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Neoadjuvant vs Adjuvant vs Perioperative therapy for Muscle-Invasive Bladder Cancer

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Conflict of Interest Disclosure

- Honoraria: Merck, Astra Zeneca, Johnson&Johnson, BMS, Gilead, Catalym
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- Travel, Accommodations, Expenses: Merck, Astra Zeneca, Johnson&Johnson, Gilead
- Employment and Stock Ownership (spouse): Bayer

Academic appointments:

- Associate Editor, Journal of Clinical Oncology®
- Vice-president of the Global Society of Rare GU Tumors (GSRGT)
- Panel member of the ASCO/EAU penile cancer guidelines committee
- Faculty GU Non-prostate cancers, ESMO (2021-2025)
- Board member – EAU Research Foundation (EAU-RF)

Multimodal Treatment(s)

Rationale

+ Select those at greatest risk
+ Can solve local problems first

- Compliance lower
- Late systemic treatment

+ Compliance higher
+ Treat all
+ Early systemic treatment (MIBC is a systemic disease)
+ Can spare radical local therapy in outlier responders
+ Matched pre-post therapy samples for biomarker discovery
+ Possibility to monitor MRD with utDNA

- Delays radical treatment in nonresponders
- Unnecessary treatment for a few patients (minimal T2, ctDNA- patients baseline)
- Can be difficult if rapidly deteriorating symptoms/problems

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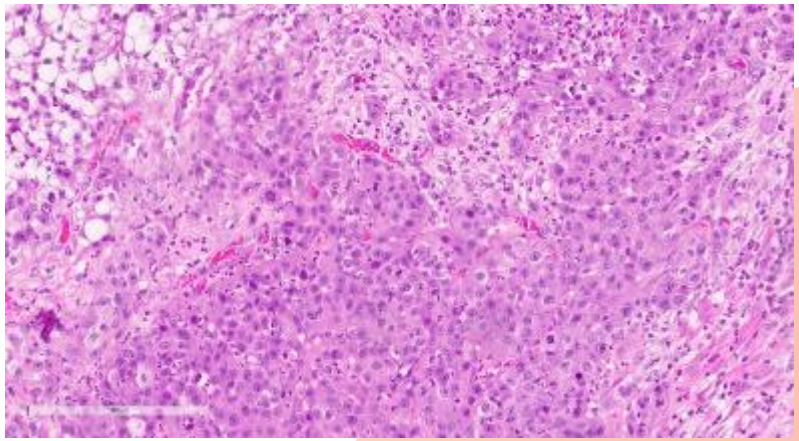
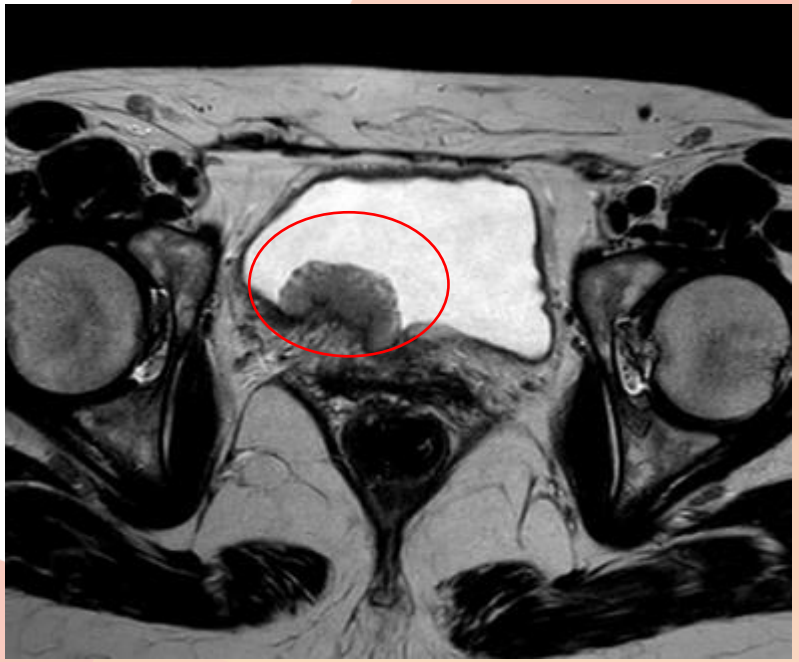
Case Study

42 years old
Female

Family history	▪ No family history of cancer, no smoking, no alcohol use, no allergies ▪ Athlete, no comorbidities
Treatment history	▪ TURBT and right ureteral stenting ▪ Pathologic findings consistent with a muscle-invasive urothelial carcinoma with squamous-cell variant histology (40%) ▪ Serum creatinine 1.04 mg/dL (GFR: 51 mL/min) ▪ Pelvic MRI: 16×34×33–mm sessile mass in the posterior-right lateral bladder wall, VI-RADS 2





MRI, magnetic resonance imaging; VI-RADS, Vesical Imaging Reporting and Data System.

Neoadjuvant Immunotherapy

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Neoadjuvant IO or IO-IO therapy trials for MIBC

	PURE-01[1]	ABACUS[2,3]	NABUCCO[4,5]			DUTRENEO[6]	MDACC[7]	PrE0807[8]	AURA-ONCODISTINCT-004[9]	OPTIMUS[10]
	PEMBRO	ATEZO	IPI > IPI/NIVO > NIVO	IPI3-NIVO1	IPI1-NIVO3	DURVA/TREME	DURVA/TREME	NIVO mono, NIVO + lirilumab	AVE	Retifanlimab
N	143	95	24	15	15	23	28	40	28	20
cT2	49%	74%	0	0	0	78.2%	43%	80%	N/A	85%
cN1-3	0	0	42%	47%	53	8.7%	0	10%	N/A	0
pT0N0	**39%**	**31%**	**46%**	**43%**	**7%**	**34.8%**	**37.5%**	**17%, 21%**	**32%[a]**	**40%**
pT≤1N0	56%	39%	58%	57%	29%	56.5%	58%	8%; 11%	N/A	50%

- **Among these trials, is there an interim signal of clinical activity? YES**
- **Are these results sufficient to envision a bladder-sparing opportunity? NO (in unselected patients)**

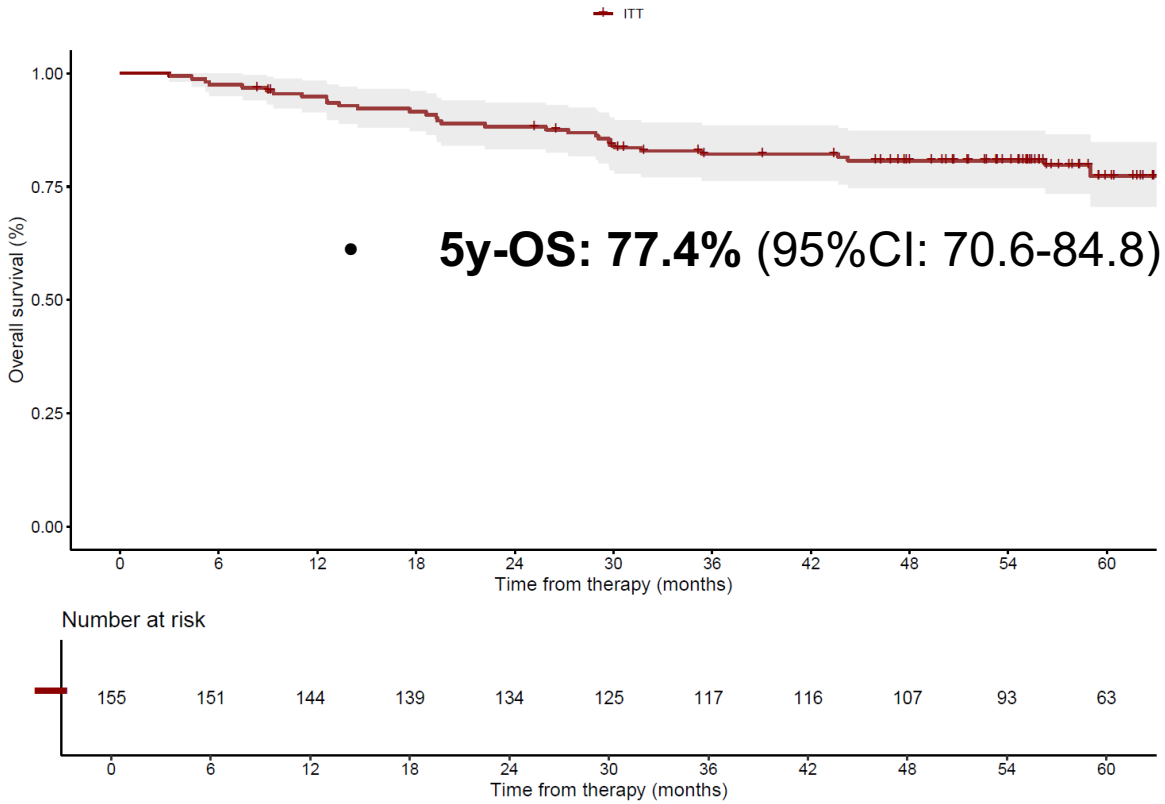
Side-by-side presentations is not intended to imply any head-to-head study comparisons. For informational/descriptive purposes only. Cross-trial comparisons should not be made due to different study designs and patient populations. This slide contains information related to therapies that are investigational and/or beyond their approved indications.

[a]Including ypT0N0 and ypT$_{is}$N0. ATEZO, atezolizumab; AVE, avelumab; DURVA, durvalumab; I-O, immuno-oncology; IPI, ipilimumab; NIVO, nivolumab; PEMBRO, pembrolizumab; TREME, tremelimumab.

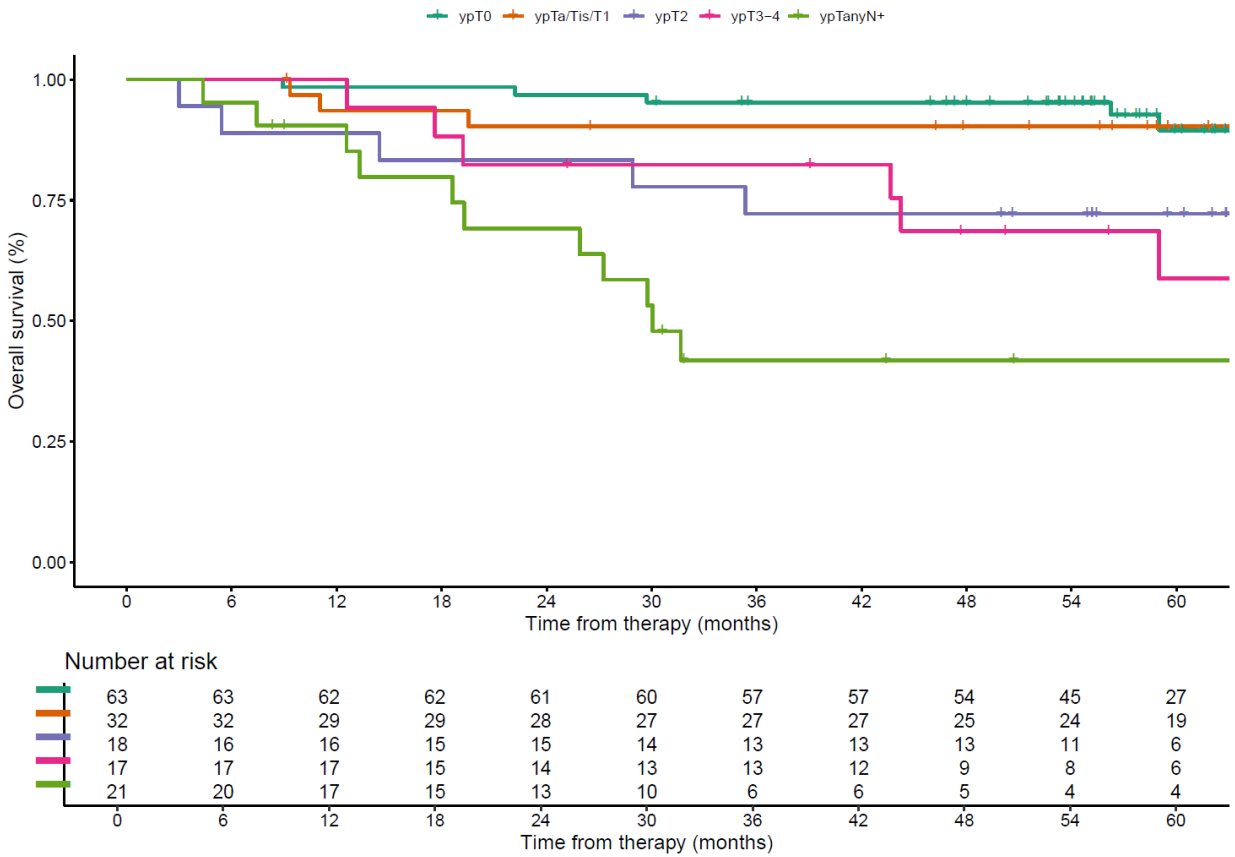
1. Bandini M et al. *Ann Oncol*. 2020;31:1755–1763. 2. Powles T et al. *Nat Med*. 2019;25:1706–1714. 3. Szabados B et al. *Eur Urol*. 2022;82:212–222. 4. van Dijk N et al. *Nat Med*. 2020;26:1839–1844. 5. van Dorp J et al. *Nat Med*. 2023 Mar;29(3):588-592. 6. Grande E et al. *J Clin Oncol*. 2020;38(Suppl15): abstr 5012. 7. Gao J et al. *Nat Med*. 2020;26:1845–1851. 8. Grivas P et al. *Eur Urol Oncol*. 2023:S2588-9311(23)00288-2. 9. Blanc J et al. *J Clin Oncol*. 2024;42(suppl 16): abstr 4516. 10. Necchi A, et al. IBCN meeting 2024; September 19-21, 2024, Bern, Switzerland.

Five-year median follow-up update of PURE-01:

- **OS and prognostic value of pathological response**



- **5y-OS: 77.4%** (95%CI: 70.6-84.8)



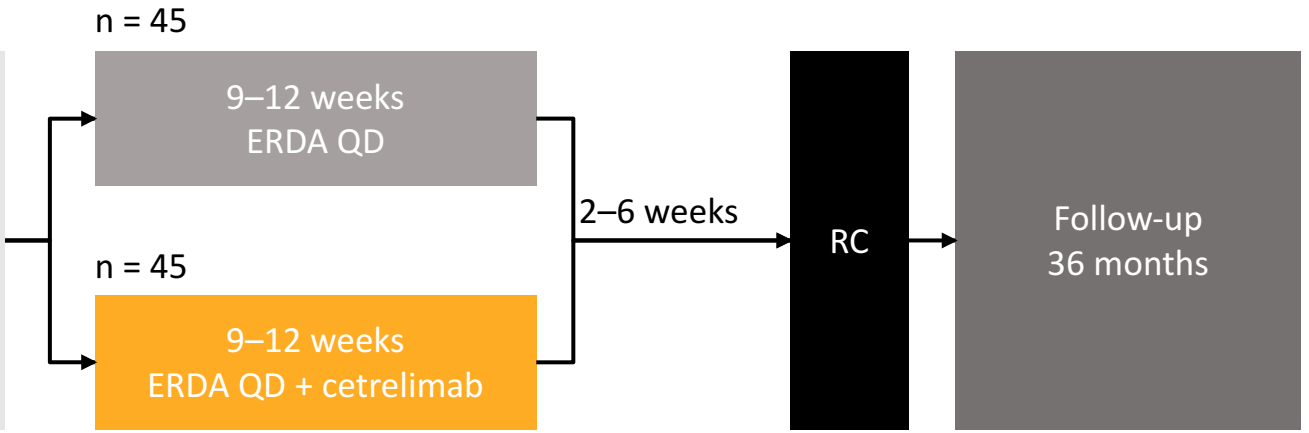
Tateo V, et al. ASCO 2025 Annual Meeting (Abstr. #4595)

NEOWIN: ERDA vs ERDA + cetrelimab as neoadjuvant treatment in cis-ineligible patients with MIBC with selected *FGFR* gene alterations

N = 90

Key eligibility criteria

- cT2-T4a N0/N1 M0
- FGFR positive by central lab[a]
- ECOG PS 0–1
- Candidate for RC
- Ineligible/refuse neoadjuvant cis
- No prior anti-FGFR or anti-PD-(L)1 systemic therapy



Total study duration:

63 months from FPI to LPO

Estimated accrual:

24 months

20 sites in 4 countries

Co-primary endpoints:

- pCR and downstaging rate (< ypT2)

Secondary endpoints:

- Efficacy: any downstaging rate, EFS, OS, ORR[b] after neoadjuvant treatment
- Safety
- Rate of delay to surgery

Exploratory endpoints

- Tumor response via PET-MRI
- QOL
- Biomarkers of response
- Changes in biomarker expression
- Genomic data in plasma, urine, and feces

[a]Local reports based on validated test can be accepted. [b]According to RECIST v1.1.
cis, cisplatin; EFS, event-free survival; ERDA, erdafitinib; FGFR, fibroblast growth factor receptor; FPI, first patient enrolled; LPO, last patient out; MIBC, muscle-invasive bladder cancer;
ORR, objective response rate; OS, overall survival; pCR, pathologic complete response; PD-1, programmed death-1; PD-L1, programmed death ligand 1; PET, positron emission tomography;
PS, performance status; QD, daily; QOL, quality of life; RC, radical cystectomy; vs, versus. Hussain SA et al. Poster at the American Society of Clinical Oncology (ASCO) Annual Meeting. May 31–June 4, 2024. Chicago, IL. Abstract TPS4623.

Neoadjuvant ADC therapies for MIBC

EV		SG	DV
EV-103 Cohort H[1] **EV 1.25 mg/kg IV D1,8 Q3W** **3 cycles** **N = 22**	**EV-103 Cohort L[2]** **EV 1.25 mg/kg IV D1,8 Q3W** **3 cycles → adjuvant EV** **N = 51**	**SURE-01[3]** **SG 10 mg/kg (amended to 7.5 mg/kg) IV D1,8 Q3** **4 cycles** **N = 33**	**Disitamab vedotin[4]** **HER2 1+/2+/3+ MIBC** **DV 2 mg/kg IV D1 Q2W + TOPA 3 mg/kg D1 Q2W** **6 cycles** **N = 47**

- Among these trials of neoadjuvant therapy with ADC, ypT0N0 rates ranged **34% - 63.6%;** ypT≤1N0 rates ranged **34% - 75.8%**
- The number of patients experiencing a grade 5 AE were low, ranging from 0 to 3 patients, but are still quite concerning

Side-by-side presentations is not intended to imply any head-to-head study comparisons. For informational/descriptive purposes only. Cross-trial comparisons should not be made due to different study designs and patient populations. This slide contains information related to therapies that are investigational and/or beyond their approved indications.
ADC, antibody-drug conjugate; AE, adverse event; D, day; DV, disitamab vedotin; EV, enfortumab vedotin; MIBC, muscle-invasive bladder cancer; SG, sacituzumab govitecan.
1. O'Donnell PH, et al. Poster at the American Society of Clinical Oncology (ASCO) Annual Meeting; May 31–June 4, 2024; Chicago, IL. Abstract 4564. 2. Sridhar S et al. Presentation at the European Society for Medical Oncology (ESMO) Annual Meeting; October 20–24, 2023; Madrid, Spain. Abstract 2365MO. 3. Maiorano BA, et al. ASCO 2025 (Abstract #4591). 4. Sheng X et al. *J Clin Oncol 43, 2025 (suppl 5; abstr 665)*

Perioperative Immunotherapy

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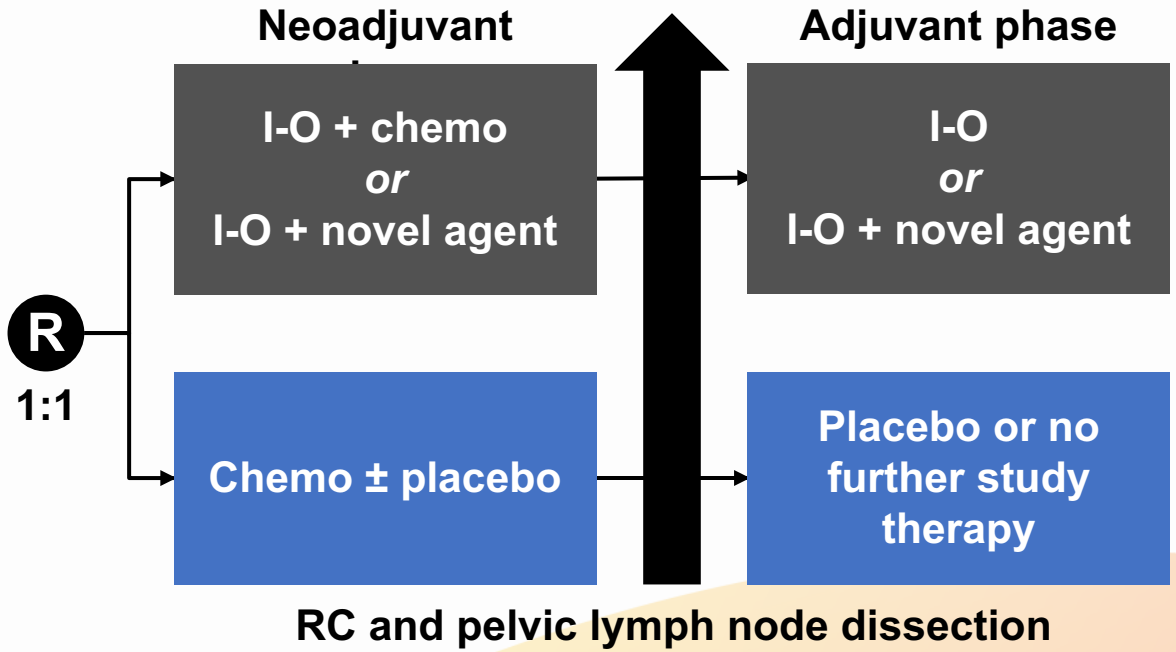
Several phase 3 trials with perioperative I-O are underway

Cisplatin eligible[1,2,4,5]



Cisplatin-eligible trials

CA017-078[1,a]
• Gem/cis ± NIVO • Fully accrued N = 861
NIAGARA[2]
• Gem/cis ± DURVA • Fully accrued N = 1063 ↑△ EFS and OS[3]
KEYNOTE-866[4]
• Gem/cis ± PEMBRO • Fully accrued N = 907
KEYNOTE-B15/EV-304[5]
• PEMBRO + EV • Enrollment ongoing, estimated N = 784

chemo, chemotherapy; cis, cisplatin; DURVA, durvalumab; EFS, event-free survival; EV, enfortumab vedotin; gem, gemcitabine; I-O, immuno-oncology; NIVO, nivolumab; OS, overall survival; PEMBRO, pembrolizumab; R, randomization; RC, radical cystectomy. 1. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT03661320. 2. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT03732677. 3. AstraZeneca [press release]. https://www.astrazeneca.com/media-centre/press-releases/2024/imfinzi-improved-efs-and-os-in-bladder-cancer.html 4. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT03924856. 5. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT04700124. All URLs accessed August 26, 2024.

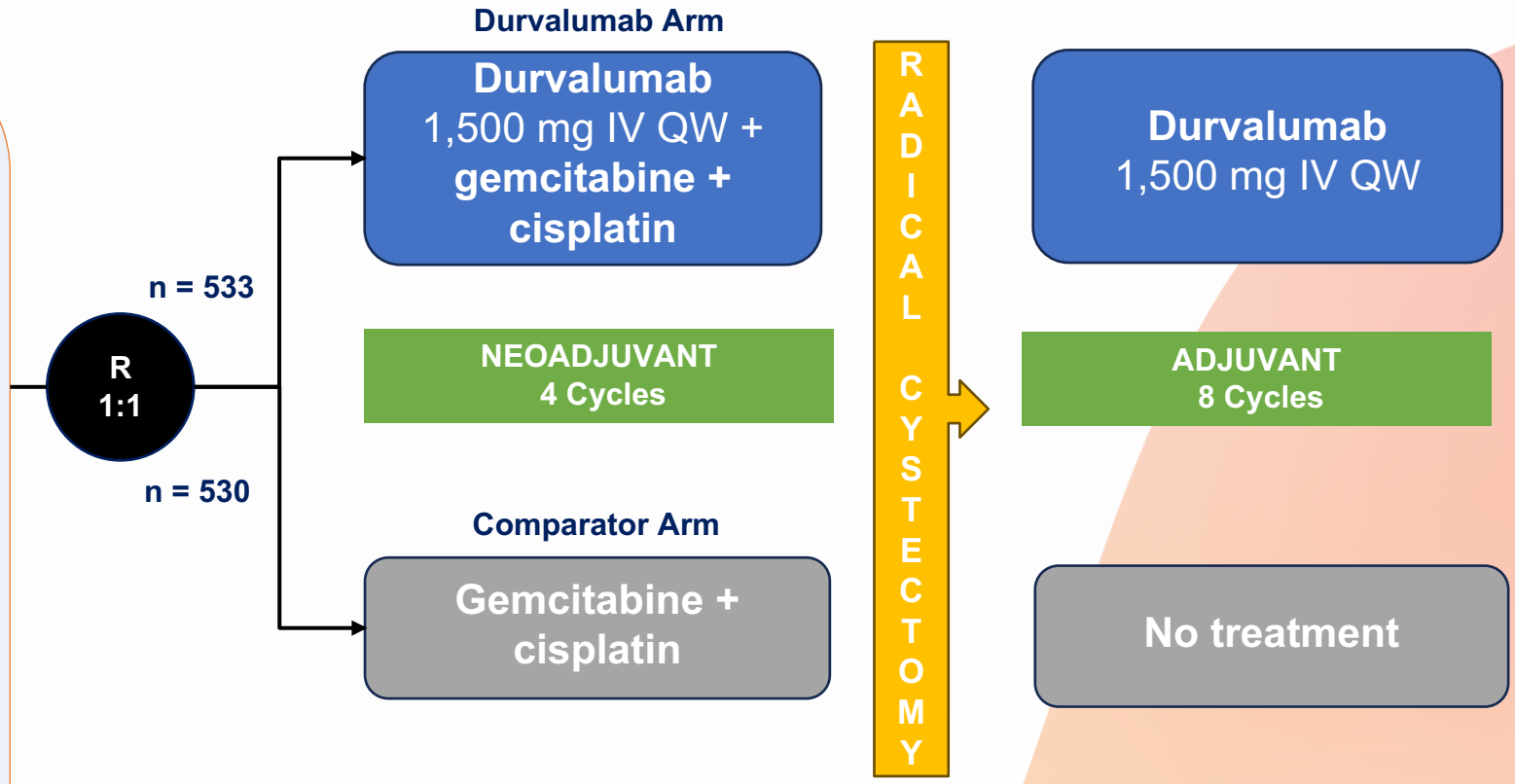
Phase 3 NIAGARA: Perioperative Durvalumab With Neoadjuvant Chemotherapy in Operable Bladder Cancer[1]

Key Eligibility Criteria

- Cisplatin-eligible MIBC
- Clinical stage T2-T4aN0/N1/M0
- UC or UC with divergent differentiation or histologic subtypes
- Evaluated and confirmed for radical cystectomy
- CrCl >40 mL/min per 1.73 m^2 per BSA

Stratification Factors

- Clinical tumor stage (T2N0 vs >T2N0)
- Renal function (CrCl >60 mL/min vs >40 to <60 mL/min)
- PD-L1 status (high vs low or negative)



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: DFS, DSS, MFS, HRQoL, 5-year OS

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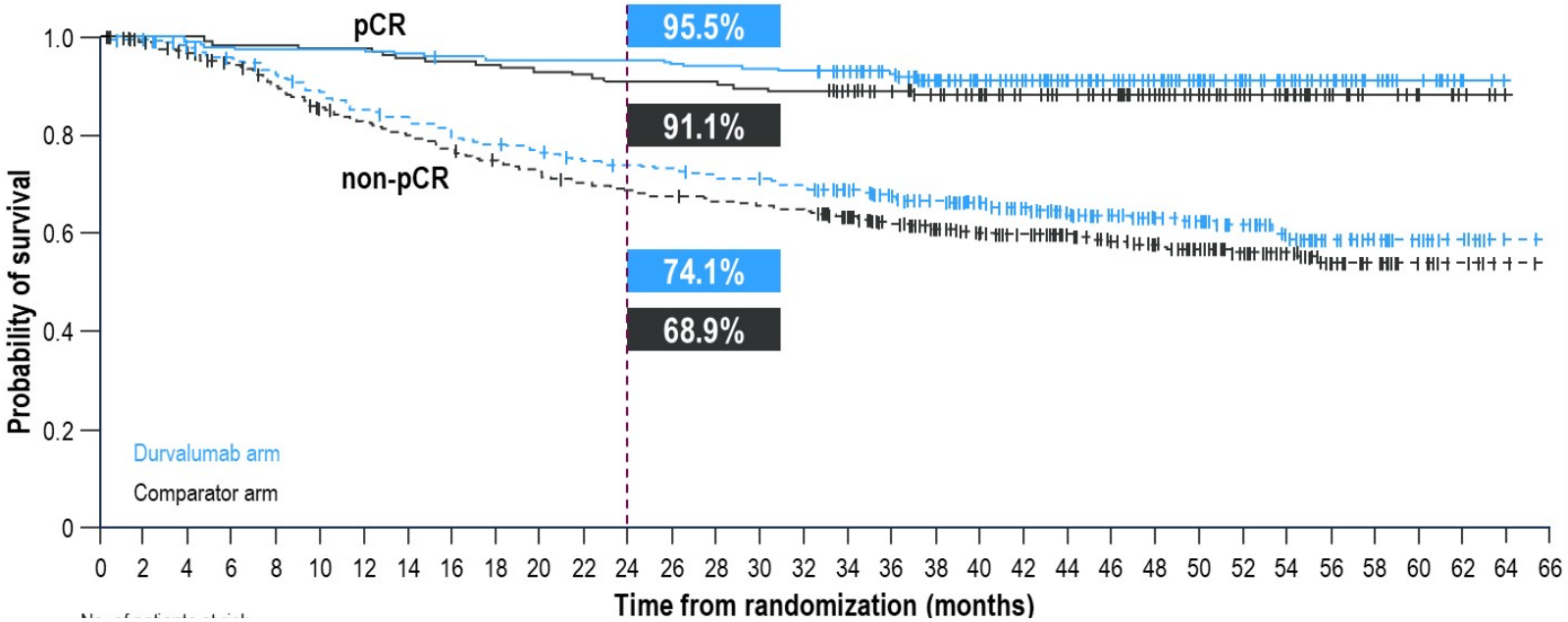
1. Powles TB et al. *N Engl J Med*. 2024; 391:1773-1786.

NIAGARA: Overall Survival in pCR and Non-pCR Groups



- pCR prognostic regardless of how it is achieved
- Established surrogate of outcome in MIBC
- Improved OS with Durva also in non-pCR subgroup
- **Unclear what contribution of adjuvant Durva is**
- No predictive biomarkers of response

In the durvalumab arm:
The risk of an MFS event was reduced by 33%; the risk of a DSS event was reduced by 31%

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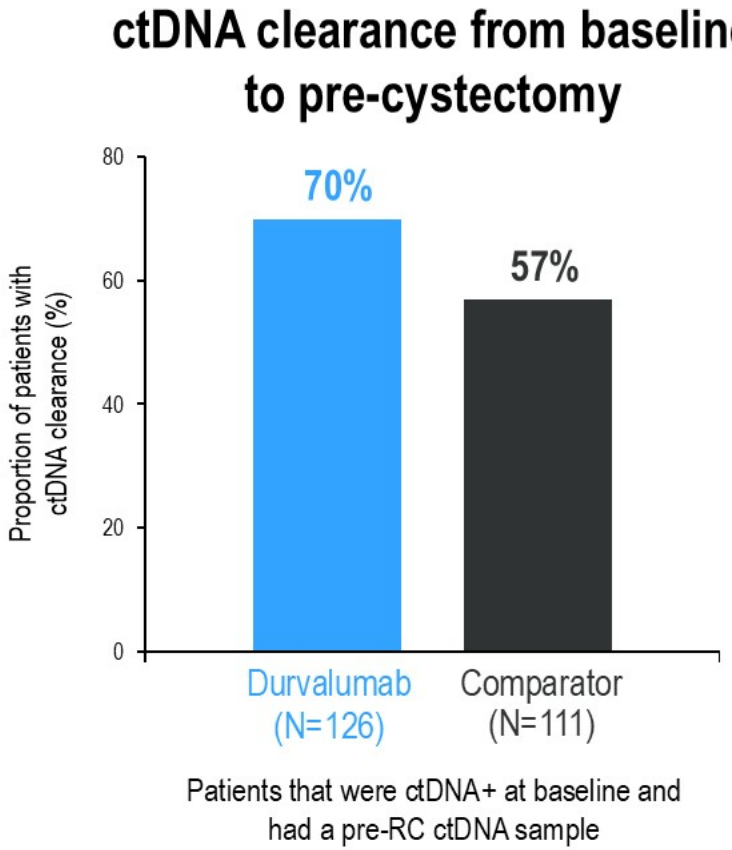
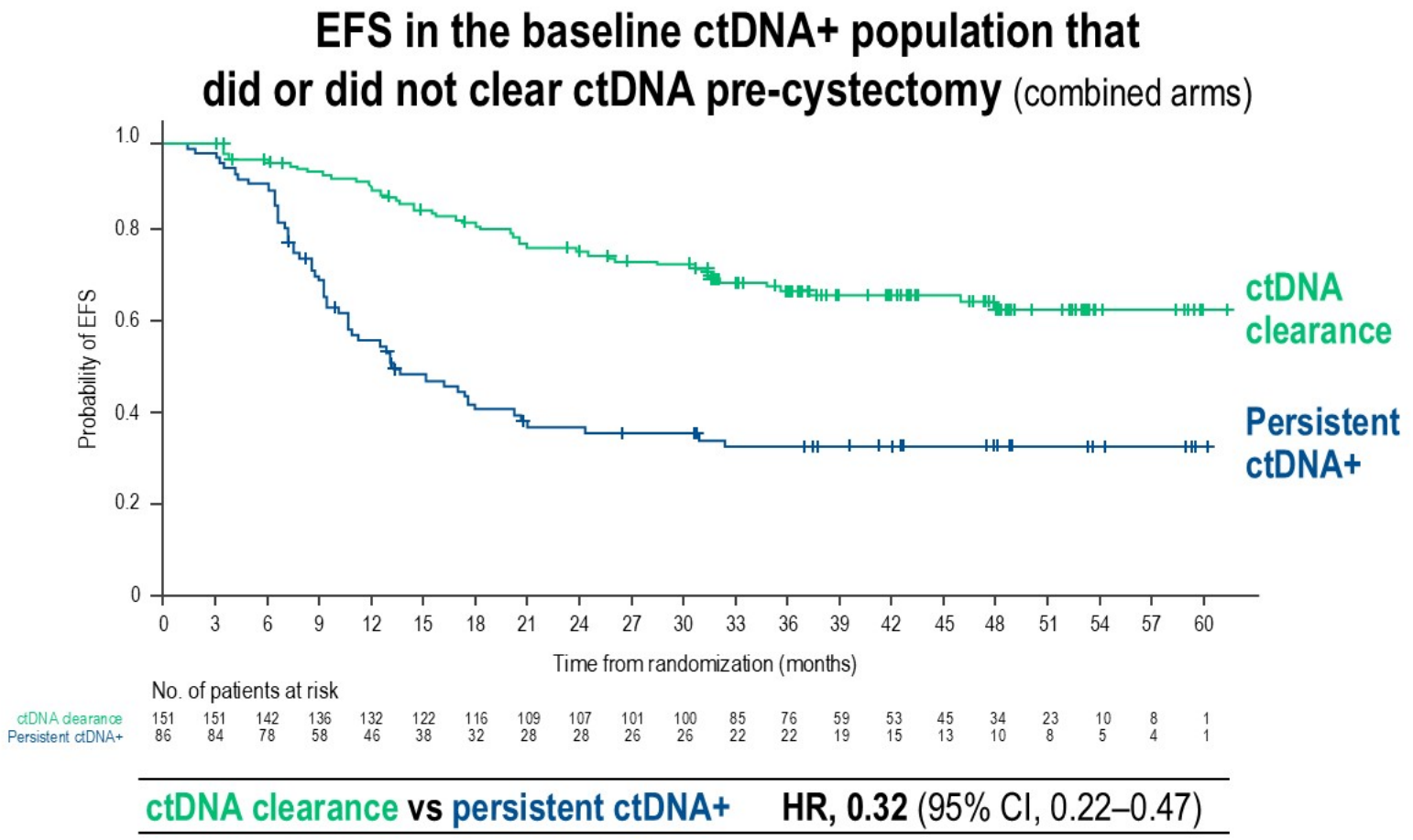
Powles T, et al. N Engl J Med. 2024;391:1773-1786.

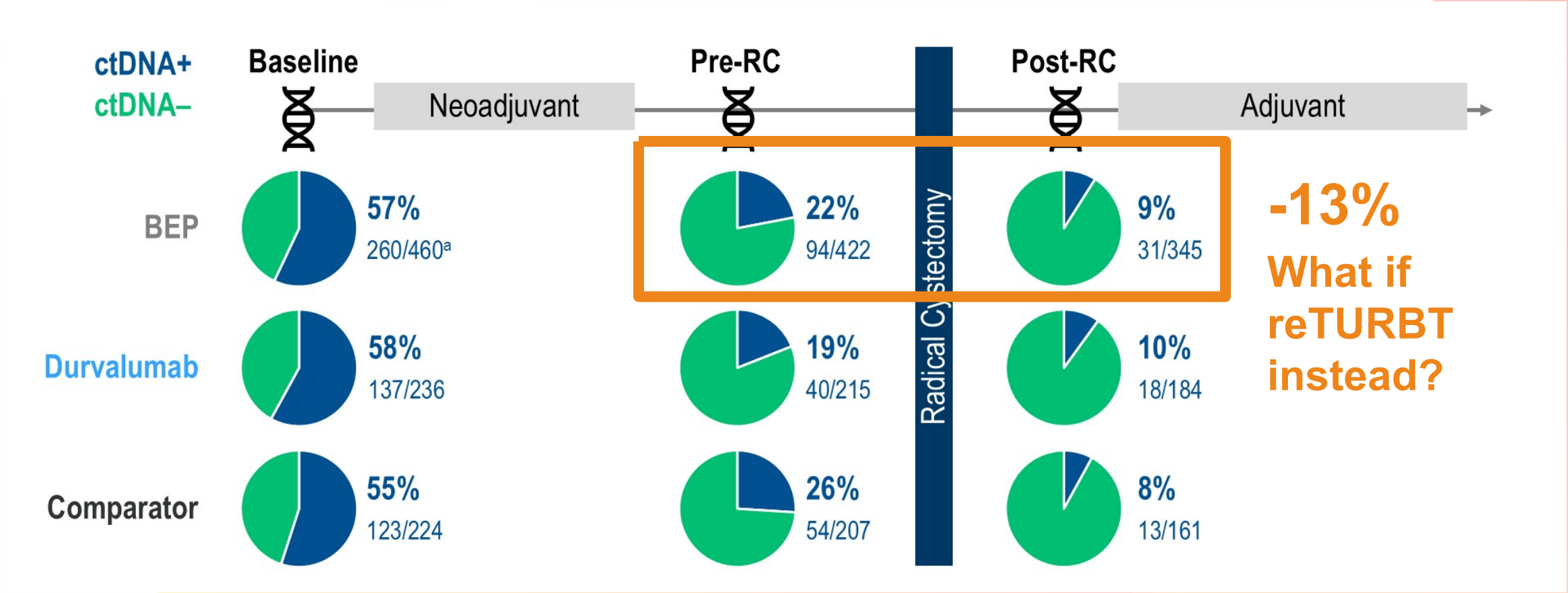
Prognostic value of ctDNA clearance in NIAGARA





Powles T, et al. ASCO 2025 (Abstract #4503)

Can we quantify the contribution of RC towards perioperative Durva+chemo or Chemo?



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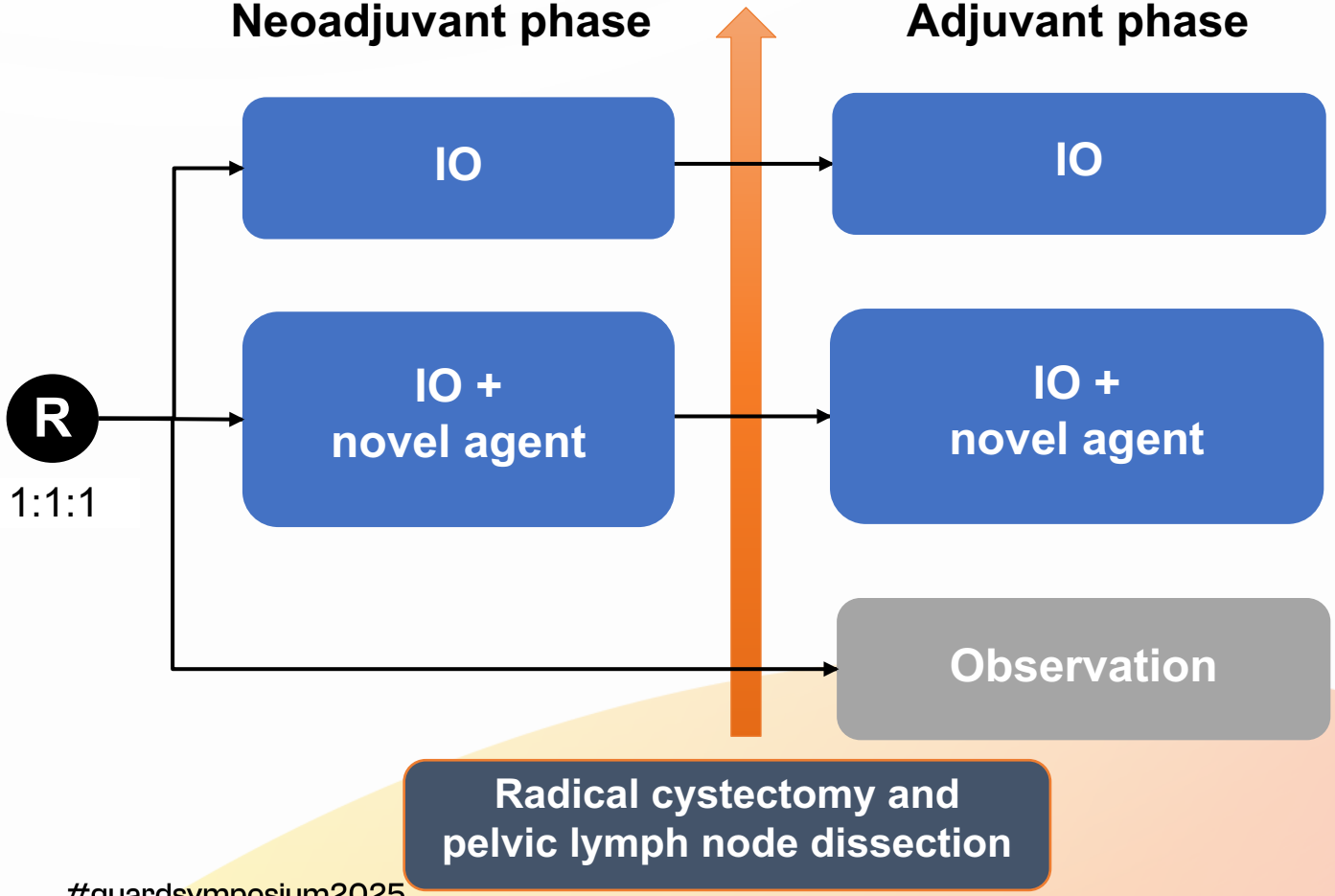
Powles T, et al. ASCO 2025 (Abstract #4503)

Several Ongoing Phase 3 Trials With Perioperative Immunotherapy

Cisplatin Ineligible



Cisplatin-Ineligible Trials

KEYNOTE-905/EV-303[1]
• Pembrolizumab + EV • Enrollment ongoing (estimated N = 857)
VOLGA[2,3]
• Durvalumab + tremelimumab + EV • Enrollment ongoing (estimated N = 830)
SunRISe-4[4,5] (phase 2)
• TAR-200 + cetrelimab • Enrollment ongoing (estimated N = 160)

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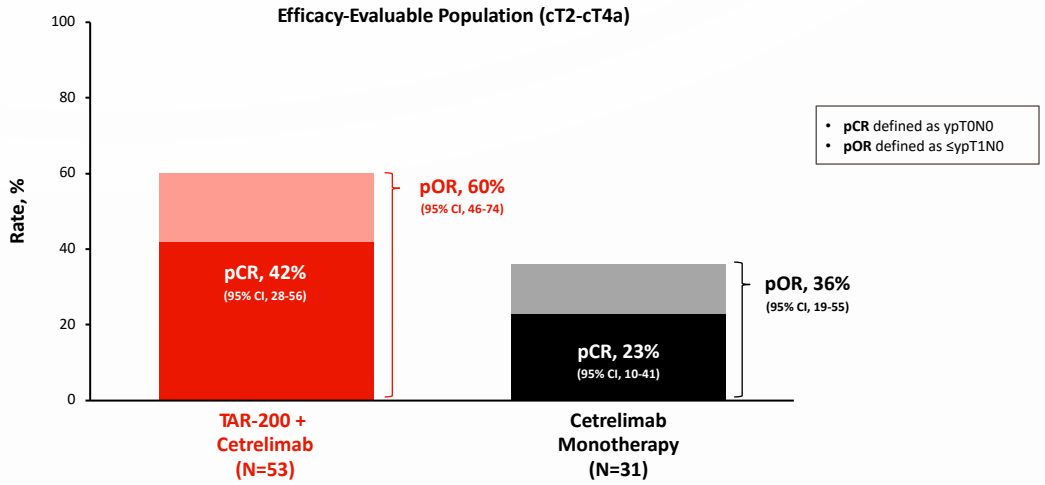
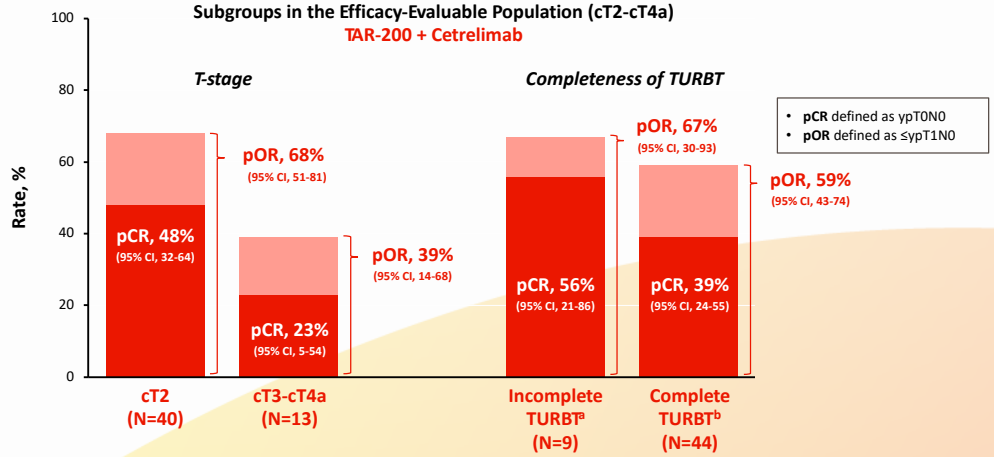
1. https://www.clinicaltrials.gov/study/NCT03924895. 2. https://clinicaltrials.gov/study/NCT04960709. 3. Powles T et al. ASCO-GU 2022. Abstract TPS579.
4. https://clinicaltrials.gov/study/NCT04919512. 5. Necchi A et al. ESMO 2024. Abstract LBA84.

Combining intravesical and systemic therapy in MIBC:

SunRISe-4: TAR-200 + Cetrelimab





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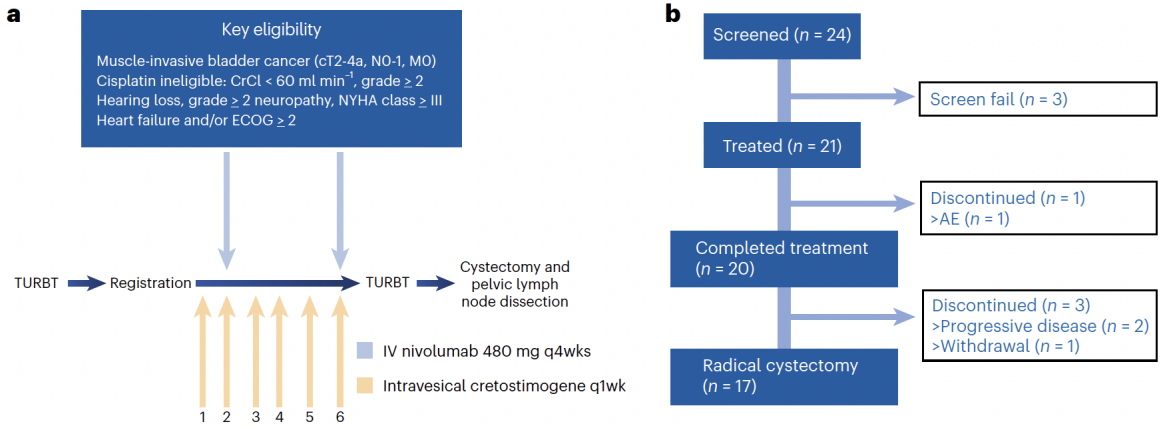
Necchi A, et al. ESMO 2024

CORE-002 trial: cretostimogene + nivolumab



- Primary Endpoint: Safety (CTCAE)
- 68% cT2N0 stage
- Chemotherapy refusal for eligibility: 9.5%
- **ypT0N0 rate: 8/19 (42.1%)**
- 1-y RFS rate: 70.4%
- Grade 3-4 TRAE: 57%

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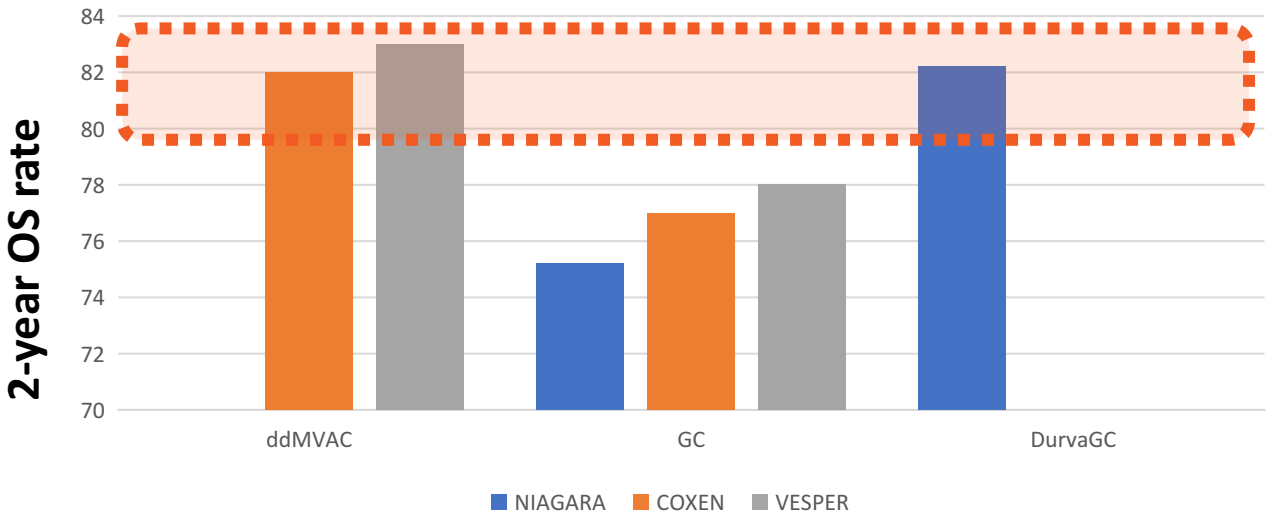
Li R, et al. *Nat Med*. 2024 Nov 9. doi: 10.1038/s41591-024-03324-9. Online ahead of print.

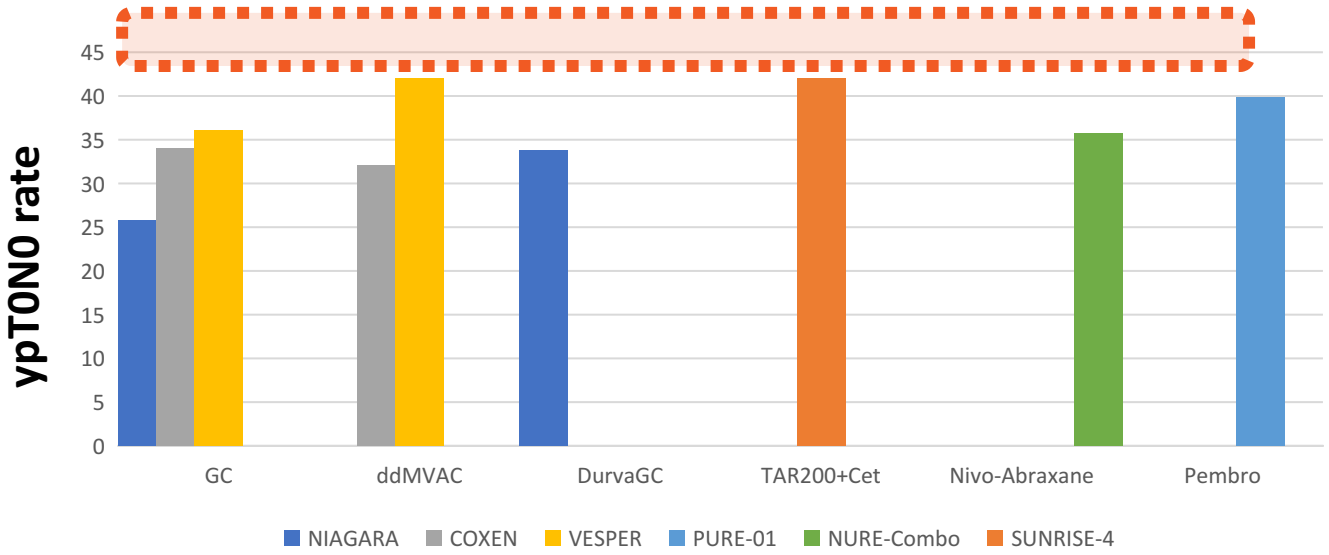
Definitions of therapeutic success are multifold and will likely change based on patient expectations

Goal: Cure from MIBC



'Success' area >80%

Goal: Cure with intact and unirradiated bladder from MIBC



'Success' area >45-50%

Powles T, et al. *N Engl J Med*. 2024 Sep 15. doi: 10.1056/NEJMoa2408154. Online ahead of print; Flaig T.W. et al. *Clin Cancer Res.* 2021;27:2435-41; Pfister C. et al. *J Clin Oncol*. 2022 Jun 20;40(18):2013-2022; Necchi A, et al. ESMO 2024; Mercinelli C, et al. *J Clin Oncol*. 2024 Sep 6:JCO2400576. doi: 10.1200/JCO.24.00576. Online ahead of print.

Adjuvant Immunotherapy

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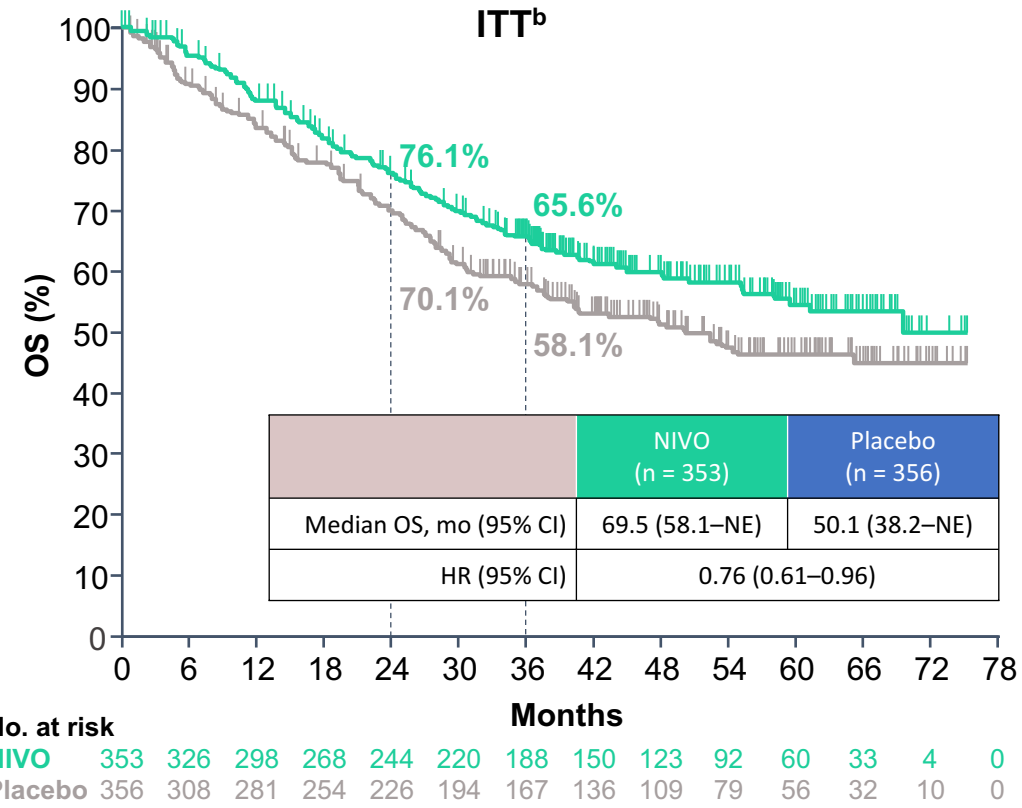
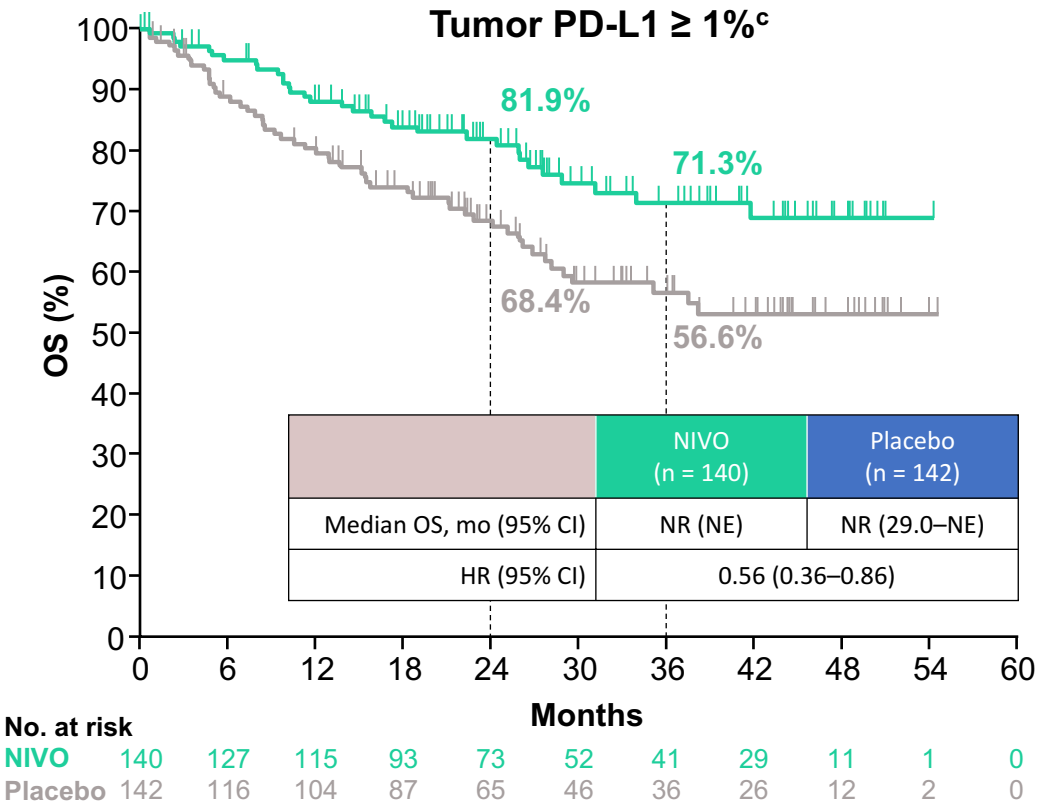
CheckMate 274: interim OS favored NIVO vs placebo in both populations[a]

ASCO
ascopubs.org/journal/jco
Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal





- Grade ≥ 3 any-cause AEs occurred in 50.6% and 31% of patients receiving NIVO and placebo, respectively

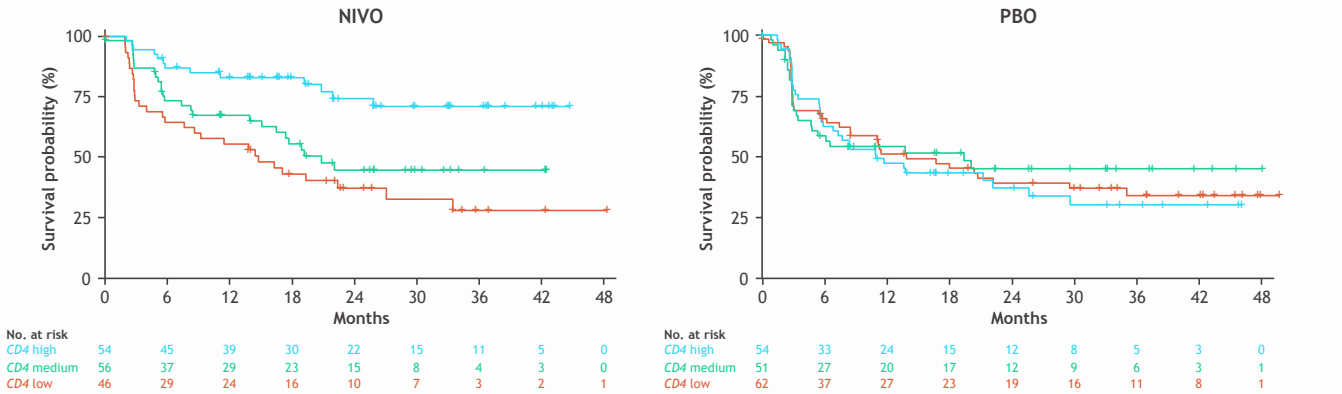
FDA & EMA Approved

Global clinical trial

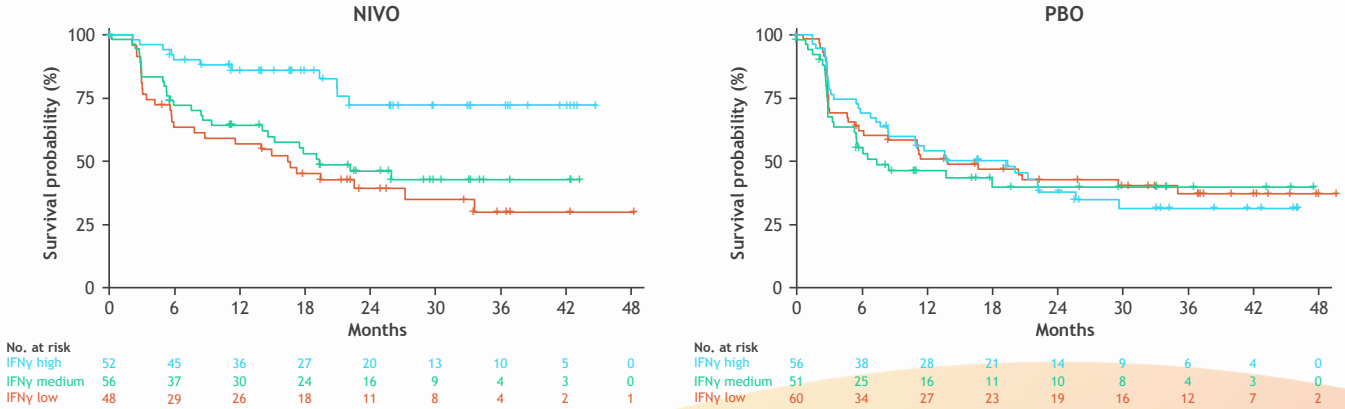
This slide contains information related to therapies that are investigational and/or beyond their approved indication(s).
[a]OS follow-up is ongoing. [b]Median (minimum) follow-up 36.1 (31.6) months. [c]Median (minimum) follow-up 23.4 (11.4) months. mo, month; NE, not evaluable; NIVO, nivolumab; NR, not reached; OS, overall survival; PD-L1, programmed death ligand 1; TRAE, treatment-related adverse event; vs, versus.

Galsky MD et al. *J Clin Oncol*. 2024 Oct 11:JCO2400340. doi: 10.1200/JCO.24.00340. Online ahead of print.

Determinants of adjuvant nivolumab benefit in CheckMate-274



Kaplan-Meier estimates of DFS for each arm stratified by *CD4* gene expression tertile



Kaplan-Meier estimates of DFS for each arm stratified by IFNγ gene signature score tertile

Necchi A, et al. ESMO 2022 (Paper in press)

If neoadjuvant IO is used:

- Neoadjuvant IO depends on CD8 + T-cells and IFNγ
- Enhanced efficacy of neoadjuvant Treg depletion to eradicate metastases
- Neoadjuvant IO increases tumor-specific CD8+ T-cells in peripheral blood and organs

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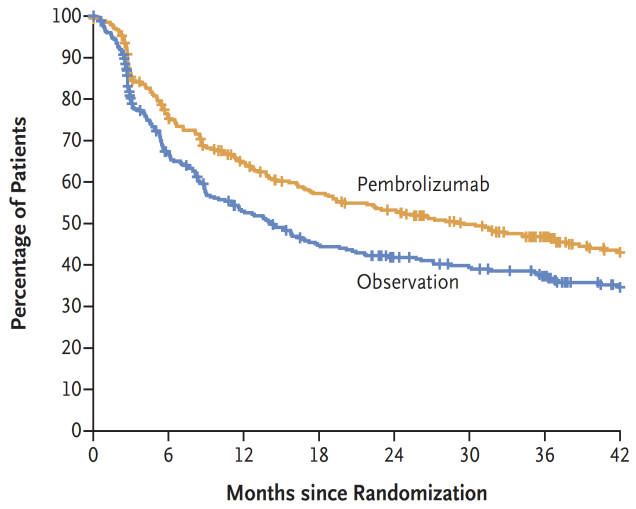
AMBASSADOR: PEMBRO demonstrated DFS benefit

DFS (ITT)[a,b]

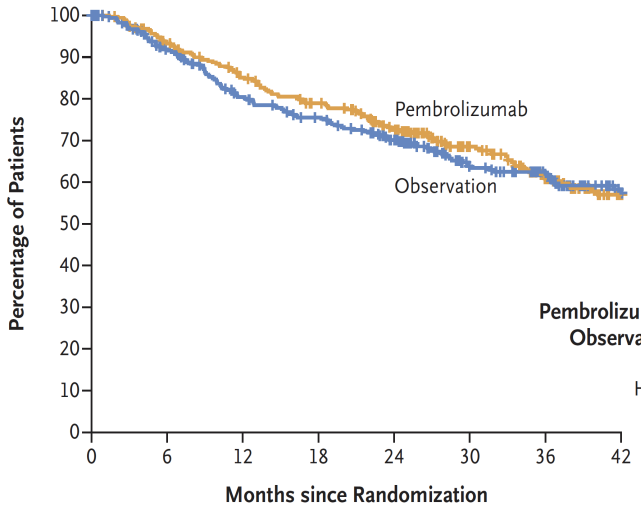


	No. of Events/ Total No. of Patients	Median Disease-free Survival (95% CI)
		mo
Pembrolizumab	185/354	29.6 (20.0–40.7)
Observation	194/348	14.2 (11.0–20.2)

Hazard ratio for disease progression or death, 0.73 (95% CI, 0.59–0.90)
Stratified P=0.003 by log-rank test

No. at Risk								
Pembrolizumab	354	247	202	174	159	137	114	85
Observation	348	198	150	124	107	96	81	58

OS[c]



	No. of Events/ Total No. of Patients	3-Yr Survival (95% CI)
		percent
Pembrolizumab	131/354	60.8 (95% CI, 55.3 to 66.9)
Observation	126/348	61.9 (95% CI, 56.5 to 67.9)

Hazard ratio for death, 0.98 (95% CI, 0.76–1.26)

No. at Risk								
Pembrolizumab	354	313	280	253	218	152	115	69
Observation	348	296	249	227	195	139	117	65

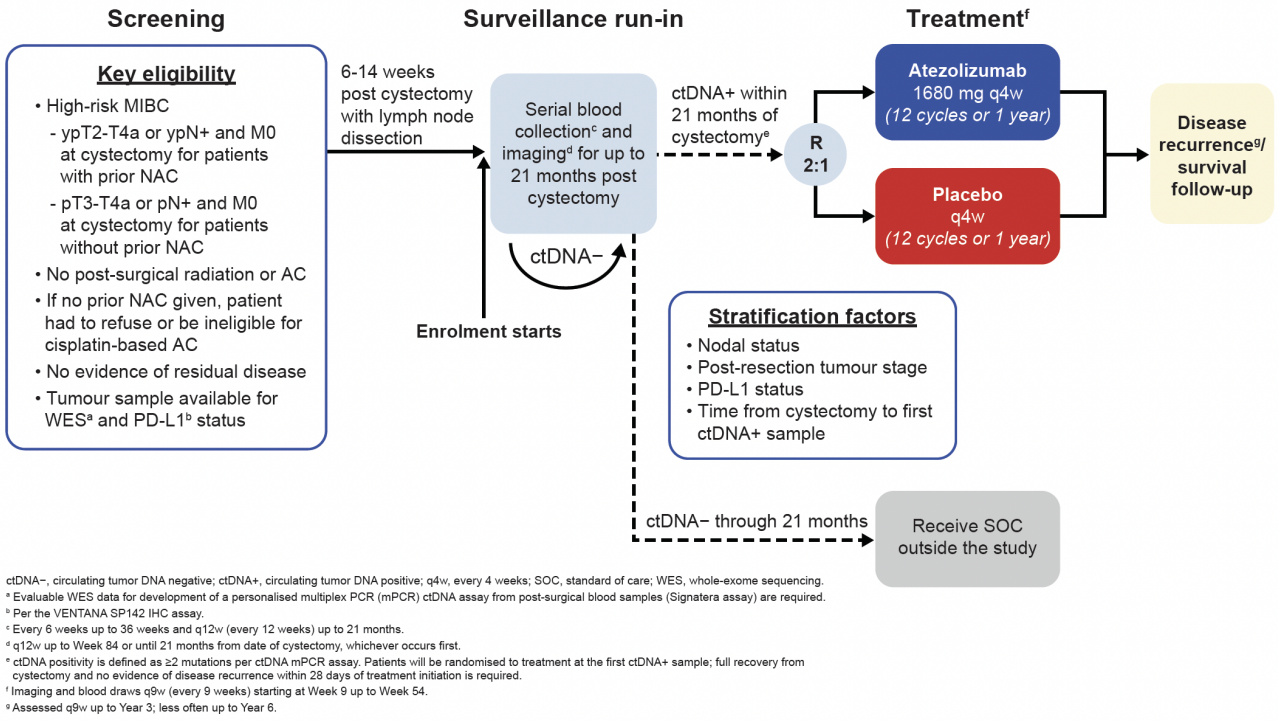
- Grade ≥ 3 TRAEs occurred in 48.4% and 31.8% of patients receiving PEMBRO and observation, respectively

US-based clinical trial

[a]Median follow-up (range) 22.3 months (0.03–48.9). [b]DFS defined as new MIUC, metastatic disease, or death without recurrence. [c]Median follow-up (range) 36.9 months (0–63.9).
DFS, disease-free survival; IA, interim analysis; MIUC, muscle-invasive urothelial carcinoma; NR, not reached; Obs, observation; OS, overall survival; PEMBRO, pembrolizumab.
Apolo AB et al., *N Engl J Med*. 2024 Sep 15. doi: 10.1056/NEJMoa2401726. Online ahead of print

Ongoing adjuvant trials designed to validate the ctDNA utility of adjuvant IO

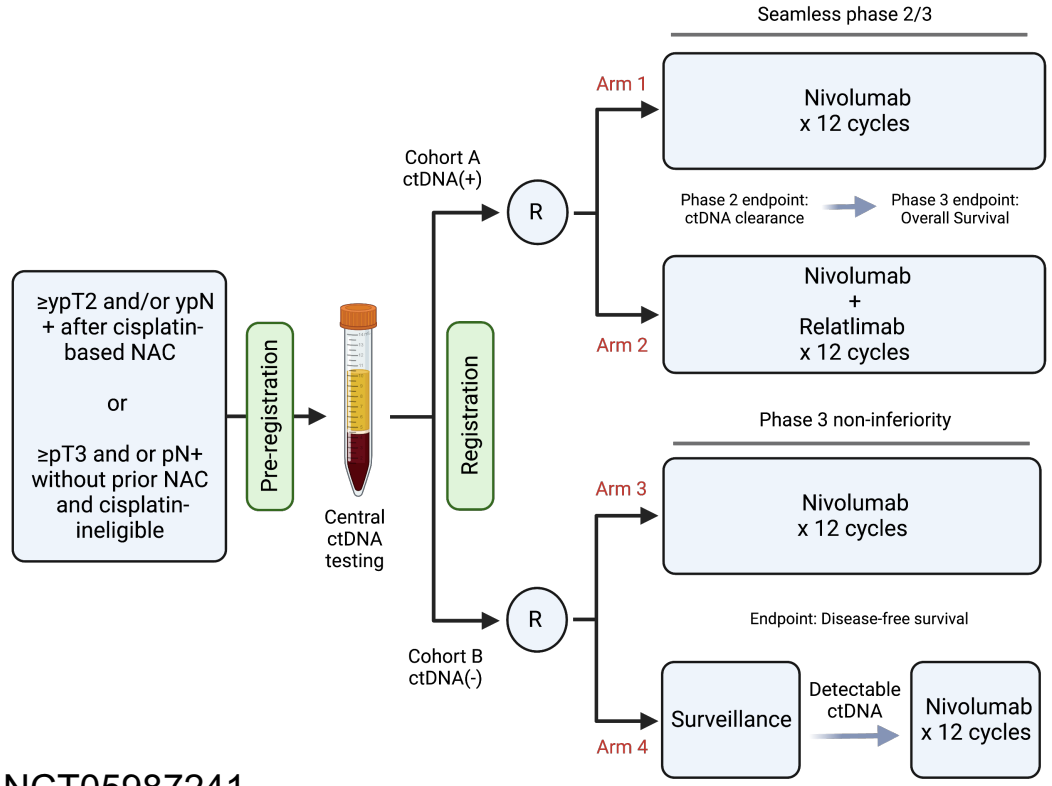
IMvigor-011



ctDNA−, circulating tumor DNA negative; ctDNA+, circulating tumor DNA positive; q4w, every 4 weeks; SOC, standard of care; WES, whole-exome sequencing.
[a] Evaluable WES data for development of a personalised multiplex PCR (mPCR) ctDNA assay from post-surgical blood samples (Signatera assay) are required.
[b] Per the VENTANA SP142 IHC assay.
[c] Every 6 weeks up to 36 weeks and q12w (every 12 weeks) up to 21 months.
[d] q12w up to Week 84 or until 21 months from date of cystectomy, whichever occurs first.
[e] ctDNA positivity is defined as ≥2 mutations per ctDNA mPCR assay. Patients will be randomised to treatment at the first ctDNA+ sample; full recovery from cystectomy and no evidence of disease recurrence within 28 days of treatment initiation is required.
[f] Imaging and blood draws q9w (every 9 weeks) starting at Week 9 up to Week 54.
[g] Assessed q9w up to Year 3; less often up to Year 6.

NCT04660344

A032103 (MODERN): An integrated Phase 2/3 and Phase 3 Trial of MRD-based Optimization of aDjuvant thErapy in uRothelial caNcer



NCT05987241

Phase 3 design & results of perioperative studies across tumor types

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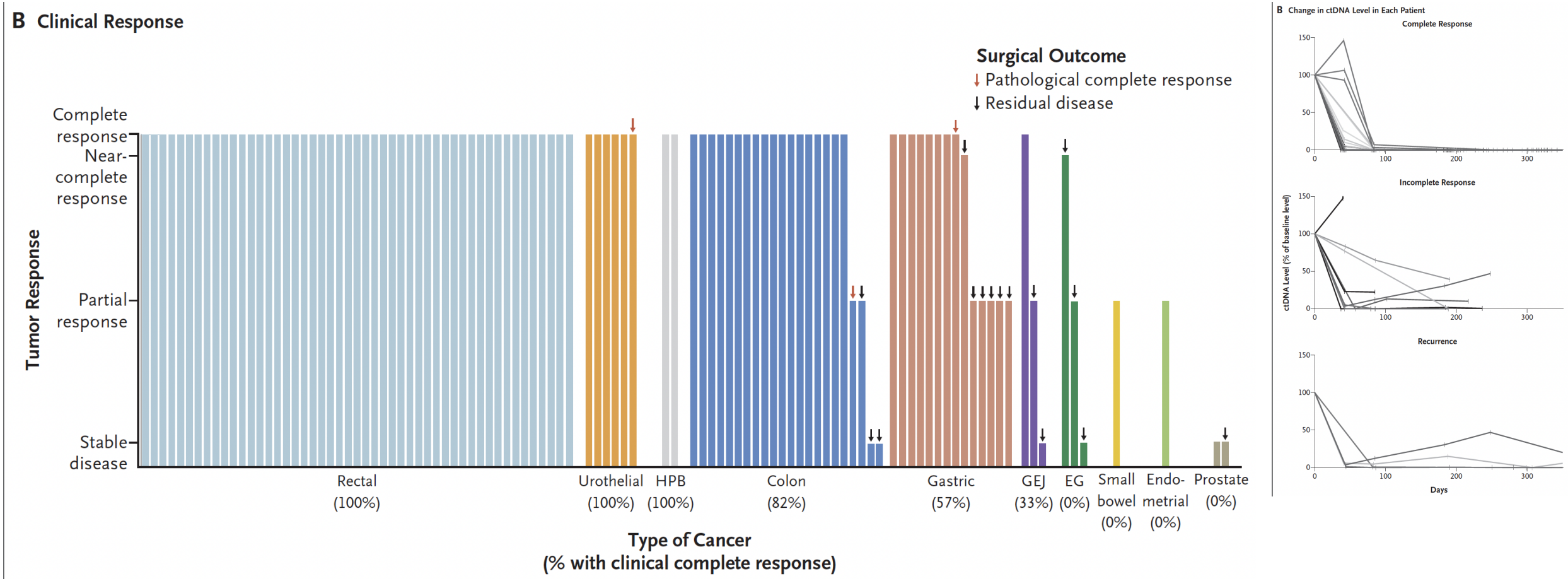
Non operative management of mismatch repair deficient tumors

Neoadjuvant dostarlimab for locally advanced mismatch repair deficient cancers could eliminate the need for surgical resection, regardless of tumor type



Cercek A, et al. *N Engl J Med*. 2025 Jun 19;392(23):2297-2308

2025 treatment landscape for MIBC

- pCR is largely prognostic across trials and tumor types
- Lower % of high-risk pathological features is observed in IO or IO+chemo vs control arms, suggesting a contribution of neoadjuvant part
- The decrease % of ctDNA suggests a contribution of RC to the overall benefit

Key questions remain unanswered with current studies:

- What is the prognostic difference between pCR induced by IO alone vs IO+chemo?
- Can pCR achieved after neoadjuvant IO be used to omit adjuvant IO across tumor types
- What is the contribution of organ-sparing treatments (reTURBT vs chemoRT) on the efficacy of perioperative IO

2025 treatment landscape for MIBC

Neoadjuvant-Perioperative Therapy

- Novel chemo + I-O regimens will become the new SOC
- ADC + I-O trials may further change the therapeutic paradigm
- **Patients have raised the bar for therapeutic success: removing the surgical part of perioperative studies is now a required goal**

Adjuvant Therapy:

- What are important patient discussion points if/when initiating adjuvant immune-checkpoint inhibitor therapy?
- What AEs do you and your team look out for and when should patients call in?
- Perceived missed opportunities: implications of metastatic disease in the EV+Pembro era weight heavily

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