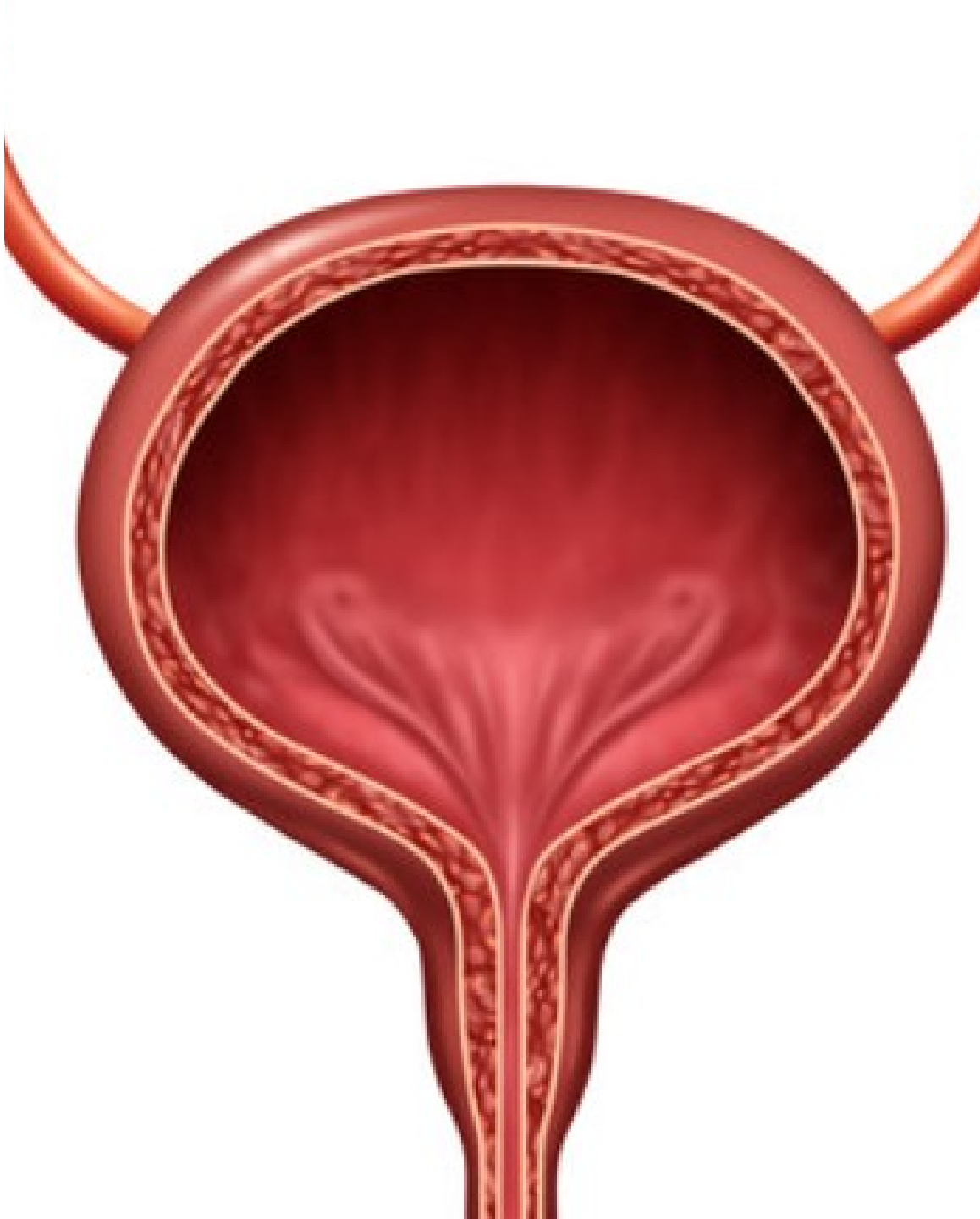
Case based Panel discussion: Muscle Invasive Bladder cancer

Moderator: Dr Maheboob Basade

"Disclaimer: This Presentation is intended for educational purposes only and do not affect independent professional judgment. Statements of fact and opinions expressed are those of the speakers individually and, unless expressly stated to the contrary, are not the opinions or position of AstraZeneca. AstraZeneca does not endorse or approve and assumes no responsibility for the accuracy or completeness of the information presented"

Transparency statement: *You agree and consent that AstraZeneca may record or take photographs or collect, retain, use and disclose your information, including personal, in order for AstraZeneca to comply with any legal or regulatory obligations or transparency requirements that apply to AstraZeneca's activities anywhere in the world, as well as comply with AstraZeneca's internal policies, sharing of practices, standard operating procedures and guidelines. You can also access our Privacy Policy at www.astrazeneca.com.*



How would you proceed in this patient?

SKM, 62 Yrs, Male, K/C/o hypertension

Clinically presented with:

- Painless haematuria for 2 months
- Increased urinary frequency and mild dysuria for 2 months

Physical examination was unremarkable with no palpable abdominal masses or suprapubic tenderness. P/R : Grade I prostatomegaly

Disclaimer: This is a hypothetical case for the purpose of discussions only

Lab tests and Imaging studies

CBC: Normal

RFT: Normal (Creatinine: 0.9 mg/dl, eGFR: 75ml/min/1.73 m2)

LFT: Normal

Urine Cytology: Positive for malignant cells

USG Abdomen and pelvis

Mass lesion at the posterior wall of urinary bladder as well as dome without any back pressure changes

CT Urogram:

Thickened bladder wall in the post wall and dome

No evidence of lymphadenopathy or distant metastasis

MRI: Mass at posterior wall of UB with muscle invasion without any pelvic lymph node involvement

Cytology and Biopsy and TURBT findings:

Findings: Ulcerative lesions in the posterior wall as well as dome

Histopathology: High grade Urothelial carcinoma invading the superficial muscularis propria (ct2)

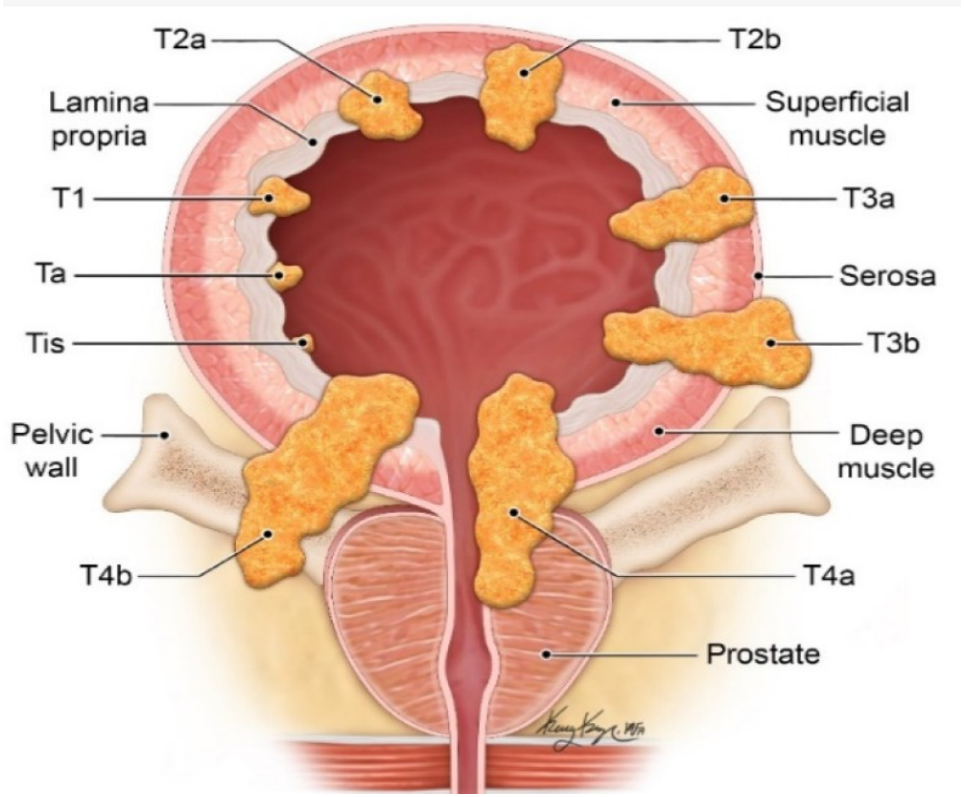
- *Disclaimer: This is a hypothetical case for the purpose of discussions only*

What is the stage of the tumour?

T Stage	Description
Tx	Primary tumor unable to be evaluated
T0	No evidence of primary tumor
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ
T1	Tumor invades lamina propria but does not involve bladder muscle
T2	Tumor invades bladder muscle
T2a	Tumor invades superficial muscle (inner half)
T2b	Tumor invades deep muscle (outer half)
T3	Tumor invades perivesical tissue
T3a	Microscopic perivesical invasion
T3b	Macroscopic perivesical invasion
T4	Tumor invades adjacent organs
T4a	Tumor invades prostate, seminal vesicles, uterus, or vagina
T4b	Tumor invades pelvic wall or abdominal wall
N stage	
Nx	Regional lymph nodes cannot be evaluated
N0	Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N1	2+ regional lymph node metastases in the true pelvis
N3	Lymph node metastasis to common iliac lymph nodes
M stage	
M0	No distant metastasis
M1	Distant metastasis

	T	N	M		T	N	M
Stage 0a	Ta	N0	M0	**Stage IIIB**	T1-T4a	N2,N3	M0
Stage 0is	Tis	N0	M0	**Stage IVA**	T4b	Any N	M0
Stage I	T1	N0	M0		Any T	Any N	M1a
Stage II	T2a	N0	M0	**Stage IVB**	Any T	Any N	M1b
	T2b	N0	M0				
Stage IIIA	T3a	N0	M0				
	T3b	N0	M0				
	T4a	N0	M0				
	T1-T4a	N1	M0				

Stage II - cT2aN0M0



Do we have to add any molecular workup at this stage?

Would you send samples for FGFR, PDL1, HER2?

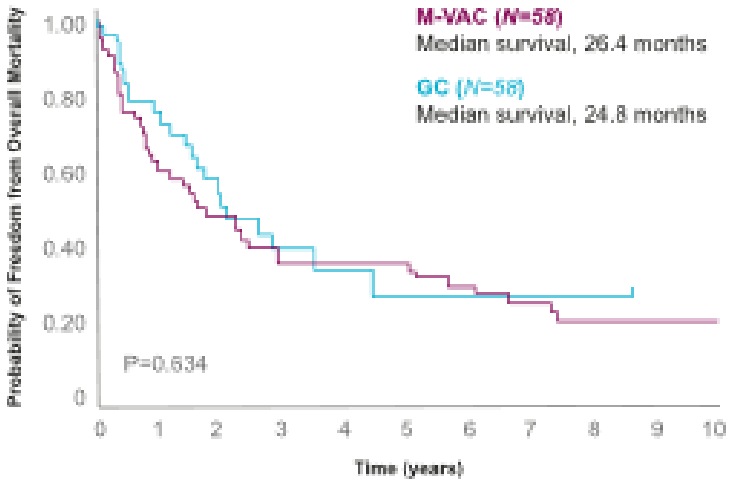
Role of ctDNA?

How do you usually manage MIBC?

Retrospective analysis indicates neoadjuvant GC and MVAC have comparable efficacy, but GC is better tolerated[1,2]

- However, cumulative recurrence was lower with MVAC vs. GC in patients with lymph node-positive (LN+) disease·

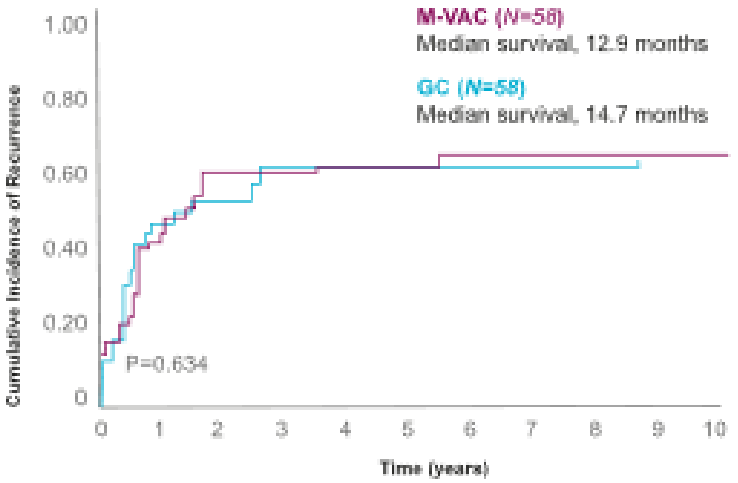
Overall survival (overall population)[1]



No. at Risk

M-VAC	58	25	18	14	10
GC	58	17	6	2	2

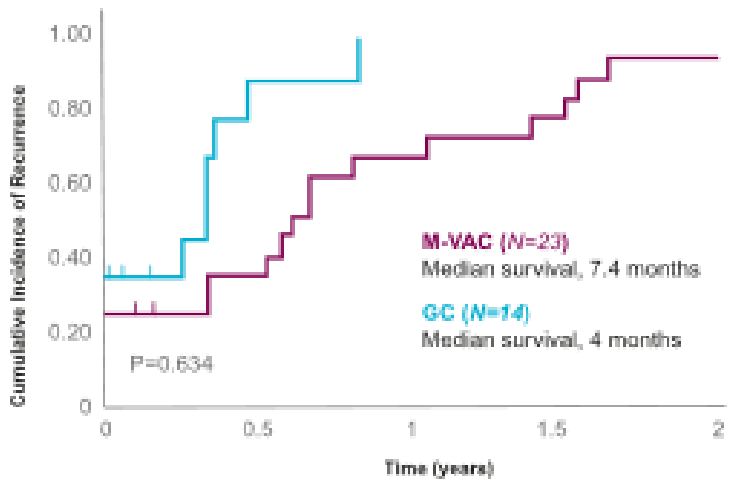
Cumulative recurrence (overall population)[1]



No. at Risk

M-VAC	58	18	16	14	10
GC	58	12	5	2	2

Cumulative recurrence (LN+ patients)[1]



No. at Risk

M-VAC	58	18	16	14	10
GC	58	12	5	2	2

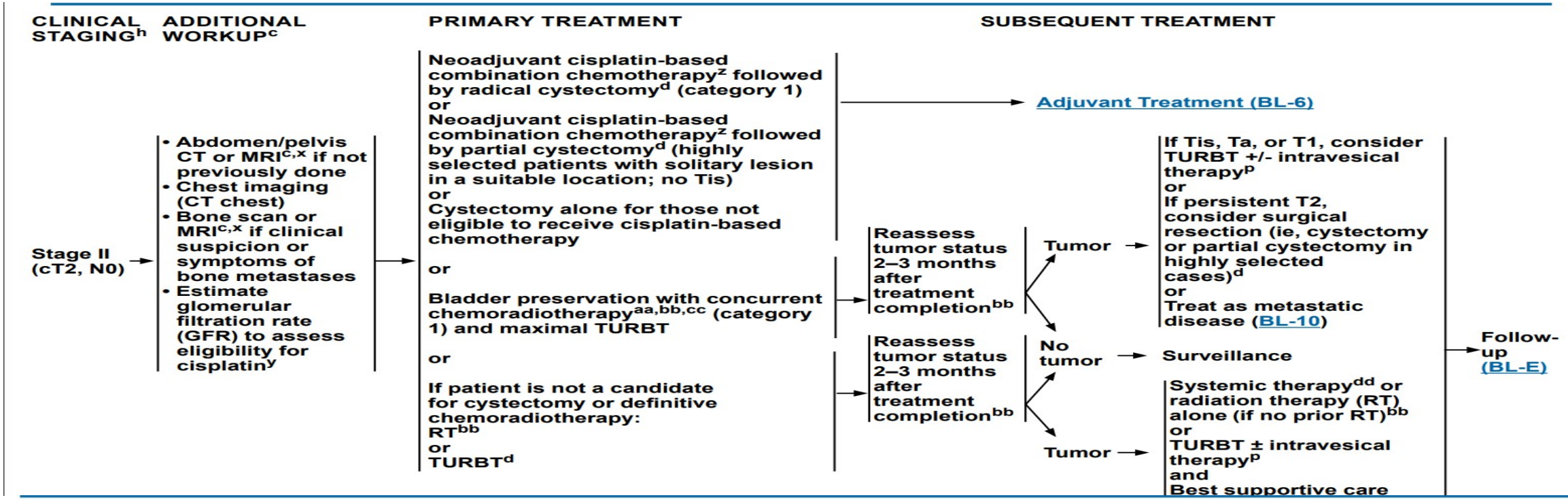
GC=gemcitabine-cisplatin; LN=lymph node; MIBC=muscle-invasive bladder cancer; MVAC=methotrexate, vinblastine, doxorubicin and cisplatin.

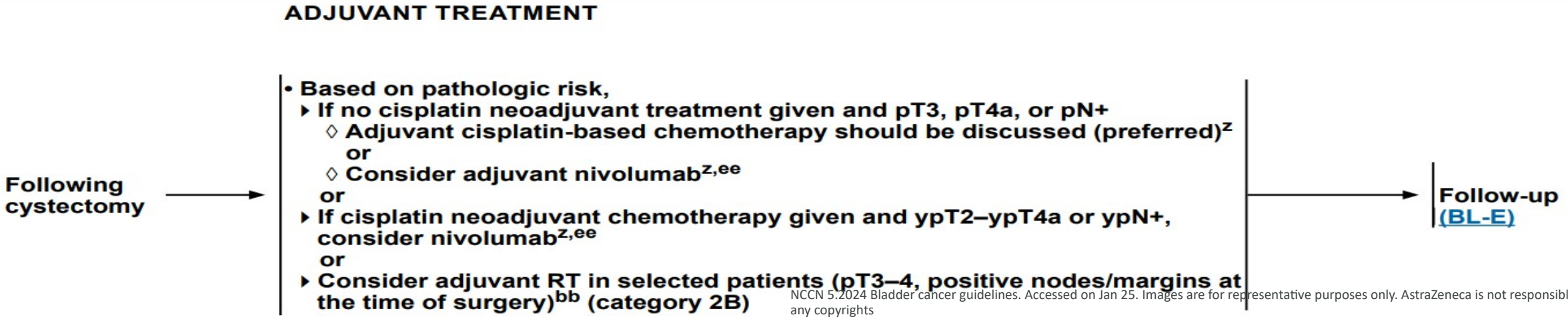
1. Fairey AS, et al. *Urol Oncol.* 2013;31(8):1737–1743; 2. Von der Maase H, et al. *J Clin Oncol.* 2000;18(17):3068–3077.

2. Images are for representation purpose only. AstraZeneca is not responsible for any copyright.

Would you give chemotherapy in patients having CrCl<50 ml/min?

NCCN recommendation





Why neoadjuvant chemotherapy? Is there any advantage evidence?

	SWOG-8710 [6]	BA06 30894 [8]	Choueiri et al. [13] (NCT00808639)	Plimack et al. [14] (NCT01031420)	Dash et al. [18]	MSK [20]
N	317	976	39	40	42	154
Phase	3	3	2	2	R	R
Regimen	MVAC	CMV	ddMVAC	aaMVAC	GC	GC
Duration of NAC, weeks	14	NA	8	6	12	12
Median time to definitive treatment after randomization, weeks	16	NA	14	9.7	19	17
Planned surgery rates, %	82	NA	97	98	NA	NA
pCR (pT0N0) rates, %	38	NA	26	38	26	21
Downstaging (<pT2) to non-muscle invasive disease, %	44	NA	49	53	36	46

To date, cisplatin based NAC is the SOC for MIBC, associated with 5% absolute survival benefit at 5 yrs and 14% relative risk

Kim Ho et al. Perioperative Systemic Treatment for Muscle-Invasive Bladder Cancer: Current Evidence and Future Perspectives

July 2021. International Journal of Molecular Sciences·

Images are for representation purpose only. AstraZeneca is not responsible for any copyright.

22(13):7201

Why perioperative treatment ?

Clinical Advantages: Perioperative vs Adjuvant Immunotherapy

Parameter	Perioperative Immunotherapy	Adjuvant Immunotherapy
Timing of Immune Activation	Before surgery, higher antigen load	After tumor removal, lower antigen exposure
Antigen Exposure	Tumor antigens present	Reduced post-surgery
T-cell Clonal Expansion	Enhanced neoantigen-specific expansion	Possibly suboptimal
Micrometastatic Control	Early systemic effect	Delayed action on micrometastases
Pathologic Response Assessment	Possible (pCR, MPR)	Not feasible
Treatment Compliance	Higher (pre-surgery)	Lower (post-surgical deconditioning)
Predictive Biomarkers	Enables early biomarker exploration	Limited due to absence of tumor
Survival Evidence	Improved EFS (e.g., CheckMate 816)	Shown in select settings
Immunoediting/Memory	More effective immune priming	Less optimal
Drawbacks	Surgical delay risk due to irAEs	Generally no surgical delay

Summary of Landmark Trials

Tumor Type	Trial Name / ID	Phase	Perioperative Arm	Adjuvant Arm / Comparator	Key Results / Findings
NSCLC	CheckMate 816	III	Neoadj. Nivolumab + chemo	Neoadj. chemo alone	↑ pCR, ↑ EFS, better downstaging
NSCLC	AEGEAN	III	Durvalumab + neoadj. chemo → adj. durva	Chemo + placebo → placebo	↑ EFS, ↑ pCR
NSCLC	IMpower030	III	Atezolizumab + neoadj. chemo → adj. atezo	Chemo → placebo	Ongoing; EFS primary
NSCLC	KEYNOTE-671	III	Chemo + neoadj. pembro → adj. pembro	Chemo + placebo	↑ EFS, ↑ pCR
Melanoma	OpACIN/OpACIN-neo	II	Neoadj. ipi+nivo ± adj.	Adjuvant ipi+nivo	↑ T-cell response, ↓ relapse
Melanoma	PRADO	II	Neoadj. ipi+nivo → tailored adj.	Historical adjuvant	61% MPR, reduced overtreatment
Melanoma	SWOG S1801	III	Neoadj. + adj. pembrolizumab	Adjuvant pembro only	↑ EFS (72% vs 49%)
Bladder	NIAGARA	III	Chemo + durva → adj. durva	Chemo only	We are discussing
Bladder	PURE-01 / ABACUS	II	Neoadj. atezo/pembro	No adjuvant	↑ pCR, immune markers
Bladder	CheckMate 274	III	Adjuvant nivolumab	Placebo	↑ DFS esp. in PD-L1 ≥1%
TNBC	KEYNOTE-522	III	Neoadj. chemo + pembro → adj. pembro	Chemo + placebo	↑ pCR, ↑ 3-yr EFS
Esophageal	CheckMate 577	III	Adjuvant nivolumab	Placebo	↑ DFS (22.4 vs 11 mo)

The Phase III CheckMate 274 study evaluated nivolumab vs. placebo for adjuvant treatment of MIBC[1,2]

- Eligible patients had undergone radical surgery with or without cisplatin-based NACT and were at high risk
- of recurrence, irrespective of PD-L1 status[1,2]

- Adults age ≥18 years
- Radical surgery within 120 days ± neoadjuvant cisplatin or ineligible for/declined cisplatin-based chemotherapy
- Evidence of urothelial cancer at high risk of recurrence per pathologic staging
- Disease free by imaging

1:1

Nivolumab
240 mg IV Q2W
(n=353)

Placebo
Q2W
(n=356)

Treatment for up to 1 year

Primary endpoints:
- DFS (INV)
- DFS (PD-L1 ≥1% population)

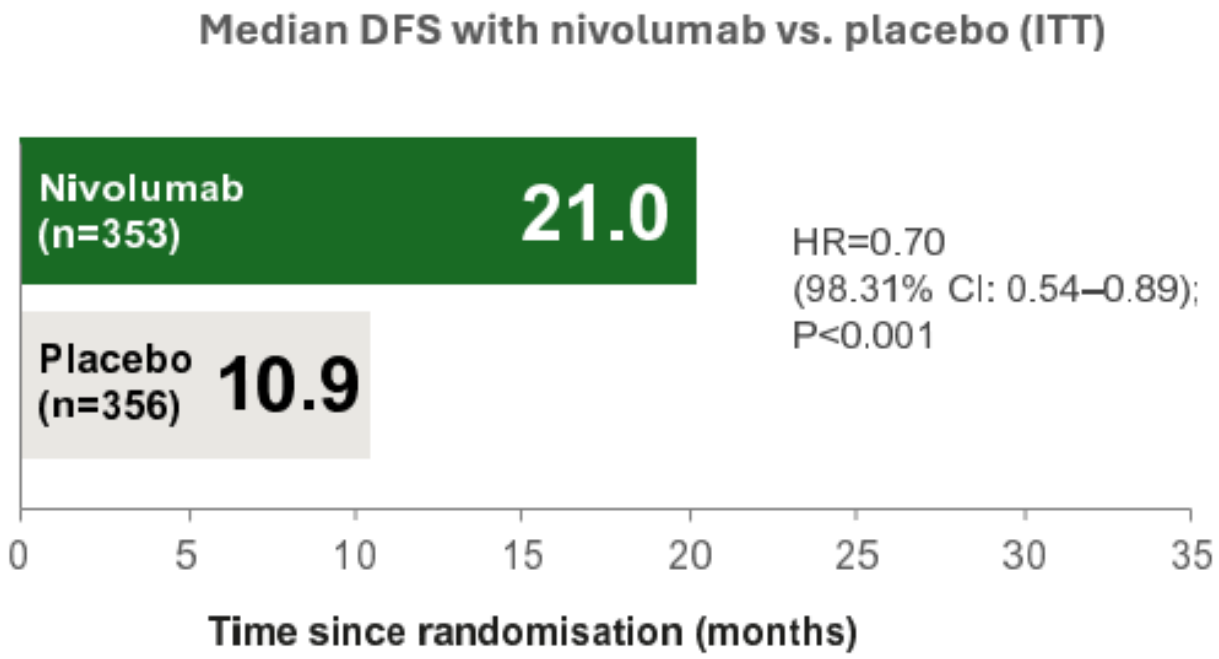
Secondary endpoints:
- OS
- NUTRFS
- DSS
- Safety/tolerability (exploratory)

1. Bajorin DF, et al. Presented at ASCO Annual Meeting; 17–19 February 2020; Virtual Congress; 2. NCT02632409. Available at: https://clinicaltrials.gov/ct2/show/NCT02632409.

2. Images are for representation purpose only. AstraZeneca is not responsible for any copyright.

Patients who received adjuvant nivolumab significantly improved DFS vs. placebo

- DFS was similarly improved in both the ITT population and PD-L1 subgroup. AEs were manageable and consistent with observations from previous studies



AE, %	Nivolumab (n=351)	Placebo (n=348)
Any Grade TRAE	77.5	55.5
Grade 3–4 TRAEs	17.9	7.2

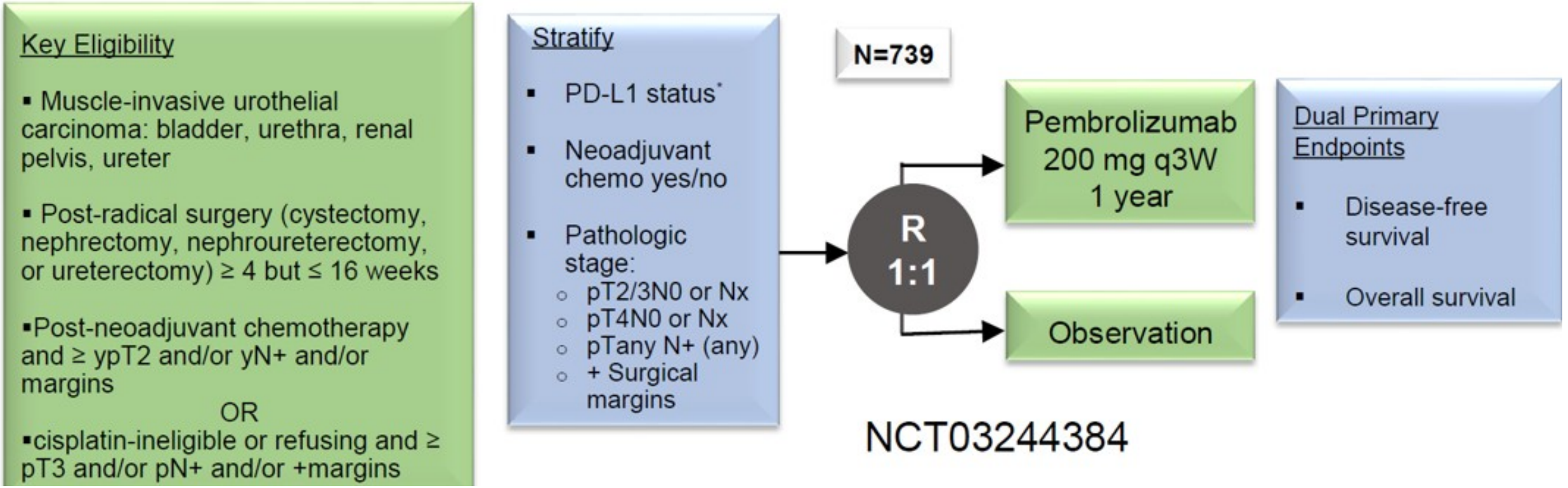
Nivolumab received FDA and EMA approvals for patients with PD-L1 ≥1% in August 2021 and April 2022 respectively[2,3]

1. Bajorin DF, et al. Presented at ASCO GU Annual Meeting; 11–13 February 2021; Virtual Congress; 2. FDA. FDA approves nivolumab for adjuvant treatment of urothelial carcinoma. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-nivolumab-adjuvant-treatment-urothelial-carcinoma ; 3. Bristol Myers Squibb. Bristol Myers Squibb Receives European Commission Approval for Opdivo (nivolumab) as Adjuvant Treatment for Patients with Radically Resected, High-Risk Muscle-Invasive Urothelial Carcinoma with Tumor Cell PD-L1 Expression ≥1%. April 2022. Available from: https://news.bms.com/news/details/2022/Bristol-Myers-Squibb-Receives-European-Commission-Approval-for-Opdivo-nivolumab-as-Adjuvant-Treatment-for-Patients-with-Radically-Resected-High-Risk-Muscle-Invasive-Urothelial-Carcinoma-with-Tumor-Cell-PD-L1-Expression-1/default.aspx

2. Images are for representation purpose only. AstraZeneca is not responsible for any copyright.

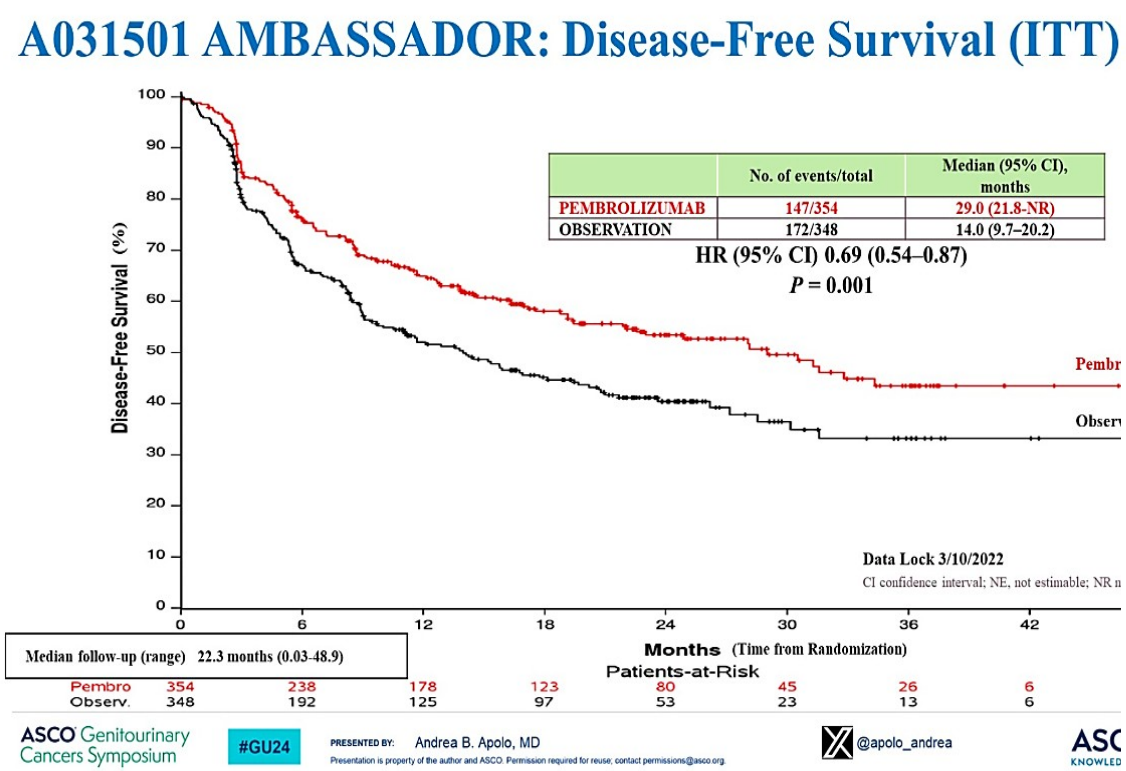
A031501 Ambassador study design

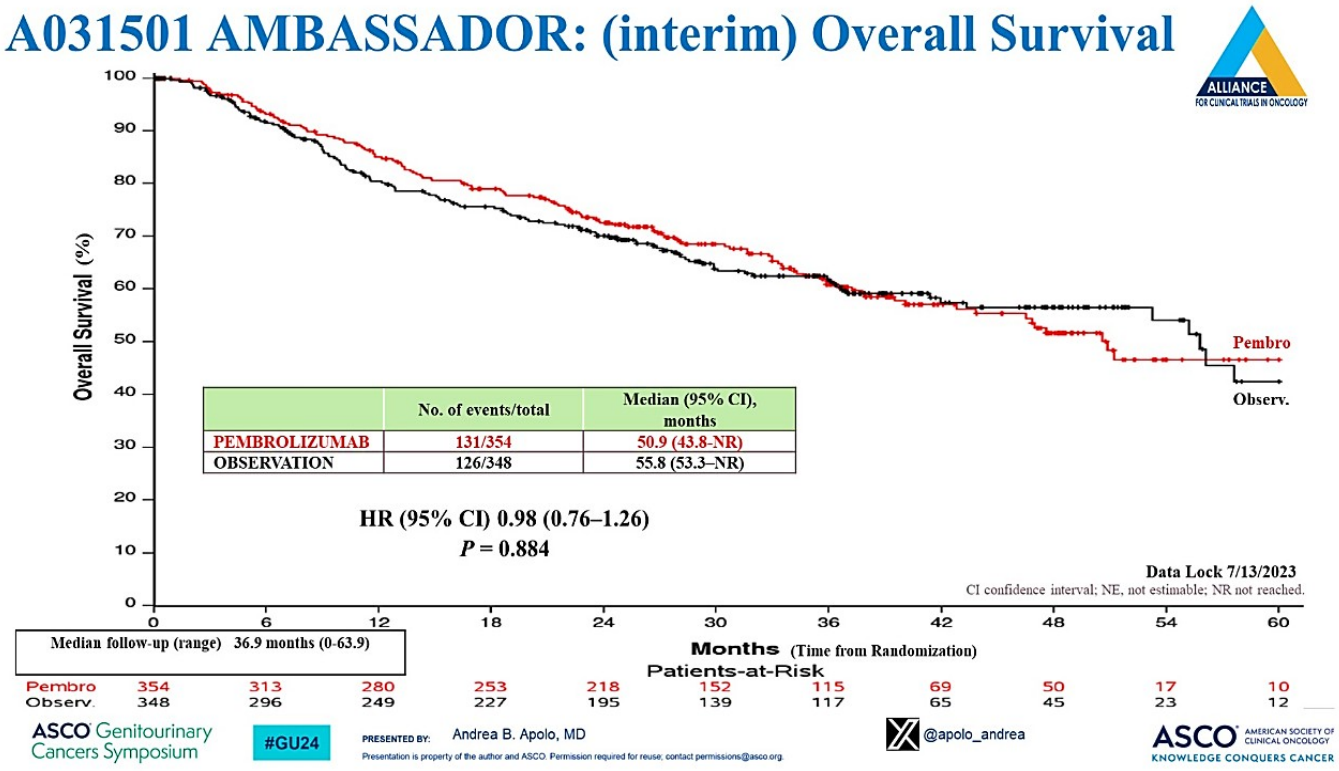
- Phase 2 randomised open label multicentre study of adjuvant pembrolizumab vs observation with patients with high risk MIBC



AMBASSADOR (ASCO-GU 2024)

- With medical f/u of 22.3 months,
- AMBASAADOR met DFS primary endpoint, DFS HR: 0.69 (95% CI, 0.54 – 0.87);
- But not OS primary endpoint, OS IA HR 0.98 (95% CI, 0.76 – 1.26)

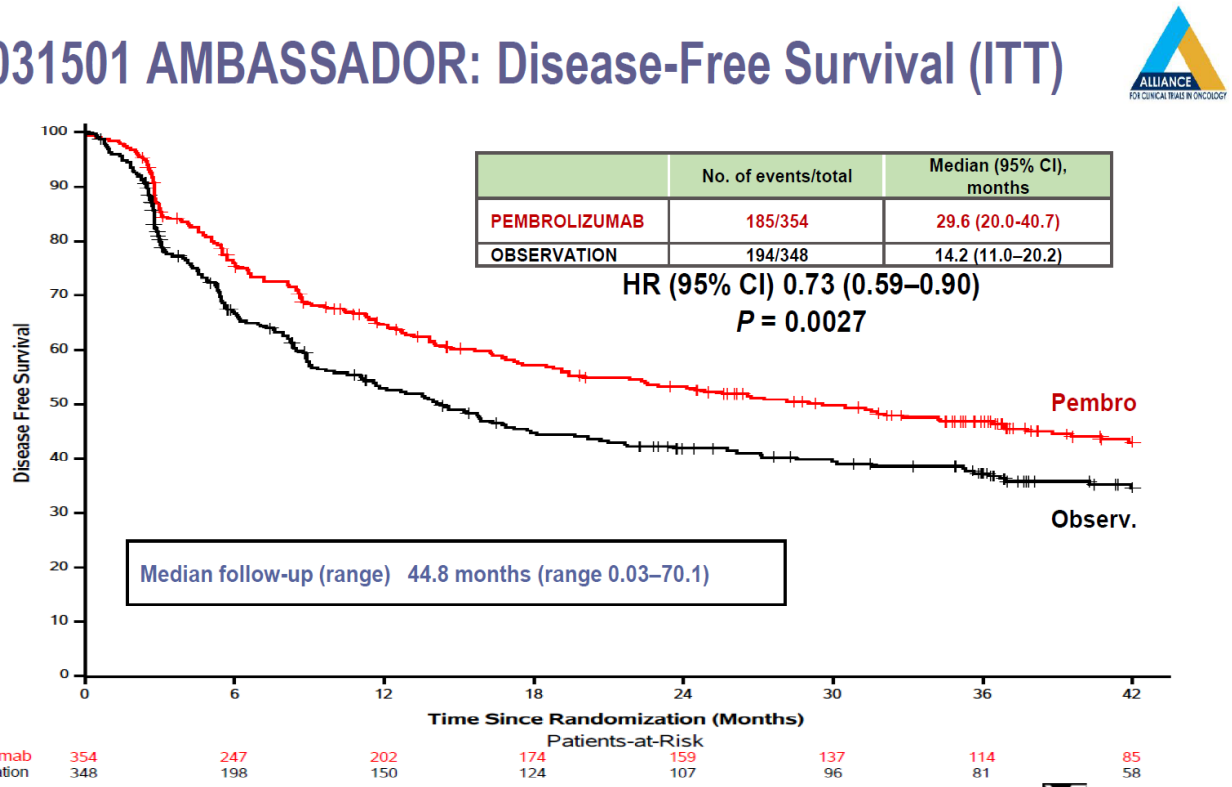




AMBASSADOR (ESMO 2024)

- With medical f/u of 44.8 months,
- AMBASAADOR showed a consistent DFS benefit, DFS HR: 0.73 (95% CI, 0.59 – 0.90);

  DFS benefit was shown regardless of PD-L1 expression and LN status
- But did not present OS result



Images are for representative purposes only. AstraZeneca is not responsible for any copyrights

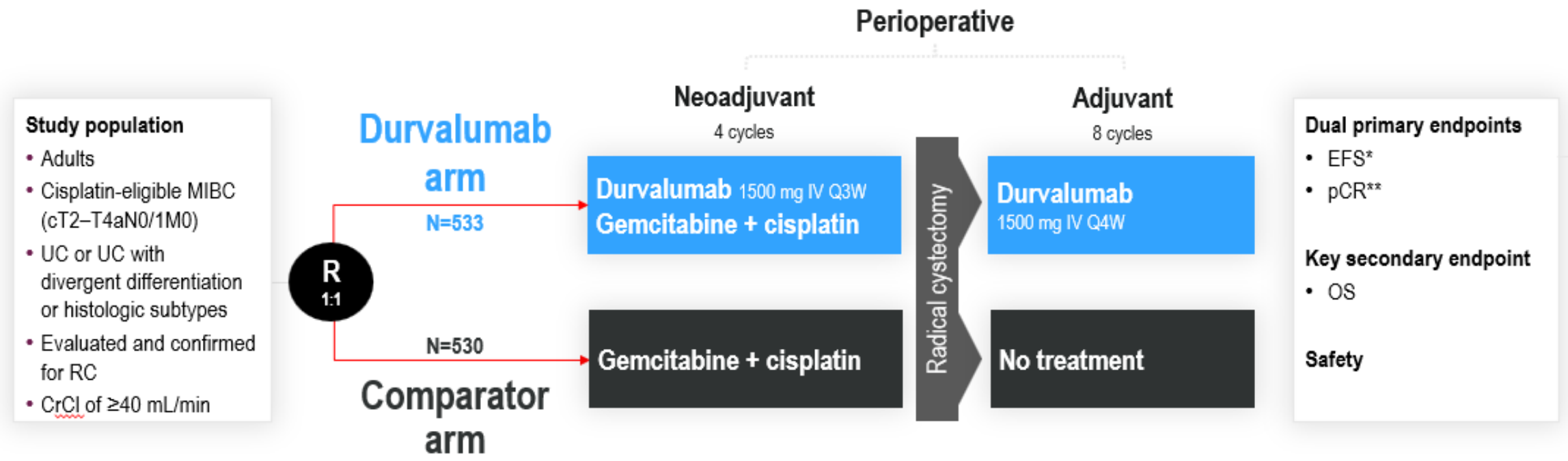
Apolo et al. Ambassador Journal of Clinical Oncology

Volume 42, Number 4_suppl

Andrea B. Apolo, MD @apolo_andrea

NIAGARA:
A Randomised Phase 3 Trial of Neoadjuvant Durvalumab Plus Chemotherapy Followed by Radical Cystectomy and Adjuvant Durvalumab in Muscle-invasive Bladder Cancer

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 was 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

July 2021. International Journal of Molecular Sciences·

NIAGARA: Baseline Characteristics (ITT)

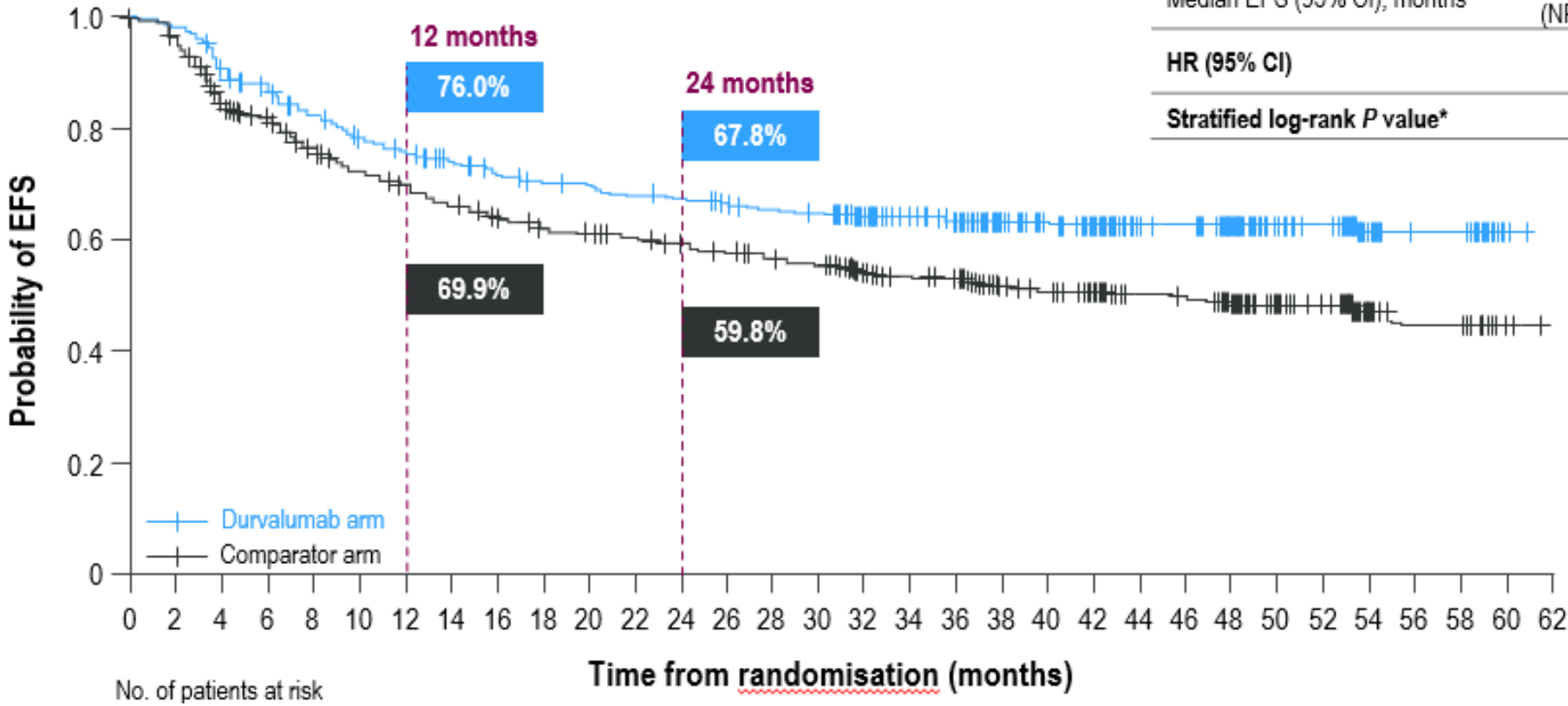
Characteristics		Durvalumab arm N=533	Comparator arm N=530
Age	Median, years (range)	65 (34–84)	66 (32–83)
Sex, %	Male	82	82
Race, %	White	66	68
	Asian	29	27
	Black/Other	2	1
	Not reported	3	4
ECOG PS, %	0	78	78
	1	22	22
Smoker, %	Yes (current or former)	71	75
Renal function, %	CrCl ≥60 mL/min	81	81
	CrCl ≥40–<60 mL/min	19	19
Tumour stage*, %	T2N0	40	40
	>T2N0	60	60
PD-L1 expression†, %	High	73	73
	Low/negative	27	27
Histology, %	UC	86	83
	UC with divergent differentiation or histologic subtypes	14	17
Regional lymph nodes, %	N0	95	94
	N1	5	6

Ki

July 2021. International Journal of Molecular Sciences·

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

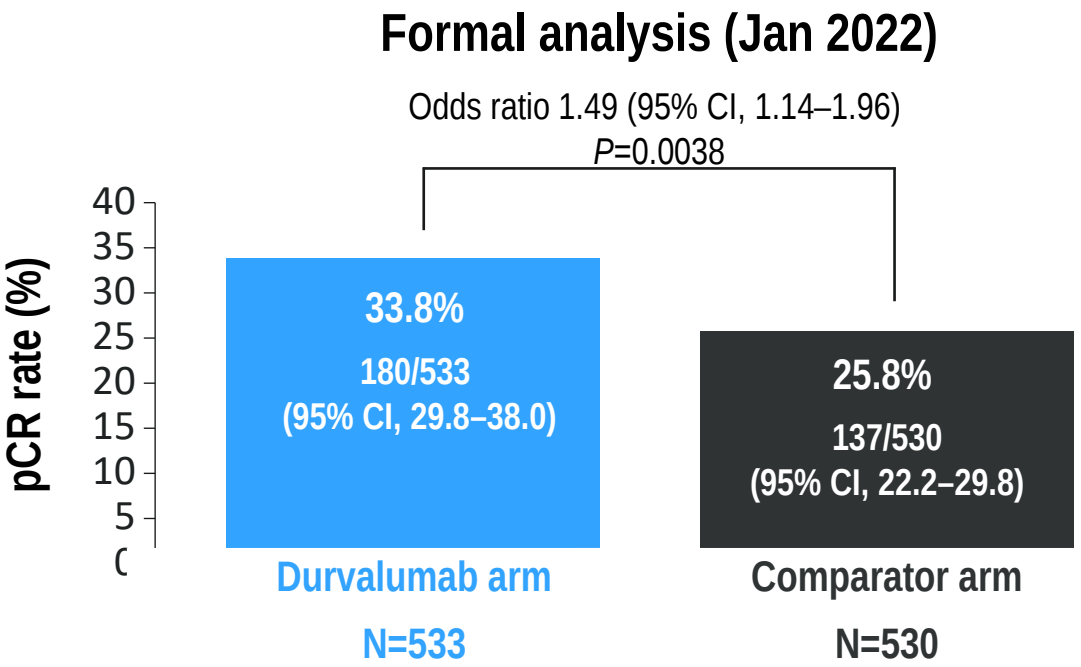
	Durvalumab arm N=533	Comparator arm N=530
Number of events, n (%)	187 (35.1)	246 (46.4)
Median EFS (95% CI), months	NR (NR–NR)	46.1 (32.2–NR)
HR (95% CI)	**0.68 (0.56–0.82)**	
Stratified log-rank *P* value*	**<0.0001**	

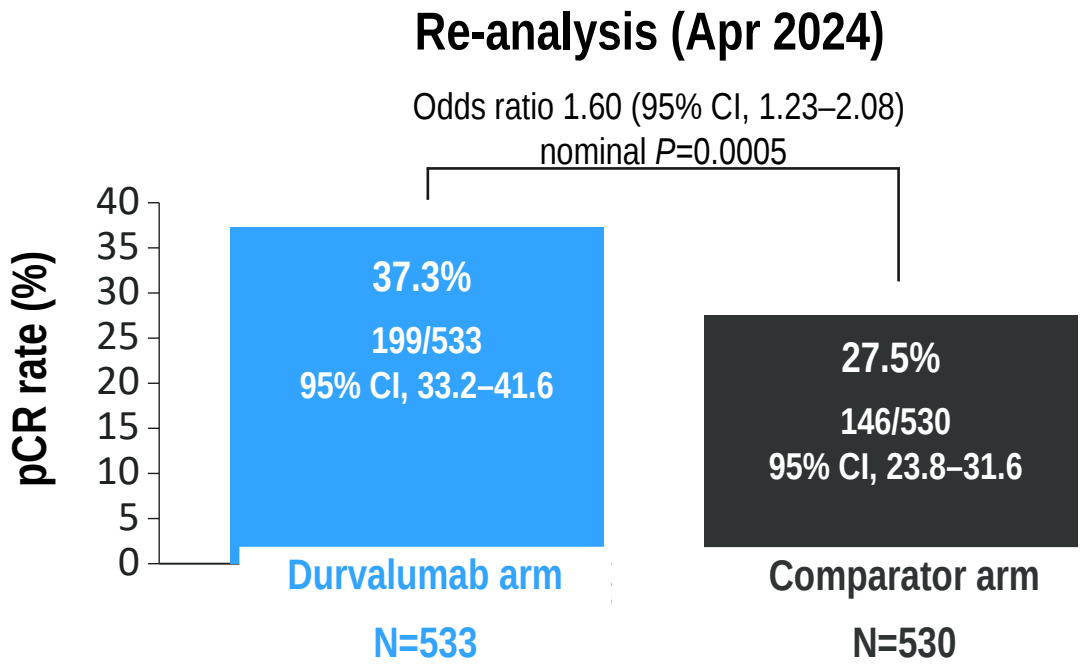


Median follow-up in censored patients: 42.3 months (range, 0.03–61.3)

July 2021. International Journal of Molecular Sciences·

NIAGARA: Pathologic Complete Response (ITT)



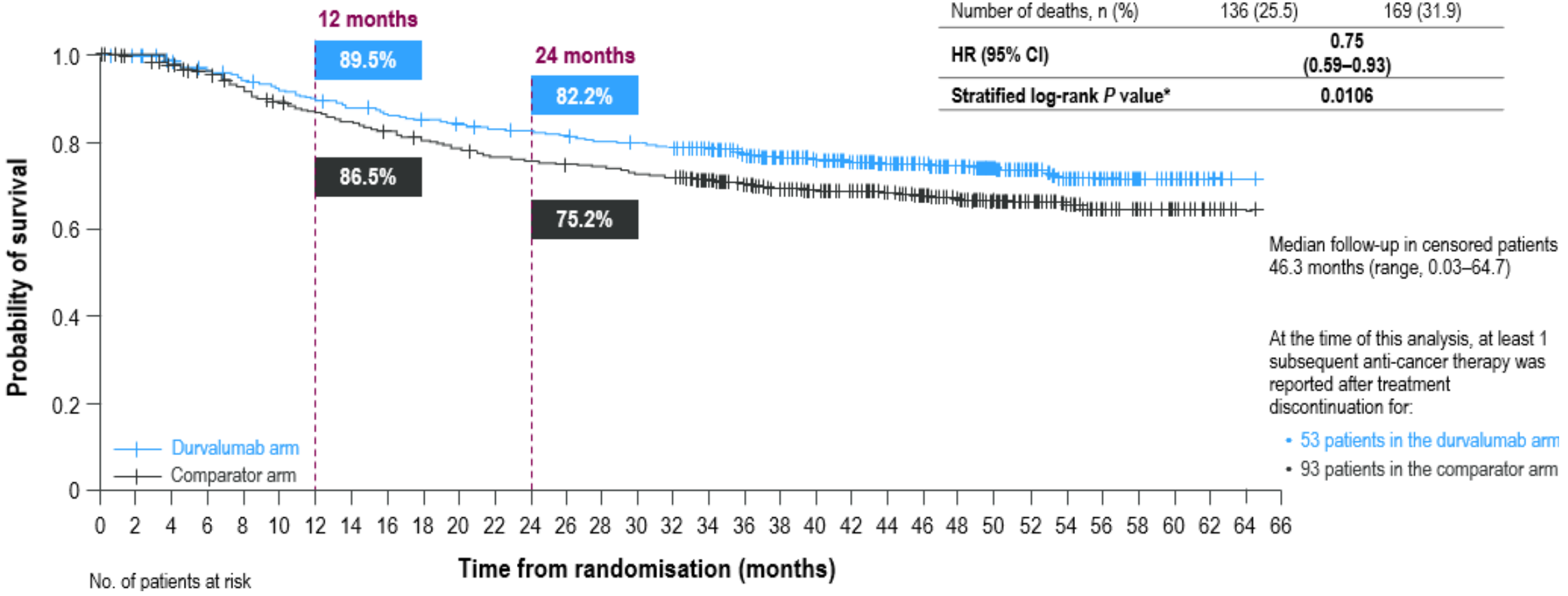


- The planned formal analysis for pCR was not statistically significant (threshold for significance, p-value 0.001)
- Due to a programming error, some results of 59 evaluable samples were incorrectly considered non-responders rather than their true result*

- The re-analysis showed nominal statistical significance in favour of the durvalumab arm
- This analysis includes the results of the 59 omitted samples (28 additional pCRs)*

Powels T et al. Perioperative Durvalumab with Neoadjuvant Chemotherapy in Operable Bladder Cancer. Presented at ESMO 2024. Presidential symposia. Published on 15 Sep NEJM Kim Ho et al. Perioperative Therapy for Muscle-Invasive Bladder Cancer: Current Evidence and Future Perspectives July 2021. International Journal of Molecular Sciences·

NIAGARA: Overall Survival (ITT)



	Durvalumab arm N=533	Comparator arm N=530
Number of deaths, n (%)	136 (25.5)	169 (31.9)
HR (95% CI)	0.75 (0.59–0.93)	
Stratified log-rank *P* value*	0.0106	

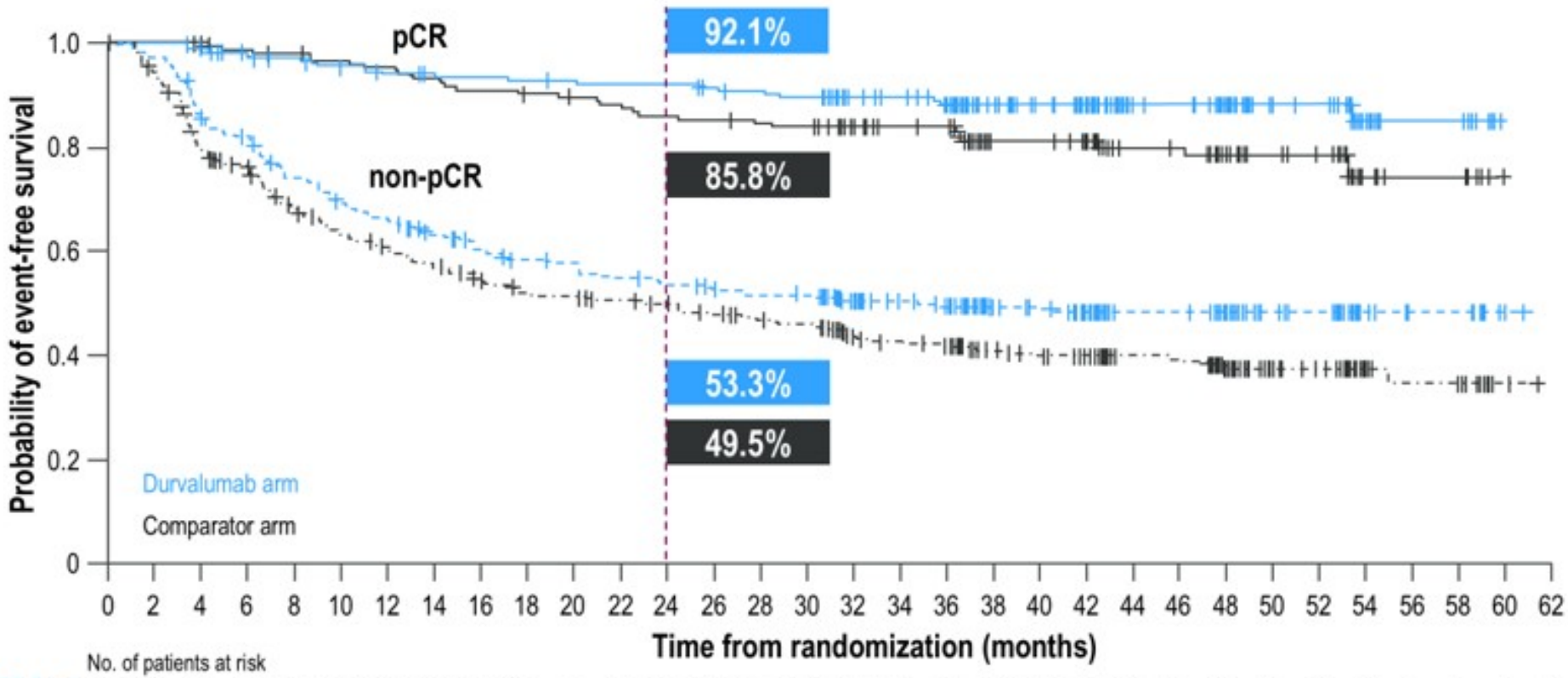
Median follow-up in censored patients 46.3 months (range, 0.03–64.7)

At the time of this analysis, at least 1 subsequent anti-cancer therapy was reported after treatment discontinuation for:

- 53 patients in the durvalumab arm
- 93 patients in the comparator arm

July 2021. International Journal of Molecular Sciences·

NIAGARA: EFS pCR and non pCR group



No. of patients at risk

pCR: D arm	199	199	195	188	185	180	176	174	173	172	171	170	170	166	164	162	145	142	134	111	103	90	70	69	57	40	39	14	9	9	0	0
pCR: C arm	146	146	144	140	139	136	134	131	128	126	124	121	119	118	116	115	105	101	100	79	79	73	58	57	38	30	27	9	6	6	0	0
non-pCR: D arm	334	320	280	266	239	221	210	196	183	176	173	165	160	155	151	150	137	127	121	103	99	89	71	71	58	46	42	18	11	11	1	0
non-pCR: C arm	384	352	293	275	242	222	209	197	185	174	172	167	162	155	148	144	123	118	114	98	93	86	74	72	56	39	35	15	12	10	2	0

pCR

	Durvalumab N=199	Comparator N=146
No. events, n (%)	23 (12)	29 (20)
Median EFS (95% CI), months	NR (NR–NR)	NR (NR–NR)
EFS HR (95% CI)	**0.58** (0.332–0.999)	

non-pCR

	Durvalumab N=334	Comparator N=384
No. events, n (%)	164 (49)	217 (57)
Median EFS (95% CI), months	34.7 (20.5–NR)	22.8 (15.5–30.6)
EFS HR (95% CI)	**0.77** (0.631–0.948)	

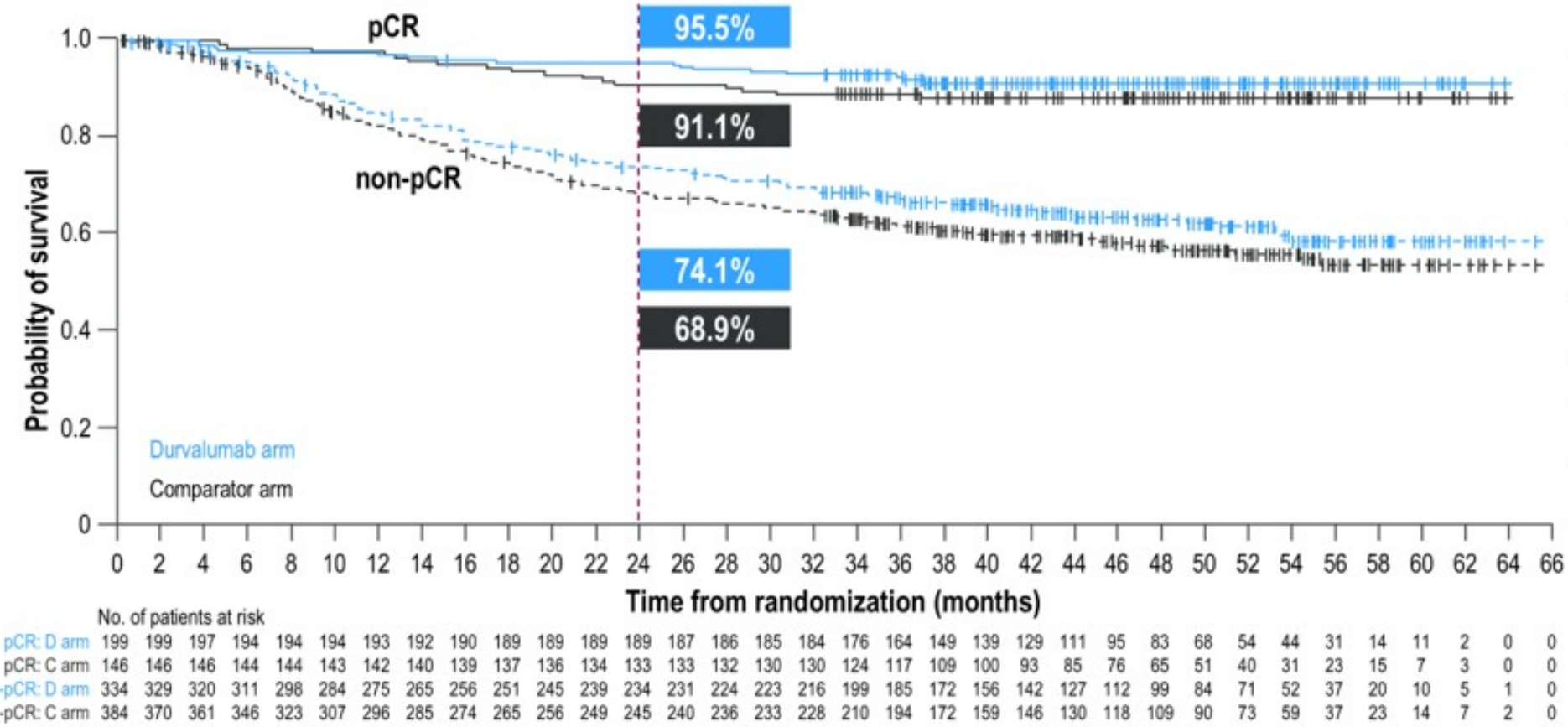
ITT

EFS HR	**0.68**
(95% CI)	(0.56–0.82)

Data cutoff Apr 29, 2024. Exploratory post-hoc analysis. Event-free survival by blinded independent central review or by central pathology review. Tick marks indicate patients with censored data. C, comparator; D, durvalumab; EFS, event-free survival; HR, hazard ratio; ITT, intent-to treat population; NAC, neoadjuvant chemotherapy; pCR, pathological complete response.

July 2021. International Journal of Molecular Sciences·

NIAGARA: Overall survival pCR and non pCR group



pCR

	Durvalumab N=199	Comparator N=146
No. deaths, n (%)	17 (9)	17 (12)
Median OS (95% CI), months	NR (NR–NR)	NR (NR–NR)
OS HR (95% CI)	**0.72** (0.367–1.426)	

non-pCR

	Durvalumab N=334	Comparator N=384
No. deaths, n (%)	119 (36)	152 (40)
Median OS (95% CI), months	NR (NR–NR)	NR (53.9–NR)
OS HR (95% CI)	**0.84** (0.660–1.068)	

ITT

OS HR (95% CI)	**0.75** (0.59–0.93)

Data cutoff Apr 29, 2024. Exploratory post-hoc analysis. Tick marks indicate patients with censored data. C, comparator; D, durvalumab; HR, hazard ratio; ITT, intent-to treat; NAC, neoadjuvant chemotherapy; pCR, pathological complete response; OS, overall survival.

Kim Ho et al. Perioperative Systemic Treatment for Muscle-Invasive Bladder Cancer: Current Evidence and Future Perspectives

July 2021. International Journal of Molecular Sciences·

NIAGARA: AE Summary (Safety Population)

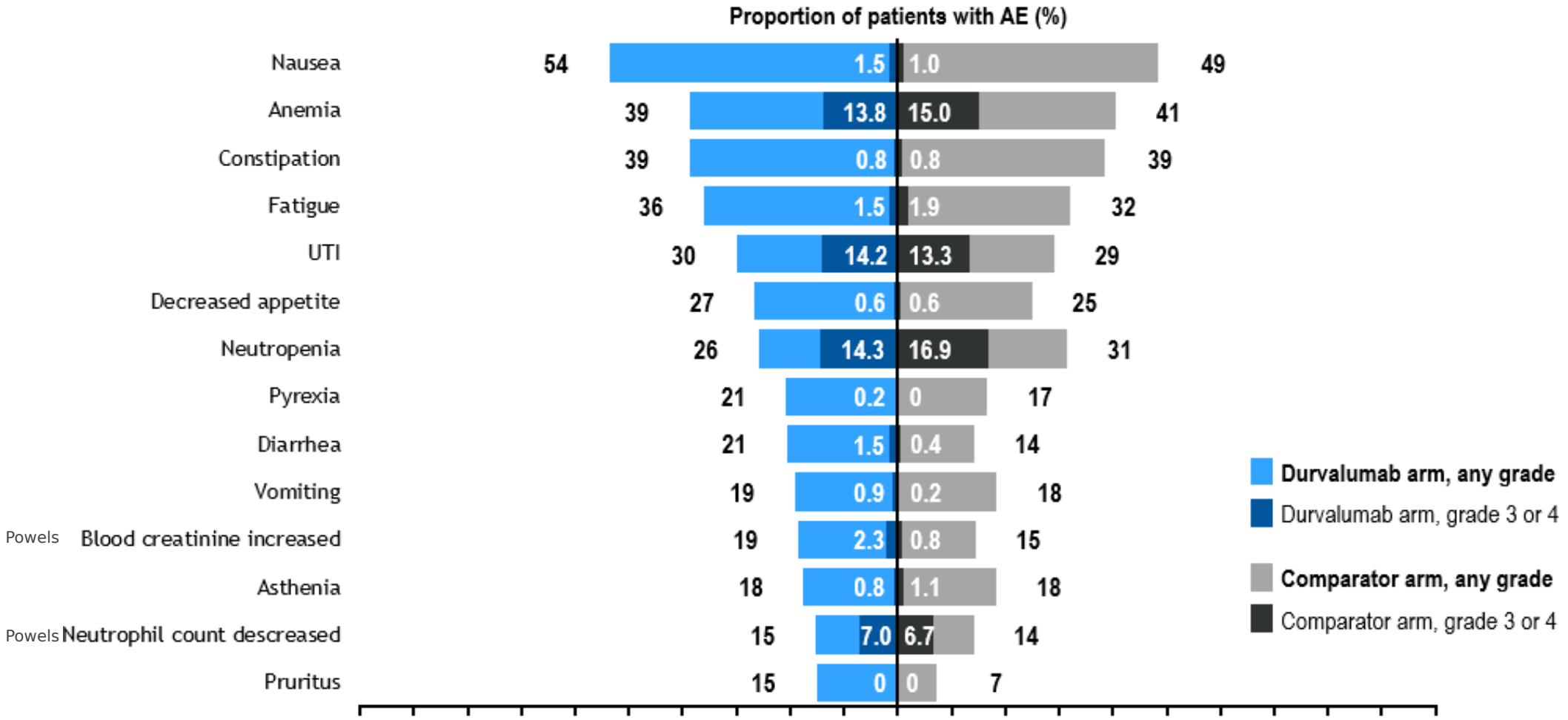
Overall study period (unless otherwise stated)	Durvalumab arm N=530	Comparator arm N=526
AEs of any cause, n (%)	527 (99)	525 (100)
Grade 3 or 4	368 (69)	355 (68)
Serious AEs	326 (62)	287 (55)
Outcome of death	27 (5)	29 (6)
Leading to discontinuation of study treatment	112 (21)	80 (15)
Leading to discontinuation of neoadjuvant durvalumab	50 (9)	---
Leading to discontinuation of NAC	72 (14)	80 (15)
Leading to patient not undergoing RC	6 (1)	7 (1)
Leading to delay in surgery*	9 (2)	6 (1)
Leading to discontinuation of adjuvant durvalumab	30/383† (8)	---
AEs possibly related to any treatment, n (%)‡	502 (95)	487 (93)
Grade 3 or 4 (treatment related)	215 (41)	215 (41)
Outcome of death (treatment related)	3 (0.6)	3 (0.6)
Any-grade immune-mediated AEs	111 (21)	16 (3)

Pow

Kim Ho et al. Perioperative Systemic Treatment for Muscle-Invasive Bladder Cancer: Current Evidence and Future Perspectives

July 2021. International Journal of Molecular Sciences·

NIAGARA: Most Frequently Reported AEs (Overall)



Kim Ho et al. Perioperative Systemic Treatment for Muscle-Invasive Bladder Cancer: Current Evidence and Future Perspectives

July 2021. International Journal of Molecular Sciences·

What are your thoughts on efficacy end points?

Would you consider giving chemotherapy in patients with CrCl of 40-60 ml/min?

What do you think about the side effect profile of the NIAGARA regimen?

How do you decide which patient should receive perioperative or adjuvant IO therapy?

Would you offer perioperative Chemo-IO in this patient?

What do you feel are the strengths and weakness of the NIAGARA study?

Strength of NIAGARA trial

1. First Study on IO in Perioperative MIBC – Evaluates the role of immunotherapy in both neoadjuvant and adjuvant settings.
2. Modified Cisplatin Eligibility – Included patients with CrCl >40 ml/min, using a split-dose regimen for CrCl 40–60 ml/min.
3. Broad Patient Inclusion – Enrolled pure UC and UC with divergent differentiation/histologic subtypes.
4. Practice-Changing Trial – First to demonstrate an OS benefit in the perioperative MIBC setting.

Powels T et al. Perioperative Durvalumab with Neoadjuvant Chemotherapy in Operable Bladder Cancer . Presented at ESMO 2024. Presidential symposia. Published on 15 Sep NEJM

Limitation of NIAGARA trial

1. pCR as a Primary Endpoint – Reasonable for Phase II trials, but not yet validated as a surrogate for EFS/OS in neoadjuvant ICI therapy.
2. pCR vs. Survival Outcomes – Unclear if a 10% difference in pCR alone explains significant EFS/OS improvements.
3. Neo-Adjuvant vs. Adjuvant Impact – Study design does not distinguish the individual contributions of neoadjuvant vs. adjuvant therapy.
4. Need for Adjuvant Durvalumab – Should all patients, including ypT0/Tis/T1N0, receive adjuvant durvalumab?
5. Role of ctDNA – Could ctDNA incorporation guide treatment decisions and de-intensification strategies?
6. Post-Progression Management – Need clarity on treatment options after progression, including IO rechallenge in metastatic urothelial carcinoma (mUC).

Powels T et al. Perioperative Durvalumab with Neoadjuvant Chemotherapy in Operable Bladder Cancer . Presented at ESMO 2024. Presidential symposia. Published on 15 Sep NEJM

Thank you!

AstraZeneca PLC, 1 Francis Crick Avenue, Cambridge Biomedical Campus, Cambridge, CB2 0AA, UK
+44(0)203 749 5000
www.astrazeneca.com