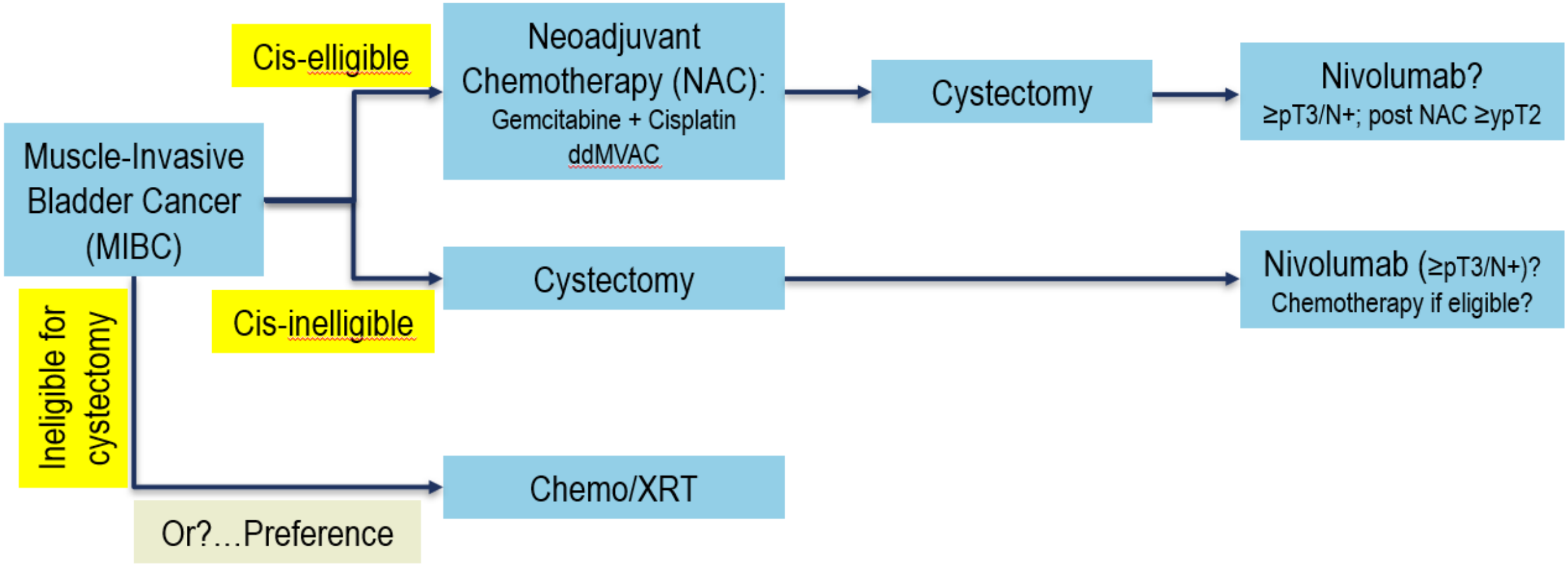
Peri-Operative Therapy in Urothelial Carcinoma

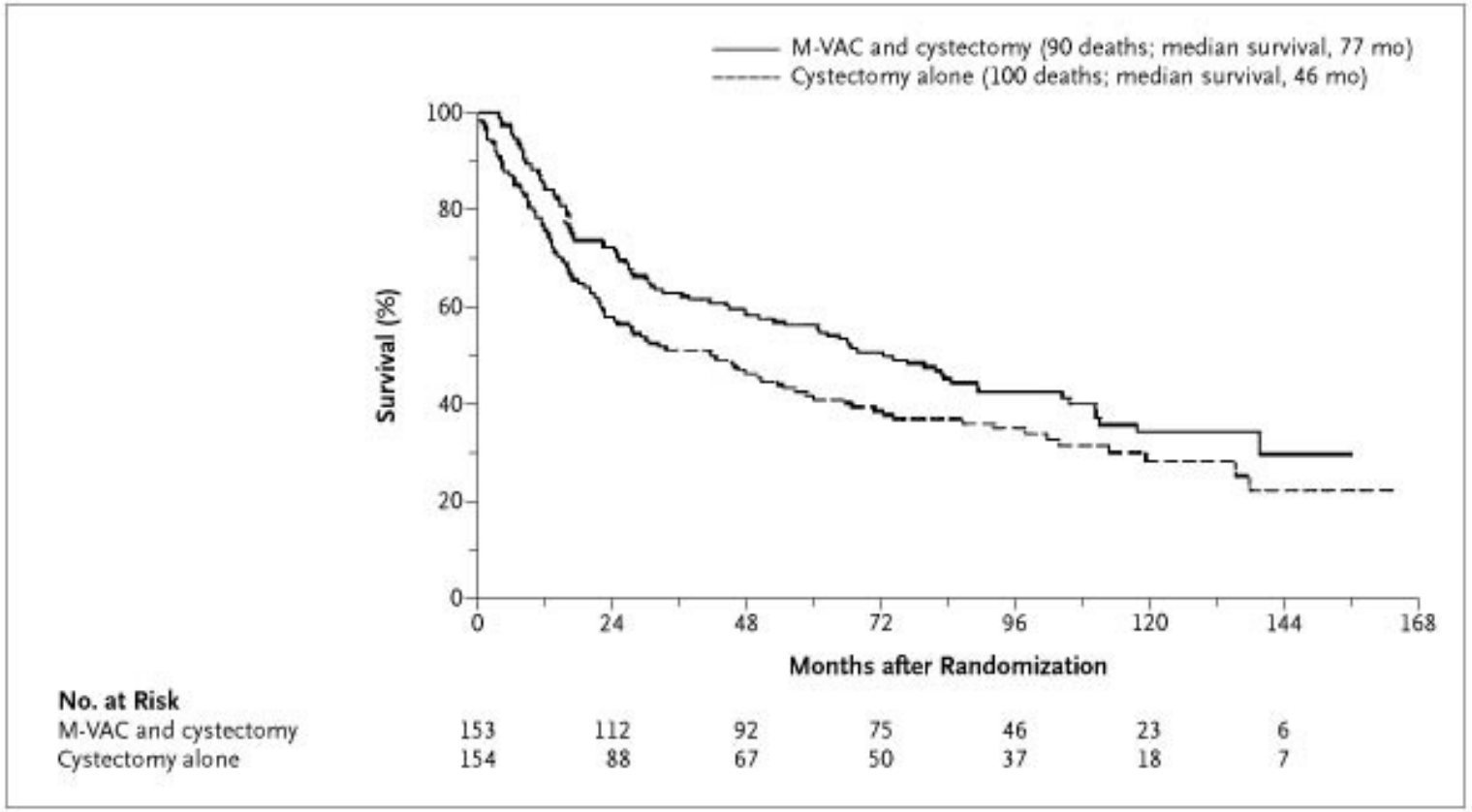
Benjamin Garmezy, MD
Associate Director of Genitourinary Research, Sarah Cannon Research Institute
GU Medical Oncologist, SCRI Oncology Partners, Nashville TN

March 22nd, 2025

SCRI Sarah Cannon Research Institute



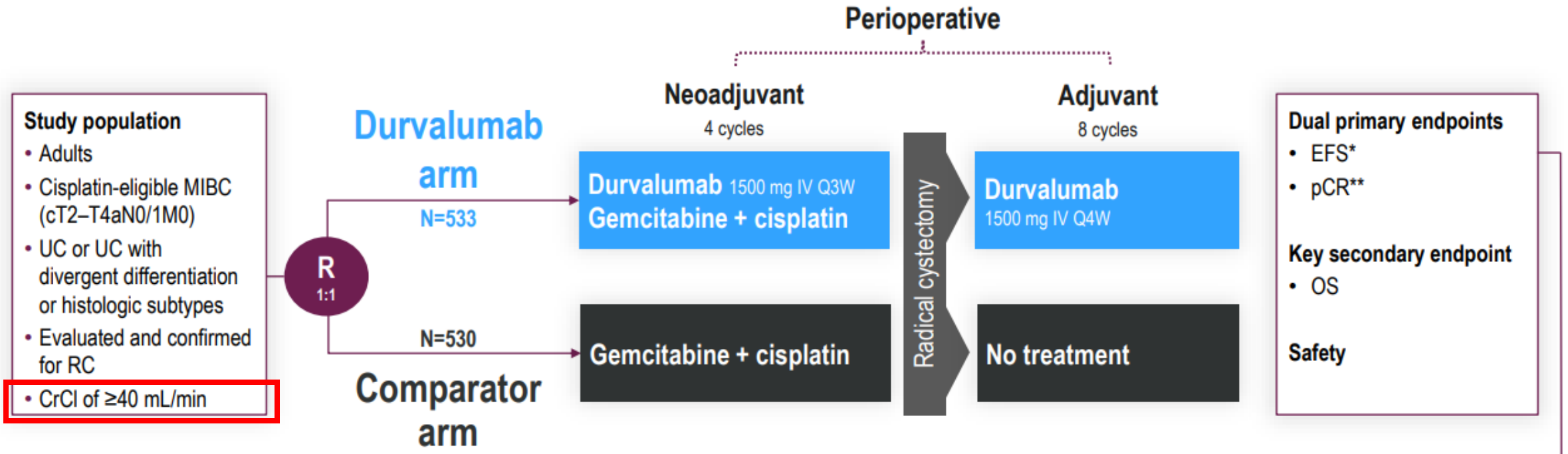
Neoadjuvant Platinum Chemotherapy



Risk of death reduced by 33% with addition of MVAC to cystectomy

Grossman et al, NEJM 2003

NIAGRA: Gem/Cis/Durvalumab vs Gem/Cis



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

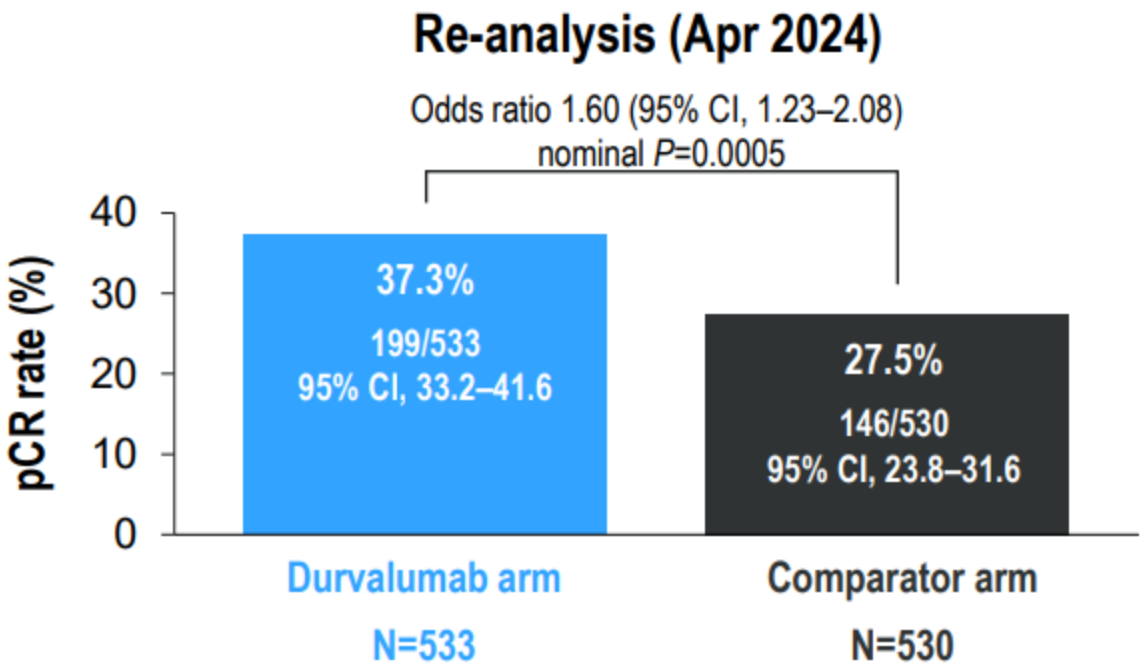
CrCl ≥40–<60 mL/min: Split-dose cisplatin 35 mg/m^2 + gemcitabine 1000 mg/m^2 Days 1 and 8, Q3W for 4 cycles

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

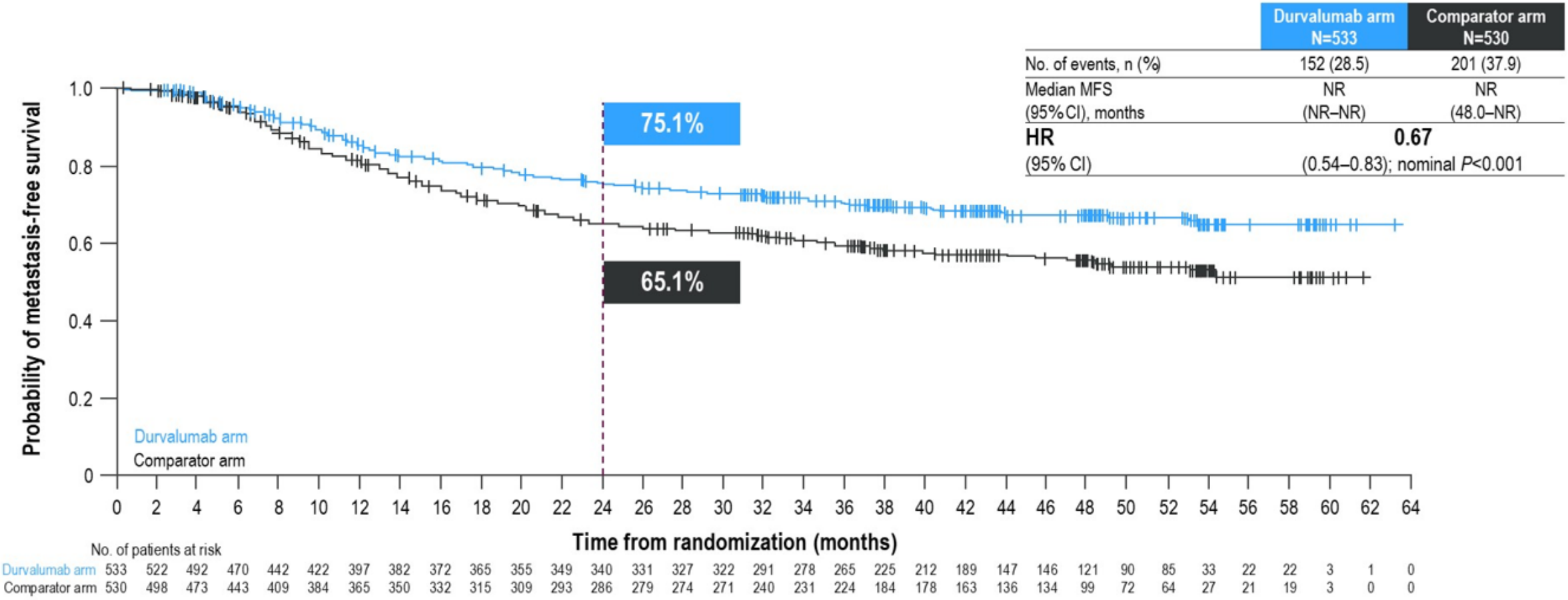
Powels et al, ESMO 2024

NIAGRA: Gem/Cis/Durvalumab vs Gem/Cis



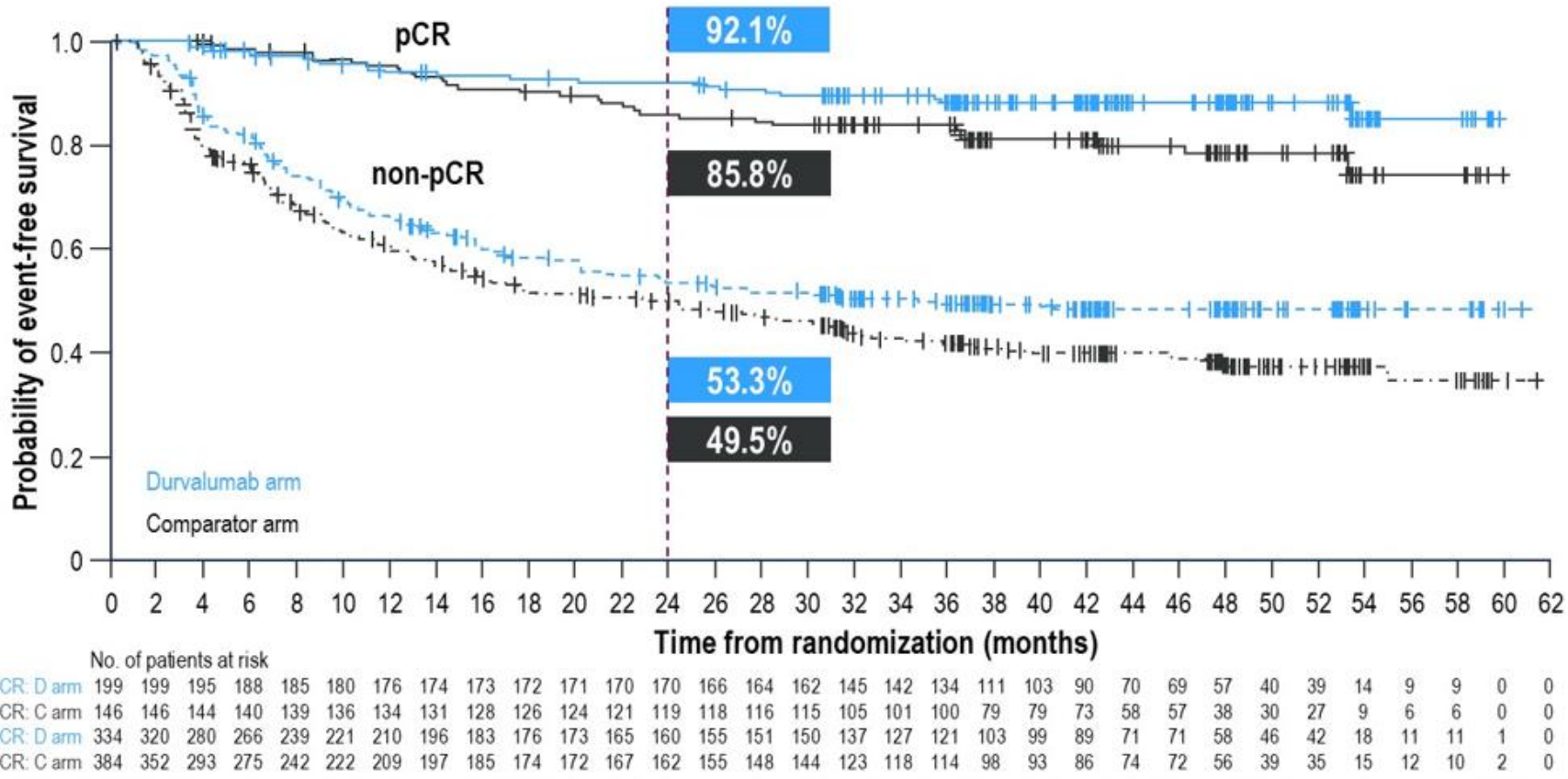
Powels et al, ESMO 2024

NIAGRA: Gem/Cis/Durvalumab vs Gem/Cis



Data cutoff Apr 29, 2024. Metastasis-free survival is defined as the time from date of randomization until the first recognition of distant metastases or death, whichever occurs first. Tick marks indicate patients with censored data. CI, confidence interval; D, durvalumab; HR, hazard ratio; ITT, intent-to-treat population; MFS, metastasis-free survival; NAC, neoadjuvant chemotherapy; NR, not reached.

NIAGRA: Gem/Cis/Durvalumab vs Gem/Cis



pCR

	Durvalumab N=199	Comparator N=146
No. events, n (%)	23 (12)	29 (20)
Median EFS (95% CI), months	NR (NR–NR)	NR (NR–NR)
EFS HR (95% CI)	**0.58** (0.332–0.999)	

non-pCR

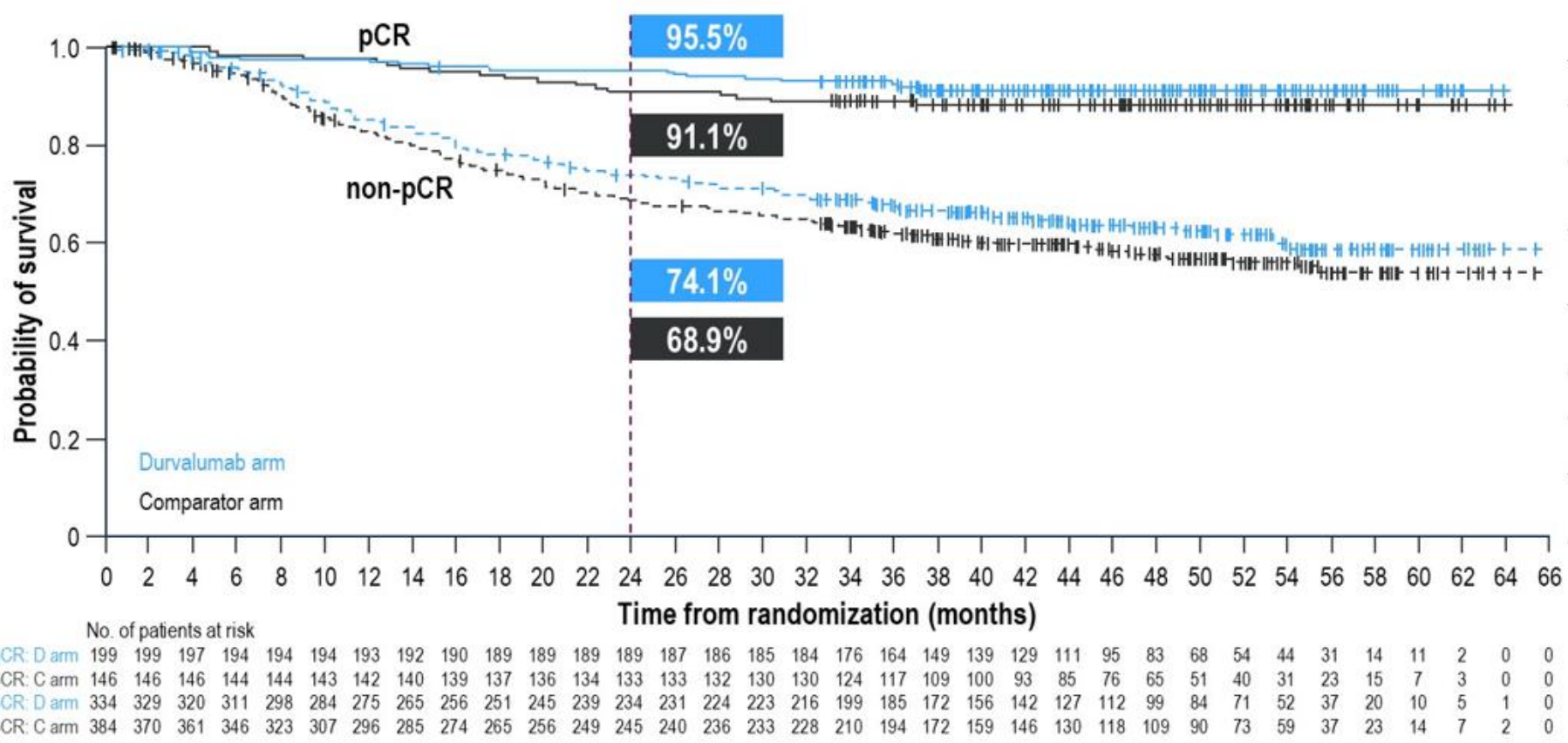
	Durvalumab N=334	Comparator N=384
No. events, n (%)	164 (49)	217 (57)
Median EFS (95% CI), months	34.7 (20.5–NR)	22.8 (15.5–30.6)
EFS HR (95% CI)	**0.77** (0.631–0.948)	

ITT

EFS HR (95% CI)	**0.68** (0.56–0.82)

Data cutoff Apr 29, 2024. Exploratory post-hoc analysis. Event-free survival by blinded independent central review or by central pathology review. Tick marks indicate patients with censored data. C, comparator; D, durvalumab; EFS, event-free survival; HR, hazard ratio; ITT, intent-to treat population; NAC, neoadjuvant chemotherapy; pCR, pathological complete response.

NIAGRA: Gem/Cis/Durvalumab vs Gem/Cis



pCR

	Durvalumab N=199	Comparator N=146
No. deaths, n (%)	17 (9)	17 (12)
Median OS (95% CI), months	NR (NR–NR)	NR (NR–NR)
OS HR (95% CI)	**0.72 (0.367–1.426)**	

non-pCR

	Durvalumab N=334	Comparator N=384
No. deaths, n (%)	119 (36)	152 (40)
Median OS (95% CI), months	NR (NR–NR)	NR (53.9–NR)
OS HR (95% CI)	**0.84 (0.660–1.068)**	

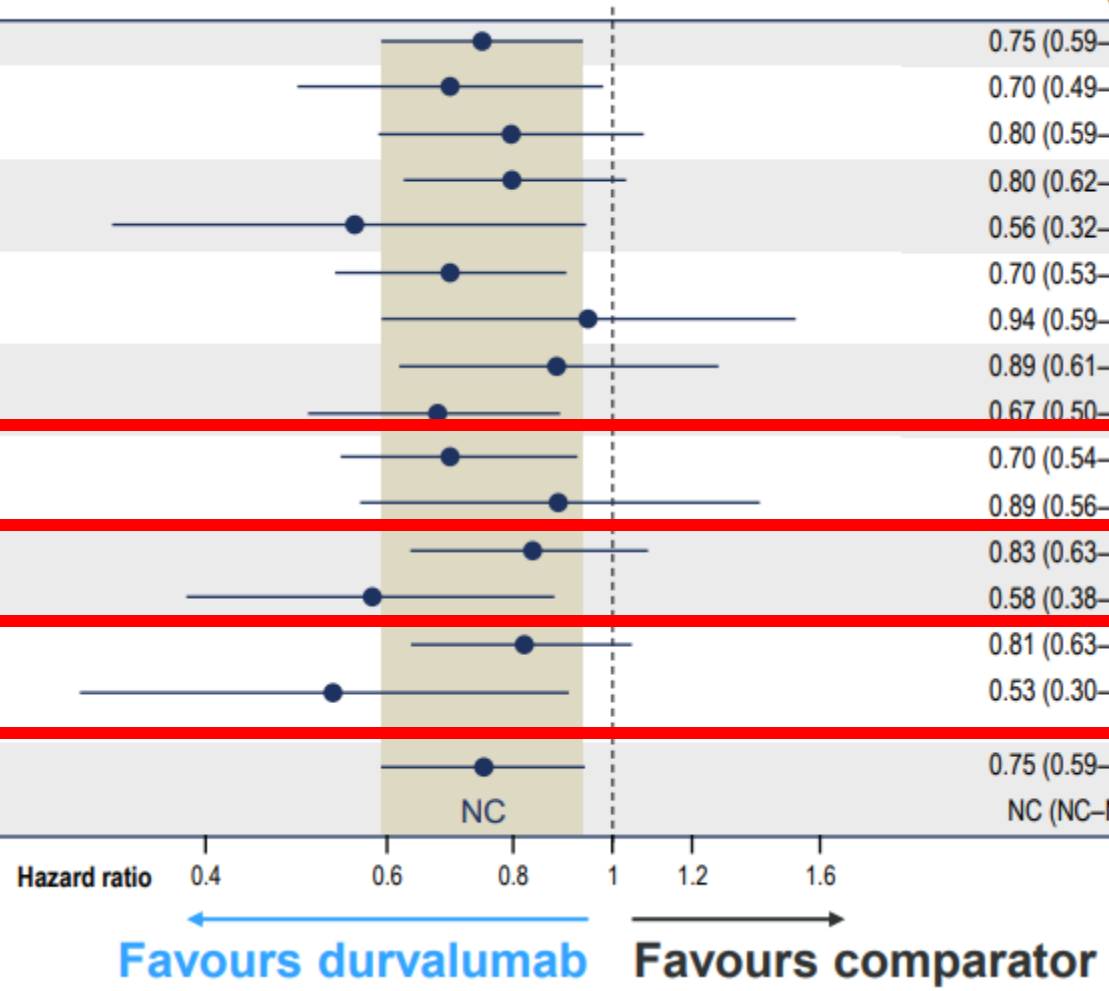
ITT

OS HR (95% CI)	**0.75 (0.59–0.93)**

Data cutoff Apr 29, 2024. Exploratory post-hoc analysis. Tick marks indicate patients with censored data. C, comparator; D, durvalumab; HR, hazard ratio; ITT, intent-to treat; NAC, neoadjuvant chemotherapy; pCR, pathological complete response; OS, overall survival.

NIAGRA: Gem/Cis/Durvalumab vs Gem/Cis

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)

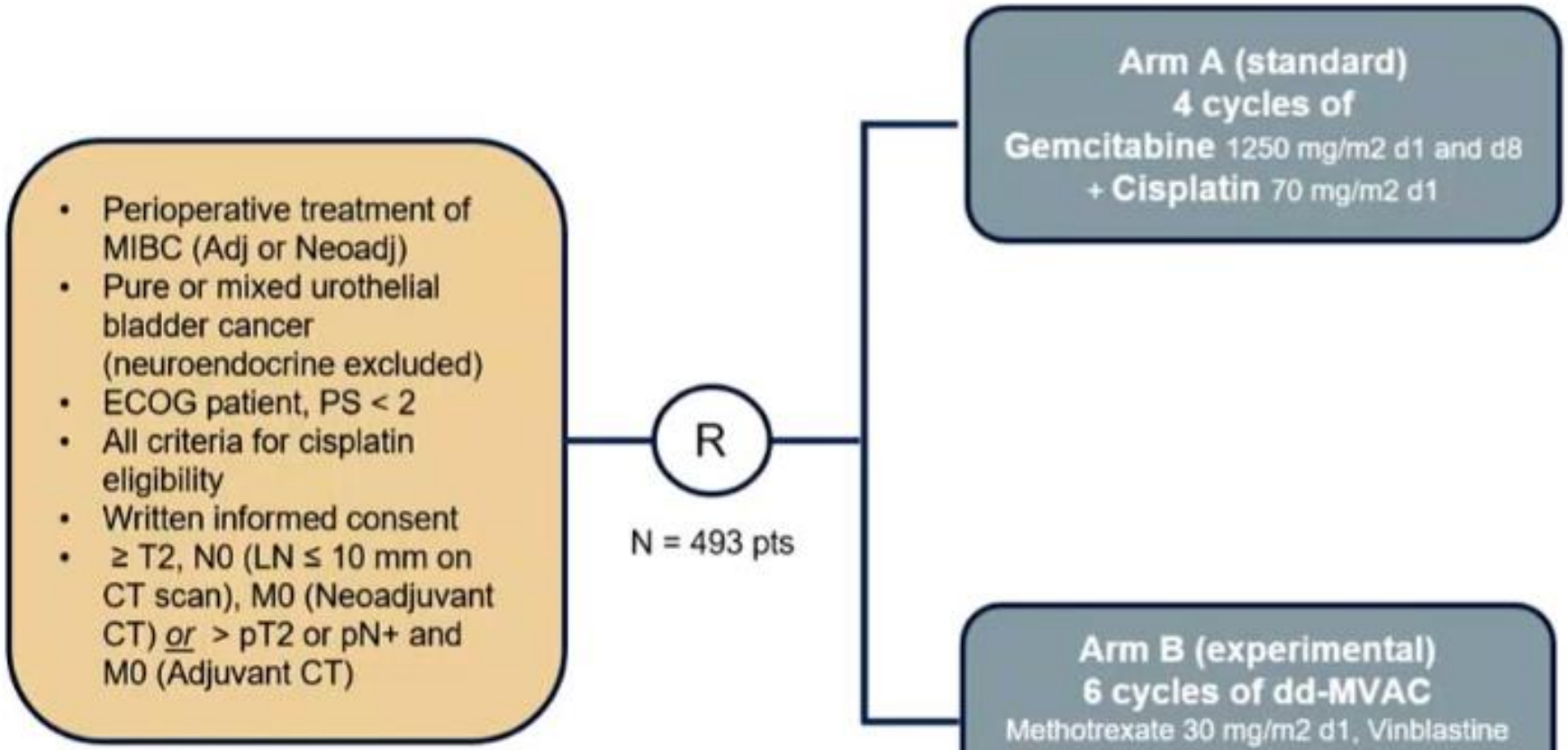


Powels et al, ESMO 2024

NIAGRA: Gem/Cis/Durvalumab vs Gem/Cis

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)**

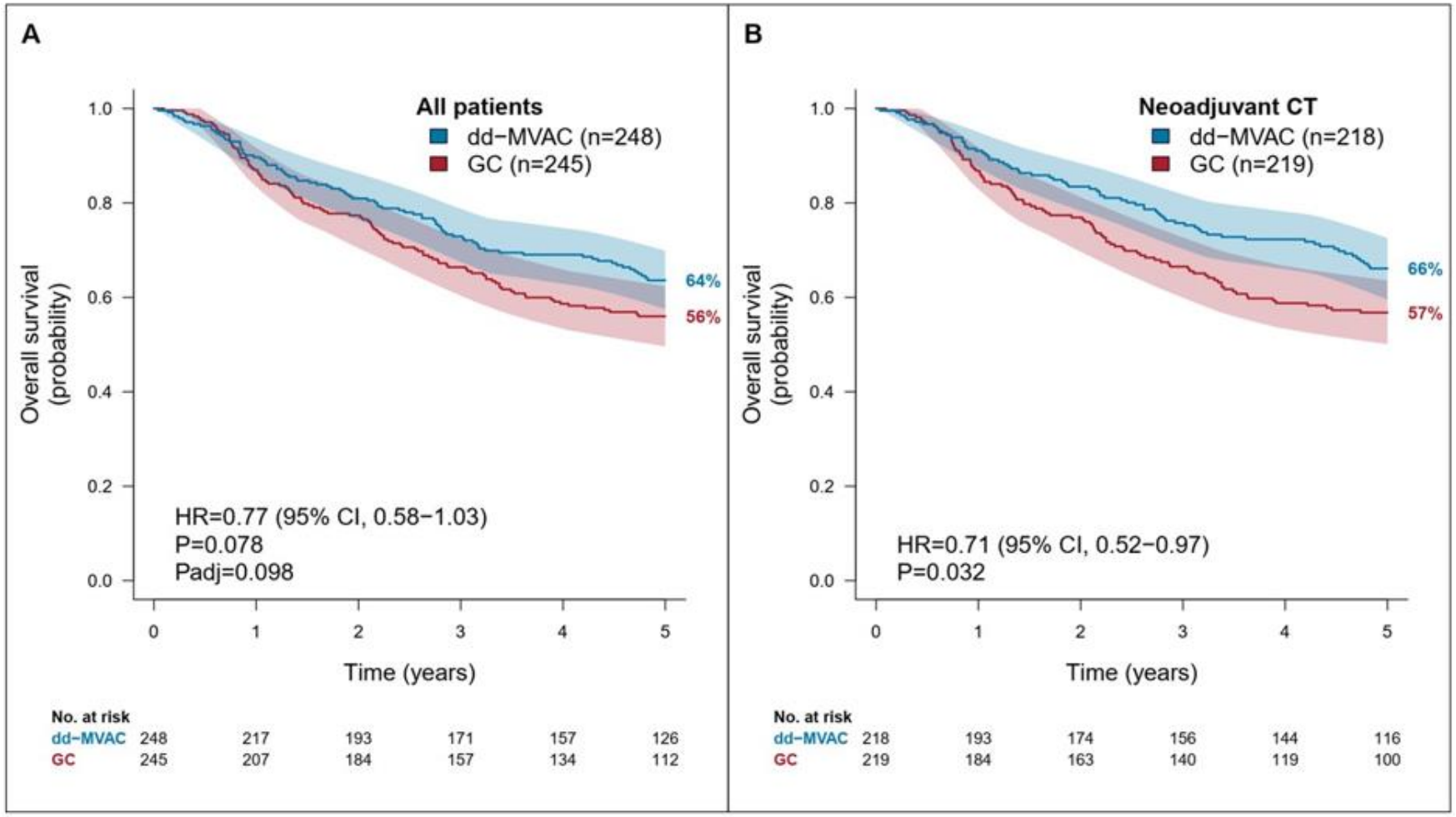
GETUG/AFU V05 VESPER Phase III Trial



- **Primary endpoint: PFS at 3 years**
- **median follow-up 40 months**

Pfister C et al, ASCO 2023

GETUG-AFU VESPER: Perioperative Chemo



Neoadjuvant Chemotherapy (88%)

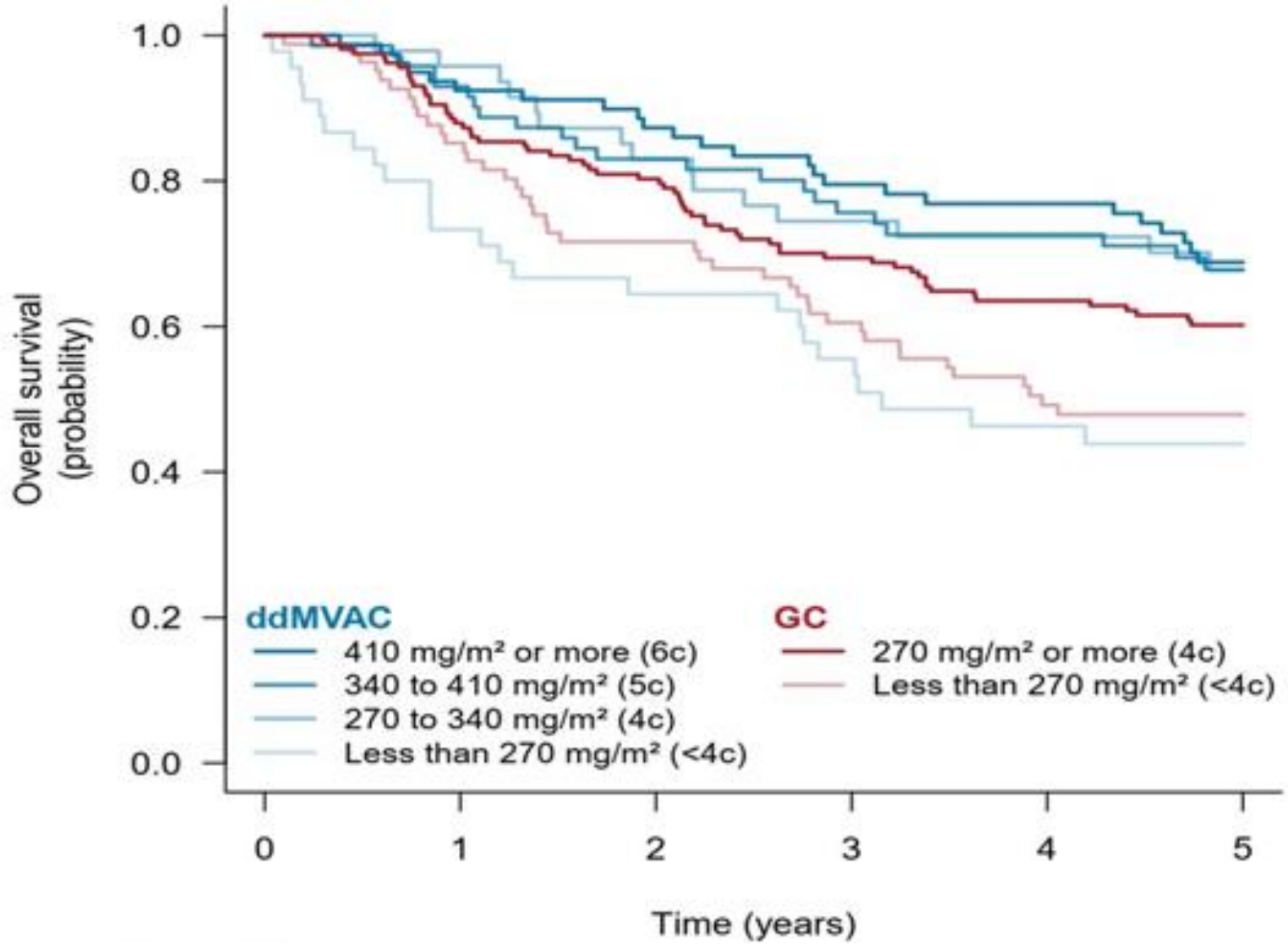
- 84% received GC x 4
- 60% received ddMVAC x6
- Radical cystectomy performed in >90% of cases

Adjuvant Chemo (12%)

- 81% received GC x 4
- 40% received ddMVAC x6

Pfister C et al, ASCO 2023

GETUG-AFU VESPER: Cisplatin Dose



Pfister C et al, ASCO 2023

AURA: Phase II Neoadjuvant Avelumab + Chemo

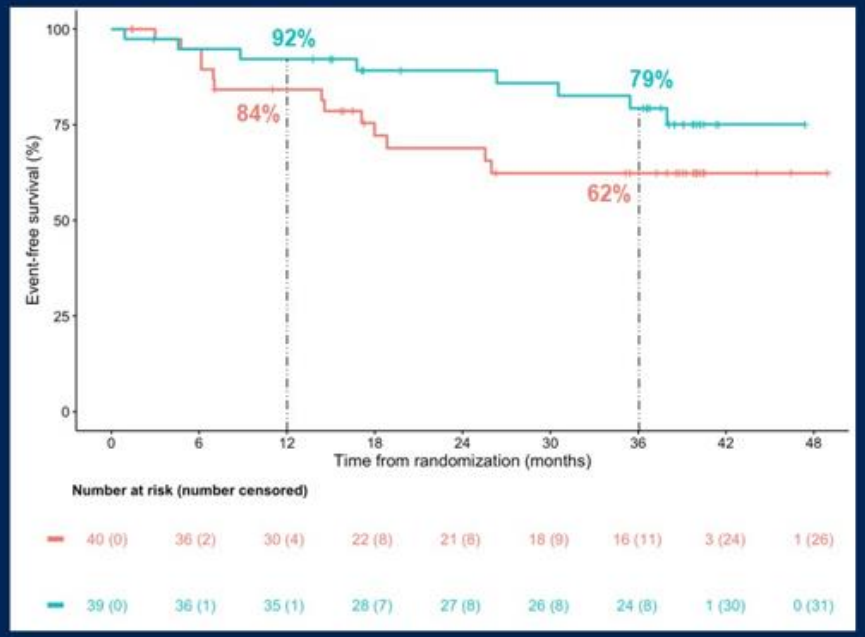
Primary endpoint was pCR

Blanc et al, ASCO 2024

AURA: Phase II Neoadjuvant Avelumab + Chemo

Survival in the **cisplatin-eligible** cohort

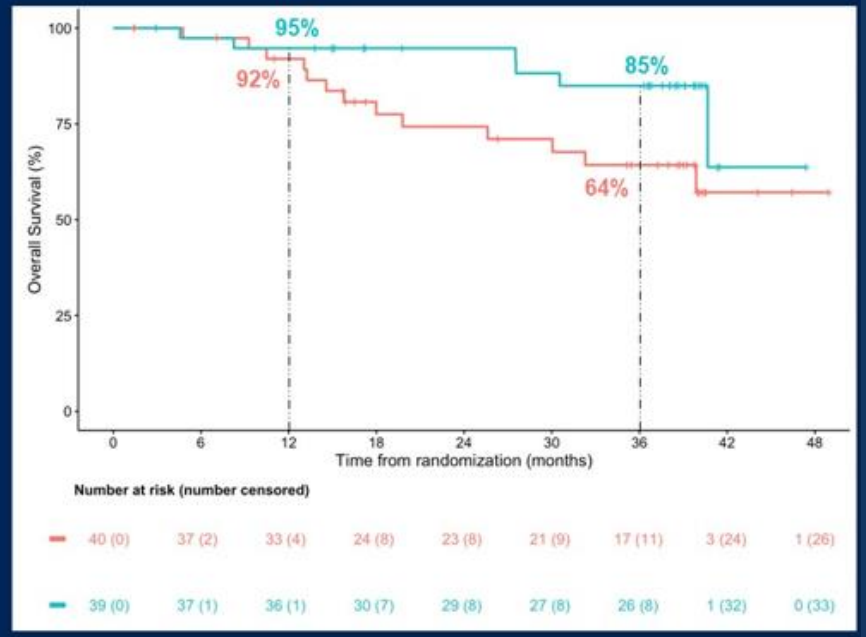
Event-free survival



ddMVAC-A

GC-A

Overall survival



12-month EFS	92% ddMVAC-A 84% GC-A
Preliminary 36-month EFS	79% ddMVAC-A 62% GC-A

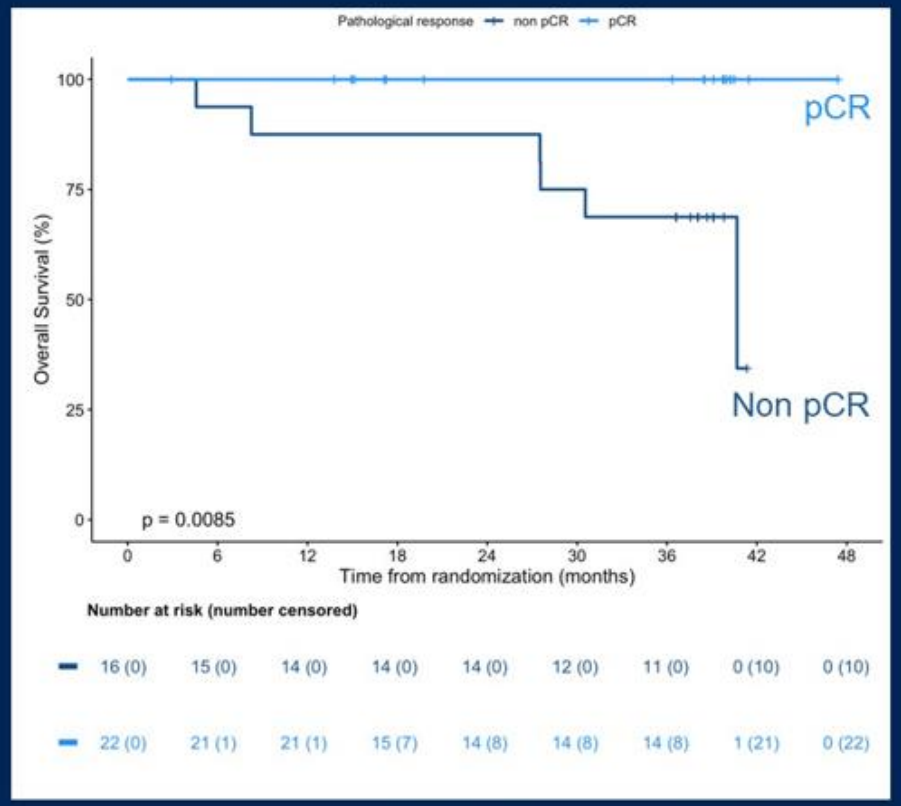
12-month OS	95% ddMVAC-A 92% GC-A
Preliminary 36-month OS	85% ddMVAC-A 64% GC-A

Blanc et al, ASCO 2024

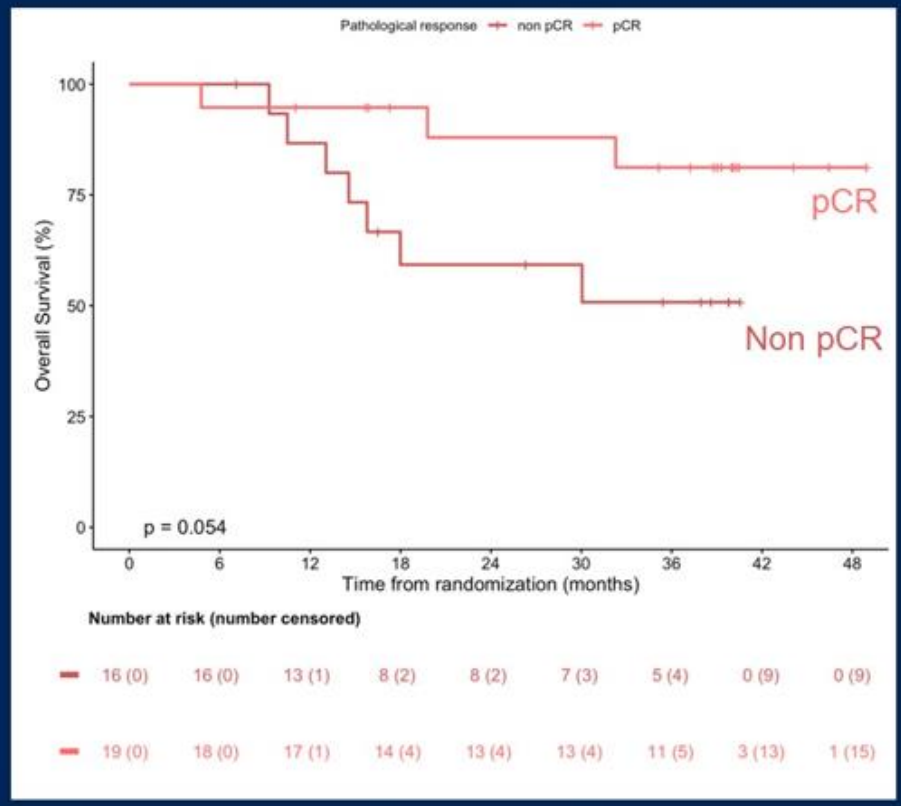
AURA: Phase II Neoadjuvant Avelumab + Chemo

Overall survival in the **cisplatin-eligible** cohort according to pCR

ddMVAC-A arm



GC-A arm



Achieving a **pCR** is associated with **longer overall survival**

Blanc et al, ASCO 2024

Pathologic Complete Response Rates

Trial	Therapy (Cycles)	pCR (%)
ddMVAC	Meta-analysis (3-6)	35.2
Cisplatin/Gemcitabine	Meta-analysis (3-4)	25.1
PURE-01	Pembrolizumab (x3)	42
ABACUS	Atezolizumab (x2)	29
NABUCCO (Cohort 2A)	Nivo 1 mg/kg + Ipi 3 mg/kg (x2)	43
NABUCCO (Cohort 2B)	Nivo 3 mg/kg + Ipi 1 mg/kg (x2)	7
NCT02812420	Durva/Tremi (x2)	37.5
BLASST-2	Durvalumab (x3)	12.5
NIAGRA	Gem/Cis/Durva (x4)	37.3
NIAGRA	Gem/Cis (x4)	27.5

Trial	Therapy (Cycles)	pCR (%)
NCT02989584	Gem/Cis Atezo	44%
BLASST-1	Gem/Cis/Nivo	34%
SAKK06/17	Gem/Cis/Durva	33%
GU14-188 Cohort 1	Gem/Cis/Pembro	44%
NCT03532451	Gem/Pembro	45%
GETUG-AFU V09	ddMVAC/Durva/Tremi	47%
GETUG-AFU V09	ddMVAC/Durva	49%

Grivas et al, ESMO 2024; Powles et al, ESMO 2024; Lee et al, Cancers 2022; Chung et al, Cancers 2021; Wei et al, ASCO GU 2020; Gao et al, Nat Med 2020; Powles et al, ASCO 2018; Necchi et al, JCO 2018; Van Dorp et al, Nat Med, 2023; Thibault et al, ESMO 2023.

ASCO GU 2025: Disitamab vedotin 63.6% (Sheng, ASCO GU 2025)

What about Adjuvant Nivolumab: CM-274

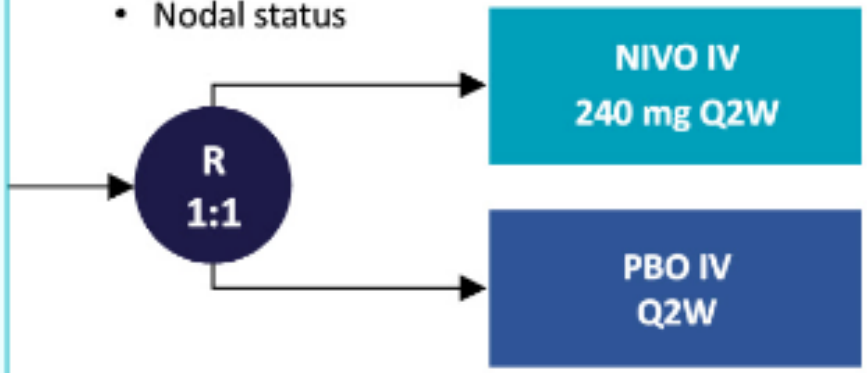
N = 709

Key inclusion criteria

- Patients with ypT2-ypT4a or ypN+ MIUC who had neoadjuvant cisplatin chemotherapy
- Patients with pT3-pT4a or pN+ MIUC without prior neoadjuvant cisplatin chemotherapy and not eligible/refuse adjuvant cisplatin chemotherapy
- Radical surgery within the past 120 days
- Disease-free status within 4 weeks of dosing

Stratification factors

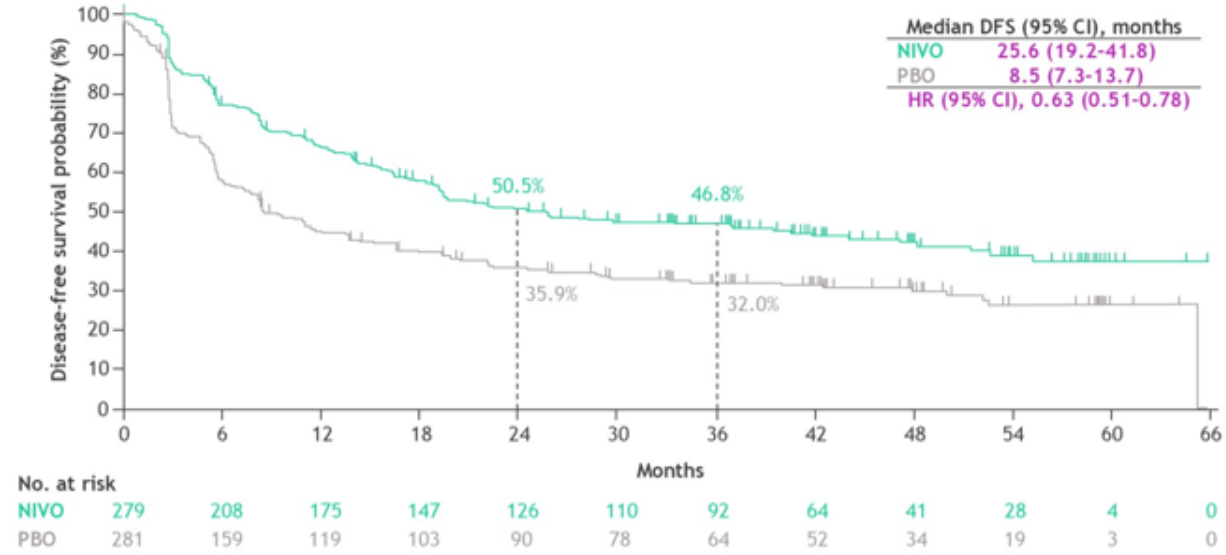
- PD-L1 status (<1% vs ≥1%)[a]
- Prior neoadjuvant cisplatin-based chemotherapy
- Nodal status

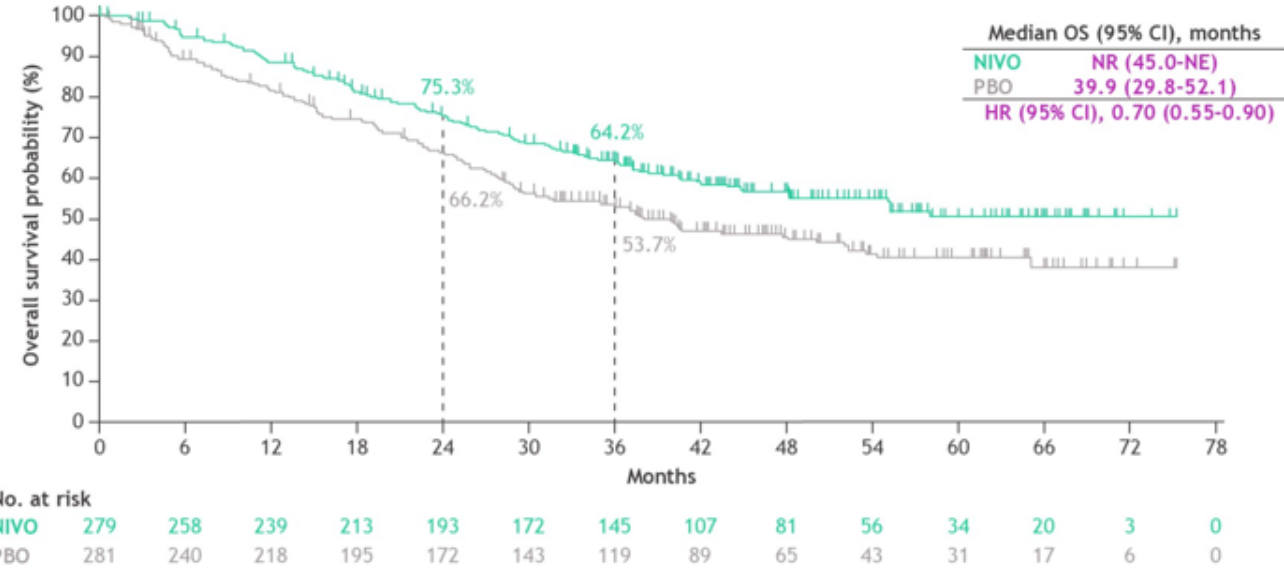


Treat for up to 1 year of adjuvant therapy

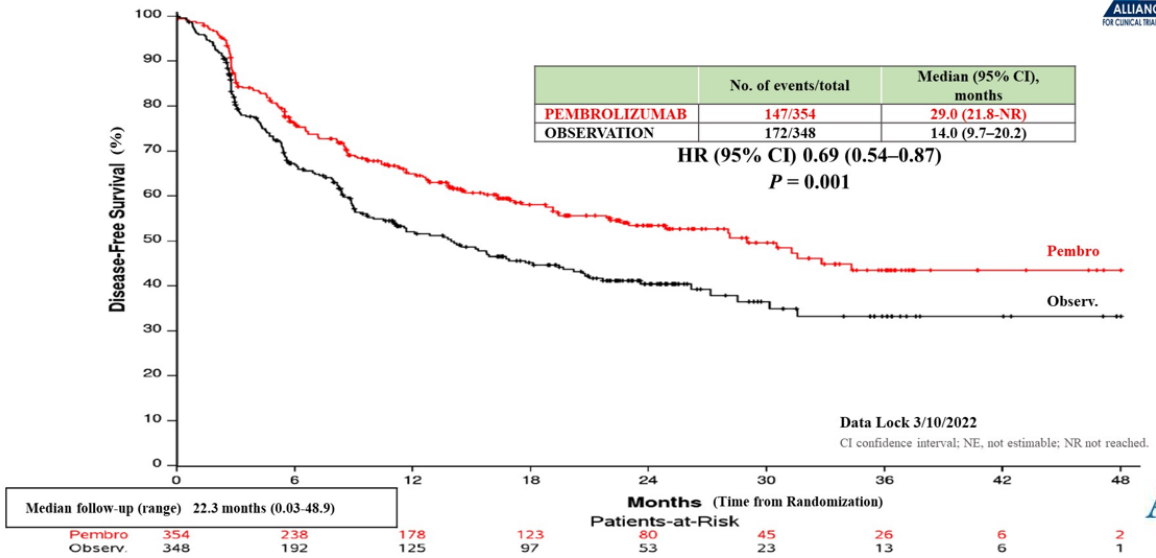
Galsky et al, JCO 2024

What about Adjuvant Nivolumab: CM-274

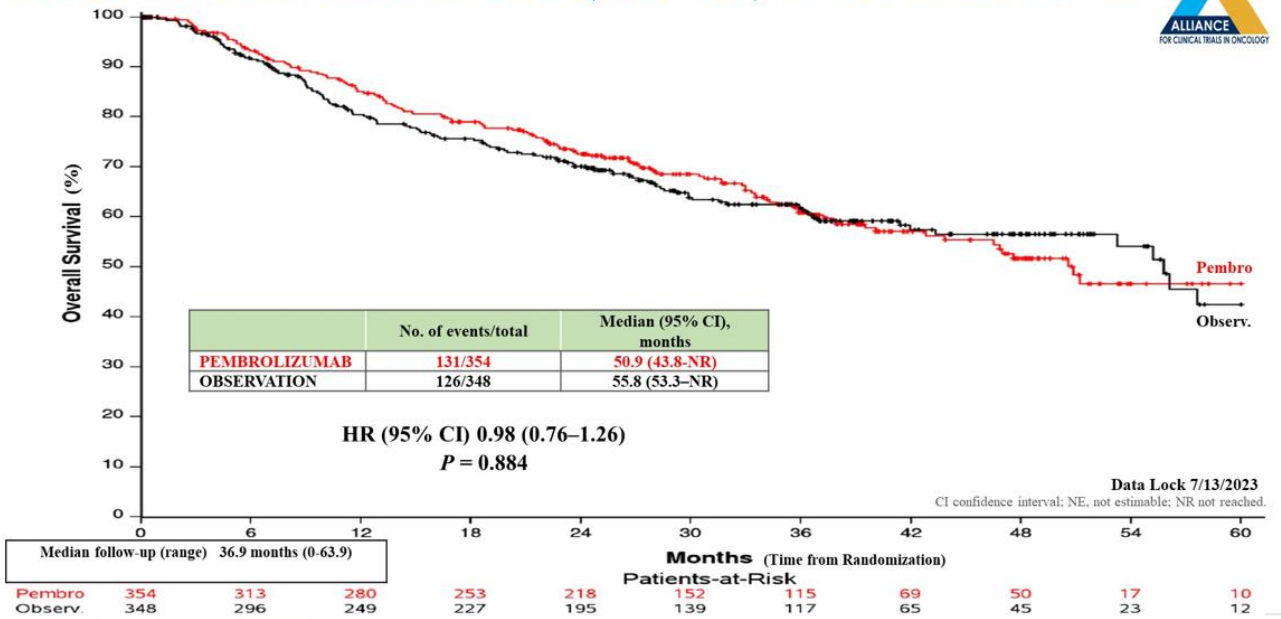




A031501 AMBASSADOR: Disease-Free Survival (ITT)



A031501 AMBASSADOR: (interim) Overall Survival



A.B. Apolo et al. ASCO GU 2024. Abstract #LBA531.

How do we treat CIS-Eligible mUC Patients?

Gemcitabine + Cisplatin + Durvaluamb -> Cystectomy -> Durvalumab (possible to de-escalate? Not yet.)

CIS Eligible with CrCl ≥ 40 ml/min

OR

ddMVAC -> Analyze pathology +/- ctDNA -> Nivolumab

ctDNA to Select Patients for Adjuvant Therapy?

IMvigor010 in MIBC

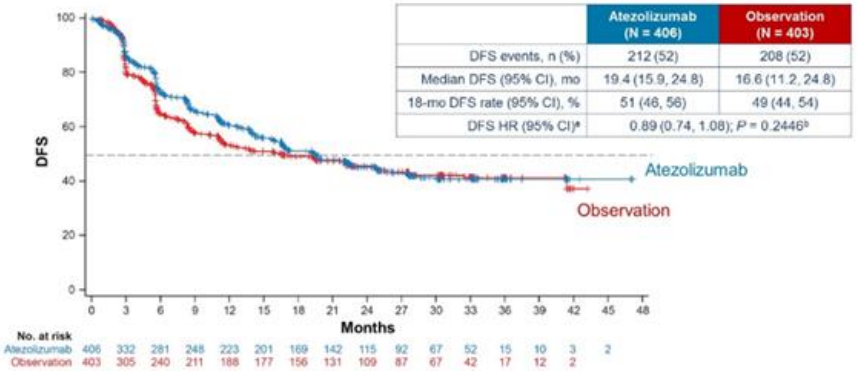
Key eligibility
- High-risk MIUC (bladder or upper tract)
- Radical surgery with lymph node dissection within ≤14 weeks
- Tissue sample for PD-L1 testing

R 1:1

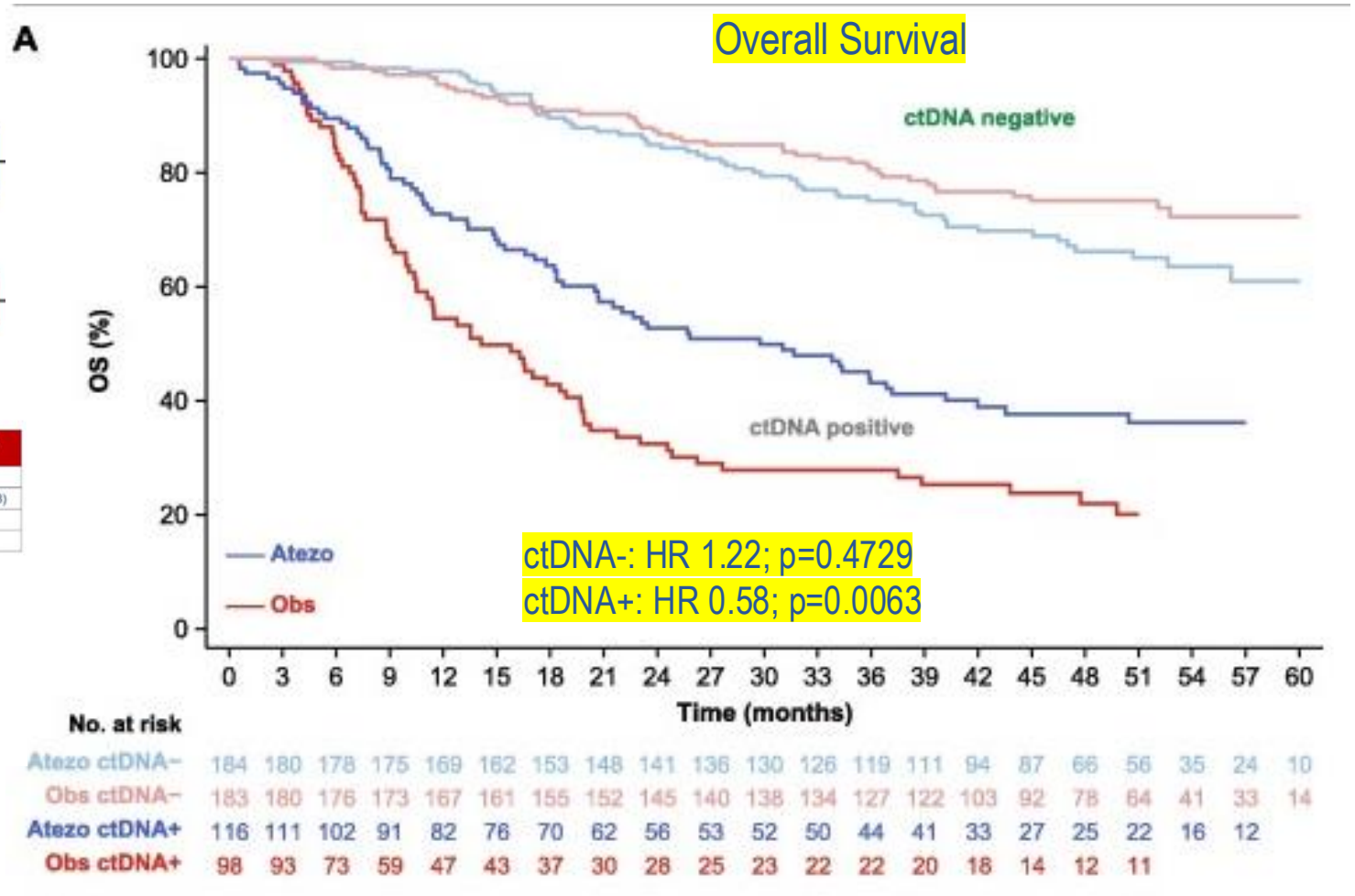
- Atezolizumab 1200 mg q3w *(16 cycles or 1 year)*
- Observation q3w

No crossover allowed

DFS in ITT Population

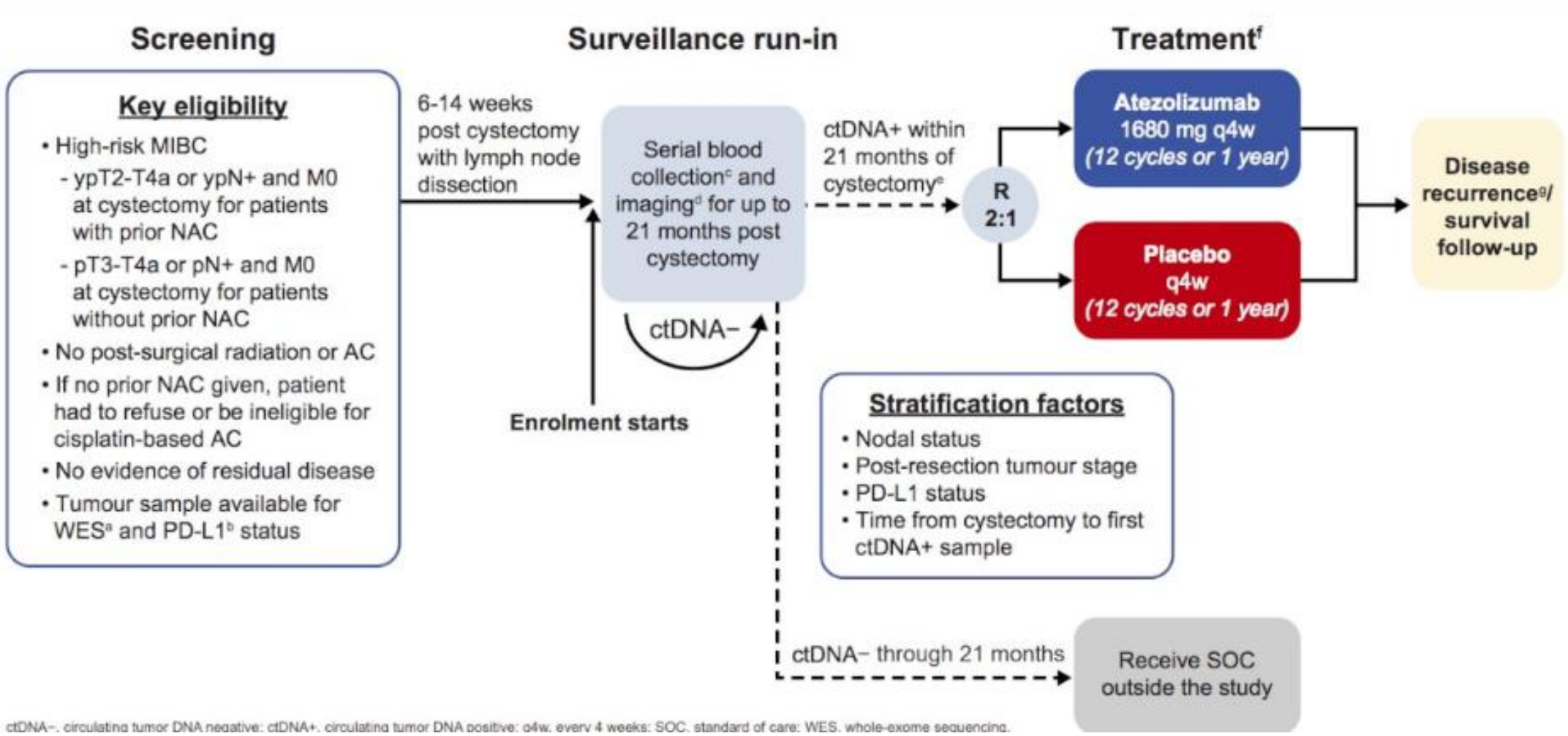


	Atezolizumab (N = 406)	Observation (N = 403)
DFS events, n (%)	212 (52)	208 (52)
Median DFS (95% CI), mo	19.4 (15.9, 24.8)	16.6 (11.2, 24.8)
18-mo DFS rate (95% CI), %	51 (46, 56)	49 (44, 54)
DFS HR (95% CI)[a]	0.89 (0.74, 1.08); *P* = 0.2446[b]	



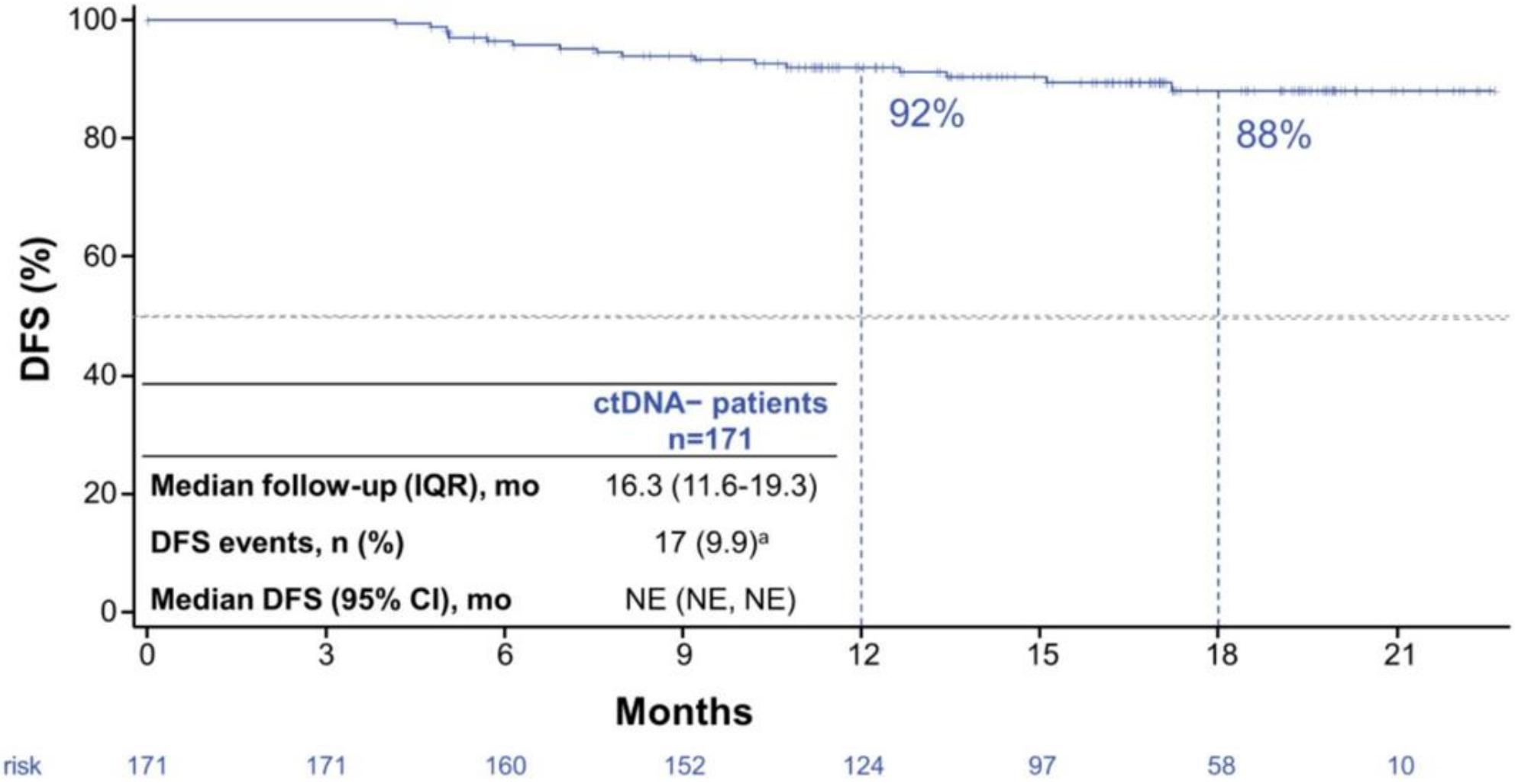
Powles et al, Nature 2021

IMvigor011: Surveillance Group



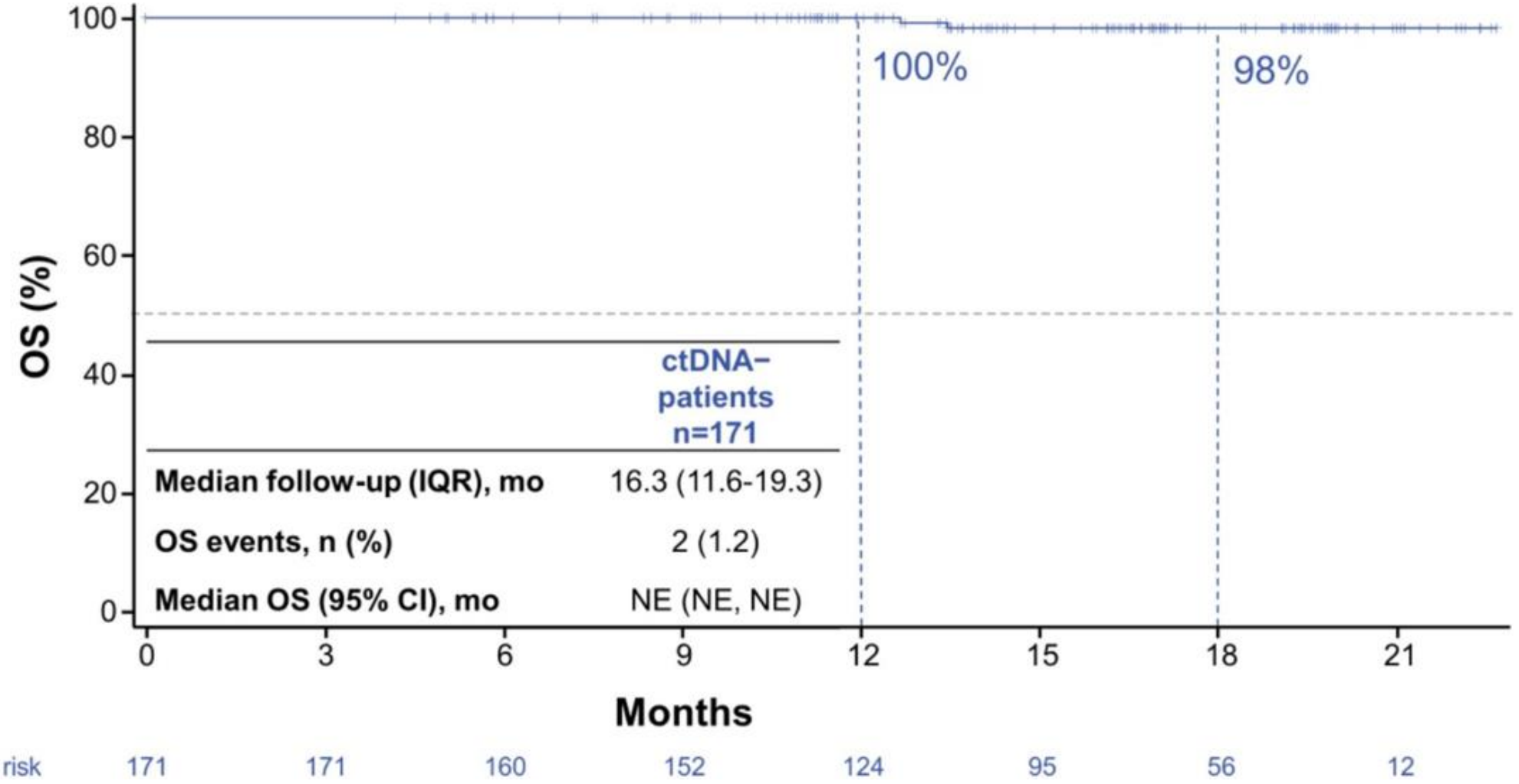
Powles, EAU 2024

IMvigor011: DFS in the ctDNA- Population



Powles, EAU 2024

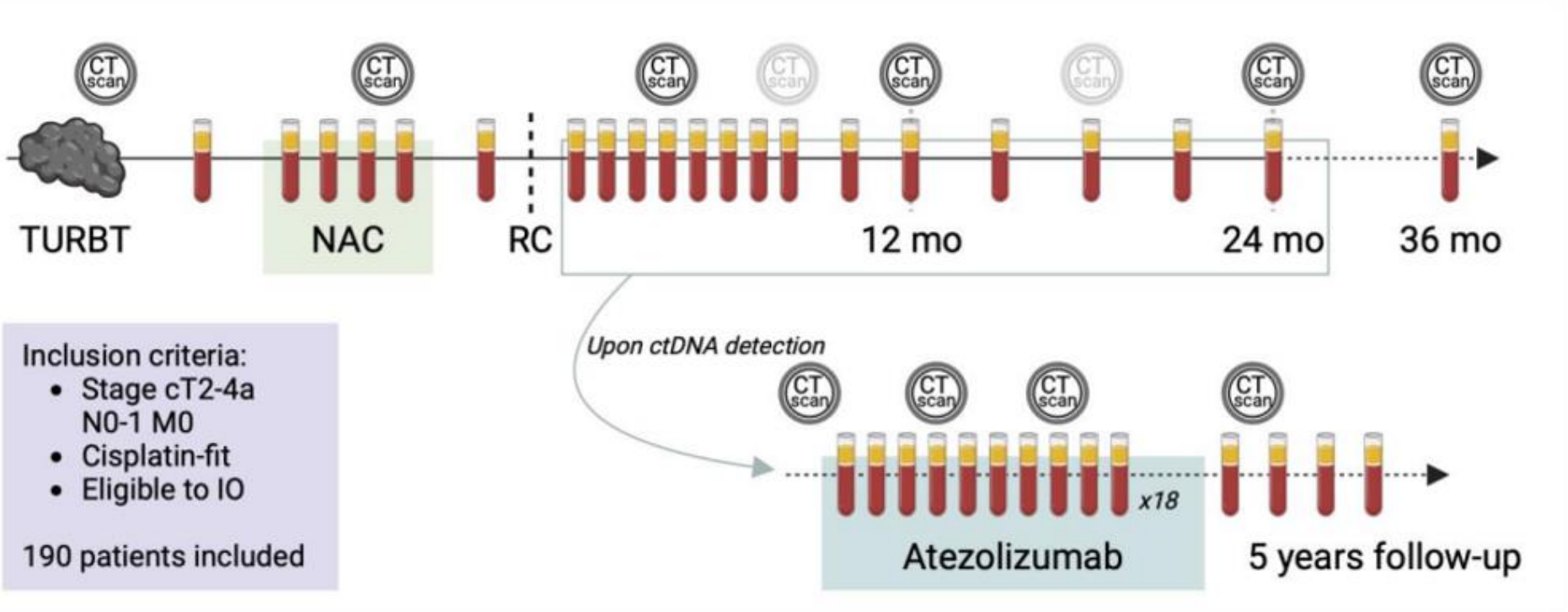
IMvigor011: OS in the ctDNA- Population



Patients who are ctDNA- after surgery can be spared potential toxicity of adjuvant immunotherapy

Powles, EAU 2024

TOMBOLA: Non-Randomized ctDNA Intervention Study

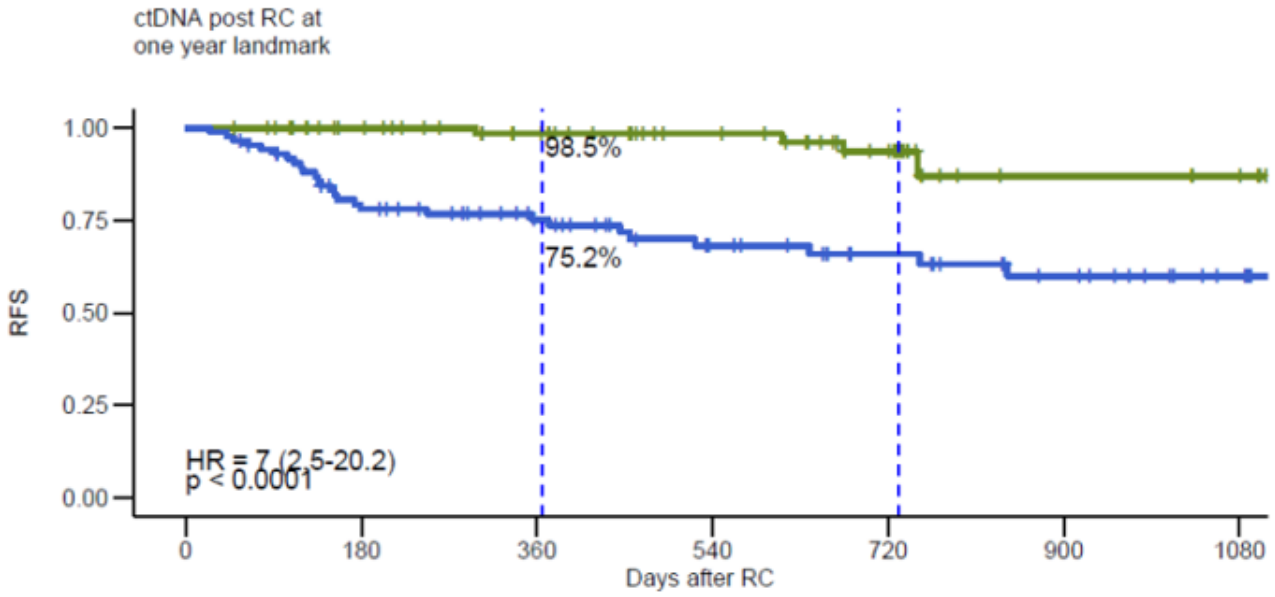


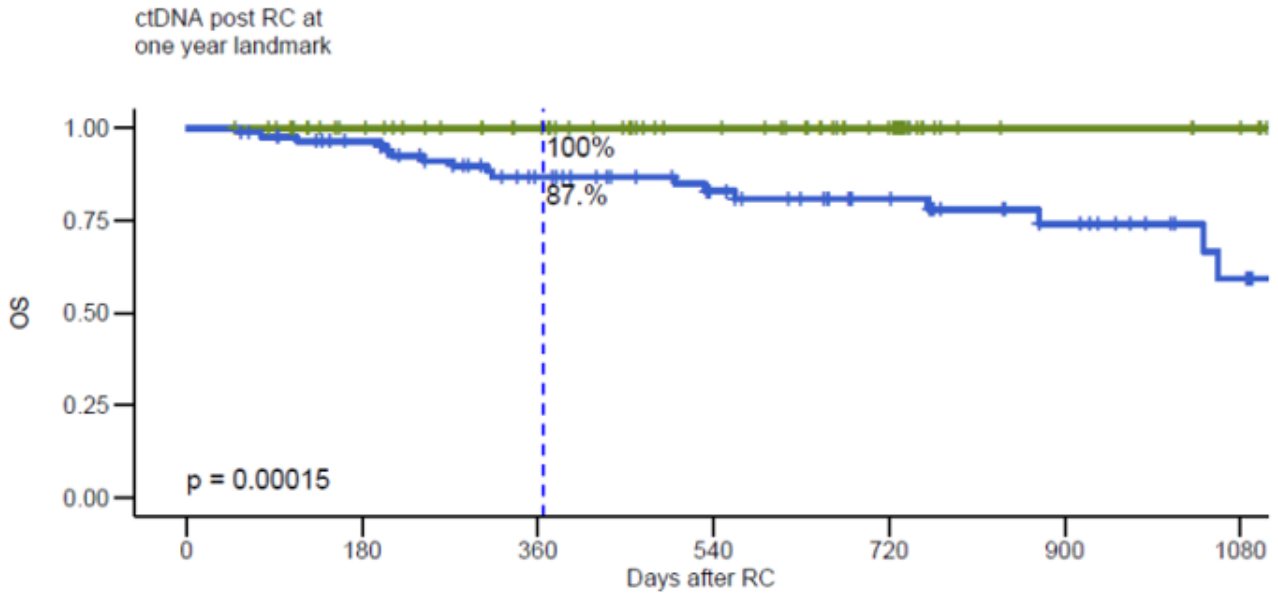
Inclusion criteria:
- Stage cT2-4a N0-1 M0
- Cisplatin-fit
- Eligible to IO

190 patients included

Jensen, ESMO 2024

TOMBOLA: Non-Randomized ctDNA Intervention Study



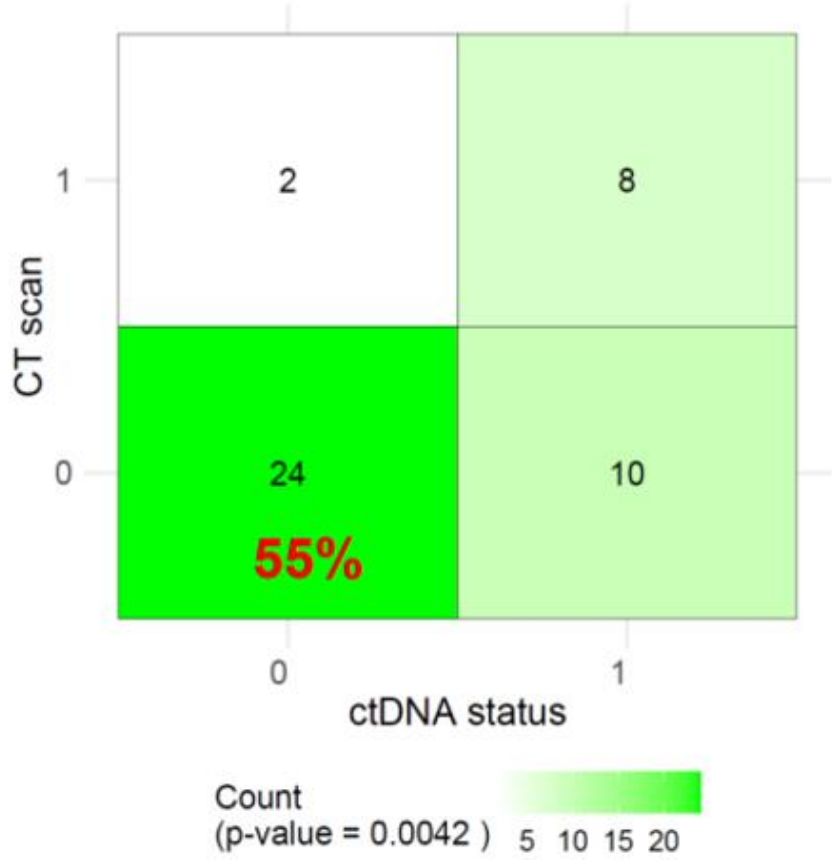


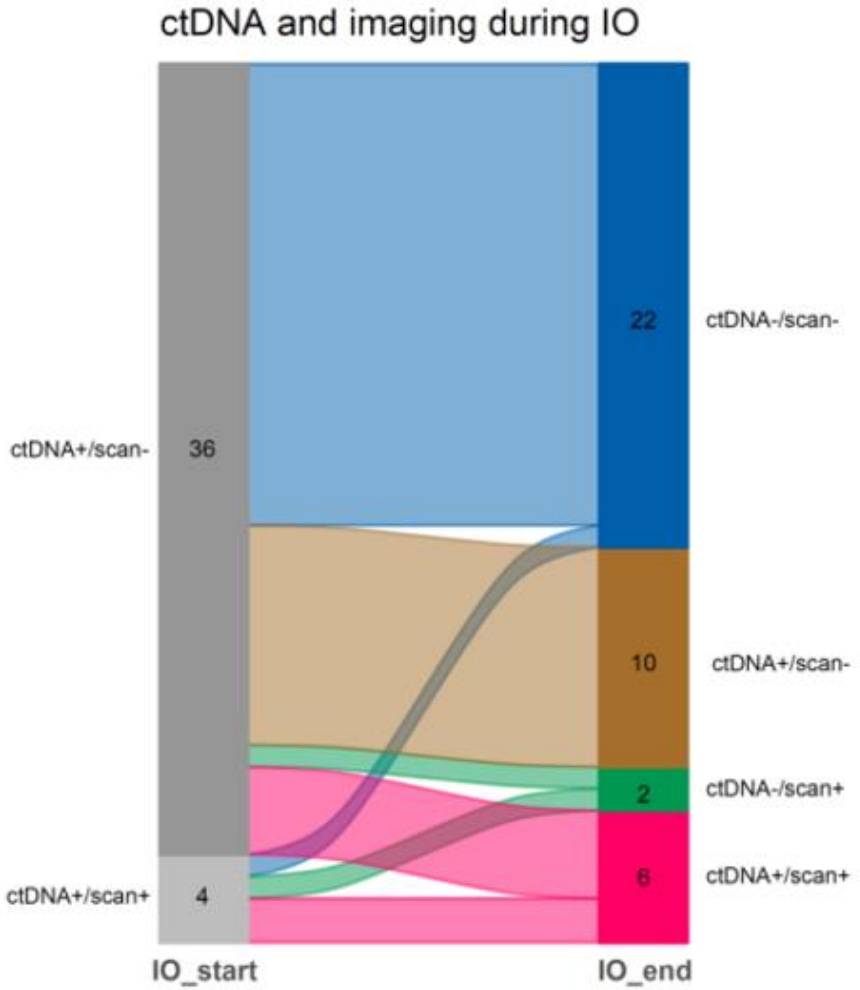
Negative	81	70	59	46	33	7	5
Positive	86	62	48	34	25	17	8

Negative	81	70	60	46	33	7	5
Positive	86	75	55	41	28	18	8

TOMBOLA: Non-Randomized ctDNA Intervention Study

NED (No evidense of disease) (CT and ctDNA-) following immunotherapy





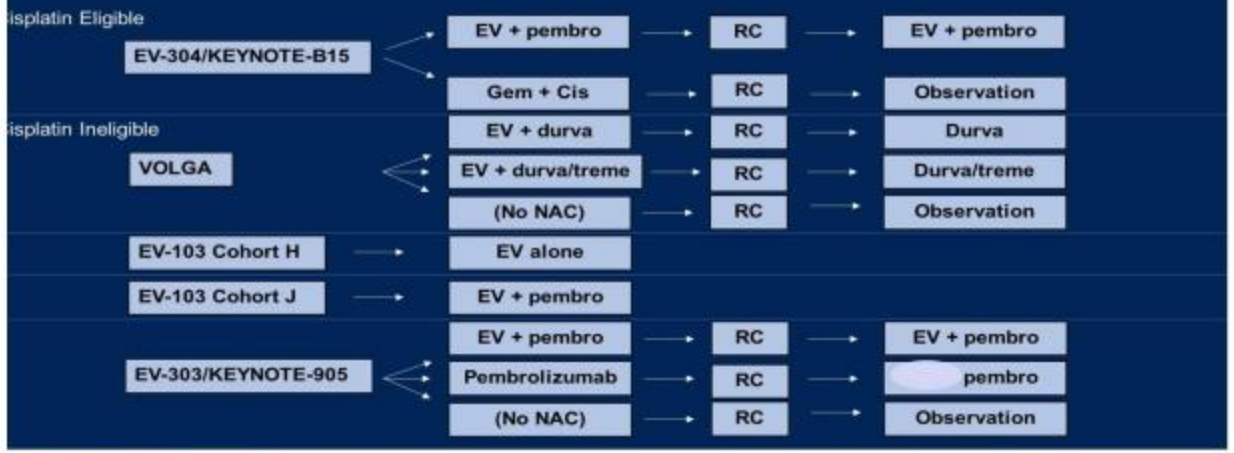
Jensen, ESMO 2024

Randomized trials are investigating combination chemo-immunotherapy in MIBC

Trial	n	Immunotherapy	Chemotherapy	Primary Outcome	Adjuvant?
NIAGARA	1050	Durvalumab	Gemcitabine + Cisplatin	Co: pCR + EFS	Yes – durva arm only
Keynote-866	790	Pembrolizumab	Gemcitabine + Cisplatin	Co: pCR + EFS	Yes – pembro arm only
[redacted]	976	Nivolumab *or* Nivolumab + IDO1-inhibitor linrodostat	Gemcitabine + Cisplatin	Co: pCR + EFS	Yes – nivo arms only

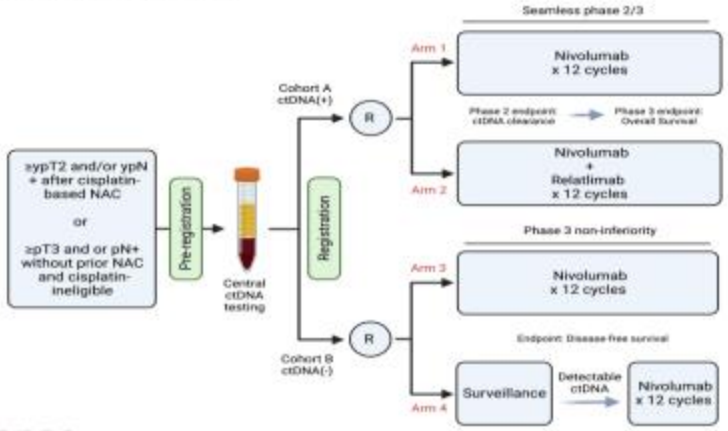
2022 ASCO ANNUAL MEETING #ASCO22 Matthew Milowsky, MD

Enfortumab vedotin as peri-operative therapy in MIBC



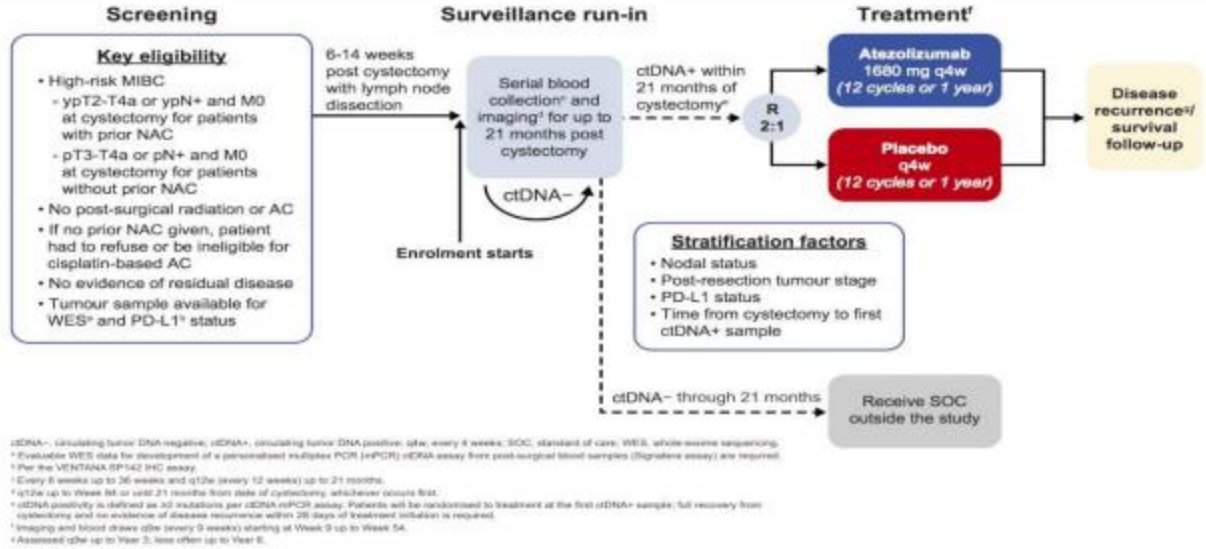
2022 ASCO ANNUAL MEETING #ASCO22 Matthew Milowsky, MD

A032103 (MODERN) Schema



Alliance for Clinical Trials in Oncology

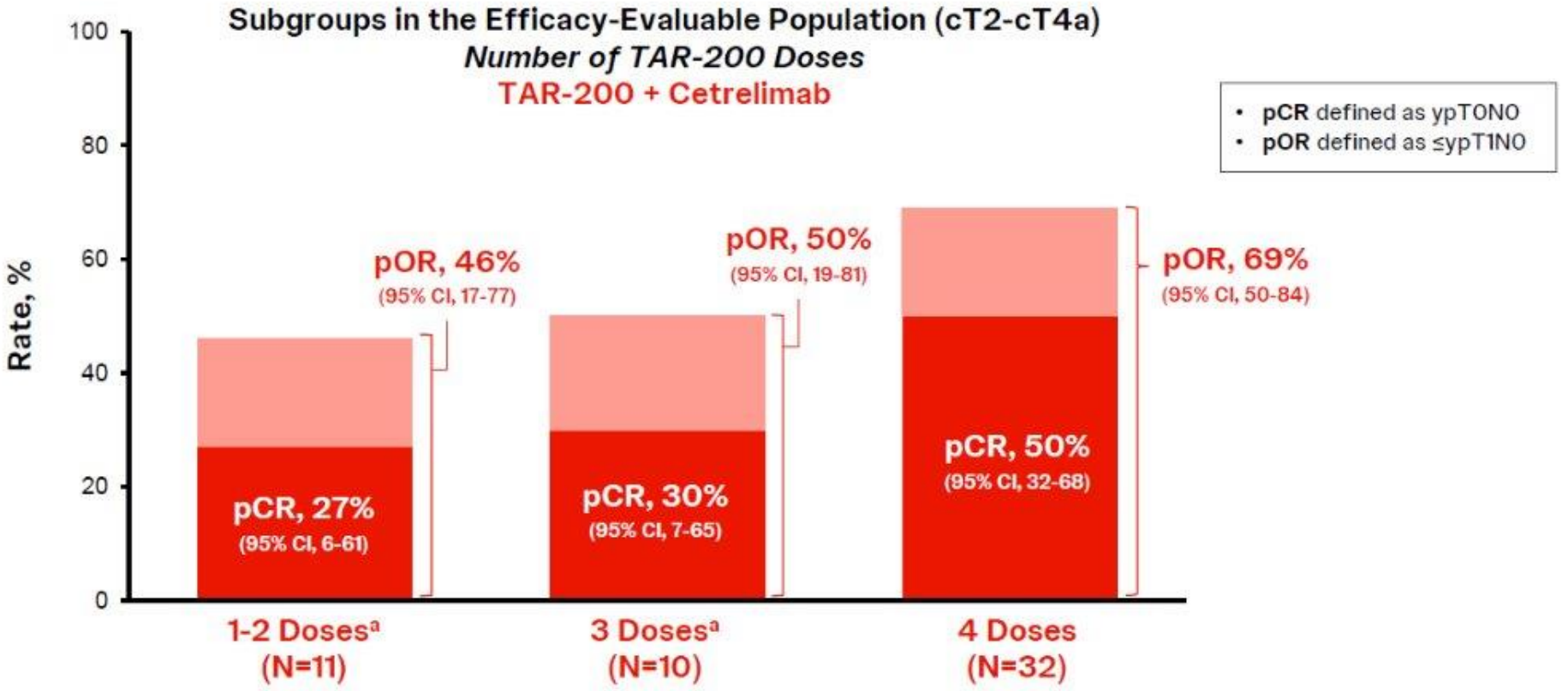
PI: Matthew Galsky, MD



TARIS Platform?

Grivas, ESMO 2024

SunRISe-4: Neoadjuvant TAR 200 + Cetrelimab



Necchi, A. et al. ESMO Congress 2024.

Thank you!

ben.garmezy@scri.com
@BGarmezy