

foro debate oncología

Zaragoza 26-29 septiembre 2023



Tratamiento Adyuvante y Neoadyuvante: Estado del Arte

Dr. Ovidio Fernández Calvo
Servicio Oncología Médica.
C. H.U. Ourense
Zaragoza 27 Septiembre 2023

Disclosures

- **Consultant or Advisory Role:** Astellas Pharma, Pfizer, Bristol-Myers-Squibb, Ipsen, Merck, Eisai
- **Speaking honoraria:** Novartis, Bristol-Myers-Squibb, Ipsen, Roche, Astellas Pharma, Bayer,
- **Travel/Accommodations:** Bristol-Myers-Squibb, Ipsen, Astellas



1. Neoadjuvant qt
2. Adjuvant qt
3. Adjuvant immunotherapy



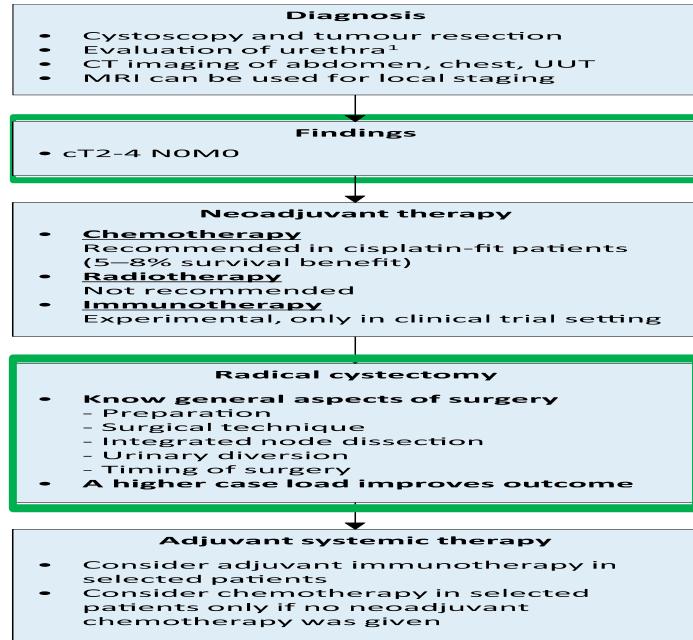
1. Neoadjuvant qt

2. Adjuvant qt

3. Adjuvant immunotherapy

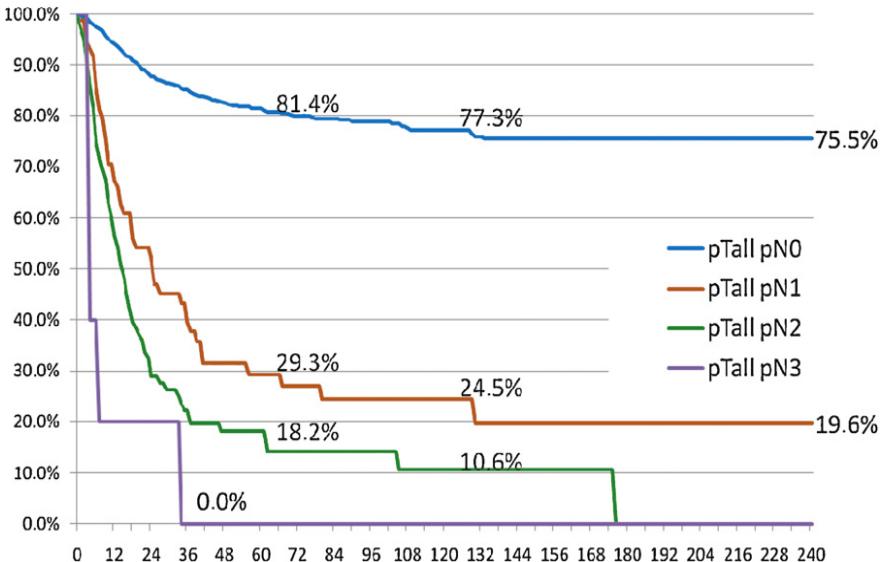
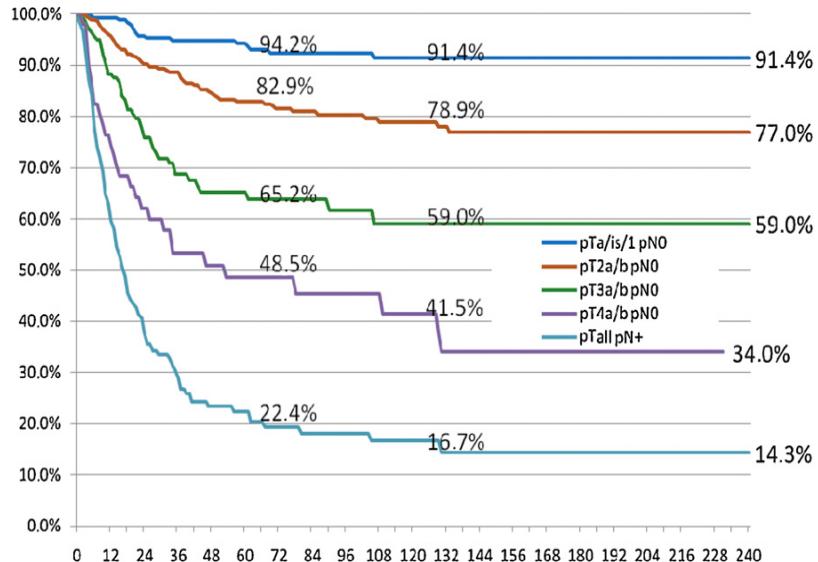


Therapeutic landscape in muscle-invasive UC



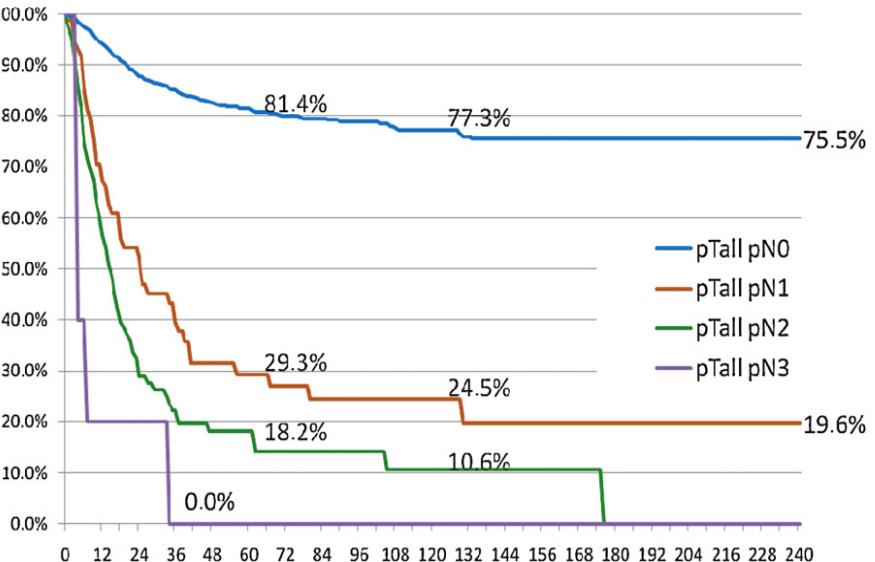
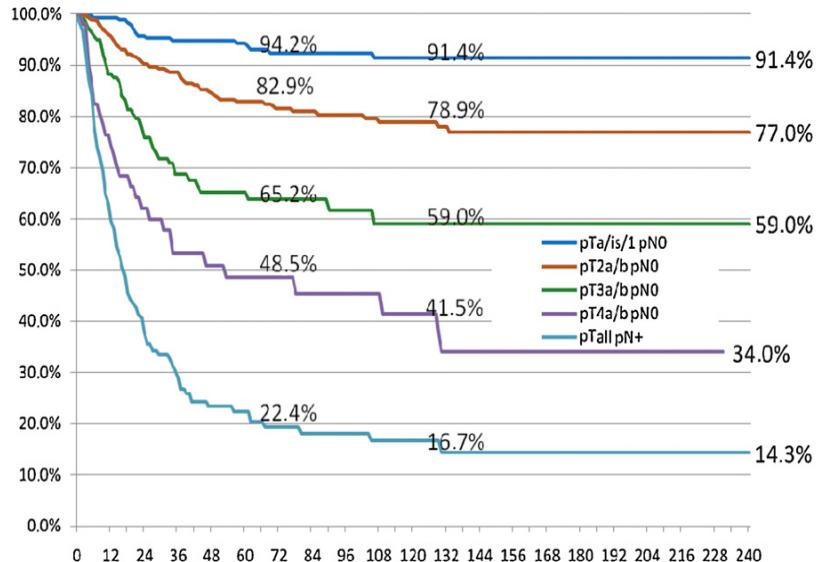


Disease specific survival according to the maximum tumor stage and lymph node status





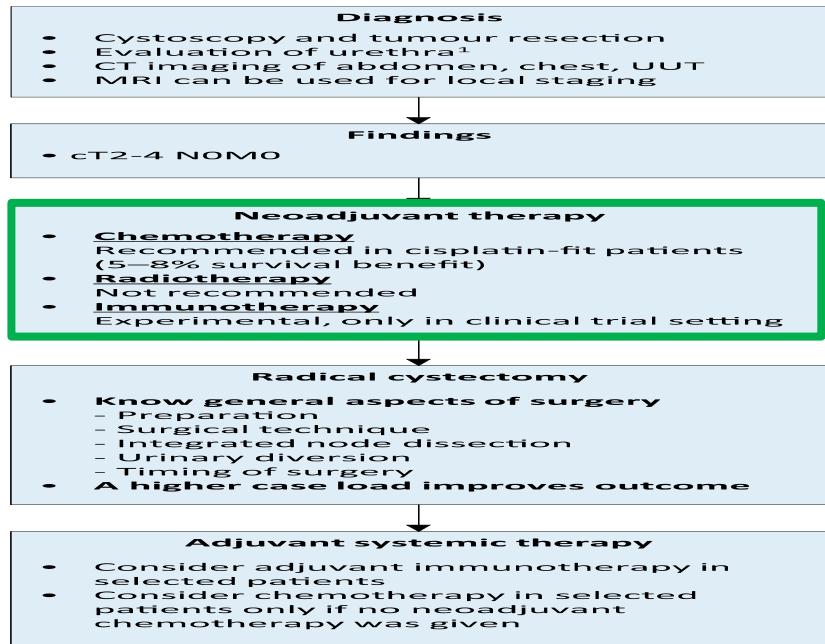
Disease specific survival according to the maximum tumor stage and lymph node status



Hautmann RE et al, Eur Urol 2012

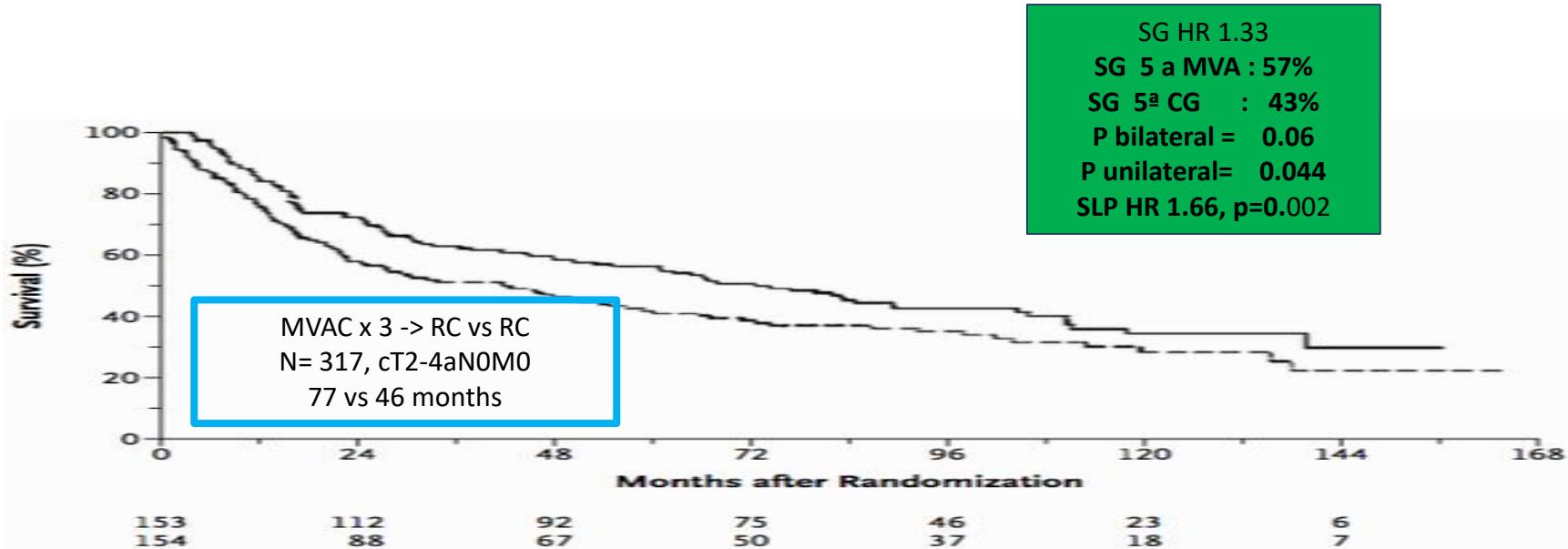


Therapeutic landscape in muscle-invasive UC





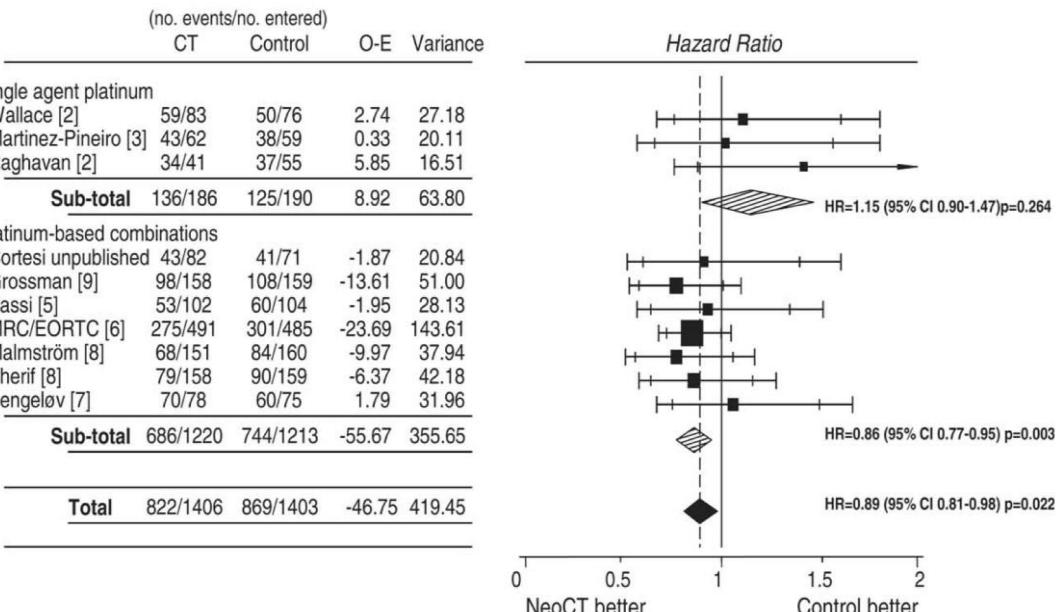
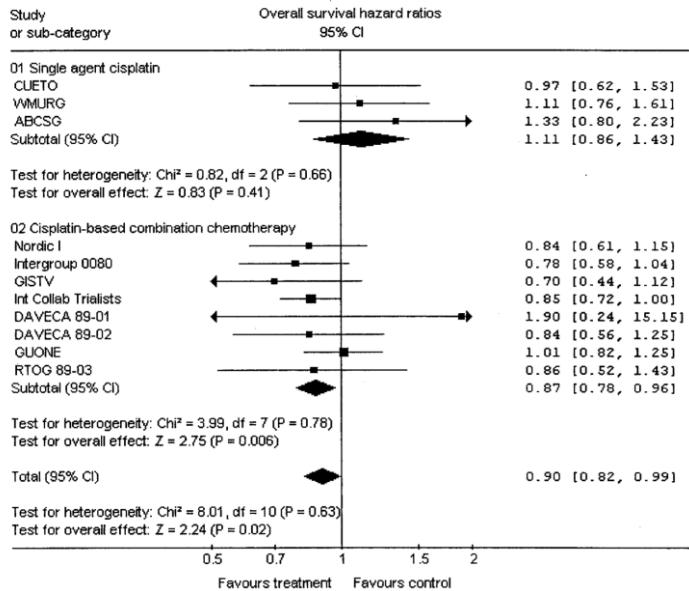
Neoadjuvant QT: SWOG 8710



Grossman HB et al. N Engl J Med 2003; 349:859



Neoadjuvant QT: Meta-analysis





Vesper Trial

Chemotherapy



Vesper Trial

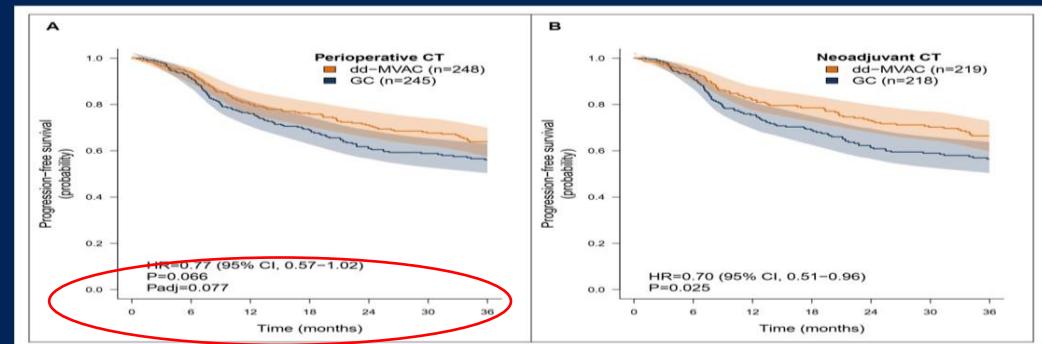
- **500 patients included in 28 centers from 2013 to 2018**
(493 patients available for intent-to-treat analysis)
- **Adjuvant (n=56) and Neoadjuvant (n=437) (88%)**
- **Primary end-point : Progression Free Survival at 3 years**
- **Final analysis : Overall and Specific Survival at 5 years**



Vesper Trial

PFS at 3 years

2021 ESMO congress
16-21 September 2021



Perioperative dd-MVAC improve 3-y PFS over GC

In the neoadjuvant group, better bladder tumor local control with a significant improvement on 3-y PFS in the dd-MVAC arm

Pfister et al. J Clin Oncol 2022

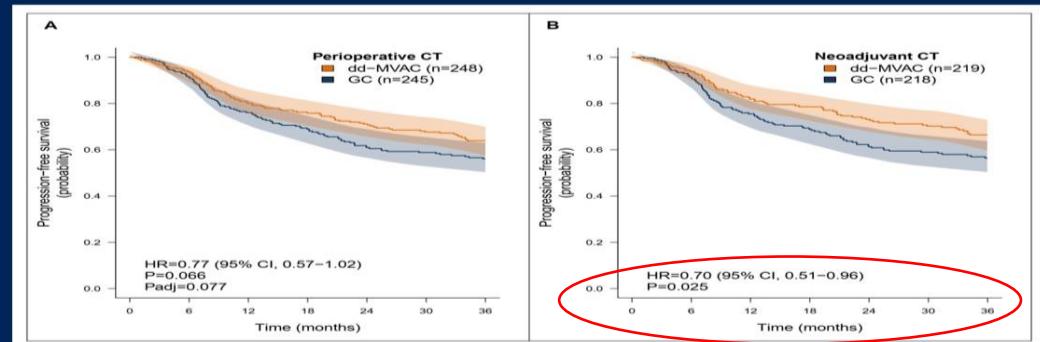
Pfister C, et al. ASCO 2023



Vesper Trial

PFS at 3 years

2021 ESMO congress
16-21 September 2021



Perioperative dd-MVAC improve 3-y PFS over GC

In the neoadjuvant group, better bladder tumor local control with a significant improvement on 3-y PFS in the dd-MVAC arm

Pfister et al. J Clin Oncol 2022

Pfister C, et al. ASCO 2023

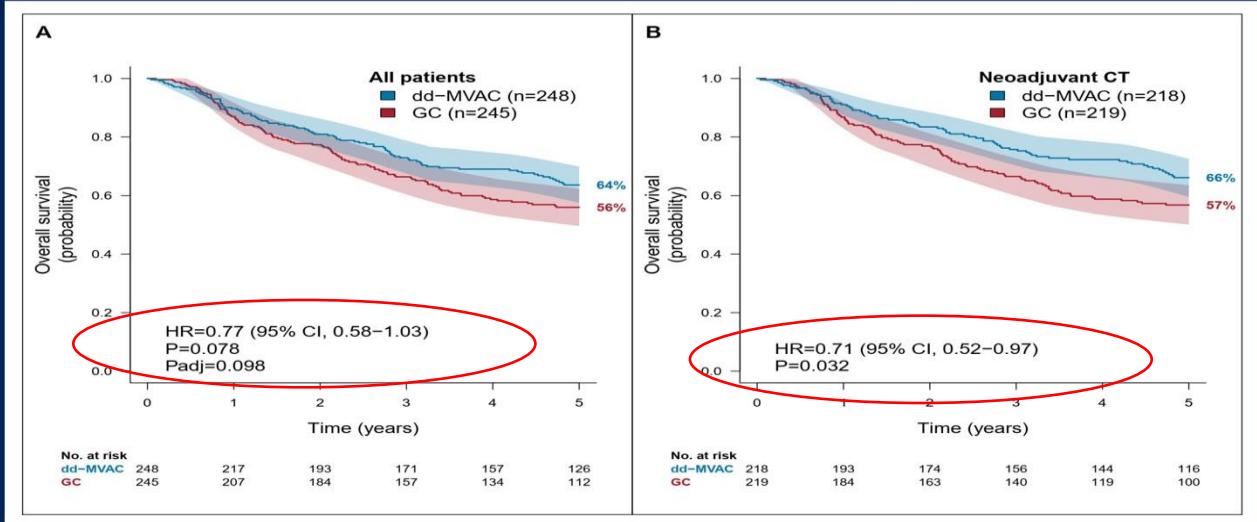


Vesper Trial

10

Results (1)

Overall Survival at 5 years





Therapeutic landscape in muscle-invasive UC

MIUC T2-T4a: Realizar QT neoadyuvante
basada en Cisplatino siempre que sea posible



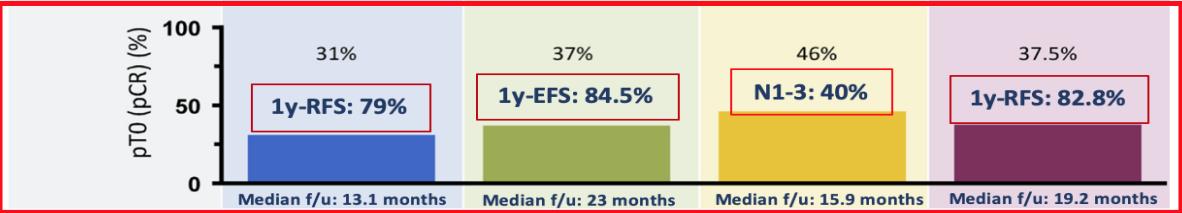
Neoadjuvant Cisplatin-Based Chemotherapy

- Meta-analyses show an absolute 5-yr OS improvement of 5%-8% with NAC
- dd-M-VAC and GC are both standard options
- High risk of recurrence despite NAC and surgery
- 50% of patients deemed ineligible for NAC
- Lack of neoadjuvant treatment options for cisplatin-ineligible patients with MIBC



IO neoadjuvant studies

	Atezolizumab	Pembrolizumab	Nivolumab + Ipilimumab	Durvalumab + Tremelimumab
Study phase	II ABACUS	II PURE-01	Ib NABUCCO	I/II MDACC
No. patients	95	114	24	28
Cisplatin eligibility	No Residual disease	Yes Predominant VH (16%)	No	No High-risk features
Schedule	2 cycles	3 cycles	3 cycles	2 cycles
Prevalence PD-L1 positivity	41%	59%	63%	N/A
PD-L1 positivity cut-off values	IC ≥5%	CPS ≥10%	CPS ≥10%	N/A
Pre-treatment clinical tumor stage				



- ✓ > 90% patients underwent radical cystectomy
- ✓ Neoadjuvant IO did not delay planned surgery
- ✓ No unexpected toxicities

Powles T, et al. Nat Med 2019;25(11):1706.
Necchi A, et al. Eur Urol 2020;77(4):439.

Van Dijk N, et al. Nat Med 2020 [online ahead of print].
Gao J, et al. Nat Med 2020 [online ahead of print].
Weis XX, et al. J Clin Oncol 2020;38(suppl 6;abstr507).



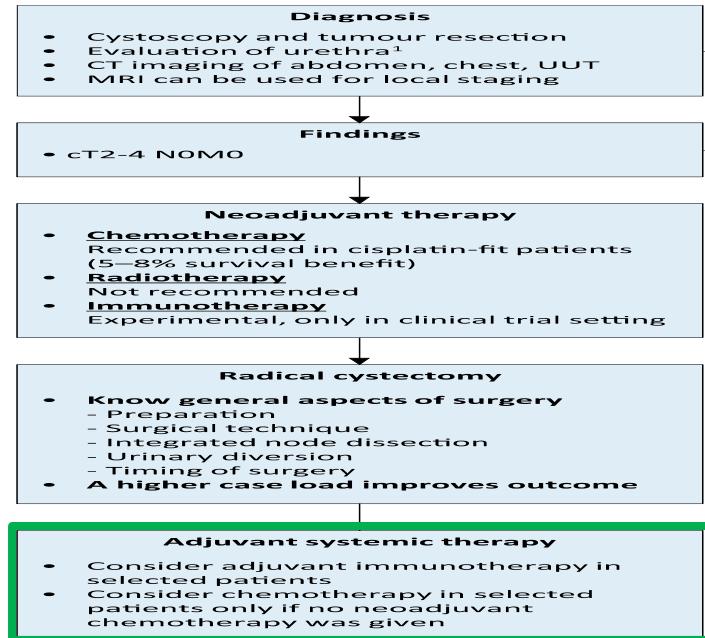
1. Neoadjuvant qt

2. Adjuvant qt

3. Adjuvant immunotherapy



Therapeutic landscape in muscle-invasive UC





Adjuvant Chemotherapy

Summary of phase 3 clinical trial for adjuvant chemotherapy

	EORTC 30994	SOGUG 99/01	Cognetti et al.
N	284	142	194
Phase	3	3	3
Stage	pT3-T4 pN1-3	pT3-pT4 pN+	pT2-pT4 pN0-2
Regimen	CDDP/gemcitabine MVAC Dd-MVAC	CDDP 70 mg/m ² D1 Gemcitabine 1000mg/m ² D1,D8 Paclitaxel 80 mg/m ² D1,D8	CDDP 70mg/m ² D1 Gemcitabine 1000mg/m ² D1,D8;D15
Primary endpoint	Overall survival	Overall survival	Overall survival
Follow up	7 years	29.8 months	35 months
5 years DFS	47.6 % vs 31.8%	NA	37.2% vs 42.3%
5 years OS	53.6% vs 47.7%	60% vs 31%	43.4% vs 53.7%

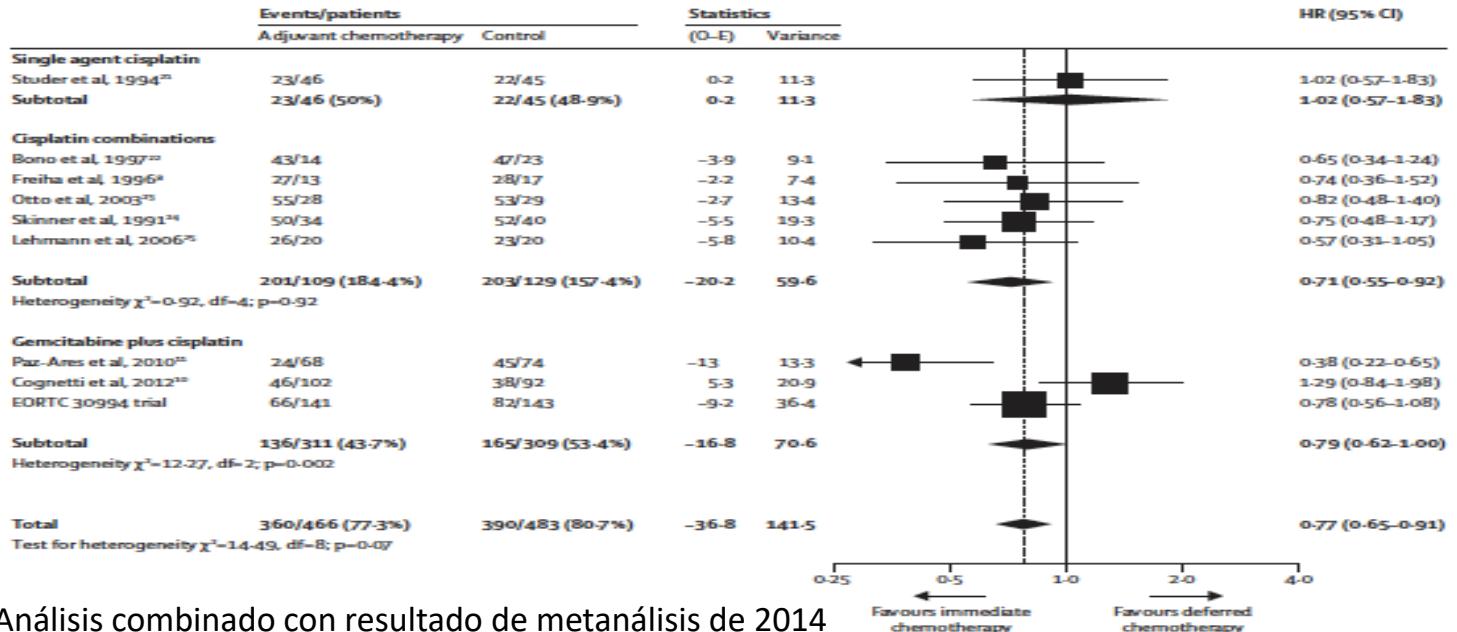
Sternberg CN, et al. Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3–pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial. Lancet Oncol 2015; 16:76-88

Paz A, et al. Randomized phase III trial comparing adjuvant paclitaxel/gemcitabine/cisplatin (PGC) to observation in patients with resected invasive bladder cancer: Results of the Spanish Oncology Genitourinary Group (SOGUG) 99/01 study. Journal of Clinical Oncology 2010 28:18_suppl, LBA451B-LBA451B

Cognetti F, et al. Adjuvant chemotherapy with cisplatin and gemcitabine versus chemotherapy at relapse in patients with muscleinvasive bladder cancer submitted to radical cystectomy: an Italian, multicenter, randomized phase III trial. Ann Oncol 2012; 23:695-700



Adjuvant QT meta-analysis

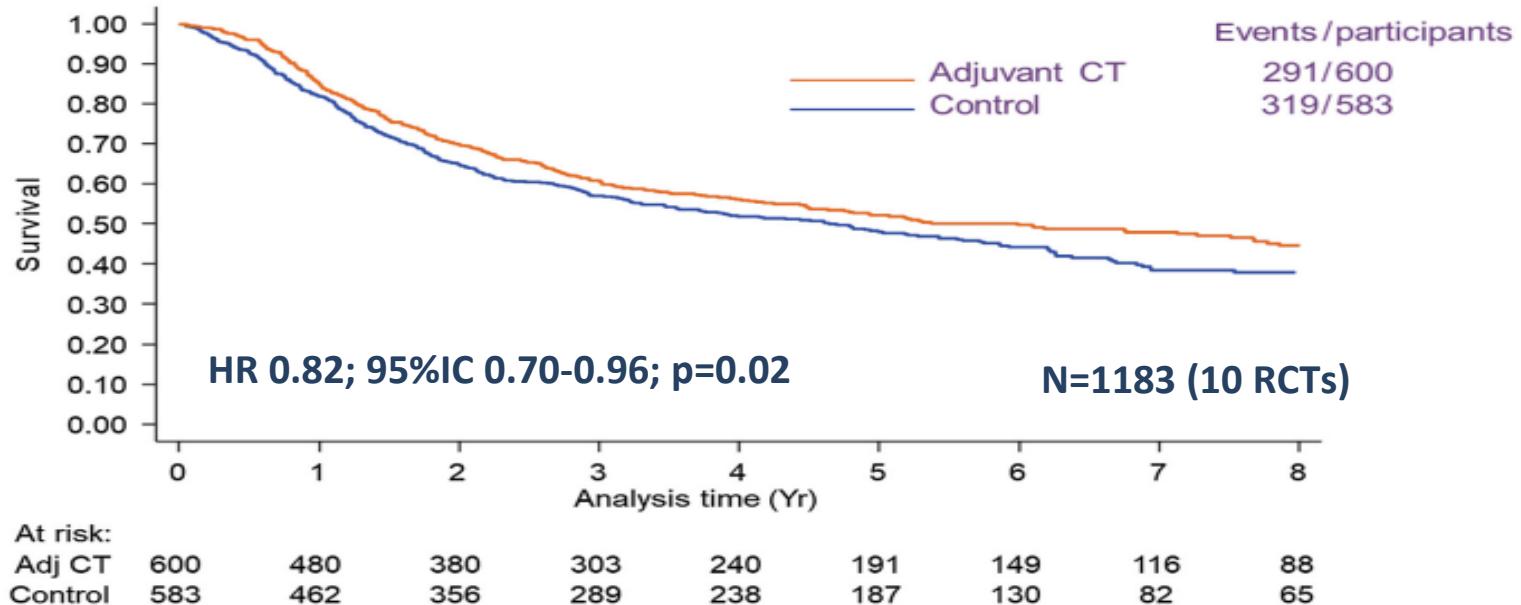


- Análisis combinado con resultado de metanálisis de 2014
- Reducción del riesgo de muerte: 23%

Sternberg CN et al, Lancet Oncol 2015;16:76



Adjuvant Chemotherapy



1. ABC Meta-Analysis Collaborators Group. Eur Urol. 2022; 81:50.



Unmet needs in high-risk MIBC

- High risk of recurrence and mortality in MIUC
- Cisplatin ineligibility (Neo and adjuvant scenario)
- Barriers to implement perioperative treatment
- High risk of relapse although perioperative QT + RC



Are these the only criteria that we use?

Panel: Consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy

Patients meeting at least one of the following are considered "unfit"

- WHO or ECOG performance status of 2, or Karnofsky performance status of 60–70%
- Creatinine clearance (calculated or measured) less than 1 mL/s
- CTCAE version 4, grade 2 or above audiometric hearing loss
- CTCAE version 4, grade 2 or above peripheral neuropathy
- NYHA class III heart failure

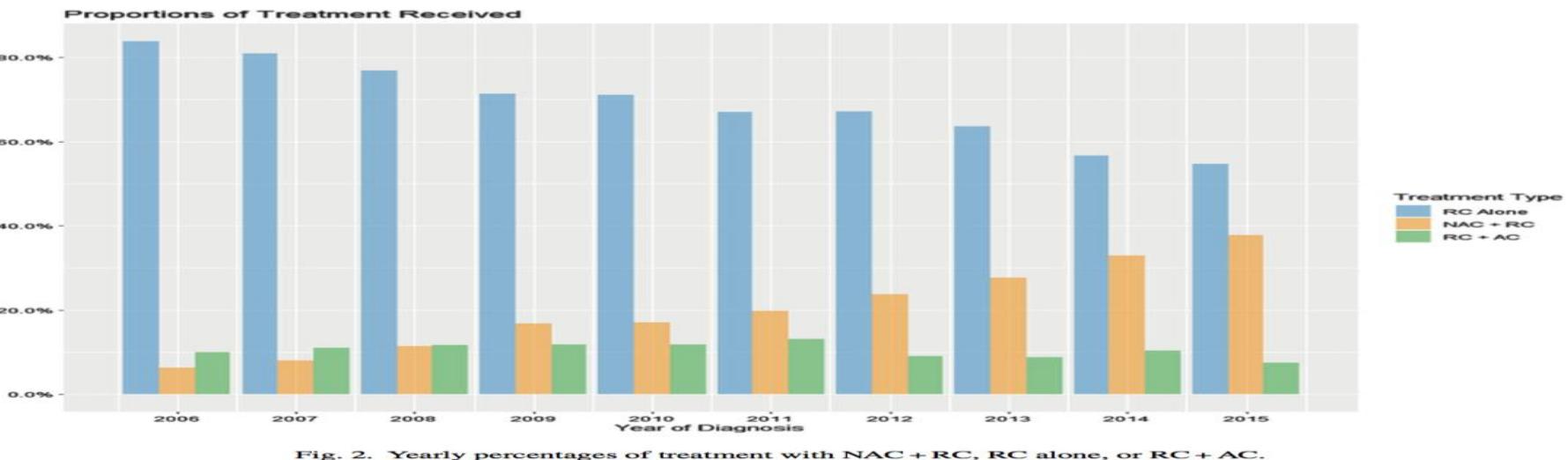
ECOG=Eastern Cooperative Oncology Group. CTCAE=Common Terminology Criteria for Adverse Events. NYHA=New York Heart Association.



- Age
- Other comorbidities

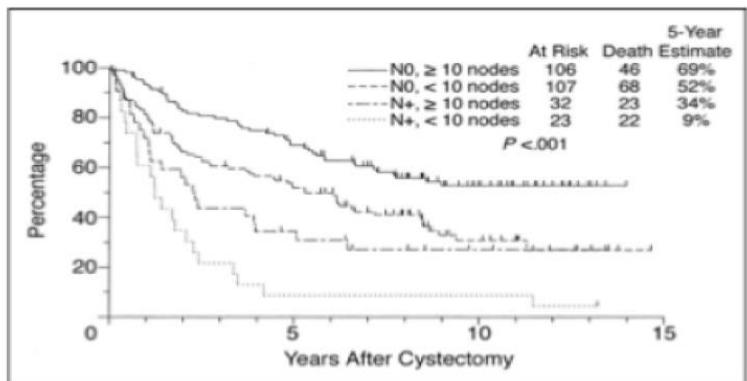


How do we treat our patients?





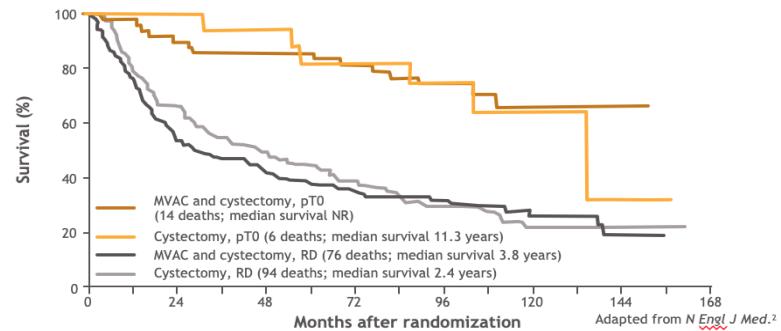
Unmet needs in high-risk MIBC



Characteristic	No.	Median OS, y	HR (95% CI)
Pathologic stage			
P0	46	13.6	1.0
P1/CIS/Pa	22	10.6	2.05 (0.99-4.24)
P2+	47	3.7	2.75 (1.54-4.89)*

pT0=24%

Survival according to treatment group and whether patients were pT0 or had RD at the time of cystectomy



Rate of pT0 was 38% with chemo vs 15% without^{2,3}

8-year survival:

- pT0: ~ 75%
- > pT0: ~ 30%

Grossman HB, et al. *N Engl J Med* 2003;349:859.

Herr HW, et al. *J Clin Oncol* 2004;22:2781.

International Collaboration of Trialists et al. *J Clin Oncol* 2011;29:2171-2177.



Unmet needs in high-risk MIBC



40%-67%
of patients with
pT3-T4a or lymph
node-positive disease
relapse after RC alone,
with a poor 5-year OS
(25%-30%)^{1,2}



**Only
10%-21%**
of patients with MIBC
undergoing RC
receive NAC, despite
current guidelines³



66%
of patients with T2
disease receiving NAC
prior to RC may not
respond and are at risk
of progression to \geq pT2
disease; 5-year DFS
may be as low as 40%⁴



**Up to
83% and 52%**
of patients may be
ineligible for
neoadjuvant and
adjuvant cisplatin-based
therapy, respectively;
there is no SOC for
these patients⁵

DFS, disease-free survival; MIBC, muscle-invasive bladder cancer; NAC, neoadjuvant chemotherapy;
1. Gschwend JE et al. *Eur Urol*. 2002;41:440-448. 2. Shariat SF et al. *J Urol*. 2006;176:2414-2422. 3.

5, overall survival; RC, radical cystectomy; SOC, standard of care.
Reardon ZD et al. *Eur Urol*. 2015;67:165-170. 4. Manoharan M et al. *BJU Int*. 2009;104:1646-1649.

5. Dash A et al. *Cancer*. 2006;107:506-513.



How can we improve these results?



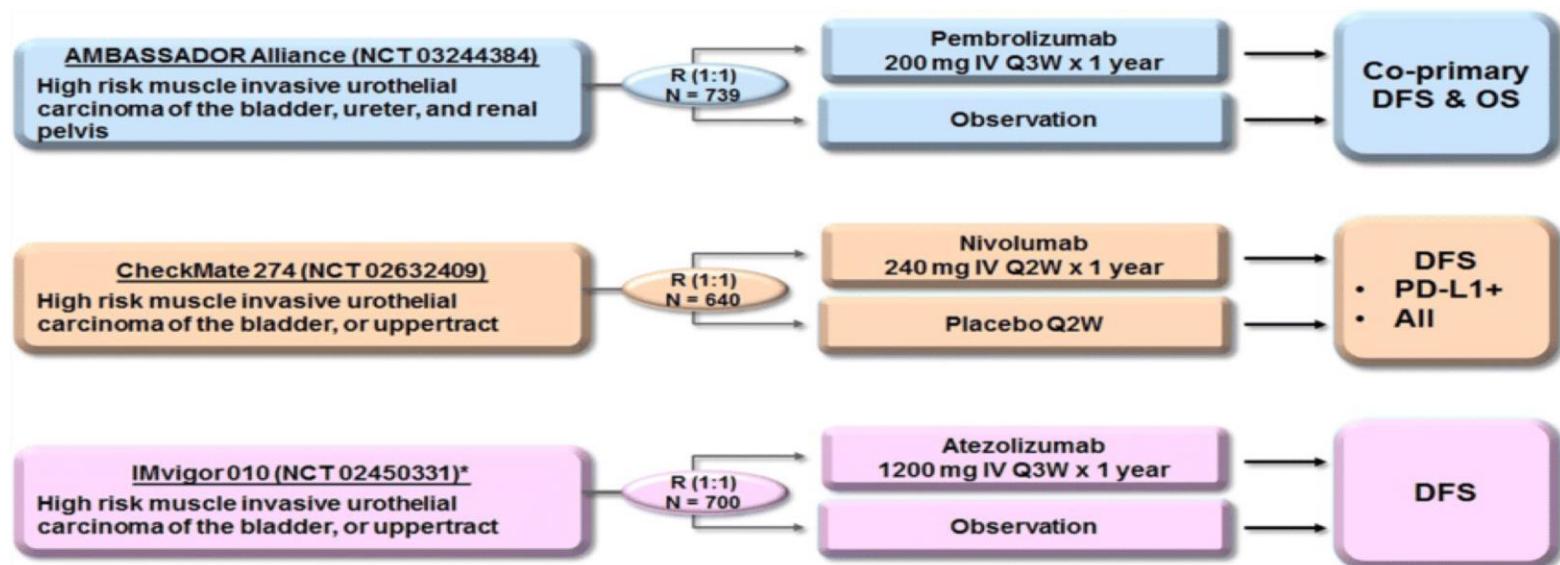
1. Neoadjuvant qt

2. Adjuvant qt

3. Adjuvant immunotherapy

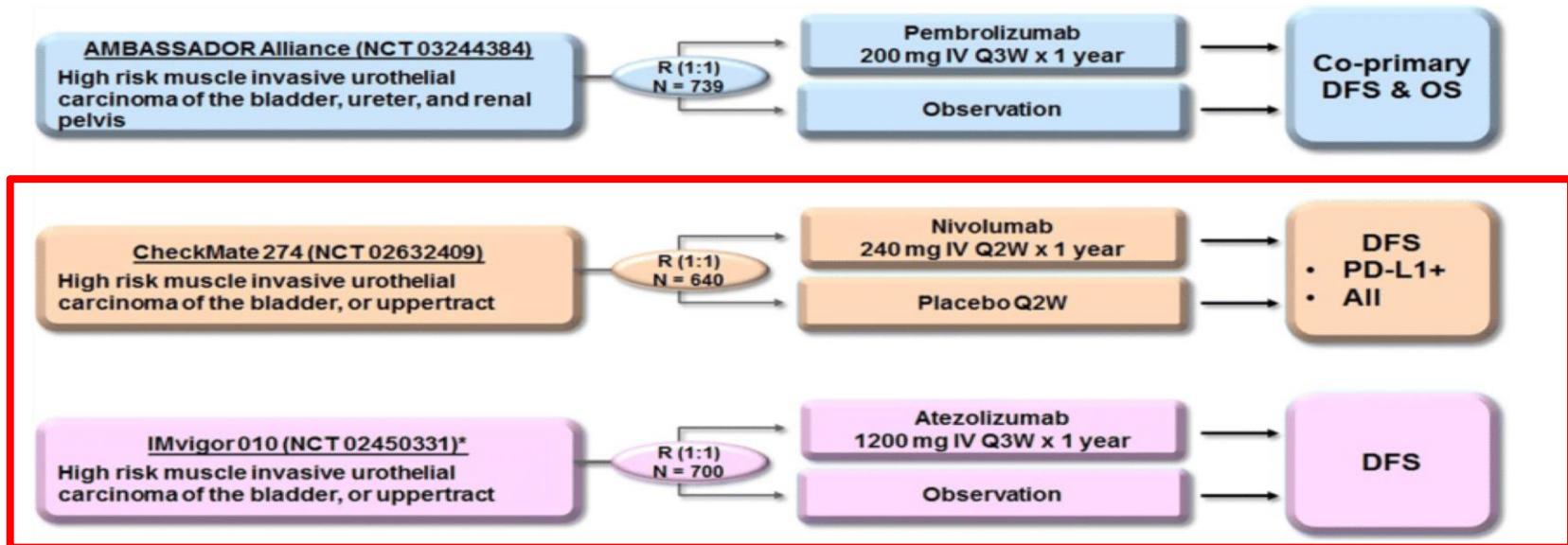


Phase 3 Immunotherapy studies in adjuvant setting





Phase 3 Immunotherapy studies in adjuvant setting





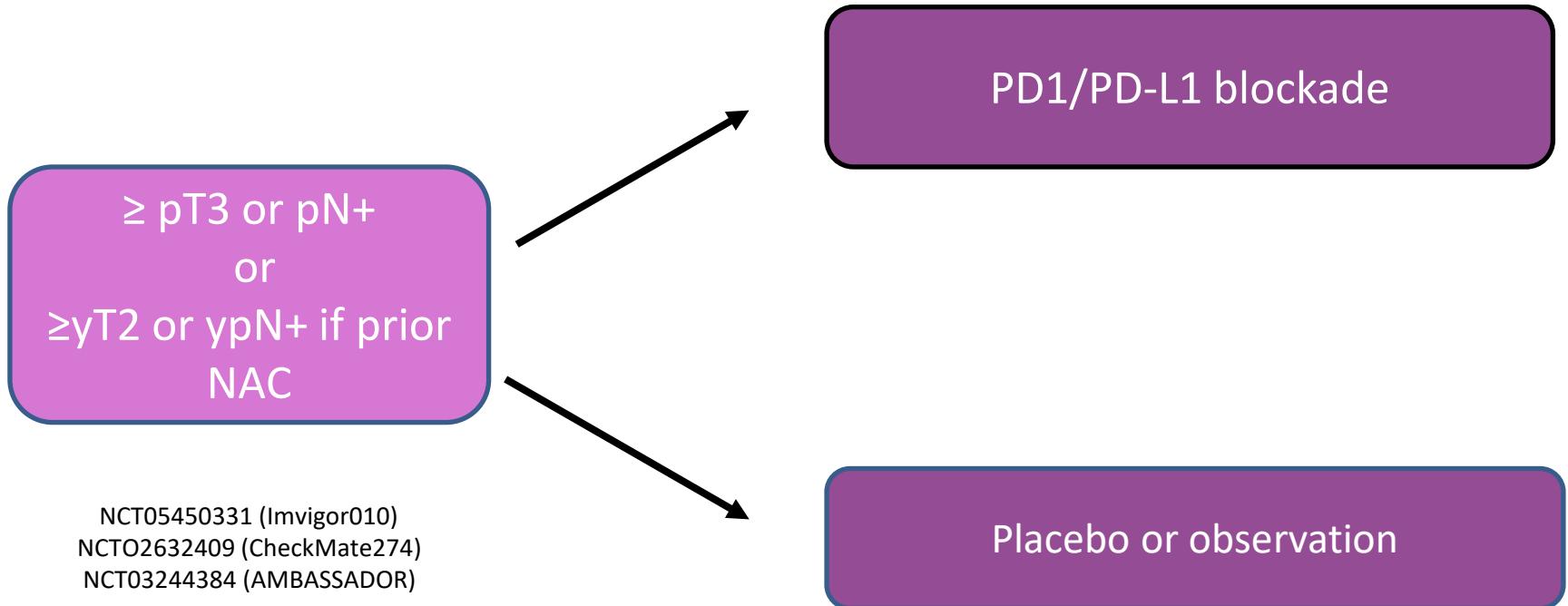
What is the high risk population?

If prior NAC:

\geq yT2 or ypN+

No prior NAC QT:

\geq pT3 or pN+





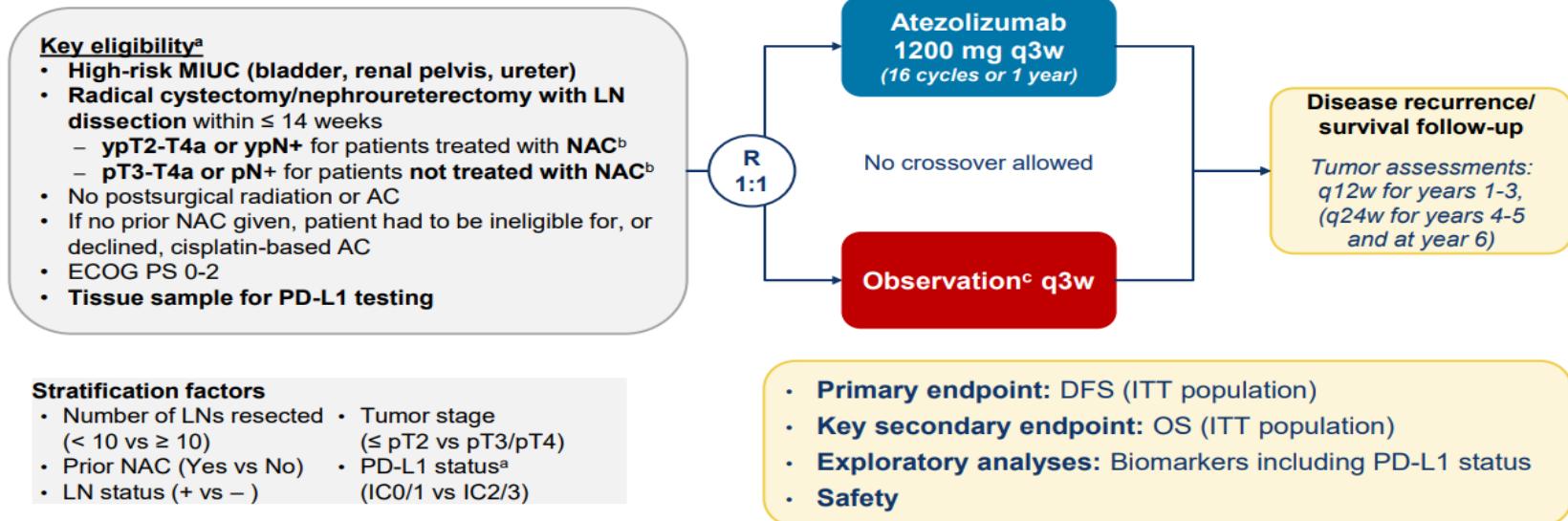
Summary of phase 3 clinical trial for adjuvant immunotherapy

	CheckMate274			
	Nivolumab (N=353)	Placebo (N=356)	Atezolizumab (N=406)	Observation (N 403)
Age, years	65.3	65.9	67	66
Male (%)	75.1	77.2	79	78
ECOG PS 0-1 (%)	98.0	97.5	96	96
Tumor origin				
Bladder (%)	79.0	78.9	93	94
UTUC (%)	21	21.1	7	6
Prior NAC (%)	43.3	43.5	48	47
Pathologic T stage at resection				
pT2-pNO (%)	7.1	8.1	8	10
pT3-T4pNO (%)	44.8	44.7	39	38
Nodal status at resection				
N+ (%)	47.3	47.2	52	52
<10 lymph nodes resected (%)	26.6	27.8	23	23
PDL-1 positive(%)	39.7	39.9	48	49
Median treatment duration (months)	8.8	8.2	10.3	-
Treatment related adverse events (TRAEs) ≤G3 (%)	17.9	7.2	16	-
TRAEs leading to discontinuation (%)	7.1	1.4	16	-
Completed treatment (%)	40.7	37.9	51	50
Disease recurrence (%)	25.6	42.2	29	39
Discontinued treatment (%)	53.3	56.3	49	50
Follow-up (months)	20.9	19.5	21.9	
Median disease free survival (months)	20.8	10.8	19.4	16.6

Bellmunt J, et al. Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2021; 22:525-37
 Bajorin DF, et al. Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. N Engl J Med 2021; 384:2102-14



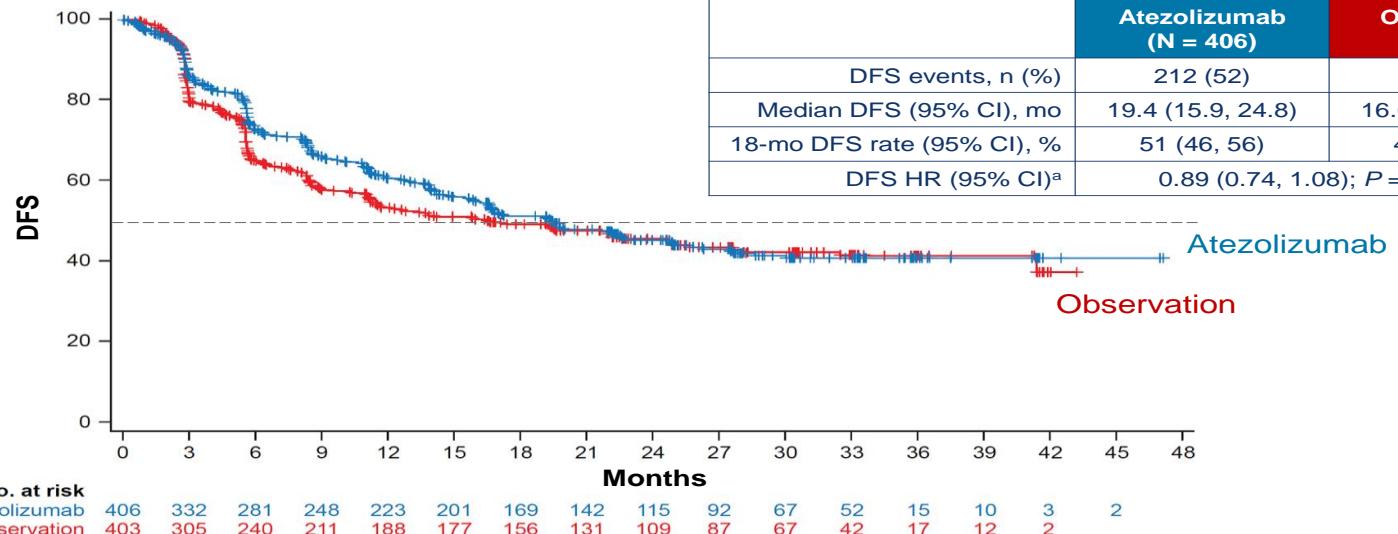
IMvigor010 Study Design



AC, adjuvant chemotherapy; DFS, disease-free survival; ITT, intention to treat; LN, lymph node; MIUC, muscle-invasive UC. ^aProtocol 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). ^bUpper-tract UC staging: ypT2-4 or ypN+ (with NAC) and pT3-4 or pN+ (without NAC). ^cAlternating clinic visits and phone calls.



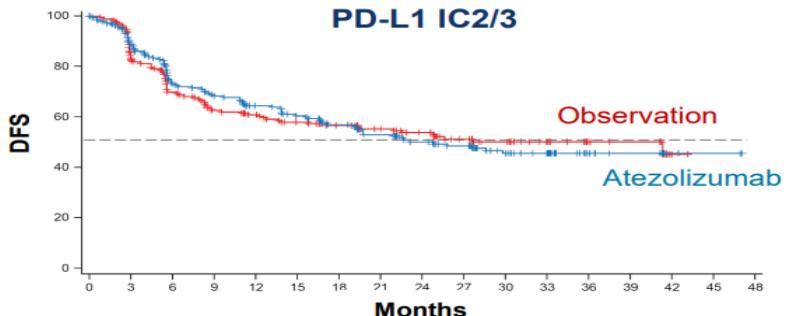
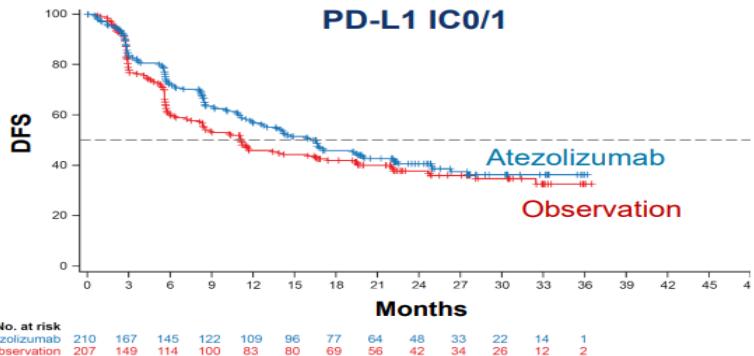
Imvigor 010: DFS in ITT Population



Data cutoff: November 30, 2019. Median follow-up: 21.9 mo. ^aStratified by post-resection tumor stage, nodal status and PD-L1 status. ^b2-sided.



Imvigor 010: DFS by PD-L1 status



	Atezolizumab (n = 210)	Observation (n = 207)
DFS events, n (%)	118 (56)	120 (58)
HR (95% CI) ^a	0.81 (0.63, 1.05)	

	Atezolizumab (n = 196)	Observation (n = 196)
DFS events, n (%)	94 (48)	88 (45)
HR (95% CI) ^a	1.01 (0.75, 1.35)	

Data cutoff: November 30, 2019. IC2/3, PD-L1-expressing IC on ≥ 5% of tumor area (VENTANA SP142 assay); IC0/1, < 5%. ^a Stratified by tumor stage and nodal status.



Checkmate 274: Study design

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

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

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

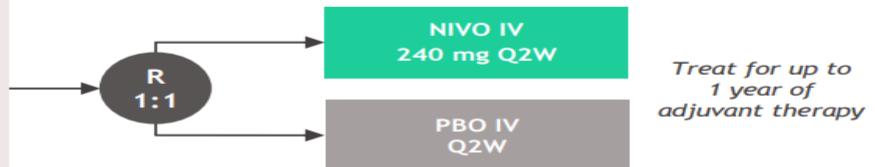
Median (range) follow-up^c (PD-L1 ≥ 1% population),
37.1 (0.0-75.3) months (39.8 months for NIVO, 33.3 months for PBO)

Database lock, October 20, 2022.

^aNCT02632409. ^bDefined 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. ^cDefined as time between randomization date and last known date alive (for patients who are alive) and death. ^dDefined as time from clinical cut-off date to last patient's randomization date. ^eOS 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.

Stratification factors

- Tumor PD-L1 status ($\geq 1\%$ vs $< 1\%$ or indeterminate)^b
- Prior neoadjuvant cisplatin-based chemotherapy
- Nodal status



Primary endpoints: DFS in all randomized patients (ITT population) and DFS in all randomized patients with tumor PD-L1 $\geq 1\%$

Secondary endpoints: NUTRFS, DSS, and OS^e

Exploratory endpoints included: DMFS, PFS2, safety, HRQoL

Minimum follow-up of 31.6 months (median follow-up, 36.1 months)

Galsky MD, ASCO GU 2023



Select baseline demographic and clinical characteristics

	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

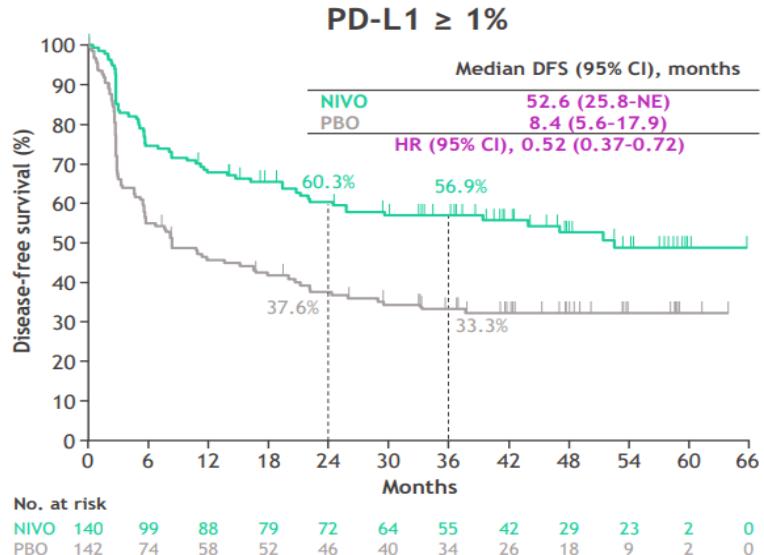
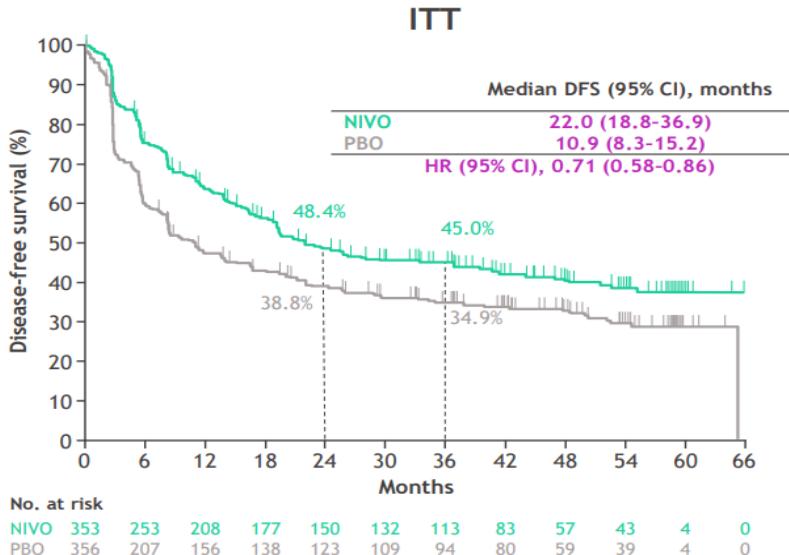
^aNot reported for 1 patient in the PBO arm. ^bpTX in 1% of patients in the NIVO arm; pTis in 1% of patients in the NIVO arm and 1% of patients in the PBO arm. ^cNot reported for 1 patient each in the NIVO and PBO arm.

ECOG PS, Eastern Cooperative Oncology Group performance status; IVRS, interactive voice-response system.



Disease-free survival (Primary endpoint)

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



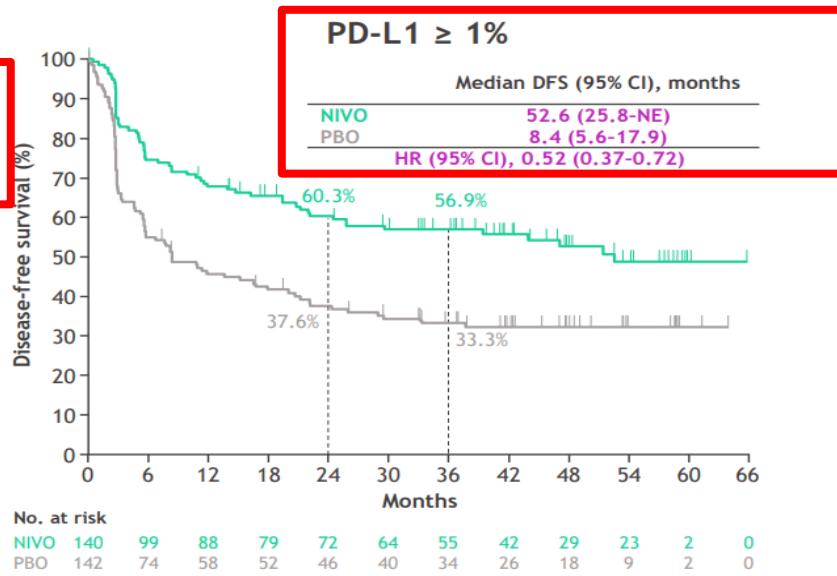
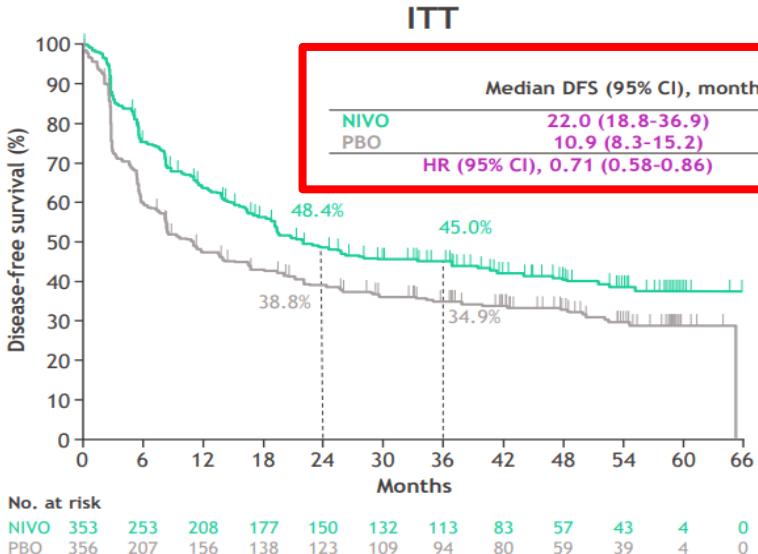
Minimum follow-up in the ITT population, 31.6 months. DFS was defined as the time between the date of randomization and the date of first recurrence (local urothelial tract, local non-urothelial tract or distant) or death.

NE, not estimable.



Disease-free survival (Primary endpoint)

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

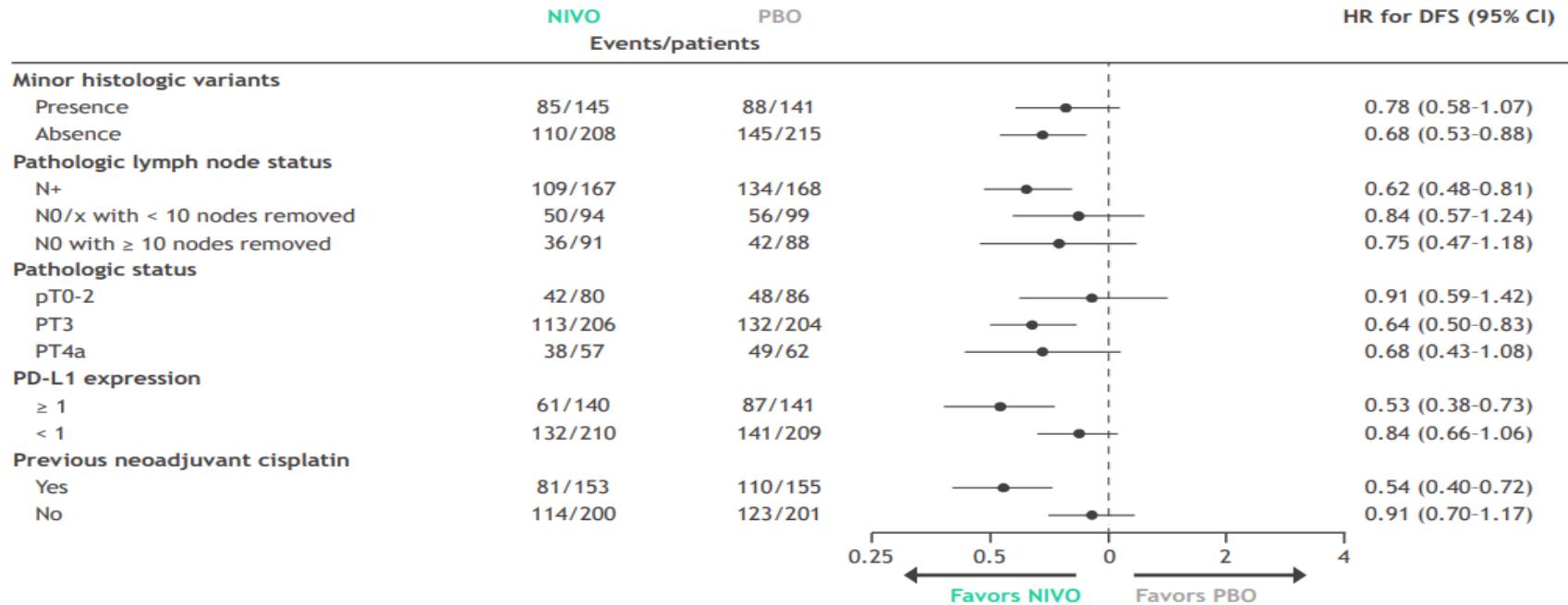


Minimum follow-up in the ITT population, 31.6 months. DFS was defined as the time between the date of randomization and the date of first recurrence (local urothelial tract, local non-urothelial tract or distant) or death.

NE, not estimable.



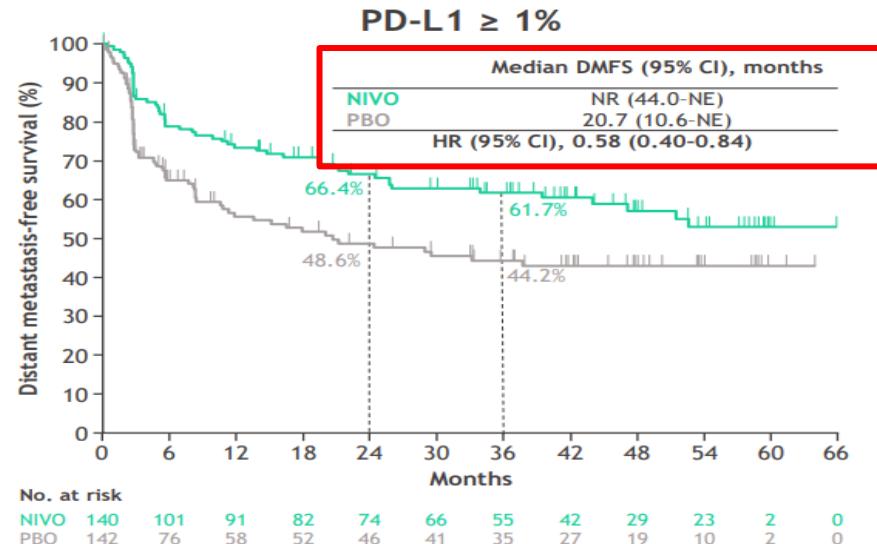
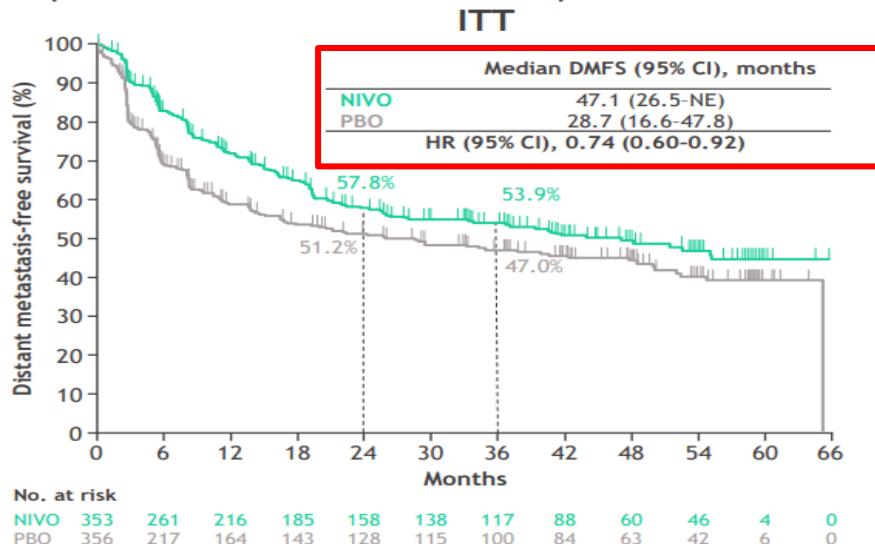
Disease-free survival by subgroup in the ITT





Distant metastasis-free survival

- Continued DMFS benefit was observed with NIVO versus PBO both in the ITT population and in patients with tumor PD-L1 expression $\geq 1\%$



Minimum follow-up in the ITT population, 31.6 months. DMFS was defined as the time between the date of randomization and the date of first distant recurrence (non-local) or date of death. NR, not reached.



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%

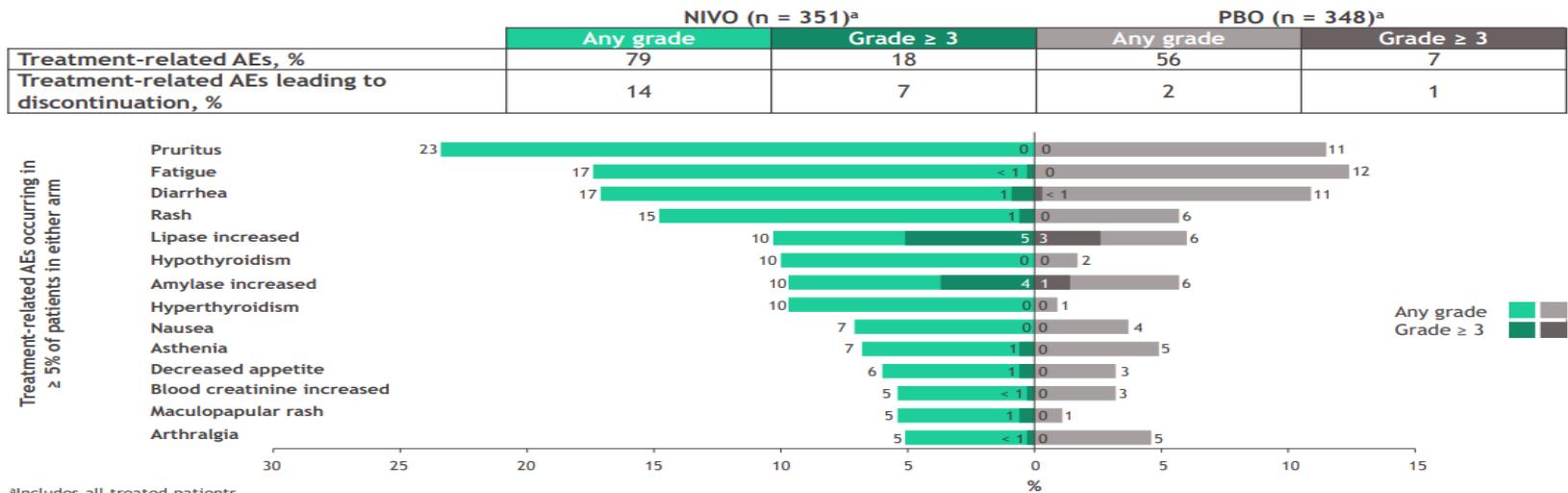
	NIVO (N = 140)	PBO (N = 142)	NIVO (N = 140)	PBO (N = 142)	NIVO (N = 140)	PBO (N = 142)
Minimum follow-up in the ITT population, months	31.6		11.0 ¹		5.9 ²	
Median DFS, months	52.6	8.4	NR	8.4	NR	8.4
DFS HR (95% CI)	0.52 (0.37-0.72)		0.53 (0.38-0.75)		0.55 (0.35-0.85) ^b	
Median NUTRFS, months	52.6	8.4	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)	

^a98.22% CI. ^b98.72% CI.

1. Galsky MD, et al. Poster presentation at SUO 2021. 1514. 2. Bajorin DF, et al. *N Engl J Med* 2021;384:2102-2114.



Safety summary in all treated patients



^aIncludes 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.

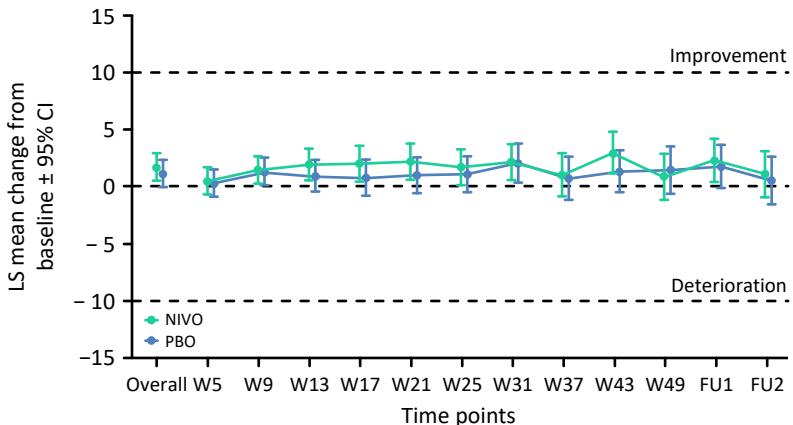
Minimum follow-up in the ITT population, 31.6 months.

AE, adverse event.

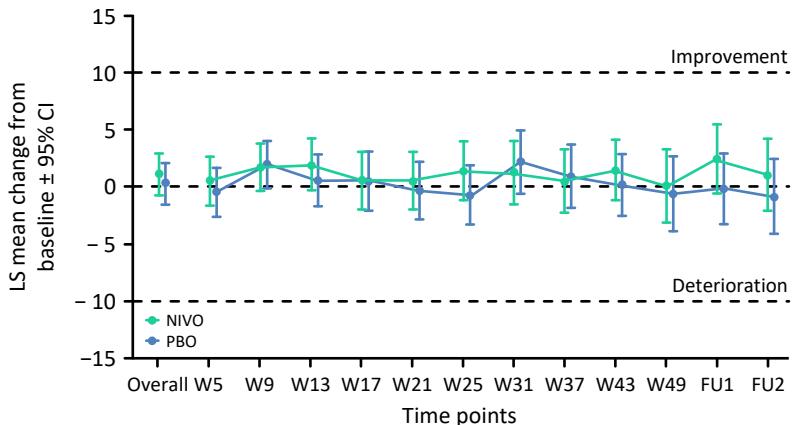


CheckMate 274: Quality of life

ITT population



Tumor PD-L1 $\geq 1\%$ population



No deterioration in HRQoL (physical functioning) with NIVO versus PBO was observed in either the ITT or PD-L1 $\geq 1\%$ populations

- Linear mixed-effect model for repeated measures LS mean change from baseline in HRQoL in physical functioning for the EORTC QLQ-C30 evaluable ITT and PD-L1 $\geq 1\%$ populations.
- EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FU, follow-up; HRQoL, health-related quality of life; LS, least squares; NIVO, nivolumab; PBO, placebo; PD-L1, programmed death ligand 1.
- Witjes JA et al. Eur Urol Oncol. 2022;S2588-9311(22)00028-1. under the creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>)



Therapeutic landscape in muscle-invasive UC



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2023 Muscle Invasive Bladder Cancer

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

ADJUVANT TREATMENT

Following
cystectomy

- Based on pathologic risk,
 - ▶ If no cisplatin neoadjuvant treatment given and pT3, pT4a, or pN+
 - ◊ Adjuvant cisplatin-based chemotherapy should be discussed (preferred)^y or
 - ◊ Consider adjuvant nivolumab ^{y,cc}
 - or
 - ▶ If cisplatin neoadjuvant chemotherapy given and ypT2–ypT4a or ypN+, consider nivolumab ^{y,cc}
 - or
 - ▶ Consider adjuvant RT in selected patients (pT3–4, positive nodes/margins at the time of surgery)^{aa} (category 2B)

→ See
Follow-up
(BL-E)



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 $\geq 1\%$, who are at high risk of recurrence after undergoing radical resection of MIUC (see section 5.1).

- EMA, European Medicines Agency; MIUC, muscle-invasive urothelial carcinoma; PD-L1, programmed death ligand 1.
- European Medicines Agency, 2022. Accessed July, 2022. <https://www.ema.europa.eu/en/medicines/human/EPAR/opdivo>.



Resolución definitiva de Financiación Nivolumab Adyuvante

- OPDIVO en monoterapia está financiado para el tratamiento adyuvante de adultos con carcinoma urotelial músculo invasivo (CUMI) con expresión de PD-L1 en células tumorales $\geq 1\%$, después de someterse a resección radical del CUMI en pacientes que:
 - No hayan recibido quimioterapia neoadyuvante con cisplatino y presenten tras la resección tumores pT3-4 o afectación ganglionar regional y que, tras valoración por el oncólogo médico, no sean candidatos a recibir quimioterapia adyuvante basada en cisplatino;
 - Habiendo recibido quimioterapia neoadyuvante basada en cisplatino, presenten tras la resección tumores \geq pT2 o afectación ganglionar regional.



PD-L1 Determination

available at www.sciencedirect.com
journal homepage: www.europeanurology.com



Bristol Myers Squibb has obtained appropriate permissions to externally share this material with
Healthcare Professionals upon request.



Bladder Cancer

Disease-free Survival Analysis for Patients with High-risk Muscle-invasive Urothelial Carcinoma from the Randomized CheckMate 274 Trial by PD-L1 Combined Positive Score and Tumor Cell Score

Matthew D. Galsky^{a,*}, Dean F. Bajorin^b, Johannes Alfred Witjes^c, Jürgen E. Gschwend^d, Yoshihiko Tomita^e, Federico Nasrullah^f, Jun Li^f, Sandra Collette^g, Begoña P. Valderrama^h, Marc-Oliver Grimmⁱ, Leonard Appleman^j, Gwenaelle Gravis^k, Andrea Necchi^l, Dingwei Ye^m, Frank Stennerⁿ, Megan Wind-Rotolo^{f,k}, Joshua Zhang^f, Keziban Ünsal-Kaçmaz^{f,k}

PD-L1 immunohistochemistry was performed on formalin-fixed, paraffin-embedded tumor samples from the resected site of disease, obtained before randomization, using the Dako PD-L1 IHC 28-8 pharmDx assay and assessed by a pathologist. Specimens with ≥ 100 evaluable tumor cells were eligible for PD-L1 scoring. TC was determined from central laboratory testing before randomization, calculated as follows:

$$TC = \frac{\text{No. of PD-L1-positive tumor cells}}{\text{Total no. of viable tumor cells}} \times 100.$$

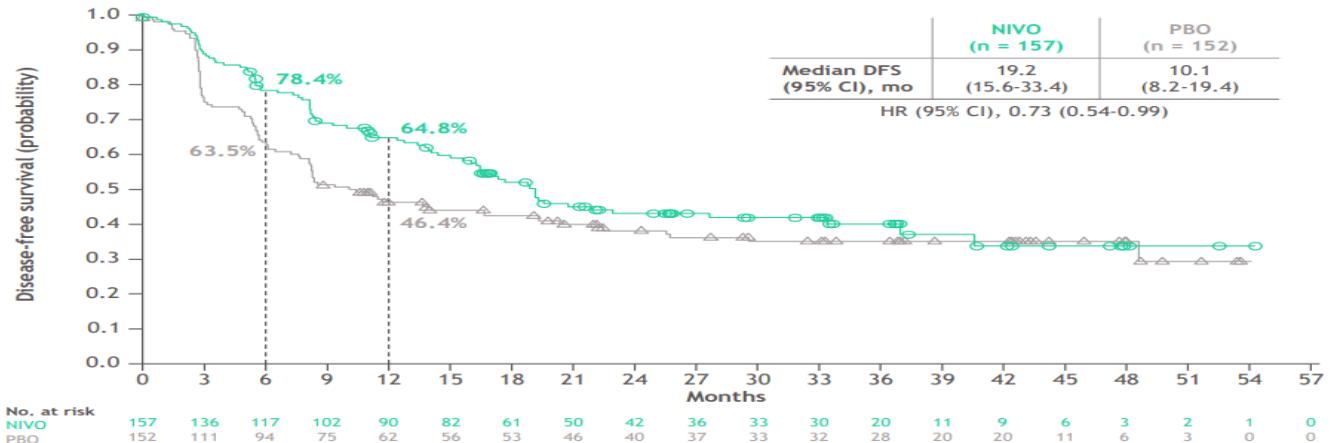
In this post hoc analysis, CPS was determined retrospectively at a central laboratory from the previously stained immunohistochemistry slides (using the Dako PD-L1 IHC 28-8 pharmDx assay). CPS was calculated as follows:

$$CPS = \frac{\text{No. of PD-L1-positive tumor and immune cells (lymphocytes and macrophages)}}{\text{Total no. of viable tumor cells}} \times 100.$$



PD-L1 Determination

Figure 4. DFS in patients with TC < 1% and CPS ≥ 1



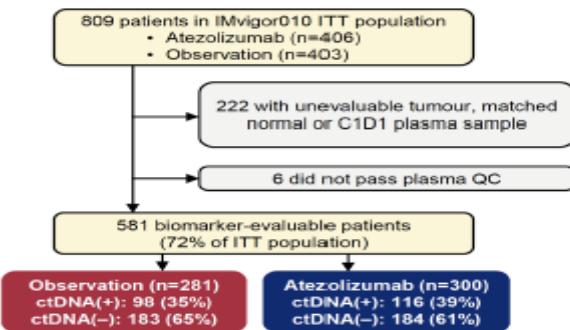
Galsky et al. ASCO GU 2022



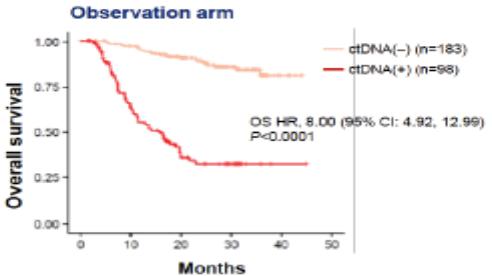
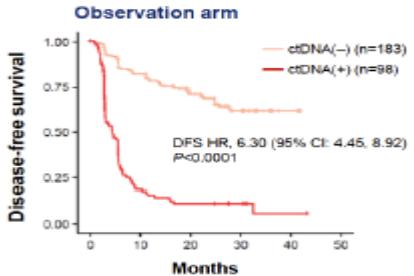
Biomarkers?



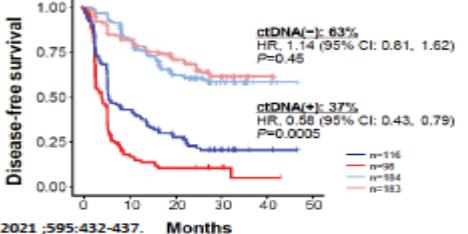
Clinical Outcomes in Post-Operative ctDNA(+) Muscle-Invasive Urothelial Carcinoma Patients After Atezolizumab Adjuvant Therapy



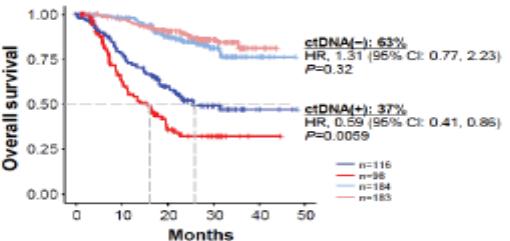
ctDNA(+) patients have poor prognosis



ctDNA(+) patients had improved DFS and OS with **atezolizumab** vs observation



	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)

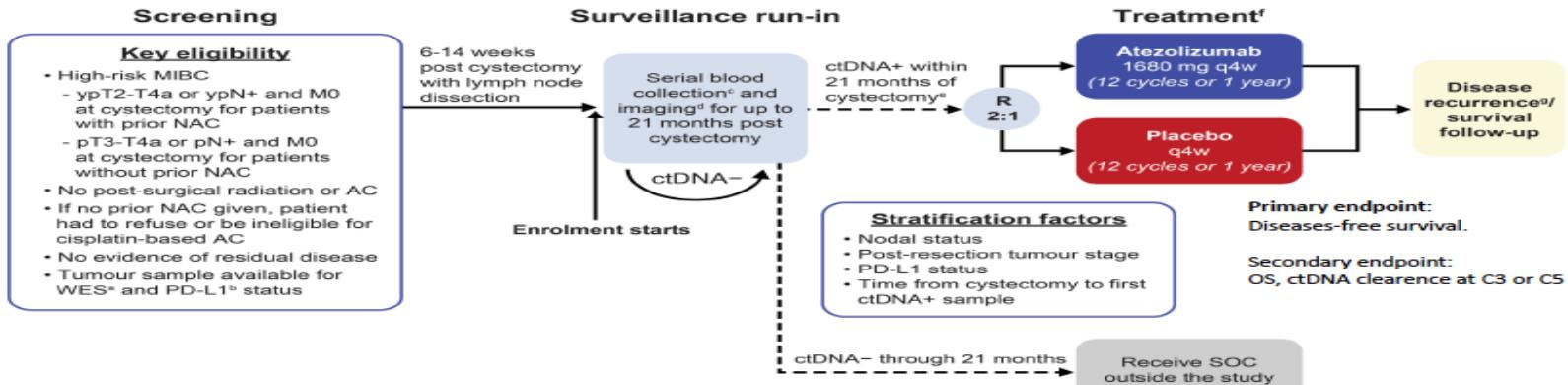


Powles T, et al. ESMO IMMUNO-ONCOLOGY 2020

Powles T, et al. ctDNA guiding adjuvant immunotherapy in urothelial carcinoma. Nature 2021;595:432-437.



IMvigor011 Study Design



ctDNA-, circulating tumor DNA negative; ctDNA+, circulating tumor DNA positive; q4w, every 4 weeks; SOC, standard of care; WES, whole-exome sequencing.

* Evaluable WES data for development of a personalised multiplex PCR (mPCR) ctDNA assay from post-surgical blood samples (Signatera assay) are required.

^a Per the VENTANA 142 IHC assay.

^b Every 12 weeks up to 36 weeks and q12w (every 12 weeks) up to 21 months.

^c q12w up to Week 84 or until 21 months from date of cystectomy, whichever occurs first.

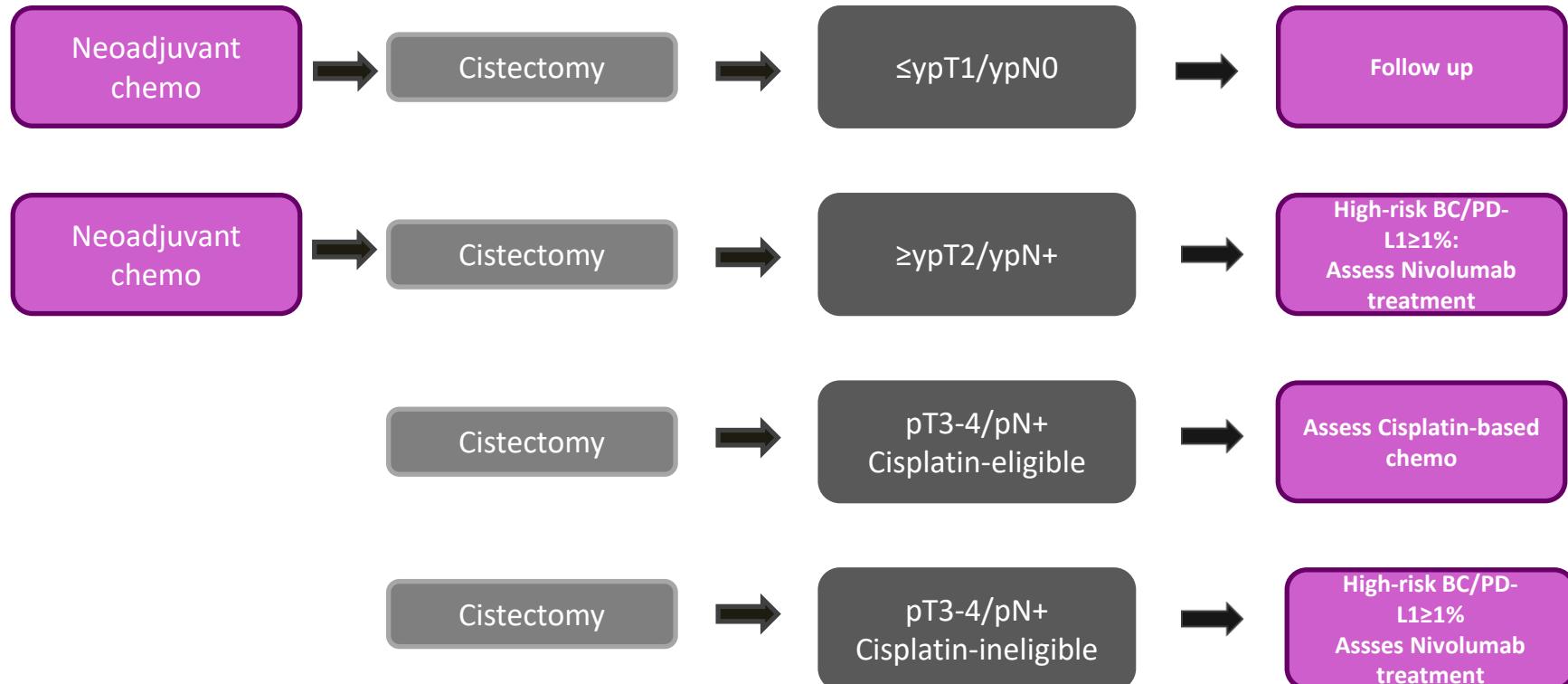
^d ctDNA positivity is defined as ≥2 mutations per ctDNA mPCR assay. Patients will be randomised to treatment at the first ctDNA+ sample; full recovery from cystectomy and no evidence of disease recurrence within 28 days of treatment initiation is required.

^e Imaging and blood draws q9w (every 9 weeks) starting at Week 9 up to Week 54.

^f Assessed q9w up to Year 3; less often up to Year 6.



Muscle-invasive bladder cancer treatment





Conclusiones

- Ca urotelial músculo–invasivo presenta una alta tasa de recurrencia y mortalidad
- QT basada en Cisplatino mejora la SG, no siempre es posible
- Nivolumab mejora la DFS en población ITT y PD-L1 positivo
- Indicación pacientes alto riesgo (\geq ypT2 y/o ypN+ tras Nac o pT3/4 y/o pN+ sin NAC)
- Es necesario un abordaje multidisciplinar para un plan terapéutico integral



Muchas gracias!!!

Dr. Ovidio Fernández Calvo

Servicio Oncología Médica

Complejo Hospitalario Universitario Ourense

foro debate oncología

