Second Opinion: Integrating Novel Approaches into the Management of Non-Muscle-Invasive and Muscle-Invasive Bladder Cancer

A CME Symposium Held Adjunct to the
2026 ASCO® Genitourinary Cancers Symposium

Thursday, February 26, 2026
7:00 PM – 9:00 PM PT (10:00 PM – 12:00 AM ET)

Faculty

Matthew D Galsky, MD
Shilpa Gupta, MD
Andrea Necchi, MD

Moderator

Terence Friedlander, MD

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Moderator

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Second Opinion

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Dr Galsky — Disclosures
Faculty

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Dr Gupta — Disclosures
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Prof Necchi — Disclosures
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Moderator

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Second Opinion: Clinical Investigators Provide Perspectives on the Future Role of AKT Inhibition in the Management of Prostate Cancer

A CME Symposium Held Adjunct to the
2026 ASCO® Genitourinary Cancers Symposium

Friday, February 27, 2026
6:00 PM – 7:30 PM PT (9:00 PM – 10:30 PM ET)

Faculty

Professor Karim Fizazi, MD, PhD
Daniel George, MD

Moderator

Elisabeth I Heath, MD

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Save The Date

Fifth Annual
National General Medical Oncology Summit

A Multitumor CME/MOC-, NCPD- and ACPE-Accredited Educational Conference Developed in Partnership with Florida Cancer Specialists & Research Institute

Friday to Sunday, April 24 to 26, 2026

The Ritz-Carlton Orlando, Grande Lakes | Orlando, Florida

Moderated by Neil Love, MD

Clinicians in the Meeting Room

Please refer to the printed handout provided with your meeting syllabus, and scan the corresponding QR code to

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Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: We will aim to address as many questions as possible during the program.

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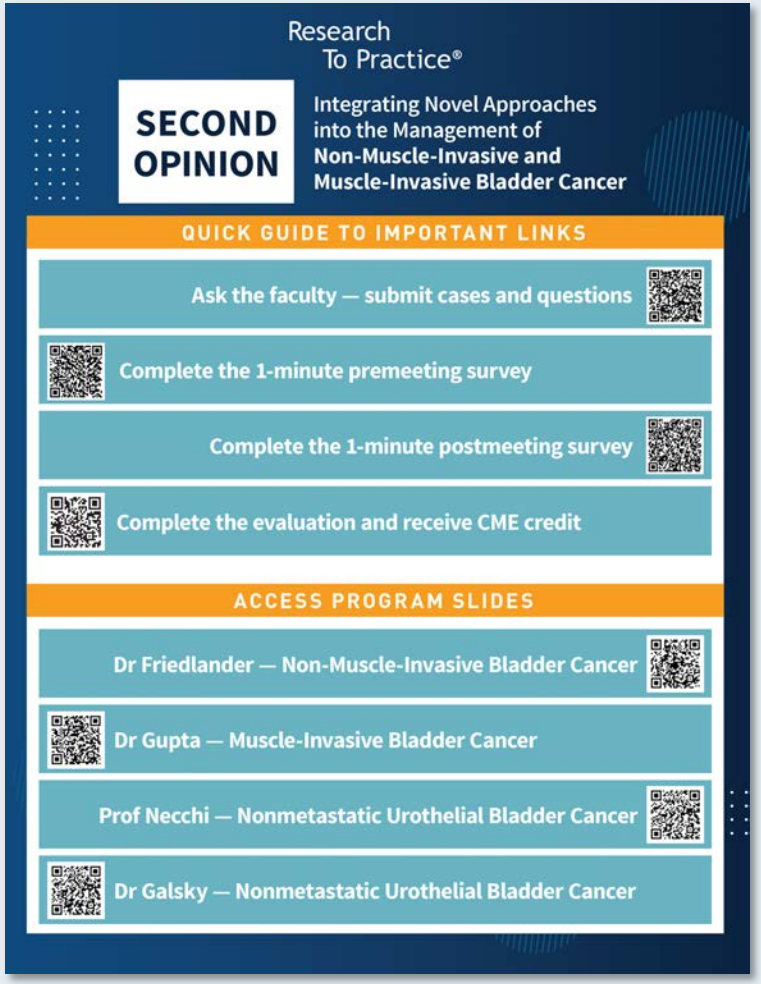

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Clinicians Attending via Zoom

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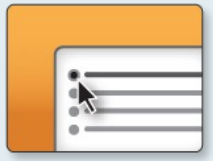

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based program.
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Agenda

Module 1: Optimal Use of Anti-PD-1/PD-L1 Antibodies in Non-Muscle-Invasive Bladder Cancer — Dr Friedlander

Module 2: Evolving Management of Muscle-Invasive Bladder Cancer — Dr Gupta

Module 3: Current and Future Role of Novel Intravesical Therapies in Nonmetastatic Urothelial Bladder Cancer (UBC) — Dr Necchi

Module 4: Emerging Utility of Circulating Tumor DNA Evaluation in Nonmetastatic UBC — Dr Galsky

Agenda

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Optimal Use of Anti-PD-1/PD-L1 Antibodies in Non-Muscle-Invasive Bladder Cancer (NMIBC)

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Robert and Virginia O'Reilly Family Endowed Chair
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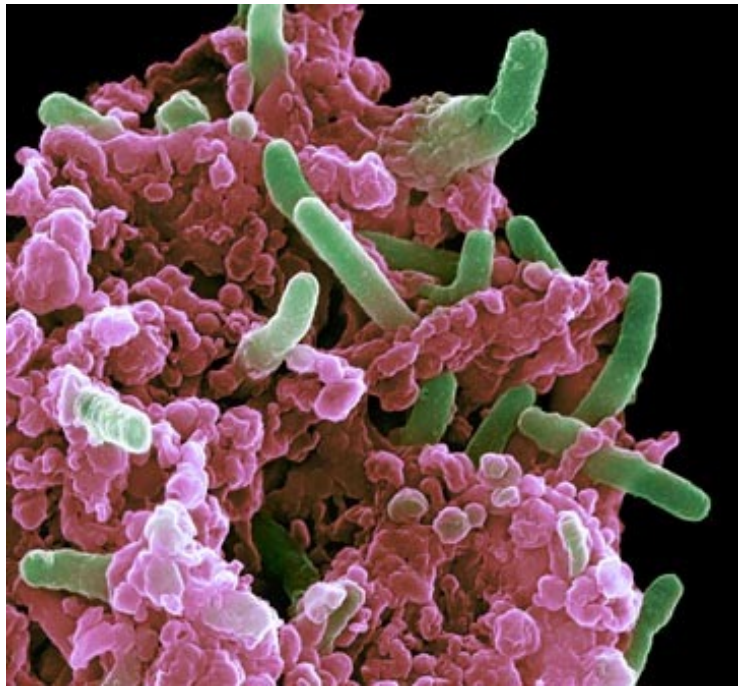
Outline

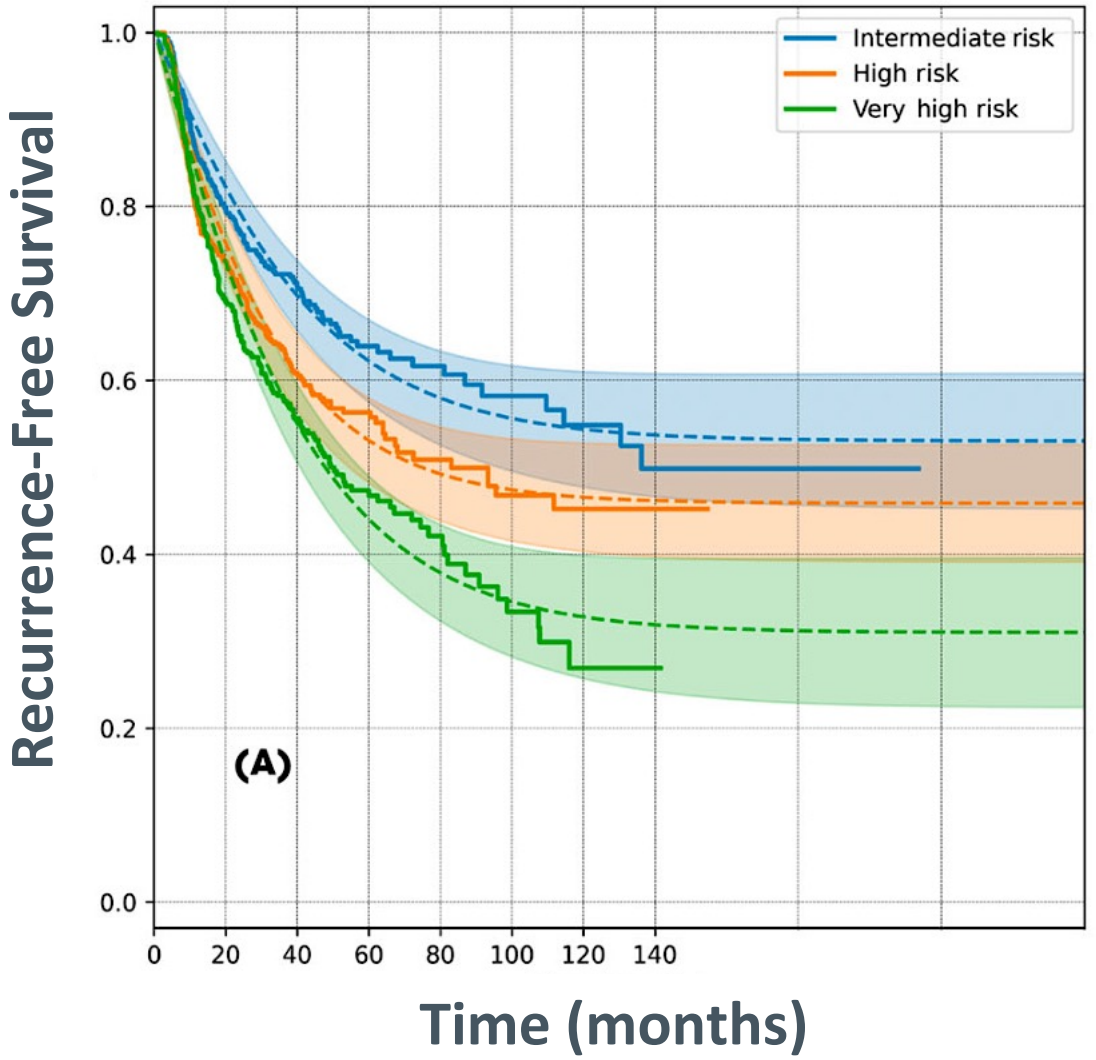
- Rationale for use of PD-1 immunotherapy + BCG for treatment-naïve, high-risk NMIBC

- Safety and Efficacy from recent Phase III trials
  - CREST
  - POTOMAC
  - ALBAN

- Future Directions

BCG is the Standard of Care for treatment-naïve NMIBC





Nature Medicine 2011, www.nccn.org, Subiela et al BJUI 2026

Why add PD-1 immunotherapy to BCG?

- Immunologically
  - BCG upregulates PD-L1 on tumors and tumor infiltrating lymphocytes (TIL)
  - BCG-resistant tumors have higher PD-L1 expression
  - Resistance associated with T-cell exhaustion

- Clinically
  - Unmet need for better therapies for high-risk NMIBC
  - Synergy of 2 immunotherapies
    - BCG addresses localized disease
    - PD-1 addresses any disease beyond the urothelium

Fukumoto et al Ann Surg Onc 2018, Hashizume et al Oncotarget 2018, Lim et al Front Immunol 2021

2025 ASCO ANNUAL MEETING

Sasanlimab in combination with Bacillus Calmette-Guérin (BCG) in BCG-naive, high-risk non–muscle-invasive bladder cancer (NMIBC): Event-free survival (EFS) subgroup analyses based on disease stage from the CREST study

Thomas B. Powles,[1] Neal D. Shore,[2] Jens Bedke,[3] Matthew D. Galsky,[4] Joan Palou Redorta,[5] Hailong Hu,[6] Evanguelos Xylinas,[7] Javier Puente ,[8] Jason M. Hafron,[9] Michele Lodde,[10] Alketa Hamzaj,[11] Julia Brinkmann,[12] Anna-Maria Calella,[13] Rossano Cesari,[14] Jennifer Vermette,[15] Caimiao Wei,[16] Gary D. Steinberg[17]

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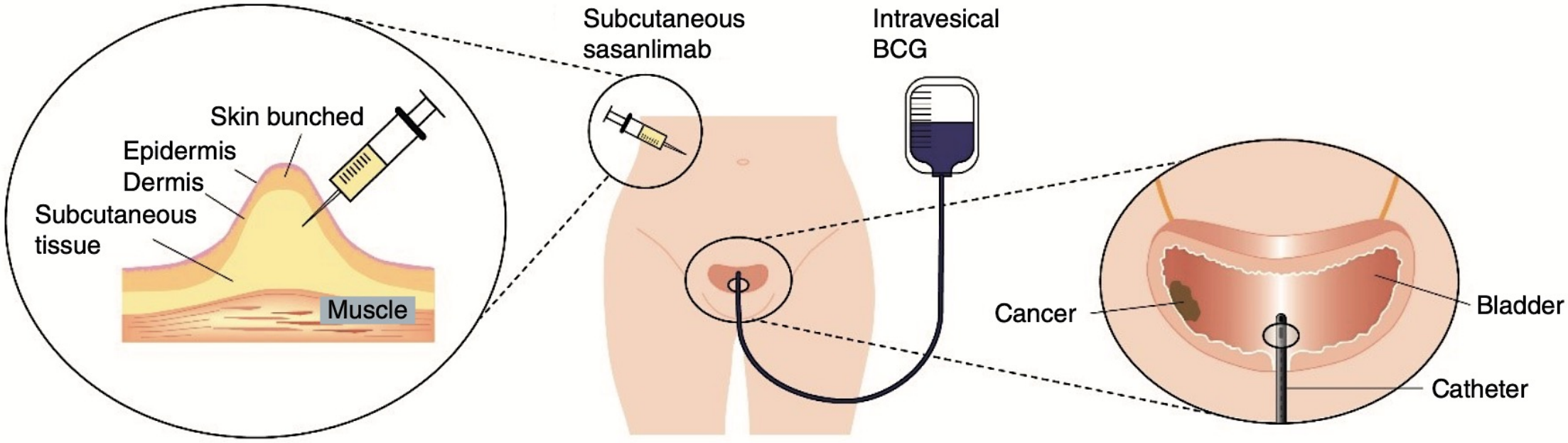
Prof Thomas Powles, MBBS, MRCP, MD

CREST Study (NCT04165317)



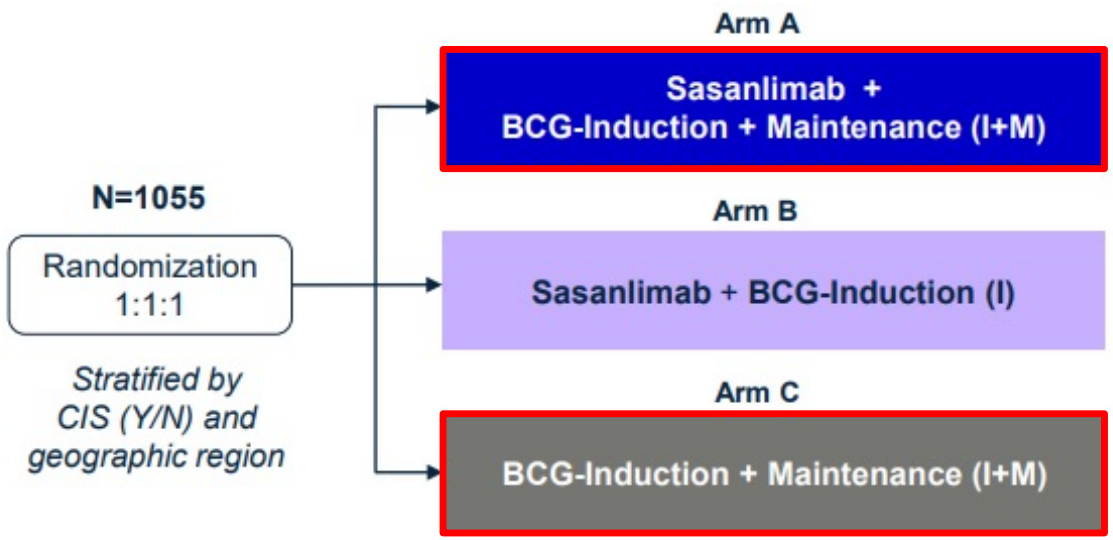
- Sasanlimab
  - Novel humanized IgG4 monoclonal anti-PD-1 ab
  - **Subcutaneous dosing** 300mg q4 weeks

Steinberg et al Future Onc 2024

CREST Study (NCT04165317)

Patient Population:

- BCG-naive, high-risk NMIBC: T1, high-grade Ta, and/or CIS
- No prior PD-(L)1, PD-L2, or CTLA-4 inhibitors or immunostimulatory agents



Primary endpoint
EFS: A vs C
(recurrence of high-grade disease, progressive disease, persistence of CIS, death from any cause)

Key secondary endpoints
EFS: B vs C
OS

Select secondary endpoints
CR (patients with CIS)
Duration of CR (patients with CIS)
Safety
QoL

Final EFS analysis data cut-off date: Dec 2, 2024
Median follow-up for EFS: 36.3 mo

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

Here we present exploratory EFS subgroup analyses based on disease stage at randomization and PD-L1 status

[a]Re-induction was permitted for pts with CIS at randomization who had persistent disease or recurrence of high-grade Ta disease at 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; I, induction; M, maintenance; NMIBC, non-muscle invasive bladder cancer; PD-1, Programmed cell death-1; PD-L1/PD-L2, Programmed cell death-ligand 1/2; QoL, quality of life.

Baseline Demographics and Disease Characteristics: Arm A vs Arm C

Baseline characteristics were balanced and representative of the HR-NMIBC population

	Sasanlimab + BCG-I+M (N=352)	BCG-I+M (N=351)
Median age, y (range)	67 (31–85)	67 (31–91)
Male, n (%)	280 (79.5)	284 (80.9)
Race, n (%)		
White	225 (63.9)	210 (59.8)
Asian	115 (32.7)	126 (35.9)
ECOG PS, n (%)		
0	298 (84.7)	291 (82.9)
1	54 (15.3)	59 (16.8)
Geographic region, n (%)		
US	49 (13.9)	47 (13.4)
Western Europe or Canada	85 (24.1)	86 (24.5)
Rest of world	218 (61.9)	218 (62.1)
Smoking history, n (%)		
Never smoker	127 (36.1)	126 (35.9)
Current smoker	71 (20.2)	54 (15.4)
Former smoker	154 (43.8)	171 (48.7)

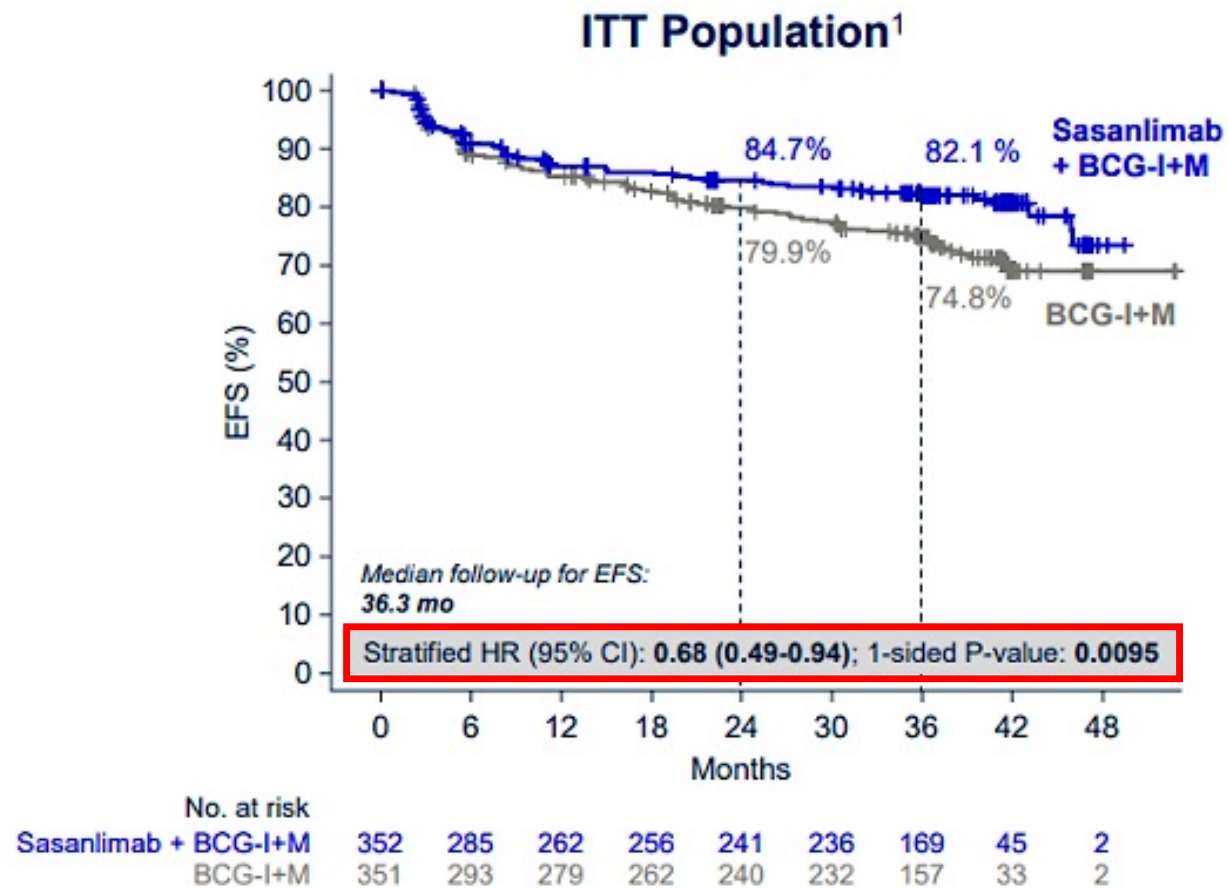
	Sasanlimab + BCG-I+M (N=352)	BCG-I+M (N=351)
Histological classification, n (%)		
UC	339 (96.3)	332 (94.6)
Disease stage, n (%)		
Ta	96 (27.3)	107 (30.5)
T1	204 (58.0)	194 (55.3)
Pure CIS	52 (14.8)	50 (14.2)
CIS ± Ta or T1	88 (25.0)	88 (25.1)
Highest grade of tumor, n (%)		
High	319 (90.6)	316 (90.0)
Low	33 (9.4)	35 (10.0)
Number of tumors, n (%)		
Single	199 (56.5)	182 (51.9)
Multiple	136 (38.6)	146 (41.6)
Size of largest tumor, n (%)		
<3 cm	193 (54.8)	190 (54.1)
≥3 cm	94 (26.7)	95 (27.1)

CIS, carcinoma in situ, ECOG PS, Eastern Cooperative Oncology Group performance status; HR, high-risk; NMIBC, non-muscle invasive bladder cancer; UC, urothelial carcinoma.

Shore et al AUA 2025

Primary Endpoint EFS by Investigator: Arm A vs Arm C

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

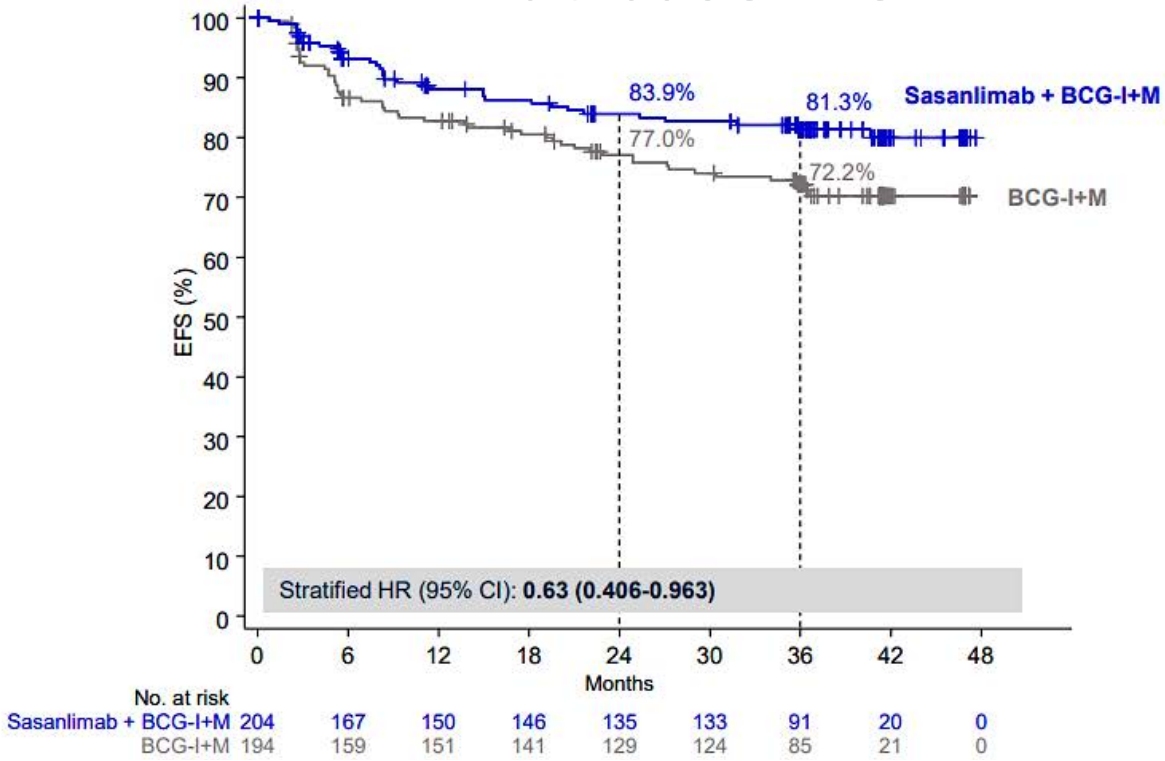


BCG, Bacillus Calmette-Guérin; CIS, carcinoma in situ; EFS, event-free survival; I, induction; ITT, intention to treat; M, maintenance.

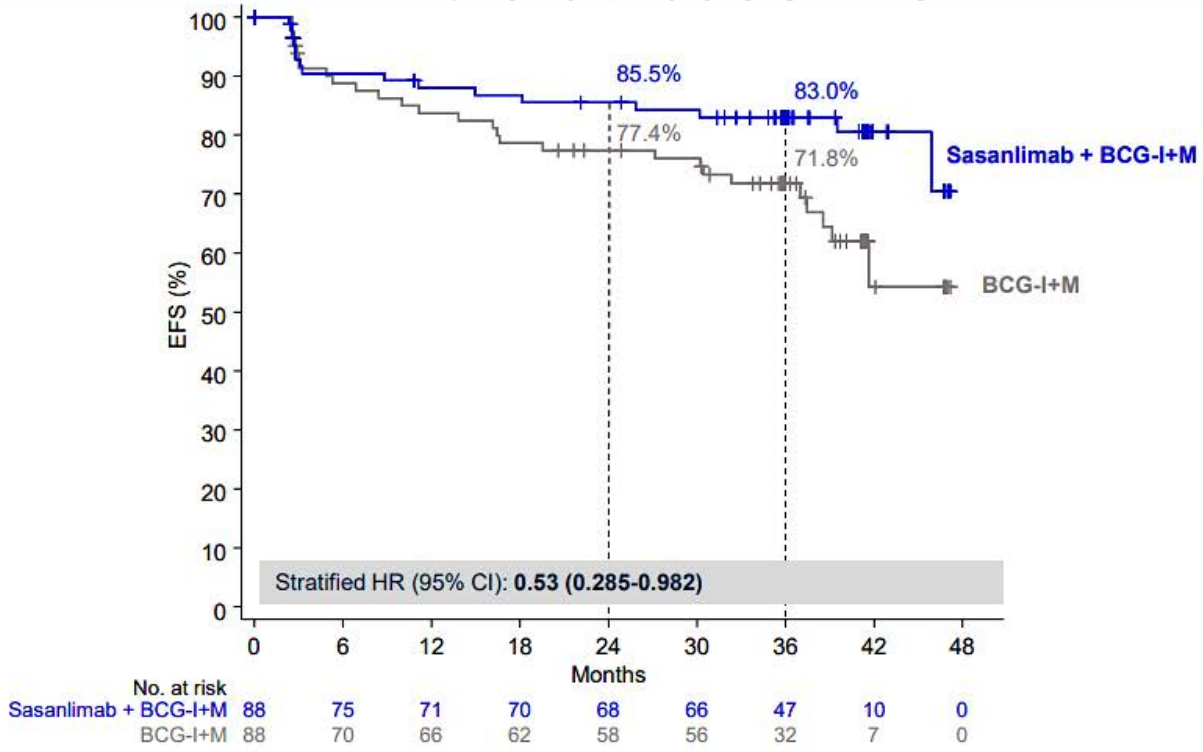
1. Shore N, et al. AUA 2025 (Oral).

EFS by T stage: Arm A vs Arm C

T1 at baseline



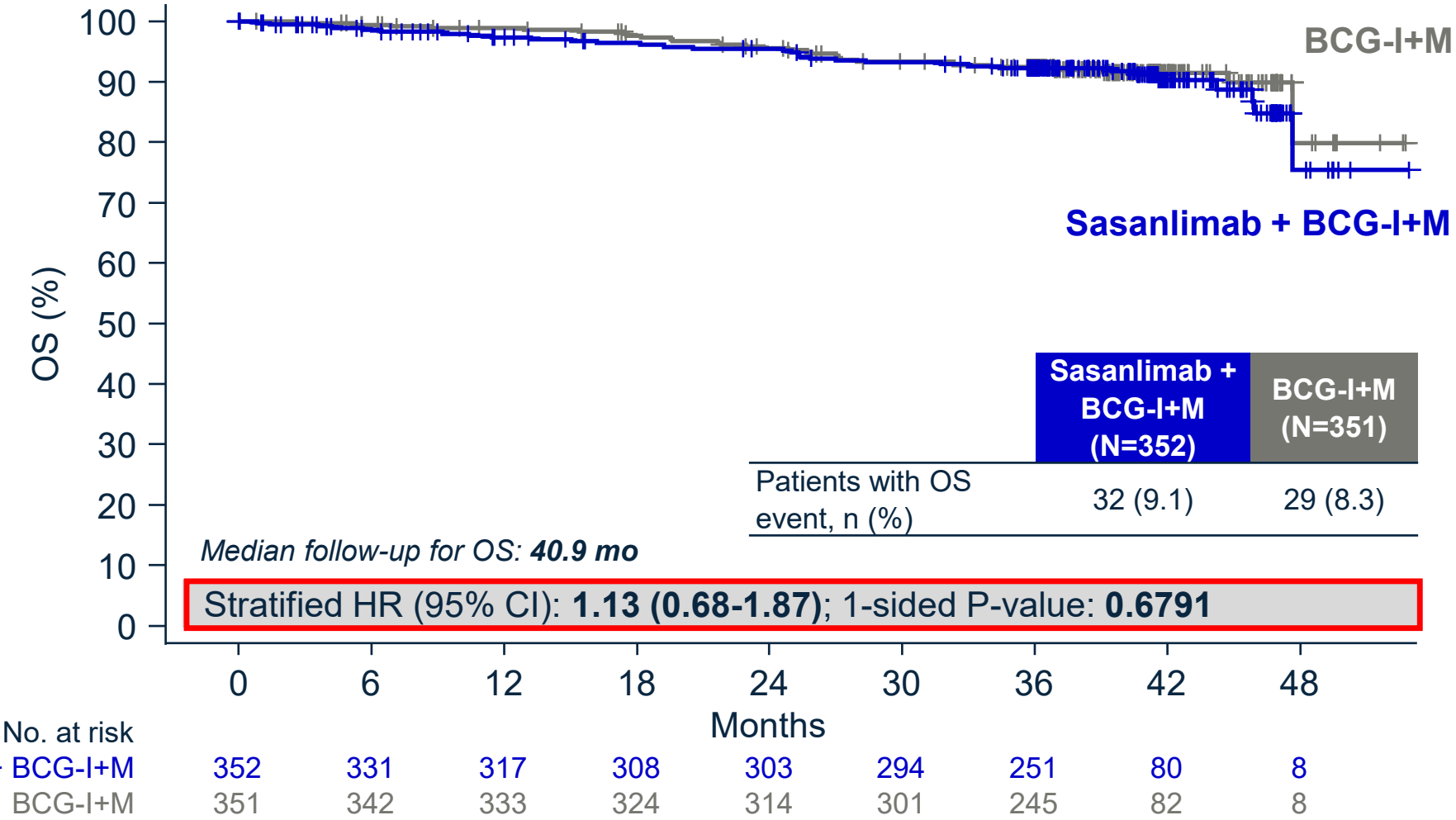
CIS at baseline



Powles et al ASCO 2025

Key Secondary Endpoint: OS for Arm A vs Arm C

Interim OS results suggest no meaningful difference between treatment arms



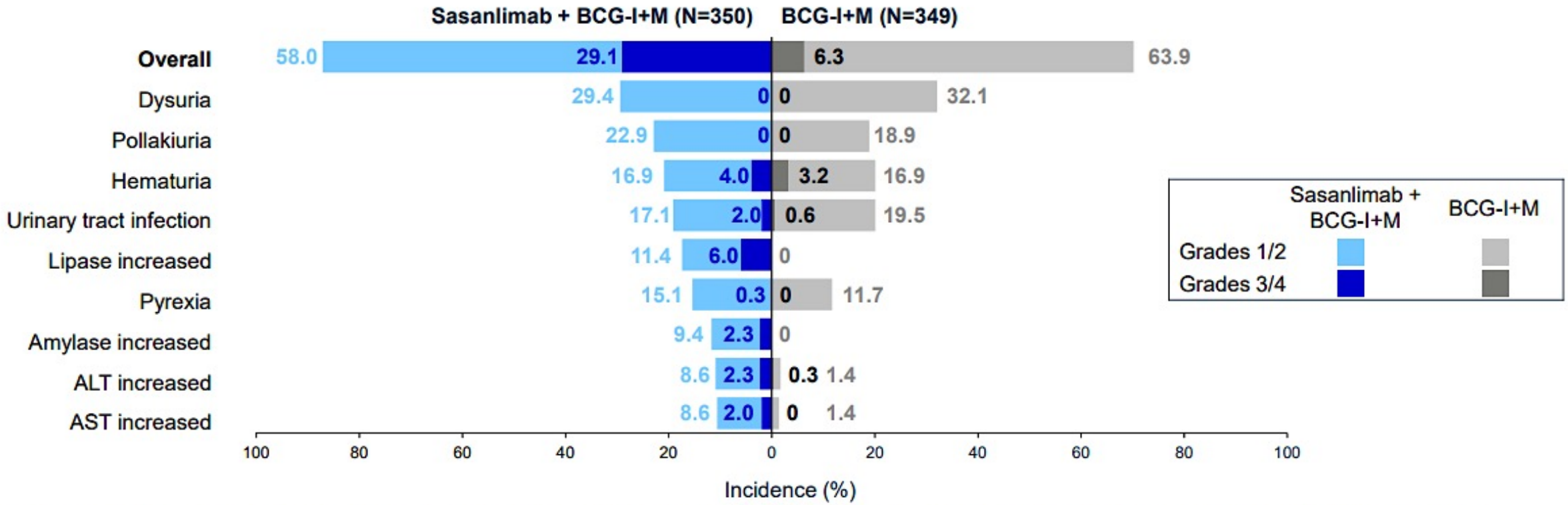
	Sasanlimab + BCG-I+M (N=352)	BCG-I+M (N=351)
Patients with OS event, n (%)	32 (9.1)	29 (8.3)

BCG, Bacillus Calmette-Guérin; I, induction; M, maintenance; OS, overall survival.

Shore et al AUA 2025

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.

Impact on Practice

- Sasanlimab combined with BCG induction and maintenance may become an option for high-risk BCG-naïve NMIBC
  - Sasanlimab is not currently FDA approved
- Is the side effect profile worth the benefit?
  - How to balance EFS (positive), OS (immature) and Toxicity (real)?
- Who will be giving this therapy? Urologists? Medical Oncologists?
- What treatment(s) will we have at recurrence? Will other immunotherapies be effective?

BERLIN 2025 ESMO congress

Durvalumab (D) in Combination With Bacillus Calmette-Guérin (BCG) for BCG-Naïve, High-Risk Non-Muscle-Invasive Bladder Cancer (NMIBC): Final Analysis of the Phase 3, Open-Label, Randomised POTOMAC Trial

Maria De Santis,[1] Joan Palou Redorta,[2] Hiroyuki Nishiyama,[3] Michał Krawczyński,[4] Artur Seytikuliev,[5] Andrey Novikov,[6] Félix Guerrero-Ramos,[7] Minoru Kato,[8] Lieven Goeman,[9] Eva Hellmis,[10] Thomas Powles,[11] Kilian M. Gust,[12] Paul Vasey,[13] Pierre Bigot,[14] Yves Fradet,[15] Jarmo C. B. Hunting,[16] Jon Armstrong,[17] Aleksandra Dąbrowska,[18] Stephan Hois,[19] Neal D. Shore[20]

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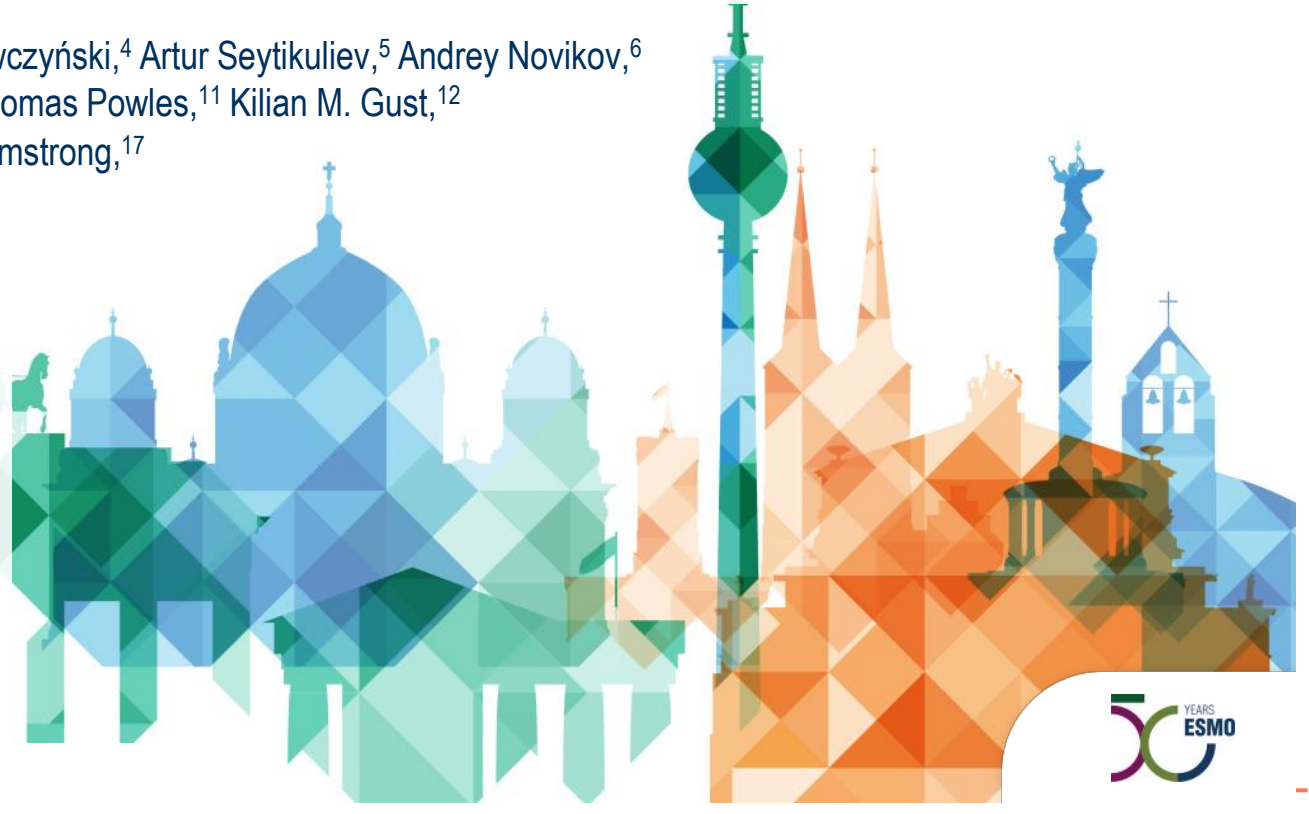


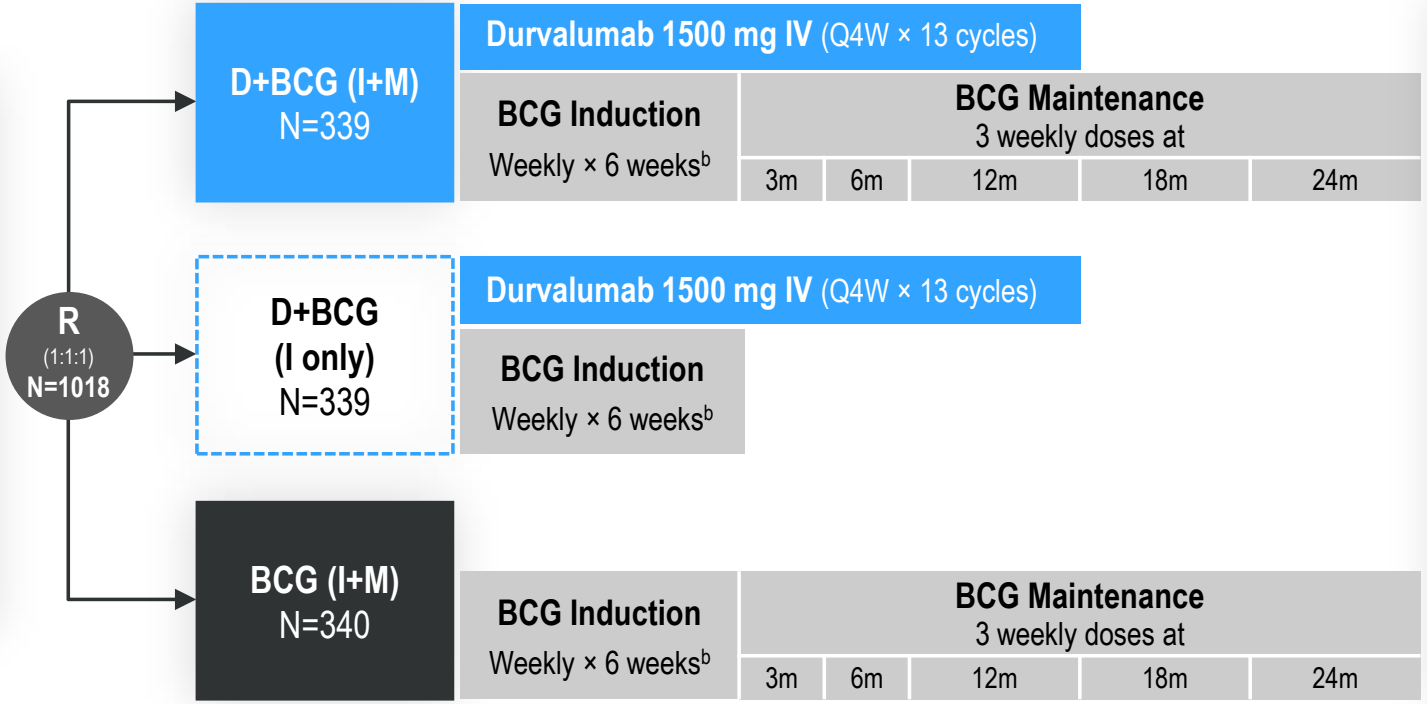
50 YEARS ESMO

POTOMAC: Study Design

A randomised, open-label, Phase 3, global study

Study population

- Age ≥18 years
- NMIBC
- BCG-naïve
- High-risk tumour defined as any of the following:
  - T1
  - High-grade/G3
  - CIS
  - Multiple and recurrent and large (≥3 cm)



Primary endpoint

- **DFS: D+BCG (I+M) vs BCG (I+M)**

Key secondary endpoints

- DFS: D+BCG (I only) vs BCG (I+M)
- DFS at 24 months
- CRR at 6 months

Other secondary endpoints

- OS at 5 years
- Safety
- EORTC QLQ-C30

Stratification factors:

- Higher risk papillary disease (yes vs no)[a]
- CIS (yes vs no)

All disease assessments were performed by the investigator. [a]Defined as T1G3/T1 high-grade or multiple and recurrent and large tumours (those with a diameter of ≥3 cm). [b]For patients with persistent CIS disease at 3 months, a single BCG re-induction was administered weekly for 6 weeks according to local standard practice. ClinicalTrials.gov, NCT03528694; EudraCT number, 2017-002979-26. BCG, bacillus Calmette-Guérin; CIS, carcinoma in situ; CRR, complete response rate; D, durvalumab; DFS, disease-free survival; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer 30-item Core Quality of Life Questionnaire; G, grade; I, induction; IV, intravenous; m, month; M, maintenance; NMIBC, non-muscle-invasive bladder cancer; OS, overall survival; Q4W, every 4 weeks; R, randomisation.

POTOMAC: Patient Characteristics – ITT

Demographic and disease characteristics were generally balanced between the study arms

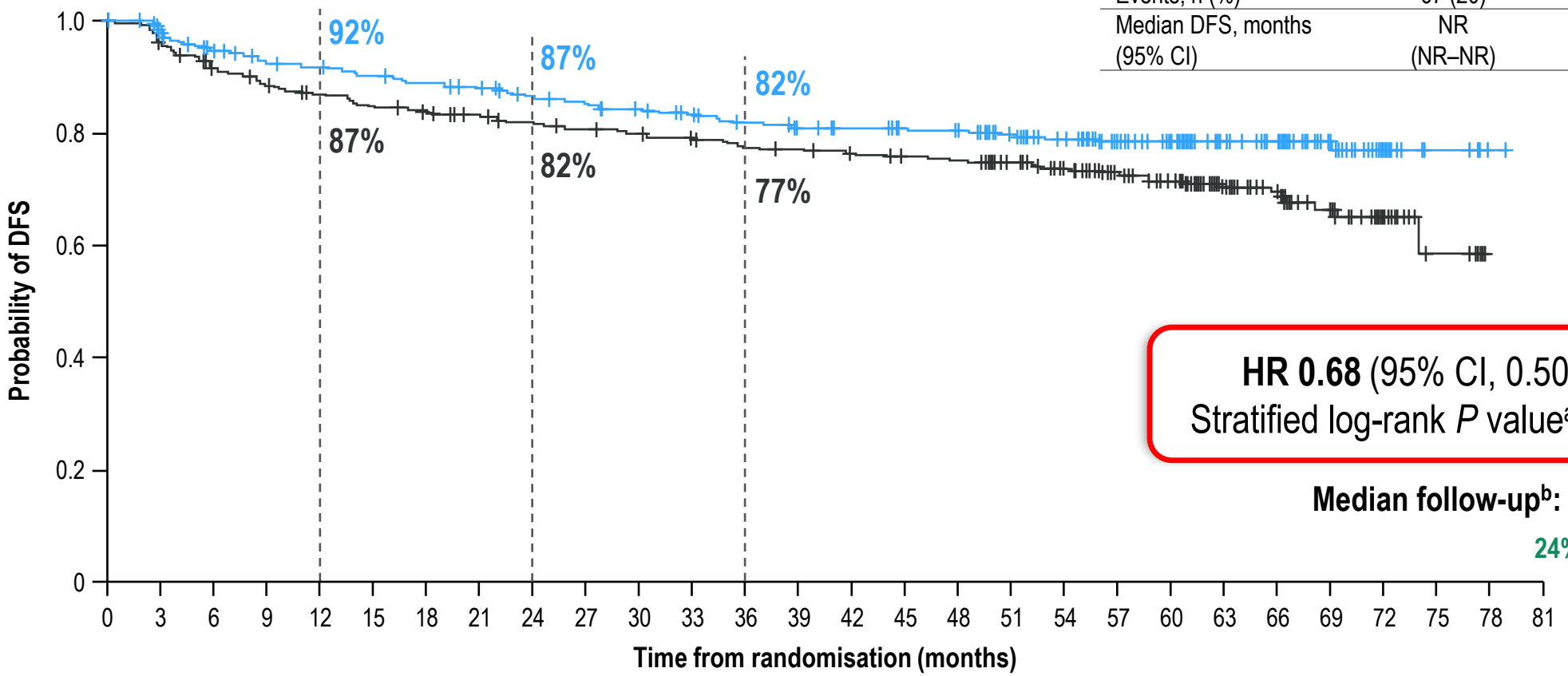
Characteristics		D+BCG (I+M) N=339	D+BCG (I only) N=339	BCG (I+M) N=340
Age, median (range), years		68 (24–90)	68 (21–87)	67 (32–86)
Sex, n (%)	**Male**	276 (81)	272 (80)	271 (80)
Region, n (%)	**Western Europe**	143 (42)	126 (37)	135 (40)
	Rest of world	196 (58)	213 (63)	205 (60)
ECOG PS, n (%)	**0**	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)

[a]With or without CIS as recorded by electronic case report form. [b]With or without papillary disease as recorded per interactive voice response system. [c]Defined as T1G3/T1 high-grade or multiple and recurrent and large tumours (those with a diameter of ≥3 cm). [d]Assessed with the investigational VENTANA PD-L1 (SP263) Assay; high PD-L1 expression was defined as any of the following: ≥25% of TC exhibit membrane staining; or ICP >1% and IC+ ≥25%; or ICP=1% and IC+=100%. Data cutoff 03 April 2025. BCG, bacillus Calmette-Guérin; CIS, carcinoma in situ; D, durvalumab; ECOG PS, Eastern Cooperative Oncology Group performance status; G, grade; I, induction; IC, immune cells; IC+, IC with staining; ICP, IC present; ITT, intent-to-treat population; M, maintenance; PD-L1, programmed cell death ligand-1; TC, tumour cells.

POTOMAC: Disease-Free Survival for D+BCG (I+M) vs BCG (I+M) – ITT

POTOMAC met its primary endpoint with early and sustained DFS benefit

	D+BCG (I+M) N=339	BCG (I+M) N=340
Events, n (%)	67 (20)	98 (29)
Median DFS, months (95% CI)	NR (NR–NR)	NR (74.0–NR)



HR 0.68 (95% CI, 0.50–0.93)
Stratified log-rank *P* value[a] = 0.0154

Median follow-up[b]: 60.7 months

24% DFS maturity

No. of patients at risk

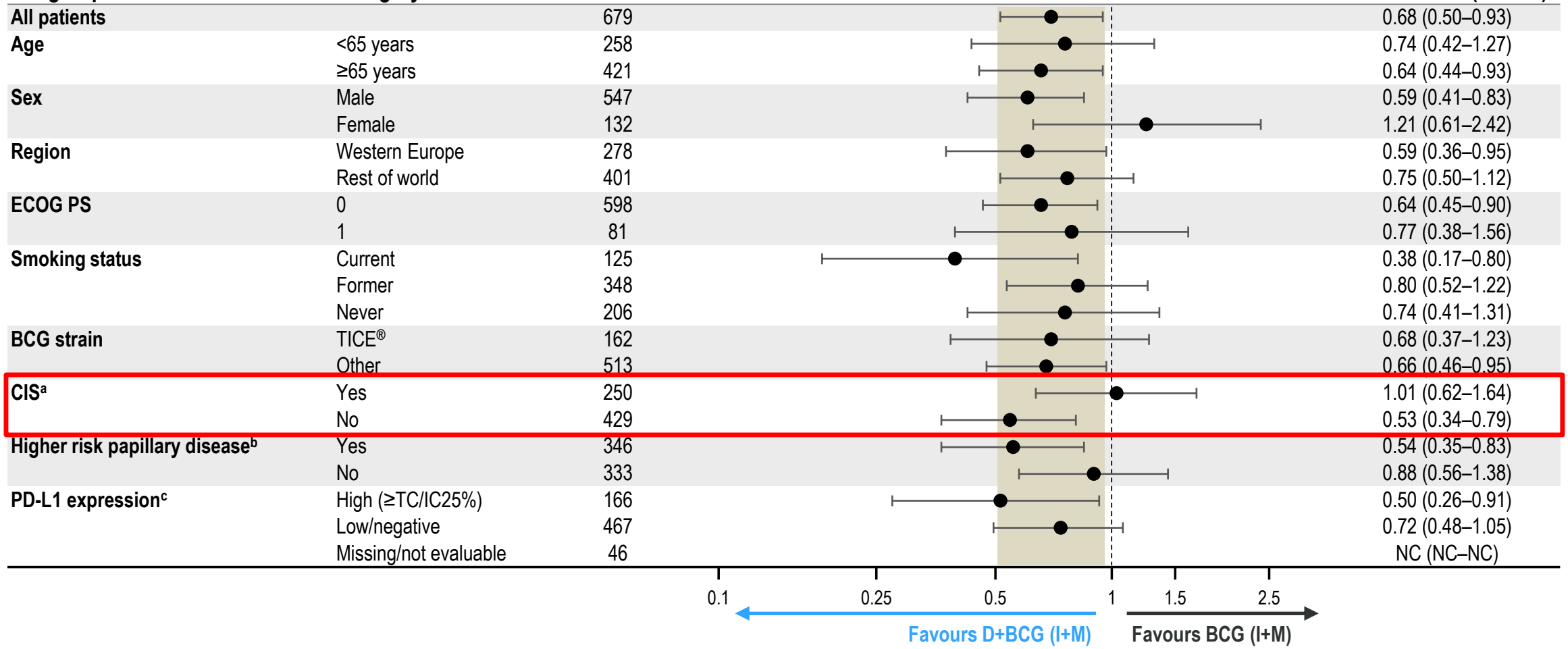
D+BCG (I+M)	339	321	304	292	289	283	278	273	262	257	250	245	235	229	226	222	220	204	195	156	145	108	94	57	26	9	1	0
BCG (I+M)	340	322	303	292	283	276	271	265	258	254	249	244	237	235	231	227	225	209	196	160	150	101	86	50	20	8	0	0

DFS is defined as the time to the first: 1) recurrence of high-risk disease (recurrence of high-grade Ta, T1, or CIS; presentation with MIBC and/or metastatic disease or persistent CIS at 6 months); 2) death by any cause in the absence of recurrence. [a]The threshold to declare statistical significance was based on a generalized Haybittle-Peto spending function – with the observed number of events, the boundary for declaring statistical significance was 0.0317 for a 5% overall 2-sided alpha. [b]In censored patients across all study arms. Data cutoff 03 April 2025. BCG, bacillus Calmette-Guérin; CI, confidence interval; CIS, carcinoma in situ; D, durvalumab; DFS, disease-free survival; HR, hazard ratio; I, induction; ITT, intent-to-treat population; M, maintenance; MIBC, muscle-invasive bladder cancer; NR, not reached.

POTOMAC: Disease-Free Survival Subgroup Analyses

Generally consistent treatment effect across subgroups for D+BCG (I+M) vs BCG (I+M) arms

Subgroup	Category	N	Hazard Ratio (95% CI)
All patients		679	0.68 (0.50–0.93)
Age	<65 years	258	0.74 (0.42–1.27)
	≥65 years	421	0.64 (0.44–0.93)
Sex	Male	547	0.59 (0.41–0.83)
	Female	132	1.21 (0.61–2.42)
Region	Western Europe	278	0.59 (0.36–0.95)
	Rest of world	401	0.75 (0.50–1.12)
ECOG PS	0	598	0.64 (0.45–0.90)
	1	81	0.77 (0.38–1.56)
Smoking status	Current	125	0.38 (0.17–0.80)
	Former	348	0.80 (0.52–1.22)
	Never	206	0.74 (0.41–1.31)
BCG strain	TICE®	162	0.68 (0.37–1.23)
	Other	513	0.66 (0.46–0.95)
CIS[a]	Yes	250	1.01 (0.62–1.64)
	No	429	0.53 (0.34–0.79)
Higher risk papillary disease[b]	Yes	346	0.54 (0.35–0.83)
	No	333	0.88 (0.56–1.38)
PD-L1 expression[c]	High (≥TC/IC25%)	166	0.50 (0.26–0.91)
	Low/negative	467	0.72 (0.48–1.05)
	Missing/not evaluable	46	NC (NC–NC)

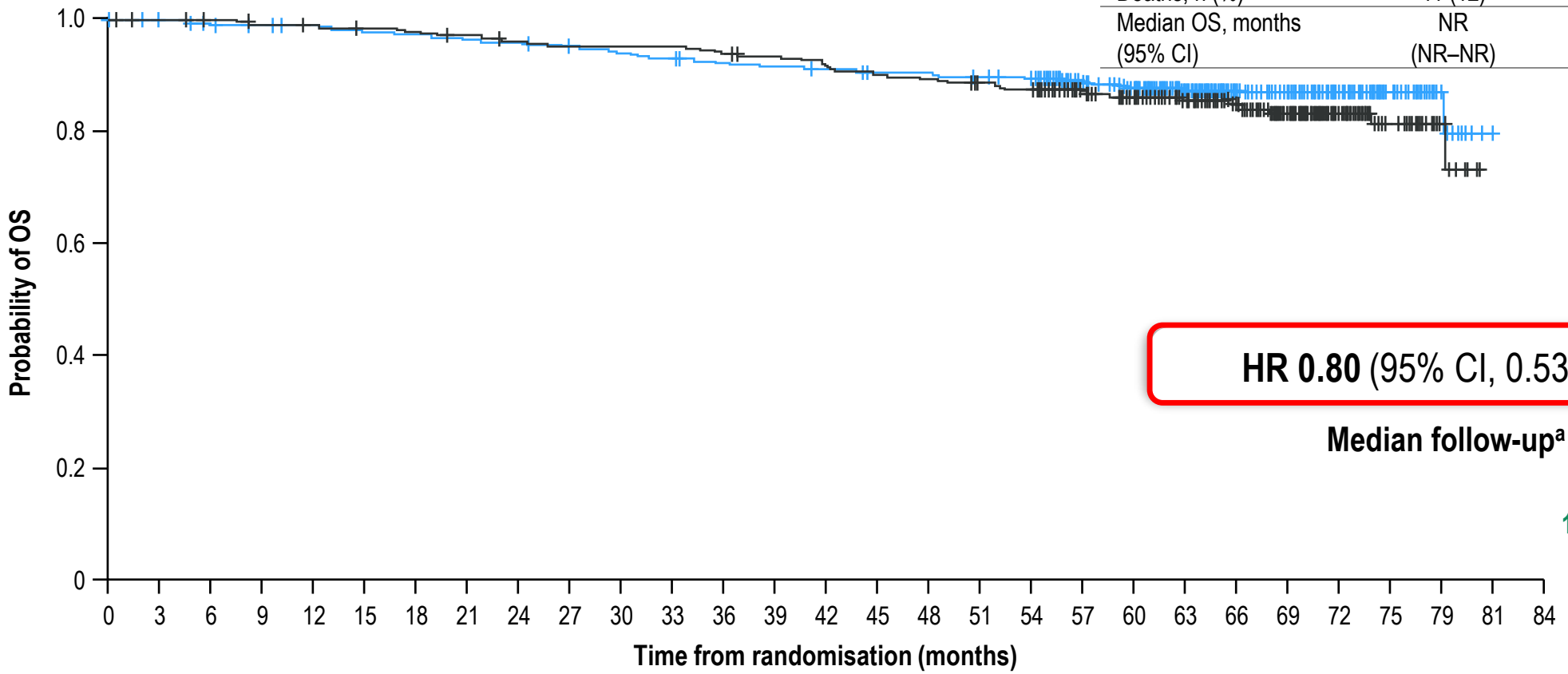


[a]With or without papillary disease as recorded per interactive voice response system. [b]Defined as T1G3/T1 high-grade or multiple and recurrent and large tumours (those with a diameter of ≥3 cm). [c]Assessed with the investigational VENTANA PD-L1 (SP263) Assay; high PD-L1 expression was defined as any of the following: ≥25% of TC exhibit membrane staining; or ICP >1% and IC+ ≥25%; or ICP=1% and IC+=100%. Data cutoff 03 April 2025. BCG, bacillus Calmette-Guérin; CI, confidence interval; CIS, carcinoma in situ; D, durvalumab; ECOG PS, Eastern Cooperative Oncology Group performance status; G, grade; I, induction; IC, immune cells; IC+, IC with staining; ICP, IC present; ITT, intent-to-treat population; M, maintenance; NC, not calculated; PD-L1, programmed cell death ligand-1; TC, tumour cells.

POTOMAC: Overall Survival – ITT

Descriptive analysis showed no detriment to OS with the addition of durvalumab to BCG (I+M) therapy

	D+BCG (I+M) N=339	BCG (I+M) N=340
Deaths, n (%)	41 (12)	52 (15)
Median OS, months (95% CI)	NR (NR–NR)	NR (NR–NR)



HR 0.80 (95% CI, 0.53–1.20)

Median follow-up[a]: 65.6 months
65.9 months
14% OS maturity

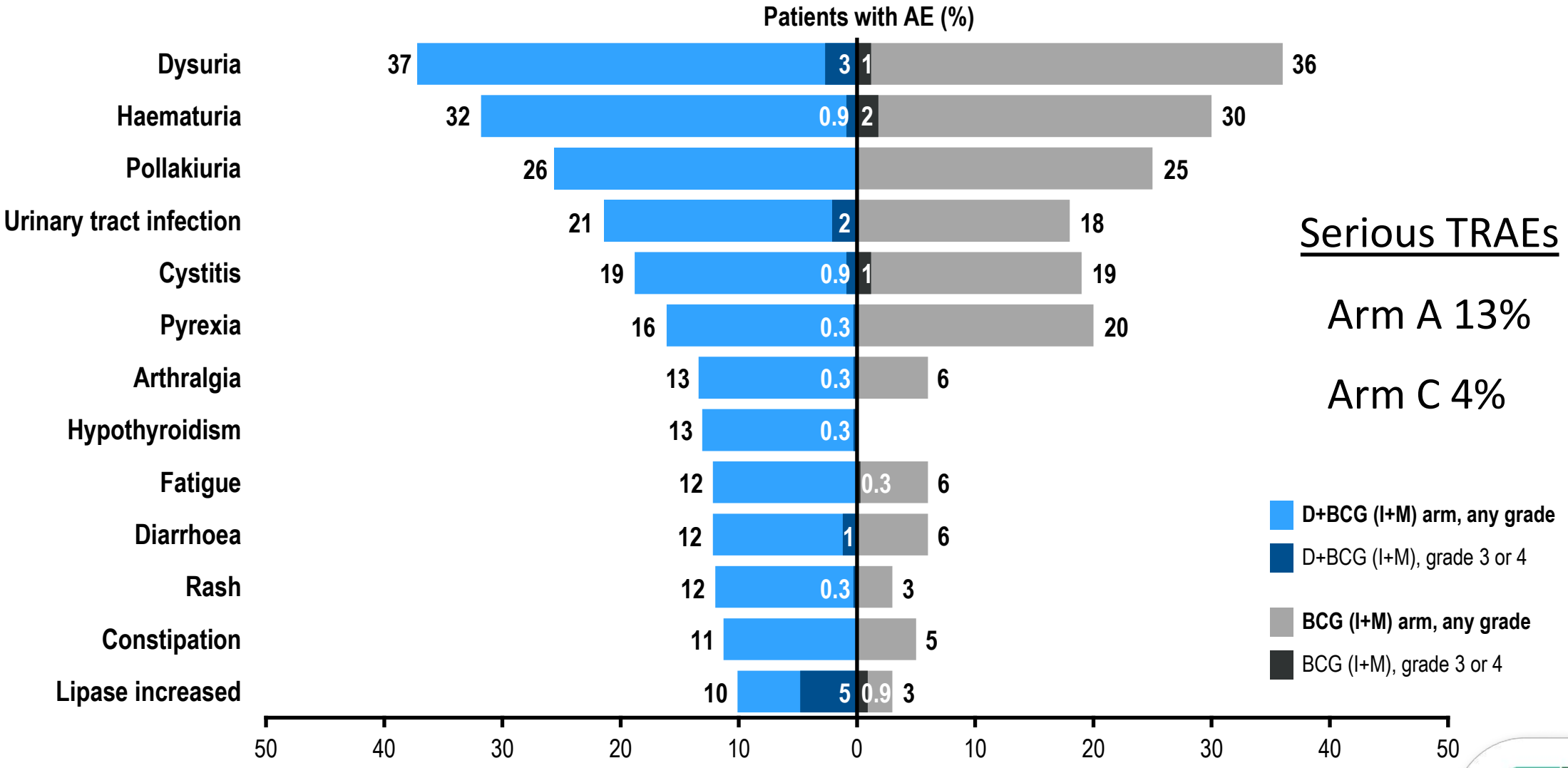
No. of patients at risk

D+BCG (I+M)	339	336	328	325	323	319	318	314	313	310	305	302	297	295	292	289	289	285	282	246	222	184	144	115	73	34	14	1	0
BCG (I+M)	340	338	336	333	330	328	326	323	318	315	315	315	311	307	303	297	294	289	285	249	228	195	147	111	71	33	12	0	0

OS is the time from randomisation until death due to any cause regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy.
[a]In censored patients. Data cutoff 03 April 2025. BCG, bacillus Calmette-Guérin; CI, confidence interval; D, durvalumab; HR, hazard ratio; I, induction; ITT, intent-to-treat population; M, maintenance; NR, not reached; OS, overall survival.

POTOMAC: Most Frequently Reported AEs – Safety Population

Overall safety profile was consistent with those of the individual therapies



Shows all-causality AEs reported for ≥10% of patients in the safety population for either arm. Data cutoff 03 April 2025. AE, adverse event; BCG, bacillus Calmette-Guérin; D, durvalumab; I, induction; M, maintenance.

Impact on Practice

- Similar results to CREST
  - Met EFS primary endpoint
  - Less activity in the CIS cohort?
    - NO – the POTOMAC control arm did exceptionally well (93% CR at 6 months)
    - The BCG + PD-1 CR rate was *higher* in POTOMAC (93%) than CREST (87%)
  - OS immature at present
  - Toxicity is as expected, but real

- What is optimal duration of PD-1?
  - 1 year (POTOMAC) vs 2 years (CREST)

- Likely we will need to see OS benefit before widely available

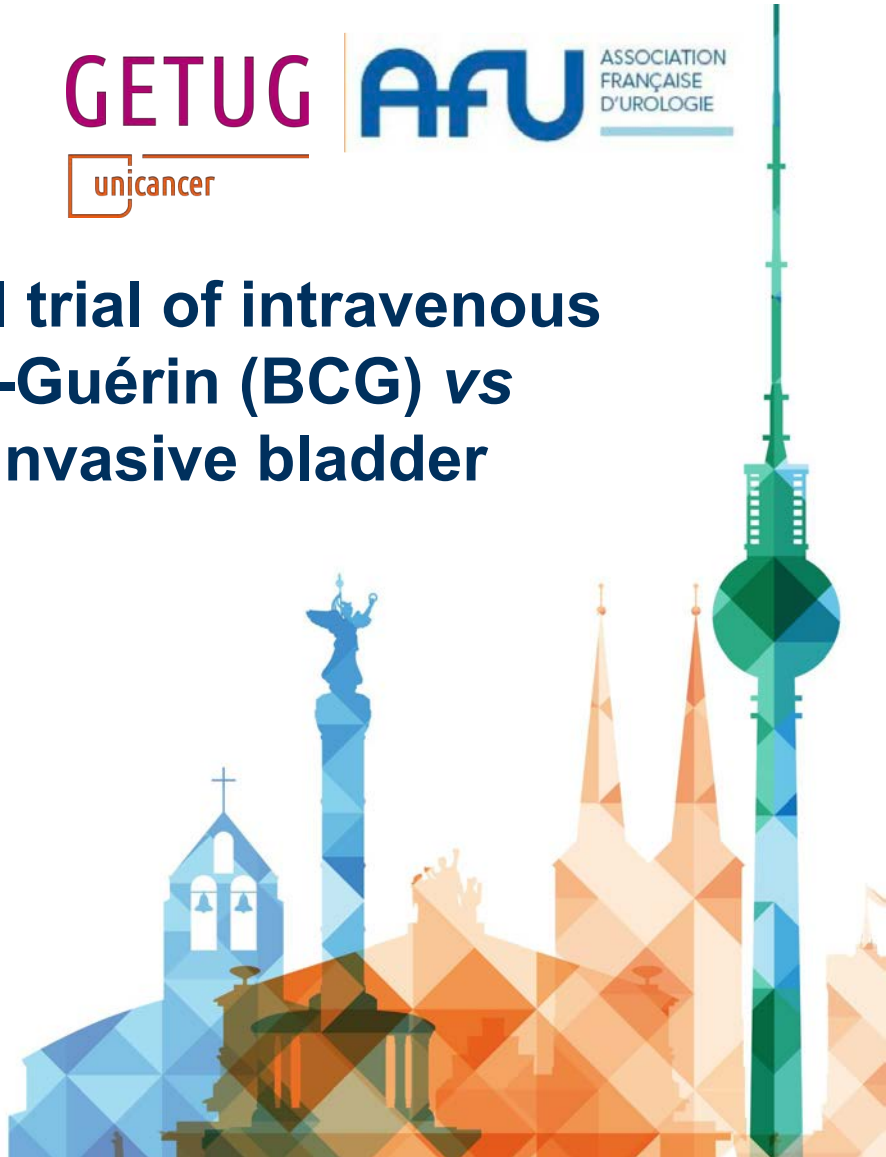
ALBAN (GETUG-AFU 37)

A phase 3, randomized, open-label, international trial of intravenous atezolizumab and intravesical Bacillus Calmette-Guérin (BCG) *vs* BCG alone in BCG-naïve high-risk, non-muscle invasive bladder cancer (NMIBC)

Prof Morgan Rouprêt
Sorbonne University, Urology, Pitie-Salpetriere Hospital, Paris, France

On behalf of ALBAN investigators, LBA107

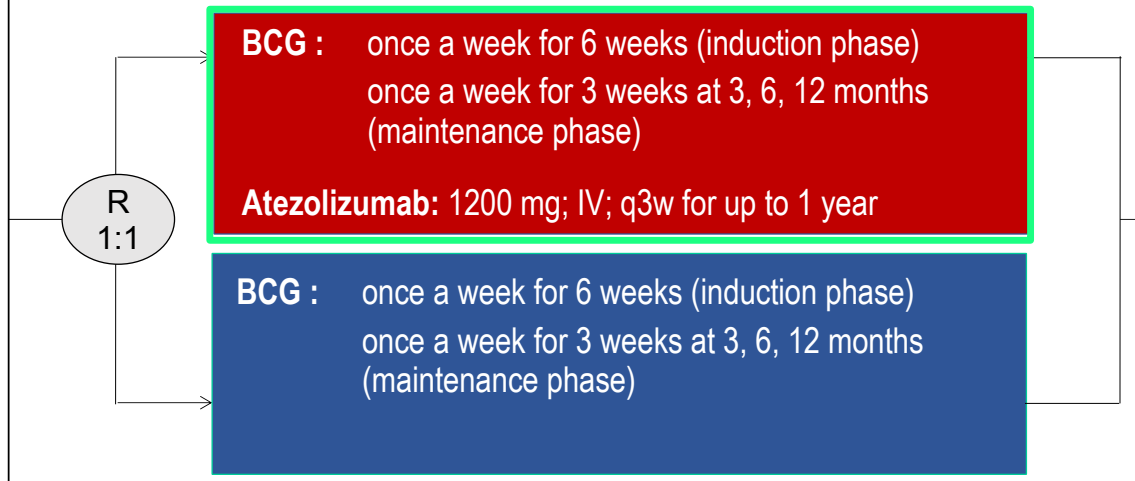
17 October 2025



ALBAN – Study design

BCG-naive 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



Primary endpoint
EFS

Key secondary endpoints
High-grade RFS
PFS
OS
DOR
Safety
QoL

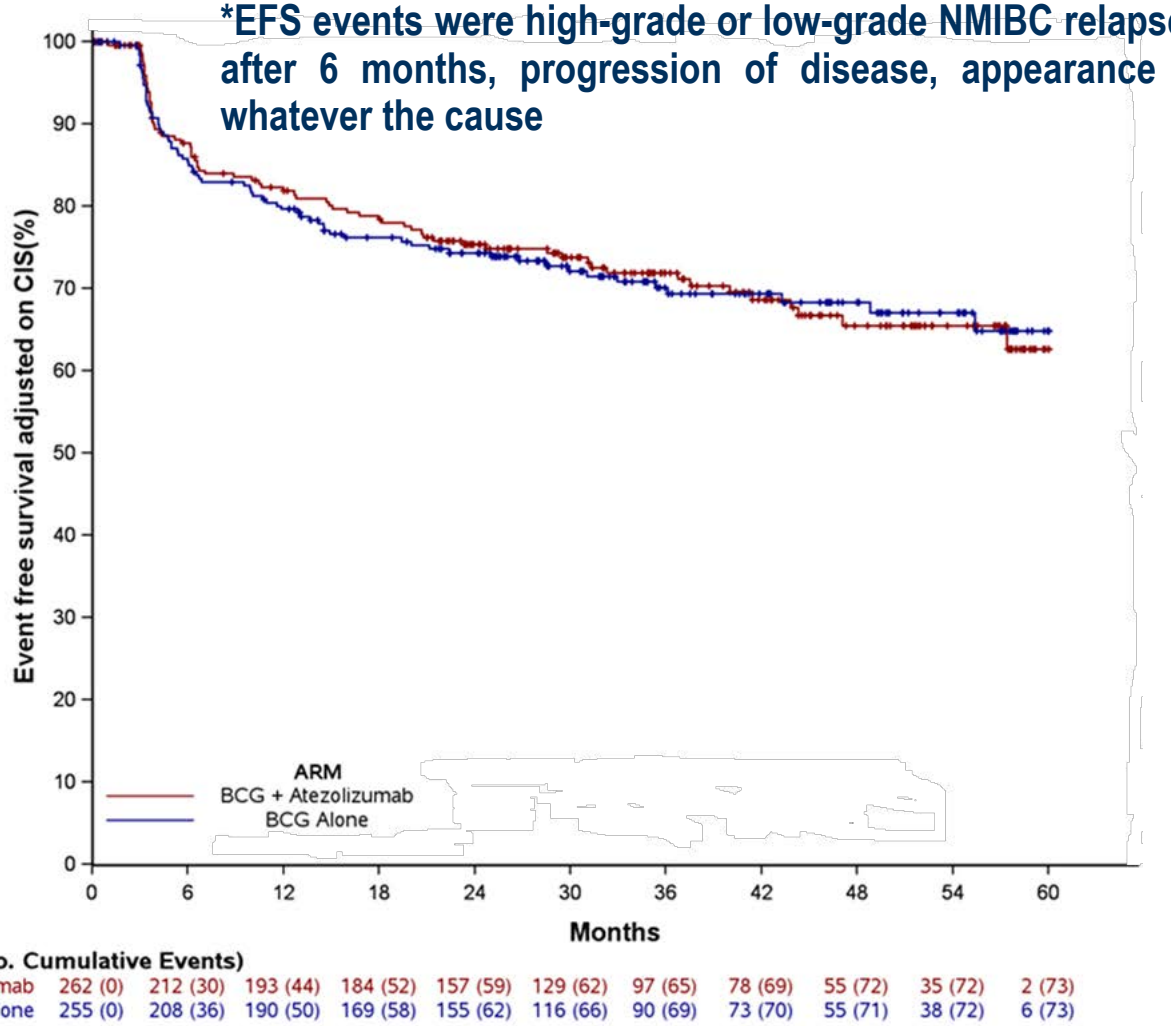
CIS: carcinoma in situ; DOR, duration of response; EFS: Event-Free Survival; OS, Overall Survival; PFS: Progression-Free survival; QoL, Quality of Life; RFS: Recurrence-Free Survival

Key statistical considerations:

- 516 patients to be included in a 1:1 ratio to BCG + atezolizumab or BCG alone
- Stratified by presence of CIS
- Follow-up period for up to 4 years after treatment completion
- 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
- 144 EFS events required to detect an improvement of 10% in EFS (HR≤0.63), power of 80%, two-sided significance level of α=5%

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



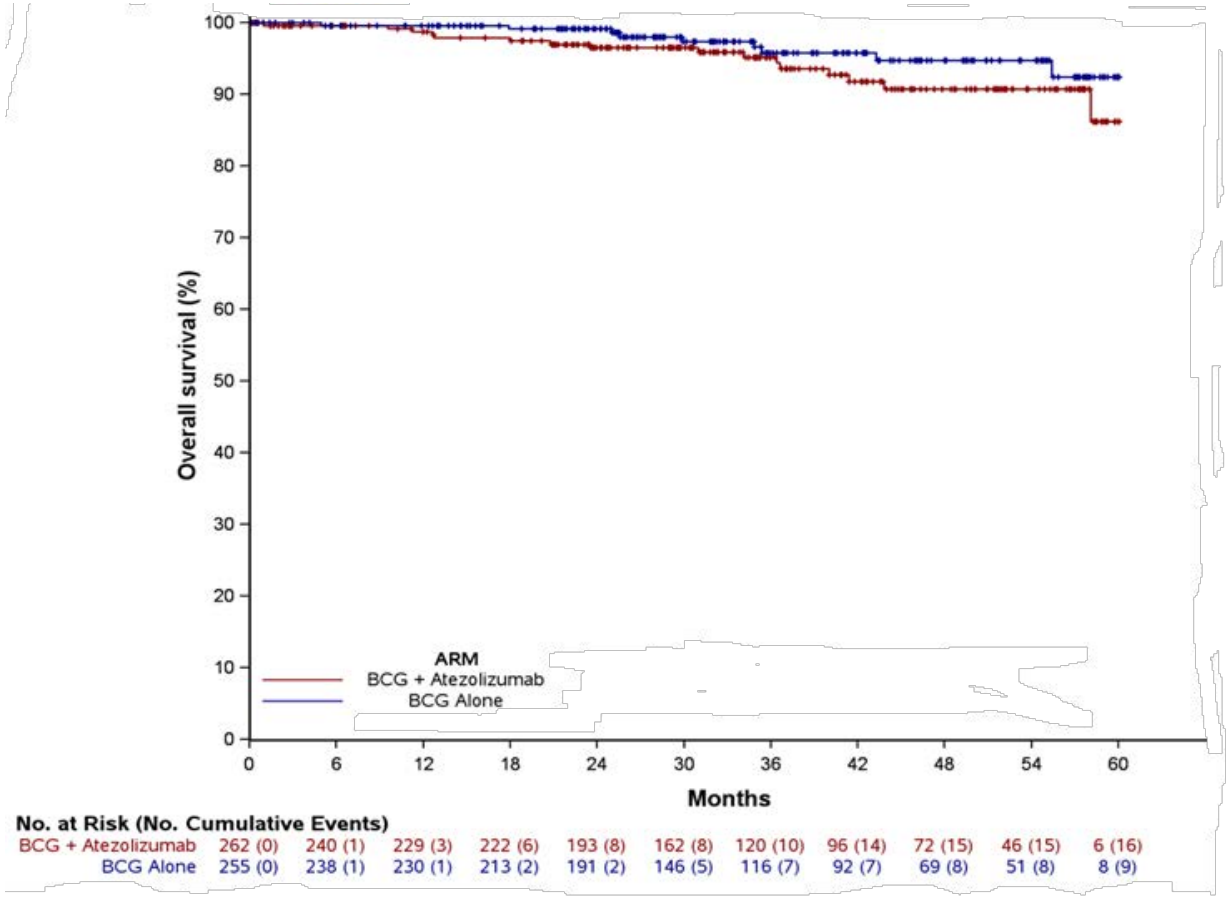
	BCG + atezolizumab	BCG
EFS events, n / N	73 / 262	73 / 255
Median EFS (95% CI), mo	NE	NE
Adjusted HR (95% CI), mo	**0.98** (0.71-1.36); *P*=0.9106	
Type of events, n (%)		
Local recurrence	62 (84.9%)	60 (82.2%)
Locoregional recurrence	3 (4.1%)	3 (4.1%)
Distant recurrence	1 (1.4%)	2 (2.7%)
UTUC	0 (0.0%)	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

Prof Morgan Rouprêt

ALBAN – Analysis of OS (secondary endpoint, ITT population)



	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

Prof Morgan Rouprêt

ALBAN – Safety summary (safety population)

Number of patients, n (%)	BCG + atezolizumab (N=255)	BCG (N=250)
Any AEs	252 (98.8%)	235 (94.0%)
Grade ≥3 AEs	102 (40.0%)	59 (23.6%)
Serious AEs	97 (38.0%)	53 (21.2%)
Any TRAEs	**240 (94.1%)**	**189 (75.6%)**
Grade ≥3 TRAEs	**58 (22.7%)**	**22 (8.8%)**
Serious TRAEs	**60 (23.5%)**	**21 (8.4%)**
irAEs TRAEs	**140 (54.9%)**	**22 (8.8%)**
Grade ≥3 irAEs TRAEs*	**14 (5.5%)**	**3 (1.2%)**
TRAEs leading to dose interruption	47 (18.4%)	19 (7.6%)
TRAEs leading to withdrawal	73 (28.6%)	22 (8.8%)
BCG withdrawal only	32 (12.5%)	22 (8.8%)
Atezolizumab withdrawal only	41 (16.1%)	0 (0.0%)
BCG + atezolizumab	8 (3.1%)	0 (0.0%)

AE, adverse event; irAE: immune related adverse event; TRAE, Treatment-related adverse event

* The most common grade ≥3 irAEs TRAEs were hepatitis (2.0%) and myositis and nephrotic syndrome (0.8% each), all occurring in BCG alone

Impact on Practice

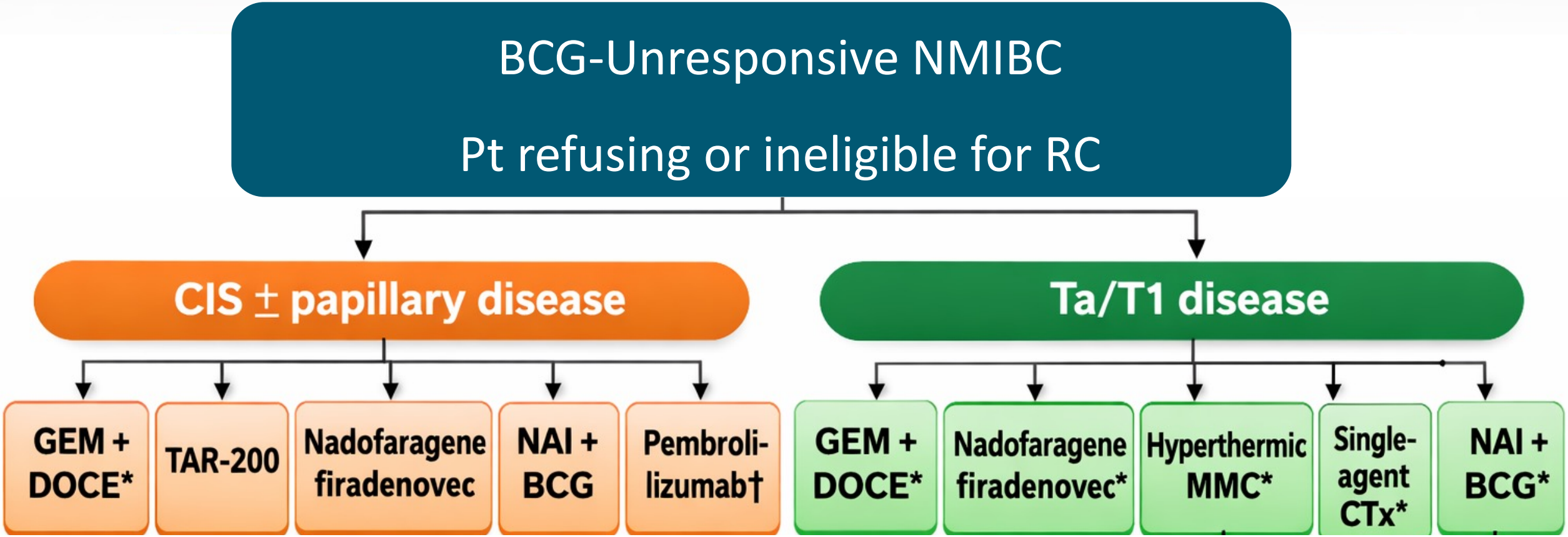
- Disappointing results
  - Did not meet primary EFS nor secondary OS endpoints

- Why?
  - Shorter duration of BCG (1 year vs 2 years)
  - Smaller study than POTOMAC and CREST (n=517 vs >1000)
  - Follows on disappointing results in BCG-unresponsive pts (SWOG 1605)
    - 27% CR at 6 months vs 41% in Keynote 057

Summary

	CREST	**POTOMAC**	**ALBAN**
ICI Agent	Sasanlimab (anti-PD-1)	Durvalumab (anti-PD-L1)	Atezolizumab (anti-PD-L1)
Route of Admin	SubQ	IV	IV
BCG Maintenance	2 years	2 years	1 year
Sample Size	1,055	1,018	517
Primary Endpoint HR	**0.68** (0.49-0.94)	**0.68** (0.50-0.93)	**0.98** (0.71-1.36)
Result	**Positive**	**Positive**	**Negative**
CIS Subgroup Benefit	Yes	No	No
OS benefit?	Immature	Immature	Immature

DeSantis et al. ESMO 2025; Powles et al. ASCO 2025; Roupret et al. ESMO 2025; Shore et al AUA 2025



Adapted from: Li and International Bladder Cancer Group, Eur Urol, 2024

Many Ongoing Trials

- Treatment naïve vs BCG-resistant
- Multiple Modalities
  - » Intravesical
  - » Systemic
  - » Combinations

Drug	FDA Approval	Study	Mechanism of Action	Number of Pts in Study	Response Rate	Reported Response Duration	Cystectomy free rate
Anktiva (N-803)	Yes	Quilt 3.302	Activation and proliferation of natural killer and CD8 + T cells	CIS (n=83); nonCIS (n=77)	CIS 71%; nonCIS 48%	24 months	CIS 91%; nonCIS 95%
Pembrolizumab	Yes	KEYNOTE-057	Monoclonal antibody binds to PD-1 inhibiting interaction with PD-L1 and PD-L2	96	41%	16.2 months	Not Reported
Atezolizumab	No	SWOG S1605	PD-L1 inhibition	129	27%	6 months	Not Reported
Sasanlimab	No	CREST	Monoclonal antibody binds to PD-1 inhibiting interaction with PD-L1 and PD-L2	Preliminary results not reported	Not yet reported	Not yet reported	Not yet reported
Durvalumab	No	PATAPSCO	Monoclonal antibody binds PD-L1 inhibiting its interaction with PD-1	Preliminary results not reported	Not yet reported	Not yet reported	Not yet reported
Nivolumab	No	CheckMate 9UT	PD-1 immune checkpoint inhibitor	Preliminary results not reported	Not yet reported	Not yet reported	Not yet reported
Nadofaragene Firadenovec	Yes	INSTILADRIN	Recombinant adenovirus vector and polyamide surfactant	157	a) 53% b) 34.2%	a) 9.7 months b) 36 months	Not Reported
CG0070	No	CORE1	Modified adenovirus that induces cell lysis paired with anti PD-1 therapy	35	a) 88% b) 73%	a) 3 months b) 12 months	Not Reported
TARA-002	No	ADVANCED-1	Lyophilized mixture of low-virulence Streptococcus pyogenes cells treated with benzylpenicillin	102	Not reported	Not yet Reported	Not yet reported
Gemcitabine & Docetaxel	No	Retrospective Review	Combination intravesical therapy	276	a) 60% b) 46%	a) 12 months b) 24 months	Not Reported
Cabazitaxel, Gemcitabine, Cisplatin	No	Phase 2 trial	Combination intravesical therapy	Preliminary results not reported	Not yet reported	Not yet reported	Not yet reported
Electromotive Drug Administration	No	Prospective Trial	Intravesical chemotherapy with mild electric current to enhance penetration	26	a) 44% b) 30.4%	a) 12 months b) 18 months	Not Reported
Hyperthermic Intravesical Chemotherapy	No	Retrospective Review	Heated intravesical therapy	56	a) 53% b) 35%	a) 12 months b) 24 months	Not Reported
TAR-200	No	SUNRISE-1 and SUNRISE-2	Investigational drug delivery system; controlled, continuous dose of gemcitabine or cetrelimab	23	Not yet reported	Not yet reported	Not yet reported

Wiesen B, et al Front. Oncol. 2025

Second Opinion

Elizabeth R Plimack, MD, MS

Neil Love, MD

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

What treatment options would you discuss with this 72-year-old man with an active lifestyle who wants to avoid cystectomy and has received BCG induction with maintenance, gemcitabine/docetaxel, and nadofaragene firadenovec with eventual recurrence of high-grade NMIBC?

The patient does not want to receive pembrolizumab due to concerns about adverse events and lack of long-term efficacy. How would this impact your discussion?

QUESTIONS FOR THE FACULTY

In general, how do you layer TAR-200 (gemcitabine intravesical system) into your treatment recommendations for patients with NMIBC? How do you describe the unique mechanism of action of TAR-200 to your patients?

What treatment would you ultimately recommend for this patient?

Second Opinion

Thomas Powles, MBBS, MRCP, MD

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Regulatory and reimbursement issues aside, what would be your preferred treatment for this man in his late 70s with newly diagnosed NMIBC? Based on the results of the Phase III CREST and POTOMAC trials, would you consider BCG in combination with an anti-PD-1/PD-L1 antibody?

From your perspective, why were the results of CREST and POTOMAC, evaluating sasanlimab and durvalumab, respectively, in combination with BCG, positive, while the results of the ALBAN study investigating atezolizumab with BCG were not?

QUESTIONS FOR THE FACULTY

Given the positive outcomes from CREST and POTOMAC, do you anticipate that anti-PD-1/PD-L1 antibodies will soon be used routinely for patients who have not experienced failure of BCG?

In your opinion, which patients represent ideal candidates for anti-PD-1/PD-L1 antibodies in combination with BCG? If this strategy were to reach the clinic, would you prefer it for all patients with high-risk disease, or are there some for whom you would still opt for BCG alone or some other strategy?

QUESTIONS FOR THE FACULTY

Are you at all concerned that as we continue to move anti-PD-1/ PD-L1 antibodies earlier in the treatment course, we may be depriving ourselves of effective therapies should disease recurrence occur?

Agenda

Module 1: Optimal Use of Anti-PD-1/PD-L1 Antibodies in Non-Muscle-Invasive Bladder Cancer — Dr Friedlander

Module 2: Evolving Management of Muscle-Invasive Bladder Cancer — Dr Gupta

Module 3: Current and Future Role of Novel Intravesical Therapies in Nonmetastatic Urothelial Bladder Cancer (UBC) — Dr Necchi

Module 4: Emerging Utility of Circulating Tumor DNA Evaluation in Nonmetastatic UBC — Dr Galsky

Cleveland Clinic

Evolving Management of Muscle-Invasive Bladder Cancer (MIBC)

Shilpa Gupta, MD
Cleveland Clinic Taussig Cancer Institute
February 26, 2026

E-mail: Guptas5@ccf.org
X: @shilpaonc

Completed Adjuvant IO trials in high-risk MIUC

High risk MIUC: if received NAC- ypT2-T4a/ypN+ or pT3-T4a/pN+ if not eligible for or declined adjuvant cisplatin-based chemotherapy

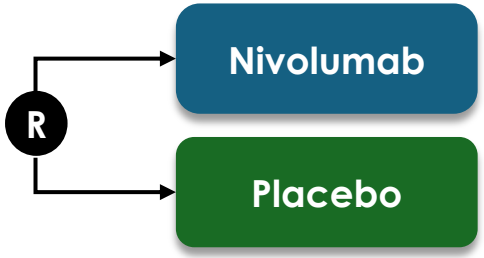
IMvigor010

Primary endpoint:
DFS

Key secondary endpoints:
OS, DSS, distant metastasis-free survival, NUTRFS

Did not meet primary endpoint

CheckMate -274



Primary endpoint:
DFS

Key secondary endpoints:
OS, NUTRFS, DSS

DFS Improvement
**OS trending **

AMBASSADOR

Coprimary endpoints:
DFS and OS

Key secondary endpoints:
OS and DFS in PD-L1–positive and PD-L1–negative patients

DFS Improvement
No OS improvement

Courtesy of Shilpa Gupta, MD

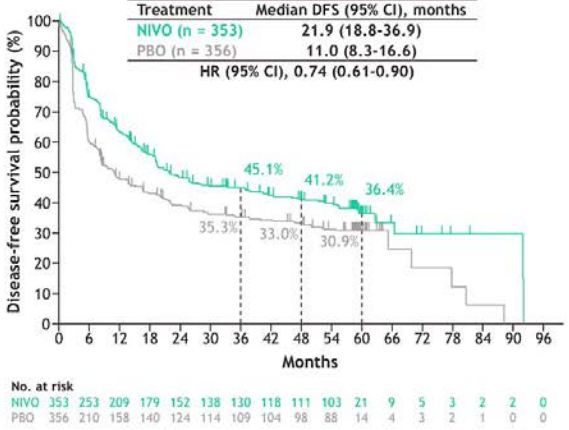
CheckMate-274 DFS 5-year follow-up

CheckMate 274

DFS: all randomized patients and patients with PD-L1 ≥ 1%

All randomized patients[a]

Treatment	Median DFS (95% CI), months
NIVO (n = 353)	21.9 (18.8-36.9)
PBO (n = 356)	11.0 (8.3-16.6)
HR (95% CI), 0.74 (0.61-0.90)	

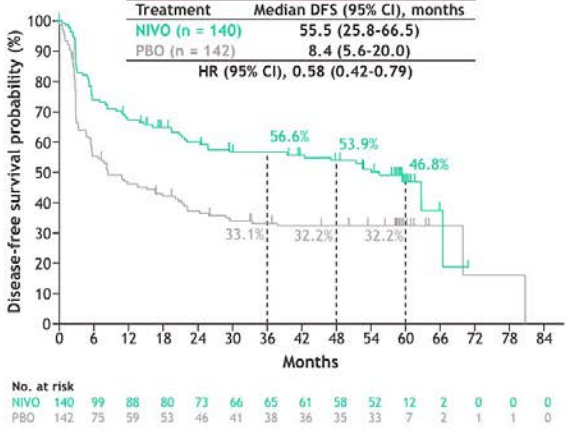


No. at risk

NIVO	353	253	209	179	152	138	130	118	111	103	21	9	5	3	2	2	0
PBO	356	210	158	140	124	114	109	104	98	88	14	4	3	2	1	0	0

Patients with PD-L1 ≥ 1%[b]

Treatment	Median DFS (95% CI), months
NIVO (n = 140)	55.5 (25.8-66.5)
PBO (n = 142)	8.4 (5.6-20.0)
HR (95% CI), 0.58 (0.42-0.79)	



No. at risk

NIVO	140	99	88	80	73	66	65	61	58	52	12	2	0	0	0	
PBO	142	75	59	53	46	41	38	36	35	33	7	2	1	1	0	

- At 5 years of follow up, long-term benefits were sustained with NIVO vs PBO in all randomized patients and patients with tumor PD-L1 expression ≥ 1%

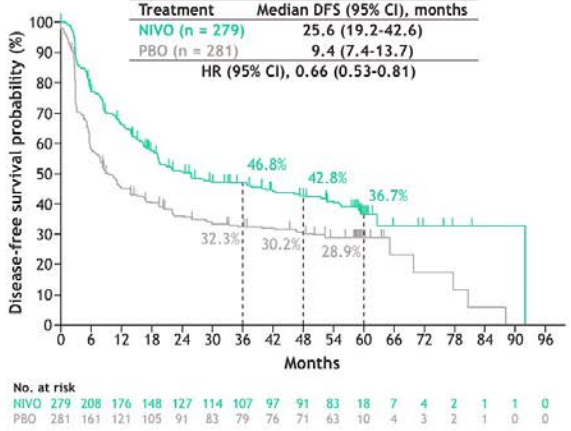
[a]Minimum follow-up, 59.6 months; median follow-up, 43.4 months. [b]Minimum follow-up, 60.0 months; median follow-up, 52.9 months. Minimum follow-up is defined as the time from last patient randomized to clinical cutoff date. Median follow-up is defined as the time from randomization to death or last known alive date (for patients who are alive).

CheckMate 274

DFS in patients with MIBC: all randomized and PD-L1 ≥ 1%

All randomized patients with MIBC

Treatment	Median DFS (95% CI), months
NIVO (n = 279)	25.6 (19.2-42.6)
PBO (n = 281)	9.4 (7.4-13.7)
HR (95% CI), 0.66 (0.53-0.81)	

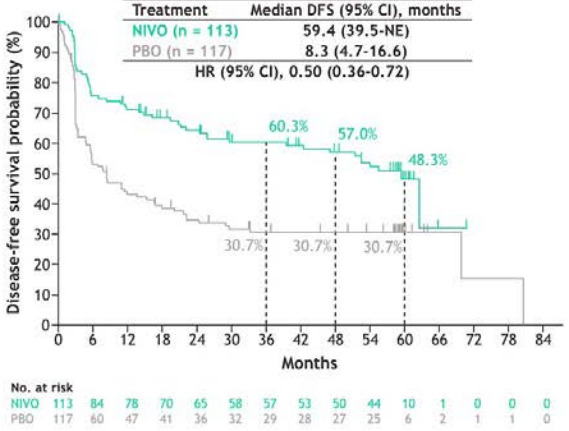


No. at risk

NIVO	279	208	176	148	127	114	107	97	91	83	18	7	4	2	1	1	0
PBO	281	161	121	105	91	83	79	76	71	63	10	4	3	2	1	0	0

Patients with MIBC and PD-L1 ≥ 1%

Treatment	Median DFS (95% CI), months
NIVO (n = 113)	59.4 (39.5-NE)
PBO (n = 117)	8.3 (4.7-16.6)
HR (95% CI), 0.50 (0.36-0.72)	



No. at risk

NIVO	113	84	78	70	65	58	57	53	50	44	10	1	0	0	0	
PBO	117	60	47	41	36	32	29	28	27	25	6	2	1	1	0	

- Median DFS in randomized patients with MIBC and patients with MIBC and tumor PD-L1 expression ≥ 1% was longer for NIVO-treated patients vs PBO-treated patients

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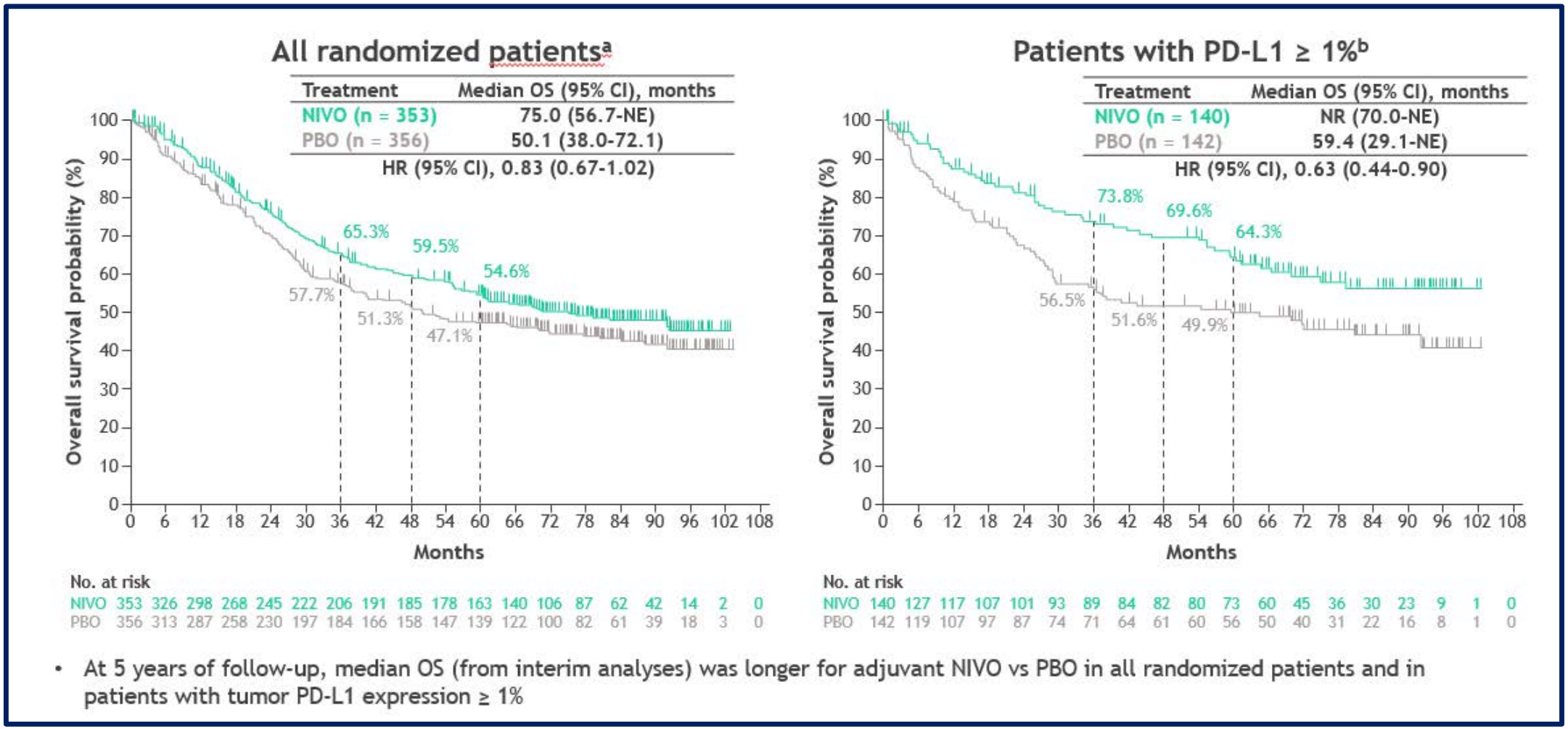
Galsky M et al. ESMO 2025

CheckMate-274 5 year OS trend with Nivo



- At 5 years of follow-up, median OS (from interim analyses) was longer for adjuvant NIVO vs PBO in all randomized patients and in patients with tumor PD-L1 expression ≥ 1%

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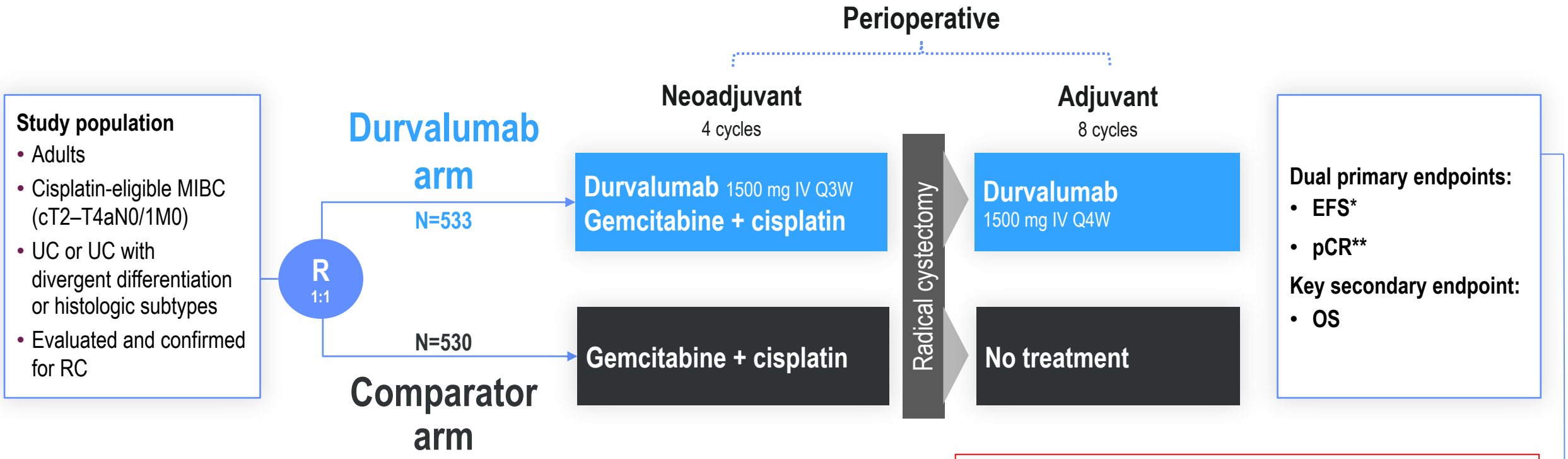
Phase 3 Peri-operative IO-based Trials in MIBC

	Clinical Trial	N	Treatment Arms	Eligibility
CISPLATIN ELIGIBLE	KEYNOTE-866	870	Pembro + GC vs GC	T2-4aN0M0
	KEYNOTE-B15/EV-304	784	Pembro +EV vs GC	T2-T4aN0M0 T1-T4aN1M0
	NIAGARA	1050	Durva+ GC vs GC	T2-4aN1M0
	ENERGIZE	1200	Nivo + GC vs GC ~~GC+ Nivo + Linrodostat~~	T2-4aN0M0
CISPLATIN-INELIGIBLE	KEYNOTE-905/ EV-303	836	RC vs Pembro+EV vs Pembro	T2-4aN0M0
	VOLGA	830	RC vs Druva/Tremi+EV vs Durva+EV	T2-4aN0M0

Primary Endpoints pCR, EFS
Adjuvant IO in experimental arm
NO adjuvant IO in control arm

Courtesy of Shilpa Gupta, MD

NIAGARA: Study Design



Stratification factors

Clinical tumour stage (T2N0 vs >T2N0)

Renal function (CrCl ≥60 mL/min vs ≥40–<60 mL/min)

PD-L1 status (high vs low/negative expression)

Gemcitabine/cisplatin dosing

CrCl ≥60 mL/min: Cisplatin 70 mg/m^2 + gemcitabine 1000 mg/m^2 Day 1, then gemcitabine 1000 mg/m^2 Day 8, Q3W for 4 cycles

CrCl ≥40–<60 mL/min: Split-dose cisplatin 35 mg/m^2 + gemcitabine 1000 mg/m^2 Days 1 and 8, Q3W for 4 cycles

EFS defined as:

- Progressive disease that precluded RC
- Recurrence after RC
- Date of expected surgery in patients who did not undergo RC
- Death from any cause

Other endpoints (not reported here):
DFS, DSS, MFS, HRQoL, 5-year OS

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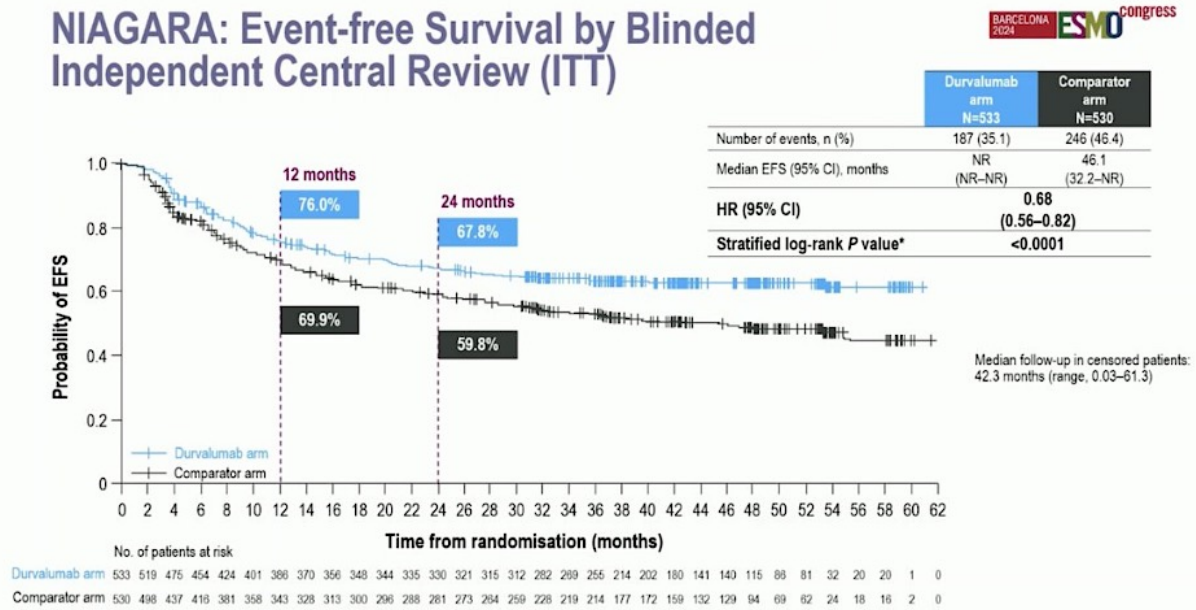
Powles T et al. ESMO 2024, NEJM 2024

NIAGARA: Event-free Survival by Blinded Independent Central Review (ITT)

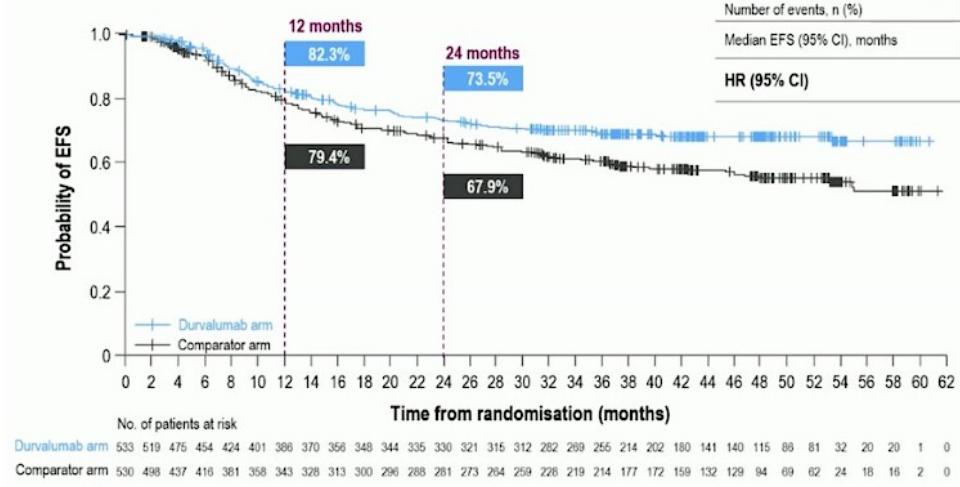


	Durvalumab arm N=533	Comparator arm N=530
Number of events, n (%)	187 (35.1)	246 (46.4)
Median EFS (95% CI), months	NR (NR–NR)	46.1 (32.2–NR)
HR (95% CI)	0.68 (0.56–0.82)	
Stratified log-rank *P* value*	<0.0001	

Median follow-up in censored patients: 42.3 months (range, 0.03–61.3)

NIAGARA: Event-free Survival Sensitivity Analysis

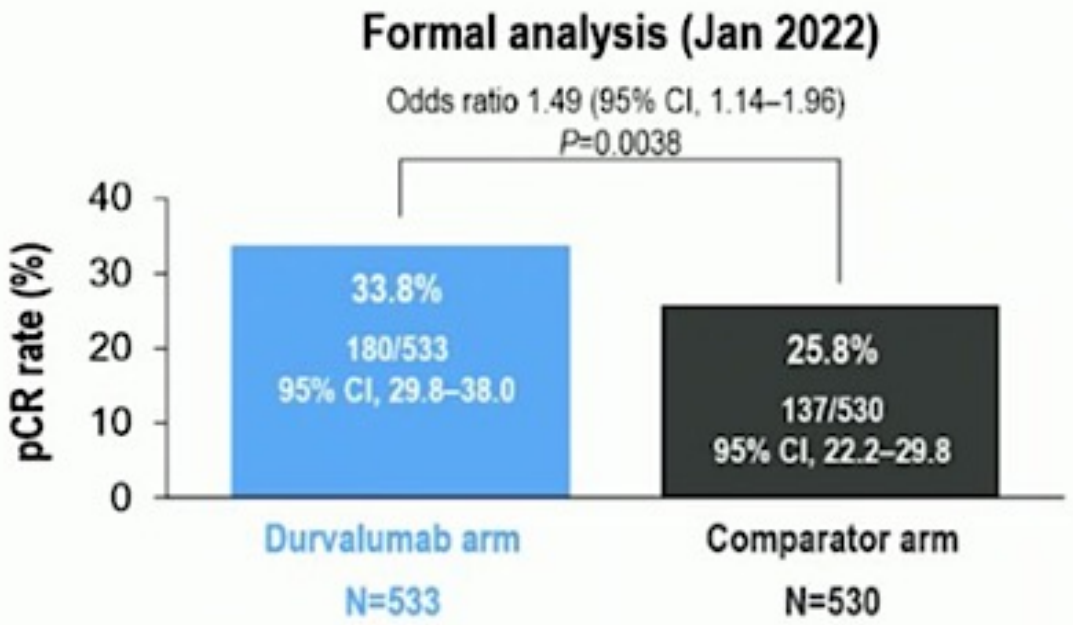
Patients who did not undergo RC were censored

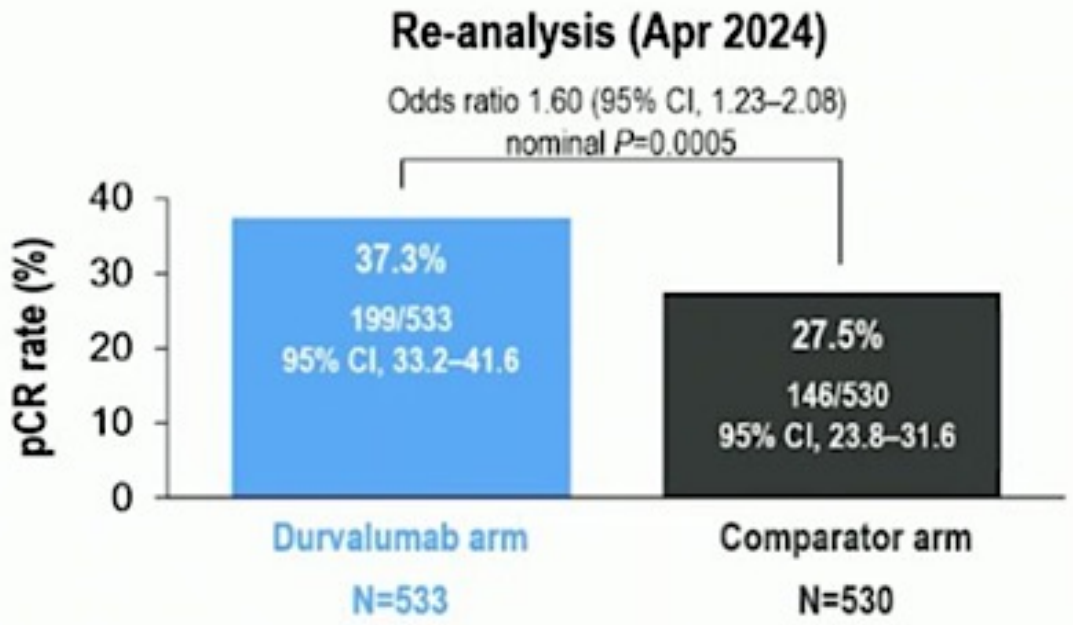


	Durvalumab arm N=533	Comparator arm N=530
Number of events, n (%)	147 (27.6)	186 (35.1)
Median EFS (95% CI), months	NR (NR–NR)	NR (53.2–NR)
HR (95% CI)	0.69 (0.56–0.86)	

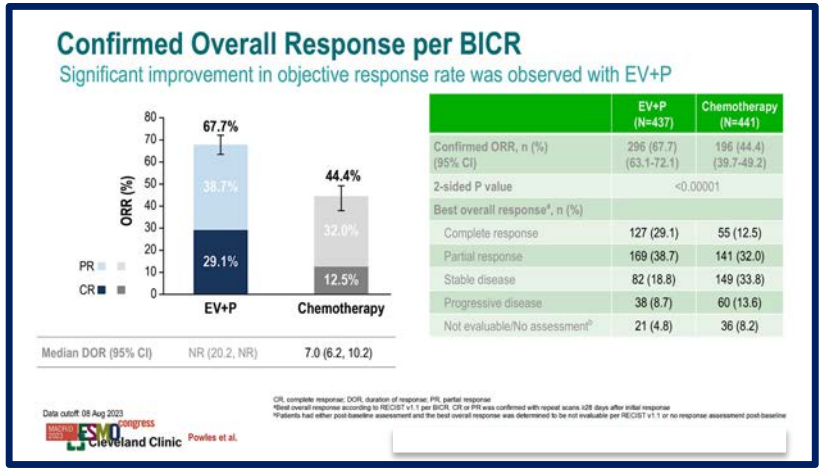
Powles T et al. ESMO 2024, NEJM 2024

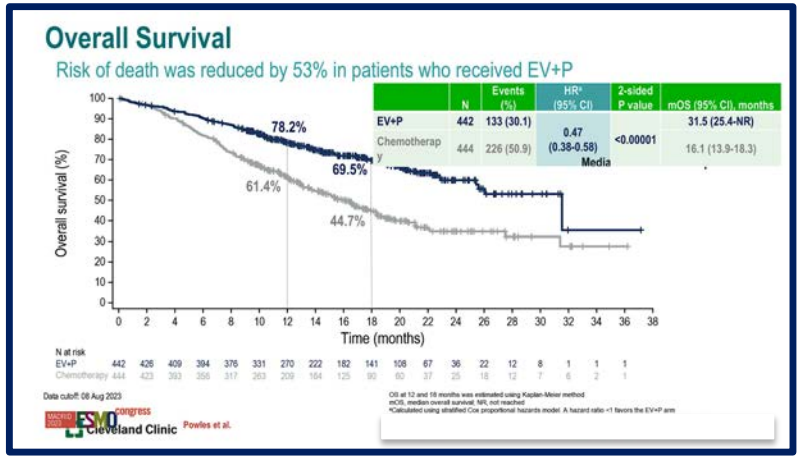
NIAGARA: Pathologic Complete Response (ITT)

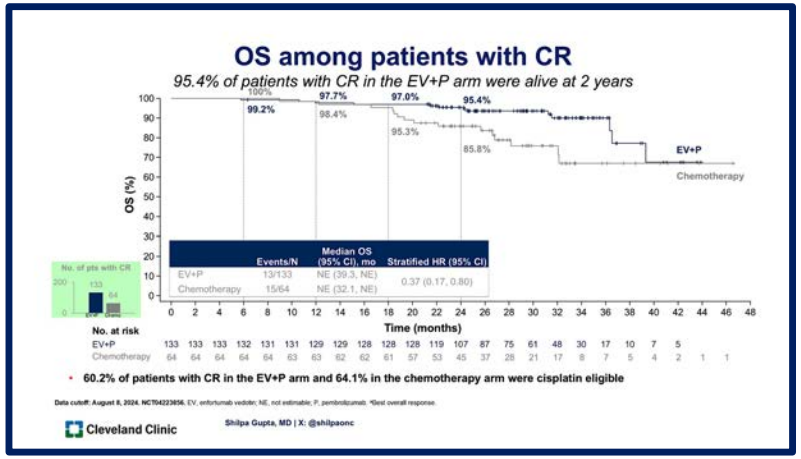




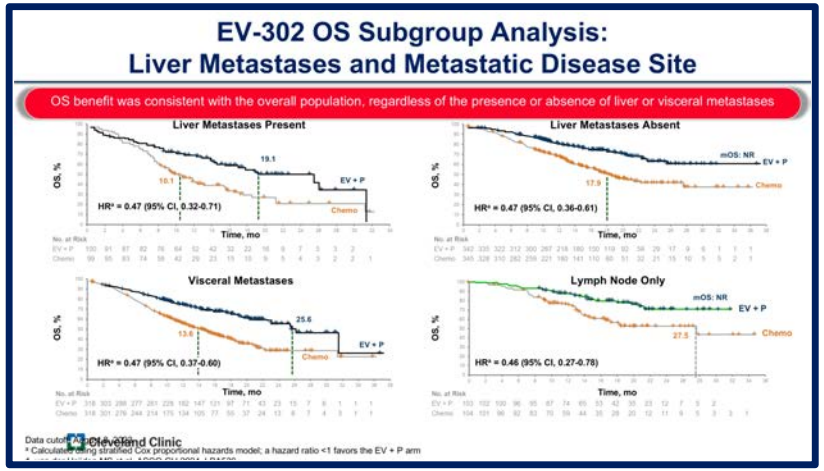
Powles T et al. ESMO 2024, NEJM 2024

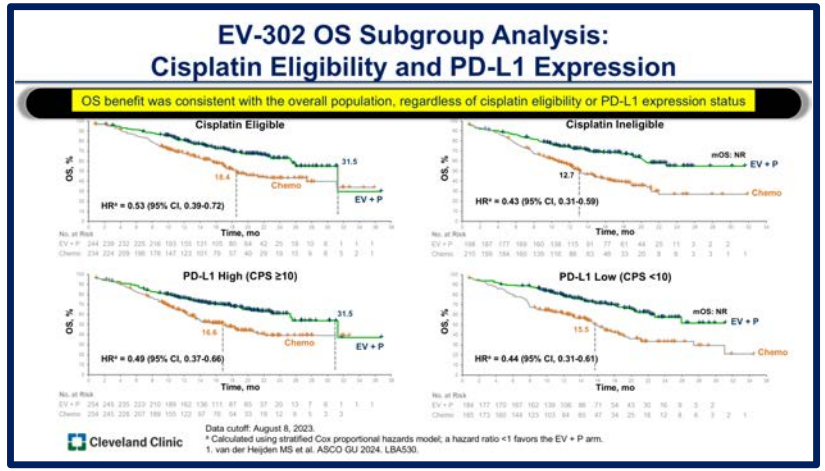


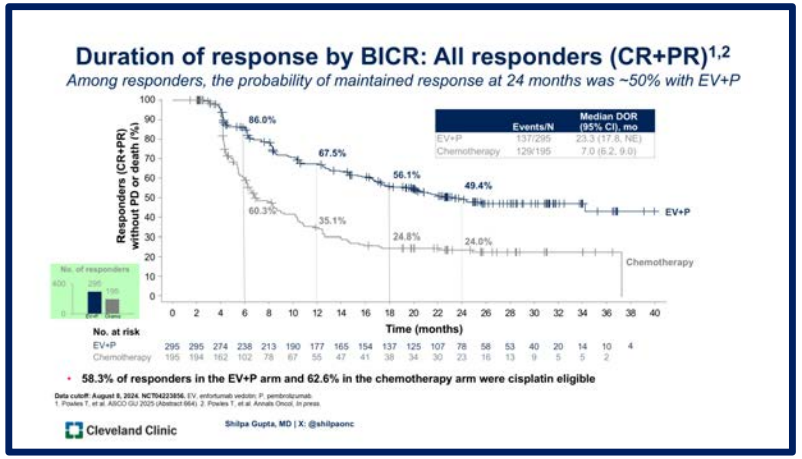




EV-Pembro has revolutionized the 1L treatment in mUC







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Gupta et al. ASCO 2025; Powles et al. Ann Oncol. 2025; Powles et al. ESMO 2023; Powles T et al. NEJM 2024; Van Der Heijden et al. ASCO GU 2024

EV-pembro sets off a domino effect in MIBC

Cleveland Clinic

NO UTUC INCLUDED

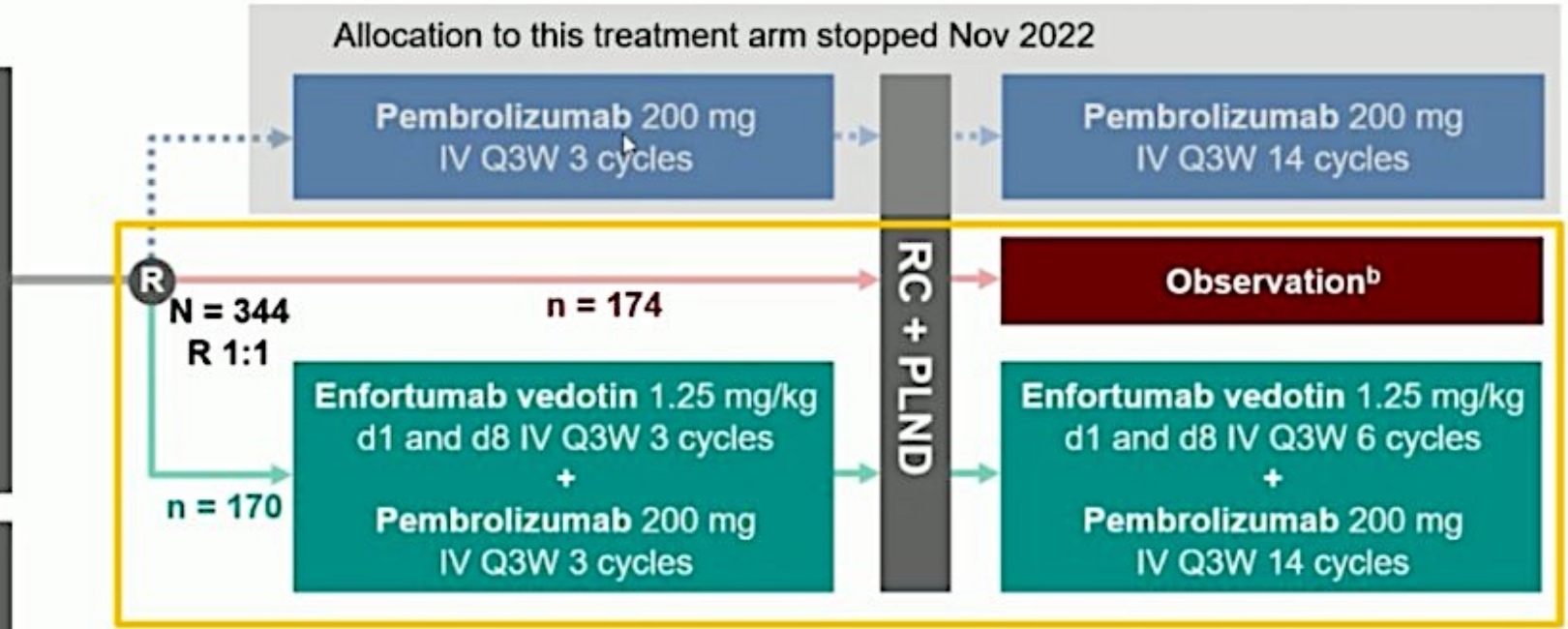
KEYNOTE-905/EV-303 Study (NCT03924895)

Key Eligibility Criteria

- Adults with MIBC
- Clinical stage T2-T4aN0M0 or T1-T4aN1M0 by central assessment
- ≥50% Urothelial histology
- Cisplatin-ineligible per Galsky criteria[a] or cisplatin-declining
- ECOG PS 0-2

Stratification Factors

- Cisplatin ineligibility (ineligible vs. eligible but declining)
- Clinical stage (T2N0 vs. T3/T4aN0 vs. T1-4aN1)
- Region (US vs. EU vs. Most of World)



Primary endpoint: Event-free survival (EFS) by BICR

Key secondary endpoints: OS and pathological complete response (pCR; pT0N0, i.e. absence of viable tumor in examined tissue from surgery) by central pathologist review

Other secondary endpoints include: Safety

Exploratory endpoints include: EFS by pCR status

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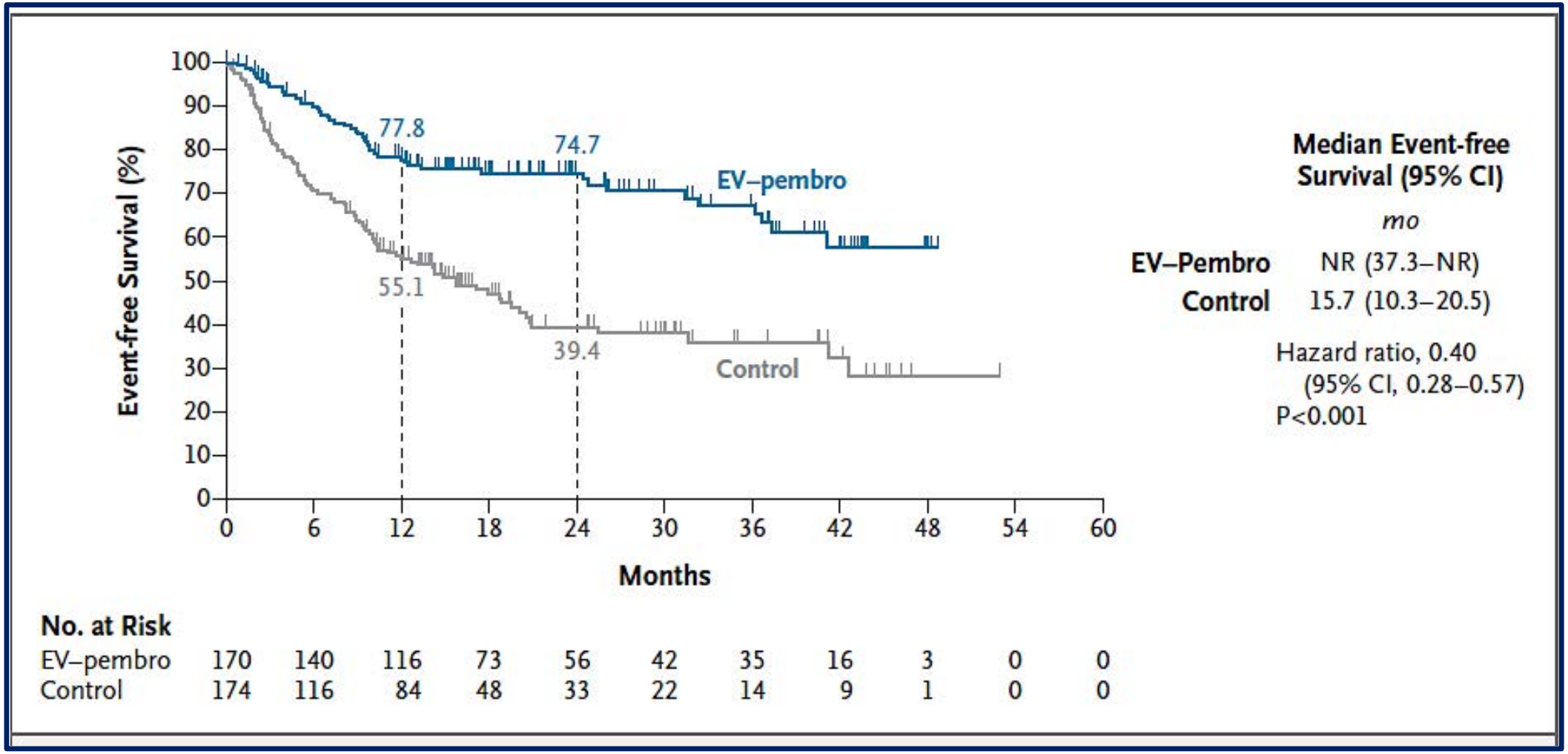
Characteristic	Enfortumab Vedotin–Pembrolizumab (N=170)	Control (N=174)
Age		
Median (range) — yr	74.0 (47–87)	72.5 (46–87)
Distribution — no. (%)		
<65 yr	29 (17.1)	29 (16.7)
65 to <75 yr	63 (37.1)	77 (44.3)
≥75 yr	78 (45.9)	68 (39.1)
Male sex — no. (%)	137 (80.6)	131 (75.3)
ECOG performance-status score — no. (%)†		
0	102 (60.0)	95 (54.6)
1	47 (27.6)	53 (30.5)
2	21 (12.4)	26 (14.9)
Cisplatin eligibility status — no. (%)		
Ineligible	142 (83.5)	139 (79.9)
Eligible but declined	28 (16.5)	35 (20.1)
Tumor stage — no. (%)¶		
T2N0	30 (17.6)	32 (18.4)
T3N0 or T4aN0	133 (78.2)	132 (75.9)
T1 to T4a with N1	7 (4.1)	10 (5.7)
Creatinine clearance — no. (%)		
<30 ml/min	0	1 (0.6)
30 to <60 ml/min	102 (60.0)	101 (58.0)
≥60 ml/min	68 (40.0)	72 (41.4)

Older and more frail patient population

Vulsteke C et al. NEJM 2026

KEYNOTE-905/EV-303 EFS



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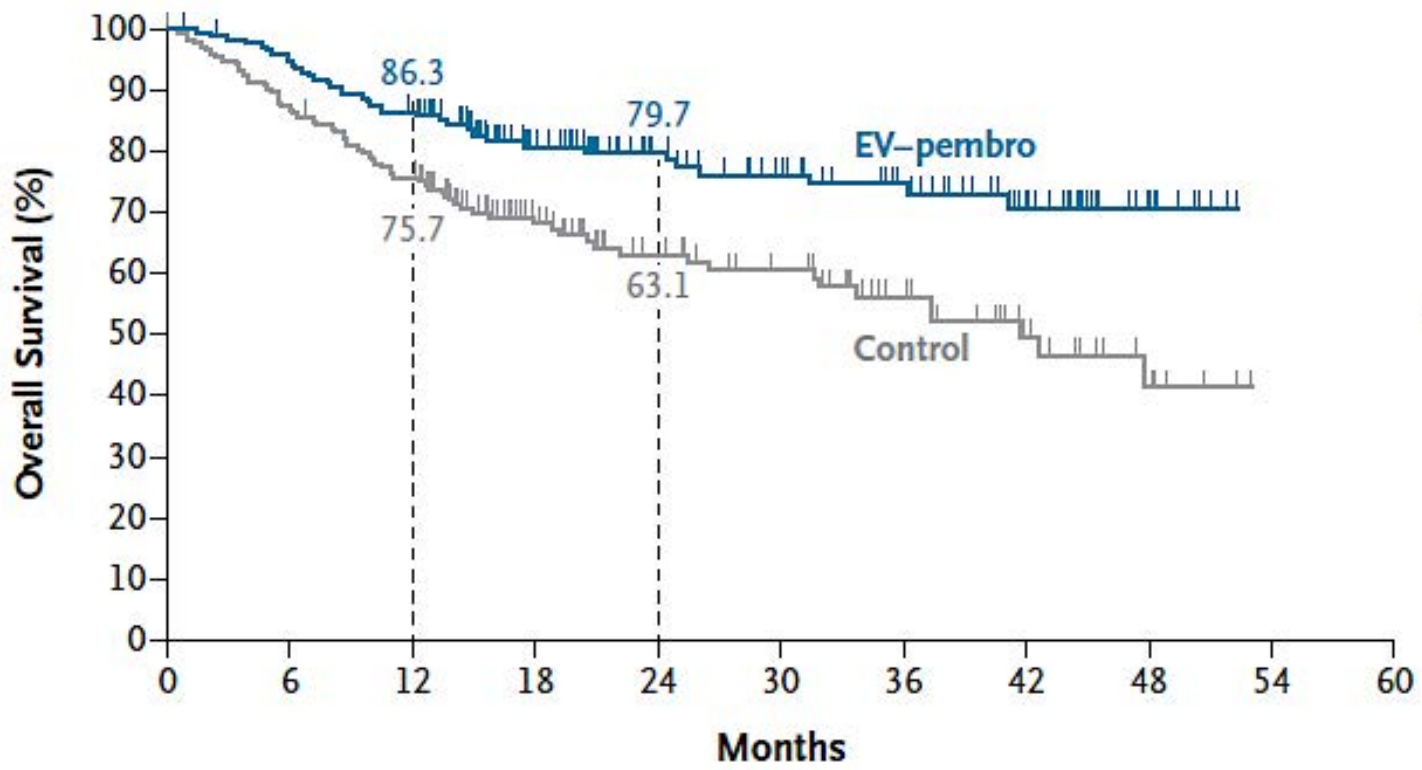
KEYNOTE-905/EV-303 OS



Median Overall Survival (95% CI)	*mo*
EV–Pembro	NR (NR–NR)
Control	41.7 (31.8–NR)

Hazard ratio, 0.50
(95% CI, 0.33–0.74)
P<0.001

No. at Risk											
EV–pembro	170	159	144	94	68	56	45	28	10	0	0
Control	174	150	130	75	54	45	30	18	6	0	0

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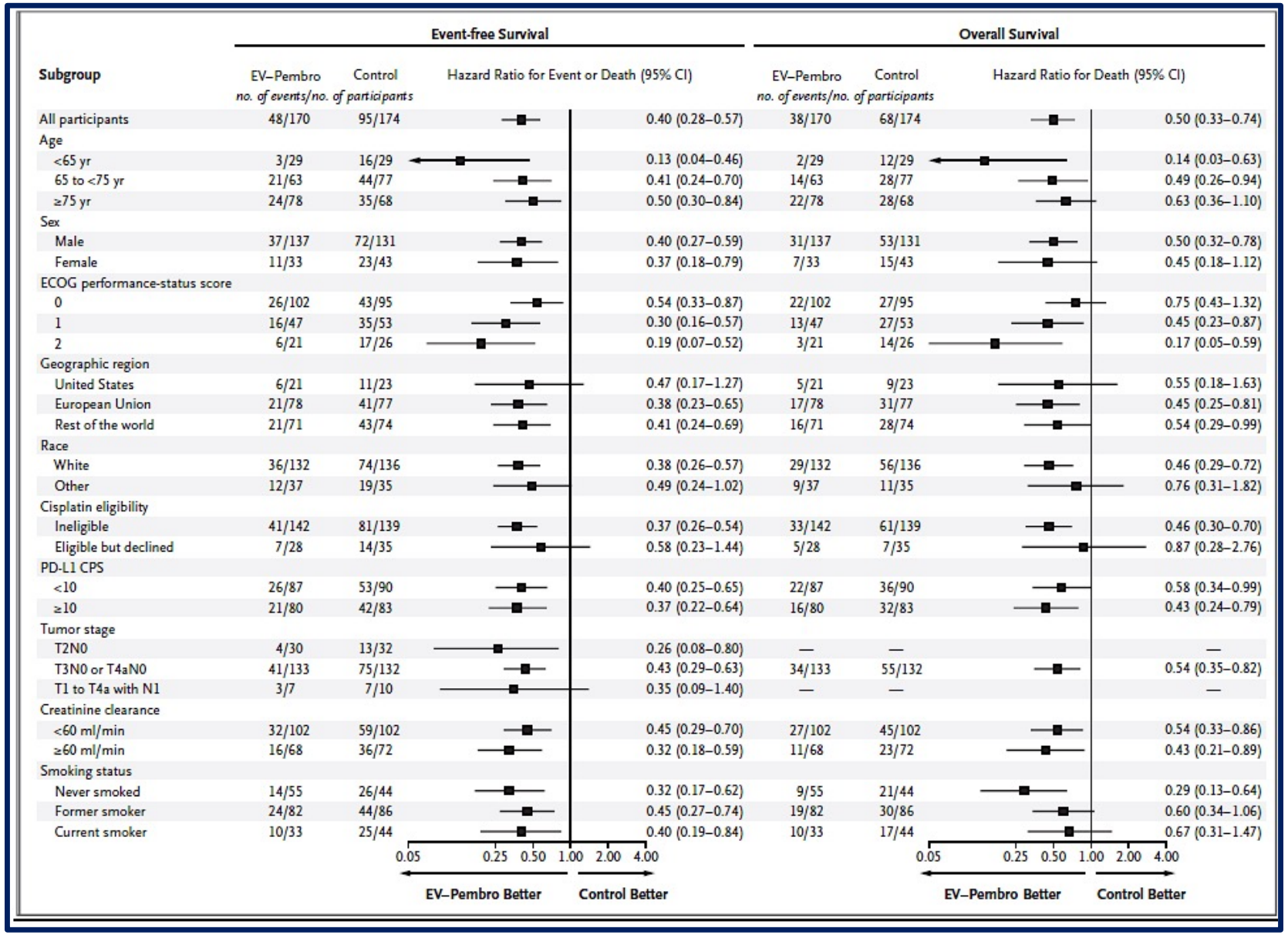
Benefit with EV-Pembro across subgroups



Subgroup	Event-free Survival: EV–Pembro (no. of events/no. of participants)	Event-free Survival: Control (no. of events/no. of participants)	Event-free Survival: Hazard Ratio for Event or Death (95% CI)	Overall Survival: EV–Pembro (no. of events/no. of participants)	Overall Survival: Control (no. of events/no. of participants)	Overall Survival: Hazard Ratio for Death (95% CI)
All participants	48/170	95/174	0.40 (0.28–0.57)	38/170	68/174	0.50 (0.33–0.74)
Age						
<65 yr	3/29	16/29	0.13 (0.04–0.46)	2/29	12/29	0.14 (0.03–0.63)
65 to <75 yr	21/63	44/77	0.41 (0.24–0.70)	14/63	28/77	0.49 (0.26–0.94)
≥75 yr	24/78	35/68	0.50 (0.30–0.84)	22/78	28/68	0.63 (0.36–1.10)
Sex						
Male	37/137	72/131	0.40 (0.27–0.59)	31/137	53/131	0.50 (0.32–0.78)
Female	11/33	23/43	0.37 (0.18–0.79)	7/33	15/43	0.45 (0.18–1.12)
ECOG performance-status score						
0	26/102	43/95	0.54 (0.33–0.87)	22/102	27/95	0.75 (0.43–1.32)
1	16/47	35/53	0.30 (0.16–0.57)	13/47	27/53	0.45 (0.23–0.87)
2	6/21	17/26	0.19 (0.07–0.52)	3/21	14/26	0.17 (0.05–0.59)
Geographic region						
United States	6/21	11/23	0.47 (0.17–1.27)	5/21	9/23	0.55 (0.18–1.63)
European Union	21/78	41/77	0.38 (0.23–0.65)	17/78	31/77	0.45 (0.25–0.81)
Rest of the world	21/71	43/74	0.41 (0.24–0.69)	16/71	28/74	0.54 (0.29–0.99)
Race						
White	36/132	74/136	0.38 (0.26–0.57)	29/132	56/136	0.46 (0.29–0.72)
Other	12/37	19/35	0.49 (0.24–1.02)	9/37	11/35	0.76 (0.31–1.82)
Cisplatin eligibility						
Ineligible	41/142	81/139	0.37 (0.26–0.54)	33/142	61/139	0.46 (0.30–0.70)
Eligible but declined	7/28	14/35	0.58 (0.23–1.44)	5/28	7/35	0.87 (0.28–2.76)
PD-L1 CPS						
<10	26/87	53/90	0.40 (0.25–0.65)	22/87	36/90	0.58 (0.34–0.99)
≥10	21/80	42/83	0.37 (0.22–0.64)	16/80	32/83	0.43 (0.24–0.79)
Tumor stage						
T2N0	4/30	13/32	0.26 (0.08–0.80)	—	—	—
T3N0 or T4aN0	41/133	75/132	0.43 (0.29–0.63)	34/133	55/132	0.54 (0.35–0.82)
T1 to T4a with N1	3/7	7/10	0.35 (0.09–1.40)	—	—	—
Creatinine clearance						
<60 ml/min	32/102	59/102	0.45 (0.29–0.70)	27/102	45/102	0.54 (0.33–0.86)
≥60 ml/min	16/68	36/72	0.32 (0.18–0.59)	11/68	23/72	0.43 (0.21–0.89)
Smoking status						
Never smoked	14/55	26/44	0.32 (0.17–0.62)	9/55	21/44	0.29 (0.13–0.64)
Former smoker	24/82	44/86	0.45 (0.27–0.74)	19/82	30/86	0.60 (0.34–1.06)
Current smoker	10/33	25/44	0.40 (0.19–0.84)	10/33	17/44	0.67 (0.31–1.47)

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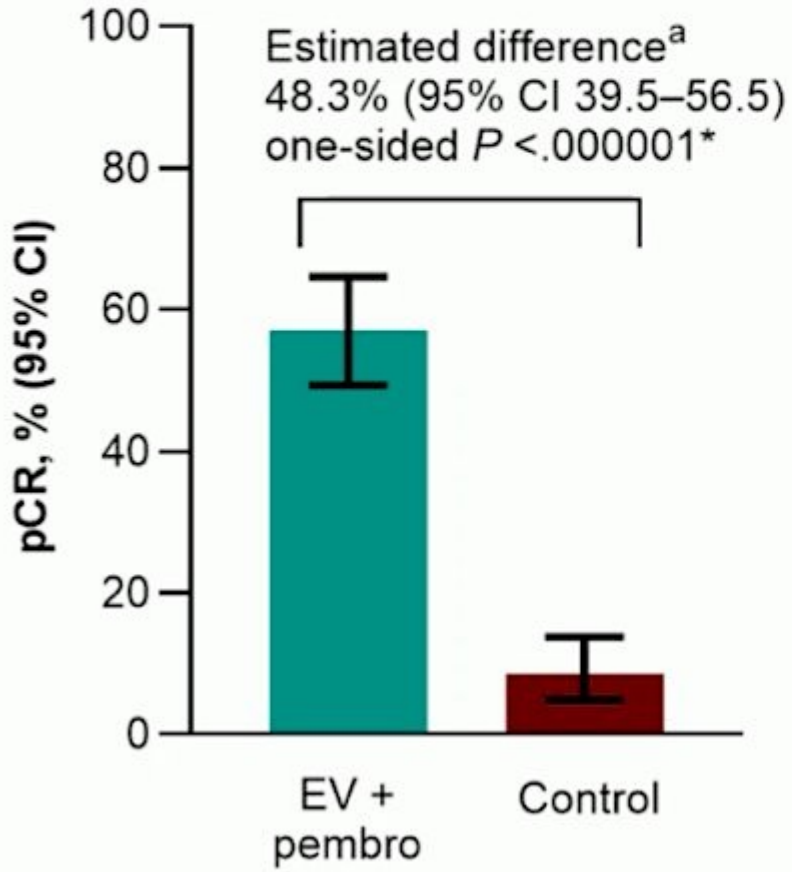
Key Secondary Endpoint: pCR by Central Pathology Review
ITT Population



	EV + pembro (N = 170)	Control (N = 174)
pCR, n	97	15
pCR rate, % (95% CI)	57.1 (49.3–64.6)	8.6 (4.9–13.8)

- **pCR:** absence of viable tumor (pT0N0) in examined tissue from RC + PLND
- Pts who did not undergo surgery, including those with clinical complete response after neoadjuvant therapy, were considered non-responders

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Safety

Adverse Event	Enfortumab Vedotin–Pembrolizumab (N=167)	Control (N=159)
	no. of participants with one or more events (%)	
Adverse events of any cause		
Any grade	167 (100)	103 (64.8)
Grade ≥3	119 (71.3)	73 (45.9)
Led to enfortumab vedotin dose reduction	28 (16.8)	NA
Led to discontinuation of any trial drug	81 (48.5)	NA
Led to death	13 (7.8)	9 (5.7)
Serious†	97 (58.1)	65 (40.9)
Drug-related adverse events as determined by the investigator		
Any grade	154 (92.2)	NA
Grade ≥3	76 (45.5)	NA
Led to enfortumab vedotin dose reduction	26 (15.6)	NA
Led to discontinuation of any trial drug	62 (37.1)	NA
Led to death	2 (1.2)	NA
Serious†	33 (19.8)	NA
Adverse events of special interest		
Any grade for pembrolizumab‡	72 (43.1)	NA
Grade ≥3 for pembrolizumab‡	30 (18.0)	NA
Drug-related any grade for enfortumab vedotin	123 (73.7)	NA
Drug-related grade ≥3 for enfortumab vedotin	27 (16.2)	NA

67% patients in EV-pembro arm got adjuvant therapy

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Press Release
EV 304: EV-P improves EFS and OS compared to Gem-Cis
Data to be presented tomorrow (Matt Galsky)

Enfortumab Vedotin-ejfv Plus Pembrolizumab Significantly Improves Survival for Patients with Muscle-Invasive Bladder Cancer Regardless of Cisplatin

Wednesday, December 17, 2025 - 06:45am

Conclusions and Future Directions

- IO is now a backbone of peri-operative treatment in MIBC, EV-pembro will revolutionize treatment further replacing platinums
- Need to personalize adjuvant therapy duration in patients with pCR using biomarkers such as ctDNA to avoid unnecessary toxicities
- Unmet need to explore bladder preservation treatment strategies in patients achieving clinical complete response to neoadjuvant treatments

Second Opinion

Elizabeth R Plimack, MD, MS

Neil Love, MD

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Do you agree with the original recommendation of adjuvant nivolumab for this 68-year-old woman with resected upper tract urothelial carcinoma? How would you have advised her?

Results of a ctDNA assay ordered for the patient were negative, and her CT scan was clear. What would be your approach to adjuvant treatment in this situation?

Do you routinely order ctDNA assays to inform treatment decisions for patients with MIBC? If so, what is your preferred platform? Are you more confident with tumor-informed versus tumor-agnostic assays? When assessing ctDNA, how often do you repeat the assay?

Second Opinion

Thomas Powles, MBBS, MRCP, MD

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

What would be your most likely post-cystectomy treatment approach for this 77-year-old man with PD-L1-negative MIBC and poor renal function? Would you consider adjuvant nivolumab? What about enfortumab vedotin with pembrolizumab (EVP)?

Based on the results of the Phase III IMvigor011 trial evaluating ctDNA-guided use of adjuvant atezolizumab versus observation, is this a strategy you would recommend in this setting? If initial ctDNA analysis is negative, are you comfortable proceeding with observation accompanied by serial testing?

QUESTIONS FOR THE FACULTY

Do you believe ctDNA analysis can be used to identify patients who are at a high risk of relapse and might derive greater benefit from adjuvant systemic therapy? Can longitudinal ctDNA monitoring be used to identify patients who can be spared adjuvant systemic therapy?

Agenda

Module 1: Optimal Use of Anti-PD-1/PD-L1 Antibodies in Non-Muscle-Invasive Bladder Cancer — Dr Friedlander

Module 2: Evolving Management of Muscle-Invasive Bladder Cancer — Dr Gupta

Module 3: Current and Future Role of Novel Intravesical Therapies in Nonmetastatic Urothelial Bladder Cancer (UBC) — Dr Necchi

Module 4: Emerging Utility of Circulating Tumor DNA Evaluation in Nonmetastatic UBC — Dr Galsky

Current and Future Role of Novel Intravesical Therapies in Nonmetastatic UBC

Andrea Necchi, MD
Vita-Salute San Raffaele University
Director of Genitourinary Medical Oncology
IRCCS San Raffaele Hospital, Milan, Italy

UniSR
Università Vita-Salute San Raffaele

Comprehensive Cancer Center
IRCCS Ospedale San Raffaele

I.R.C.C.S. Ospedale San Raffaele
Gruppo San Donato

Unmet Needs Across the Disease Spectrum

- Only one-third of patients with **NMIBC** receive intravesical BCG[1]
- Many of those with **NMIBC** who are unresponsive to BCG experience recurrence or progression[2]

- Close to half of patients with **MIBC** worldwide may not receive curative-intent therapy[3]
- Patients who have undergone radical cystectomy for **MIBC** often have impaired HRQOL and a high risk of recurrence[4,5]

- More than half of patients with **mUC** may not receive first-line systemic treatment[4,5]
- Many patients with **mUC** who progress on 1L or 2L therapy do not receive subsequent treatment[4,5]

- In NMIBC, development of effective, safe, and durable intravesical treatment remains a critical unmet clinical need for patients who want to avoid radical cystectomy
- In MIBC, effective consolidation approaches post neoadjuvant therapy in patients who refuse to undergo radical cystectomy are key to improve disease control and QoL
- Clinical trial enrollment allows for modern advances to reach patients

1. Tyson M et al. *J Clin Oncol*. 2019;37(suppl 15):e16012. 2. Shore ND et al. *Urol Oncol*. 2021;39(10):642-663. 3. Westergren DO et al. *J Urol*. 2019;202:905-912.
4. Choi H et al. *Transl Androl Urol*. 2020;9:2997-3006. 5. Roupret M et al. *Eur Urol*. 2021;79:62-79. 4. Morgans AK. ESMO 2021. Abstract 704P.
5. Bilen M. ESMO 2021. Abstract 701P.

Background

High-Risk NMIBC Is Defined as High-grade Ta, Any T1, and/or Carcinoma in situ

- **Standard of care for high-risk NMIBC:** TURBT followed by intravesical BCG
- Prognosis is poor for patients whose disease does not respond to BCG or relapses within 12 months[1]; these patients are directed to radical cystectomy

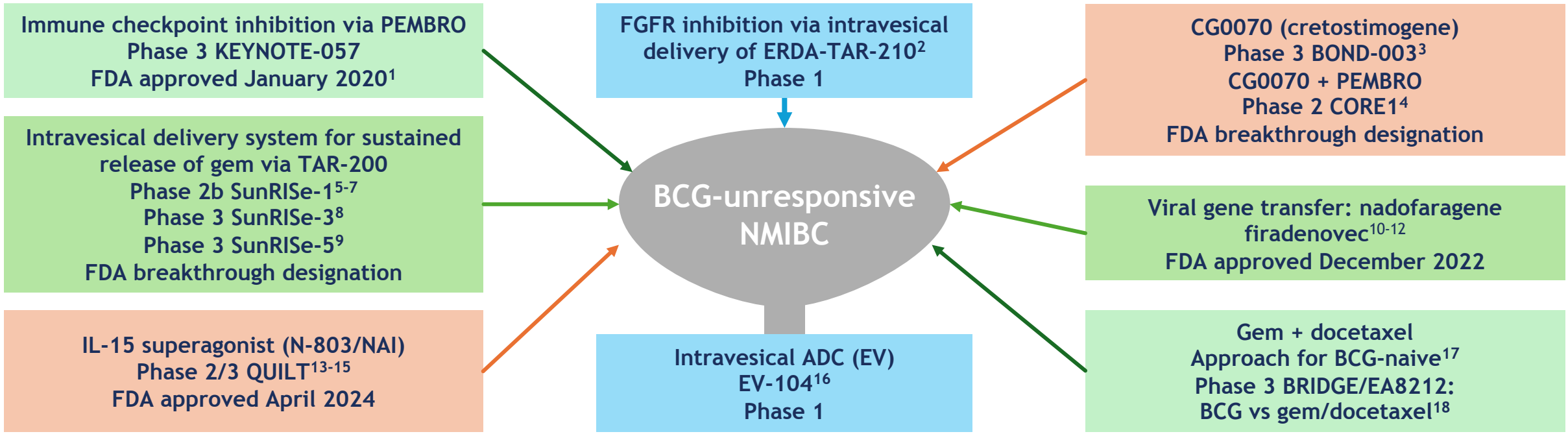
Criteria for the Definition of Adequate BCG and BCG-Unresponsive, High-Risk NMIBC Are Well Established and Endorsed by the FDA[2]

- **Adequate BCG induction:** ≥5 instillations of BCG and ≥7 instillations within 9 months of the first instillation of induction therapy
- **BCG-unresponsive, high-risk NMIBC** is defined as one of the following
  - Stage progression at 3 months despite adequate BCG induction
  - High-grade T1 disease at first evaluation after adequate BCG induction
  - Persistent high-risk NMIBC at 6 months after adequate BCG
  - Recurrent high-risk NMIBC within 9 months of the last BCG instillation despite adequate BCG

BCG, Bacillus Calmette-Guerin; NMIBC, nonmuscle-invasive bladder cancer; RC, radical cystectomy; TURBT, transurethral resection of bladder tumor.

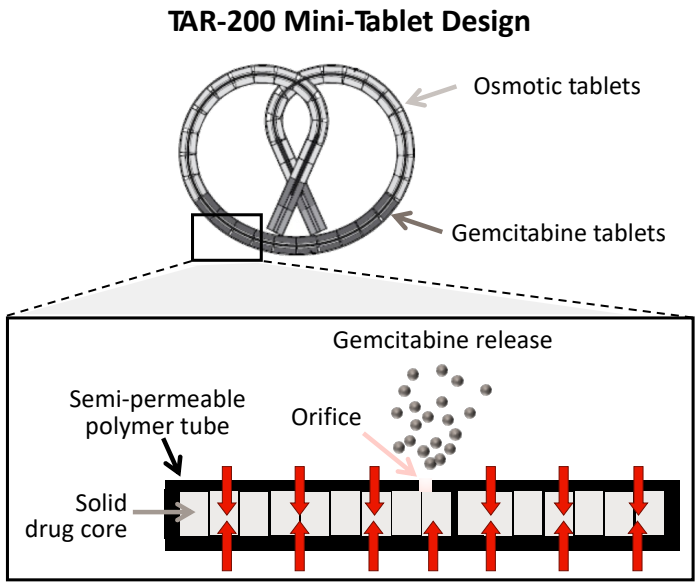
1. Jeong et al. *BMC Cancer*. 2022;22:361. 2. Kamat AM et al. *J Clin Oncol.* 2016;34:1935–1944.

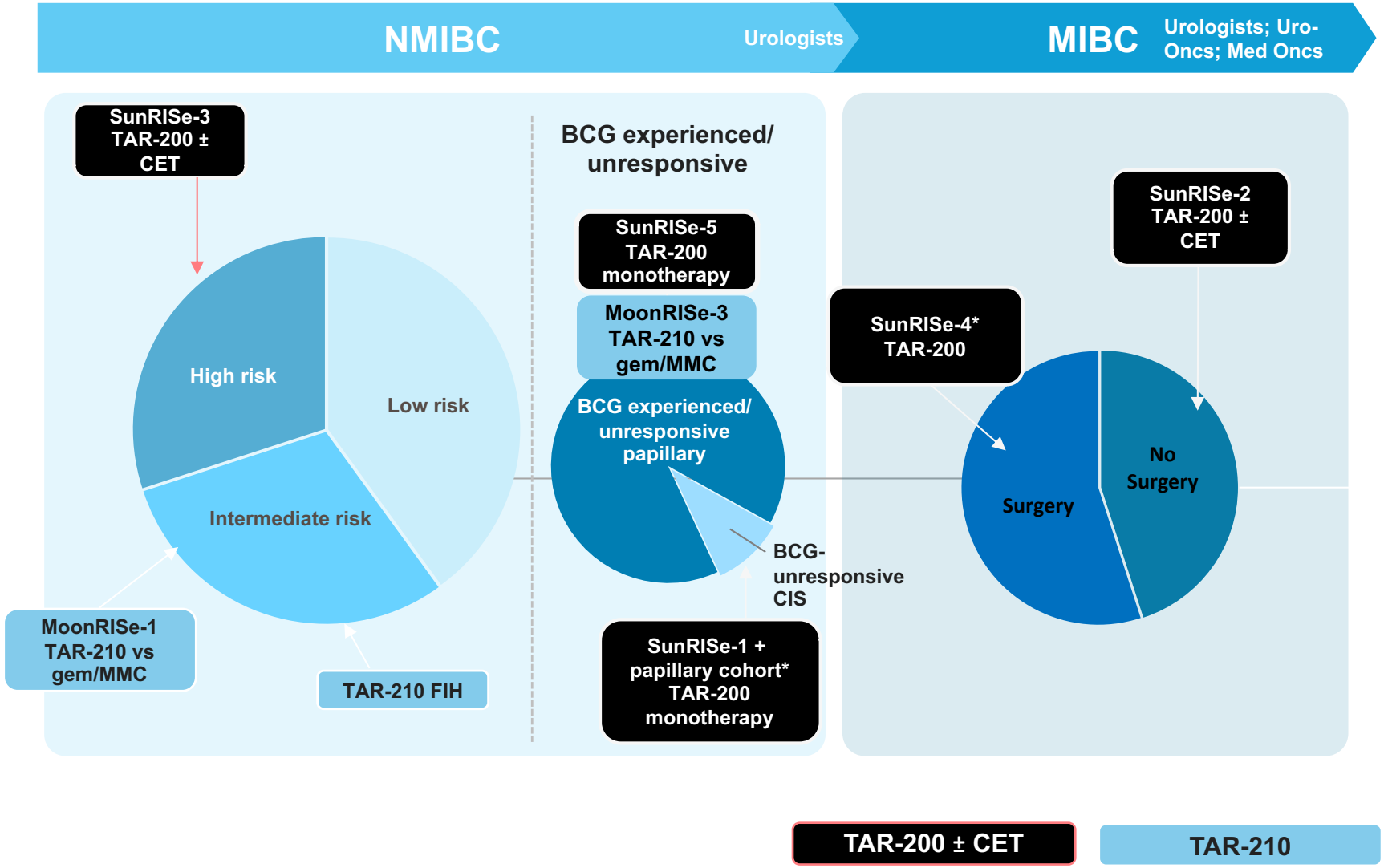
Treatment approaches for high-risk NMIBC unresponsive to BCG



- ADC, antibody-drug conjugate; BCG, Bacillus Calmette-Guerin; ERDA, erdafitinib; EV, enfortumab vedotin; FGFR, fibroblast growth factor receptor; gem, gemcitabine; IL, interleukin; NAI, nogapendekin alfa inbakicept; NMIBC, nonmuscle-invasive bladder cancer; PEMBRO, pembrolizumab. 1. Balar AV et al. *Lancet Oncol*. 2021;22:919-930. 2. Vilaseca A et al. AUA 2024. Abstract PD48-02. 3. Tyson MD et al. AUA 2024. Abstract P2-02. 4. Li R et al. *Nat Med*. 2024 Jun 6. doi: 10.1038/s41591-024-03025-3. Online ahead of print. 5. Daneshmand S et al. AUA 2023. LBA 02-03. 6. Necchi A et al. ESMO 2023. LBA105. 7. Jacob J et al. AUA 2024. Abstract P2-01. 8. ClinicalTrials.gov https://clinicaltrials.gov/study/NCT05714202. 9. ClinicalTrials.gov https://clinicaltrials.gov/study/NCT06211764. 10. Boorjian SA et al. *Lancet Oncol*. 2021;22:107–117. 11. Mitra AP et al. AUA 2022. Abstract MP54-05. 12. ADSTILADRIN® (nadofaragene firadenovec-vncg) [package insert]. Kastrup, Denmark: Ferring Pharmaceuticals; August 2024. 13. Chamie K. *NEJM Evidence*. 2022;2(1):1–11. 14. ClinicalTrials.gov https://clinicaltrials.gov/study/NCT03022825. 15. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-nogapendekin-alfa-inbakicept-pmln-bcg-unresponsive-non-muscle-invasive-bladder-cancer. Accessed August 29, 2024. 16. Kamat AM et al. *J Clin Oncol*. 2023;41(suppl 16). Abstract 4596. 17. McElree IM et al. *J Urol*. 2022;208:589-599. 18. Kates M et al. *Eur Urol Focus*. 2023;9(4):561–563.

TAR development in Nonmetastatic Bladder Cancer





*Nonregistrational. BCG, bacillus Calmette–Guerin; CET, cetrelimab; CIS, carcinoma in situ; CRT, chemoradiotherapy; FIH, first-in-human; gem, gemcitabine; MIBC, muscle-invasive bladder cancer; MMC, mitomycin C; mUC, metastatic urothelial carcinoma; NMIBC, non–muscle-invasive bladder cancer.

Phase 2b SunRISe-1 Study: Cohort 2 BCG-Unresponsive HR NMIBC CIS ± Papillary Disease

NCT04640623

Population:
- Aged ≥18 years
- Histologically confirmed HR NMIBC CIS (with or without 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

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 *Cohort 3* (N=28) — *Cohort 3 was closed*
- TAR-200 Monotherapy *Cohort 4* (N=52) — *Enrollment completed*

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

TAR-200 dosing: Q3W (indwelling) for the first 24 weeks; then Q12W through Week 96

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

Key secondary end points
- Duration of response
- Overall survival
- Safety
- Tolerability
- HRQoL

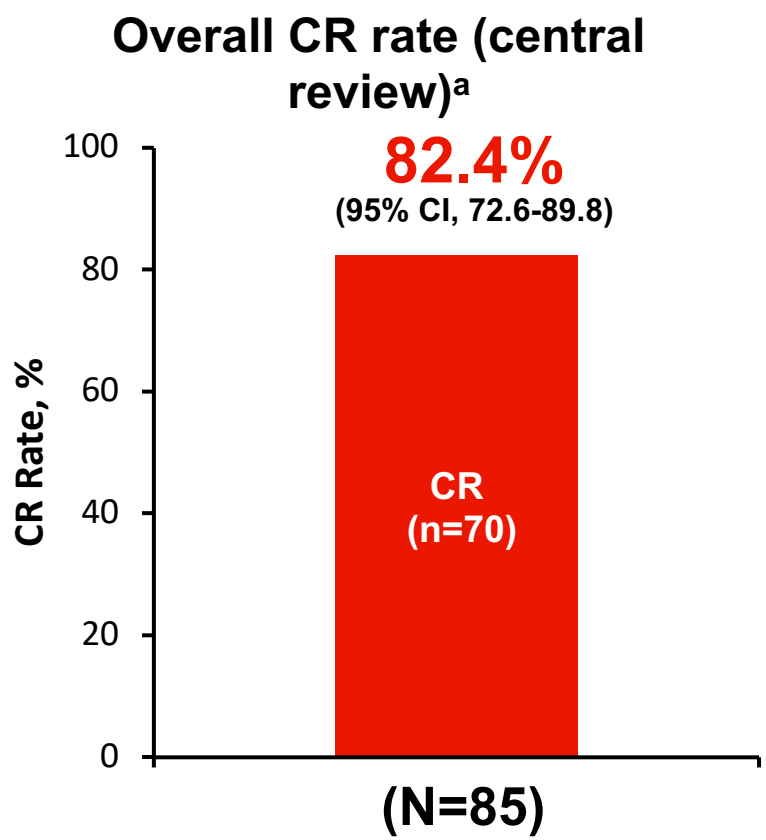
Cohort 4:
Primary end point
- DFS

- **Here we report *1-year durability data from the TAR-200 monotherapy cohort (Cohort 2) of SunRISe-1***
- Response is determined by quarterly cystoscopy, quarterly central cytology, **mandated bladder biopsy by central assessment at Weeks 24 and 48**, and local imaging Q24W
- The study protocol **did not allow re-induction for nonresponders**, consistent with US FDA guidance[2]
- As of June 2023, Cohorts 1 and 3 were closed for enrollment, and Cohort 2 enrollment continued to achieve N=85, per protocol amendment

The clinical data cutoff was March 31, 2025.
DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; Q3W, every 3 weeks; Q12W, every 12 weeks; Q24W, every 24 weeks; R, randomization.
[a]Patients with BCG-unresponsive papillary-only HR NMIBC (high-grade Ta, any T1) per protocol amendment 4. [b]Cetrelimab is an anti–programmed cell death-1[3,4]; cetrelimab dosing was Q3W through Week 78. [c]Number of patients enrolled in Cohort 1 was N=55 and number of patients treated was N=53.
1. Lerner SP, et al. *Urol Oncol*. 2009;27:155-159. 2. US Food and Drug Administration. Available at: https://www.fda.gov/media/101468/download. 3. DeAngelis N, et al. *Cancer Chemother Pharmacol*. 2022;89:515-527.
4. Felip E, et al. *Cancer Chemother Pharmacol*. 2022;89:499-514.

Presented by JM Jacob at the 120th AUA Annual Meeting; April 26-29, 2025; Las Vegas, NV, USA

Highest CR Rate to Date With Rapid Onset After TAR-200 Monotherapy in BCG-Unresponsive HR NMIBC CIS ± Papillary Disease



CR Rate From Treatment Initiation	Observed Overall CR Rate, % (n/N)
12 months[b]	**45.9** (39/85)

	KM Estimated Overall CR Rate, % (95% CI)
12 months	**52.4** (40.7-62.8)
24 months	**44.7** (33.1-55.7)

- Rapid onset of response: median time to onset, **2.8 months** (range, 2.1-8.3)
- **95.7%** (67 of 70) CRs achieved at the first (3 month) disease assessment

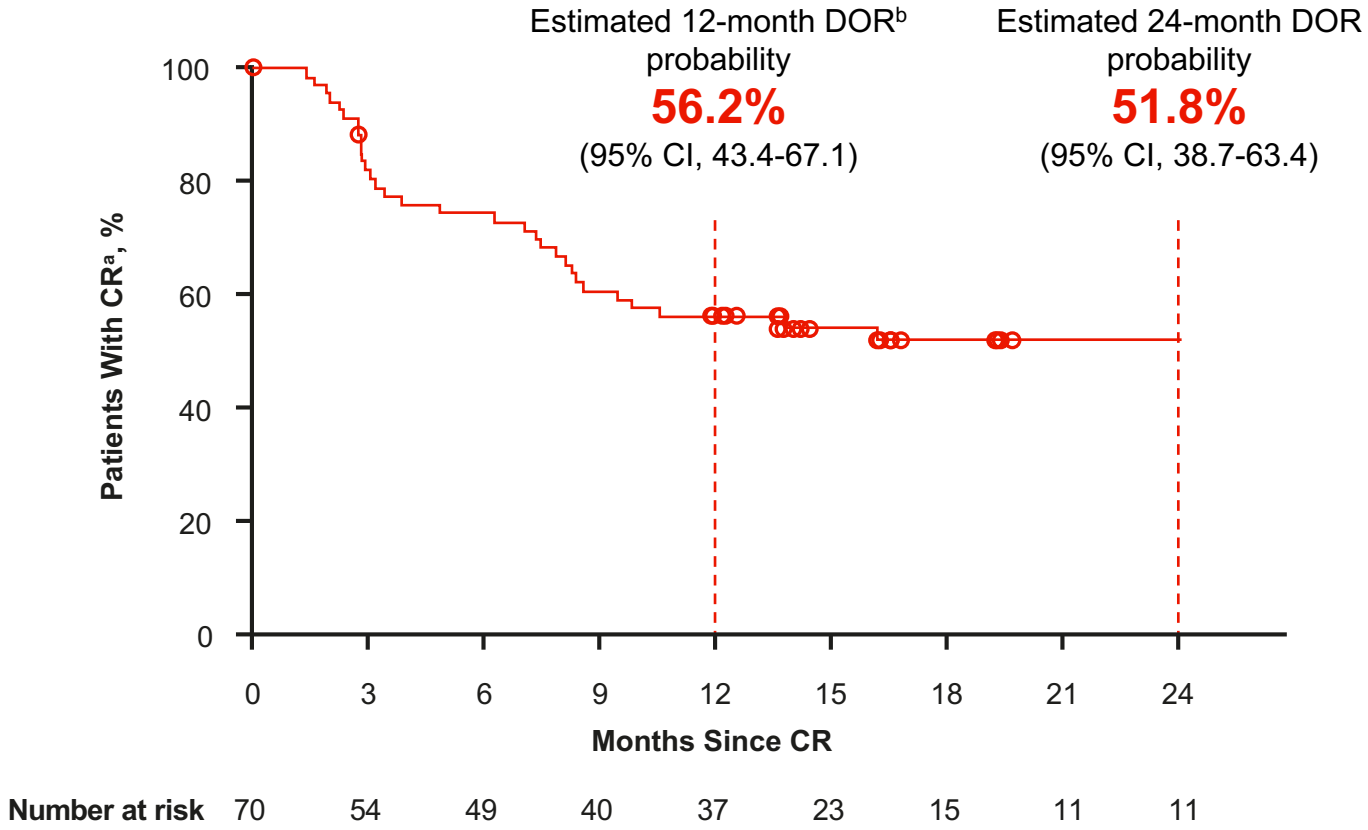
FDA Breakthrough Therapy Designation

Daneshmand S, et al. *J Clin Oncol*. 2025 Nov 20;43(33):3578-3588.

CI, confidence interval; KM, Kaplan-Meier.
[a]Response is based on centrally reviewed urine cytology, local cystoscopy, and central biopsy (if available). CRs do not have to be confirmed. A CR is defined as having a negative cystoscopy and negative (including atypical) centrally read urine cytology, or positive cystoscopy with biopsy-proven benign or low-grade NMIBC and negative (including atypical) centrally read cytology at any time point. [b]The CR rate at 12 months is represented by disease evaluation occurring at 48 weeks from first dose.

Presented by JM Jacob at the 120th AUA Annual Meeting; April 26-29, 2025; Las Vegas, NV, USA

Durable Responses With TAR-200 Monotherapy



- **25.8 months** (95% CI, 8.3-NE) median DOR
- Of 70 responders:
  - 23 (32.9%) had HR NMIBC recurrence[c]
  - 4 (5.7%) had ≥T2 progression[c]
- **86.6%** (95% CI, 76.6-92.6) cystectomy-free rate at 12 months

Daneshmand S, et al. *J Clin Oncol*. 2025 Nov 20;43(33):3578-3588.

DOR, duration of response; MIBC, muscle-invasive bladder cancer; NE, not estimable.
[a]Response is based on centrally reviewed urine cytology, local cystoscopy, and central biopsy (if available). CRs do not have to be confirmed. A CR is defined as having a negative cystoscopy and negative (including atypical) centrally read urine cytology, or positive cystoscopy with biopsy-proven benign or low-grade NMIBC and negative (including atypical) centrally read cytology at any time point. [b]Median follow-up in responders was 20.2 months (range, 5-48). [c]Stage based on investigator assessment. Three patients with no evidence of disease had recurrence/progression based on central review but was not indicated by local assessment.

Presented by JM Jacob at the 120th AUA Annual Meeting; April 26-29, 2025; Las Vegas, NV, USA

TAR-200 Monotherapy Safety Profile

- Most TEAEs were grade 1 or 2
  - TEAEs resolved after a median of 3.1 weeks
- 99% (745 of 755) insertion success rate
- 5 patients (5.9%) had ≥1 serious TRAEs[a]
- Few patients (n=3; 3.5%) discontinued treatment due to TRAEs[b]
- No treatment-related deaths were reported

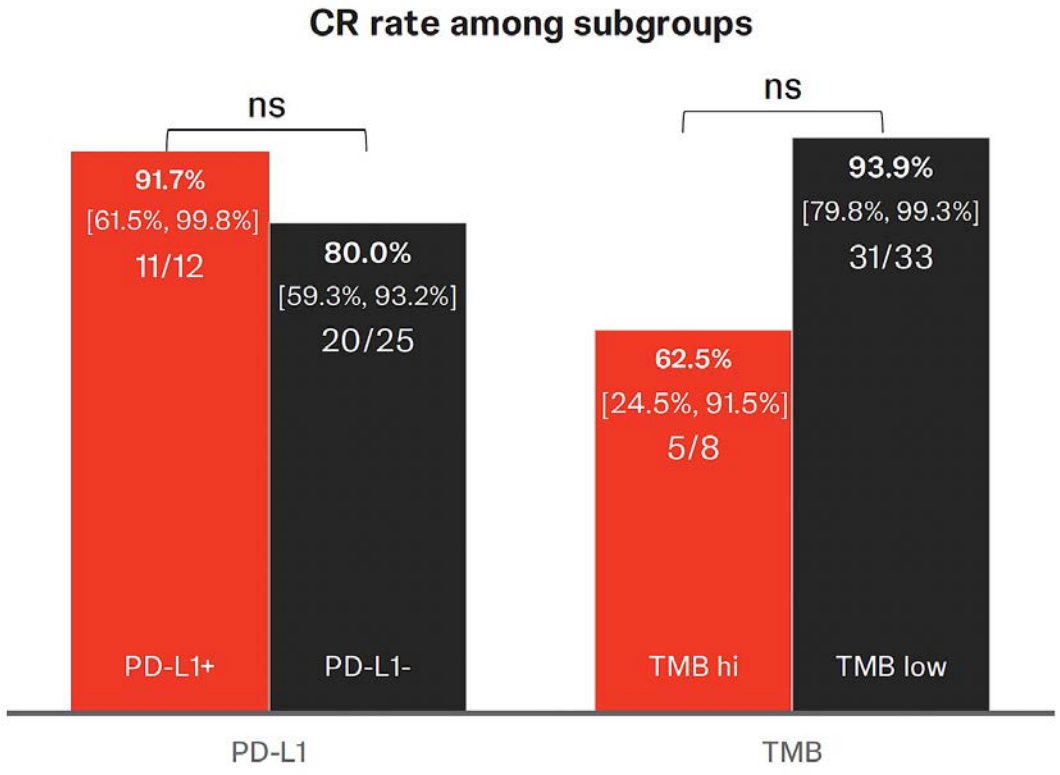
Patients With Events, n (%)	TAR-200 Monotherapy *Cohort 2* (N=85)[c]	
	Any Grade	Grade ≥3
≥1 TRAE[d]	71 (83.5)	11 (12.9)
Most frequent TRAEs[e,f]		
Pollakiuria	37 (43.5)	0
Dysuria	34 (40.0)	0
Micturition urgency	21 (24.7)	0
Urinary tract infection	19 (22.4)	1 (1.2)
Hematuria	14 (16.5)	0
Urinary tract pain	9 (10.6)	4 (4.7)
Bladder pain	7 (8.2)	2 (2.4)
Bladder spasm	7 (8.2)	0
Noninfective cystitis	6 (7.1)	0
Urinary incontinence	5 (5.9)	0

TEAE, treatment emergent adverse event; TRAE, treatment-related adverse event.
[a]1 event each of acute kidney injury, bladder pain, cystitis, cystitis pseudomonal, urinary tract infection, urinary tract pain, and urosepsis. Note, patients may have had ≥1 serious TRAE. [b]TRAEs leading to discontinuation were noninfective cystitis (n=2), bladder pain (n=1), pollakiuria (n=1), and urinary tract disorder (n=1). Note, patients who discontinued may have had ≥1 TRAE. [c]Safety is shown for all patients who received at least 1 dose of TAR-200 in the safety analysis set (N=85). [d]An AE was categorized as related if the investigator determined that there was a possible, probable, or causal relationship between the AE and TAR-200 or the insertion or removal procedure or urinary placement catheter. [e]Reported in ≥5% of patients. [f]TRAEs of grade ≥3 reported in ≥2% of patients. All other TRAEs of grade ≥3 were reported in only 1 patient each and included acute kidney injury, cystitis, urinary retention, cystitis pseudomonal, and urosepsis. Note, patients may have had ≥1 grade ≥3 TRAE.

Presented by JM Jacob at the 120th AUA Annual Meeting; April 26-29, 2025; Las Vegas, NV, USA

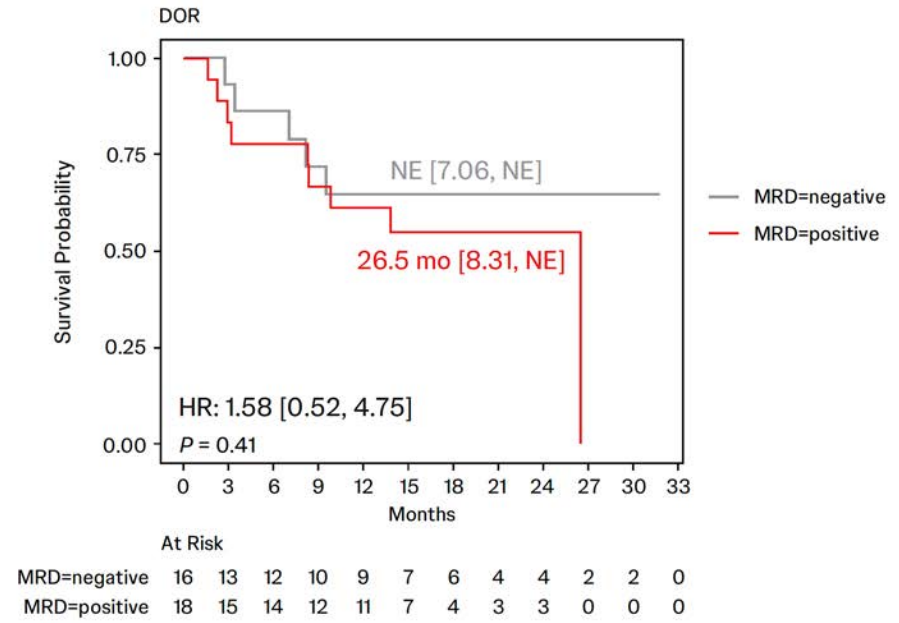
Translational Results With TAR-200 Monotherapy (SR1 – Cohort 2)

PD-L1 and TMB status and association with response



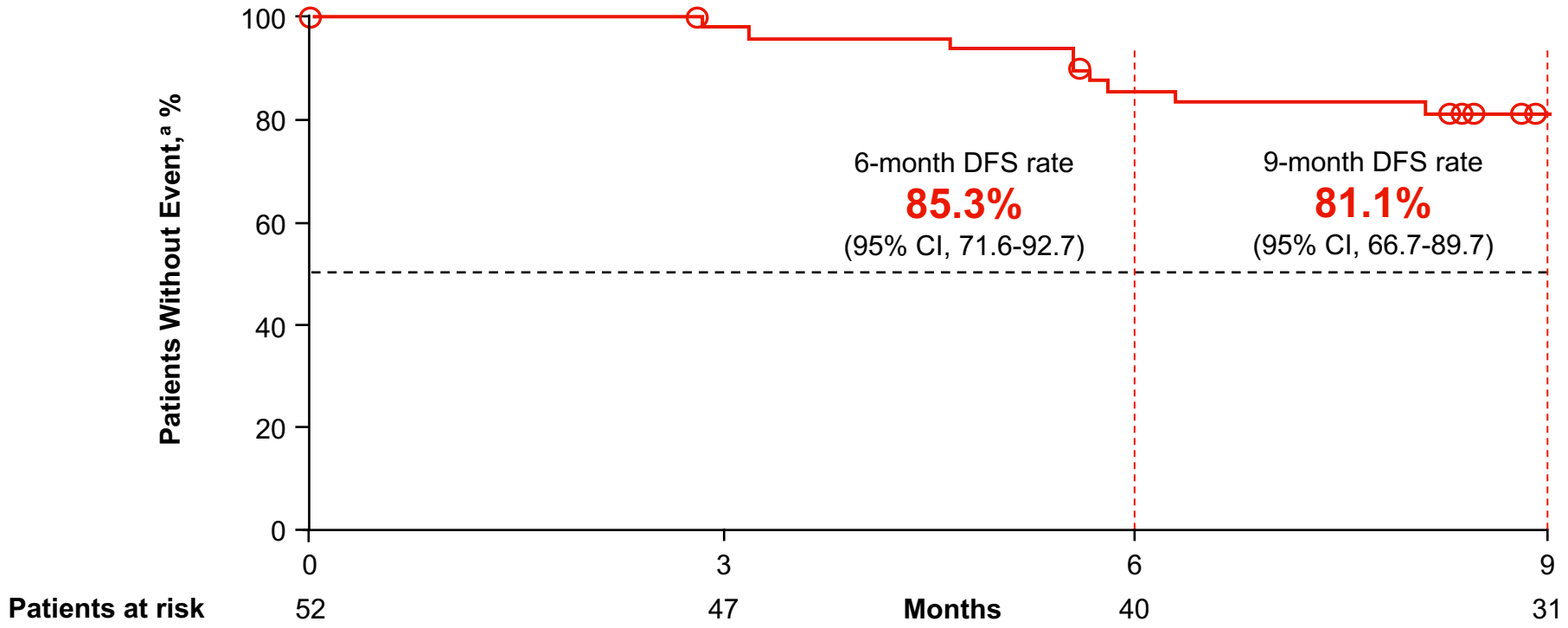
Association of MRD status with response

	CR rate [95% CI]	*P* value	1 yr DOR rate (%) [95% CI]	*P* value
MRD-positive	78.2% [56.3%, 92.5%]	0.820	64.6% [34.7%, 83.5%]	0.41
MRD-negative	88.9% [65.3%, 98.6%]		61.1% [35.3%, 79.2%]	



Guerrero-Ramos F, et al. Presented at European Society for Medical Oncology (ESMO) Congress 2025; Berlin, Germany; October 17–21, 2025

Cohort 4 interim results: 6- and 9-Month DFS Rates With TAR-200 Monotherapy in Papillary Disease–Only HR NMIBC



- Median follow-up was 12.8 months
- **Median DFS was not reached** (95% CI, 12.1-NE)
- Overall, only **5.8%** (3 of 52) of patients had **RC**

NE, not estimable.
[a]**An event is defined as recurrence, progression, or death.**

Presented by F Guerrero-Ramos at the 120th AUA Annual Meeting; April 26-29, 2025; Las Vegas, NV, USA

SunRISe-3 (NCT05714202) Is a Phase 3, Open-Label, Multicenter Randomized Study

Key eligibility criteria

- Patients with histologically confirmed HR NMIBC (high grade Ta, any T1, or CIS)
- BCG naive (no prior BCG or last exposure >3 years prior to randomization)

Additional criteria:

- Aged ≥18 years
- ECOG PS of 0, 1, or2
- All visible papillary disease must be fully resected (absent) prior to randomization and documented at baseline cystoscopy
- Local urine cytology at screening must be negative or atypical for high-grade urothelial carcinoma in patients with papillary-only disease
- All adverse events associated with any prior surgery and/or intravesical therapy must have resolved to CTCAE v5.0 grade <2 prior to date of randomization

1:1:1 (N≈1050)

R

Group A (n≈350)
TAR-200 + cetrelimab[a]

Group C (n≈350)
TAR-200

Group B (n≈350)
BCG

Primary end point

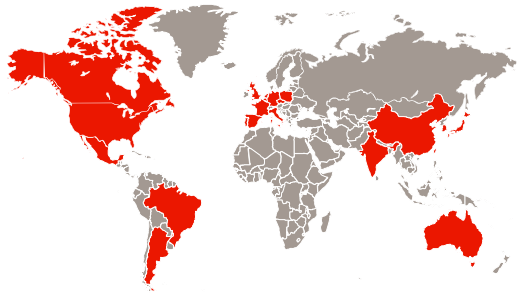
Event-free survival

Time from randomization to first occurrence of:

- High-risk disease recurrence
- Disease progression[b]
- Any-cause death
- For patients with CIS, persistent disease at 6 months is also an EFS event

Secondary end points

- Overall CR rate (CIS only)[c]/duration of CR[d]
- Recurrence-free survival
- Time to progression
- Overall survival
- Cancer-specific survival
- Safety and tolerability
- Patient-reported outcomes



CR, complete response, CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival.
[a]Cetrelimab is an anti–programmed death-1 antibody. [b]Progression is defined as stage increase from Ta to T1 or from CIS to T1 or progression to MIBC (T≥2) or to lymph node (N+) or distant (M+) disease (whichever occurs first).
[c]Proportion of patients with CIS who have no presence of high-risk disease at 6 months. [d]Time from first CR achieved to first evidence of recurrence, progression, or any-cause death, whichever occurs first.

Presented by SS Chang at the 119th AUA Annual Meeting; May 3-6, 2024; San Antonio, TX, USA

SunRISe-5 (NCT06211764) Is an Open-Label, Multicenter Phase 3 Study

Key eligibility criteria

- Histologically confirmed, papillary-only HR NMIBC (high grade Ta or any T1),[1,2] recurrent within the first year of last dose of BCG
- No CIS at time of papillary recurrence
- RC refusing or ineligible
- ECOG PS <3

Stratification factors

- T-stage
- Prior BCG

1:1
(N≈250)

R

Group A (n≈125)
TAR-200 monotherapy
Q3W during an induction phase
Q12W during a maintenance phase

Crossover
Patients in Group B may receive TAR-200 after positive study result at any planned analyses

Group B (n≈125)
Intravesical gemcitabine
OR
Intravesical mitomycin
Weekly during an induction phase
Monthly during a maintenance phase

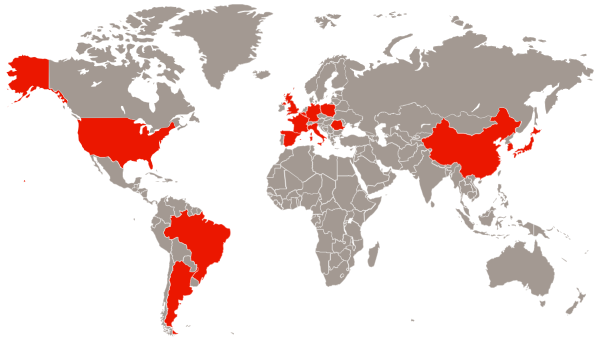
Primary end point

Disease-free survival

Secondary end points

- Recurrence-free survival
- Time to next intervention
- Time to progression
- Time to disease worsening
- Overall survival
- Safety and tolerability
- PROs/HRQoL

- Disease-free survival is defined as time from randomization to first recurrence of HR NMIBC (high grade Ta, any T1 or CIS), progression, or any cause death, whichever occurs first

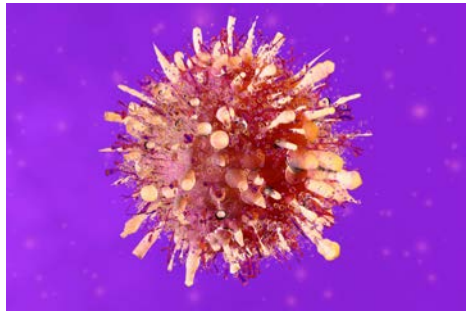


The study will evaluate whether TAR-200 will prolong disease-free survival when compared with intravesical chemotherapy in patients with papillary-only HR NMIBC recurrent after BCG therapy who refuse or are unfit for RC

ECOG PS, Eastern Cooperative Oncology Group performance status; PRO, patient-reported outcome; HRQoL, health-related quality of life; Q3W, every 3 weeks; Q12W, every 12 weeks.

1. NCCN Clinical Practice Guidelines in Oncology. Bladder Cancer. Version 1. 2024. 2. EAU Guidelines. Edn. presented at the EAU Annual Congress Milan 2023. ISBN 978-94-92671-19-6.

Presented by S Porten at the 119th AUA Annual Meeting; May 3-6, 2024; San Antonio, TX, USA



Cretostimogene Grenadenorepvec – BOND-003 Trial

FDA Breakthrough Therapy Designation

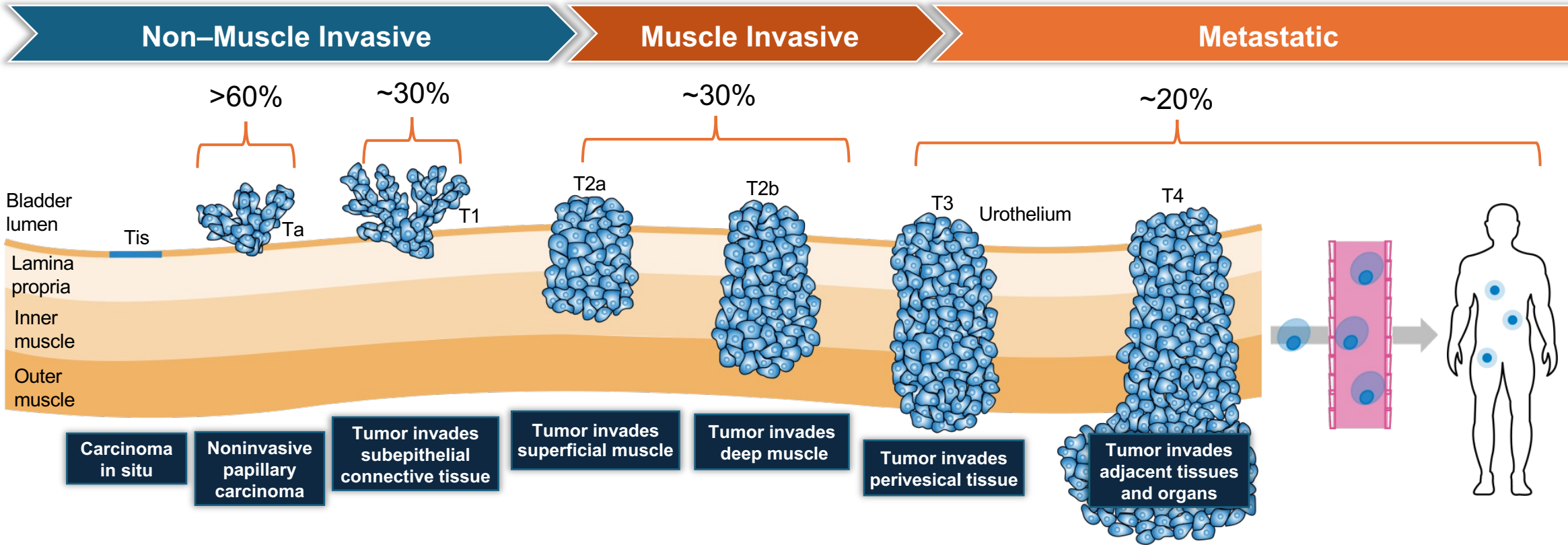
US-based clinical trial

76% CR at Any Time; 74.4% of Responders Maintained Response ≥ 6 Months

Response Evaluation	Cretostimogene Monotherapy	
	%, (n/N)	Confidence Interval (CI)
Complete Response		
Complete Response, Any Time	75.7% (50/66)	95% CI: 63% - 85%
Complete Response, 3 Months	68.2% (45/66)	95% CI: 55% - 79%
Complete Response, 6 Months	63.6% (42/66)	95% CI: 51% - 75%
Duration of Complete Response		
Duration of Response ≥ 3 Months	84.0% (42/50)	95% CI: 70% - 92%
Duration of Response ≥ 6 Months	74.4% (32/43)[1]	95% CI: 58% - 86%

Tyson MD, et al. AUA 2024

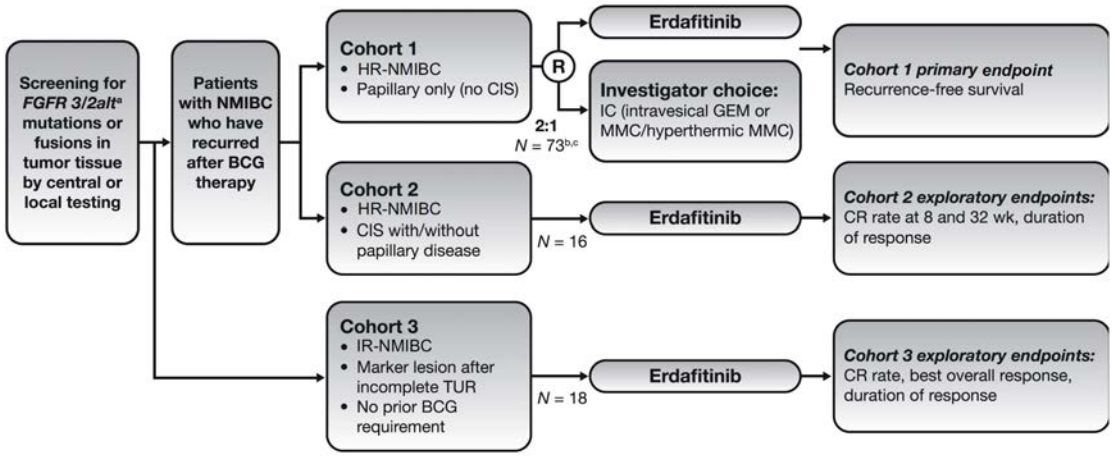
FGFR Mutations Are Frequently Observed in Bladder Cancer[1]



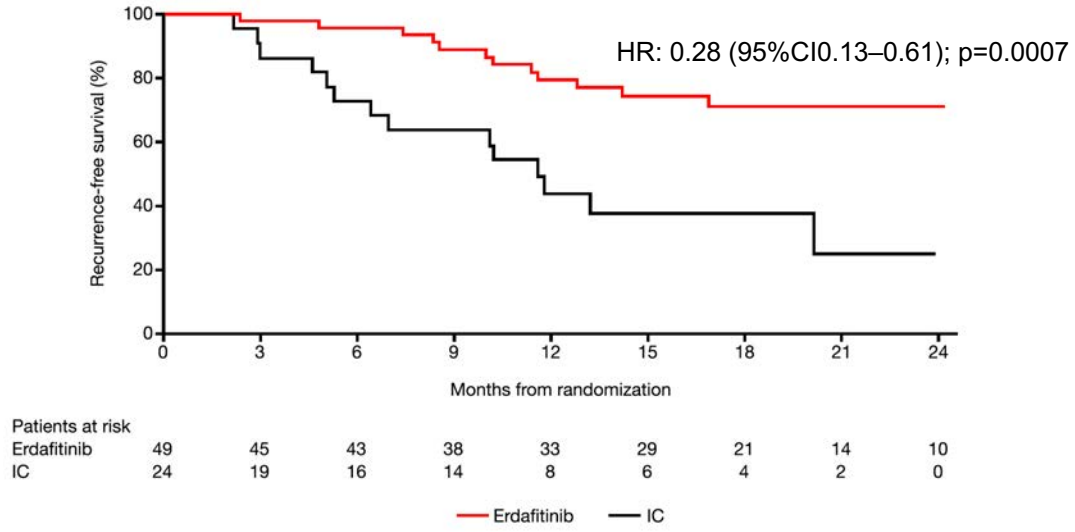
FGFR inhibitors can be effective across the disease spectrum

1. Knowles MA et al. *Nat Rev Cancer*. 2015;15:25-41.

THOR-2: Oral Erdafitinib Final Results

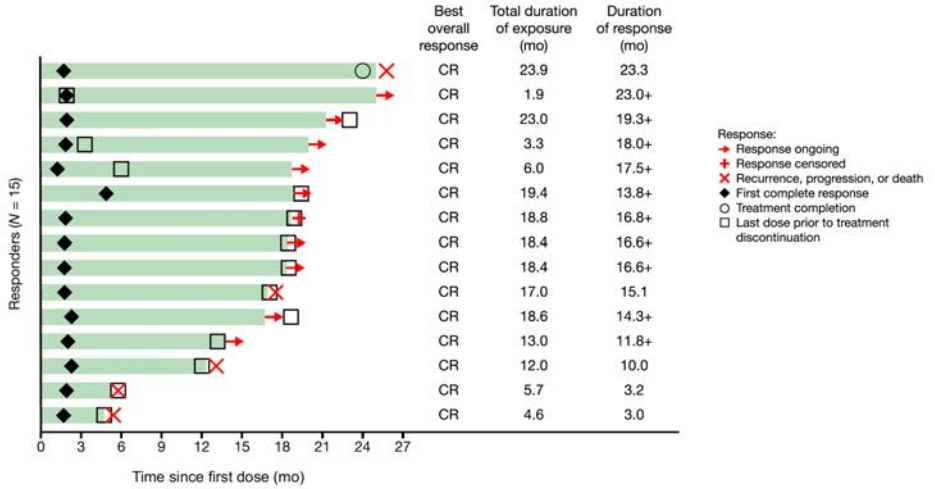


Cohort 1



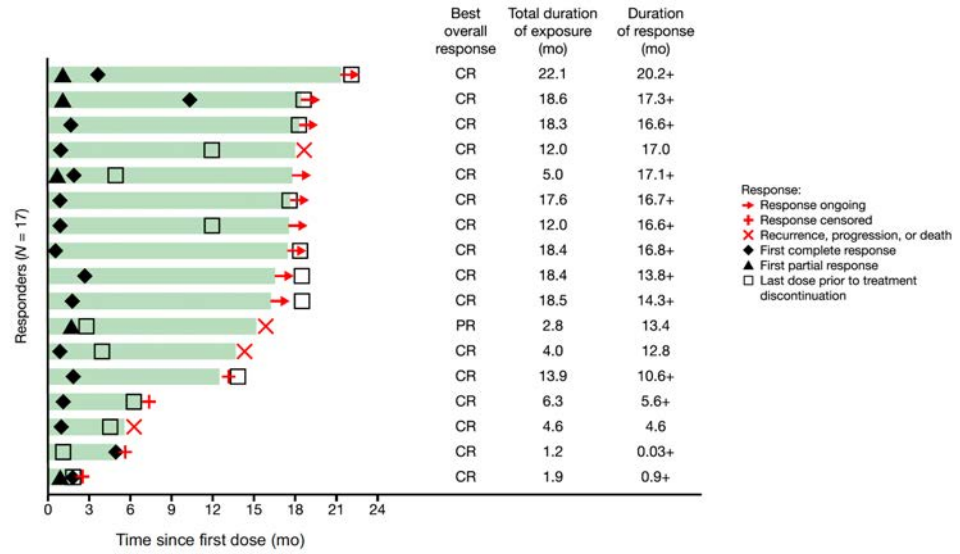
Cohort 2:

- CR (8w): 94%; (32w): 81%
- median DoR: 23.3mo



Cohort 3:

- CR (3m): 89%
- median DoR was NR

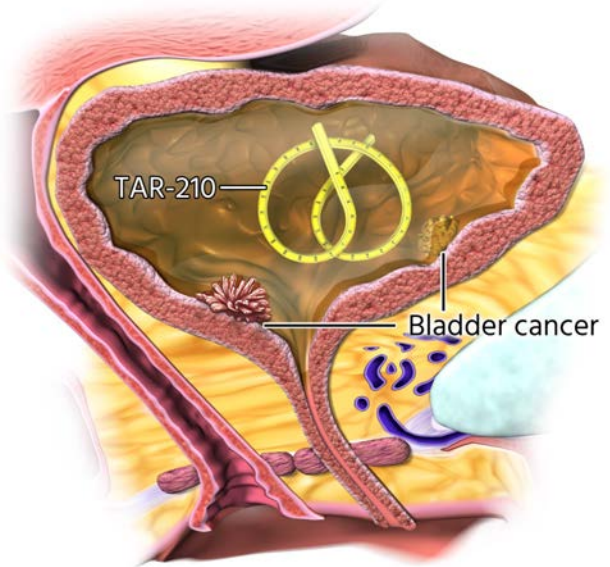


Daneshmand S et al. *Eur Urol*. 2026 Feb;89(2):165-173.

TAR-210 is a Novel Intravesical Targeted Releasing System Designed to Deliver Erdafitinib for Patients With Bladder Cancer

- Despite available treatment options for patients with IR NMIBC, recurrence rates remain high, underscoring the need for effective therapies[1]
- *FGFR* alterations are prevalent in ~50% to 80% of low-grade NMIBC and may function as oncogenic drivers[2-4]
- **Erdafitinib** is a selective pan-FGFR tyrosine kinase inhibitor[5]
  - Oral erdafitinib is approved in the United States to treat adults with locally advanced or mUC with susceptible *FGFR3* alterations following progression on or after at least 1 prior systemic treatment, with additional approvals across geographies[6-9]
- Oral erdafitinib demonstrated clinical efficacy in HR and IR NMIBC populations, but was limited by challenging systemic toxicities[10-12]
  - In an interim analysis of THOR-2 Cohort 3, 15/18 patients with *FGFR*-altered IR NMIBC had CR (83%) with median DOR of 12.8 months[13]

TAR-210 is a novel targeted releasing system designed for sustained local delivery of erdafitinib over 3 months in the bladder



TAR-210 is placed using a urinary placement catheter in a 2-3 minute in-office procedure.

In a first-in-human study, TAR-210 was well tolerated with promising clinical activity in *FGFR*-altered **HR NMIBC (RFS rate: 82%)** and **IR NMIBC (CR rate: 87%)**.[14]

CR, complete response; FGFR, fibroblast growth factor receptor; HR, high risk; IR, intermediate risk; mUC, metastatic urothelial carcinoma; NMIBC, non–muscle-invasive bladder cancer; RFS, recurrence free survival.

1. Ritch CR, et al. *J Urol.* 2020;203:505-511. 2. Hernández S, et al. *J Clin Oncol.* 2008;24:3664-3671. 3. Knowles MA, Hurst CD. *Nat Rev Cancer*. 2014;15:25-41. 4. Khalid S, et al. *Eur Urol Open Sci.* 2020;21:61-68. 5. Perera TPS, et al. *Mol Cancer Ther*. 2017;16:1010-1020. 6. Erdafitinib [package insert]. Horsham, PA: Janssen Products, LP; 2024. 7. Loriot Y, et al. *N Engl J Med.* 2019;381:338-348. 8. Siefker-Radtke AO, et al. *Lancet Oncol.* 2022;23:248-258. 9. Loriot Y, et al. *N Engl J Med*. 2023;21:1961-1971. 10. Daneshmand S, et al. *J Clin Oncol.* 2023;41(Suppl 6):504. 11. Catto JWF, et al. *J Clin Oncol.* 2023;41(Suppl 6):503. 12. Catto JWF, et al. *Ann Oncol.* 2024;35:98-106. 13. Daneshmand S, et al. *Urol Oncol: Sem Orig Investig*. 2024;42:S58. 14. Vilaseca A, et al. *Ann Oncol*. 2023;34:S1343.

Presented by R Li at the 119th AUA Annual Meeting; May 3-6, 2024; San Antonio, TX, USA

TAR-210 First-in-Human Phase 1: Cohorts 1 and 3

Study Design

NCT05316155

Molecular Eligibility

FGFR alterations:

- Flexible molecular eligibility strategy used
  - Local or central fresh/ archival **tissue-based** testing by NGS or PCR

—*or*—

  - Central **urine cell-free DNA** NGS testing

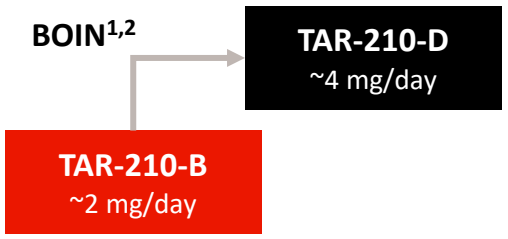
HR NMIBC (Cohort 1)

- Recurrent, high-grade Ta/T1, papillary only, no CIS
- BCG-experienced[a] and not undergoing radical cystectomy
- TURBT with complete resection of all visible disease prior to treatment

IR NMIBC (Cohort 3)

- Recurrent, history of low-grade only Ta/T1 disease
- **Visible target lesions** prior to treatment (chemoablation design)

Part 1: Dose Escalation



- Placement every 3 months

Part 2: Dose Expansion

- Expansion of both dose levels

Response assessed every 3 months with continued treatment for up to 1 year if recurrence free (Cohort 1) or complete response (Cohort 3).

Clinical cutoff date: **March 22, 2024**.

BCG, bacillus Calmette-Guérin; BOIN, Bayesian optimization interval; CIS, carcinoma in situ; HR, high risk; IR, intermediate risk; NGS, next-generation sequencing; PCR, polymerase chain reaction; PK, pharmacokinetics; TURBT, transurethral resection of bladder tumor.

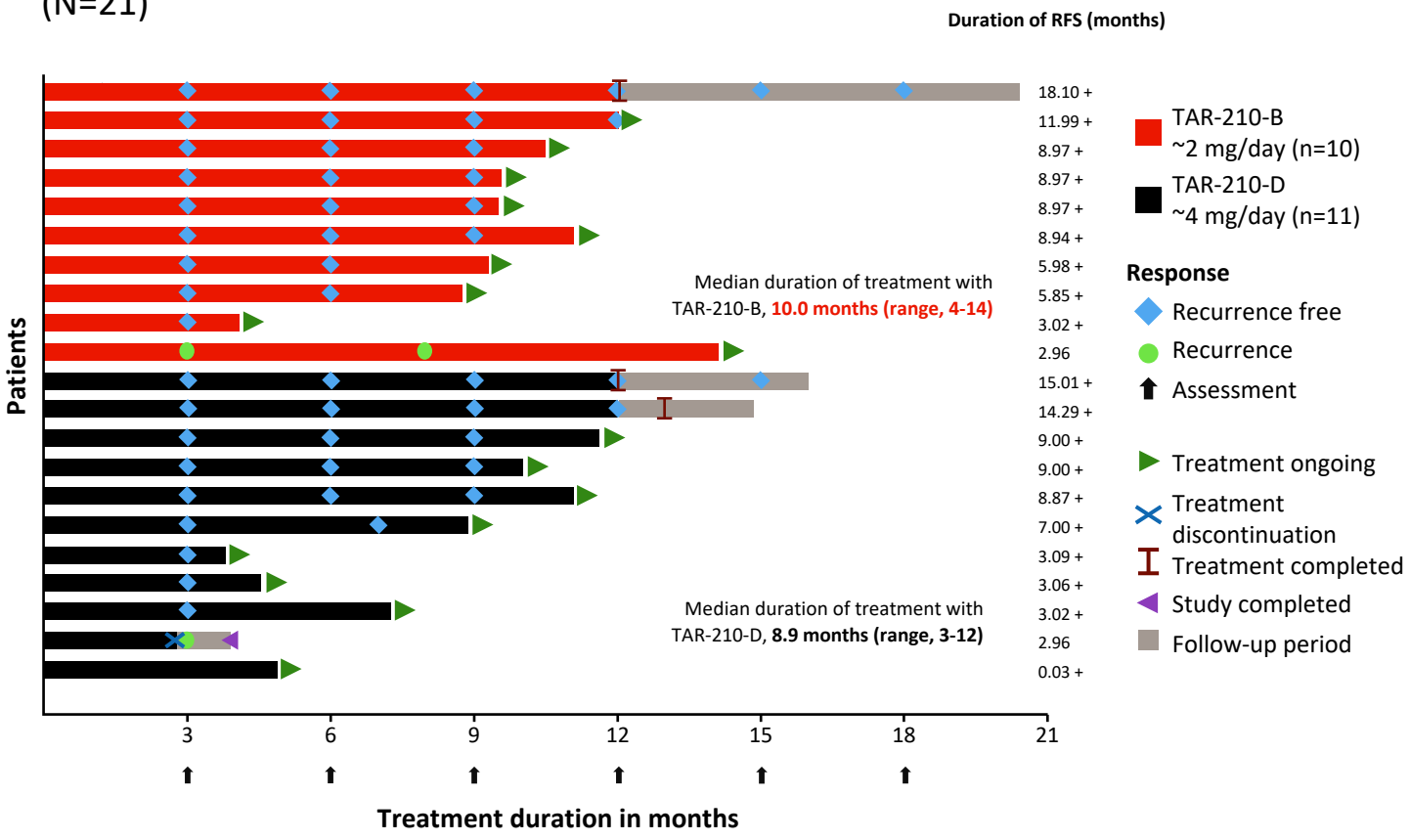
[a]BCG experienced is defined as 5 of 6 induction doses with or without maintenance or intolerant of BCG.

1. Liu S, Yuan Y. *J R Stat Soc Ser C Appl Stat.* 2015;64:507-523. 2. Yuan Y, et al. *Clin Cancer Res.* 2016;22:4291-4301.

Presented by A Vilaseca at the 119th AUA Annual Meeting; May 3-6, 2024; San Antonio, TX, USA

TAR-210 HR NMIBC (Cohort 1): Results

HR NMIBC With *FGFR* Alterations (Cohort 1)
(N=21)



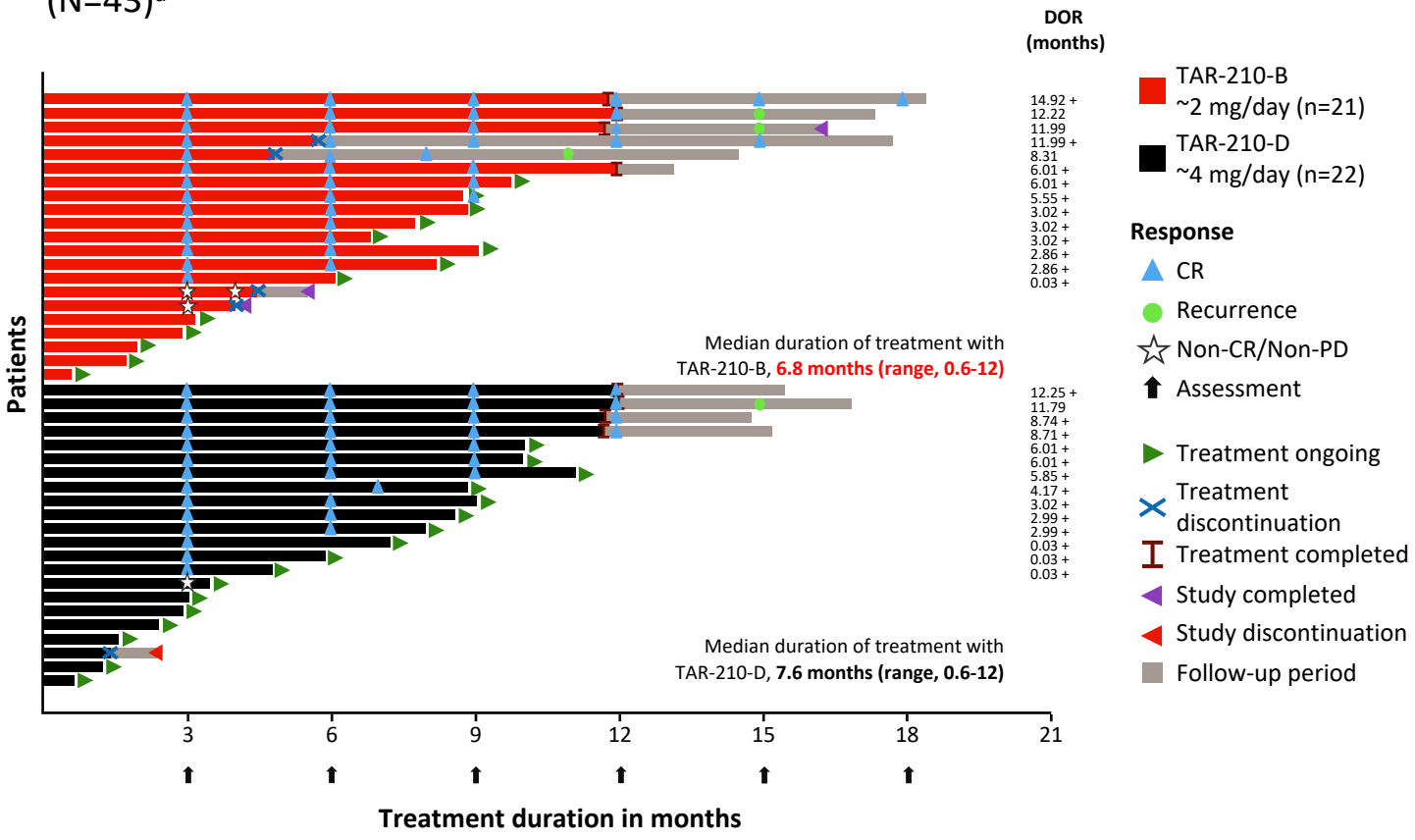
- **90% estimated 12-month RFS rate[a]** (n=21)
  - Median RFS was not estimable
  - 2 of 21 patients have recurred
  - Median duration of follow-up 8.9 months
- No difference observed in RFS between the TAR-210 dose levels

+ Indicates patient was censored; CI, confidence interval; CR, complete response; NE, non-estimable; RFS, recurrence-free survival.
[a]All treated patients were efficacy evaluable. RFS was estimated using the Kaplan-Meier method.

Presented by A Vilaseca at the 119th AUA Annual Meeting; May 3-6, 2024; San Antonio, TX, USA

TAR-210 IR NMIBC (Cohort 3): Results

IR NMIBC With *FGFR* Alterations (Cohort 3)
(N=43)[a]



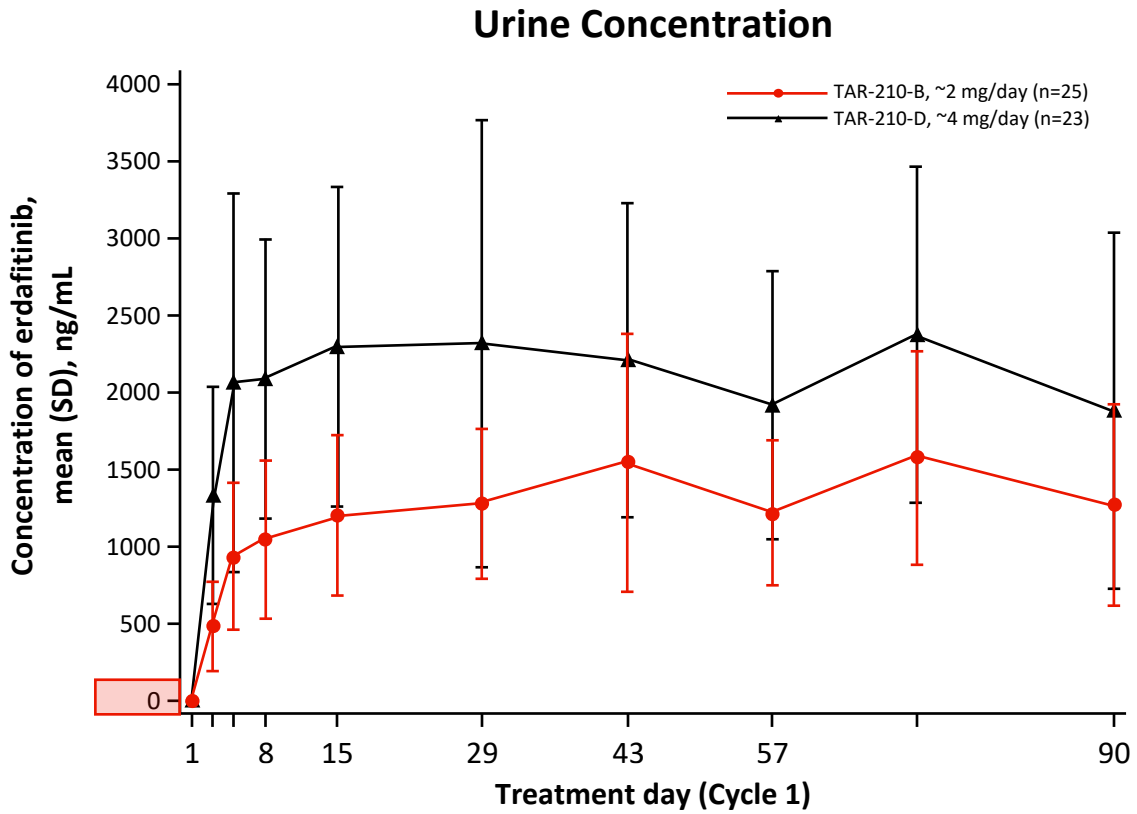
- Overall, 31 patients were evaluable for response[b]
- **90% CR rate,** with 28/31 patients achieving a CR at Week 12
- Overall, **100% of patients achieved a clinical response**; 3 patients had a non-CR/non-PD response
- Consistent CR rate across both doses
- 86% (24/28) of CRs are ongoing at time of clinical cutoff

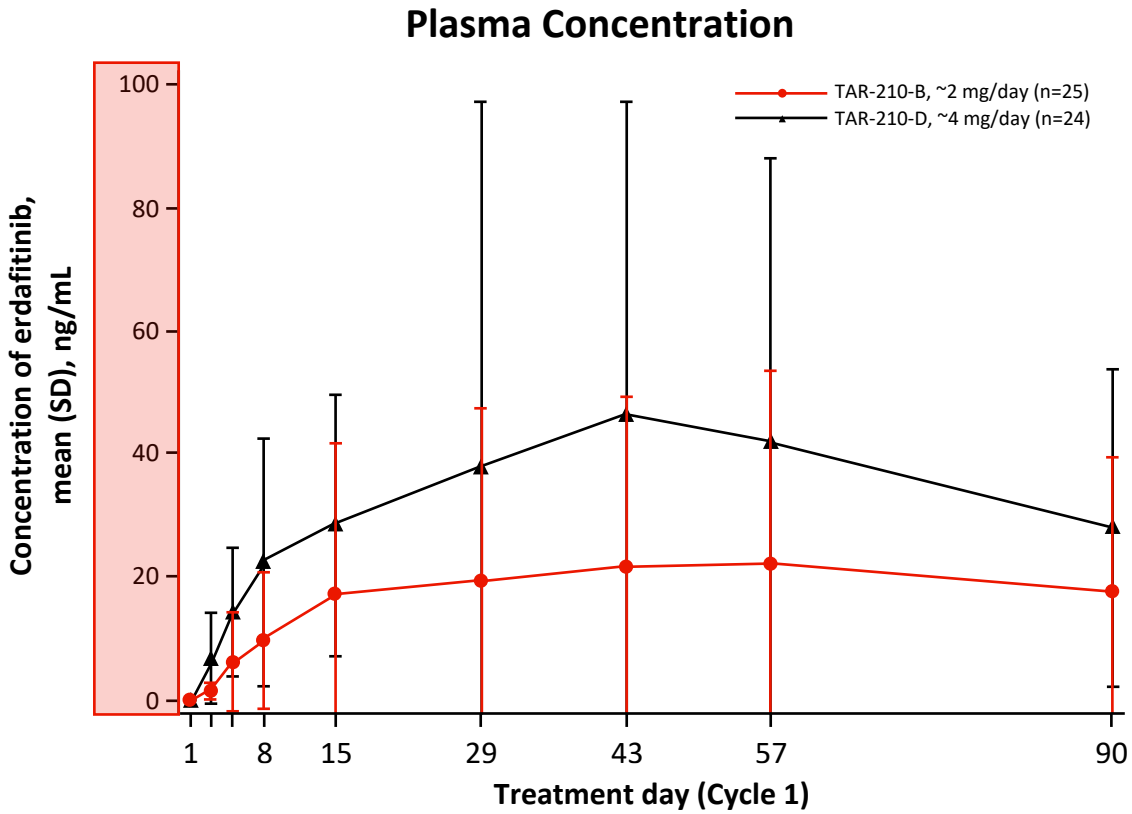
Durable response rate at specific landmarks[c]	% (95% CI)
6 months	100 (100-100)
9 months	89 (43-98)

+ Indicates patient was censored; DOR, duration of response; PD, progressive disease.
[a]43 patients were treated; 31 patients were efficacy evaluable for CR and DOR. [b]Efficacy evaluable patients were those having at least one disease evaluation or discontinuing treatment prior to their first disease evaluation for either PD or recurrence. [c]DOR was estimated using the Kaplan-Meier method.

Presented by A Vilaseca at the 119th AUA Annual Meeting; May 3-6, 2024; San Antonio, TX, USA

TAR-210 Provided Sustained Erdafitinib Concentrations in Urine With Very Low Plasma Concentrations





- No hyperphosphatemia was reported, consistent with the very low plasma concentrations observed with TAR-210
- Mean plasma erdafitinib concentrations were >50 × lower than mean urine concentrations

Presented by A Vilaseca at the 119th AUA Annual Meeting; May 3-6, 2024; San Antonio, TX, USA

Safety and Tolerability of TAR-210 in HR NMIBC (Cohort 1) and IR NMIBC (Cohort 3)

- The majority of AEs were grade 1/2 lower urinary tract AEs
- Few patients discontinued due to AEs
  - 2 patients (3%) discontinued due to TRAEs of low-grade urinary symptoms
- 2 patients had serious TRAEs with pyelonephritis and sepsis or UTI and sepsis, respectively
  - Both events resolved with antibiotics and patients were able to continue TAR-210
- No dose-limiting toxicities were identified

Patients with events, n (%)	HR NMIBC (Cohort 1)		IR NMIBC (Cohort 3)		All patients (N=64)
	TAR-210-B ~2 mg/day (n=10)	TAR-210-D ~4 mg/day (n=11)	TAR-210-B ~2 mg/day (n=21)	TAR-210-D ~4 mg/day (n=22)	
≥1 AE	10 (100)	9 (82)	20 (95)	15 (68)	54 (84)
≥1 TRAE[a]	9 (90)	5 (55)	9 (43)	6 (27)	30 (47)
Hematuria	5 (50)	2 (18)	7 (33)	4 (18)	18 (28)
Dysuria	4 (40)	2 (18)	4 (19)	2 (9)	12 (19)
Micturition urgency	2 (20)	1 (9)	5 (24)	0	8 (13)
UTI	0	1 (9)	3 (14)	1 (5)	5 (8)
Urethral pain	1 (10)	1 (9)	1 (5)	0	3 (5)
Cystitis noninfective	0	0	1 (5)	1 (5)	2 (3)
≥1 TRAE of grade ≥2	3 (30)	3 (27)	6 (29)	2 (9)	14 (22)

AE, adverse event; TRAE, treatment-related adverse event; UTI, urinary tract infection.
[a]Listed are AEs related to TAR-210 by preferred term that were reported in >1 patient in either cohort.

Presented by A Vilaseca at the 119th AUA Annual Meeting; May 3-6, 2024; San Antonio, TX, USA

MoonRISe-1: An Open-Label, Multicenter, Randomized Phase 3 Study to Evaluate Efficacy and Safety of TAR-210 vs Intravesical Chemotherapy in Patients With *FGFR*-Altered, Low-Grade IR NMIBC

Key eligibility criteria

- Adults (aged ≥18 years)
- Histologically confirmed **IR NMIBC** (diagnosed ≤90 days prior to randomization):
  - Ta LG/grade 1
    - Primary
    - Recurrent

    —*or*—
  - Ta LG/grade 2
    - Primary
    - Recurrent
- With **≥1 risk factor**[a]
- Susceptible *FGFR2/3* alterations by central or local tissue or urine testing

Stratification factors

- Anticipated choice of intravesical chemotherapy
- Newly diagnosed vs recurrent disease
- Cystoscopic assessment method (white light vs enhanced assessment method)

1:1 (N≈540)

R

TAR-210
(n≈270)
Q12W for 1 year

Investigator's choice of intravesical chemotherapy
(n≈270)
MMC or gemcitabine
QW for 4 to 6 doses (induction)
and maintenance for 6 months to 1 year

Primary end point

- Disease-free survival[b]

Secondary end points

- Time to next-line treatment
- High-grade recurrence-free survival
- Progression-free survival
- Rate of diagnostic and therapeutic urological interventions
- Safety and tolerability

NCT06319820

- All visible papillary disease must be fully resected prior to randomization
- Assessments of recurrence or progression include urine cytology, cystoscopy, for-cause TURBT or biopsy of bladder lesions, ultrasound, and urography
- The follow-up phase for patients meeting the primary end point is up to ≈5 years

[a]Risk factors include multiple Ta LG tumors, tumors ≥3 cm, early (<1 year) recurrence, frequent (>1 per year) recurrences, or recurrence after prior adjuvant intravesical chemotherapy. [b]Disease-free survival defined as time from randomization to first documented recurrence of any-grade NMIBC, disease progression, or death from any cause, whichever occurs first.
LG, low grade; MMC, mitomycin C; NMIBC, non–muscle-invasive bladder cancer; Q12W, every 12 weeks; QW, every week; R, randomized; TURBT, transurethral resection of bladder tumor.

Presented by R Li at the 120th AUA Annual Meeting; April 26-29, 2025; Las Vegas, NV, USA

MoonRISe-3: Phase 3 Study of TAR-210 vs Intravesical Chemotherapy in Patients With BCG-treated, *FGFR*-altered Papillary-only HR NMIBC

Key eligibility criteria

- Adults (aged ≥18 years)
- Histologically confirmed **papillary-only HR NMIBC**:
  - High-grade Ta
    —*or*—
    Any T1 (no CIS)
  - Recurrent after BCG
    —*or*—
    Intolerant of BCG
- ECOG performance status of ≤2
- Susceptible *FGFR* mutation or fusion by urine or tumor tissue testing

Stratification factors

- T stage (high-grade Ta or any T1)
- Prior BCG treatment (BCG unresponsive, experienced, or intolerant)
- Choice of intravesical chemotherapy

1:1
(N≈220)

R

TAR-210
(n≈110)
Q12W for 2 years

Investigator's choice of single-agent intravesical chemotherapy
(n≈110)
MMC or gemcitabine
QW for 6 doses (induction) followed by Q4W for 1-2 years (maintenance)

Primary end point

- Disease-free survival[a]

Key secondary end points

- Recurrence-free survival
- Time to next intervention
- Time to disease worsening
- Time to progression
- Overall survival
- Safety and tolerability

NCT06919965

- Assessments of recurrence or progression will be based on central urine cytology, bladder biopsy, and imaging results
- After a positive interim analysis, the IDMC may recommend a crossover option for patients with recurrence in the intravesical chemotherapy arm

[a]Disease-free survival defined as time from randomization to first documented recurrence of HR NMIBC (high-grade Ta, any T1, or CIS), disease progression, or death from any cause, whichever occurs first.
IDMC, independent data monitoring committee; MMC, mitomycin C; NMIBC, non–muscle-invasive bladder cancer; Q12W, every 12 weeks; Q4W, every 4 weeks; QW, every week; R, randomized.

Presented by N Shore at the 120th AUA Annual Meeting; April 26-29, 2025; Las Vegas, NV, USA

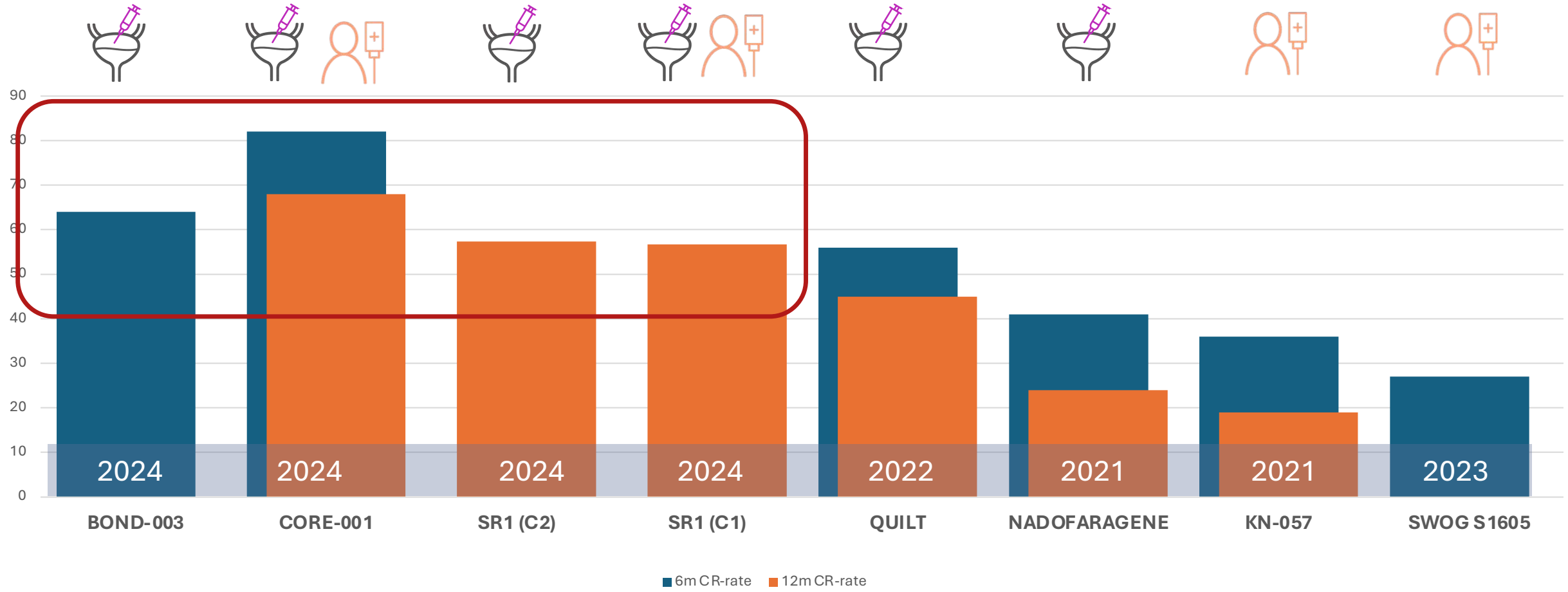
Summary of the Key Efficacy and Safety Outcomes of Novel Therapies for the Treatment of HR NMIBC

Trial	BOND-003[1]	CORE-001[2]	Sunrise-1[3]	Sunrise-1[3]	QUILT 3.032[4]	NCT02773849[5]	Keynote-057[6,7]	SWOG S1605[8]
Intervention	Cretostimogene	Cretostimogene + pembrolizumab	TAR-200	TAR-200 Cetrelimab	N-803+BCG	Nadofaragene	Pembrolizumab	Atezolizumab
Mechanism	Oncolytic immunotherapy	Oncolytic immunotherapy + ICI	Chemotherapy	Chemotherapy + ICI	IL-15 superagonist + BCG	Gene therapy secreting IFN	ICI	ICI
Delivery	Intravesical	Intravesical + intravenous	Intravesical	Intravesical + intravenous	Intravesical	Intravesical	Intravenous	Intravenous
Stage	Phase 3 **FDA BTD***	Phase 2	Phase 2 **FDA BTD**	Phase 2	**FDA approved** April 22, 2024	**FDA approved**	**FDA approved** (CIS)	Phase 2
N	116	35	85	53	77	98	96 (A)	129
6m CR-rate	**64%**	**82%**	**N/A**	**N/A**	**56%**	**41%**	**36%**	**27%**
12m CR-rate	**N/A**	**68%**	**57.4%**	**56.7%**	**45%**	**24%**	**19% (A)**	**N/A**
Safety	0% G3-4 TRAE	14.3% G3 TRAE	9.4% G3-4 TRAE	35.8% G3-4 TRAE	16% SAE	4% G3-4 TRAE	A: 11% G3 TRAE; 2% G4 TRAE	16% G3-5 TRAE

*BTD: breakthrough therapy designation; ICI: immune-checkpoint inhibitor

1. Tyson MD et al. AUA 2024. Abstract P2-02. 2. Li R et al. *Nat Med.* 2024 Aug;30(8):2216-2223. 3. Presented by MS van der Heijden at the European Society of Medical Oncology Congress 2024; September 13-17, 2024; Barcelona, Spain. 4. Chamie K. *NEJM Evidence*. 2022;2. 5. Boorjian SA et al. *Lancet Oncol*. 2021;22:107-117. 6. Balar AV et al. *Lancet Oncol*. 2021 Jul;22:919-930. 7. Necchi A et al. *Lancet Oncol*. 2024;S1470-2045:00178-5. 8. Black PC et al. *Eur Urol*. 2023;84:536-544.

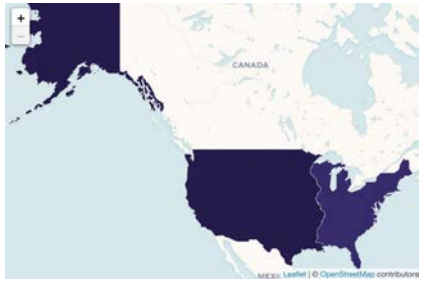
BCG-unresponsive CIS: do we measure the IO effect?

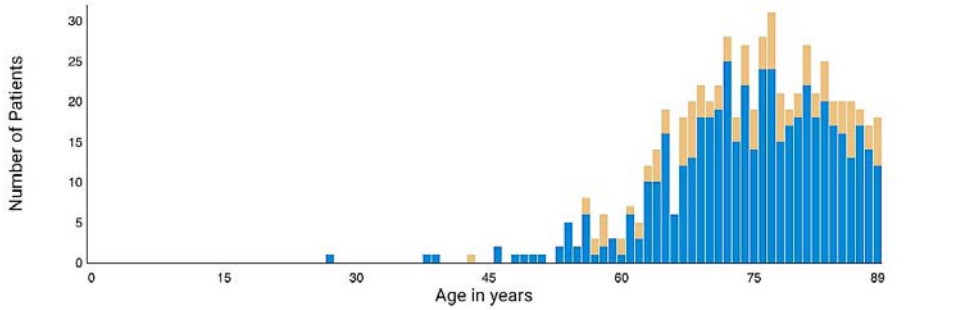


- Thus far the results favor the intravesical monotherapy strategy
- Uncertainties related to the contribution of systemic ICI towards monotherapies

1. Tyson MD et al. AUA 2024. Abstract P2-02. 2. Li R et al. *Nat Med.* 2024 Aug;30(8):2216-2223. 3. Presented by MS van der Heijden at the European Society of Medical Oncology Congress 2024; September 13-17, 2024; Barcelona, Spain. 4. Chamie K. *NEJM Evidence*. 2022;2. 5. Boorjian SA et al. *Lancet Oncol*. 2021;22:107-117. 6. Balar AV et al. *Lancet Oncol*. 2021 Jul;22:919-930. 7. Necchi A et al. *Lancet Oncol*. 2024;S1470-2045:00178-5. 8. Black PC et al. *Eur Urol*. 2023;84:536-544.

Real world U.S. data of therapeutic pathways for BCG-unresponsive HR-NMIBC





Patients 90 and Older: 60

Total Patients	Minimum Age	Maximum Age	Mean Age	Standard Deviation
708	27	90	76	10

Sex

Male	74.86%
Female	18.93%
Unknown	6.21%

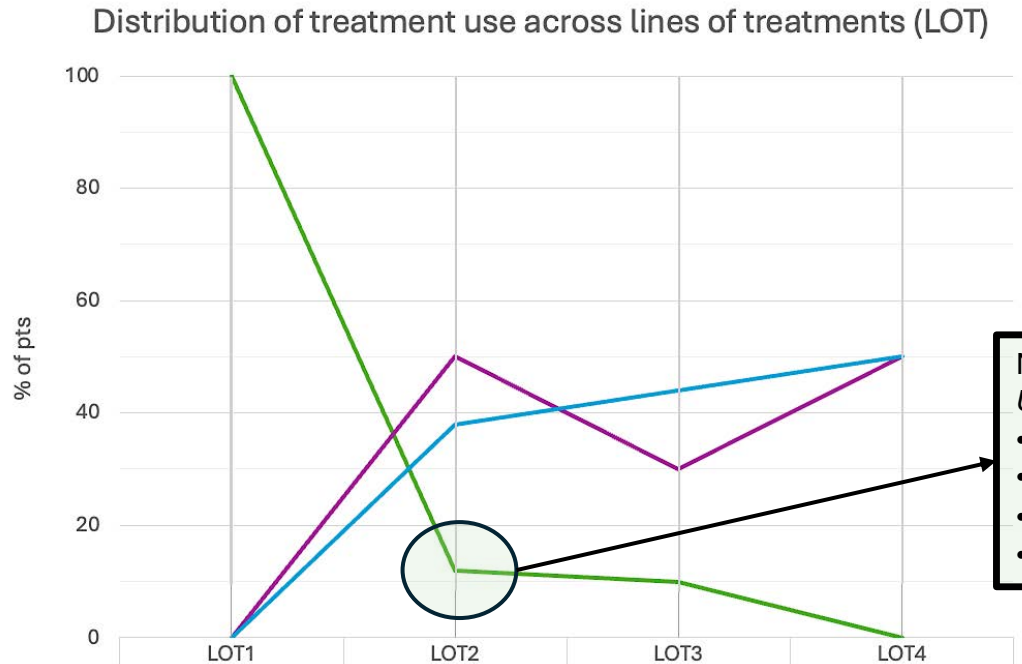
Ethnicity

Not Hispanic ...	84.88%
Unknown Eth...	11.02%
Hispanic or L...	4.10%

Race

White	82.48%
Unknown Race	9.03%
Black or Afric...	5.79%
Asian	1.55%
Other Race	1.41%
American Indi...	0.00%
Native Hawaii...	0.00%

Generated by TriNetX



Myers AA, et al. *Eur Urol.* 2024:

- **N=36**
- **75% CR rate**
- **12m-DFS: 69%**
- **24m RC-free: 74%**

Generated by TriNetX

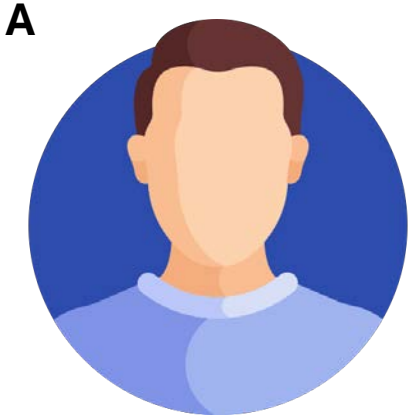
N=708 pts

Source: TrinetX (TirnetX.com); courtesy: Dr. Brigida Maiorano

Contributing sites from USA (see worldmap)

Geographical disparities in radical cystectomy destiny

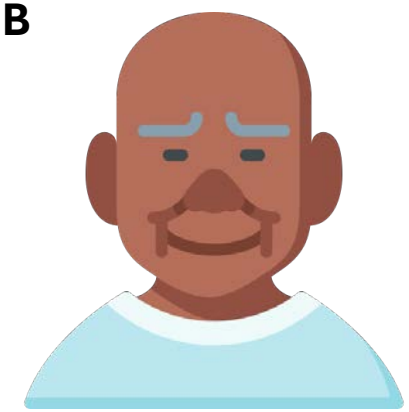
Patient A



N-803+BCG | Pembrolizumab | TAR200 | Nadofaragene | Cretostimogene

BCG rechallenge | (Gem/Doce) | chemoRT

Patient B



BCG rechallenge | (Gem/Doce)

chemoRT

Sunrise-4: Primary results

Population:
- Aged ≥18 years
- Histologically confirmed cT2-T4a N0M0 MIBC (absence of nodal or metastatic disease at screening)
- Predominant UC histology
- ECOG PS of 0-1
- Ineligible for or refusing cisplatin-based chemotherapy
- Scheduled for RC

Stratification:
- Visible residual disease at TURBT: complete vs incomplete (≤3 cm)
- Tumor stage at MIBC diagnosis: cT2 vs cT3-4a

NCT04919512

R 5:3

Cohort 1 (N=101): Gemcitabine intravesical system (TAR-200) 225 mg gemcitabine Q3W (indwelling) 12 weeks + cetrelimab monotherapy 360 mg IV Q3W for 12 weeks

Cohort 2 (N=58): Cetrelimab monotherapy 360 mg IV Q3W for 12 weeks

Radical cystectomy Week 12[a]

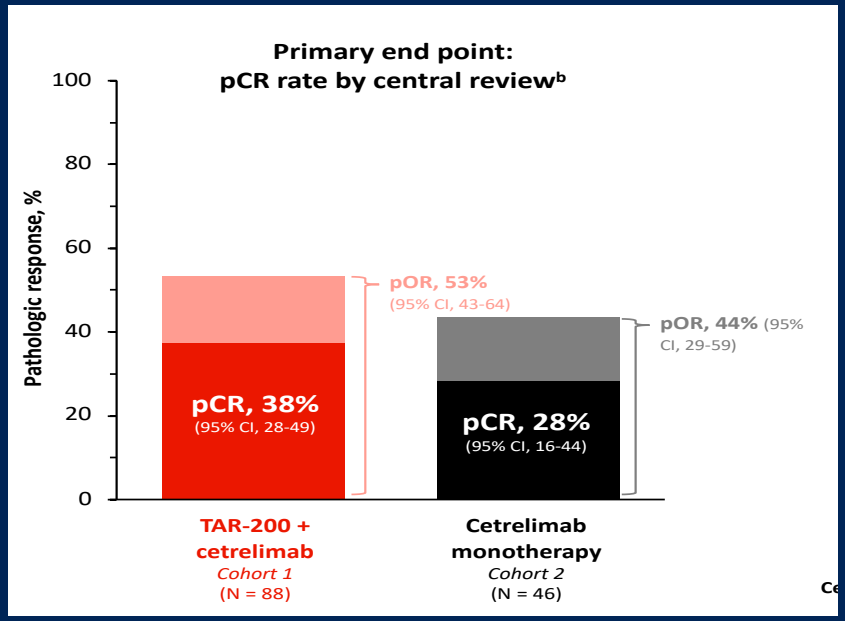
Follow-up[b] Weeks 4-108
- Every 4 weeks until Week 12 post cystectomy
- Every 12 weeks until Week 108 post cystectomy (end of study)

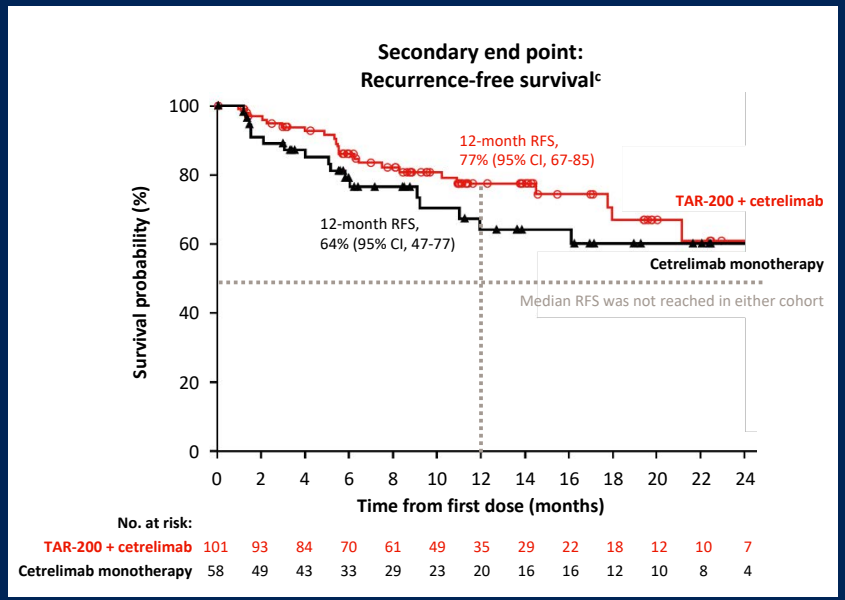
Baseline (pre-treatment) — Blood and urine samples collected for exploratory biomarker analysis — Week 12 (pre-RC)

Primary end point
- Pathologic CR rate (ypT0N0)

Secondary end points
- Recurrence-free survival
- Safety

Exploratory end points
- Pathologic OR rate (≤ypT1N0)
- Overall survival
- Time to symptomatic progression
- Quality of life according to FACT-BI
- Pharmacokinetics
- Biomarker analysis





Necchi A, et al. *J Clin Oncol*. 2025 Dec 3:JCO2502382. doi: 10.1200/JCO-25-02382. Online ahead of print.

Evolving treatment landscape for NMIBC

- BCG-naive HR-NMIBC: the future of systemic ICI is uncertain based on the results of phase 3 studies
- HR-NMIBC unresponsive to BCG: intravesical therapies (e.g., TAR-200, cretostimogene) are best positioned to become the new SOC
- Similar to MIBC trials, the contribution of systemic ICI towards the cCR rate is unknown
- Patients have raised the bar for therapeutic success: low rates of Grade 3-4 TRAE or long-lasting G1-2 TRAE may count
- In general, simplifying the therapeutic burden of these patients is an important goal for the ongoing research
- Geographical disparities in therapeutic access (as standard therapy or clinical trial therapy) are huge!

Second Opinion

Elizabeth R Plimack, MD, MS

Neil Love, MD

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

What would be your most likely treatment approach for this cisplatin-eligible 80-year-old man who develops MIBC and prefers to avoid cystectomy?

Based on the recent FDA approval of neoadjuvant EVP for patients with MIBC who are cisplatin ineligible, how are you integrating this regimen into your clinical practice?

Are you recommending EVP for all patients who are cisplatin ineligible? Have you employed it for patients who are cisplatin eligible? How do you determine the ideal patient to receive this regimen?

QUESTIONS FOR THE FACULTY

How would you assess the tolerability of neoadjuvant EVP? What are the most common side effects experienced by patients who are receiving it?

Second Opinion

Thomas Powles, MBBS, MRCP, MD

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Which treatment would you most likely recommend for this man in his late 70s with BCG-refractory CIS? Would you proceed with cystectomy? Would you offer the TAR-200 gemcitabine intravesical system?

Now that the TAR-200 gemcitabine intravesical system has received FDA approval, how are you integrating it into patient care? Which patients do you feel are ideal candidates for this approach?

Based on available data and your clinical experience, how would you compare the tolerability of the TAR-200 gemcitabine intravesical system to that of other available systemic agents?

QUESTIONS FOR THE FACULTY

If the results of the ongoing Phase III SunRISe-3 trial evaluating TAR-200 with cetrelimab or TAR-200 alone versus BCG for patients with treatment-naïve high-risk NMIBC are positive, how do you see this approach being integrated with other available options in this setting?

Would you encourage a patient with FGFR-altered NMIBC in your own practice to enroll on a clinical trial with the TAR-210 erdafitinib intravesical delivery system? Do the early findings with TAR-210 lead you to believe that biomarker-based intravesical therapy is likely to become standard practice in the near future?

Agenda

Module 1: Optimal Use of Anti-PD-1/PD-L1 Antibodies in Non-Muscle-Invasive Bladder Cancer — Dr Friedlander

Module 2: Evolving Management of Muscle-Invasive Bladder Cancer — Dr Gupta

Module 3: Current and Future Role of Novel Intravesical Therapies in Nonmetastatic Urothelial Bladder Cancer (UBC) — Dr Necchi

Module 4: Emerging Utility of Circulating Tumor DNA Evaluation in Nonmetastatic UBC — Dr Galsky

Emerging Utility of Circulating Tumor DNA (ctDNA) Evaluation in Nonmetastatic UBC

Matthew D. Galsky, MD FASCO

Lillian and Henry Stratton Professor of Medicine

Icahn School of Medicine at Mount Sinai

Director, Genitourinary Medical Oncology

Deputy Director

The Tisch Cancer Center at Mount Sinai

Overview

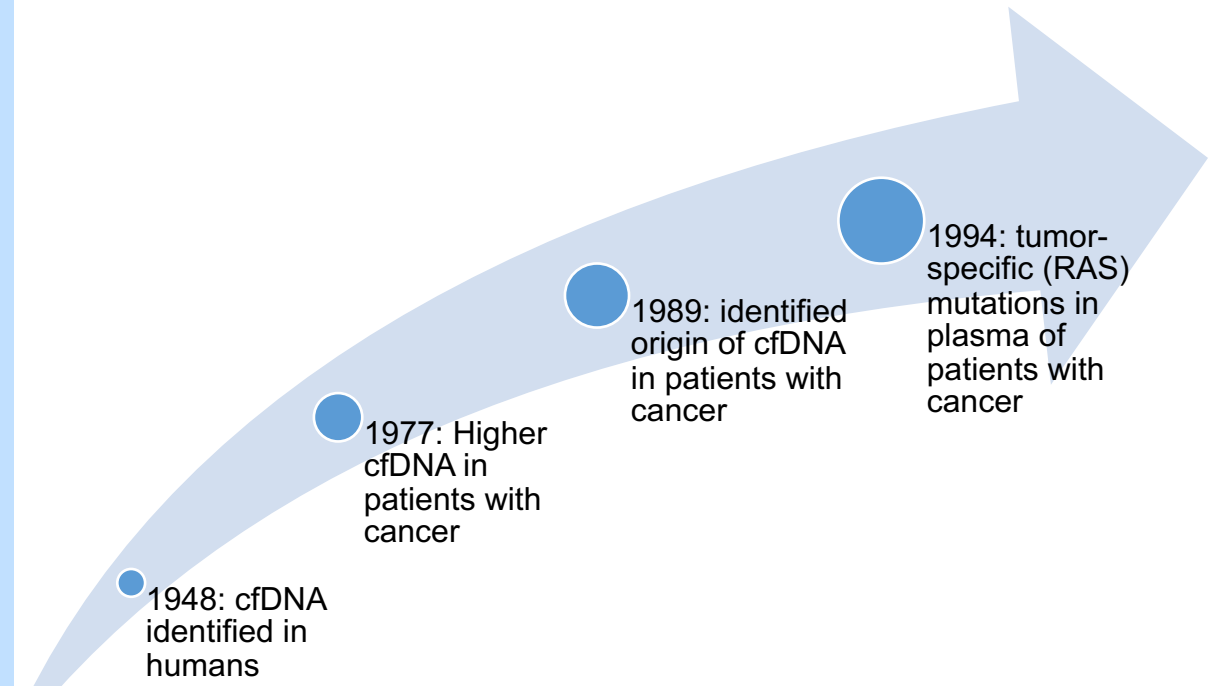
What do we know?

✅ ctDNA tells us who needs adjuvant treatment

⚠️ ctDNA tells us who doesn’t need adjuvant treatment

⛔ ctDNA tells us who doesn’t need neoadjuvant treatment

Evolution of ctDNA as a Tool to Assess MRD




TECHNICAL REPORTS

nature medicine

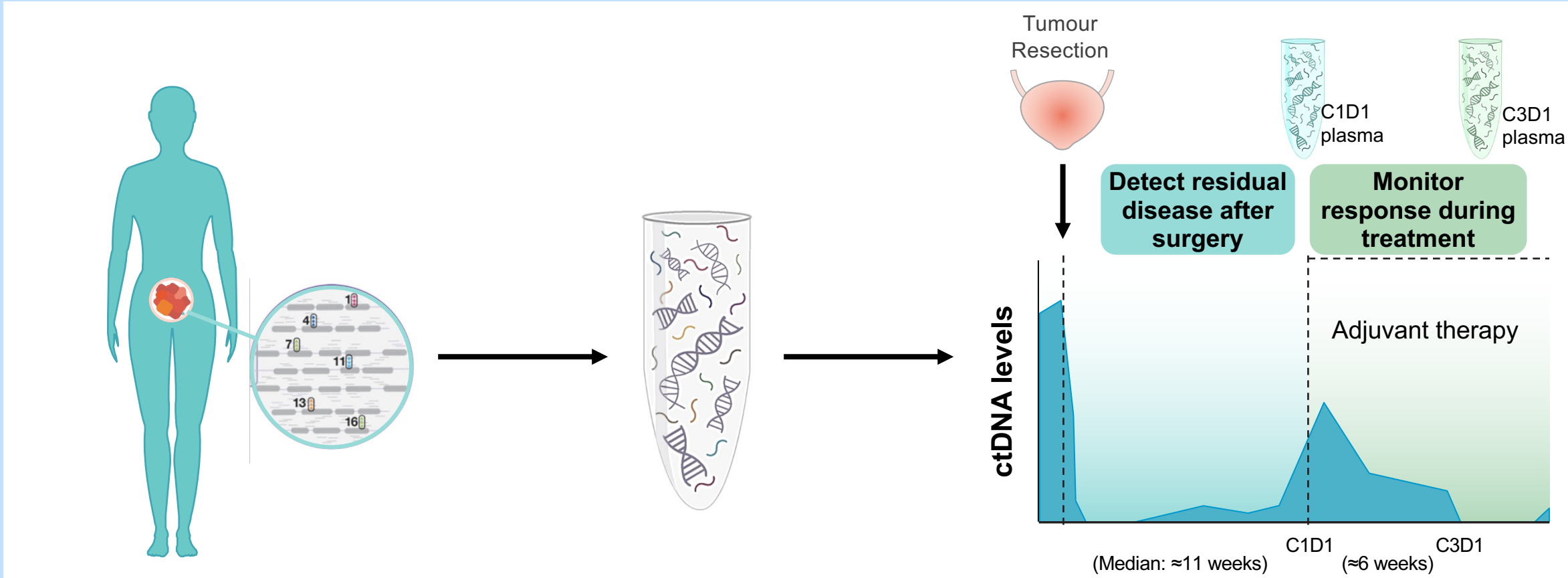
2008

Circulating mutant DNA to assess tumor dynamics

Frank Diehl[1,5], Kerstin Schmidt[1,5], Michael A Choti[2], Katharine Romans[1], Steven Goodman[3], Meng Li[1], Katherine Thornton[1], Nishant Agrawal[1], Lori Sokoll[4], Steve A Szabo[1], Kenneth W Kinzler[1], Bert Vogelstein[1] & Luis A Diaz Jr[1]

Mandel P et al. *C R Seances Soc Biol Fil.* 1948 ;142(3-4):241-3. Leon SA et al. *Cancer Res.* 1977;37(3):646-50. Stroun M et al. *Oncology.* 1989;46(5):318-22. Sorenson GD et al. *Cancer Epidemiol Biomarkers Prev.* 1994;3(1):67-71. Diehl F et al. *Nature Medicine.* 2008;14:985–990.

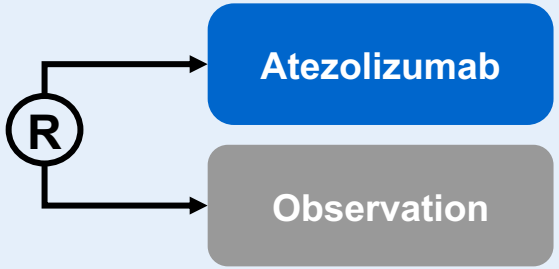
Tumor-Informed MRD Testing



Powles T et al. *Nature 2021*:595(7867):432-437.

Adjuvant PD-1/PD-L1 Blockade

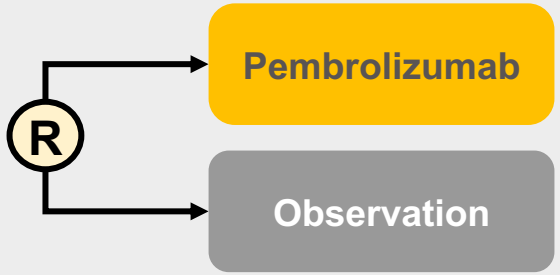
IMvigor010
NCT02450331



Primary endpoint
DFS

Secondary endpoints
OS, DSS, distant metastasis-free survival, AEs and ATAs

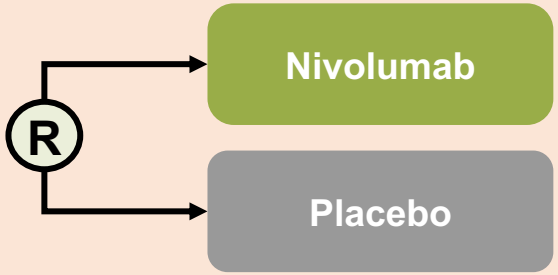
AMBASSADOR
NCT03244384



Co-primary endpoints
DFS and OS

Secondary endpoints
OS and DFS in PD-L1+ and PD-L1– patients

CheckMate 274
NCT02632409



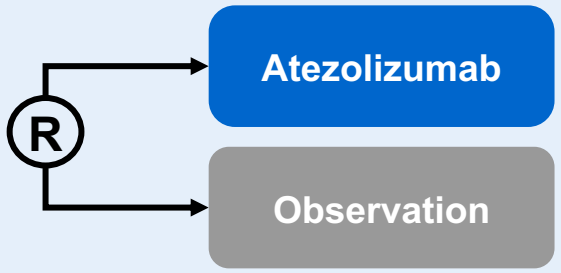
Primary endpoint
DFS in ITT and PD-L1≥1%

Secondary endpoints
OS,
non-urothelial tract RFS,
disease-specific survival

Bellmunt J et al. *Lancet Oncol.* 2021;22(4):525-537. Apolo AB et al. *N Engl J Med.* 2025; 392(1):45-55. Bajorin DF et al. *N Engl J Med.* 2021;384(22):2102-2114. Galsky MD et al. *J Clin Oncol.* 2025;43(1):15-21.

Adjuvant PD-1/PD-L1 Blockade

IMvigor010
NCT02450331



Did not meet primary endpoint

metastasis-free survival, AEs and ATAs

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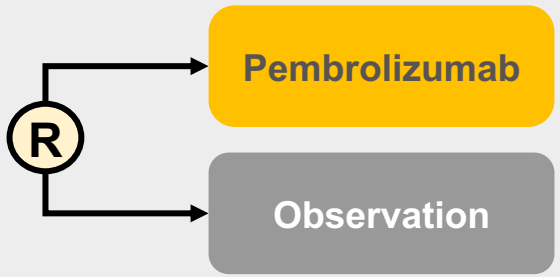
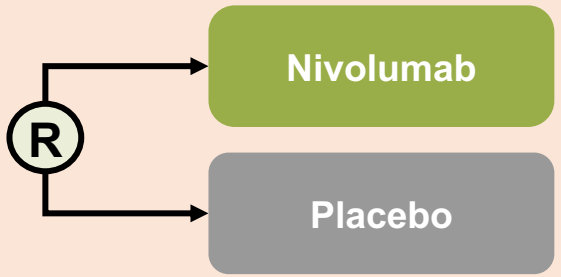
NCT03244384



Met DFS primary endpoint

and PD-L1– patients

CheckMate 274
NCT02632409

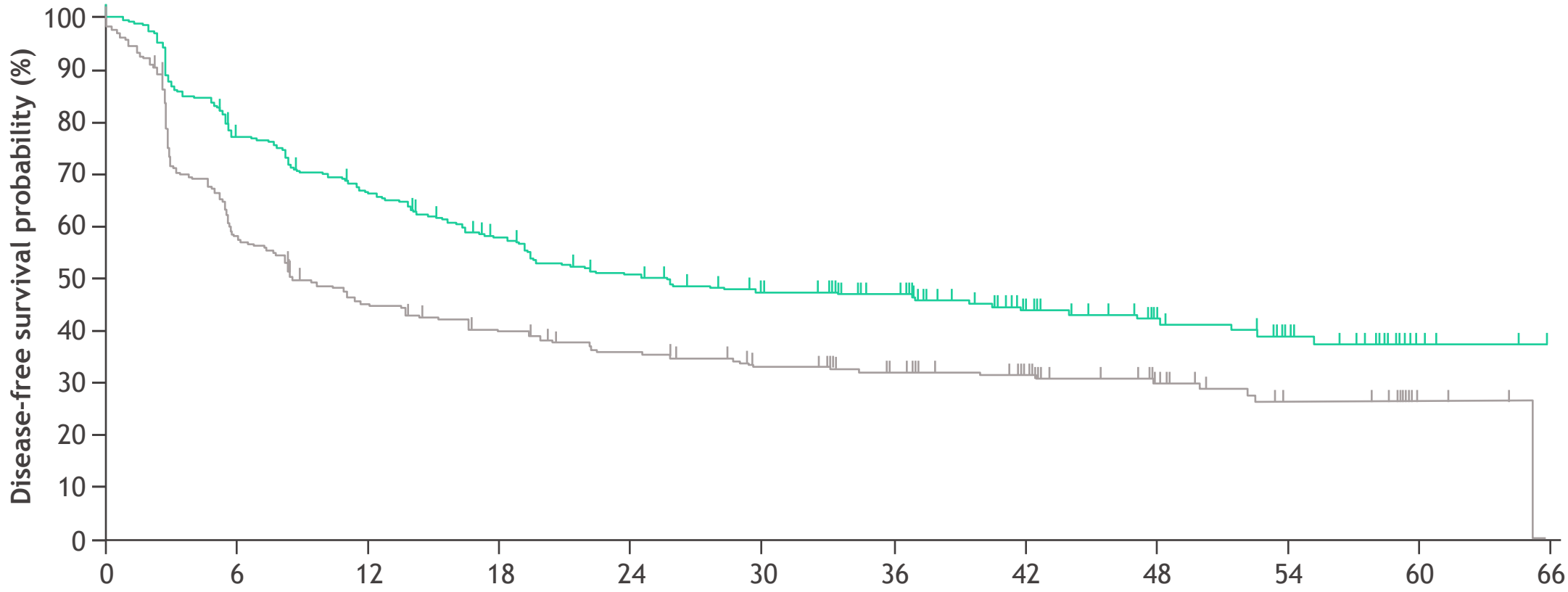


Met DFS primary endpoint(s)

non-urothelial tract RFS, disease-specific survival

Bellmunt J et al. *Lancet Oncol.* 2021;22(4):525-537. Apolo AB et al. *N Engl J Med.* 2025; 392(1):45-55. Bajorin DF et al. *N Engl J Med.* 2021;384(22):2102-2114. Galsky MD et al. *J Clin Oncol.* 2025;43(1):15-21.

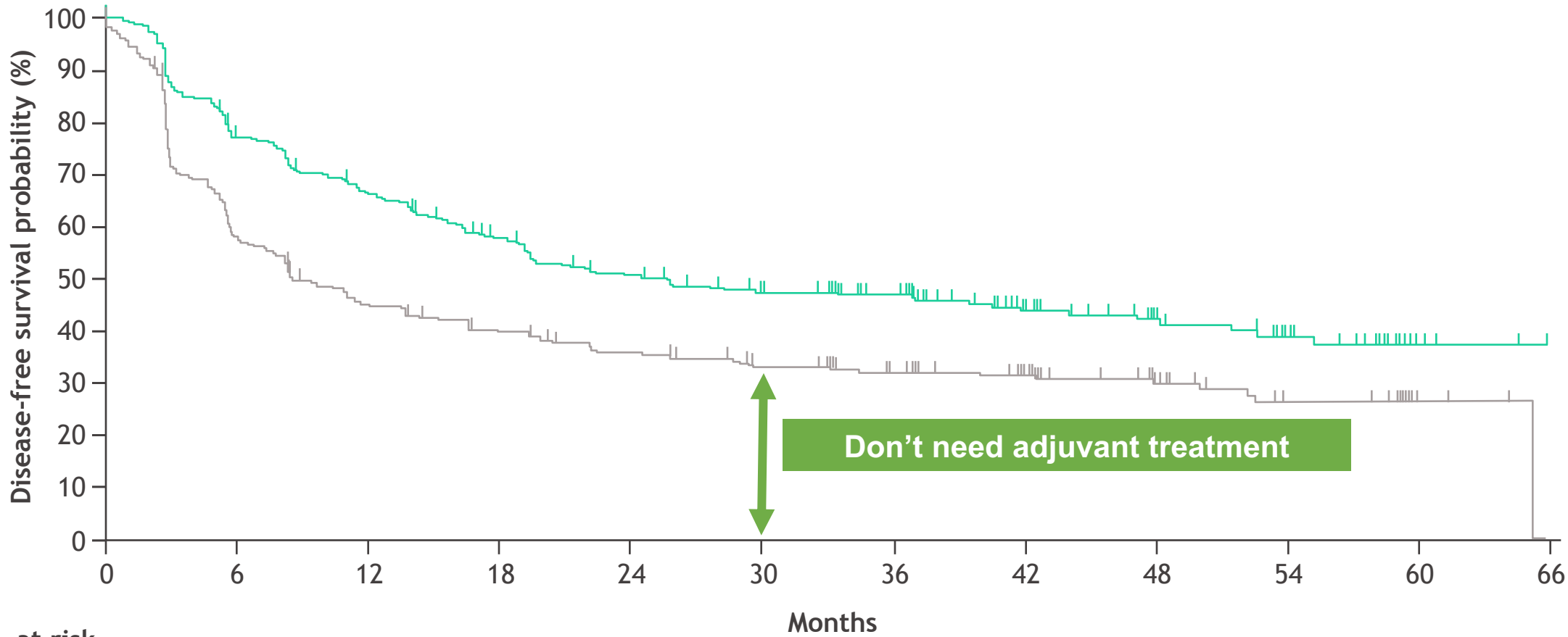
Adjuvant Nivolumab in Patients with MIBC



No. at risk											
NIVO	279	208	175	147	126	110	92	64	41	28	4	0
PBO	281	159	119	103	90	78	64	52	34	19	3	0

Galsky MD, et al. *J Clin Oncol* 2025

Adjuvant Nivolumab in Patients with MIBC



No. at risk												
NIVO	279	208	175	147	126	110	92	64	41	28	4	0
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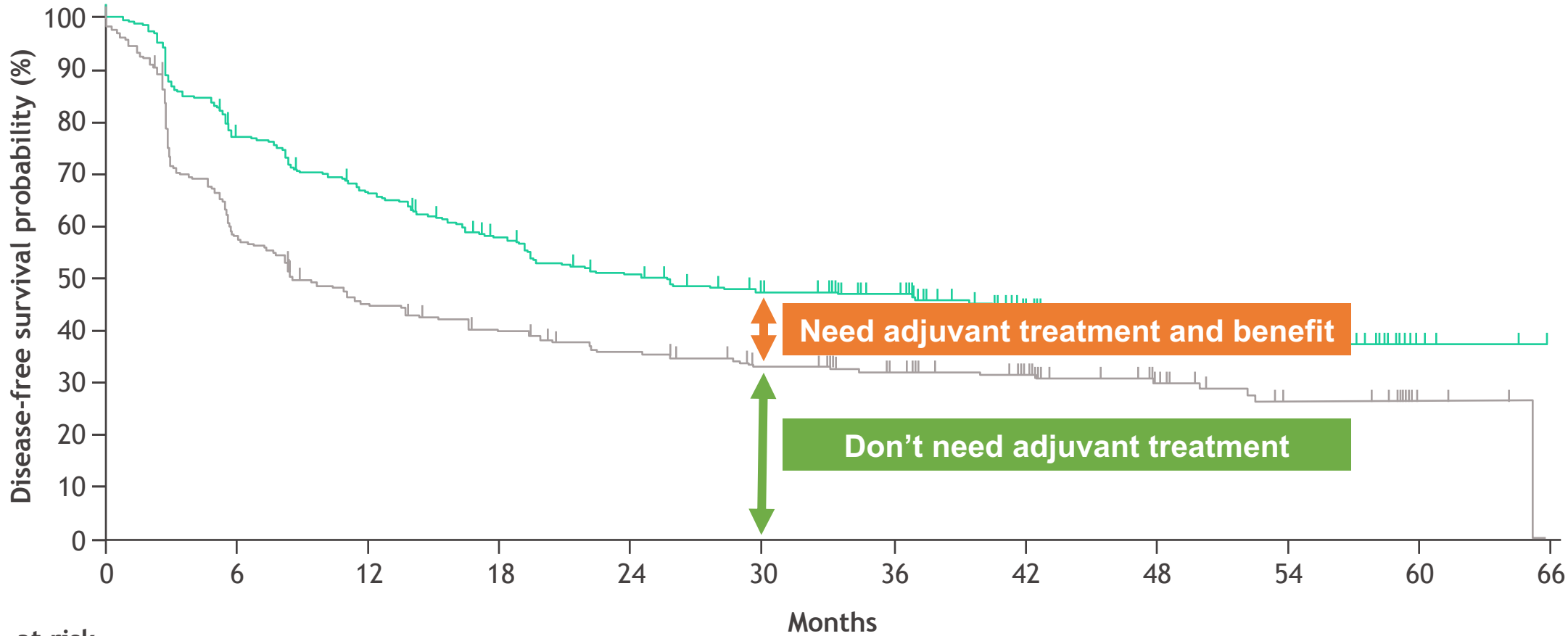
Galsky MD et al. *J Clin Oncol*. 2025; 43(1):15-21.

Adjuvant Nivolumab in Patients with MIBC



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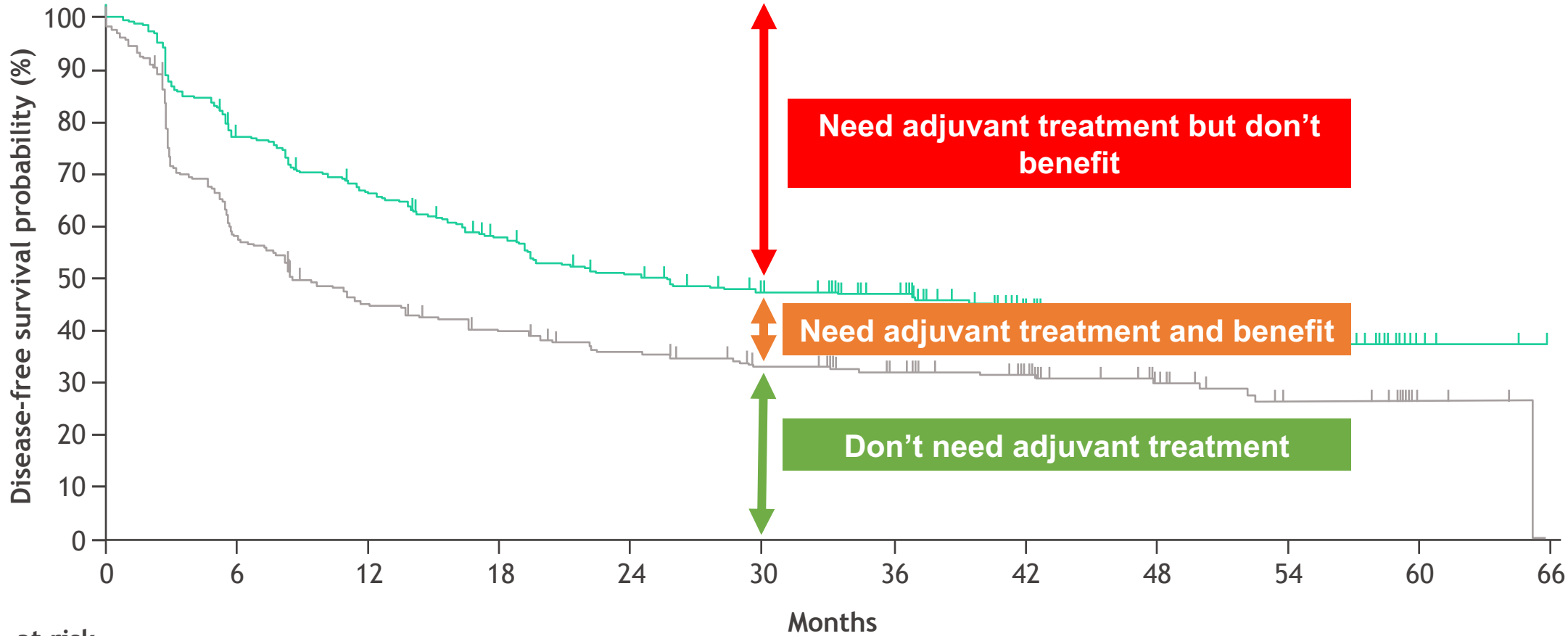
Galsky MD et al. *J Clin Oncol*. 2025; 43(1):15-21.

Adjuvant Nivolumab in Patients with MIBC



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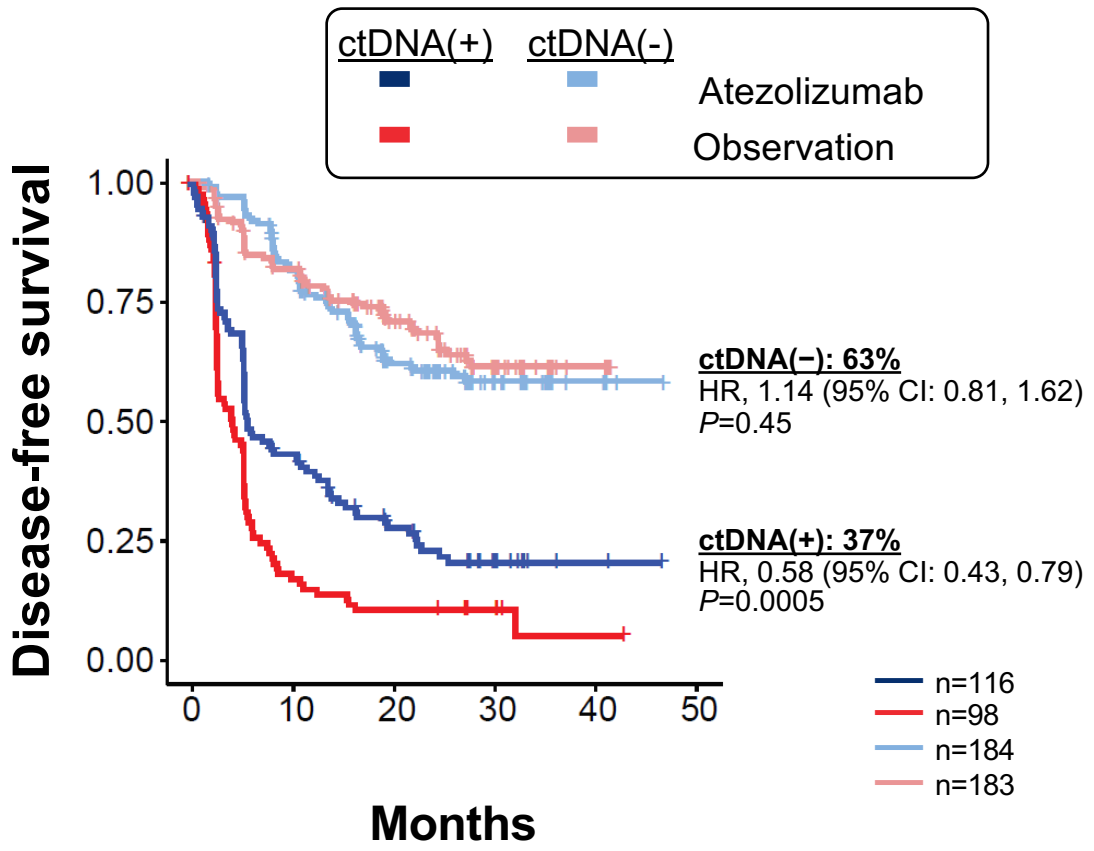
Galsky MD et al. *J Clin Oncol*. 2025; 43(1):15-21.

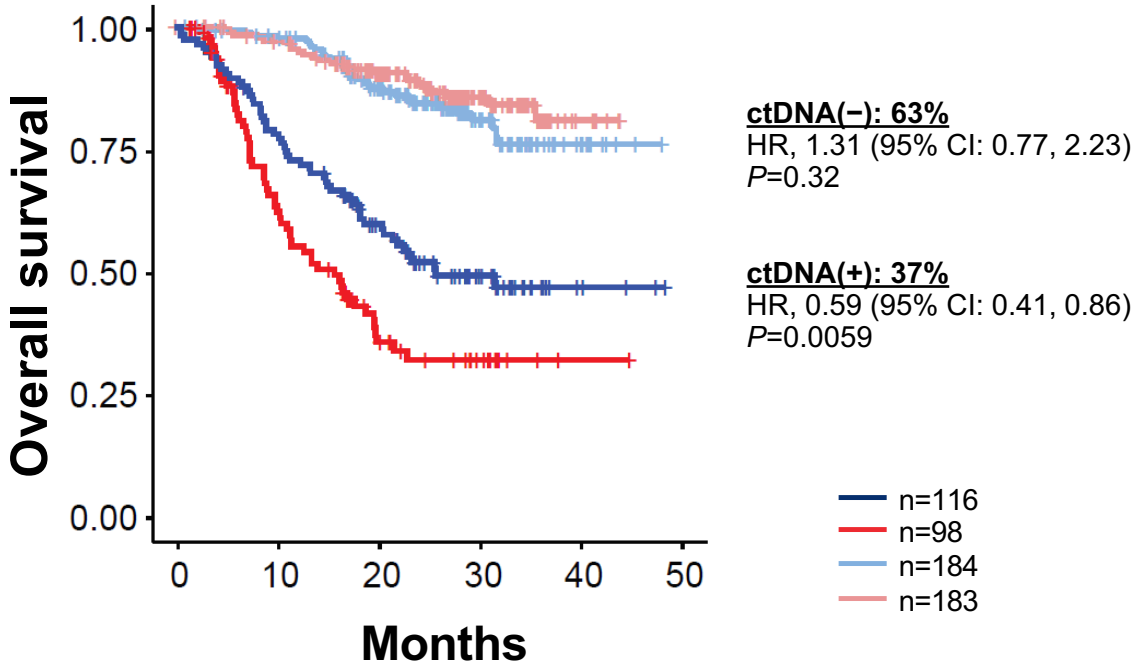
The "Double Biomarker Dilemma"

Who needs treatment?

Who benefits from treatment?

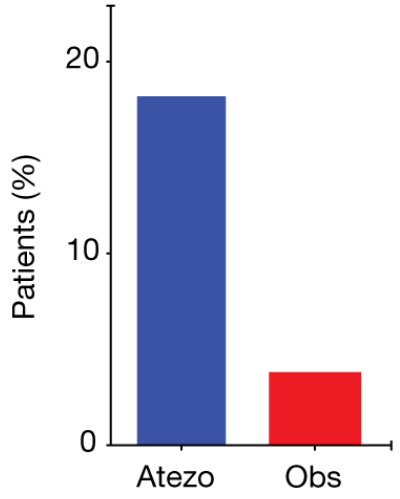
Retrospective Analysis of ctDNA in IMvigor 010



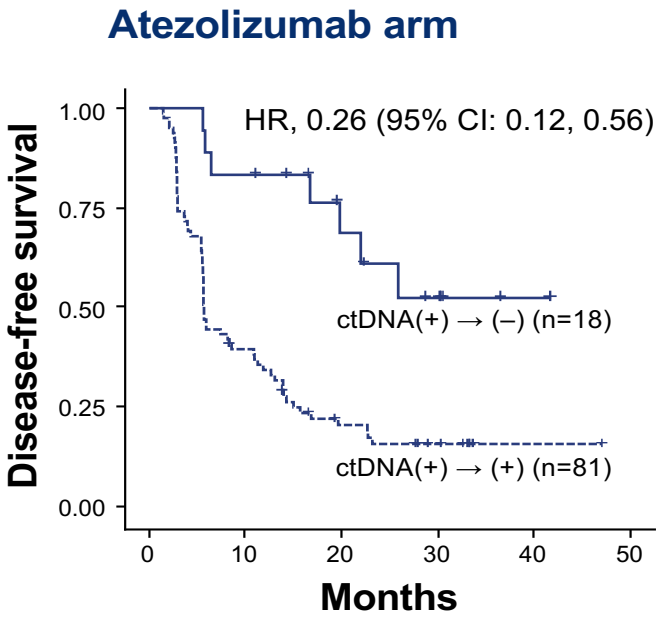


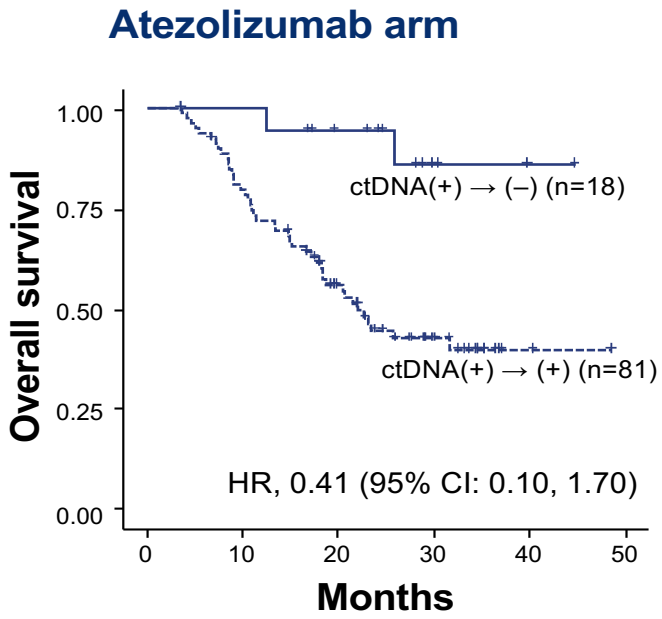
Powles T et al. *Nature.* 2021;595(7867):432-437.

Can ctDNA-Based MRD Serve as an Intermediate Clinical Endpoint?



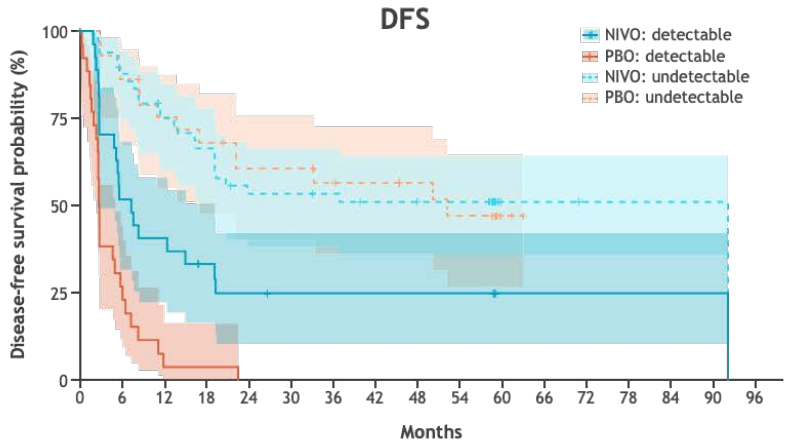
ctDNA⁺ patients at C1D1	*n* = 99	*n* = 79
Pos > Pos	81 (81.8%)	76 (96.2%)
Pos > Neg	18 (18.2%)	3 (3.8%)





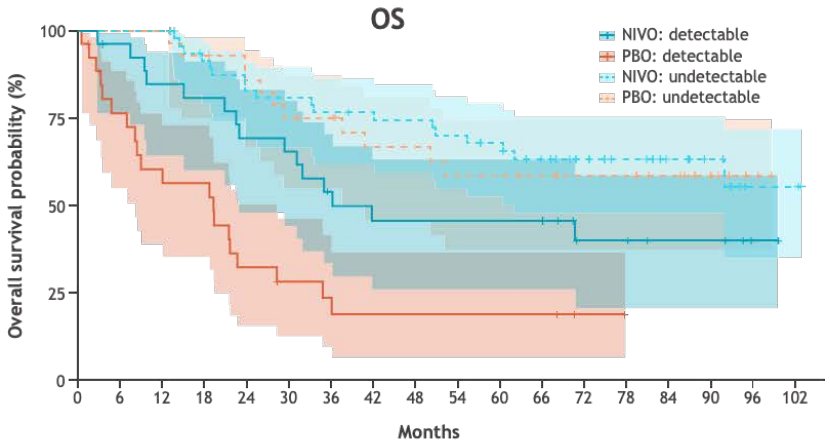
Powles T et al. *Nature.* 2021;595(7867):432-437.

Retrospective Analysis of ctDNA in Checkmate 274



ctDNA detectable	NIVO (n = 27)	PBO (n = 27)
Median DFS (95% CI), months	7.4 (2.8-19.2)	2.8 (2.4-5.0)
DFS HR (95% CI)	0.35 (0.18-0.66)	

ctDNA undetectable	NIVO (n = 50)	PBO (n = 29)
Median DFS (95% CI), months	91.9 (19.2-NE)	52.2 (16.9-NE)
DFS HR (95% CI)	0.99 (0.51-1.93)	

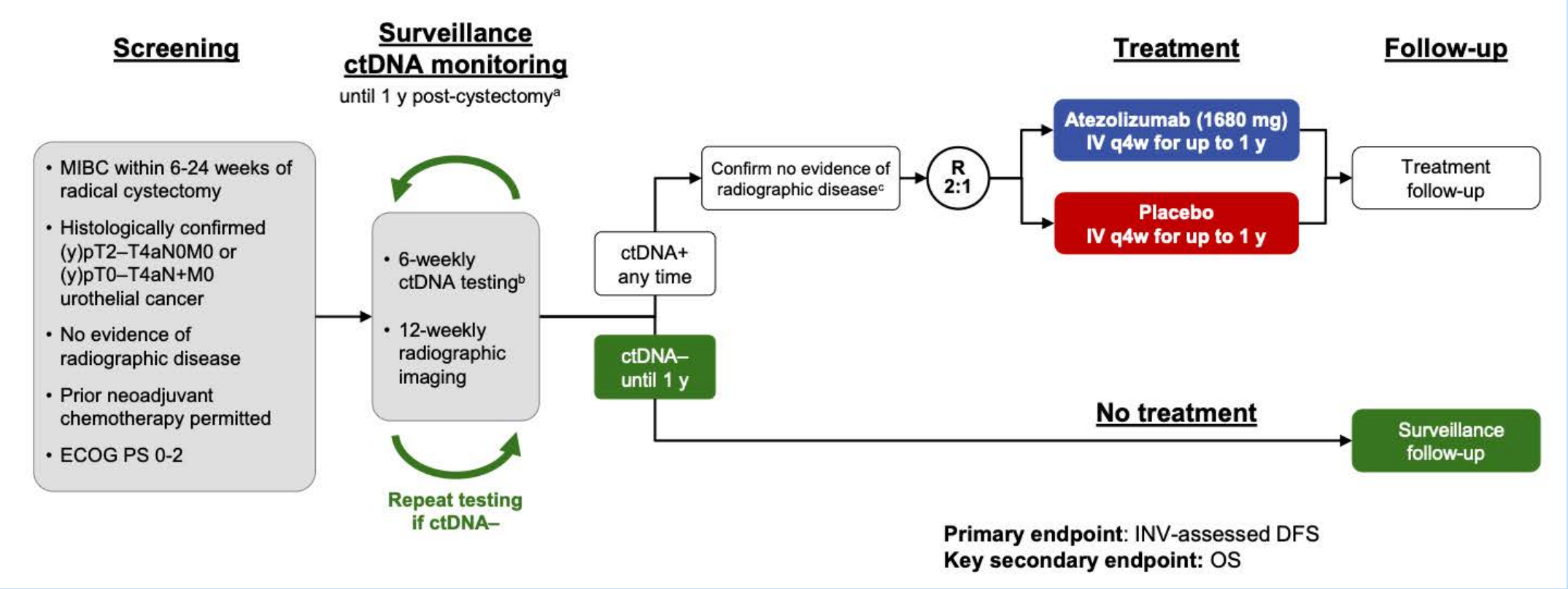


ctDNA detectable	NIVO (n = 27)	PBO (n = 27)
Median OS (95% CI), months	36.2 (23.0-NE)	19.3 (8.1-28.2)
OS HR (95% CI)	0.41 (0.20-0.83)	

ctDNA undetectable	NIVO (n = 50)	PBO (n = 29)
Median OS (95% CI), months	NR (62.0-NE)	NR (40.7-NE)
OS HR (95% CI)	0.87 (0.41-1.84)	

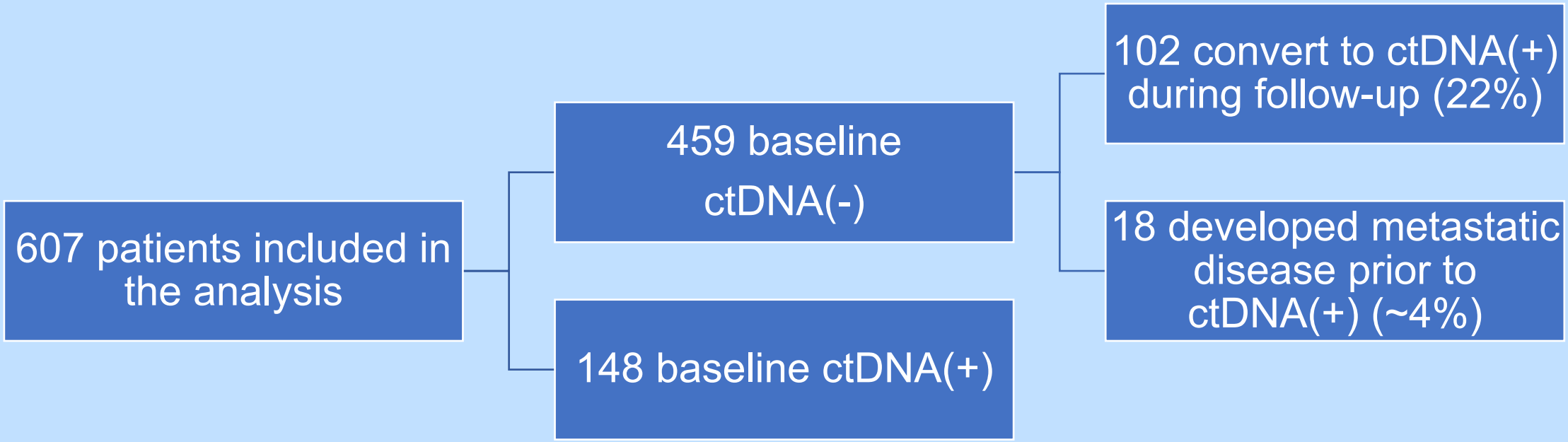
Galsky MD et al. *Ann Oncol.* 2025:S0923-7534(25)04930-0.

IMvigor 011: Study Schema

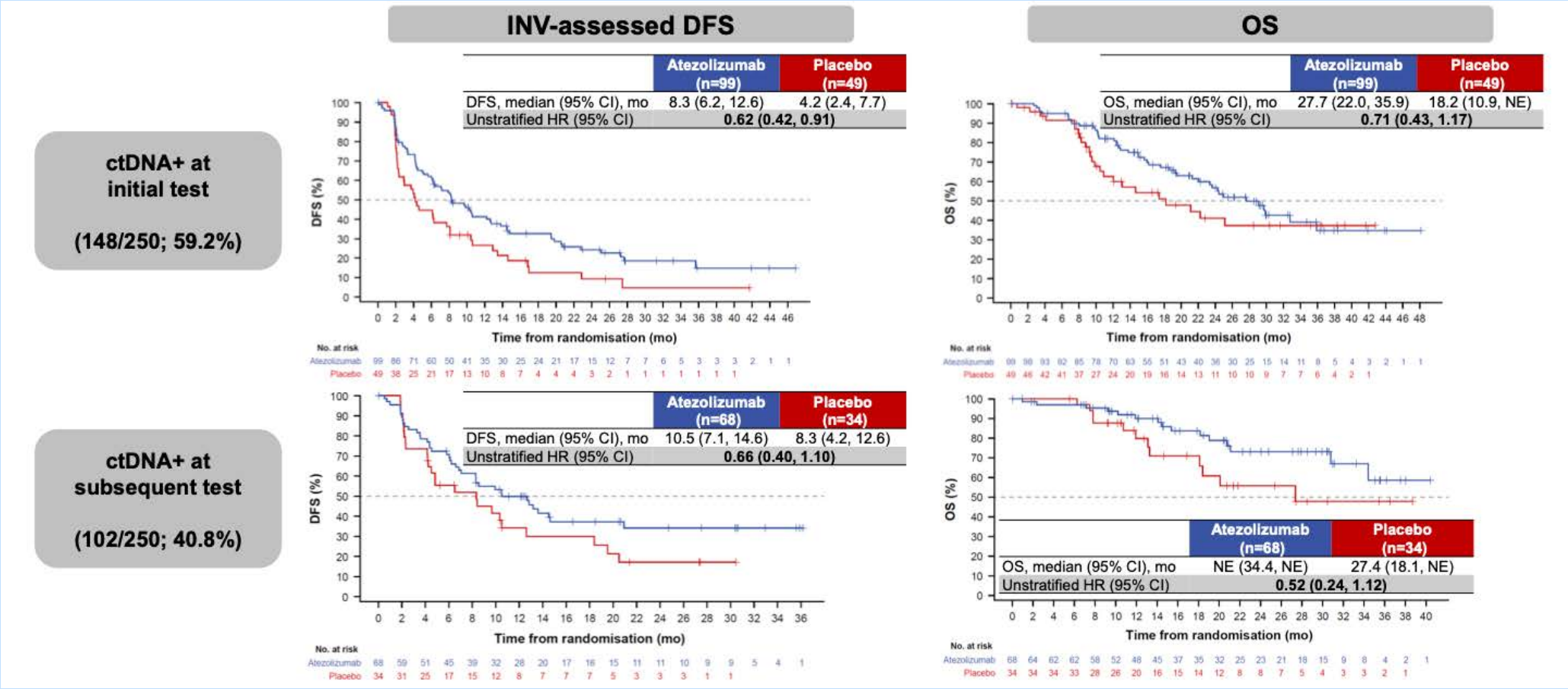


Powles T et al. *N Engl J Med.* 2025 Oct 20.

IMvigor 011: ctDNA kinetics

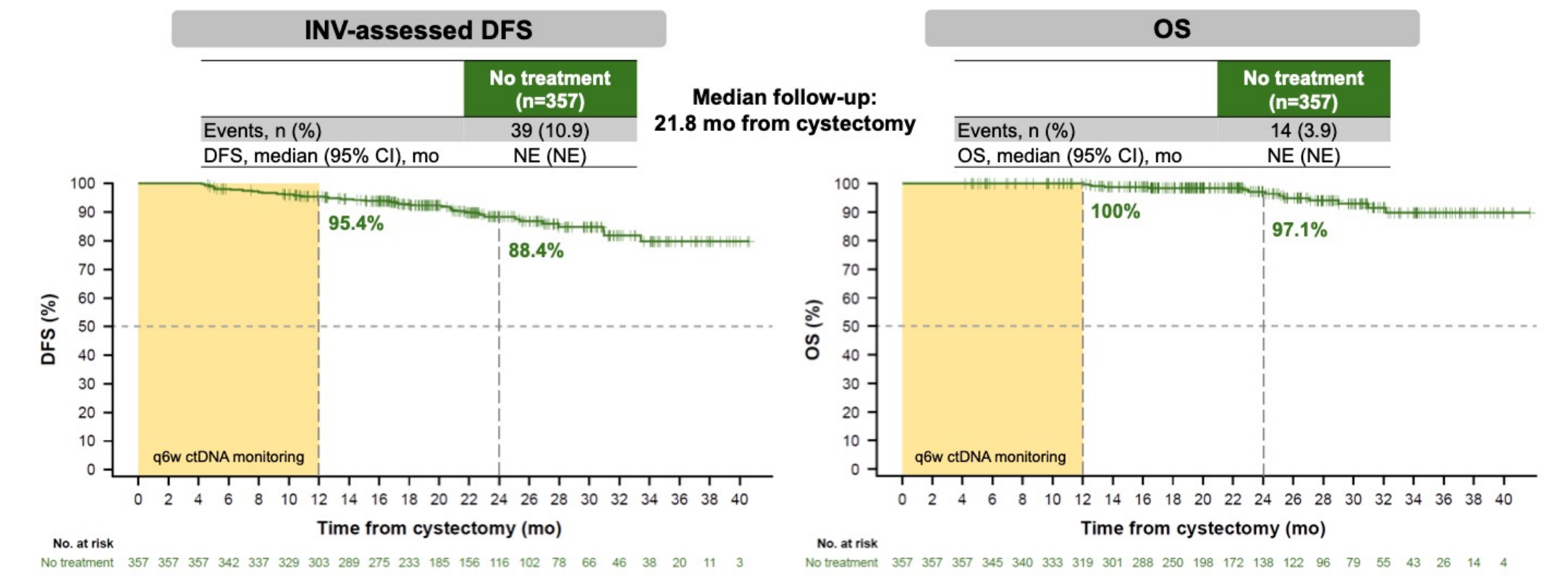


IMvigor 011: Outcomes in patients who tested ctDNA(+)



Powles T et al. ESMO 2025*; N Engl J Med.* 2025 Oct 20.

IMvigor 011: Outcomes in patients who tested *persistently* ctDNA(-)



Powles T et al. ESMO 2025*; N Engl J Med.* 2025 Oct 20.

IMvigor 011: Take Home

- ✓ Patients with ctDNA(+) assays after radical surgery for urothelial cancer need adjuvant treatment.
- ✓ Molecular recurrence is a new clinical disease state that can be meaningfully intervened upon with immune checkpoint blockade.

- ✓ Patients with serial ctDNA(-) assays *overall* have an excellent prognosis (conditional probability) – one does not know that the assay will be serially negative at the time standard adjuvant decisions need to be made.

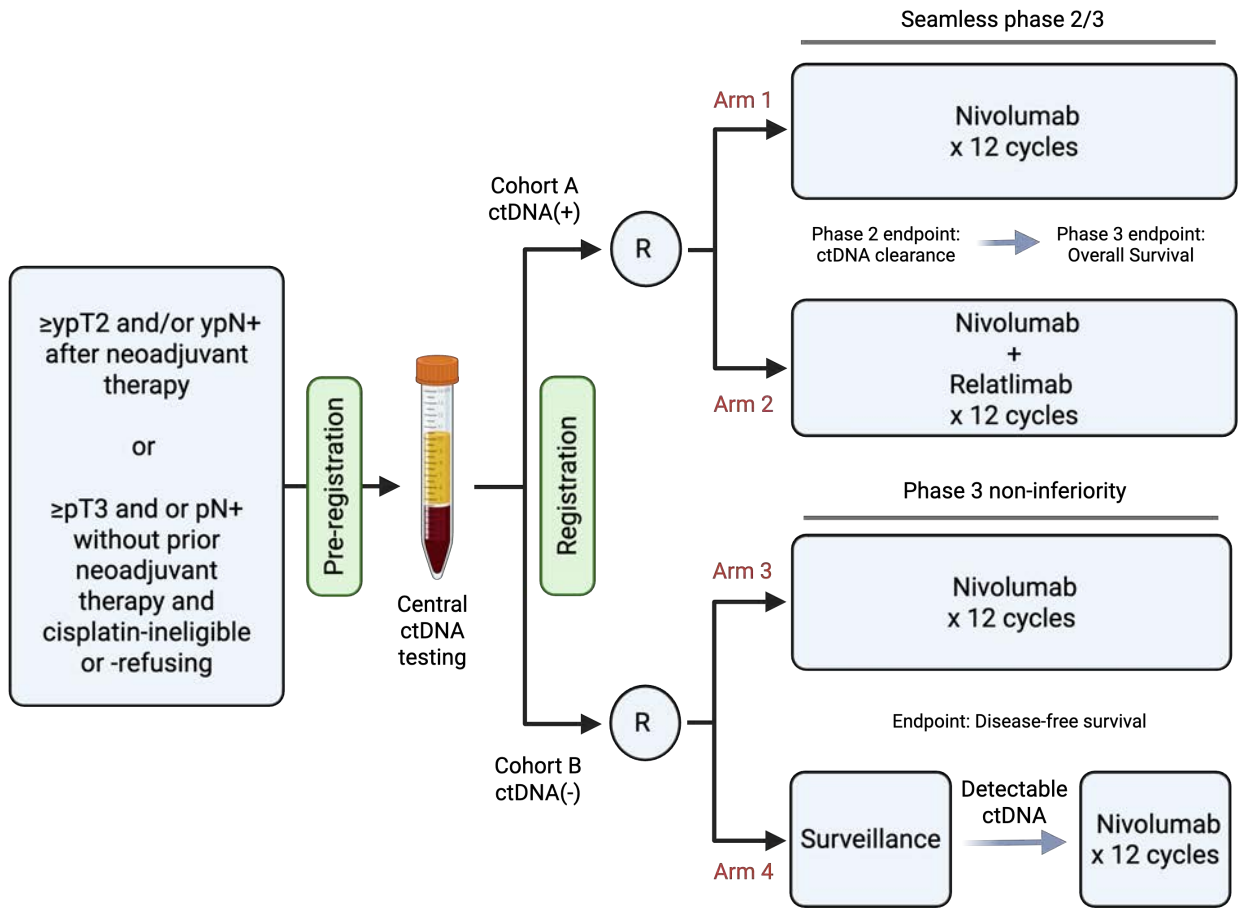
Whether treatment upon molecular recurrence is non-inferior to standard adjuvant therapy was not tested…and has not yet been answered.

Powles T et al. ESMO 2025*; N Engl J Med.* 2025 Oct 20.

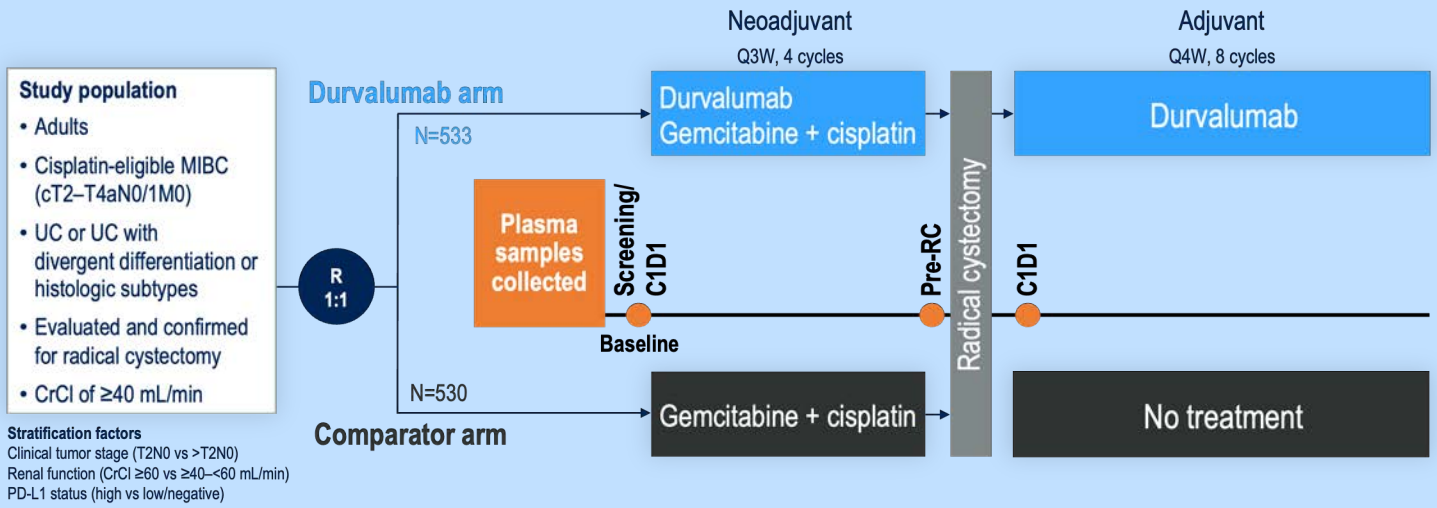
Alliance A032103: MODERN

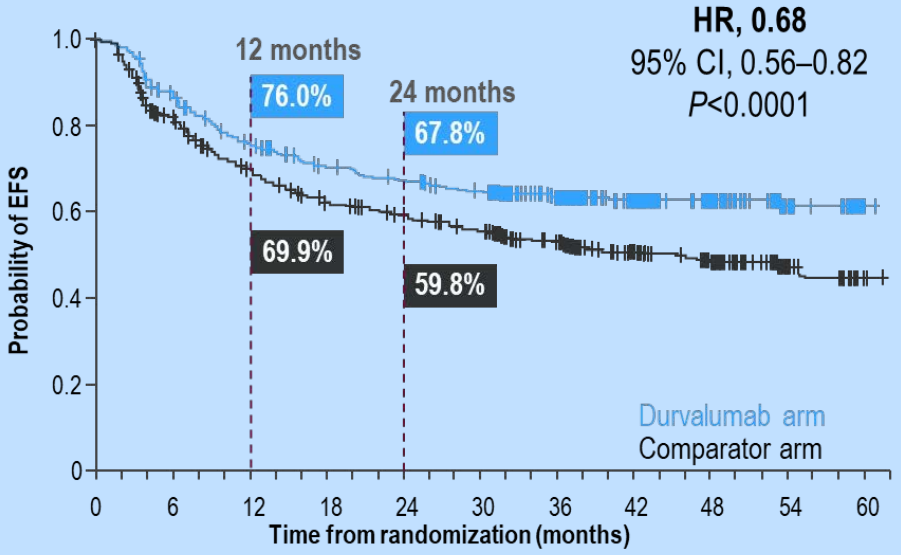
MODERN
Advancing Bladder Cancer Care Through ctDNA

Alliance for Clinical Trials in Oncology



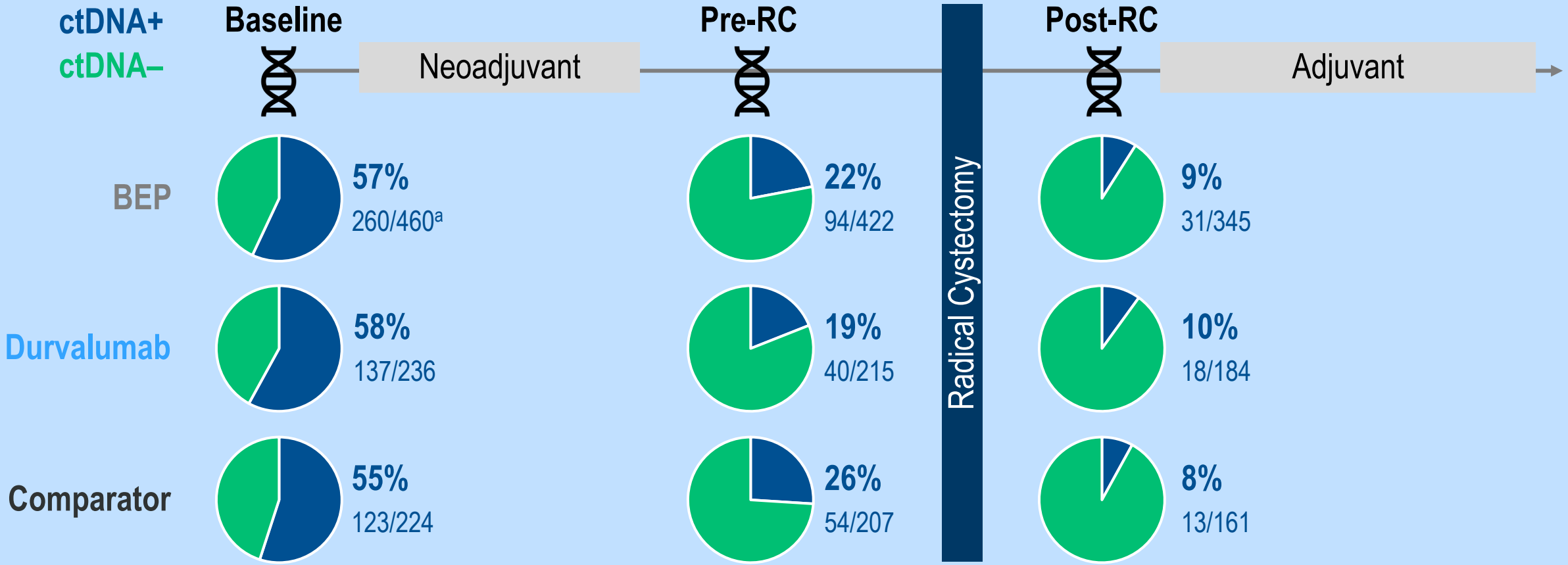
NIAGARA demonstrated an improvement in outcomes adding PD-L1 blockade to neoadjuvant/adjuvant therapy





Powles J et al. *N Engl J Med.* 2024;391(19):1773-1786.

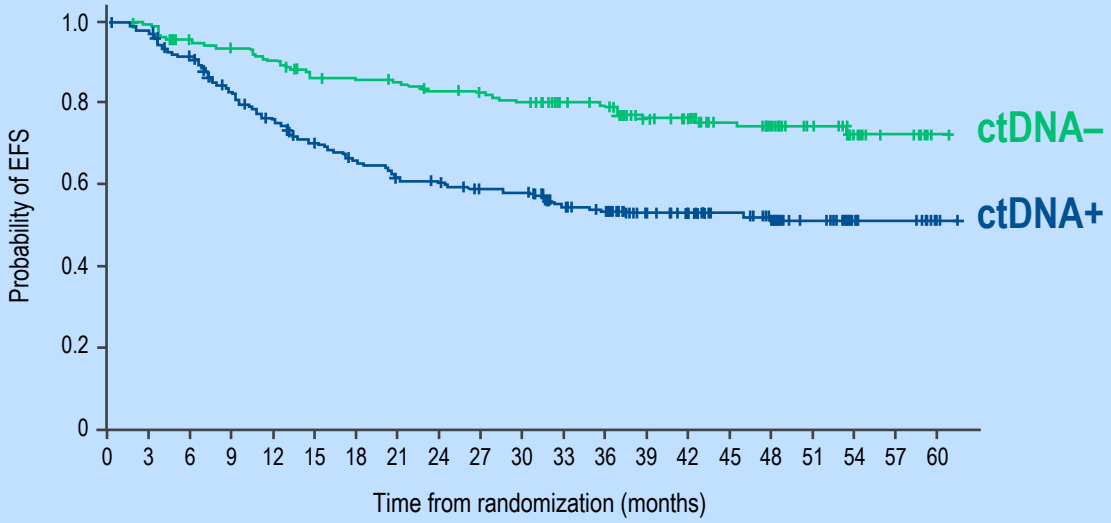
ctDNA detection rates in NIAGARA



Powles T et al. ASCO 2025. Abstract 4503.

Prognostic impact of *baseline* ctDNA in NIAGARA

EFS (combined arms)

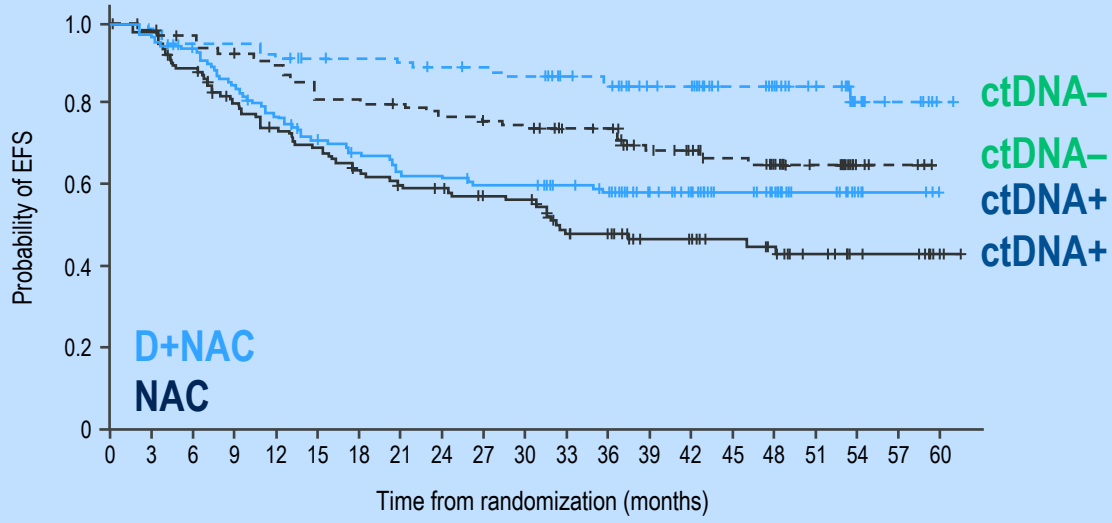


No. of patients at risk

ctDNA–	200	197	185	180	174	162	160	158	153	150	146	131	127	104	95	76	60	48	20	10	1
ctDNA+	260	253	233	206	188	170	156	145	143	135	134	114	105	83	72	61	47	33	16	13	2

ctDNA– vs ctDNA+	**HR, 0.42** (95% CI, 0.30–0.60)

EFS (per arm)



No. of patients at risk

ctDNA– D+NAC	99	99	91	91	88	84	83	82	80	79	77	69	66	55	51	39	35	29	14	7	1
ctDNA– NAC	101	98	94	89	86	78	77	76	73	71	69	62	61	49	44	37	25	19	6	3	0
ctDNA+ D+NAC	137	133	126	113	103	91	85	79	78	75	75	69	63	49	42	35	26	17	7	5	0
ctDNA+ NAC	123	120	107	93	85	79	71	66	65	60	59	45	42	34	30	26	21	16	9	8	2

ctDNA–: D+NAC vs NAC	**HR, 0.45** (95% CI, 0.24–0.84)
ctDNA+: D+NAC vs NAC	**HR, 0.73** (95% CI, 0.51–1.05)

Durvalumab arm = D+NAC; Comparator arm = NAC

Powles T et al. ASCO 2025. Abstract 4503.

Conclusions

What do we know?

- ✅ ctDNA tells us who needs adjuvant treatment
- ⚠️ ctDNA tells us who doesn’t need adjuvant treatment
- ⛔ ctDNA tells us who doesn’t need neoadjuvant treatment

Second Opinion

Elizabeth R Plimack, MD, MS

Neil Love, MD

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

What treatment approach would you most likely recommend for a patient who presented with T4 disease and a 2-cm pelvic lymph node and attained a CR on imaging after 6 cycles of EVP?

Would you refer for surgery? Or would you consider this patient to have metastatic disease and use ctDNA to monitor continued response and potentially avoid surgery?

QUESTIONS FOR THE FACULTY

How would you compare the sensitivity of serial ctDNA monitoring to that of radiological assessments in detecting disease progression?

If a patient with no clinical or radiologic evidence of relapse were found to have a positive ctDNA test, would it change your approach to monitoring or management in any way?

Second Opinion

Thomas Powles, MBBS, MRCP, MD

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

How would you approach the management of this 72-year-old man who received neoadjuvant chemoimmunotherapy and was found to have a positive ctDNA analysis prior to cystectomy and a negative ctDNA result after surgery?

Would you draw from the IMvigor011 results and be more inclined to forgo the use of adjuvant immune checkpoint inhibitor therapy? If so, how often would you repeat ctDNA testing?

QUESTIONS FOR THE FACULTY

Ultimately, do you believe ctDNA will be used to inform treatment decision-making for patients with nonmetastatic UBC in routine clinical practice in the near future?

Outside of a clinical trial, should medical oncologists in community-based practice be ordering these assays for their own patients and acting on the results?

Second Opinion: Clinical Investigators Provide Perspectives on the Future Role of AKT Inhibition in the Management of Prostate Cancer

A CME Symposium Held Adjunct to the
2026 ASCO® Genitourinary Cancers Symposium

Friday, February 27, 2026
6:00 PM – 7:30 PM PT (9:00 PM – 10:30 PM ET)

Faculty

Professor Karim Fizazi, MD, PhD
Daniel George, MD

Moderator

Elisabeth I Heath, MD

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RESEARCH TO PRACTICE

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Please complete the survey currently available via the corresponding QR code on the printed handout for attendees in the room and on Zoom for those attending virtually. The survey will remain open up to 5 minutes after the meeting ends.

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In-person attendees: Please refer to the program syllabus for the CME credit link or QR code. Online/Zoom attendees: The CME credit link is posted in the chat room.

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