VGO NORTE INTERNATIONAL GU DEBATES

New IO based treatments are not ready for prime time in BCG naïve NMIBC patients

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Disclosures

Research support/PI	Johnson & Johnson, Pfizer, Taris, BMS, Roche, Seagen, AstraZeneca, Combat Medical, Cepheid, Fidia, Astellas, UroGen, MSD, enGene, Tyra Bio
Employee	SERMAS (Servicio Madrileño de Salud)
Consultant	Johnson & Johnson, Pfizer, Merck, Roche, Taris, Combat Medical, AstraZeneca, MSD, BMS, enGene, Nanobots Therapeutics, Gebro, Photocure
Stockholder	CG Oncology, Johnson & Johnson, Pfizer, Danae Urogenomics
Speaker bureau	Nucleix, MSD, Pfizer, Merck, BMS, AstraZeneca, Palex, Combat Medical, Johnson & Johnson, Recordati, Gebro
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, Gebro
Others	CEO & Co-founder of Danae Urogenomics

Would you like to have this drug in your practice?

Intravesical

Unexpensive

At 3 years, 75% of the patients are **event-free**

At 3 years, 15% of the patients have a **HG recurrence**

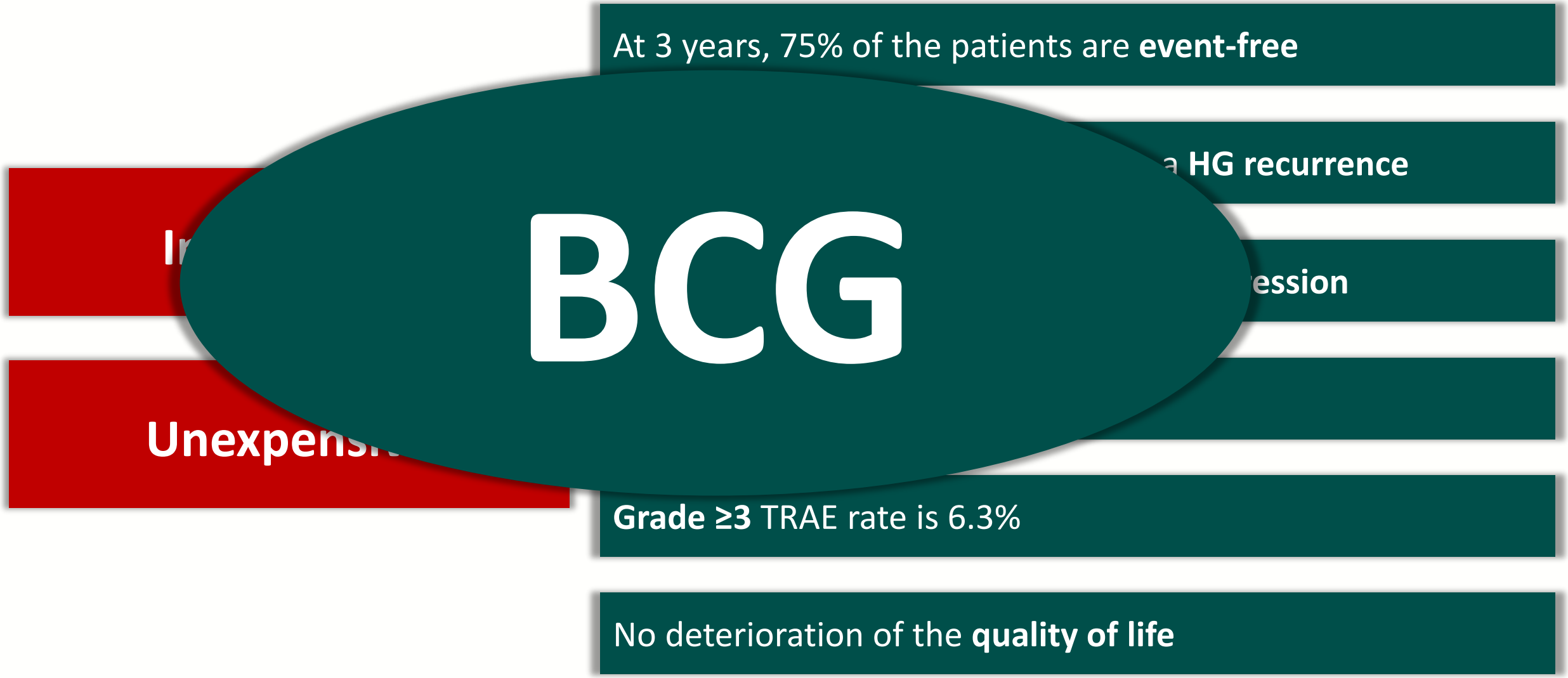
At 3 years, 6% of the patients have a **progression**

For **CIS**, the CR rate is 85%

Grade ≥3 TRAE rate is 6.3%

No deterioration of the **quality of life**

Would you like to have this drug in your practice?



Shore ND, Guerrero-Ramos F, Nat Med 2025

Current clinical research landscape

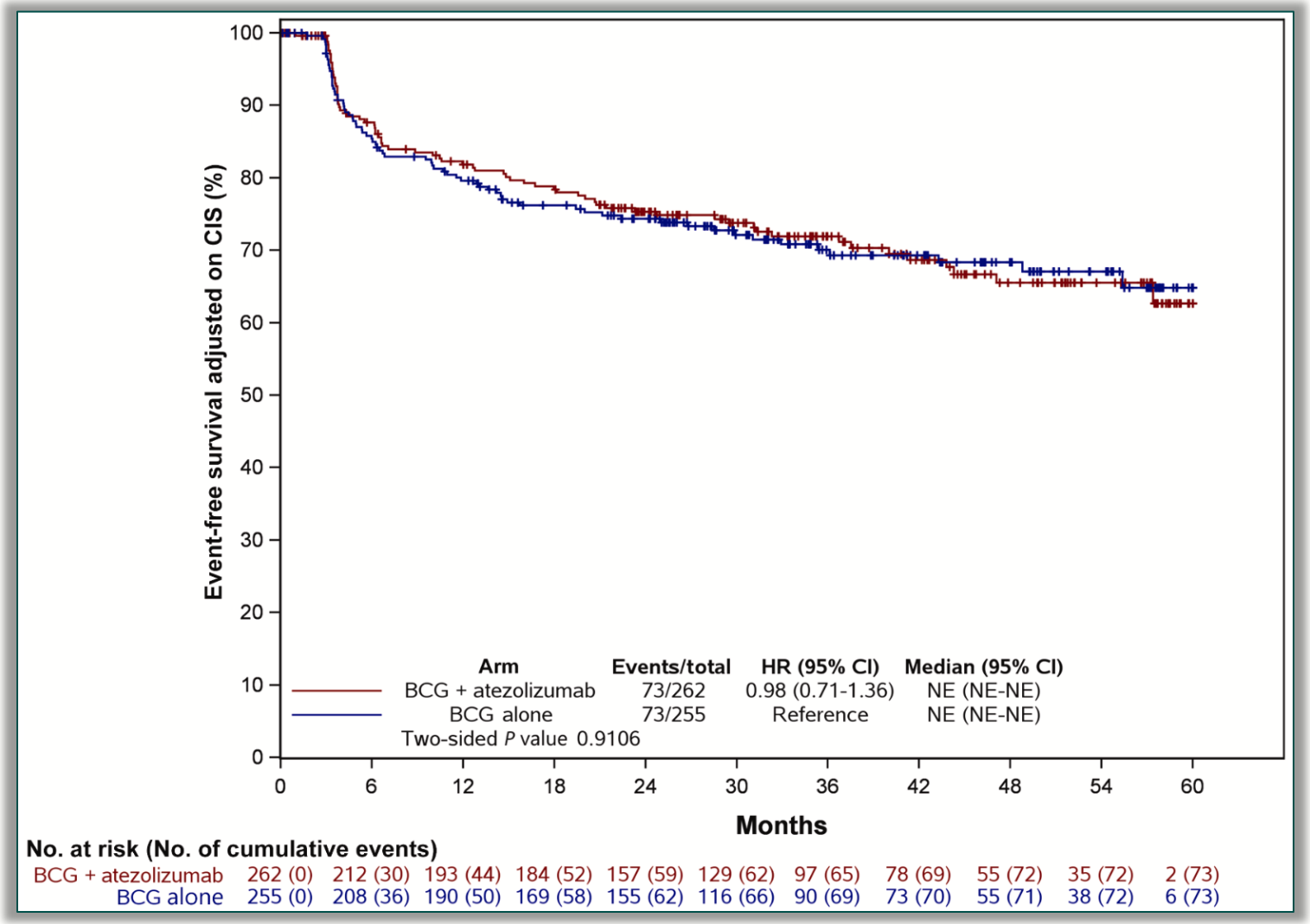
Table 1 – Comparative designs of the largest trials assessing novel agents in BCG-naïve high-risk non–muscle invasive bladder cancer

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.

Guerrero-Ramos F, Eur Urol Oncol 2024

Atezolizumab + BCG is NOT better than BCG alone



Rouprêt M, Ann Oncol 2026

Atezolizumab + BCG is NOT better than BCG alone

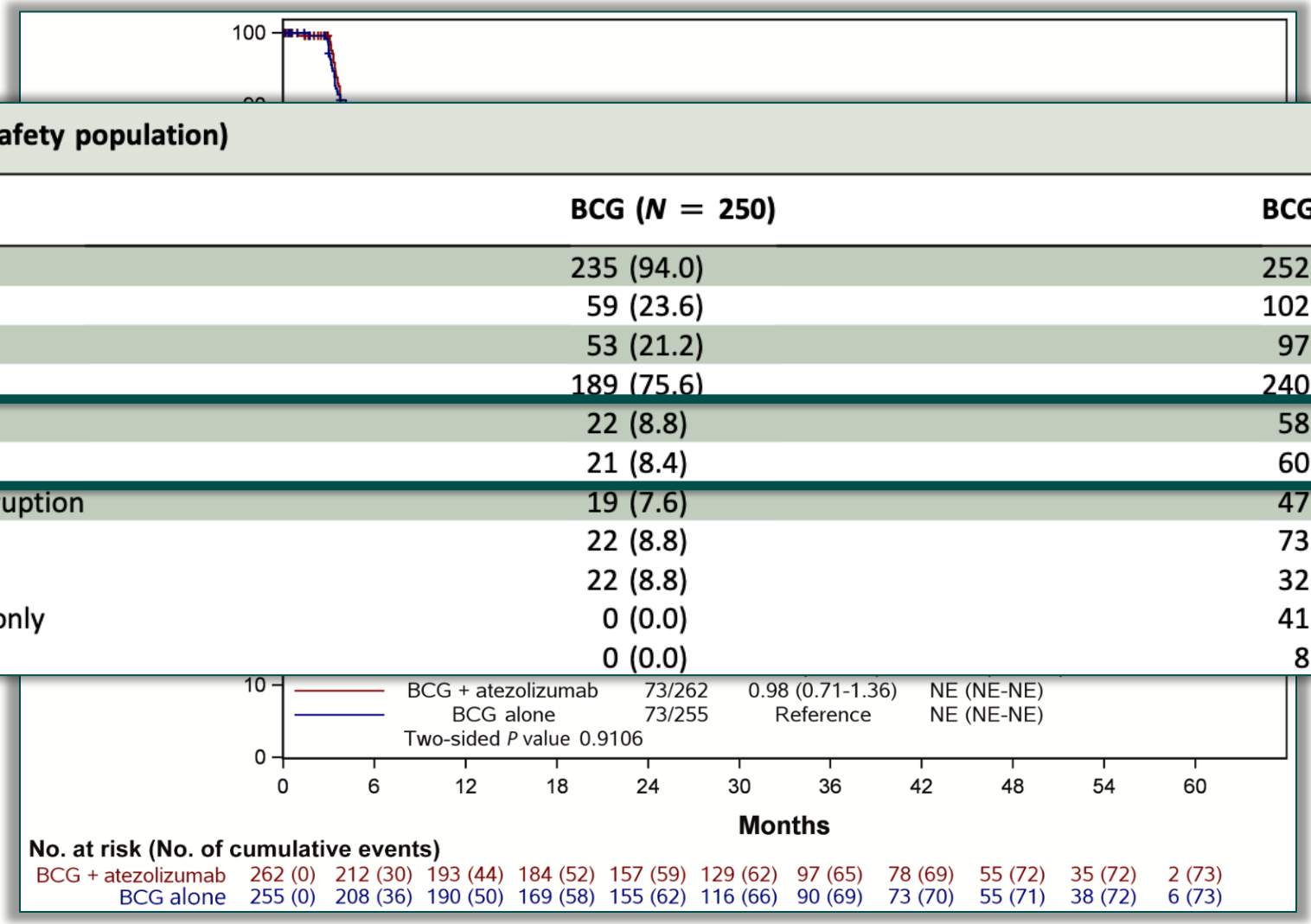
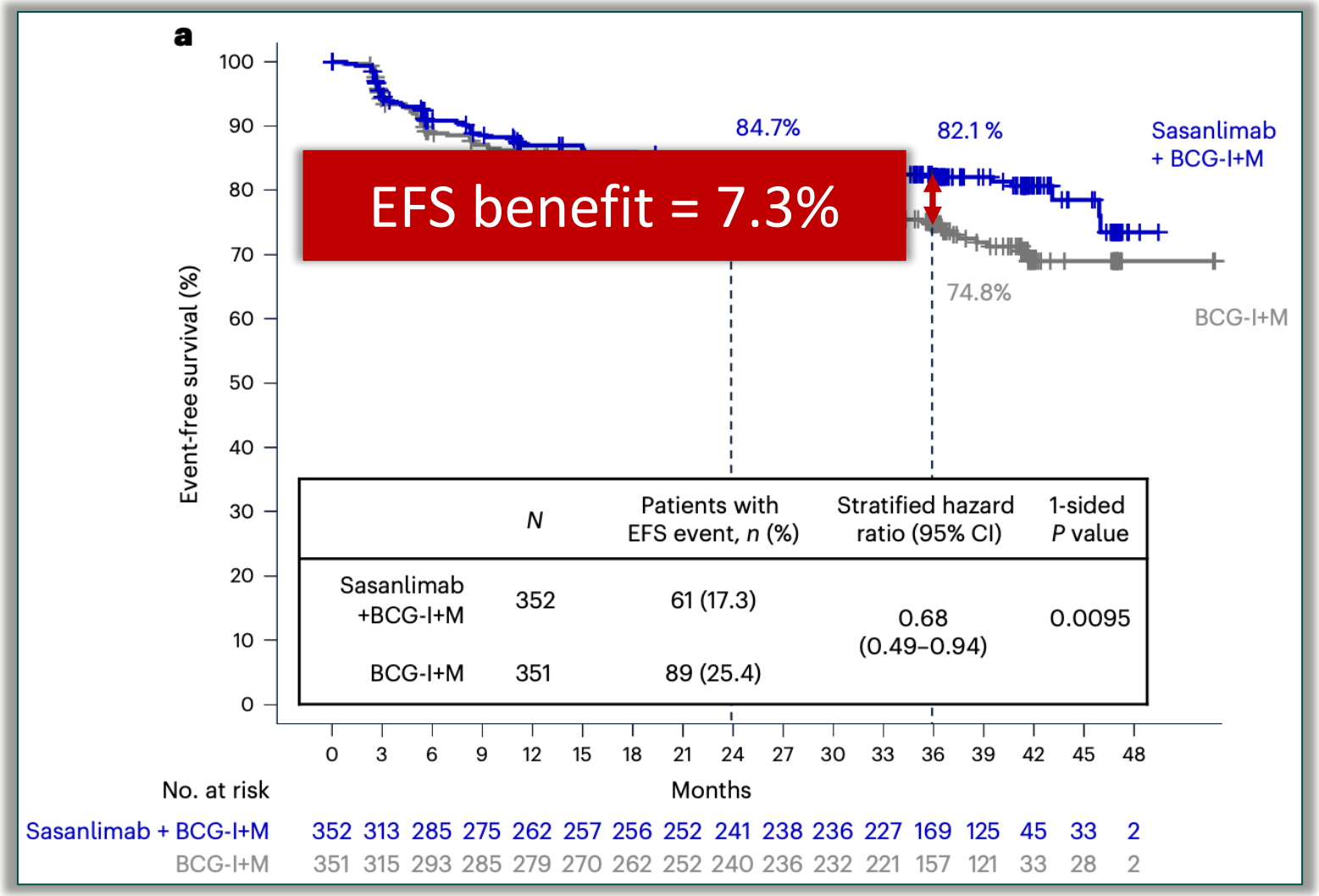


Table 2. Safety summary (safety population)

Events, *n* (%)	BCG (*N* = 250)	BCG + atezolizumab (*N* = 255)
Any AEs	235 (94.0)	252 (98.8)
Grade ≥3 AEs	59 (23.6)	102 (40.0)
Serious AEs	53 (21.2)	97 (38.0)
Any TRAEs	189 (75.6)	240 (94.1)
Grade ≥3 TRAEs	22 (8.8)	58 (22.7)
Serious TRAEs	21 (8.4)	60 (23.5)
TRAEs leading to dose interruption	19 (7.6)	47 (18.4)
TRAEs leading to withdrawal	22 (8.8)	73 (28.6)
BCG withdrawal only	22 (8.8)	32 (12.5)
Atezolizumab withdrawal only	0 (0.0)	41 (16.1)
BCG + atezolizumab	0 (0.0)	8 (3.1)

What about sasanlimab + BCG?



Shore ND, Guerrero-Ramos F, Nat Med 2025

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What about sasanlimab + BCG?

Rate of recurrence of high-grade disease was reduced by >50% with sasanlimab + BCG-I+M vs BCG-I+M

	Sasanlimab + BCG-I+M (N=352)	BCG-I+M (N=351)
Patients with EFS event, n (%)	61 (17.3)	89 (25.4)
Recurrence of high-grade disease	**26 (7.4)**	**53 (15.1)**
Persistence of CIS	1 (0.3)	1 (0.3)
Progressive disease	18 (5.1)	22 (6.3)
Progression to N+/M+, n	3	7
Progression to MIBC (≥T2), n	7	7
Stage Progression (high-grade Ta, T1), n	7	7
Unknown, n	1	1
Death	16 (4.5)	13 (3.7)

No. at risk	Months																
Sasanlimab + BCG-I+M	352	313	285	275	262	257	256	252	241	238	236	227	169	125	45	33	2
BCG-I+M	351	315	293	285	279	270	262	252	240	236	232	221	157	121	33	28	2

Shore ND, Guerrero-Ramos F, Nat Med 2025

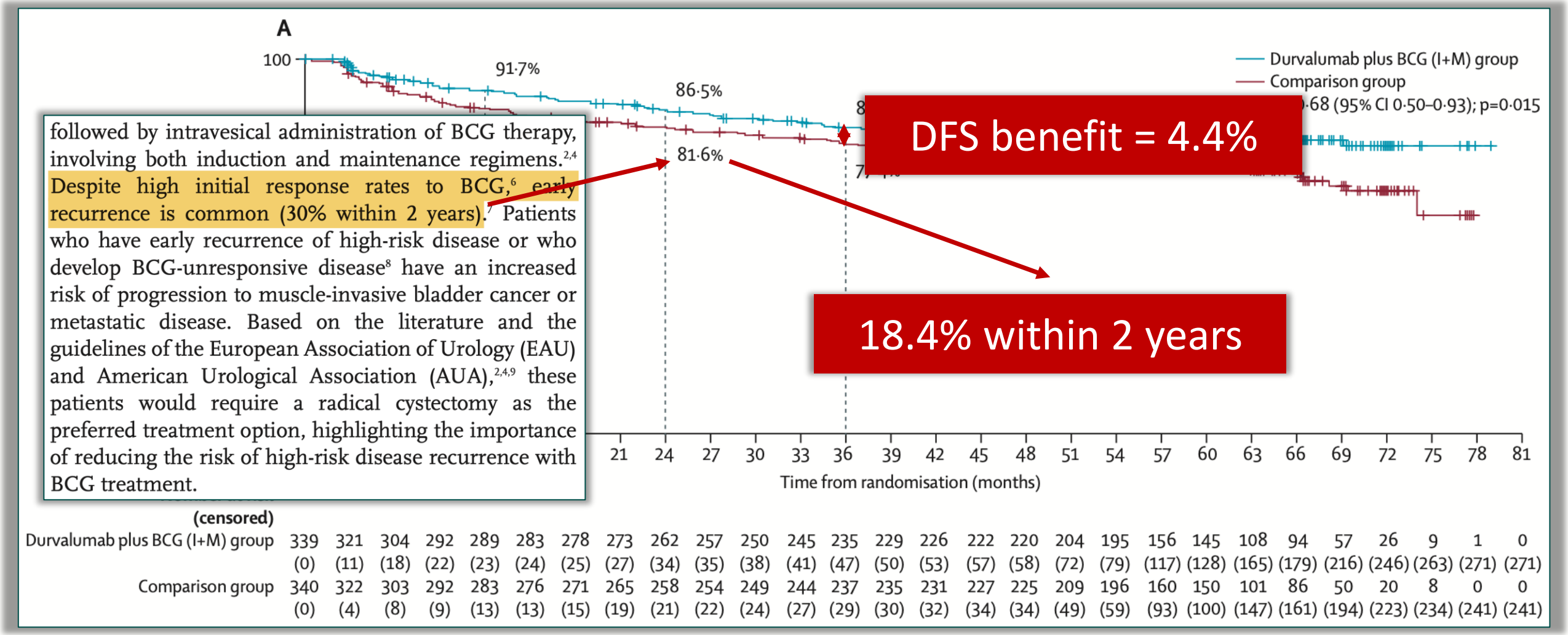
What about sasanlimab + BCG?

Table 2 | TRAEs by preferred term and maximum CTCAE grade during the on-treatment period in the safety analysis set

	Sasanlimab + BCG-I+M (*N*=350)		Sasanlimab + BCG-I (*N*=348)		BCG-I+M (*N*=349)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Patients with any event, *n* (%)	305 (87.1)	102 (29.1)	275 (79.0)	76 (21.8)	245 (70.2)	22 (6.3)
Dysuria	103 (29.4)	0	46 (13.2)	0	112 (32.1)	0
Pollakiuria	80 (22.9)	0	27 (7.8)	0	66 (18.9)	0
Hematuria	73 (20.9)	14 (4.0)	31 (8.9)	5 (1.4)	70 (20.1)	11 (3.2)
Urinary tract infection	67 (19.1)	7 (2.0)	28 (8.0)	2 (0.6)	70 (20.1)	2 (0.6)
Lipase increased	61 (17.4)	21 (6.0)	42 (12.1)	5 (1.4)	0	0
Pyrexia	54 (15.4)	1 (0.3)	35 (10.1)	0	41 (11.7)	0
Hypothyroidism	50 (14.3)	2 (0.6)	44 (12.6)	0	0	0
Amylase increased	41 (11.7)	8 (2.3)	33 (9.5)	3 (0.9)	0	0
Alanine aminotransferase increased	38 (10.9)	8 (2.3)	24 (6.9)	2 (0.6)	6 (1.7)	1 (0.3)
Cystitis	38 (10.9)	1 (0.3)	10 (2.9)	0	30 (8.6)	0
Aspartate aminotransferase increased	37 (10.6)	7 (2.0)	21 (6.0)	4 (1.1)	5 (1.4)	0
Micturition urgency	36 (10.3)	0	11 (3.2)	0	37 (10.6)	0
Fatigue	35 (10.0)	1 (0.3)	26 (7.5)	1 (0.3)	11 (3.2)	0
Pruritus	34 (9.7)	0	37 (10.6)	1 (0.3)	1 (0.3)	0
Asthenia	27 (7.7)	1 (0.3)	19 (5.5)	0	9 (2.6)	0
Hyperthyroidism	27 (7.7)	0	26 (7.5)	0	0	0

Shore ND, Guerrero-Ramos F, Nat Med 2025

Then, let's see durvalumab

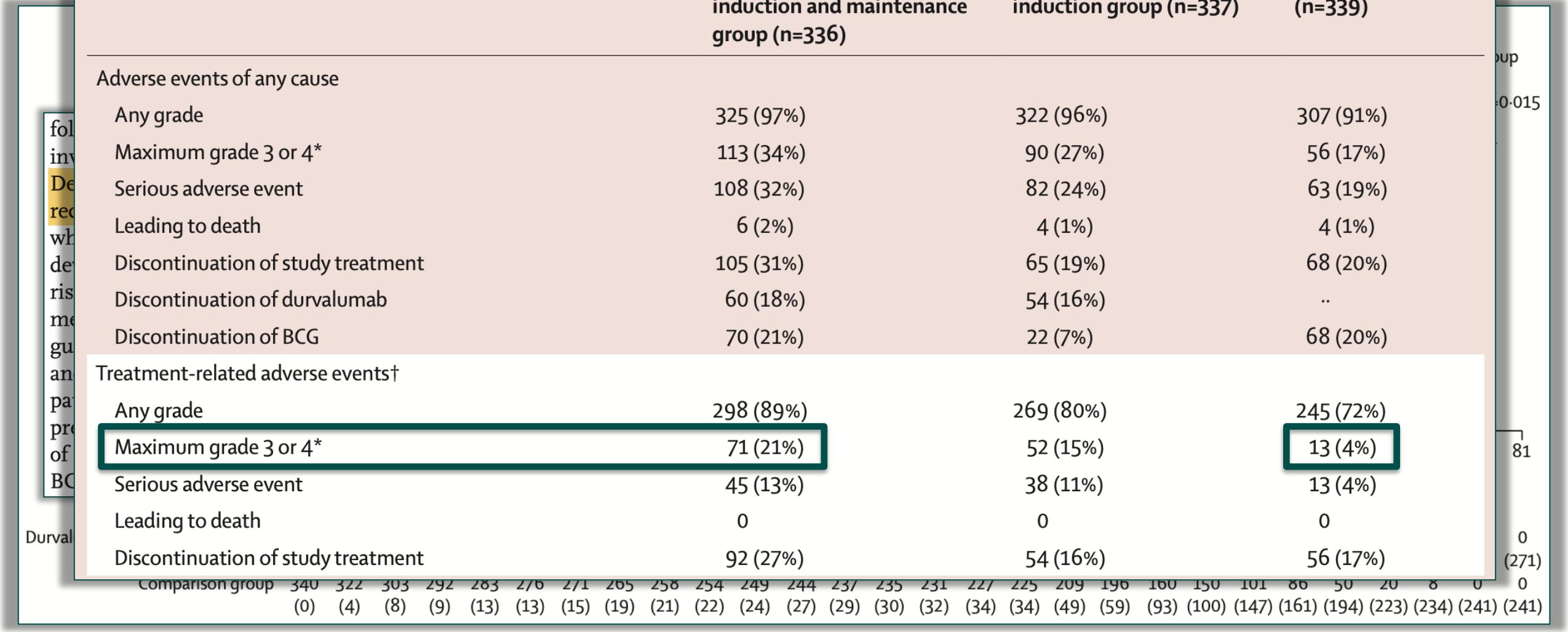


followed by intravesical administration of BCG therapy, involving both induction and maintenance regimens.[2,4] Despite high initial response rates to BCG,[6] early recurrence is common (30% within 2 years).[7] Patients who have early recurrence of high-risk disease or who develop BCG-unresponsive disease[8] have an increased risk of progression to muscle-invasive bladder cancer or metastatic disease. Based on the literature and the guidelines of the European Association of Urology (EAU) and American Urological Association (AUA),[2,4,9] these patients would require a radical cystectomy as the preferred treatment option, highlighting the importance of reducing the risk of high-risk disease recurrence with BCG treatment.

De Santis M, Guerrero-Ramos F, Lancet 2025

Then, let's see durvalumab

	Durvalumab plus BCG induction and maintenance group (n=336)	Durvalumab plus BCG induction group (n=337)	Comparison group (n=339)
Adverse events of any cause			
Any grade	325 (97%)	322 (96%)	307 (91%)
Maximum grade 3 or 4*	113 (34%)	90 (27%)	56 (17%)
Serious adverse event	108 (32%)	82 (24%)	63 (19%)
Leading to death	6 (2%)	4 (1%)	4 (1%)
Discontinuation of study treatment	105 (31%)	65 (19%)	68 (20%)
Discontinuation of durvalumab	60 (18%)	54 (16%)	..
Discontinuation of BCG	70 (21%)	22 (7%)	68 (20%)
Treatment-related adverse events†			
Any grade	298 (89%)	269 (80%)	245 (72%)
Maximum grade 3 or 4*	71 (21%)	52 (15%)	13 (4%)
Serious adverse event	45 (13%)	38 (11%)	13 (4%)
Leading to death	0	0	0
Discontinuation of study treatment	92 (27%)	54 (16%)	56 (17%)



Recurrence after BCG…

IS NO LONGER EQUAL TO IMMEDIATE RC!!!

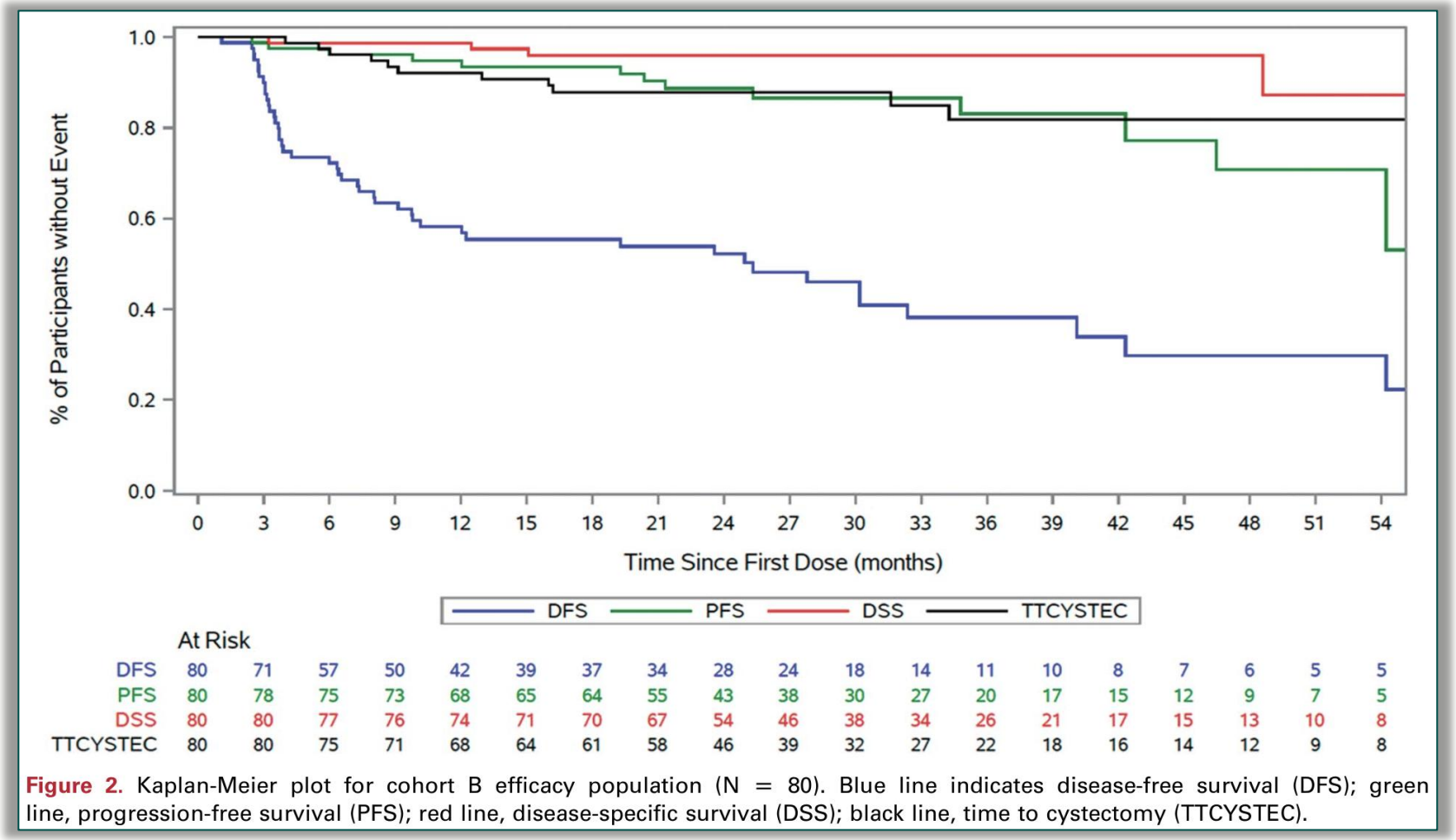


Figure 2. Kaplan-Meier plot for cohort B efficacy population (N = 80). Blue line indicates disease-free survival (DFS); green line, progression-free survival (PFS); red line, disease-specific survival (DSS); black line, time to cystectomy (TTCYSTEC).

Chang SS, J Urol 2026

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Recurrence after BCG… FDA approvals (CIS)

2020	**FDA approves pembrolizumab for BCG-unresponsive, high-risk non-muscle invasive bladder cancer**	CRR 41%
2022	**FDA D.I.S.C.O. Burst Edition: FDA approval of Adstiladrin (nadofaragene firadenovec-vncg) for patients with high-risk Bacillus Calmette-Guérin unresponsive non-muscle invasive bladder cancer with carcinoma in situ with or without papillary tumors**	CRR 53.4%
2024	**FDA approves nogapendekin alfa inbakicept-pmln for BCG-unresponsive non-muscle invasive bladder cancer**	CRR 71%
2025	**FDA approves gemcitabine intravesical system for non-muscle invasive bladder cancer**	CRR 82.4%

Recurrence after BCG… FDA approvals (CIS)

2020 — FDA approves pembrolizumab for BCG-unresponsive, high-risk non-muscle invasive bladder cancer — CRR 41%

	AMONG RESPONDERS…		OVERALL	
Agent, mFU (mo)	*12 mo DoR*	*Median DoR (months)*	*Cystectomy rate*	*Upstaging to ≥MIBC*
Pembrolizumab (36.4)	46%	16.2	49%	12%
Nadofaragene (20)	24.3%	9.7	26%	12.5%
BCG + N-803 (23.9)	61.6%	26.6	15.6%	N/R
TAR-200 (20.2)	56.2%	25.8	21.2%	8.2%

2024 — …pmln for BCG-unresponsive non-muscle invasive bladder cancer — CRR 71%

2025 — FDA approves gemcitabine intravesical system for non-muscle invasive bladder cancer — CRR 82.4%

Balar AV, Lancet Oncol 2021; Boorjian SA, Lancet Oncol 2021; Chamie K, NEJM Evid 2022; Daneshmand S, Guerrero-Ramos F, J Clin Oncol 2025

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Grade ≥3 TRAEs (for IVES therapies):

- Nadofaragene firadenovec = 4%
- Gem iDRS (TAR-200) = 12.9%
- BCG + N-803 = 23%

Balar AV, Lancet Oncol 2021; Boorjian SA, Lancet Oncol 2021; Chamie K, NEJM Evid 2022; Daneshmand S, Guerrero-Ramos F, J Clin Oncol 2025

High efficacy of intravesical for papillary-only

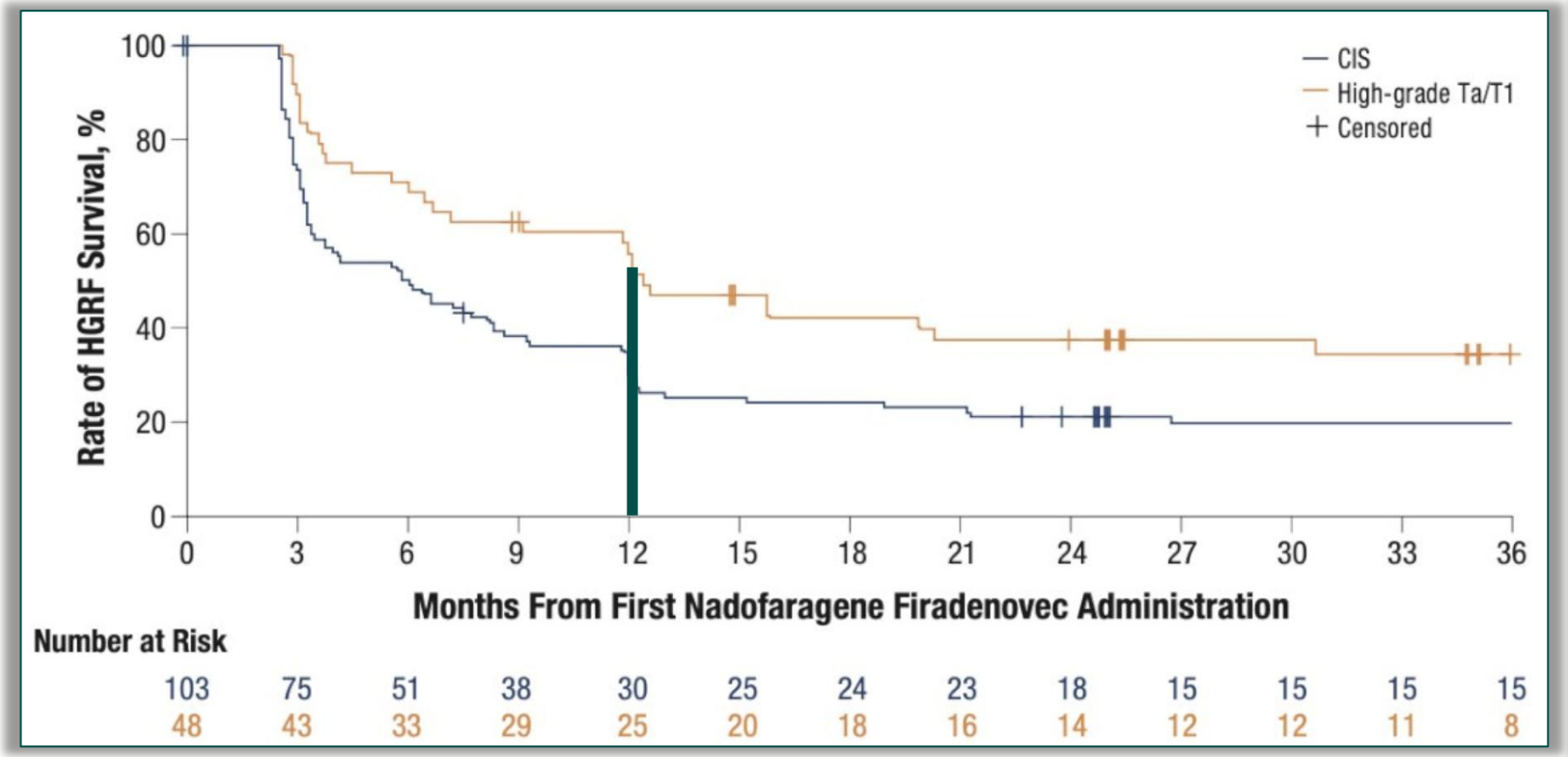


Table 2. Summary of Efficacy in Cohort B.*

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)†	19.3 (7.4 to upper bound not reached)
Disease-free survival rate — % (95% CI)†	
12 mo	55.4 (42.0–66.8)
18 mo	51.1 (37.6–63.1)
24 mo	48.3 (34.5–60.7)
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)

Dinney CP, EAU 2024; Chamie K, NEJM Evid 2022

High efficacy of intravesical for papillary-only

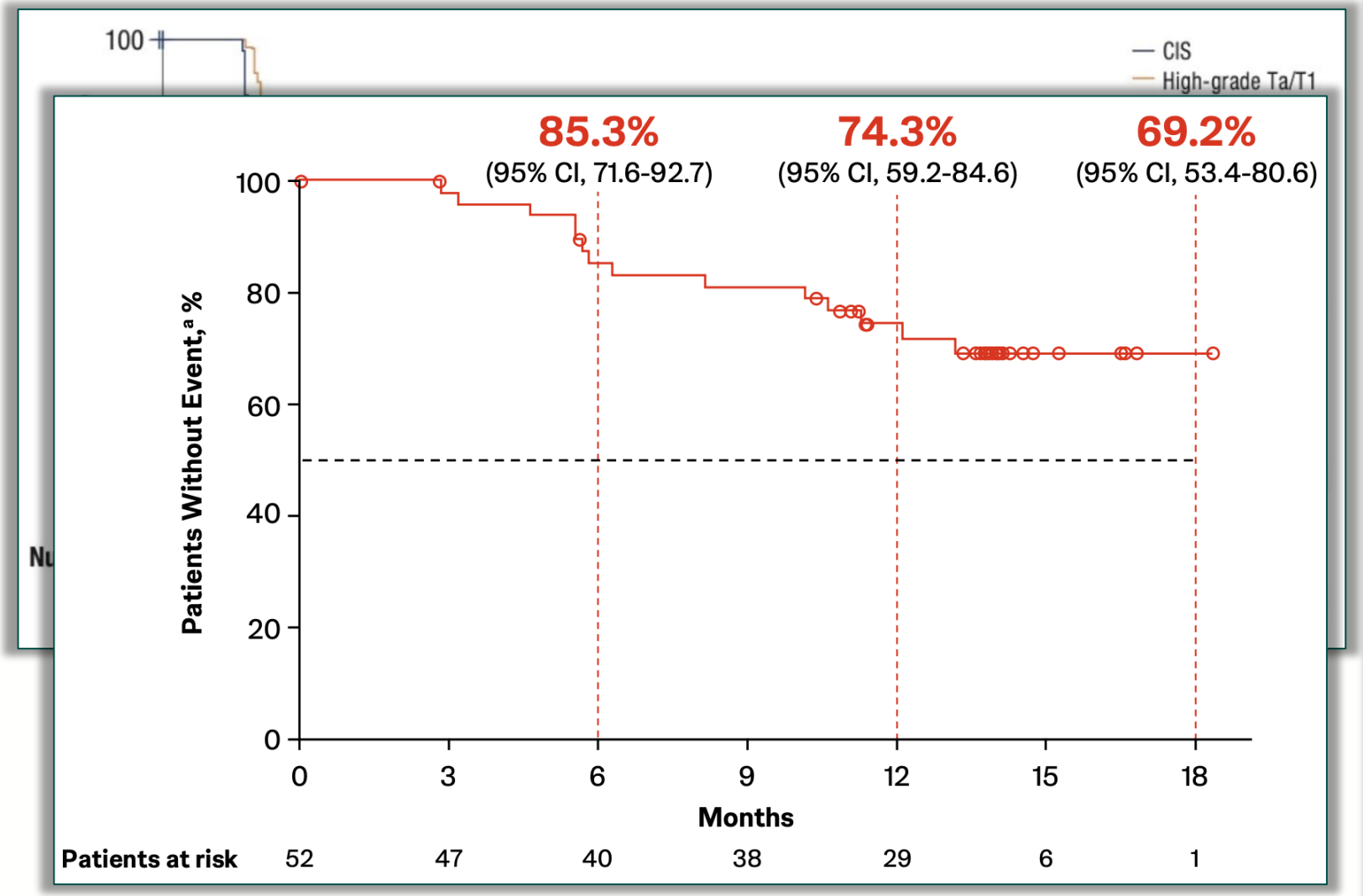
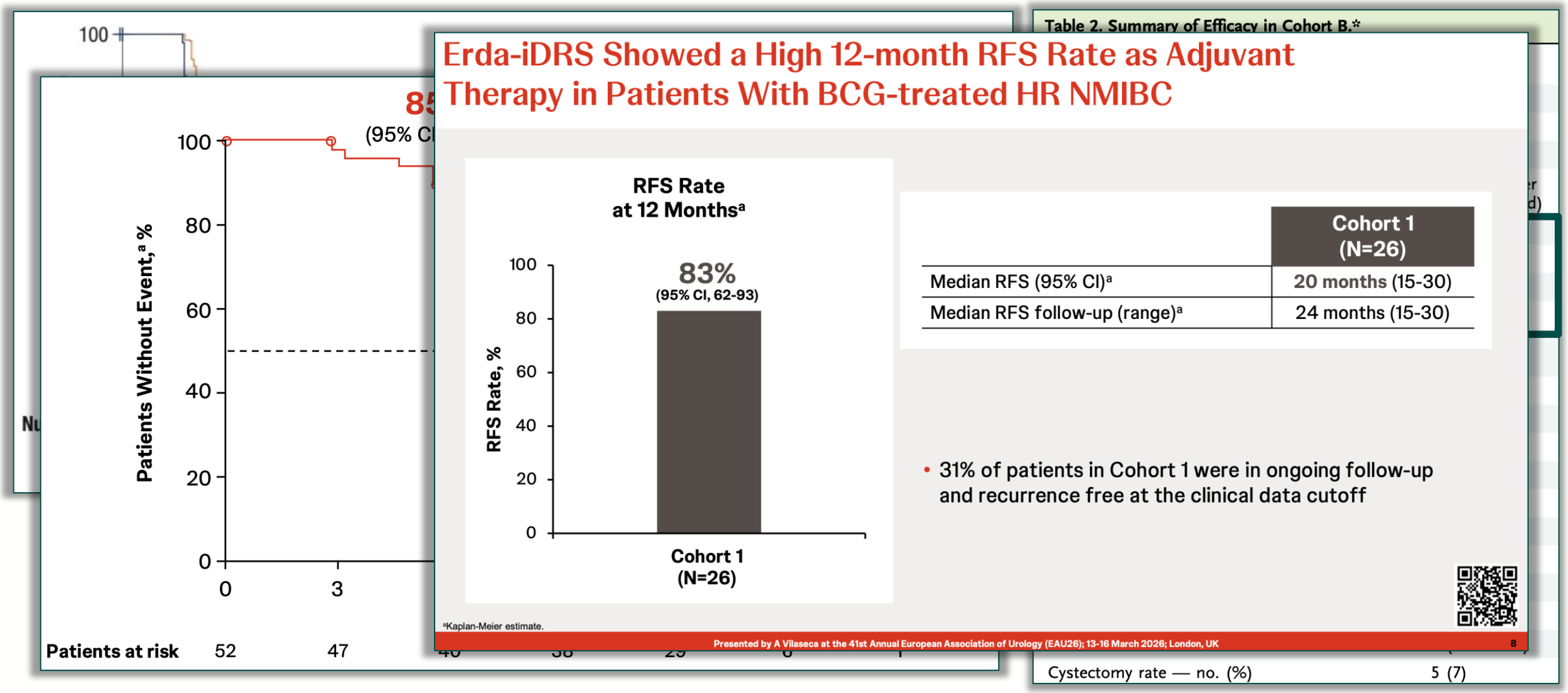


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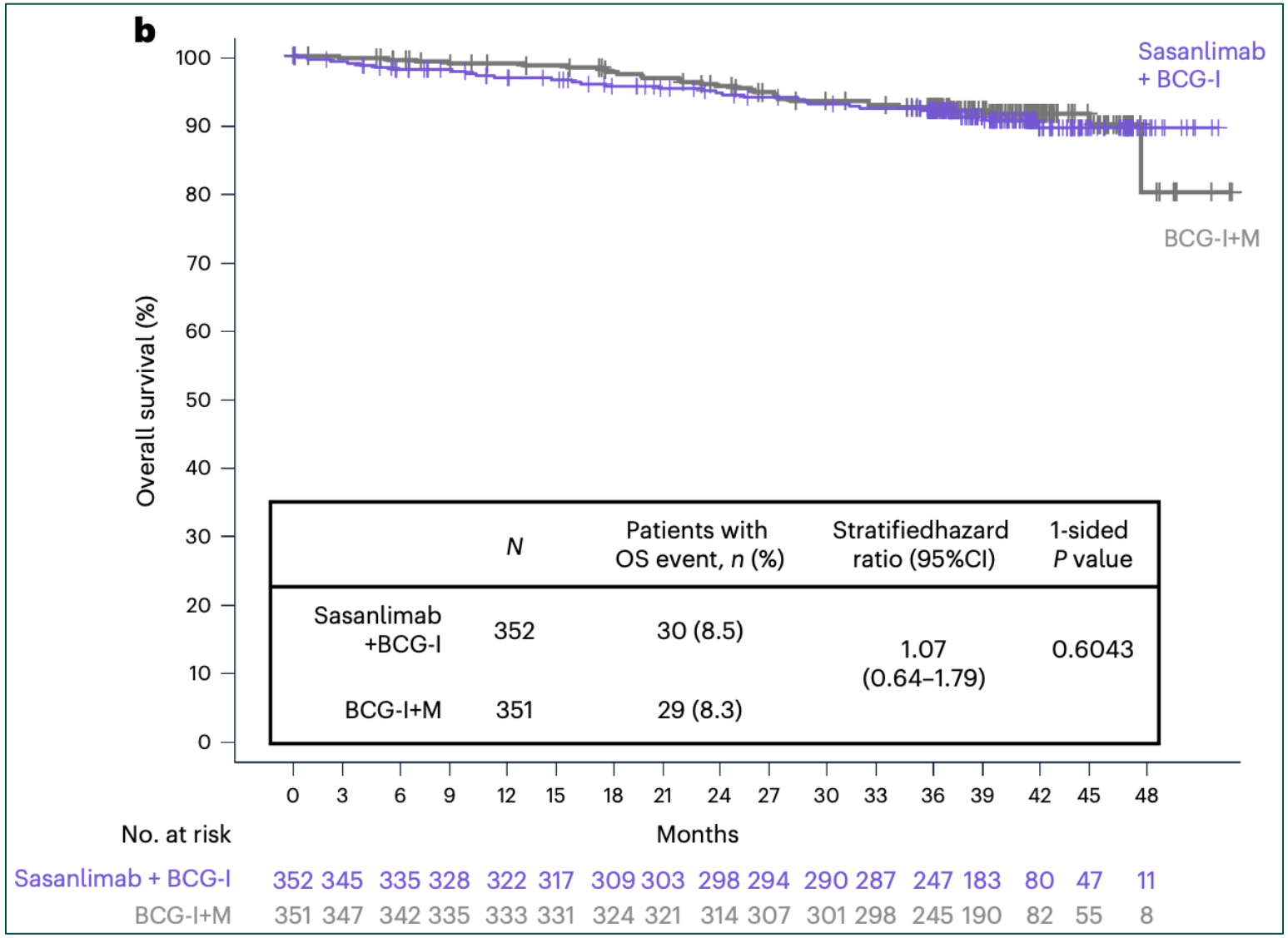
Dinney CP, EAU 2024; Chamie K, NEJM Evid 2022; Daneshmand S, Guerrero-Ramos F, SUO 2025

High efficacy of intravesical for papillary-only



Dinney CP, EAU 2024; Chamie K, NEJM Evid 2022; Daneshmand S, Guerrero-Ramos F, SUO 2025; Vilaseca A, Guerrero-Ramos F, EAU 2026

We DO need BCG maintenance

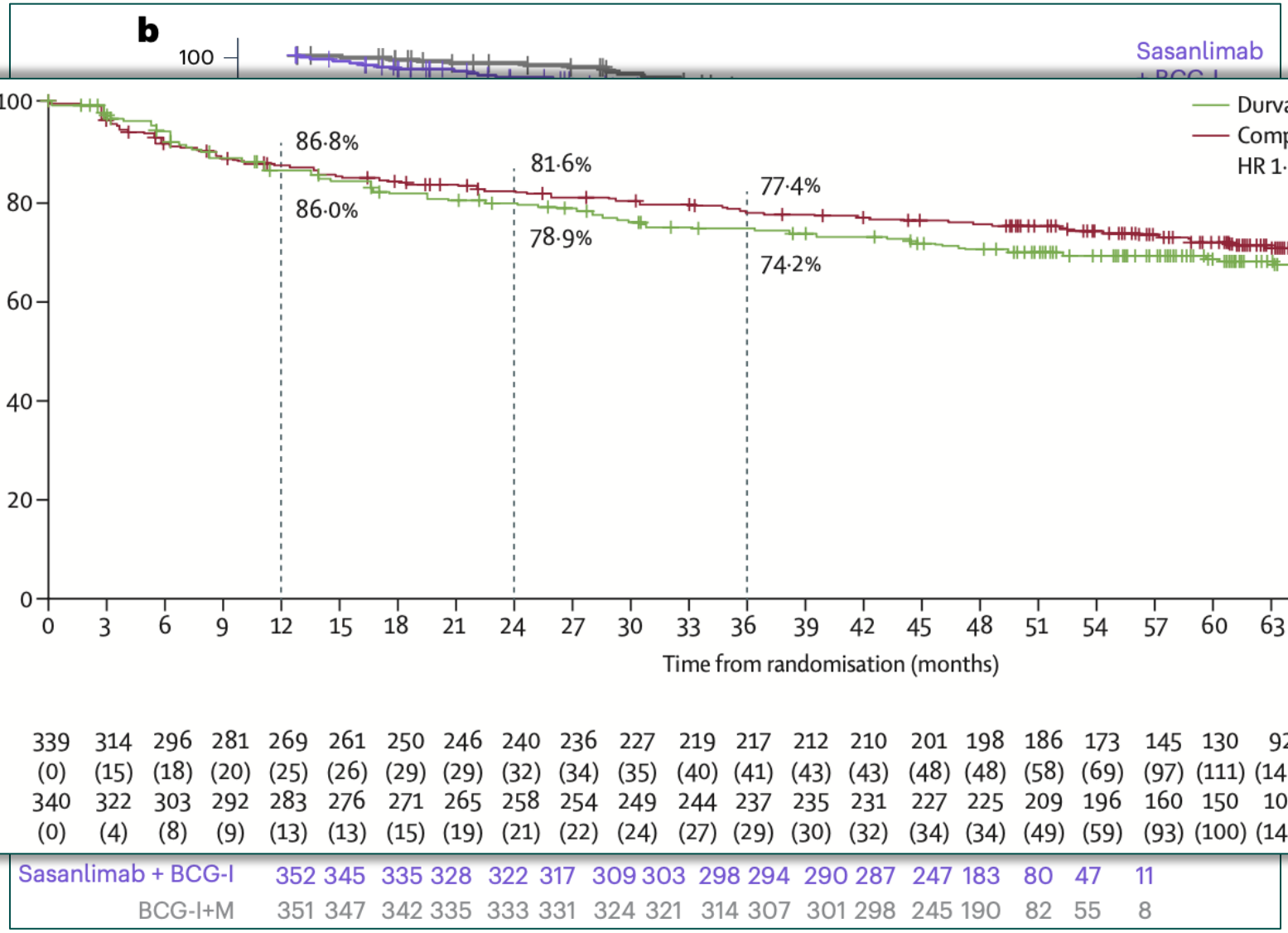


	N	Patients with OS event, *n* (%)	Stratifiedhazard ratio (95%CI)	1-sided *P* value
Sasanlimab +BCG-I	352	30 (8.5)	1.07 (0.64–1.79)	0.6043
BCG-I+M	351	29 (8.3)		

Shore ND, Guerrero-Ramos F, Nat Med 2025

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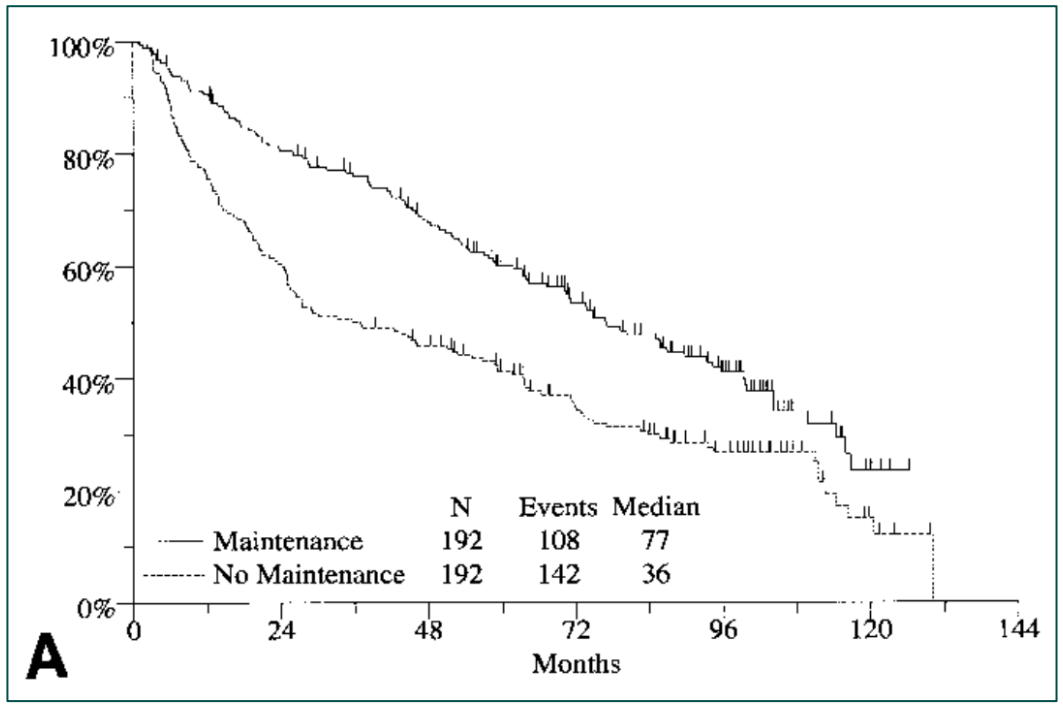
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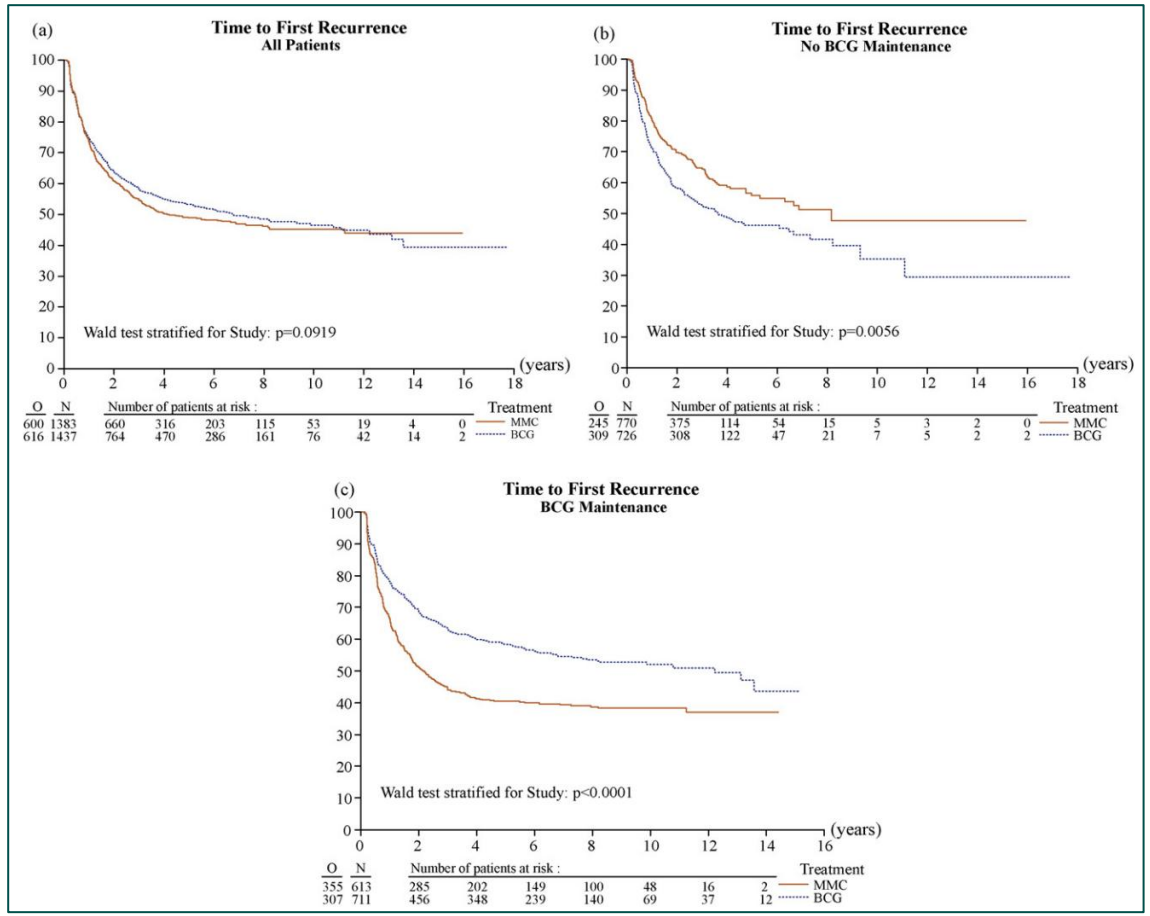


Shore ND, Guerrero-Ramos F, Nat Med 2025; De Santis M, Guerrero-Ramos F, Lancet 2025

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We DO need BCG maintenance, and this is not new





Lamm DL, J Urol 2000; Malmström PU, Eur Urol 2009

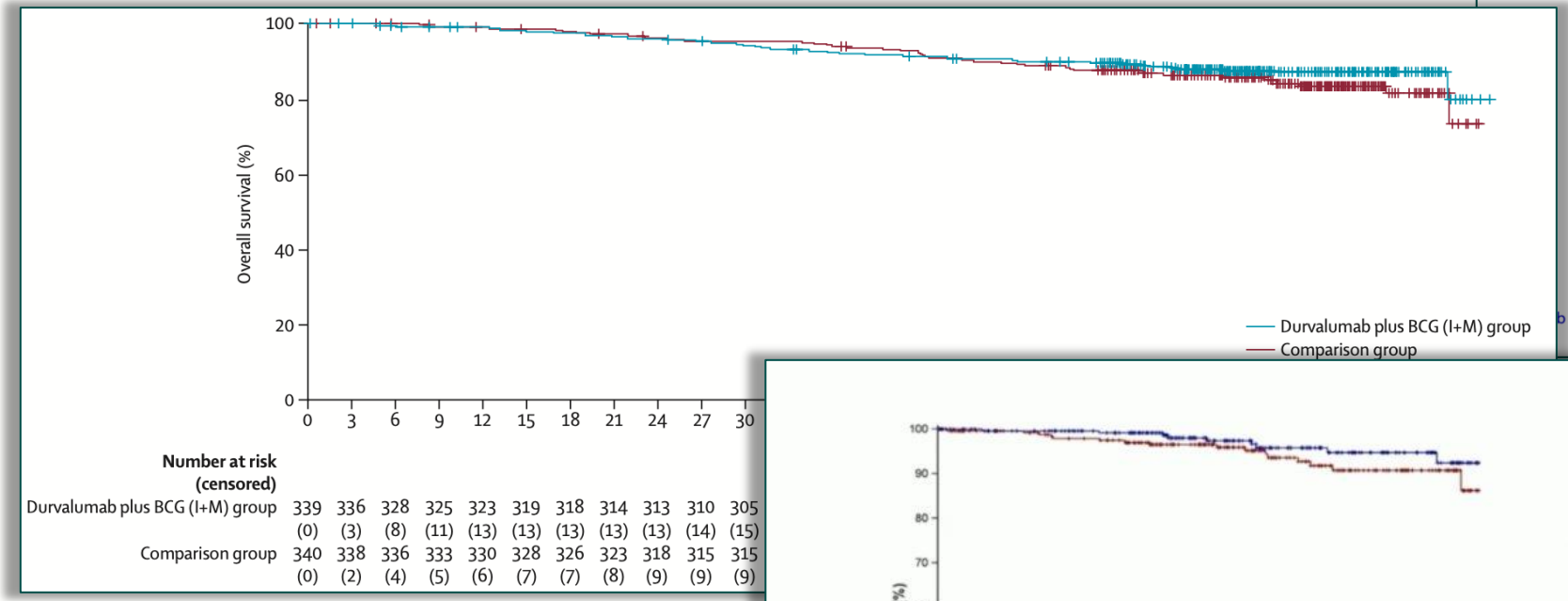
BCG currently performs much better than we thought

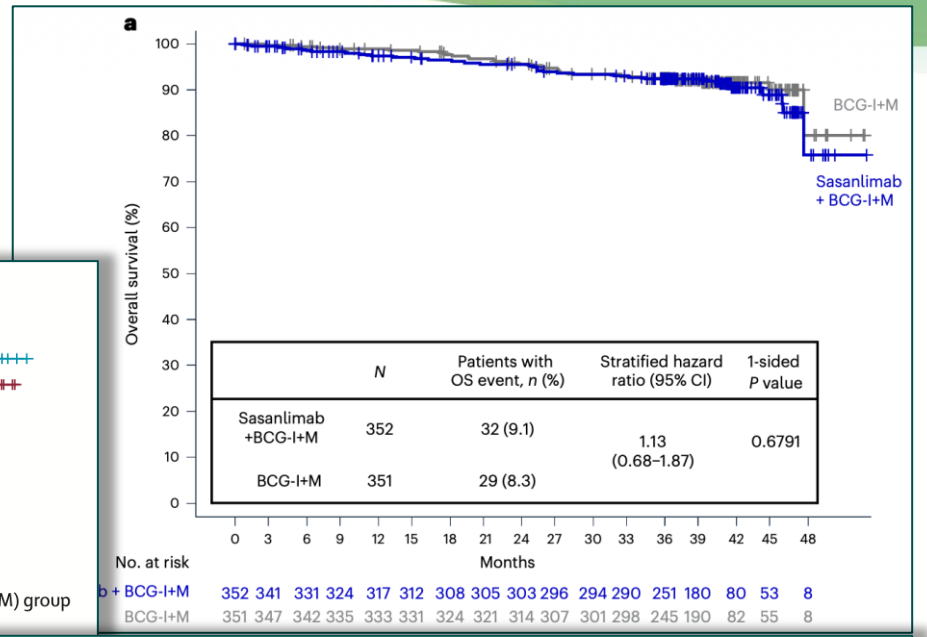
Table 2. *Survival analysis based on Kaplan-Meier estimates at 1, 3 and 5-year time points*

	RFS-HG			PFS			CFS			OS			
	1 Yr	3 Yrs	5 Yrs	1 Yr	3 Yrs	5 Yrs	1 Yr	3 Yrs	5 Yrs	1 Yr	3 Yrs	5 Yrs	Median Mos Followup
% Overall	81	76	74	97	93	92	95	89	86	99	93	86	47.8
% EAU risk group:													
Intermediate	95	92	86	100	100	100	98	96	90	98	94	79	43.1
High	80	74	72	96	92	91	95	88	86	99	93	87	49.4
% AUA NMIBC risk group:													
Intermediate	89	85	82	98	98	98	93	91	88	99	96	86	46.9
High	79	73	71	96	94	93	96	89	86	99	92	86	48.2
% Presence of CIS:													
LG Ta/T1 only	94	90	85	100	100	100	98	96	92	98	94	82	43.0
HG Ta/T1 only	81	77	75	97	93	92	96	91	89	99	94	88	44.8
CIS only	77	70	66	91	91	91	81	74	74	97	90	80	42.3
Ta/T1+CIS	77	68	67	96	92	89	94	85	81	99	91	86	65.3

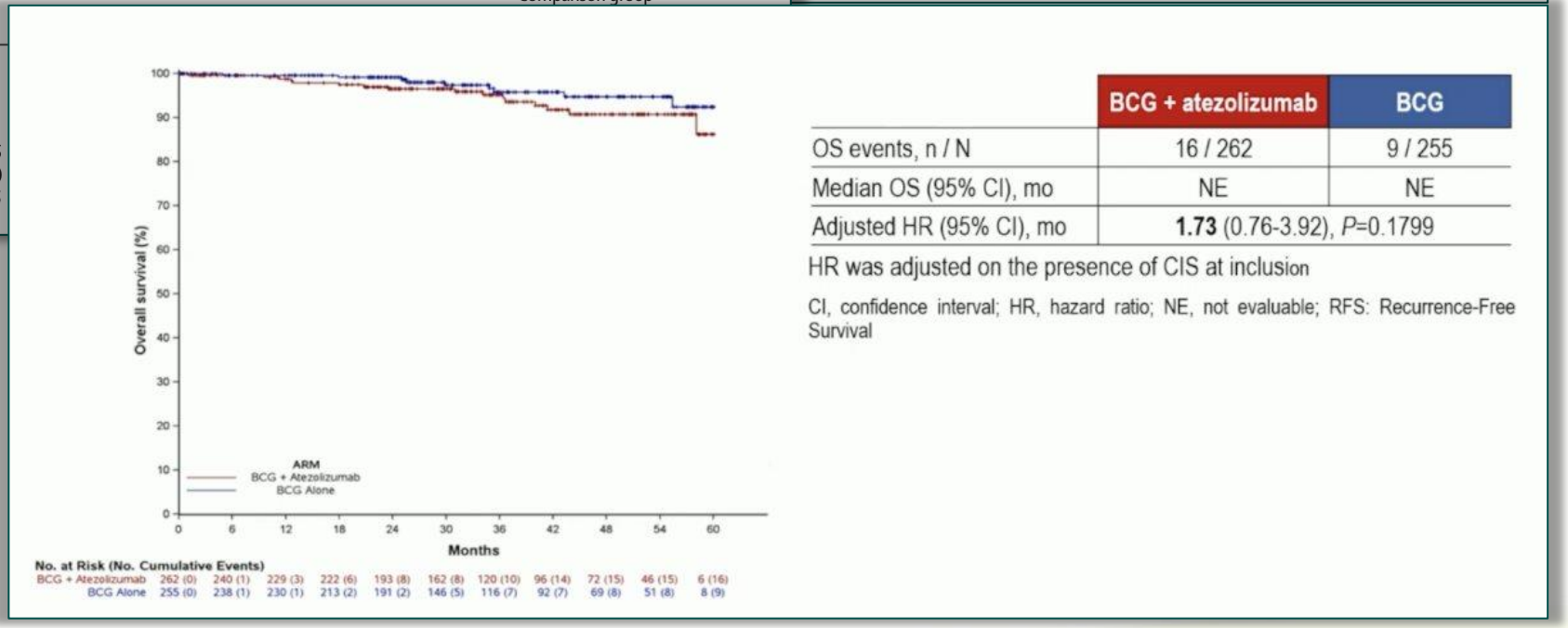
Matulay JT, J Urol 2021

Overall survival





	N	Patients with OS event, n (%)	Stratified hazard ratio (95% CI)	1-sided P value
Sasanlimab +BCG-I+M	352	32 (9.1)	1.13 (0.68–1.87)	0.6791
BCG-I+M	351	29 (8.3)		



	BCG + atezolizumab	BCG
OS events, n / N	16 / 262	9 / 255
Median OS (95% CI), mo	NE	NE
Adjusted HR (95% CI), mo	**1.73** (0.76-3.92), *P*=0.1799	

HR was adjusted on the presence of CIS at inclusion

CI, confidence interval; HR, hazard ratio; NE, not evaluable; RFS: Recurrence-Free Survival

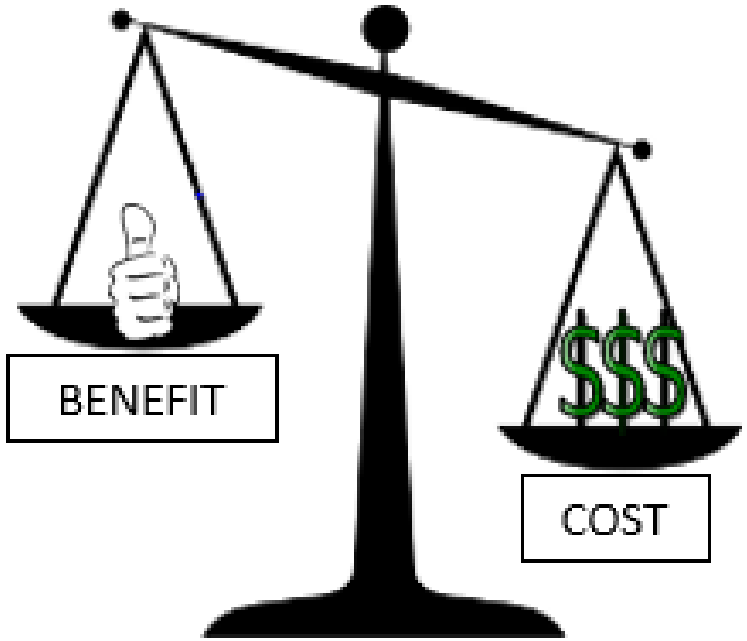
Economical burden

- **INDIVIDUAL cost** for intravesical therapies in BCG unresponsive disease is higher than BCG + IO for BCG naïve HR-NMIBC

- **HOWEVER**, a scarce number of patients will need these therapies, given the low rates of BCG unresponsiveness with BCG alone

- **THEREFORE**: overall **lower cost for BCG alone in HR-NMIBC** (followed by rescue therapies if needed)

Economical burden… and logistics



Box 1 Challenges to address for the introduction and practical implementation of novel PD-(L)1 inhibitors for NMIBC.

- Optimal management of irAEs by a well-trained, vigilant multidisciplinary team.
- Identification of provision barriers after PD-(L)1-based treatments are approved by the appropriate regulatory body.
- Review and adjustment of infrastructure to ensure that clinics in which PD-(L)1 inhibitors will be used are streamlined, thus permitting appropriate patient monitoring and management.
- Creative and up-to-date electronic systems for AE monitoring and management.
- Education for all members of the multidisciplinary team, on an ongoing basis (possibly included in CME programs), to optimize knowledge and management of AEs, particularly irAEs.
- Integrated patient management—especially between medical oncologists and urologists—wherever medical oncologists are administering the PD-(L)1 inhibitors.
- Define the optimal route of administration.
- AE = adverse event; CME = continuing medical education; irAE = immune-related adverse event; NMIBC = non-muscle-invasive bladder cancer; PD-(L)1 = programmed cell death-(ligand) 1.

Bedke J, Guerrero-Ramos F, Urol Oncol 2023

IO treatments NOT ready for prime time in BCG naïve NMIBC

- Modest efficacy benefit with the addition of systemic ICIs
  - One negative trial, two positive trials
  - Avoiding mainly HG recurrences…
  - …at the expense of relevant toxicity
- BCG maintenance schedule is the key
  - Modern data exceed historical benchmarks
- HG recurrence ≠ radical cystectomy anymore
  - IVES therapies for BCG unresponsive are effective and safe
- BCG is unexpensive and easy to deliver (no logistic challenges)

IO treatments NOT ready for prime time in BCG naïve NMIBC

- Modest efficacy benefit with the addition of systemic ICIs
  - …positive trials
  - …rrences…
  - …ant toxicity

5-7% EFS/DFS benefit

VS

20-30% grade ≥3 TRAEs

- BCG maintenance schedule is the key
  - Modern data exceed historical
- HG recurrence ≠ radical cystec
  - IVES therapies for BCG unrespo
- BCG is unexpensive and easy to deliver (no logistic challenges)

NNT ≃ 14-20

&

NNH ≃ 3-5

IO treatments NOT ready for prime time in BCG naïve NMIBC

BCG is a **MUST** in NMIBC…

M: maintenance achieves excellent efficacy

U: unexpensive therapy

S: second line effective therapies

T: tolerable safety profile

…until we find those patients who really benefit from the combination

VGO NORTE
INTERNATIONAL
GU DEBATES

¡GRACIAS!

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