Novel biomarkers in urothelial carcinoma

Predictive biomarkers

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Metastatic Urothelial Carcinoma (mUC) therapy March 2025

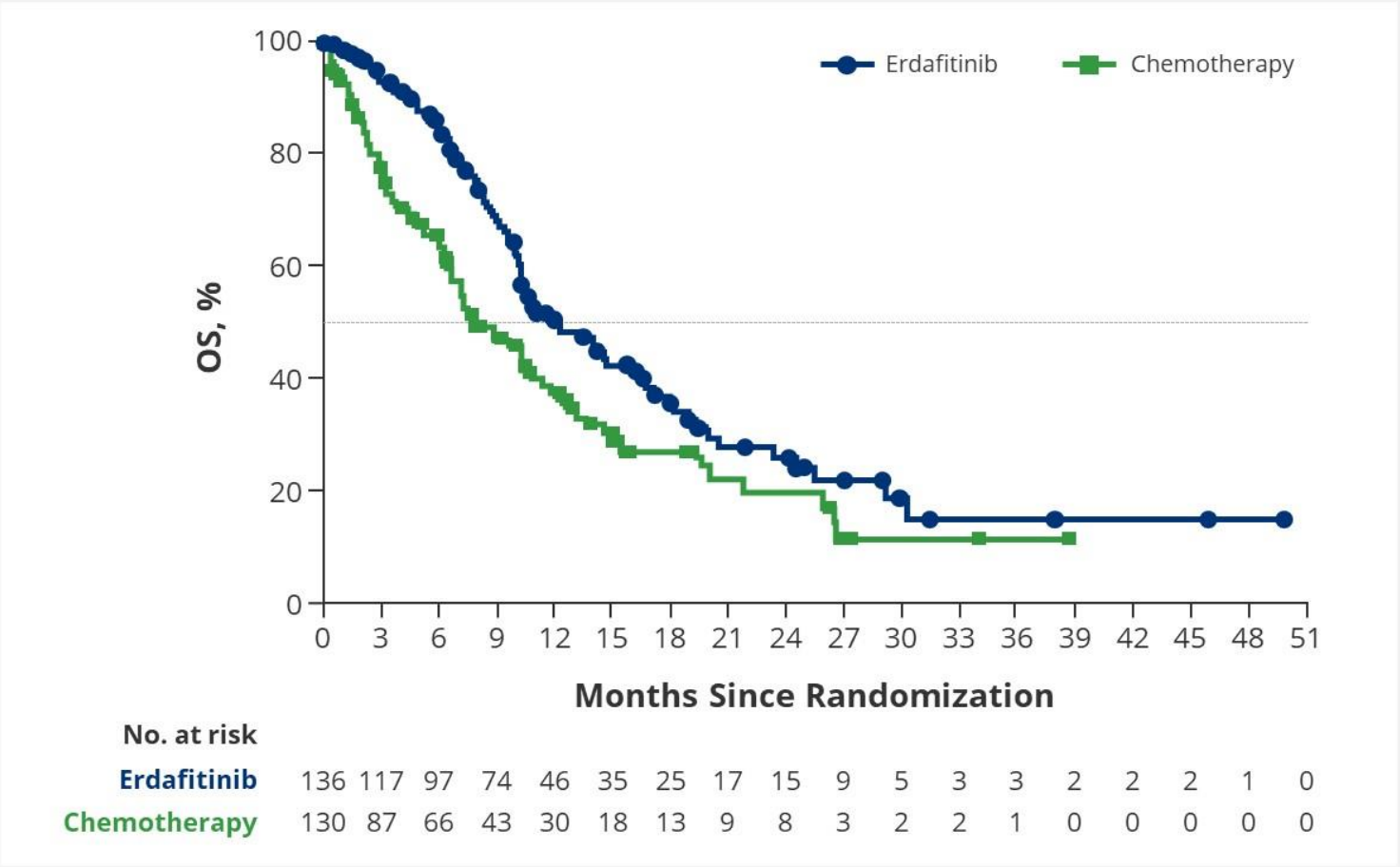
Treatment	First-Line	Second-line	Late salvage
Cisplatin-eligible	•EV + Pembro •Gem-Cis-Nivo •Gem-Cisplatin→ Avelumab (Javelin)	**Post-EV-pembro** •Gem-platinum •Erdafitinib (FGFR3 mutations/fusions) •T-Dxd (Her2 IHC 3+) **Post GC-Nivo/Javelin** •Erdafitinib (FGFR3 mutations/fusions) •EV •~~Sacituzumab Govitecan~~ •T-Dxd (Her2 IHC 3+) **Post-PD1 inhibitor** •Gem-Platinum •EV (cisplatin-ineligible) •Erdafitinib (FGFR3 mutations/fusions) •T-Dxd (Her2 IHC 3+) **Post-platinum** •Pembrolizumab (or nivolumab or avelumab) •EV (cis-ineligible) •T-Dxd (Her2 IHC 3+)	•EV •T-Dxd (Her2 IHC 3+) •~~Sacituzumab Govitecan~~ •Erdafitinib •Taxane •Vinflunine
Cisplatin-ineligible	•EV + Pembro •Gem-Carbo →Avelumab		
Platinum-ineligible (chemo-ineligible)	•Pembrolizumab		

Impact of prior peri-operative therapy on metastatic disease therapy unclear:

1. Prior last cycle of peri-op cisplatin-based chemotherapy <1 year considered a line of therapy
2. Prior last cycle of peri-op PD1/L1 inhibitor <6 months ago should be considered a line of therapy?

~~Sacituzumab Govitecan~~ withdrawn from US October 2024 for treating mUC following negative TROPiCS-04 Phase III trial

Overall Survival for Erdafitinib Was Superior to Investigator's Choice of Chemotherapy



- Median follow-up was 15.9 months
- Median OS was 12.1 months for erdafitinib versus 7.8 months for chemotherapy
- Erdafitinib reduced the risk of death by 36% versus chemotherapy
  - HR, 0.64 (95% CI, 0.47-0.88; *P* = 0.005)[a]
- Based on these interim analysis results, the IDMC recommended to stop the study, unblind data, and cross over patients from chemotherapy to erdafitinib

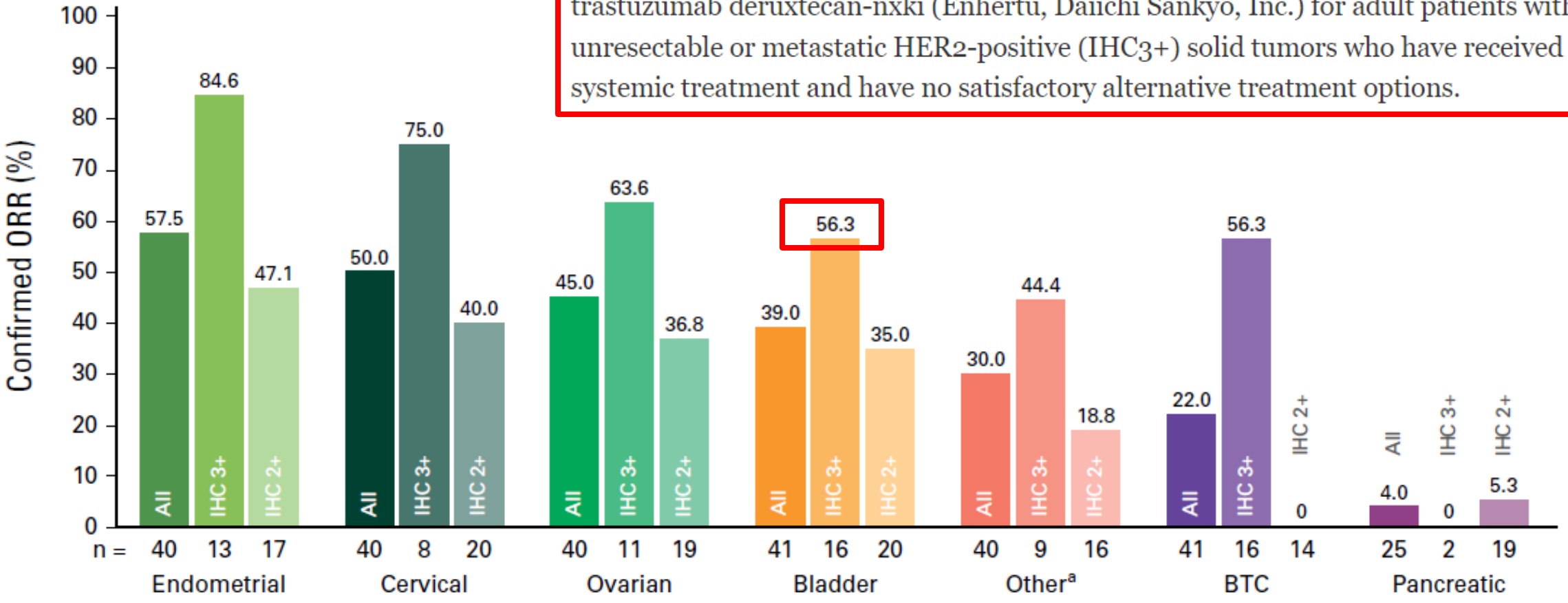
CI, confidence interval; HR, hazard ratio; IDMC, independent data monitoring committee; OS, overall survival.
[a]The significance level for stopping for efficacy was p=0.019, corresponding to a HR of 0.69.

THOR trial. Loriot Y, et al. ASCO 2023, NEJM 2023.

Trastuzumab-Deruxtecan (T-Dxd) approved by FDA for Her2 IHC 3+ tumors

HER2 binding ADC with Topo1 inhibitor payload

On April 5, 2024, the Food and Drug Administration granted accelerated approval to fam-trastuzumab deruxtecan-nxki (Enhertu, Daiichi Sankyo, Inc.) for adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.



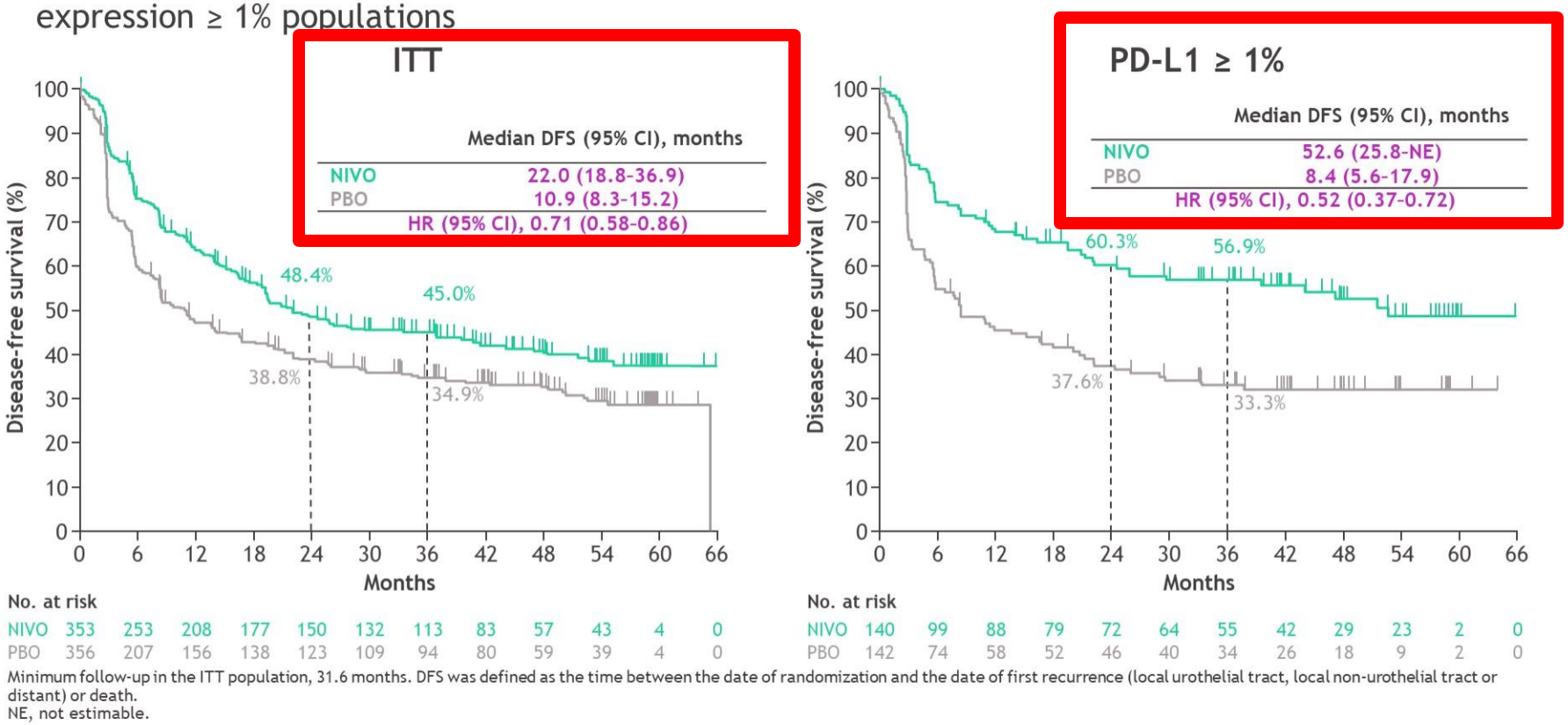
Merc-Bernstam F, et al. J Clin Oncol 2023; 42:47-58

CHECKMATE274: Adjuvant nivolumab for high-risk muscle-invasive urothelial carcinoma

CheckMate 274

Disease-free survival (primary endpoint)

- Continued DFS benefit was observed with NIVO versus PBO both in the ITT and tumor PD-L1 expression ≥ 1% populations



Minimum follow-up in the ITT population, 31.6 months. DFS was defined as the time between the date of randomization and the date of first recurrence (local urothelial tract, local non-urothelial tract or distant) or death.
NE, not estimable.

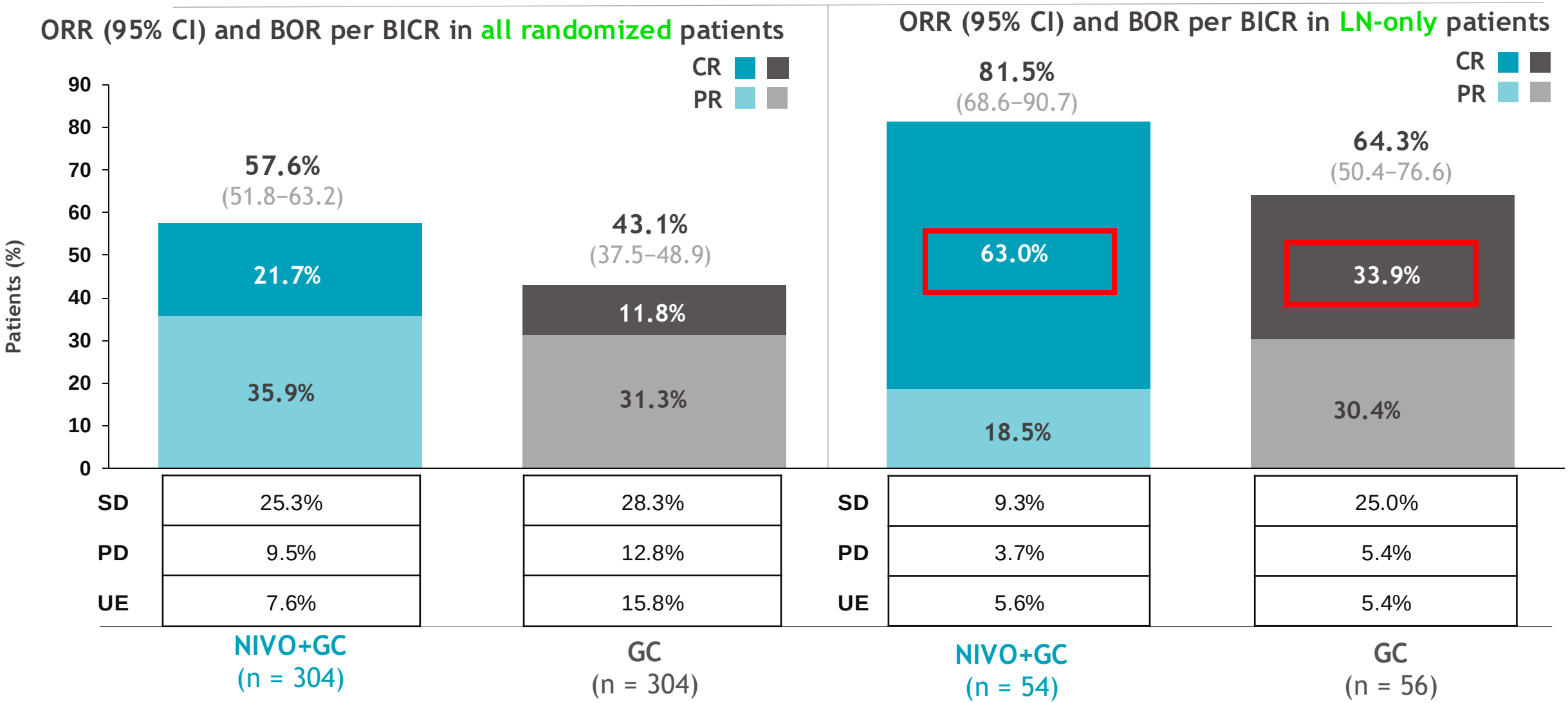
Approved in USA for all-comers, but in EU for PD-L1+ only

Bajorin D, et al. GU ASCO Feb 2021, NEJM Jun 2021, Galsky M, et al, GU-ASCO 2023

Response per BICR: patients with LN-only mUC

Galsky M, Sonpavde G, Powles T, et al. ASCO 24

- CR rates for NIVO+GC-treated patients with LN-only mUC were approximately twice that of GC-treated patients



EV-pembrolizumab: ORR in EV302 trial based on site of metastasis

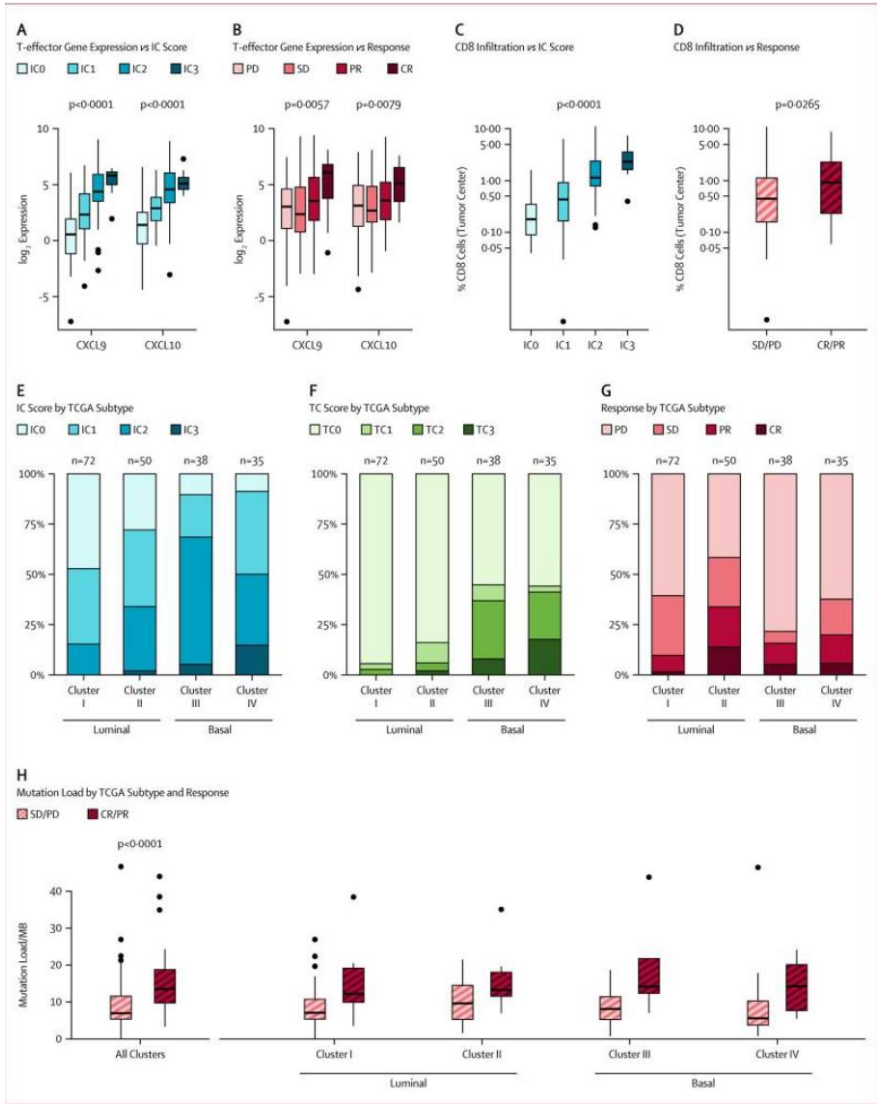
No striking differential activity in LN-only disease

Subgroup	Events/N: Enfortumab vedotin-pembrolizumab	Events/N: Chemotherapy	Absolute difference, % (95% CI)
Overall	296/437 (67.7)	196/441 (44.4)	23.3 (16.8–29.6)
Age			
<65 years	98/142 (69.0)	70/134 (52.2)	16.8 (5.3–27.9)
≥65 years	198/295 (67.1)	126/307 (41.0)	26.1 (18.2–33.6)
Race			
White	204/307 (66.4)	130/289 (45.0)	21.5 (13.6–29.1)
Other	92/130 (70.8)	66/152 (43.4)	27.3 (15.9–38.0)
Region			
North America	66/103 (64.1)	42/85 (49.4)	14.7 (0.4–28.4)
Europe	112/171 (65.5)	91/196 (46.4)	19.1 (8.9–28.8)
Rest of world	118/163 (72.4)	63/160 (39.4)	33.0 (22.5–42.8)
Sex			
Female	64/97 (66.0)	44/107 (41.1)	24.9 (11.2–37.6)
Male	232/340 (68.2)	152/334 (45.5)	22.7 (15.3–29.9)
ECOG PS			
0	161/222 (72.5)	106/213 (49.8)	22.8 (13.7–31.5)
1-2	135/215 (62.8)	89/226 (39.4)	23.4 (14.2–32.3)
Primary disease site of origin			
Upper tract	90/133 (67.7)	42/103 (40.8)	26.9 (14.2–38.8)
Lower tract	205/302 (67.9)	154/337 (45.7)	22.2 (14.6–29.5)
Liver metastases			
Present	60/100 (60.0)	41/99 (41.4)	18.6 (4.7–31.8)
Absent	236/337 (70.0)	155/342 (45.3)	24.7 (17.4–31.8)
PD-L1 expression			
Low (CPS <10)	114/180 (63.3)	75/183 (41.0)	22.3 (12.1–32.1)
High (CPS ≥10)	180/253 (71.1)	118/253 (46.6)	24.5 (16.0–32.6)
Cisplatin eligibility			
Eligible	172/243 (70.8)	123/232 (53.0)	17.8 (9.1–26.2)
Ineligible	124/194 (63.9)	73/209 (34.9)	29.0 (19.4–38.0)
Metastatic disease site			
Visceral metastases	202/315 (64.1)	126/318 (39.6)	24.5 (16.8–31.9)
Lymph node only	79/102 (77.5)	55/103 (53.4)	24.1 (11.1–36.3)
Renal function			
Normal	58/84 (69.0)	53/95 (55.8)	13.3 (-1.0–26.9)
Mild	111/163 (68.1)	72/160 (45.0)	23.1 (12.4–33.3)
Moderate/Severe	127/190 (66.8)	71/186 (38.2)	28.7 (18.7–38.0)

Powles et al. ESMO 23, NEJM 2024

Multimodal: TMB + Intrinsic subtype + PD-L1 IHC to predict PD1/L1 inhibitor monotherapy activity

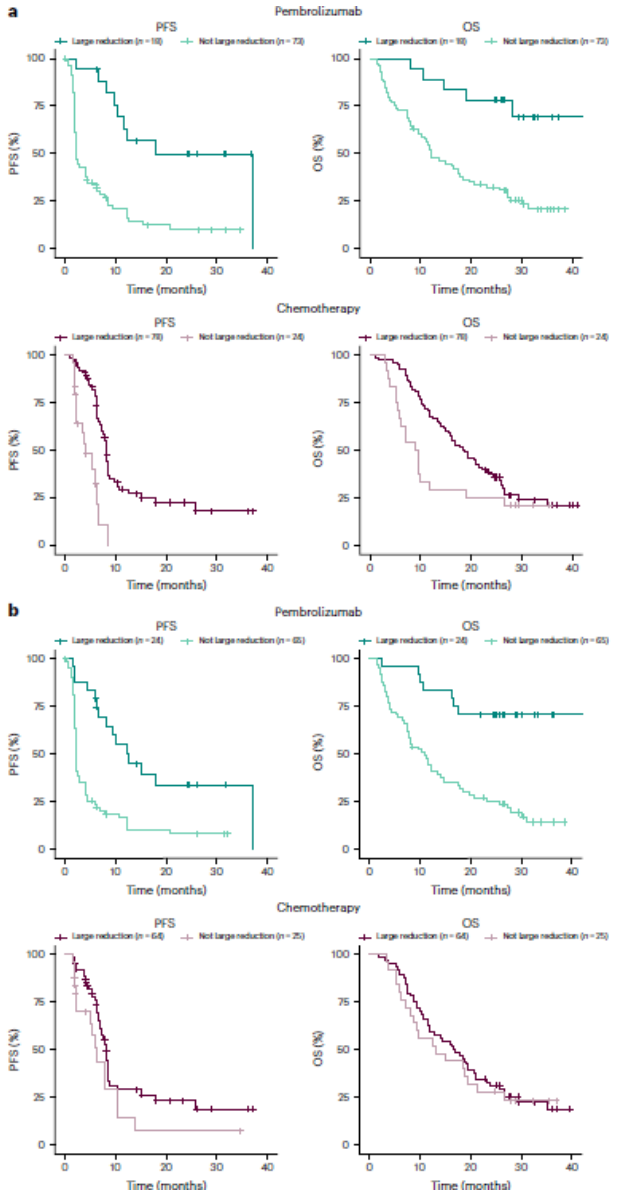
- Luminal cluster II subtype, high mutation load and high PD-L1 IC expression provide complementary information to predict response.
- Tumor CD8+ T cell infiltration was associated with both PD-L1 IC and response to atezolizumab (p=0·0265).
- Additional data and larger sample sizes are required.



Rosenberg JE, et al. Lancet 2016 May 7;387(10031):1909-20

ctDNA to inform metastatic urothelial carcinoma therapy

- pre- and posttreatment ctDNA with clinical outcomes in a subset of patients who received pembrolizumab (n = 130) or chemotherapy (n = 130) in KEYNOTE-361 Phase III trial.
- In the pembrolizumab arm, lower baseline tumor-informed maxVAF was associated with improved BOR (*P* = 0.009), PFS (*P* < 0.001) and OS. In the chemotherapy arm, lower baseline tumor-informed maxVAF was not associated with improved outcomes.
- Chemotherapy induced larger ctDNA decreases from baseline to treatment cycle 2 than pembrolizumab; however, change with pembrolizumab (n = 87) was more associated with BOR ($P = 4.39 \times 10^{-5}$) and OS ($P = 7.07 \times 10^{-5}$) than chemotherapy (n = 102; BOR: $P = 1.01 \times 10^{-4}$; OS: P = 0.018).

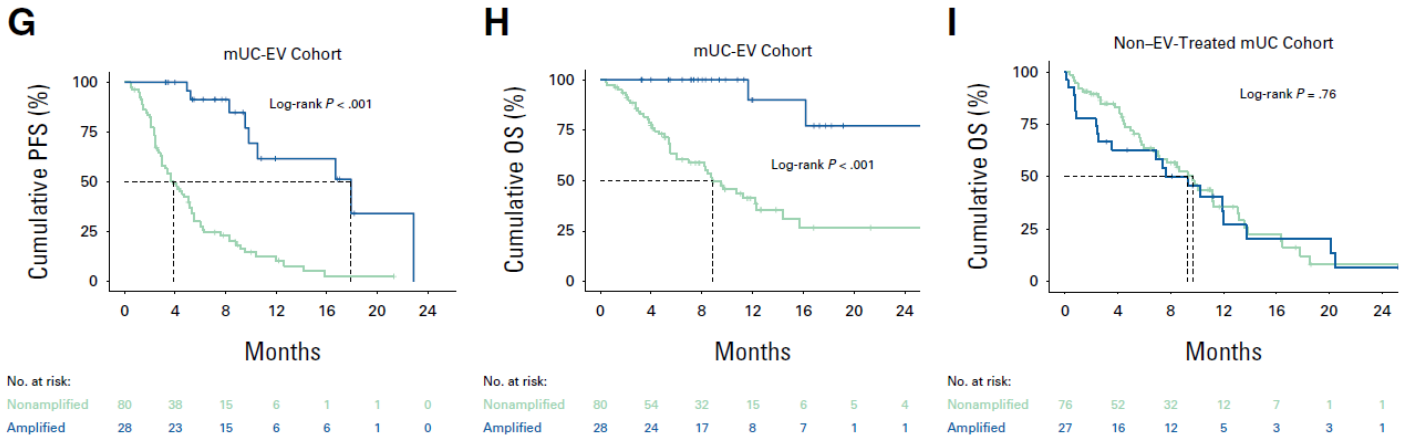


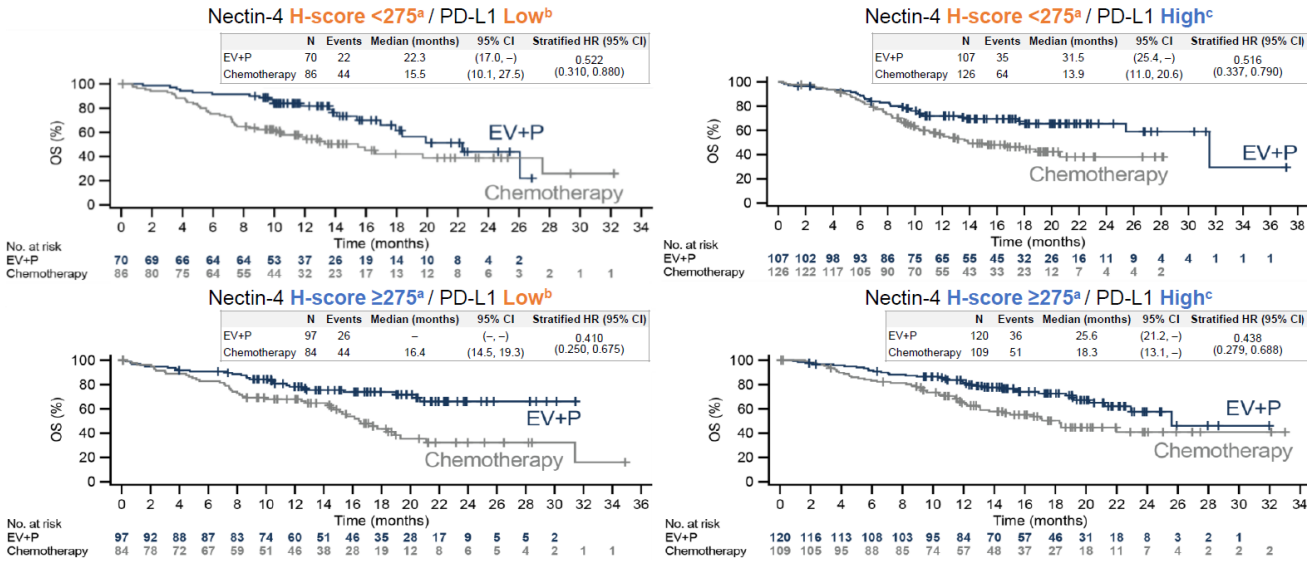
Powles T, et al. Nat Med 2024 Sep;30(9):2508-2516

Nectin4 gene amplification to predict EV activity

- NECTIN4 amplifications occurred in approximately 25% of mUC.
- 96% with NECTIN4 amplifications showed responses to EV compared with 32% in the nonamplified subgroup.
- Nectin4 amp correlates with membranous Nectin4 protein expression.

The observed benefit of EV+P remains regardless of Nectin-4 protein expression and PD-L1 status

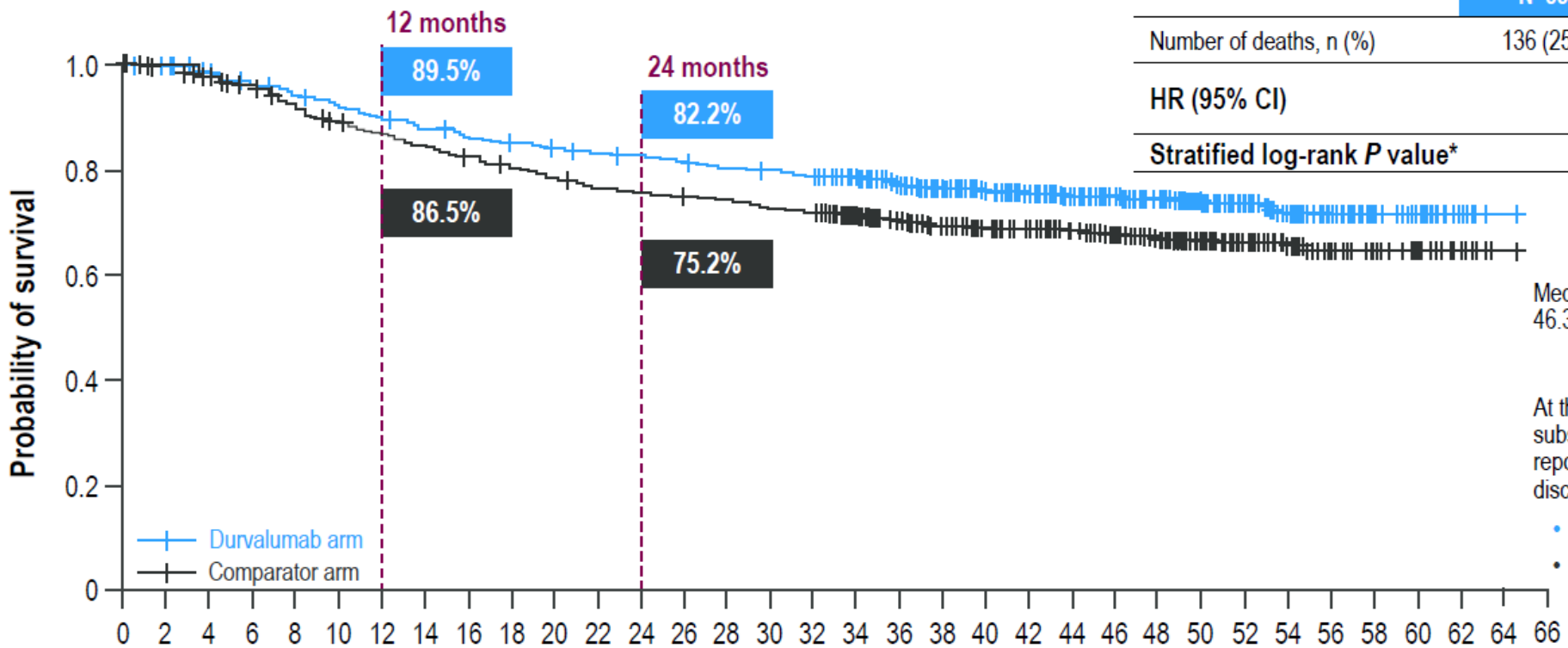




Data cutoff: 8 August 2023.
CPS, combined positive score; EV, enfortumab vedotin; P, pembrolizumab; PD-L1, programmed death ligand 1.
[a]The median Nectin-4 H-score was 275 across patients in both arms. [b]CPS <10. [c]CPS ≥10.

Klumper N, et al. J Clin Oncol 2024; 42(20):2446-2455.
Powles T, et al. Annals of Oncology (2024) 35 (suppl_2): S1135-S1169.

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

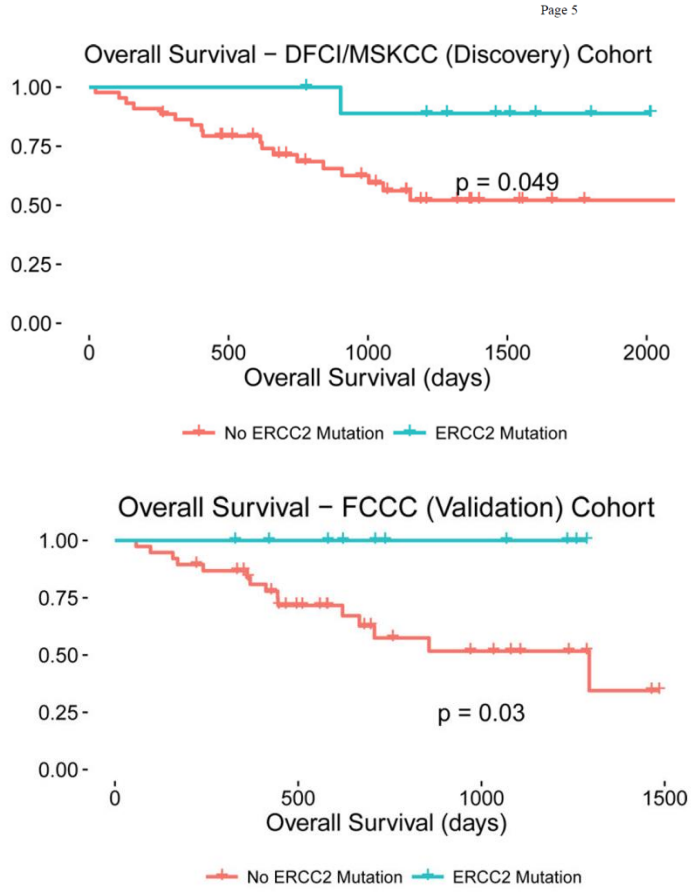
Durvalumab arm	533	528	517	505	492	478	468	457	446	440	434	428	423	418	410	408	400	375	349	321	295	271	238	207	182	152	125	96	68	34	21	7	1	0
Comparator arm	530	516	507	490	467	450	438	425	413	402	392	383	378	373	368	363	358	334	311	281	259	239	215	194	174	141	113	90	60	38	21	10	2	0

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.

Powles T, et al. NEJM 2024

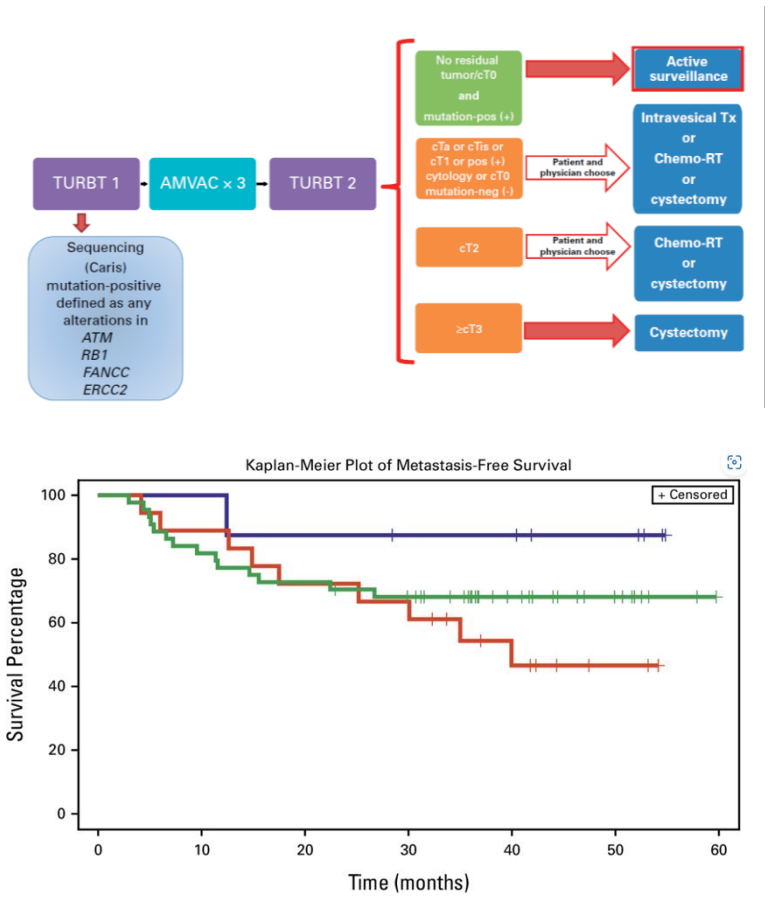
ERCC2 mutations as predictive genomic biomarker for benefit from neoadjuvant cisplatin-based chemo

Liu D, et al. JAMA Oncol 2016 Aug 1;2(8):1094-6



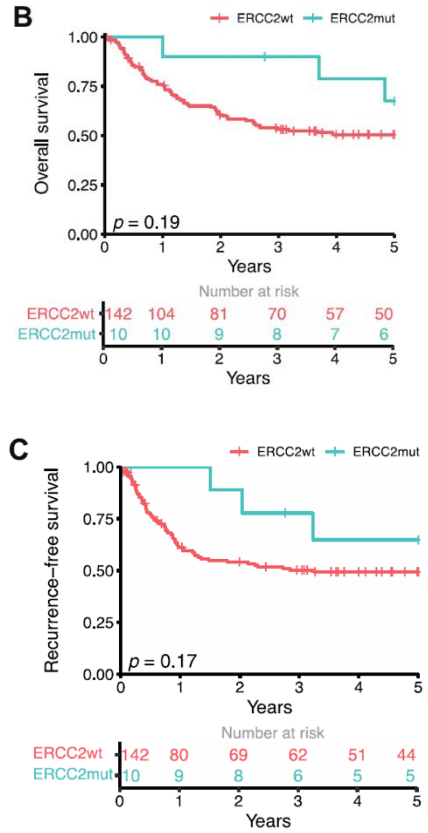
- ERCC2 was associated with response: 40% responders & 7% non-responders had ERCC2 alteration (p=0.010).
- There was a statistically significant difference in overall survival among patients with ERCC2 alterations in the validation (p = 0.03) and discovery cohorts (p = 0.049).

Geynisman DM, et al. J Clin Oncol. 2024 Dec 16.



- The primary end point was not met: metastasis-free survival (MFS) at 2 years for the entire cohort with the null hypothesis rejected if the lower bound one-sided 95% CI >64%.
- Trend toward improved MFS in those with *ERCC2* mutations was observed

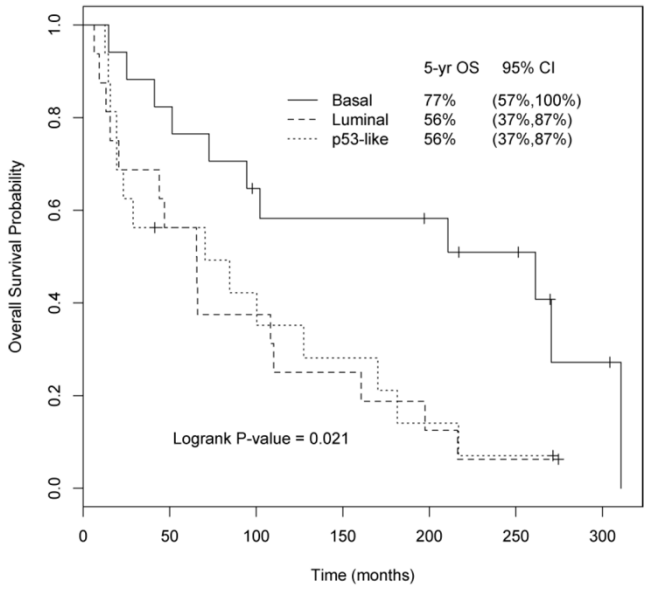
Gil-Jimenez A, et al. Eur Urol 2023; 83(4):313-317.



- Association between deleterious mutations in *ERCC2* and pathological response to NAC, but not overall survival or recurrence-free survival.
- No correlation was between response and alterations in *ERBB2*, *ATM* , *RB1* , or *FANCC*

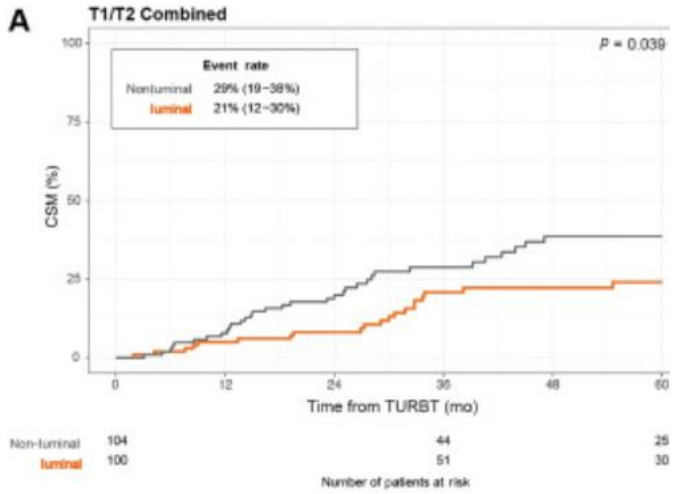
Transcriptomic predictive biomarkers for benefit from neoadjuvant cisplatin-based chemo: disappointing

McConkey DJ et al. Eur Urol 2016;69(5):855-62.



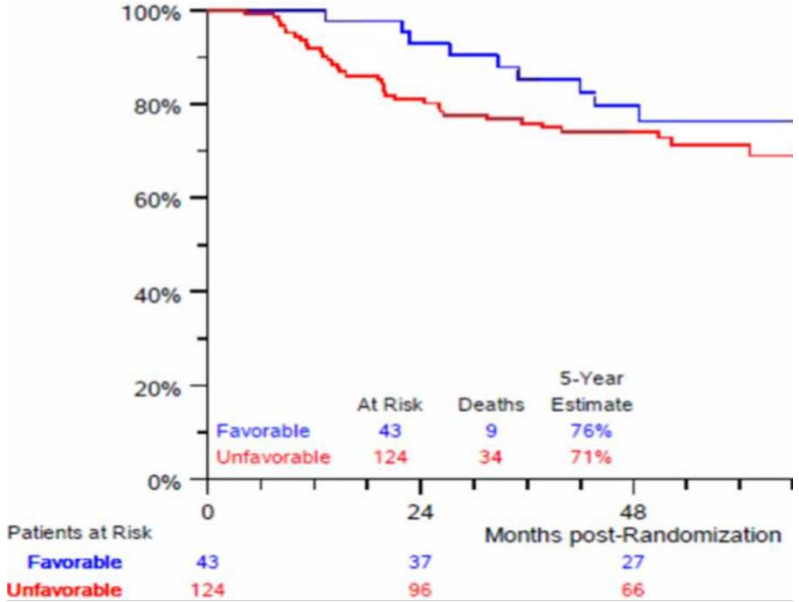
In validation cohort treated with perioperative MVAC: 5-yr OS 77% for basal, 56% for luminal, and 56% for p53-like; p=0.021).

Lotan Y, et al. Eur Urol 2019 Aug;76(2):200-206



Patients with luminal tumors had lower CSM than patients with nonluminal tumors (p = 0.039)

Flaig T, et al. CCR 2021, Eur Urol 2023 Sep;84(3):341-347

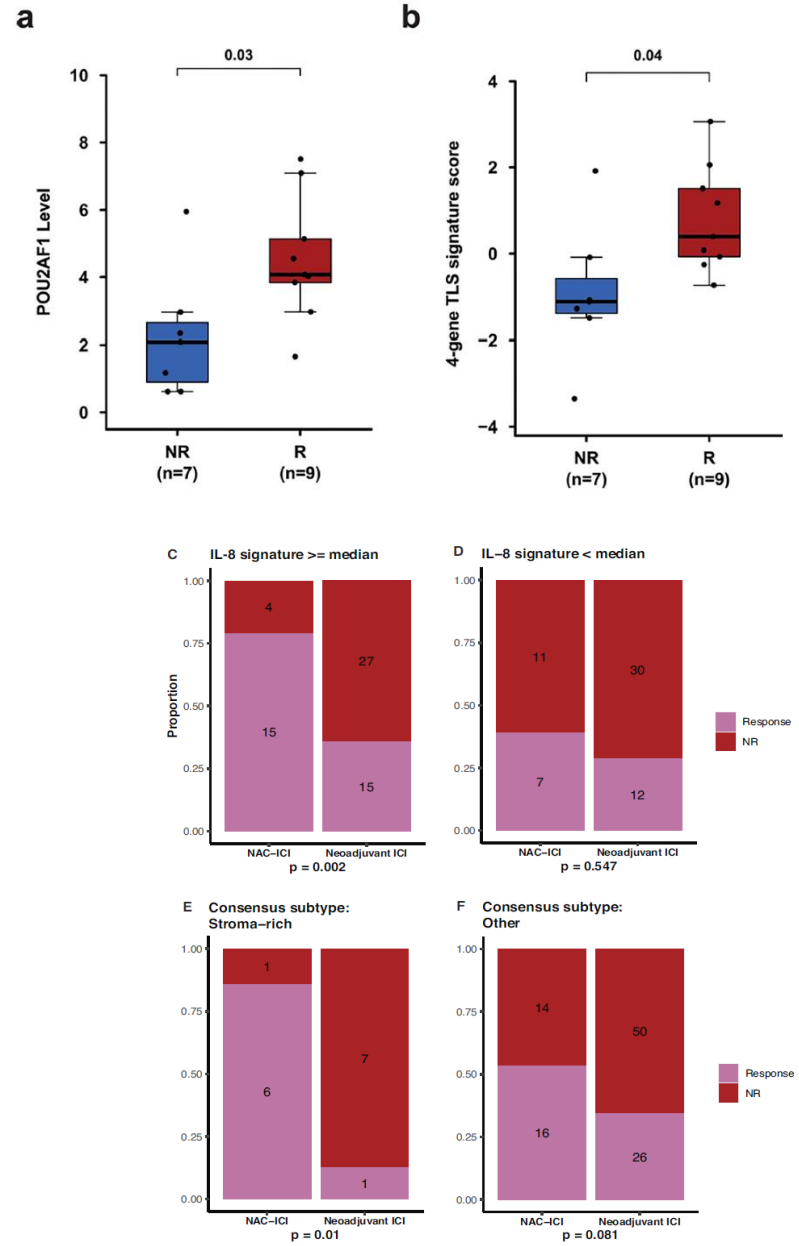


- Coexpression extrapolation (COXEN) is a gene expression–based biomarker, which uses in vitro data in NCI-60 cell lines.
- The individual COXEN score for GC and ddMVAC did not provide prognostic differentiation.
- GC COXEN score had a HR=0.45 (p = 0.047) when the GC and ddMVAC arms were pooled.

Prediction of ICI or chemo-ICI neoadjuvant activity

4-gene Tertiary Lymphoid Structure (TLS) signature comprised of POU2AF1, LAMP3, CD79A and MS4A1 significantly higher in responders (N=9) as compared to non-responders (N=7) to IPI-NIVO

- Plasma IL-9, tumor IL-8 gene signature levels, and tumor stroma-rich subtype represent potential biomarkers of response to NAC-ICI.

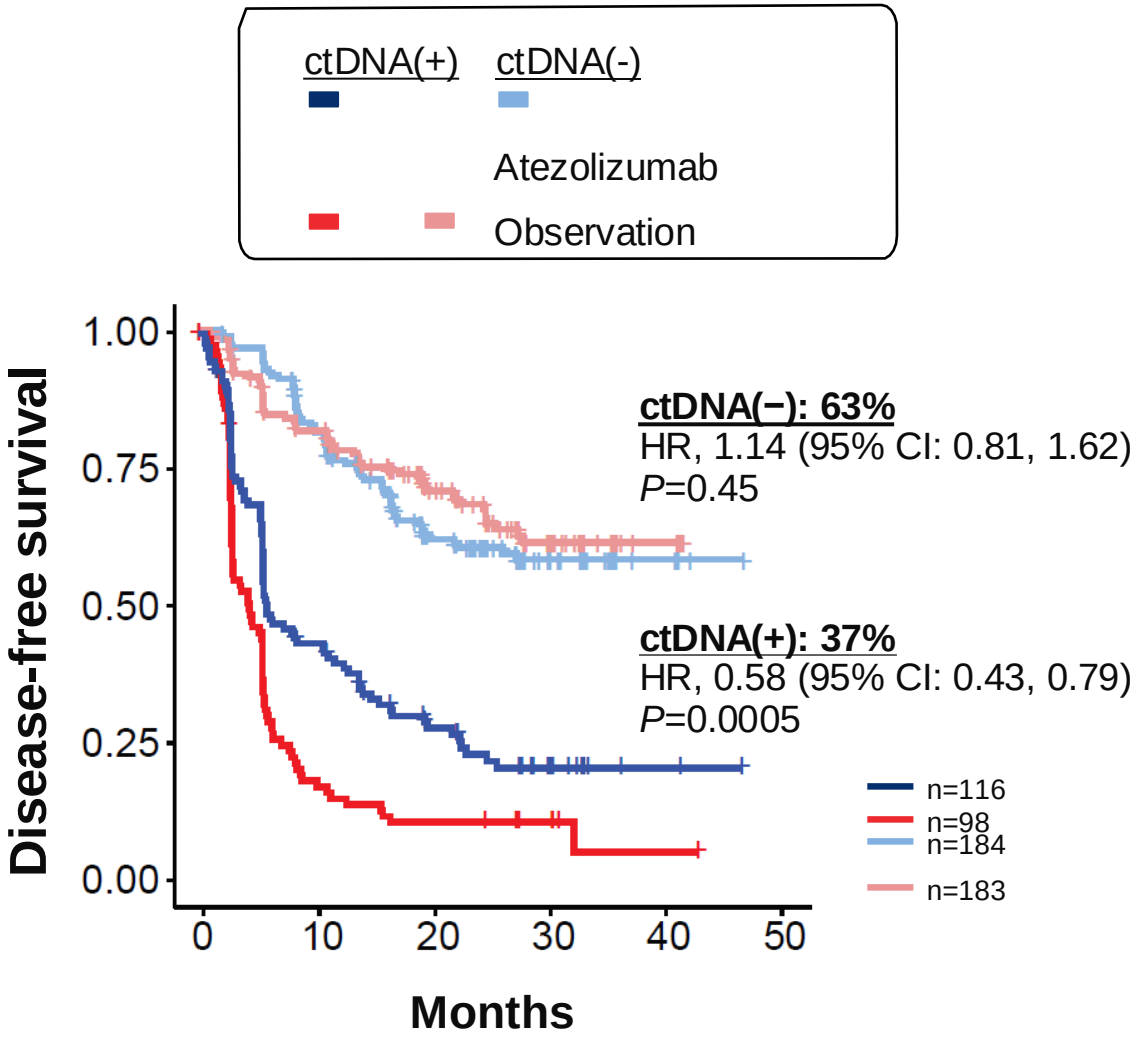


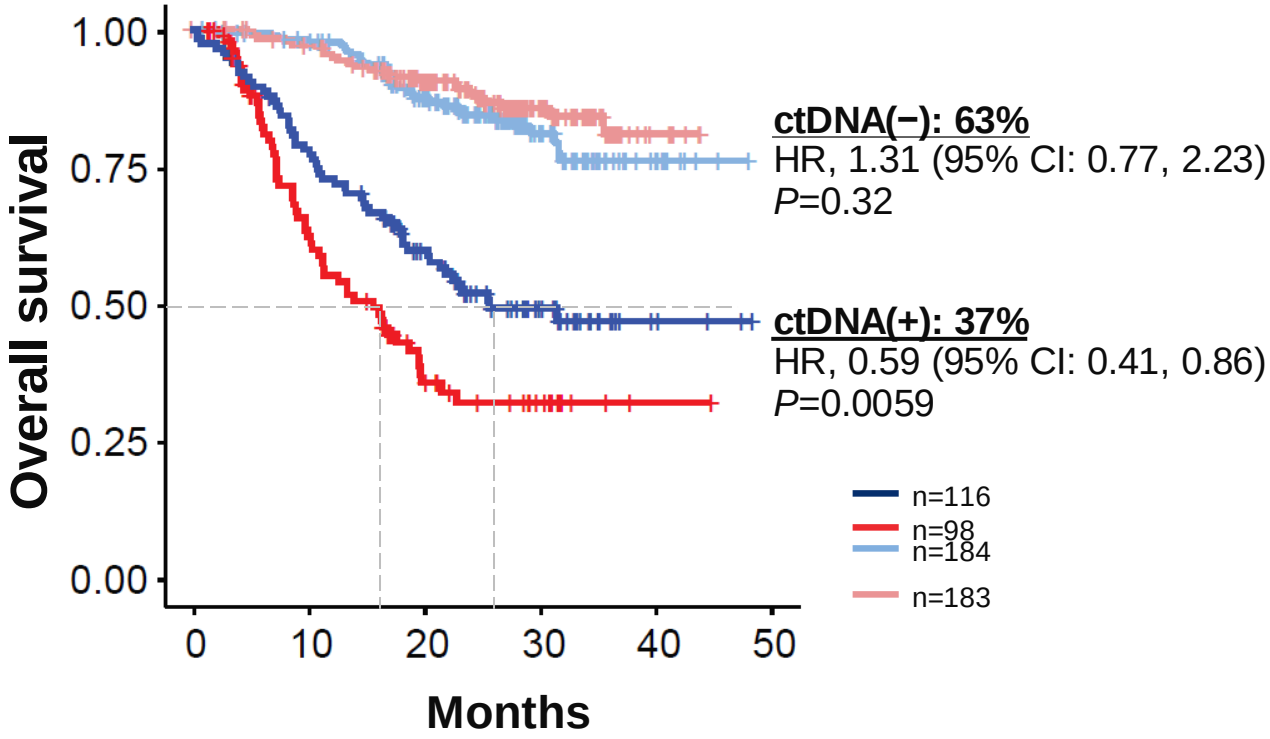
Gao J, et al. Nat Med 2020 Dec;26(12):1845-1851.
Beckabir W, et al. Nat Commun 2024 May 24;15(1):4448.

Minimal residual disease using post-op ctDNA to select for adjuvant atezolizumab:

retrospective IMvigor010 analysis- ctDNA(+) patients had improved DFS and OS with atezo

	ctDNA(+) patients	
	Atezolizumab	Observation
Median DFS (95% CI), mo	5.9 (5.6, 11.2)	4.4 (2.9, 5.6)
Median OS (95% CI), mo	25.8 (20.5, NR)	15.8 (10.5, 19.7)



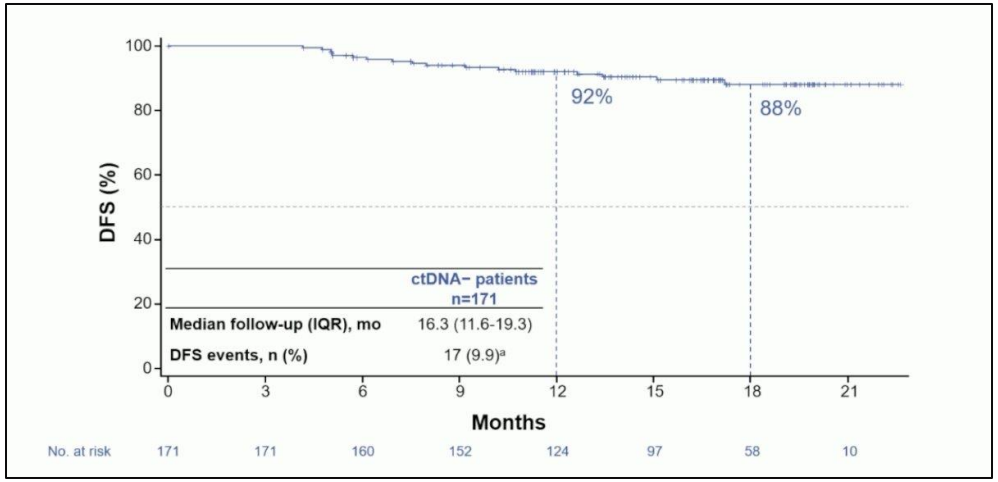


NR, not reached.

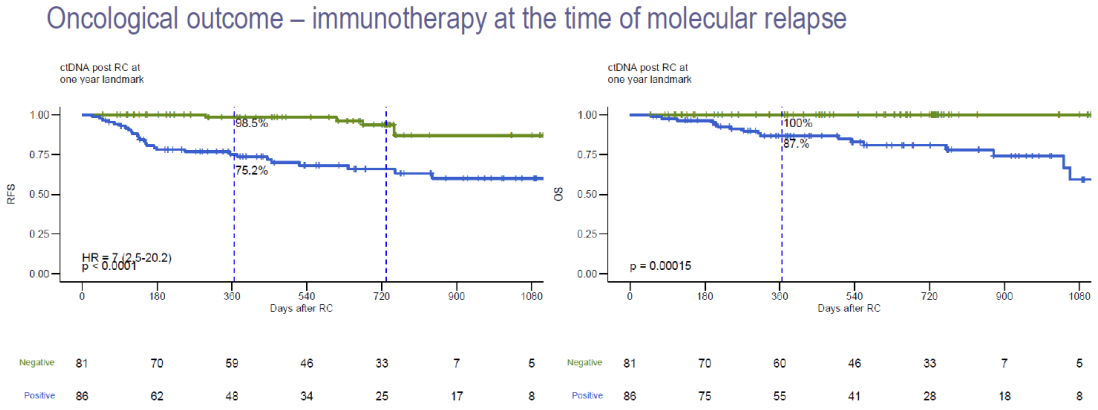
Powles T, ESMO IO 12/2020

Preliminary validation data for ctDNA to predict MRD

- Early analysis of Imvigor-011 Phase III trial with median follow-up of 16.3 months
- Continuously ctDNA- population (n=171)
- 17 recurrence events (9.9%) that did not appear to be related to pathologic stage or PD-L1 status
- 12-month DFS rate was 92% and 18-month DFS rate 88%



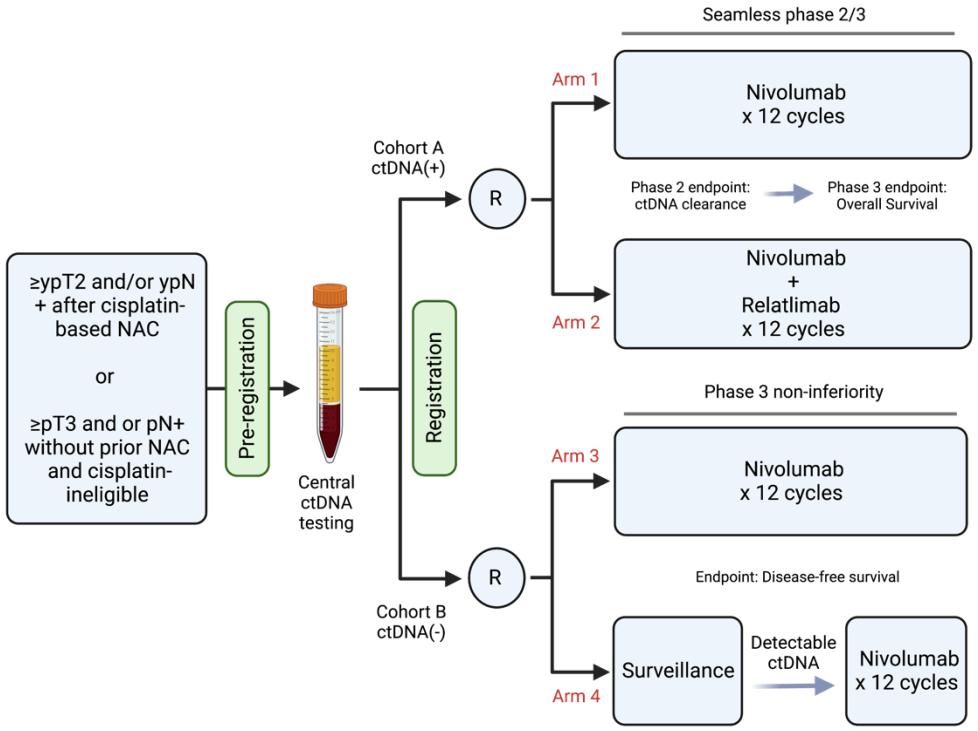
- TOMBOLA Phase II trial
- Of the ctDNA- patients, only 2 (3%) recurred.
- Atezolizumab at time of molecular ctDNA relapse improved outcomes



Powles T, et al. EAU Annual Meeting April 2024
Jensen JB, et al. ESMO Congress September 2024

Ongoing trials of adjuvant therapy

A032103 (MODERN)



Interpath-005

Pembrolizumab + V940 (individualized mRNA therapy encoding up to 34 neoantigens) as adjuvant therapy for high-risk muscle-invasive urothelial carcinoma: V940-005 randomized Phase II trial

Eligibility
- Muscle-invasive urothelial carcinoma
- h/o radical cystectomy or nephroureterectomy
- pT2-4aNany or pTanyN+ post-neoadjuvant cisplatin -based chemotherapy
  OR
  pT3-4Nany or pN+ post surgery with no neoadjuvant chemotherapy (cisplatin-ineligible or declined adjuvant cisplatin-based chemo)
- ECOG-PS 0-2
- Predominant urothelial carcinoma
- Tissue adequate for NGS and V940 production
- Blood sample for V940 manufacture process and tumor-informed ctDNA assay

Stratify: ctDNA NAC

RANDOMIZE

N=200

Pembrolizumab q6W IV x 9 + Placebo q3W IM x 9

Pembrolizumab q6W IV x 9 + V940 q3W IM x 9

V940 may begin as soon as Cycle 1 Day 22

Primary endpoint
DFS (Investigator assessed)

Secondary endpoints
OS
DMFS
Safety

NCT06305767

Novel biomarkers for bladder cancer: Take home message

Setting / Biomarkers	1L	Salvage	Adjuvant	Neoadjuvant	Bladder preservation
Validated or used in clinic	None	• FGFR3 mutation / fusion • HER2 IHC 3+	PD-L1 IHC (Europe)	None	None
Potential biomarkers	• Deep learning on WES, RNAseq • Spatial transcriptomics • Computational pathology • Tertiary Lymphoid Structures (TLS) • Radiomics • Plasma proteomics		Tumor-informed ctDNA (MRD)	ERCC2	• DDR alterations • ctDNA

Upfront development of predictive biomarkers should be given high priority as we expand the therapeutic armamentarium to predict:

1) durable response
2) primary refractory disease (significant attrition of patients with successive lines of therapy)
3) Severe / life-threatening toxicities