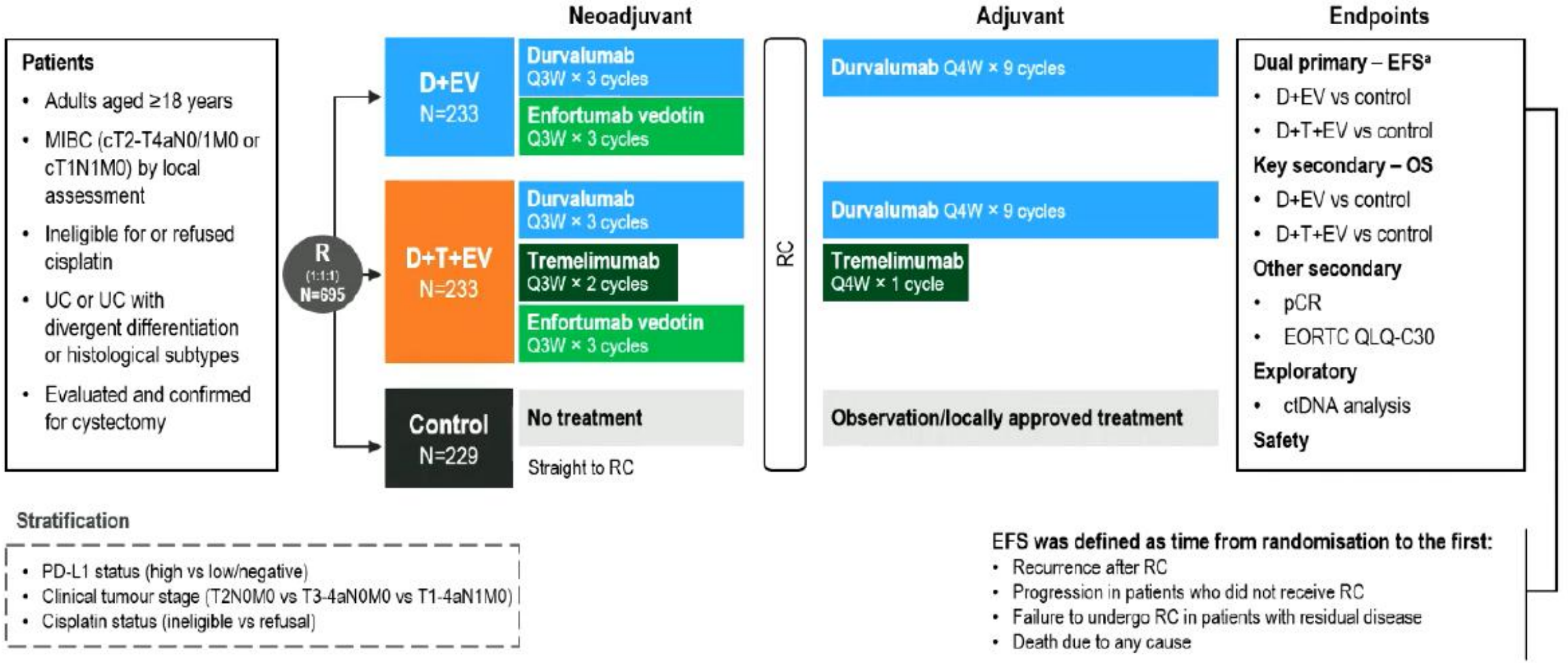
Perioperative Durvalumab With or Without Tremelimumab Plus Neoadjuvant Enfortumab Vedotin in Muscle-Invasive Bladder Cancer: Results From the Phase 3 VOLGA Trial

VOLGA: Background

- Patients with muscle-invasive bladder cancer (MIBC) treated with radical cystectomy (RC) alone have high rates of recurrence and a poor prognosis[1]
- Integration of immune checkpoint inhibitors into treatment regimens improved outcomes for these patients[2,3]
  - Durvalumab (anti–PD-L1 antibody) was the first immunotherapy approved for perioperative treatment of MIBC, when combined with neoadjuvant chemotherapy and RC[3]
  - Tremelimumab (anti–CTLA-4 antibody), in combination with durvalumab, is approved for use in metastatic non-small cell lung cancer and unresectable hepatocellular carcinoma[4,5]
- Recently, perioperative treatment strategies incorporating enfortumab vedotin (nectin-4 ADC) and pembrolizumab have further expanded the therapeutic landscape for MIBC[6,7]

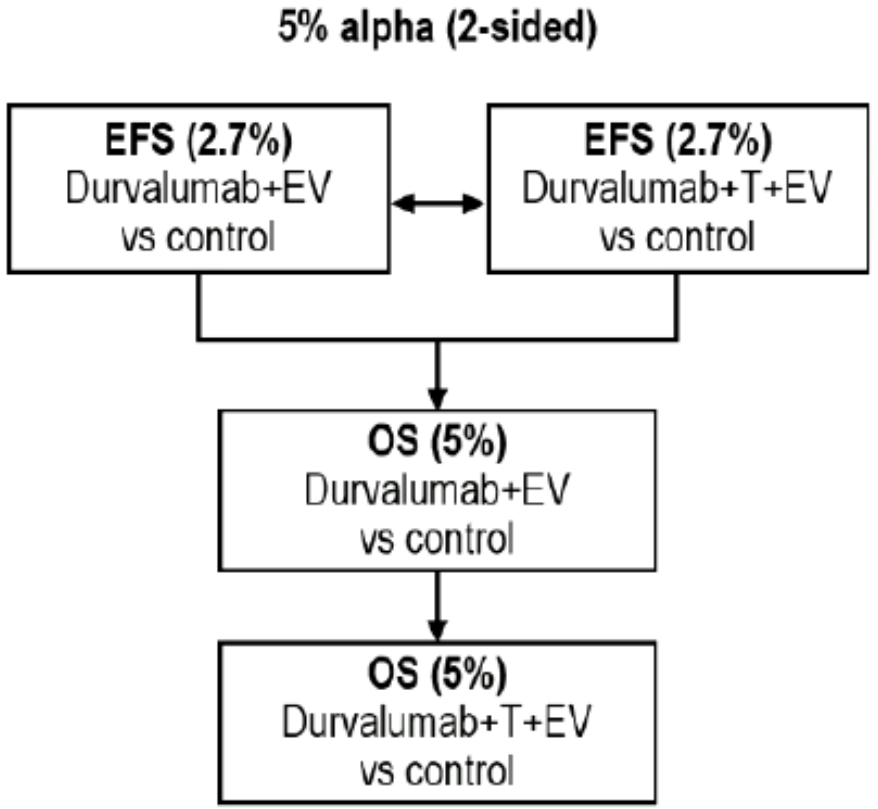
VOLGA is a Phase 3 study evaluating perioperative durvalumab ± tremelimumab plus neoadjuvant enfortumab vedotin in cisplatin-ineligible/refusing patients with MIBC

VOLGA: Study Design



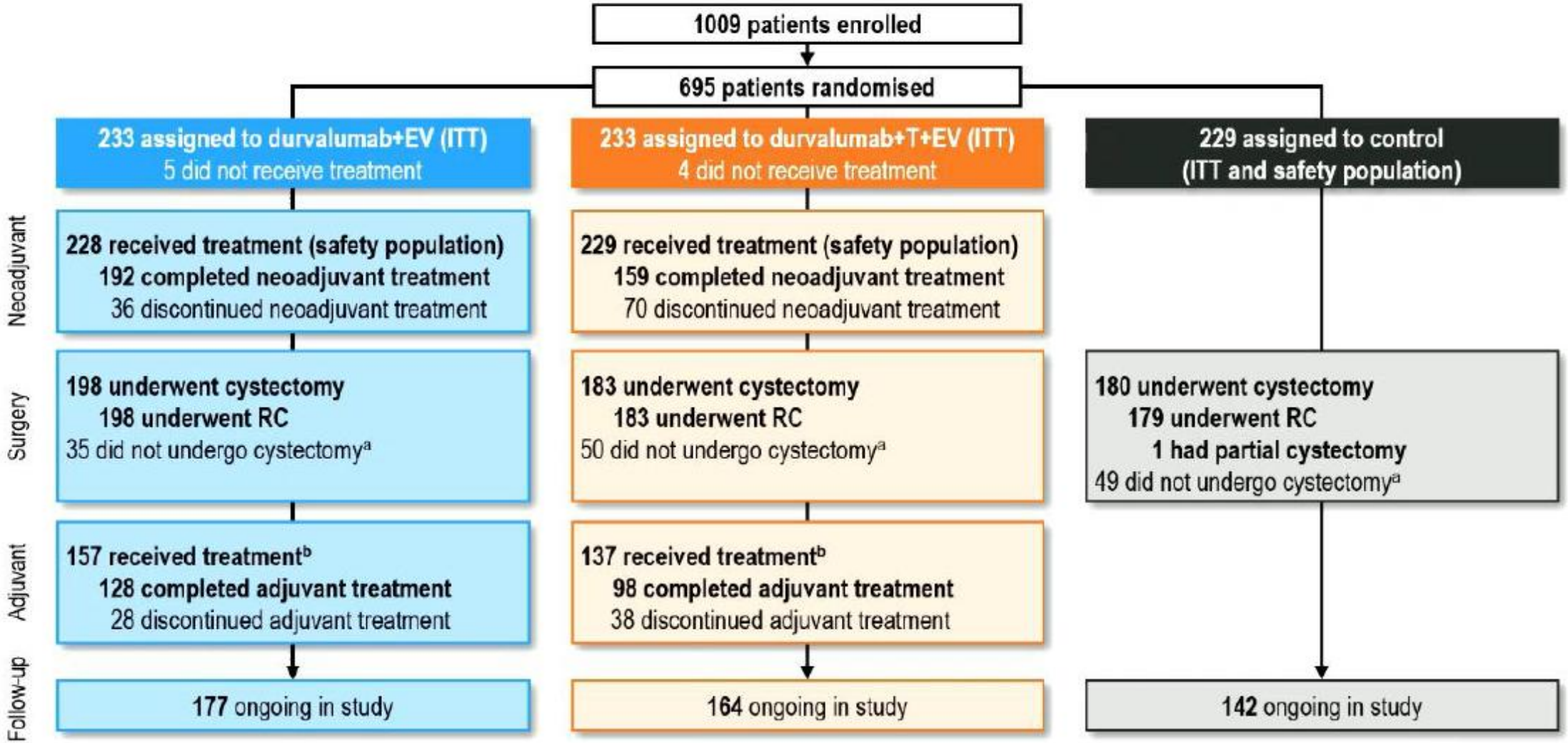
VOLGA: Statistical Analysis Plan

- A multiple testing procedure with a gatekeeping strategy was used across the dual primary endpoints of EFS and the key secondary endpoint of OS
- From a data cutoff of 02 March 2026, an interim analysis of EFS and OS was performed
  - The actual number of EFS events was 207 (durvalumab+EV vs control) and 215 (durvalumab+T+EV vs control)
  - EFS alpha spend calculated based on the observed number of events was 0.0218 (durvalumab+EV vs control) and 0.0270 (durvalumab+T+EV vs control)
  - Similarly, OS alpha spend was 0.0104 (durvalumab+EV vs control) and 0.0138 (durvalumab+T+EV vs control)
- *P* values were based on stratified log-rank tests; hazard ratios and 95% confidence intervals were estimated using stratified Cox proportional hazards models
- Medians and landmarks were estimated using the Kaplan-Meier method



VOLGA: Patient Disposition

First patient randomised: Apr 2022
Last patient randomised: Jan 2025



[a]The most common reasons for not undergoing cystectomy were patient decision (D+EV, n=15; D+T+EV, n=14; control, n=30), death (D+EV, n=7; D+T+EV, n=12; control, n=1), and disease progression (D+EV, n=4; D+T+EV, n=9; control, n=6). [b]One patient in the D+EV arm and one in the D+T+EV arm were ongoing adjuvant treatment at data cutoff. Data cutoff 02 March 2026. D, durvalumab; EV, enfortumab vedotin; ITT, intention-to-treat population; RC, radical cystectomy; T, tremelimumab.

VOLGA: Patient Characteristics – ITT

Baseline demographic and disease characteristics were generally balanced between the study arms

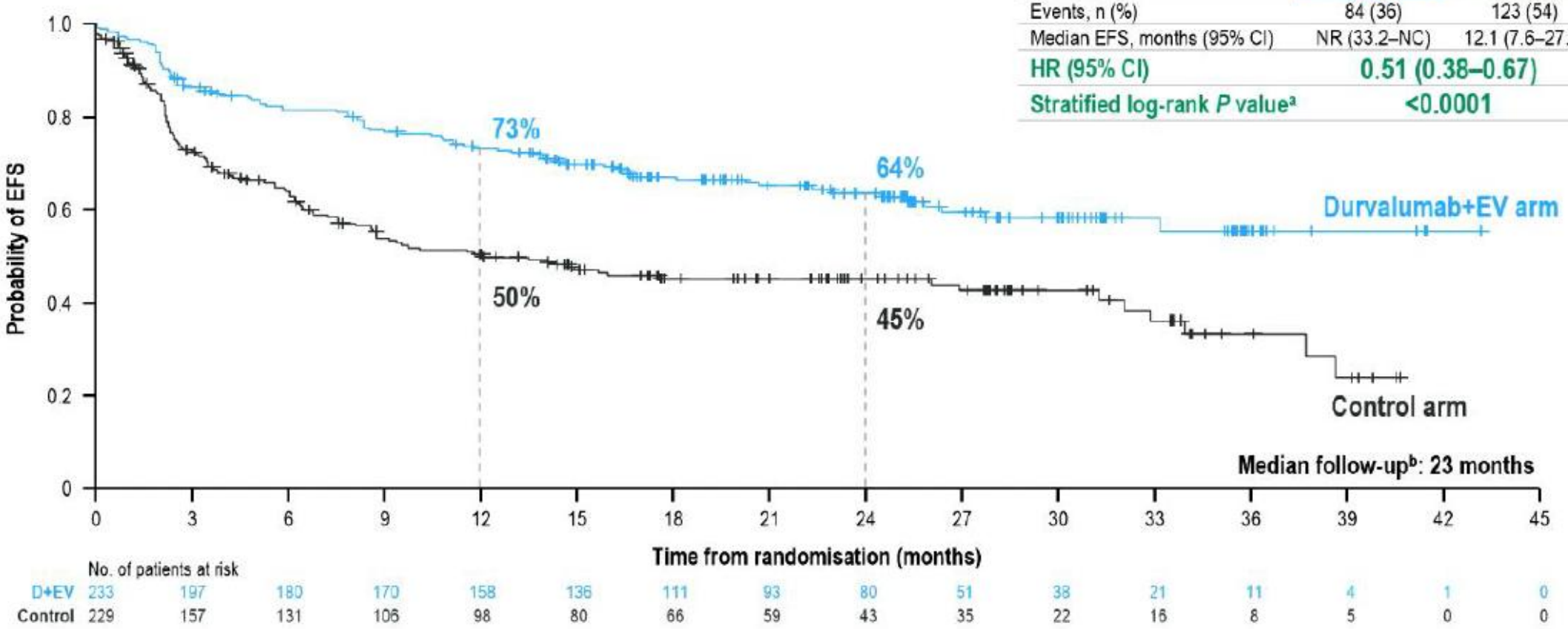
Characteristics		Durvalumab+EV N=233	Durvalumab+T+EV N=233	Control N=229
Age, median (range), years		72 (31–87)	71 (30–87)	72 (38–87)
Sex	**Male**	82%	79%	82%
Region	**Europe**	60%	52%	56%
	Asia	19%	20%	20%
	Americas	21%	28%	24%
ECOG PS[a]	**0**	67%	62%	66%
	1	24%	29%	25%
	2	9%	9%	8%
Nicotine use	**Current**	24%	17%	14%
	Former	49%	58%	57%
Tumour PD-L1 expression[b,c]	**High**	52%	52%	52%
	Low/negative	48%	48%	48%
Tumour stage[b,d]	**T2N0M0**	35%	37%	36%
	T3-4aN0M0	48%	48%	48%
	T1-4aN1M0	16%	14%	15%
Cisplatin status[b]	**Ineligible**	75%	76%	77%
	Refusal	25%	24%	23%

[a]ECOG PS missing for 1 patient in the control arm. [b]As reported by electronic case report form. [c]Assessed with the clinical trial assay for PD-L1 (SP263) (Roche Diagnostics); high PD-L1 expression was defined as any of the following: ≥25% of tumour cells exhibited membrane staining; or ICP >1% and IC+ ≥25%; or ICP=1% and IC+=100%. [d]Five patients (D+EV, n=1; D+T+EV, n=2; control, n=2) with T1-4aN0-1M1 tumour stage were enrolled and randomised in error and did not receive study treatment. Data cutoff 02 March 2026. D, durvalumab; ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; IC+, immune cells with PD-L1 staining; ICP, tumour-associated immune cells present; ITT, intention-to-treat population; PD-L1, programmed cell death ligand-1; T, tremelimumab.

VOLGA: EFS by BICR for Durvalumab+EV vs Control – ITT

Durvalumab+EV demonstrated a statistically significant improvement in EFS vs control

	D+EV N=233	Control N=229
Events, n (%)	84 (36)	123 (54)
Median EFS, months (95% CI)	NR (33.2–NC)	12.1 (7.6–27.0)
HR (95% CI)	0.51 (0.38–0.67)	
Stratified log-rank *P* value[a]	<0.0001	

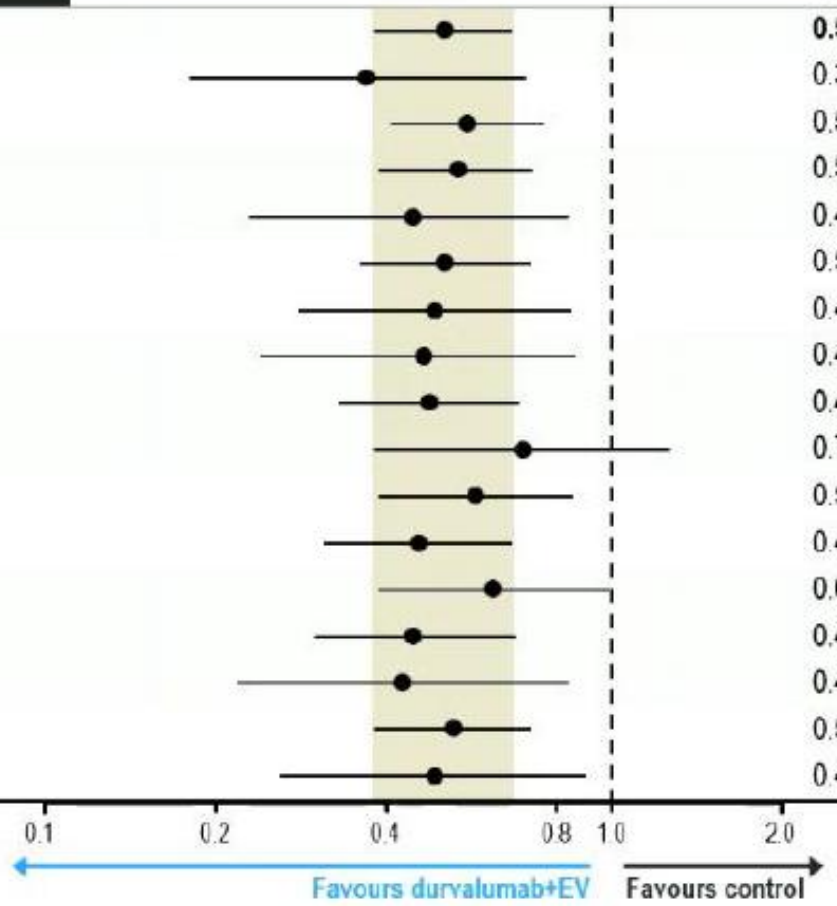


EFS is the time from randomisation to the first: 1) recurrence after RC, 2) progression in patients who did not receive RC, 3) failure to undergo RC in patients with residual disease, or 4) death due to any cause.
[a]The threshold to declare statistical significance was based on a based on a Lan-DeMets alpha spending function with O'Brien-Fleming boundary – with the observed number of events, the boundary for declaring statistical significance was 0.0218 for a 2.7% overall 2-sided alpha. [b]In censored patients across all study arms. Data cutoff 02 March 2026. BICR, blinded independent central review; CI, confidence interval; D, durvalumab; EFS, event-free survival; EV, enfortumab vedotin; HR, hazard ratio; ITT, intention-to-treat population; NC, not calculated; NR, not reached; RC, radical cystectomy.

VOLGA: EFS Subgroup Analyses for Durvalumab+EV vs Control

EFS benefit was consistent across subgroups for durvalumab+EV vs control

Subgroup	Category	Events/patients: Durvalumab+EV	Events/patients: Control	HR (95% CI)
All patients		84/233	123/229	**0.51 (0.38–0.67)**
Age at randomisation	<65 years	15/49	22/40	0.37 (0.18–0.71)
	≥65 years	69/184	101/189	0.56 (0.41–0.76)
Sex	Male	69/191	97/187	0.54 (0.39–0.73)
	Female	15/42	26/42	0.45 (0.23–0.84)
Race	White	55/153	82/158	0.51 (0.36–0.72)
	Non-White	20/56	34/54	0.49 (0.28–0.85)
Geographic region	Asia	15/44	29/46	0.47 (0.24–0.87)
	Europe	50/139	68/129	0.48 (0.33–0.69)
	Americas	19/50	26/54	0.70 (0.38–1.27)
Tumour PD-L1 expression[a,b]	High	41/120	60/120	0.58 (0.39–0.86)
	Low/negative	43/113	63/109	0.46 (0.31–0.67)
Tumour stage[a]	T2N0M0	31/82	41/83	0.62 (0.39–0.99)
	T3-4aN0M0	36/113	59/109	0.45 (0.30–0.68)
	T1-4aN1M0	16/37	21/35	0.43 (0.22–0.84)
Cisplatin status[a]	Ineligible	67/175	100/176	0.53 (0.38–0.72)
	Refusal	17/58	23/53	0.49 (0.26–0.91)

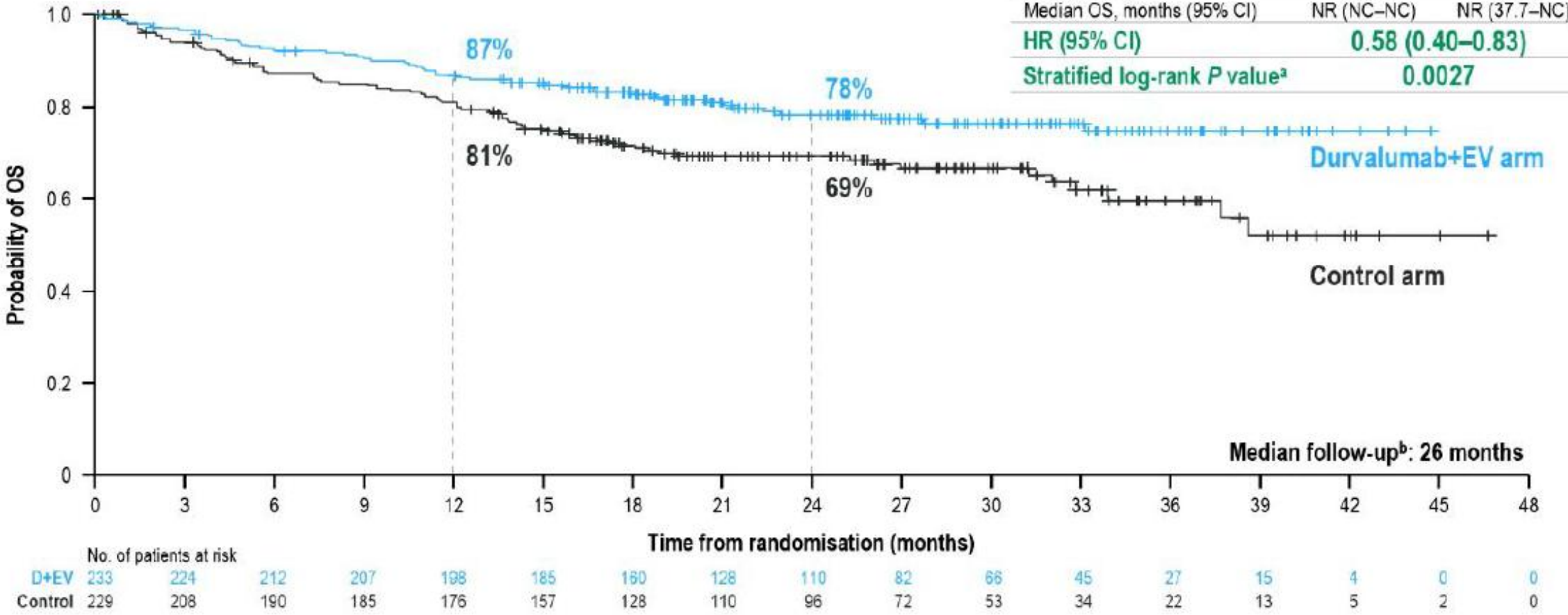


[a]As reported by electronic case report form. [b]Assessed with the clinical trial assay for PD-L1 (SP263) (Roche Diagnostics); high PD-L1 expression was defined as any of the following: ≥25% of tumour cells exhibited membrane staining; or ICP >1% and IC+ ≥25%; or ICP=1% and IC+=100%. Data cutoff 02 March 2026. CI, confidence interval; EFS, event-free survival; EV, enfortumab vedotin; HR, hazard ratio; IC+, immune cells with PD-L1 staining; ICP, tumour-associated immune cells present; PD-L1, programmed cell death ligand-1.

VOLGA: OS for Durvalumab+EV vs Control – ITT

Durvalumab+EV demonstrated a statistically significant improvement in OS vs control

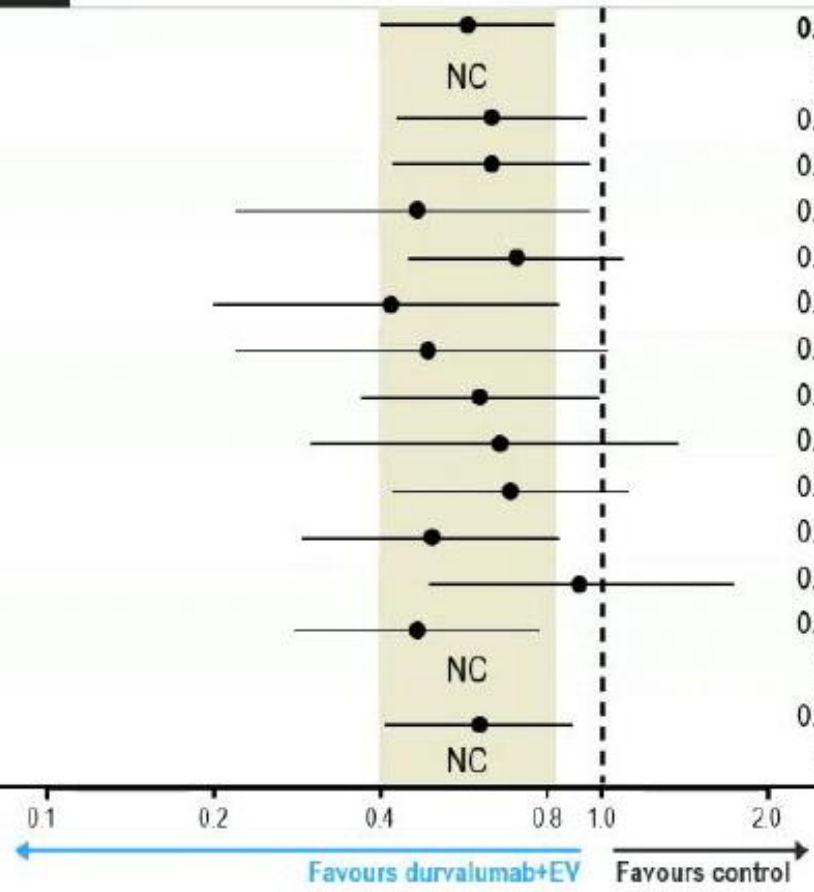
	D+EV N=233	Control N=229
Deaths, n (%)	49 (21)	74 (32)
Median OS, months (95% CI)	NR (NC–NC)	NR (37.7–NC)
HR (95% CI)	0.58 (0.40–0.83)	
Stratified log-rank *P* value[a]	0.0027	



VOLGA: OS Subgroup Analyses for Durvalumab+EV vs Control

OS benefit was consistent across subgroups for durvalumab+EV vs control

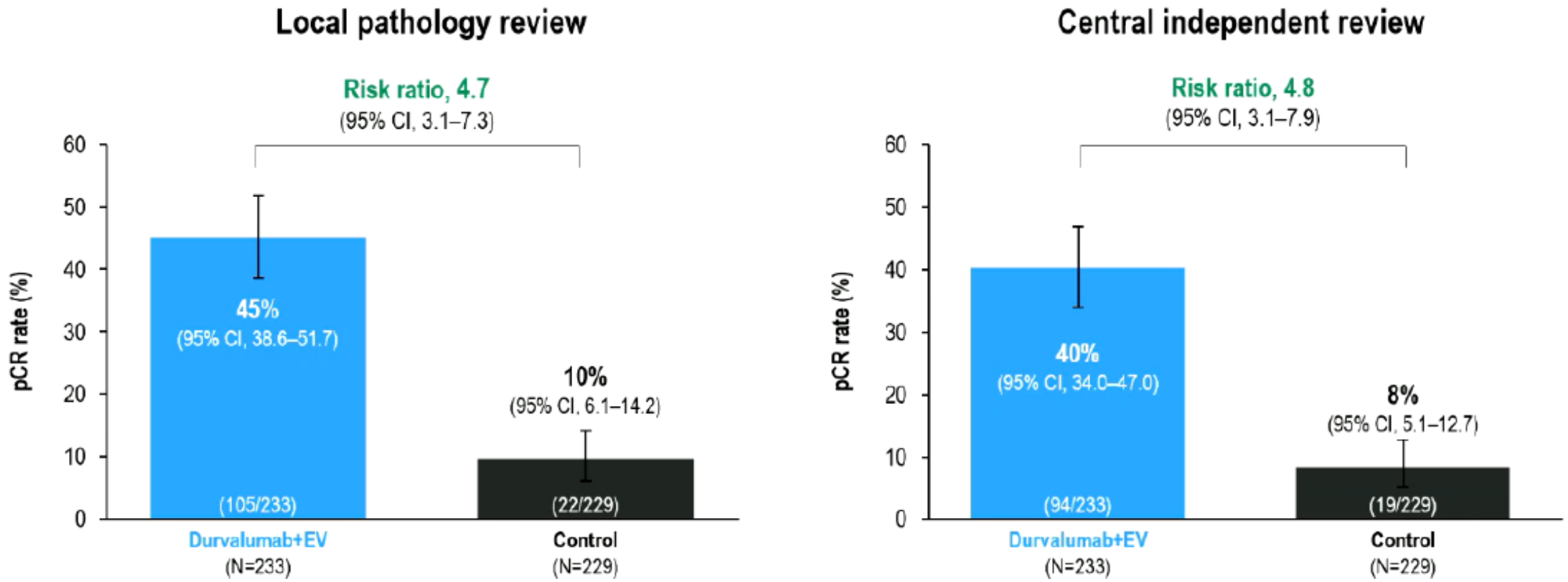
Subgroup	Category	Events/patients: Durvalumab+EV	Events/patients: Control	HR (95% CI)
All patients		49/233	74/229	**0.58 (0.40–0.83)**
Age at randomisation	<65 years	6/49	11/40	NC (NC–NC)
	≥65 years	43/184	63/189	0.64 (0.43–0.95)
Sex	Male	38/191	53/187	0.64 (0.42–0.96)
	Female	11/42	21/42	0.47 (0.22–0.96)
Race	White	34/153	45/158	0.71 (0.45–1.10)
	Non-White	11/56	23/54	0.42 (0.20–0.84)
Geographic region	Asia	10/44	19/46	0.49 (0.22–1.03)
	Europe	28/139	37/129	0.61 (0.37–1.00)
	Americas	11/50	18/54	0.66 (0.30–1.39)
Tumour PD-L1 expression[a,b]	High	27/120	38/120	0.69 (0.42–1.13)
	Low/negative	22/113	36/109	0.50 (0.29–0.84)
Tumour stage[a]	T2N0M0	19/82	20/83	0.92 (0.49–1.74)
	T3-4aN0M0	23/113	41/109	0.47 (0.28–0.78)
	T1-4aN1M0	7/37	12/35	NC (NC–NC)
Cisplatin status[a]	Ineligible	43/175	63/176	0.61 (0.41–0.89)
	Refusal	6/58	11/53	NC (NC–NC)



OS HR and CI were not calculated for subgroups with <20 events across both treatment arms. [a]As reported by electronic case report form. [b]Assessed with the clinical trial assay for PD-L1 (SP263) (Roche Diagnostics); high PD-L1 expression was defined as any of the following: ≥25% of tumour cells exhibited membrane staining; or ICP >1% and IC+ ≥25%; or ICP=1% and IC+=100%. Data cutoff 02 March 2026. CI, confidence interval; EV, enfortumab vedotin; HR, hazard ratio; IC+, immune cells with PD-L1 staining; ICP, tumour-associated immune cells present; NC, not calculated; OS, overall survival; PD-L1, programmed cell death ligand-1.

VOLGA: pCR for Durvalumab+EV vs Control – ITT

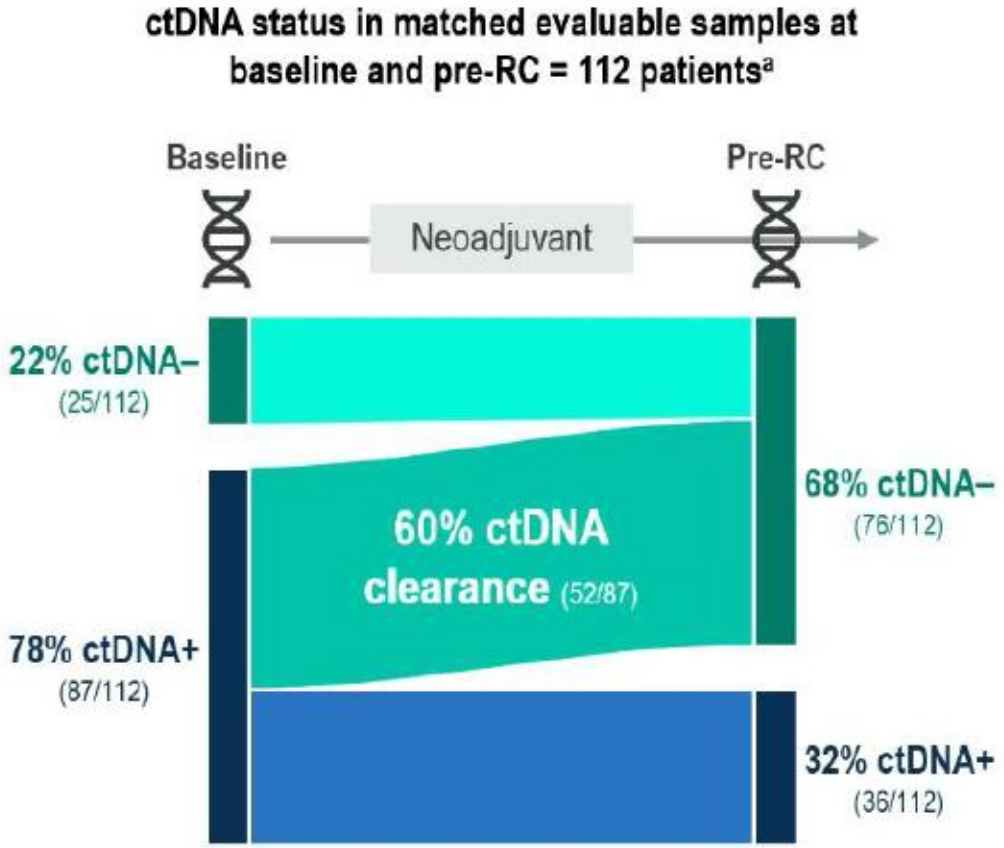
Durvalumab+EV showed improvements in pCR rate vs control

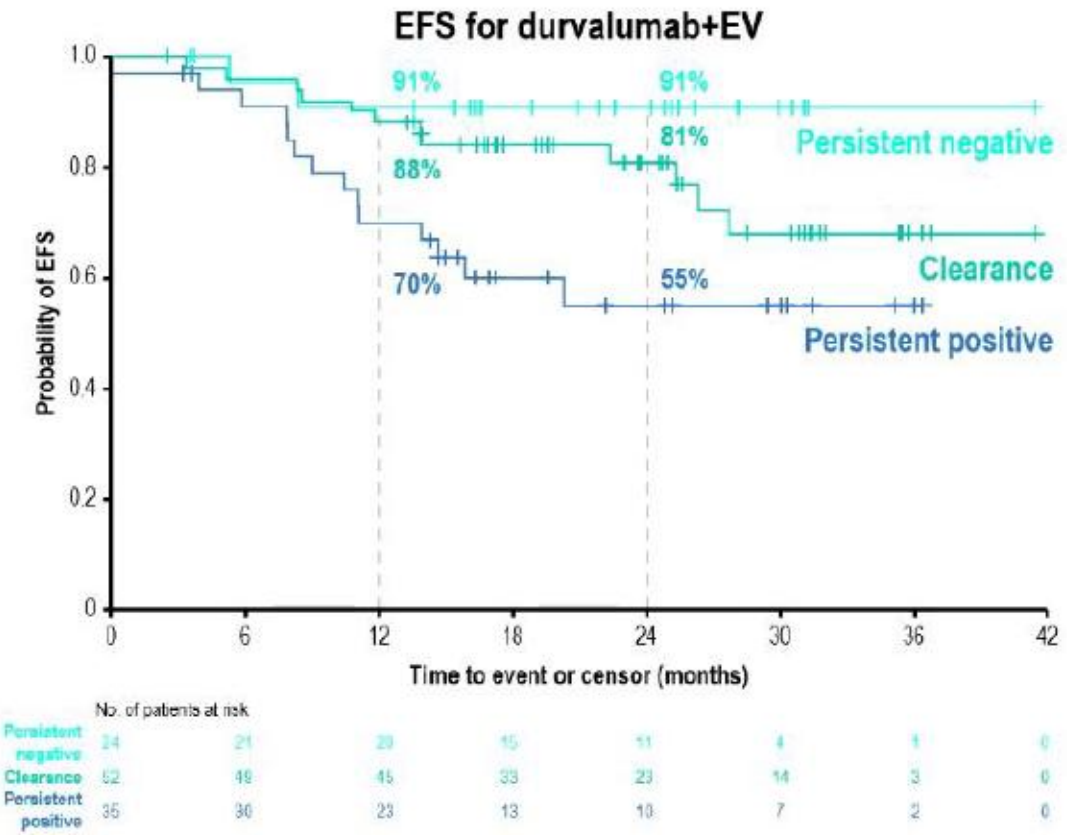


Analysis performed using log-binomial models adjusted using stratification factors: PD-L1 status, tumour stage and cisplatin status per interactive-response technology. Patients who did not undergo surgery or those with a missing or non-evaluable assessment were considered non-responders. Data cutoff 02 March 2026. CI, confidence interval; EV, enfortumab vedotin; ITT, intention-to-treat population; pCR, pathological complete response; PD-L1, programmed cell death ligand-1.

VOLGA: Pre-RC ctDNA Dynamics and Association With EFS for D+EV

60% of baseline ctDNA+ patients achieved ctDNA clearance in this exploratory analysis, as assessed using Natera's ultrasensitive Signatera™ Genome with Phased and Structural Variants Assay



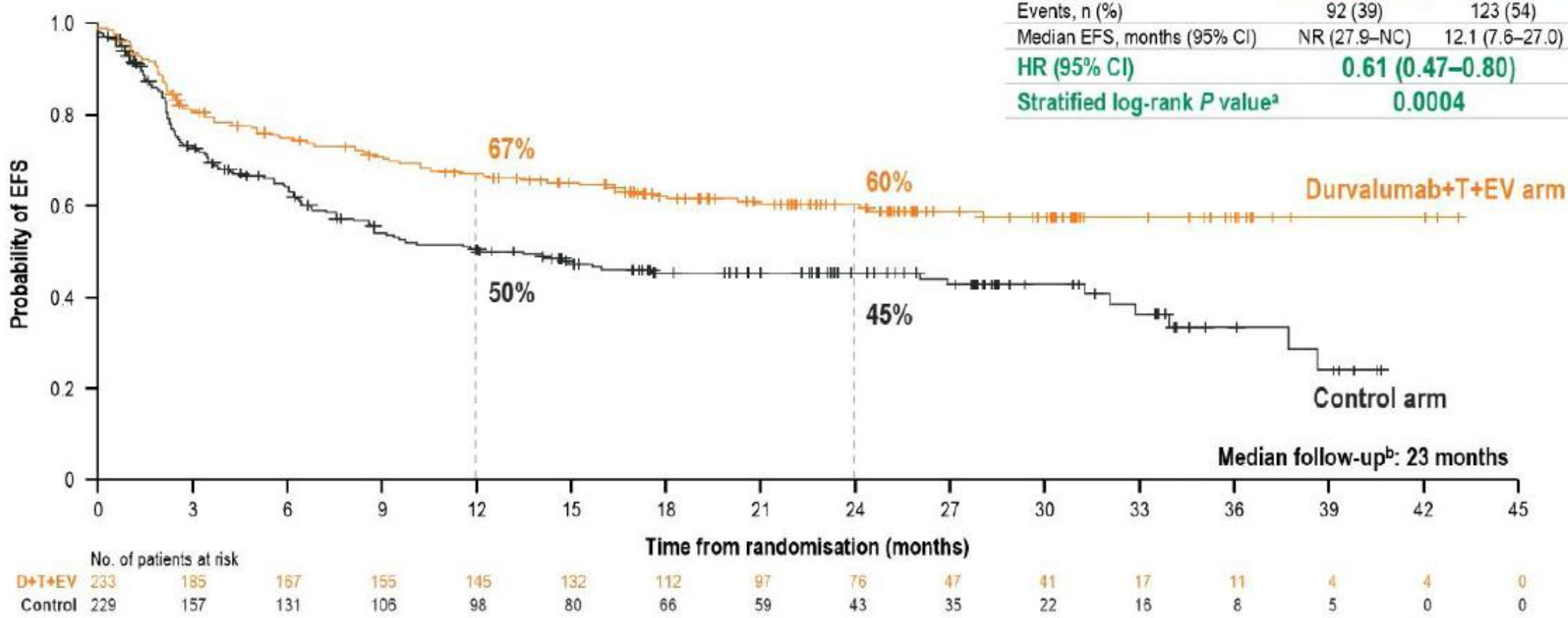


[a]Analysis based on currently available ctDNA biomarker evaluable population as of July 2026; additional patient data pending. One patient with ctDNA– to ctDNA+ status is not shown in the Sankey plot and was not included in the EFS Kaplan-Meier analysis. ctDNA, circulating tumour DNA; D, durvalumab; EFS, event-free survival; EV, enfortumab vedotin; RC, radical cystectomy.

VOLGA: EFS by BICR for Durvalumab+T+EV vs Control – ITT

Durvalumab+T+EV also demonstrated a statistically significant improvement in EFS vs control

	D+T+EV N=233	Control N=229
Events, n (%)	92 (39)	123 (54)
Median EFS, months (95% CI)	NR (27.9–NC)	12.1 (7.6–27.0)
HR (95% CI)	0.61 (0.47–0.80)	
Stratified log-rank *P* value[a]	0.0004	

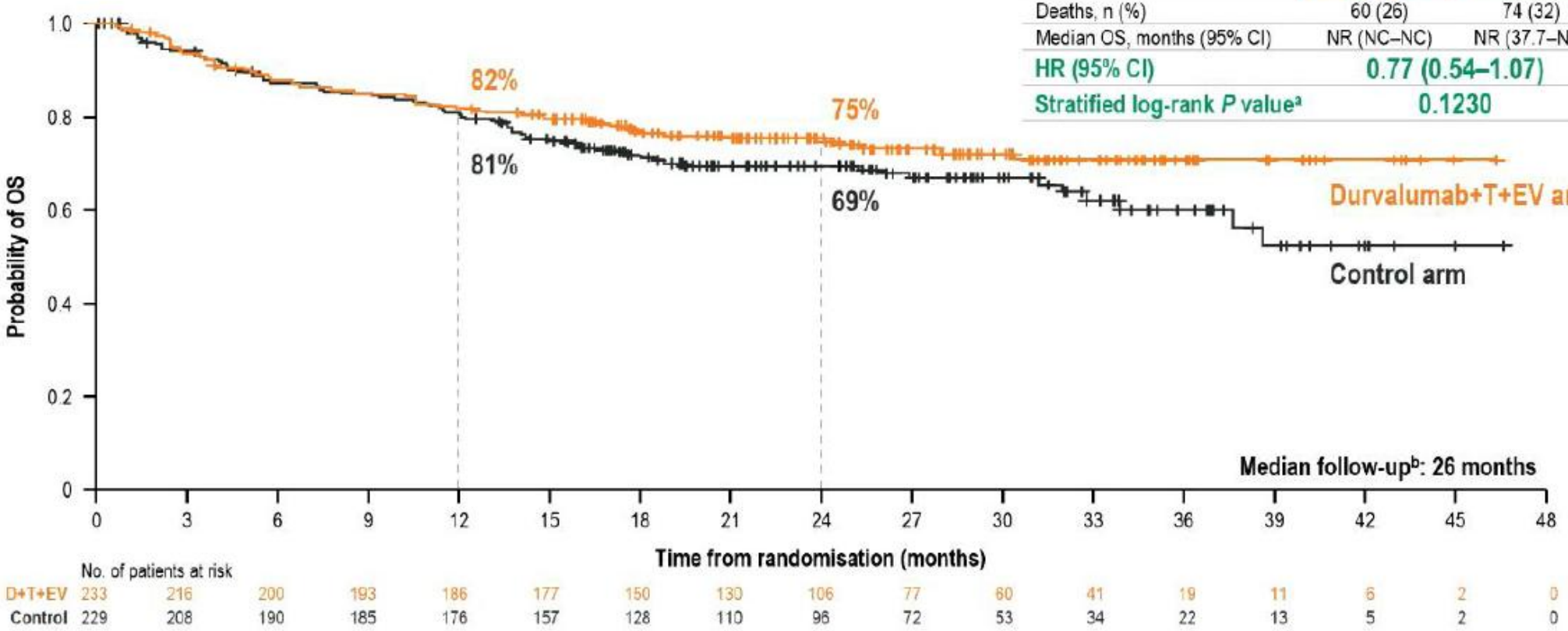


EFS is the time from randomisation to the first: 1) recurrence after RC, 2) progression in patients who did not receive RC, 3) failure to undergo RC in patients with residual disease, or 4) death due to any cause.
[a]The threshold to declare statistical significance was based on a Lan-DeMets alpha spending function with O'Brien-Fleming boundary – with the observed number of events, the boundary for declaring statistical significance was 0.0270 for a 2.7% overall 2-sided alpha. [b]In censored patients across all study arms. Data cutoff 02 March 2026. BICR, blinded independent central review; CI, confidence interval; D, durvalumab; EFS, event-free survival; EV, enfortumab vedotin; HR, hazard ratio; ITT, intention-to-treat population; NC, not calculated; NR, not reached; RC, radical cystectomy; T, tremelimumab.

VOLGA: OS for Durvalumab+T+EV vs Control – ITT

OS did not reach statistical significance at this interim analysis, and follow-up is ongoing

	D+T+EV N=233	Control N=229
Deaths, n (%)	60 (26)	74 (32)
Median OS, months (95% CI)	NR (NC–NC)	NR (37.7–NC)
HR (95% CI)	0.77 (0.54–1.07)	
Stratified log-rank *P* value[a]	0.1230	



OS is the time from randomisation until death due to any cause, regardless of whether the patient withdraws from randomised therapy or receives another anticancer therapy. [a]The threshold to declare statistical significance was based on a Gamma family (-3) spending function – with the observed number of events, the boundary for declaring statistical significance was 0.0138 for a 5% overall 2-sided alpha. [b]In censored patients across all study arms. Data cutoff 02 March 2026. CI, confidence interval; D, durvalumab; EV, enfortumab vedotin; HR, hazard ratio; ITT, intention-to-treat population; NC, not calculated; NR, not reached; OS, overall survival; T, tremelimumab.

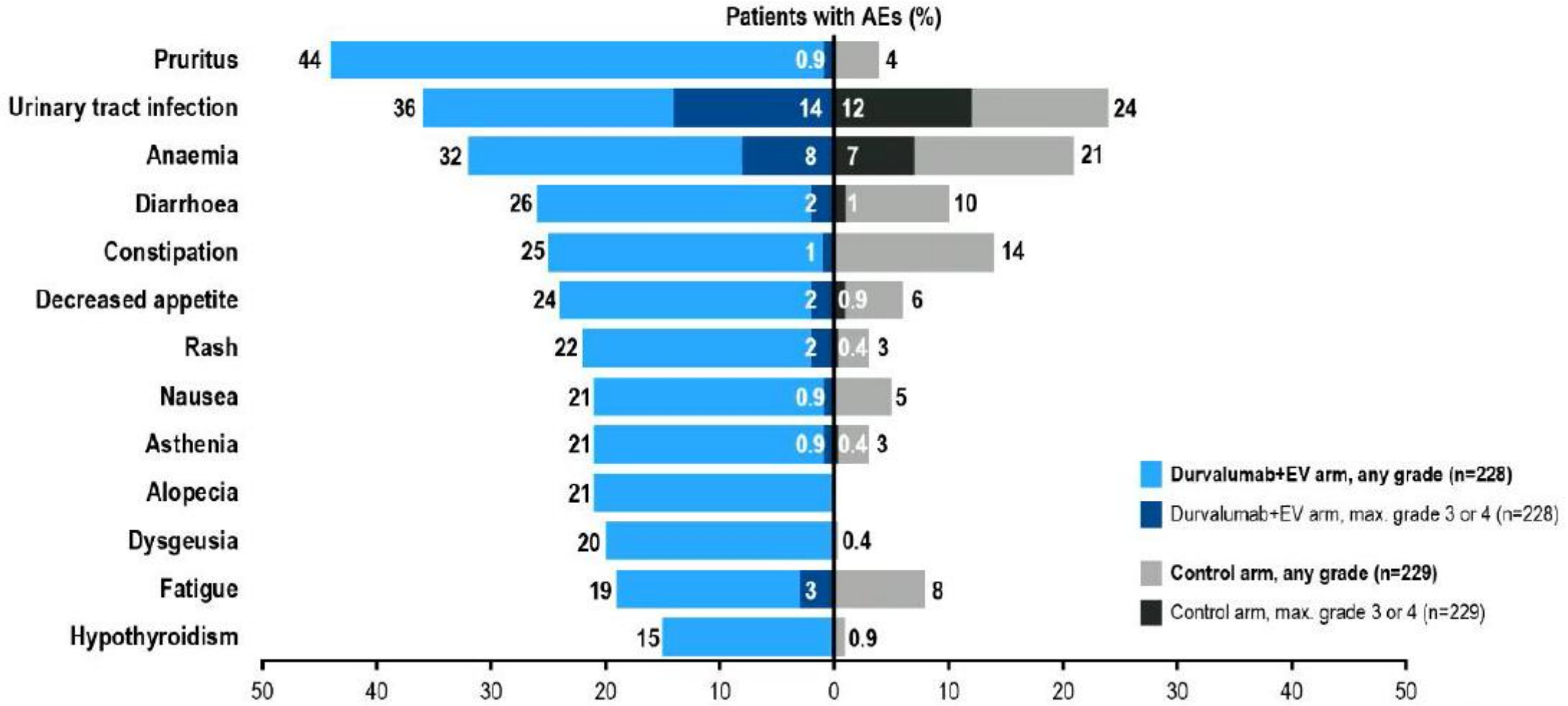
VOLGA: AE Summary – Safety Population (Overall Trial Period)

Events, n (%)	Durvalumab+EV n=228	Control n=229
AEs of any cause	**227 (>99)**	**170 (74)**
Maximum grade 3 or 4 AEs	145 (64)	101 (44)
Serious AEs	143 (63)	101 (44)
Leading to death	17 (7)	14 (6)
Leading to discontinuation of any study treatment	48 (21)	NA
Leading to discontinuation of durvalumab	37 (16)	NA
Leading to discontinuation of tremelimumab	NA	NA
Leading to discontinuation of enfortumab vedotin	26 (11)	NA
Leading to cancellation of surgery	2 (0.9)	0
Leading to delay in surgery[a]	8 (4)	1 (0.4)
AEs possibly related to any treatment	**207 (91)**	**NA**
Maximum grade 3 or 4 AEs	69 (30)	NA
Serious AEs	45 (20)	NA
Leading to death	1 (0.4)	NA
Any-grade immune-mediated AEs	**75 (33)**	**8 (3)**
Maximum grade 3 or 4	24 (11)	2 (0.9)
Leading to death	0	0

The safety population includes all patients who received study treatment (D+EV arm) or who were randomised (control arm). Investigator-assessed causality. [a]Recommended timeframe for surgery was within 56 days after the last dose of neoadjuvant treatment (D+EV arm), and within 12 weeks of diagnosis (control arm). Data cutoff 02 March 2026. AE, adverse event; D, durvalumab; EV, enfortumab vedotin; NA, not applicable.

VOLGA: Most Frequently Reported AEs for Durvalumab+EV vs Control

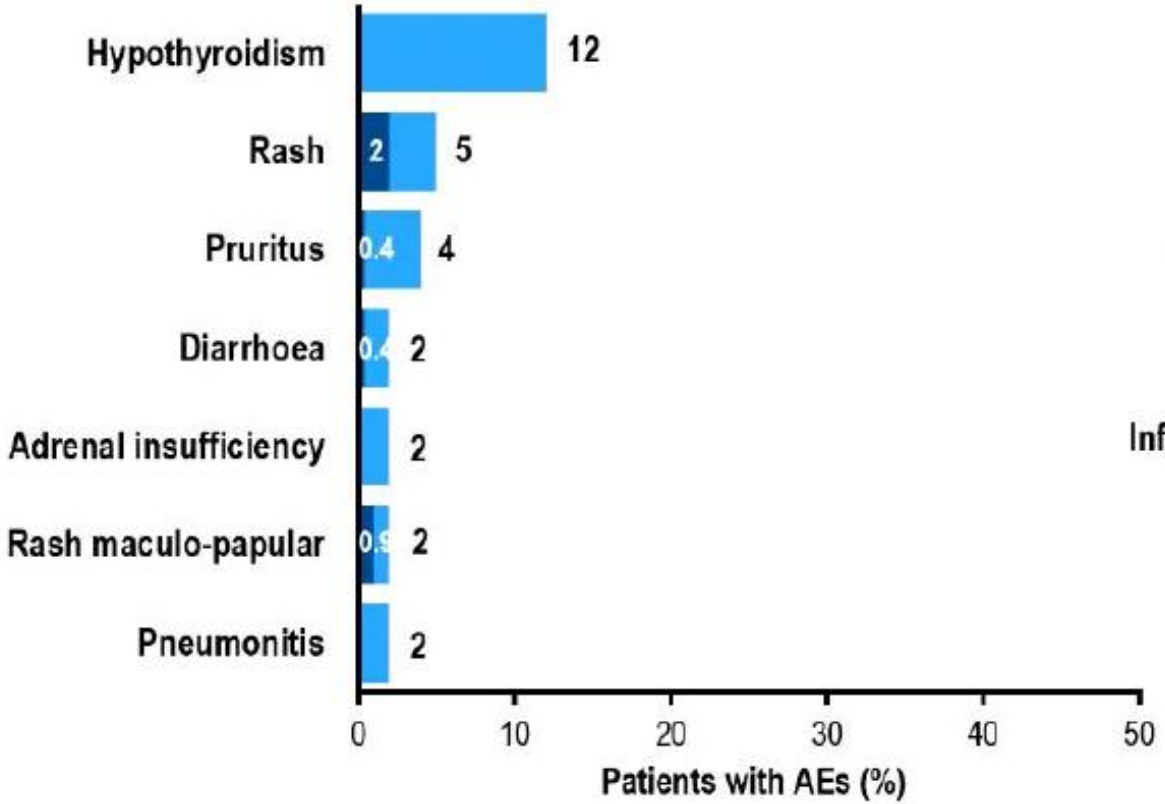
The safety profile was consistent with those of the individual agents



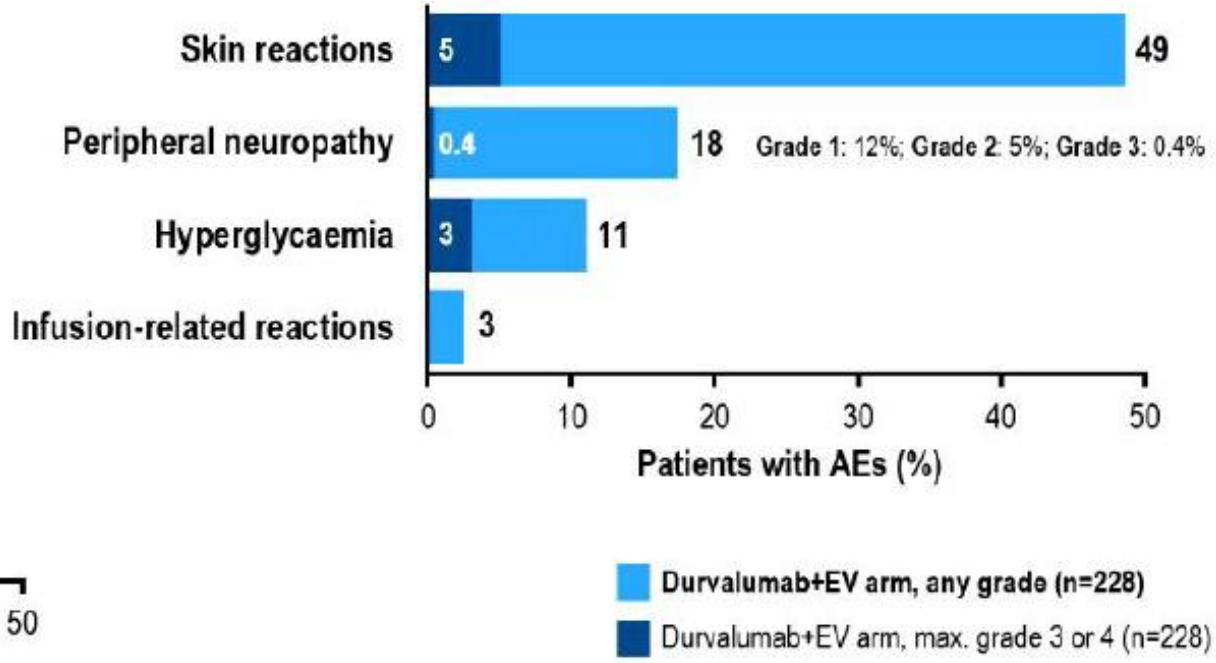
VOLGA: AEs Known to be Associated With Durvalumab or EV

Durvalumab+EV had a safety profile consistent with exposure to perioperative D plus 3 cycles of neoadjuvant EV

Immune-mediated AEs per preferred term[a]



Treatment-related AEs known to be associated with EV per grouped term[b]



[a]Shows immune-mediated AEs in ≥1% of patients in the safety population of the D+EV arm. [b]Grouped terms are based on multiple, similar preferred terms for EV: Rosenberg JE, et al. *J Clin Oncol*. 2019;37:2592–2600 and The Astellas Group. European Union Risk Management Plan for Enfortumab Vedotin, Version 5.3, May 2026. Available at: https://www.ema.europa.eu/en/documents/rmp/padcev-epar-risk-management-plan_en.pdf. Access date: 23 September 2026. Investigator-assessed causality. Data cutoff 02 March 2026. AE, adverse event; D, durvalumab; EV, enfortumab vedotin.

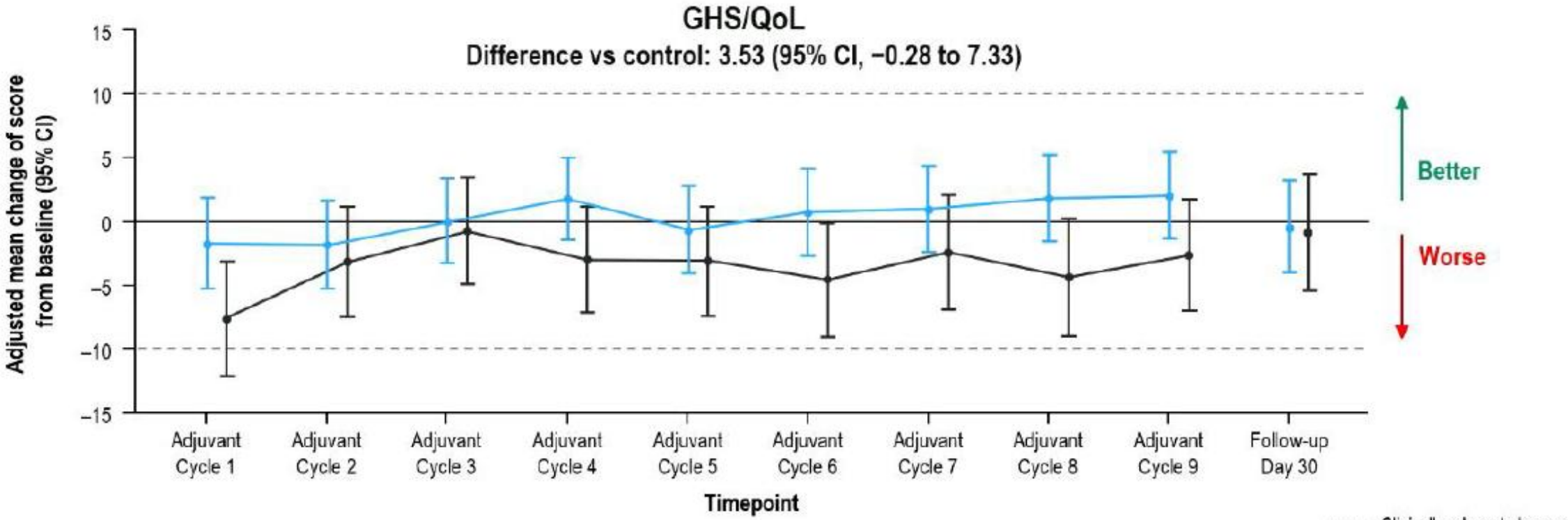
VOLGA: AE Summary – Safety Population (Overall Trial Period)

Events, n (%)	Durvalumab+EV n=228	Durvalumab+T+EV n=229	Control n=229
AEs of any cause	**227 (>99)**	**227 (99)**	**170 (74)**
Maximum grade 3 or 4 AEs	145 (64)	161 (70)	101 (44)
Serious AEs	143 (63)	161 (70)	101 (44)
Leading to death	17 (7)	21 (9)	14 (6)
Leading to discontinuation of any study treatment	48 (21)	72 (31)	NA
Leading to discontinuation of durvalumab	37 (16)	50 (22)	NA
Leading to discontinuation of tremelimumab	NA	37 (16)	NA
Leading to discontinuation of enfortumab vedotin	26 (11)	52 (23)	NA
Leading to cancellation of surgery	2 (0.9)	6 (3)	0
Leading to delay in surgery[a]	8 (4)	8 (3)	1 (0.4)
AEs possibly related to any treatment	**207 (91)**	**216 (94)**	**NA**
Maximum grade 3 or 4 AEs	69 (30)	97 (42)	NA
Serious AEs	45 (20)	70 (31)	NA
Leading to death	1 (0.4)	5 (2)	NA
Any-grade immune-mediated AEs	**75 (33)**	**109 (48)**	**8 (3)**
Maximum grade 3 or 4	24 (11)	46 (20)	2 (0.9)
Leading to death	0	3 (1)	0

The safety population includes all patients who received study treatment (D+EV and D+T+EV arms) or who were randomised (control arm). Investigator-assessed causality. [a]Recommended timeframe for surgery was within 56 days after the last dose of neoadjuvant treatment (D+EV and D+T+EV arms), and within 12 weeks of diagnosis (control arm). Data cutoff 02 March 2026. AE, adverse event; D, durvalumab; EV, enfortumab vedotin; NA, not applicable; T, tremelimumab.

VOLGA: Quality of Life as Assessed by EORTC QLQ-C30

Patient-reported quality of life was maintained after surgery in the durvalumab+EV arm



No. of patients in analysis										
Durvalumab+EV	98	93	92	97	92	85	86	81	84	62
Control	61	58	57	55	55	44	45	39	47	37

Questionnaire compliance in the D+EV and control arms was 84% and 60% at baseline, 71% and 54% at adjuvant cycle 1, 66% and 64% at adjuvant cycle 9, and 34% and 29% at follow-up day 30, respectively.
A positive difference favours D+EV vs control. MMRM analysis of change from baseline in EORTC QLQ-C30 scores with fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, PD-L1 status, tumour stage, and cisplatin status and the continuous fixed covariate of baseline score-by-visit interaction. A clinically relevant change was defined as a ≥10-point change in score compared with baseline.[1]

1. Osoba D, et al. *J Clin Oncol*. 1998;16:139–144. Data cutoff 02 March 2026. CI, confidence interval; D, durvalumab; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer 30-item Core Quality of Life Questionnaire; EV, enfortumab vedotin; GHS/QoL, global health status/quality of life; MMRM, mixed model for repeated measures; PD-L1, programmed cell death ligand-1.

VOLGA: Conclusions

- Perioperative durvalumab plus 3 cycles of neoadjuvant enfortumab vedotin demonstrated statistically significant improvements in EFS and OS vs control in patients with MIBC ineligible for or who refused cisplatin-based chemotherapy
  - EFS HR 0.51 (95% CI, 0.38–0.67), *P*<0.0001
  - OS HR 0.58 (95% CI, 0.40–0.83), *P*=0.0027
  - EFS and OS benefits were consistent across subgroups
- Durvalumab plus enfortumab vedotin had a tolerable and manageable safety profile that was consistent with the known safety profiles of the individual agents, with quality of life maintained after surgery
- Durvalumab and tremelimumab plus enfortumab vedotin also demonstrated a statistically significant improvement in EFS vs control
  - OS analysis was not statistically significant at this interim analysis; follow-up is ongoing

VOLGA supports perioperative durvalumab plus 3 cycles of neoadjuvant enfortumab vedotin as a potential new standard of care for patients with MIBC ineligible for or who refused cisplatin-based chemotherapy