LIVESTREAM SESSION

Peri-Operative Therapy in Urothelial Cancer

MODERATOR

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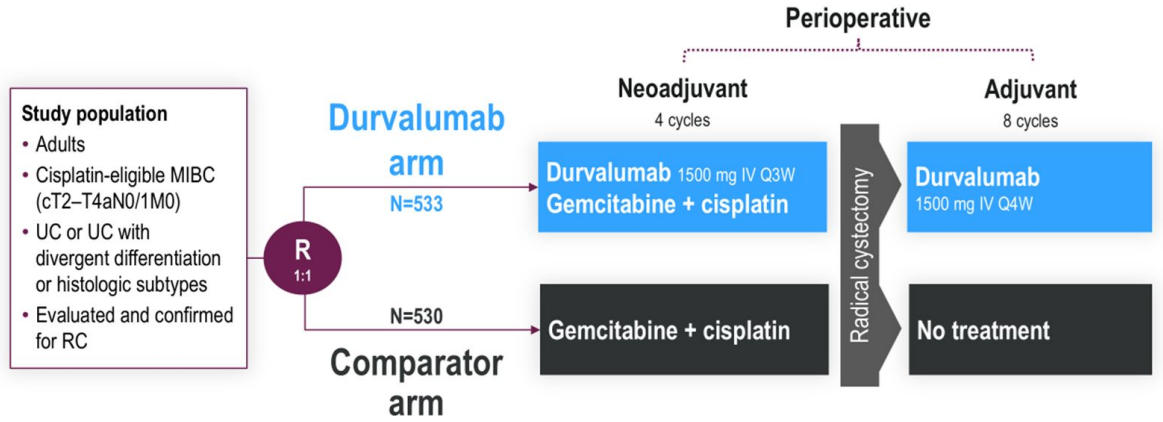
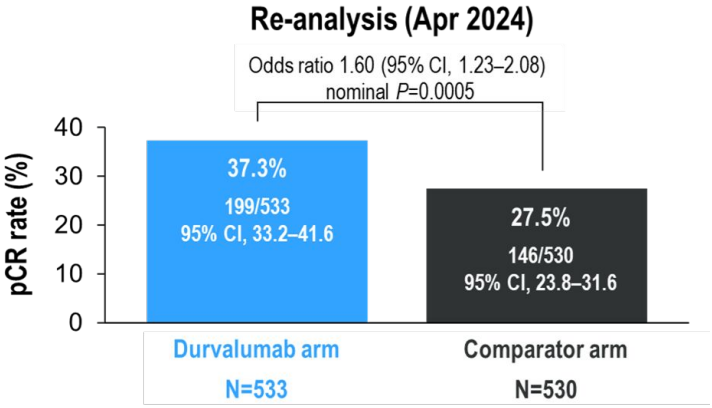
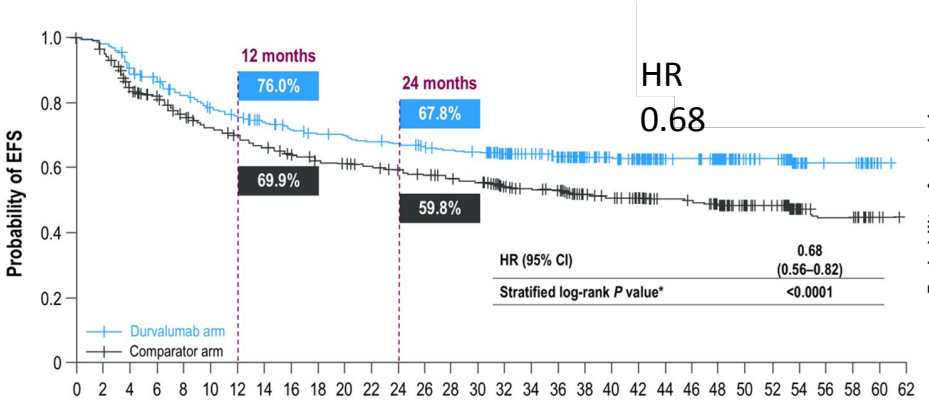
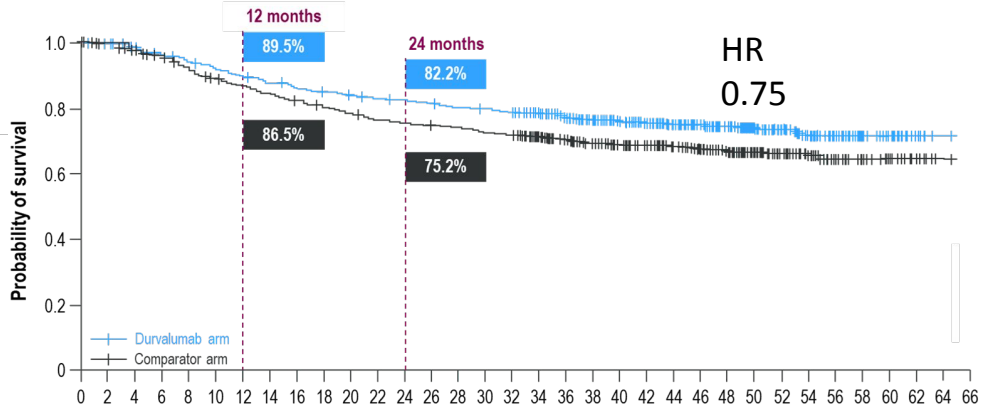
Cancer Center

NIAGARA: Study Design









Summary of perioperative immune therapy trials in UC

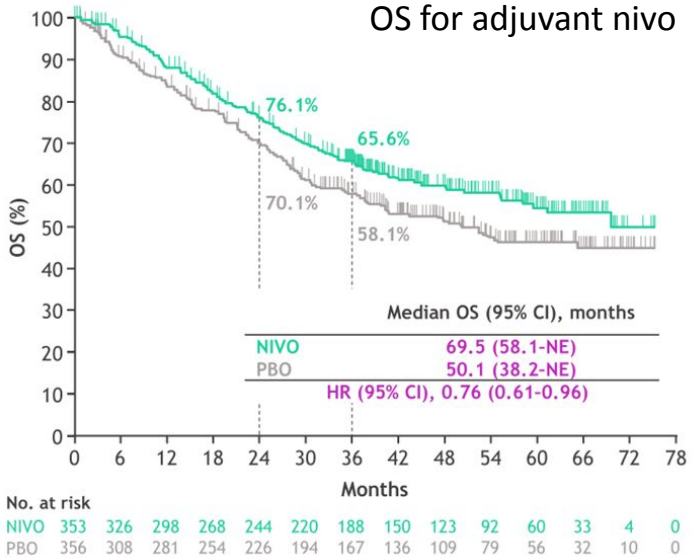
Perioperative	T2 %	pCR	EFS 24 mnth	G3+TRAE
Durva + GC	40%	37%	82%	41%
Gem/cis	40%	27%	75%	41%
PII GC durva	NA	34%	76%	NA

Summary of perioperative immune therapy trials in UC

Cystectomy → Adjuvant pembrolizumab

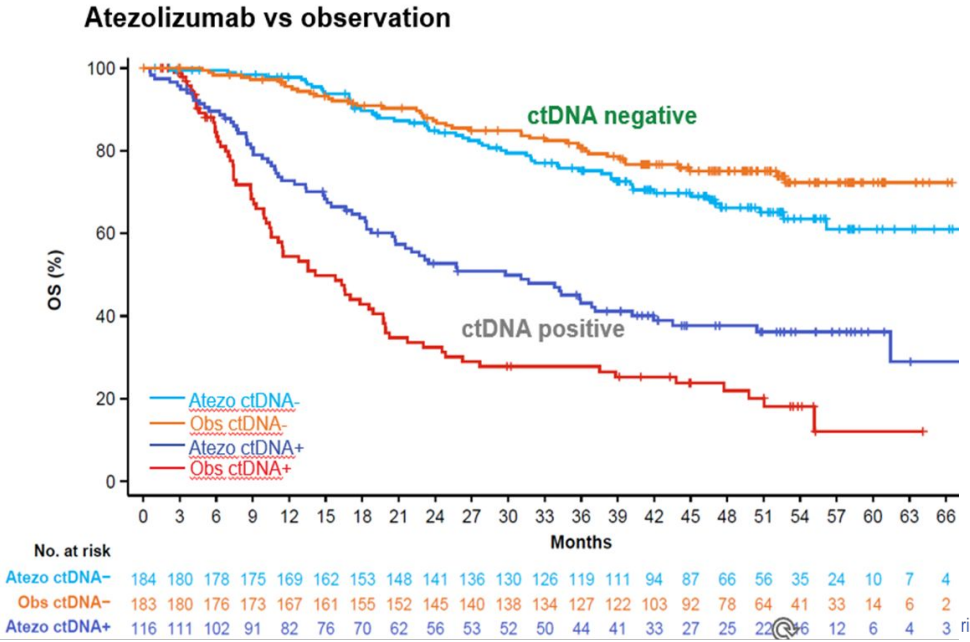
- Eligible by path stage
- Starts IO 10 wks post op
- NAC for some
- Excludes patients with post-op issues or relapse

ITT
OS for adjuvant nivo

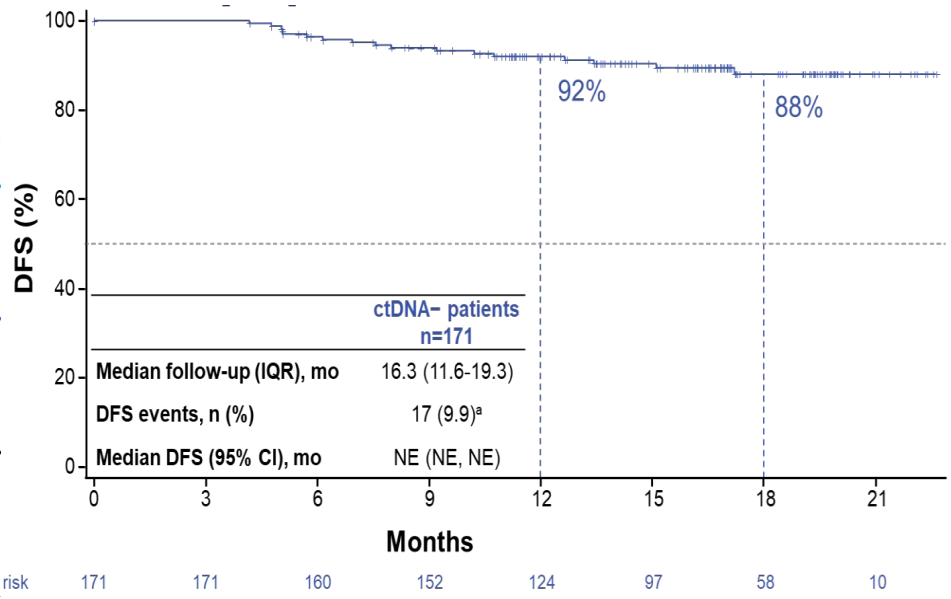


adjuvant	node +ve/NAC	24 mnth DFS	G3+ TRAE
Nivo	47%/43%	48%	18%
Atezo ctDNA +ve	48%/52%	25%	
Gem/cis	/0%	60%	>26%
pembro	51%/65%	~44%	

ctDNA identifies a high-risk population which benefits from adjuvant atezolizumab.



Relapse in the persistently ctDNA-ve surveillance population from IM011



IMVIGOR011 tests atezolizumab vs placebo in ctDNA-positive patients within 1st year of surgery (enrolment complete)
MODERN Trial tests nivolumab + LAG3 vs nivolumab alone in ctDNA+ve and nivolumab vs placebo in ctDNA -ves

Summary of perioperative immune therapy trials in UC

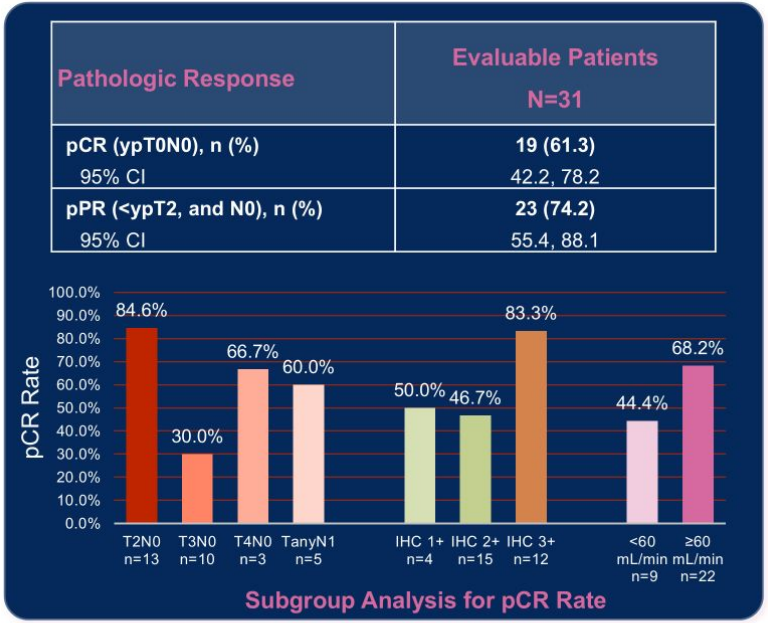
Neoadjuvant → Cystectomy

- Eligible by TURBT
- Starts IO more quickly

neoadjuvant	cT2 %	pCR	24 mnth EFS	G3+ TRAE
Atezo (95)	74%	28%	68%	7%
Pembro (114)	48%	37%	71%	5%
TAR200+PD1 (53) vs PD1 (31)	80%	42%/23%	NA	11%/5%
MVAC(153)		48/153 (31%)		
DDMVAC (218)	95%	84/218 (39%)	~75%	>55%
Gem/Cis nivo	66%	35%	73%	~40%
EV	68%/66%	36%		
SG (21)	66%	20-46%		58%
DV+Toripalimab (31)	46%	61%		

Immature data for Disitamab vedotin & Toripalimab In NMIBC (46% T2 RC data on 31/47)

Pathologic Response	Evaluable Patients N=31
pCR (ypT0N0), n (%)	19 (61.3)
95% CI	42.2, 78.2
pPR (<ypT2, and N0), n (%)	23 (74.2)
95% CI	55.4, 88.1



Xinan Sheng, MD

Neoadjuvant durvalumab/tremelimumab/enfortumab vedotin resulting in high ctDNA clearance

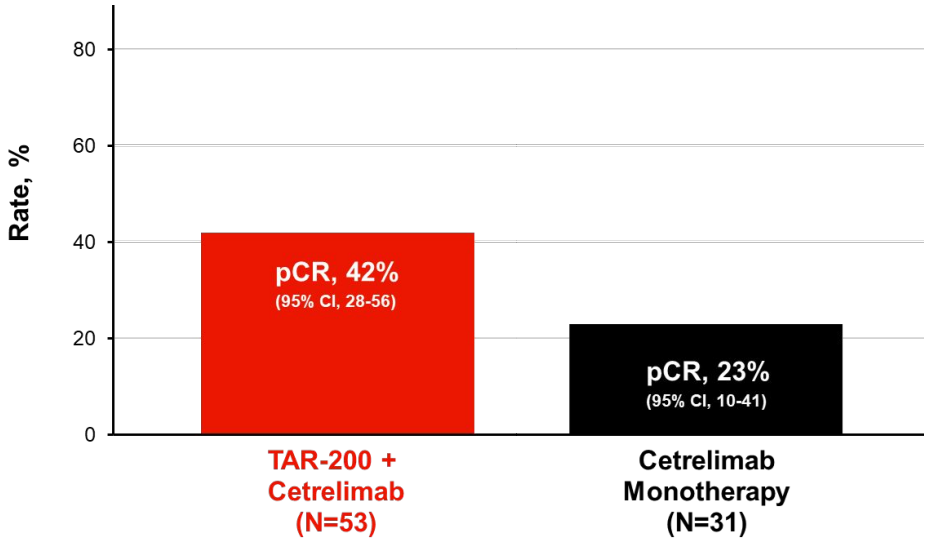
Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Cystectomy	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N
Clinical stage at baseline	T2	**>T2**	T2	T2	T2	T2	T2	T2	T2	T2	T2	**>T2**	T2	**>T2**	T2	T2	**>T2**
Pathological assessment at RC			pCR				Downstaged			No change		Upstaged			NA	NA	NA
Baseline ctDNA status	+	+	+	+	+	–	–	–	–	+	+	+	+	+	–	–	NS
Pre-RC ctDNA status	–	–	–	–	–	–	NS	–	–	–	–	+	+	+	–	NS	NS

- At baseline, the overall ctDNA-positive rate was 62.5% (10/16 patients) and the overall ctDNA-negative rate was 37.5% (6/16 patients)
- After neoadjuvant treatment, the pre-RC ctDNA-negative rate was 78.6% (11/14 patients)
- A total of **7 out of 10 patients had ctDNA clearance** (baseline ctDNA positive, then pre-RC ctDNA negative)

Neoadjuvant atezolizumab alone in x patients showed 60% were ctDNA positive at baseline and 18% ctDNA clearance rate.

SunRISe-4: Cetrelimab +/- TAR200 in MIBC

Characteristic	TAR-200 + Cetrelimab (N=79)	Cetrelimab Monotherapy (N=41)
ECOG PS 1, n (%)	14 (17.7)	10 (24.4)
NAC, n (%)		
Ineligible	31 (39.2)	15 (36.6)
Refusing	48 (60.8)	26 (63.4)
Residual disease (visibly incomplete TURBT), n (%)	16 (20.3)	6 (14.6)
Tumor stage, n (%)		
cT2	62 (78.5)	35 (85.4)
cT3-4a	17 (21.5)	6 (14.6)
Urothelial carcinoma with variant histology, n (%)	16 (20.3)	11 (26.8)
Prior intravesical therapy, n (%)	10 (12.7)	8 (19.5)



ECOG PS, Eastern Cooperative Oncology Group performance status;
NAC, neoadjuvant cisplatin-based chemotherapy; TURBT, transurethral resection of bladder tumor.

Perioperative immune therapy trials in UC

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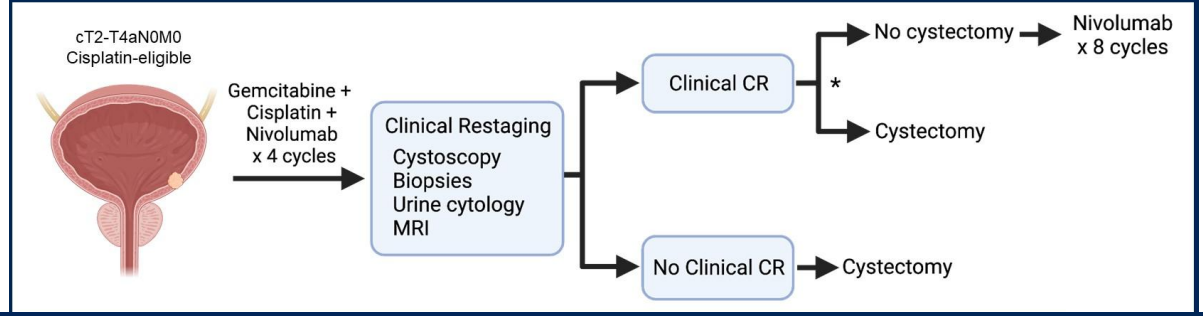
pCR as a % of ITT not RC population only

Ongoing Phase 3 Neoadjuvant IO-based Trials in MIBC

	Clinical Trial	N	Treatment Arms	Eligibility
CISPLATIN ELIGIBLE	KEYNOTE-866	870	Pembro+GC vs GC	T2-4aN0M0
	KEYNOTE-B15/EV-304	784	Pembro+EV vs GC	T2-T4aN0M0 T1-T4aN1M0
	NIAGARA	1050	Durva+GC vs GC	T2-4aN0M0
	ENERGIZE	1200	Nivo+GC vs GC	T2-4aN0M0
CISPLATIN-IN ELIGIBLE	KEYNOTE-905/ EV-303	836	RC vs Pembro+EV vs Pembro	T2-4aN0M0
	VOLGA	830	RC vs Durva/Trem+EV vs Durva+EV	T2-4aN0M0
	SWOG GAP	196	Surgery vs Gem/Carbo+Avelumab	T2-4aN0M0

There are also RIII trials with TMT and ICI therapy: These studies may have wider influences.



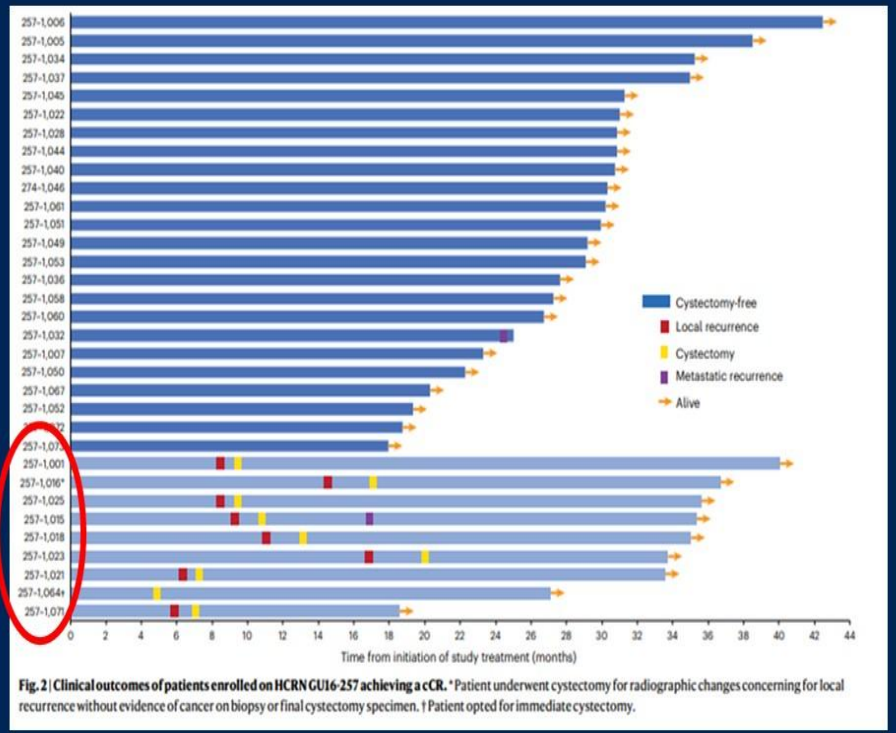
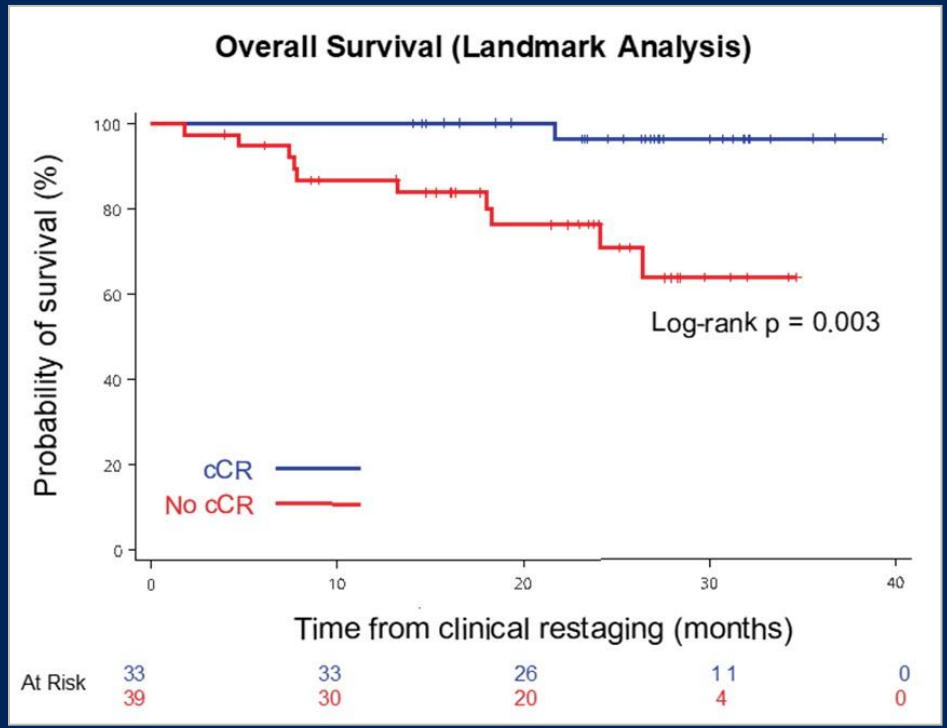
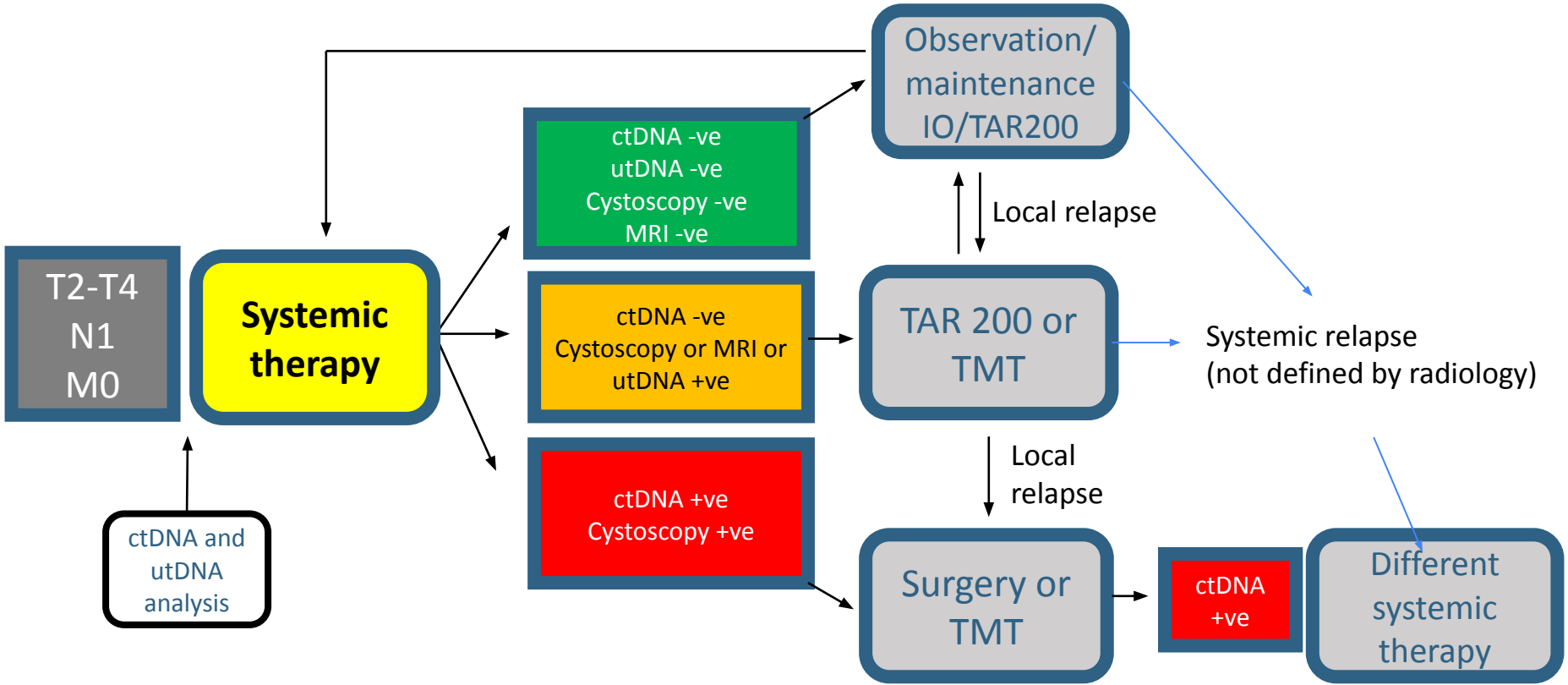


Fig. 2 | Clinical outcomes of patients enrolled on HCRN GU16-257 achieving a cCR. * Patient underwent cystectomy for radiographic changes concerning for local recurrence without evidence of cancer on biopsy or final cystectomy specimen. † Patient opted for immediate cystectomy.



Curing most patients with MIBC without surgery or RT



Audience Question

Is gemcitabine/cisplatin+durvalumab the new standard of care for patients eligible for cisplatin-based chemotherapy?

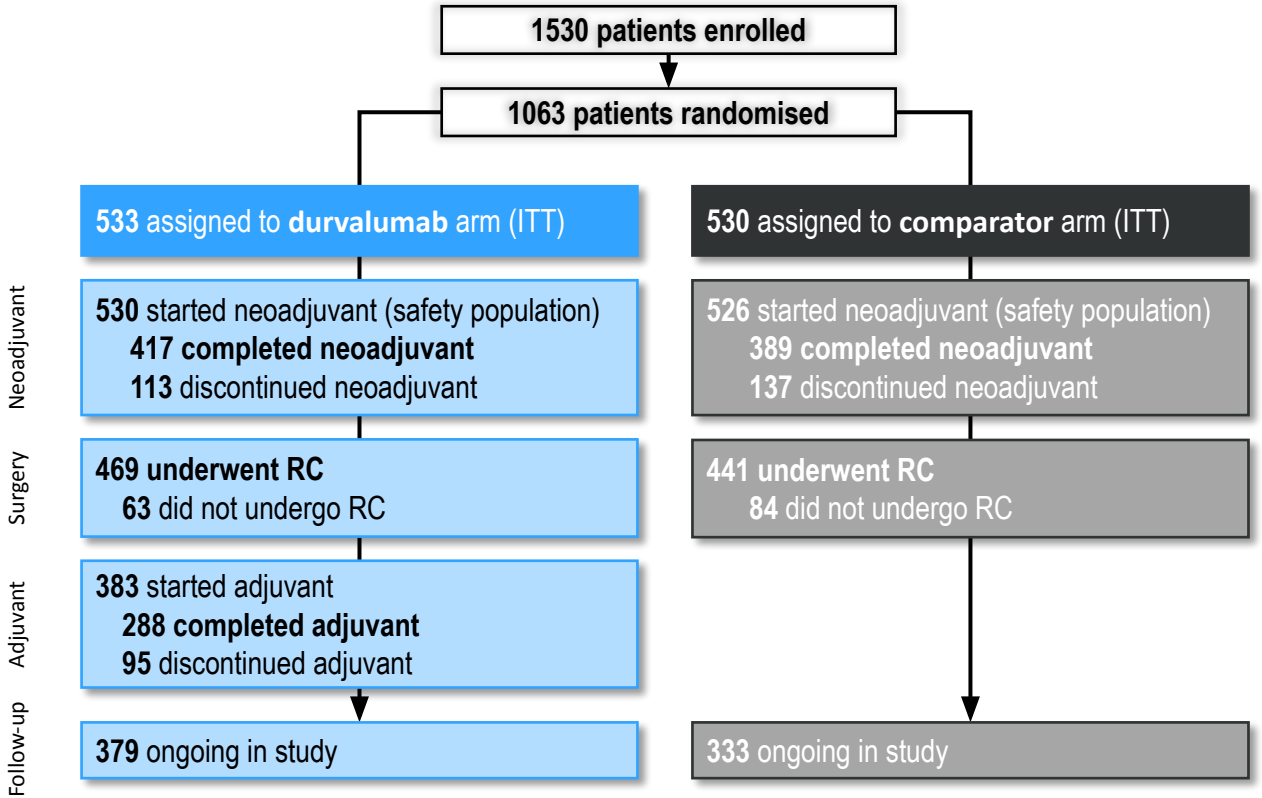
1. Yes
2. No

Audience Question

Would you give EVP for a patients whose cancer has progressed after gem/cis+durvalumab for MIBC?

1. Yes
2. Yes, but there needs to be at least a 6 month gap since durvalumab
3. Yes, but there needs to be at least 12 months gap since durvalumab

NIAGARA: Patient Disposition



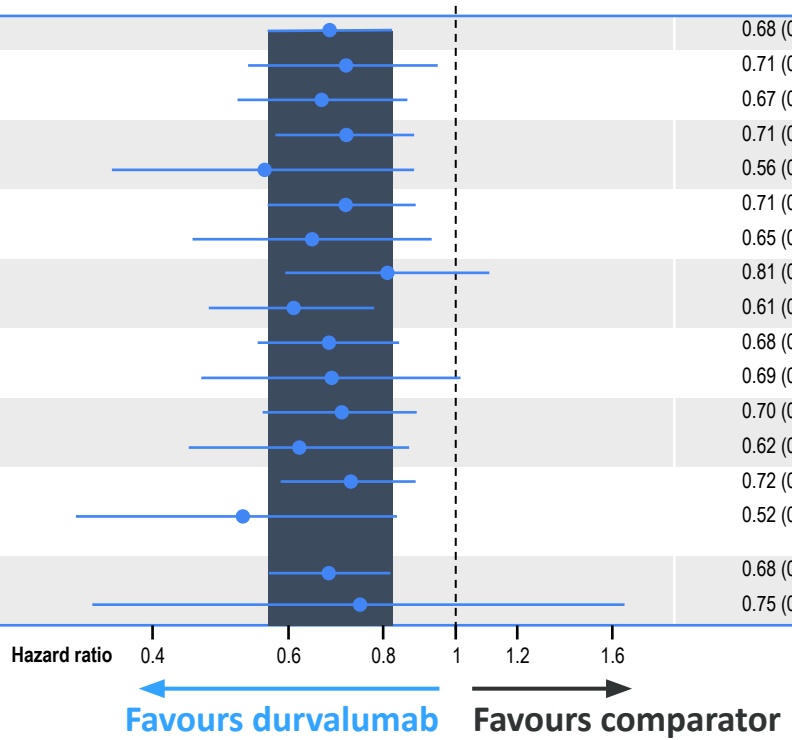
- No patients were ongoing on study treatment at data cutoff
- Median time from the last dose of neoadjuvant therapy to cystectomy:
  - 39.0 days (range, 8–118) for the durvalumab arm
  - 38.0 days (range, 12–333) for the comparator arm

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.

NIAGARA: Event-free Survival Subgroup Analyses

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 (0.60–1.10)
	>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 (0.32–0.84)
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 using 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.

NIAGARA: Overall Survival Subgroup Analyses

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 (0.62–1.03)
	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)
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	Low/negative	286	0.58 (0.38–0.80)
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)
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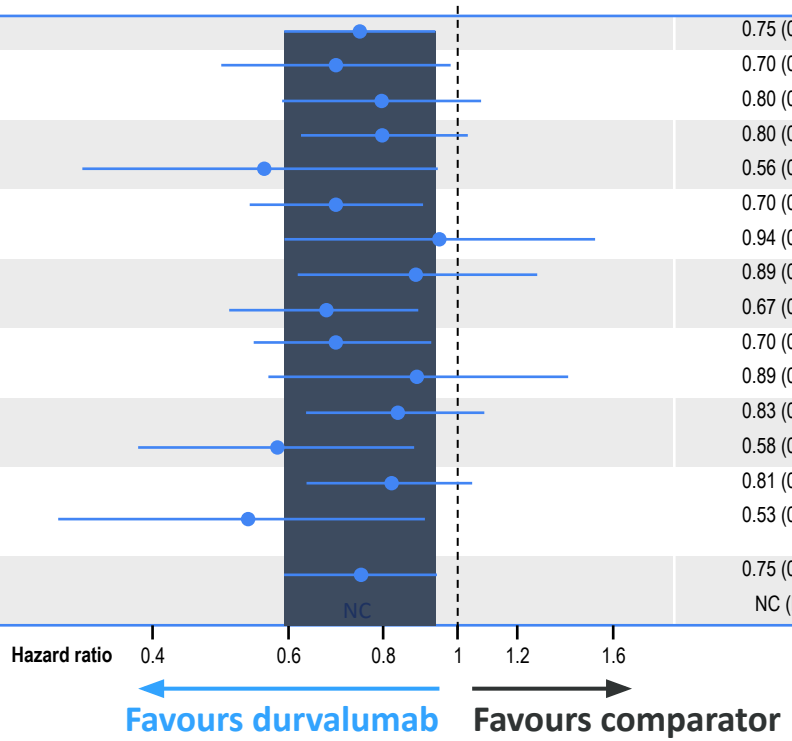
	N1	58	NC (NC–NC)



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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.