ASOPROCÁNCER
Asociación Pro Congreso de Cancerología

XXII Congreso Colombiano de Cáncer

19, 20 y 21 de marzo de 2026

Inteligencia artificial en oncología
Atención integral centrada en el paciente

Centro de convenciones Neomundo
Bucaramanga

Con el aval de:

Dr. Juan Pablo Rojas Manrique

Carcinoma Urotelial Músculo-Invasivo Rol 2026:

¿Quién recibe Neoadyuvancia y quien Adyuvancia ?

XXII Congreso Colombiano de Cáncer

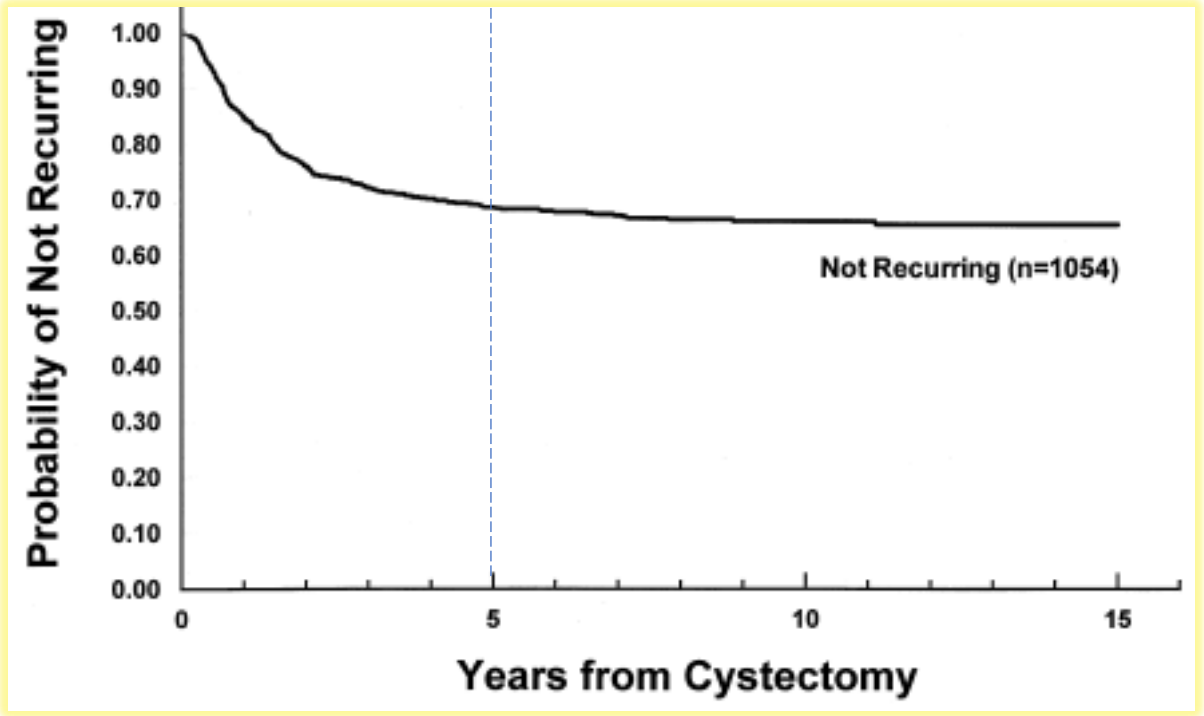
Disclosures

- Speaker honoraria: Adium, AstraZeneca, Bayer, Johnson & Johnson, Ipsen, MSD
- Advisory Board: Pfizer, Johnson & Johnson
- Clinical trials:
  - Site PI: MK-3475-B15, MK-3475-905 (perioperative bladder cancer trials)
  - Site SI: MK-5684-003, MK-5684-004 (mCRPC), EMBRACE trial (Janssen)

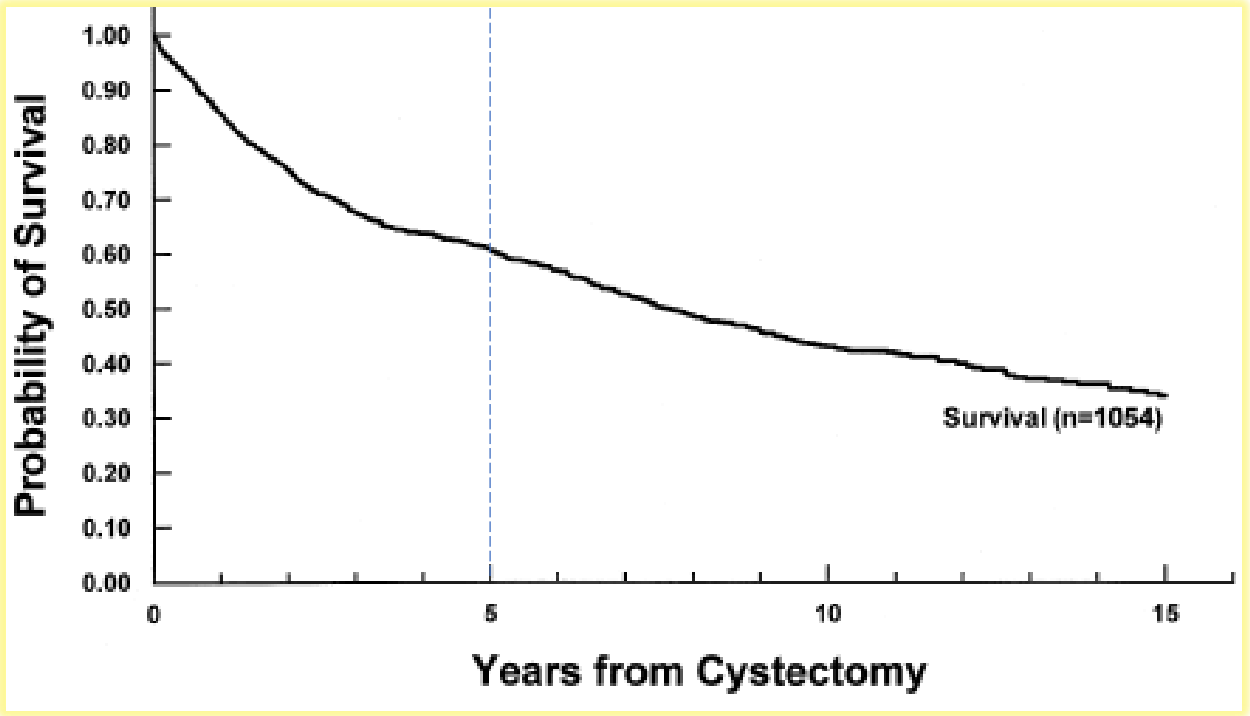
Rational for Perioperative Chemotherapy

University of Southern California – 1054 patients

Recurrence Free Survival



Overall Survival



Stein et. al., J Clin Oncol 2001.

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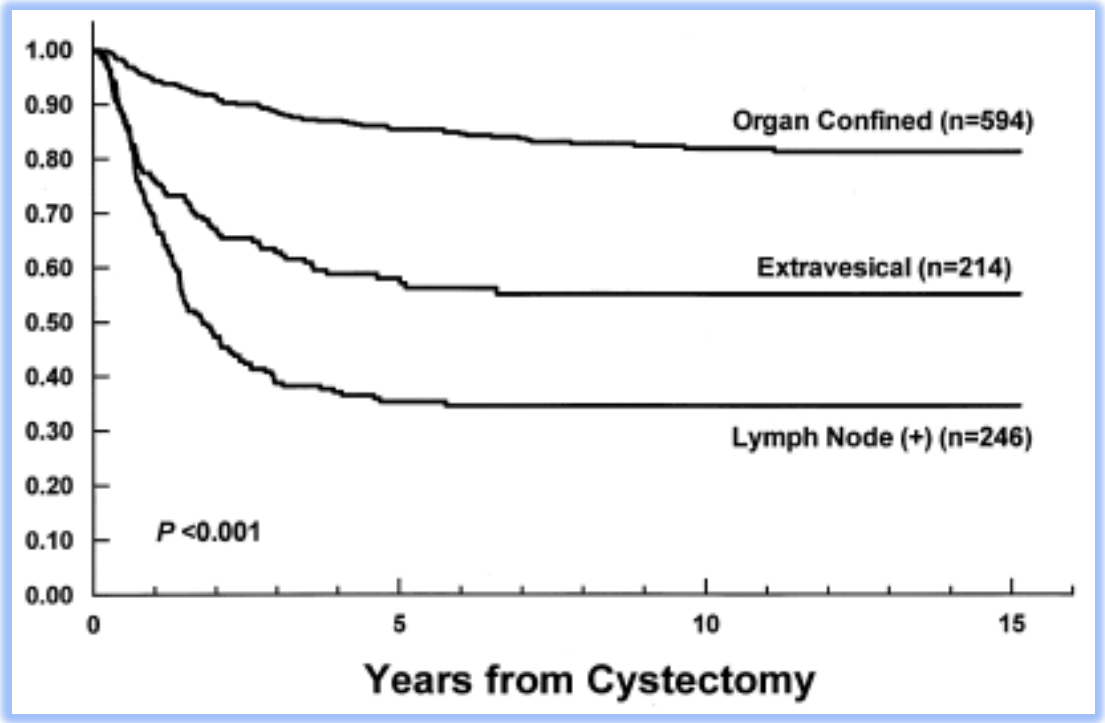
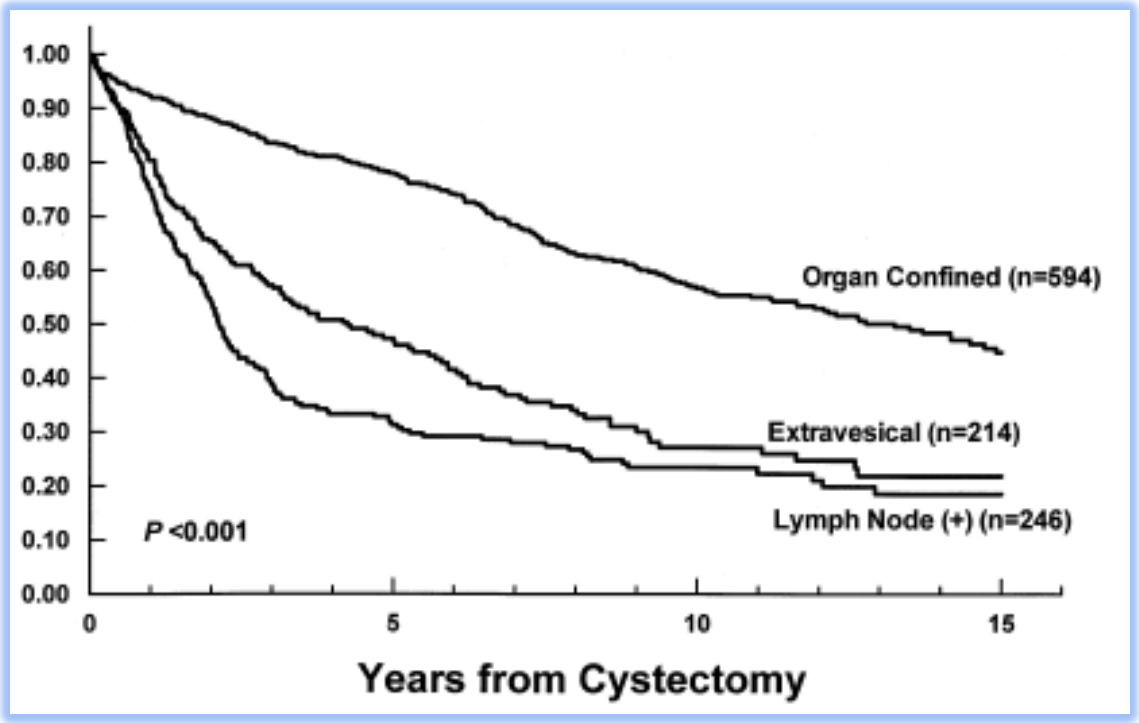


Overall Survival



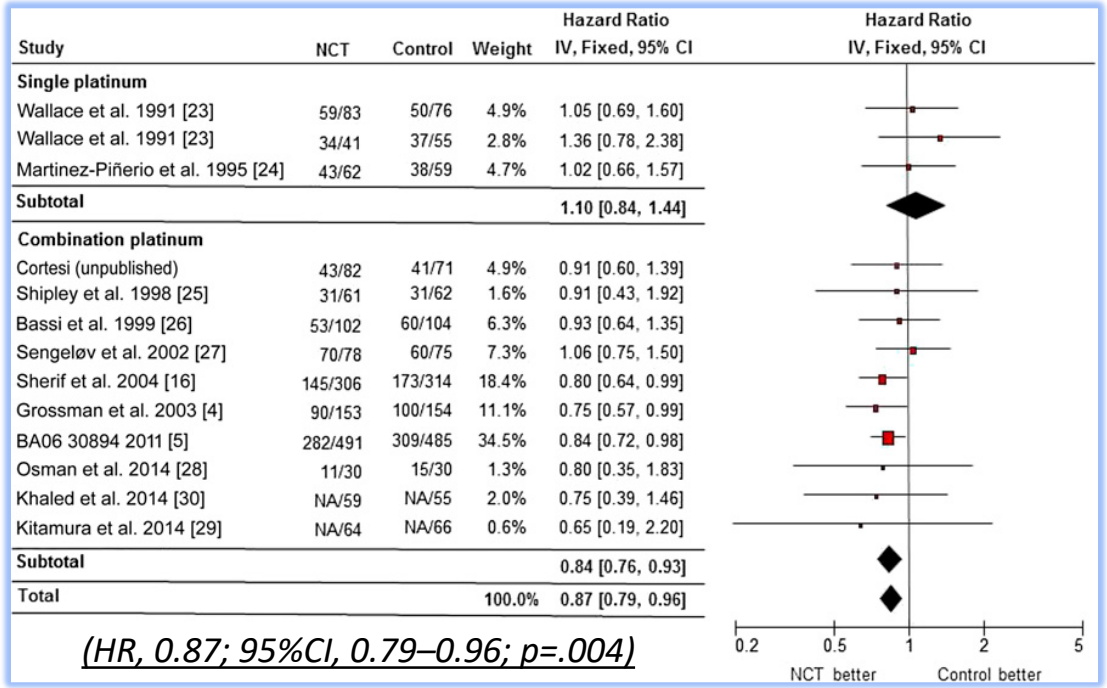
Stein et. al., J Clin Oncol 2001.

Neoadjuvant Chemotherapy

1. Meta Analysis (ABC MA Collaboration. Lancet 2003).
2. Meta Analysis (E. Winquist et. al. J Urol 2004).
3. Meta Analysis (ABC MA Collaboration. Eur Urol 2005).
4. Meta Analysis (M Yin. Oncologist 2016).
   - 3285 patients
   - 15 RCT Cisplatin based

LEVEL OF EVIDENCE 1A

OS cisplatin-based NCT vs Locoregional therapy alone



(HR, 0.87; 95%CI, 0.79–0.96; p=.004)

Cisplatin based combination Chemotherapy
5 – 8% absolute increase in OS

Neoadjuvant Chemotherapy Benefits

Downstaging of the primary tumor

Complete Response (***ypT0 N0***)

- 38% (Grossman et. al. NEJM 2003)
- 22.7% (Zargar et. al. Eur Urol 2016)

55% lower risk of death

81% lower risk of recurrence

- 5 yr OS: 80%
- 5 yr CSS: 96%

Pathologic stage is the main prognostic factor for survival

Rosenblatt et al., Eur Urol 2012; Petrelli et al., Eur Urol 2014.

Neoadjuvant Chemotherapy Regimens

GETUG/AFU V05 VESPER Trial Phase 3 RCT

Gem/Cis 4 Cycles	Vs	dd-MVAC 6 Cycles
Complete Response (***ypT0 N0***)		
71 pts (36%)	Vs	84 pts (42%)
	(p = 0.2)	

ddMVAC

- **Higher Local Control** rate (pCR, tumor downstaging or organ confined)
- Manageable Toxicity (**more anemia, nausea/vomiting and asthenia**)

Pfister et al., J Clin Oncol, 2022; Pfister et al., Eur Urol, 2021.

Adjuvant Chemotherapy
Meta-analysis from RCT

1183 patients - 10 RCT

Adjuvant cisplatin-based chemotherapy

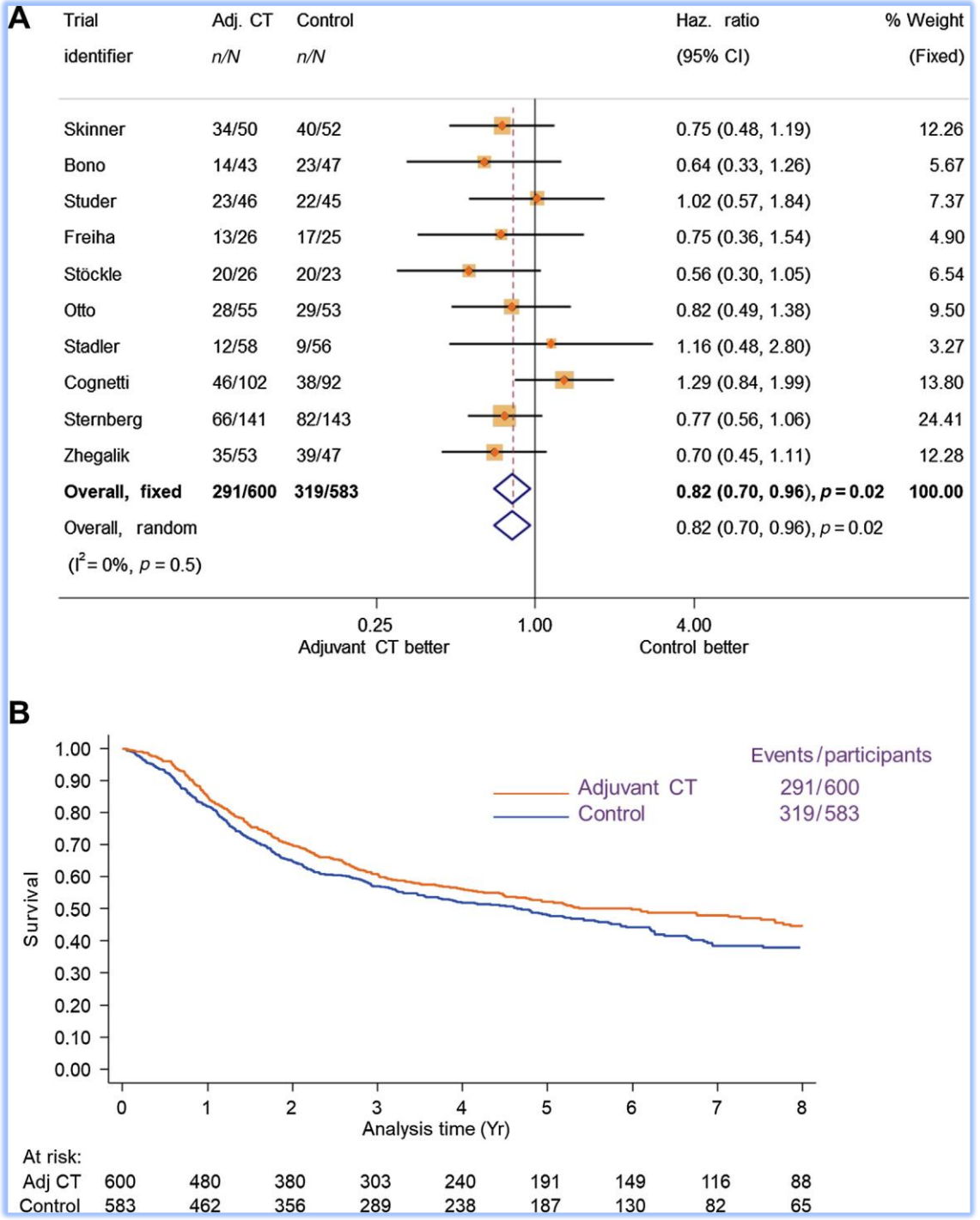
Vs

Observation

Key results

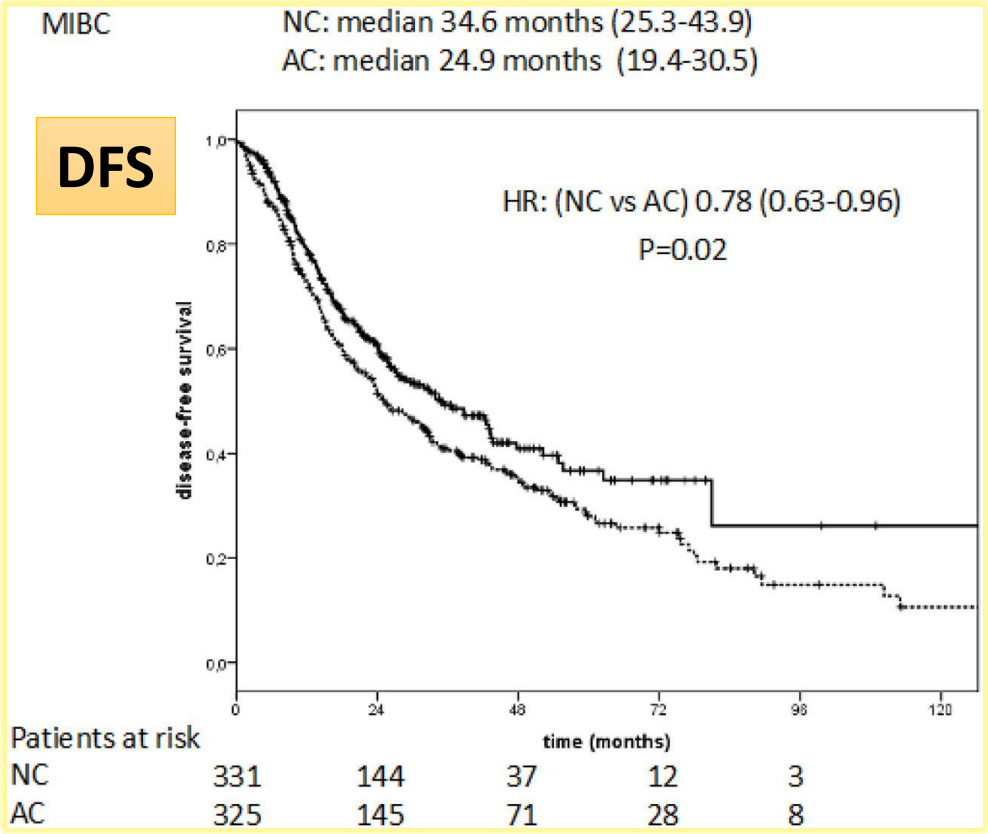
- **Overall survival: HR 0.82**
- Absolute OS benefit at 5 years: ~6%

ABC/ABCM Collaborators, Eur Urol 2022.



Neoadjuvant Vs. Adjuvant Chemotherapy

Retrospective International Study of Cancers of the Urothelial Tract



Del Bene et al., Frontiers in Oncology 2018.

Cisplatin eligibility after RC

- **~25% of patients** lose eligibility
- Mainly to **pop renal function decline**

	Neoadjuvant	Adjuvant
Initiation	**88.6%**	68.0%
Completion	**83.5%**	35.5%

Thompson et al. *BJU Int* 2014; Eldefrawy et al. *Urol Oncol* 2013.

Lessons from the Chemotherapy Era

- Both neoadjuvant and adjuvant chemotherapy improve outcomes
- Neoadjuvant chemotherapy has the strongest level of evidence
- Higher rates of treatment delivery and completion with NAC
- Retrospective studies generally favor neoadjuvant strategies

Neoadjuvant > Adjuvant

Inclusion Criteria of Adjuvant ICI Trials

CheckMate-274
(Nivolumab)

- **Inclusion criteria**
  - Radical surgery for muscle-invasive urothelial carcinoma
  - High risk of recurrence:
    - ypT2–ypT4a or ypN+ (after NAC)
    - pT3–pT4a or pN+ (no NAC)
  - Bladder or upper tract urothelial carcinoma

Primary endpoints:

- Disease-free survival (DFS) in intention-to-treat population
- Disease-free survival (DFS) in PD-L1 ≥1% population

Bajorin et al. *N Engl J Med.* 2021

IMvigor010
(Atezolizumab)

- **Inclusion criteria**
  - Radical surgery for muscle-invasive urothelial carcinoma
  - High risk of recurrence:
    - ypT2–ypT4a or ypN+ (after NAC)
    - pT3–pT4a or pN+ (no NAC)
  - Bladder or upper tract urothelial carcinoma

Primary endpoint:

- Disease-free survival (DFS) (investigator-assessed)

Bellmunt et al. *Lancet Oncol.* 2021

AMBASSADOR
(Pembrolizumab)

- **Inclusion criteria**
  - Radical surgery for muscle-invasive urothelial carcinoma
  - High risk of recurrence:
    - ypT2–ypT4a or ypN+ (after NAC)
    - pT3–pT4a or pN+ (no NAC)
  - Bladder or upper tract urothelial carcinoma

Co-primary endpoints:

- Disease-free survival (DFS)
- Overall survival (OS)

Apolo et al. *N Engl J Med.* 2024

CheckMate 274
NCT02632409

Phase 3, multicenter, double-blind, randomized trial
Randomization 1:1

Nivolumab n = 335 | Placebo n = 356

Median age: 65 years
Prior history of neoadjuvant treatment: 308 (43%)
Presence of pN+: 335 (47%)
PD-L1 expression (≥ 1%): 282 (40%)

Cancer location	No. (%) participants	
	Urinary bladder	Upper urinary tract
709 (100)	560 (79)	149 (21)

Median follow-up: 21.9 months

DFS **PD-L1 ≥ 1%:** 74.5% and 55.7%
HR, 0.55; 98.72% CI, 0.35 to 0.85
P<0.001

OS:
HR: 0.72 (95% CI, 0.59 to 0.89) p<0.001

Bajorin et al, NEJM 2021

IMvigor010
NCT02450331

Phase 3, multicentre, open-label, randomized trial
Randomization 1:1

Atezolizumab n = 406 | Placebo n = 403

Median age: 66-67 years
Prior history of neoadjuvant treatment: 385 (46%)
Presence of pN+: 420 (52%)
PD-L1 expression (IC0-1): 417 (52%)

Cancer location	No. (%) participants	
	Urinary bladder	Upper urinary tract
809 (100)	755 (93)	54 (7)

Median follow-up: 20 months

DFS:
19.4 mo. atezolizumab vs. 16.6 mo. placebo,
HR: 0.89 (95% CI 0.74–1.08), p=0.24

OS:
HR: 0.85 (95% CI 0.66-1.09), p>0.5

Bellmunt et al, Lancet Oncol 2021

AMBASSADOR
NCT03244384

Phase 3, multicentre, open-label, randomized trial
Randomization 1:1

Pembrolizumab n = 354 | Placebo n = 348

Median age: 68 years
Prior history of neoadjuvant treatment: 447 (64%)
Presence of pN+: 350 (50%)
PD-L1 expression (score ≥ 10): 404 (58%)

Cancer location	No. (%) participants	
	Urinary bladder	Upper urinary tract
702 (100)	548 (78)	154 (22)

Median follow-up: 44.8 months

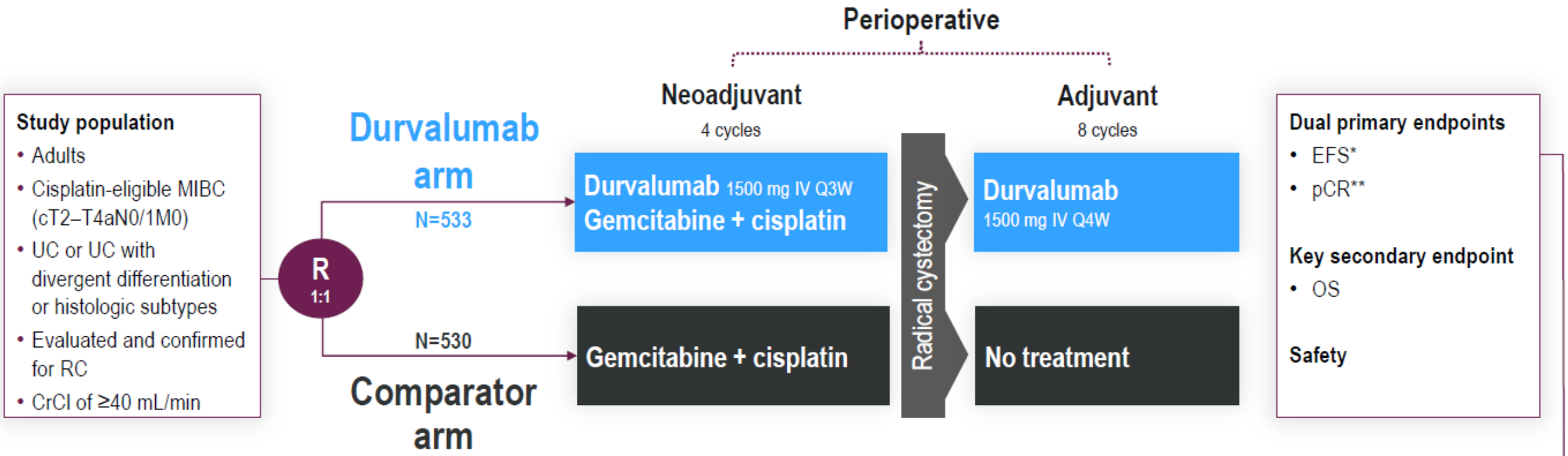
DFS:
29.6 mo. pembrolizumab vs. 14.2 mo. placebo,
HR: 0.73 (95% CI 0.59–0.90), p=0.003

OS:
HR: 0.98 (95% CI 0.76-1.26), p>0.5

Apolo et al, NEJM 2024

Adapted from UroToday (Scilipoti, Moschini & Briganti), 2024.

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

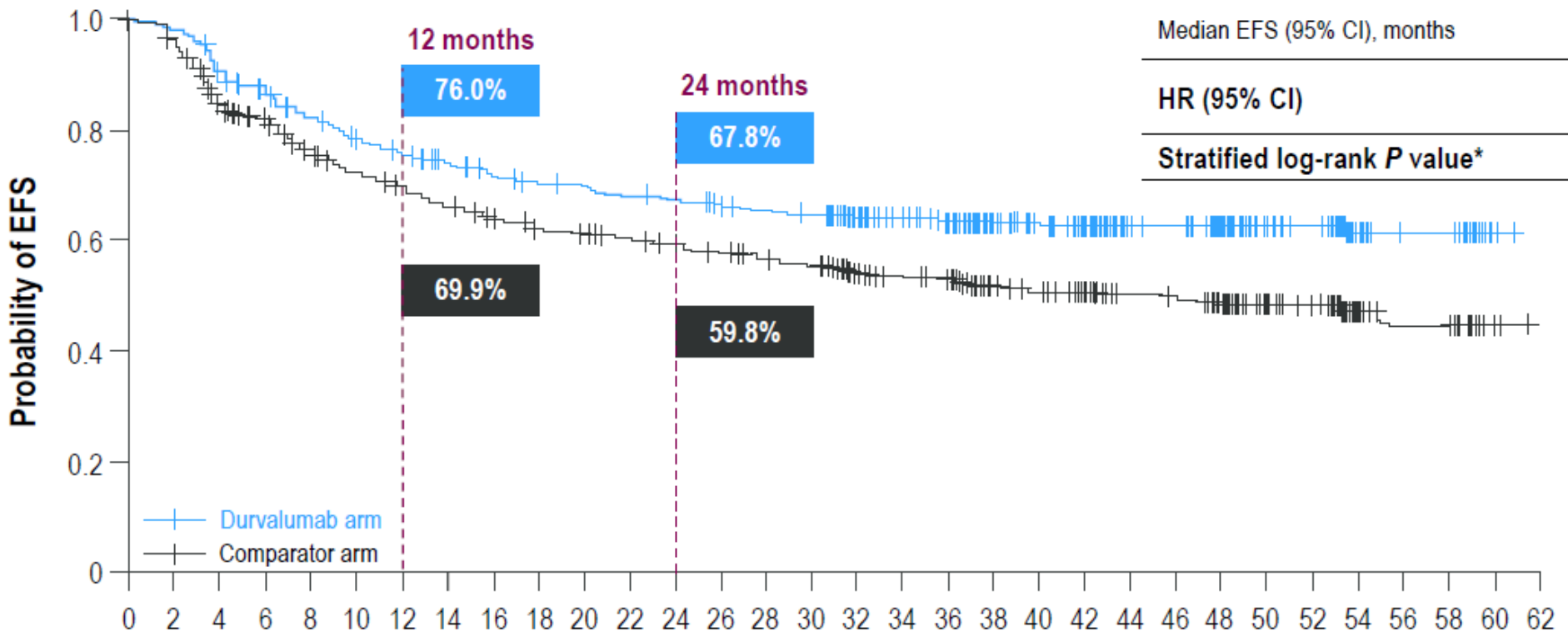
Other endpoints (not reported here): DFS, DSS, MFS, HRQoL, 5-year OS

*Evaluated by blinded independent central review or central pathology review (if a biopsy was required for a suspected new lesion). **Evaluated by blinded central pathology review.

ClinicalTrials.gov, NCT03732677; EudraCT number, 2018-001811-59. CrCl, creatinine clearance; DFS, disease-free survival; DSS, disease-specific survival; EFS, event-free survival; HRQoL, health-related quality of life; IV, intravenous; MFS, metastasis-free survival; MIBC, muscle-invasive bladder cancer; OS, overall survival; pCR, pathologic complete response; PD-L1, programmed cell death ligand-1; Q3W, every 3 weeks; Q4W, every 4 weeks; R, randomised; RC, radical cystectomy; UC, urothelial carcinoma..

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**	



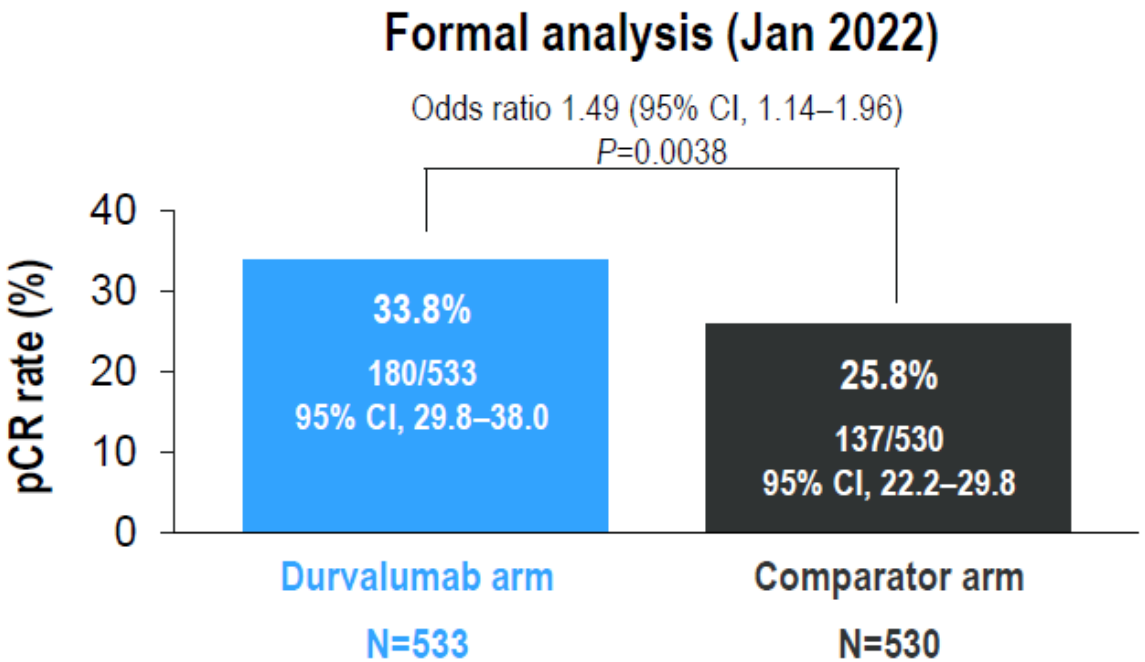
Median follow-up in censored patients: 42.3 months (range, 0.03–61.3)

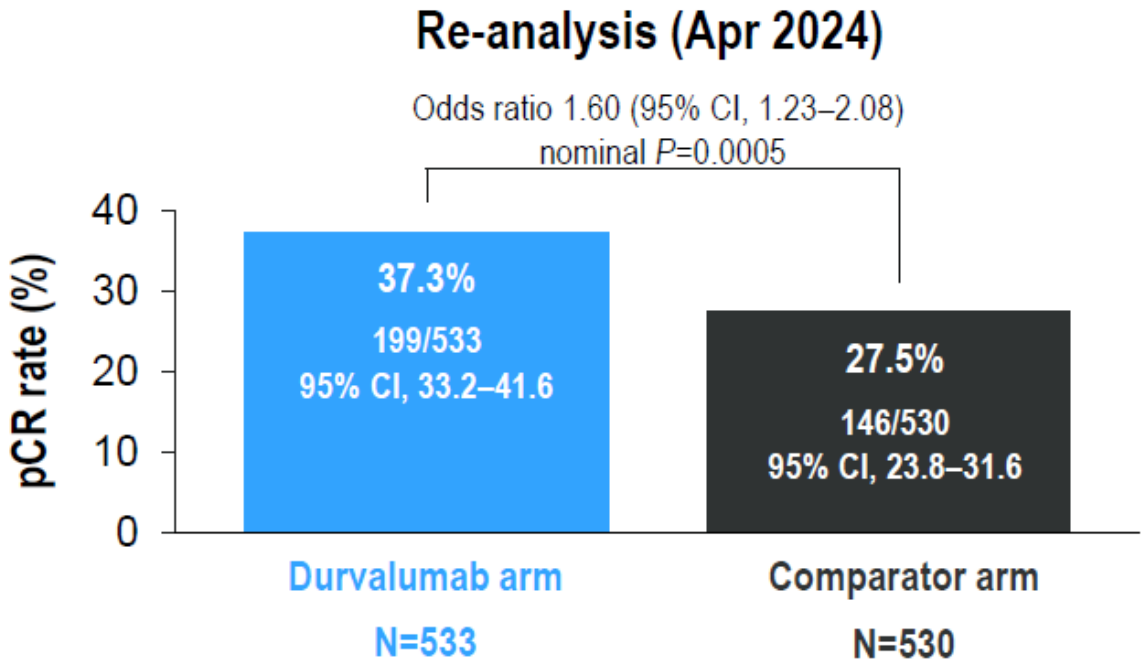
No. of patients at risk

Durvalumab arm	533	519	475	454	424	401	386	370	356	348	344	335	330	321	315	312	282	269	255	214	202	180	141	140	115	86	81	32	20	20	1	0
Comparator arm	530	498	437	416	381	358	343	328	313	300	296	288	281	273	264	259	228	219	214	177	172	159	132	129	94	69	62	24	18	16	2	0

EFS was assessed using RECIST v1.1. EFS is defined as the time from randomisation to the first: 1) progressive disease that precluded RC; 2) recurrence after RC; 3) date of expected surgery in patients who did not undergo RC; 4) death from any cause.
*The threshold to declare statistical significance was based on a Lan-DeMets alpha spending function with O'Brien-Fleming boundary – with the observed number of events, the boundary for declaring statistical significance was 0.04123 for a 4.9% overall 2-sided alpha.
Data cutoff 29 Apr 2024. CI, confidence interval; EFS, event-free survival; HR, hazard ratio; ITT, intent-to-treat population; NR, not reached; RC, radical cystectomy; RECIST, Response Evaluation Criteria In Solid Tumors.

NIAGARA: Pathologic Complete Response (ITT)



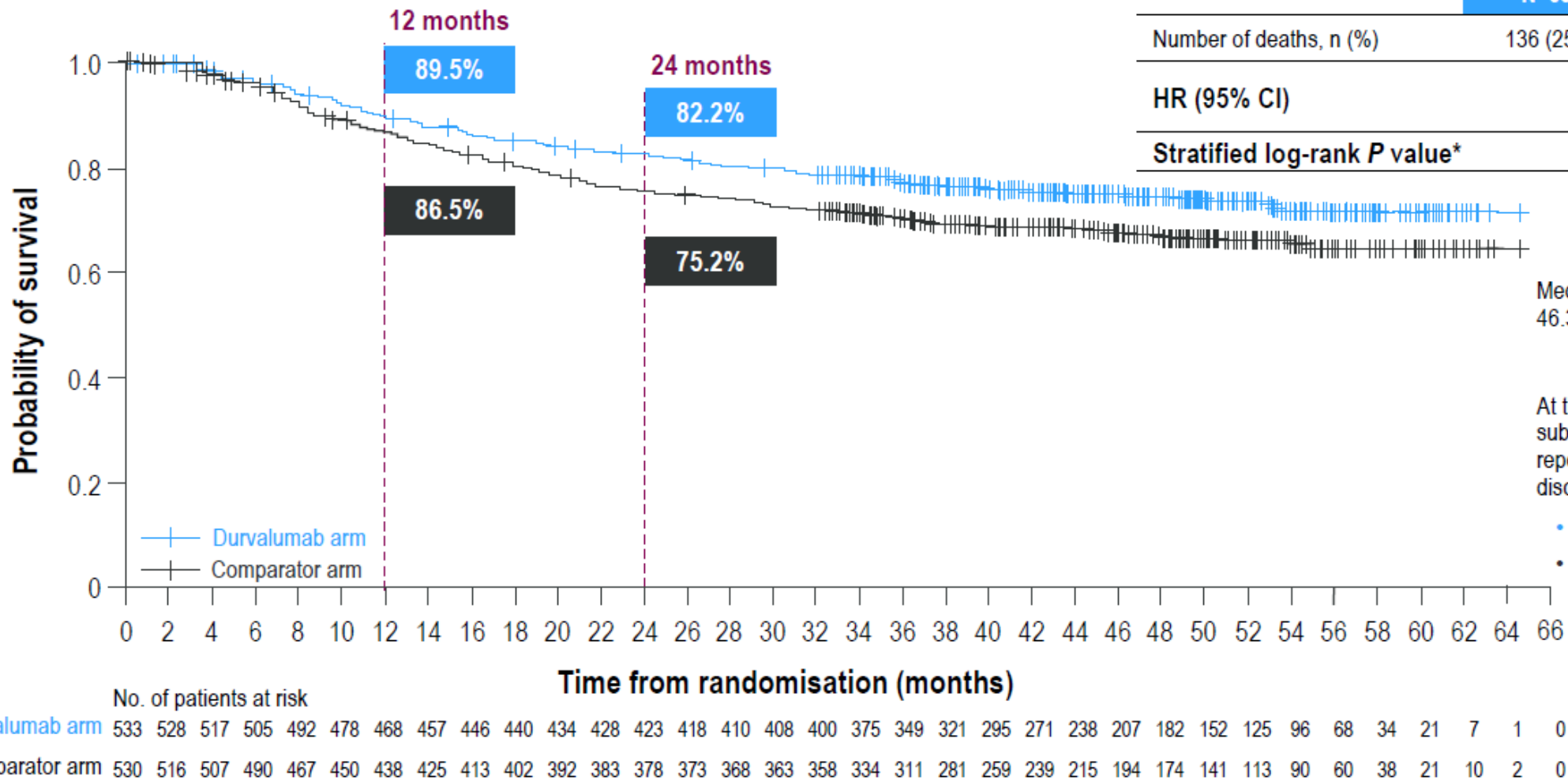


- The planned formal analysis for pCR was not statistically significant (threshold for significance, p-value 0.001)
- 59 evaluable samples were incorrectly considered non-responders rather than their true result*

- 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)*

*pCR was statistically tested as the final analysis in Jan 2022 (formal analysis). The results of 59 evaluable samples were omitted due to applying the DCO to the date of central review, rather than date of surgery. The re-analysis is a descriptive analysis of pCR rate and associated odds ratios that includes all samples from the formal pCR analysis and applies the DCO to the date of surgery for all samples. Alpha spend for the multiple testing procedure is associated with the formal pCR analysis only. pCR statistical significance was set at a threshold of 0.001.
95% CIs for the pCR rate are calculated using the Clopper-Pearson method. Odds ratio, corresponding CI, and *P* value are obtained using logistic regression adjusted for the stratification factors (renal function, tumour stage, and PD-L1 status). Pathological staging of samples taken during RC was performed centrally; pCR was the proportion of patients with stage T0N0M0 at RC (American Joint Committee on Cancer 8th edition classification). CI, confidence interval; DCO, data cutoff; ITT, intent-to-treat population; pCR, pathologic complete response; RC, radical cystectomy.

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

No. of patients at risk

Durvalumab arm	533	528	517	505	492	478	468	457	446	440	434	428	423	418	410	408	400	375	349	321	295	271	238	207	182	152	125	96	68	34	21	7	1	0
Comparator arm	530	516	507	490	467	450	438	425	413	402	392	383	378	373	368	363	358	334	311	281	259	239	215	194	174	141	113	90	60	38	21	10	2	0

OS is the time from the date of randomisation until death due to any cause regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy. *The threshold for statistical significance was based on a Lan-DeMets alpha spending function with O'Brien-Fleming boundary – with the observed number of events, the boundary for declaring statistical significance was 0.01543 for a 4.9% overall 2-sided alpha.
Data cutoff 29 Apr 2024. CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat population; OS, overall survival.

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)**

The safety population includes all patients who received treatment. *Recommended timeframe for RC was within 56 days after the last dose of NAC. †In patients who started adjuvant durvalumab. ‡Investigator-assessed causality.
The overall study period includes AEs that occurred between the first dose of study treatment, and whichever occurred first: 1) 90 days after the last dose of treatment, surgery, or last adjuvant visit; 2) date of first dose of subsequent anti-cancer therapy; or 3) data cutoff date.
Data cutoff 29 Apr 2024. AE, adverse event; NAC, neoadjuvant chemotherapy; RC, radical cystectomy.

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Data cutoff 29 Apr 2024. AE, adverse event; NAC, neoadjuvant chemotherapy; RC, radical cystectomy.

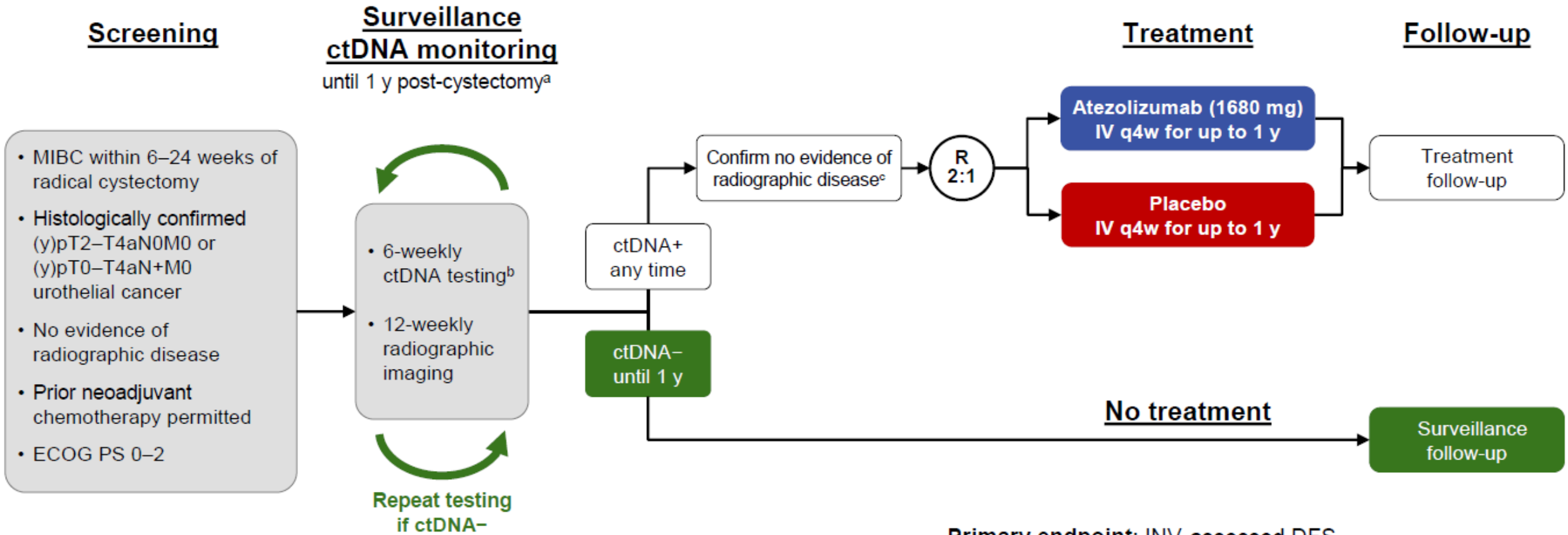
Emerging Biomarkers

from static to dynamic biomarkers

ctDNA

utDNA

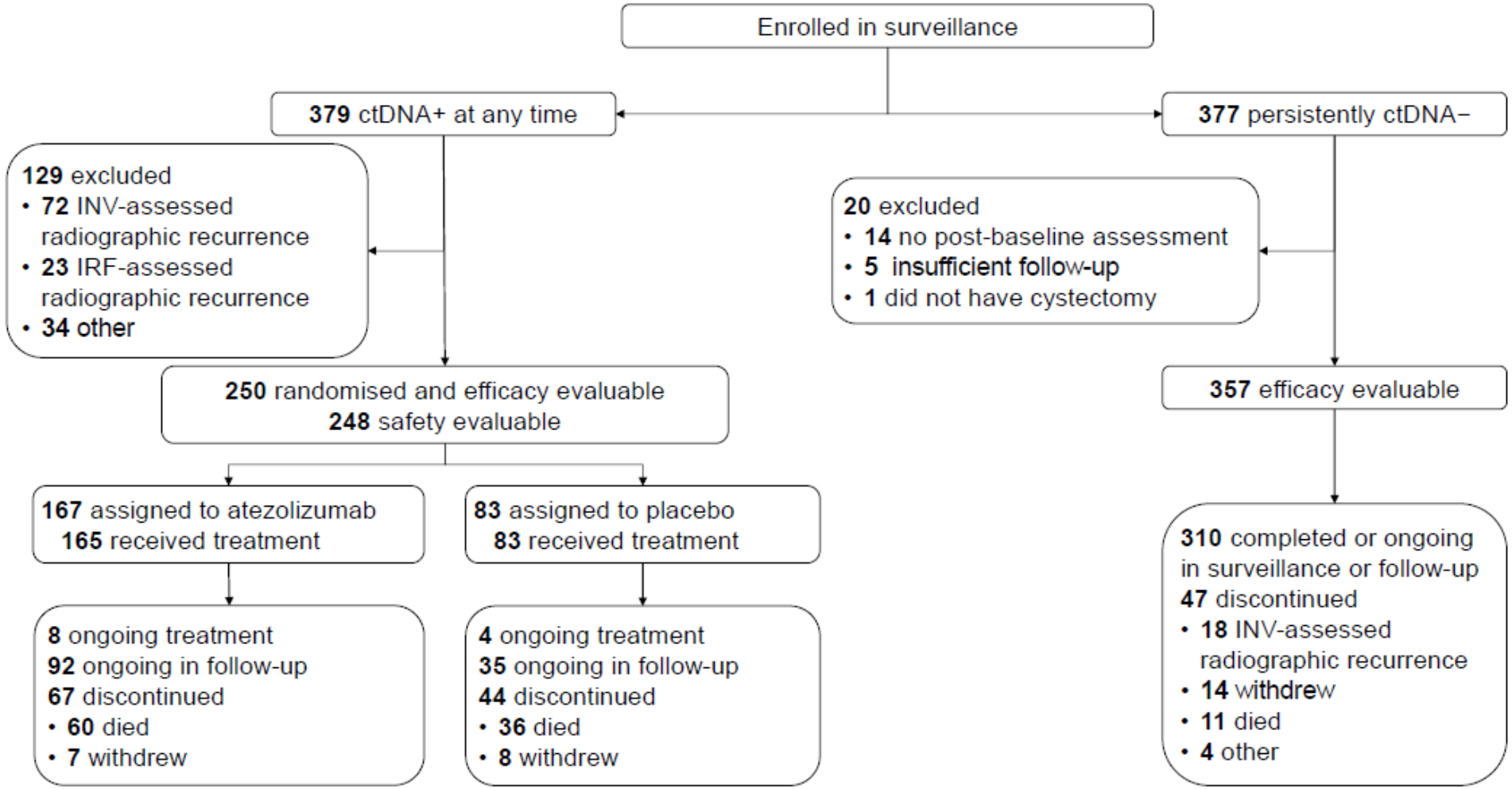
IMvigor011 study design



ClinicalTrials.gov number, NCT04660344. Stratification factors were nodal status (positive vs negative), tumour stage at cystectomy (≤pT2 vs pT3/pT4), PD-L1 status (IC0/1 [<5%] vs IC2/3 [≥5%] by VENTANA SP142 immunohistochemistry assay) and time from cystectomy to first ctDNA+ sample (≤20 weeks vs >20 weeks). [a] Early versions of the protocol included a 21-mo surveillance ctDNA monitoring period.
[b] ctDNA status was determined by the Natera Signatera™ MRD test (outside of mainland China) and by the BGI MRD test (in mainland China). [c] By INV and IRF assessment. ECOG PS, Eastern Cooperative Oncology Group performance status; IC, immune cells; INV, investigator; IRF, independent review facility; IV, intravenous; mo, month; PD-L1, programmed death-ligand 1; R, randomised; y, year.
Adapted from Powles T, et al. ESMO 2021 (Abstract 3716) with permission.

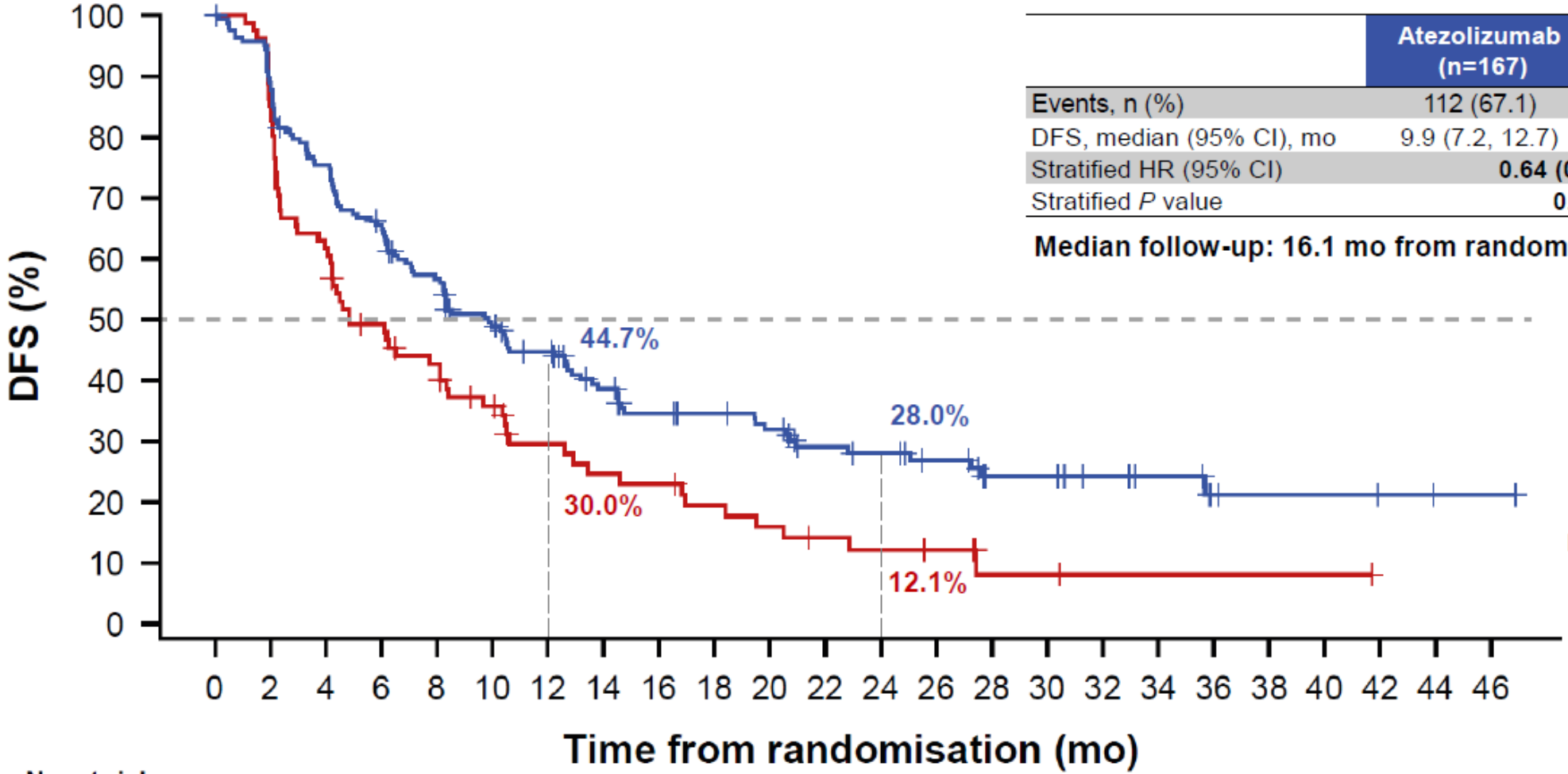
Presented by: Thomas Powles, MBBS, MRCP, MD

CONSORT diagram



Clinical cutoff: 15 June 2025; median follow-up: 16.1 mo from randomisation (ctDNA+) and 21.8 mo from cystectomy (ctDNA−). Patients were grouped according to final ctDNA status at the end of the 1-y surveillance monitoring period. ctDNA+ status refers to patients with a positive test who were eligible for randomisation; the positive test could have occurred at any time during the ctDNA monitoring period. ctDNA− status refers to patients with ≥1 negative test result and no positive test result. To be included in the persistently ctDNA− efficacy-evaluable population, patients must have had ≥1 post-baseline clinical outcome assessment and completed 1 y of surveillance or discontinued from surveillance without a ctDNA+ result. CONSORT, Consolidated Standards of Reporting Trials.

INV-assessed DFS in patients who tested ctDNA+



	Atezolizumab (n=167)	Placebo (n=83)
Events, n (%)	112 (67.1)	66 (79.5)
DFS, median (95% CI), mo	9.9 (7.2, 12.7)	4.8 (4.1, 8.3)
Stratified HR (95% CI)	**0.64 (0.47, 0.87)**	
Stratified *P* value	**0.0047**	

Median follow-up: 16.1 mo from randomisation

Consistent benefit in relevant secondary endpoints:

DFS per IRF:
HR, 0.66 (95% CI: 0.48, 0.91)

Distant-metastasis free survival:
HR, 0.66 (95% CI: 0.47, 0.94)

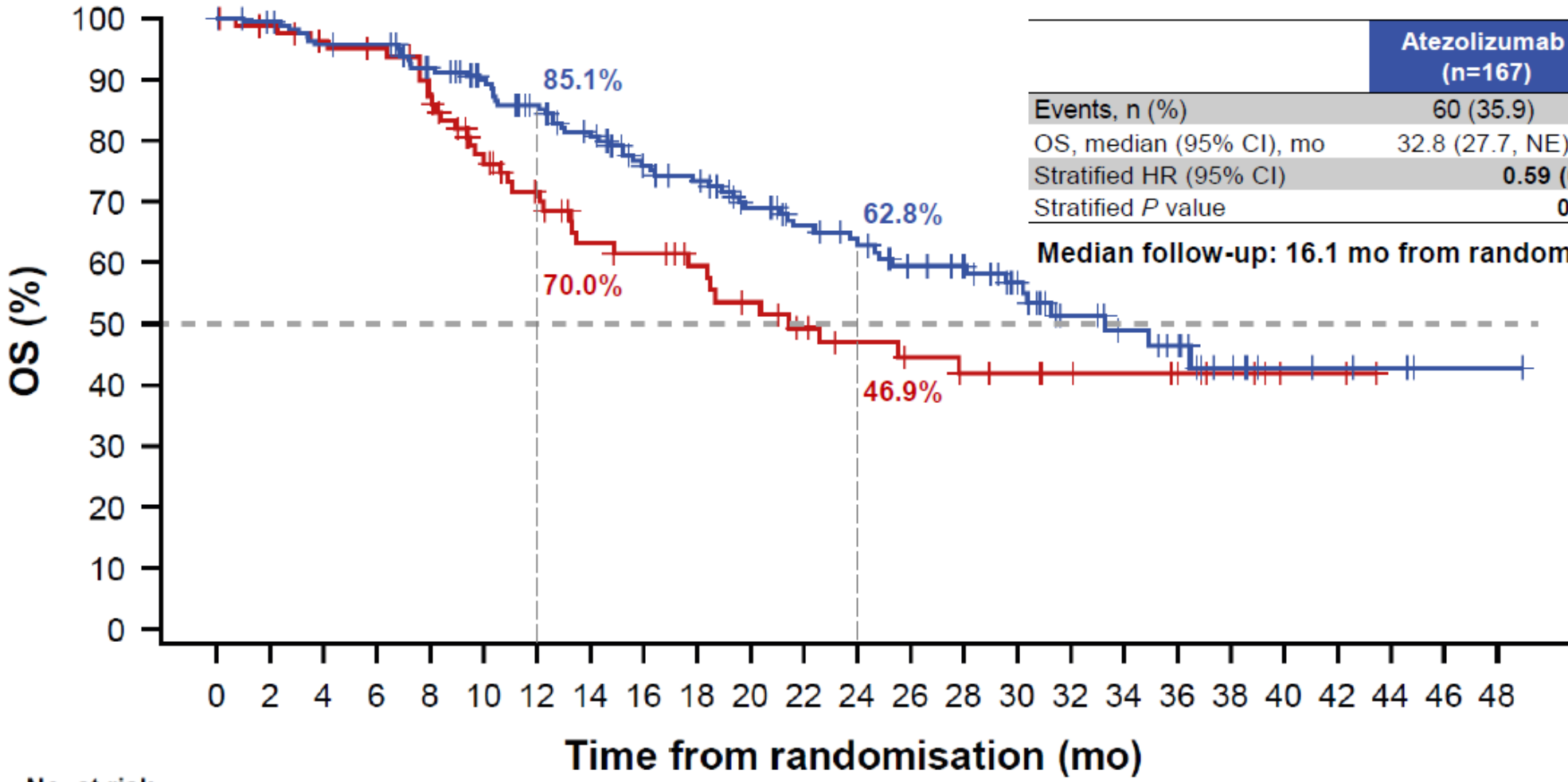
No. at risk

Atezolizumab	167	145	122	105	89	73	63	50	42	40	36	28	26	22	16	16	11	9	4	3	3	2	1	1
Placebo	83	69	50	38	32	25	18	15	14	11	9	7	6	5	2	2	1	1	1	1	1			

Clinical cutoff: 15 June 2025. CI, confidence interval.

Presented by: Thomas Powles, MBBS, MRCP, MD

OS in patients who tested ctDNA+



	Atezolizumab (n=167)	Placebo (n=83)
Events, n (%)	60 (35.9)	36 (43.4)
OS, median (95% CI), mo	32.8 (27.7, NE)	21.1 (14.7,NE)
Stratified HR (95% CI)	**0.59 (0.39, 0.90)**	
Stratified *P* value	**0.0131**	

Median follow-up: 16.1 mo from randomisation

Consistent benefit in relevant secondary endpoints:

Disease-specific survival:
HR, 0.64 (95% CI: 0.40, 1.05)

No. at risk

Atezolizumab	167	162	155	154	143	130	118	108	92	86	75	65	59	51	43	30	23	19	12	7	5	3	2	1	1
Placebo	83	80	76	74	65	53	44	36	34	30	26	21	19	17	15	13	10	10	8	5	2	1			

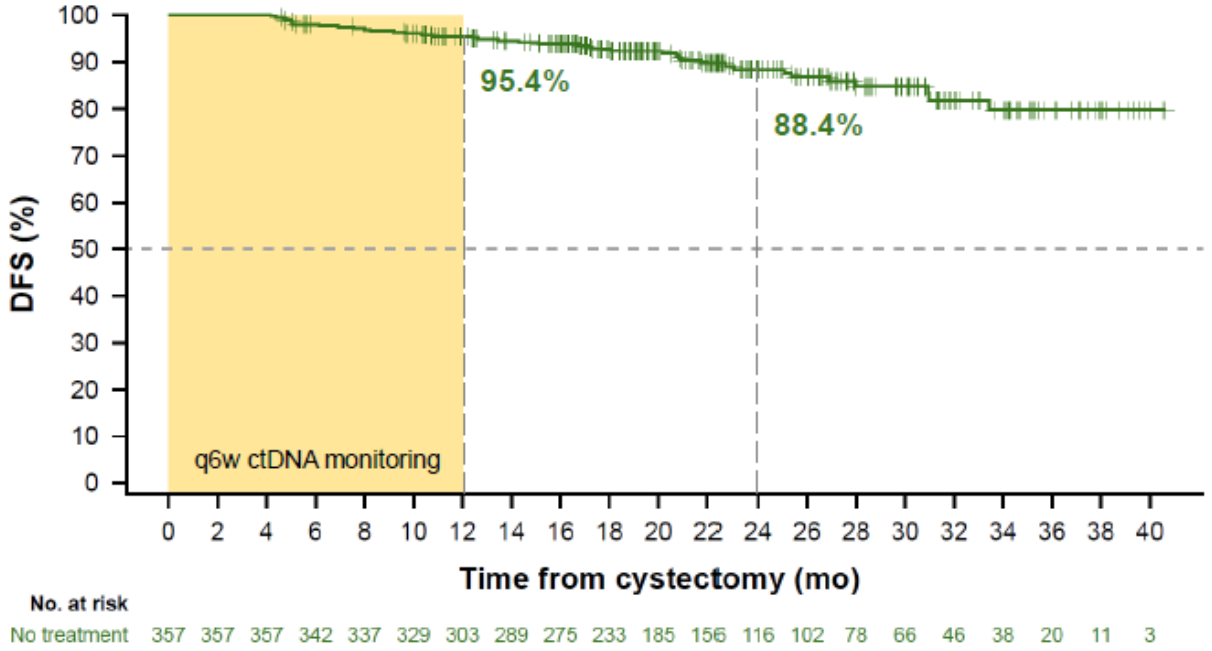
Clinical cutoff: 15 June 2025. NE, not evaluable.

Presented by: Thomas Powles, MBBS, MRCP, MD

DFS and OS in patients who persistently tested ctDNA−

INV-assessed DFS

	No treatment (n=357)
Events, n (%)	39 (10.9)
DFS, median (95% CI), mo	NE (NE)



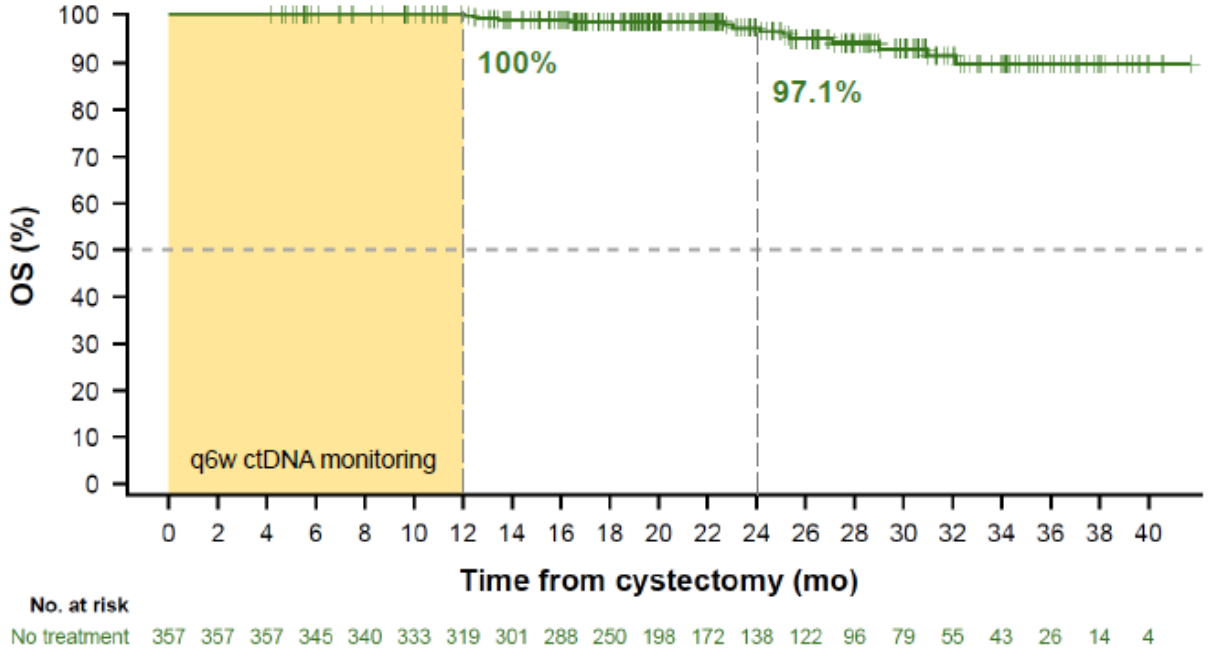
No. at risk

No treatment	357	357	357	342	337	329	303	289	275	233	185	156	116	102	78	66	46	38	20	11	3

Median follow-up: 21.8 mo from cystectomy

OS

	No treatment (n=357)
Events, n (%)	14 (3.9)
OS, median (95% CI), mo	NE (NE)



No. at risk

No treatment	357	357	357	345	340	333	319	301	288	250	198	172	138	122	96	79	55	43	26	14	4

8 DFS events were deaths not clearly attributed to disease recurrence

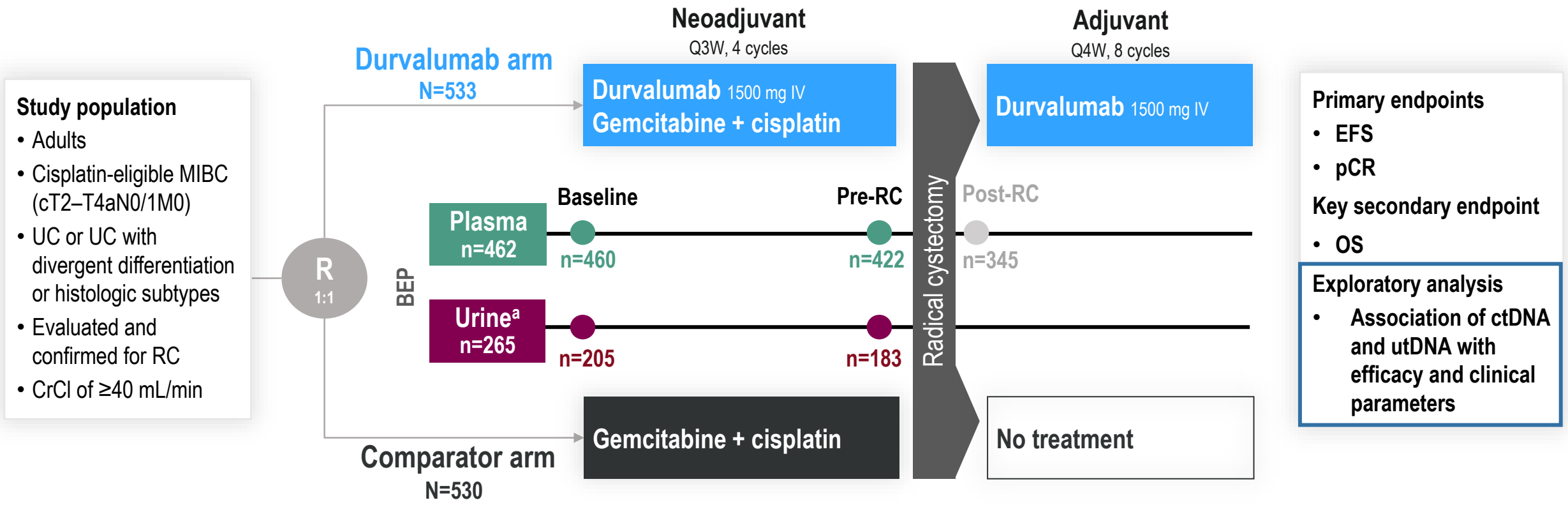
15 patients (4.2%) who experienced disease recurrence during the ctDNA monitoring period were discontinued from the study and censored for OS

Clinical cutoff: 15 June 2025. To be included in the ctDNA− efficacy-evaluable population, patients must have ≥1 negative test result and no positive test result, had ≥1 post-baseline clinical outcome assessment and completed 1 y of surveillance or discontinued from surveillance without a ctDNA+ result. q6w, every 6 weeks

Presented by: Thomas Powles, MBBS, MRCP, MD

BERLIN 2025 ESMO congress

NIAGARA: Study Design and ctDNA/utDNA Analysis

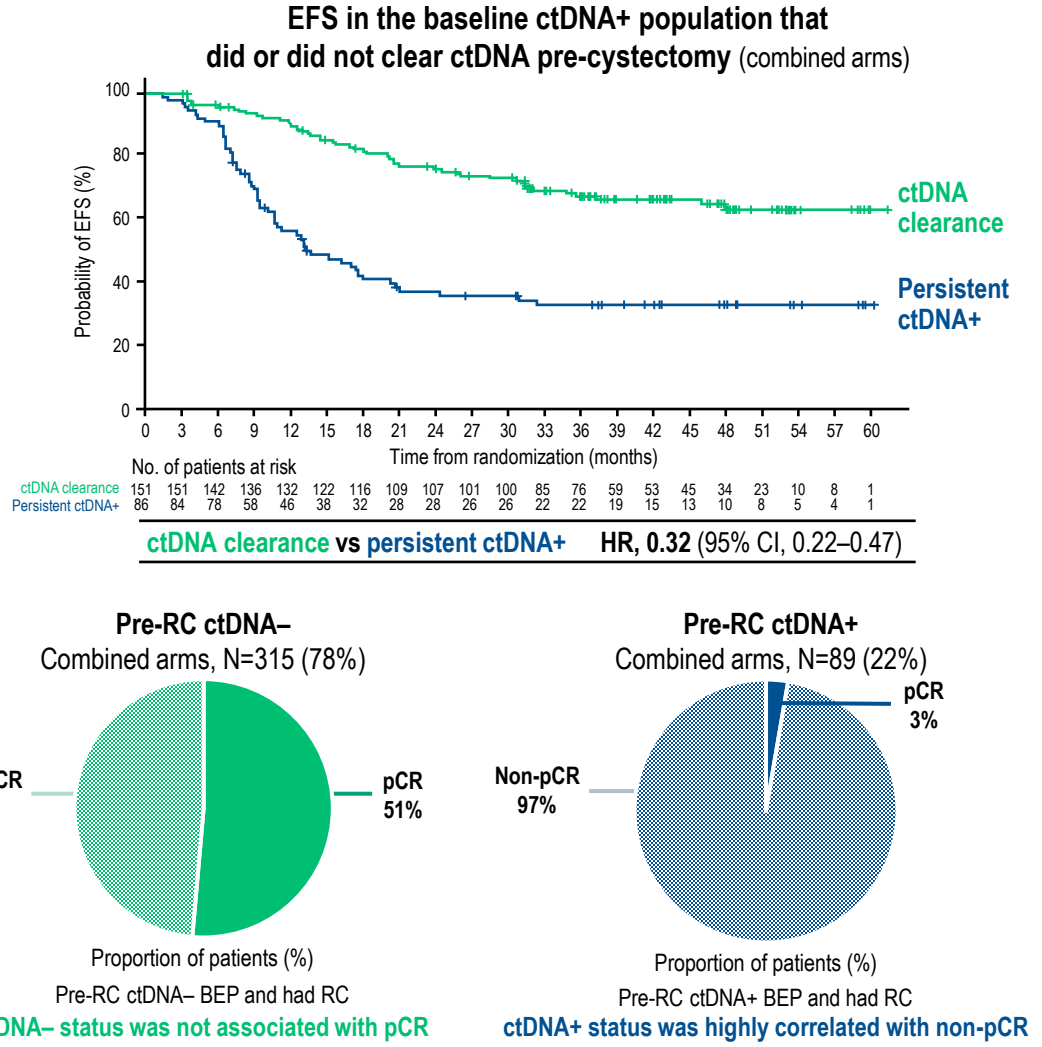


- Baseline characteristics were generally similar between the BEP and ITT populations
- ctDNA/utDNA assessed using Signatera™ assay (Natera, Inc, Austin, TX, USA)

Study design in Powles T, et al. *N Engl J Med*. 2024;391:1773–1786. ClinicalTrials.gov, NCT03732677. Data cutoff Apr 29, 2024. [a]Urine samples collected in ~50% of patients with evaluable ctDNA.
BEP, biomarker-evaluable population; CrCl, creatinine clearance; ctDNA, circulating tumor DNA; EFS, event-free survival; IV, intravenous; MIBC, muscle-invasive bladder cancer;
OS, overall survival; pCR, pathological complete response; Q3W, every 3 weeks; Q4W, every 4 weeks; R, randomized; RC, radical cystectomy; UC, urothelial carcinoma; utDNA, urinary tumor DNA.

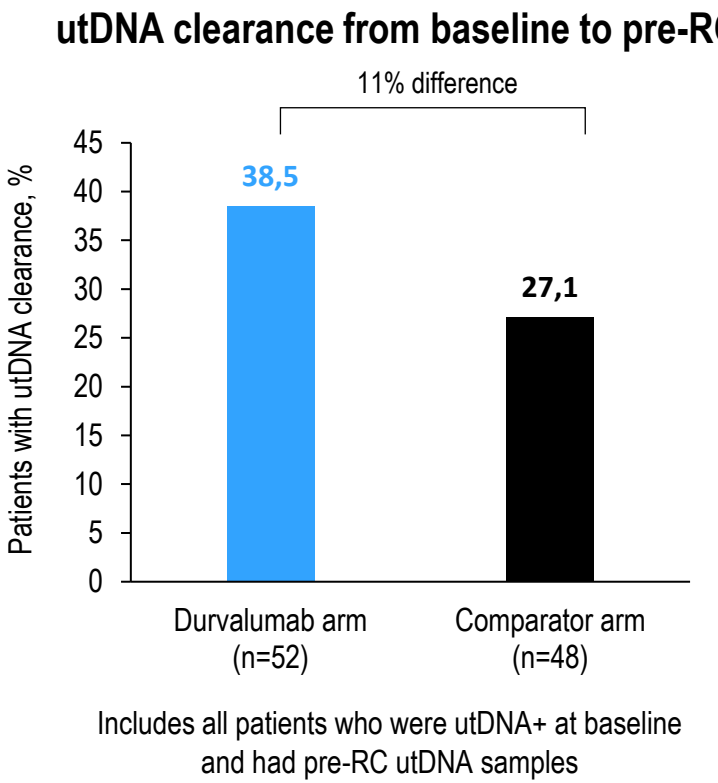
NIAGARA: Background

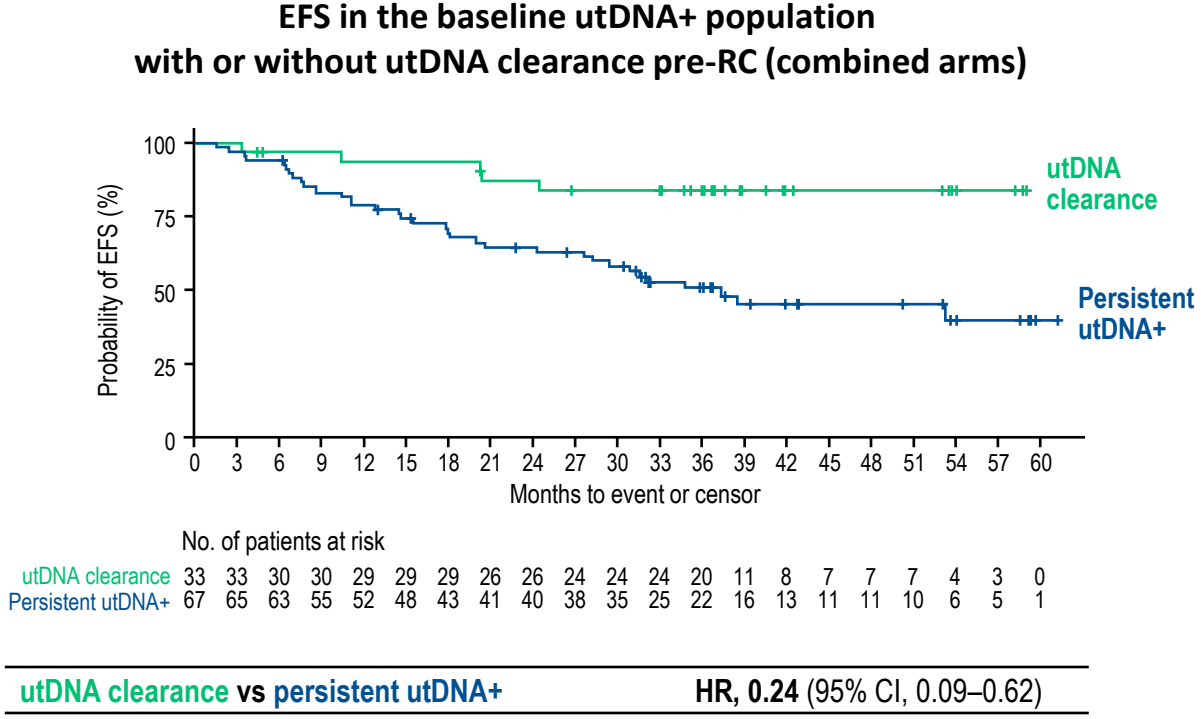
- In NIAGARA, the addition of perioperative durvalumab to NAC demonstrated:
  - Statistically significant improvement in
    - EFS: HR, 0.68 (95% CI, 0.56–0.82), *P*<0.0001
    - OS: HR, 0.75 (95% CI, 0.59–0.93), *P*=0.0106
  - 10% improvement in pCR rate[1]
- In prior exploratory analysis, plasma ctDNA– status after neoadjuvant treatment was not associated with pCR but was prognostic for EFS[2]
- Here, we expanded the analysis to assess potential utility of utDNA testing in MIBC management



1. Powles T, et al. *N Engl J Med*. 2024;391:1773–1786. 2. Powles T, et al. *J Clin Oncol*. 2025;43:16_suppl:4503. Pre-RC denotes sample collection after neoadjuvant treatment but before RC.
BEP, biomarker-evaluable population; CI, confidence interval; ctDNA, circulating tumor DNA; EFS, event-free survival; HR, hazard ratio; MIBC, muscle-invasive bladder cancer; NAC, neoadjuvant chemotherapy; OS, overall survival; pCR, pathological complete response; RC, radical cystectomy; utDNA, urinary tumor DNA.

NIAGARA Neoadjuvant: utDNA Clearance Was 11% Higher in the Durvalumab Arm and Appears to Be Prognostic for EFS

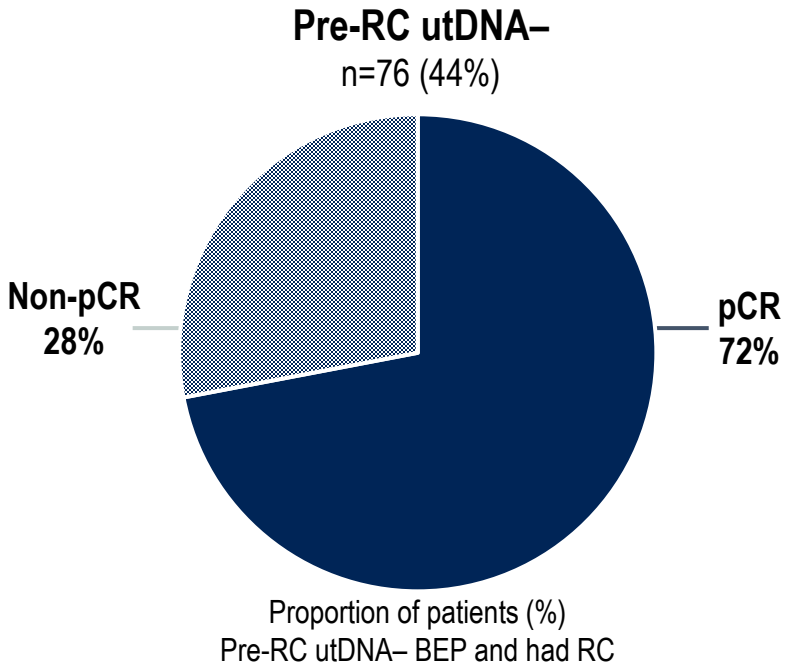




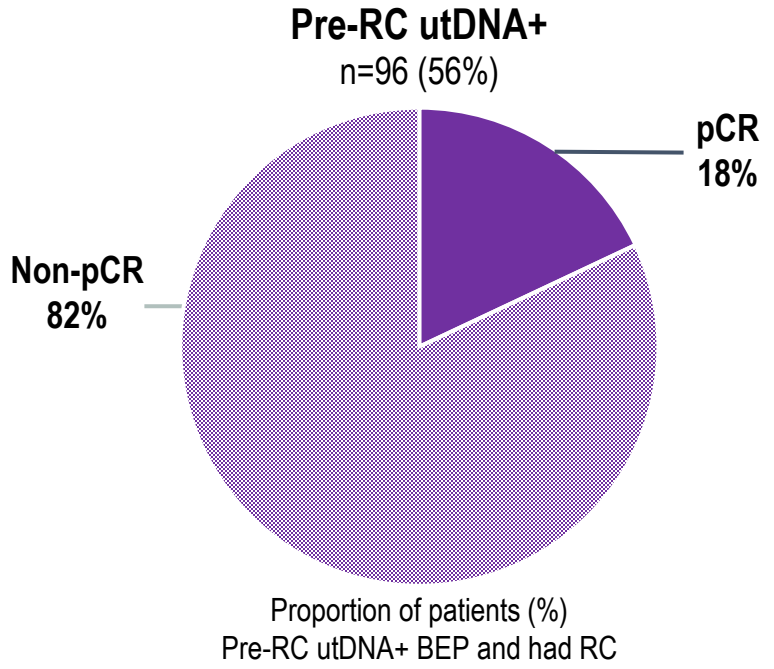
- Similar results were also observed with plasma ctDNA clearance[1]
- 85% of patients were utDNA positive at baseline, which reduced to 55% following neoadjuvant treatment (combined arms)

1. Powles T, et al. *J Clin Oncol*. 2025;43:16_suppl:4503. Pre-RC denotes sample collection after neoadjuvant treatment but before RC. CI, confidence interval; ctDNA, circulating tumor DNA; EFS, event-free survival; HR, hazard ratio; RC, radical cystectomy; utDNA, urinary tumor DNA.

NIAGARA Pre-cystectomy: utDNA– Status Is Associated With pCR



utDNA– status at pre-RC is associated with higher likelihood of pCR



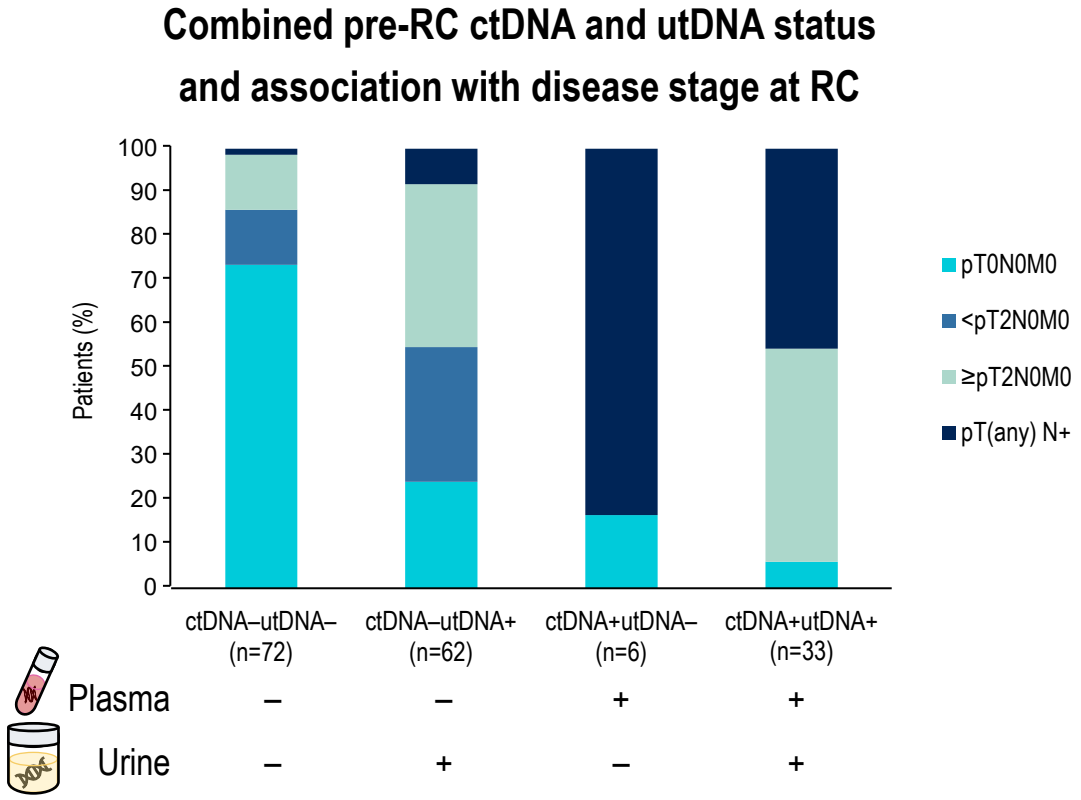
utDNA+ status at pre-RC is associated with higher likelihood of non-pCR

- In contrast, 51% of patients with plasma ctDNA– status after neoadjuvant treatment had pCR[1]

Pre-RC BEP with recorded pCR/non-pCR result, n=172 patients

1. Powles T, et al. *J Clin Oncol*. 2025;43:16_suppl:4503. Pre-RC denotes sample collection after neoadjuvant treatment but before RC. BEP, biomarker-evaluable population; ctDNA, circulating tumor DNA; pCR, pathological complete response; RC, radical cystectomy; utDNA, urinary tumor DNA.

NIAGARA Pre-cystectomy: utDNA and ctDNA Status Is Differentially Associated With Disease Stage at Cystectomy

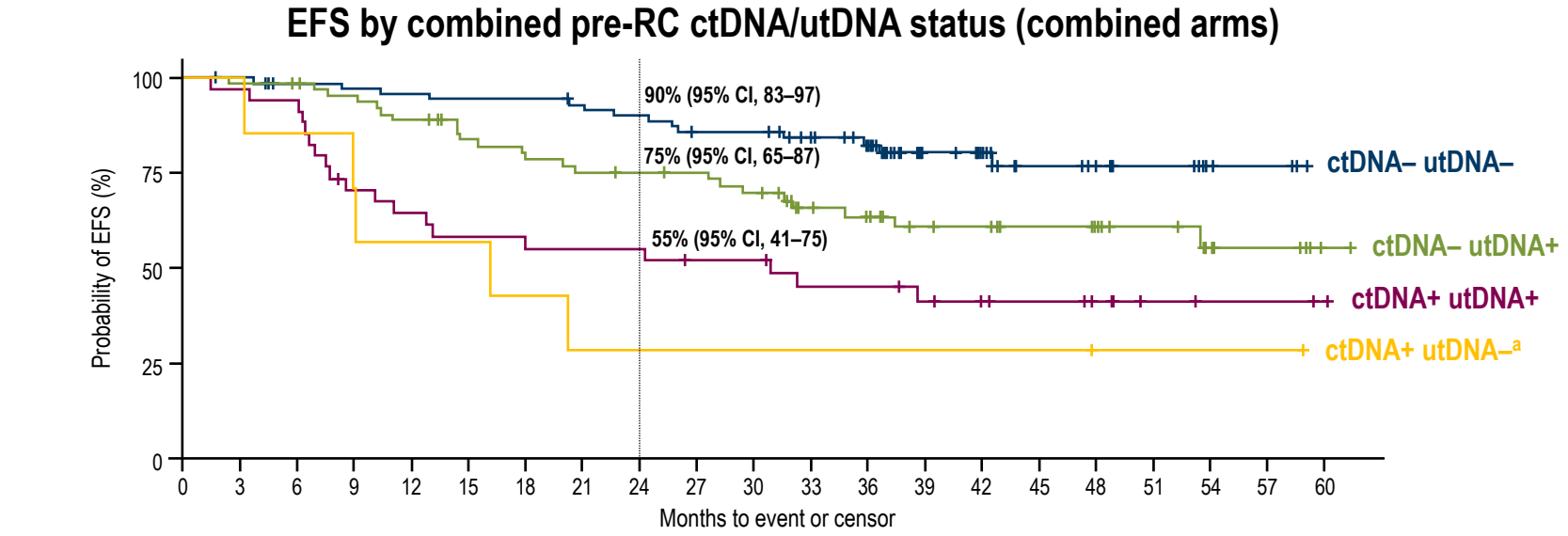


- utDNA+ status is associated with a higher frequency of non–invasive disease (<pT2N0M0), consistent with detection of local residual disease
- ctDNA+ status is associated with a higher frequency of invasive disease (≥pT2N0M0) and nodal involvement (N+), reflecting systemic spread

Pre-RC BEP with ctDNA and utDNA results, n=179[a]

Pre-RC denotes sample collection after neoadjuvant treatment but before RC. [a]Pathological staging was not available for n=6 patients. BEP, biomarker evaluable population; ctDNA, circulating tumor DNA; RC, radical cystectomy; utDNA, urinary tumor DNA.

NIAGARA: 24-Month EFS Was Highest for Patients With Dual-Negative Status at Pre-cystectomy



No. of patients at risk

ctDNA– utDNA–	74	73	69	68	67	66	66	64	62	58	58	53	47	30	25	17	13	9	4	3	0
ctDNA– utDNA+	64	63	62	59	55	49	46	44	43	42	39	30	26	21	20	17	15	12	8	6	1
ctDNA+ utDNA–[a]	7	7	6	5	4	4	3	2	2	2	2	2	2	2	2	2	1	1	1	1	0
ctDNA+ utDNA+	34	33	32	23	21	19	18	18	18	16	16	13	13	11	9	8	6	3	2	2	1

ctDNA– utDNA– vs ctDNA– utDNA+	**HR, 0.46** (95% CI, 0.23–0.89)
ctDNA– utDNA– vs ctDNA+ utDNA+	**HR, 0.25** (95% CI, 0.12–0.49)
ctDNA– utDNA+ vs ctDNA+ utDNA+	**HR, 0.51** (95% CI, 0.27–0.93)

Pre-RC BEP with ctDNA and utDNA results, n=179

Pre-RC denotes sample collection after neoadjuvant treatment but before RC. [a]Note, due to the small sample size for the ctDNA+ and utDNA– group, HRs for group comparisons were not calculated.
BEP, biomarker evaluable population; CI, confidence interval; ctDNA, circulating tumor DNA; EFS, event-free survival; HR, hazard ratio; RC, radical cystectomy; utDNA, urinary tumor DNA.

Enfortumab Vedotin: Practice-Changing Evidence

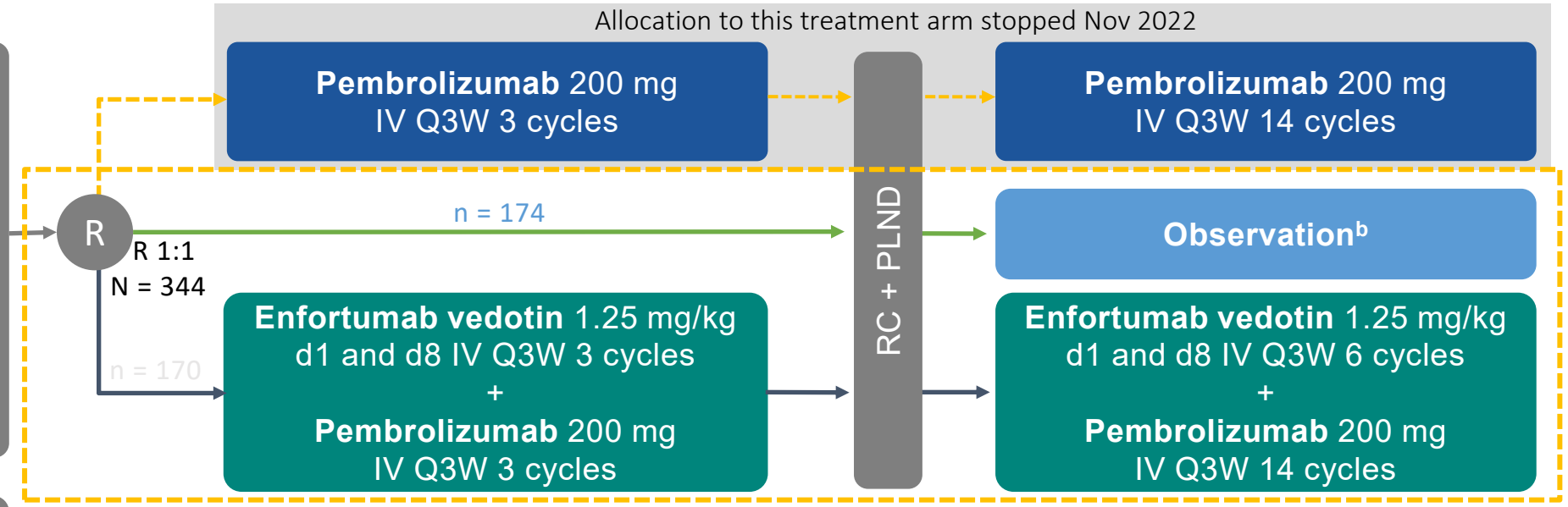
KEYNOTE-905/EV-303 Study (NCT03924895)

KEYNOTE-B15/EV-304 Study (NCT04700124)

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[a] or cisplatin declining
- ECOG PS score 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)



End points

Primary: EFS by BICR

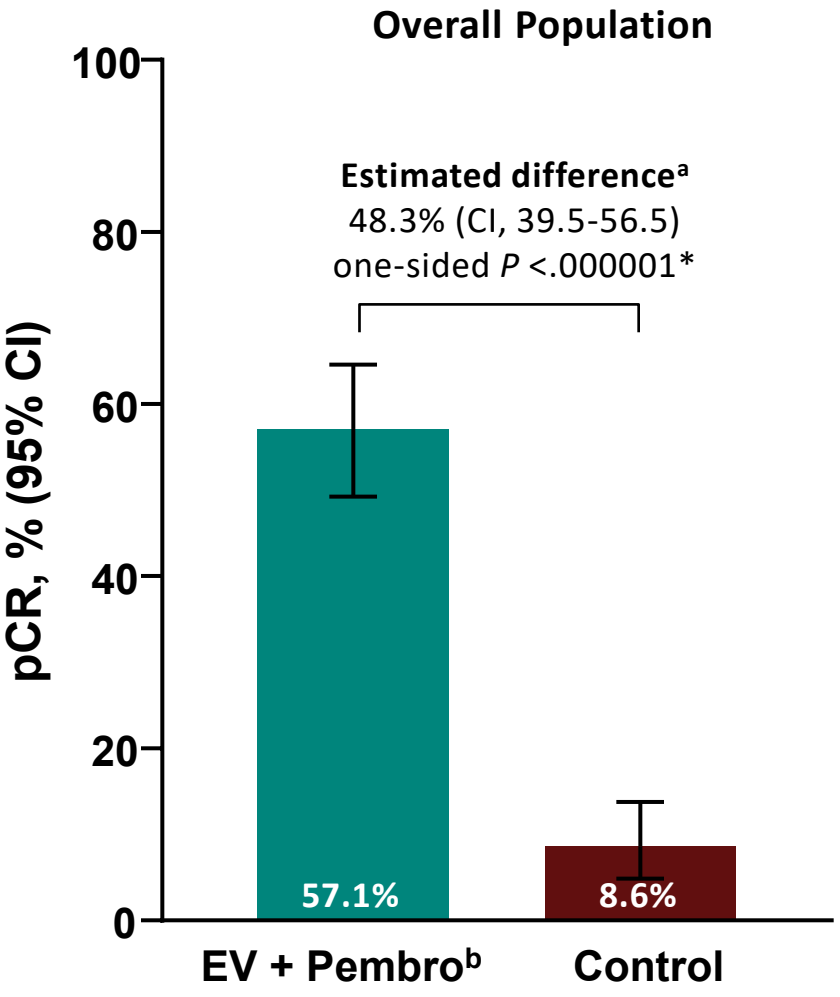
Key secondary:
- OS
- Pathologic complete response (pCR; absence of viable tumor in tissue from RC + PLND [pT0N0])[c]

Other secondary:
- Pathologic downstaging (pDS; <pT2 [pT0, pTis, pTa, pT1] and N0 in tissue from RC + PLND)[c]
- Disease-free survival (DFS; time from post-surgery scan to local/distant recurrence or death)[c,d]

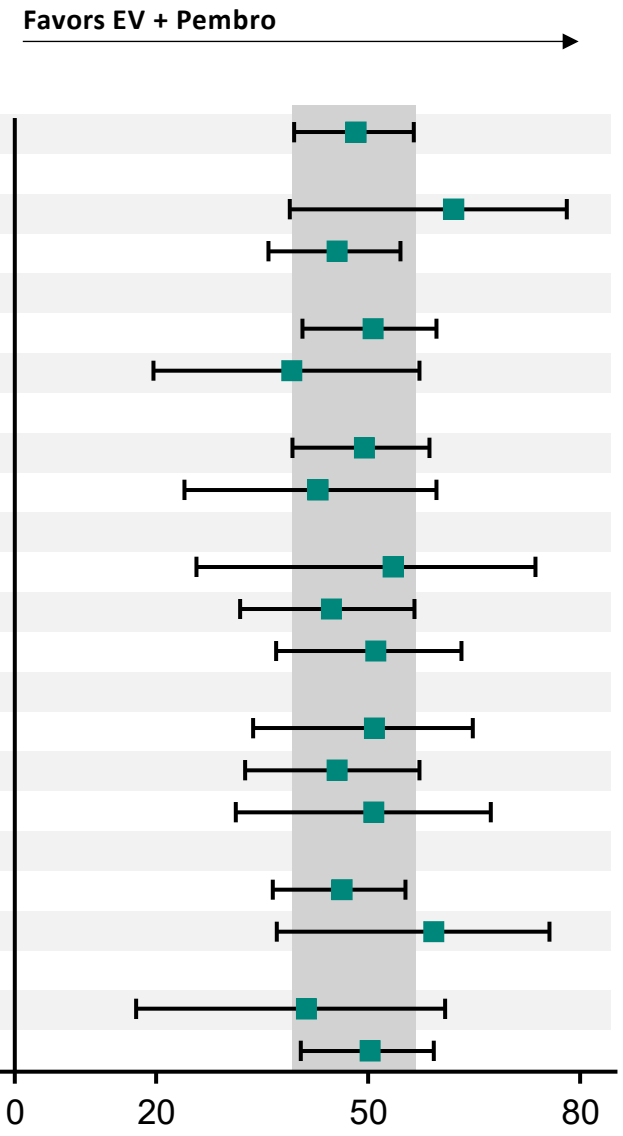
BICR, blinded independent central review; d, day; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; IV, intravenous; MIBC, muscle-invasive bladder cancer; NYHA, New York Heart Association; OS, overall survival; PLND, pelvic lymph node dissection; Q3W, every 3 weeks; R, randomization; RC, radical cystectomy.

[a]Protocol defined as having ≥1 of the following: impaired renal function (creatinine clearance, 30 to 59 mL/min), ECOG PS score 2, CTCAE v4 grade ≥2 audiometric hearing loss, or NYHA Class III heart failure. [b]As of November 2022, adjuvant nivolumab was permitted when clinically indicated and regionally available. [c]Assessed by central pathology or BICR. [d]Participants were considered disease-free after RC + PLND if they had complete resection (no gross residual disease) and no evidence of disease on a post-surgery scan.

pCR by BICR in the ITT Population



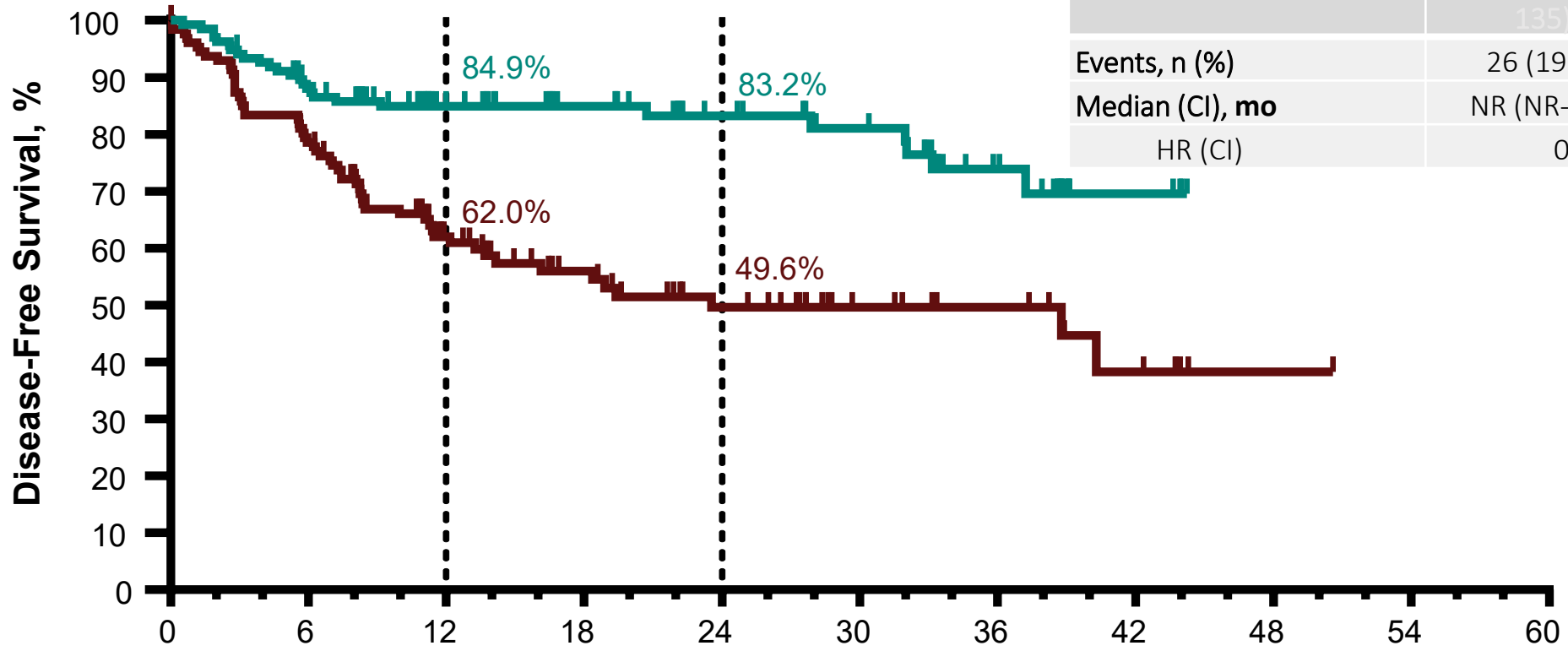
	Number with pCR/N		pCR difference, % (CI)
	EV + Pembro	Control	
Overall	97/170	15/174	48.3 (39.5-56.5)
Age, years			
<65	21/29	3/29	62.1 (38.9-78.1)
≥65	76/141	12/145	45.6 (35.9-54.6)
Sex			
Male	81/137	11/131	50.7 (40.7-59.7)
Female	16/33	4/43	39.2 (19.6-57.3)
Race			
White	78/132	13/136	49.5 (39.3-58.7)
All others	18/37	2/35	42.9 (24.0-59.7)
Geographic region			
US	14/21	3/23	53.6 (25.7-73.7)
EU	40/78	5/77	44.8 (31.9-56.6)
MOW	43/71	7/74	51.1 (37.0-63.2)
Smoking status			
Never	33/55	4/44	50.9 (33.7-64.8)
Former	45/82	8/68	45.6 (32.6-57.3)
Current	19/33	3/44	50.8 (31.3-67.4)
Cisplatin status			
Ineligible	78/142	12/139	46.3 (36.5-55.3)
Declining	19/28	3/35	59.3 (37.1-75.7)
Tumor stage			
T2N0	18/30	6/32	41.3 (17.2-60.9)
T3/T4aN0	76/133	9/132	50.3 (40.5-59.3)



MOW, most of world.
*Denotes statistical significance (one-sided boundary .00025). [a]Based on the stratified Miettinen and Nurminen method.
[b]97 of 149 participants (65.0%) who underwent surgery and received EV + pembro had a pCR. Data cutoff date: June 6, 2025.

Disease-Free Survival by BICR[a]

	EV + Pembro (n = 135)	Control (n = 129)
Events, n (%)	26 (19.3)	57 (44.2)
Median (CI), mo	NR (NR-NR)	23.6 (13.7-NR)
HR (CI)	0.37 (0.23-0.59)[b]	



No. at Risk										
EV + pembro	135	115	75	58	43	36	18	5	0	0
Control	129	98	57	38	27	16	12	6	1	0

HR, hazard ratio; NR, not reached.

[a]Participants were considered disease-free after RC + PLND for DFS analysis if they had complete resection (no gross residual disease) and no evidence of disease on a post-surgery scan. [b]Based on Cox regression model with the Efron method of tie handling with treatment as a covariate. Data cutoff date: June 6, 2025.

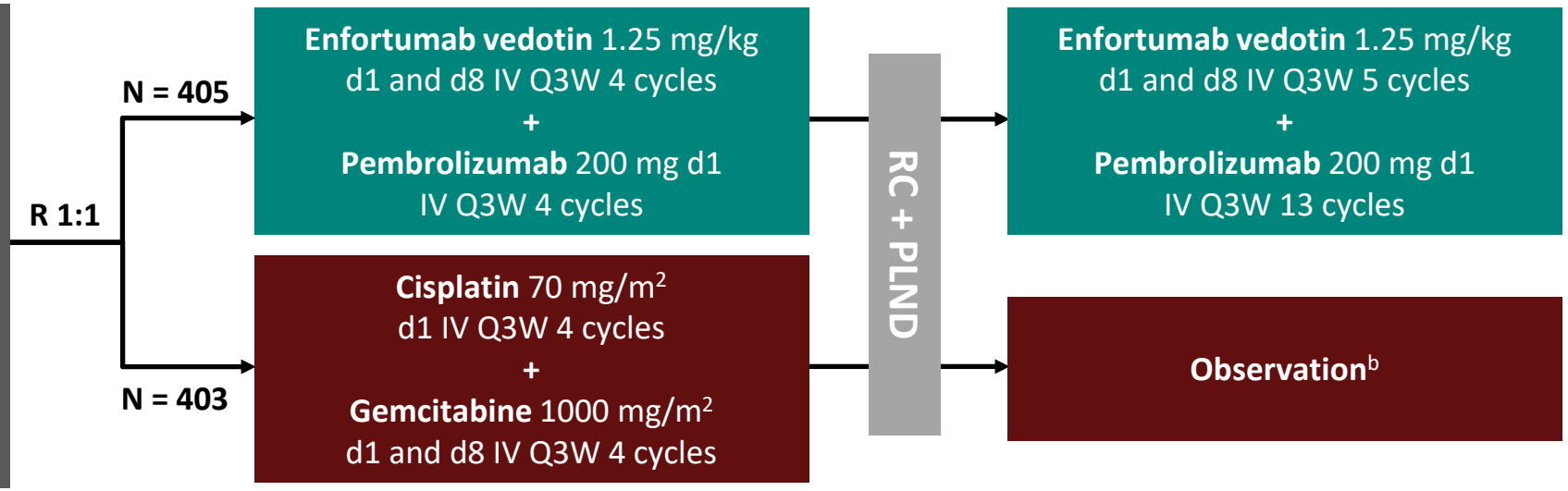
KEYNOTE-B15/EV-304 Study (NCT04700124)

Key Eligibility Criteria

- Adults with MIBC
- Clinical stage T2-T4aN0M0 or T1-T4aN1M0 by central assessment
- Urothelial histology ≥50%
- Eligible for RC + PLND
- Did not meet any Galsky criteria for cisplatin ineligibility
- ECOG PS 0-1

Stratification Factors

- PD-L1 status (CPS ≥10 vs. <10)[a]
- Clinical stage (T2N0 vs. T3/T4aN0 vs. T1-4aN1)
- Geographic 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

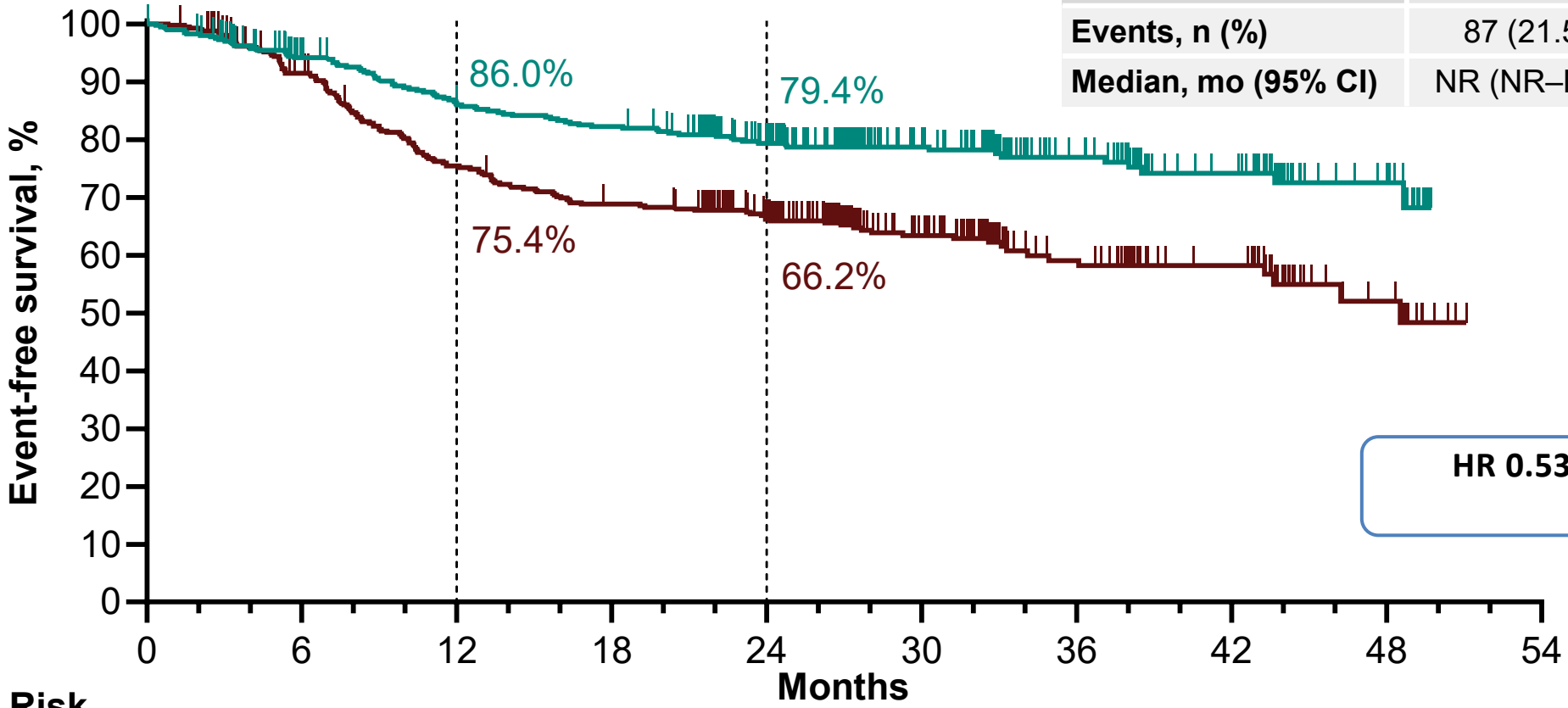
BICR, blinded independent central review; CPS, combined positive score; IV, intravenous; Q3W, every 3 weeks.
[a]Assessed by PD-L1 IHC 22C3 pharmDx (Agilent, Carpinteria, CA); CPS = # PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) ÷ total # viable tumor cells × 100.
[b]As of Feb 2023, adjuvant nivolumab was permitted when clinically indicated and regionally available.

Data cutoff date: 27 October 2025

Primary Endpoint: EFS by BICR

ITT Population

	EV + pembro N = 405	Cis + gem N = 403
Events, n (%)	87 (21.5)	146 (36.2)
Median, mo (95% CI)	NR (NR–NR)	48.5 (43.3–NR)



HR 0.53, 95% CI 0.41–0.70, 1-sided *P* <.0001*

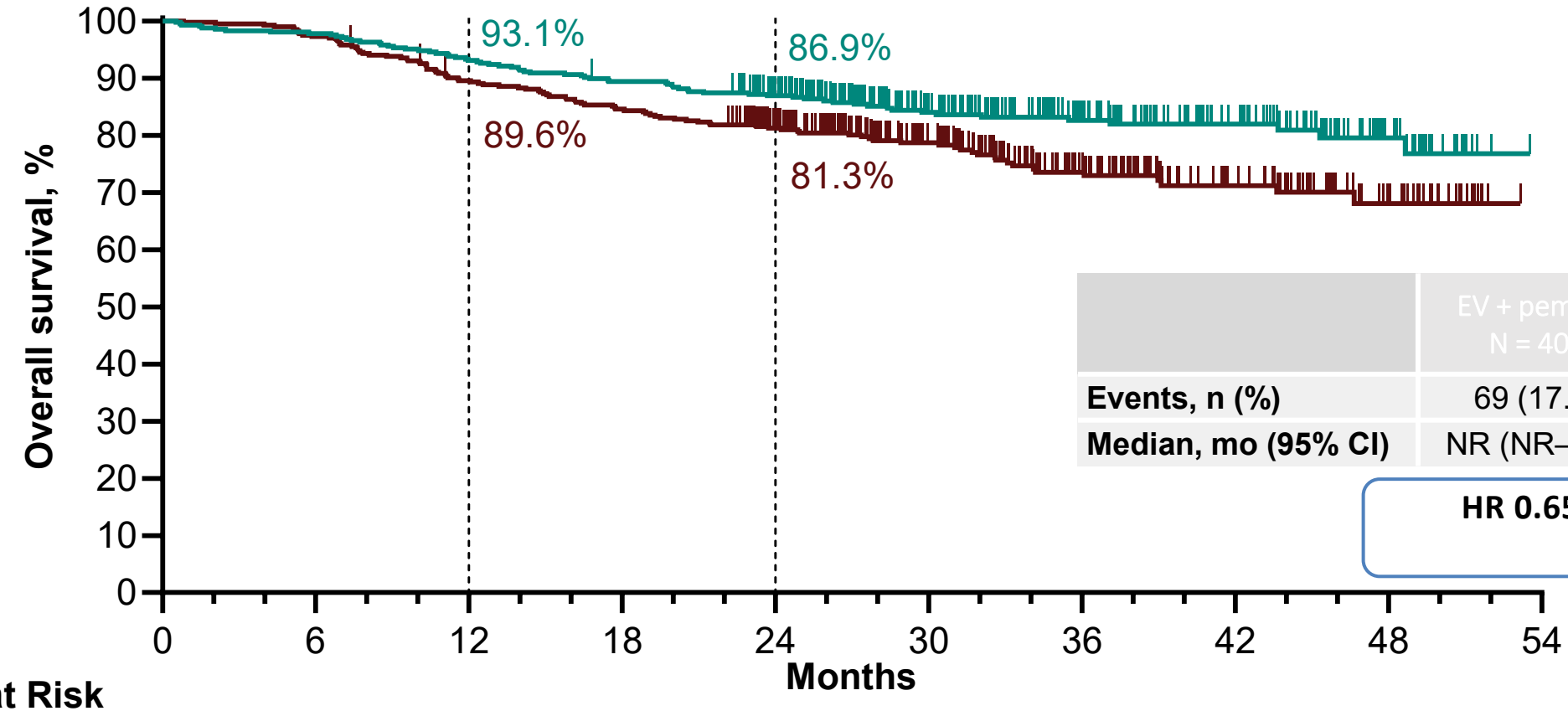
No. at Risk

EV + pembro	405	351	317	303	257	154	100	63	23	0
Cis + gem	403	350	286	259	216	131	70	45	16	0

NR, not reached. * denotes statistical significance (one-sided boundary 0.0082).

Data cutoff date: 27 October 2025

Key Secondary Endpoint: OS
ITT Population



	EV + pembro N = 405	Cis + gem N = 403
Events, n (%)	69 (17.0)	99 (24.6)
Median, mo (95% CI)	NR (NR–NR)	NR (NR–NR)

HR 0.65, 95% CI 0.48–0.89, 1-sided *P* =.0029*

No. at Risk

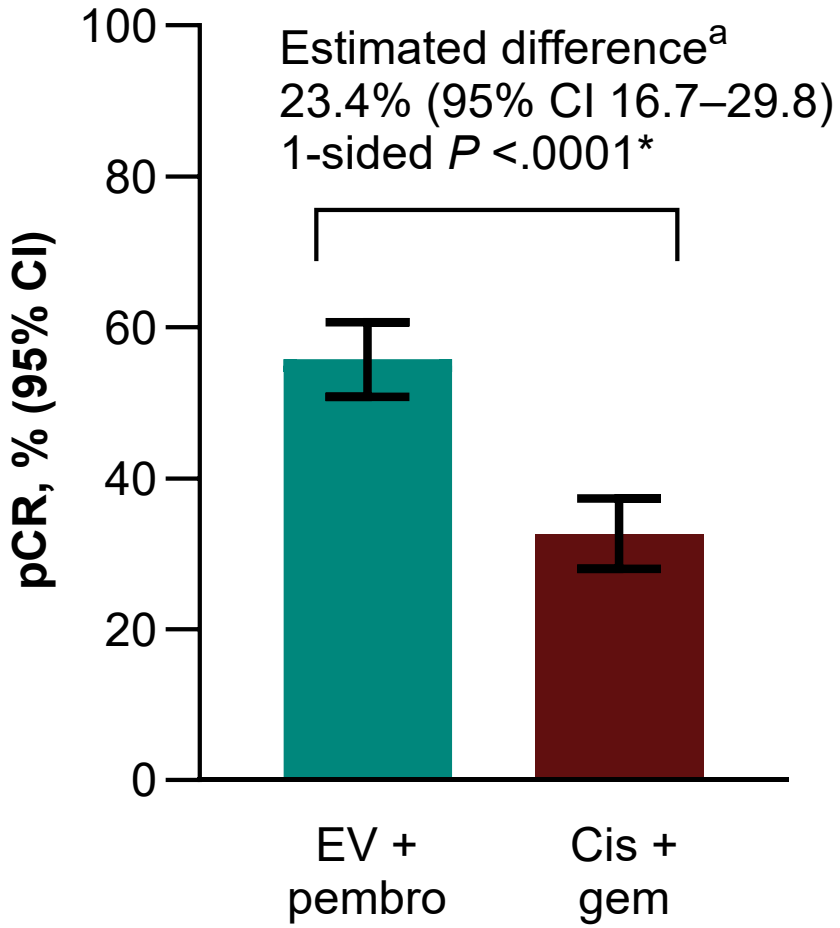
EV + pembro	405	396	377	361	325	215	142	90	34	0
Cis + gem	403	392	358	338	295	201	119	67	29	0

- In total, 44/87 (50.6%) of pts with an EFS event in the EV + pembro arm and 86/146 (58.9%) of pts with an EFS event in the cis + gem arm received any subsequent systemic therapy

NR, not reached. * denotes statistical significance (one-sided boundary 0.0038).

Data cutoff date: 27 October 2025

Key Secondary Endpoint: pCR by Central Pathology Review
ITT Population



	EV + pembro N = 405	Cis + gem N = 403
pCR, n	226	131
pCR rate, % (95% CI)	55.8 (50.8–60.7)	32.5 (28.0–37.3)

- **pCR:** defined as absence of viable tumor in examined tissue from RC + PLND (pT0N0)
- Pts who discontinued study therapy prior to definitive surgery were classified as non-responders
- Out of pts who underwent surgery, 226/351 (64.4%) in the EV + pembro arm and 131/361 (36.3%) in the cis + gem arm had pCR

* denotes statistical significance (one-sided boundary 0.001).
[a]Based on stratified Miettinen and Nurminen method.

Data cutoff date: 27 October 2025

Summary of Treatment Exposure and Safety
Safety Analysis Population

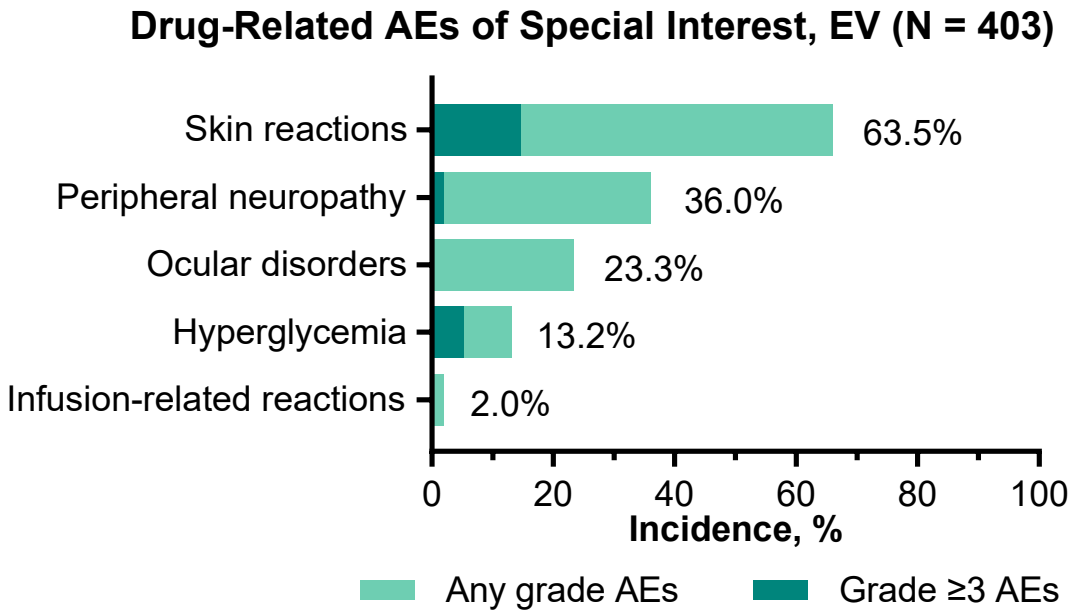
	EV + pembro	Cis + gem
Median (range) total duration of therapy, months	**N = 403** 10.2 (0.03–25.5)	**N = 396** 3.5 (0.03–16.8)
Median (range) cycles, neoadjuvant phase Enfortumab vedotin Pembrolizumab Gemcitabine Cisplatin	**N = 403** 4.0 (1.0–4.0) 4.0 (1.0–4.0) NA NA	N = 396 NA NA 4.0 (1.0–4.0) 4.0 (1.0–4.0)
Median (range) cycles, adjuvant phase Enfortumab vedotin Pembrolizumab	N = 262 5.0 (1.0–5.0) 13.0 (1.0–13.0)	NA NA NA
Pts with AE,[a] n (%)	**EV + pembro, N = 403**	**Cis + gem, N = 396**
Any-grade TEAE	395 (98.0)	389 (98.2)
Grade ≥3 TEAE	305 (75.7)	266 (67.2)
Serious TEAE	255 (63.3)	190 (48.0)
TEAE leading to death Treatment-related AEs leading to death[b]	17 (4.2) 2 (0.5)	11 (2.8) 1 (0.3)
Neoadjuvant phase TEAE leading to drug discontinuation	101 (25.1)	61 (15.4)
Adjuvant phase TEAE leading to drug discontinuation, n/N (%)	75/262 (28.6)	NA

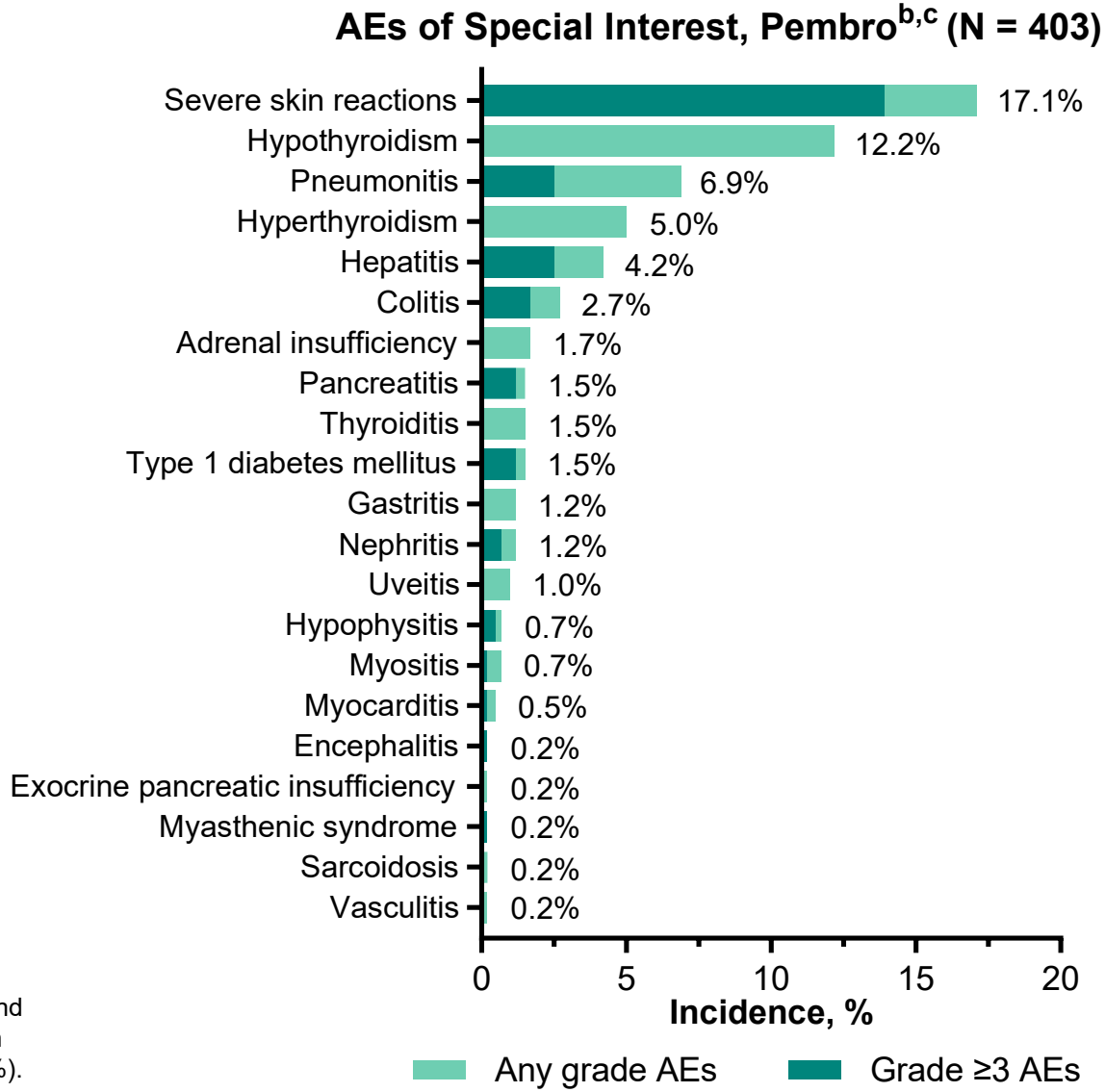
[a]Collected up to 30 days after cessation of study treatment (90 days for serious AEs); EV + pembro reporting window included neoadjuvant, surgery, and adjuvant phases, cis + gem reporting window included neoadjuvant and surgery phases. [b]EV + pembro arm: multiple organ dysfunction syndrome (n = 2); cis + gem arm: pneumonia (n = 1).

Data cutoff date: 27 October 2025

AEs of Special Interest[a]

Safety Analysis Population, EV + Pembro Arm





[a]Based on separate prespecified lists of preferred terms (grouped) of known risks associated with EV and pembro treatment. [b]Considered regardless of attribution to study treatment by the investigator. [c]Infusion reactions, reported separately, occurred in 12 pt (3.0%); grade ≥3 infusion reactions occurred in 3 (0.7%).
Data cutoff date: 27 October 2025

Conclusions

Current standard in Colombia

- Neoadjuvant Cisplatin-based chemotherapy (cisplatin-eligible patients)
- Adjuvant cisplatin-based chemotherapy (pT3/4 and/or pN+ disease if no neoadjuvant systemic therapy has been given)
- Adjuvant Nivolumab (high-risk ≥ ypT2N0 after NAC or pT3/4 and/or pN+) PD-L1 tumour cell expression ≥ 1%.

Conclusions

Emerging new standard (PERIOPERATIVE)

- Durvalumab + Gem/Cis (NIAGARA)
  - cisplatin elegible only

- Enfortumab Vedotin + Pembrolizumab (KN905/EV303, KNB15/EV304)
  - Cisplatin elegible
  - Cisplatin inelegible or cisplatin declining

Do all patients requiere Adjuvant therapy?

A major unmet need: absence of robust and validated predictive biomarkers to optimize patient selection and persolalize therapy

GRACIAS.

XXII Congreso Colombiano de Cáncer