XVII SIMPOSIUM
BASES BIOLÓGICAS DEL CÁNCER
E INNOVACIÓN TERAPÉUTICA

MÁS DE 20 AÑOS A LA VANGUARDIA DE LA FORMACIÓN
EN LA BIOLOGÍA Y TRATAMIENTO DEL CÁNCER

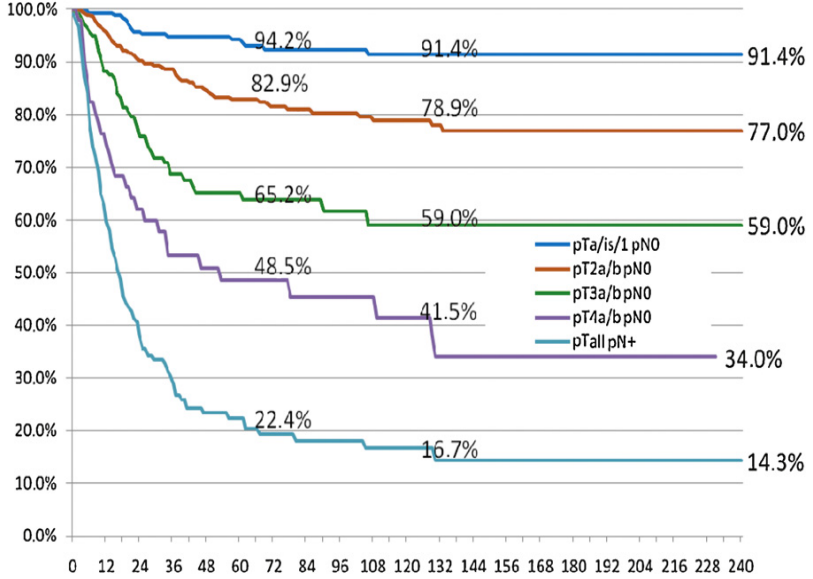
SALAMANCA, 22 Y 23 DE MAYO DE 2025

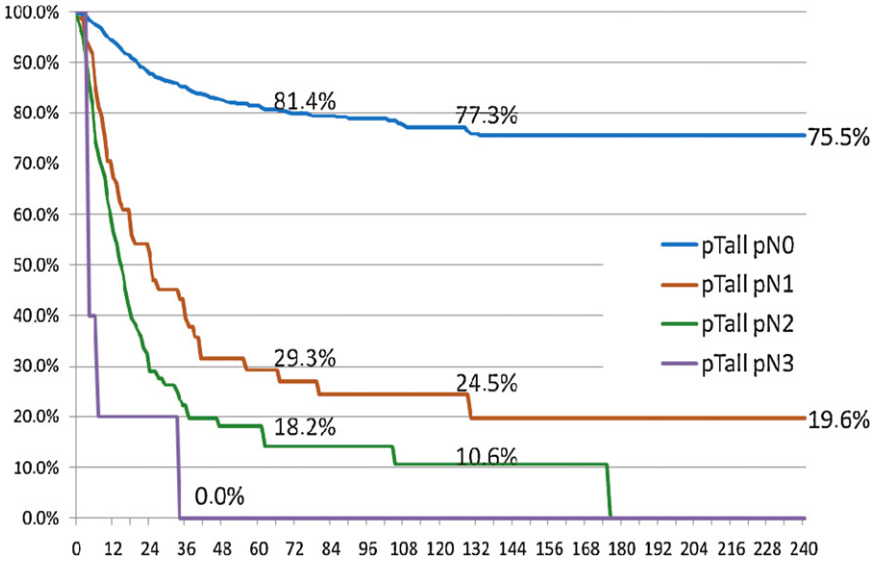
Manejo perioperatorio en carcinoma urotelial músculo-invasivo: ¿todos los pacientes se benefician de la inmunoterapia?

Javier Cassinello. Servicio de Oncología Médica. Hospital Universitario de Guadalajara

Disease specific survival in muscle invasive UC

Resectable MIBC	T2-T4, N0-N1, M0	Tumor extends into or through the muscularis propria, with or without minimal lymph node involvement

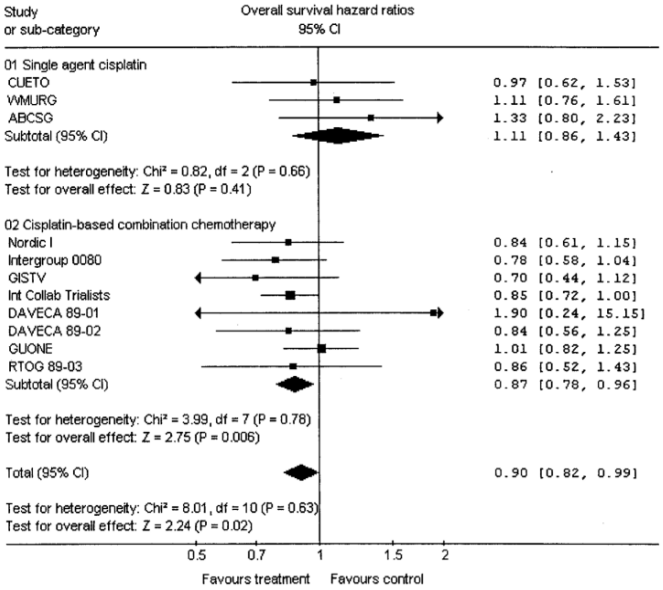




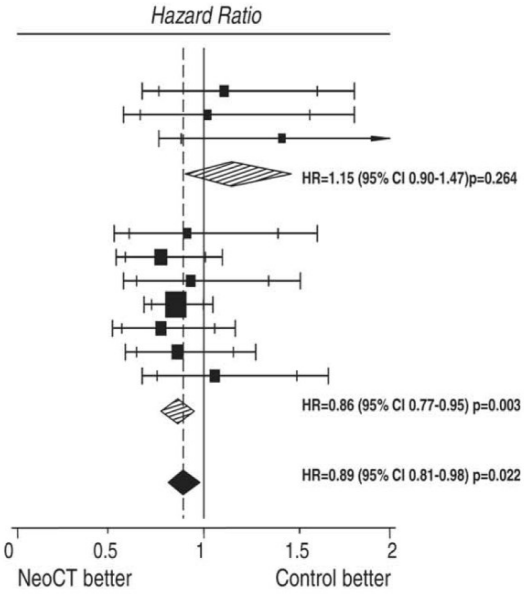
MIUC is an aggressive disease, and a large subset of patients experience recurrence within 3 years of radical surgery.

Renner A,
Ther Adv Urol 13:12. 2021

Neoadjuvant QT: Meta-analysis



	(no. events/no. entered) CT	Control	O-E	Variance
Single agent platinum				
Wallace [2]	59/83	50/76	2.74	27.18
Martinez-Pineiro [3]	43/62	38/59	0.33	20.11
Raghavan [2]	34/41	37/55	5.85	16.51
Sub-total	136/186	125/190	8.92	63.80
Platinum-based combinations				
Cortesi unpublished	43/82	41/71	-1.87	20.84
Grossman [9]	98/158	108/159	-13.61	51.00
Bassi [5]	53/102	60/104	-1.95	28.13
MRC/EORTC [6]	275/491	301/485	-23.69	143.61
Malmström [8]	68/151	84/160	-9.97	37.94
Sherif [8]	79/158	90/159	-6.37	42.18
Sengeløv [7]	70/78	60/75	1.79	31.96
Sub-total	686/1220	744/1213	-55.67	355.65
Total	822/1406	869/1403	-46.75	419.45



Absolute Benefit 6%

Winquist E, et al J Urol Feb; 171: 561: 9;
ABC Meta-análisis Collaboration: Eur Urol 48 (2005): 202-206

Estudio VESPER: ddMVAC vs CG en contexto neoadyuvante y adyuvante

N=500

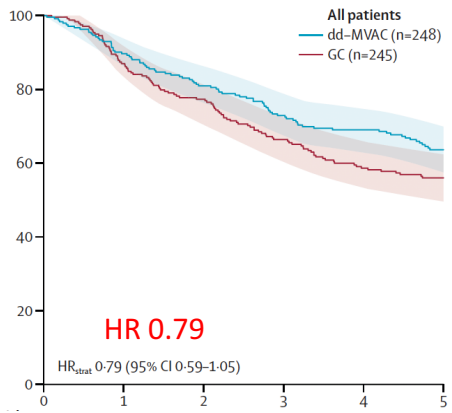
Muscle-invasive UBC (pure o mixed histology) eligible for cisplatin
- Neoadjuvant: ≥T2 N0 M0
- Adjuvant: >pT2 or pN+ M0

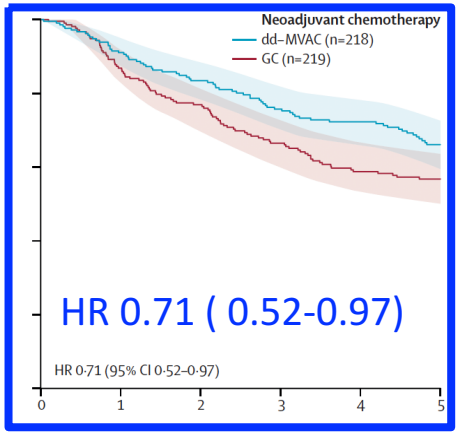
Randomization 1:1

ddMVAC
6 cycles (Q2W)

Cisplatin/Gemcitabine
4 cycles (Q3W)

Radical cystectomy





Perioperative dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin in muscle-invasive bladder cancer (VESPER): survival endpoints at 5 years in an open-label, randomised, phase 3 study

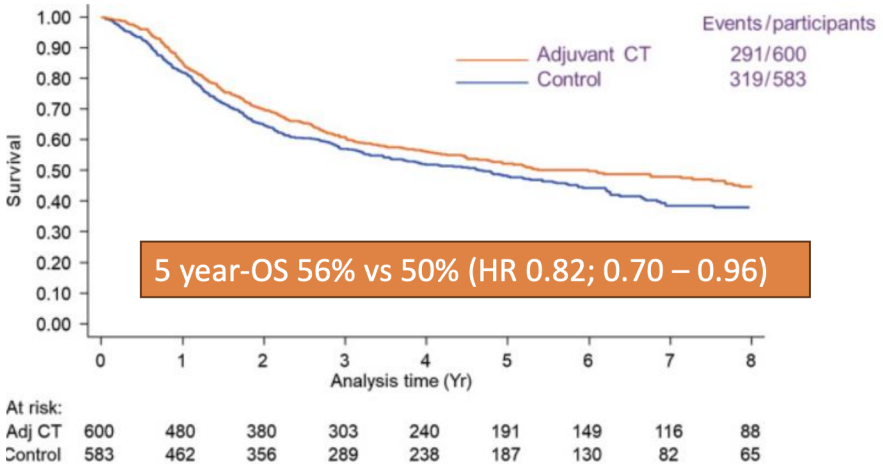
*Christian Pfister, Gwenaelle Gravis, Aude Flechon, Christine Chevreau, Hakim Mahammedi, Brigitte Laguerre, Aline Guillot, Florence Joly, Michel Soulie, Yves Allory, Valentin Harter, Stéphane Culine, for the VESPER Trial Investigators**

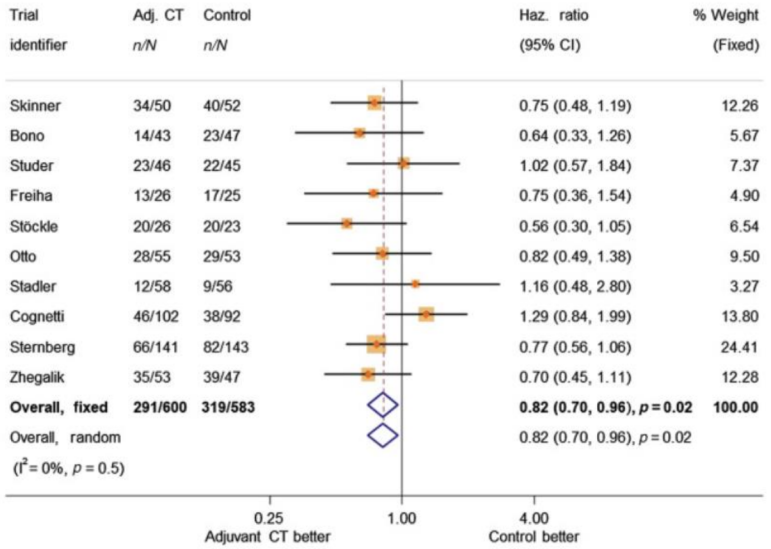
Neoadjuvant QT: ddMVAC > cis/gem

Pfister C, et al. Lancet Oncol 2024;25(2):255-64.

Adjuvant treatment chemotherapy-based.

Meta analysis 10 randomized clinical trials (1183 participants)

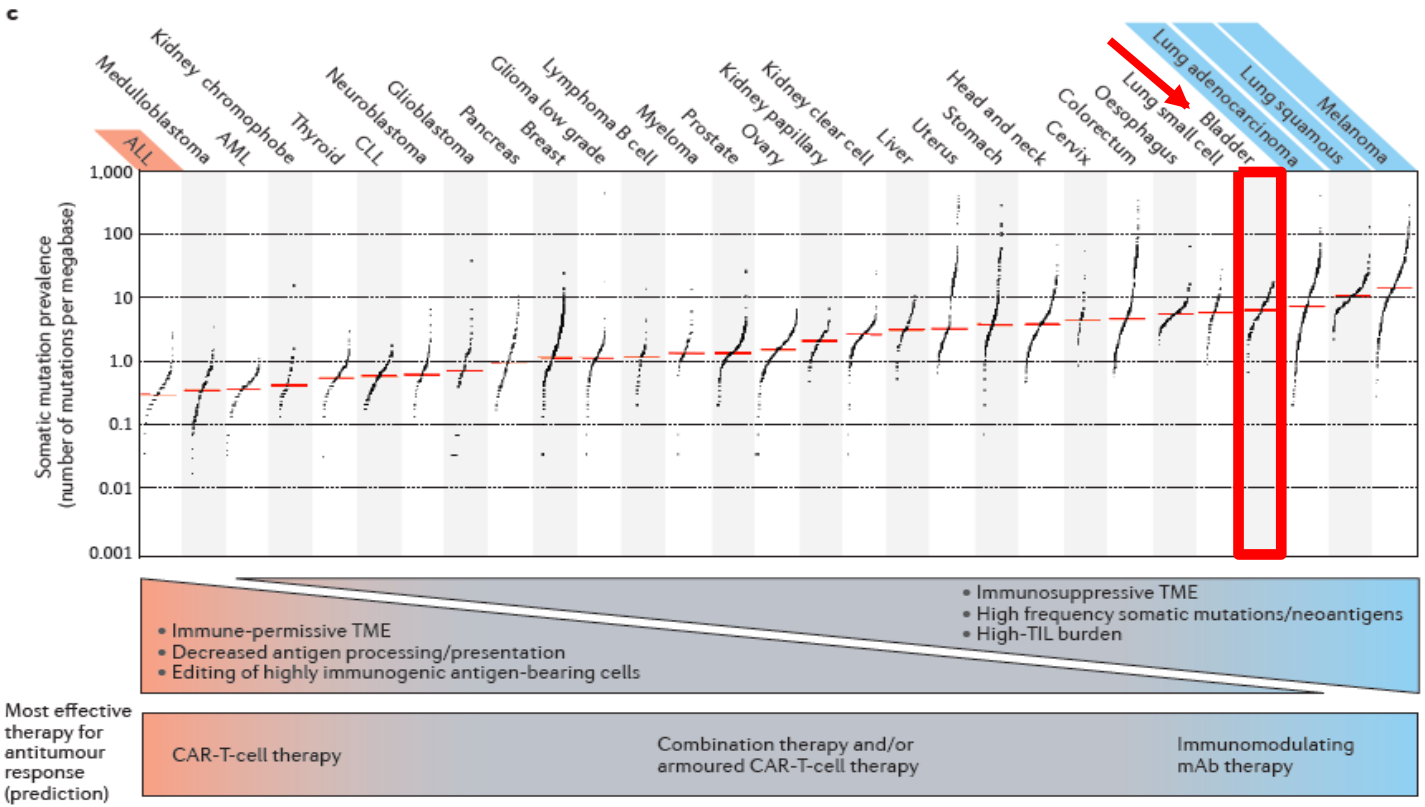




The effect (Non-stratified) of adjuvant chemotherapy on overall survival

Advanced Bladder Cancer (ABC) Meta-analysis Collaborators Group. Eur Urol 2021
S. Burdett, et al. European Urology 2022 (10 trials, n=1183)

Bladder Cancer:
SOMATIC MUTATION PREVALENCE



1 Neoadyuvancia

Pure, Abacus, Nabucco, BLASST

2 Adyuvancia

CM274, Ambassador, IMvigor

3 Tratamiento perioperatorio:

Niágara y otros

4 Primera línea en inelegibles para cisplatino

KN 052, IMvigor 210

5 Primera línea en elegibles para cisplatino

CM901

6 Primera linea combinaciones sin platino:

EV 302

7 Mantenimiento tras QT basada en platino en 1L

Javelin Bladder 100

8 Segunda línea y sucesivas

KN 045

9 Estudios en NMIBC

KN057

La IO está presente hoy día en *todos* los escenarios del cancer de vejiga

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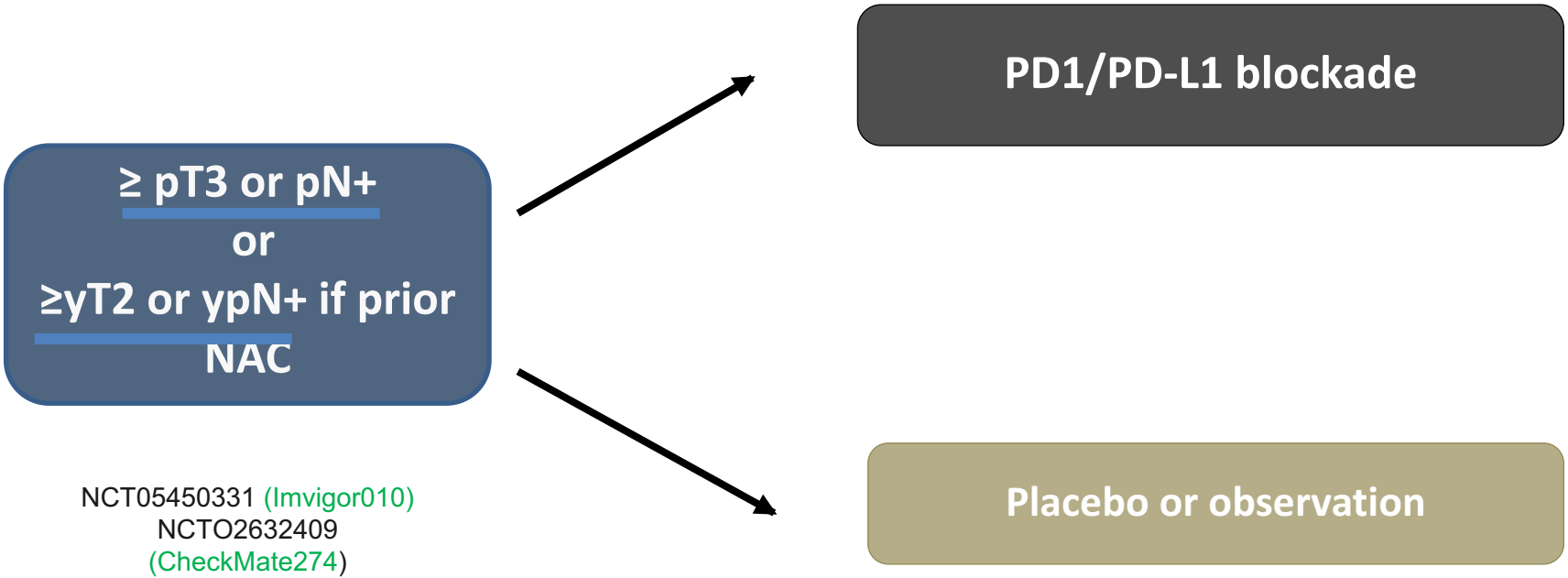
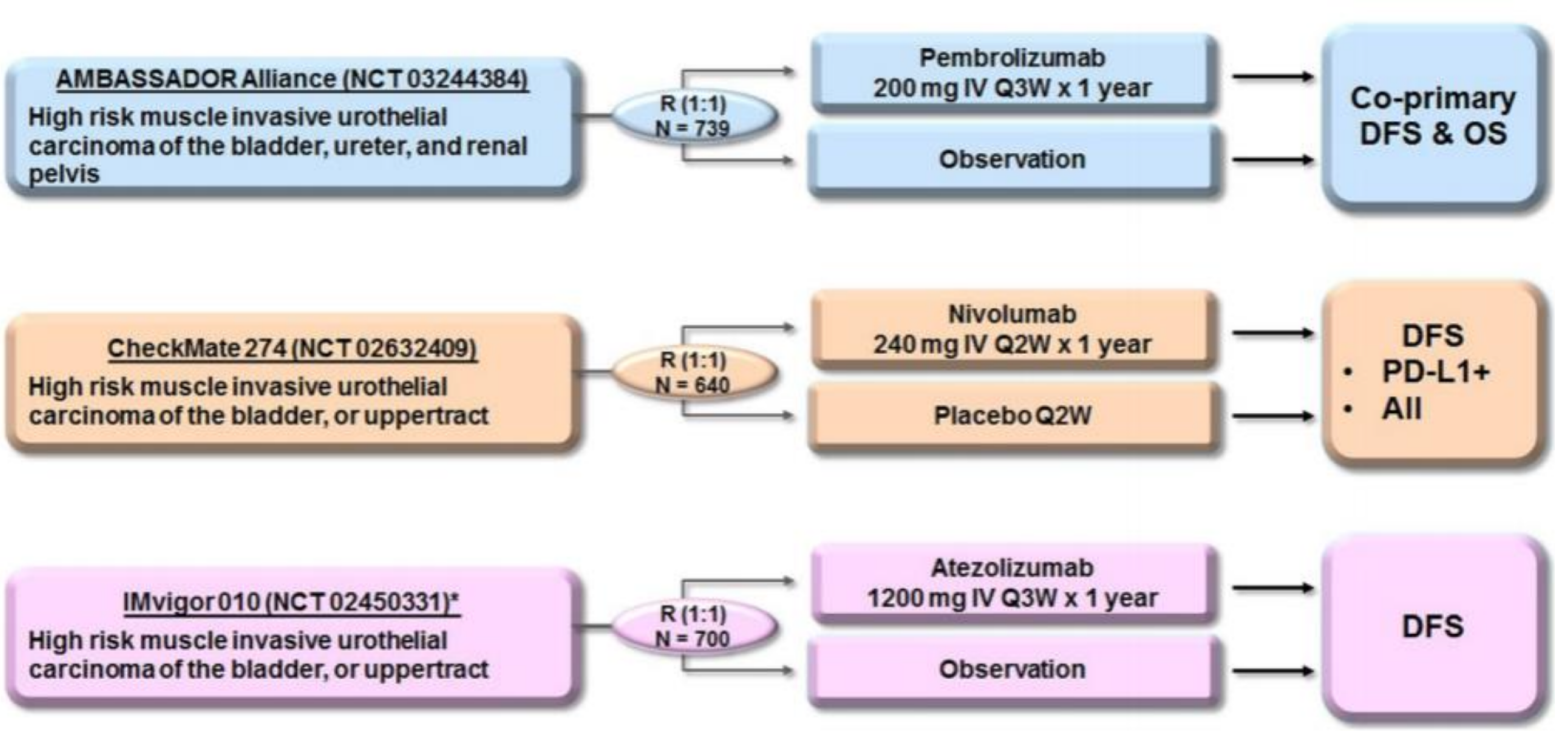
1 TRATAMIENTO ADYUVANTE con IO

High risk population where adyuvant IO must be test



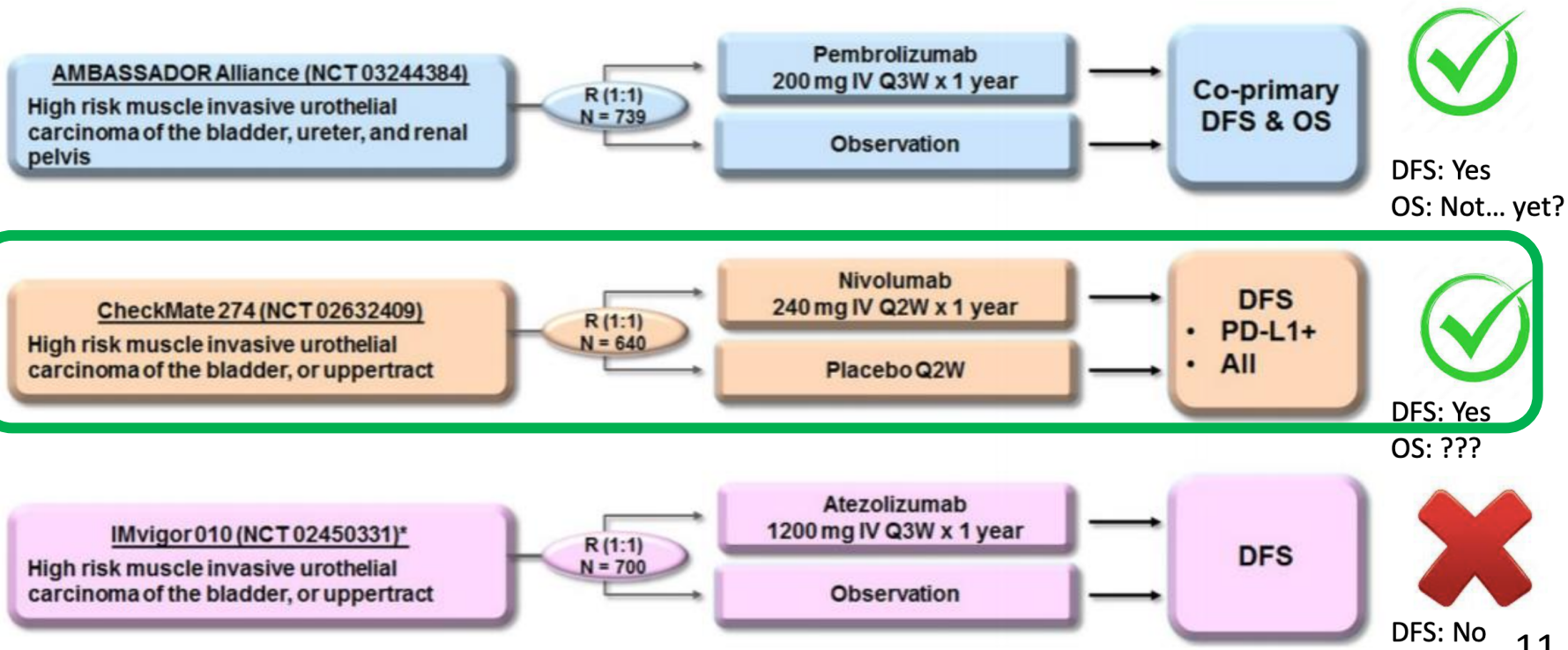
NCT05450331 (Imvigor010)
NCTO2632409
(CheckMate274)
NCT03244384
(AMBASSADOR)

Adjuvant treatment with PD-1/PD-L1 inhibitors



Nadal R and Apolo A. Curr Treat Options Oncol. 2018

Adjuvant treatment with PD-1/PD-L1 inhibitors



Nadal R and Apolo A. Curr Treat Options Oncol. 2018

Study design: CheckMate 274

- Phase 3, randomized, double-blind, multicenter study of adjuvant NIVO vs PBO for high-risk MIUC[a]

N = 709

Key inclusion criteria

- Patients with ypT2-ypT4a or ypN+ MIUC who had NAC chemotherapy
- Patients with pT3-pT4a or pN+ MIUC without prior NAC 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 NAC-based chemotherapy
- Nodal status

Treat for up to 1 year of adjuvant therapy

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

Post hoc analysis endpoints reported here:

- DFS in all randomized patients with MIBC, and in patients with MIBC according to prior NAC
- OS in all randomized patients with MIBC, patients with MIBC and tumor PD-L1 ≥ 1%, and MIBC according to prior NAC

[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 assay. [c]OS is being tested using a hierarchical procedure in each population (ITT and PD-L1 ≥ 1%), per the statistical analysis plan. OS data are from preplanned interim analyses for the ITT and PD-L1 ≥ 1% populations. OS follow-up is ongoing, as the prespecified statistical boundary for significance was not met at the time of these analyses.
Bajorin D, et al. *N Engl J Med* 2021;384:2102-2114.

Baseline clinical and demographic characteristics

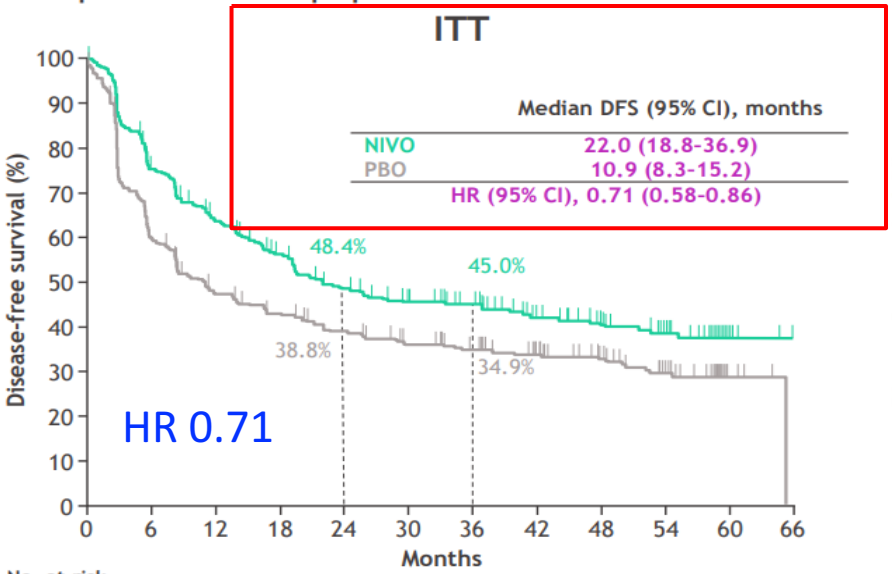
	ITT[1]		MIBC[2]	
	NIVO (N = 353)	PBO (N = 356)	NIVO (n = 279)	PBO (n = 281)
Mean age (range), years	65.3 (30-92)	65.9 (42-88)	64.8 (37-83)	65.7 (42-88)
Male, %	75	77	78	79
Race or ethnic group, %				
White	75	76	83	82
Asian	23	21	14	15
Black	1	1	< 1	1
Other	2	1	3	2
Unreported	0	< 1	0	< 1
ECOG PS,[a] %				
0	63	62	63	58
1	35	35	35	39
2	2	3	2	3
Tumor origin at initial diagnosis, %				
Urinary bladder	79	79	100	100
Renal pelvis	12	15	0	0
Ureter	8	6	0	0
Tumor PD-L1 expression ≥ 1% as recorded at randomization, %	40[b]	40[b]	40[c]	41[c]
Prior neoadjuvant cisplatin, %	43	44	51	51
Pathologic T stage at resection, %				
pTX	1	0	2	0
pT0	1	2	2	2
pTis	1	1	1	1
pT1	4	4	3	5
pT2	18	18	20	23
pT3	58	57	52	49
pT4a	16	17	19	20
Not reported	< 1	< 1	< 1	< 1
Nodal status at resection, %				
N+	47	47	53	55
N0/x with < 10 nodes removed	27	28	17	16
N0 with ≥ 10 nodes removed	26	25	30	28
Not reported	< 1	< 1	< 1	< 1

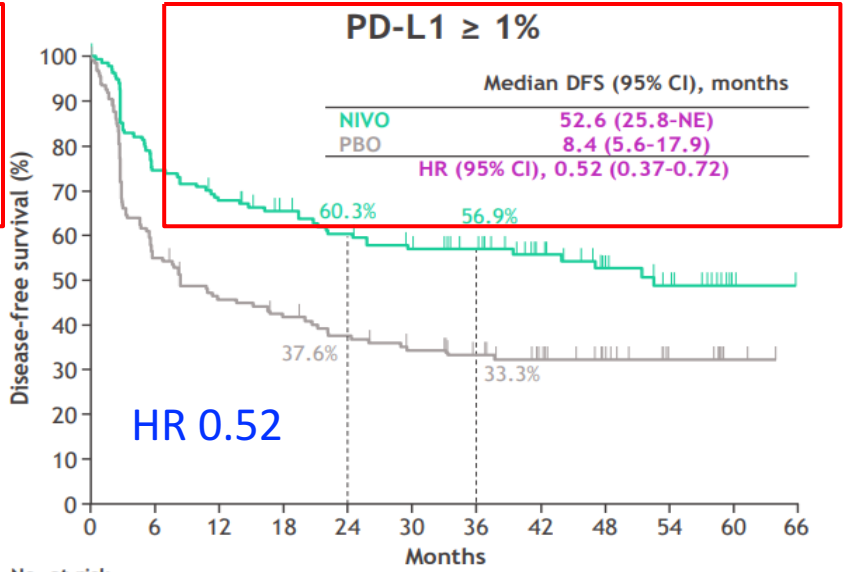
[a]Not reported for 1 patient in the PBO arm. [b]By interactive voice response system. [c]By clinical source.

1. Bajorin DF, et al. *N Engl J Med* 2021;384:2102-2114. 2. Witjes JA, et al. Poster presentation at the ASCO 2022 Annual Meeting; June 3-7, 2022; Chicago, IL & Online. Abstract 4585.

Disease-free survival (Primary endpoint)

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



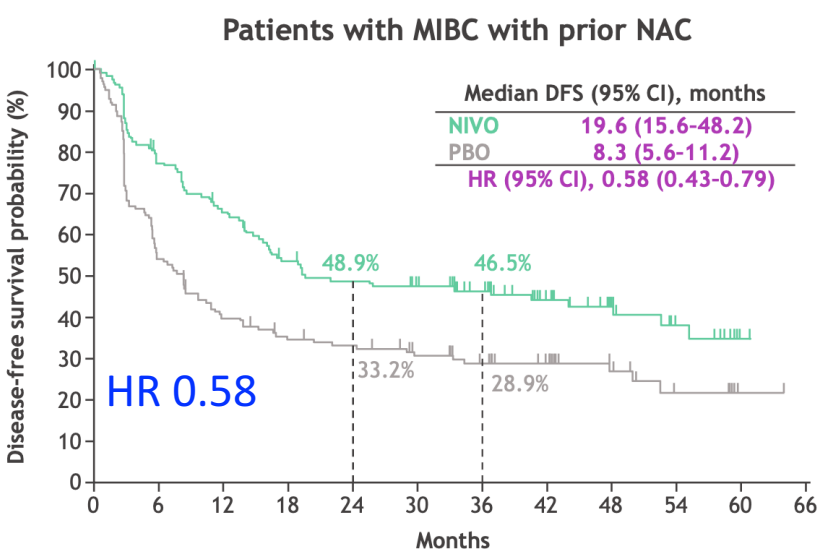


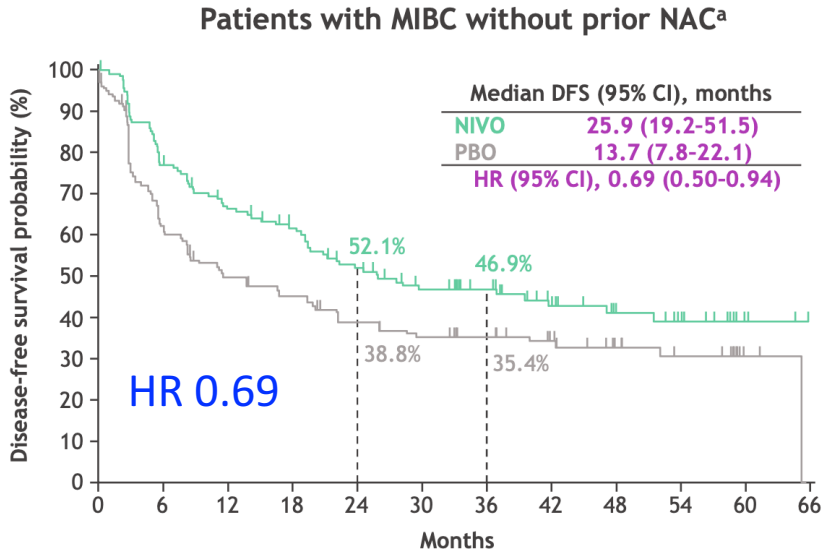
Minimum follow-up in the ITT population, 31.6 months. DFS was defined as the time between the date of randomization and the date of first recurrence (local urothelial tract, local non-urothelial tract or distant) or death.
NE, not estimable.

Follow up: 31 meses

Galsky MD, EAU 2024

DFS: patients with MIBC according to prior NAC



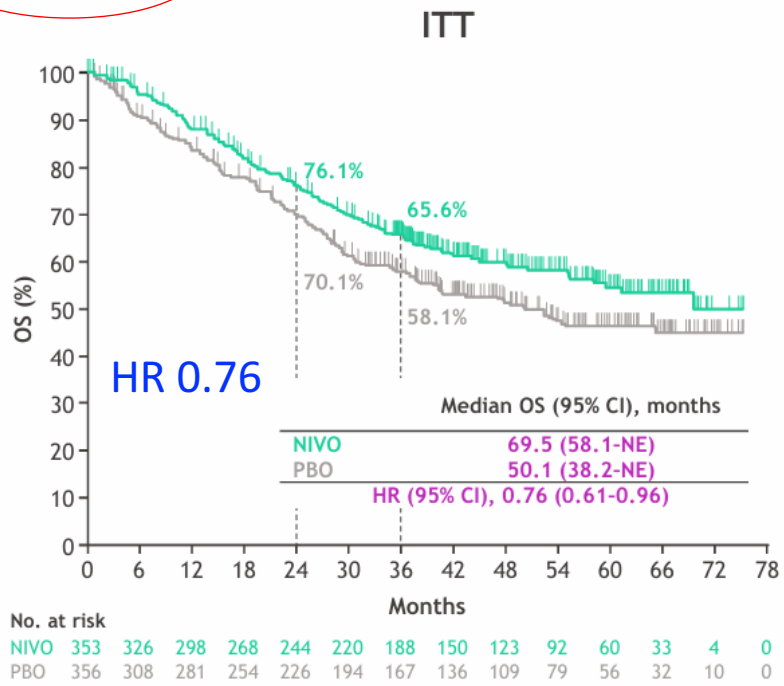


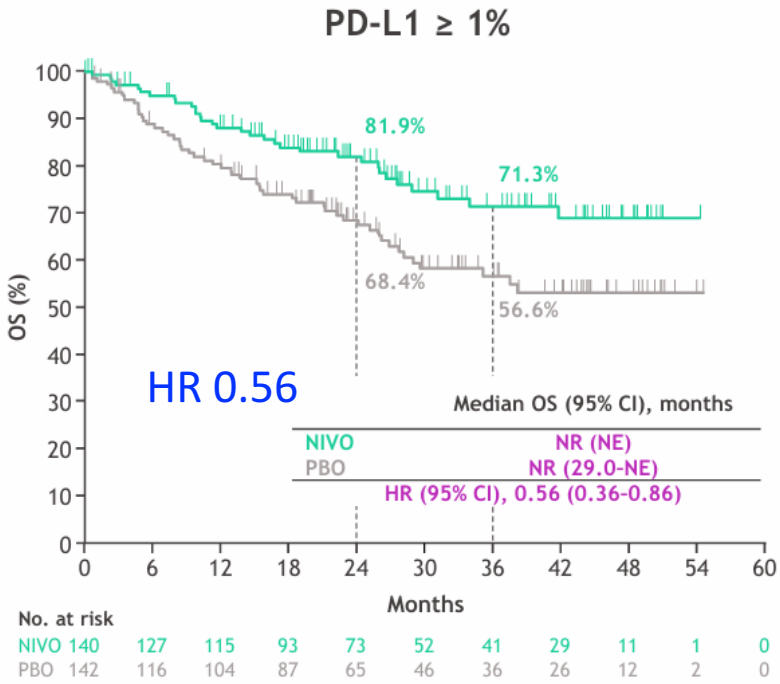
Follow up: 36 meses

Median follow-up of 36.1 months in the ITT population and 34.5 months in the MIBC population.
[a]This includes patients who had not received neo-adjuvant cisplatin chemotherapy and are not eligible for or refuse adjuvant cisplatin chemotherapy.

Overall survival

- Interim OS data favored NIVO versus PBO in the ITT and tumor PD-L1 ≥ 1% populations





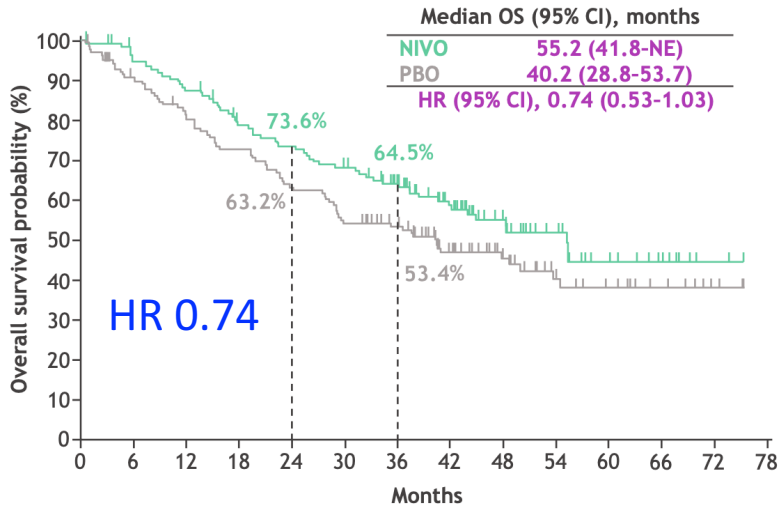
OS follow-up is ongoing, as the prespecified statistical boundary for significance was not met at the time of these analyses. Median (minimum) follow-up in the ITT population, 36.1 (31.6) months; median (minimum) follow-up in PD-L1 ≥ 1% population, 23.4 (11.4) months. OS was defined as time from date of randomization to date of death (from any cause).

Follow up: 31 meses

Galsky MD, EAU 2024

OS: patients with MIBC according to prior NAC

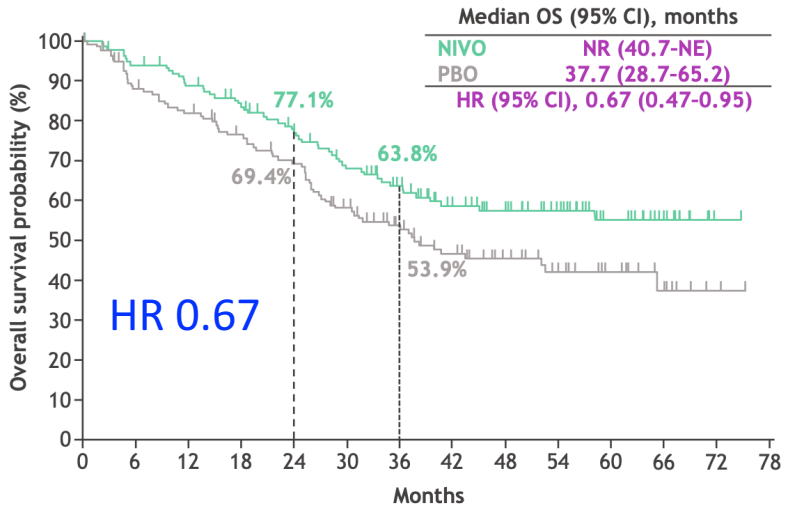
Patients with MIBC with prior NAC



No. at risk

NIVO	142	131	121	105	98	90	76	55	37	23	14	9	2	0
PBO	142	123	110	98	85	73	64	45	31	18	14	9	4	0

Patients with MIBC without prior NAC



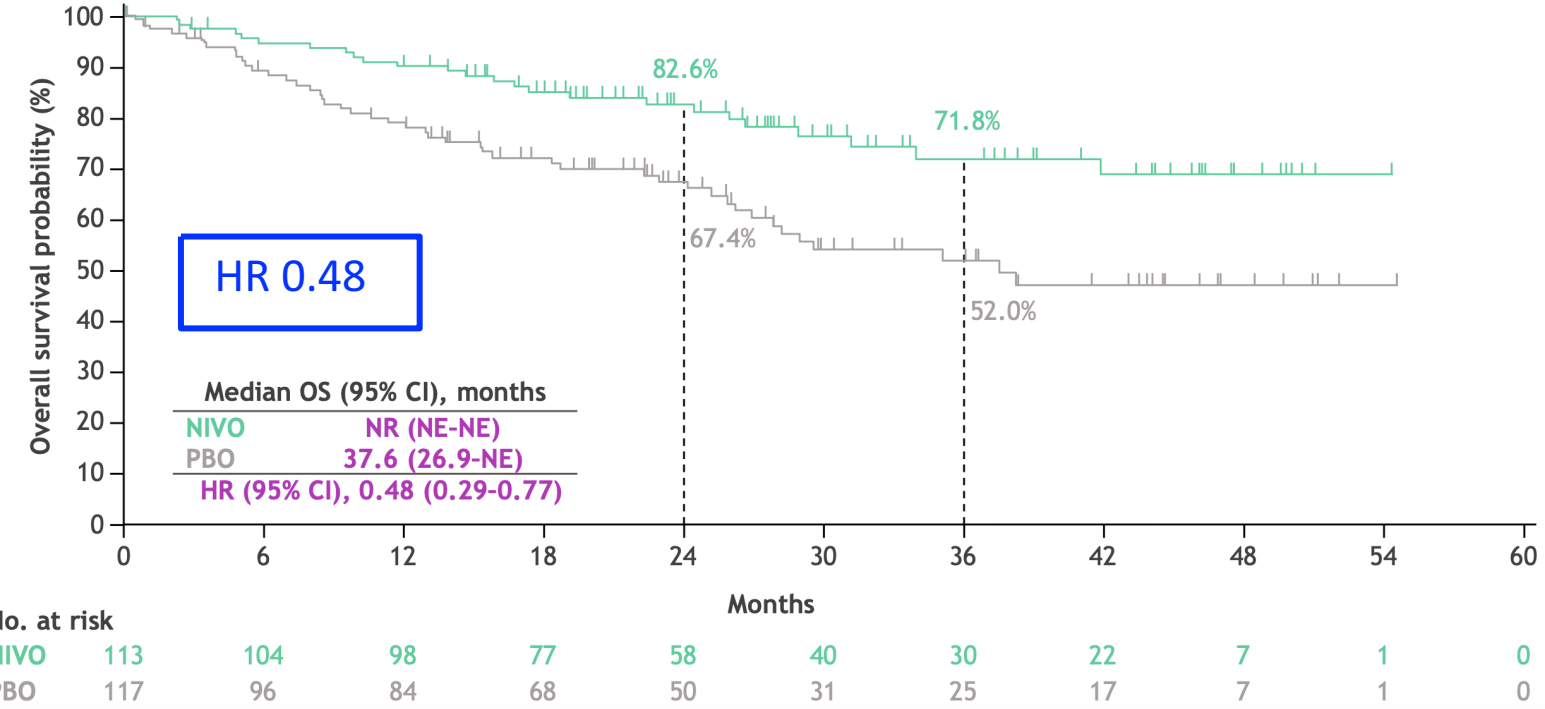
No. at risk

NIVO	137	127	118	108	95	82	69	52	44	33	20	11	1	0
PBO	139	117	108	97	87	70	55	44	34	25	17	8	2	0

Follow up: 36 meses

Median follow-up of 36.1 months in the ITT population and 34.5 months in the MIBC population.

OS[a]: all randomized patients with MIBC and tumor PD-L1 ≥ 1%



CM274 shows clear OS benefit with nivolumab vs placebo

Absolute EFS benefit at 3 years: **15%**
Absolute OS benefit at 3 years: **11%**

- Patients with ypT2-ypT4a or ypN+ MIUC who had NAC chemotherapy

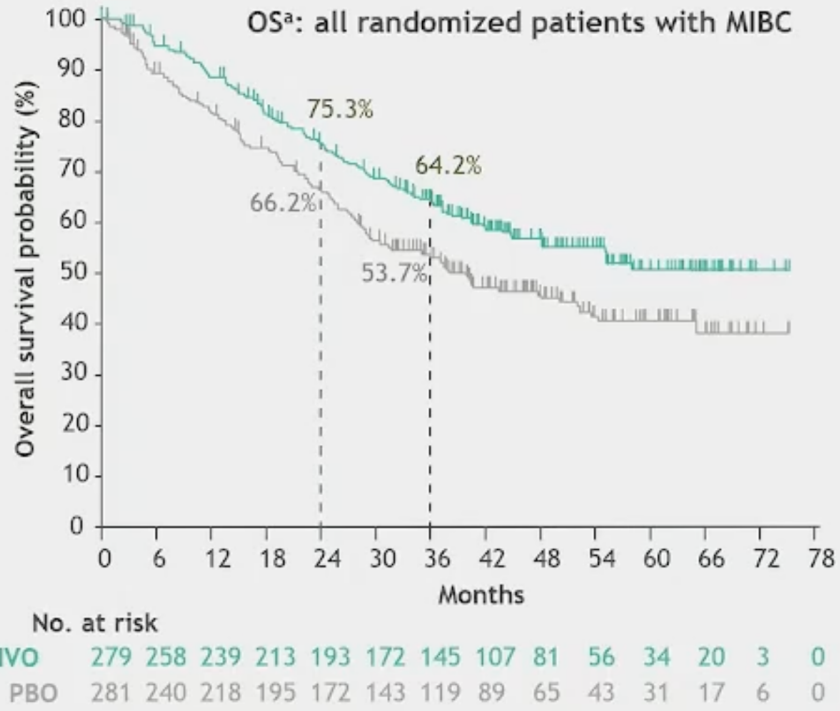
  N=284

- Patients with pT3-pT4a or pN+ MIUC without prior NAC chemotherapy and not eligible/refuse adjuvant cisplatin chemotherapy

  N=276

R 1:1

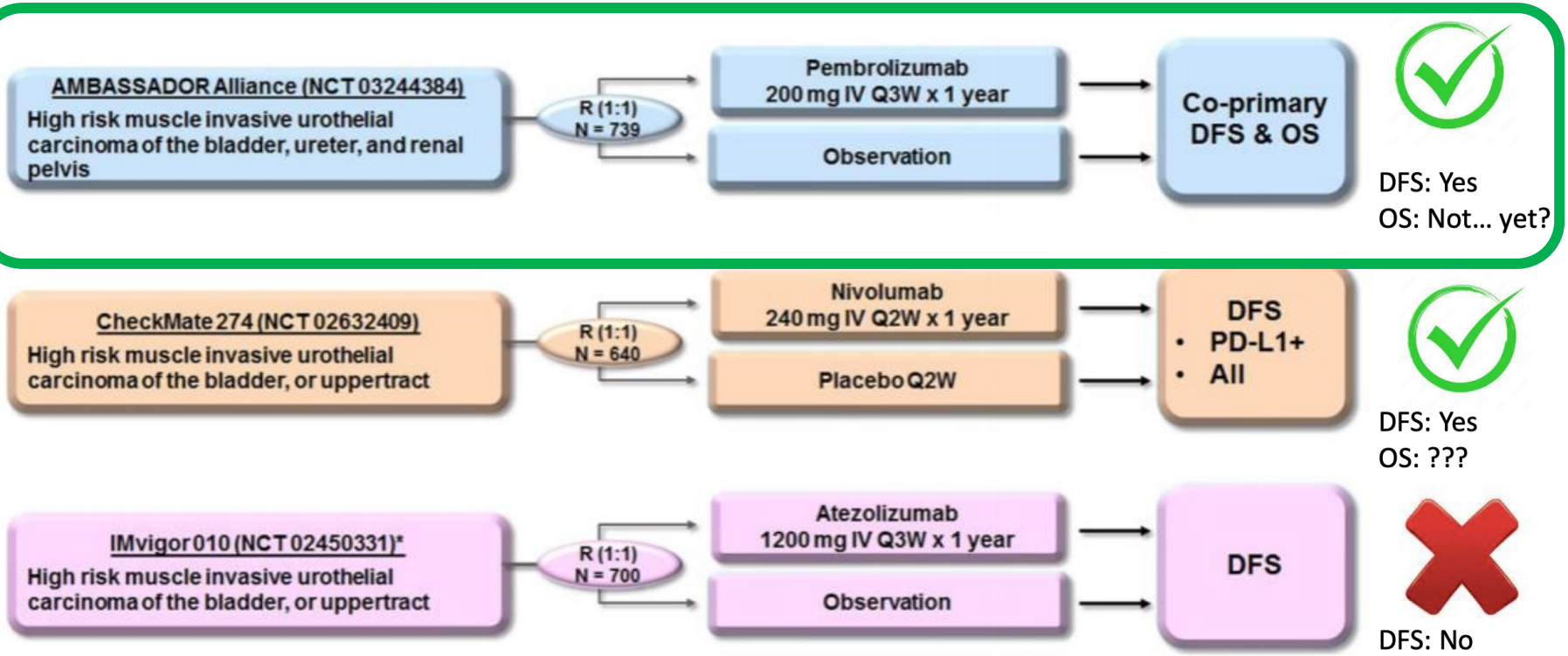
- NIVO IV 240 mg Q2W
- PBO IV Q2W



Comparison of Adjuvant Regimens for Cancer (Intent to Treat vs Placebo)

	Absolute DFS Benefit	Absolute OS Benefit	Trial
NSCLC (EGFRmut)	41%	12%	ADAURA https://ascopubs.org/doi/pdf/10.1200/JCO.22.02186 https://www.nejm.org/doi/full/10.1056/NEJMoa2304594
Bladder Cancer	**15%**	**11%**	**CHECKMATE 274** Milowsky et al. ASCO GU 2025
Breast (TN)	9%	8%	KEYNOTE-522 https://www.nejm.org/doi/full/10.1056/NEJMoa2409932
Breast (HER2+)	14%	5%	KATHERINE https://www.nejm.org/doi/full/10.1056/NEJMoa2406070
RCC	8%	5%	KEYNOTE-564 https://doi.org/10.1056/NEJMoa2312695
Melanoma	14%	Awaiting events Expected at year 10	KEYNOTE-054 https://pubmed.ncbi.nlm.nih.gov/39288737/
Colorectal Cancer	6%	3%	MOSAIC https://doi.org/10.1200/JCO.2008.20.6771
NSCLC	8%	2%	KEYNOTE 091 https://doi.org/10.1016/S1470-2045(22)00518-6
NSCLC	6%	1%	IMPower010 https://ascopubs.org/doi/10.1200/JCO.2024.42.17_suppl.LBA8035
Breast (HR+)	7%	1%	MonarchE https://doi.org/10.1200/JCO.23.01994

Adjuvant treatment with PD-1/PD-L1 inhibitors



Nadal R and Apolo A. Curr Treat Options Oncol. 2018

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

ORIGINAL ARTICLE

Adjuvant Pembrolizumab versus Observation in Muscle-Invasive Urothelial Carcinoma

A.B. Apolo, K.V. Ballman, G. Sonpavde, S. Berg, W.Y. Kim, R. Parikh, M.Y. Teo, R.F. Sweis, D.M. Geynisman, P. Grivas, G. Chatta, Z.R. Reichert, J.W. Kim, M.A. Bilen, B. McGregor, P. Singh, A. Tripathi, S. Cole, N. Simon, S. Niglio, L. Ley, L. Cordes, S. Srinivas, J. Huang, M. Odegaard, C. Watt, D. Petrylak, J. Hoffman-Censits, Y. Wen, O. Hahn, C. Mitchell, A. Tan, H. Streicher, E. Sharon, H. Moon, M. Woods, S. Halabi, G. Perez Burbano, M.J. Morris, and J.E. Rosenberg

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

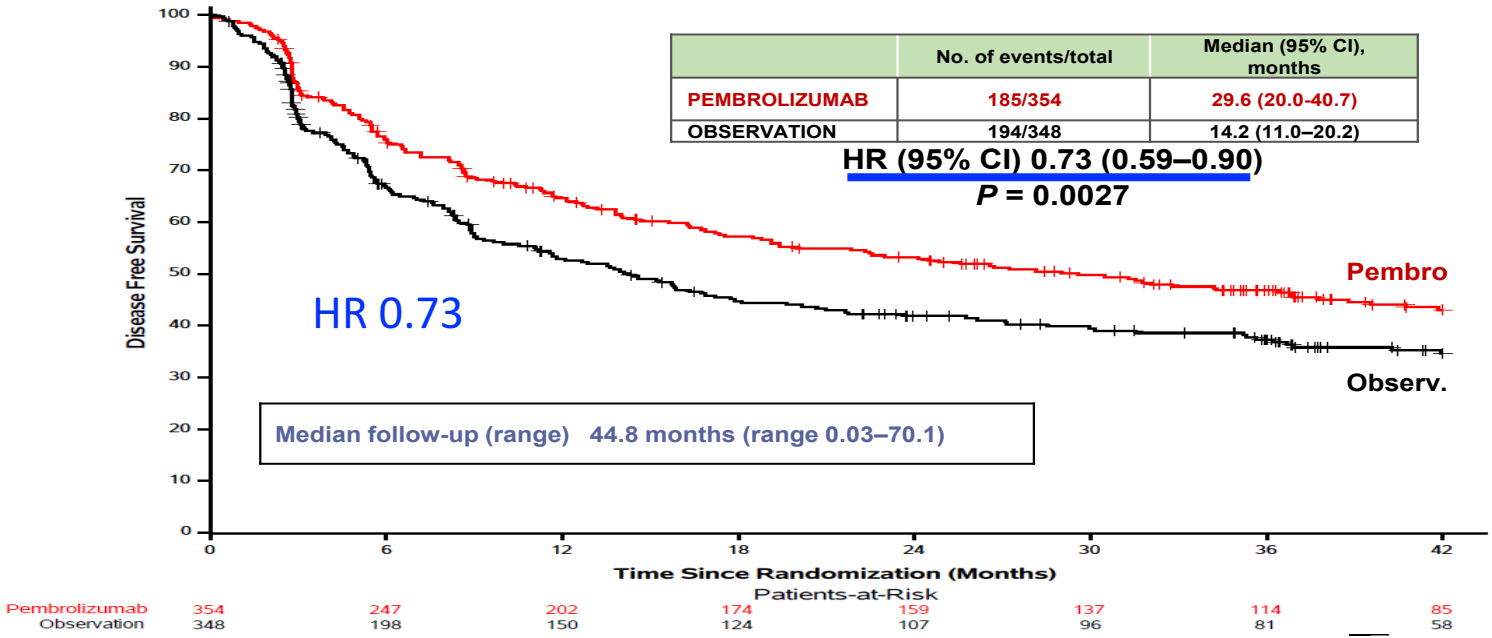
- DFS/OS PD-L1 +/-
- Safety

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

AMBASSADOR: Disease-Free Survival (ITT)

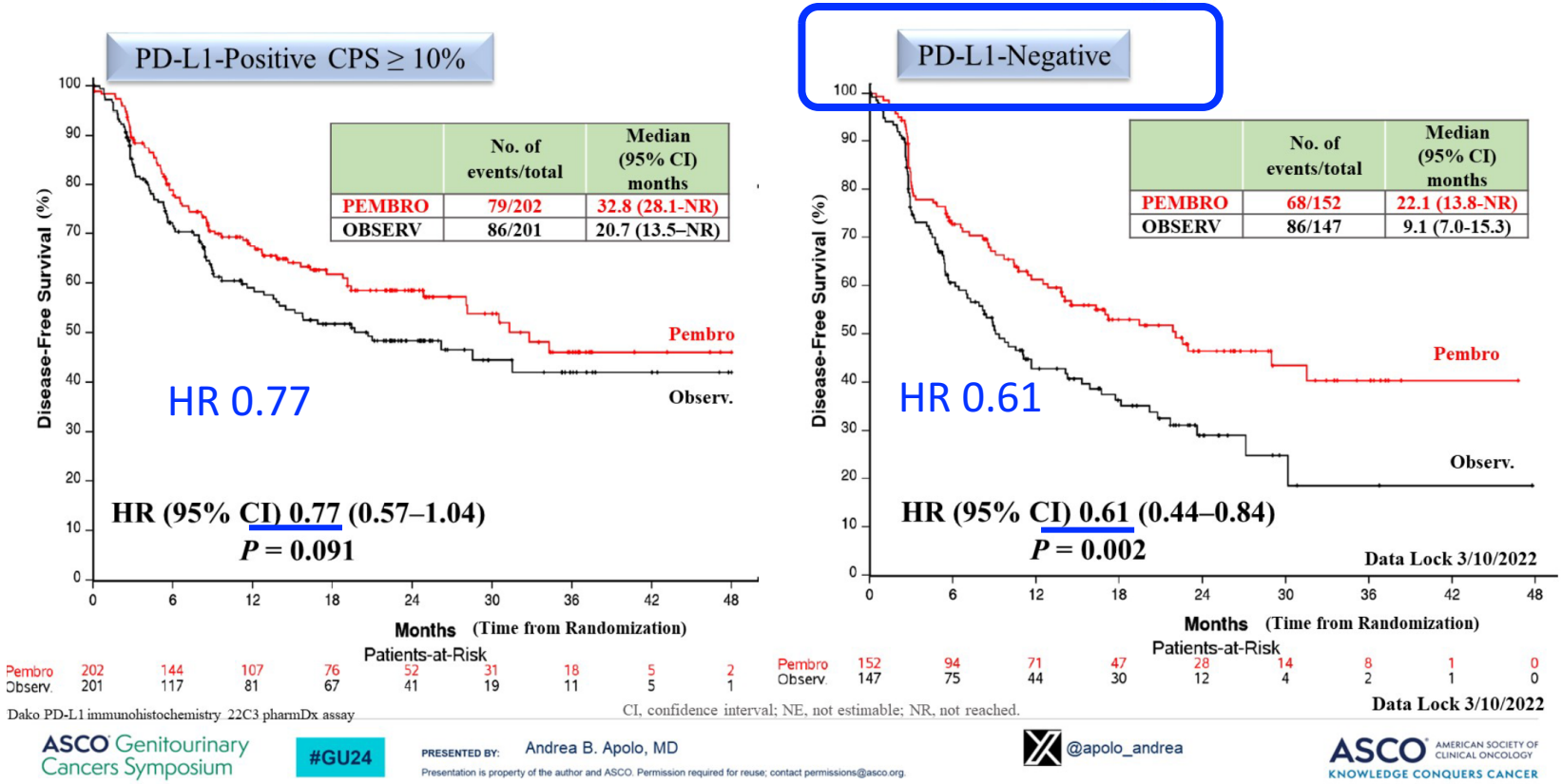


	No. of events/total	Median (95% CI), months
PEMBROLIZUMAB	185/354	29.6 (20.0-40.7)
OBSERVATION	194/348	14.2 (11.0–20.2)

HR (95% CI) 0.73 (0.59–0.90)

***P* = 0.0027**

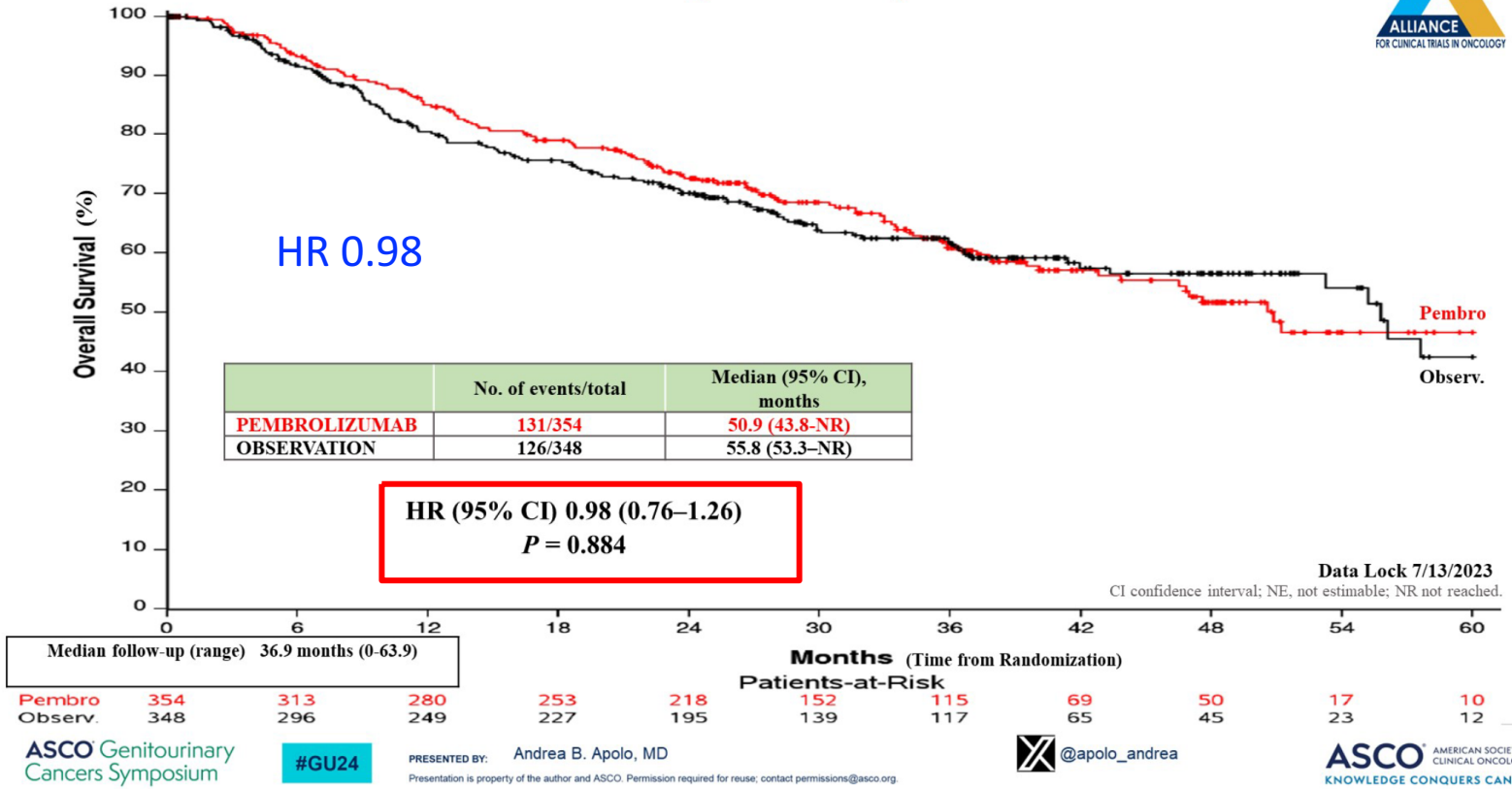
A031501 AMBASSADOR: Disease-Free Survival by PD-L1* Status



Dako PD-L1 immunohistochemistry 22C3 pharmDx assay

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

A031501 AMBASSADOR: (interim) Overall Survival



	No. of events/total	Median (95% CI), months
PEMBROLIZUMAB	131/354	50.9 (43.8-NR)
OBSERVATION	126/348	55.8 (53.3–NR)

HR (95% CI) 0.98 (0.76–1.26)
***P* = 0.884**

Data Lock 7/13/2023

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

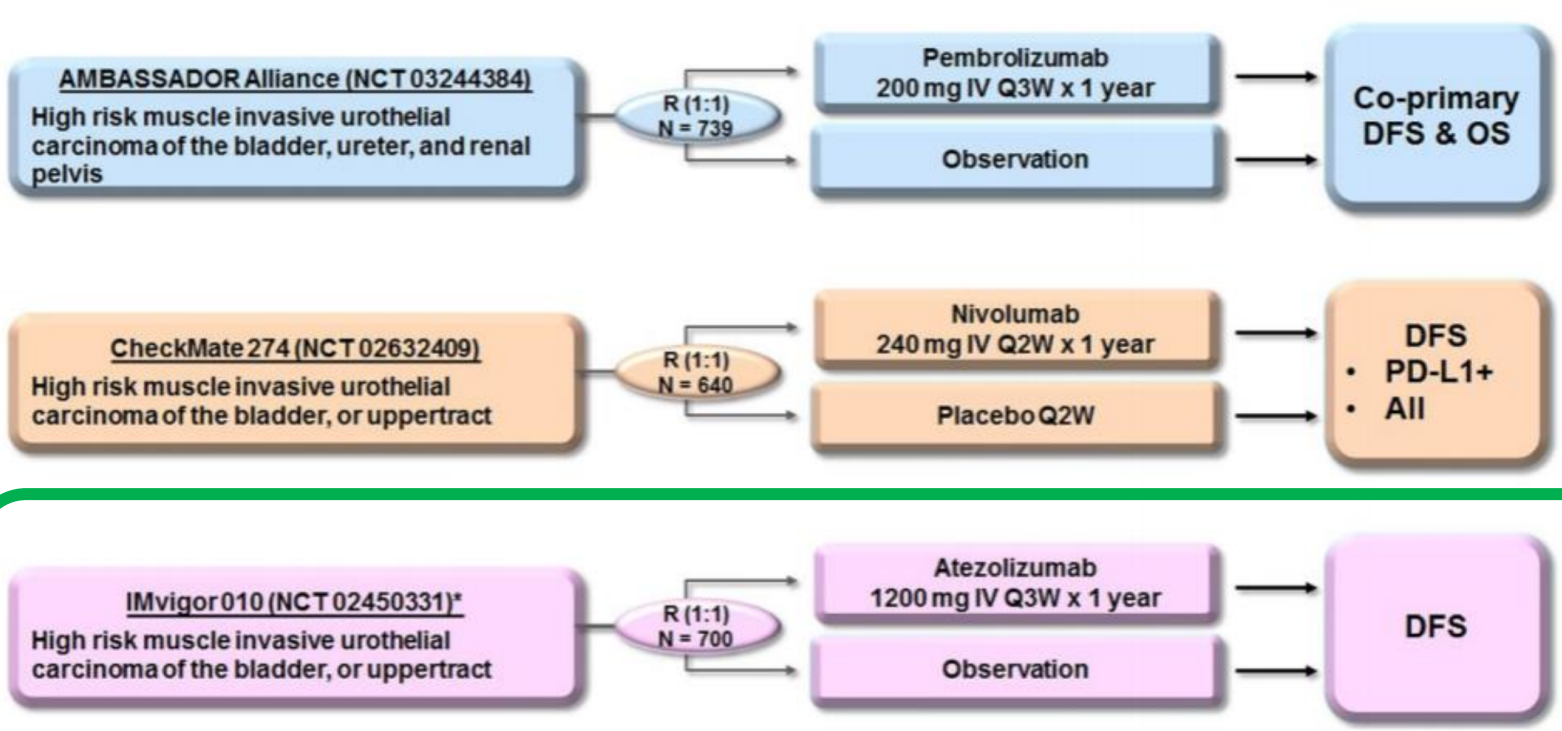
ASCO Genitourinary Cancers Symposium #GU24

PRESENTED BY: Andrea B. Apolo, MD

@apolo_andrea

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Adjuvant treatment with PD-1/PD-L1 inhibitors



Madal R and Apolo A. Curr Treat Options Oncol. 2018

IMVIGOR 010

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**

R 1:1

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

No crossover allowed

Observation[c] **q3w**

Completed treatment: A 51% vs O 50%%

Disease recurrence/ survival follow-up

Tumor assessments: q12w for years 1-3, (q24w for years 4-5 and at year 6)

Stratification factors

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

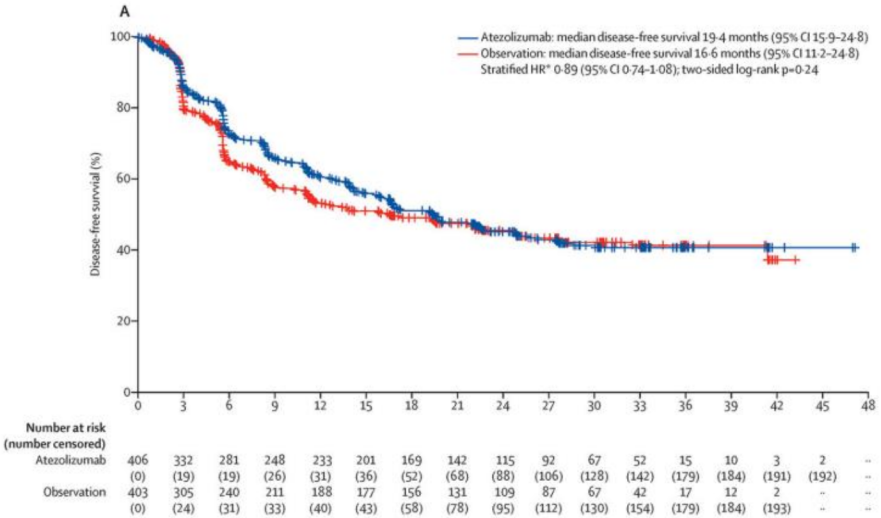
- **Primary endpoint:** DFS (ITT population)
- **Key secondary endpoint:** OS (ITT population)
- **Exploratory analyses:** Biomarkers including PD-L1 status
- **Safety**

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.

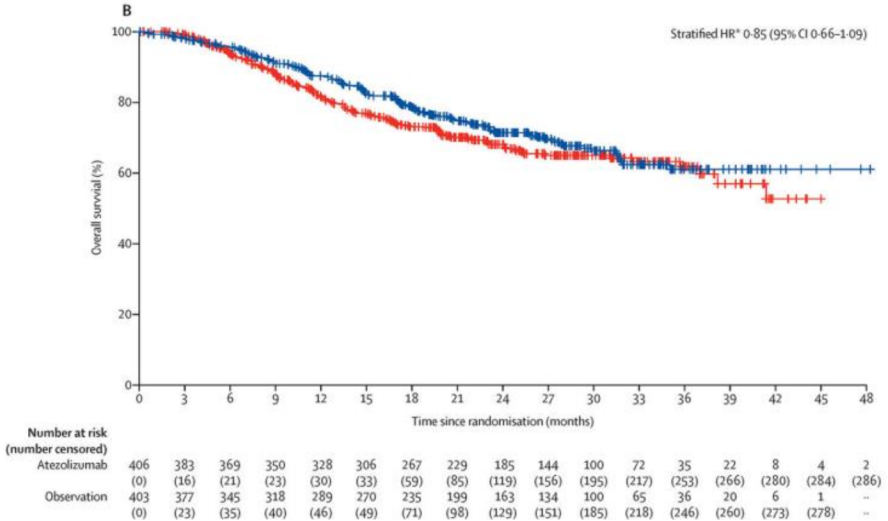
Hussain M, et al. ASCO 2020, Abstract #5000

IMVIGOR 010

DISEASE FREE SURVIVAL (INV. ASSESSED)



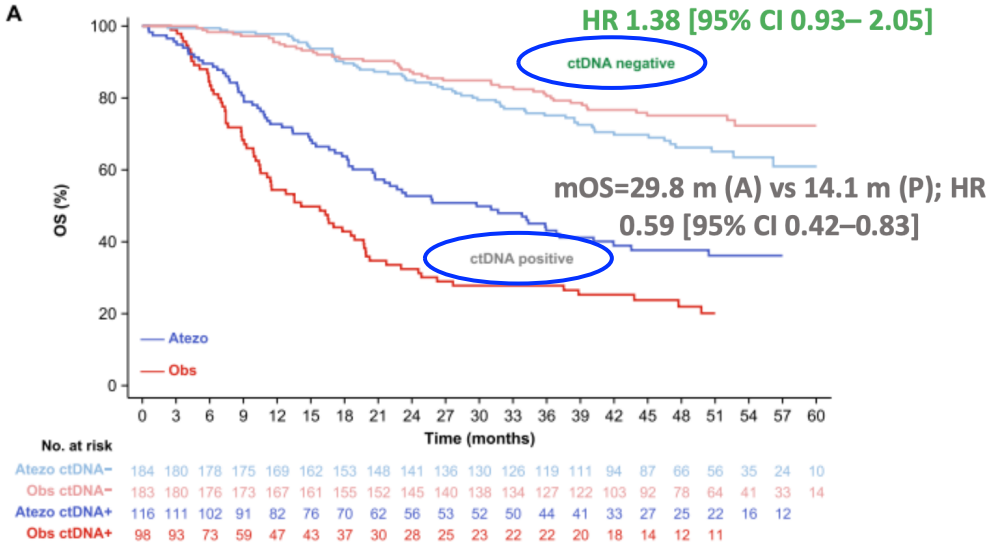
OVERALL SURVIVAL (ITT POPULATION)



Bellmunt J, et al. Lancet Oncol. 2021 Apr;22(4):525-537.

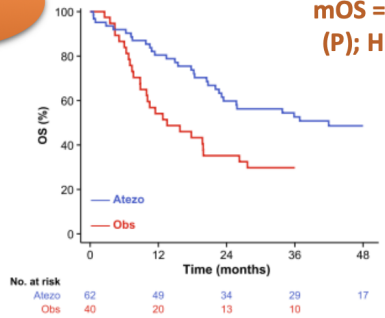
IMVIGOR 010: ANALYSIS AT BASELINE

Kaplan-Meier estimate of OS with atezolizumab versus observation in subgroups defined by baseline ctDNA status



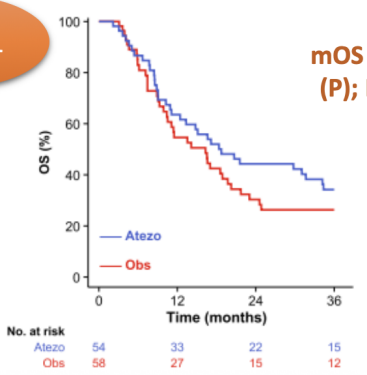
Kaplan-Meier estimates of OS with atezolizumab versus observation in patients positive for ctDNA by baseline PD-L1 status

IHC 2/3



mOS = 42.0 m (A) vs 13.5 m (P); HR 0.51 [95% CI 0.30–0.85])

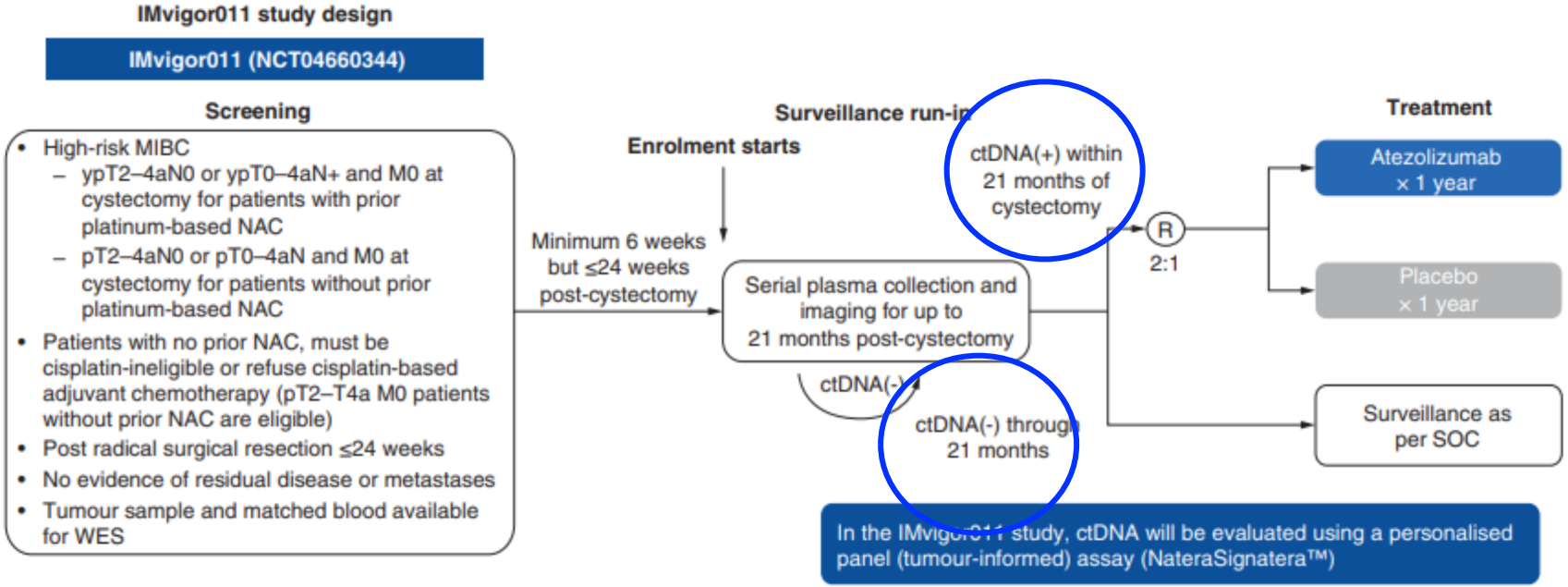
IHC 0/1



mOS = 18.7 m (A) vs 16.3 m (P); HR 0.75 [95% CI 0.49–1.16]

Powles T, et al. Eur Urol. 2024 Feb;85(2):114-122.

IMVIGOR 011

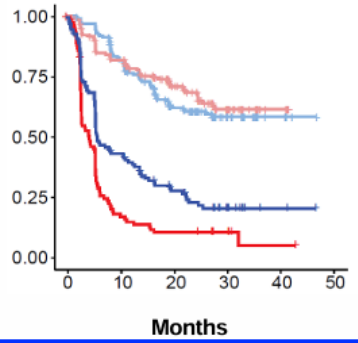


Jackson-Spence F, et al. Future Oncol. 2023 Mar;19(7):509-515.

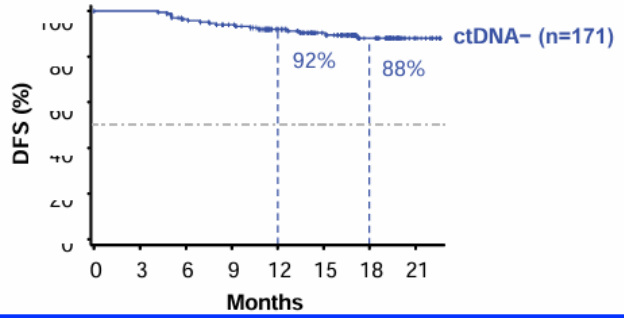
IMvigor011: Surveillance group analysis

- This analysis suggests that serial ctDNA testing may have greater clinical utility than landmark ctDNA testing as a risk stratification tool using Natera Signatera assay

IMvigor010: landmark testing in a high-risk population (DFS)[1,a]

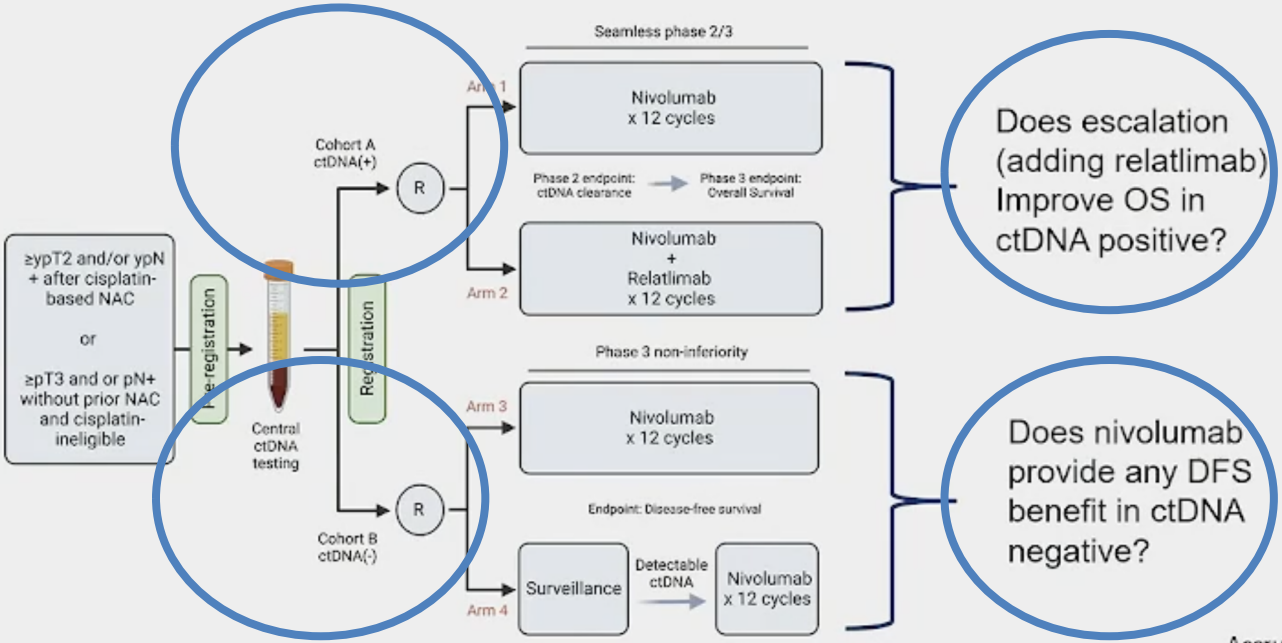


IMvigor011 serial testing: DFS in ctDNA– patients (surveillance group)



- These data lend increasing confidence that patients with high-risk MIBC who have persistent ctDNA− status after cystectomy may be spared from adjuvant treatment
- This analysis was limited to ctDNA− patients and suggests that ctDNA status selects for patients with favourable clinical prognosis regardless of PD-L1 status and pathologic staging at cystectomy

Risk adapted adjuvant therapy: MODERN



Accrual to date 93/1190

PRESENTED BY: Elizabeth Plimack, MD MS FASCO

Galsky. Personal communication

ADJUVANT TREATMENT

Following cystectomy →

- If gemcitabine + cisplatin + durvalumab given preoperatively, then durvalumab should be used postoperatively.
- Based on pathologic risk,
  - If no cisplatin neoadjuvant treatment given and pT3, pT4a, or pN+
    - ◊ Adjuvant cisplatin-based chemotherapy should be discussed (preferred)[z]
      or
    - ◊ Consider adjuvant nivolumab[ee] or pembrolizumab[z,ee]

  or
  - If cisplatin neoadjuvant chemotherapy given and ypT2–ypT4a or ypN+, consider nivolumab[ee] or pembrolizumab[z,ee]

  or
  - Consider adjuvant RT in selected patients (pT3–4, positive nodes/margins at the time of surgery)[bb] (category 2B)

→ Follow-up (BL-E)

2 TRATAMIENTO PERI-OPERATORIO con IO

Combinations: Ongoing phase III trials

	Clinical Trial	N	Treatment Arms
CISPLATIN ELIGIBLE	KEYNOTE-866[1]	907	Pembro + GC vs GC
	KEYNOTE-B15/EV-304[2]	784	Pembro + EV vs GC
	NIAGARA[3]	1063	Durva + GC vs GC
	ENERGIZE[4]	861	Nivo + GC vs GC
CISPLATIN INELIGIBLE	KEYNOTE-905/EV-303[5]	857	RC vs Pembro + EV vs Pembro
	VOLGA[6]	830	RC vs Durva/Treme + EV vs Durva + EV
	SWOG GAP[7]	196	Surgery vs Gem/Carbo + Avelumab

1. NCT03924856; 2. NCT04700124; 3. NCT03732677; 4. NCT03661320; 5. NCT03924895; 6. NCT04960709; 7. NCT04871529

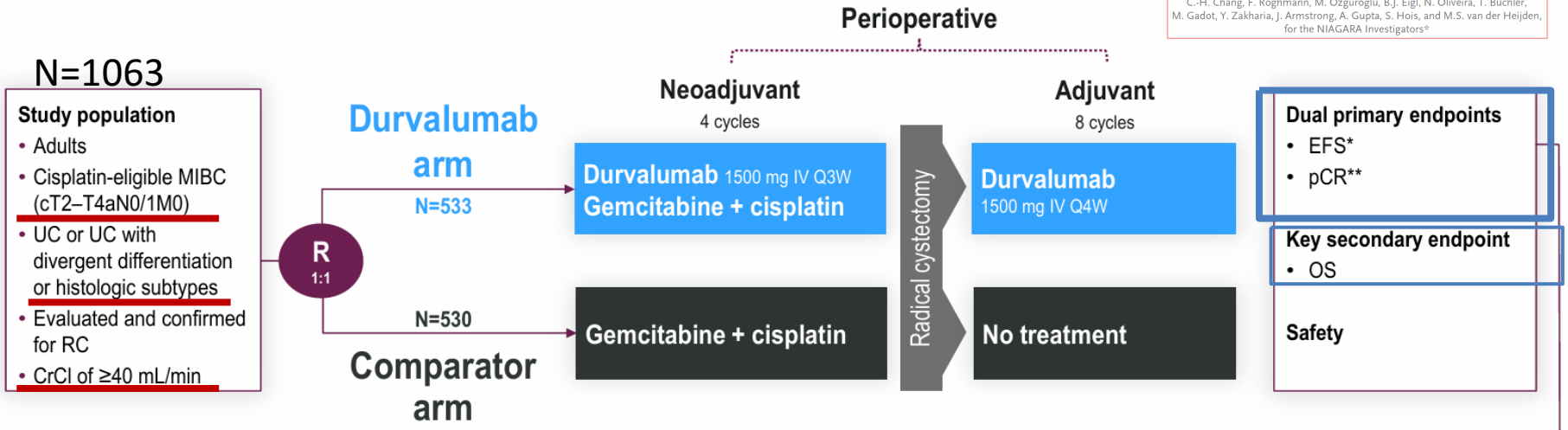
Modificado de Gupta S. GUCS 2023

Niagara: Study desing

ORIGINAL ARTICLE

Perioperative Durvalumab with Neoadjuvant Chemotherapy in Operable Bladder Cancer

T. Powles, J.W.F. Catto, M.D. Galsky, H. Al-Ahmadie, J.J. Meeks, H. Nishiyama, T.Q. Vu, L. Antonuzzo, P. Wiechno, V. Atduev, A.G. Kann, T.-H. Kim, C. Suárez, C.-H. Chang, F. Roghmann, M. Özgüroğlu, B.J. Eigl, N. Oliveira, T. Buchler, M. Gadot, Y. Zakharia, J. Armstrong, A. Gupta, S. Hois, and M.S. van der Heijden, for the NIAGARA Investigators*



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

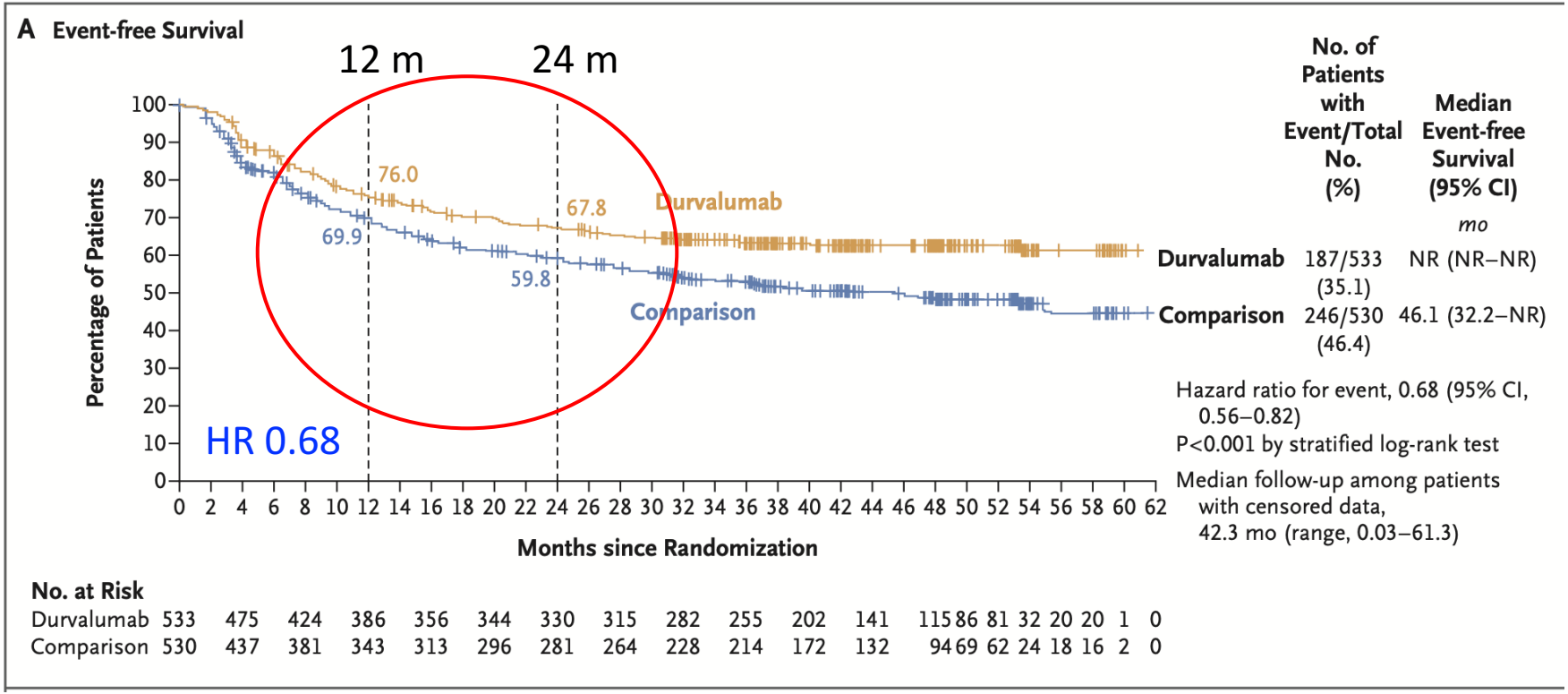
Other endpoints (not reported here): DFS, DSS, MFS, HRQoL, 5-year OS

*Evaluated by blinded independent central review or central pathology review (if a biopsy was required for a suspected new lesion). **Evaluated by blinded central pathology review.

ClinicalTrials.gov, NCT03732677; EudraCT number, 2018-001811-59. CrCl, creatinine clearance; DFS, disease-free survival; DSS, disease-specific survival; EFS, event-free survival; HRQoL, health-related quality of life; IV, intravenous; MFS, metastasis-free survival; MIBC, muscle-invasive bladder cancer; OS, overall survival; pCR, pathologic complete response; PD-L1, programmed cell death ligand-1; Q3W, every 3 weeks; Q4W, every 4 weeks; R, randomised; RC, radical cystectomy; UC, urothelial carcinoma..

Powles T, et al. N Engl J Med 2024;391(19):1773.

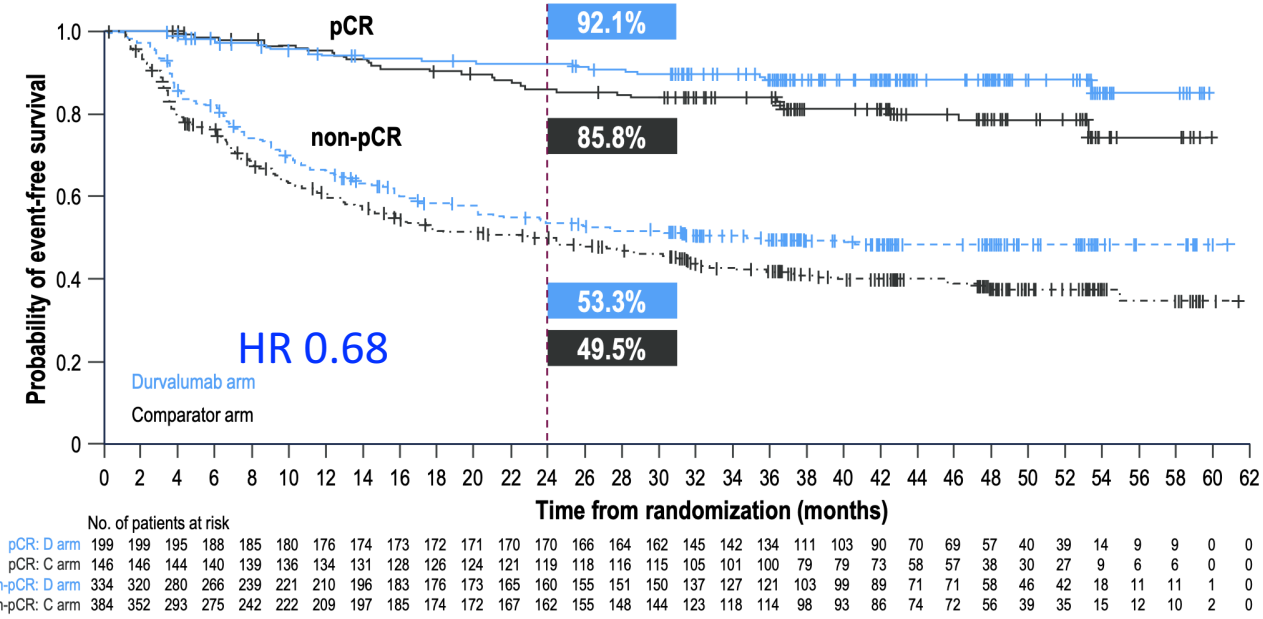
Event-free Survival by Blinded Independent Central Review (ITT)



Powles T, et al. N Engl J Med 2024;391(19):1773.

NIAGARA: Event-free Survival (pCR and Non-pCR Groups)

Perioperative D + NAC improved EFS in both groups



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)

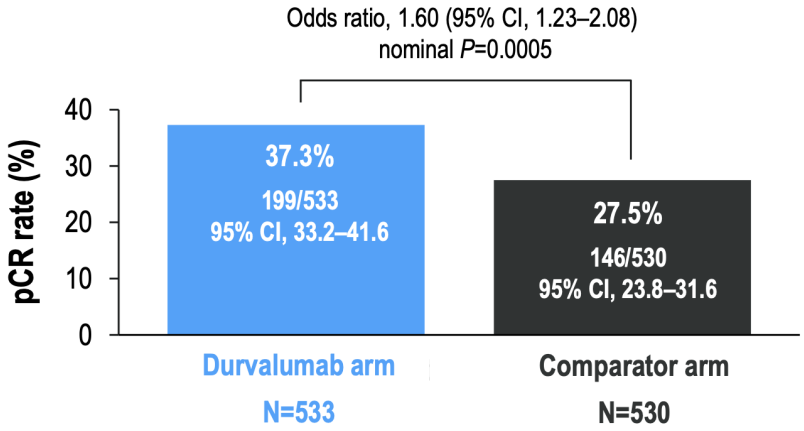
Data cutoff Apr 29, 2024. Exploratory post-hoc analysis. Event-free survival by blinded independent central review or by central pathology review. Tick marks indicate patients with censored data. C, comparator; D, durvalumab; EFS, event-free survival; HR, hazard ratio; ITT, intent-to treat population;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

39b

PRESENTED BY: Prof Matthew D. Galsky

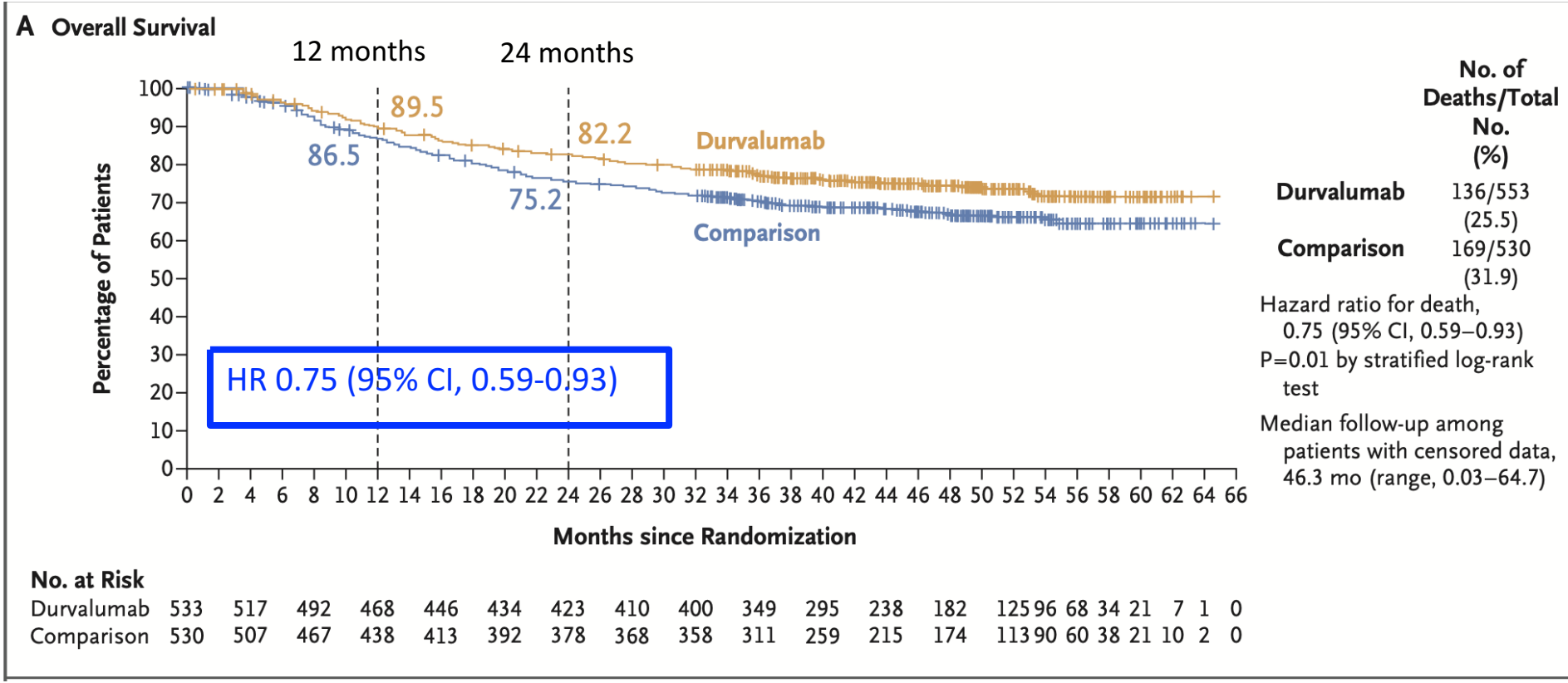
NIAGARA: Pathological Complete Response (ITT)

10% improvement in pathological complete response rate in favor of the durvalumab arm



Further details are available in Powles T, et al. *N Engl J Med*. 2024;391:1773–1786.
Data cutoff Apr 29, 2024. Odds ratio, corresponding CI, and *P* value are obtained using logistic regression adjusted for the stratification factors (renal function, tumor stage, and PD-L1 status). Pathological staging of samples taken during RC was performed centrally; pCR was the proportion of patients with stage T0N0M0 at RC (American Joint Committee on Cancer 8th edition classification). CI, confidence interval; ITT, intent-to-treat population; pCR, pathological complete response; RC, radical cystectomy.

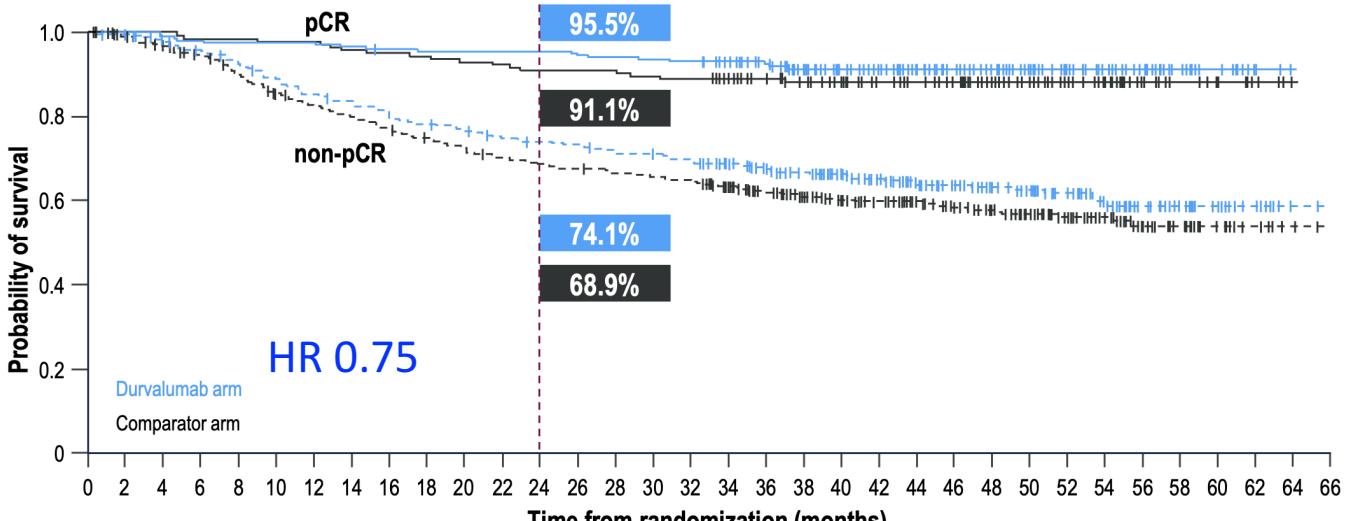
Niagara: Overall Survival



Powles T, et al. N Engl J Med 2024;391(19):1773.

NIAGARA: Overall Survival in pCR and Non-pCR Groups

Perioperative D + NAC improved OS in both groups



No. of patients at risk

pCR: D arm	199	199	197	194	194	194	193	192	190	189	189	189	189	187	186	185	184	176	164	149	139	129	111	95	83	68	54	44	31	14	11	2	0	0
pCR: C arm	146	146	146	144	144	143	142	140	139	137	136	134	133	133	132	130	130	124	117	109	100	93	85	76	65	51	40	31	23	15	7	3	0	0
non-pCR: D arm	334	329	320	311	298	284	275	265	256	251	245	239	234	231	224	223	216	199	185	172	156	142	127	112	99	84	71	52	37	20	10	5	1	0
non-pCR: C arm	384	370	361	346	323	307	296	285	274	265	256	249	245	240	236	233	228	210	194	172	159	146	130	118	109	90	73	59	37	23	14	7	2	0

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

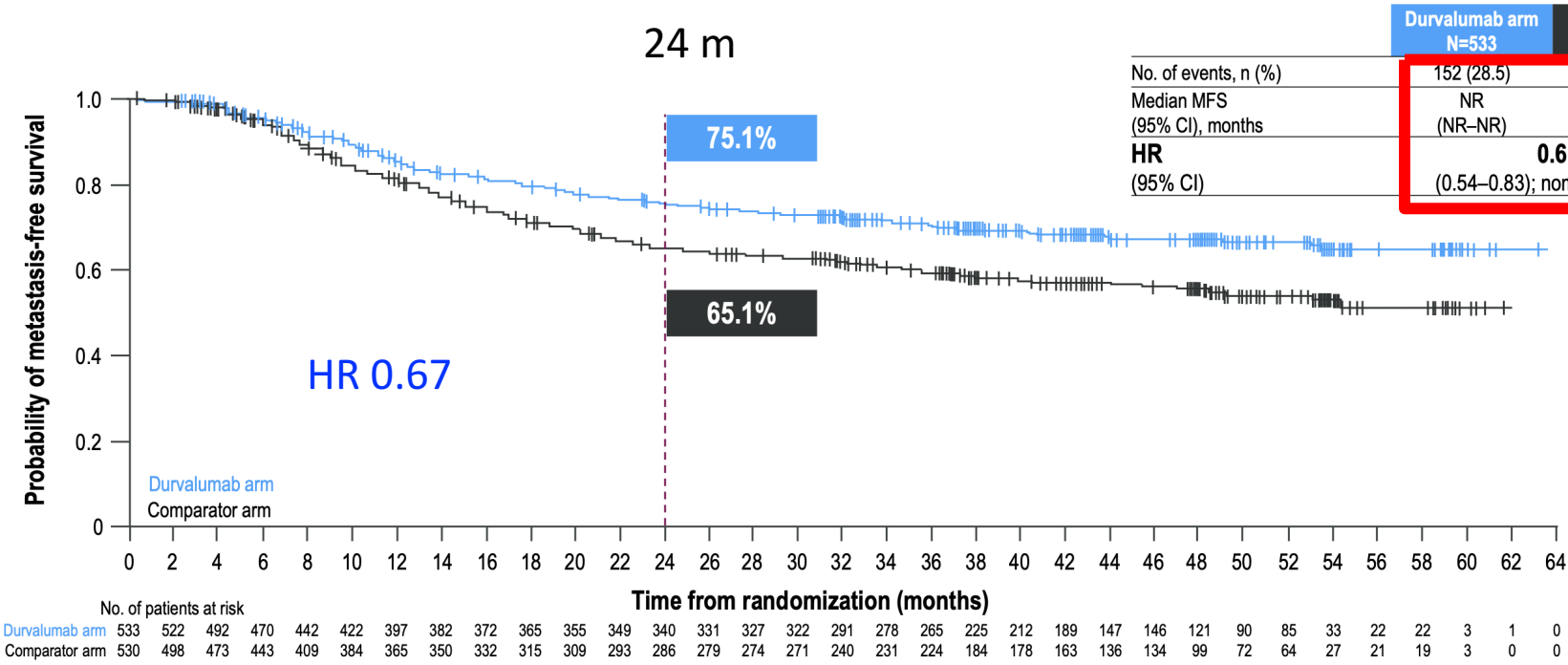
OS HR (95% CI)	**0.75** (0.59–0.93)

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.

PRESENTED BY: Prof Matthew D. Galsky

NIAGARA: Metastasis-free Survival (ITT)

Perioperative D + NAC reduced the risk of distant metastases or death by 33%



	Durvalumab arm N=533	Comparator arm N=530
No. of events, n (%)	152 (28.5)	201 (37.9)
Median MFS (95% CI), months	NR (NR–NR)	NR (48.0–NR)
HR (95% CI)	**0.67** (0.54–0.83); nominal *P*<0.001	

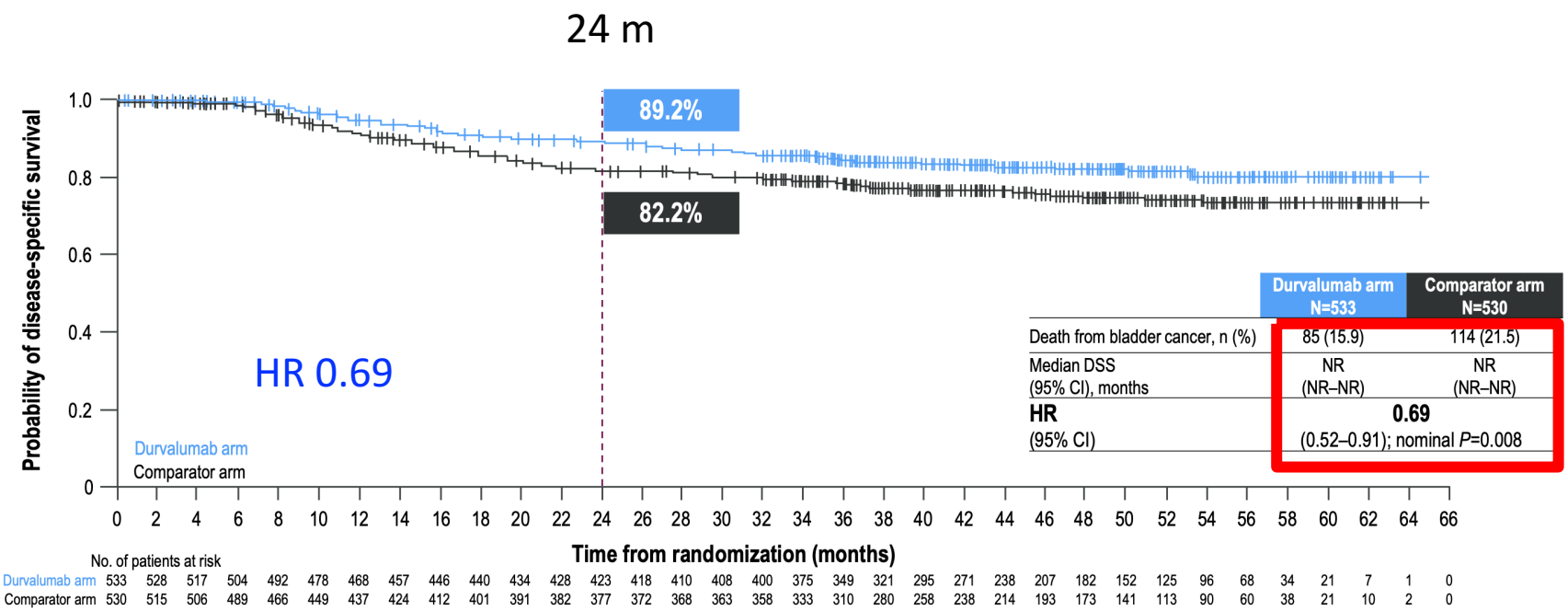
No. of patients at risk

Durvalumab arm	533	522	492	470	442	422	397	382	372	365	355	349	340	331	327	322	291	278	265	225	212	189	147	146	121	90	85	33	22	22	3	1	0
Comparator arm	530	498	473	443	409	384	365	350	332	315	309	293	286	279	274	271	240	231	224	184	178	163	136	134	99	72	64	27	21	19	3	0	0

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.

NIAGARA: Disease-specific Survival (ITT)

Perioperative D + NAC reduced the risk of death from bladder cancer by 31%



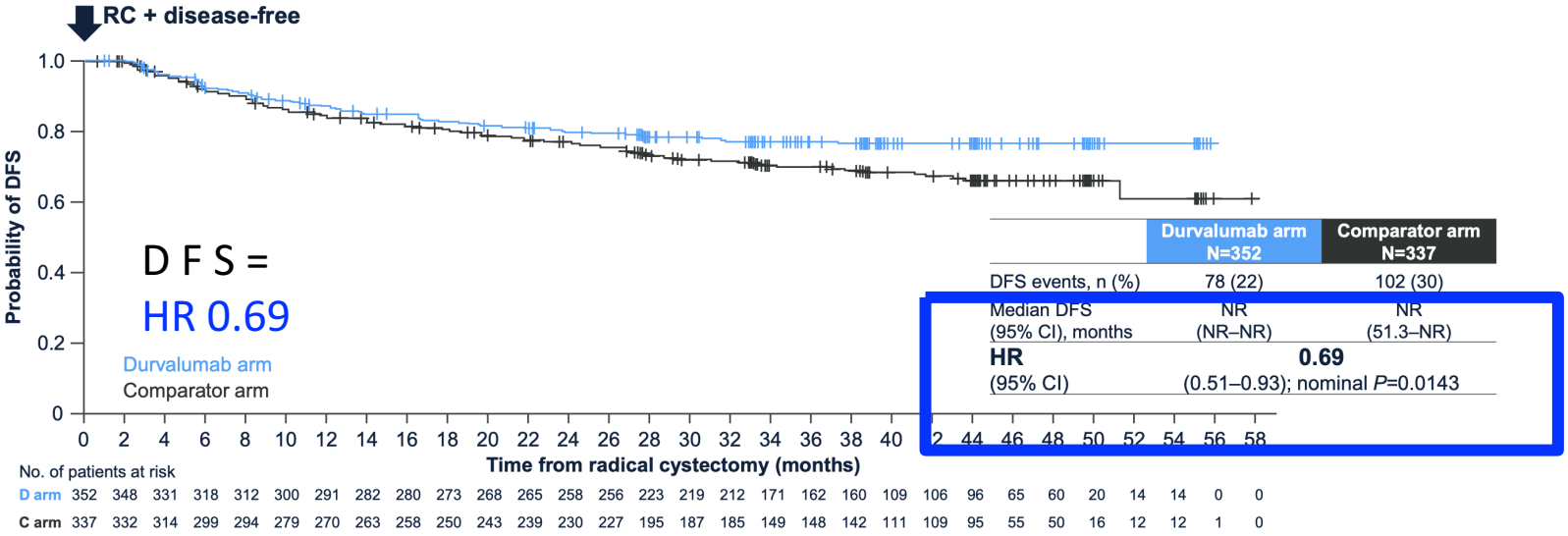
	Durvalumab arm N=533	Comparator arm N=530
Death from bladder cancer, n (%)	85 (15.9)	114 (21.5)
Median DSS (95% CI), months	NR (NR–NR)	NR (NR–NR)
HR (95% CI)	**0.69** (0.52–0.91); nominal *P*=0.008	

Data cutoff Apr 29, 2024. Disease-specific survival is defined as the time from the date of randomization until death due to bladder cancer. Tick marks indicate patients with censored data. CI, confidence interval; D, durvalumab; DSS, disease-specific survival; HR, hazard ratio; ITT, intent-to-treat population; NAC, neoadjuvant chemotherapy; NR, not reached.

AUA 2025 APRIL 26-29 Las Vegas

NIAGARA: DFS

Perioperative durvalumab + NAC reduced the risk of recurrence or death post-RC by 31%



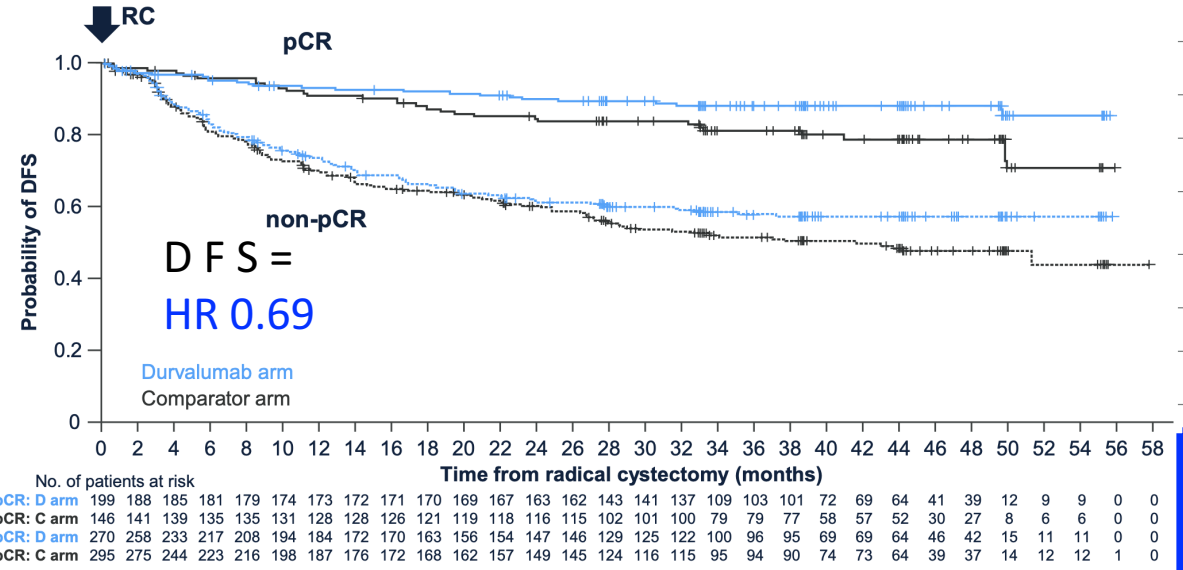
	Durvalumab arm N=352	Comparator arm N=337
DFS events, n (%)	78 (22)	102 (30)
Median DFS (95% CI), months	NR (NR–NR)	NR (51.3–NR)
HR (95% CI)	**0.69** (0.51–0.93); nominal *P*=0.0143	

Data cutoff: 29 April 2024. HR based on Cox proportional hazard model adjusted for the stratification factors (tumor stage, renal function, and PD-L1 status), with ties handled by the Efron approach. DFS is the time from date of RC to first recurrence of disease post-RC, or death due to any cause, whichever occurs first. RC population included all randomized patients who underwent RC and were disease-free at adjuvant baseline per blinded independent central review. C, comparator; CI, confidence interval; D, durvalumab; DFS, disease-free survival; HR, hazard ratio; NAC, neoadjuvant chemotherapy; NR, not reached; PD-L1, programmed cell death ligand-1; RC, radical cystectomy.

AUA 2025 APRIL 26-29 Las Vegas

NIAGARA: DFS by pCR and Non-pCR at RC

Perioperative durvalumab + NAC improved DFS in both the pCR and non-pCR groups



pCR

	Durvalumab N=199	Comparator N=146
Median DFS (95% CI), months	NR (NR–NR)	NR (NR–NR)
DFS HR (95% CI)	**0.58** (0.33–1.00)	

Non-pCR

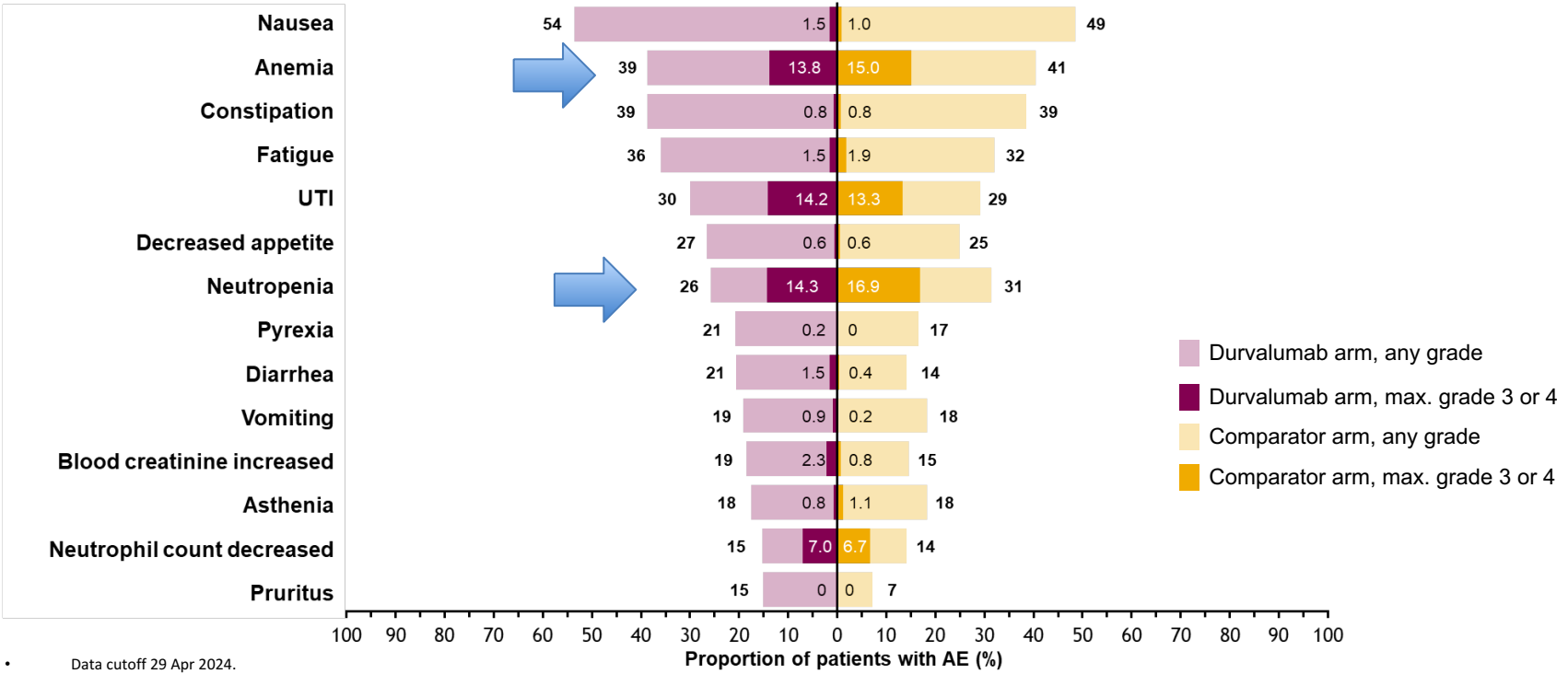
	Durvalumab N=270	Comparator N=295
Median DFS (95% CI), months	NR (NR–NR)	41.9 (27.4–NR)
DFS HR (95% CI)	**0.82** (0.64–1.05)	

Combined RC + disease-free population

DFS HR (95% CI)	**0.69** (0.51–0.93)

Data cutoff: 29 April 2024. Exploratory post hoc analysis. DFS is defined as time from date of RC to first recurrence of disease post-RC, or death due to any cause, whichever occurs first.

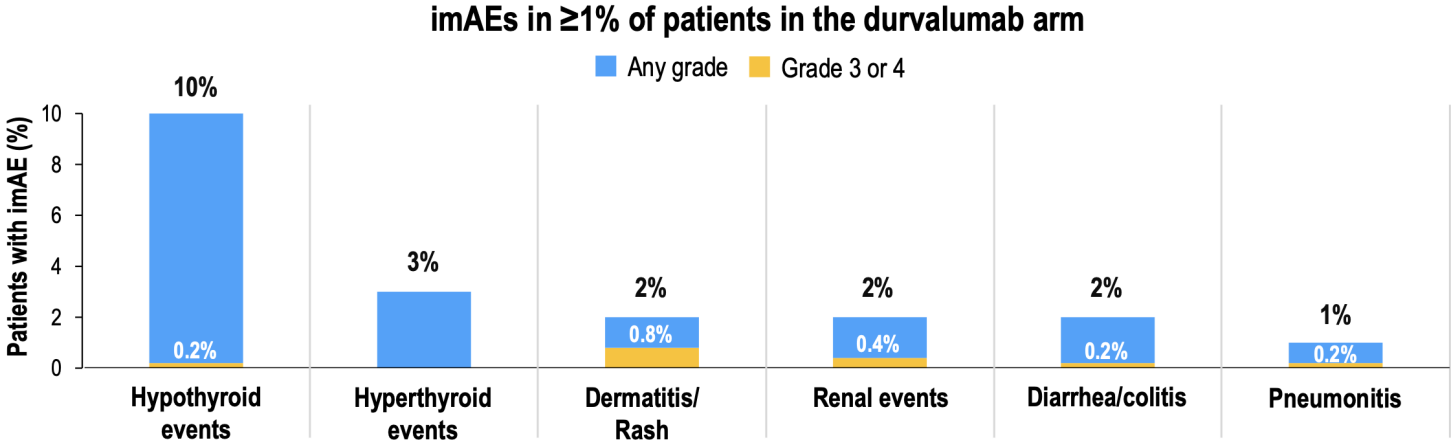
Most Frequently Reported AEs (Overall)[1,2]



- Data cutoff 29 Apr 2024.
- All-causality AEs reported for ≥15% of patients in either arm in the overall study period are shown. The overall period includes AEs that occurred between the first dose of study treatment, and which ever occurred first: 1) 90 days after the last dose of treatment, surgery, or last adjuvant visit; 2) date of first dose of subsequent anti-cancer therapy; or 3) data cutoff date.
- AE = adverse events; UTI = urinary tract infection.
- 1. Powles T, et al. Presented at: ESMO Congress; September 13-17, 2024; Barcelona, Spain. Abs#LBA5. 2. Powles T, et al. *N Engl J Med.* 2024 Nov 14;391(19):1773-1786.

NIAGARA: Immune-mediated AEs in the Overall Study Period

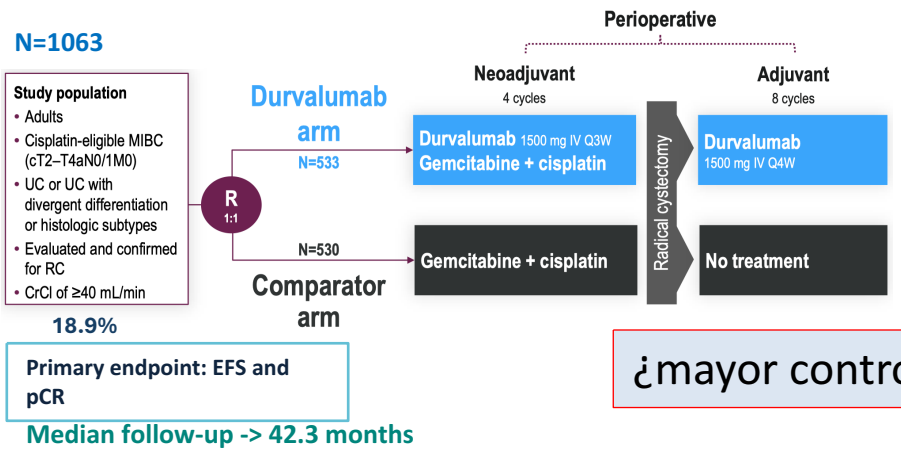
imAEs in the durvalumab arm were low grade and consistent with the known profile



- imAEs were reported in 21% (111/530; grade 3/4, 3%) of patients in the durvalumab arm
- There were 45/111 (41%) patients who had all imAEs resolved in the durvalumab arm
- Unresolved imAEs were mainly low-grade hypothyroid events, which were manageable with replacement therapy

imAEs were reported in 3% (16/526; grade 3/4 0.2% [1/526]) of patients in the comparator arm. There were 7/16 (44%) patients who had all their imAEs resolved in the comparator arm.
Data cutoff Apr 29, 2024. imAEs are defined as AEs of special interest that were consistent with an immune-mediated mechanism of action with no clear alternative cause and resulted in the use of systemic glucocorticoids, other immunosuppressants, or endocrine therapy. Resolved includes outcomes of recovered/resolved and recovered/resolved with sequelae. The overall study period includes AEs that occurred between the first dose of study treatment, and whichever occurred first: 1) 90 days after the last dose of treatment, surgery, or last adjuvant visit; 2) date of first dose of subsequent anti-cancer therapy; or 3) data cutoff date. AE, adverse event; imAE, immune mediated adverse event.

Estudio NIAGARA



¿mayor control local?

Completed neoadjuvant treatment:
- Durva arm: 78.7%
- Control arm: 74.0%

Underwent radical cystectomy:
- Durva arm: 88.0%
- Control arm: 83.2%

Completed adjuvant treatment:
- Neoadj -> Rad Cist: 75.2%
- Total: 54.3%

Powles T, et al. N Engl J Med 2024;391(19):1773.

NIAGARA-Conclusions

1 NIAGARA demonstrated statistically significant and clinically meaningful improvement in EFS (HR, 0.68; 95% CI, 0.56–0.82) and OS (HR, 0.75; 95% CI, 0.59–0.93), in both pCR and non-pCR groups in an exploratory post-hoc análisis with a 10% improvement in pCR rate

2 In the durvalumab arm, the risk of distant metastasis was reduced by 33% and the risk of death from bladder cancer event was reduced by 31%

3 Neoadjuvant durvalumab did not delay surgery and did not impact the ability of patients to undergo complete surgery

4 imAEs were mostly low grade and consistent with the known profile of durvalumab

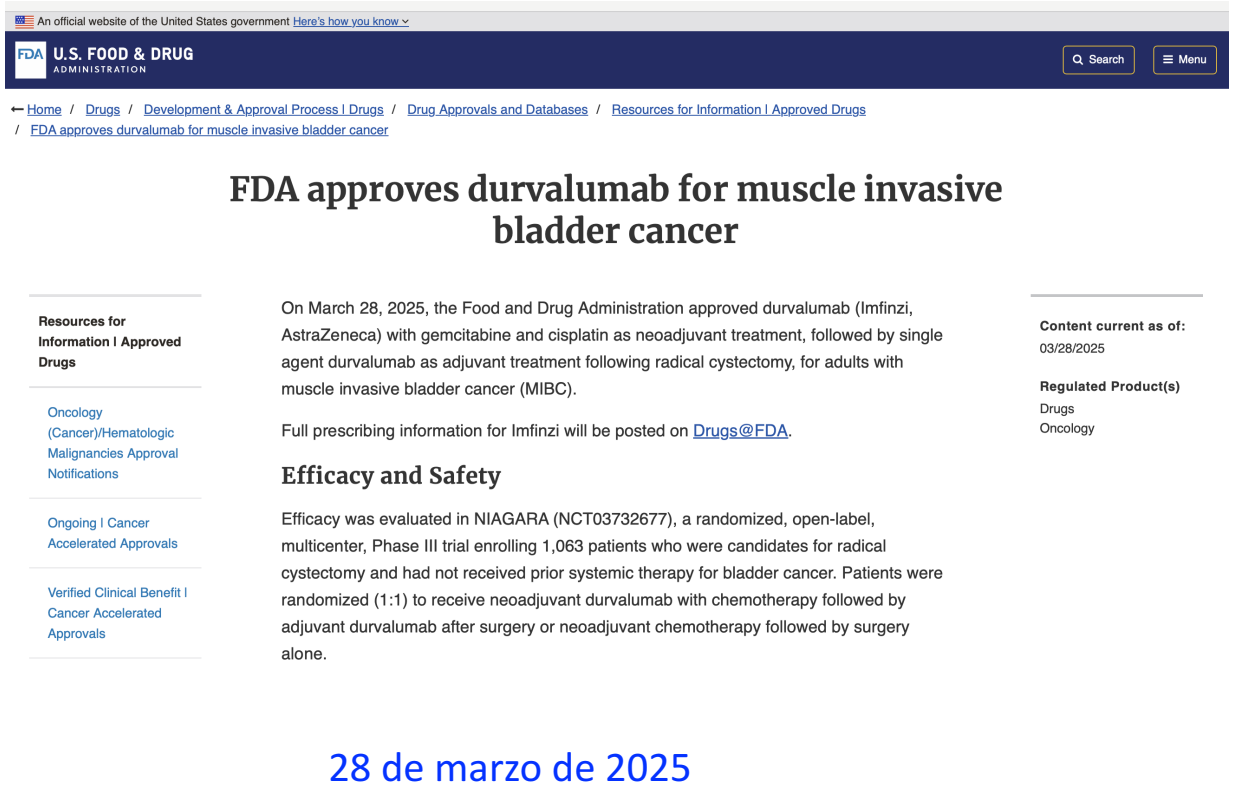
NIAGARA-Conclusions

“This additional NIAGARA data further supports perioperative durvalumab with NAC as a potential new treatment for patients with cisplatin-eligible MIBC”

Prof Matthew D. Galsky

ASCO GU 2025

48b



28 de marzo de 2025

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2025
Muscle-Invasive Bladder Cancer

NCCN Guidelines Index
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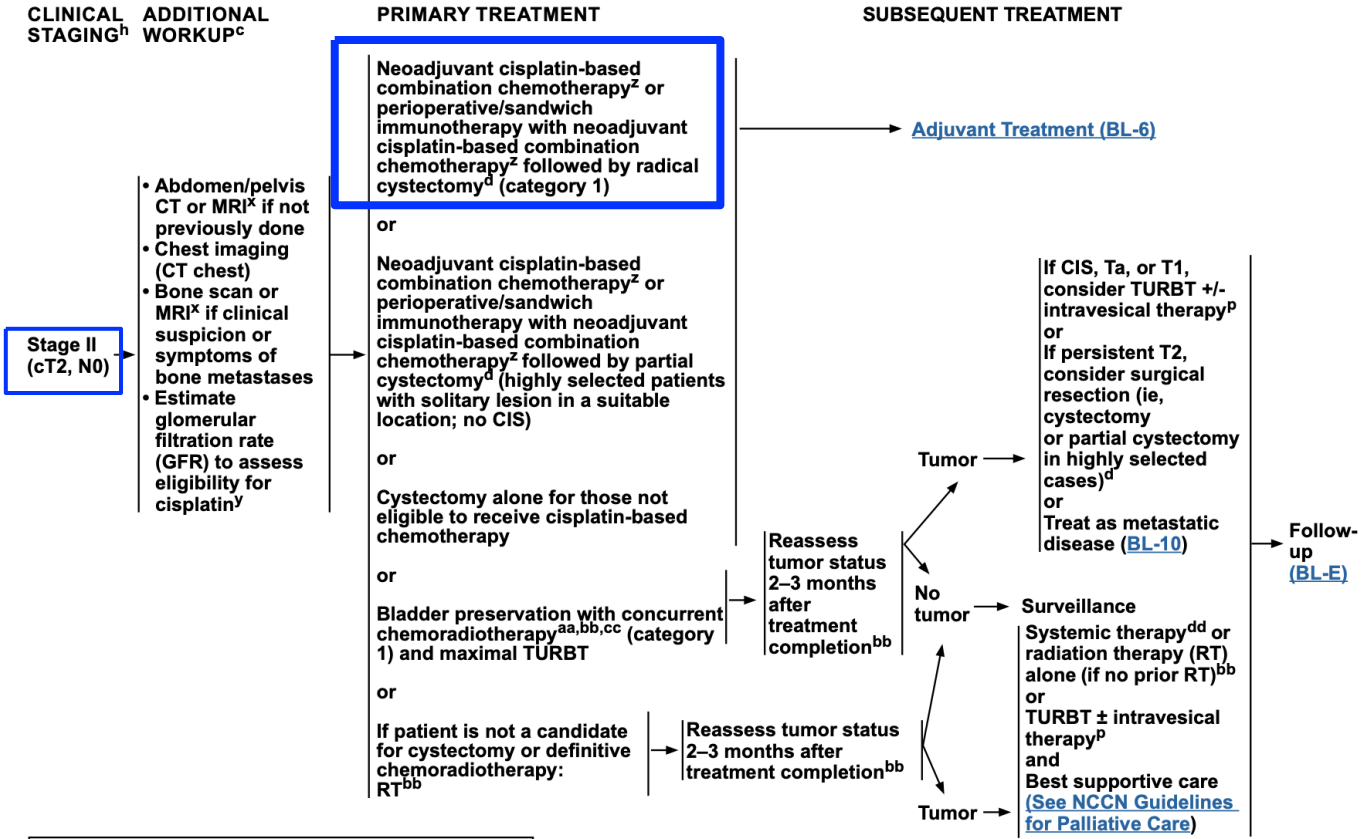
Discussion



Note: All recommendations are category 2A unless otherwise indicated.

Footnotes on BL-6

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2025
Muscle-Invasive Bladder Cancer

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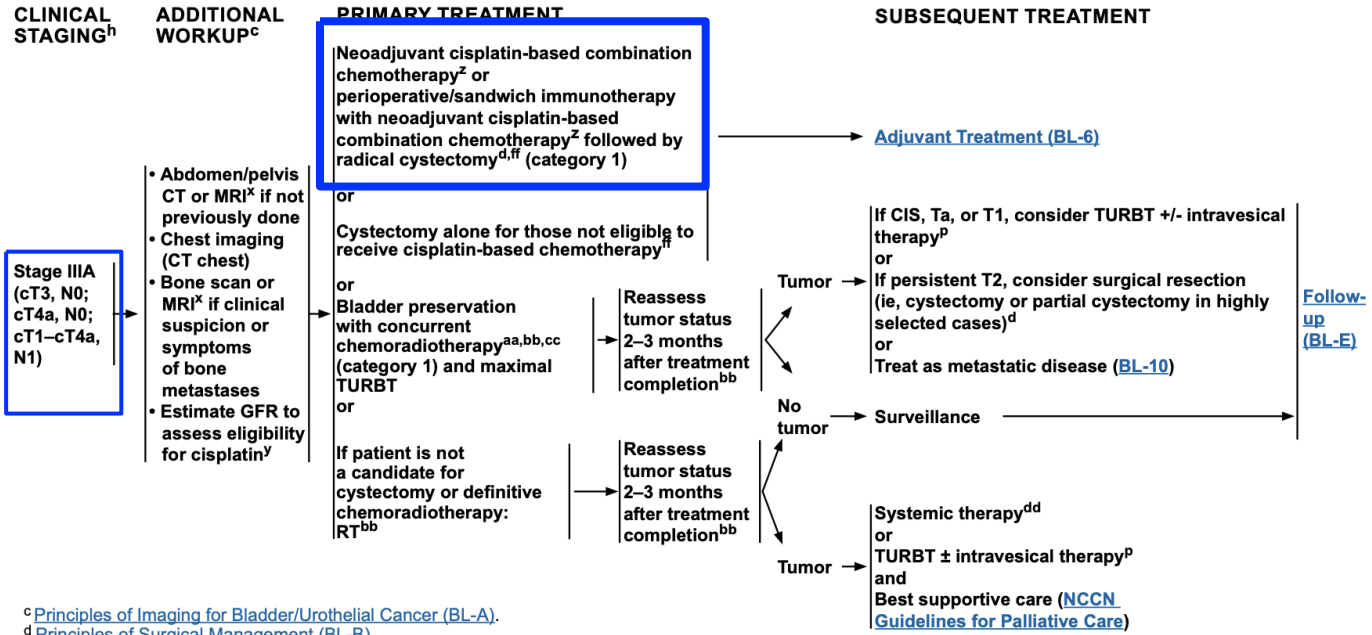


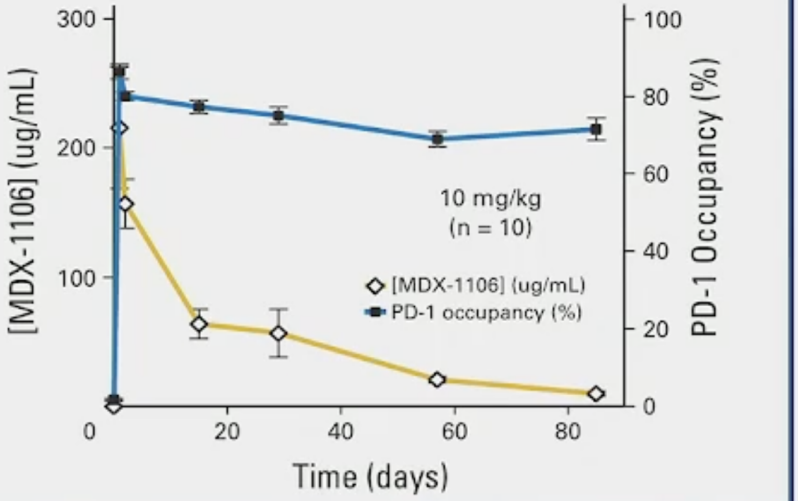
[c] Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[d] Principles of Surgical Management (BL-B).
[h] The modifier "c" refers to clinical staging based on bimanual EUA, endoscopic surgery (biopsy or TUR), and imaging studies. The modifier "p" refers to pathologic staging based on cystectomy and lymph node dissection.
[p] Principles of Instillation Therapy (BL-F).
[x] Consider FDG-PET/CT scan (skull base to mid-thigh) (category 2B).
[y] For patients with borderline GFR, consider timed urine collection, which may more accurately determine eligibility for cisplatin.
[z] Principles of Systemic Therapy (BL-G 1 of 7).
[aa] Principles of Systemic Therapy (BL-G 5 of 7).
[bb] Principles of Radiation Management of Invasive Disease (BL-H).

[cc] Optimal candidates for bladder preservation with chemoradiotherapy include patients with tumors that present without moderate/severe hydronephrosis, are without concurrent extensive or multifocal CIS, and are <6 cm. Ideally, tumors should allow a visually complete or maximally debulking TURBT. See Principles of Radiation Management of Invasive Disease (BL-H).
[dd] Principles of Systemic Therapy (BL-G 2 of 7).
[ff] Patients with cN1 disease have better outcomes if they are given neoadjuvant chemotherapy and have a response.

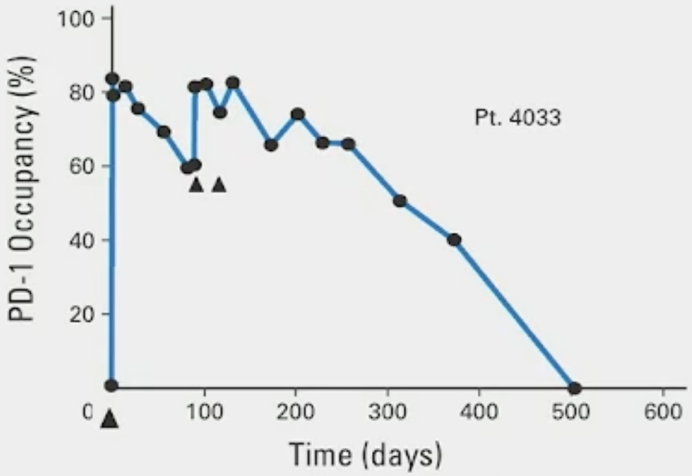
Note: All recommendations are category 2A unless otherwise indicated.

Recurrent or Persistent Disease (BL-11)

For Checkpoint inhibitors – persistent PD1 receptor occupancy suggests that effects of NAC extend into the adjuvant period even without adjuvant dosing



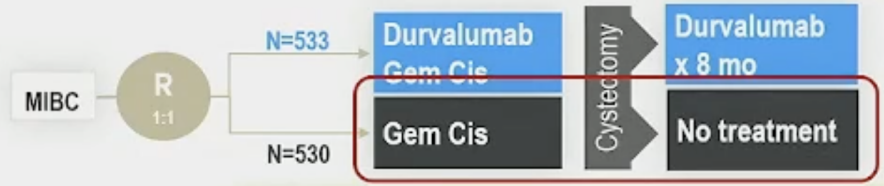
One dose of nivolumab saturates PD1 receptors out beyond 3 mo even as drug itself is cleared

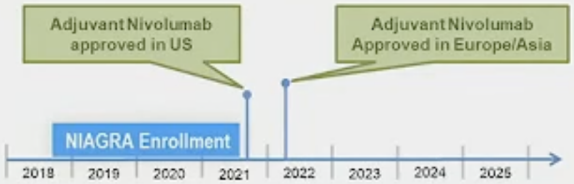


With 3 doses of nivolumab
PD1 receptors remain occupied (40%) at ~380 days from last dose

Brahmer et al., Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors. J Clin Oncol 28, 3167-3175 (2010)

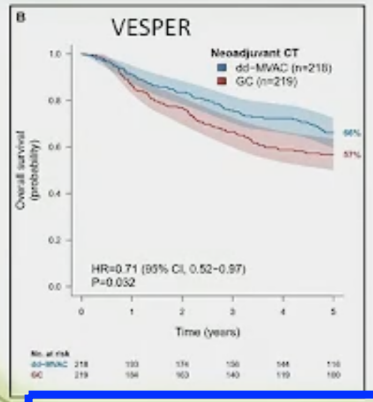
NIAGARA control arm does not reflect current standard of care





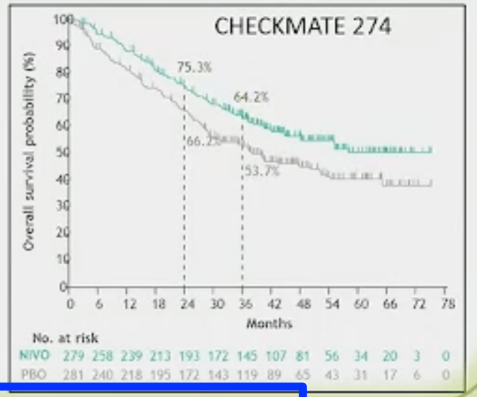
Standard of Care Now

ddMVAC OS benefit over GC 2023



Cystectomy

Adjuvant Nivolumab for high risk OS benefit vs no treatment 2021



Few patients in the NIAGARA control arm would have had access to adjuvant nivolumab, which became standard of care in 2021

VESPER and COXEN OS data resulted in 2023, after NIAGARA had fully accrued

CHECKMATE 274 Milowsky et al. ASCO GU 2025
Powles et al. N Engl J Med 391, 1773-1786 (2024)
VESPER Pfister et al. LBA4507, ASCO 2023

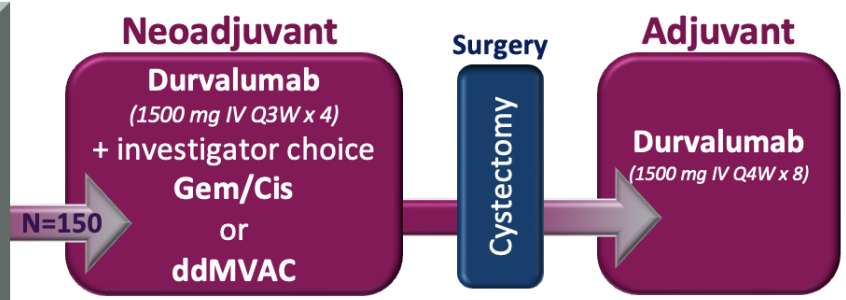
NIAGARA 2

A Phase IIIb, Open-label, Single-arm, Global Study of Perioperative Durvalumab With Neoadjuvant ddMVAC or Gem/Cis in Patients With Muscle-invasive Bladder Cancer (NIAGARA-2)

The Phase IIIb NIAGARA-2 study aims to expand on the data from the Phase III NIAGARA study by investigating perioperative durvalumab in combination with investigator-selected cisplatin-based neoadjuvant chemotherapy (either ddMVAC or gemcitabine/cisplatin) in a clinical practice setting

Population

- Participants with clinical tumour stage T2-T4aN0/1M0 or T1N1M0 with transitional or mixed transitional cell histology
- Patients must be planning to undergo radical cystectomy
- Patients who have not received prior systemic chemotherapy or immunotherapy for treatment of muscle-invasive bladder cancer
- ECOG performance status of 0 or 1
- Minimum life expectancy of 12 weeks at first dose of study medication



Non-cystectomy subgroup:

If patients achieve cCR & refuse cystectomy, adjuvant Durva will be provided upon individual risk/benefit assessment. Safety and efficacy of this cohort will be separately described.

Endpoints

Primary Endpoint:

- Safety (G3/G4 PRAEs) prior to cystectomy

Secondary Endpoints:

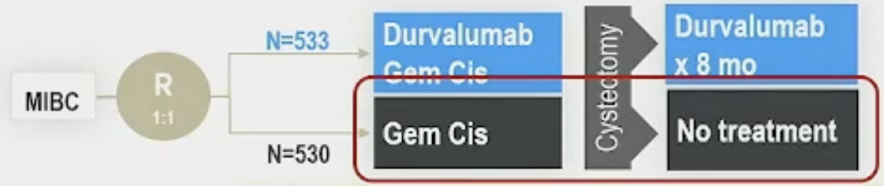
- Safety (treatment discontinuation rate, all grade imAEs, AESI, AEs, SAEs)
- pCR, pathologic response
- EFS
- DFS
- OS
- Time to surgery
- PRO

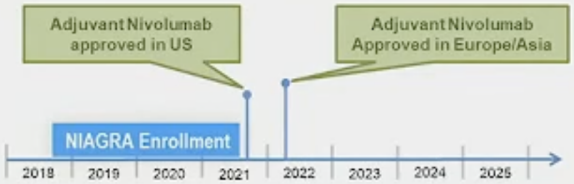
final analysis will be conducted when there is 55% EFS maturity or the Last Participant In (LPI) has had the opportunity to be followed up for a minimum of 12 months, whichever occurs first.

PRAEs: Possibly treatment-related adverse events

1 https://clinicaltrials.gov/study/NCT06960577?term=niagara%202&rank=6

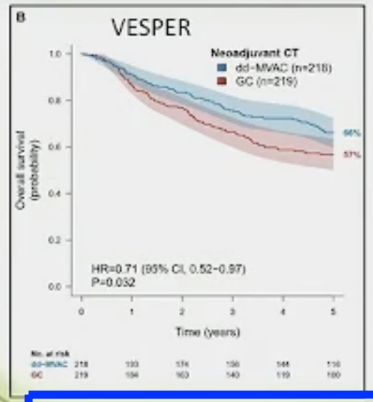
NIAGARA control arm does not reflect current standard of care





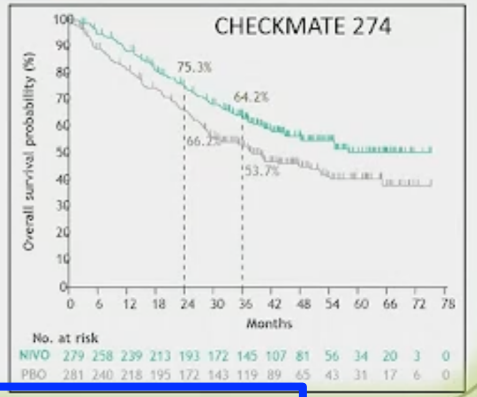
Standard of Care Now

ddMVAC OS benefit over GC 2023



Cystectomy

Adjuvant Nivolumab for high risk OS benefit vs no treatment 2021



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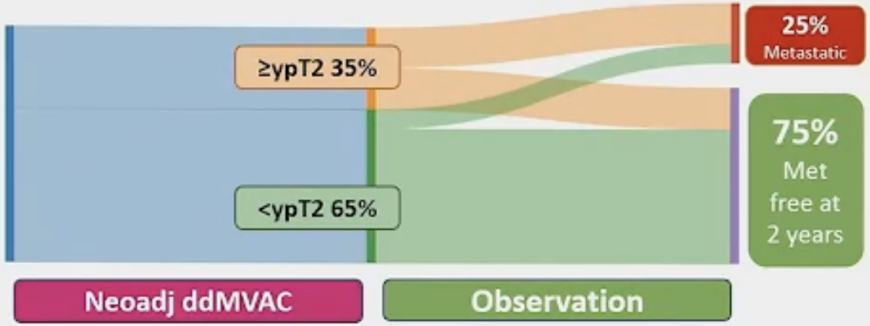
Powles et al. N Engl J Med 391, 1773-1786 (2024)
VESPER Pfister et al. LBA4507, ASCO 2023

Take Home: 2 options for clinic on Monday

Neoadjuvant ddMVAC

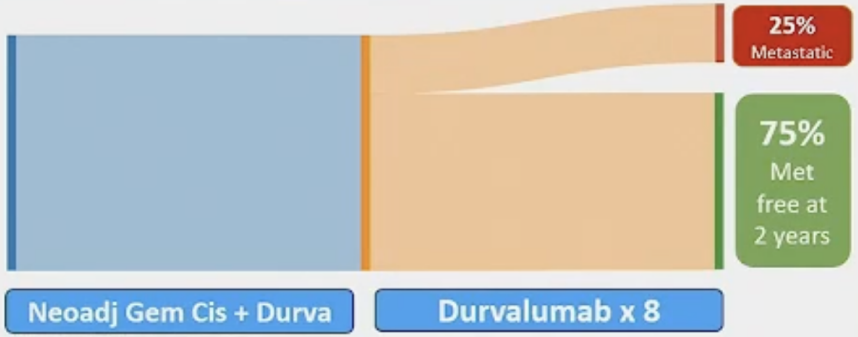


Benefits of risk adapted approach using ddMVAC

- ≥ypT2 35% patients would qualify for and may gain additional benefit from adjuvant nivolumab or the MODERN trial
- Avoids overtreatment and IO toxicity for <ypT2 65%
- Cost and time saving

ddMVAC….cistectomía…Nivo adyuvante “adaptado”

“Sandwich” Approach with GC Durva



Benefits of a “sandwich” approach

- If using Gem Cis, adding durvalumab pre and post adds benefit in direct and cross trial comparison
- Adjuvant durvalumab may benefit some of the ~10% of <ypT2 who develop metastases but would not have qualified for adjuvant nivolumab

NIÁGARA …y beneficio en <ypT2 que no “podrían” recibir Nivo

NIAGARA Galsky et al. ASCO GU 2025
VESPER Pfister et al. LBA4507, ASCO 2023
S Culine and VESPER team personal communication

PLATINO ELEGIBLES

KEYNOTE 866

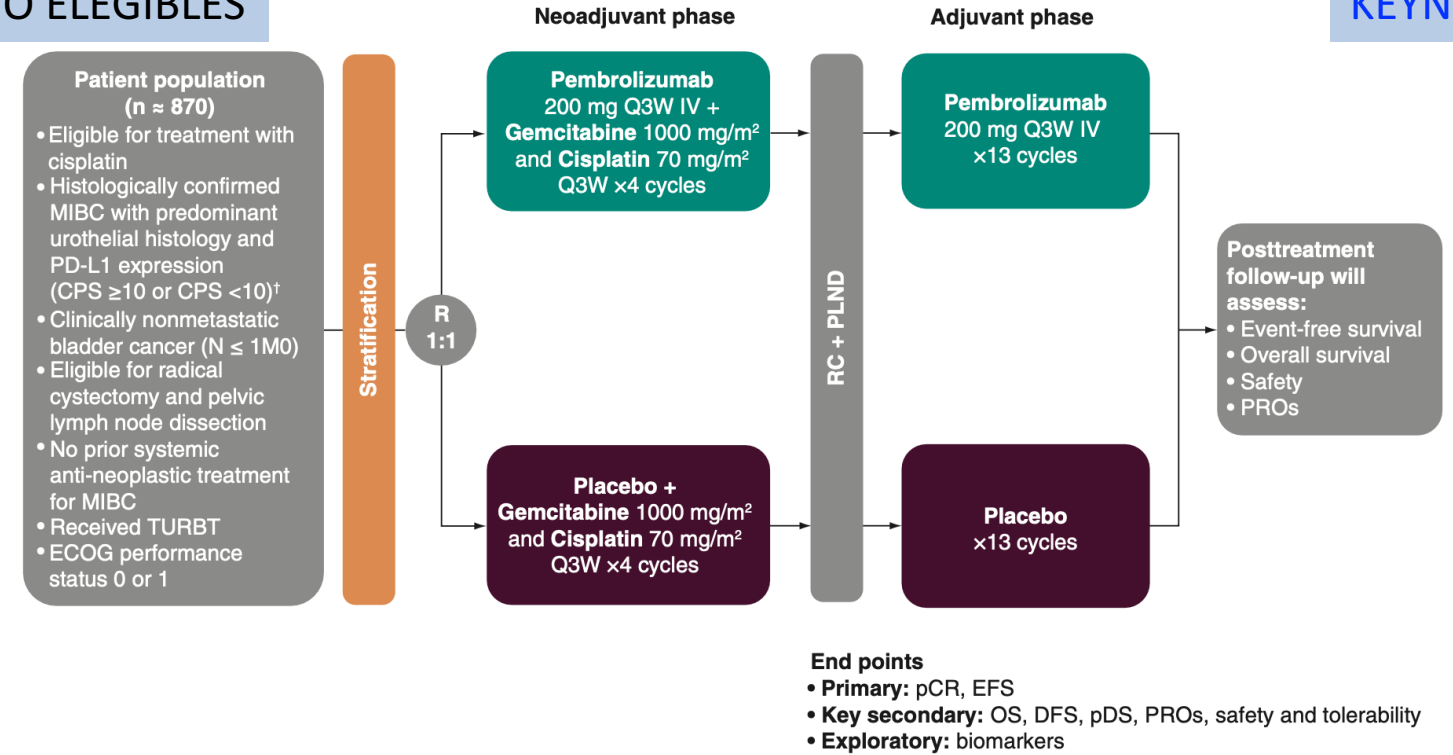


Figure 1. KEYNOTE-866 study design.

†Histology will be confirmed by blinded central pathology review. Patients with mixed histology are eligible if the urothelial component is ≥50%. Patients whose tumors contain any neuroendocrine component are not eligible. Patients with urothelial carcinomas not originating from the bladder (e.g., upper tract [ureters and renal pelvis] and urethra) are not eligible.

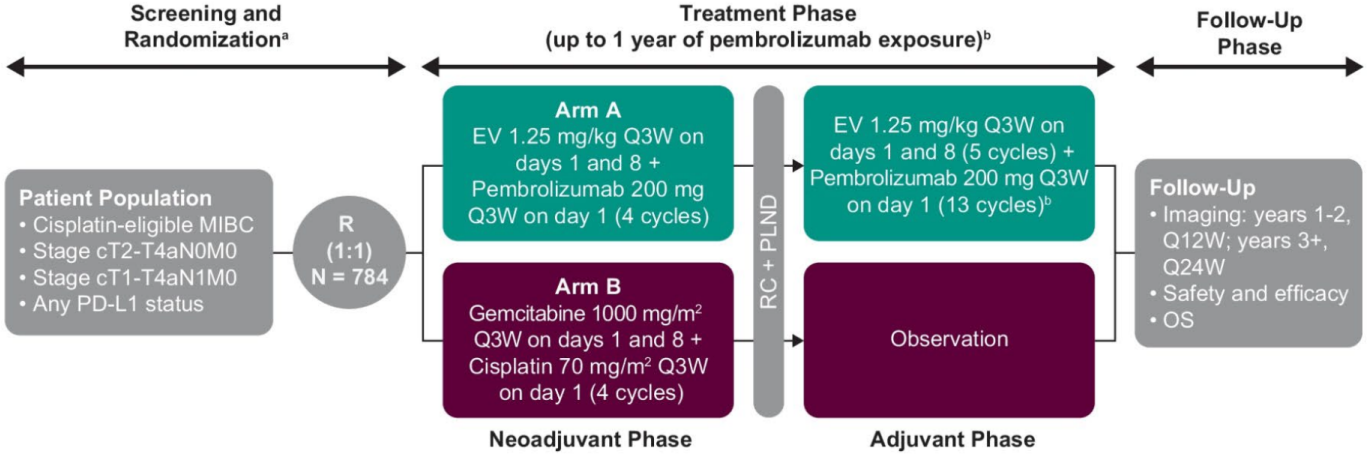
PLATINO ELEGIBLES

TPS588

Perioperative Enfortumab Vedotin Plus Pembrolizumab Versus Chemotherapy in Cisplatin-Eligible Patients With Muscle-Invasive Bladder Cancer: Phase 3 KEYNOTE-B15/EV-304

KEYNOTE B15/ EV304

Study design



AE, adverse event; BICR, blinded independent central review; CT, computed tomography; MOW, most of world; MRI, magnetic resonance imaging; Q3W, every 3 weeks; Q12W, every 12 weeks; Q24W, every 24 weeks; R, randomization.

[a]All patients will undergo baseline imaging studies (CT or MRI) for clinical staging (evaluated by BICR before randomization) and central pathology confirmation for pathologic stage pT2-T4a or pT1 (only if N1), urothelial histology, and PD-L1 expression.

[b]Until unacceptable AEs, intercurrent illness preventing further treatment administration, or investigator or patient decision to withdraw.

[c]CPS is defined as the number of PD-L1–staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100.

Patient eligibility criteria

PLATINO INELEGIBLES

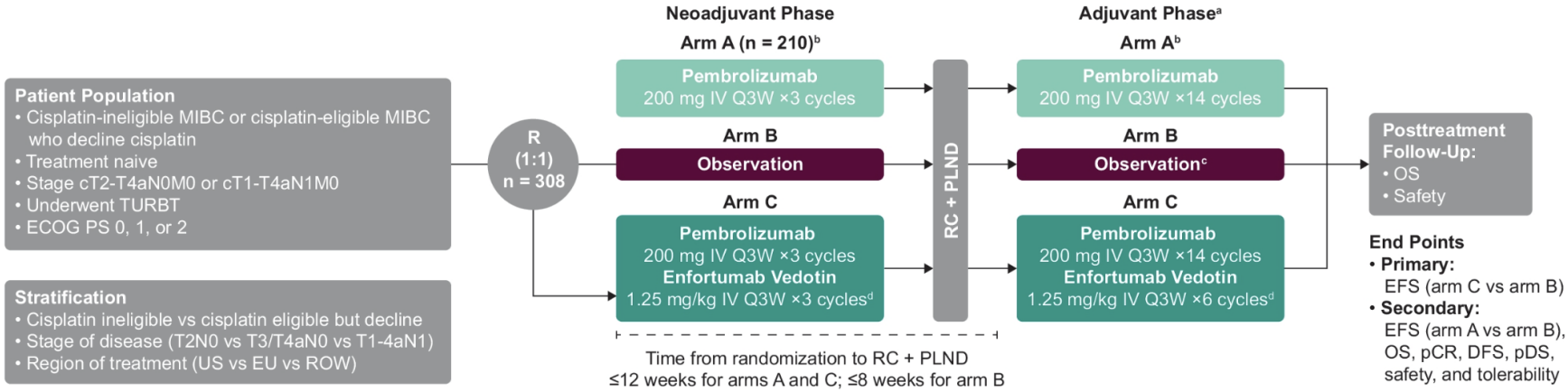
TPS4601

KEYNOTE-905/EV-303: A Phase 3 Study to Evaluate the Efficacy and Safety of Perioperative Pembrolizumab or Pembrolizumab Plus Enfortumab Vedotin for Muscle-Invasive Bladder Cancer

KEYNOTE 905/ EV303

Methods

Study design



ECOG PS, Eastern Cooperative Oncology Group performance status; EU, European Union; IV, intravenously; Q3W, every 3 weeks; R, randomization; ROW, rest of world; TURBT, transurethral resection of the bladder tumor.

[a]Until disease progression, unacceptable adverse events (AEs), intercurrent illness preventing further treatment administration, or investigator's or patient's decision to withdraw.

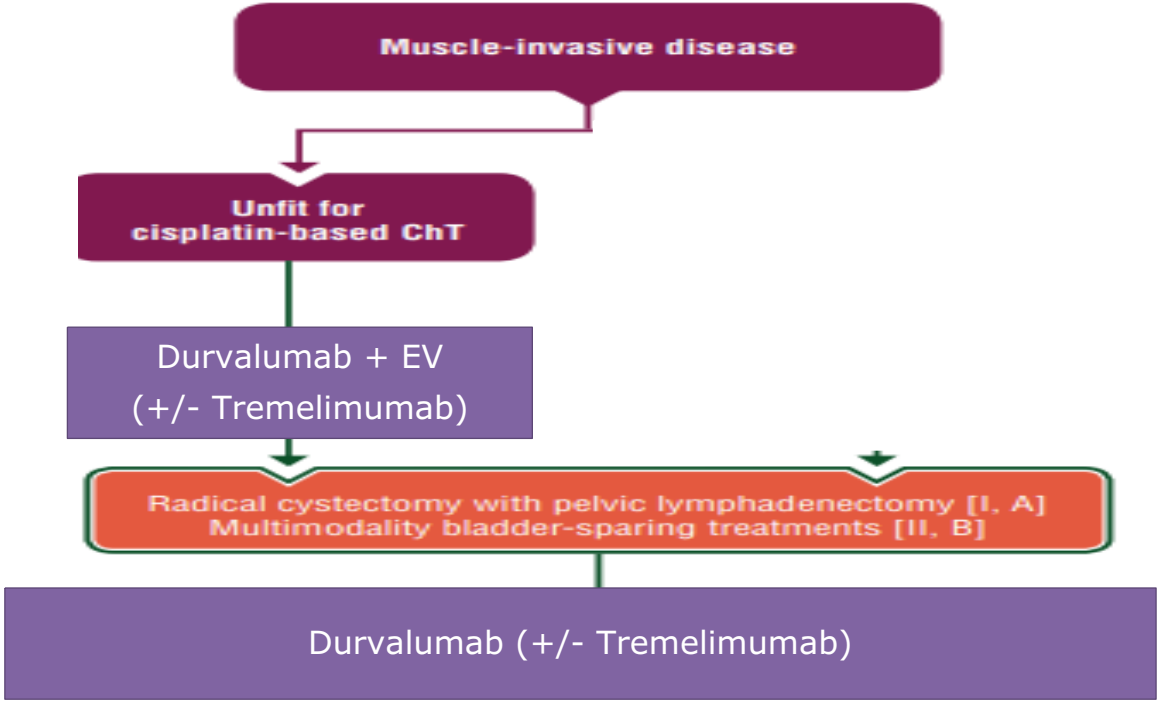
[b]Prior to the protocol amendment 8, patients were enrolled in arm A. Enrollment for that arm will be stopped once the current protocol amendment is initiated, and further randomization will focus on arms B and C.

[c]Patients at high risk of recurrence after RC + PLND may receive treatment with adjuvant nivolumab per the approved product label.

[d]Administered on days 1 and 8 of every 3-week cycle.

PLATINO INELEGIBLES

VOLGA



Resumen-Conclusiones (1)

1 Nivolumab adyuvante, según el estudio CM 274, aumenta la DFS y la SG (análisis interino) frente a placebo con independencia de quimioterapia neoadyuvante y sobre todo en pacientes con PD-L1 +.

Se considera tratamiento adyuvante estándar

(en nuestro medio sólo si PD-L1 +)

Resumen-Conclusiones (2)

2 Biomarcadores: (IMvigor 010) la determinación de ctDNA puede seleccionar pacientes con menor riesgo de recaída (ctDNA -) y en los que podríamos no tratar con IO adyuvante *vs* aquellos (ctDNA +) en los que sería conveniente dicho tratamiento.

Pendientes resultados IMvigor 011, MODERN, otros

Resumen-Conclusiones (3)

3 En el estudio NIAGARA, el tratamiento perioperatorio con durvalumab y quimiterapia aumenta la SLE (HR 0.68) y la SG (HR 0.75) con diferencias significativas e independientemente de la obtención de RCP

Resumen-Conclusiones (4)

4 El tratamiento perioperatorio en NIAGARA con durvalumab aumenta en un 10% el porcentaje de respuestas completas patológicas (37.3% vs 27.5%)

En el brazo de durvalumab se aumenta significativamente la SLM (Supervivencia Libre de Metástasis) y la SEE (Supervivencia Específica de Enfermedad)

Resumen-Conclusiones (5)

5 Durvalumab neoadyuvante en NIAGARA no retrasó la cirugía ni alteró la posibilidad de realizar una cirugía completa a estos pacientes

Controversia

El tratamiento peripeatorio (NIAGARA) es eficaz pero puede suponer un "sobretratamiento" de los pacientes al no quedar clarificada la contribución de los componentes neoadyuvante y adyuvante

HIPÓTESIS: (*Dra Plimark)* El tratamiento con QT neoadyuvante (¿ddMVAC?) con inmunoterapia adyuvante "adaptada al riesgo", podría ser tan eficaz como los modelos "sándwich" y con menor riesgo de sobretratamiento- a la espera de resultados de NIAGARA 2.

Resumen-Conclusiones (6)

6 Varios estudios fases 3 están valorando otros fármacos y combinaciones perioperatorias, tanto en pacientes elegibles [pembro+QT vs QT; enfortumab+pembro vs QT], como inelegibles a platino [pembro vs pembro + enfortumab; durva + enfortumab +/- treme vs durva + treme], que confirmarán la validez de este abordaje terapéutico en la disminución de recaídas

Respuesta a la pregunta

Manejo perioperatorio en carcinoma urotelial músculo-invasivo:
¿todos los pacientes se benefician de la inmunoterapia?

SÍ……”NIAGARA”… ↑SLE, ↑%RCP, ↑SG

Hipótesis: si se demostrara disminución de recaídas en p con ctDNA - seriado, tras dd MVAC neoadyuvante, se podría considerar NO TRATAR con IO adyuvante *(tratamiento adyuvante adaptado al riesgo)*

MUCHAS GRACIAS por su atención