Inmunoterapia perioperatoria en CVMI

Dónde estamos y visión de futuro

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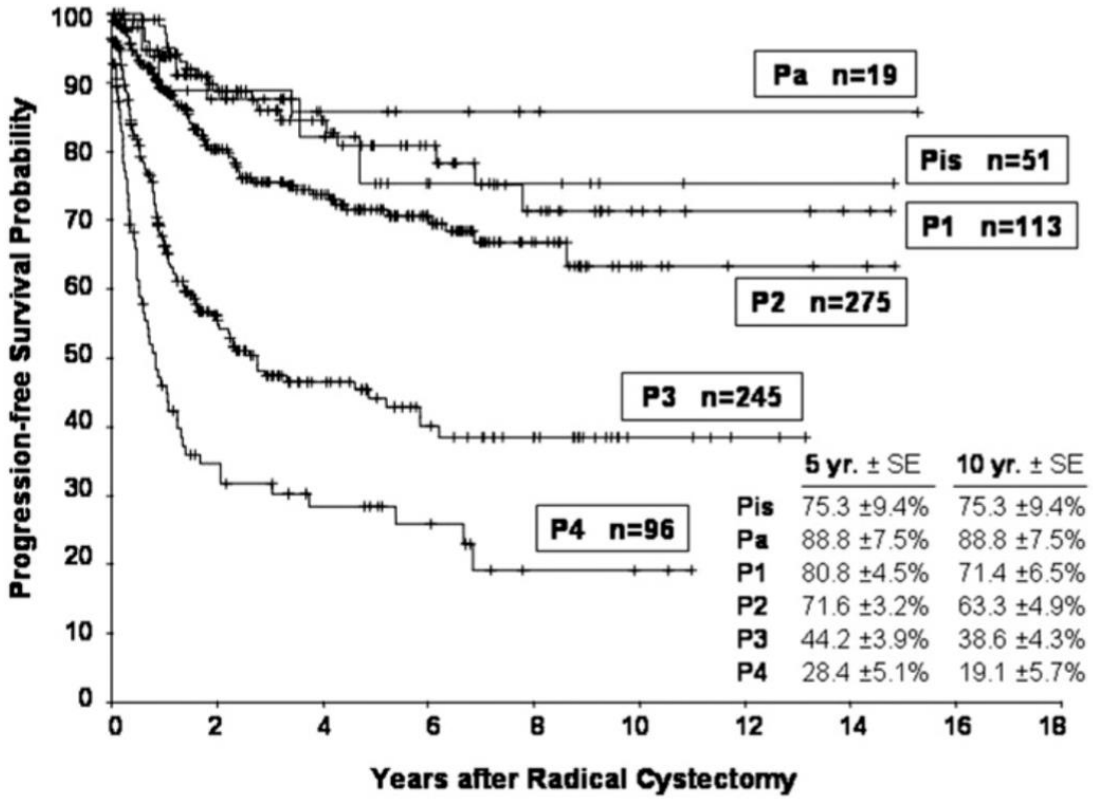
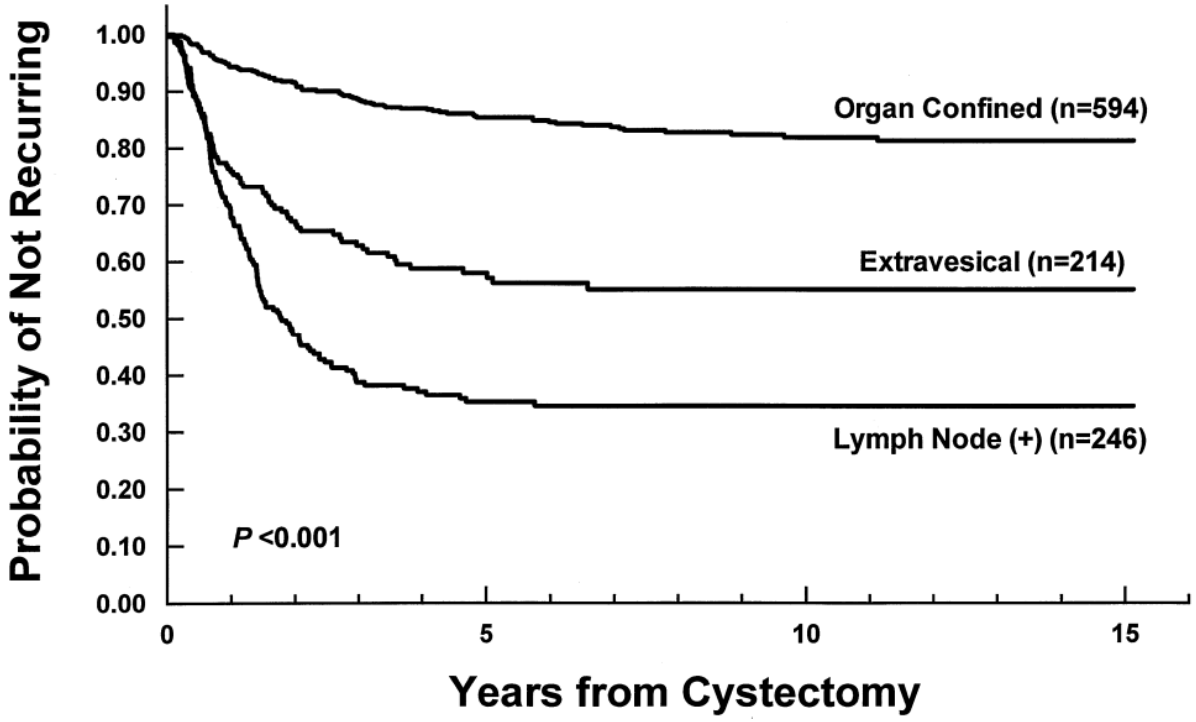
Disclosures

Me or my institution has received honoria for speaking, advisory role, research funding, travel, accomodations and expenses from

Prognostic of MIBC remains low despite radical treatment





1. Stein HP, et al. J Clin Oncol 2001 2. Shariat SF, et al. J Urol 2006

Perioperative Cisplatin-based combinations are the SoC for MIBC, but long-term OS impact remains limited

Neoadjuvant and adjuvant cisplatin-based combinations improve OS

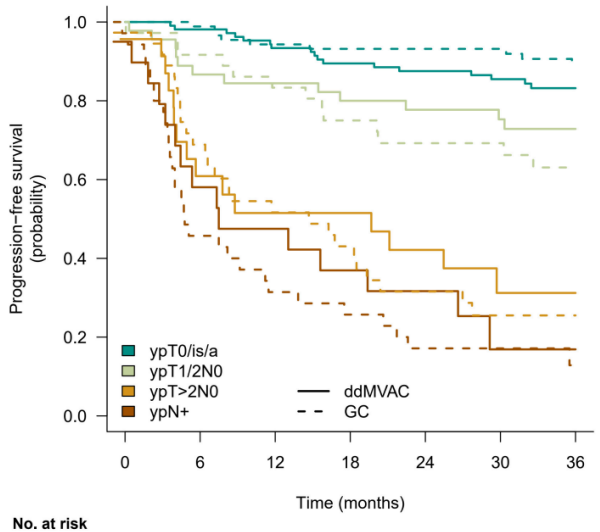
Risk of death ↓ ≈10-20%

Absolute OS benefit at 5 years ≈ 5-10%

.ABC Meta-analysis. Eur Urol 2005 (11 trials, n=3005)
S. Burdett, et al. European Urology 2022 (n=1183)

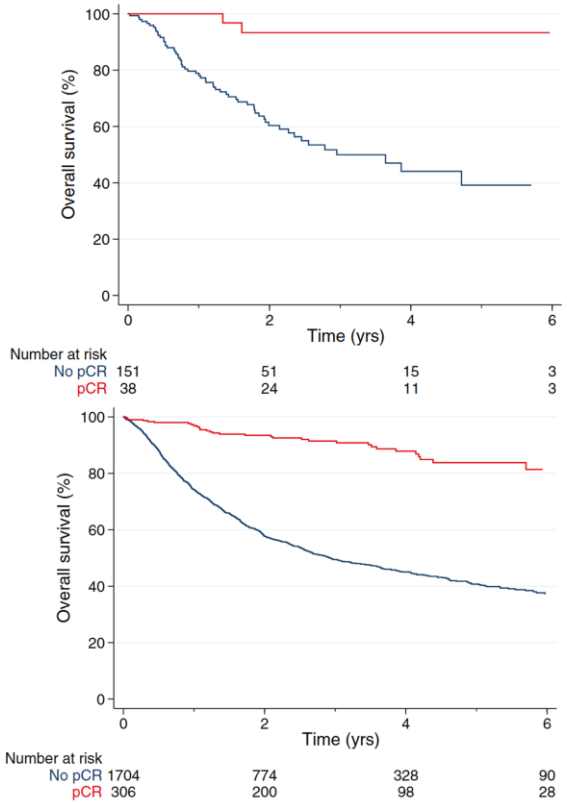
NAC response predicts outcomes

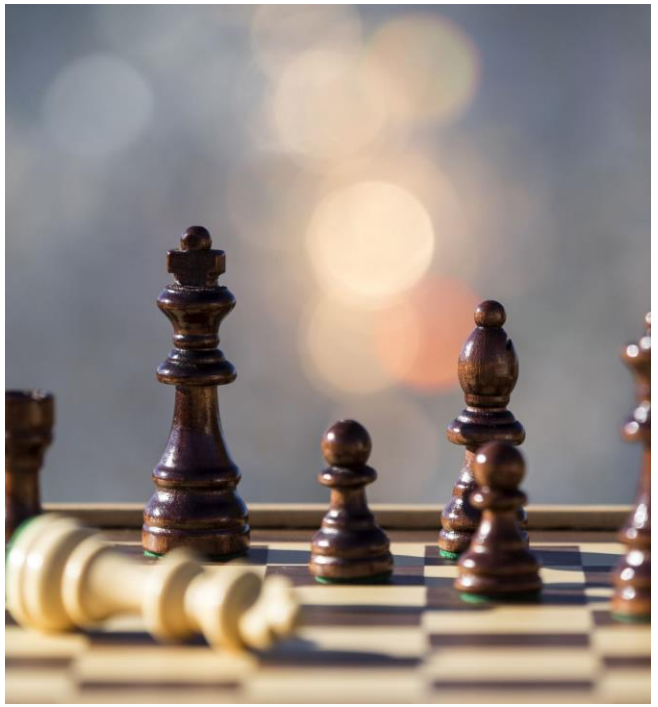
VESPER trial



	No. at risk							
ddMVAC	ypT0/is/a	109	104	98	92	89	81	44
	ypT1/2N0	45	39	38	36	34	31	15
	ypT>2N0	22	14	11	11	9	5	3
	ypN+	19	11	9	7	6	2	1
GC	ypT0/is/a	88	87	83	82	81	74	39
	ypT1/2N0	36	33	30	27	24	23	14
	ypT>2N0	36	24	18	15	11	8	5
	ypN+	34	16	11	9	6	6	2

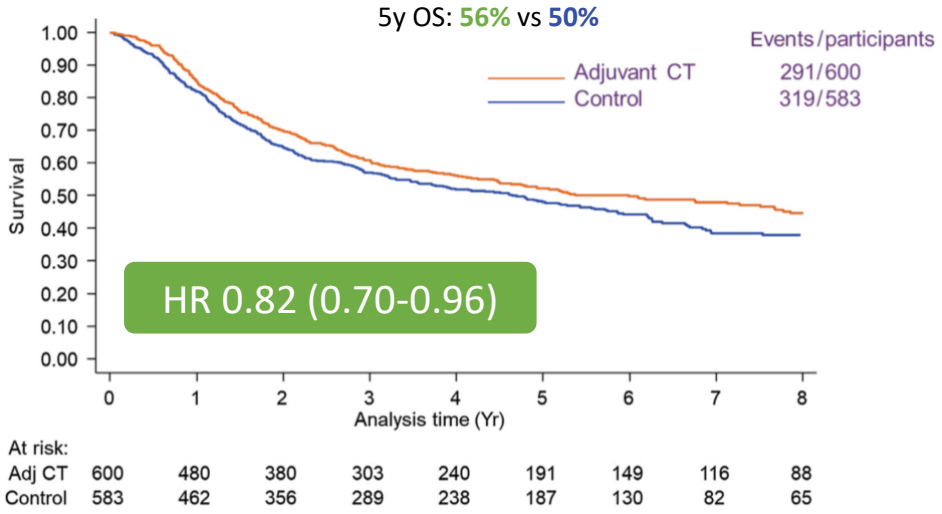
RISC & NCDB datasets

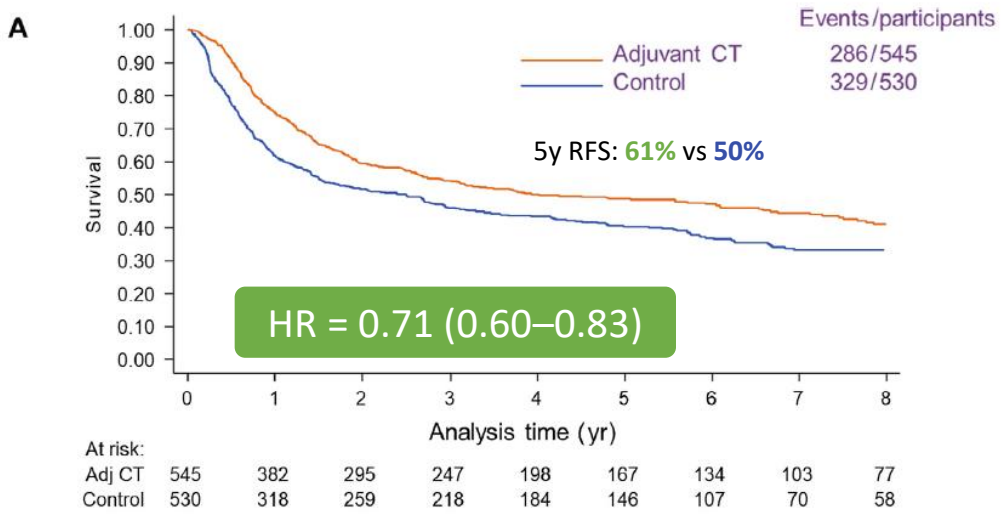




1. S Culine et al, Cancers 2023; 2. Martini A, et al. Cancer 2019

Adjuvant cisplatin-based chemotherapy should be offered to those untreated in the NA setting



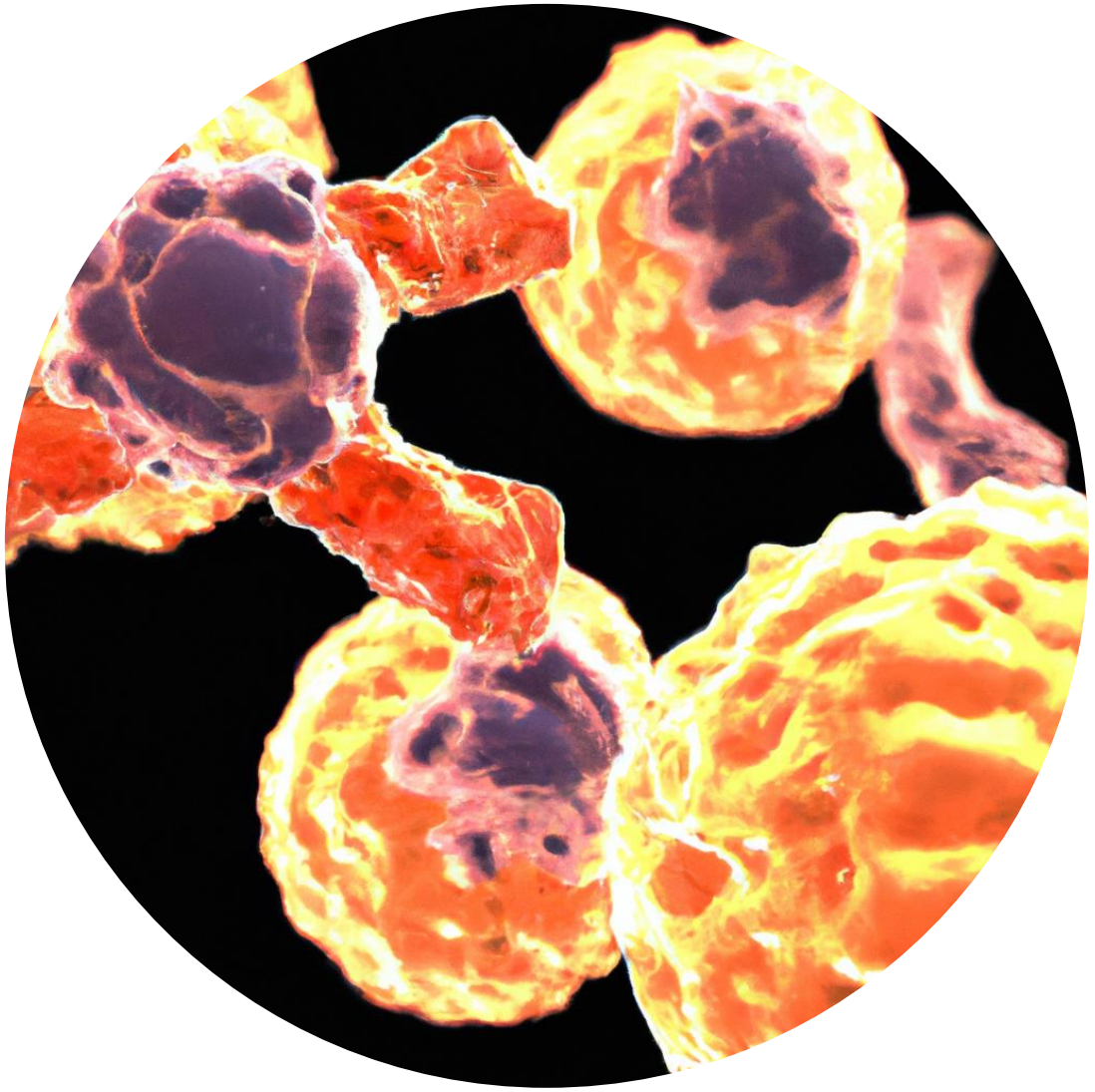


S. Burdett, et al. European Urology 2022 (10 trials, n=1183)

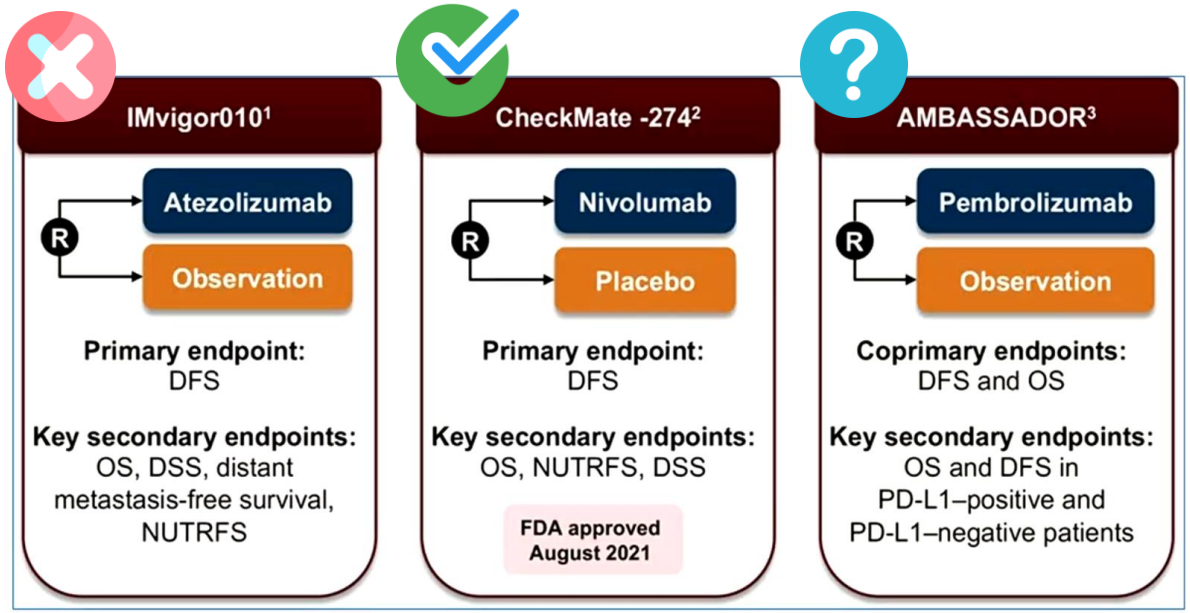
¿Rol en pacientes que no pueden recibir cisplatino?

Preguntas abiertas sobre la inmunoterapia perioperatoria en CVMI

¿Son las combinaciones de IO superiores al cisplatino?



Adjuvant immunotherapy in bladder cancer – cisplatin ineligible patients



Checkmate 274 design

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 randomization

Stratification factors

- Tumor PD-L1 status (≥ 1% vs < 1% or indeterminate)[b]
- Prior neoadjuvant cisplatin-based chemotherapy
- Nodal status

Median (range) follow-up[c] (ITT population),
36.1 (0.0-75.3) months (37.4 months for NIVO, 33.9 months for PBO)
Minimum follow-up[d] (ITT population), 31.6 months

Median (range) follow-up[c] (PD-L1 ≥ 1% population),
37.1 (0.0-75.3) months (39.8 months for NIVO, 33.3 months for PBO)

Database lock, October 20, 2022

Primary endpoints: DFS in all randomized patients (ITT population) and DFS in all randomized patients with tumor PD-L1 ≥ 1%
Secondary endpoints: NUTRFS, DSS, and OS[e]
Exploratory endpoints included: DMFS, PFS2, safety, HRQoL

[a]NCT02632409. [b]Defined by the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells using the validated Dako PD-L1 IHC 28-8 pharmDx immunohistochemistry assay. [c]Defined as time between randomization date and last known date alive (for patients who are alive) and death. [d]Defined as time from clinical cut-off date to last patient's randomization date. [e]OS will be assessed at a future database lock. OS and DSS data are not presented.
DMFS, distant metastasis-free survival; DSS, disease-specific survival; HRQoL, health-related quality of life; IV, intravenous; NUTRFS, non-urothelial tract recurrence-free survival; OS, overall survival; PFS2, second progression-free survival; Q2W, every 2 weeks; R, randomized.

DF Bajorin et al, NEJM 2021; M Galsky et al, ASCO GU 2023

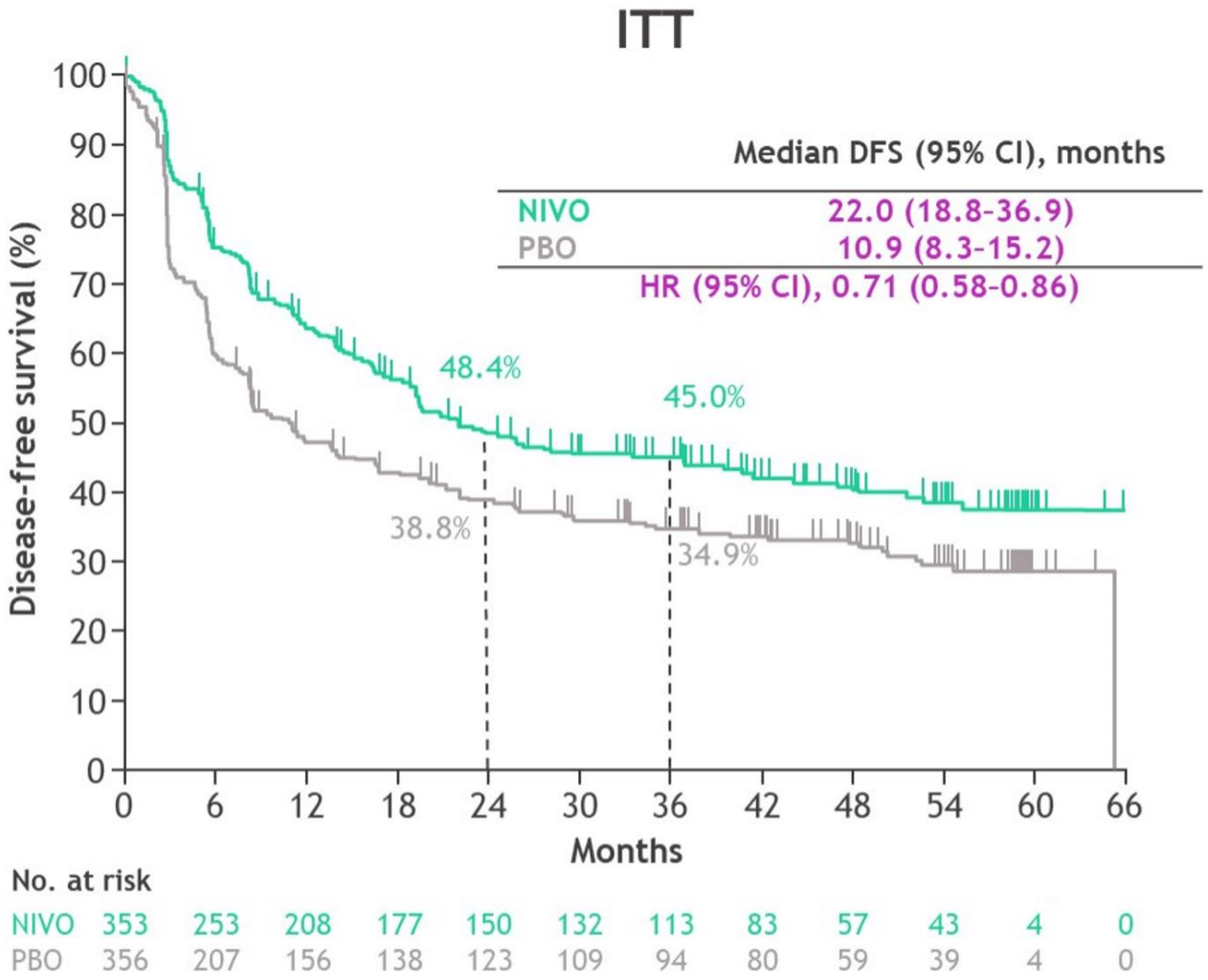
Select baseline demographic and clinical characteristics[1]

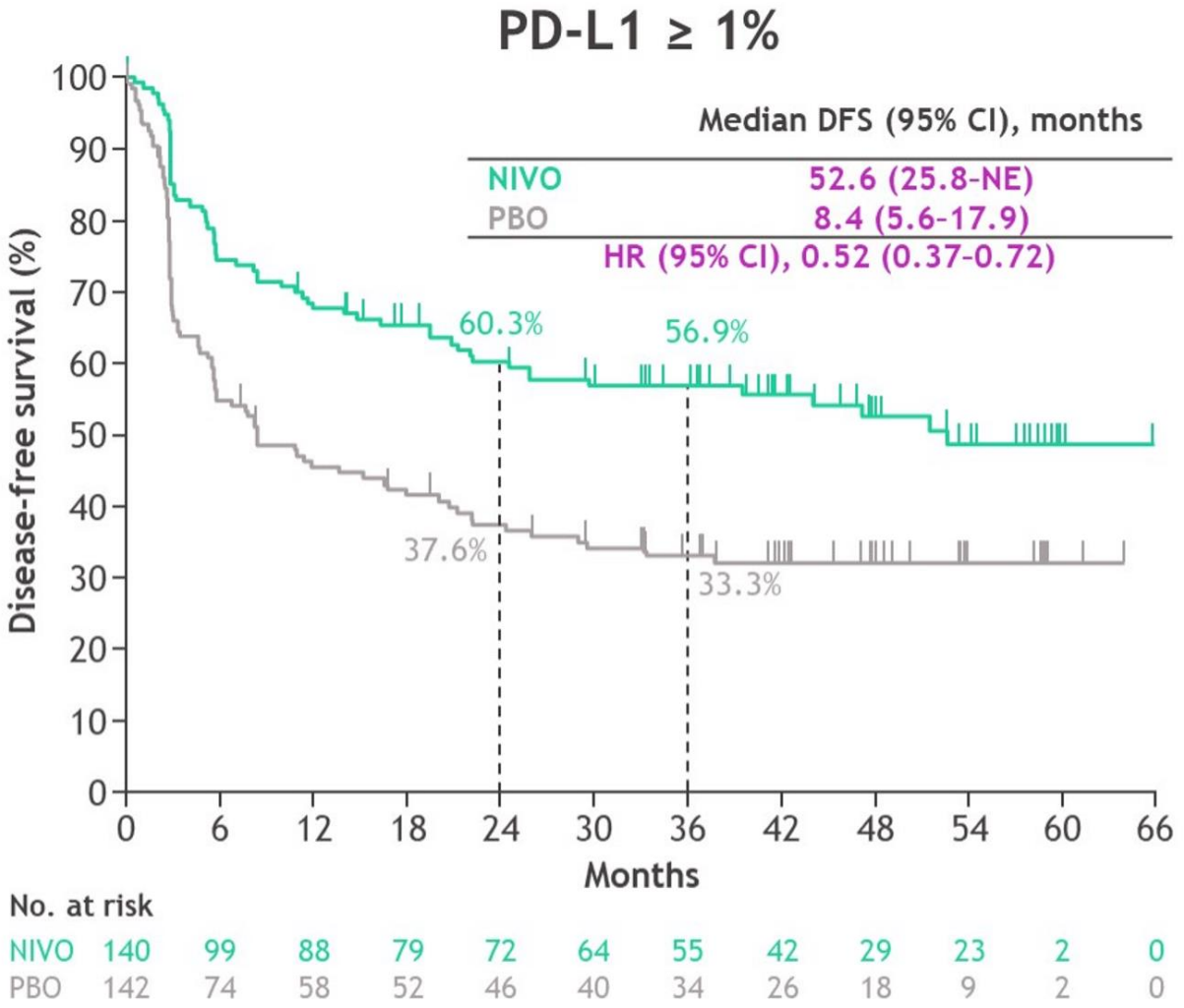
	NIVO (N = 353)	PBO (N = 356)
Mean age (range), years	65.3 (30-92)	65.9 (42-88)
Male, %	75	77
Race or ethnic group, %		
White	75	76
Asian	23	21
Black	1	1
Other/unreported	2	2
ECOG PS,[a] %		
0	63	62
1	35	35
2	2	3
Tumor origin at initial diagnosis, %		
Urinary bladder	79	79
Renal pelvis	12	15
Ureter	8	6
Tumor PD-L1 ≥ 1% as recorded at randomization by IVRS, %	40	40
Prior neoadjuvant cisplatin, %	43	44
Pathologic T stage at resection,[b,c] %		
pT0-2	23	24
pT3	58	57
pT4a	16	17
Nodal status at resection,[c] %		
N+	47	47
N0/x with < 10 nodes removed	27	28
N0 with ≥ 10 nodes removed	26	25

[a]Not reported for 1 patient in the PBO arm. [b]pTX in 1% of patients in the NIVO arm; pTis in 1% of patients in the NIVO arm and 1% of patients in the PBO arm. [c]Not reported for 1 patient each in the NIVO and PBO arm.
ECOG PS, Eastern Cooperative Oncology Group performance status; IVRS, interactive voice-response system.
1. Bajorin DF, et al. *N Engl J Med* 2021;384:2102-2114.

DF Bajorin et al, NEJM 2021; M Galsky et al, ASCO GU 2023

Adjuvant Nivolumab improves DFS



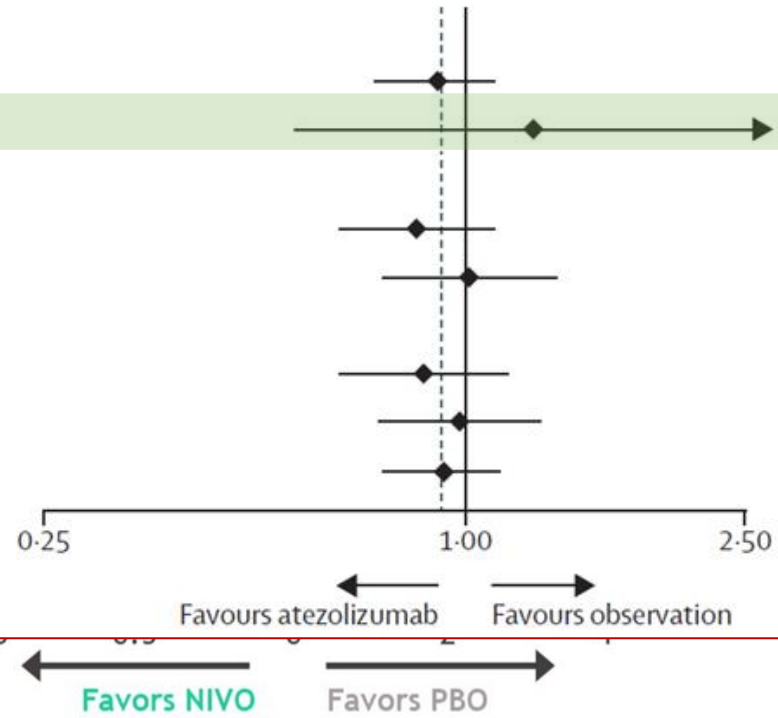


DF Bajorin et al, NEJM 2021; M Galsky et al, ASCO GU 2023

DFS by subgroups in ITT

NIVO PBO

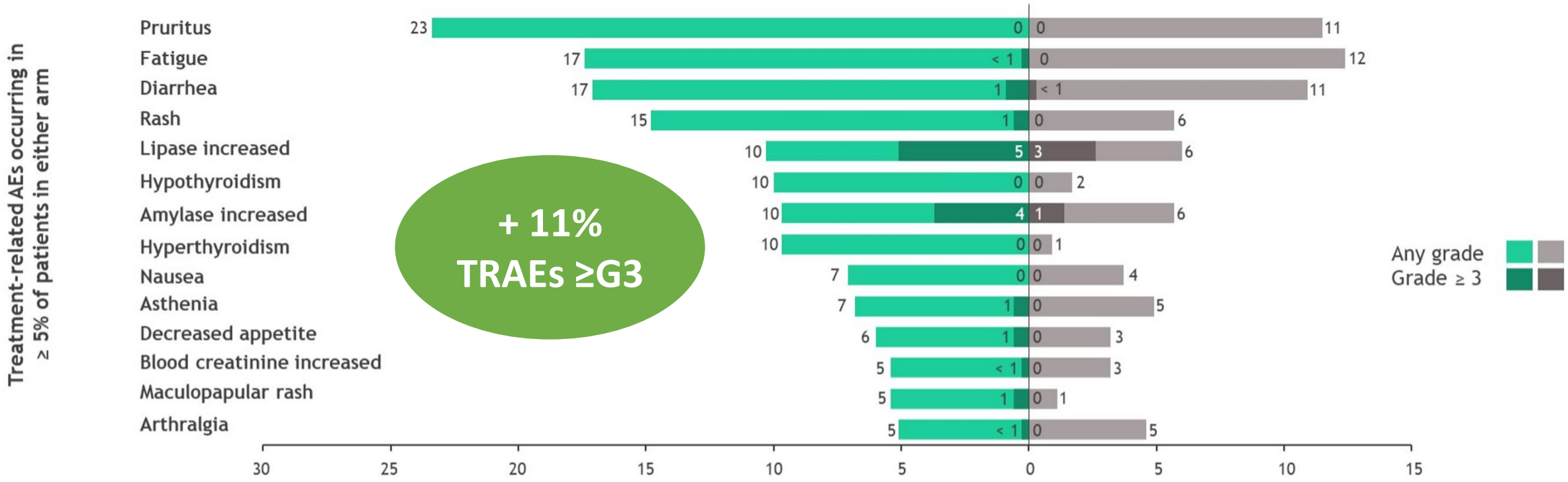
	Atezolizumab		Observation		Hazard ratio (95% CI)*
	Events/ patients	Median disease-free survival (95% CI), months	Events/ patients	Median disease-free survival (95% CI), months	
Primary tumour site†					
Bladder	197/377	19·6 (16·4–24·9)	197/378	15·8 (11·1–24·8)	0·91 (0·74–1·10)
Upper tract	15/29	14·2 (5·6–NE)	11/25	28·1 (6·8–NE)	1·25 (0·57–2·74)
PD-L1 status†					
IC0 or IC1	118/210	16·4 (12·0–20·0)	120/207	11·1 (8·3–16·6)	0·85 (0·66–1·10)
IC2 or IC3	94/196	24·8 (17·2–NE)	88/196	41·4 (17·1–NE)	1·01 (0·76–1·35)
Previous neoadjuvant chemotherapy†					
Yes	101/196	19·8 (15·9–NE)	103/189	16·5 (11·1–24·9)	0·87 (0·66–1·15)
No	111/210	16·8 (13·9–25·8)	105/214	19·4 (8·9–NE)	0·98 (0·75–1·28)
All patients	**212/406**	**19·4 (15·9–24·8)**	**208/403**	**16·6 (11·2–24·8)**	**0·93 (0·76–1·12)**



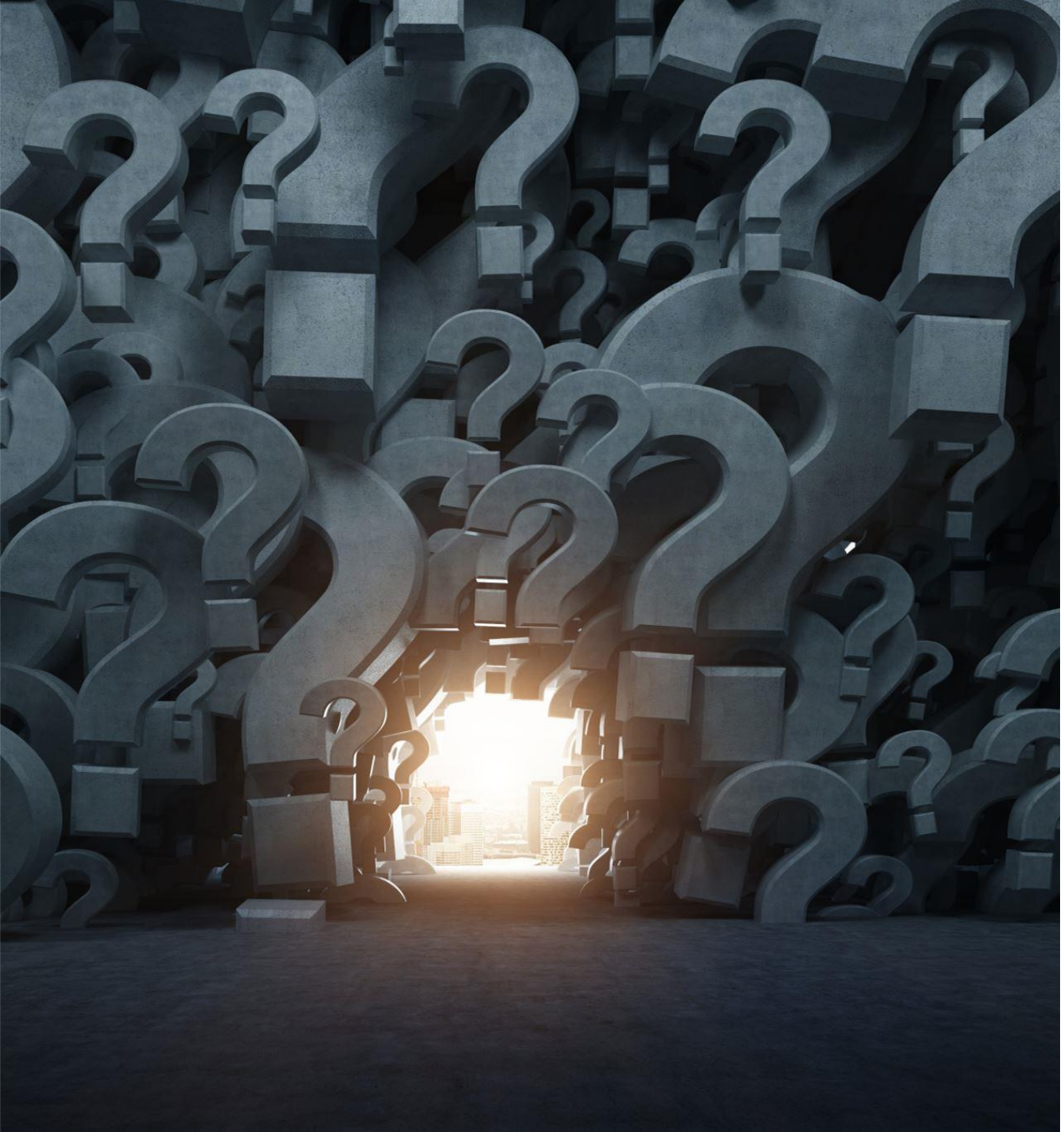
M Galsky et al, ASCO GU 2023; Bellmunt J et al, Lancet Onc 2021

Safety of adjuvant Nivolumab

	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



DF Bajorin et al, NEJM 2021; M Galsky et al, ASCO GU 2023



Will adjuvant Nivolumab derive into an OS signal?

Will adjuvant Nivolumab derive into an OS signal?

	NA Cisplatin combinations[1] N=3005	Adjuvant Cisplatin combos[2] N=1183	Adjuvant PlatGem in UTUC (POUT)[3] N=261	Adjuvant Nivolumab in ITT[4,5] N=709	Adjuvant Nivolumab in PD-L1[4,5] N=282
DFS/RFS absolute increase	9% at 5y	11% at 5y	21% at 5y	10% at 3y	24% at 3y
DFS/RFS HR	0.78 (0.71-0.86)	0.71 (0.60–0.83)	0.51 (0.35-0.76)	0.71 (0.58-0.86)	0.52 (0.37-0.72)
OS absolute increase	5% at 5y	6% at 5y	8% at 5y		
OS HR	0.86 (0.77-0.95)	HR 0.82 (0.70-0.96)	0.70 (0.46-1.06)		

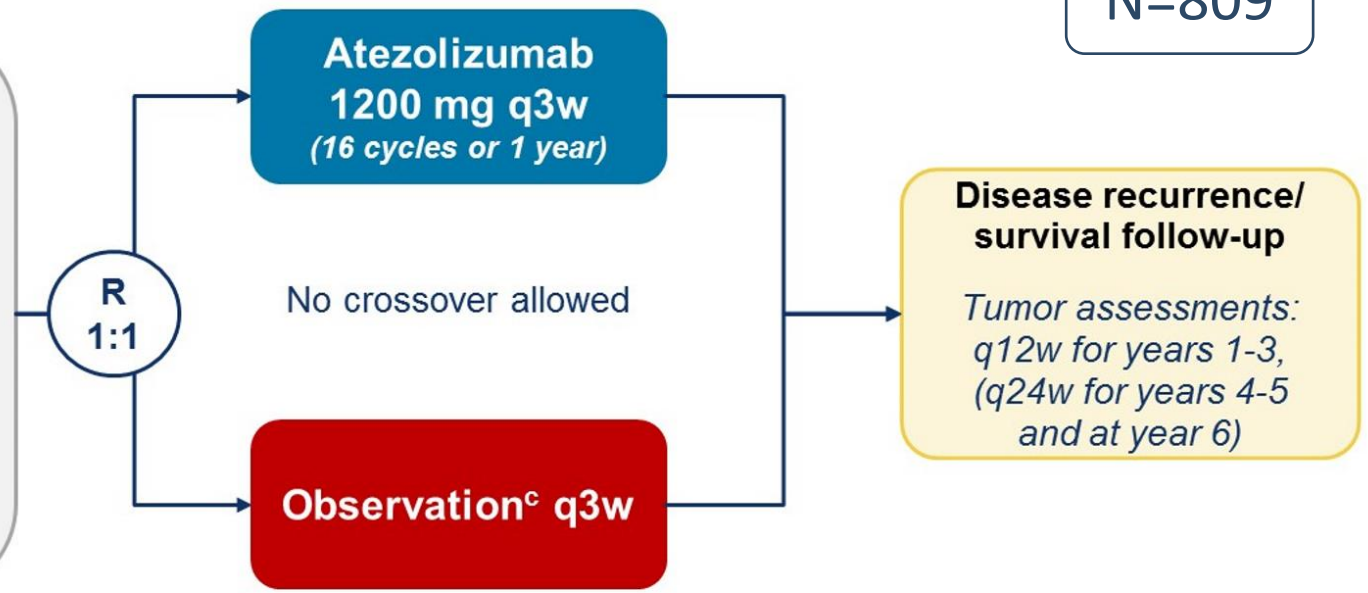
1) ABC Meta-analysis. Eur Urol 2005; 2) S. Burdett, et al. European Urology 2022; 3) Birtle et al, ASCOGU 2021; 4) DF Bajorin et al, NEJM 2021; 5) M Galsky et al, ASCO GU 2023)

IMvigor010 Study Design

N=809

Key eligibility[a]

- **High-risk MIUC (bladder, renal pelvis, ureter)**
- **Radical cystectomy/nephroureterectomy with LN dissection** within ≤ 14 weeks
  - **ypT2-T4a or ypN+** for patients treated with **NAC**[b]
  - **pT3-T4a or pN+** for patients **not treated with NAC**[b]
- No postsurgical radiation or AC
- If no prior NAC given, patient had to be ineligible for, or declined, cisplatin-based AC
- ECOG PS 0-2
- **Tissue sample for PD-L1 testing**



Stratification factors

- Number of LNs resected (< 10 vs ≥ 10)
- Prior NAC (Yes vs No)
- LN status (+ vs –)
- Tumor stage (≤ pT2 vs pT3/pT4)
- PD-L1 status[a] (IC0/1 vs IC2/3)

- **Primary endpoint:** DFS (ITT population)
- **Key secondary endpoint:** OS (ITT population)
- **Exploratory analyses:** Biomarkers including PD-L1 status
- **Safety**

AC, adjuvant chemotherapy; DFS, disease-free survival; ITT, intention to treat; LN, lymph node; MIUC, muscle-invasive UC. [a] Protocol amendments broadened eligibility to "all-comers" (initially, only PD-L1–selected patients were enrolled [IC2/3: PD-L1 expression on tumor-infiltrating immune cells (IC) ≥ 5% of tumor area [VENTANA SP142 IHC assay]) and to patients with MIUC (initially, only patients with muscle-invasive bladder cancer were enrolled). [b] Upper-tract UC staging: ypT2-4 or ypN+ (with NAC) and pT3-4 or pN+ (without NAC). [c] Alternating clinic visits and phone calls.

Bellmunt J et al, Lancet Onc 2021

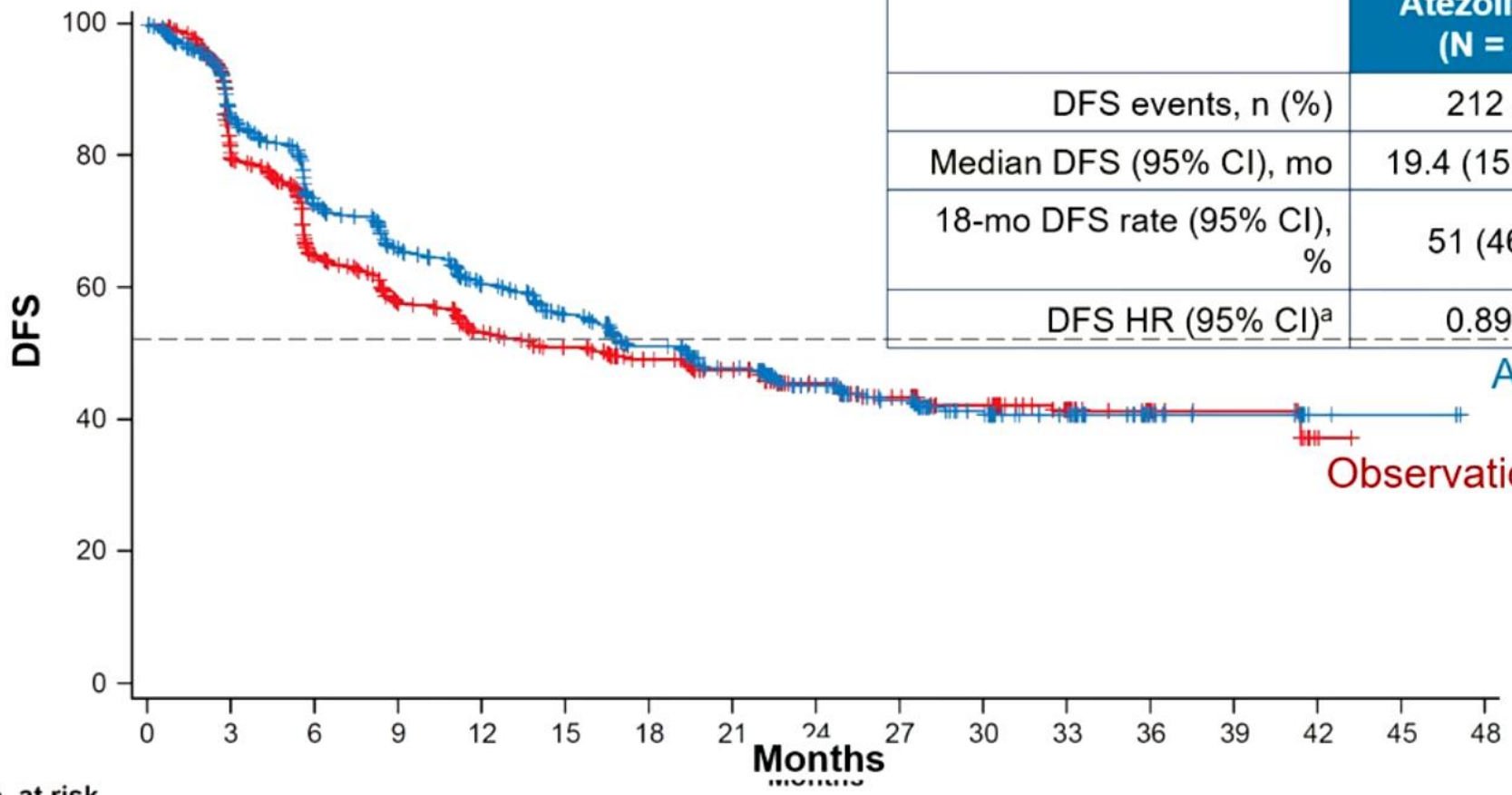
IMvigor010 patient characteristics

	Atezolizumab (N = 406)	Observation (N = 403)
Median age, years (range)	67 (31-86)	66 (22-88)
Male, n (%)	**322 (79)**	**316 (78)**
ECOG PS, n (%)		
0	248 (61)	259 (64)
1	142 (35)	130 (32)
2	16 (4)	14 (4)
Primary tumor site, n (%)		
Bladder	**377 (93)**	**378 (94)**
Upper tract (ureter, renal pelvis)	29 (7)	25 (6)
Prior neoadjuvant chemotherapy, n (%)[a]	**196 (48)**	**189 (47)**
Pathologic tumor stage, n (%)[b]		
pT2N0	34 (8)	39 (10)
pT3N0	**124 (31)**	**119 (30)**
pT4N0	**32 (8)**	**33 (8)**
≤pT2-4 and pN+, n (%)[a]	**212 (52)**	**208 (52)**
PD-L1 IHC status, n (%)[c]		
IC0	57 (14)	66 (16)
IC1	152 (37)	138 (34)
IC2	147 (36)	144 (36)
IC3	50 (12)	55 (14)

Bellmunt J et al, Lancet Onc 2021

Imvigor010: Atezo did not improve DFS against Observation

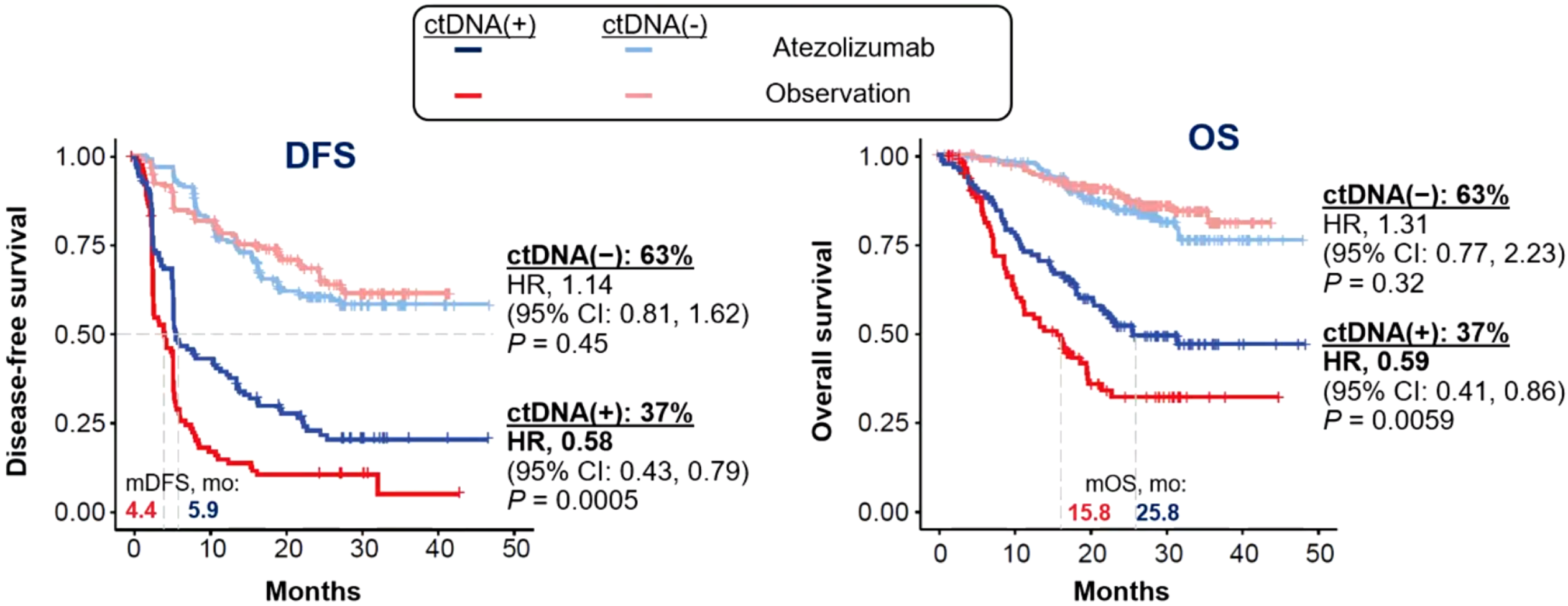
	Atezolizumab (N = 406)	Observation (N = 403)
DFS events, n (%)	212 (52)	208 (52)
Median DFS (95% CI), mo	19.4 (15.9, 24.8)	16.6 (11.2, 24.8)
18-mo DFS rate (95% CI), %	51 (46, 56)	49 (44, 54)
DFS HR (95% CI)[a]	0.89 (0.74, 1.08); *P* = 0.2446[b]	



Data cutoff: November 30, 2019.
Median follow-up: 21.9 mo. [a]
Stratified by post-resection tumor stage, nodal status and PD-L1 status. [b] 2-sided.

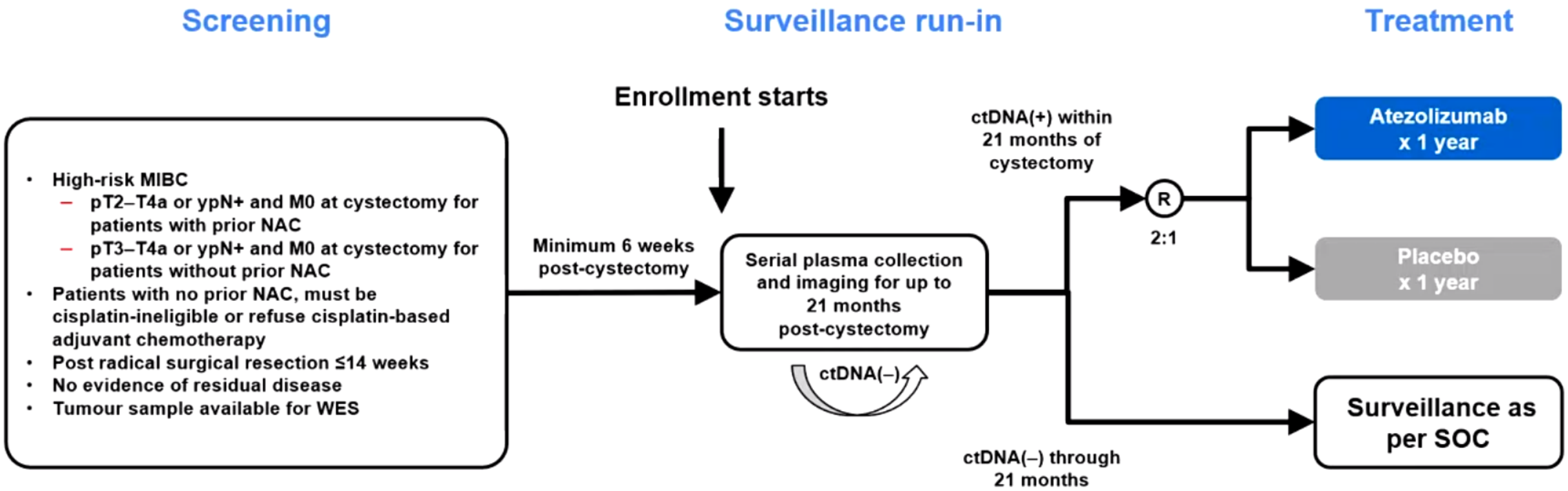
Bellmunt J et al, Lancet Onc 2021

ctDNA(+) patients had improved DFS and OS with atezolizumab vs observation in IMvigor010 adj trial



Powles T, et al. Nature 2021

IMvigor011 study design

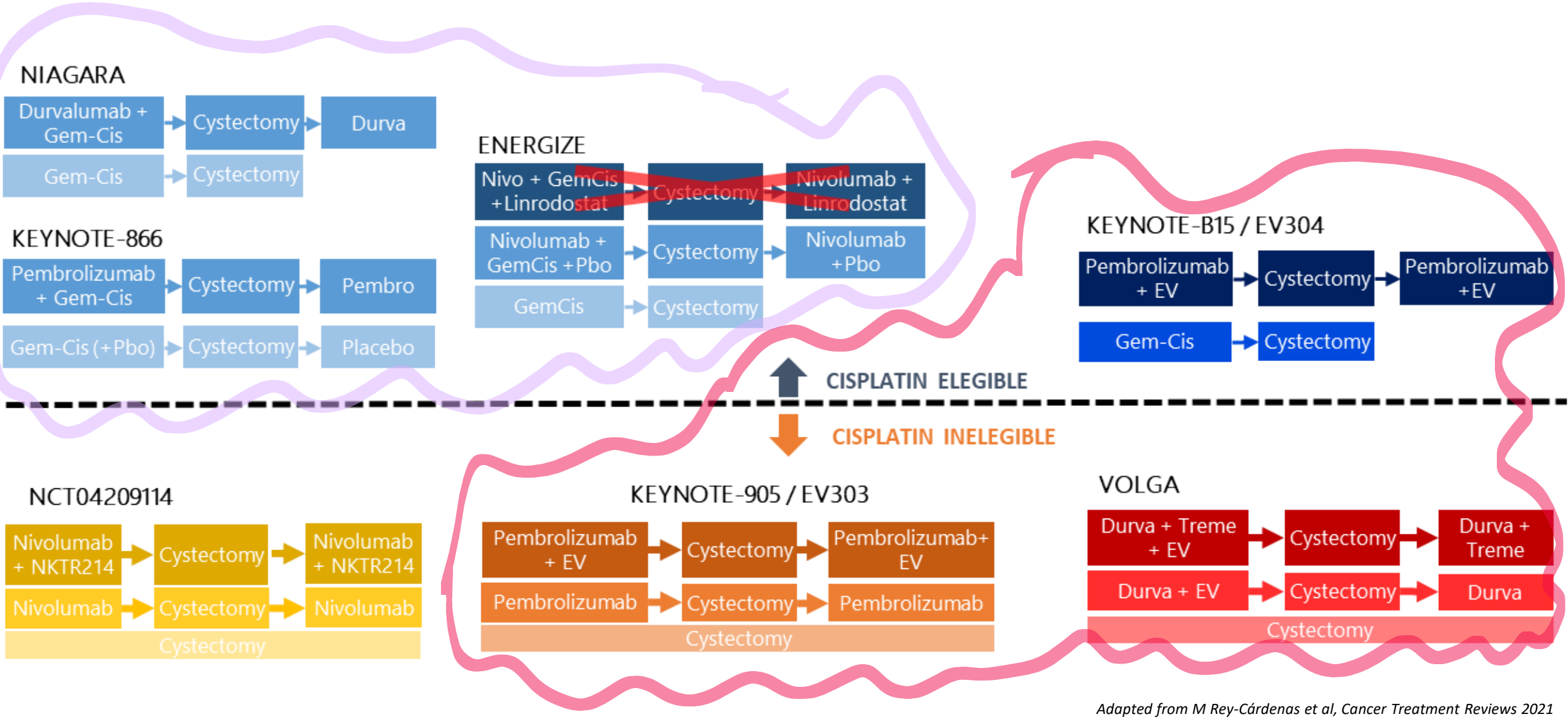


Stratification factors

- Nodal status (positive vs negative)
- Tumour stage after cystectomy (≤pT2 vs pT3/pT4)
- PD-L1 IHC status (IHC score of IC0/1 vs IC2/3)
- Time from cystectomy to first ctDNA(+) sample (≤20 weeks vs >20 weeks)

Bellmunt J et al, Lancet Onc 2021

Phase 3 trials testing perioperative IO in MIBC



Adapted from M Rey-Cárdenas et al, Cancer Treatment Reviews 2021

Will the phase 3 trials beat NA Cisplatin?

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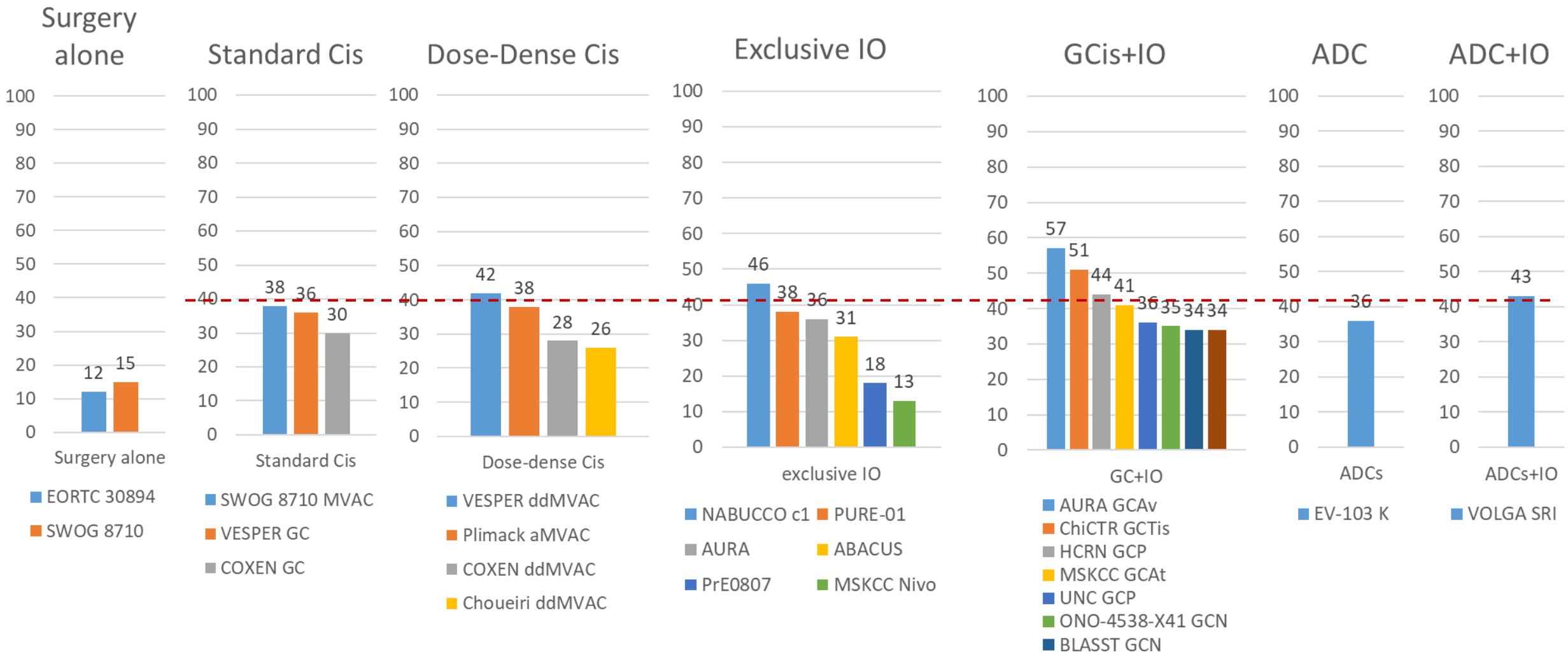
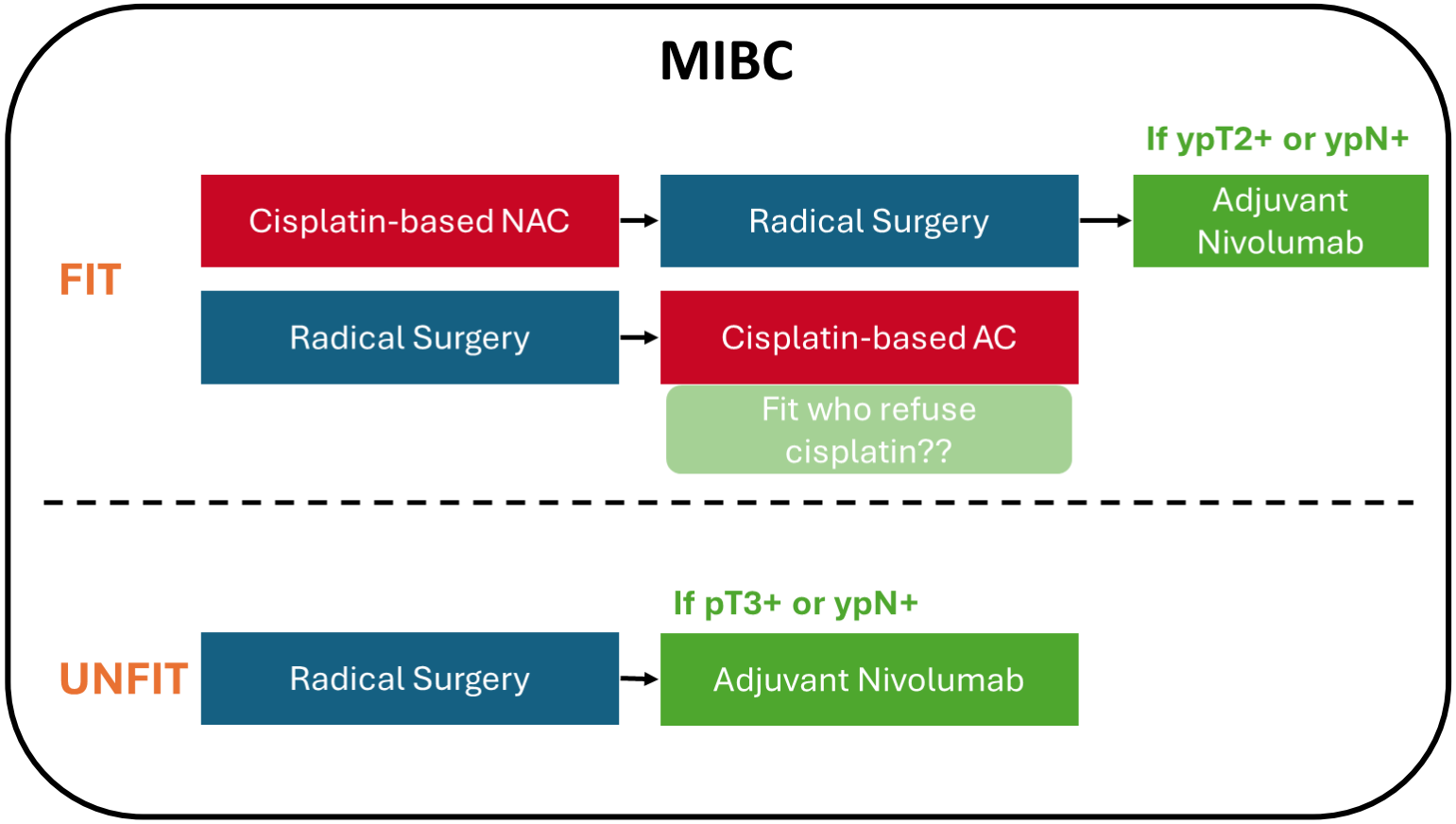
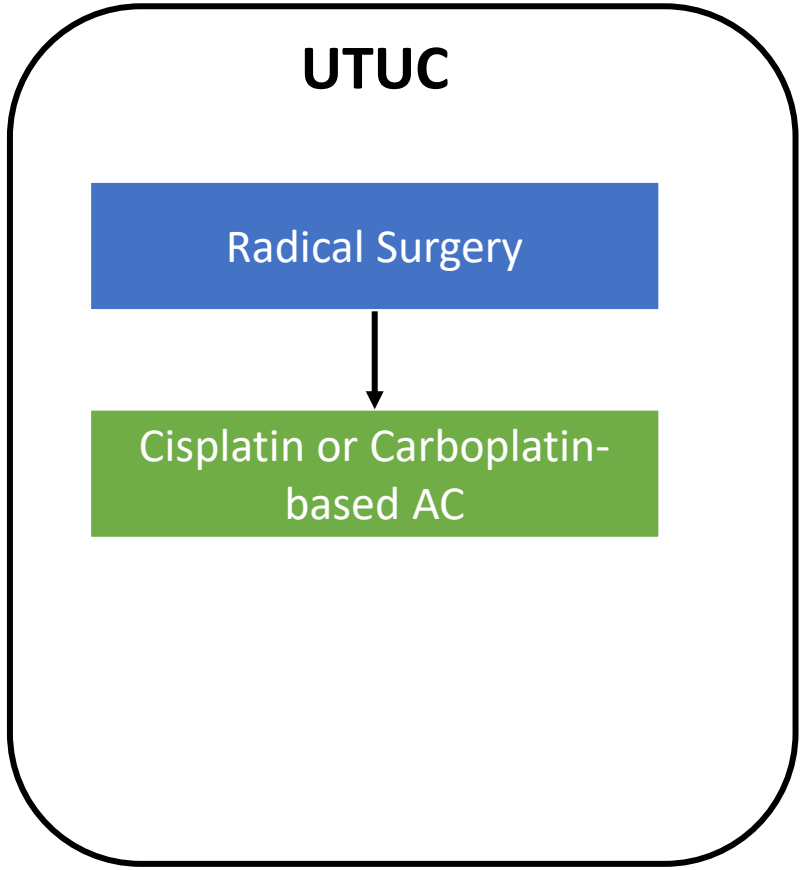


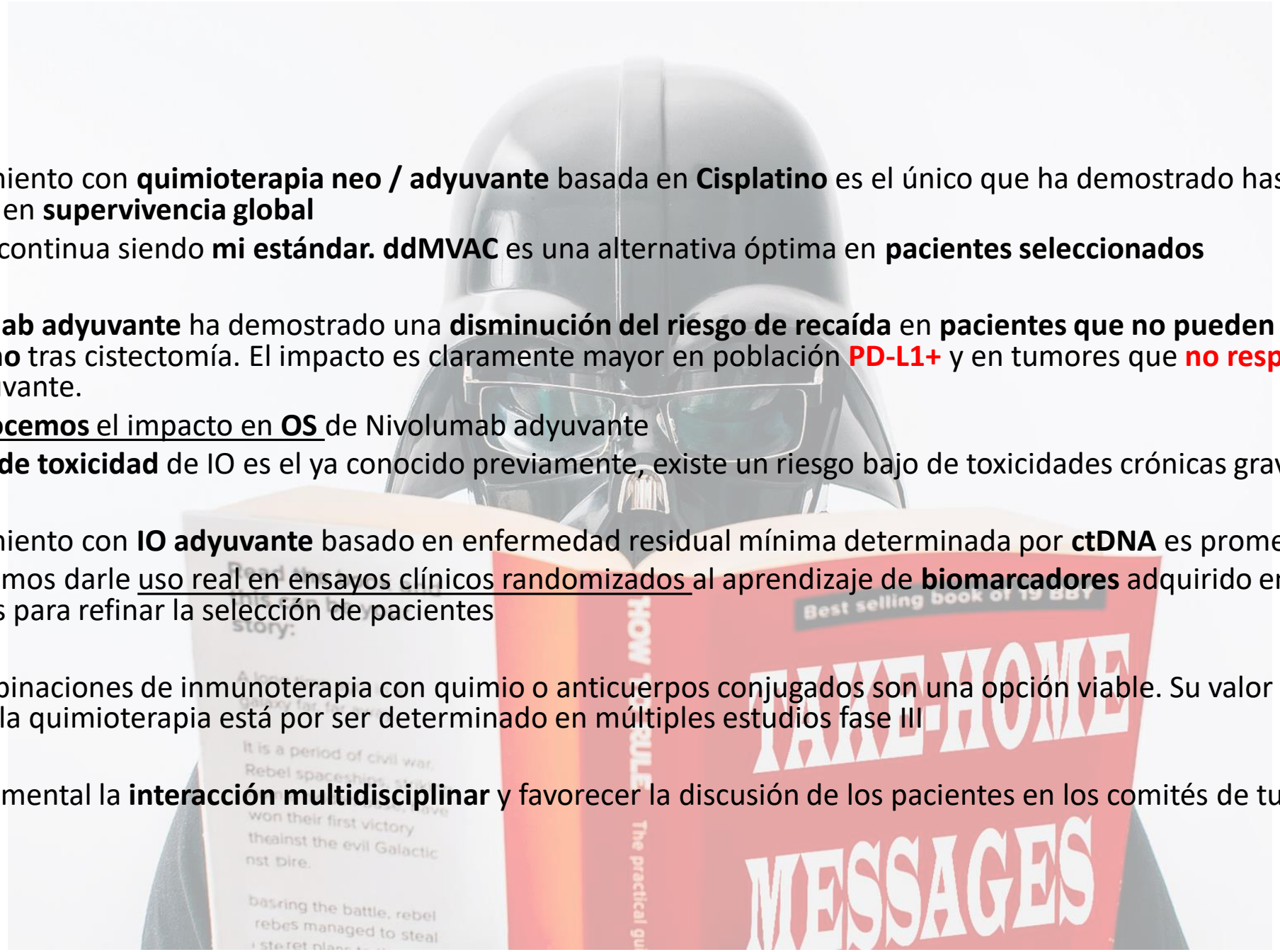
Adapted from BM Faltas, ASCO 2021

Perioperative chemo & IO in MIBC and UTUC – my point of view






Read the book and this can be your story:
A long time ago, in a galaxy far, far away...
It is a period of civil war. Rebel spaceships, striking from a hidden base, have won their first victory
HOW TO RULE
Best selling book of 19 BBY
TAKE-HOME MESSAGES



- El tratamiento con **quimioterapia neo / adyuvante** basada en **Cisplatino** es el único que ha demostrado hasta la fecha impacto en **supervivencia global**
- **CisGem** continua siendo **mi estándar. ddMVAC** es una alternativa óptima en **pacientes seleccionados**

- **Nivolumab adyuvante** ha demostrado una **disminución del riesgo de recaída** en **pacientes que no pueden recibir Cisplatino** tras cistectomía. El impacto es claramente mayor en población **PD-L1+** y en tumores que **no responden a QT** neoadyuvante.
- **Desconocemos** el impacto en **OS** de Nivolumab adyuvante
- El **perfil de toxicidad** de IO es el ya conocido previamente, existe un riesgo bajo de toxicidades crónicas graves

- El tratamiento con **IO adyuvante** basado en enfermedad residual mínima determinada por **ctDNA** es prometedor
- Necesitamos darle uso real en ensayos clínicos randomizados al aprendizaje de **biomarcadores** adquirido en los fase 3 pivotales para refinar la selección de pacientes

- Las combinaciones de inmunoterapia con quimio o anticuerpos conjugados son una opción viable. Su valor añadido frente a la quimioterapia está por ser determinado en múltiples estudios fase III

- Es fundamental la **interacción multidisciplinar** y favorecer la discusión de los pacientes en los comités de tumores


GRACIAS!!