ACTUALIZACIÓN EN
URO-ONCOLOGÍA:
UPDATE **2024**

Madrid, 28 de febrero de 2024

INMUNOTERAPIA EN EL ESCENARIO PERIOPERATORIO DEL CÁNCER DE VEJIGA MÚSCULO-INVASIVO

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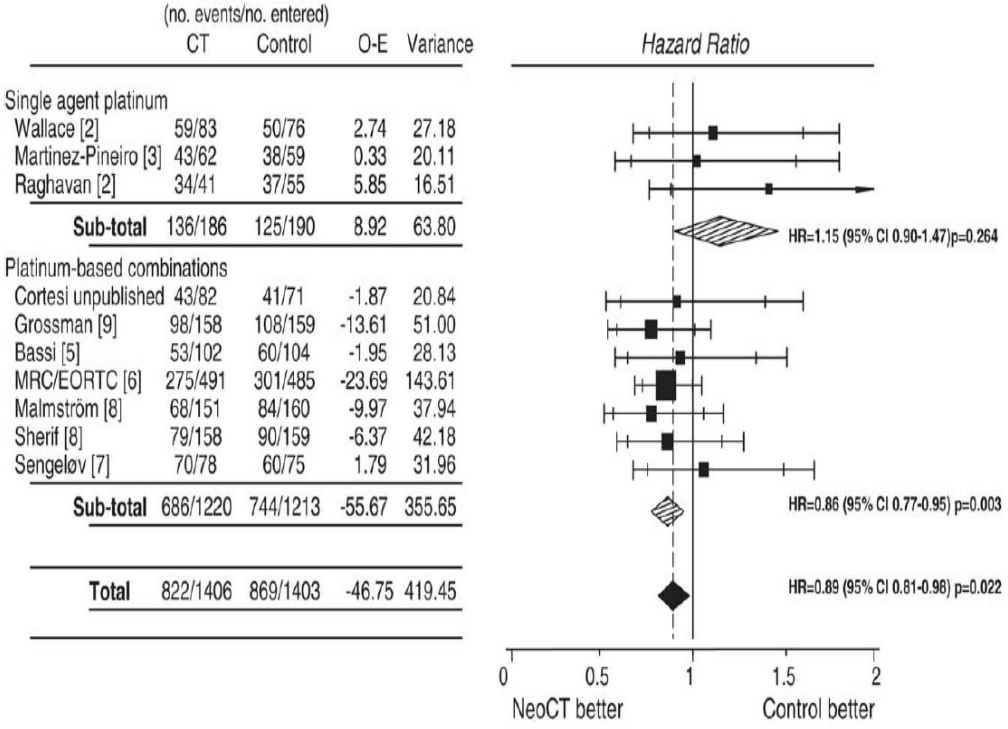
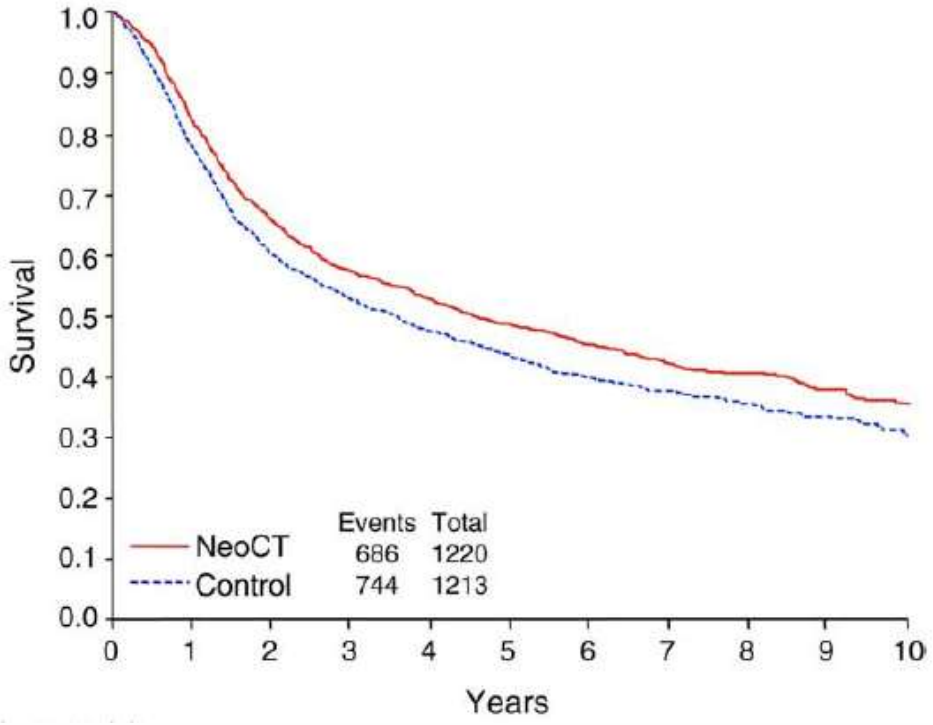
DISCLOSURES

- **Research funding:** Pfizer, BMS
- **Advisory boards:** Pfizer, Novartis, Ipsen, BMS, Janssen, Astellas, Sanofi, Bayer, Clovis, Roche, MSD, Pierre Fabre, Merck
- **Clinical trial payments:** Pfizer, Bayer, Janssen, MSD, Clovis, Pharmacyclics, BMS, Sanofi, Astra Zeneca, Roche, Eisai, Aveo
- **Travel arrangements:** Janssen, Roche, Pfizer, BMS, Ipsen, MSD

UN ESTÁNDAR DURANTE MÁS DE 20 AÑOS

Neoadjuvant Chemotherapy in Invasive Bladder Cancer: Update of a Systematic Review and Meta-Analysis of Individual Patient Data

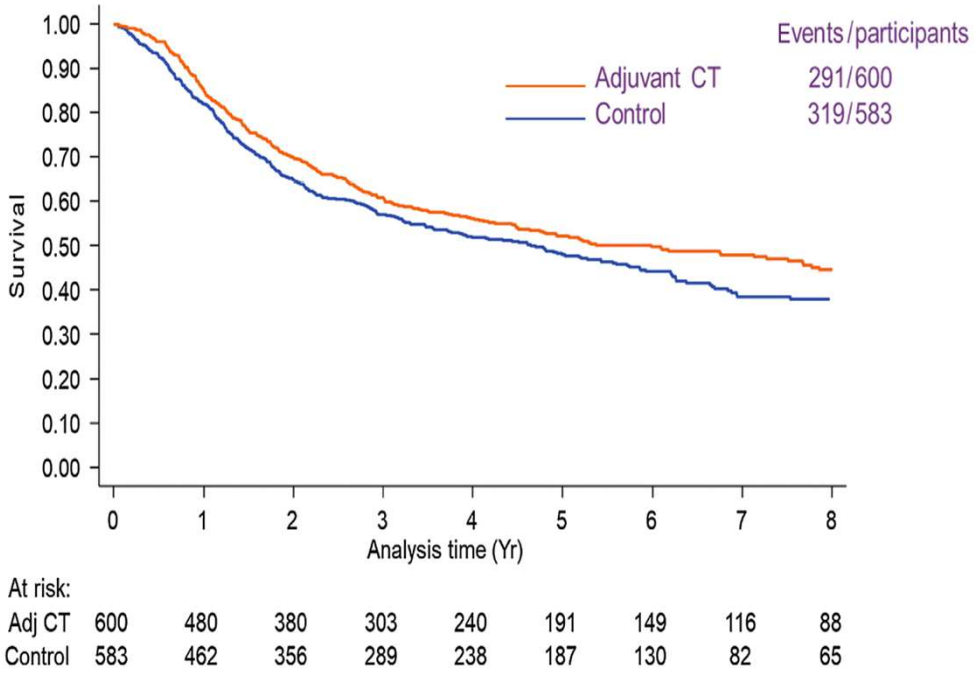




ABC meta-analysis collaboration. Eur Urol 2005

UNA "OPCIÓN" USADA EN PRÁCTICA CLÍNICA

Adjuvant Chemotherapy for Muscle-invasive Bladder Cancer: A Systematic Review and Meta-analysis of Individual Participant Data from Randomised Controlled Trials



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Bladder cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

- Three to four cycles of cisplatin-based neoadjuvant ChT should be given for MIBC [I, A]. Cross-sectional imaging should occur after ChT before RC [IV, B].
- There is weak evidence to support the use of adjuvant cisplatin-based ChT in patients who did not receive neo-adjuvant therapy [II, B]. Neoadjuvant ChT is preferred.

ABC meta-analysis collaboration. Eur Urol 2022; Powles T et al. Ann Oncol 2021

ACTUALIZACIÓN EN **URO-ONCOLOGÍA:**
UPDATE **2024**

UNA NECESIDAD NO CUBIERTA

1. Mediana de edad: **70-73 años**
2. **50%** pacientes **no elegibles** para **cisplatino**
3. **40-67%** de pacientes **pT3-T4a o N+** tratados sólo con cistectomía recaen, con pobre SG-5años **(25-30%)**
4. **40-50%** de pacientes que reciben QT-NA **tienen enfermedad residual invasiva** (mediana SG 3.5años)
5. Falta de **evaluación multidisciplinar**
6. **15-30% pacientes con CVMI reciben QT-NA**

Gschwend et al. Eur Urol 2002; Shariat et al. J Urol 2006 Burger et al. Eur Urol 2012; Huo et al. Eur Urol Oncol. 2019 Dash et al. Cancer 2006; Sonpavde et al. J Urol 2011; Galsky et al. J Clin Oncol 2011

¿CÓMO PODEMOS MEJORAR?

1. MEJORES TRATAMIENTOS SISTÉMICOS
2. NUEVOS BIOMARCADORES
3. CAMBIO DE PARADIGMA

¿CÓMO PODEMOS MEJORAR?

1. **MEJORES TRATAMIENTOS SISTÉMICOS**
2. **NUEVOS BIOMARCADORES**
3. **CAMBIO DE PARADIGMA**

- CheckMate 274 is a phase 3, randomized, double-blind, multicenter study of adjuvant nivolumab versus placebo in patients with high-risk MIUC

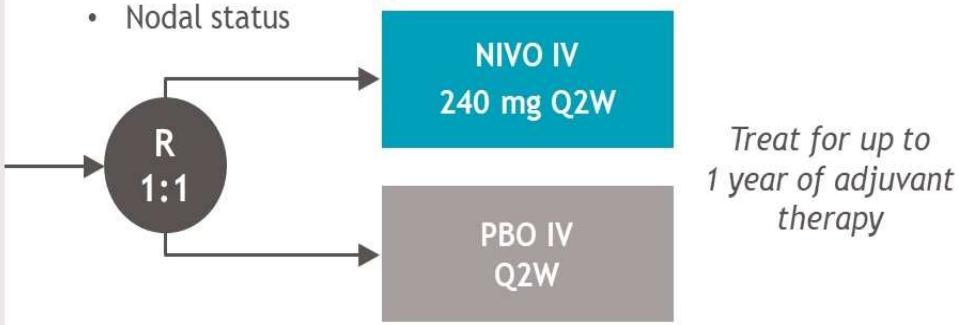
N = 709

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



Minimum follow-up, 5.9 months
Median follow-up in ITT population, 20.9 months (NIVO) and 19.5 months (PBO)

Primary endpoints: DFS in ITT population and DFS in all randomized patients with tumor PD-L1 ≥ 1%
Secondary endpoints: NUTRFS, DSS, and OS[b]
Exploratory endpoints included: DMFS, safety, HRQoL

Bajorin DF et al. N Engl J Med 2021

CheckMate 274

Disease-free survival (primary endpoint)

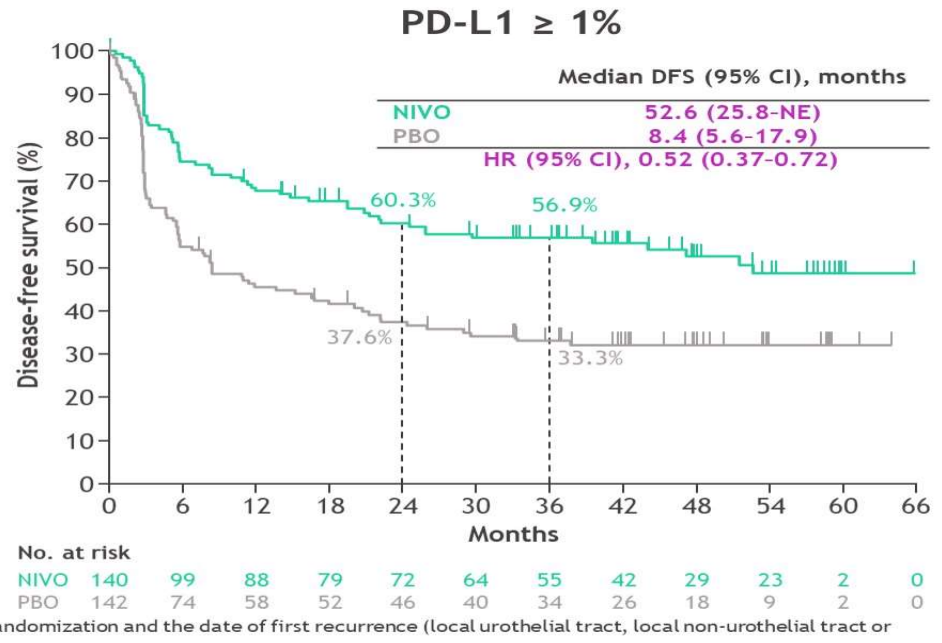
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Adjuvant treatment of urothelial carcinoma

OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC) with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC (see section 5.1).

NE, not estimable.

ersus PBO both in the ITT and tumor PD-L1

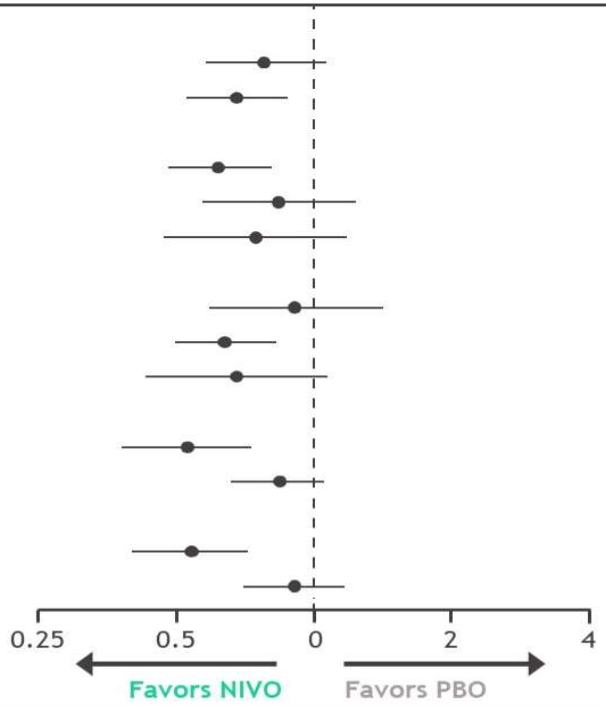


andomization and the date of first recurrence (local urothelial tract, local non-urothelial tract or

Bajorin DF et al. N Engl J Med 2021; Galsky MD et al. ASCO GU 2023

Disease-free survival by subgroup in the ITT population

	NIVO Events/patients	PBO Events/patients	HR for DFS (95% CI)
Minor histologic variants			
Presence	85/145	88/141	0.78 (0.58-1.07)
Absence	110/208	145/215	0.68 (0.53-0.88)
Pathologic lymph node status			
N+	109/167	134/168	0.62 (0.48-0.81)
N0/x with < 10 nodes removed	50/94	56/99	0.84 (0.57-1.24)
N0 with ≥ 10 nodes removed	36/91	42/88	0.75 (0.47-1.18)
Pathologic status			
pT0-2	42/80	48/86	0.91 (0.59-1.42)
PT3	113/206	132/204	0.64 (0.50-0.83)
PT4a	38/57	49/62	0.68 (0.43-1.08)
PD-L1 expression			
≥ 1	61/140	87/141	0.53 (0.38-0.73)
< 1	132/210	141/209	0.84 (0.66-1.06)
Previous neoadjuvant cisplatin			
Yes	81/153	110/155	0.54 (0.40-0.72)
No	114/200	123/201	0.91 (0.70-1.17)

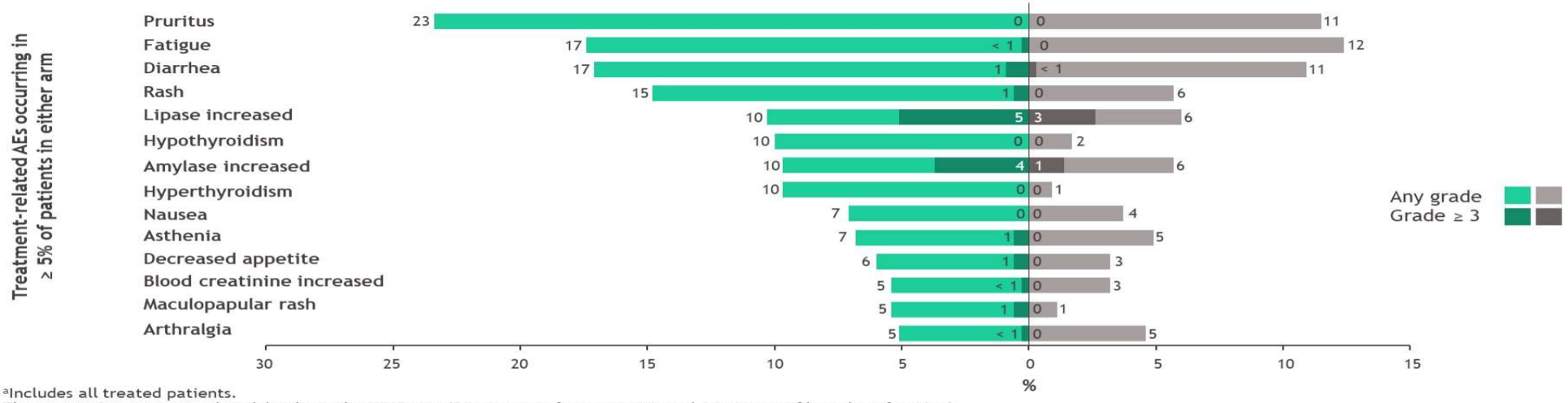


Bajorin DF et al. N Engl J Med 2021; Galsky MD et al. ASCO GU 2023

CheckMate 274

Safety summary in all treated patients

	NIVO (n = 351)[a]		PBO (n = 348)[a]	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Treatment-related AEs, %	79	18	56	7
Treatment-related AEs leading to discontinuation, %	14	7	2	1



[a]Includes all treated patients.
There were 3 treatment-related deaths in the NIVO arm (2 instances of pneumonitis and 1 instance of bowel perforation).
Includes events reported between the first dose and 30 days after the last dose of study therapy.
Minimum follow-up in the ITT population, 31.6 months.
AE, adverse event.

Bajorin DF et al. N Engl J Med 2021; Galsky MD et al. ASCO GU 2023

Summary of efficacy outcomes over time

ITT

	NIVO (N = 353)	PBO (N = 356)	NIVO (N = 353)	PBO (N = 356)	NIVO (N = 353)	PBO (N = 356)
Minimum follow-up in the ITT population, months	31.6		11.0[1]		5.9[2]	
Median DFS, months	22.0	10.9	22.0	10.9	20.8	10.8
DFS HR (95% CI)	0.71 (0.58-0.86)		0.70 (0.57-0.85)		0.70 (0.55-0.90)[a]	
Median NUTRFS, months	25.9	13.7	26.0	13.7	22.9	13.7
NUTRFS HR (95% CI)	0.72 (0.59-0.88)		0.71 (0.58-0.88)		0.72 (0.59-0.89)	
Median DMFS, months	47.1	28.7	41.1	29.2	40.5	29.5
DMFS HR (95% CI)	0.74 (0.60-0.92)		0.73 (0.58-0.92)		0.75 (0.59-0.94)	

PD-L1 ≥ 1%

	NIVO (N = 140)	PBO (N = 142)	NIVO (N = 140)	PBO (N = 142)	NIVO (N = 140)	PBO (N = 142)
Minimum follow-up in the ITT population, months	31.6		11.0[1]		5.9[2]	
Median DFS, months	52.6	8.4	NR	8.4	NR	8.4
DFS HR (95% CI)	0.52 (0.37-0.72)		0.53 (0.38-0.75)		0.55 (0.35-0.85)[b]	
Median NUTRFS, months	52.6	8.4	NR	10.8	NR	10.8
NUTRFS HR (95% CI)	0.53 (0.38-0.74)		0.54 (0.39-0.77)		0.55 (0.39-0.79)	
Median DMFS, months	NR	20.7	NR	20.7	NR	21.2
DMFS HR (95% CI)	0.58 (0.40-0.84)		0.60 (0.41-0.88)		0.61 (0.42-0.90)	

Bajorin DF et al. N Engl J Med 2021; Galsky MD et al. ASCO GU 2023

A031501 AMBASSADOR: Study Design

Phase 3 randomized, open label, multicenter study of adjuvant pembrolizumab vs observation in patients with high-risk muscle-invasive urothelial carcinoma (MIUC)

NCT03244384

Key Eligibility

- Muscle-invasive urothelial carcinoma: bladder, urethra, renal pelvis, ureter
- Post-radical surgery (cystectomy, nephrectomy, nephroureterectomy, or ureterectomy) ≥ 4 but ≤ 16 weeks
- Post-neoadjuvant chemotherapy and ≥ pT2 and/or N+/+margins
  OR
- cisplatin-ineligible or refusing and ≥ pT3 and/or pN+/+margins

Stratify

- PD-L1 status*
- Neoadjuvant chemotherapy yes/no
- Pathologic stage:
  - pT2/3/4aN0
  - pT4aN0
  - pT4bNx/N1-3
  - +surgical margins

N=739

R 1:1

- Pembrolizumab 200 mg q3W 1 year (18 cycles)
- Observation

Dual Primary Endpoints

- **Disease-free survival**
- **Overall survival**

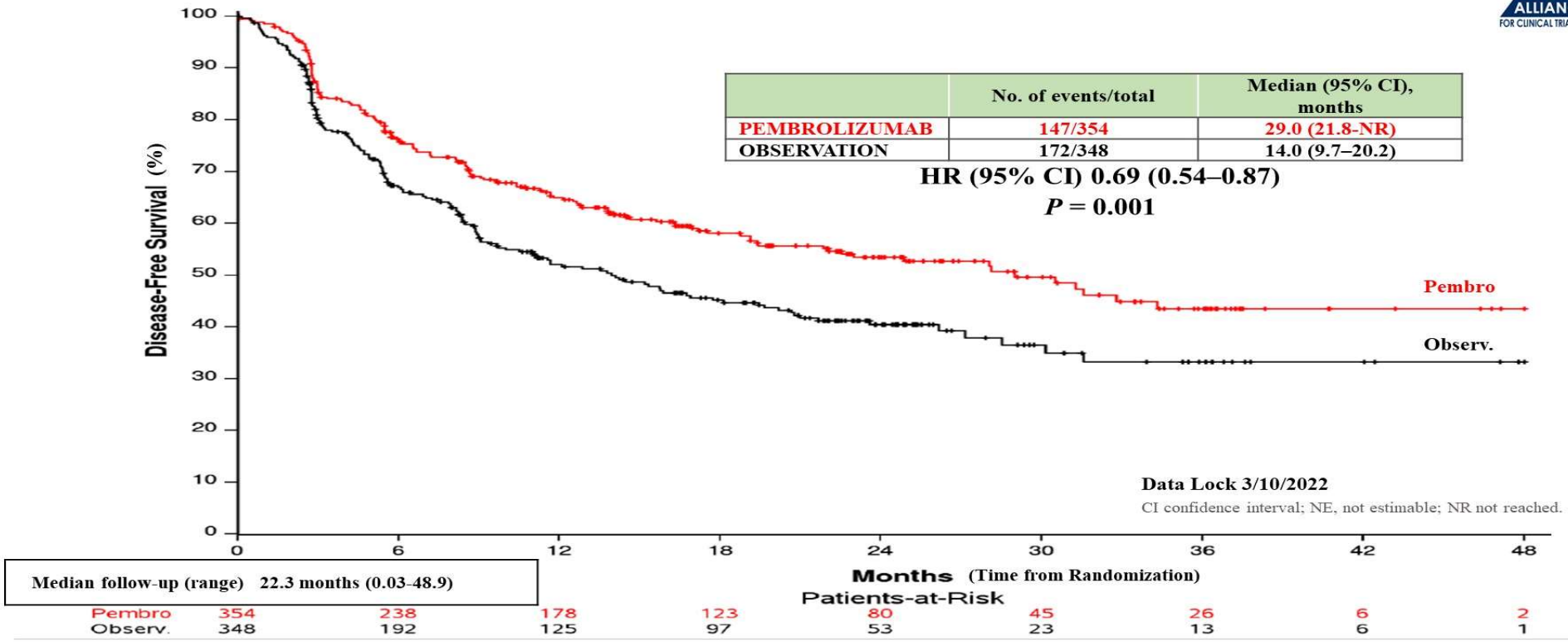
Key Secondary Endpoints
- DFS/OS PD-L1 +/-
- Safety

Correlative Endpoints
- DFS/OS ctDNA +/-
- DFS/OS immune gene signatures
- DFS/OS tumor molecular subtype
- DFS/OS TCR clonality
- QOL

*PD-L1 status was tested centrally and defined using the combined positive score: percentage of PD-L1-positive tumor cells and infiltrating immune cells relative to the total number of tumor cells. PD-L1 positive = CPS ≥ 10%, Dako PD-L1 immunohistochemistry 22C3 pharmDx assay. DFS: disease-free survival (defined as new MIUC, metastatic disease, or death without recurrence); OS: overall survival

Apolo A et al. ASCO GU 2024

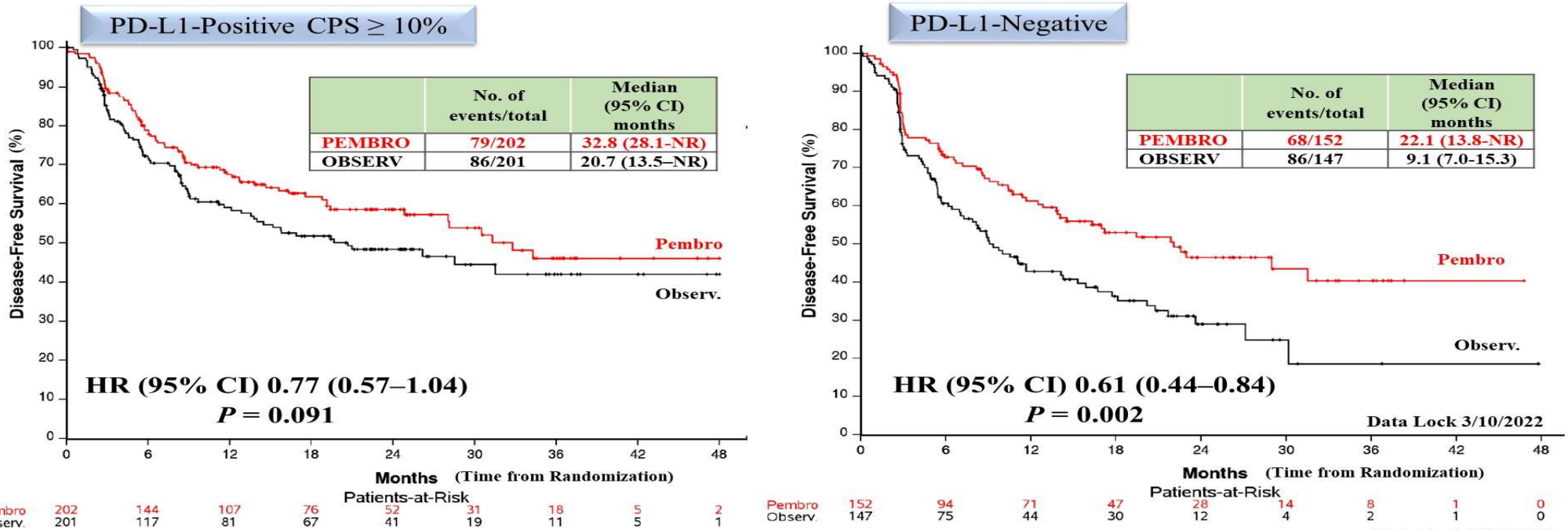
A031501 AMBASSADOR: Disease-Free Survival (ITT)



	No. of events/total	Median (95% CI), months
PEMBROLIZUMAB	147/354	29.0 (21.8-NR)
OBSERVATION	172/348	14.0 (9.7–20.2)

Apolo A et al. ASCO GU 2024

A031501 AMBASSADOR: Disease-Free Survival by PD-L1* Status



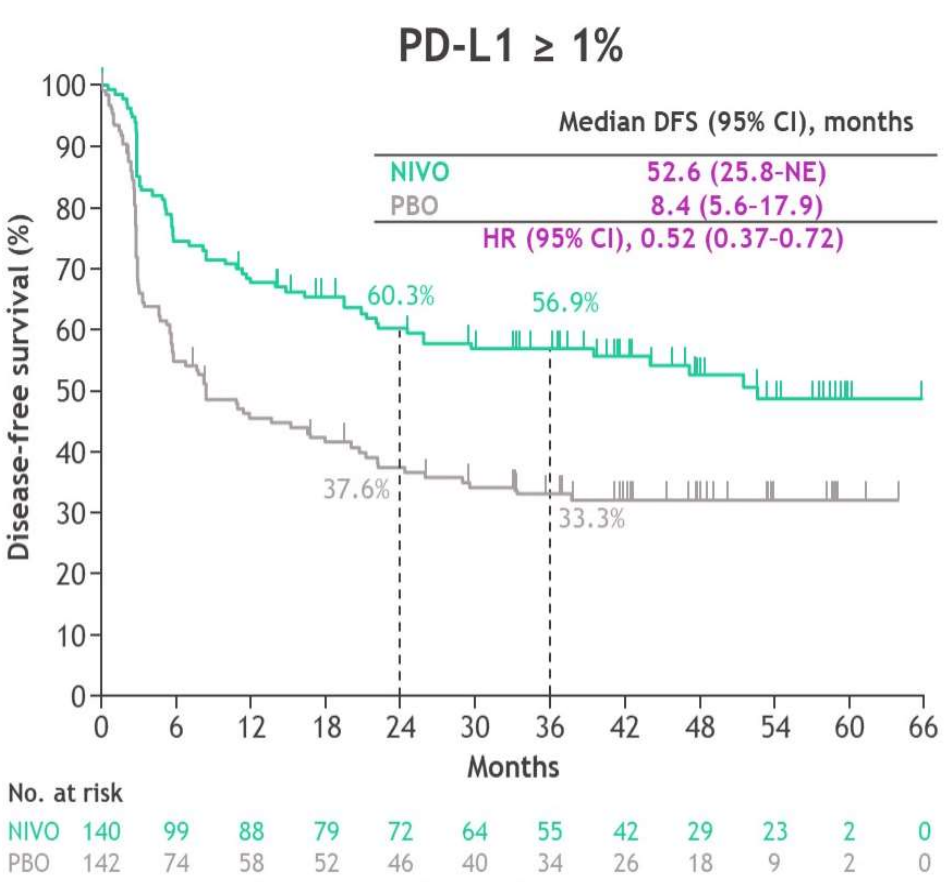
*Dako PD-L1 immunohistochemistry 22C3 pharmDx assay

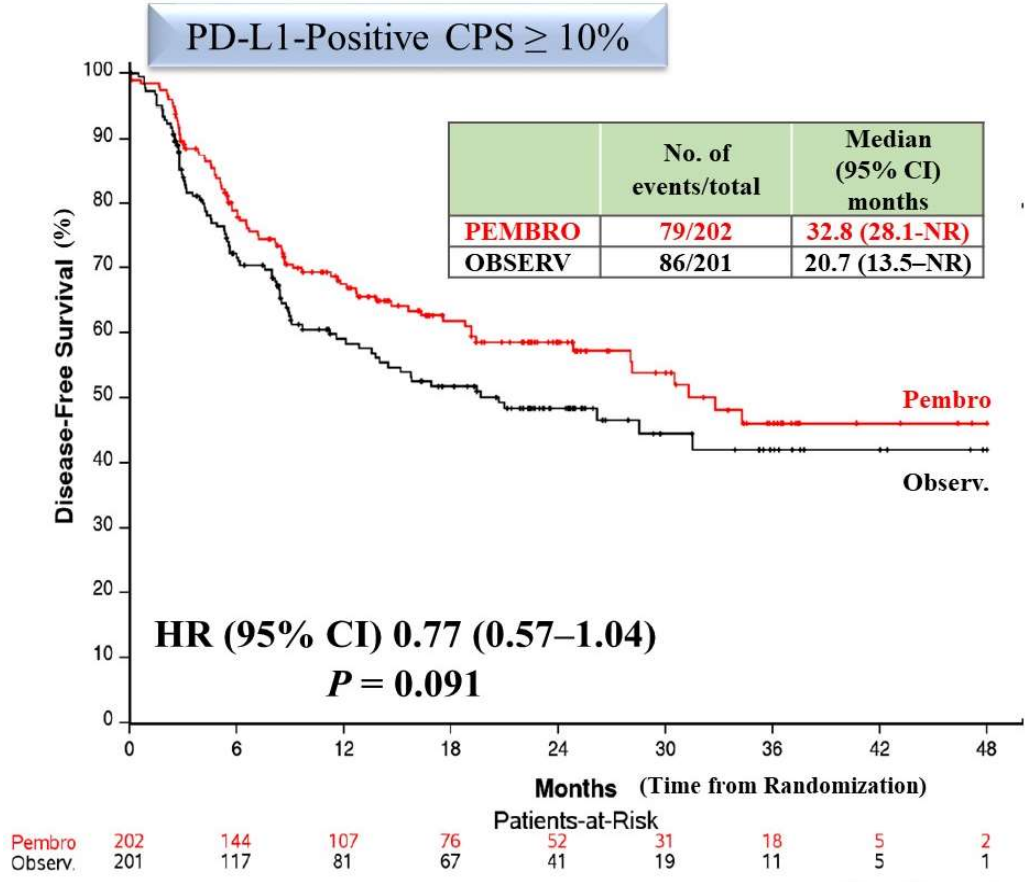
CI, confidence interval; NE, not estimable; NR, not reached.

Data Lock 3/10/2022

Apolo A et al. ASCO GU 2024

1 MEJORES TRATAMIENTOS SISTÉMICOS



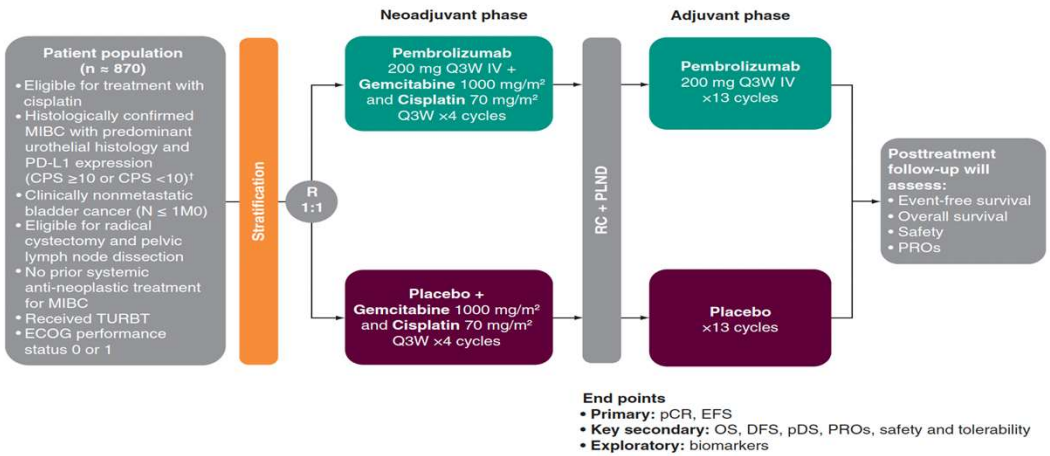


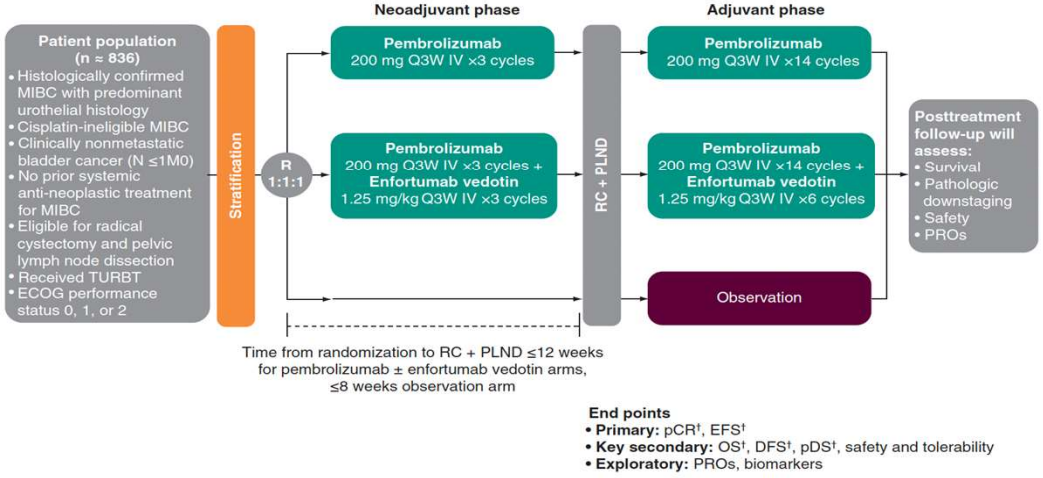
Galsky MD et al. ASCO GU 2023; Apolo A et al. ASCO GU 2024

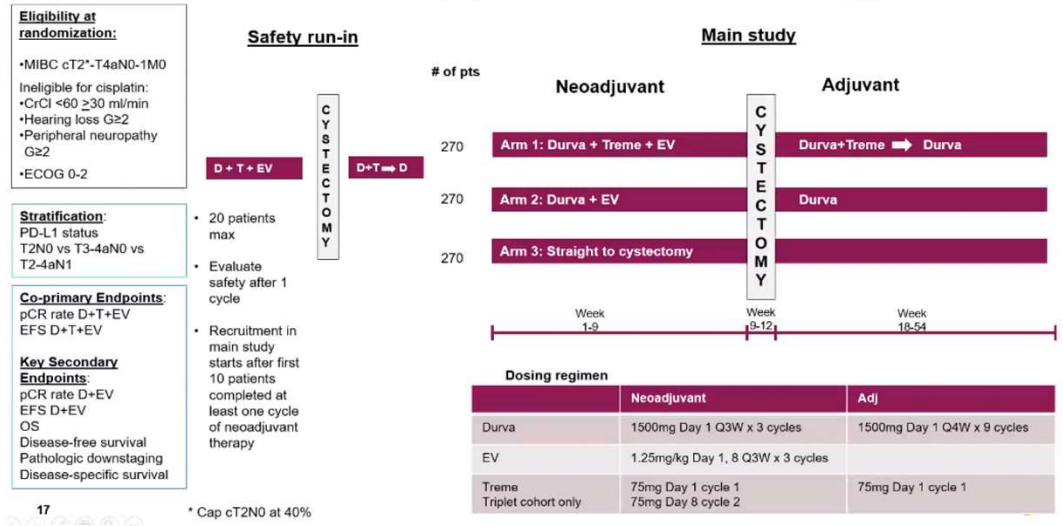
	NIVO	NIVO (PLACEBO)	PEMBRO	PEMBRO (OBS)
PFS ITT	22	10,9	29	14
PFS PD-L1+	52,6	8,4	32,8	20,7
PFS PD-L1-			22,1	9,1

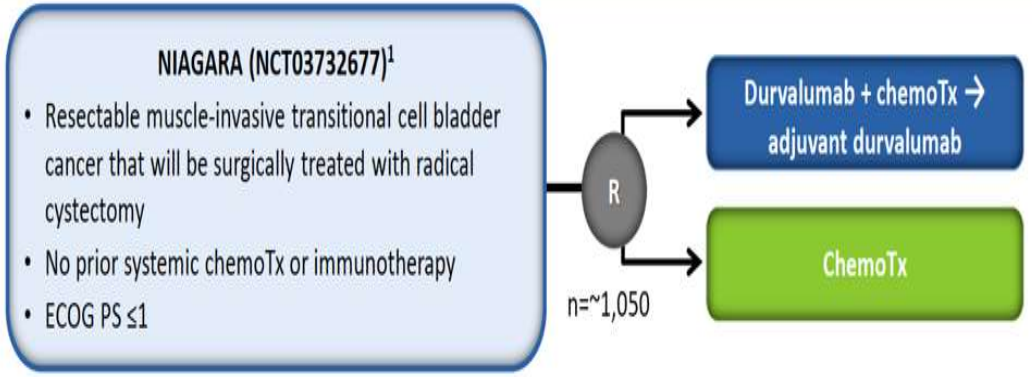
- Diferentes fármacos (Nivo vs Pembro)
- Diferente definición de PD-L1+ (TC>1% vs CPS>10%)
- Diferente población
- Diferente brazo control (placebo vs observación)
- Estudio de registro vs grupo cooperativo

1 MEJORES TRATAMIENTOS SISTÉMICOS









¿CÓMO PODEMOS MEJORAR?

1 MEJORES TRATAMIENTOS SISTÉMICOS

NUEVOS BIOMARCADORES 2

3 CAMBIO DE PARADIGMA

NUEVOS BIOMARCADORES 2

IMvigor010: phase III study of adjuvant atezolizumab in MIUC

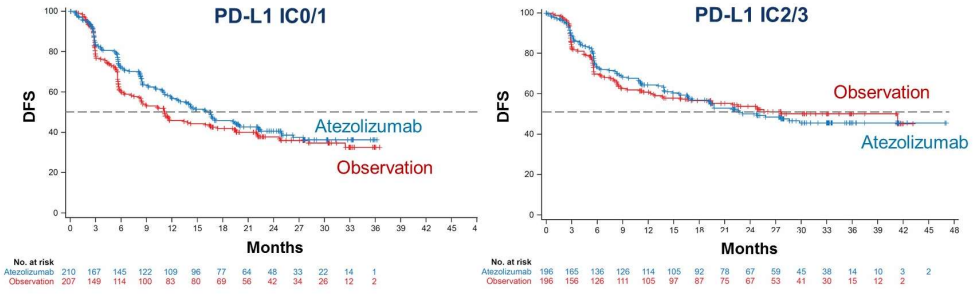
- High-risk MIUC (bladder or upper tract)
- Radical surgery with lymph node dissection within ≤14 weeks
- Tissue sample for PD-L1 testing

R 1:1 → Atezolizumab / Observation (No crossover allowed) → Disease recurrence/ survival follow-up

Endpoints
- Primary: DFS (ITT population)
- Key secondary: OS (ITT population)
- Other: safety
- **Exploratory: predictive, prognostic and pharmacodynamic biomarkers in tumour tissue and blood and their association with disease recurrence**

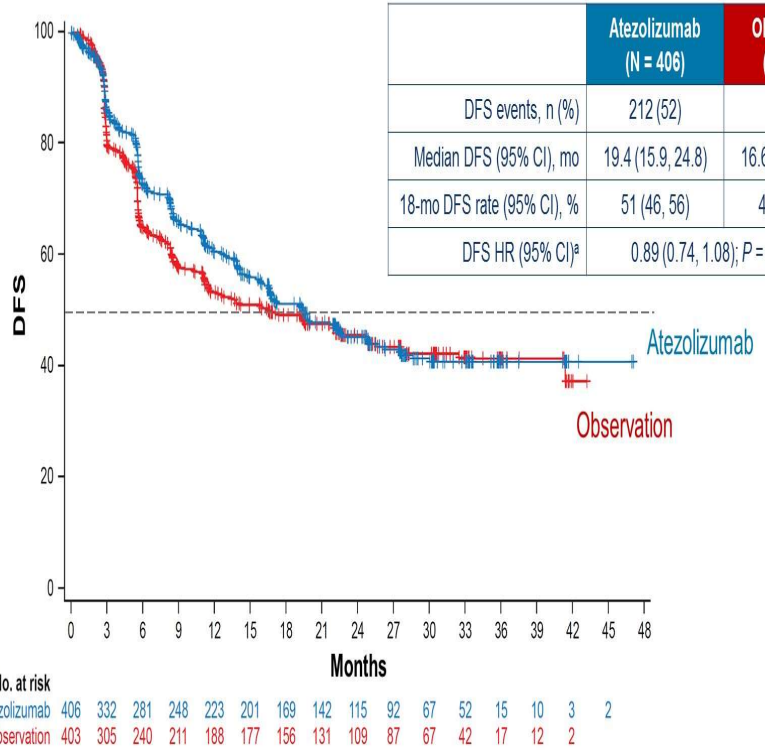
- IMvigor010 did not meet its primary endpoint (DFS in the ITT population)
  - A pre-planned interim OS analysis was performed but could not be formally tested
  - OS follow-up is immature and ongoing in the ITT population
- The PD-L1 and TMB biomarkers did not identify patients benefitting from atezolizumab vs observation in the ITT population
- A pre-specified ctDNA biomarker analysis was performed

DFS by PD-L1 Status



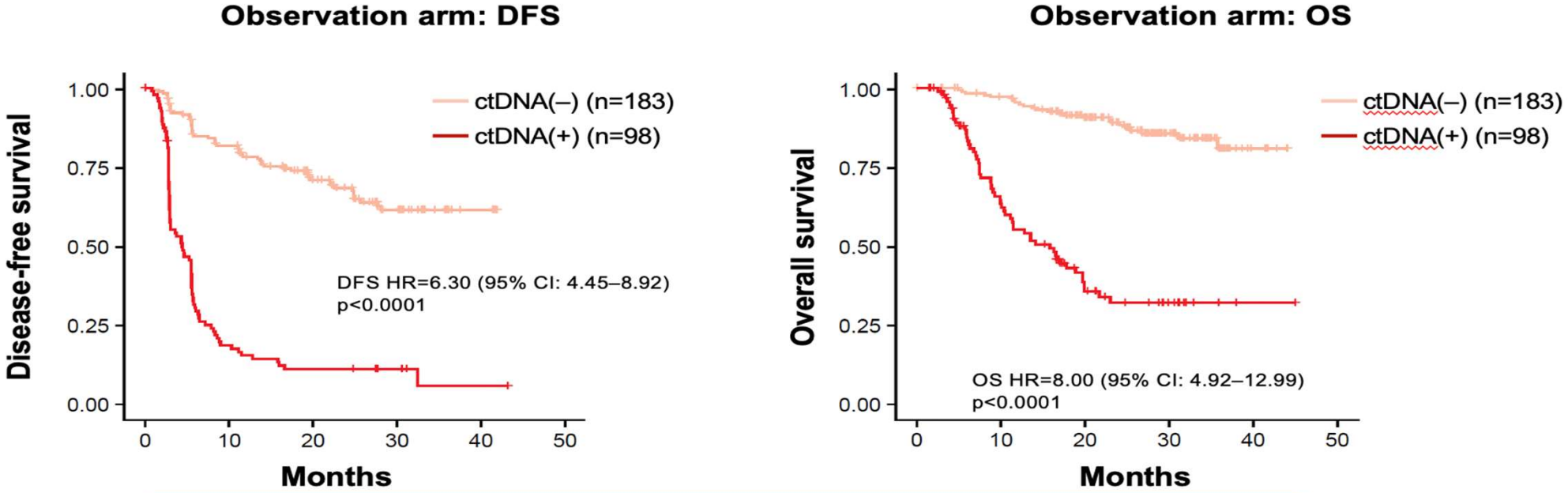
DFS in ITT Population

	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]	



Bellmunt J et al. Lancet Oncol 2021

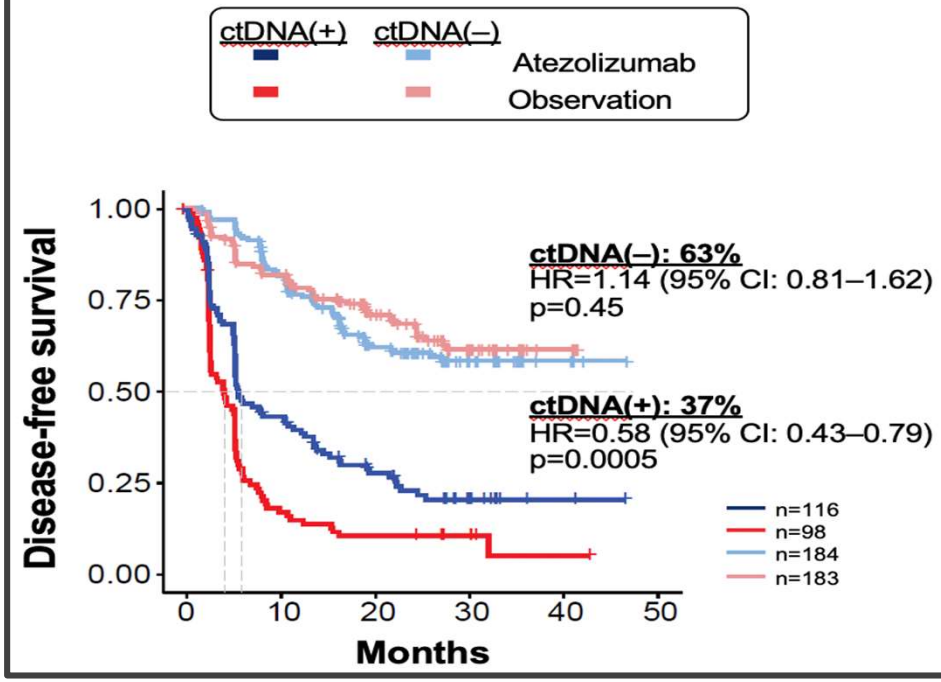
1. CT-DNA+ PATIENTS HAVE A WORSE PROGNOSIS



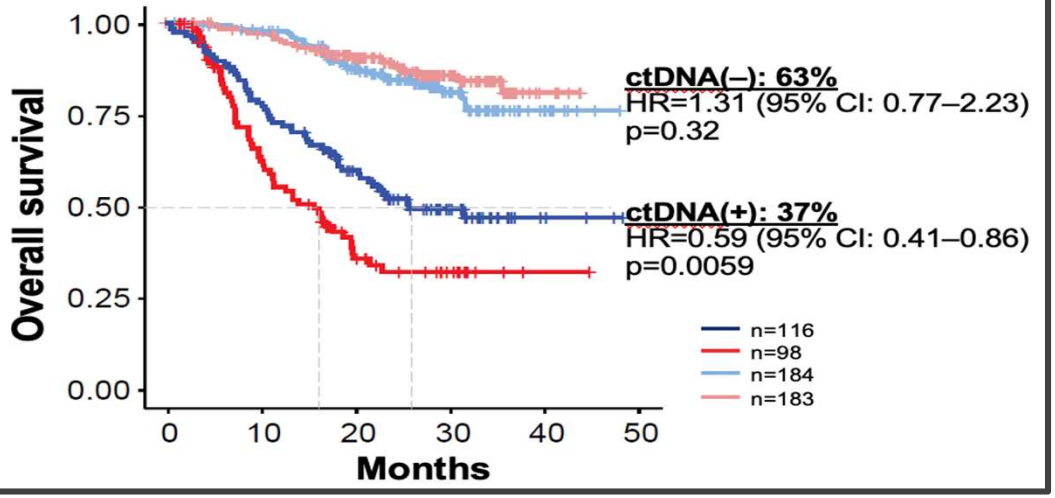
IMvigor010 confirmed the prognostic value of ctDNA status

Powles T et al. ESMO IO 2020

2. CT-DNA+ PATIENTS TREATED WITH ATEZOLIZUMAB HAD IMPROVED SURVIVAL

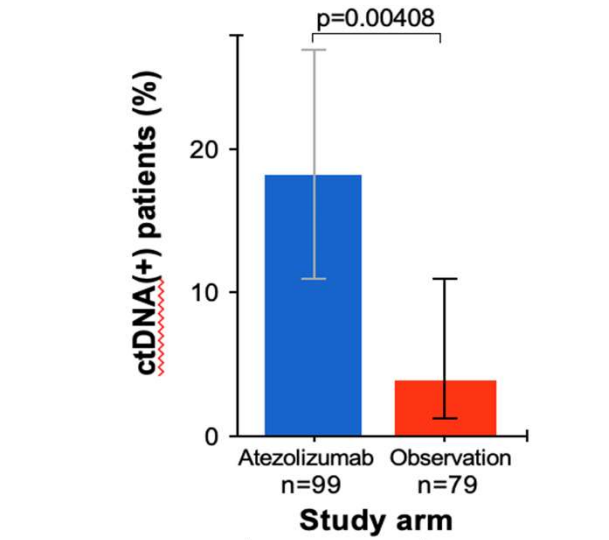


	ctDNA(+) patients	
	Atezolizumab	**Observation**
Median DFS (95% CI), months	5.9 (5.6–11.2)	4.4 (2.9–5.6)
Median OS (95% CI), months	25.8 (20.5–NR)	15.8 (10.5–19.7)

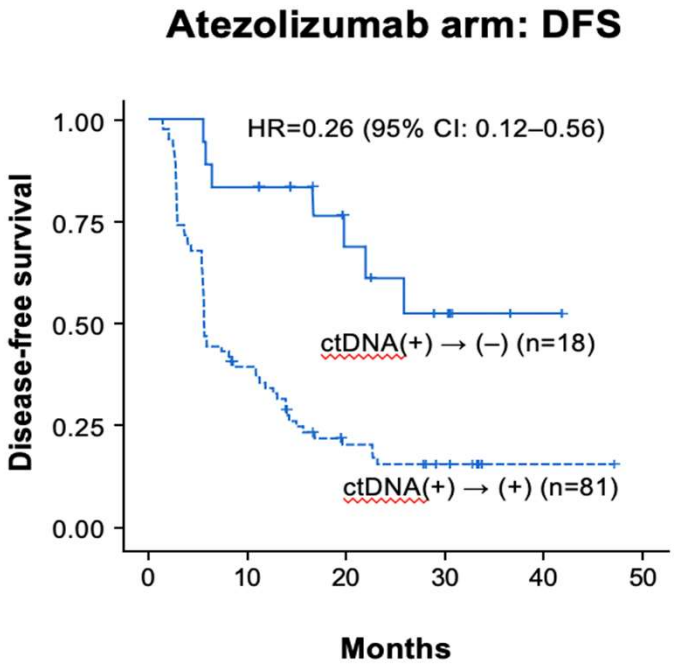


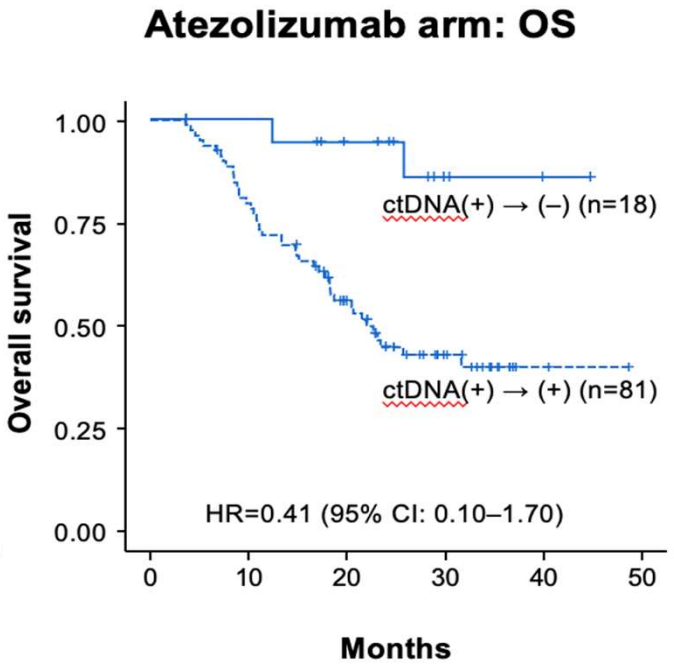
Powles T et al. ESMO IO 2020

3. CT-DNA CLEARANCE UNDER ATEZOLIZUMAB WAS ASSOCIATED WITH IMPROVED SURVIVAL



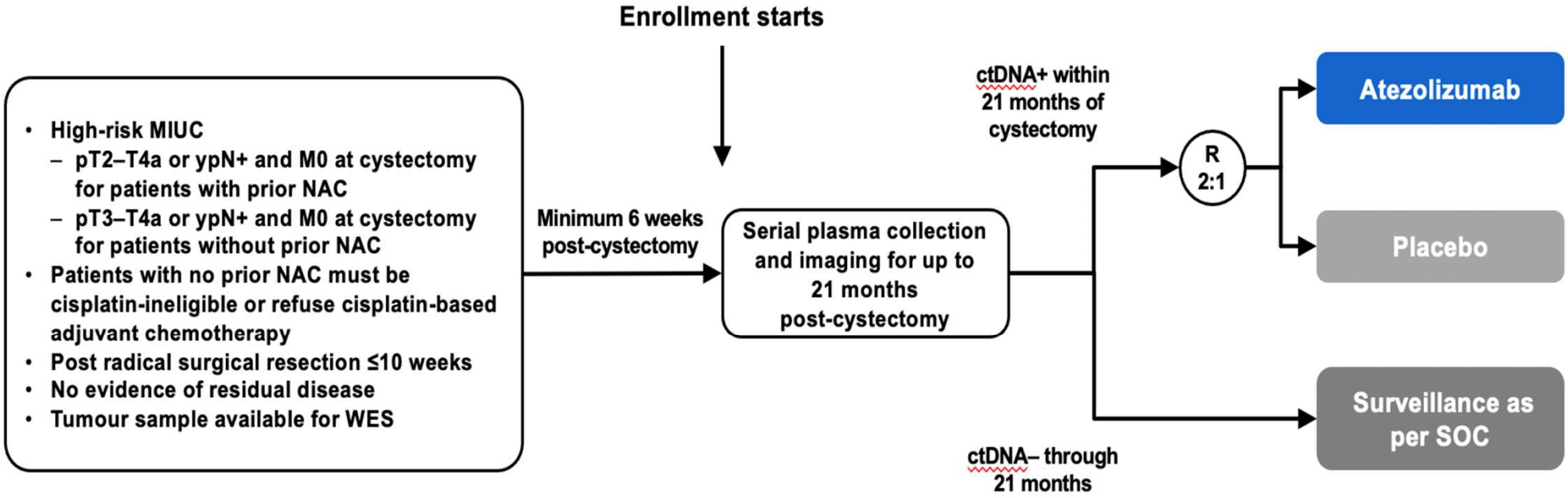
ctDNA(+) → (–)	18 (18.8%)	3 (3.8%)
ctDNA(+) → (+)	81 (81.82%)	76 (96.2%)





Powles T et al. ESMO IO 2020

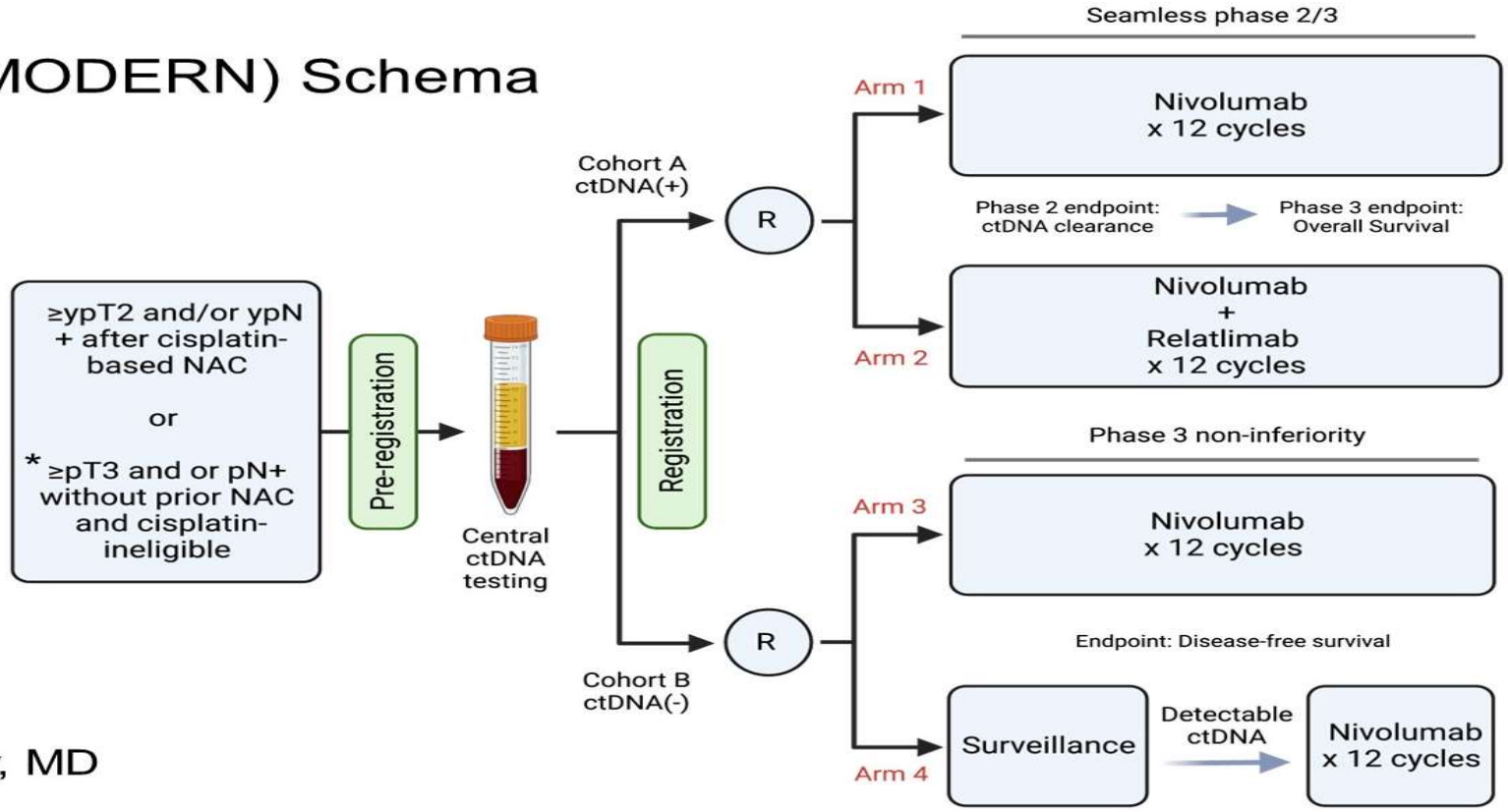
IMvigor011 (phase III study of adjuvant atezolizumab in ctDNA+ MIUC patients)



Primary endpoint: IRF-assessed DFS in patients who are ctDNA+ within 20 weeks of cystectomy

NUEVOS BIOMARCADORES 2

A032103 (MODERN) Schema



PI: Matthew Galsky, MD

*patients with pT2N0 (distinct from ypT2N0) will be eligible IF ctDNA(+)

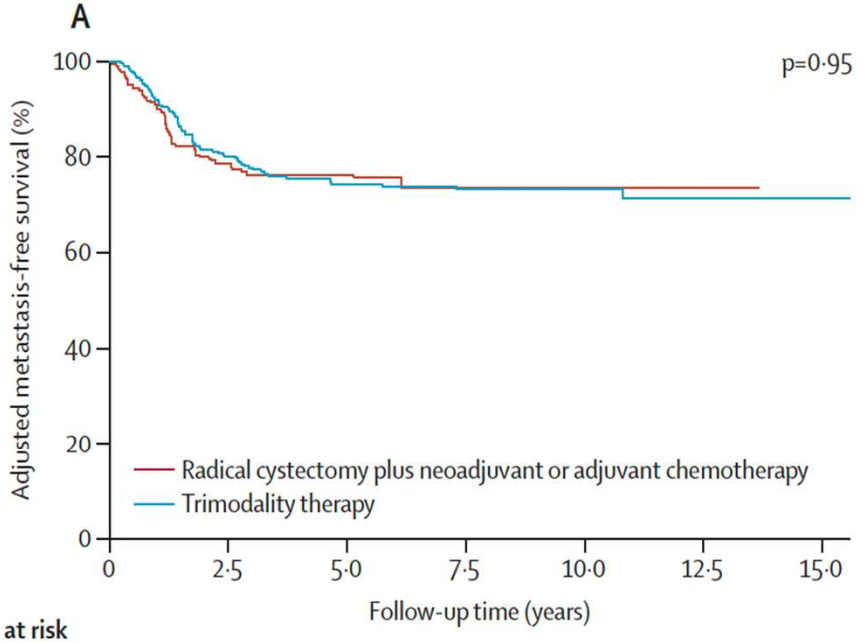
Powles T et al. ESMO IO 2020

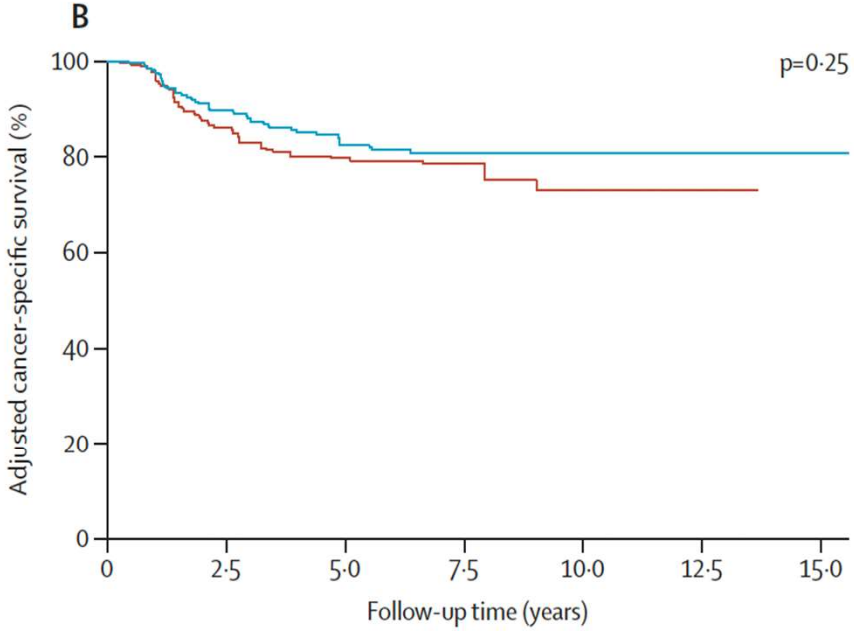
¿CÓMO PODEMOS MEJORAR?

1. MEJORES TRATAMIENTOS SISTÉMICOS
2. NUEVOS BIOMARCADORES
3. CAMBIO DE PARADIGMA

3 CAMBIO DE PARADIGMA

Radical cystectomy versus trimodality therapy for muscle-invasive bladder cancer: a multi-institutional propensity score matched and weighted analysis



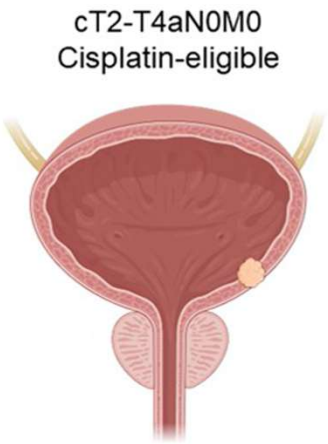


Number at risk							
Radical cystectomy plus neoadjuvant or adjuvant chemotherapy	176	118	82	34	14	4	0
Trimodality therapy	282	202	130	75	42	17	2

	176	127	86	37	14	4	0
	282	222	138	76	43	19	2

Zlotta AR et al. Lancet Oncol 2023

3 CAMBIO DE PARADIGMA



cT2-T4aN0M0
Cisplatin-eligible

Gemcitabine +
Cisplatin +
Nivolumab
x 4 cycles

Clinical Restaging
Cystoscopy
Biopsies
Urine cytology
MRI

Clinical CR
- No cystectomy → Nivolumab x 8 cycles
- *
- Cystectomy

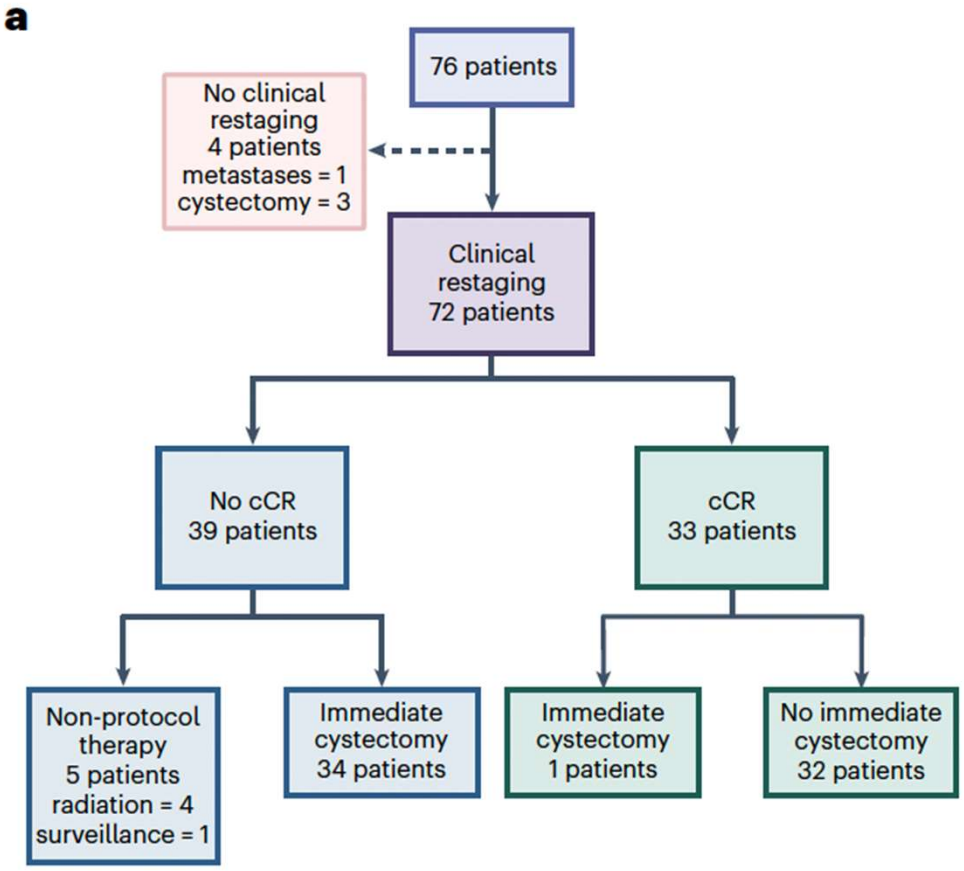
No Clinical CR → Cystectomy

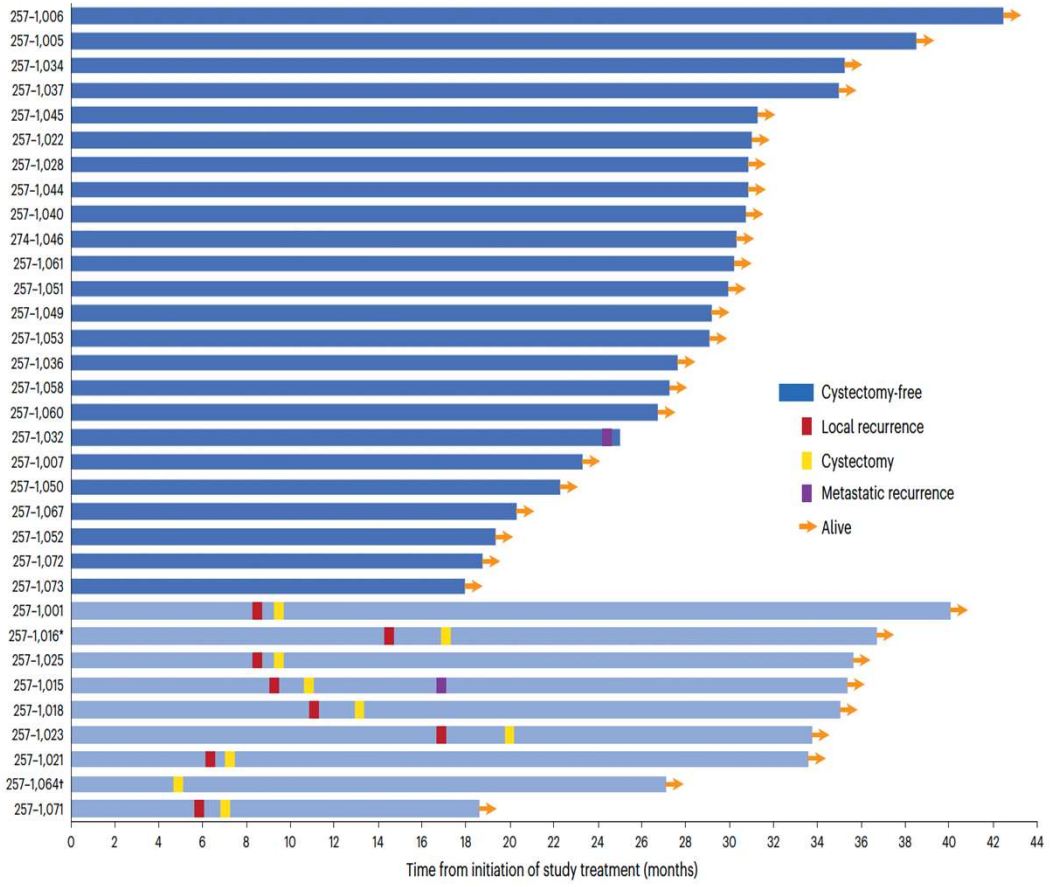
*patient choice

Co-primary endpoints
- Clinical complete response (CR) rate
- Performance of clinical CR in predicting treatment *benefit:*
  - 2 year metastasis free if no cystectomy
  - pCR in immediate cystectomy

Galsky M et al. Nat Med 2023

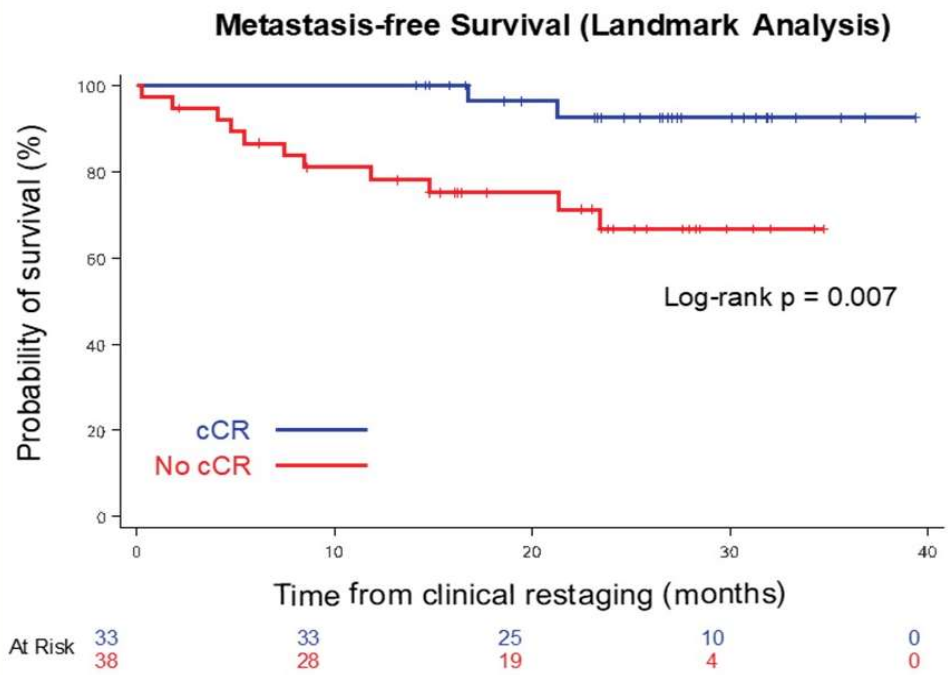
3 CAMBIO DE PARADIGMA

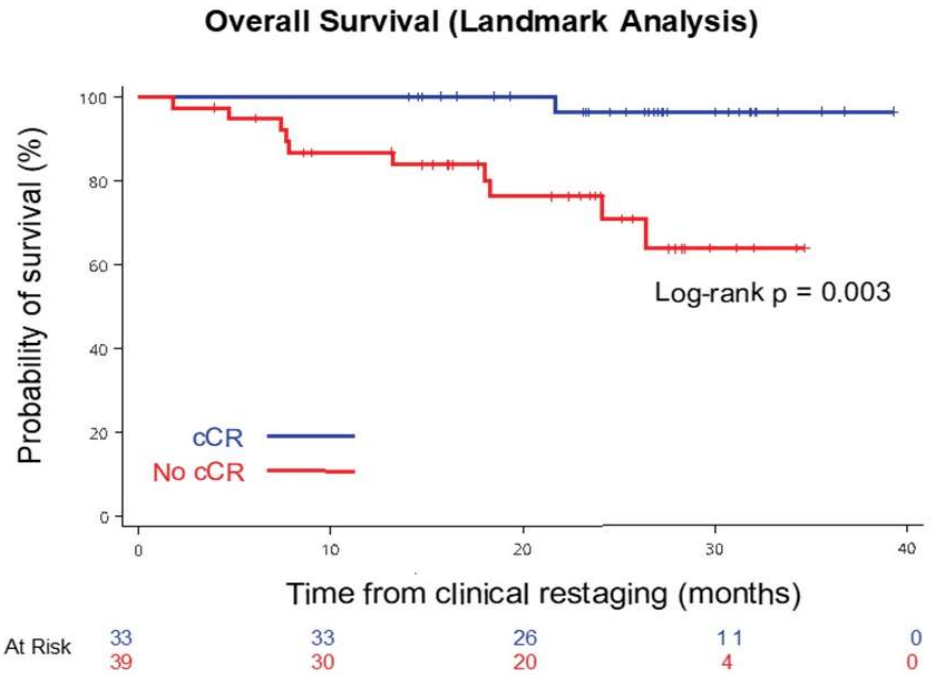




Galsky M et al. Nat Med 2023

3 CAMBIO DE PARADIGMA





***Clinical* CR predicted treatment benefit with a positive predictive value of 0.96 (95% CI, 0.89, 1)**

Galsky M et al. Nat Med 2023

CONCLUSIONES

- Quimioterapia neoadyuvante como estándar para un subgrupo de pacientes
- Inmunoterapia adyuvante como opción con impacto en DFS
  - *Nivolumab* aprobado en PD-L1+
  - *Pembrolizumab*
- Necesitamos mejores biomarcadores
- ¿Son todas las cistectomías realmente necesarias?

ACTUALIZACIÓN EN
URO-ONCOLOGÍA:
UPDATE **2024**

Madrid, 28 de febrero de 2024

MUCHAS GRACIAS POR SU ATENCIÓN

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