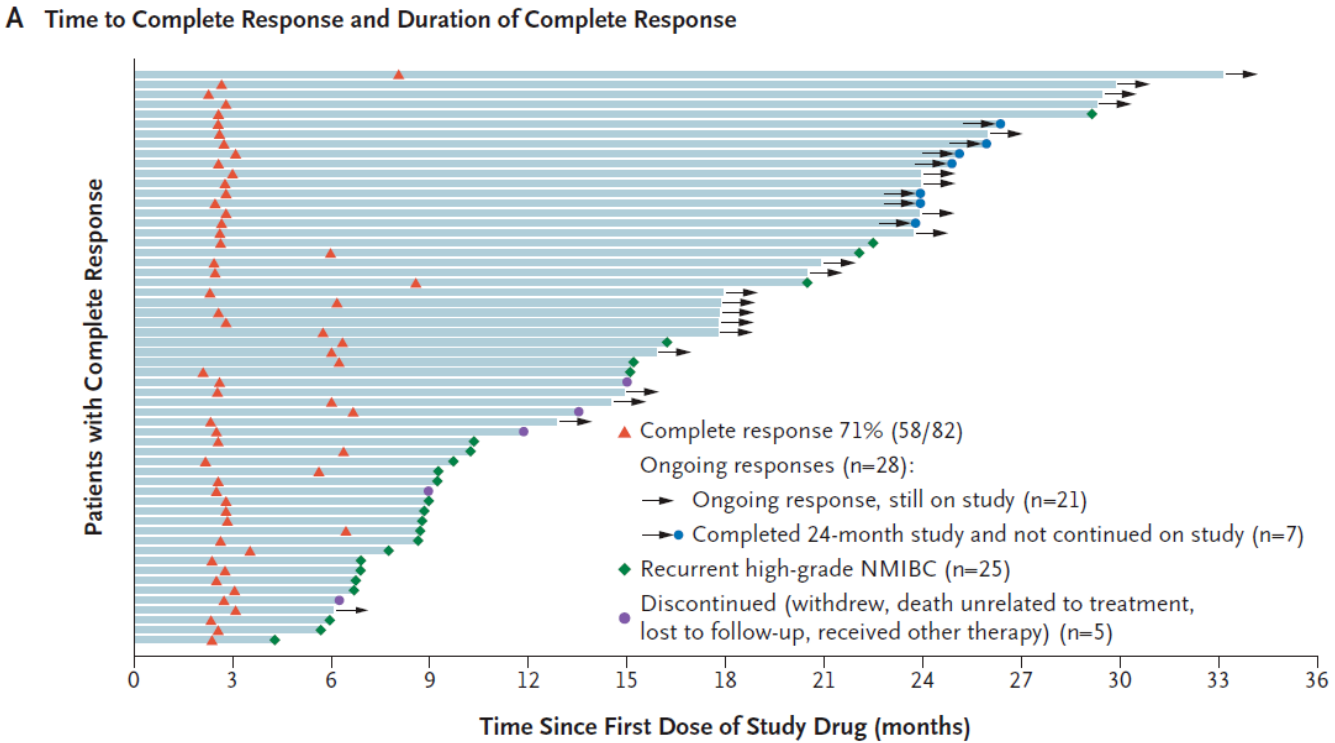
N-803 Mechanism of Action: novel IL-15 Superagonist Fusion Protein Upregulates Natural Killer (NK) & T Cells



IL-15N72D and IgG1 Fc target, activate and proliferate endogenous killing cells NK, CD8⁺ T Cells without inducing T Reg stimulation



IL-15 Superagonist: NAI (Nogapendekin alfa inbakicept, N-803)

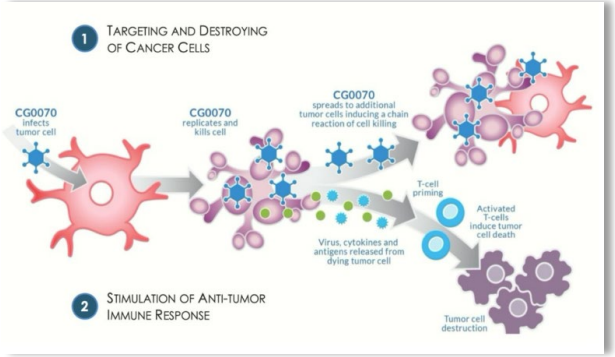


Key Efficacy Results

71% CR Rate At Any Time	**26.6** Months Median Duration of CR
62% 12 Months Complete Response	**53%** 24 Months Complete Response
90% Avoidance of Cystectomy In Responders	**89%** Cystectomy Free At 24 Months

Chamie et al, NEJM Evidence, 2022

Oncolytic Adenovirus (CG0070)



BOND-003; Phase III; single-arm

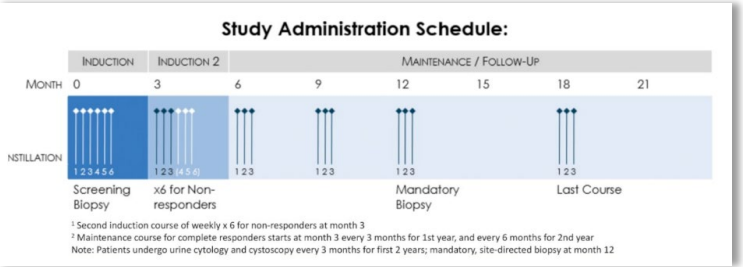
N=110 w/ Cis

Primary Endpoint→CR @ 12 mo

Mandatory Bx @ 12 mo

Recruiting

CG0070 is a serotype 5 adenovirus engineered to express GM-CSF and replicate in cells with mutated or deficient RB



SUO23: First Results from BOND-003 Study

CG0070 as MONOTHERAPY for BCG-Unresponsive NMIBC (CIS+/-Ta/T1)

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.

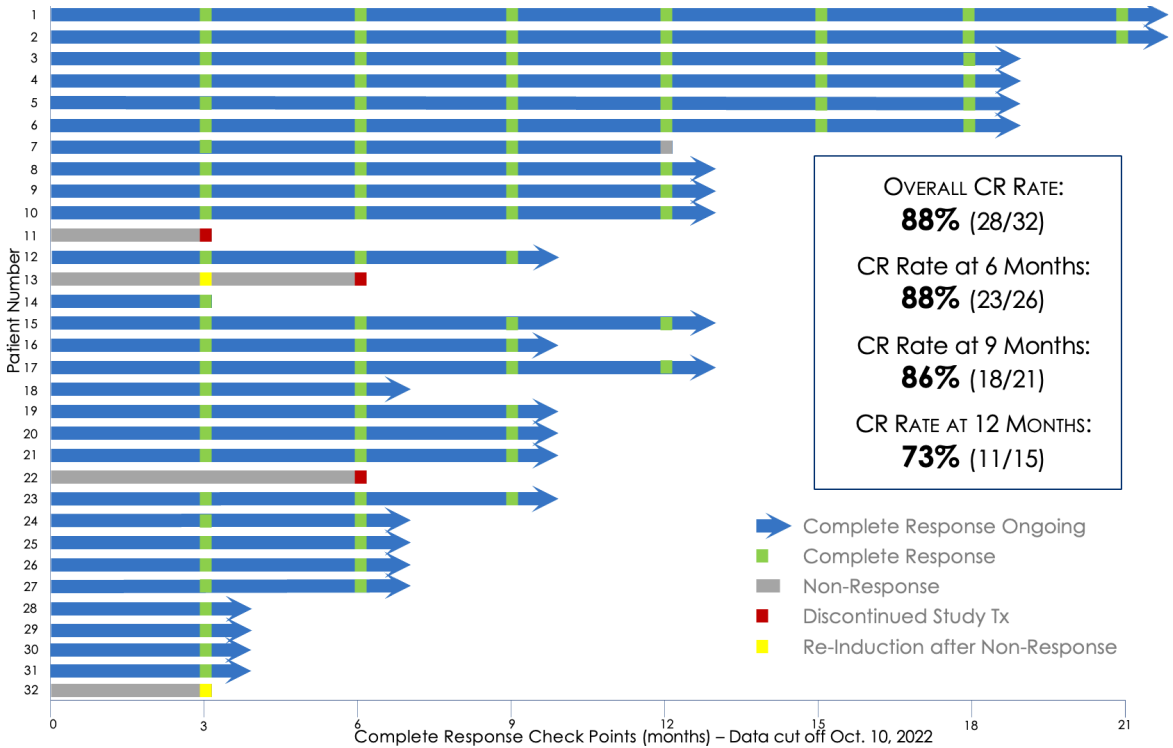
1. Seven patients yet to reach minimum duration of response evaluation and not included in durable CR lasting ≥ 6 months assessment.

MARK TYSON, EDWARD UCHIO, JONG-KIL NAM, DONALD LAMM, NEAL SHORE, WASSIM KASSOUF, GARY STEINBERG, PETER BLACK, HIROSHI KITAMURA, ASHISH M. KAMAT, JAMES BURKE, TRINITY J. BIVALACQUA, & ROGER LI

EAU23: Preliminary Data in CORE1 Study

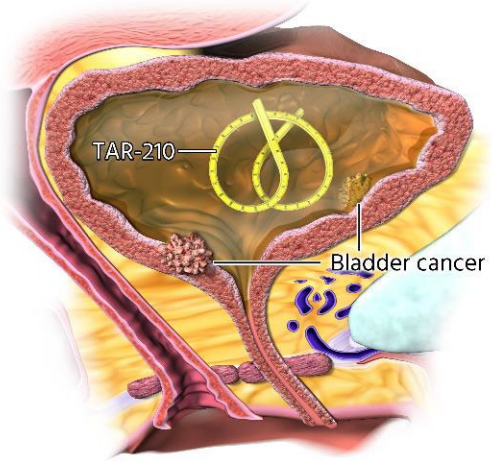
CG0070 + Pembrolizumab Combo for BCG-Unresponsive NMIBC

Design: Single-arm, intravesical (IVe) CG0070 + IV pembrolizumab



TAR-210 Is a Novel Drug Delivery System Designed to Provide Local Targeted Therapy for Patients With Bladder Cancer

TAR-210 is designed to provide local, sustained release of erdafitinib within the bladder for 3 months while limiting systemic toxicities

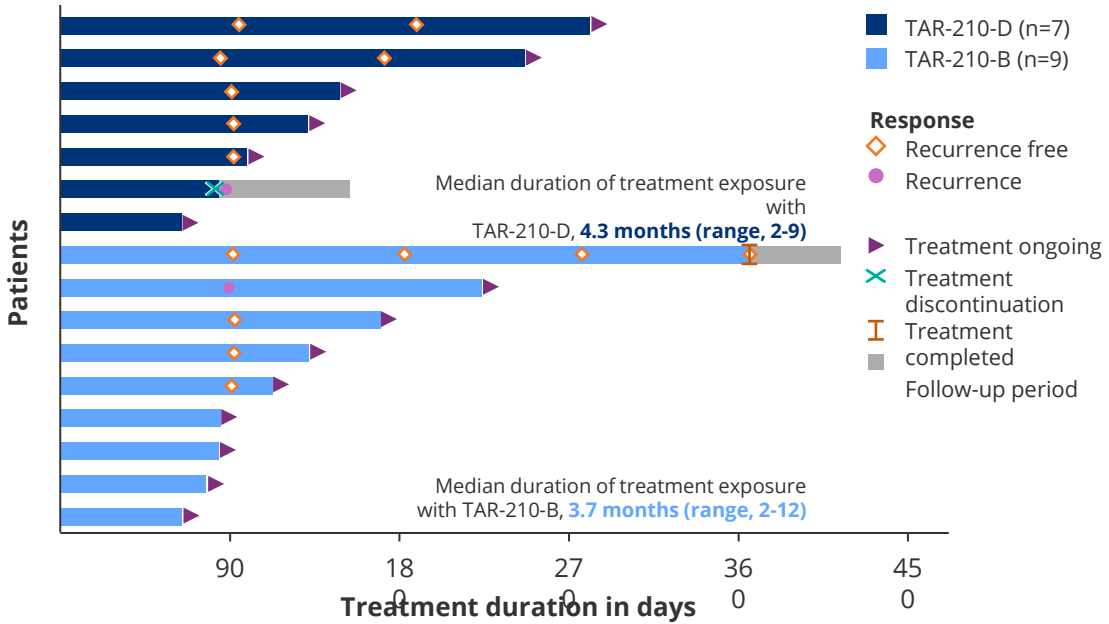


TAR-210 is inserted into the bladder through a dedicated urinary placement catheter and removed via cystoscopy.

FGFR, fibroblast growth factor receptor; HR, high risk; IR, intermediate risk; mUC, metastatic urothelial carcinoma; NMIBC, non–muscle-invasive bladder cancer.

1. Hernández S, et al. *J Clin Oncol.* 2008;24:3664-3671; 2. Knowles MA, Hurst CD. *Nat Rev Cancer*. 2014;15:25-41; 3. Khalid S, et al. *Eur Urol Open Sci.* 2020;21:61-68; 4. BALVERSA® (erdafitinib) [package insert]. Horsham, PA: Janssen Products, LP; 2023; 5. Perera TPS, et al. *Mol Cancer Ther*. 2017;16:1010-1020; 6. Loriot Y, et al. *N Engl J Med.* 2019;381:338-348; 7. Siefker-Radtke AO, et al. *Lancet Oncol.* 2022;23:248-258; 8. Loriot Y, et al. *J Clin Oncol.* 2023;41(Suppl 17):LBA4619; 9. Daneshmand S, et al. *J Clin Oncol.* 2023;41(Suppl 6):504; 10. Catto JWF, et al. *J Clin Oncol.* 2023;41(Suppl 6):503; 11. Catto JWF, et al. ESMO, 2023.

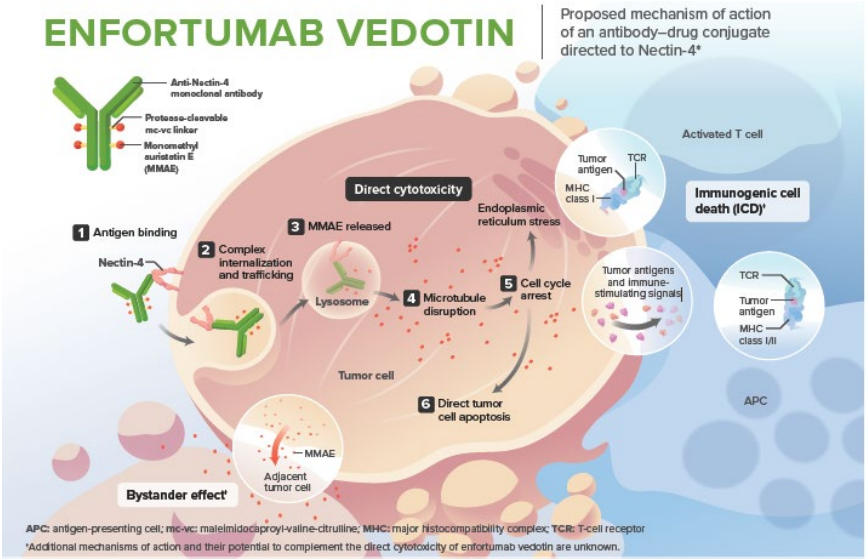
TAR-210 Activity in HR NMIBC (Cohort 1): 82% Are Recurrence Free

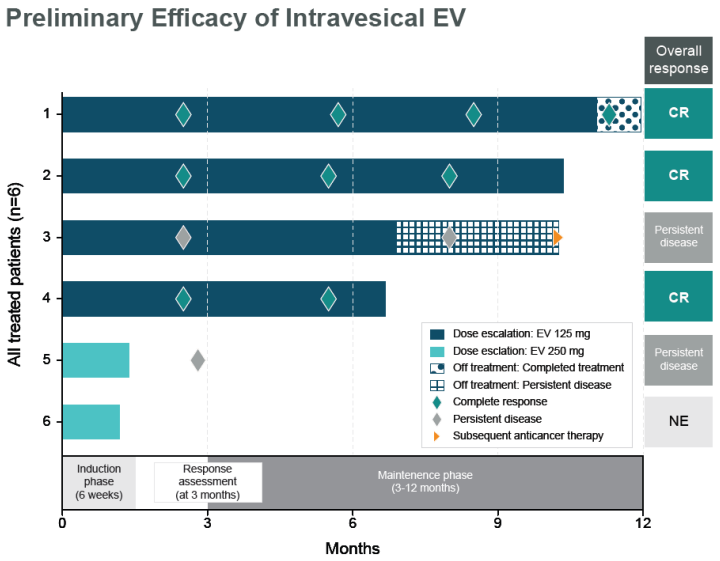


- Patient characteristics (N=16):
  - Median age was 73.5 years (range, 62-90)
  - 75% were male
  - 75% and 25% had tumor stage Ta and T1, respectively
  - 44% had multiple tumors
  - 100% had prior BCG
- In 11 patients with a response assessment, 9 were recurrence free (**recurrence-free rate, 82%**)
  - First response assessment was at 3 months
- Median recurrence-free survival was NE (95% CI, 2.96 months-NE)

CI, confidence interval; NE, non-estimable.

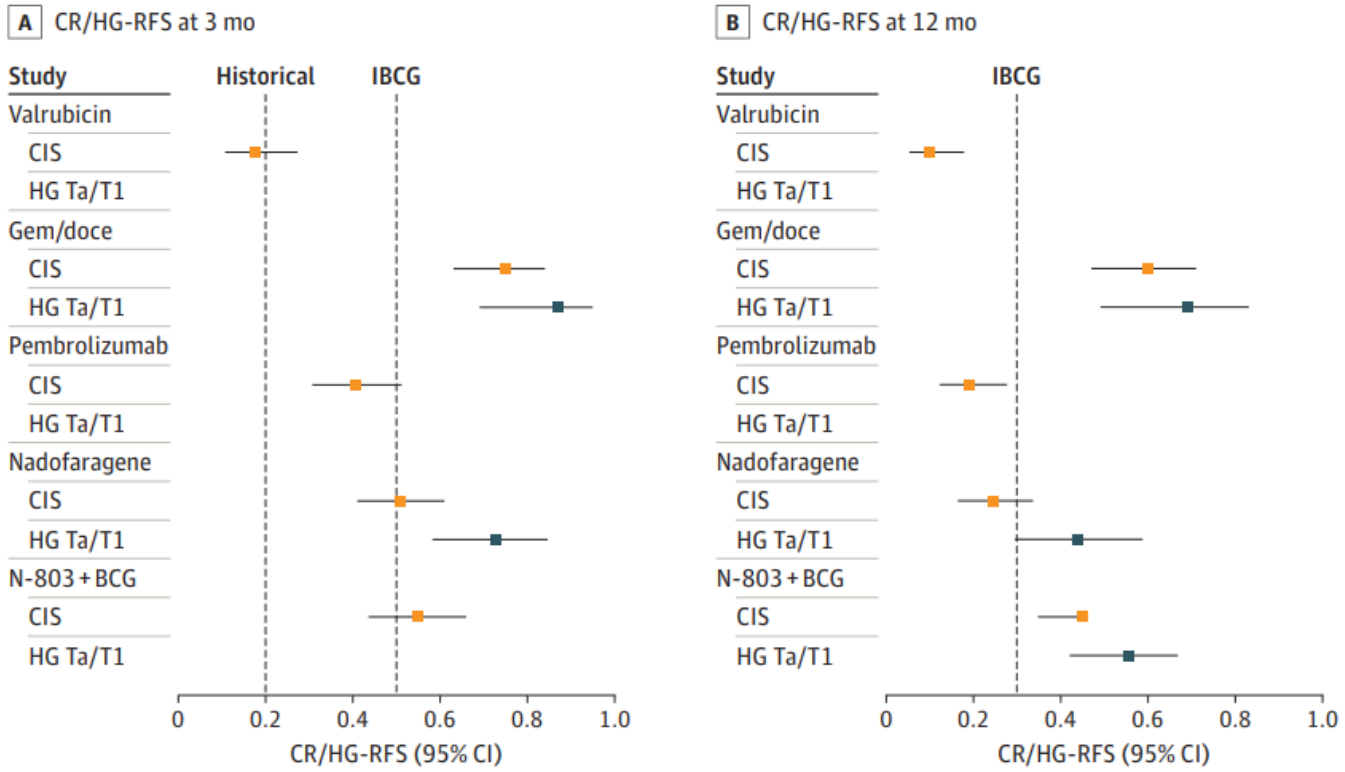
A First-In-Human Trial of Intravesical Enfortumab Vedotin (EV) in Patients with NMIBC: Interim Results of a Phase 1 Study (EV-104)





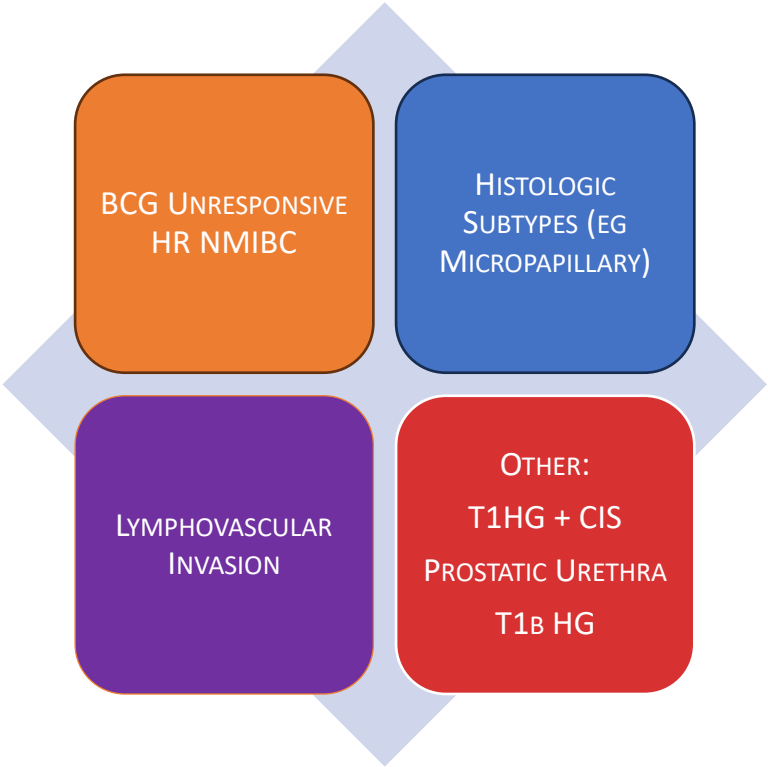
Kamat et al, ASCO 2023

Figure. CR–High-Grade Recurrence-Free Survival (HG-RFS) for Approved and Selected Investigational Agents for BCG-Unresponsive NMIBC



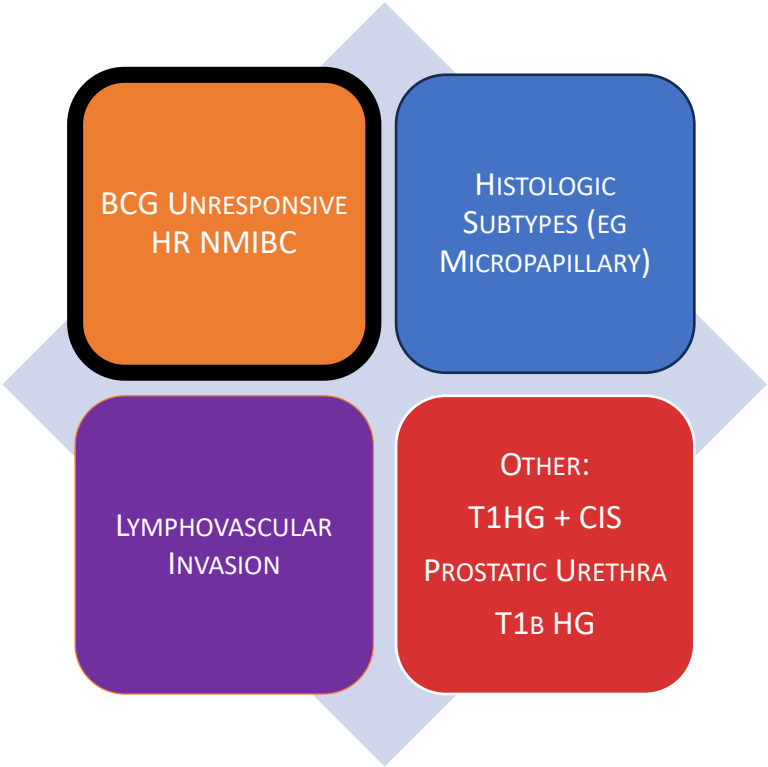
Hwang, JAMA Oncology, 2023

When to consider Radical Cystectomy in NMIBC



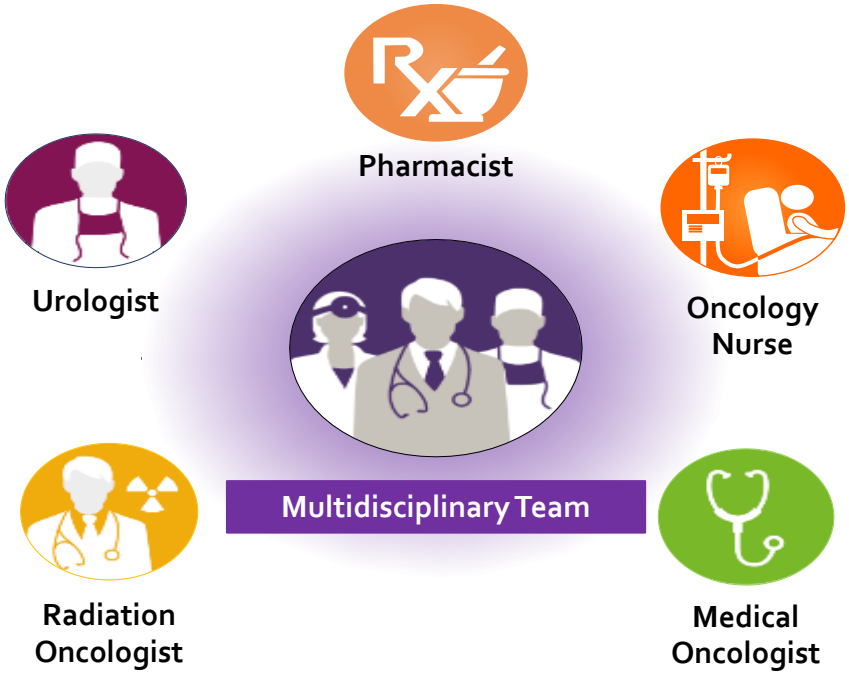
Kamat, AUA Course, 2023

When to consider Radical Cystectomy in NMIBC



Kamat, AUA Course, 2023

Optimal Management of Bladder Cancer Requires a Multidisciplinary Approach



"Providing the best management for patients with bladder neoplasia relies on close cooperation and teamwork among urologists, oncologists, radiologists, and pathologists"

—2nd International Consultation on Bladder Cancer

"Multidisciplinary input via tumor board discussions and/or directed consultations is critical to the optimal management of patients with bladder cancer"

—ASCO Clinical Practice Guideline Endorsement

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INTERNATIONAL BLADDER CANCER GROUP

EUROPEAN UROLOGY ONCOLOGY