Retos en el manejo del CVNMI, ¿a qué deberíamos dar respuesta?

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Hospital Universitario 12 de Octubre
Madrid

CONFLICTOS DE INTERÉS

Research support/PI	Johnson & Johnson, Pfizer, Taris, BMS, Roche, Seagen, AstraZeneca, Combat Medical, Cepheid, Fidia, Astellas, UroGen, MSD, enGene
Employee	SERMAS (Servicio Madrileño de Salud)
Consultant	Johnson & Johnson, Pfizer, Merck, Roche, Taris, Combat Medical, AstraZeneca, MSD, BMS, enGene, Nanobots Therapeutics
Stockholder	CG Oncology, Johnson & Johnson, Pfizer
Speaker bureau	Janssen, Nucleix, MSD, Pfizer, Merck, BMS, AstraZeneca, Palex, Combat Medical, Johnson & Johnson, Recordati
Travel	Pfizer, Recordati, Ipsen, Combat Medical, Alter, Salvat, Nucleix, AstraZeneca, Fidia, Johnson & Johnson
Scientific advisory board	AstraZeneca, BMS, Combat Medical, Johnson & Johnson, Nucleix, Pfizer, Taris, Roche, MSD, enGene
Manuscript support	Pfizer, Janssen, Combat Medical, AstraZeneca, Johnson & Johnson, BMS

Areas for improvement in NMIBC

Diagnosis	Screening, novel biomarkers, enhanced endoscopic visualization, functional imaging
Follow-up	Improved risk stratification, novel biomarkers, more tailored follow-up, cost
TURBT	Blue light cystoscopy, bladder mapping, en bloc, TURBT avoidance
Cystectomy	Robotic, fast-track protocols, complication rate, cystectomy avoidance
Recurrence	Decrease not only rates, but also time to event
Progression	

TURBT: the neglected procedure?

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European Association of Urology

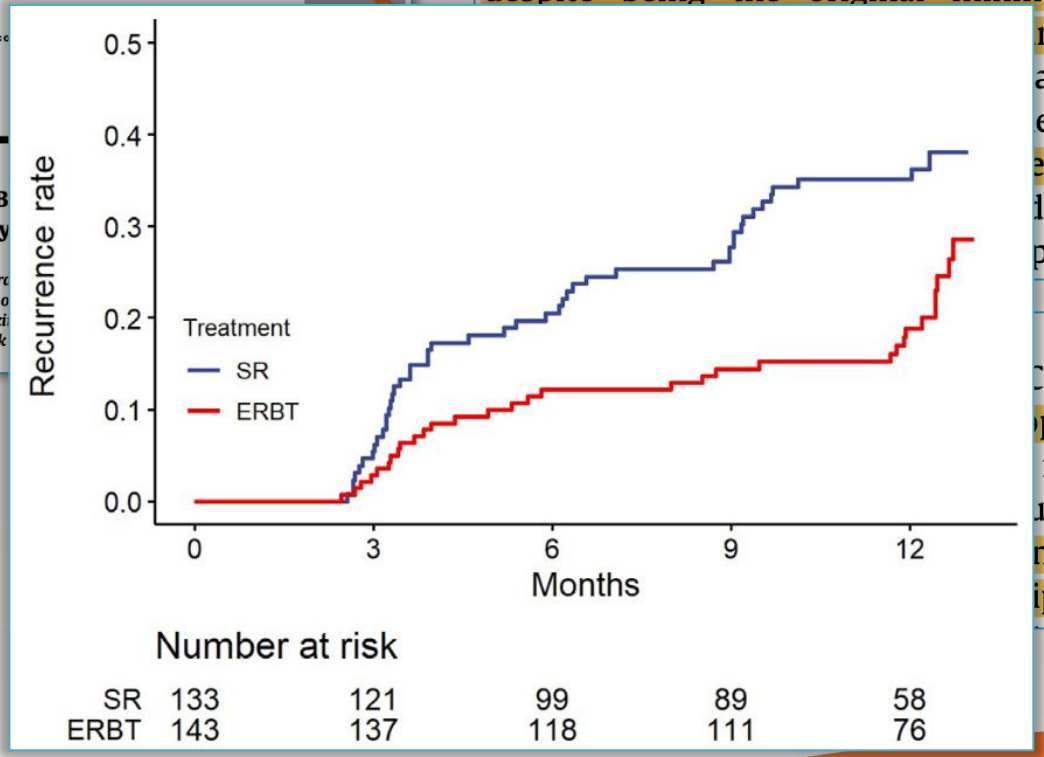
Platinum Opinion

Transurethral Resection of B
Procedure in the Technology

Hugh Mostafid[a], *Marko Babjuk*[b], *Bernard*
Morgan Roupret[g], *Sharokh Shariat*[h], *Pao*
Richard Sylvester[l], *Eva Comperat*[m], *Maxi*
Stephen Williams[q], *Peter Black*[r], *Siamak*
Jim Catto[v], *Ashish M. Kamat*[w,*]

despite being the original minimally invasive cancer
ns an anachronism in
al surgery is performed
ever designed for this
eces using a technique
described by Jones and
perhaps not surprising

in improving surgical
needs to be explored.
peration familiar to all
is therefore practiced
ut a focused interest in
ng is the historical lack
ipment manufacturers.



Teoh J, et al. Eur Urol. 2024

Current treatment landscape

EAU Risk Group: Intermediate	
In general, chemotherapy (the optimal schedule is unknown) is a reasonable first-line option in the majority of patients. One-year full-dose BCG treatment (induction plus three-weekly instillations at 3, 6 and 12 months), is an alternative option. The final choice should reflect the individual patient's risk of recurrence and progression as well as the efficacy and side effects of each treatment modality. Offer one immediate chemotherapy instillation to patients with small papillary recurrences detected more than one year after previous TURB.	Strong
EAU risk group: High	
Offer intravesical full-dose instillations for one to three years but discuss immediate radical cystectomy (RC).	Strong
EAU risk group: Very High	
Offer RC or intravesical full-dose BCG instillations for one to three years, particularly to those who decline or are unfit for RC.	Strong

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INTRACAVITARY BACILLUS CALMETTE-GUERIN IN THE TREATMENT OF SUPERFICIAL BLADDER TUMORS

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ABSTRACT

Patients with recurrent superficial bladder tumors have been treated by vesical and intradermal administration of Bacillus Calmette-Guerin. The pattern of recurrence in 9 patients has been altered favorably. Although the findings are still preliminary they appear to hold promise of a new therapeutic approach to the treatment of a group of neoplasms for which effective therapy is still lacking.

Instillation of oncolytic agents has been used for many years in the treatment and prophylaxis of superficial bladder tumor recurrences with variable success.[1-3] The location and natural history of these neoplasms and the easy accessibility of the bladder make this type of therapy particularly attractive.

The antigenicity of bladder tumors has been demonstrated repeatedly.[4, 5] This would suggest that immunotherapy may be useful in the eradication of non-invasive bladder neoplasms. Successful Bacillus Calmette-Guerin (BCG) immunotherapy must meet several criteria: 1) ability to develop an immune response to mycobacteria antigens, 2) adequate numbers of living bacilli, 3) close contact between BCG and tumor, 4) relatively small tumor load and 5) freedom from major systemic side effects.[6] Superficial bladder tumors appear to be ideally suited to this approach. The results presented summarize our initial experience with the use of BCG in the treatment and prophylaxis of these neoplasms.

MATERIALS AND METHODS

There were 2 groups of patients considered candidates for BCG immunotherapy. In group 1 were patients with a history of persistent tumor recurrences but in whom all gross evidence of cancer was eliminated by endoscopic fulguration prior to the onset of immunotherapy. In group 2 were patients with tumor recurrence in whom complete endoscopic eradication of the neoplasm was not achieved. In every case the tumor was clinically and histologically staged and considered to be superficial (T_a to T_1).

Immunological evaluation was performed in vivo and in vitro. In vivo studies consisted of the determination of delayed cutaneous hypersensitivity to a battery of recall antigens: tuberculin, histoplasmin, dermatophytin and streptokinase-streptodornase. In vitro studies included absolute peripheral lymphocyte counts and determination of T and B subpopulations as previously described.[7]

BCG administration. The vaccine was given by intradermal and per urethram routes. Five mg. BCG (Institut Armand Frappier, Montreal) was administered to the upper thigh using a multiple puncture apparatus. For the intracavitary administration 120 mg. of the vaccine reconstituted in 50 cc normal saline was injected into the bladder through a No. 8 urethral catheter. The patient was advised to retain the fluid for not less than 2 hours. Treatments were repeated at weekly intervals for 6 weeks, alternating thighs for the intradermal administration.

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* Current address: Laboratory of Immunodiagnosis, Building 8, Room 118, National Institutes of Health, Bethesda, Maryland 20014.

Four to 6 weeks after the last immunization cystoscopy was performed. Any areas suggesting the presence of tumor were biopsied, otherwise random samples were taken. Recheck cystoscopies were performed periodically thereafter.

RESULTS

Delayed cutaneous hypersensitivity. All patients exhibited a cutaneous reaction to mycobacteria antigens. In 4 cases the administration of tuberculin caused no reaction but strong reactivity was obtained 3 weeks after administration of BCG. Response to other recall antigens was found in 6 patients, the most common being to streptokinase-streptodornase. All patients tested with dinitrochlorobenzene showed reactivity to this substance.

Quantitative lymphocyte studies. The mean numbers of absolute peripheral lymphocytes and the T and B subpopulations are illustrated in figure 1. The initial values are not different from the ones found in normal subjects. This finding may well reflect the limited tumor load. Although an increase in lymphocyte populations was noted after the onset of therapy the values lack statistical significance.

Recurrence rate. The number of recurrences found in the 12-month period immediately before BCG therapy and during the post-vaccination period is illustrated in table 1. Before therapy 9 patients demonstrated a total of 22 recurrences during 77 patient months. After vaccination these 9 patients yielded 1 recurrence during a followup of 41 patient months. However, these 2 total distributions do not permit a valid statistical analysis. On the other hand, looking at 5 cases in which the pre-BCG and post-BCG periods were identical (25 patient months), it was found that 12 recurrences were detected during the pre-BCG period, while after immunization no recurrences were present. With the chi-square test in these 5 patients for the pre-BCG versus the post-BCG periods, a statistically significant difference was obtained (p less than 0.01).

Of the 9 patients who have now received BCG immunotherapy 5 were treated for prevention of recurrence and 4 for residual tumor.

CASE REPORTS

Case 1. An 80-year-old man was found to have a transitional cell carcinoma of the bladder in 1970. Elimination of tumor was achieved by endoscopic fulguration but rechecks every 3 to 4 months demonstrated persistent recurrences. In June 1974 a course of intradermal and intracavitary BCG was decided upon after conversion to purified protein derivative positivity by intradermal injection of BCG. It was well tolerated although the patient experienced fever, malaise and dysuria for 48 to 72 hours after the vaccination. After immunotherapy no recurrences have been detected endoscopically and random biopsies

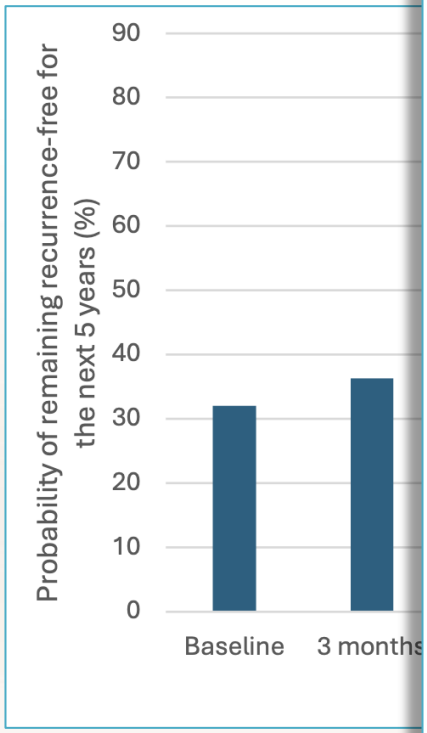
Medical therapy: the endpoint challenge

- Recurrence-free survival
- Disease-free survival
- Safety
- Low-grade vs high-grade
- Event-free survival
- Tolerability
- Cancer-specific survival
- Progression-free survival
- BI event-free survival
- QoL
- Overall survival
- Cystectomy-free survival
- Complete response
- Duration of the response

Another challenge… how to assess the response?

- Cystoscopy
- CT-scan/MRI
- Cytology
- PET-scan?
- Biopsies
- Biomarkers?
- HOW???
- What else?

NMIBC: the challenge of defining CURE



Conclusions

The evidence reviewed in this manuscript indicates that consensus on what constitutes cure and curative intent in early bladder cancer remains to be established. Such consensus would support the development of clinical trial designs that adequately capture cure endpoints and inform healthcare decision-making, both from a clinician-patient and reimbursement perspective. Based on established cure endpoints in other oncology indications, we propose 5-year RFS as a potential cure definition in early bladder cancer. RWE indicates that this endpoint would be feasible, with 5-year RFS being regularly reported.

Guerrero-Ramos F, Eur Urol Oncol, UNDER REVIEW (**PLEASE DO NOT SHARE**)

Intermediate risk

- Improved RFS (and PFS): **adjuvant** approaches
- Avoid TURBTs: **ablative** approaches
- Longer times to recurrence: **both** approaches

High risk

- Improved HG-RFS and PFS
- Minimize toxicity
- Avoid radical cystectomy

BCG unresponsive

- AVOID RADICAL CYSTECTOMY (SoC)…
- … without compromising survival
- **IMPORTANT: CIS vs papillary-only**

Intermediate-risk

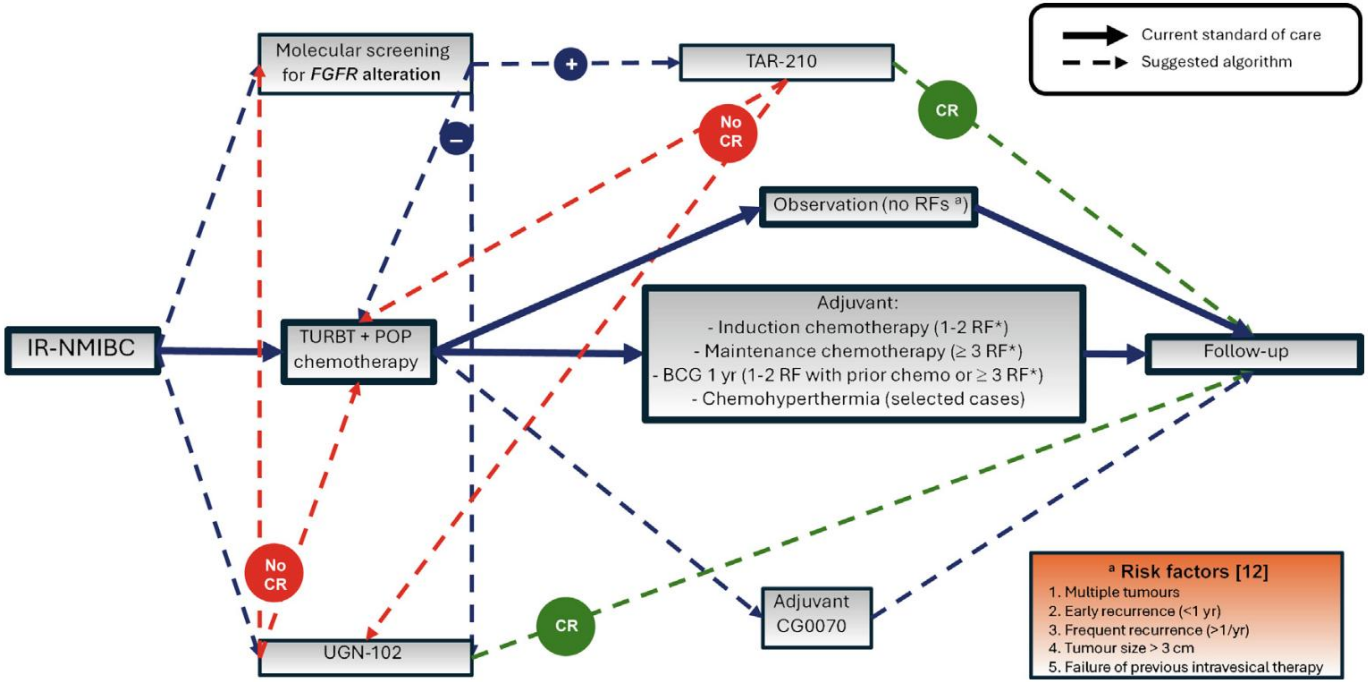


Fig. 2 – Suggested algorithm for the treatment of IR-NMIBC after the eventual approval of all new agents (all intravesical). BCG = bacillus Calmette-Guérin; CR = complete response; IR-NMIBC = intermediate-risk non–muscle-invasive bladder cancer; POP = postoperative; RFs = risk factors; TURBT = transurethral resection of bladder tumour. [a] Risk factors according to Tan et al [12].

Guerrero-Ramos F, Eur Urol Oncol 2024

High-risk

Table 1 – Comparative designs of the largest trials assessing novel agents in BCG-naïve high-risk non–muscle invasive bladder cancer

Study title	POTOMAC	ALBAN	KEYNOTE-676 (cohort B)	CREST	SunRISe-3	BRIDGE
Study ID	NCT03528694	NCT03799835	NCT03711032	NCT04165317	NCT05714202	NCT05538663
Intervention	Durv + BCG (I + M) vs Durv + BCG (I) vs BCG (I + M)	Atezolizumab + BCG (I + M) vs BCG (I + M)	Pembro + BCG (M) vs Pembro + BCG (reduced M) vs BCG (I + M)	Sasanlimab + BCG (I + M) vs Sasanlimab + BCG (I) vs BCG (I + M)	TAR-200 vs Cetrelimab + TAR-200 vs BCG (I + M)	Sequential Gem/Doc vs BCG (I + M)
Administration route	Durvalumab: i.v. BCG: IVS	Atezolizumab: i.v. BCG: IVS	Pembro: i.v. BCG: IVS	Sasanlimab: SC BCG: IVS	Cetrelimab: i.v. TAR-200: IVS BCG: IVS	Gem/Doc: IVS BCG: IVS
BCG M	24 mo	12 mo	18 mo	24 mo	24 mo (optional 36 mo)	36 mo
Participants (*n*)	1018	516	975	1070	1050	870
Primary EP	DFS	RFS	EFS	EFS	EFS	EFS
Key secondary EPs	OS, QoL, DSS, QoL	PFS, OS, CR, QoL	OS, CRR, RFS, DSS, TTC, DOR, safety/tolerability	OS, CR, duration of CR, TTC, QoL	RFS, OS, MFS, TTC, TTP, safety, QoL	QoL, safety, toxicity, PFS, CFR
BCG strain	OncoTICE	Medac, OncoTICE	OncoTICE	Various, including OncoTICE	BCG Culture	OncoTICE
Current status	Active, NRC	Active, NRC	Recruiting	Active, NRC	Recruiting	Recruiting
eSCD	September 2025	February 2028	October 2028	December 2027	May 2030	October 2030

BCG = bacillus Calmette-Guérin; CFR = cystectomy-free rate; CR = complete response; CRR = complete response rate; DFS: disease-free survival; DOR: duration of response; DSS: disease-specific survival; Durv = durvalumab; EFS = event-free survival; EP = endpoint; eSCD = estimated study completion date; Gem/Doc = gemcitabine + docetaxel; I = induction; i.v. = intravenous; IVS = intravesical; M = maintenance; MFS = metastasis-free survival; NRC = not recruiting; OS = overall survival; Pembro = pembrolizumab; PFS = progression-free survival; QoL = quality of life; RFS = recurrence-free survival; SC = subcutaneous; TTC = time to cystectomy; TTP = time to progression.

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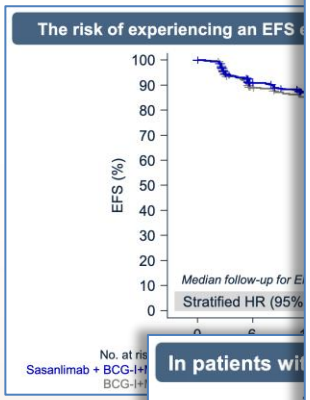
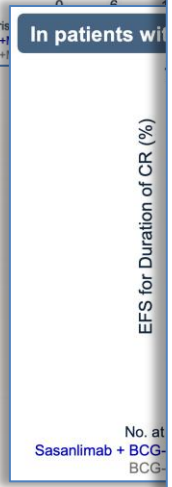
High-risk:

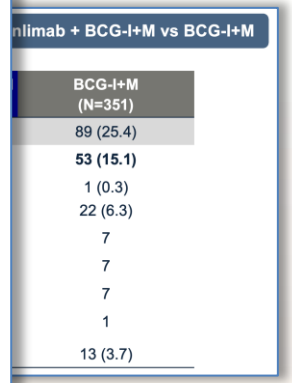




AstraZeneca

Imfinzi regimen demonstrated statistically significant and clinically meaningful improvement in disease-free survival for high-risk non-muscle-invasive bladder cancer in POTOMAC Phase III trial

PUBLISHED
9 May 2025



BCG unresponsive: CIS

FDA approves pembrolizumab for BCG-
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dition:
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patients with high-risk Bacillus Calmette-Guérin unresponsive non-muscle invasive bladder
in situ w
y tumors
ndekin alf
nsive non-
bladder cancer

2022

2024

TAR-200
82.4% AAT

CG0070 + pembrolizumab
82.9% 3m

CRR 53.4% 3m

CG0070
75.5% 3m

Detalimogene voraplasmid
67.0% 3m

www.fda.gov. Balar AV, Lancet Oncol 2021. Boorjian SA, Lancet Oncol 2021. Chamie K, NEJM Evid 2022. Jacob J, AUA 2025. Tyson MD, AUA 2025. Li R, Nat Med 2024. Taylor JA, ASCOGU 2025. Guerrero-Ramos F, Eur Urol Oncol 2024.

BCG unresponsive: papillary-only

Other a
12
(with rei

NCT04640623

Population:
- Aged ≥18 years
- Histologically confirmed HR NMIBC CIS (+/-papillary disease)
- ECOG PS of 0-2
- Persistent or recurrent disease within 12 months of completion of BCG
- Unresponsive to BCG[1,2] and not receiving RC

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

R

TAR-200 + Cetrelimab[b]
Cohort 1 (N=53)[c]
Cohort 1 was closed

TAR-200 Monotherapy
Cohort 2 (N=85)
Enrollment completed

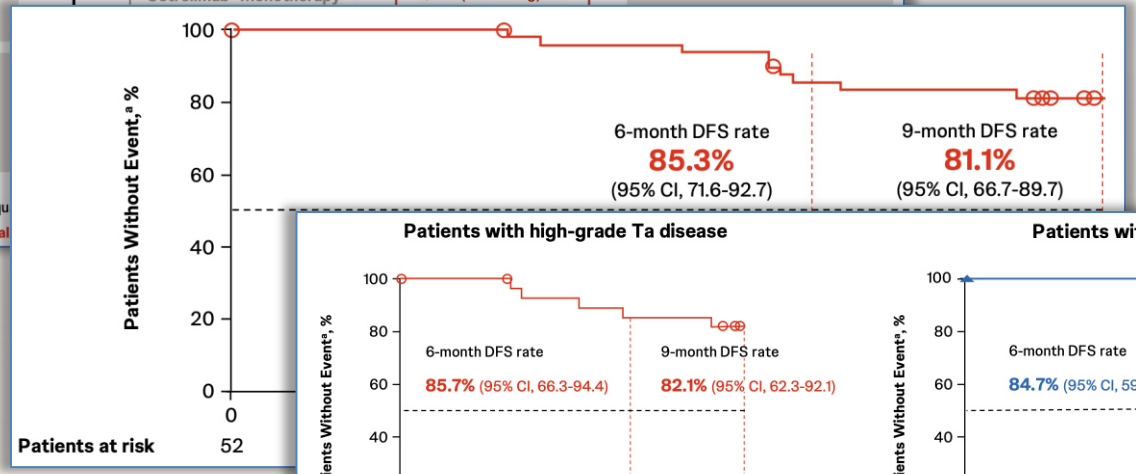
Cetrelimab[b] Monotherapy

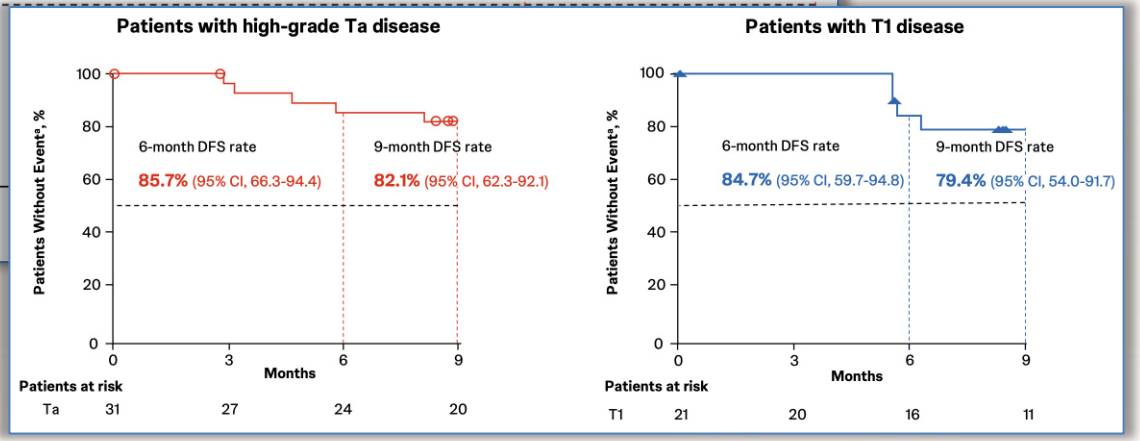
TAR-200 dosing: Q3W (indwelling) for

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

Key secondary end points
- DOR
- Safety

- Response is determined by qu
- The study protocol did not al





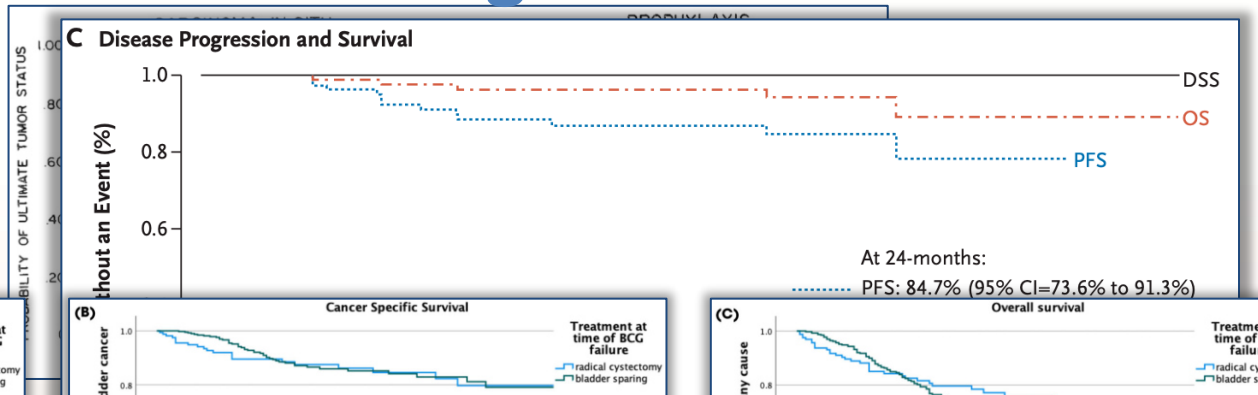
Necchi A, ASCOGU 2023; Chamie K, NEJM Evidence 2022; Boorjian SA, Lancet Oncol 2021; Guerrero-Ramos F, AUA 2025

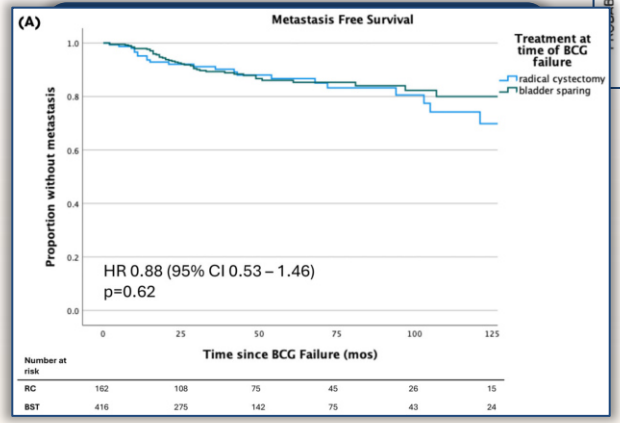
Challenges in the BCGu setting

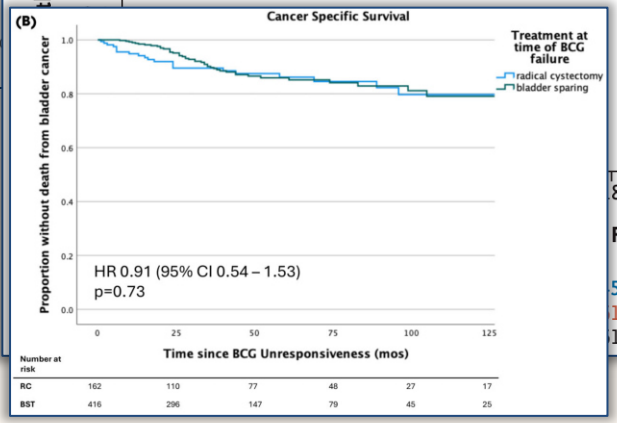
- SURVIVAL
- COST
- BIOMARKERS

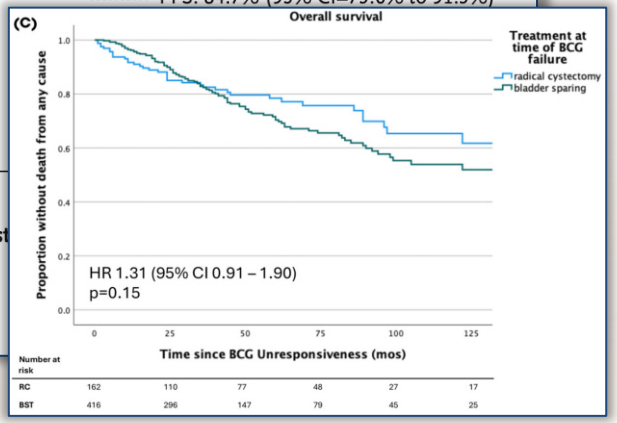
Challenges in the BCGu setting

SURVIVAL









Catalona WJ, J Urol 1987; Chamie K, NEJM Evidence 2022; Taylor JI, BJU Int 2024

Challenges in the BCGu setting

SURVIVAL

COST

BIOMARKER

	Pembrolizumab	Nadofaragene firadenovec	BCG + N-803
Price per dose	$11,957 (200 mg)	$60,000 (75 mL)	$35,800 (400 µg)
Dosage	Every 3 weeks	Every 3 months	≃SWOG-BCG
Duration	24 months	12 months	18 months
Total doses	34	4	21
Overall cost*	**$406,538**	**$240,000**	**$751,800**

Estimated cost of a radical cystectomy:
$70,000 (90 days), $150,000 (1 year)

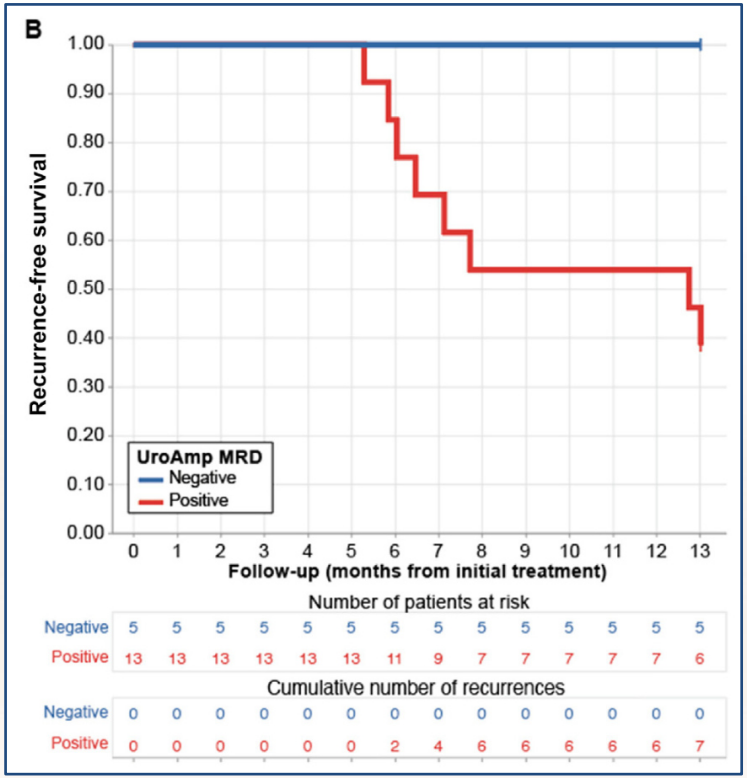
*All these are estimations; Williams SB, JAMA Surgery 2019

Challenges in the BCGu setting

SURVIVAL

COST

BIOMARKERS



Narayam VM, Eur Urol Oncol 2024

CONCLUSIONS

- Bladder cancer is not the same at all stages → **different endpoints**
- NMIBC requires a high **individualized approach**
  - Offer the right **drug** to the right patient
  - Offer the right **plan** to the right patient
- Understand the concept of **cure** in this stage of the disease
- **New therapies** are a reality
  - But… not exempt of **challenges**
- In certain scenarios, we will have to **work together** (even more)

¡Muchas gracias!

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