Under the aegis of CANCER RESEARCH AND STATISTIC FOUNDATION

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Perioperative Durvalumab with Neoadjuvant Chemotherapy in Operable Bladder Cancer

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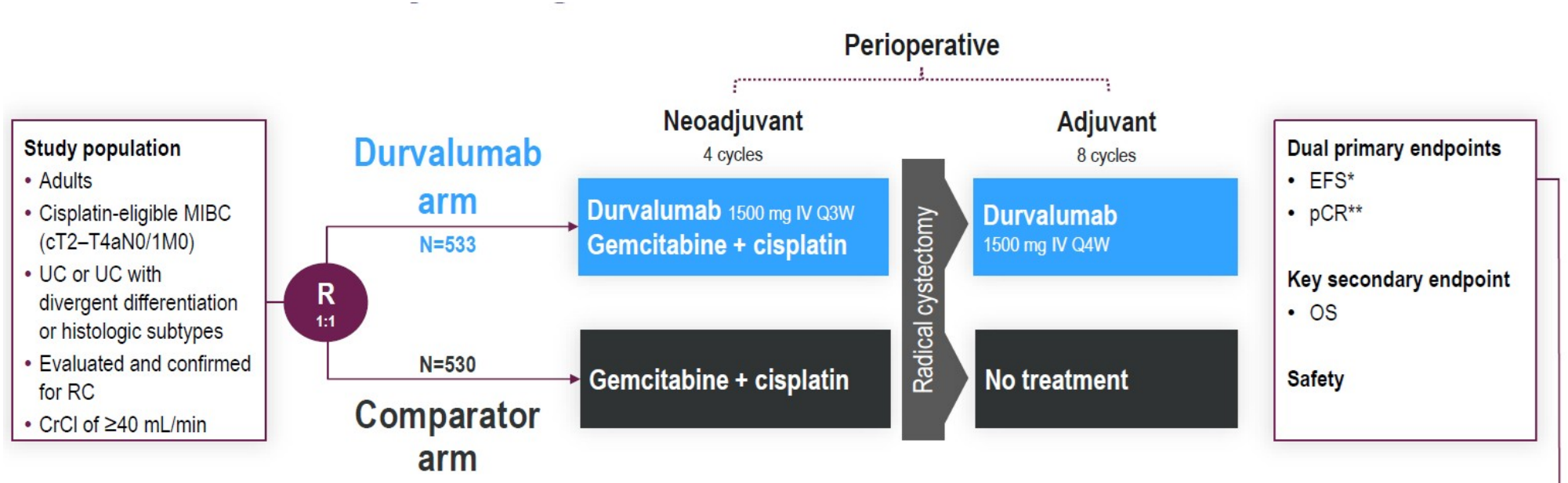
BACKGROUND

- Neoadjuvant cisplatin-based chemotherapy (NAC) with radical cystectomy (RC) improves overall survival (OS) versus RC alone and has been the recommended treatment for muscle-invasive bladder cancer (MIBC) for the past 40 years
- However, ~50% of patients experience recurrence within 3 years
- In the setting of MIBC, immune checkpoint inhibitors as adjuvant monotherapy have demonstrated improved disease-free survival in Phase 3 studies in patients at high risk of recurrence after surgery (CheckMate 274, AMBASSADOR)
- Perioperative immune checkpoint inhibitors could improve long-term clinical outcomes by priming anti-tumour immunity before surgery and eradicating micrometastatic disease after surgery
- Perioperative durvalumab was shown to be safe and efficacious in a Phase 2 study of MIBC

NIAGARA is the first global Phase 3 study to evaluate a perioperative immune checkpoint inhibitor, durvalumab, combined with NAC in cisplatin eligible patients with MIBC

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

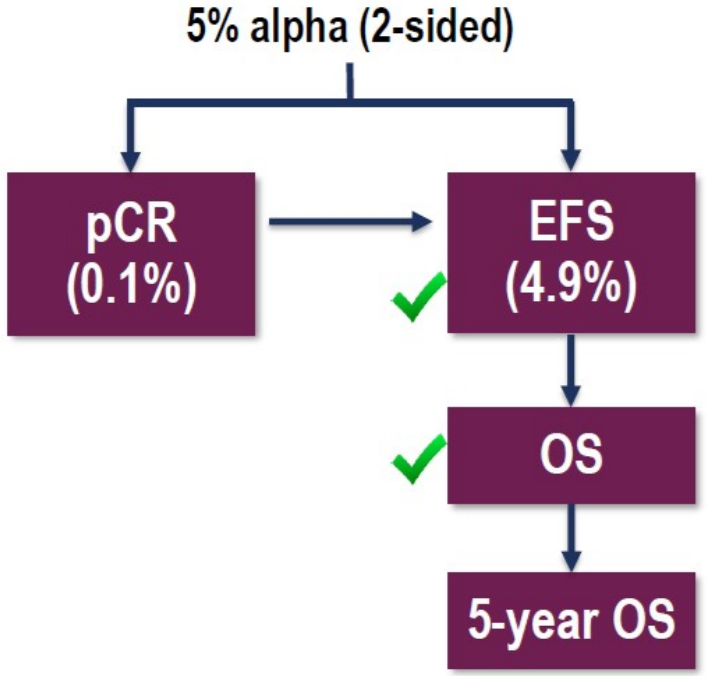
EFS was defined as:

- 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

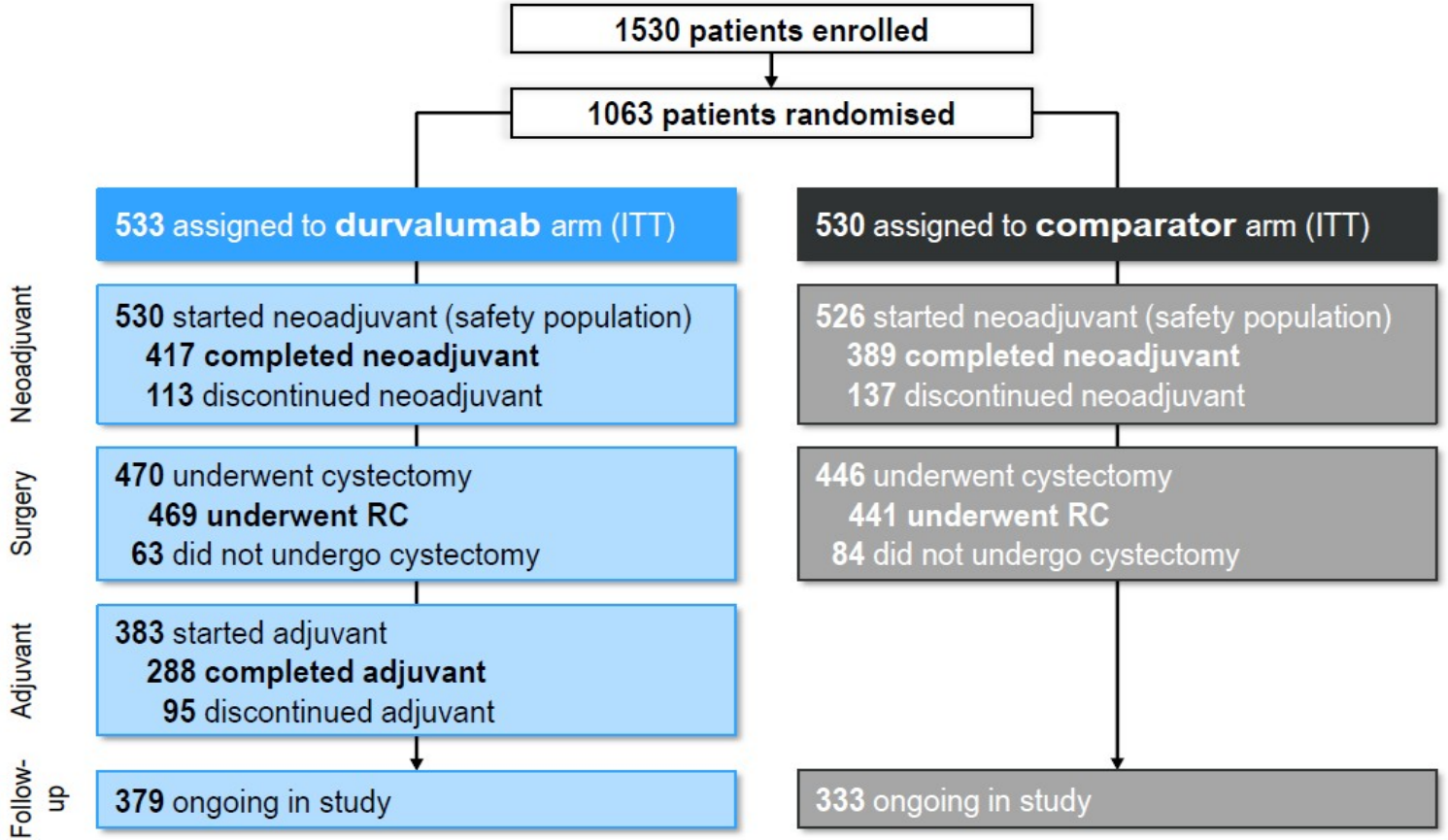
STATISTICAL ANALYSIS

- Multiple testing procedure with an alpha-exhaustive recycling strategy and gatekeeping strategy was used across the dual primary endpoints and then the secondary endpoints of OS and 5-year OS
- One pCR analysis was planned ~6 months after the last patient was randomised (ITT)
  - Comparison between study arms was analysed with logistic regression and summarised with odds ratio, 95% CI, and *P* value
- In interim analysis, the estimated number of events across the 2 arms was 410 for EFS and 288 for OS (ITT)
  - The actual numbers of events were 433 for EFS and 305 for OS
  - *P* value comparison between study arms was analysed using a stratified log-rank test
  - HRs and 95% CIs were estimated from stratified Cox PH models
  - Medians and landmarks were estimated using the KM method



Study considered positive if either of the dual primary endpoints were met

PATIENT DISPOSITION



- No patients were ongoing on study treatment at data cutoff
- Median time from the last dose of neoadjuvant therapy to cystectomy:
  - 39.0 days (range, 8–118) for the durvalumab arm
  - 38.0 days (range, 12–333) for the comparator arm

First patient enrolled: Nov 2018
Last patient enrolled: Jul 2021
Last RC: Nov 2021

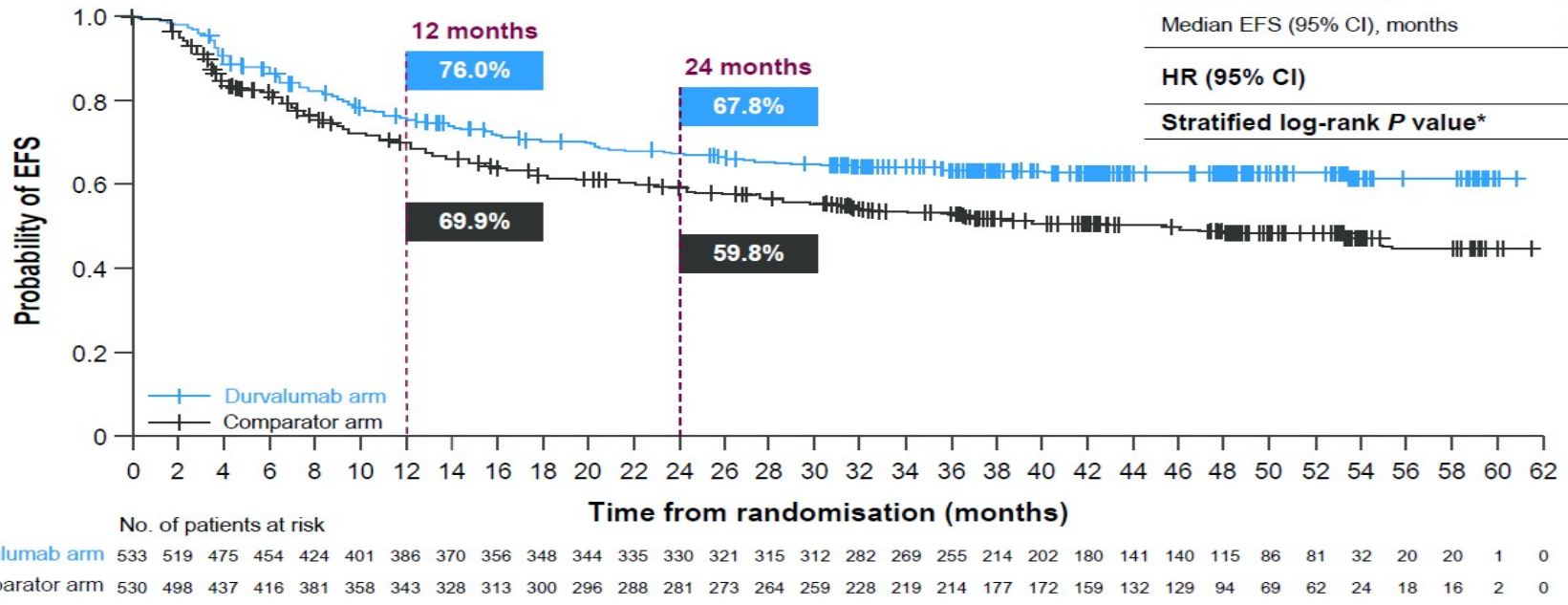
Data cutoff 29 Apr 2024. ITT, intent-to-treat population; RC, radical cystectomy.

BASELINE CHARACTERISTICS

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

*The study design capped recruitment of patients with tumour stage T2 at 40% and CrCl of <60 mL/min to 20%. †Assessed with the VENTANA PD-L1 (SP263) Assay using the TC/IC25% algorithm; high PD-L1 expression was defined as ≥25% of TCs with any membrane staining or ICs staining for PD-L1 at any intensity. Data cutoff 29 Apr 2024. CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, immune cell; ITT, intent-to-treat population; PD-L1, programmed cell death ligand-1; TC, tumour cell; UC, urothelial carcinoma.

EVENT FREE SURVIVAL BY BLINDED INDEPENDENT CENTRAL REVIEW



	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

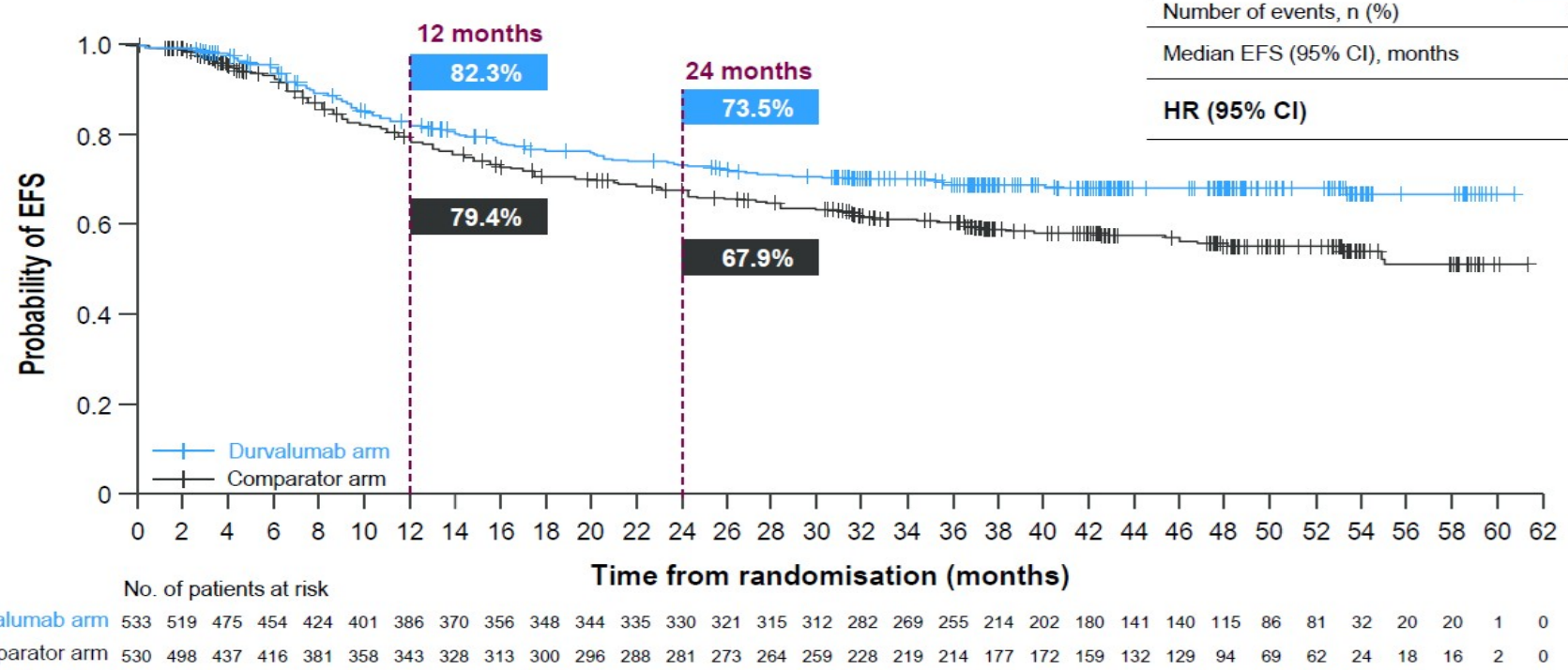
Durvalumab arm	533	519	475	454	424	401	386	370	356	348	344	335	330	321	315	312	282	269	255	214	202	180	141	140	115	86	81	32	20	20	1	0
Comparator arm	530	498	437	416	381	358	343	328	313	300	296	288	281	273	264	259	228	219	214	177	172	159	132	129	94	69	62	24	18	16	2	0

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.

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)**	



No. of patients at risk

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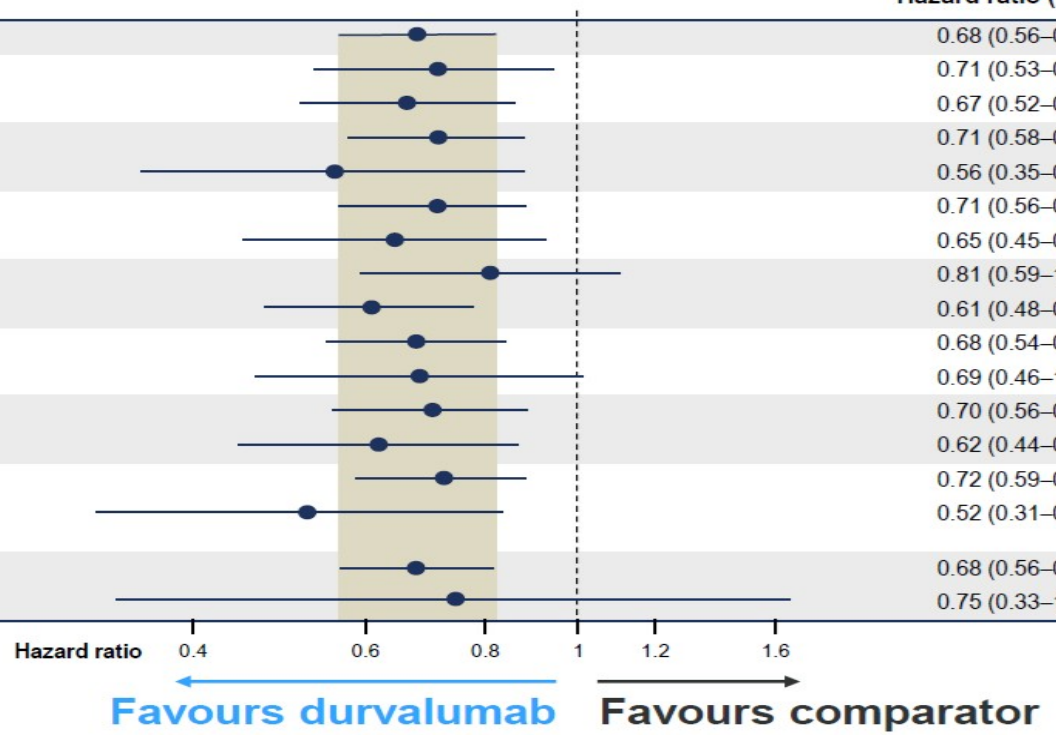
Data cutoff 29 Apr 2024. CI, confidence interval; EFS, event-free survival; HR, hazard ratio; NR, not reached; RC, radical cystectomy; RECIST, Response Evaluation Criteria In Solid Tumors.

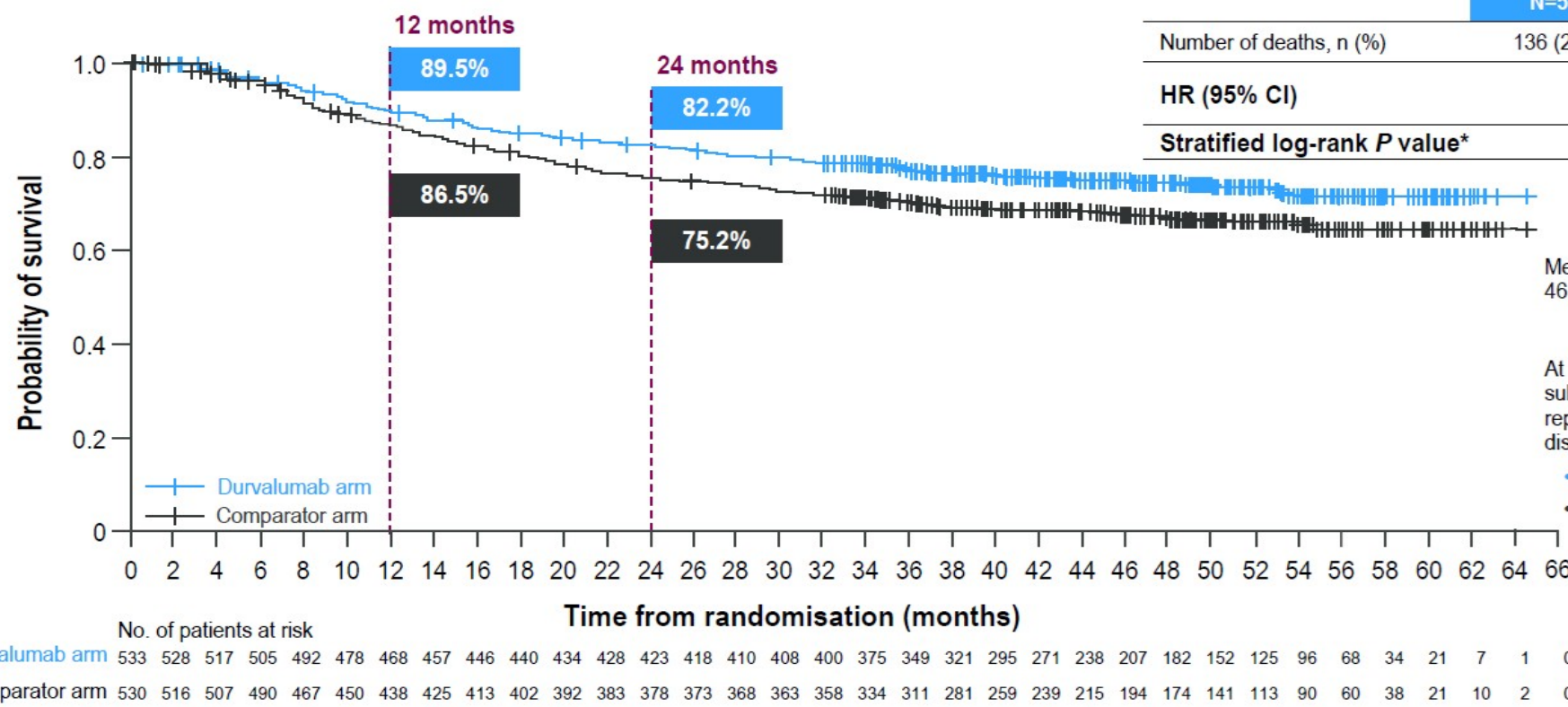
EVENT FREE SURVIVAL SUBGROUP ANALYSIS

Subgroup	Category	N	Hazard ratio (95% CI)
All patients		1063	0.68 (0.56–0.82)
Age at randomisation	<65 years	499	0.71 (0.53–0.94)
	≥65 years	564	0.67 (0.52–0.86)
Sex	Male	870	0.71 (0.58–0.88)
	Female	193	0.56 (0.35–0.88)
Race	White	712	0.71 (0.56–0.89)
	Non-White	315	0.65 (0.45–0.92)
Tumour stage at baseline	T2N0	428	0.81 (0.59–1.10)
	>T2N0	635	0.61 (0.48–0.78)
Renal function at baseline	CrCl ≥60 mL/min	862	0.68 (0.54–0.84)
	CrCl ≥40–<60 mL/min	201	0.69 (0.46–1.01)
PD-L1 expression at baseline*	High	777	0.70 (0.56–0.88)
	Low/negative	286	0.62 (0.44–0.87)
Histology at baseline	UC	898	0.72 (0.59–0.89)
	UC with divergent differentiation or histologic subtypes	165	0.52 (0.31–0.84)
Lymph node positive at baseline	N0	1005	0.68 (0.56–0.83)
	N1	58	0.75 (0.33–1.64)



EFS was assessed by blinded independent central review or by central pathology review, using RECIST v1.1. The plot is of hazard ratio and 95% CI. Tan-coloured band represents the 95% CI for the overall (all patients) hazard ratio. The subgroup analyses were performed using an unstratified Cox proportional hazard model, with treatment as only covariate and ties handled by Efron approach.
*Assessed with the VENTANA PD-L1 (SP263) Assay using the TC/IC25% algorithm; high PD-L1 expression was defined as ≥25% of TCs with any membrane staining or ICs staining for PD-L1 at any intensity. Due to observed inconsistencies between central laboratories in PD-L1 IC prevalence, but not TC prevalence, in the PD-L1 TC/IC25% algorithm, additional analyses of EFS by TC expression levels of 1% and 25% were performed and the results were consistent with those in the intent-to-treat population.
Data cutoff 29 Apr 2024. CI, confidence interval; CrCl, creatinine clearance; EFS, event-free survival; IC, immune cell; PD-L1, programmed cell death ligand-1; RECIST, Response Evaluation Criteria In Solid Tumors; TC, tumour cell; UC, urothelial carcinoma.

OVERALL SURVIVAL



	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

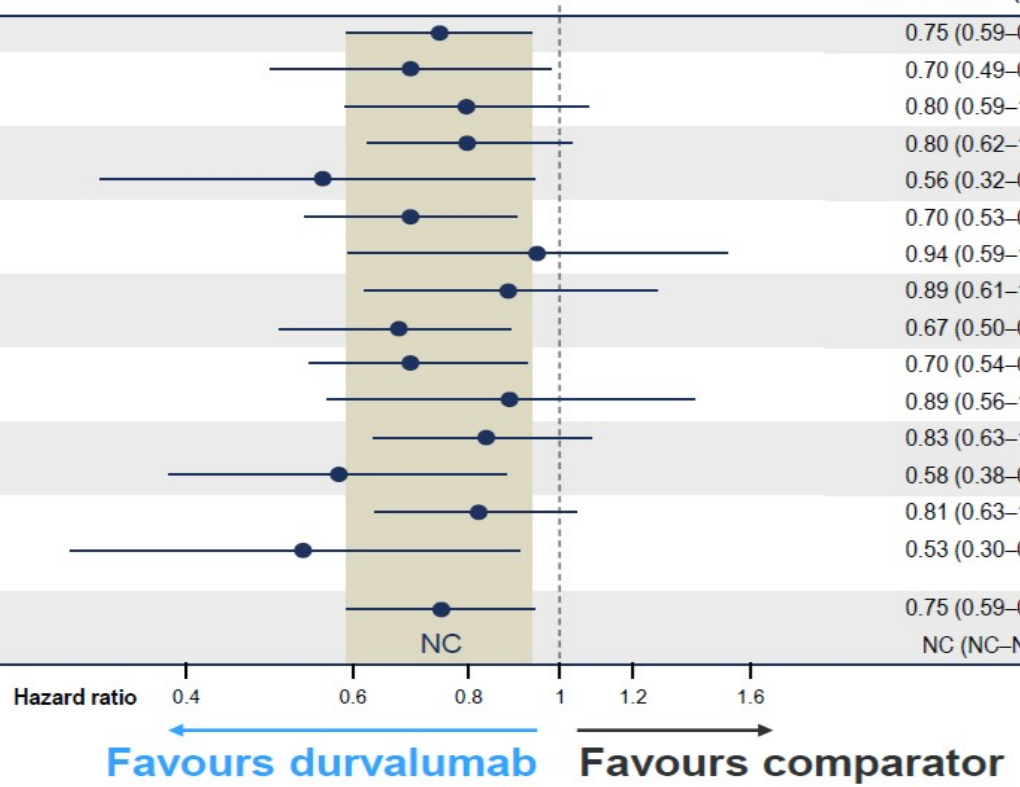
No. of patients at risk

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.

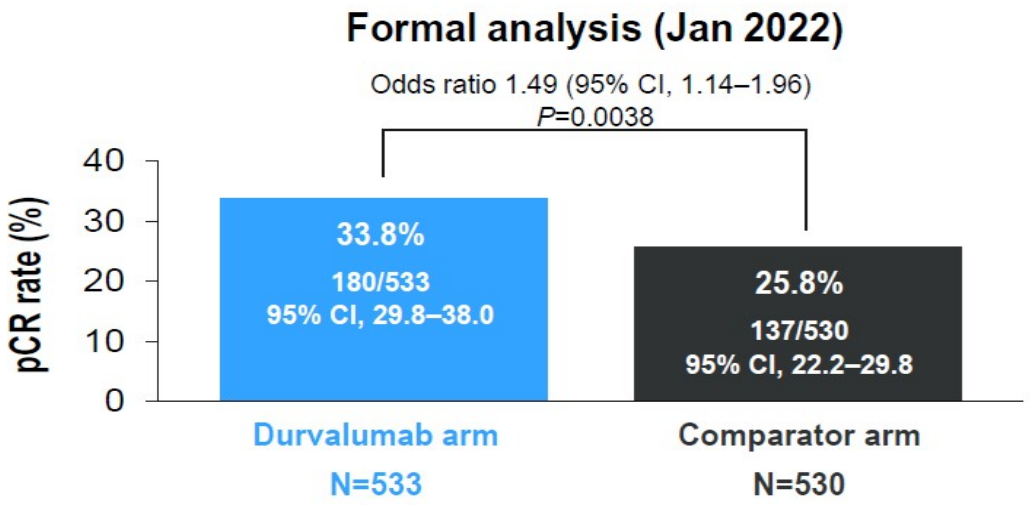
OVERALL SURVIVAL SUBGROUP ANALYSIS

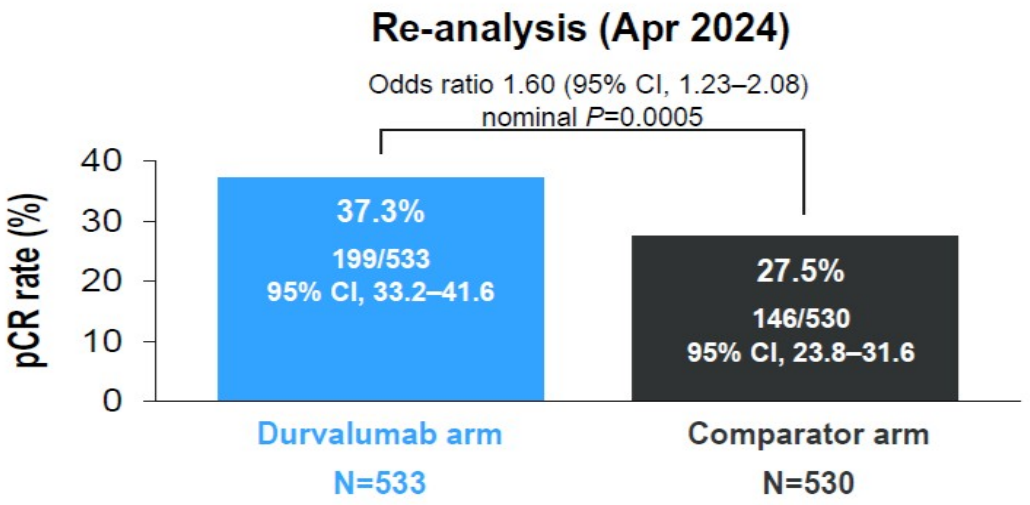
Subgroup	Category	N	Hazard ratio (95% CI)
All patients		1063	0.75 (0.59–0.93)
Age at randomisation	<65 years	499	0.70 (0.49–0.98)
	≥65 years	564	0.80 (0.59–1.07)
Sex	Male	870	0.80 (0.62–1.02)
	Female	193	0.56 (0.32–0.94)
Race	White	712	0.70 (0.53–0.90)
	Non-White	315	0.94 (0.59–1.51)
Tumour stage at baseline	T2N0	428	0.89 (0.61–1.28)
	>T2N0	635	0.67 (0.50–0.89)
Renal function at baseline	CrCl ≥60 mL/min	862	0.70 (0.54–0.91)
	CrCl ≥40–<60 mL/min	201	0.89 (0.56–1.40)
PD-L1 expression at baseline*	High	777	0.83 (0.63–1.09)
	Low/negative	286	0.58 (0.38–0.88)
Histology at baseline	UC	898	0.81 (0.63–1.04)
	UC with divergent differentiation or histologic subtypes	165	0.53 (0.30–0.91)
Lymph node positive at baseline	N0	1005	0.75 (0.59–0.94)
	N1	58	NC (NC–NC)



The plot is of hazard ratio and 95% CI. Tan-coloured band represents the 95% CI for the overall (all patients) hazard ratio. The subgroup analyses were performed using an unstratified Cox proportional hazard model, with treatment as only covariate and ties handled by Efron approach.
*Assessed with the VENTANA PD-L1 (SP263) Assay using the TC/IC25% algorithm; high PD-L1 expression was defined as ≥25% of TCs with any membrane staining or ICs staining for PD-L1 at any intensity.
Data cutoff 29 Apr 2024. CI, confidence interval; CrCl, creatinine clearance; IC, immune cell; NC, not calculated; PD-L1, programmed cell death ligand-1; TC, tumor cell; UC, urothelial carcinoma.

PATHOLOGICAL COMPLETE RESPONSE





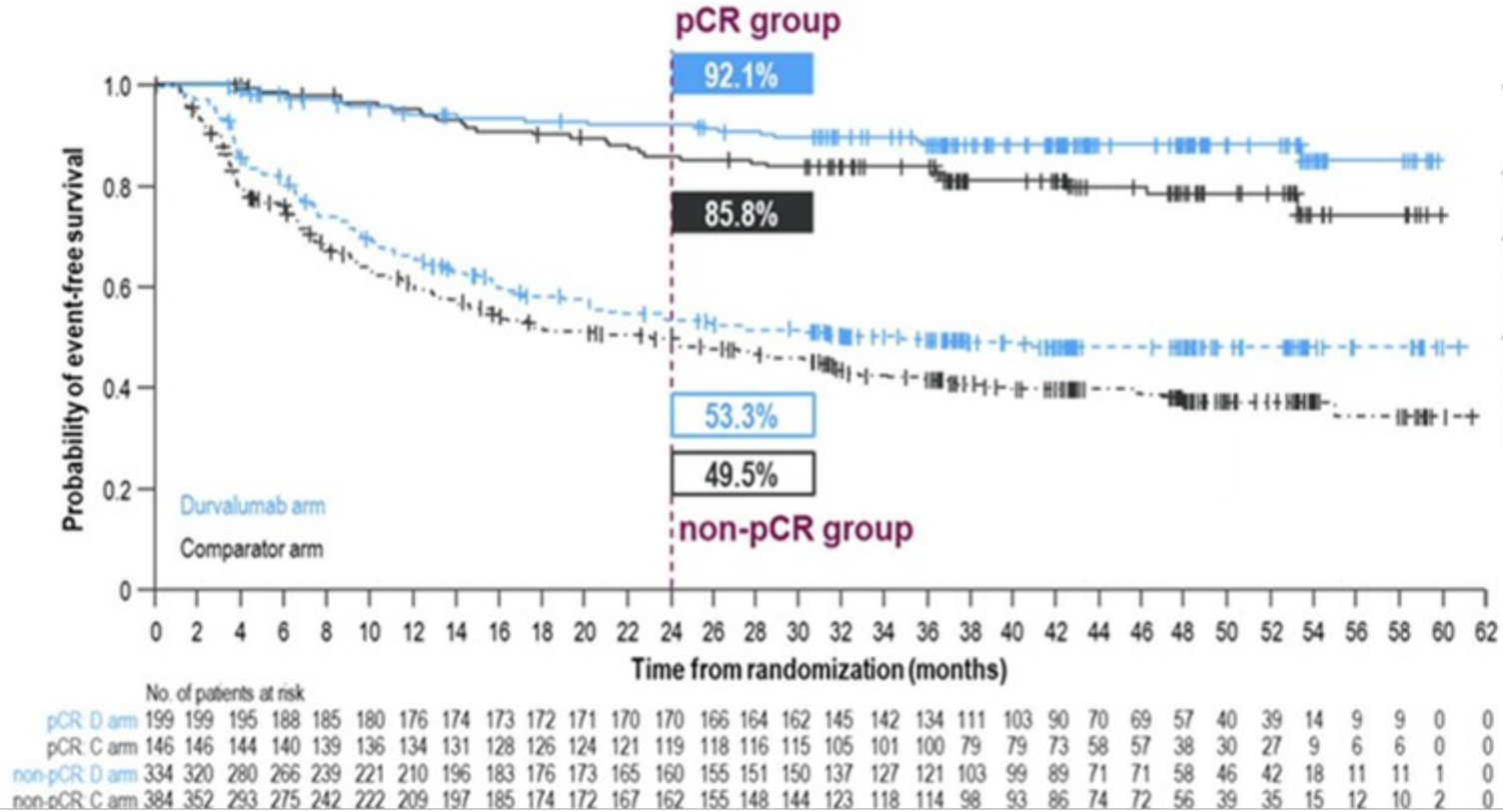
- The planned formal analysis for pCR was not statistically significant (threshold for significance, p-value 0.001)
- 59 evaluable samples were incorrectly considered non-responders rather than their true result*

- 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.

EVENT FREE SURVIVAL BY PATHOLOGICAL STAGING

Peri operative D+NAC improved EFS in both groups

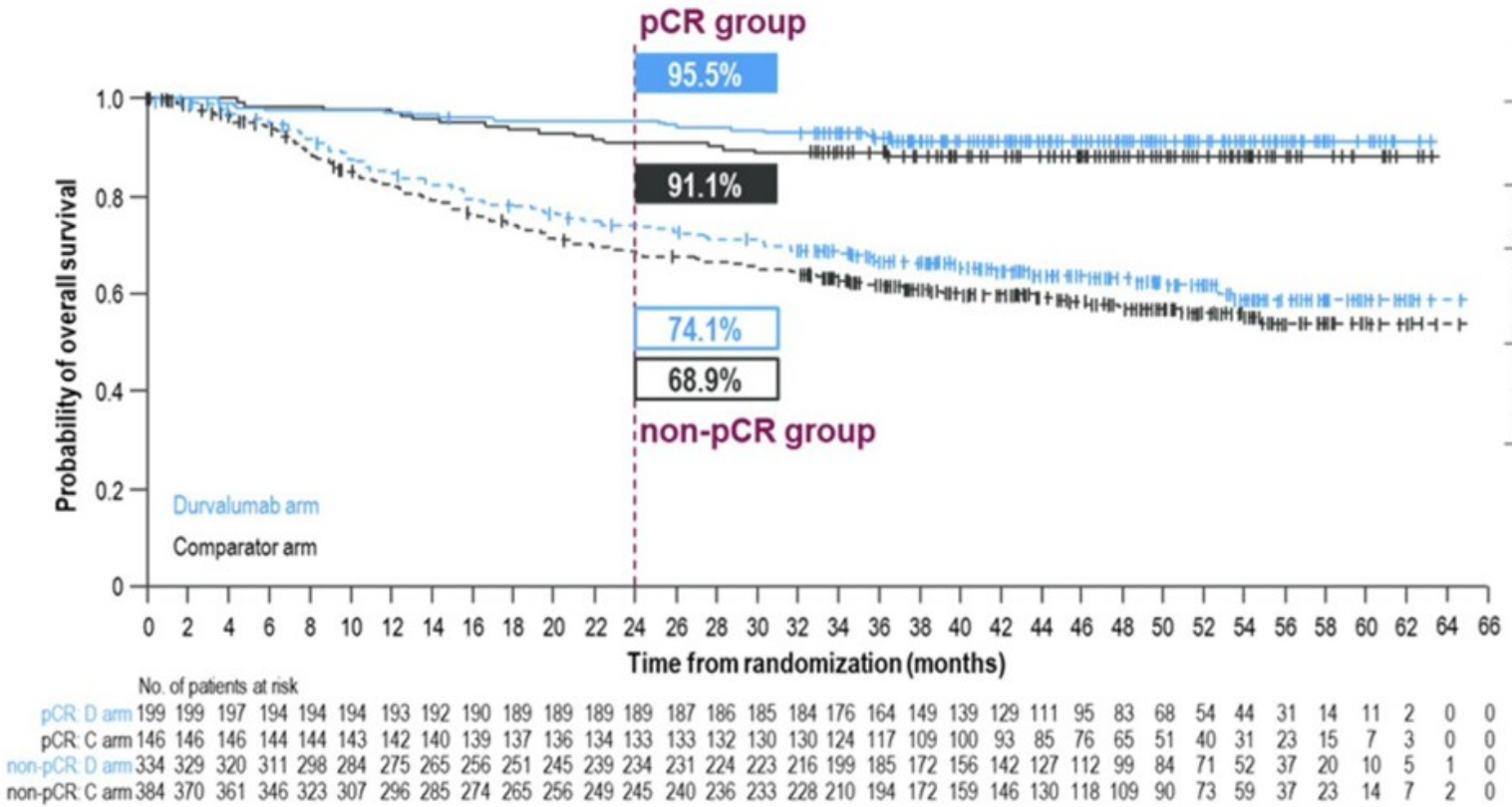


	pCR		non-pCR	
	D N=199	C N=146	D N=334	C N=384
Number of events, n (%)	X	X	X	X
Median EFS (95% CI), months	NR (NR–NR)	NR (NR–NR)	34.7 (20.5–NR)	22.8 (15.5–30.6)
HR (95% CI)	**0.58 (0.332–0.999)**		**0.77 (0.631–0.948)**	

	EFS in the ITT
HR	**0.68**
95% CI	(0.56–0.82)

OVERALL SURVIVAL BY PATHOLOGICAL STAGING

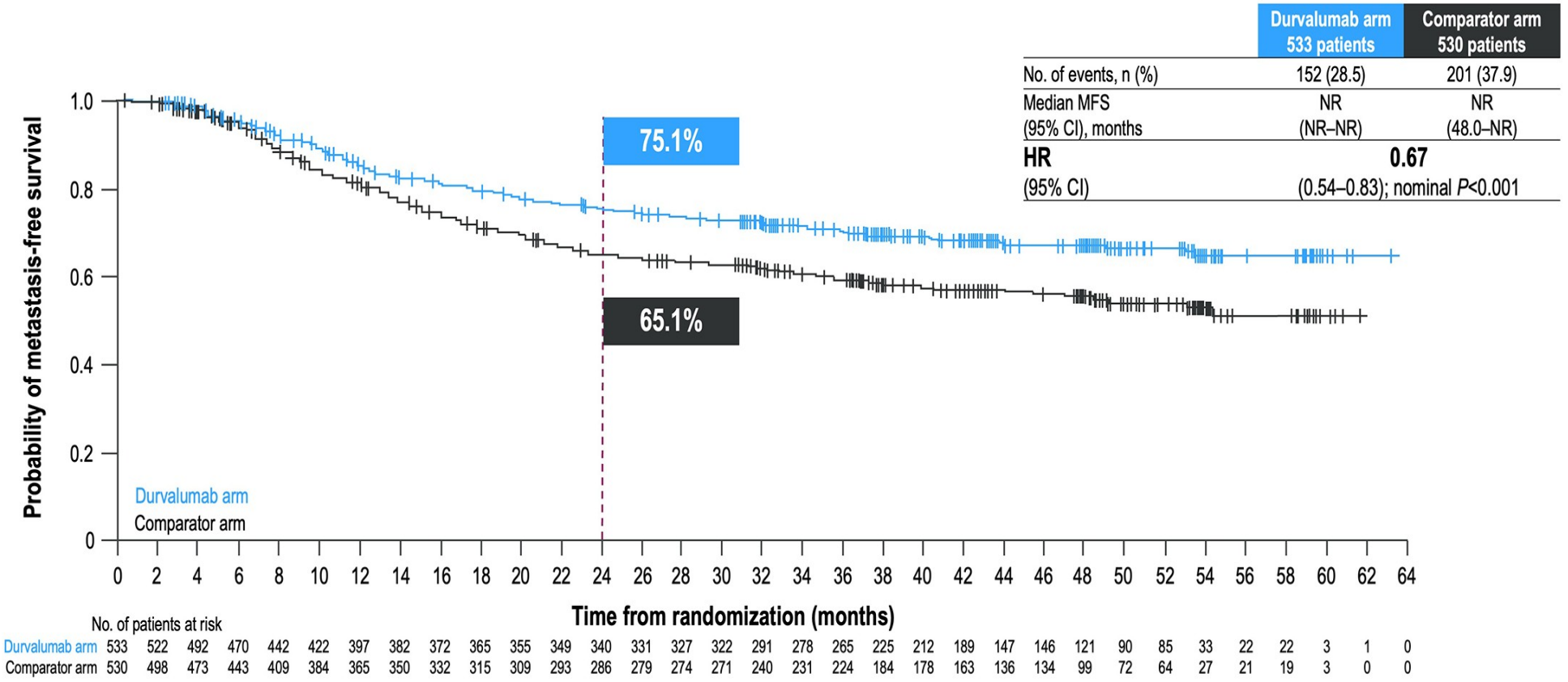
Peri operative D+NAC improved OS in both groups



	pCR		non-pCR	
	D N=199	C N=146	D N=334	C N=384
Number of deaths, n (%)	X	X	X	X
Median OS (95% CI), months	NR (NR–NR)	NR (NR–NR)	NR (NR–NR)	NR (53.9–NR)
HR (95% CI)	**0.72 (0.367–1.426)**		**0.84 (0.660–1.068)**	

	OS in the ITT
HR	**0.75**
95% CI	(0.59–0.93)

METASTASIS FREE SURVIVAL



ADVERSE EVENTS

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.

ADVERSE EVENTS

Overall study period (unless otherwise stated)	Durvalumab arm N=530	Comparator arm N=526
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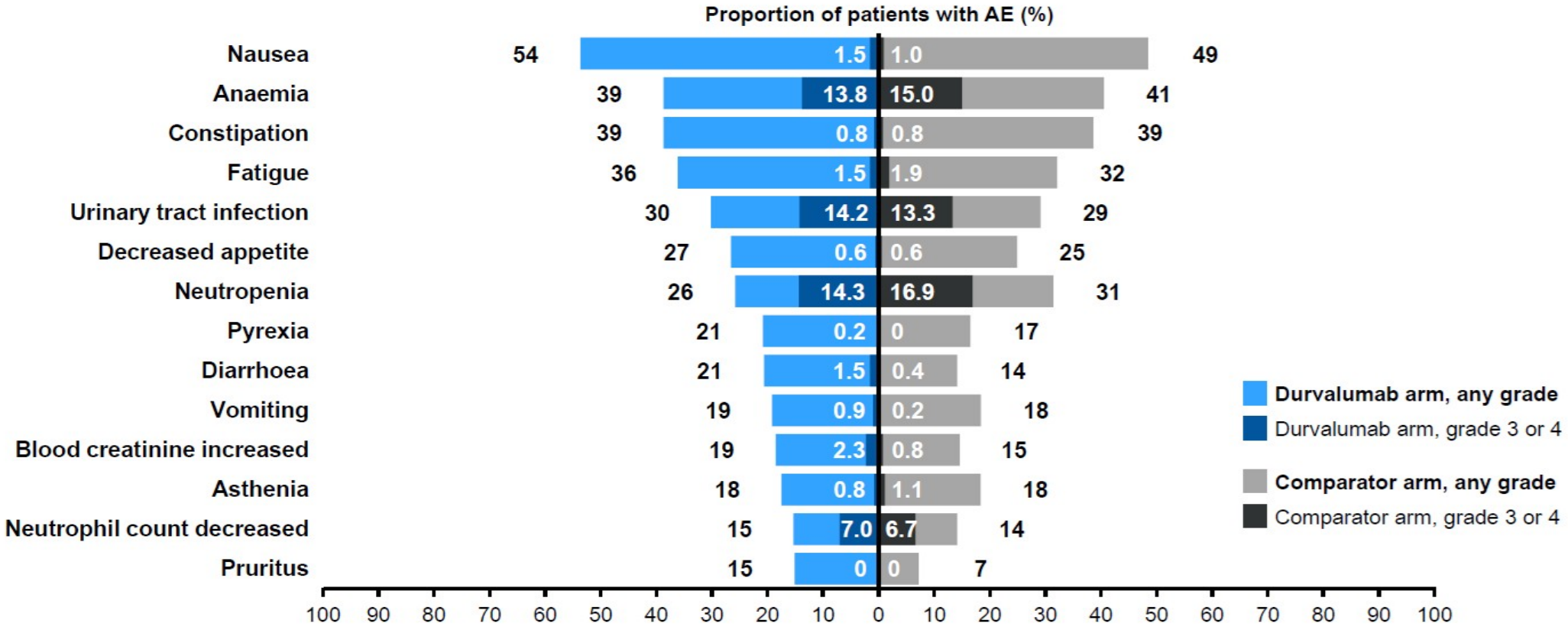
Any-grade immune-mediated AEs	111 (21)	16 (3)

ADVERSE EVENTS

Adjuvant treatment phase*	Durvalumab arm (N=383)	Comparator arm (N=383)
AEs of any cause, n (%)	331 (86)	273 (71)
Grade 3 or 4	119 (31)	91 (24)
Serious AEs	101 (26)	85 (22)
Outcome of death	7 (2)	6 (2)
Leading to discontinuation of adjuvant durvalumab	30 (8)	---
AEs possibly related to treatment, n (%)†	156 (41)	23 (6)
Grade 3 or 4 (treatment related)	21 (6)	3 (1)
Outcome of death (treatment related)	0	0

ADVERSE EVENTS



All-causality AEs reported for ≥15% of patients in the safety population from either arm in the overall study period are shown. The overall 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.

CONCLUSION

- NIAGARA is the first Phase 3 perioperative immunotherapy study in MIBC and has demonstrated a statistically significant and clinically meaningful improvement in EFS and OS
- **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**
- EFS and OS benefits with durvalumab were consistent across subgroups
- The pCR results and the significant OS benefit support the perioperative approach
- Addition of perioperative durvalumab to NAC was tolerable and manageable, with no new safety signals
- Neoadjuvant durvalumab did not delay surgery and did not impact the ability of patients to undergo/complete surgery

NIAGARA supports perioperative durvalumab with NAC as a potential new standard treatment for patients with cisplatin-eligible MIBC

CONCLUSION

- In new analysis, both metastasis-free survival (MFS) and disease-specific survival were improved with durvalumab
- Pathological complete responses (pCRs) were more likely among patients who received durvalumab (37.3% vs 27.5%), but benefit with durvalumab was seen both in patients who did and did not achieve a pCR

Where do we go from here …

- Biomarkers beyond PDL1- ctDNA escalate/de-escalate
- Can we avoid surgery and consider for bladder preservation approaches
- Post progression therapies - impact on OS and accessibility
- Role of the neo vs adjuvant component - future studies
- Shorter duration, Lower doses –future studies


THANK YOU!