Sasanlimab + BCG in BCG-naïve, high-risk NMIBC: The randomized phase 3 CREST trial

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Sasanlimab plus BCG in BCG-naive, high-risk non-muscle invasive bladder cancer: the randomized phase 3 CREST trial

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BCG-Unresponsive NMIBC – Focus

- Significant research efforts in BCG-unresponsive NMIBC

What about BCG-naïve HR NMIBC?

  - 2022: Nadofaragene firadenovec
  - 2024: N-803 (Anktiva) + BCG – QUILT-3.032

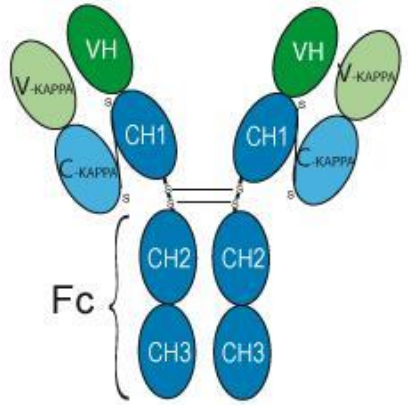
Balar et al. Lancet Oncol, 2021
Boorjian et al. Lancet Oncol, 2021
Chamie et al. NEJM Evid, 2022

BCG-Naïve HR NMIBC

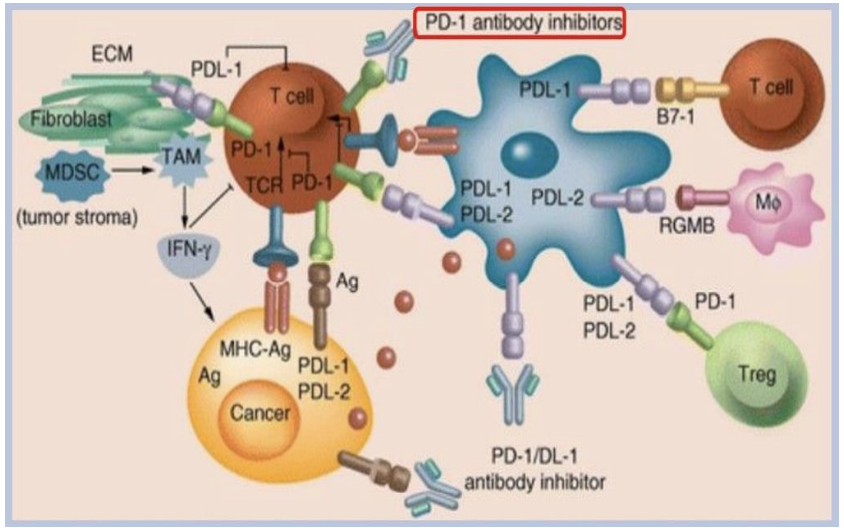
- Standard of care: TURBT + adjuvant intravesical BCG induction (6-weekly) + maintenance x 3 years
- 2-year rate of disease recurrence/progression: **40%**
- Novel agents/combinations needed to:
  - Avoid radical cystectomy + systemic therapies (multi-agent – e.g. EV + pembro; Gem-Cis)
  - Maintain QoL

High Risk
HG T1
Any recurrent, HG Ta
HG Ta, >3cm (or multifocal)
Any CIS[d]
Any BCG failure in HG patient
Any variant histology
Any LVI[e]
Any HG prostatic urethral involvement

Sasanlimab



- Anti-PD-1 mAb administered SQ (or IV)
- Demonstrated safety & efficacy in phase I trial in 40 pts w/ locally advanced/metastatic solid tumors:
  - ORR: 18%
  - Gr ≥3 TRAEs w/ SQ: 6.7%
- Ph Ib/II trial in NSCLC (n=68) & UC (n=38) w/ disease progression/intolerance to systemic therapy:
  - ORR: 18.4%
  - mPFS: 3 mo
  - mOS: 11 mo

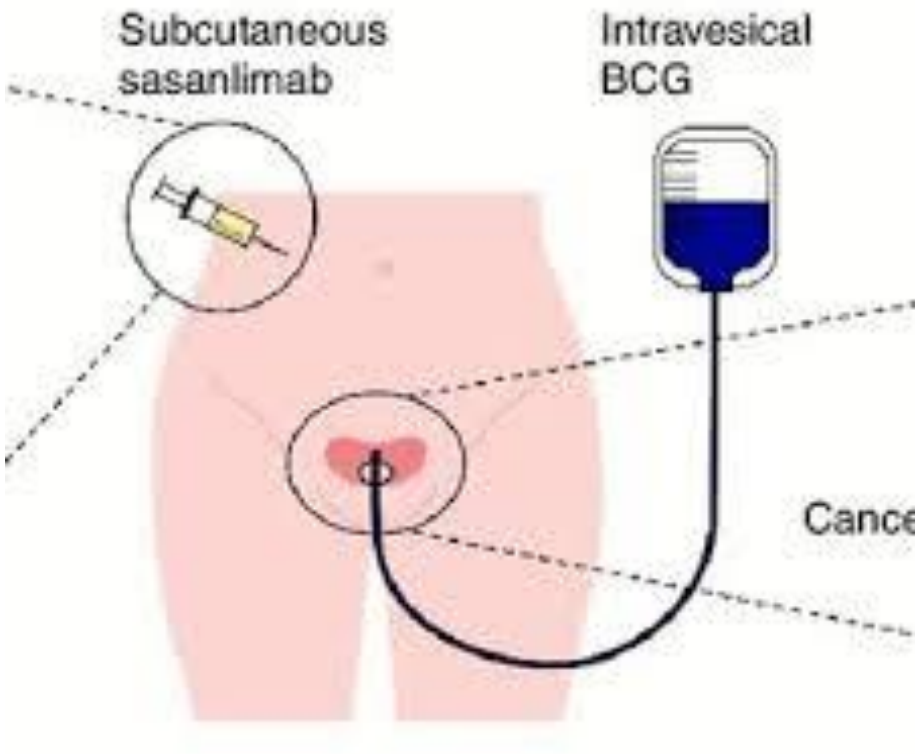


Johnson et al. JAMA Oncol, 2019
Cho et al. ESMO Open, 2023

Why Sasanlimab + BCG?

- BCG exposure → increased PD-L1 expression → contribute to the immune escape mechanism in bladder cancer cells

- Ph Ib/II trial by Cho et al:
  - Higher PD-L1 expression (≥25%): → Improved ORR, PFS, OS



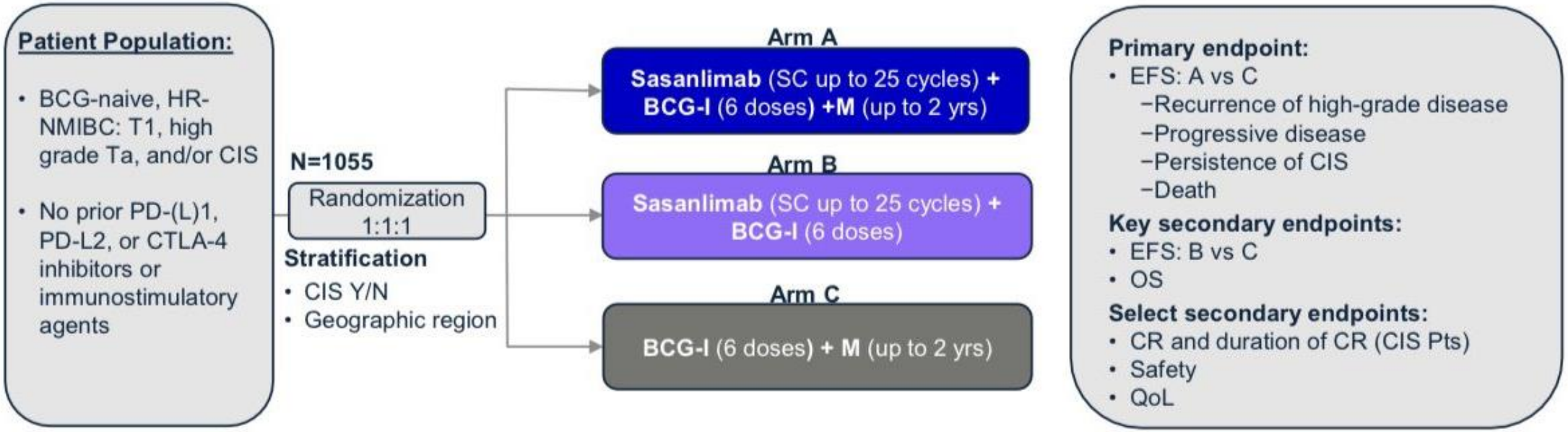
Cho et al. ESMO Open, 2023

Main Study Objective

Compare the efficacy and safety of sasanlimab SQ + BCG induction + maintenance to BCG induction + maintenance only

CREST Study Design

CREST Study (NCT04165317)



Statistical Considerations:

Data cut-off date Dec 2, 2024 (3 yrs after last randomized pt)

- EFS final analysis, significance threshold: 1-sided $\alpha = 0.025$
- Interim OS analysis, nominal $\alpha=0.0001$

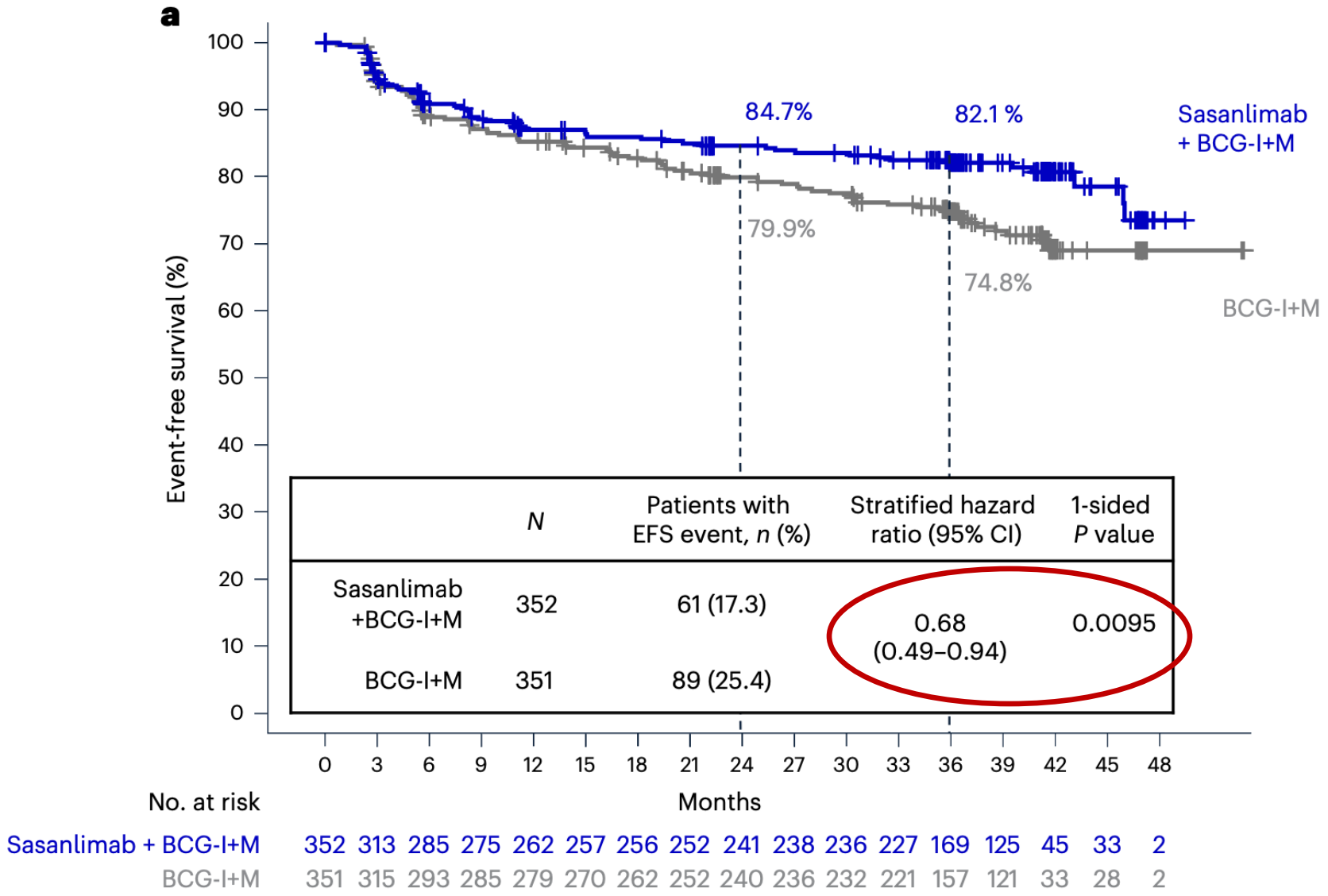
Study Objectives

- Primary:
  - Sasanlimab + BCG I+M (Arm A) superior to BCG I+M (Arm C) for prolonging investigator-assessed EFS
    - Event: HG recurrence, disease progression, CIS persistence, or death
- Secondary:
  - EFS for sasanlimab + BCG I-only (Arm B) vs BCG I+M (Arm C)
  - OS (Arms A & B vs C)
  - CR in CIS pts
  - Duration of CR
  - Safety/adverse events
  - QoL

Demographic and Baseline Disease Characteristics in the ITT Population

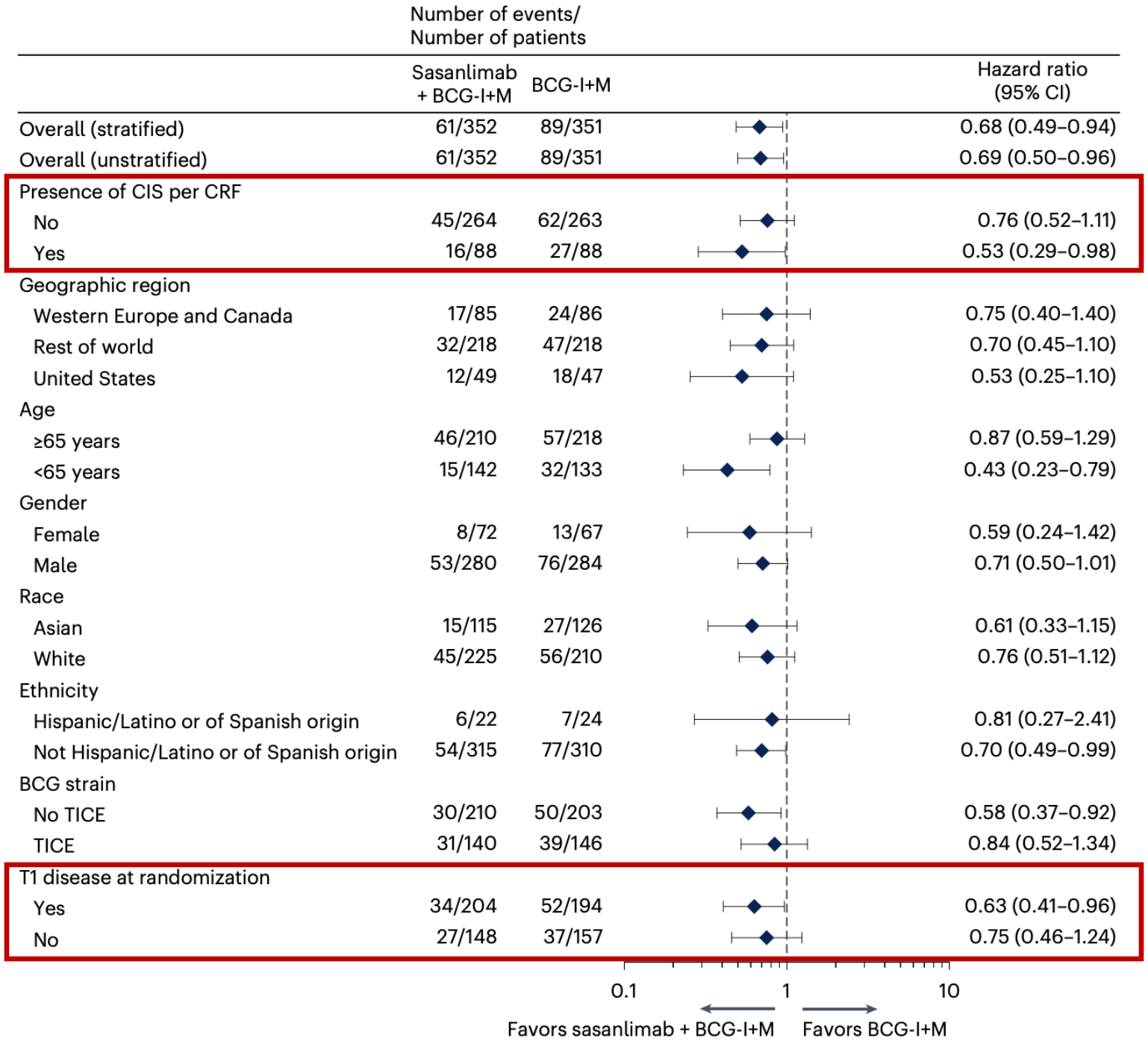
	Sasanlimab + BCG-I+M (*N*=352)	Sasanlimab + BCG-I (*N*=352)	BCG-I+M (*N*=351)
Median age (range), years	67 (31–85)	67 (34–90)	67 (31–91)
Male, *n* (%)	280 (79.5)	299 (84.9)	284 (80.9)
Race, *n* (%)			
White	225 (63.9)	211 (59.9)	210 (59.8)
Asian	115 (32.7)	133 (37.8)	126 (35.9)
Black or African American	3 (0.9)	2 (0.6)	5 (1.4)
Unknown	9 (2.6)	6 (1.7)	10 (2.8)
Eastern Cooperative Oncology Group performance status, *n* (%)			
0	298 (84.7)	293 (83.2)	291 (82.9)
1	54 (15.3)	57 (16.2)	59 (16.8)
2	0	2 (0.6)	1 (0.3)
Presence of CIS per CRF at randomization, *n* (%)	88 (25.0)	93 (26.4)	88 (25.1)
Geographic region, *n* (%)			
United States	49 (13.9)	47 (13.4)	47 (13.4)
Western Europe or Canada	85 (24.1)	87 (24.7)	86 (24.5)
Rest of world	218 (61.9)	218 (61.9)	218 (62.1)
Histological classification, *n* (%)			
UC	339 (96.3)	346 (98.3)	332 (94.6)
UC with squamous differentiation	6 (1.7)	2 (0.6)	8 (2.3)
UC with glandular differentiation	2 (0.6)	4 (1.1)	3 (0.9)
UC with variant histology	4 (1.1)	0	6 (1.7)
Other	1 (0.3)	0	2 (0.6)
Worst T stage, *n* (%)			
CIS	52 (14.8)	42 (11.9)	50 (14.2)
Ta	96 (27.3)	136 (38.6)	107 (30.5)
T1	204 (58.0)	174 (49.4)	194 (55.3)
Smoking history, *n* (%)			
Never smoker	127 (36.1)	108 (30.7)	126 (35.9)
Current smoker	71 (20.2)	70 (19.9)	54 (15.4)
Former smoker	154 (43.8)	174 (49.4)	171 (48.7)
PD-L1 status			
High[a]	77 (22.6)	68 (20.2)	73 (21.7)
Low[b]	252 (74.1)	256 (76.0)	253 (75.1)
Unknown	11 (3.2)	13 (3.9)	11 (3.3)

EFS: Sasanlimab + BCG (I+M) vs BCG (I+M)

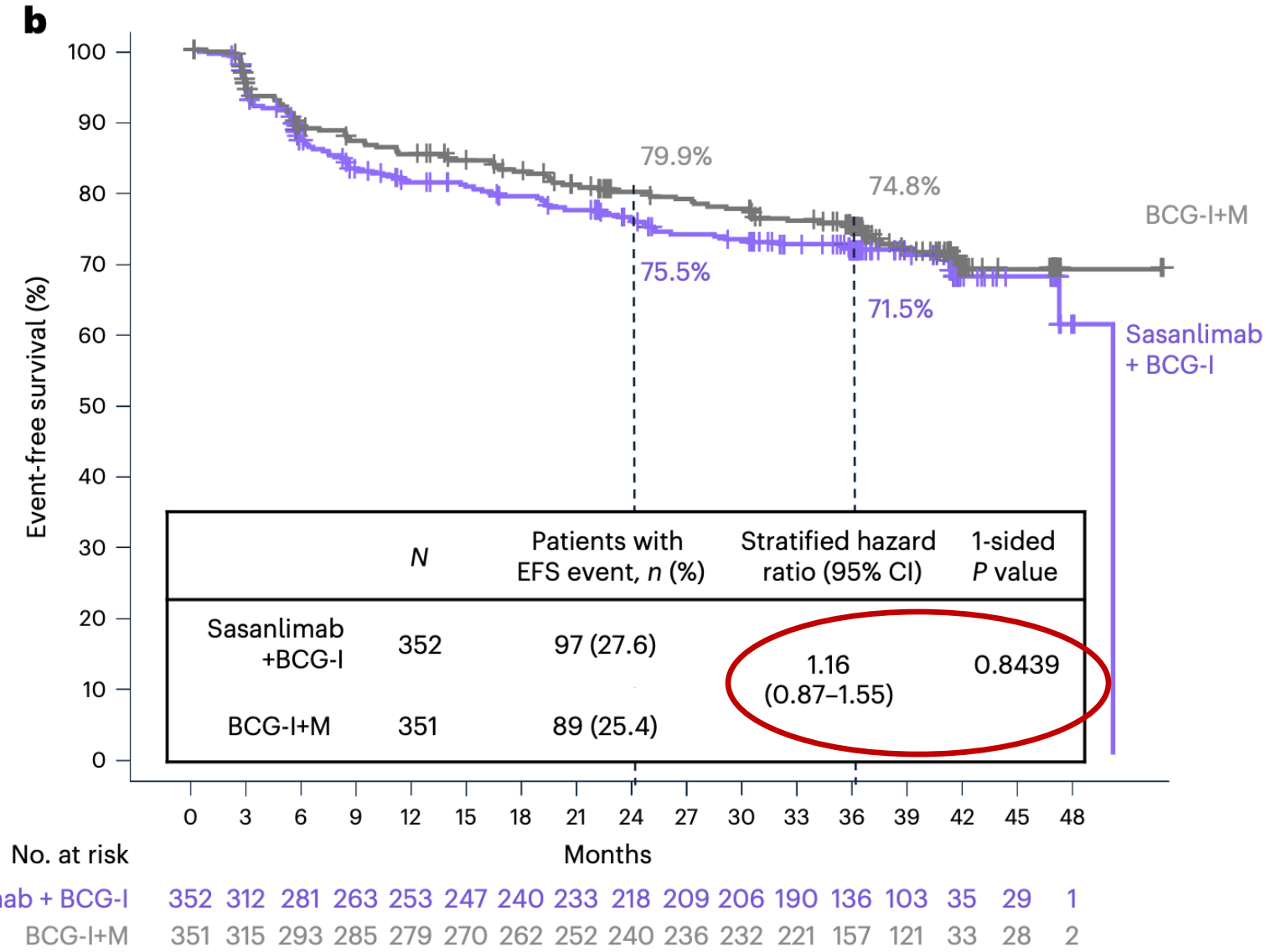


	N	Patients with EFS event, *n* (%)	Stratified hazard ratio (95% CI)	1-sided *P* value
Sasanlimab +BCG-I+M	352	61 (17.3)	0.68 (0.49–0.94)	0.0095
BCG-I+M	351	89 (25.4)		

Sasanlimab + BCG (I+M) vs BCG (I+M) EFS Subgroup Analyses



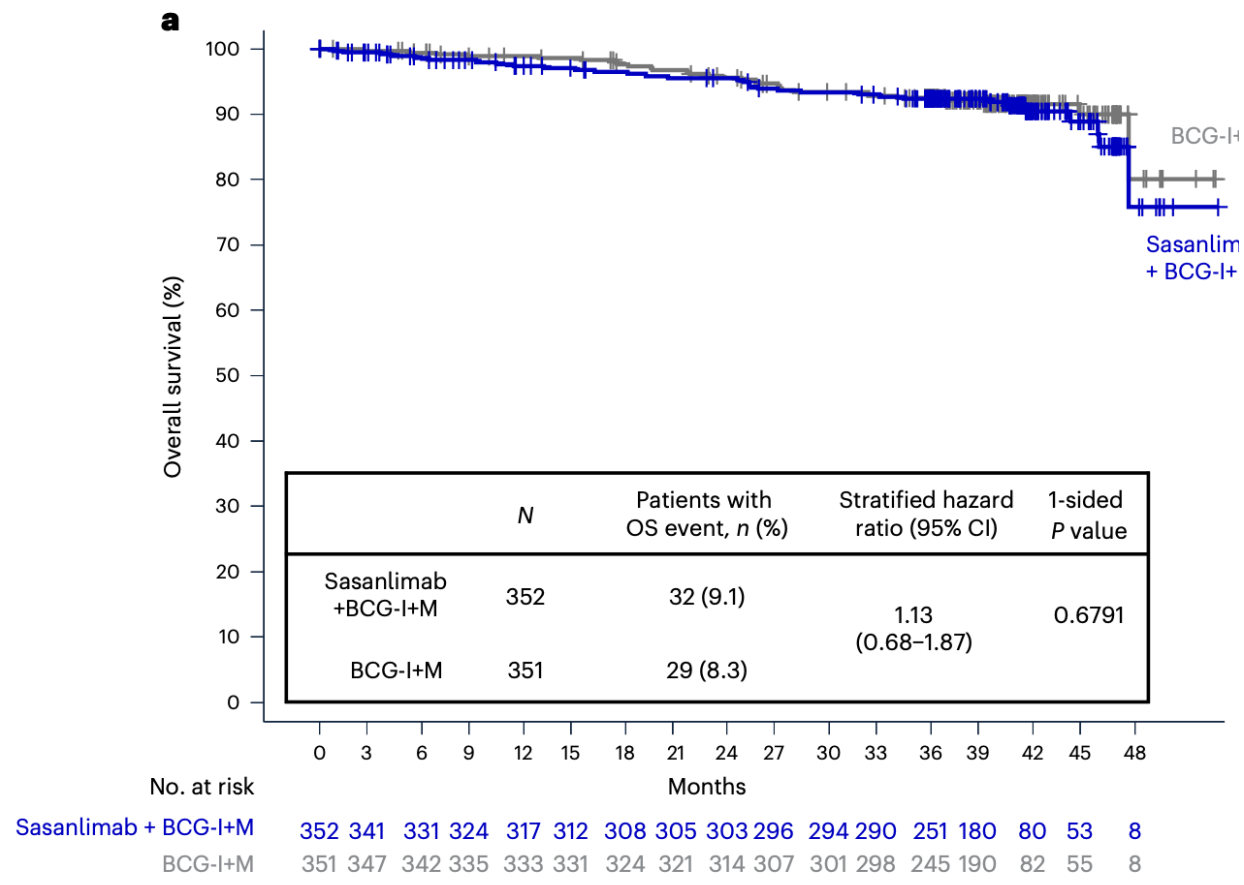
EFS: Sasanlimab + BCG (I) vs BCG (I+M)



EFS in the ITT Population

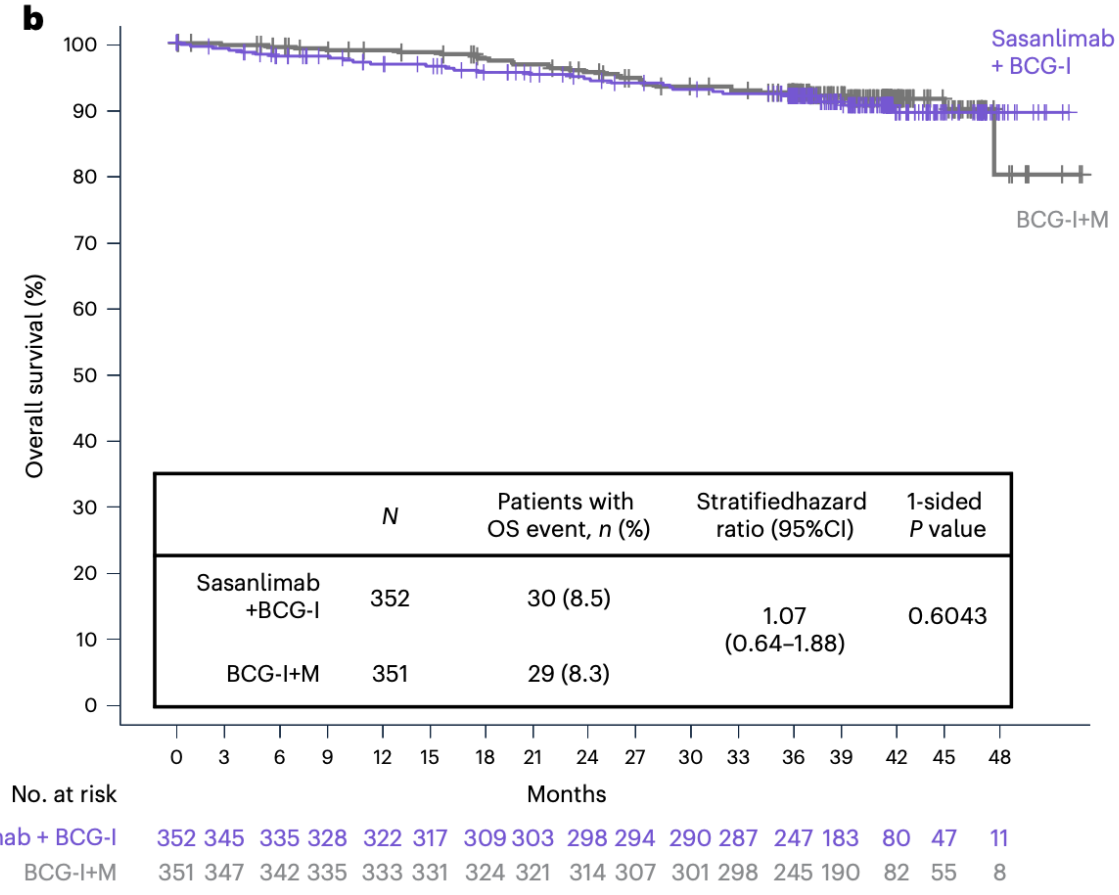
	Sasanlimab + BCG-I+M (*N*=352)	Sasanlimab + BCG-I (*N*=352)	BCG-I+M (*N*=351)
Patients with EFS event, *n* (%)	61 (17.3)	97 (27.6)	89 (25.4)
Progressive disease	18 (5.1)	14 (4.0)	22 (6.3)
Progression to metastatic disease (N+, M+), *n*	3	2	7
Progression to muscle-invasive disease (≥T2), *n*	7	3	7
Stage progression (Ta high-grade, T1), *n*	7	9	7
Unknown, *n*	1	0	1
Recurrence of high-grade disease, *n* (%)	26 (7.4)	61 (17.3)	53 (15.1)
Persistence of CIS, *n* (%)	1 (0.3)	2 (0.6)	1 (0.3)
Death, *n* (%)	16 (4.5)	20 (5.7)	13 (3.7)
Probability of being event free (95% CI), %			
12 mo	87.0 (82.8-90.2)	81.2 (76.5-85.0)	85.3 (81.0-88.7)
24 mo	84.7 (80.2-88.2)	75.5 (70.4-79.9)	79.9 (75.2-83.9)
36 mo	82.1 (77.4-85.9)	71.5 (66.1-76.2)	74.8 (69.7-79.2)
EFS stratified hazard ratio versus Arm C (95% CI); 1-sided stratified log-rank test P-value	0.68 (0.49-0.94); 0.0095	1.16 (0.87-1.55); 0.8439	–

OS in the ITT Population



	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)		

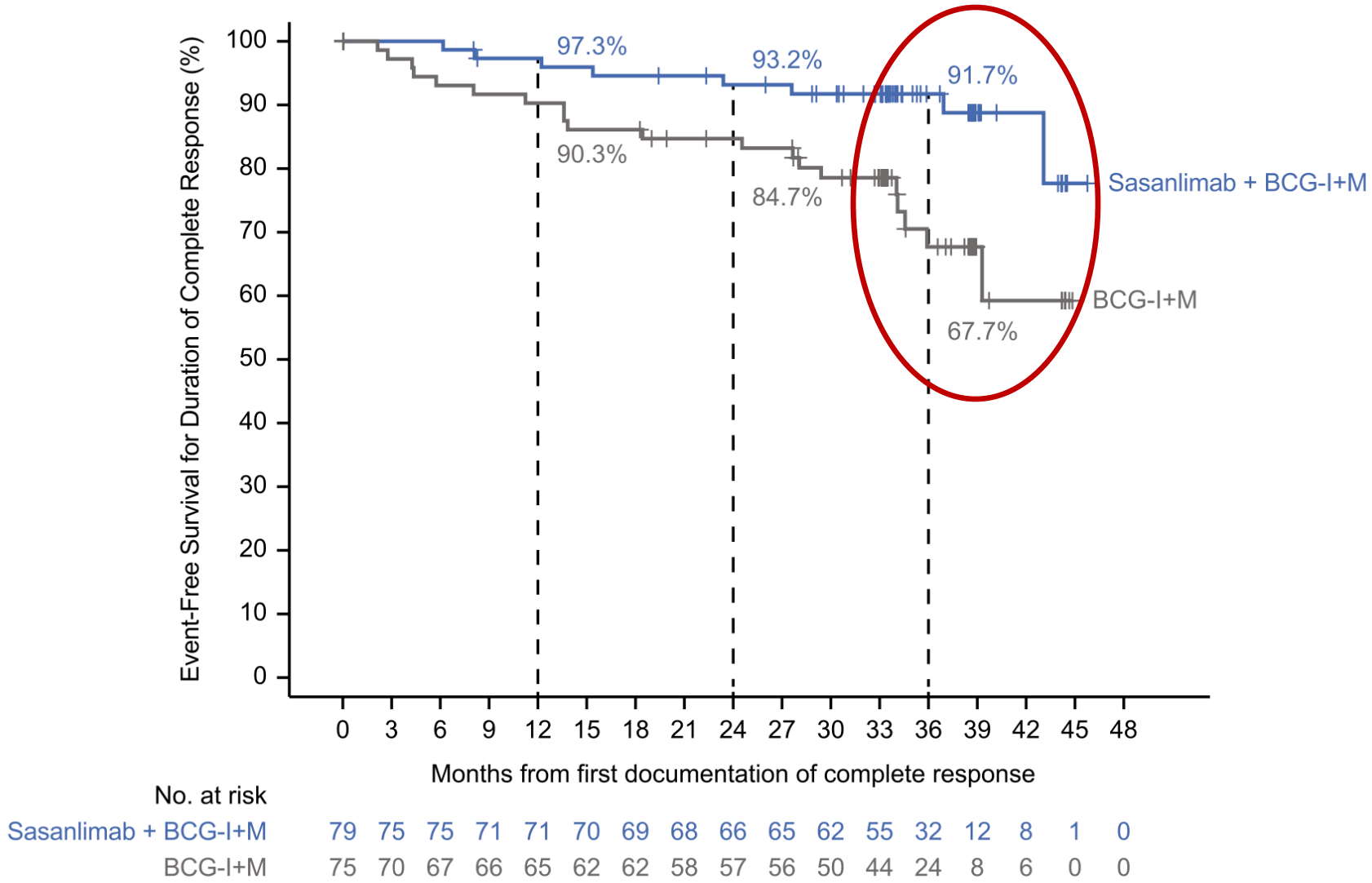
Sasanlimab + BCG (I+M) vs (BCG I+M)



	N	Patients with OS event, n (%)	Stratifiedhazard ratio (95%CI)	1-sided P value
Sasanlimab +BCG-I	352	30 (8.5)	1.07 (0.64–1.88)	0.6043
BCG-I+M	351	29 (8.3)		

Sasanlimab + BCG (I) vs BCG (I+M)

Probability of Remaining in CR for CIS Patients who Achieved CR - *Sasanlimab + BCG (I+M) vs BCG (I+M)*



TRAEs During the On-Treatment Period

	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

Summary of Immune-Related AEs

	Sasanlimab + BCG-I+M (*N*=350)		Sasanlimab + BCG-I (*N*=348)		BCG-I+M (*N*=349)	
Cluster terms *n* (%)	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
* THYROID DISORDERS	62 (17.7)	2 (0.6)	71 (20.4)	1 (0.3)	5 (1.4)	0
* RASH	46 (13.1)	10 (2.9)	48 (13.8)	8 (2.3)	0	0
* HEPATITIS	15 (4.3)	12 (3.4)	14 (4.0)	11 (3.2)	0	0
* PANCREATITIS	14 (4.0)	7 (2.0)	10 (2.9)	6 (1.7)	0	0
ADRENAL INSUFFICIENCY	12 (3.4)	6 (1.7)	12 (3.4)	5 (1.4)	0	0
* PNEUMONITIS	10 (2.9)	4 (1.1)	4 (1.1)	1 (0.3)	0	0
* COLITIS	9 (2.6)	5 (1.4)	9 (2.6)	3 (0.9)	0	0
HYPOPHYSITIS/ HYPOPITUITARISM	8 (2.3)	4 (1.1)	9 (2.6)	3 (0.9)	0	0
TYPE 1 DIABETES MELLITUS	7 (2.0)	6 (1.7)	4 (1.1)	4 (1.1)	0	0
NEPHRITIS AND RENAL DYSFUNCTION	6 (1.7)	4 (1.1)	9 (2.6)	7 (2.0)	0	0
MYASTHENIC SYNDROME/MYASTHENIA GRAVIS	2 (0.6)	1 (0.3)	0	0	0	0
MYOCARDITIS	1 (0.3)	1 (0.3)	3 (0.9)[a]	1 (0.3)	0	0
MYOSITIS	1 (0.3)	1 (0.3)	2 (0.6)	1 (0.3)	0	0
UVEITIS	1 (0.3)	1 (0.3)	0	0	0	0
Other irAEs	8 (2.3)	1 (0.3)	16 (4.6)	4 (1.1)	0	0
Psoriasis	5 (1.4)	0	3 (0.9)	1 (0.3)	0	0
Vitiligo	2 (0.6)	0	3 (0.9)	0	0	0
Rheumatoid arthritis	1 (0.3)	1 (0.3)	1 (0.3)	0	0	0
Polymyalgia rheumatica	1 (0.3)	0	5 (1.4)	2 (0.6)	0	0
Dermatitis psoriasiform	1 (0.3)	0	1 (0.3)	0	0	0
Sjogren's syndrome	1 (0.3)	0	1 (0.3)	0	0	0
Immune thrombocytopenia	0	0	1 (0.3)	1 (0.3)	0	0
Pulmonary sarcoidosis	0	0	1 (0.3)	0	0	0

Discussion

- **<u>Key finding</u>**: The risk of an EFS event was 32% lower in the sasanlimab + BCG (I+M) arm vs BCG (I+M) arm

- Sasanlimab + BCG (I) did not result in prolongation of EFS vs BCG (I+M)
  - Underscores the need for BCG maintenance not only as current SOC treatment but also in combination with sasanlimab

- As expected, higher frequencies of any grade TRAEs and grade 3+ TRAEs (including irAEs) were observed in sasanlimab + BCG (I+M) vs BCG (I+M)
  - Suggests no relevant safety differences between shorter vs longer exposure to BCG
  - The benefit/risk of adding sasanlimab to BCG in clinical practice will heavily rely on SDM

- **Outstanding questions:**
  1. What will be the urologist's comfort level be for SQ sasanlimab? Partner with med onc?
  2. Impact of the ongoing BCG shortage?

Take Home Messages

- The significant reduction in the risk of recurrence of high-grade disease, persistence of CIS, disease progression or death led to durable disease control in patients receiving sasanlimab + BCG (I+M)

- The safety profile of the combination was manageable

- ***Sasanlimab + BCG (I+M) has the potential to redefine the treatment paradigm and clinical decision making for patients with aggressive (CIS or T1) BCG-naïve NMIBC***