Novel Treatment Options in Non-Muscle Invasive Bladder Cancer (NMIBC)

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EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

NCI Designated Comprehensive Cancer Center

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Disclosures:

Member of advisory board: Exelixis

Consultant: Cardinal Health

Educational Presentation: Intellisphere LLC

Paid Participant in Case Discussion: AmerisourceBergen, Targeted Oncology

NON-MUSCLE INVASIVE BLADDER CANCER - NMIBC

75% of bladder cancer cases

Tx: removal of all visible tumors

Intravesical BCG: cornerstone Tx

High-risk NMIBC unresponsive to BCG: notoriously difficult to treat

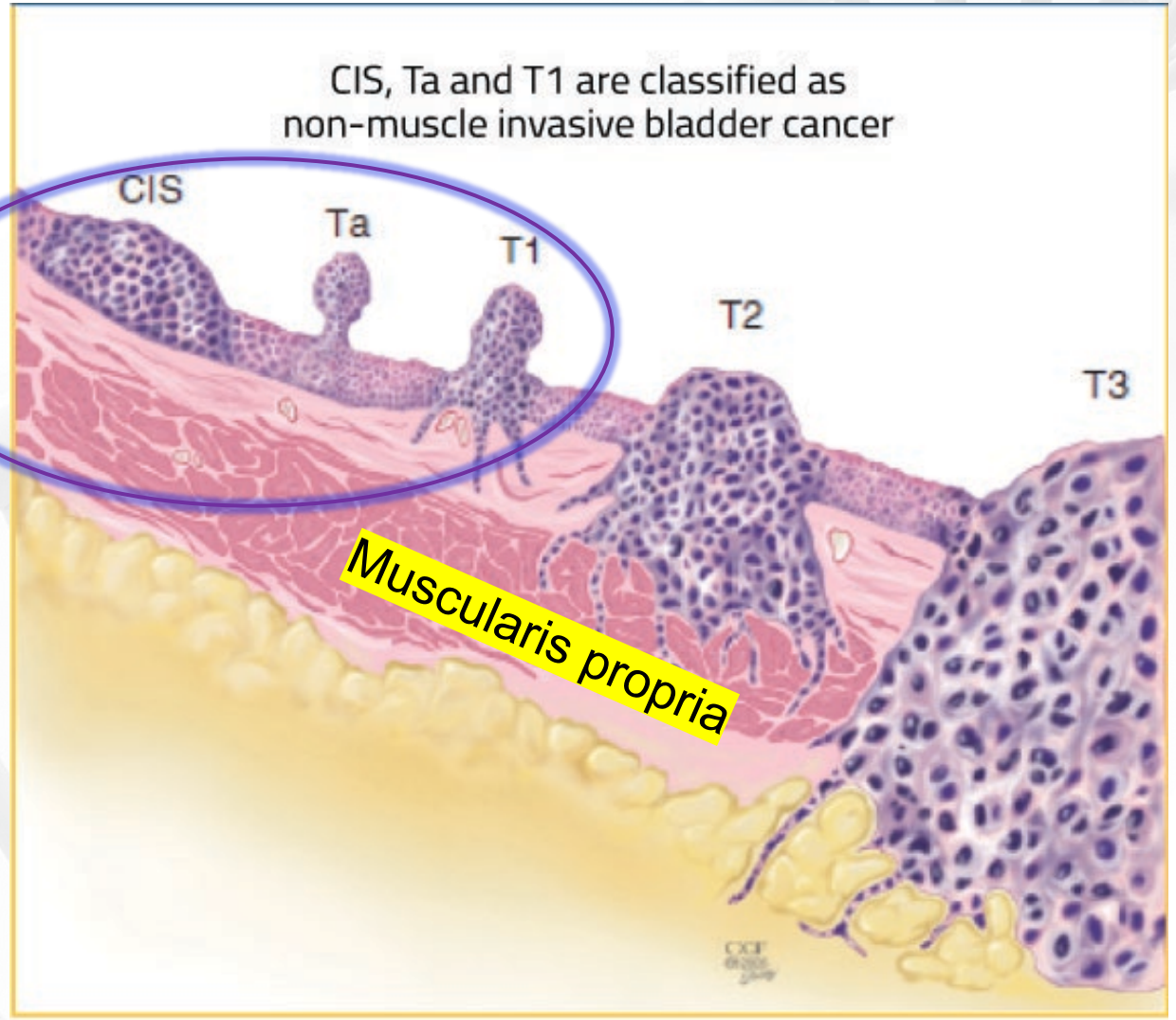
→ Radical cystectomy is curative

STAGES OF BLADDER CANCER

Low Risk

Intermediate Risk

High Risk



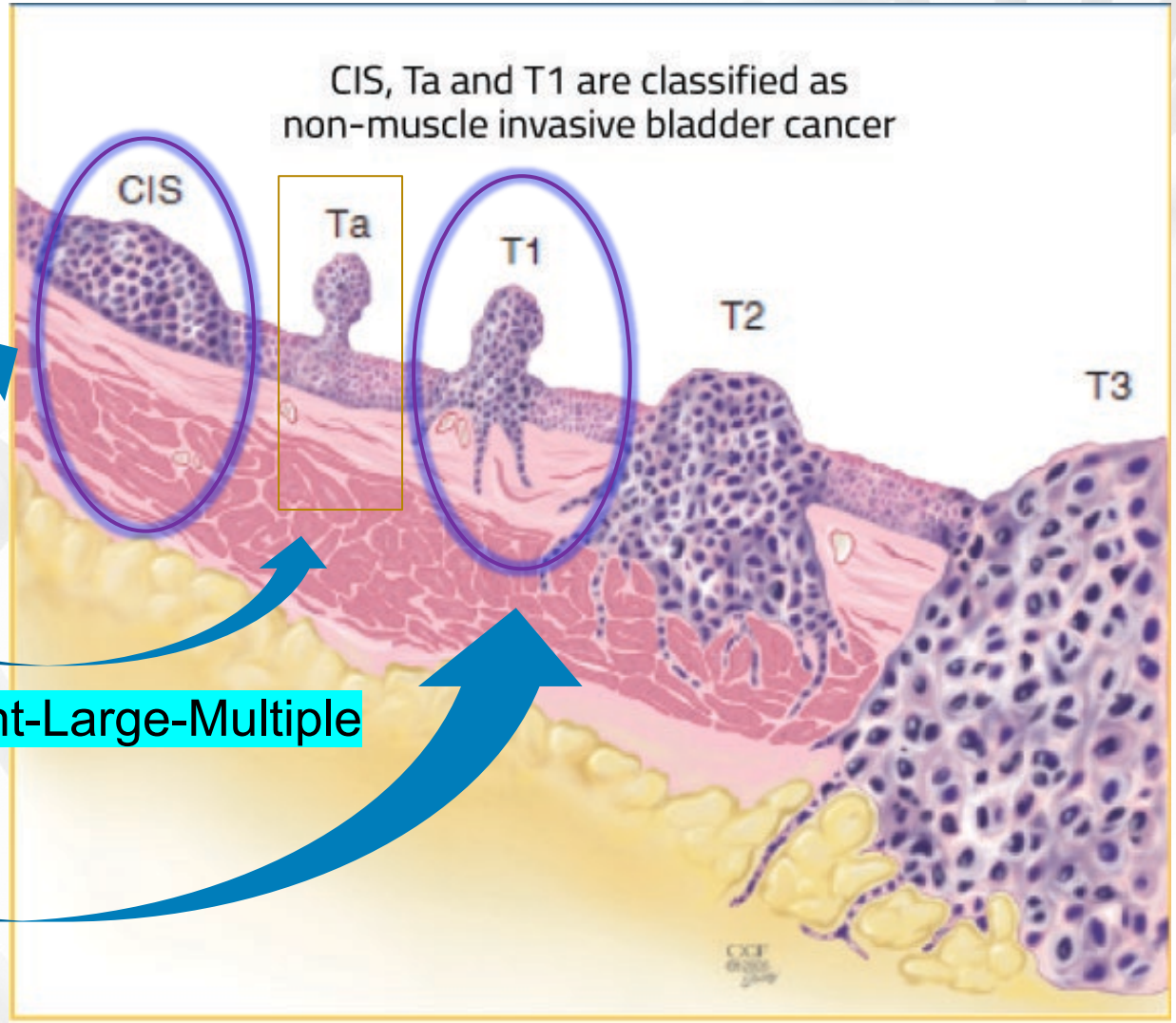
Adapted from Campbell-Walsh Urology, 11th edition, Chapter 93

STAGES OF BLADDER CANCER

High-grade

High Risk

Recurrent-Large-Multiple



Adapted from Campbell-Walsh Urology, 11th edition, Chapter 93

Cancer Specific Survival

T1 high-grade Bladder Cancer

=

cT3b
Gleason Grade 5
12/12 positive cores
PSA 75

(courtesy: Navai, N MDACC)

NCCN Guidelines Version 3.2023
Non-Muscle Invasive Bladder Cancer

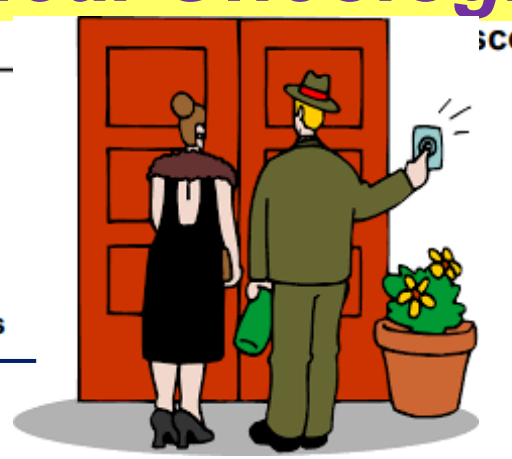
NCCN Guidelines Index
Table of Contents
Discussion

UROLOGISTS

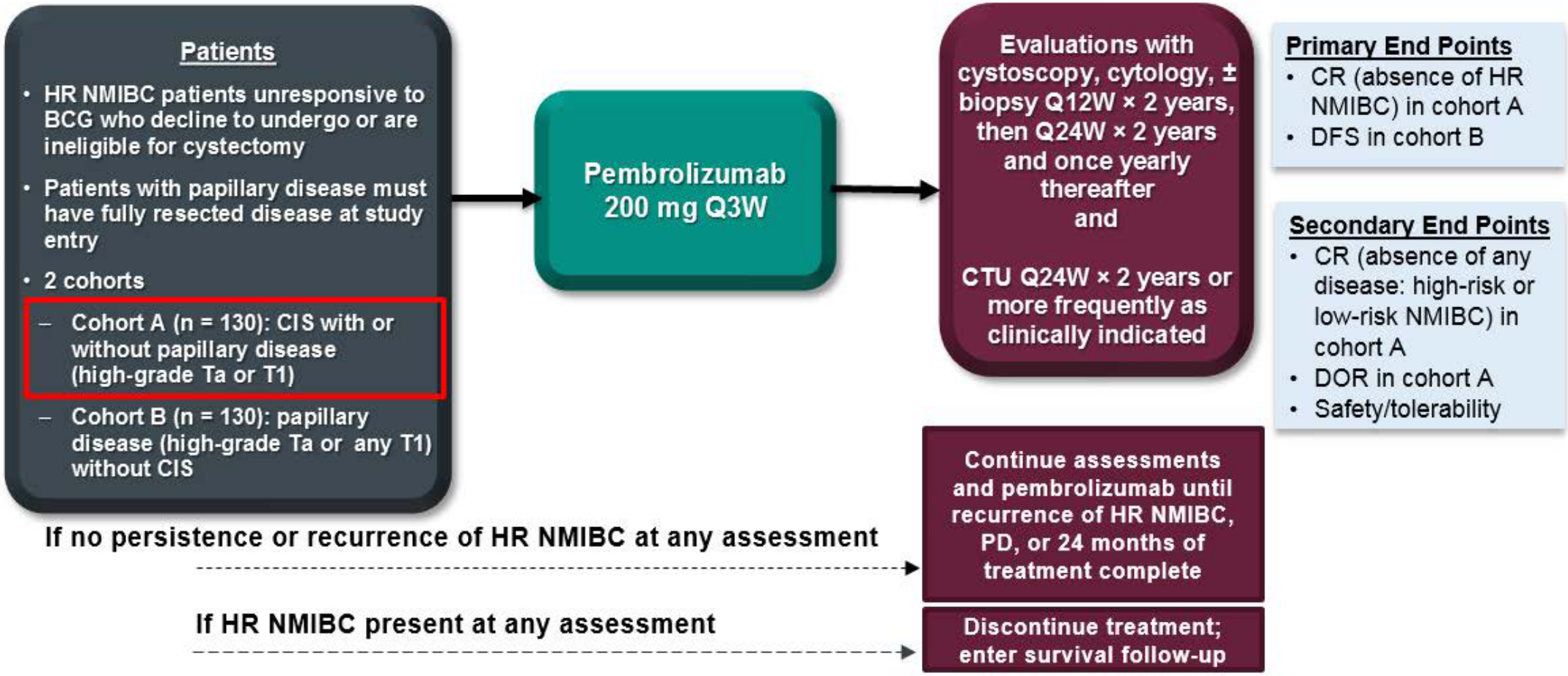
MANAGEMENT PER NMIBC RISK GROUP

AUA RISK GROUP (SEE BL-2)	INITIAL MANAGEMENT	FOLLOW-UP
Low	Surveillance[o]	• Cytology positive • Imaging negative • Cystoscopy negative → See BL-4
Intermediate	Intravesical therapy[p,q] (preferred) or Surveillance	See Follow-up (BL-E)
High: Bacillus Calmette-Guérin (BCG) naïve: Very-high-risk features[n]	Cystectomy (preferred) or BCG[p]	If prior BCG,
High: Bacillus Calmette-Guérin (BCG) naïve: No very-high-risk features	BCG[p] (category 1, preferred) or Cystectomy	scopy positive → Reclassify AUA Risk Group and manage accordingly
High: BCG unresponsive or BCG intolerant	Cystectomy (preferred) or Intravesical chemotherapy[p,r] or Pembrolizumab (select patients)[s] or Nadofaragene firadenovec-vncg[t]	

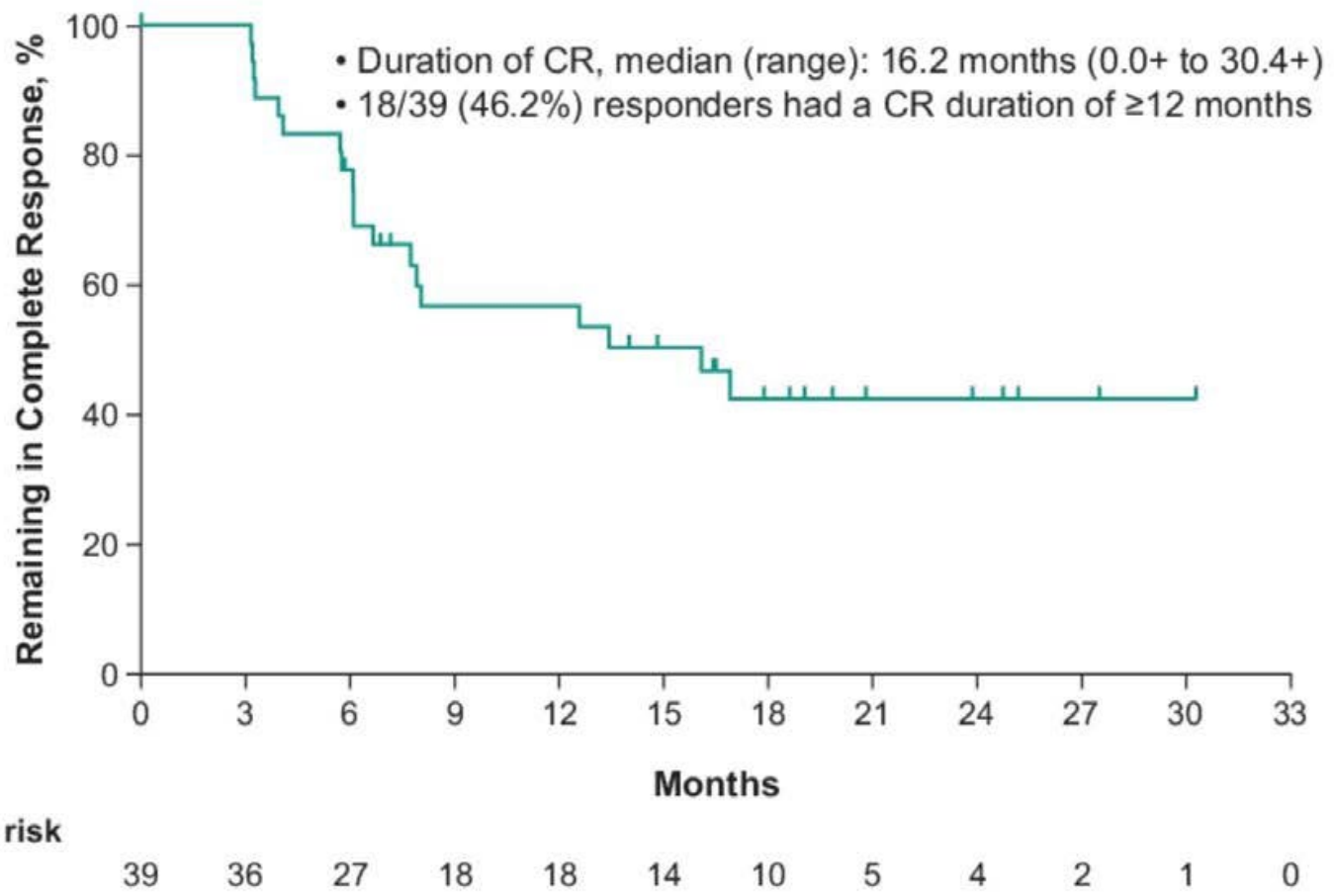
Medical Oncologists



KEYNOTE 057: SINGLE ARM PHASE 2 STUDY OF PEMBROLIZUMAB FOR PATIENTS WITH HIGH-RISK NMIBC UNRESPONSIVE TO BCG



KEYNOTE 057 COHORT A: CIS (+/- PAPILLARY DISEASE) COHORT



" + " indicates ongoing response.

[a]Month 0 = time point when initial CR was achieved. The onset of response was 3 months for most patients.

Plimack E, Nov 2022

N=102

19% complete response at 12 months

No progression to MIBC based on study assessments

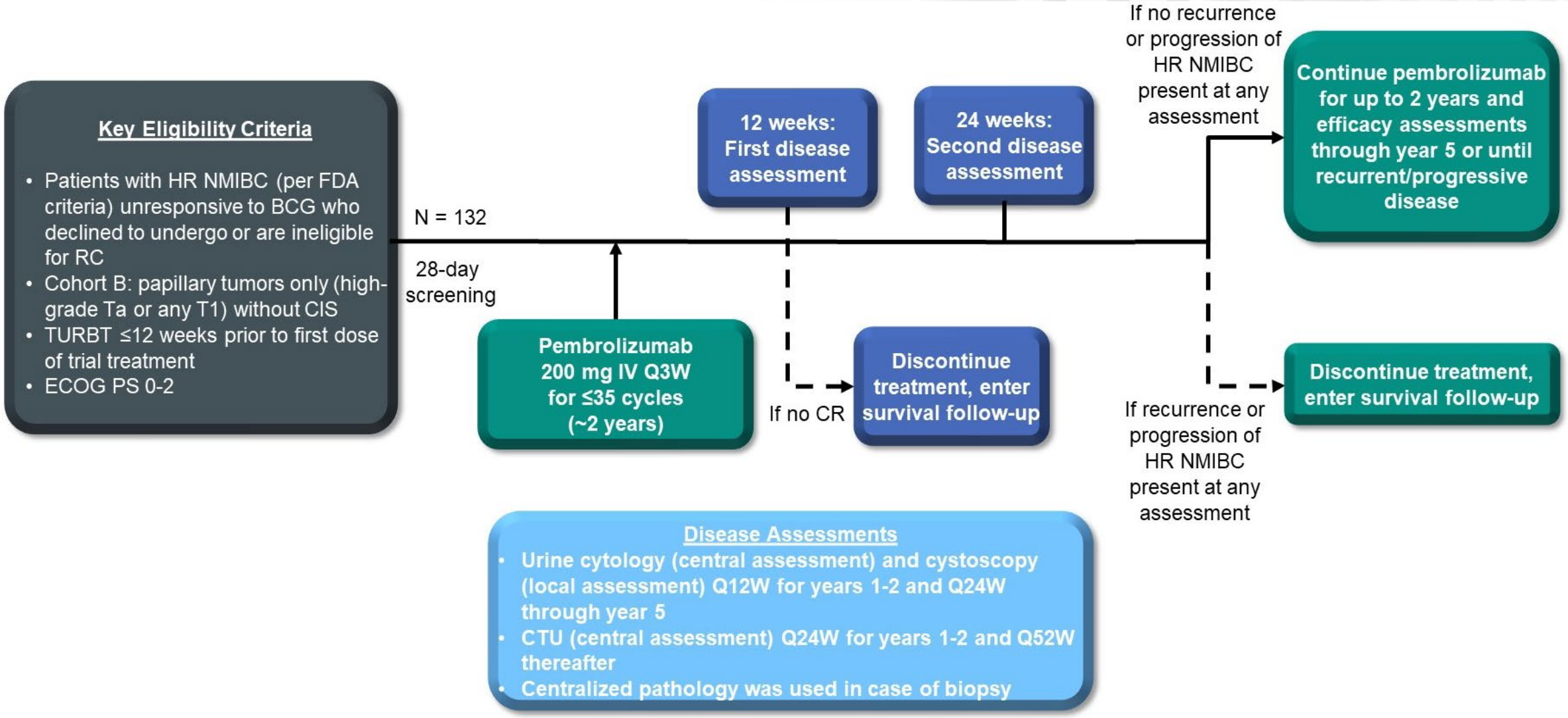
↓ in number at risk:

Very few patients had a maintained CR beyond 18 months

January 8, 2020

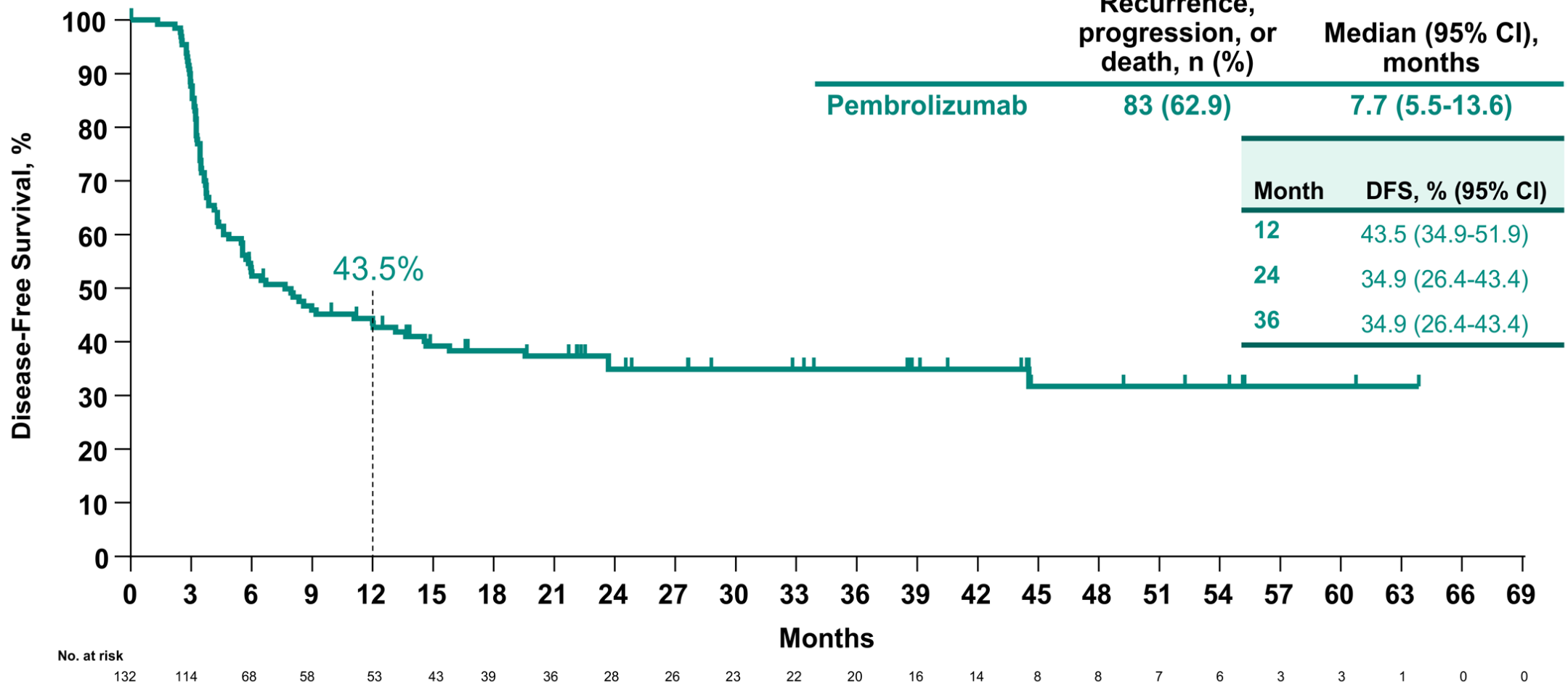
Pembrolizumab for *BCG-unresponsive, high-risk, NMIBC with CIS with or without papillary tumors* who are ineligible for or have elected not to undergo cystectomy.

KEYNOTE 057 COHORT B: TA OR T1 (NO CIS)



TU, computed tomography urography; ECOG PS, Eastern Cooperative Oncology Group performance status.

KEYNOTE 057 COHORT B: TA OR T1 (NO CIS)



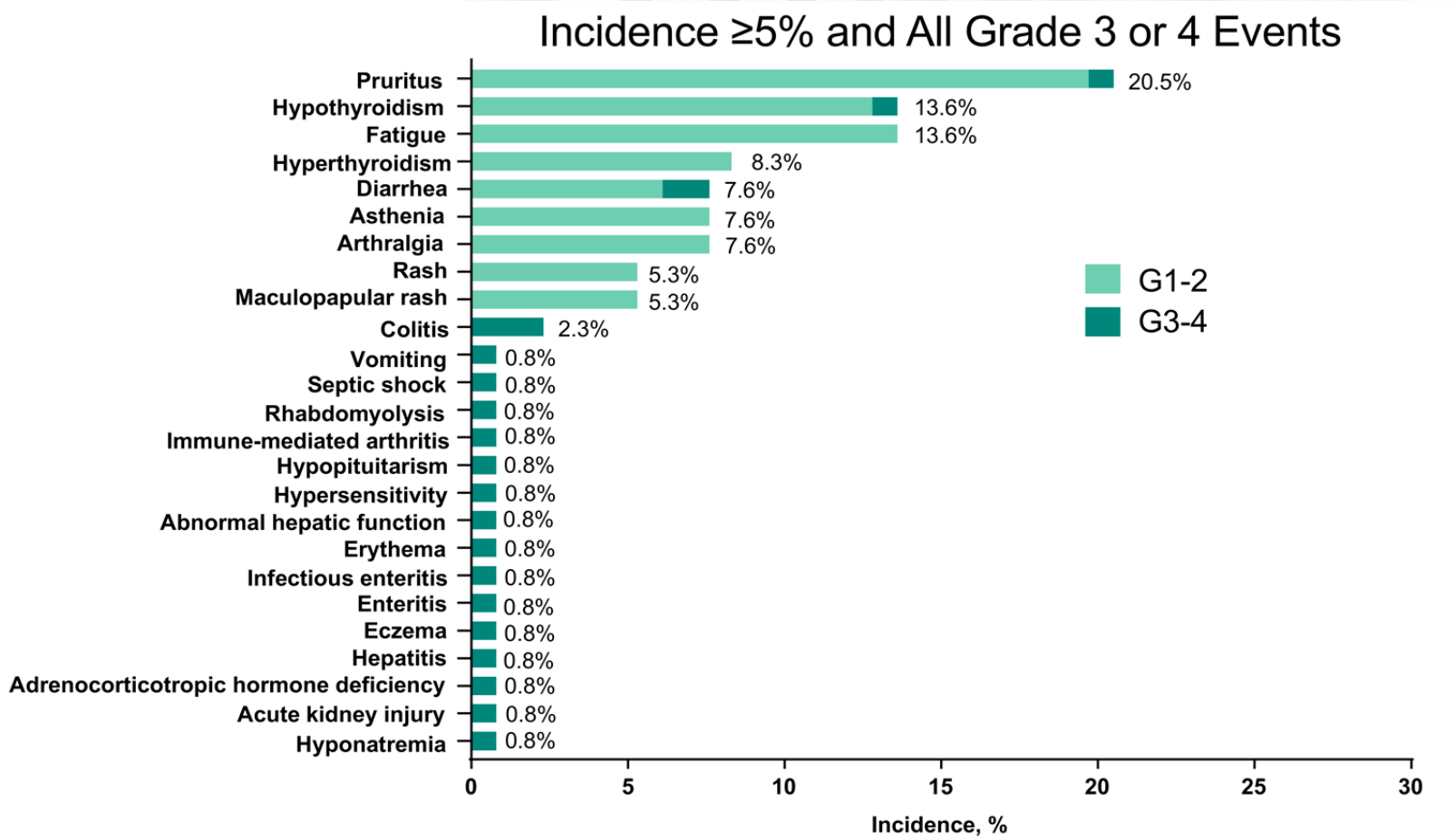
	Recurrence, progression, or death, n (%)	Median (95% CI), months
Pembrolizumab	83 (62.9)	7.7 (5.5-13.6)

Month	DFS, % (95% CI)
12	43.5 (34.9-51.9)
24	34.9 (26.4-43.4)
36	34.9 (26.4-43.4)

[a]Per central pathology/radiology review.
Data cutoff: October 20, 2022.

KEYNOTE 057 COHORT B: TA OR T1 (NO CIS)

Summary	Cohort B N = 132
Treatment-related AEs	97 (73.5)
Grade 3 or 4	19 (14.4)
Serious	17 (12.9)
Discontinuations	14 (10.6)
Deaths	0 (0)



- Median duration of treatment: 6.3 months (range, 0-26.9)

Values are n (%) unless otherwise noted. Data cutoff: October 20, 2022.

NMIBC REFERRAL TO MED ONC

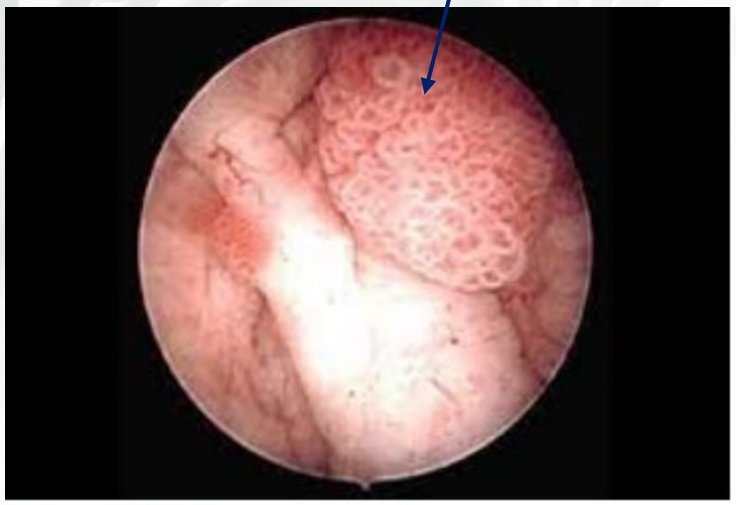
62 y.o. man referred for recurrent CIS (with papillary tumor) urothelial bladder cancer without muscle invasion.

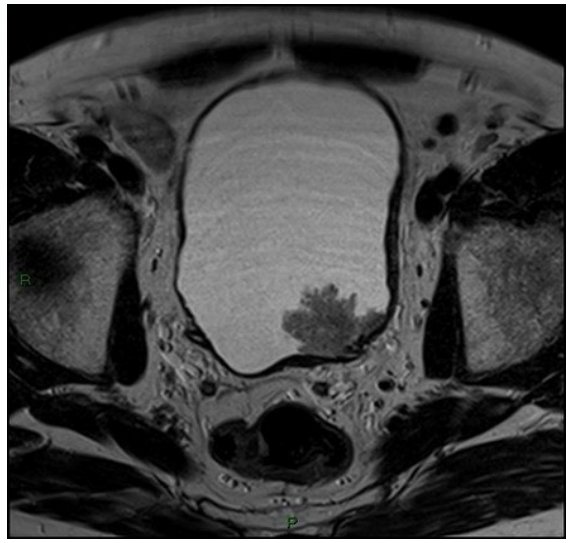
s/p BCG-therapy

intravesical docetaxel/gemcitabine

repeat TURBT

The patient declined radical cystectomy





Cystoscopy image curtsey: Meeks J MD, Research to Practice 2023

WHAT WE TELL PATIENTS RE: PEMBROLIZUMAB IN NMIBC

Still need cystoscopies every 3 months

Appropriate for patients with poor bladder function

Very portable treatment option

24 months, potential side effects

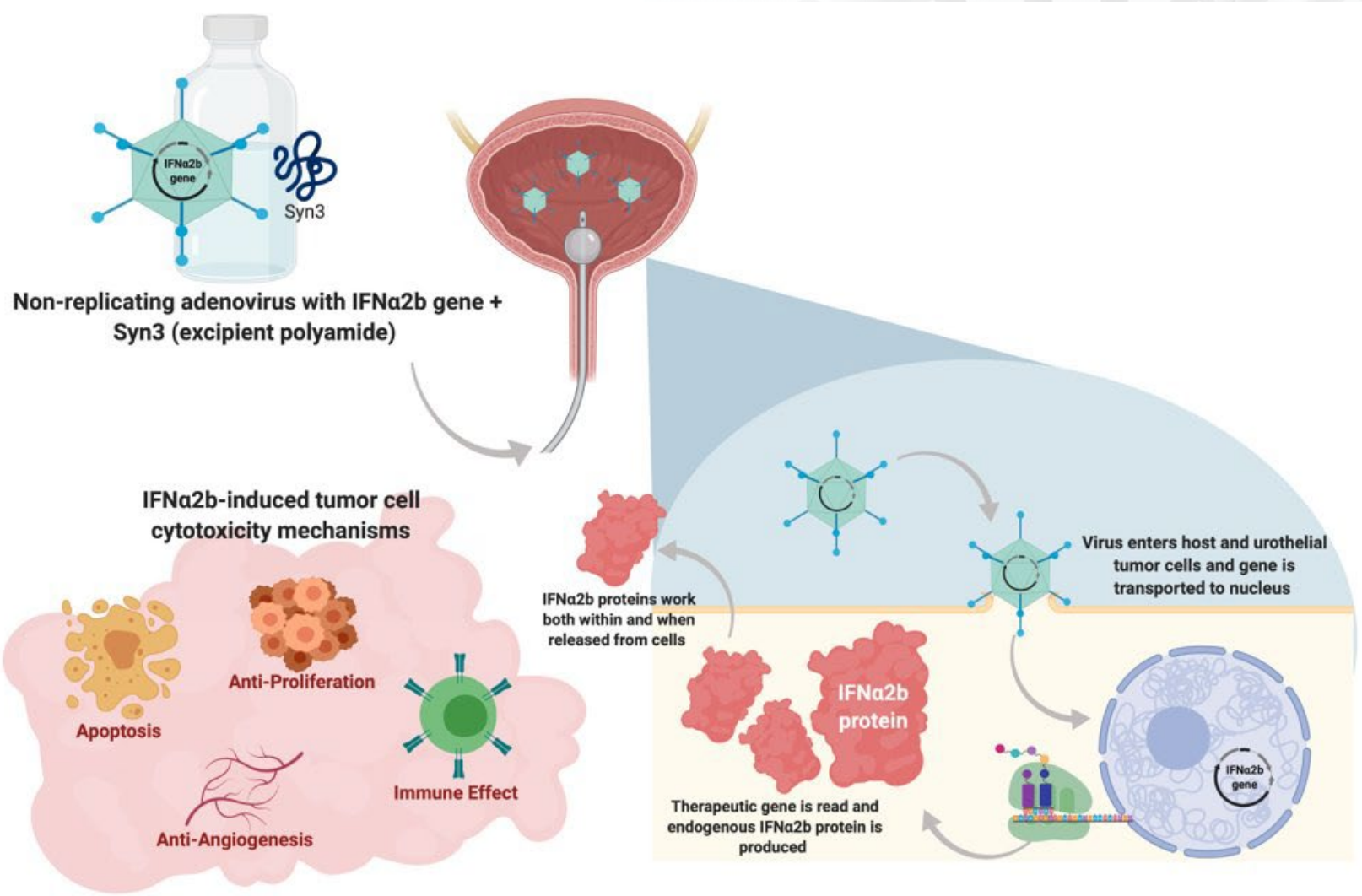
Efficacy questions remain

NMIBC IO TRIALS IN PROGRESS – SELECT PHASE III

Design	n	Study Name/NCT#
BCG +/- pembrolizumab High risk recurrent or persistent after BCG induction	550	KEYNOTE-676 NCT03711032
BCG induction and maintenance + durvalumab Vs. BCG induction only + durvalumab Vs. BCG High-risk BCG/IO naïve NMIBC	975	POTOMAC NCT03528694
BCG Vs BCG + atezolizumab High-risk BCG/IO naïve NMIBC	614	ALBAN NCT03799835

Plimack E, IO for Patients with Nonmetastatic Urothelial Bladder Cancer, 2022

NADOFARAGENE FIRADENOVEC



Narayan and Dinney, *Urol Clin N Am* 2020

THE LANCET
Oncology

ARTICLES | VOLUME 22, ISSUE 1, P107-117, JANUARY 2021

Intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive non-muscle-invasive bladder cancer: a single-arm, open-label, repeat-dose clinical trial

Prof Stephen A Boorjian, MD • Mehrdad Alemozaffar, MD • Prof Badrinath R Konety, MD • Neal D Shore, MD • Prof Leonard G Gomella, MD • Prof Ashish M Kamat, MD • et al. Show all authors

Published: November 27, 2020 • DOI: https://doi.org/10.1016/S1470-2045(20)30540-4 •

Phase III
Single-arm

High-Grade
BCG-unresponsive
NMIBC

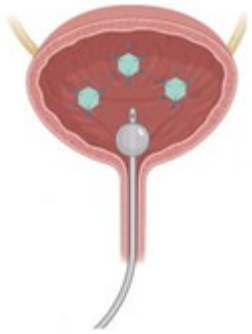
N=157

Cohorts

- CIS +/- Ta/T1

- High-grade Ta/T1

Nadofaragene Firadenovec



75 mL (3x10$_{11}$ vp/mL)

once every 3 months

3, 6, and 9 months

- Cytology

- Cystoscopy

12 months

- Cytology

- Cystoscopy

- Mandatory biopsy

EFFICACY OF NADOFARAGENE FIRADENOVEC

Patients who have achieved HGRF survival at: (n, %)	CIS ± Ta/T1 (N=55)	HG Ta/T1 (N=35)
3 months	55 (100)	35 (100)
6 months	42 (76)	30 (86)
9 months	36 (66)	28 (80)
12 months	25 **(46)**	21 **(60)**

24% CR at 12 months for patients with CIS±Ta/T1 among the entire cohort

Narayan V, 2023

NADOFARAGENE FIRADENOVEC HAS A FAVORABLE SAFETY PROFILE

	Grade 1–2	Grade 3
TOTAL	**103 (66%)**	**6 (4%)**
Discharge around the catheter during instillation	39 (25%)	0
Fatigue	31 (20%)	0
Bladder spasm	24 (15%)	1 (1%)
Micturition urgency	22 (14%)	2 (1%)
Chills	18 (12%)	0
Dysuria	17 (11%)	0
Pyrexia	16 (10%)	0
Syncope	0	1 (1%)
Hypertension	2 (1%)	1 (1%)
Urinary incontinence	4 (3%)	1 (1%)

Majority of AEs are local, some are systemic

Low incidence of Grade 3 toxicities

No Grade 4/5 toxicities

2% treatment discontinuation due to AEs

December 16, 2022

Nadofaragene firadenovec-vncg

for BCG-unresponsive, high-risk, NMIBC with CIS with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.

REFERRAL TO MED ONC

62 y.o. man referred for recurrent CIS
(with p
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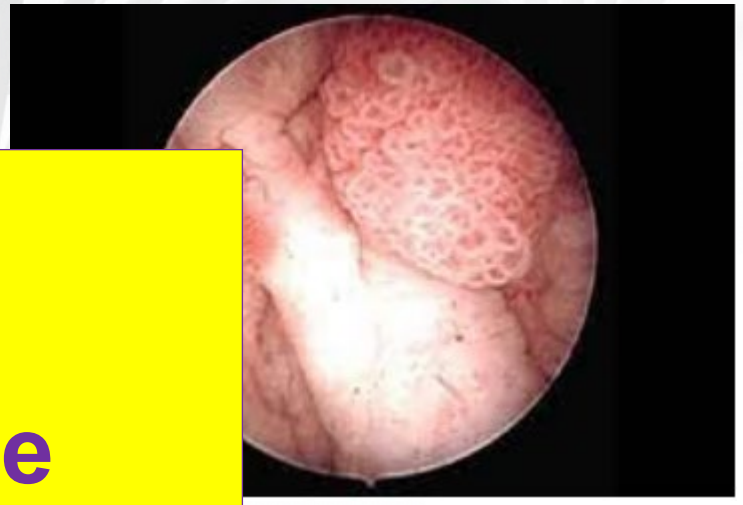
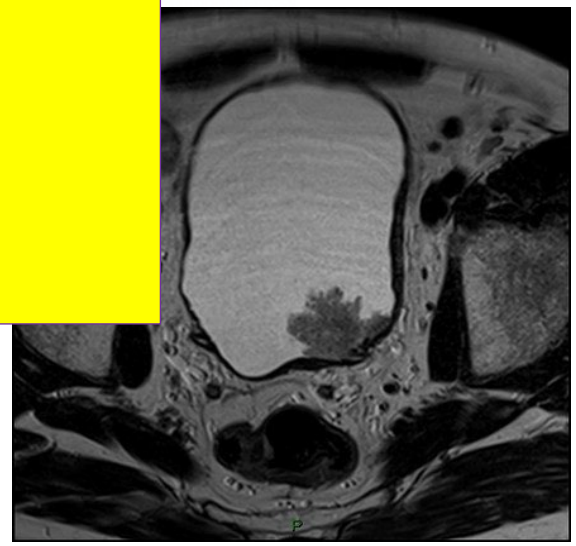
s/p BC
int
re

The patient declined radical cystectomy

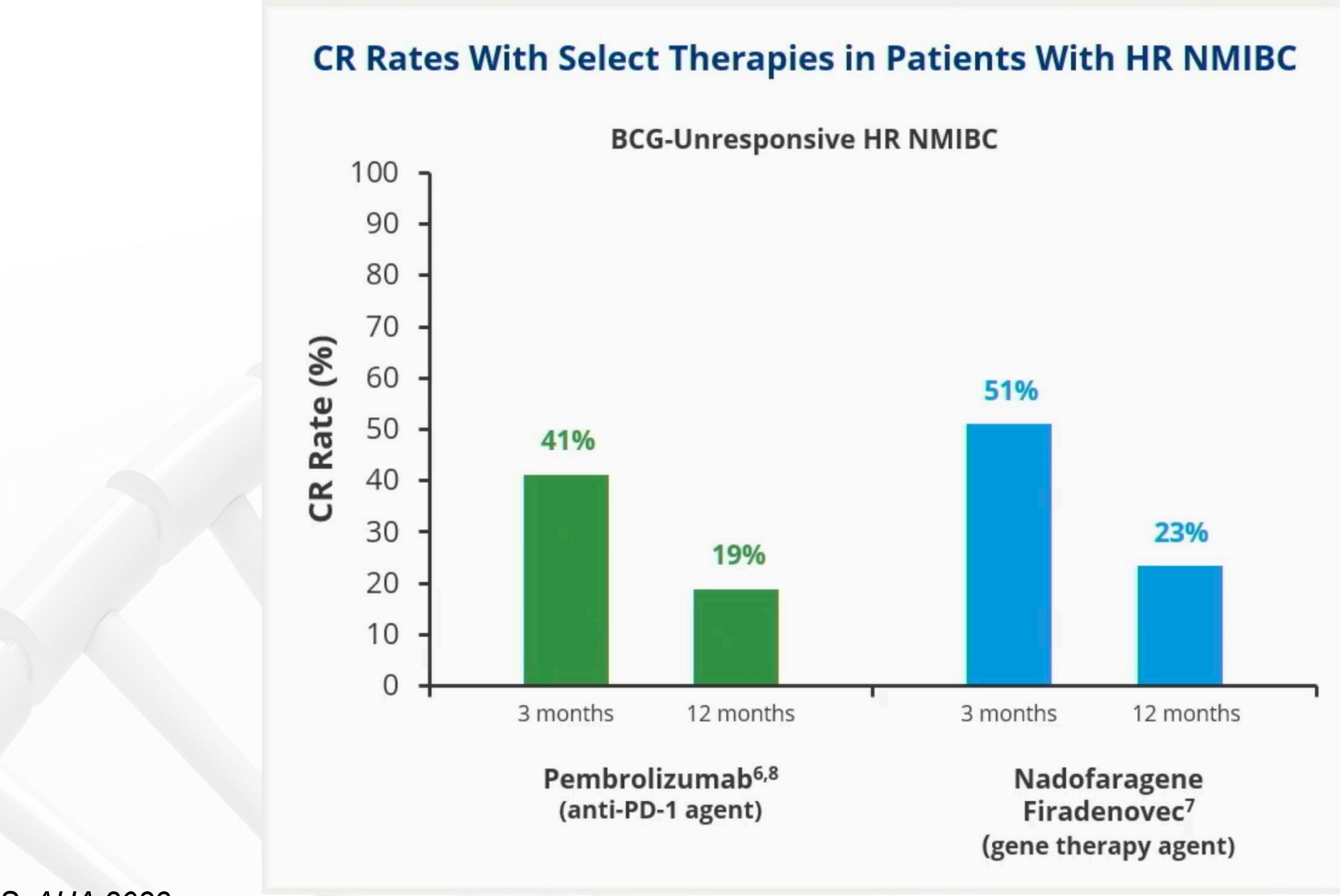




✔ **Eligible for Nadofaragene Firadenovec**

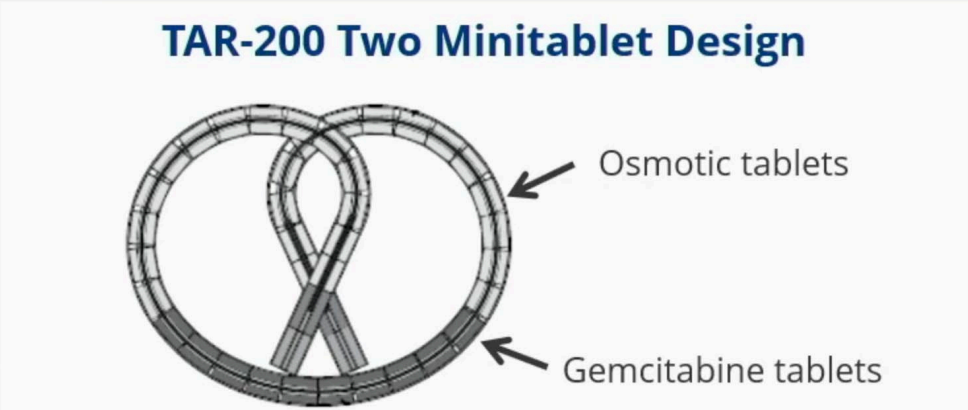
Image curtsey: Joshua J Meeks, MD, PhD

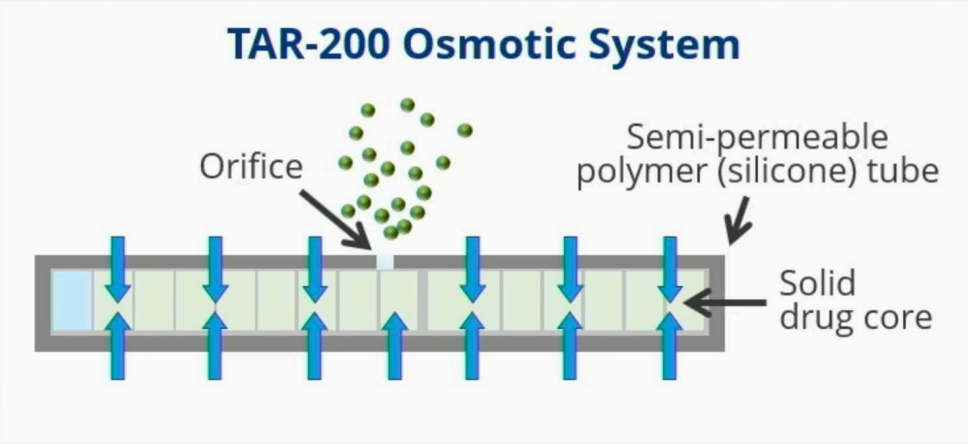
HIGH-RISK NMBIC REMAINS AN AREA OF NEED

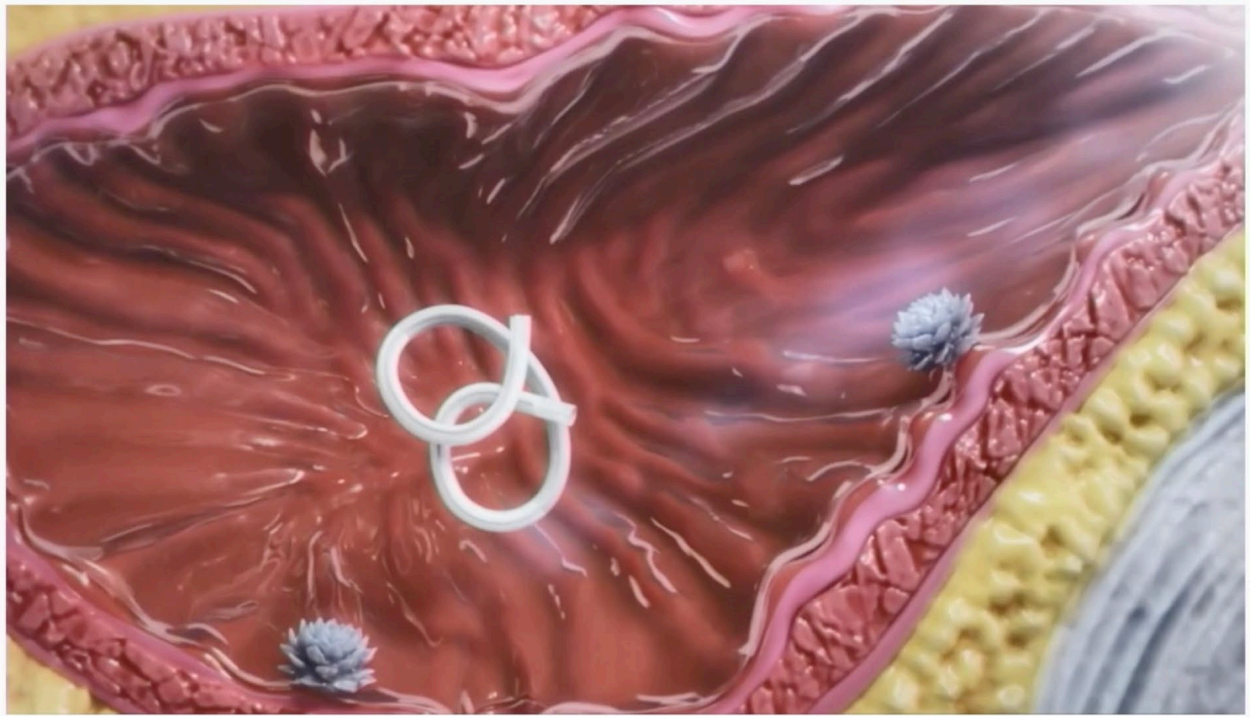


Daneshmand S, AUA 2023

TAR-200: SUSTAINED LOCAL RELEASE OF GEMCITABINE IN THE BLADDER

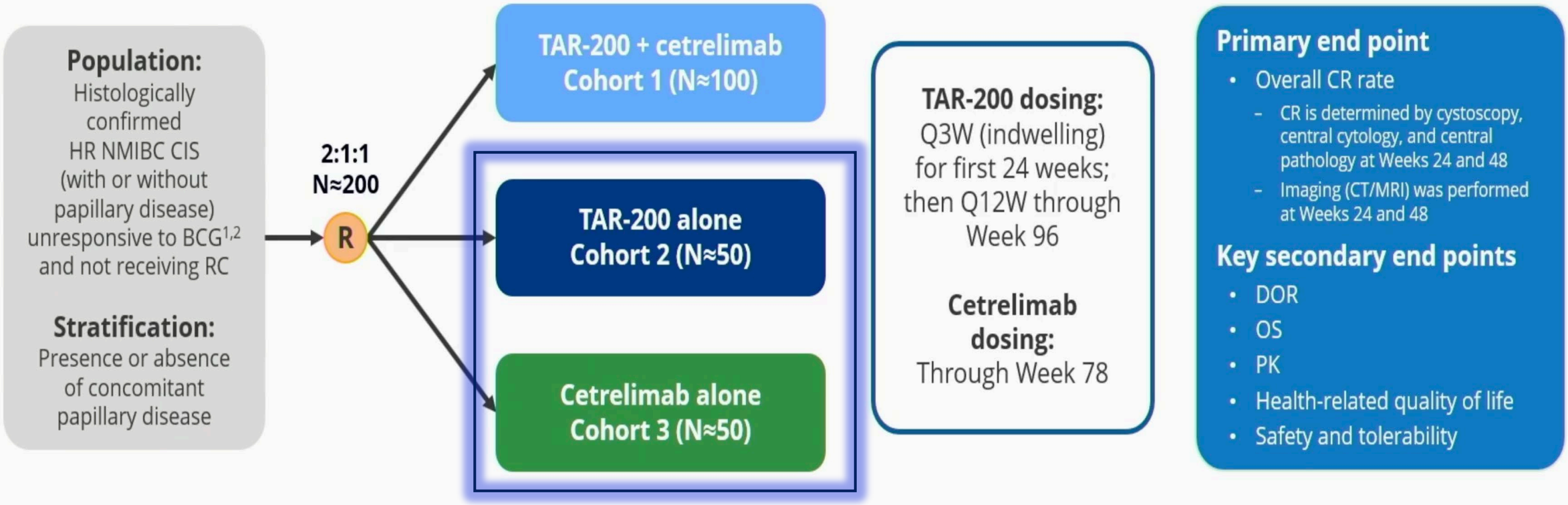






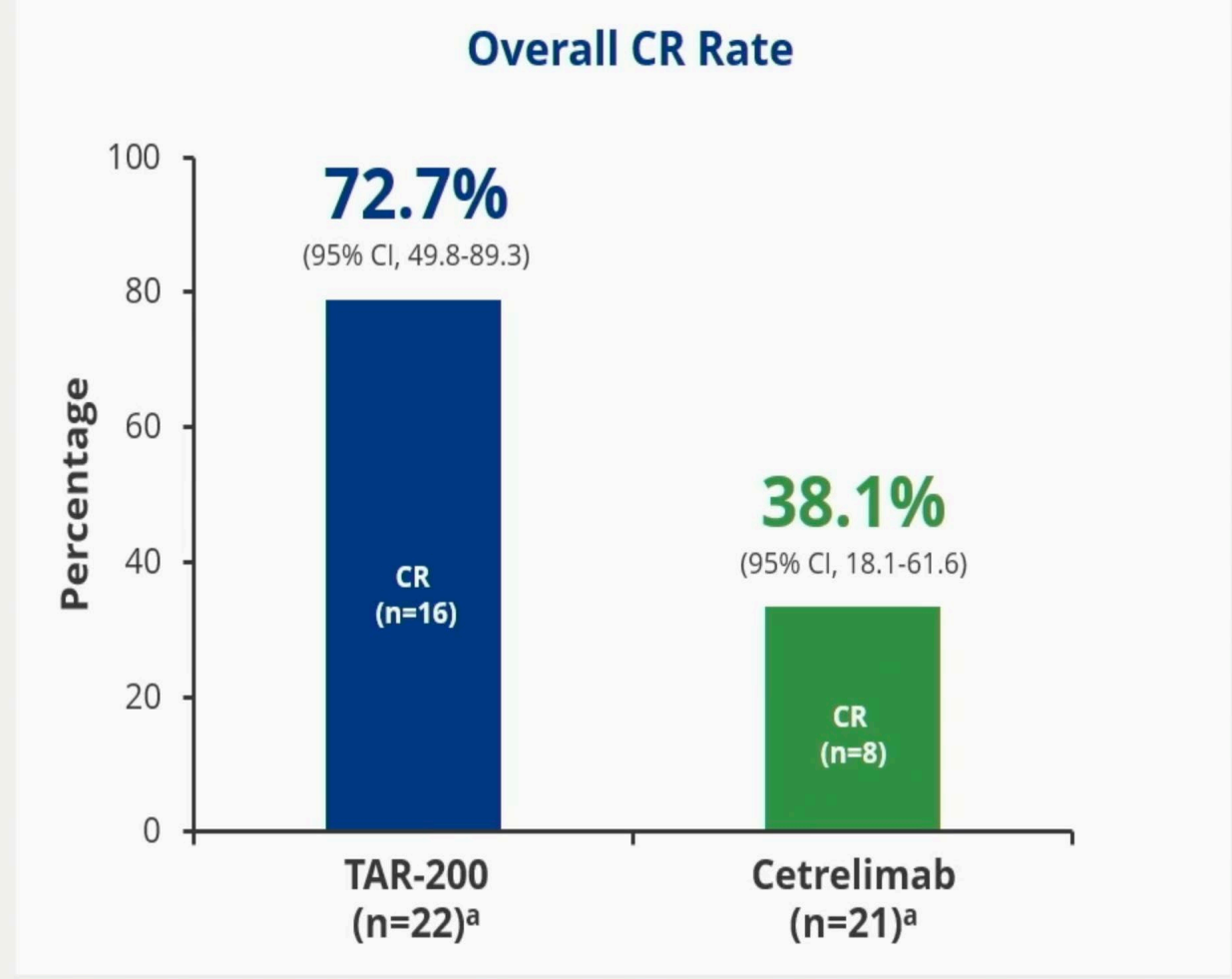
Janssen; Daneshmand S, AUA 2023
2023

SUNRISE-1 (NCT04640623): PHASE 2B, RANDOMIZED, OPEN-LABEL STUDY



Daneshmand S, AUA 2023

SUNRISE-1 EFFICACY



SUNRISE-1 SAFETY

Patients with events, n (%)[b]	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

Daneshmand S, AUA 2023

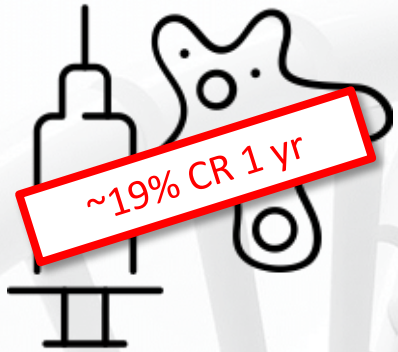
Patients with high-risk BCG-unresponsive NMIBC now have more than one choice

GOLD STANDARD

Radical cystectomy

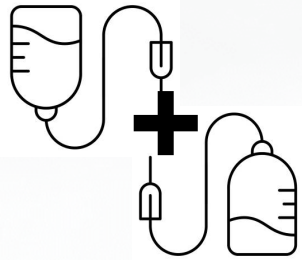
BLADDER SPARING

Intravesical Valrubicin



Pembrolizumab

Intravesical Nadofaragene firadenovec



Intravesical Gemcitabine/Docetaxel

Off Label

CLINICAL TRIAL

~71% CR at ?? yr

TAR-200 + IO

Radiation + IO

Oncolytic adenovirus + IO

BCG + IO

Electromotive Drug Administration

Chemohyperthermia

Adapted from Narayan V 2023

CONCLUDING THOUGHTS ON NMIBC (BCG-REFRACTORY)

Combination of intravesical and systemic Tx is a future direction for patients ineligible for or declining radical cystectomy

Role of IO (and medical oncologists) will grow

Randomized, multi-arm trials in NMIBC are ongoing

Escalation of therapy requires balancing potential benefit with clinical and financial toxicities

Thank you

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