

Manejo actual del cáncer de vejiga NMIBC alto riesgo (Pro manejo sistémico)

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Risk stratification

Clinical composition of the EAU NMIBC prognostic factor risk groups

Risk group	
Low Risk	• A primary, single, Ta/T1 LG/G1 tumour < 3 cm in diameter without CIS in a patient < 70 years
	• A primary Ta LG/G1 tumour without CIS with at most ONE of the additional clinical risk factors (see above*)
Intermediate Risk	Patients without CIS who are not included in either the low, high or very high-risk groups
High Risk	• 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
	Stage, grade with additional clinical risk factors: • Ta LG/G2 or T1 G1, no CIS with all 3 risk factors • Ta HG/G3 or T1 LG, no CIS with at least 2 risk factors • T1 G2 no CIS with at least 1 risk factor
Very High Risk	Stage, grade with additional clinical risk factors: • Ta HG/G3 and CIS with all 3 risk factors • T1 G2 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

- Additional clinical risk factors are:

- age > 70;
- multiple papillary tumours;
- tumour diameter > 3 cm.

Table 6.2: Probabilities of disease progression in 1, 5 and 10 year(s) for the new EAU NMIBC risk groups [227]*

Risk group	Probability of Progression and 95% Confidence Interval (CI)		
	1 Year	5 Years	10 Years
New Risk Groups with WHO 2004/2016			
Low	0.06% (CI: 0.01%–0.43%)	0.93% (CI: 0.49%–1.7%)	3.7% (CI: 2.3%–5.9%)
Intermediate	1.0% (CI: 0.50%–2.0%)	4.9% (CI: 3.4%–7.0%)	8.5% (CI: 5.6%–13%)
High	3.5% (CI: 2.4%–5.2%)	9.6% (CI: 7.4%–12%)	14% (CI: 11%–18%)
Very High	16% (CI: 10%–26%)	40% (CI: 29%–54%)	53% (CI: 36%–73%)
New Risk Groups with WHO 1973			
Low	0.12% (CI: 0.02%–0.82%)	0.57% (CI: 0.21%–1.5%)	3.0% (CI: 1.5%–6.3%)
Intermediate	0.65% (CI: 0.36%–1.2%)	3.6% (CI: 2.7%–4.9%)	7.4% (CI: 5.5%–10%)
High	3.8% (CI: 2.6%–5.7%)	11% (CI: 8.1%–14%)	14% (CI: 10%–19%)
Very High	20% (CI: 12%–32%)	44% (CI: 30%–61%)	59% (CI: 39%–79%)

WHO = World Health Organization.

**Table 6.2 does not include patients with subtypes of urothelial carcinoma (variant histologies), LVI, CIS in the prostatic urethra, primary CIS or recurrent patients.*

**Please note that these percentages refer to patients who were not (immediately) treated with adjuvant BCG instillations after their primary TUR.*

5-Year Overall Survival After Radical Cystectomy

Bladder cancer stage groups

pT0–pT1	pT2–pT4
High-risk non–muscle-invasive / downstaged disease	Muscle-invasive disease
86%	54%
5-year overall survival	5-year overall survival

Approximate grouped values



Source: Adapted from Nikulainen et al. *Acta Oncologica*, 2023 (5-year OS by pathologic stage after radical cystectomy: pT0 87%, pTa/pTis/pT1 85%, pT2 70%, pT3 50%, pT4 41%).

BCG-naïve

Table 1 – Clinical trials including systemic immunotherapy for BCG-naïve high-risk non-muscle-invasive bladder cancer ^a

	ALBAN	CREST	POTOMAC	KEYNOTE 676	SunRISe-3
Immunotherapy	Atezolizumab	Sasanlimab	Durvalumab	Pembrolizumab	Cetrelimab
Type of immunotherapy	PD-L1	PD-1	PD-L1	PD-1	PD-1
Duration of Immunotherapy (yr)	1	2	1	1	2
Administration of immunotherapy	Intravenous Every 3 wk	Subcutaneous Every 4 wk	Intravenous Every 4 wk	Intravenous Every 3 wk	Intravenous Every 3 wk
Start date	Dec 2018	Dec 2019	May 2018	Dec 2018	May 2023
Trial design	Randomized, open-label, parallel-group, multicenter	Randomized, open-label, parallel-group, multicenter	Randomized, open-label, parallel-group, multicenter	Randomized, open-label, parallel-group, multicenter	Randomized, open-label, parallel-group, multicenter
Estimated number of enrolled patients	516	999	1018	975	1050
Treatment arms	Atezolizumab + BCG (IND + MAIN) vs BCG control	Sasanlimab + BCG (IND + MAIN) or sasanlimab + BCG (IND) vs BCG control	Durvalumab + BCG (IND + MAIN) or durvalumab + BCG (IND) vs BCG control	Pembrolizumab + BCG (IND + MAIN) vs BCG (IND + MAIN)	Cetrelimab + TAR 200 vs TAR 200 vs BCG control (IND + MAIN)
Primary endpoint	RFS	EFS	DFS	CR (CIS)	EFS
Secondary endpoints	PFS, OS, CSS, CRR, DW, QLQ, safety	OS, CRR (CIS), DOR (CIS) DSS, time to RC, QLQ, safety	DFS at 24 mo, OS at 5 yr, QLQ, safety	12-mo EFS, 12-mo DOR, RFS, OS, DSS, time to RC, QLQ, safety	CRR (CIS), DOR, RFS, CSS, OS, QLQ, safety
Results on the primary endpoint	Awaiting	Positive	Positive	Awaiting	Awaiting
Expected results date	2025	2025	2025	2025	2030

	ALBAN		CREST		POTOMAC	
	A/I/M	I/M	S/I/M	I/M	D/I/M	I/M
2-year EFS (%)	81	82	85	80	87	82
3-year EFS (%)	79	79	82	75	82	77
HR	0.98 (0.71-1.36)		0.68 (0.49-0.94)		0.68 (0.5-0.93)	
3-year ΔEFS	0%		7%		5%	

Gabriel PE, Roumiguié M, Marcq G, Allory Y, Audenet F, Bajiot AS, Leon P, Masson-Lecomte A, Pradère B, Seisen T, Thibault C, Rouprêt M, Xylinas E; Cancer Committee of The French Association of Urology (CC-AFU). The Evolving Landscape of Systemic Immunotherapy for Bacillus Calmette-Guérin-naïve High-risk Non-muscle-invasive Bladder Cancer: At the Edge of a Tsunami? *Eur Urol Oncol*. 2025 Aug;8(4):1174-1181. <https://www.urotoday.com/conference-highlights/esmo-2025/esmo-2025-bladder-cancer/164039-esmo-2025-discussant-systemic-treatment-for-non-muscle-invasive-bladder-cancer-clinical-precision-or-overreaction.html>

EFFECTIVITY

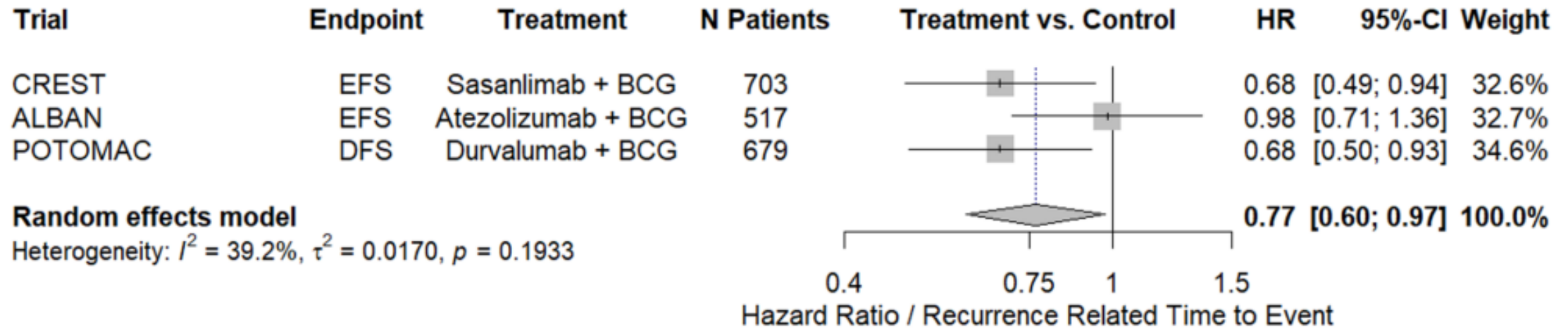


Fig. 2 Forest-Plot: Meta-analysis of recurrence-related time to event for intravesical BCG combined with systemic immunotherapy

ALBAN – Study design

BCG-naïve patients, with high-risk NMIBC after first and second look TURBT:

- High-risk defined as the presence of any high-grade/grade 3 Ta, T1 tumors and/or CIS
- No prior BCG therapy
- Absence of metastatic disease in the pelvis, abdomen, or chest
- ECOG PS of 0-2

R
1:1

BCG : once a week for 6 weeks (induction phase)
once a week for 3 weeks at 3, 6, 12 months
(maintenance phase)

Atezolizumab: 1200 mg; IV; q3w for up to 1 year

BCG : once a week for 6 weeks (induction phase)
once a week for 3 weeks at 3, 6, 12 months
(maintenance phase)

Primary endpoint

EFS

Key secondary endpoints

High-grade RFS

PFS

OS

DOR

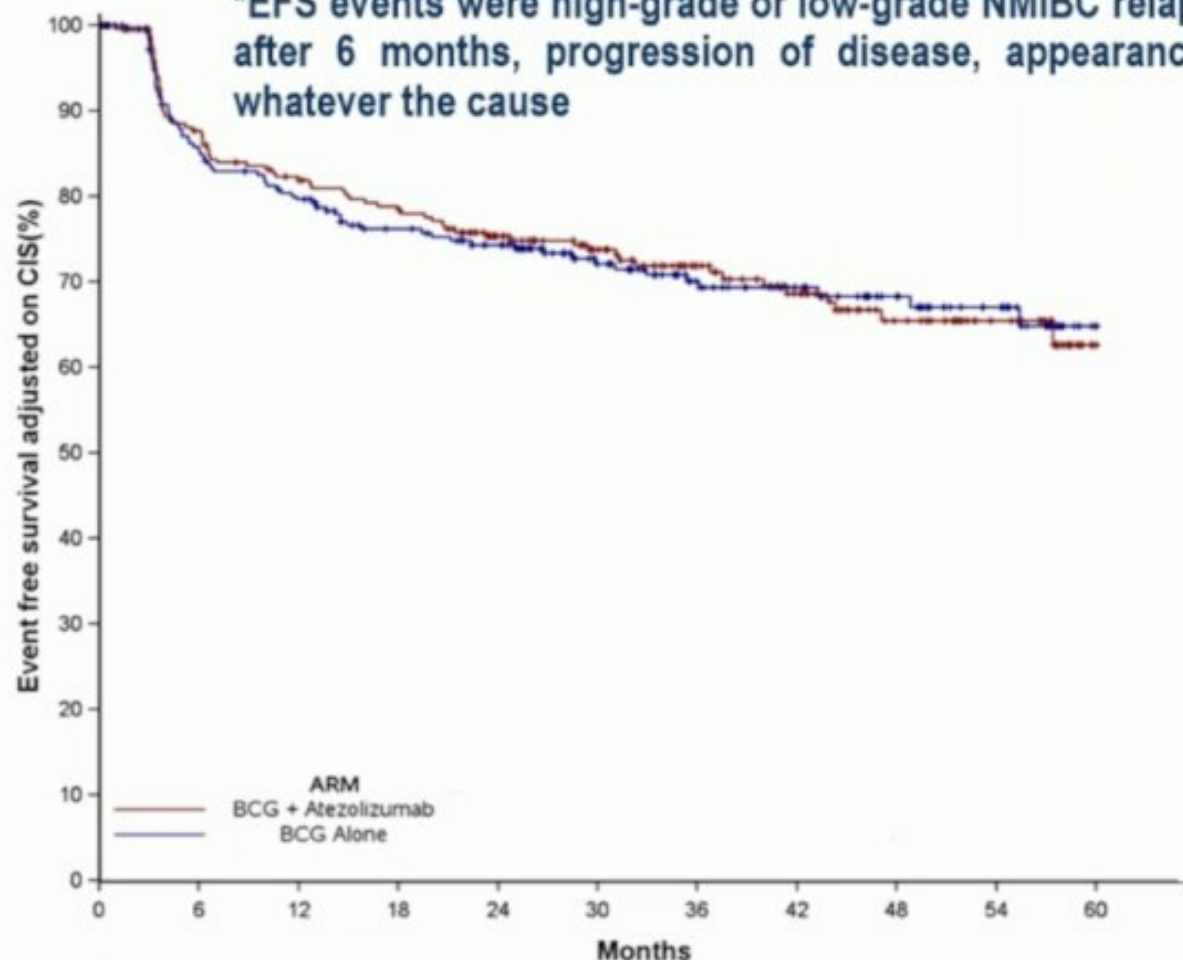
Safety

QoL

CIS: carcinoma in situ; DOR, duration of response; EFS: Event-Free Survival; OS, Overall Survival; PFS: Progression-Free survival; QoL, Quality of Life; RFS: Recurrence-Free Survival

ALBAN – Analysis of EFS* (primary endpoint, ITT population)

*EFS events were high-grade or low-grade NMIBC relapse, persistence of CIS after 6 months, progression of disease, appearance of UTUC, or death whatever the cause



Risk (No. Cumulative Events)											
Atezolizumab	262 (0)	212 (30)	193 (44)	184 (52)	157 (59)	129 (62)	97 (65)	78 (69)	55 (72)	35 (72)	2 (73)
BCG Alone	255 (0)	208 (36)	190 (50)	169 (58)	155 (62)	116 (66)	90 (69)	73 (70)	55 (71)	38 (72)	6 (73)

Prof Morgan Rouprêt

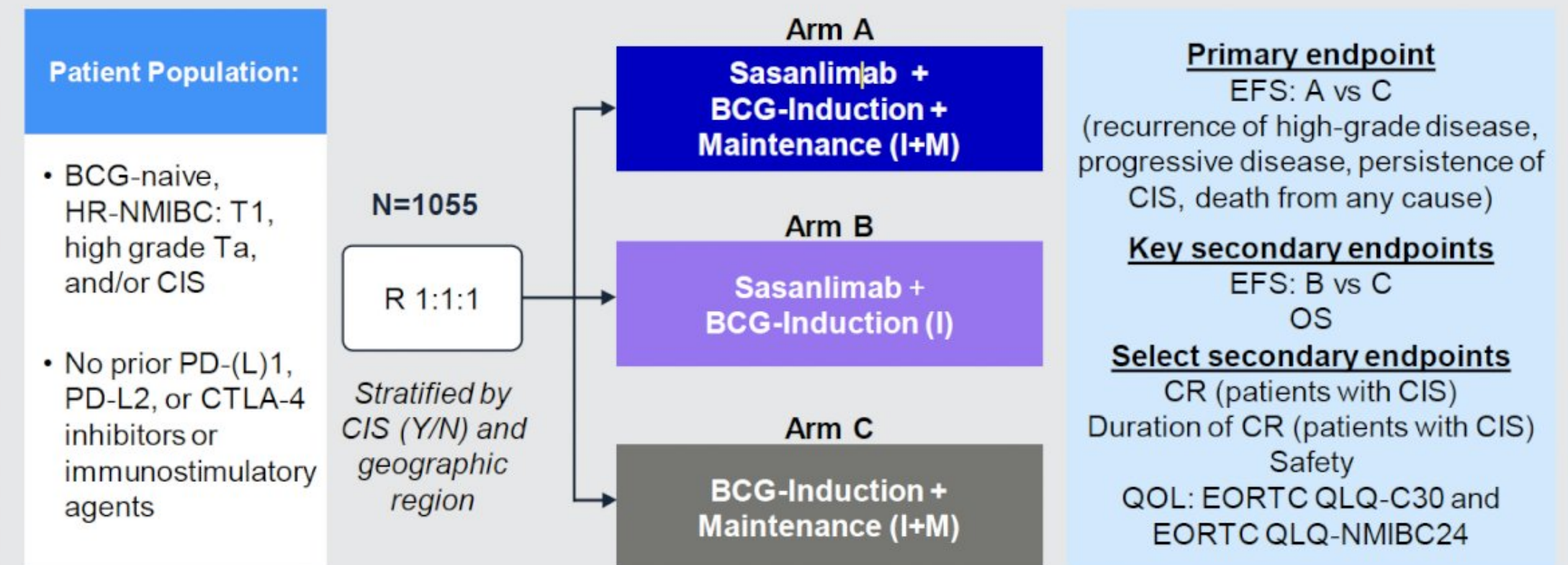
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of UTUC, or death	BCG + atezolizumab	BCG
EFS events, n / N	73 / 262	73 / 255
Median EFS (95% CI), mo	NE	NE
Adjusted HR (95% CI), mo	0.98 (0.71-1.36); <i>P</i> =0.9106	
<u>Type of events, n (%)</u>		
Local recurrence	62 (84.9%)	60 (82.2%)
Locoregional recurrence	3 (4.1%)	3 (4.1%)
Distant recurrence	1 (1.4%)	2 (2.7%)
UTUC	0 (0.0%)	2 (2.7%)
Death from any cause	7 (9.6%)	6 (8.2%)

HR was adjusted on the presence of CIS at inclusion

CI, Confidence Interval; CIS, Carcinoma In Situ; EFS, Event-Free Survival; HR, Hazard Ratio; ITT, Intent To Treat; NE not evaluable

Figure 1. CREST Study Design



Final EFS analysis data cut-off date: Dec 2, 2024

BCG-I+M: BCG induction (6 doses)^a and maintenance (up to 2 years) therapy

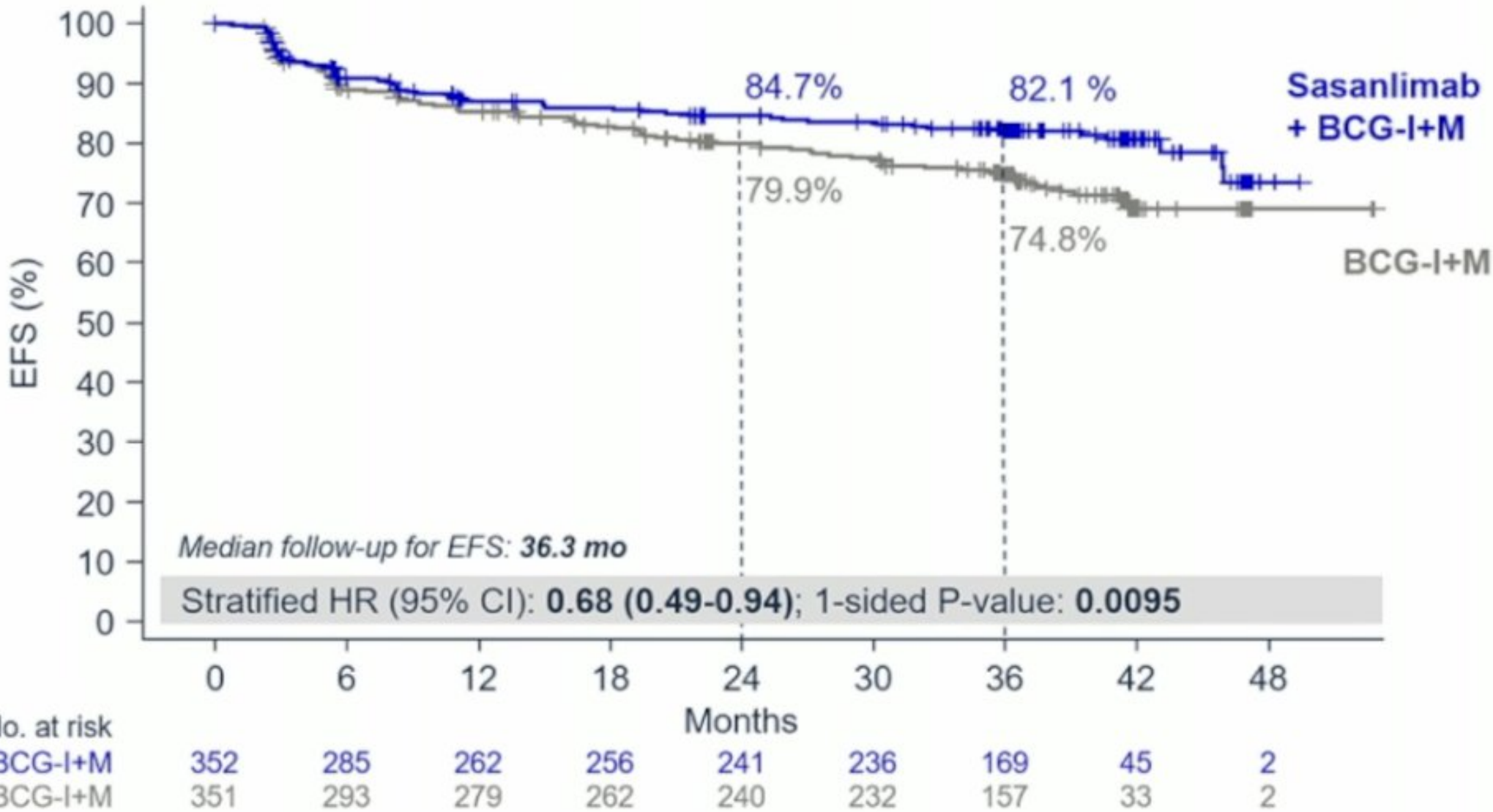
BCG-I: BCG induction (6 doses)^a only

Sasanlimab: Administered SC for up to 25 four-week cycles

^aRe-induction permitted for patients with CIS at randomization who had persistent disease or recurrence of high-grade Ta disease 3 months after initiating study treatment. BCG, Bacillus Calmette-Guérin; CIS, carcinoma in situ; CR, complete response; CTLA-4: cytotoxic T lymphocyte-associated antigen 4; EFS, event-free survival; EORTC, European Organization for Research and Treatment of Cancer; HR, high-risk; I, induction; M, maintenance; PD-1, Programmed cell death-1; PD-L1/PD-L2, Programmed cell death-ligand 1/2; QLQ-C30, Core Quality of Life questionnaire; QLQ-NMIBC24, Non-Muscle-Invasive Bladder Cancer Quality of Life questionnaire; QOL, quality of life, R, randomization.

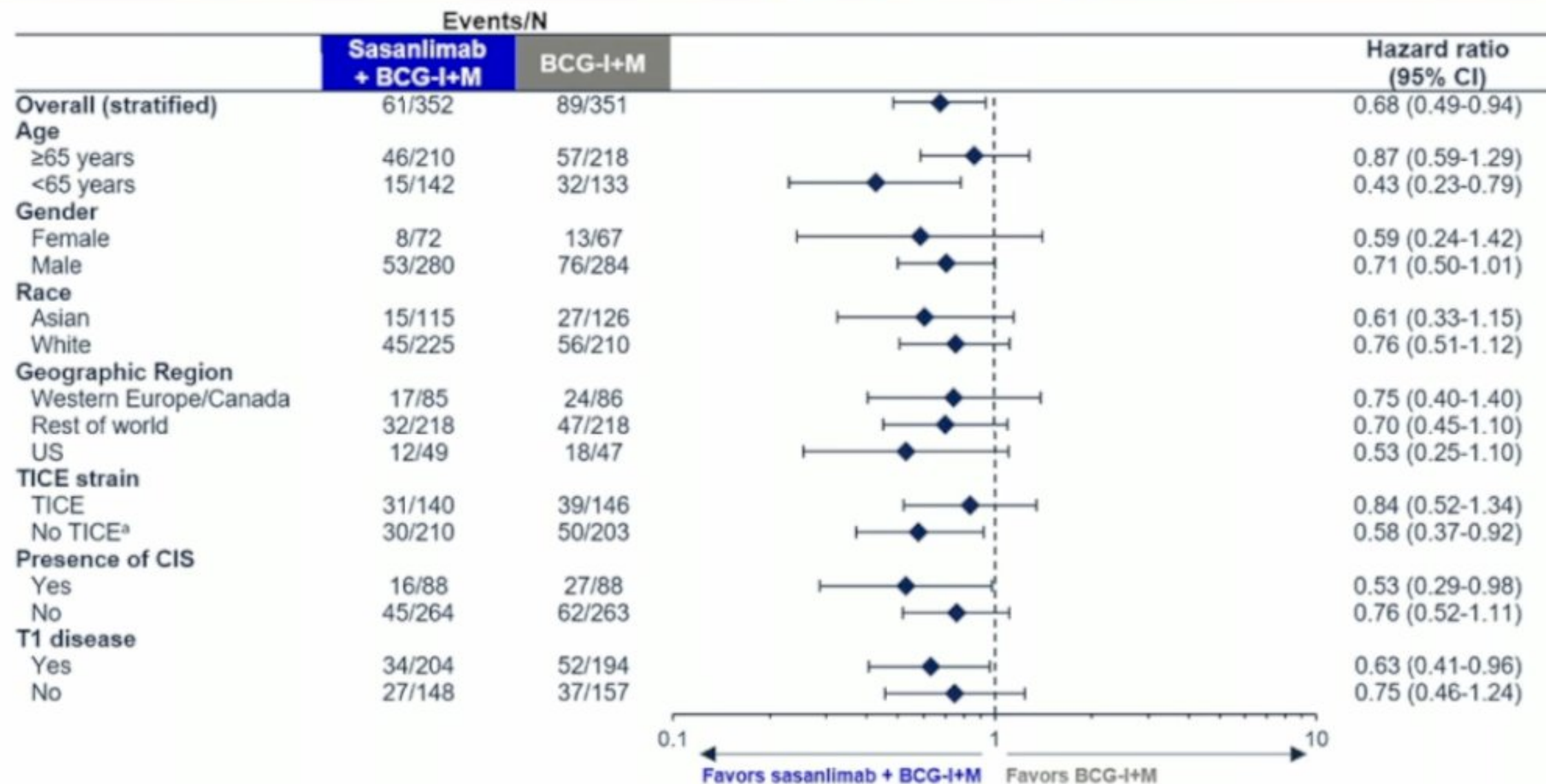
Primary Endpoint EFS by Investigator: Arm A vs Arm C

The risk of experiencing an EFS event was 32% lower with sasanlimab + BCG-I+M vs BCG-I+M



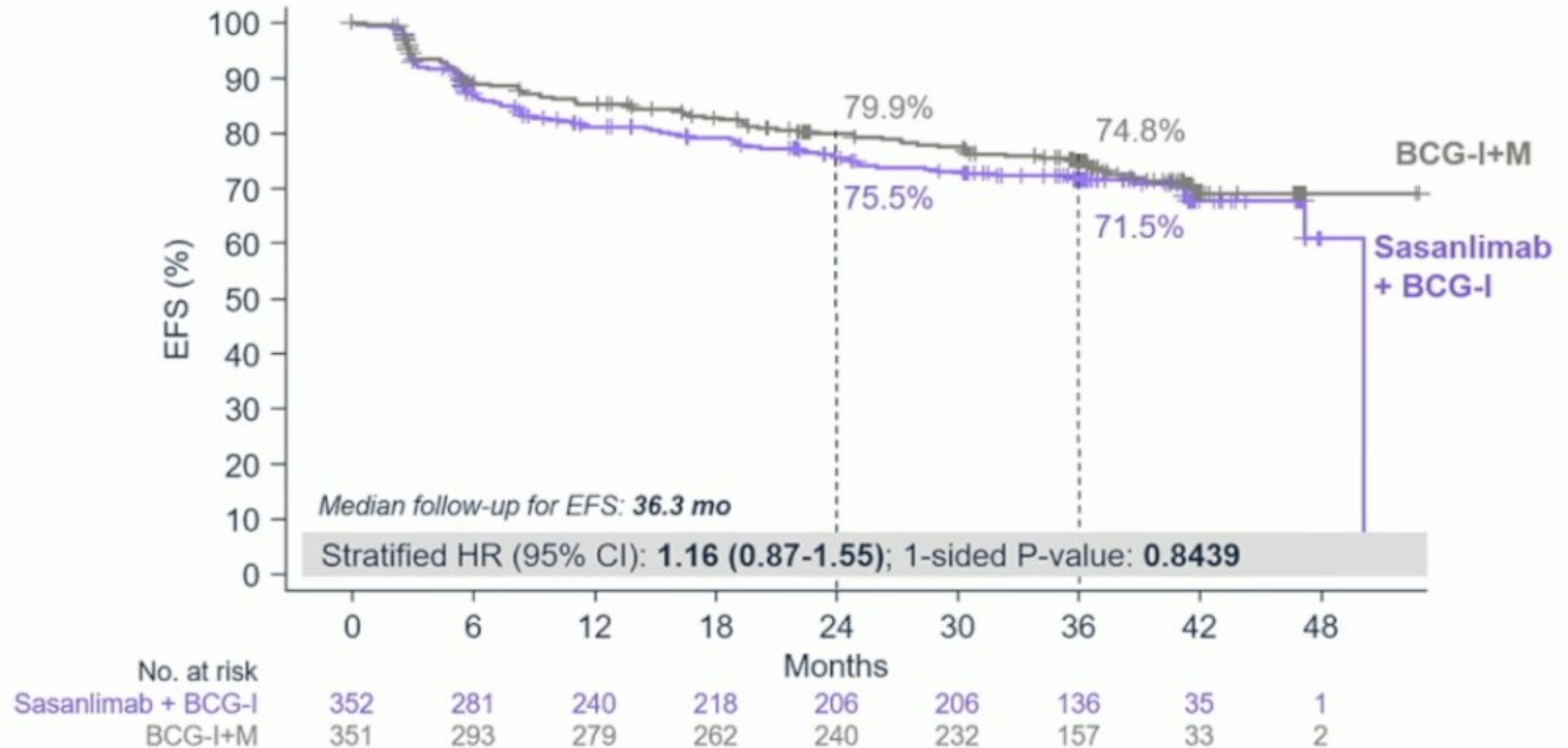
Prespecified Subgroup Analysis of EFS: Arm A vs C

EFS benefit was consistent across subgroups including patients with CIS and T1



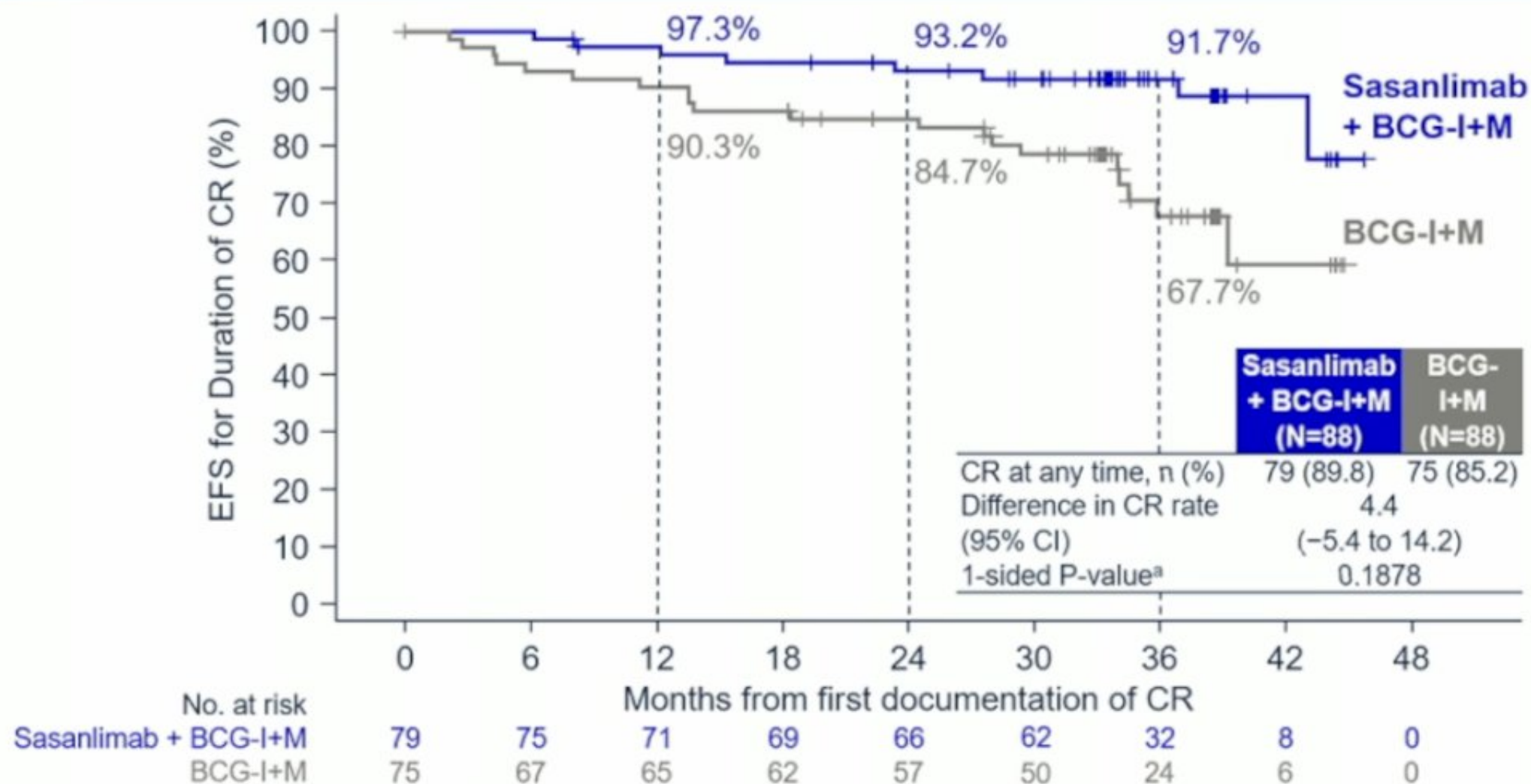
Key Secondary Endpoint EFS by Investigator: Arm B vs Arm C

EFS was not different for sasanlimab + BCG-I vs BCG-I+M



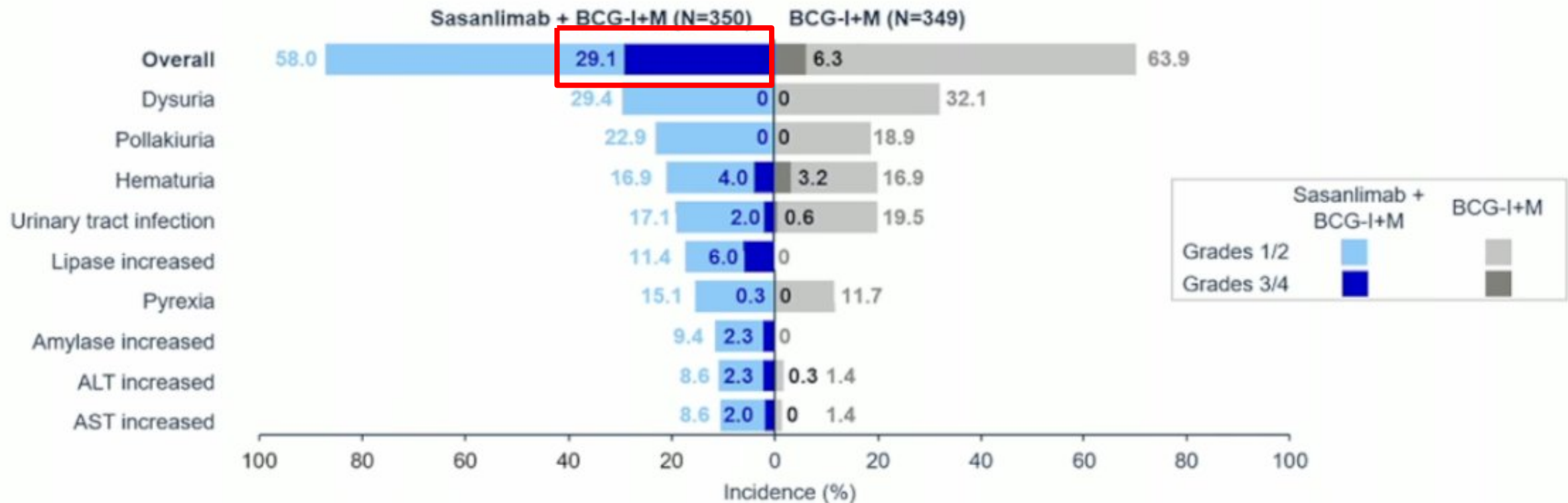
CR and Duration of Response in Patients With CIS: Arm A vs Arm C

In patients with CIS, probability of continued CR at 36 months was 92% for sasanlimab + BCG-I+M



Treatment Related Adverse Events: Arm A vs Arm C

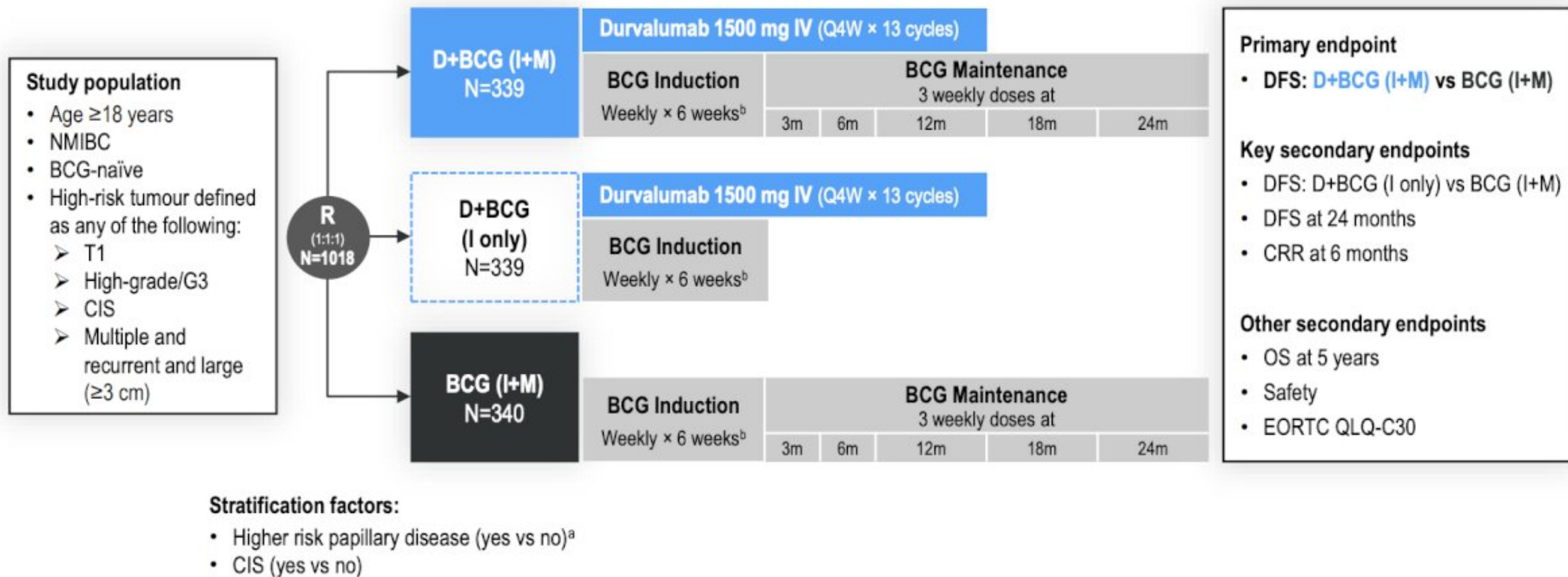
The observed safety profile was consistent with the known safety profile for each individual agent



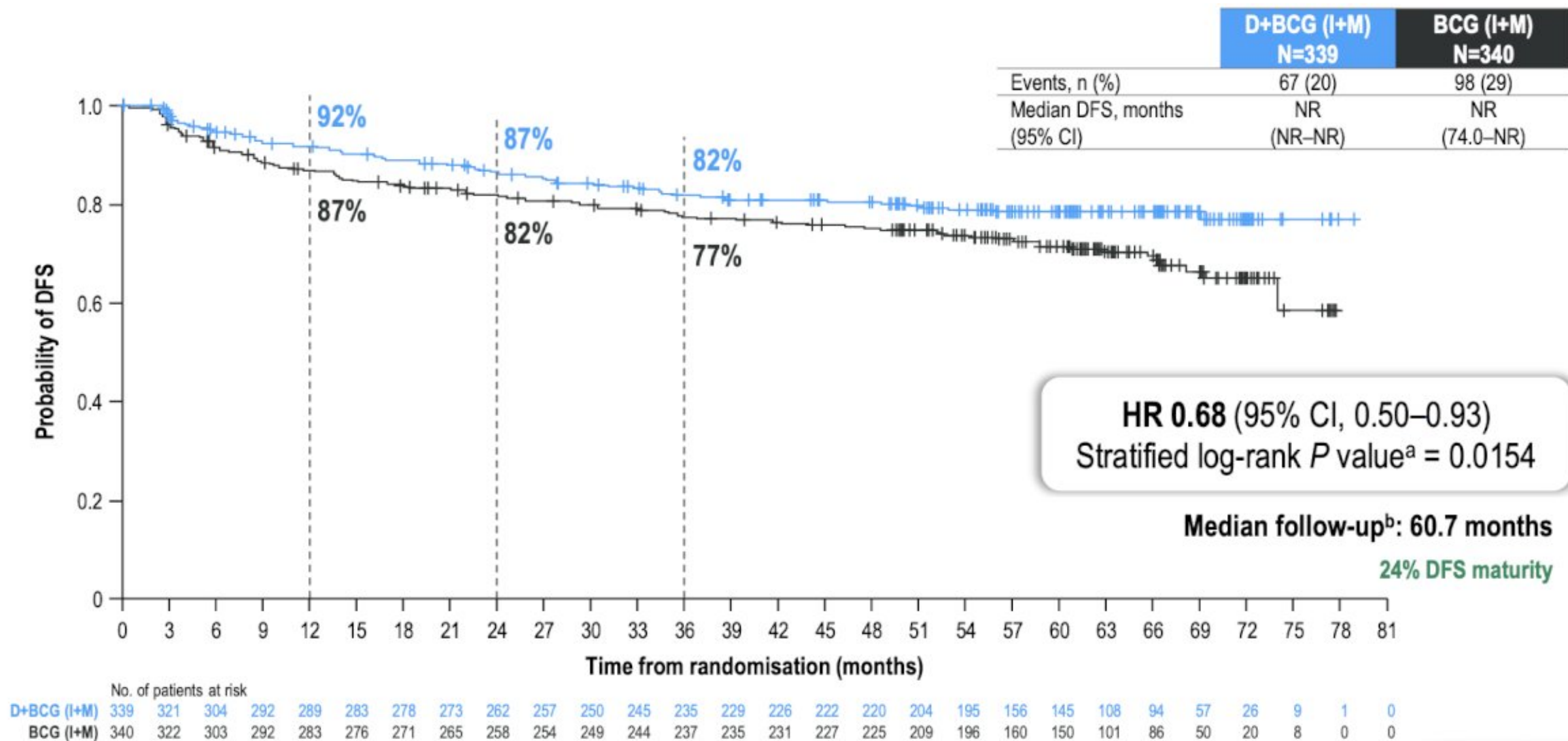
- The median duration (range) of sasanlimab was 80.3 weeks (4.0-103.9) for the sasanlimab + BCG-I+M arm. The median duration (range) of BCG was 98.1 weeks (2.0, 125.1) for the sasanlimab + BCG-I+M arm and 98.9 weeks (2.0, 110.0) for the BCG-I+M arm
- Serious TRAEs were reported in 62 (17.7%) and 5 (1.4%) patients in Arms A and C, respectively
- There were no TRAEs leading to death in Arm A or Arm C

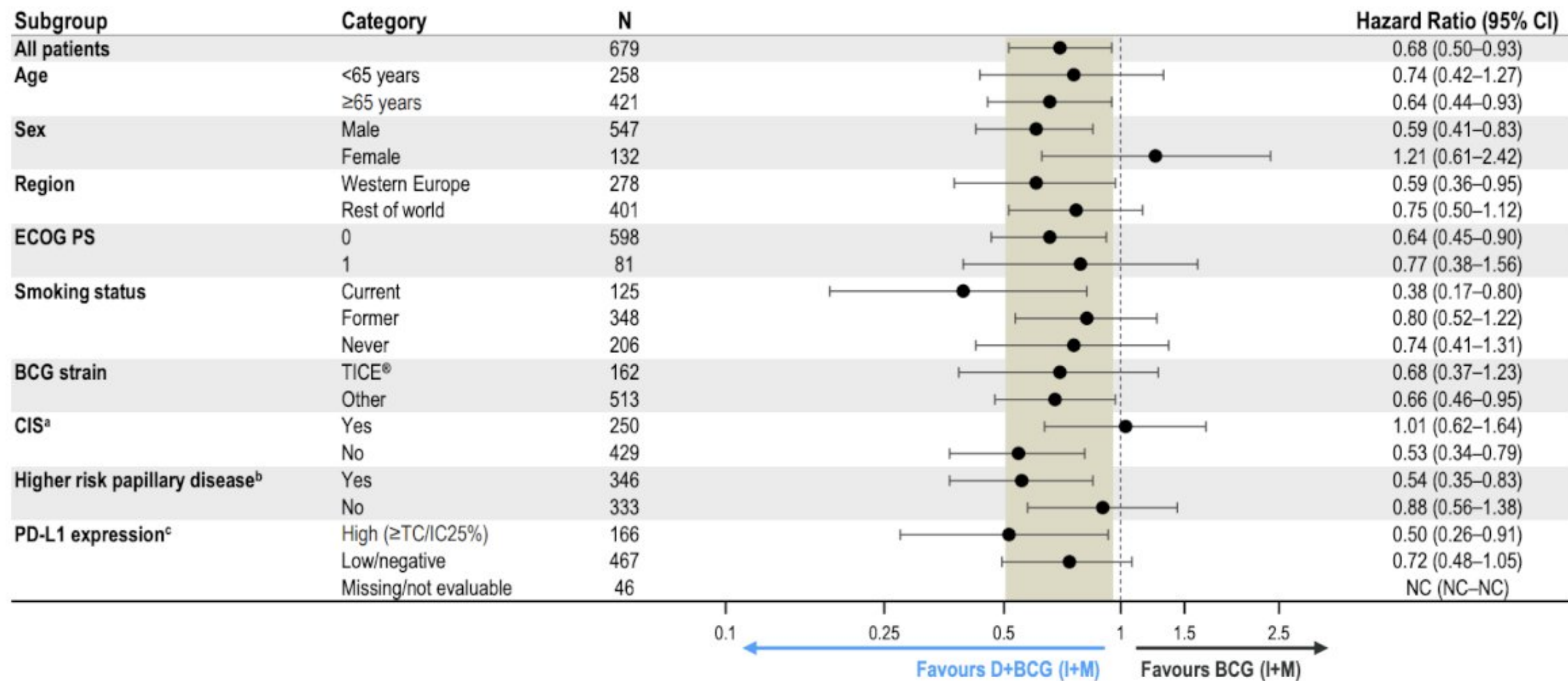
Included are TRAEs that occurred in at least 15% of the patients in any treatment group or grade ≥3 TRAEs that occurred in at least 2% of the patients in any treatment group. BCG, Bacillus Calmette-Guérin; I, induction; M, maintenance; TRAE, treatment-related treatment-emergent adverse event.

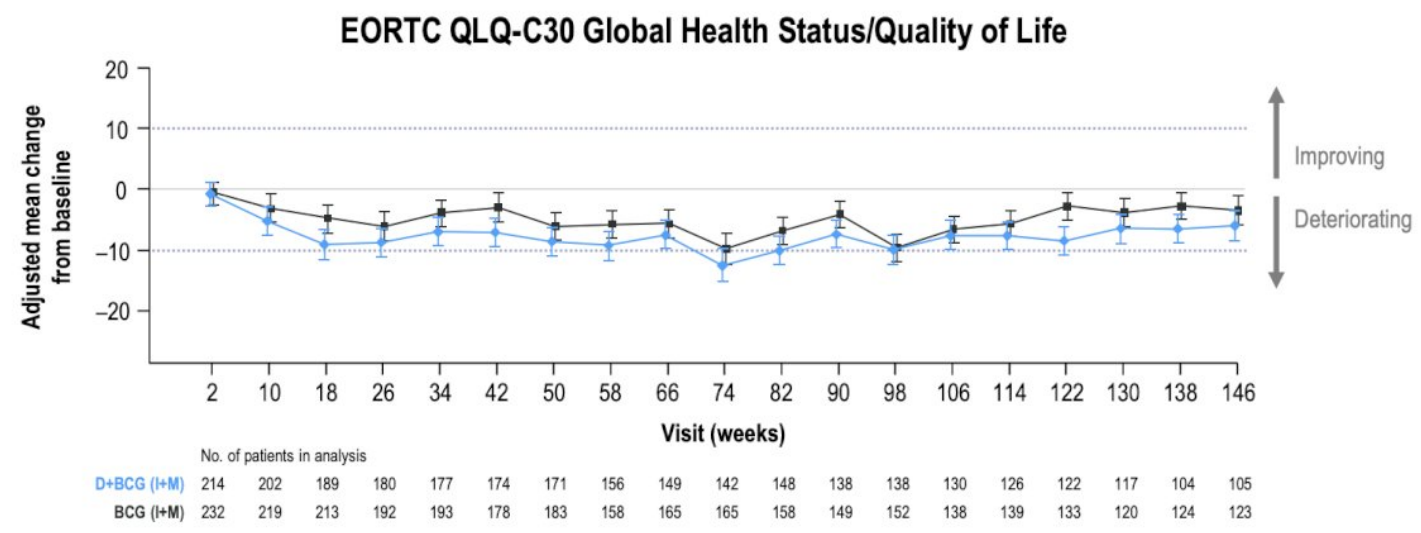
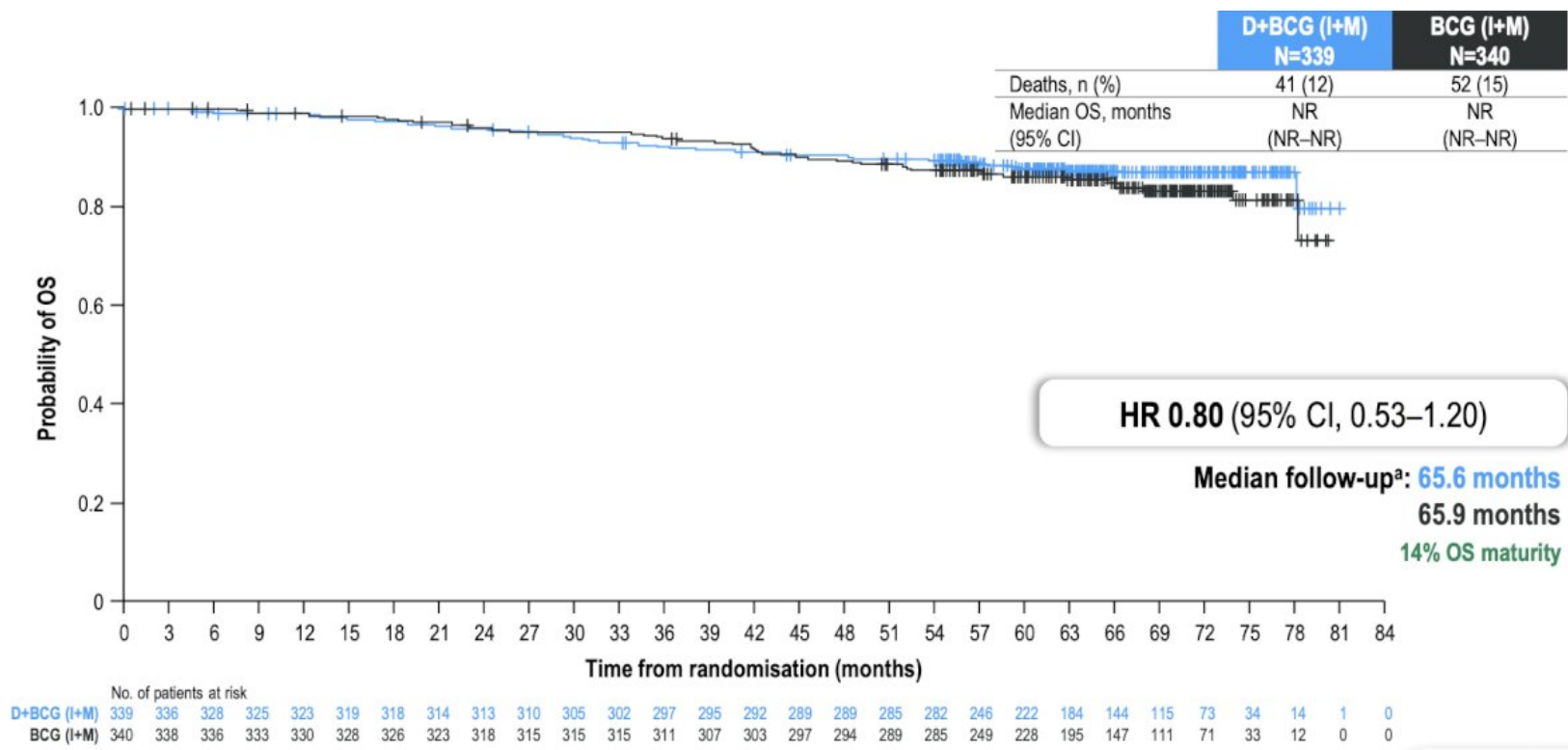
POTOMAC



Characteristics		D+BCG (I+M) N=339	D+BCG (I only) N=339	BCG (I+M) N=340
Age, median (range), years		68 (24–90)	68 (21–87)	67 (32–86)
Sex, n (%)	Male	276 (81)	272 (80)	271 (80)
Region, n (%)	Western Europe	143 (42)	126 (37)	135 (40)
	Rest of world	196 (58)	213 (63)	205 (60)
ECOG PS, n (%)	0	294 (87)	305 (90)	304 (89)
	1	45 (13)	34 (10)	36 (11)
Smoking, n (%)	Current	62 (18)	60 (18)	63 (19)
	Former	175 (52)	182 (54)	173 (51)
	Never	102 (30)	97 (29)	104 (31)
Disease stage, n (%)	T1 ^a	195 (58)	191 (56)	211 (62)
	Ta ^a	112 (33)	114 (34)	99 (29)
	CIS ^b	125 (37)	125 (37)	125 (37)
Papillary disease only, n (%)	Yes	217 (64)	222 (65)	220 (65)
Higher risk papillary disease, ^c n (%)	Yes	173 (51)	173 (51)	173 (51)
PD-L1 expression, ^d n (%)	High (≥TC/IC25%)	81 (24)	90 (27)	85 (25)
	Low/negative	235 (69)	228 (67)	232 (68)
	Missing/not evaluable	23 (7)	21 (6)	23 (7)

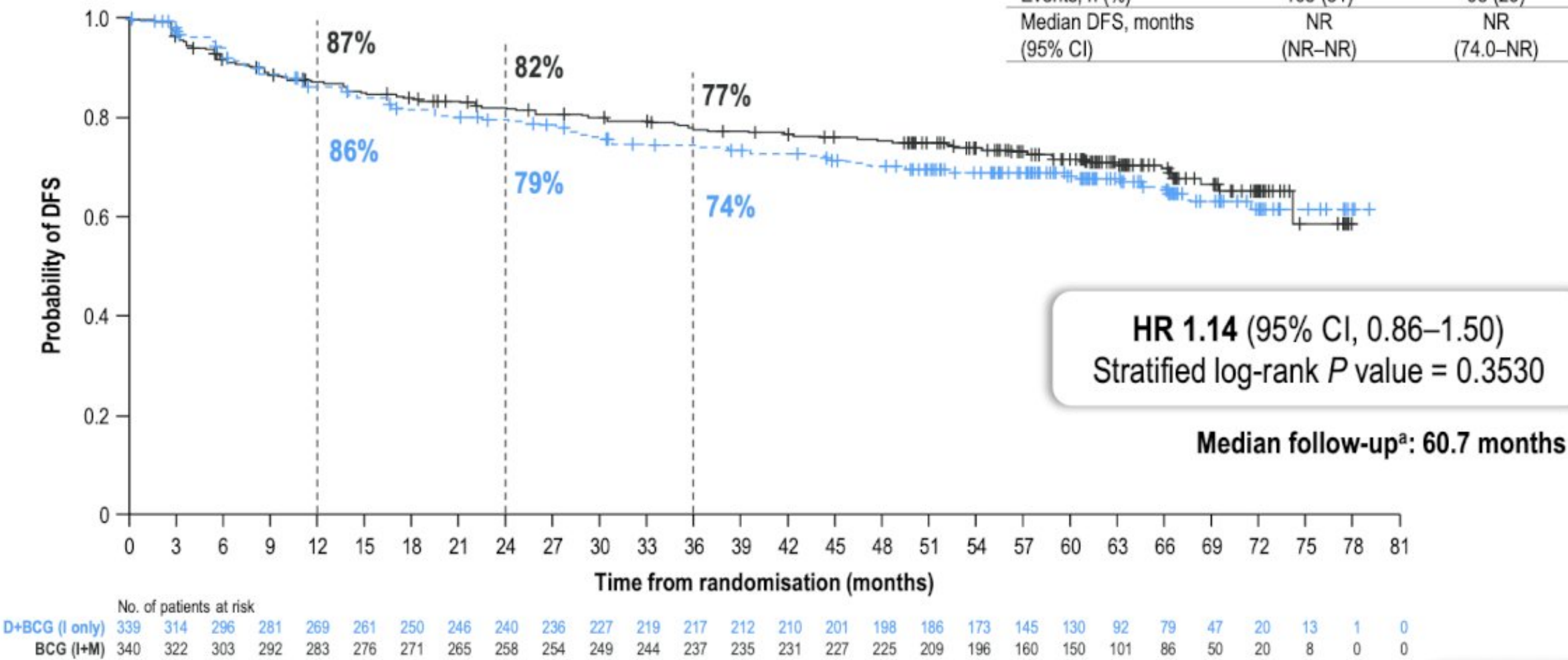






Difference in DFS between D+BCG (I only) vs BCG (I+M) arms was not statistically significant
(key secondary endpoint)

	D+BCG (I only) N=339	BCG (I+M) N=340
Events, n (%)	105 (31)	98 (29)
Median DFS, months (95% CI)	NR (NR–NR)	NR (74.0–NR)



Events, n (%)	D+BCG (I+M) n=336	D+BCG (I only) n=337	BCG (I+M) n=339
AEs of any cause	325 (97)	322 (96)	307 (91)
Possibly related to any treatment	298 (89)	269 (80)	245 (72)
Maximum grade 3 or 4 AEs	113 (34)	90 (27)	56 (17)
Possibly related to any treatment	71 (21)	52 (15)	13 (4)
Serious AEs	108 (32)	82 (24)	63 (19)
Possibly related to any treatment	45 (13)	38 (11)	13 (4)
AEs leading to death	6 (2)	4 (1)	4 (1)
Possibly related to any treatment	0	0	0
AEs leading to discontinuation of study treatment	105 (31)	65 (19)	68 (20)
Possibly related to durvalumab	54 (16)	44 (13)	1 (0.3)^a
Possibly related to BCG	55 (16)	15 (4)	55 (16)
Any-grade immune-mediated AEs	91 (27)	113 (34)	4 (1)
Maximum grade 3 or 4	27 (8)	27 (8)	1 (0.3)
Leading to death	0	0	0

EFFECTOS ADVERSOS GRAVES

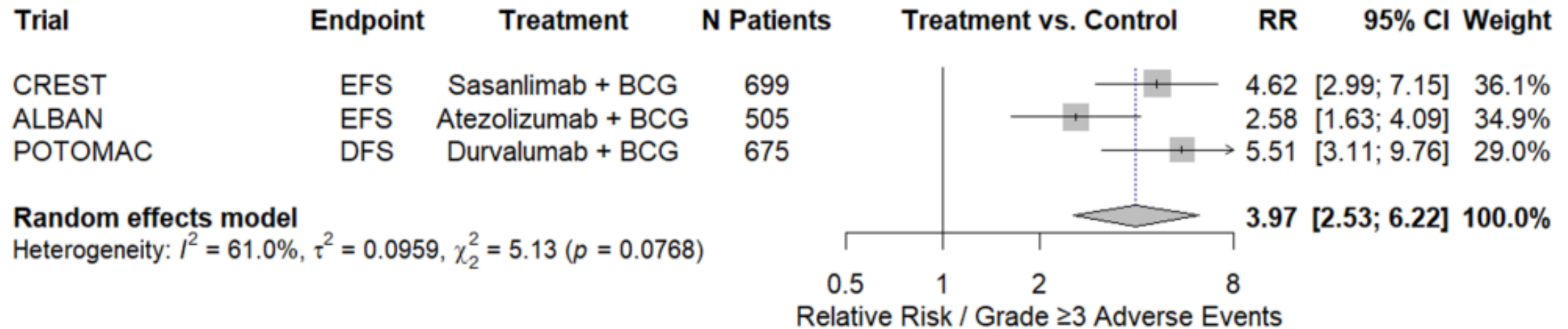
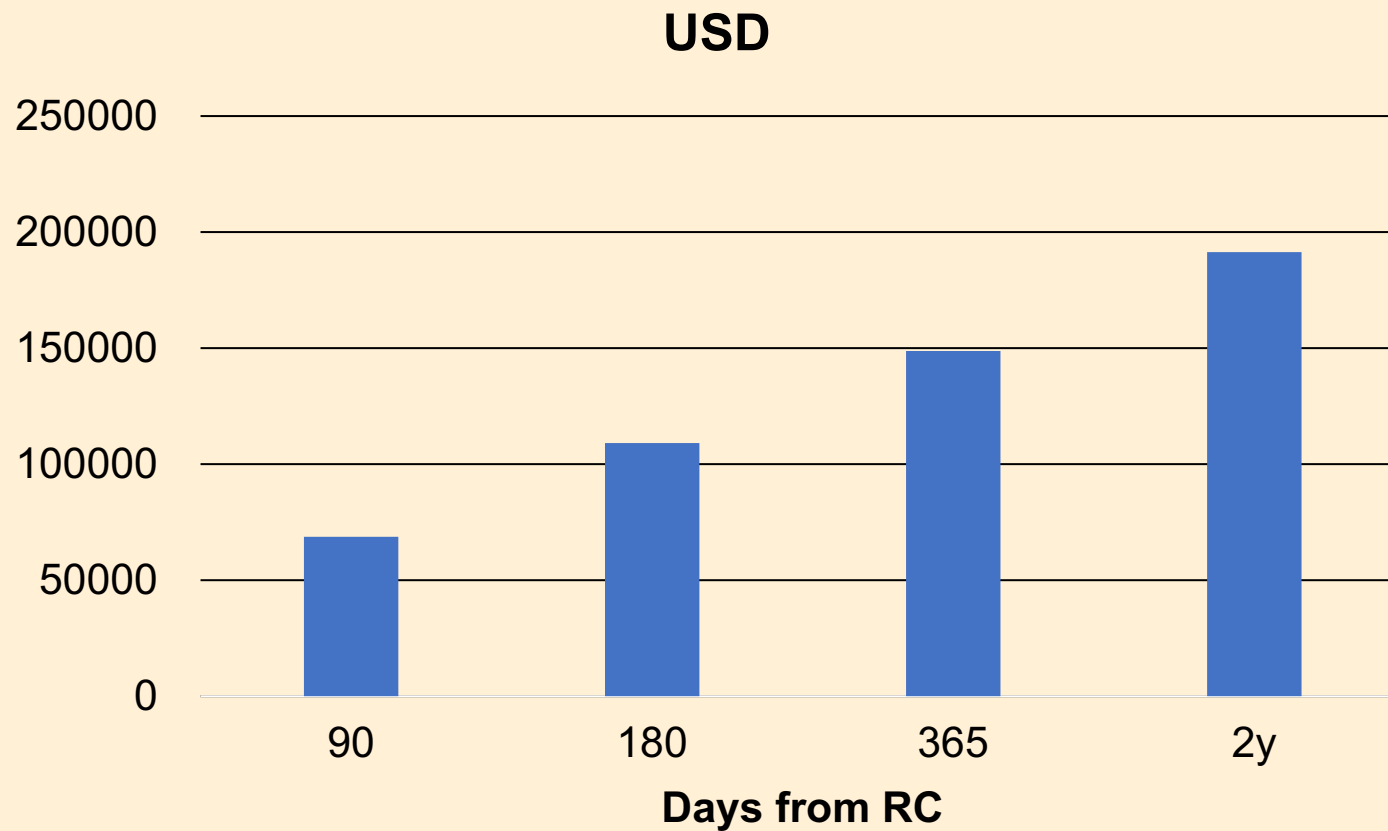


Fig. 3 Forest-Plot: meta-analysis of treatment-related severe adverse events for systemic immunotherapy combined with intravesical BCG



- 30K – 80K USD

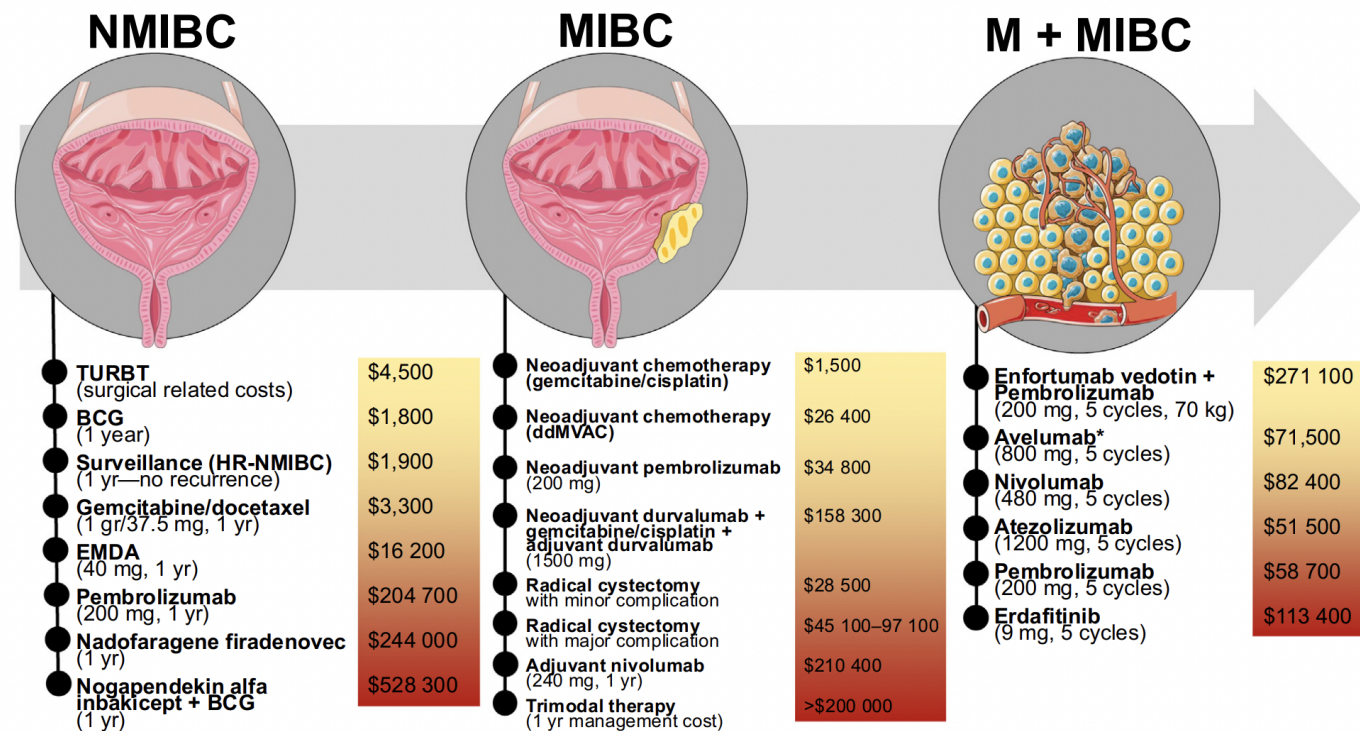
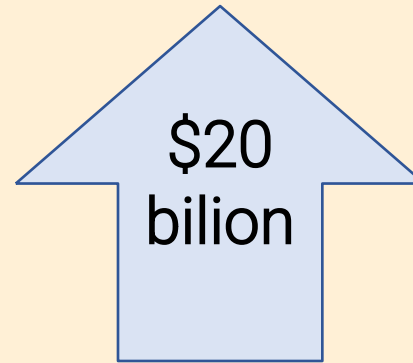


Fig. 2 – Graphical representations of the main direct costs of drugs and procedures related to different stages of bladder cancer (realized with <https://smart.servier.com>). The gradient illustrates the chronological progression of treatment indications. Detailed cost data can be found in Supplementary Tables 4 and 5. Drug pricing was obtained from publicly available sources and literature, and does not reflect confidential discounts negotiated between manufacturers and health care systems. Indirect costs of treatment are not included. For avelumab, one cycle is defined as two infusions within a 21-d period, matching the cycle length used for atezolizumab and pembrolizumab, but requiring two infusions due to the half-life of avelumab. Nivolumab (480 mg) is given every 4 wk per cycle. One cycle of erdafitinib was defined as an infusion at 21 d. BCG = bacillus Calmette-Guerin; ddMVAC = dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; EMDA = electromotive drug administration; HR = high risk; M = metastatic; MIBC = muscle-invasive bladder cancer; NMIBC = non-muscle-invasive bladder cancer; TURBT = transurethral resection of a bladder tumor.

- Increasing bladder cancer incidence
- Implementation of costly new treatments



- Health economic studies
 - Risk stratification and enhanced patient selection
 - Comparative efficacy and sequencing
 - Creative payment structures
 - Strategies for prevention and early detection of bladder cancer
- Emphasize quality of life

In the control arms of **BCG-naïve trials**, maintenance 1yr vs 2 yrs has an impact

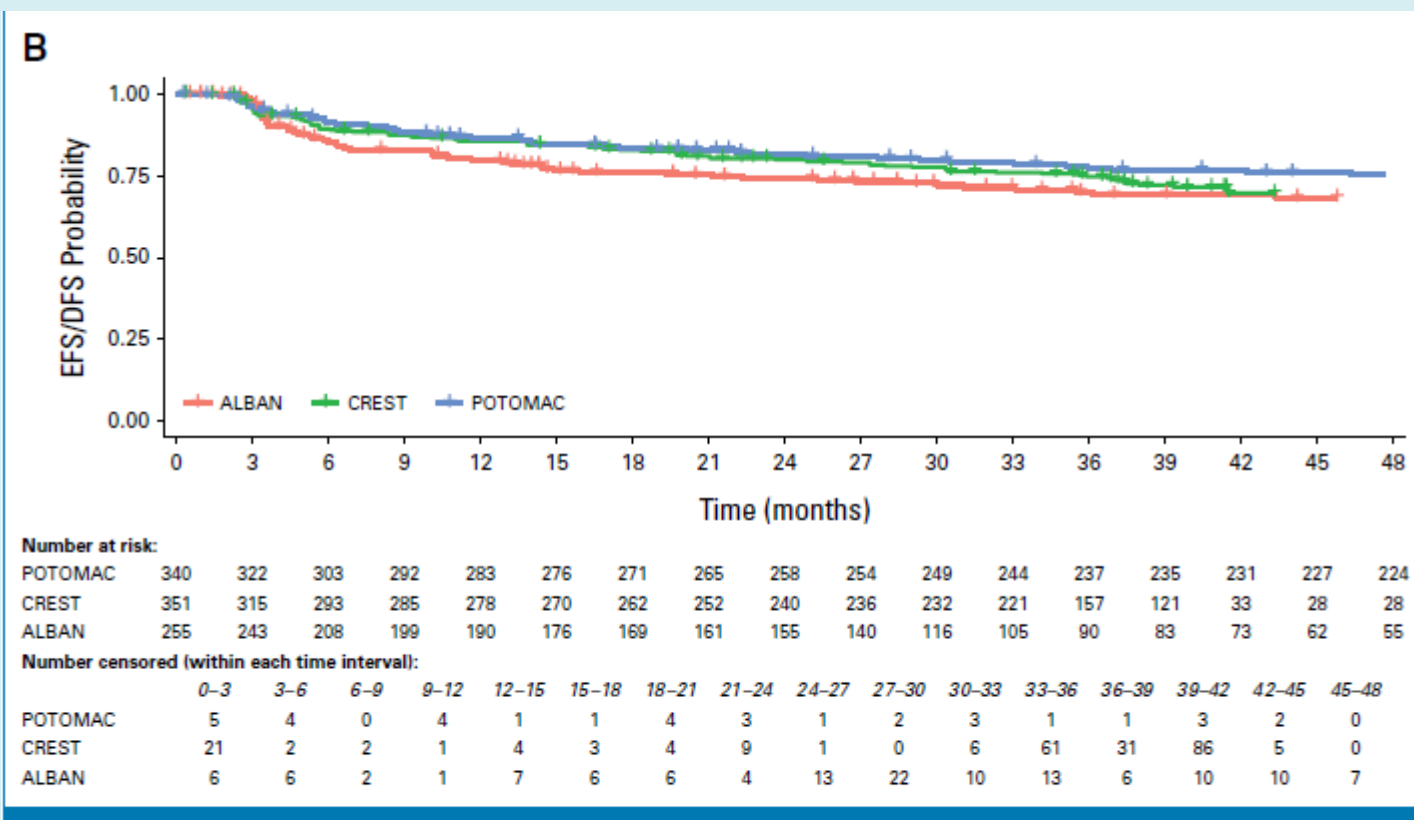


FIG 1. Reconstruction and comparison of EFS/DFS curves across trials. (A) EFS/DFS survival probability of the experimental arms across the included trials. (B) EFS/DFS survival probability of the control arms of the included trials. DFS, disease-free survival; EFS, event-free survival.



LOW COST



ENABLES EQUITY

