New options in the adjuvant setting including ctDNA

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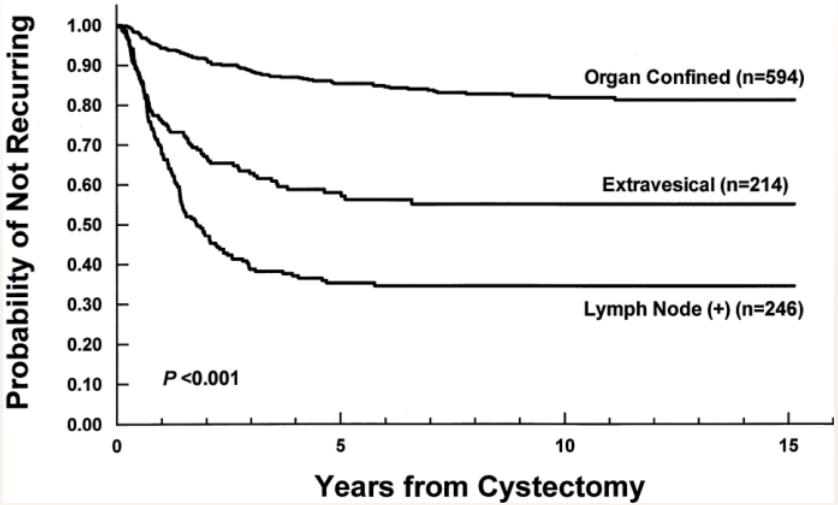
Dr. Alonso Gordoa financial interests:

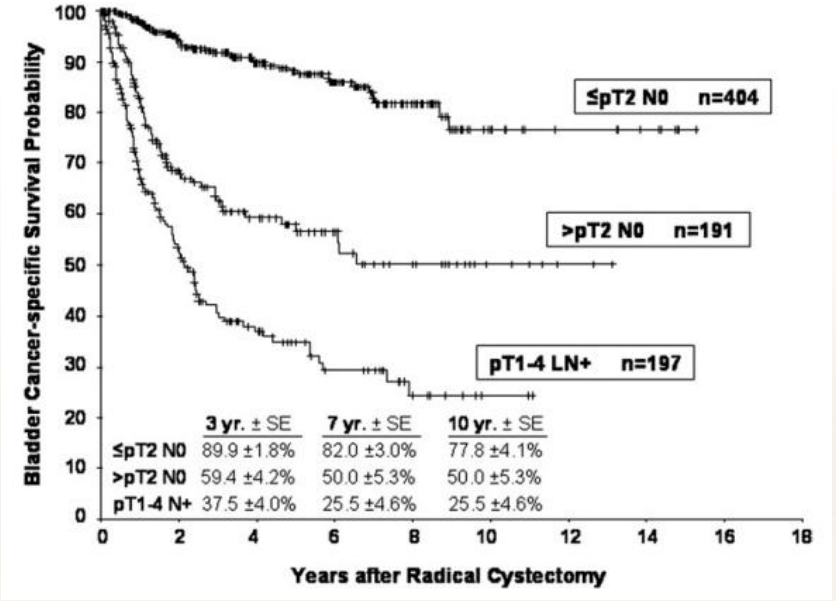
Personal conflicts of interest Scientific consultancy role (speaker and advisory roles) from Lilly, Ipsen, Bayer, Johnson & Johnson, Astellas, Eisai, Advanced Accelerator Applications, MSD, BMS, Pfizer.

Research support Research grants from IPSEN, Johnson & Johnson.

Why do we need perioperative treatment in MIBC

888 consecutive patients with bladder TCC
3 academic centers in US

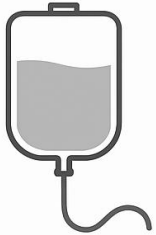




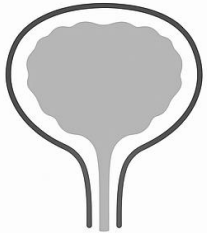
creating a selection bias. In addition, because the study period spans more than 20 years, data may not represent current practice patterns. For example, neoadjuvant chemotherapy was relatively underused in our series compared to current recommendations. Moreover, surgical techniques, such as nerve sparing radical cystectomy and the number of LNs removed, indications for surgery and followup protocols have changed with time. Furthermore, assigning cause of

Stein H et al. JCO 2001
Shariat S et al. J Urol 2006

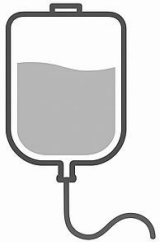
NEOADJUVANT



SURGERY



ADJUVANT



*Stop early

Adjuvant treatment chemotherapy-based.

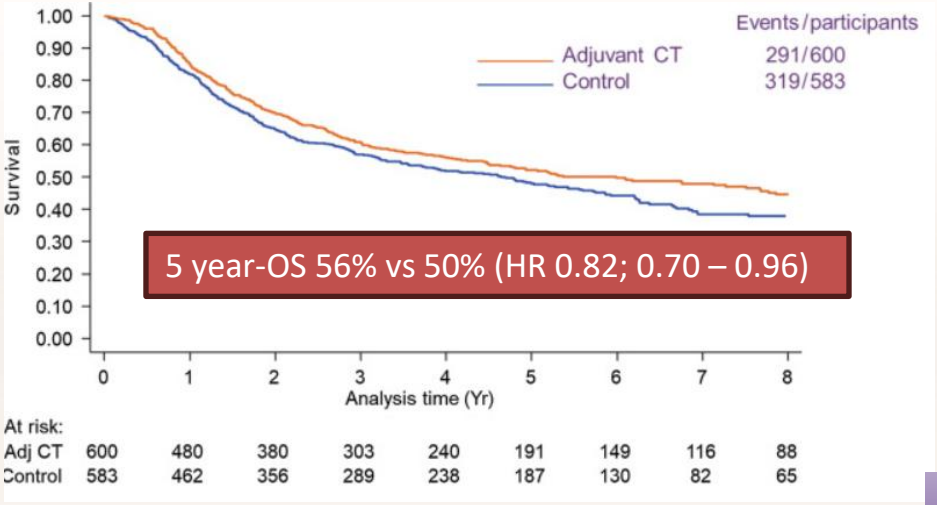
CISPLATIN-BASED

Trial	Accrual years	N	Stage	Treatment	Control arm
Skinner*	1980-88	102	pT3-pT4, pN+, M0	Cystectomy + 4c of CAP	Cystectomy
Bono	1984-87	90	pT2-pT4a, pN0, M0	Cystectomy + 4c of Cisplatin + Methotrexate	Cystectomy
Studer*	1984-89	91	pT1 (grade 2)-pT4, pN1–2, M0	Cystectomy + 3c of cisplatin	Cystectomy
Stockle*, Lehmann*	1987-90	49	pT3b-pT4a, pN+, M0	Cystectomy + 3c of MVEC or MVAC	Cystectomy
Otto	1993-99	108	pT3, N1–2, M0	Cystectomy + 3c of MVEC	Cystectomy
Stadler*	1997-2006	114	pT1-pT2, pN0, M0 (all p53+)	Cystectomy + 3c of MVAC	Cystectomy
Freiha*	1986-93	51	pT3b-pT4, any pN, M0	Cystectomy + 4c of CMV	Cystectomy + (same) CT on relapse
Cognetti*	2001-07	194	pT2 (grade 3) pT3-pT4, pN0–2, M0	Cystectomy + 4c GC	Cystectomy + (same) CT on relapse
Sternberg*	2002-14	284	pT3-pT4 or pN1–3, M0	Cystectomy + 4c of: MVAC, high-dose MVAC or GC	Cystectomy + 6 cycles (same) CT on relapse
Zhegalik	2007-13	100	pT3-pT4 and/or pN+, M0	Cystectomy + 2c of GC	Cystectomy + (same) CT on relapse

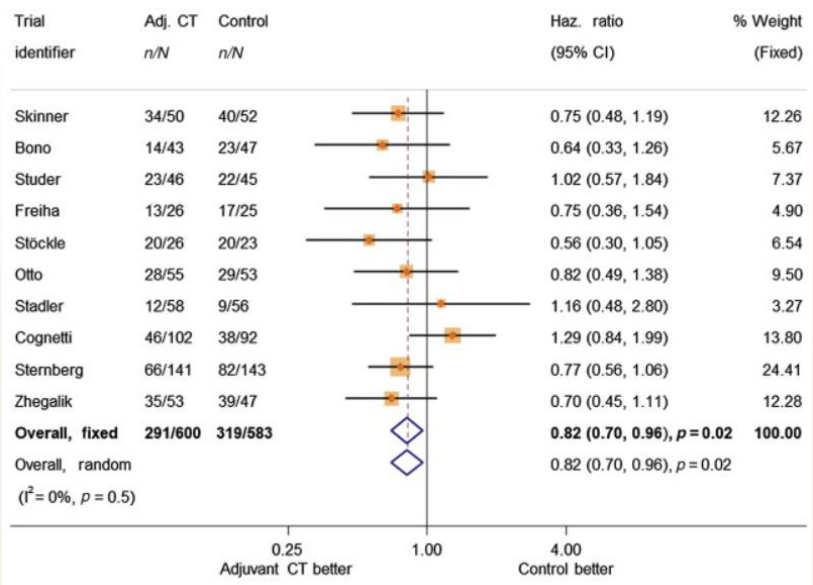
Advanced Bladder Cancer (ABC) Meta-analysis Collaborators Group. Eur Urol 2021
S. Burdett, et al. European Urology 2022 (10 trials, n=1183)

Adjuvant treatment chemotherapy-based

Meta analysis 10 randomized clinical trials (1183 participants)



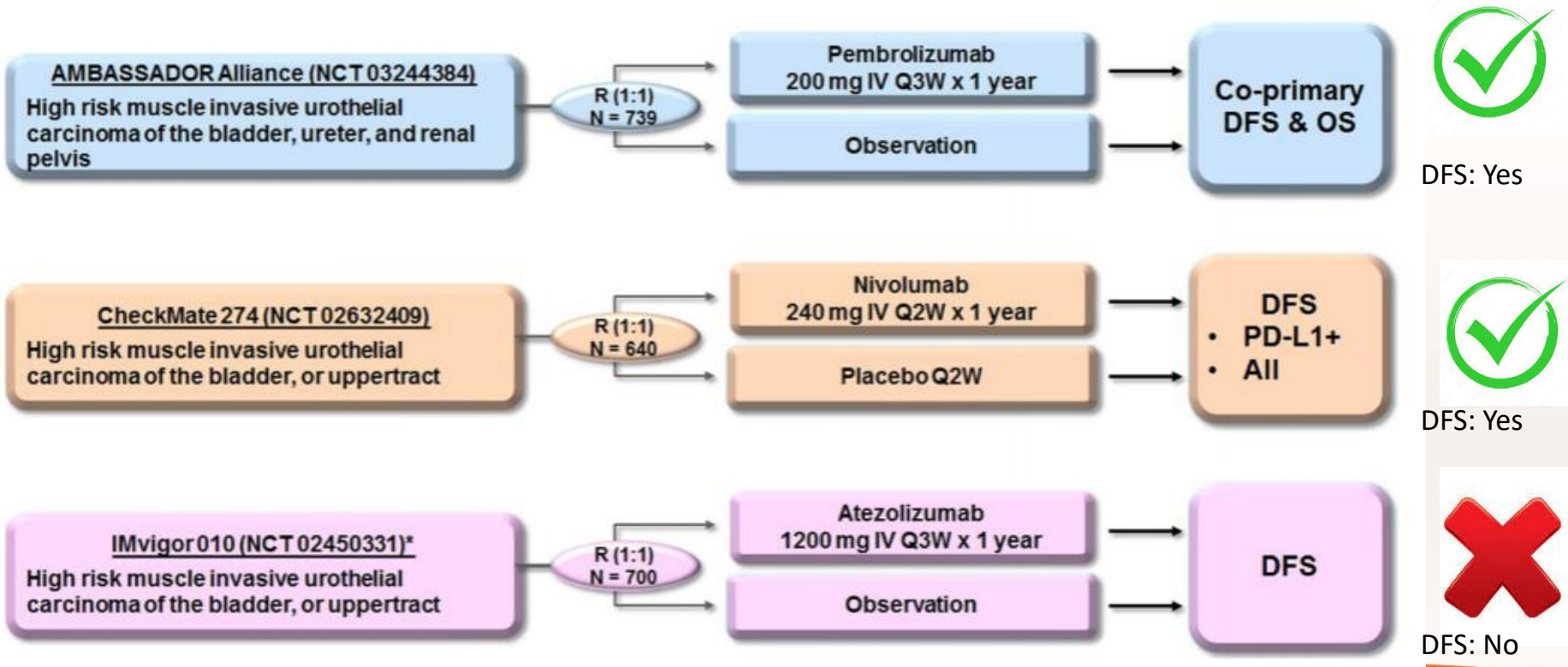
The effect (Non-stratified) of adjuvant chemotherapy on overall survival



Limitation in recruitment, treatment schedules, treatment compliance, and in the profile of eligible patients to cisplatin-based therapy

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

Adjuvant treatment with PD-1/PD-L1 inhibitors



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

CHECKMATE 274

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

N = 709

Key inclusion criteria

- Patients with ypT2-ypT4a or ypN+ MIUC who had neoadjuvan cisplatin chemotherapy
- Patients with pT3-pT4a or pN+ MIUC adjuvant cisplatin chemotherapy and not eligi nt cisplatin chemotherapy
- Radical surgery within the past 120 d
- Disease-free status within 4 weeks of dos

43%
pT2=18%
pT3=58%
pT4a=16%
N+=47%

Stratification factors

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

R 1:1

NIVO IV 240 mg Q2W

PBO IV Q2W

Treat for up to 1 year of adjuvant therapy

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

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

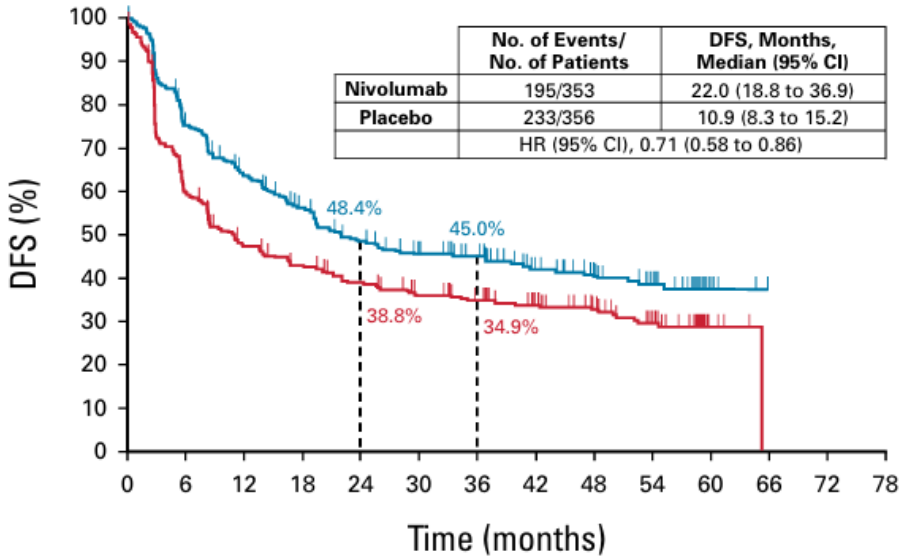
[a]Defined by the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells using the PD-L1 IHC 28-8 PharmDx immunohistochemistry assay.
[b]OS data were not mature at the time of the first planned interim analysis. OS and DSS data are not presented.
DFS, disease-free survival; DMFS, distant metastasis-free survival; DSS, disease-specific survival; HRQoL, health-related quality of life; IHC, immunohistochemistry; ITT, intent-to-treat; NUTRFS, non-urothelial tract recurrence-free survival; OS, overall survival; PD-L1, programmed death ligand 1; Q2W, every 2 weeks; R, randomized.

Bajorin D et al. ASCO GU 2021

CHECKMATE 274

PRIMARY ENDPOINT: DISEASE FREE SURVIVAL (3 YEAR MEDIAN FUP)

ITT

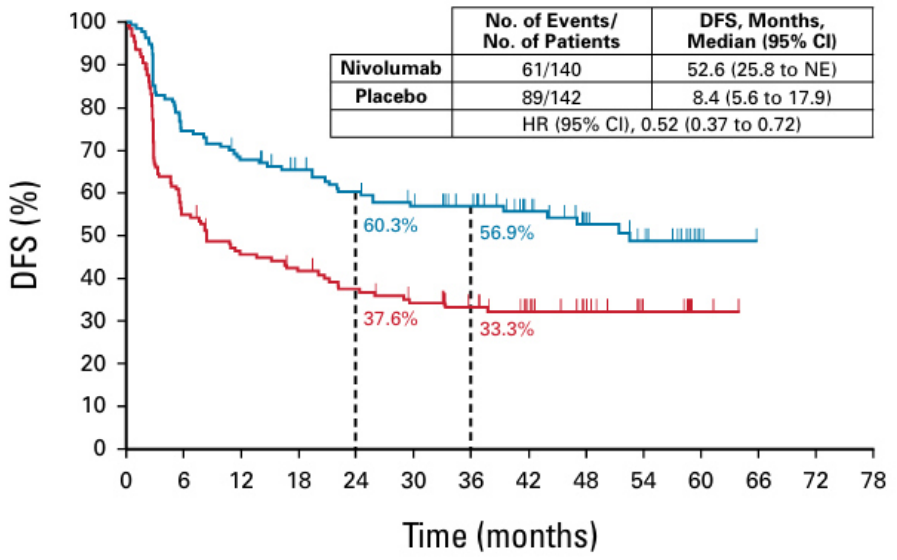


	No. of Events/ No. of Patients	DFS, Months, Median (95% CI)
Nivolumab	195/353	22.0 (18.8 to 36.9)
Placebo	233/356	10.9 (8.3 to 15.2)
	HR (95% CI), 0.71 (0.58 to 0.86)	

Number at risk

Nivolumab	353	253	208	177	150	132	113	83	57	43	4	0	0	0
Placebo	356	207	156	138	123	109	94	80	59	39	4	0	0	0

PD-L1 ≥ 1%



	No. of Events/ No. of Patients	DFS, Months, Median (95% CI)
Nivolumab	61/140	52.6 (25.8 to NE)
Placebo	89/142	8.4 (5.6 to 17.9)
	HR (95% CI), 0.52 (0.37 to 0.72)	

Number at risk

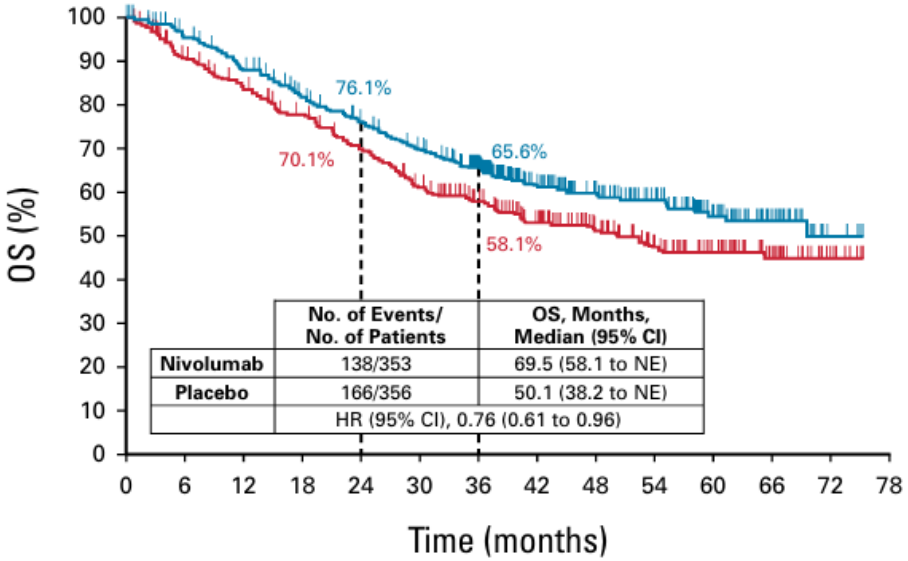
Nivolumab	140	99	88	79	72	64	55	42	29	23	2	0	0	0
Placebo	142	74	58	52	46	40	34	26	18	9	2	0	0	0

Galsky M, et al. J Clin Oncol. 2025 Jan;43(1):15-21.

CHECKMATE 274

SECONDARY ENDPOINT: OVERALL SURVIVAL (3 YEAR MEDIAN FUP)

ITT

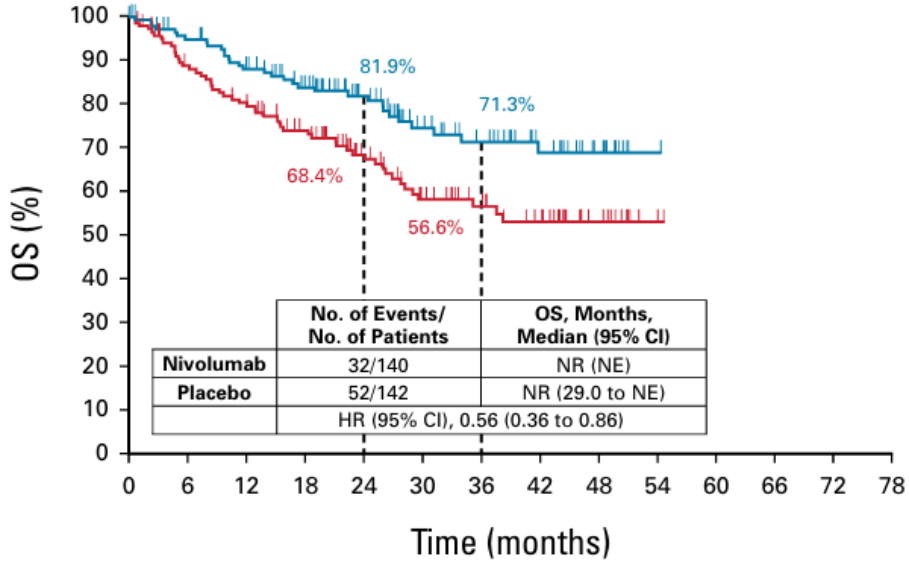


	No. of Events/ No. of Patients	OS, Months, Median (95% CI)
Nivolumab	138/353	69.5 (58.1 to NE)
Placebo	166/356	50.1 (38.2 to NE)
	HR (95% CI), 0.76 (0.61 to 0.96)	

Number at risk

Nivolumab	353	326	298	268	244	220	188	150	123	92	60	33	4	0
Placebo	356	308	281	254	226	194	167	136	109	79	56	32	10	0

PD-L1 ≥ 1%



	No. of Events/ No. of Patients	OS, Months, Median (95% CI)
Nivolumab	32/140	NR (NE)
Placebo	52/142	NR (29.0 to NE)
	HR (95% CI), 0.56 (0.36 to 0.86)	

Number at risk

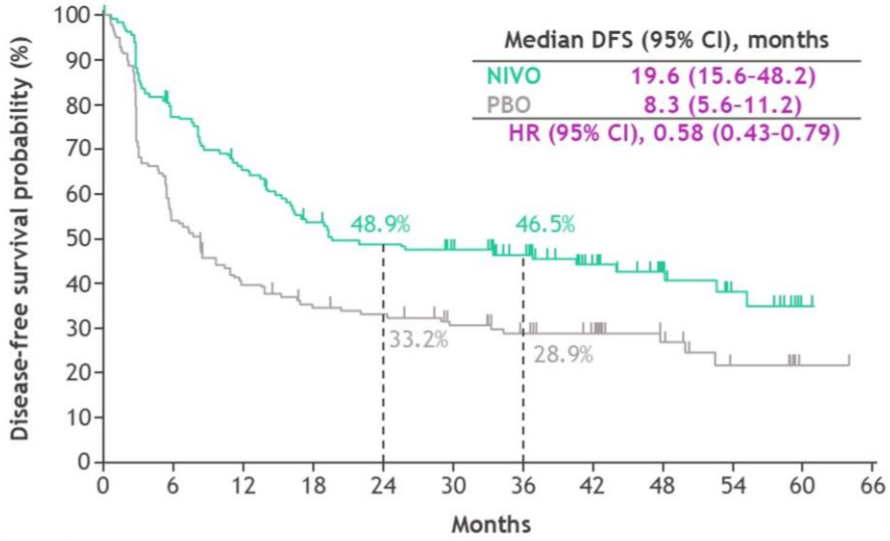
Nivolumab	140	127	115	93	73	52	41	29	11	1	0	0	0	0
Placebo	142	116	104	87	65	46	36	26	12	2	0	0	0	0

Galsky M, et al. J Clin Oncol. 2025 Jan;43(1):15-21.

CHECKMATE 274

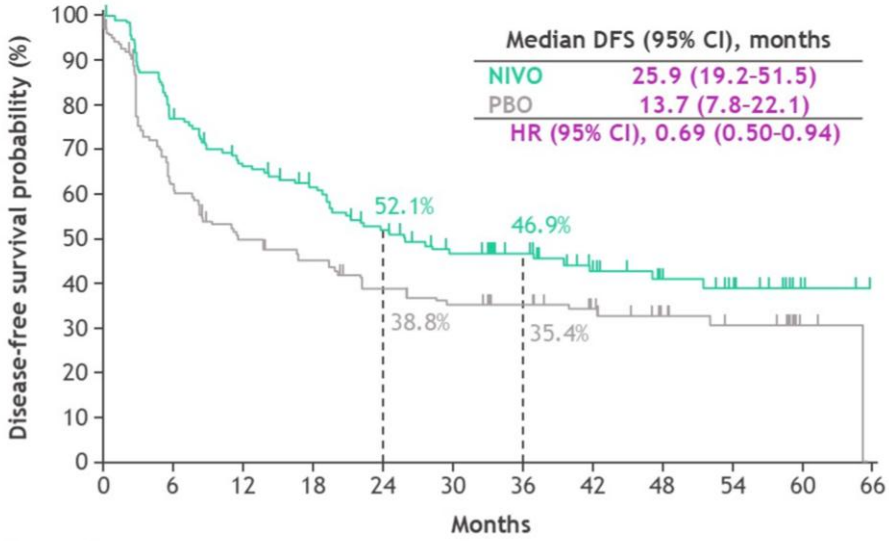
IMPACT OF NEOADJUVANT TREATMENT

Patients with MIBC with prior NAC



No. at risk												
NIVO	142	105	88	70	63	58	48	34	20	12	1	0
PBO	142	77	55	46	43	36	29	24	15	7	1	0

Patients with MIBC without prior NAC[a]



No. at risk												
NIVO	137	103	87	77	63	52	44	30	21	16	3	0
PBO	139	82	64	57	47	42	35	28	19	12	2	0

Milowsky MI, et al. ASCO GU 2025

AMBASSADOR

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

Second interim DFS analysis = 319
Second interim OS analysis = 257

AMBASSADOR

Started enrollment Sept 2017
Closed to accrual Aug 2021

Early closure due to US FDA approval of nivolumab for MIUC

Enrolled N=702

PEMBROLIZUMAB* N=354
- Never started treatment N=24

OBSERVATION N=348
- Never started observation N=4

Disease-Free Survival

207 (58.5%)	**DFS CENSORED**	**176 (50.6%)**
166 (80.2)	Alive & disease-free and in follow-up	117 (66.5%)
5 (2.4%)	Alternative therapy	11 (6.3%)
36 (17.4%)	Withdrew (clinical follow-up/study) (without event)	48 (27.2)
147 (41.5%)	**DFS EVENTS**	**172 (49.4%)**
121 (82.3%)	Progression/recurrence	143 (83.1%)
26 (17.7%)	Death	29 (16.9%)

19.8 %

33.5 %

A higher number of patients were censored in the observation vs the pembro arm

Overall Survival

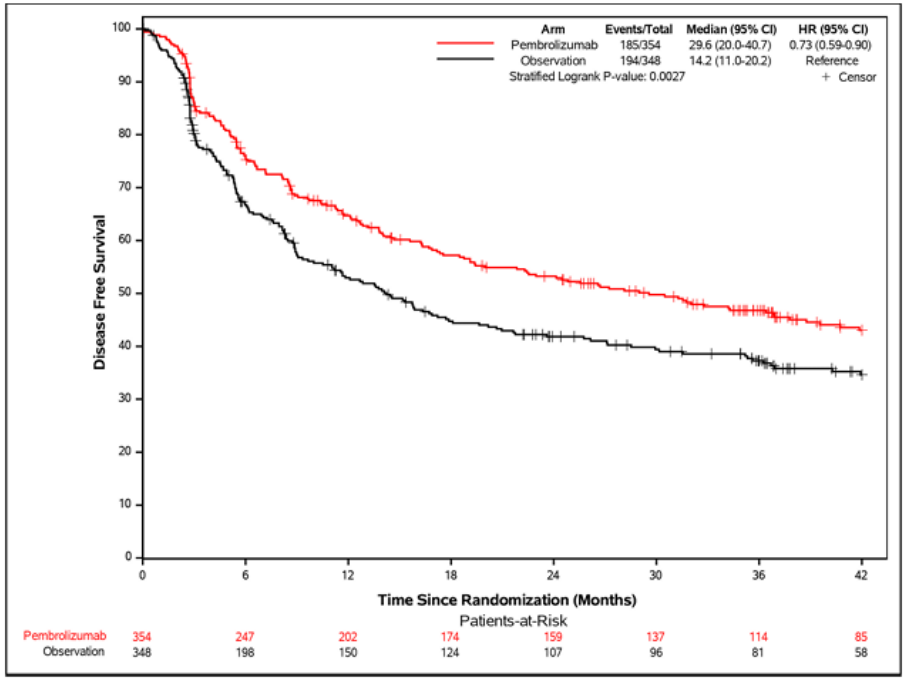
223 (63.0%)	**OS CENSORED**	**222 (63.8%)**
36 (16.1%)	Withdrew from study	42 (18.9%)
187 (83.9%)	Alive and in follow-up	179 (80.6%)
131 (37.0%)	**OS EVENTS**	**126 (36.2%)**

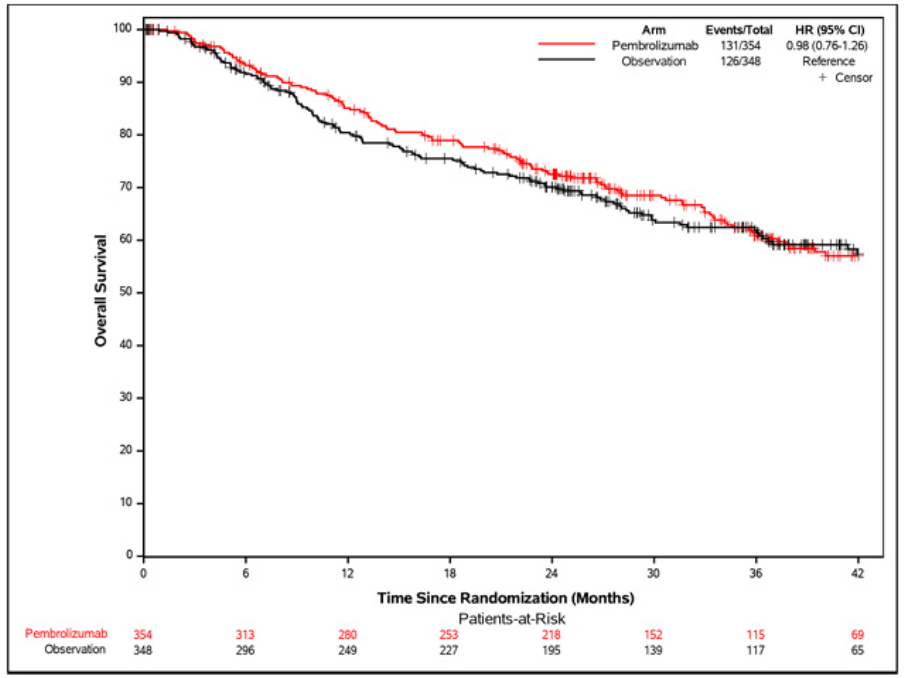
*Mean Number of Cycles (range) 11 (1-18)

All patients are currently off treatment

AMBASSADOR

CO-PRIMARY ENDPOINTS: DISEASE FREE SURVIVAL (45 MONTHS MEDIAN FUP)





Apolo AB, et al. N Engl J Med. 2025 Jan 2;392(1):45-55.

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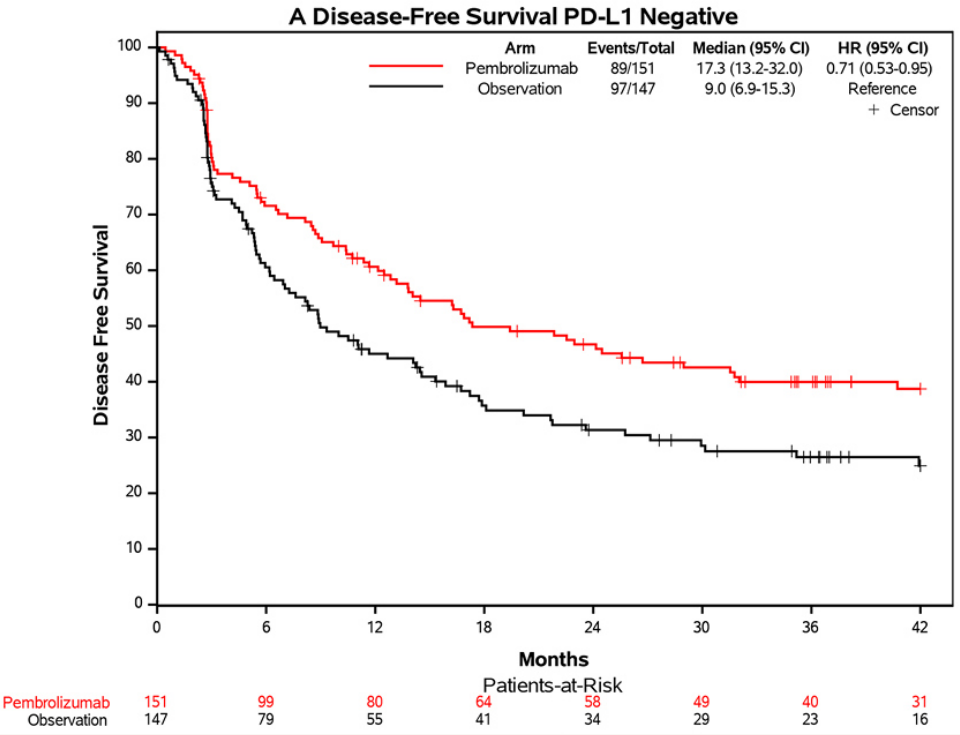
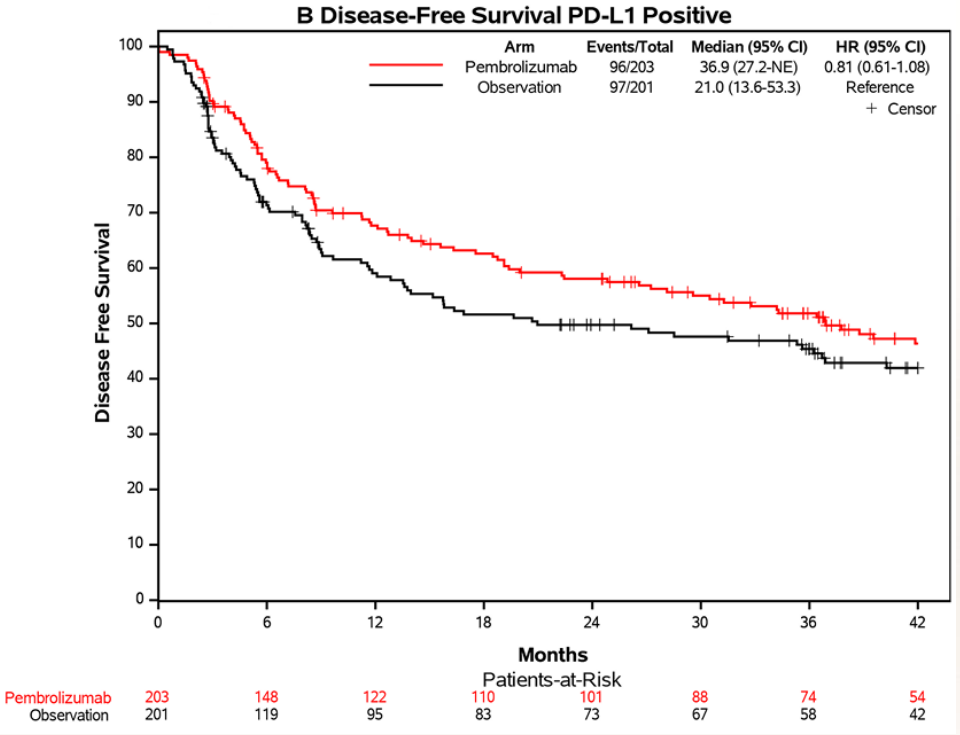
DISEASE FREE SURVIVAL ACCORDING TO PD-L1 STATUS





Apolo AB, et al. N Engl J Med. 2025 Jan 2;392(1):45-55.

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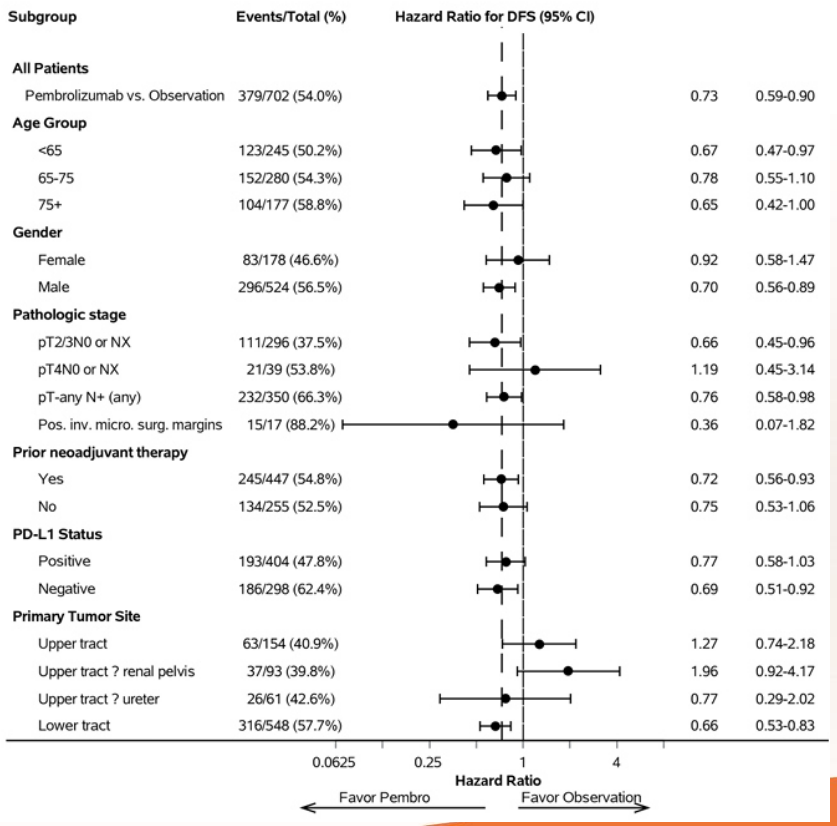
PRIMARY ENDPOINT: DISEASE FREE SURVIVAL SUBGROUPS



Apolo AB, et al. N Engl J Med. 2025 Jan 2;392(1):45-55.

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**

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)

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)

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

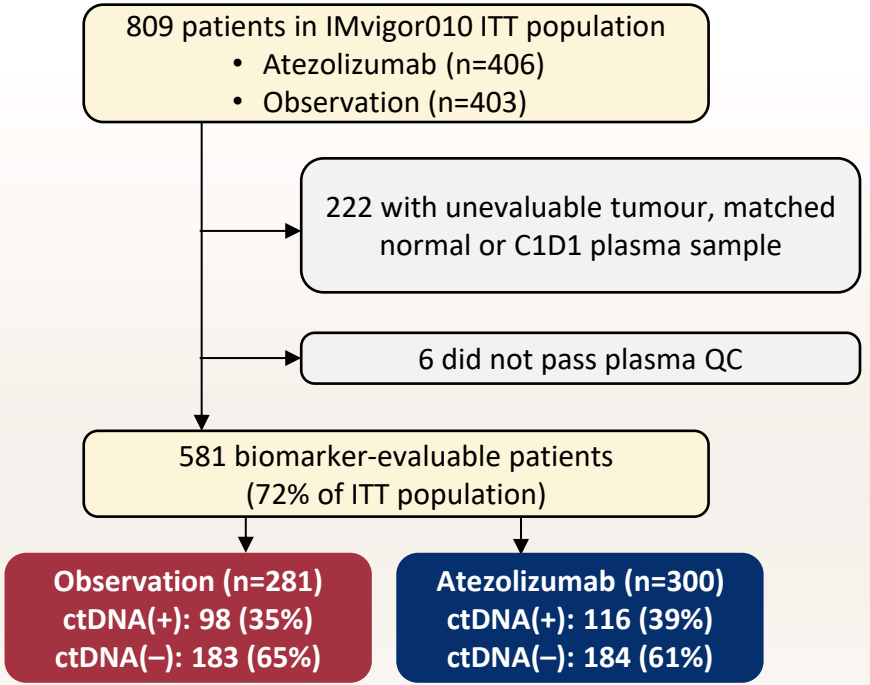
AC, adjuvant chemotherapy; DFS, disease-free survival; ITT, intention to treat; LN, lymph node; MIUC, muscle-invasive UC. [a] Protocol amendments broadened eligibility to "all-comers" (initially, only PD-L1–selected patients were enrolled [IC2/3: PD-L1 expression on tumor-infiltrating immune cells (IC) ≥ 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.

CONTACTO SIGNATERA

IMVIGOR 010

Prespecified exploratory analysis of ctDNA

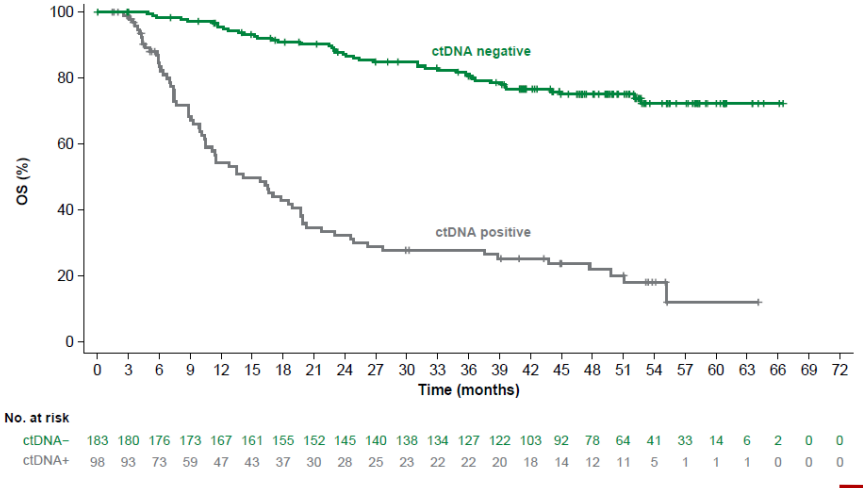
- Measure ctDNA status at C1D1 and C3D1 using a personalized assay
- Evaluate potentially prognostic and/or predictive roles of ctDNA(+) and ctDNA clearance in IMvigor010
- HRs determined by univariate Cox proportional-hazards model, unless otherwise indicated
- *P* values are for descriptive purposes and only shown for prespecified analyses



ctDNA positivity was associated with nodal status (*P*<0.001)

Powles T, et al. ESMO IO 2020

IMVIGOR 010



	ctDNA positive (n = 98)	ctDNA negative (n = 183)
Events, n (%)	70 (71)	43 (23)
Median OS (95% CI), mo	14.1 (10.5–19.7)	NR (NE)
HR[a] (95% CI)	**6.30 (4.30–9.30)**	

809 patients in IMvigor010 ITT population
- Atezolizumab (n=406)
- Observation (n=403)

222 with unevaluable tumour, matched normal or C1D1 plasma sample

6 did not pass plasma QC

581 biomarker-evaluable patients (72% of ITT population)

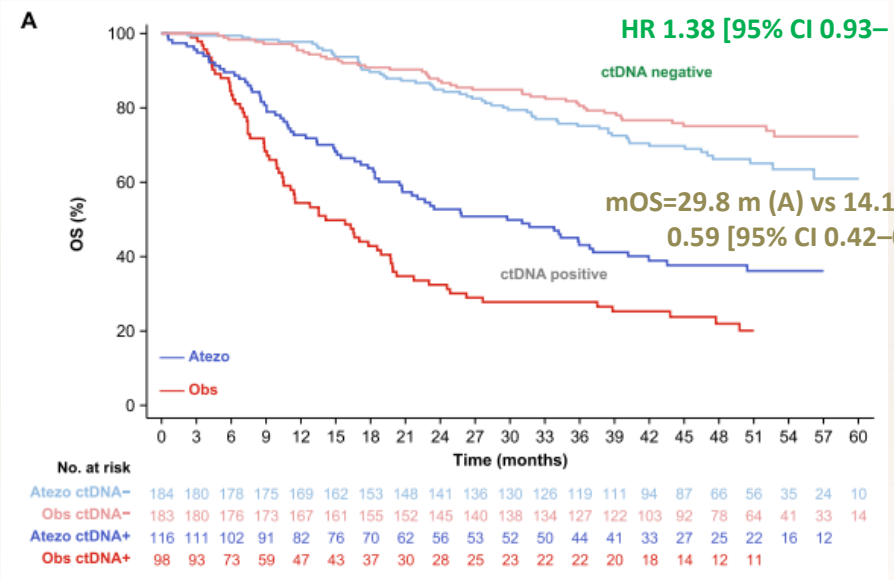
Observation (n=281)
ctDNA(+): 98 (35%)
ctDNA(–): 183 (65%)

Atezolizumab (n=300)
ctDNA(+): 116 (39%)
ctDNA(–): 184 (61%)

Powles T, et al. ESMO IO 2020
Powles T, et al. Eur Urol. 2024 Feb;85(2):114-122.

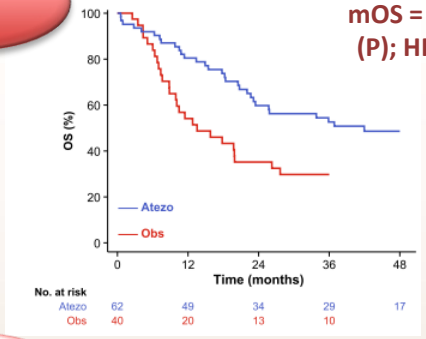
IMVIGOR 010: ANALYSIS AT BASELINE

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



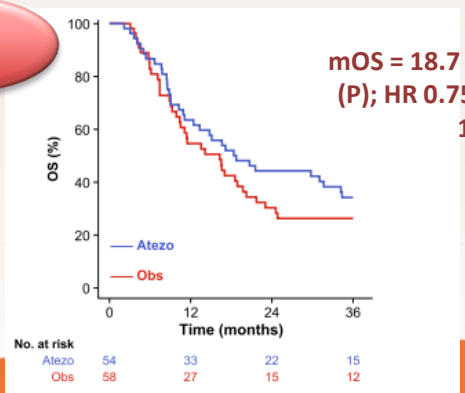
Kaplan-Meier estimates of OS with atezolizumab versus observation in patients positive for ctDNA by baseline PD-L1 status

IHC 2/3



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

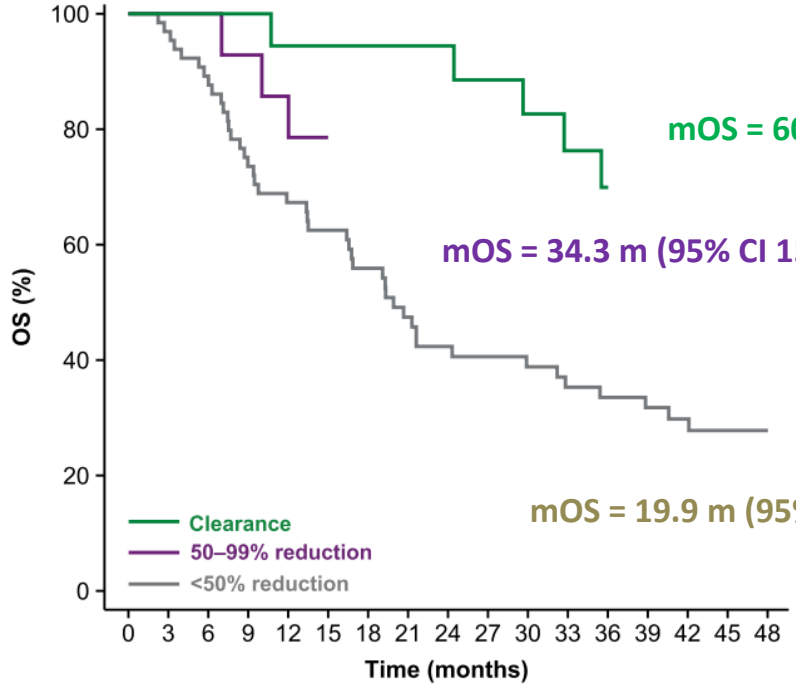
IHC 0/1



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 010: ANALYSIS DURING ADJUVANT TREATMENT



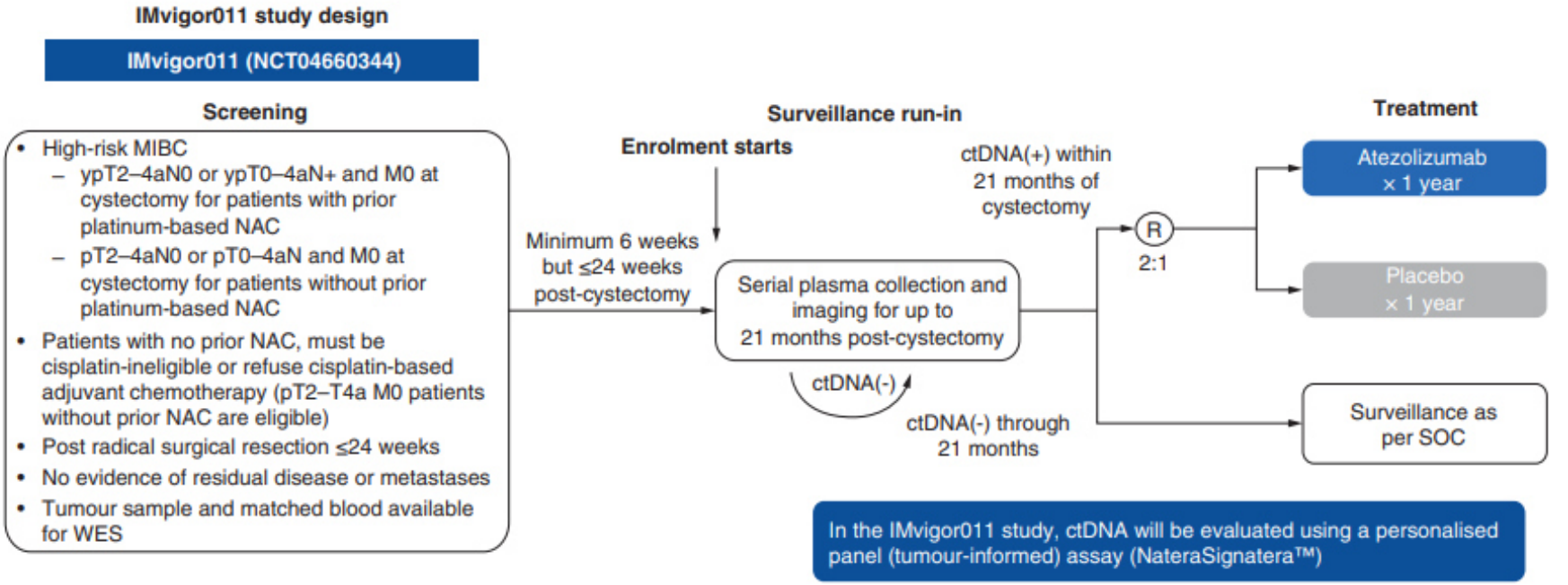
mOS = 60.0 m (95% CI 35.5–NE)

mOS = 34.3 m (95% CI 15.2–NE)

mOS = 19.9 m (95% CI 16.4–32.2)

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.

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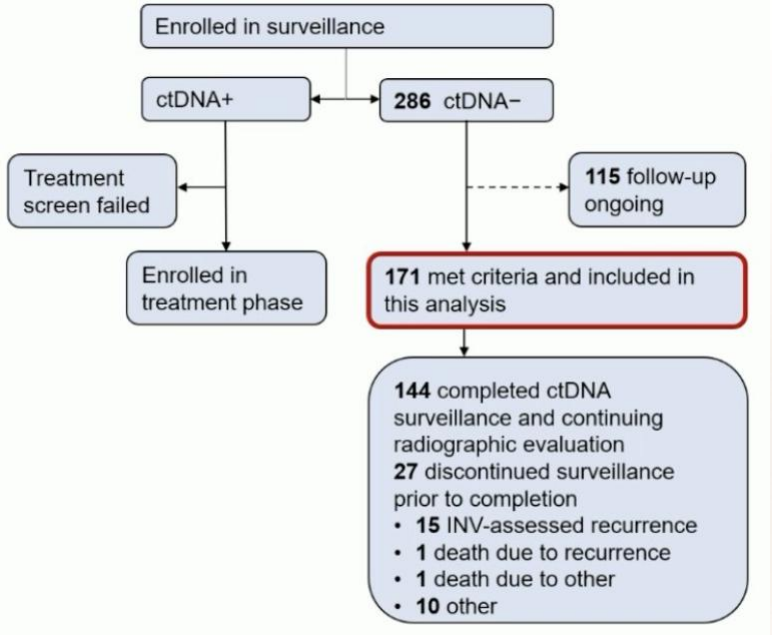

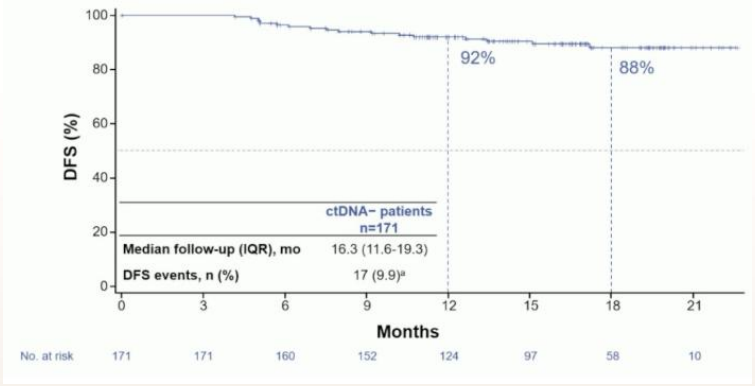

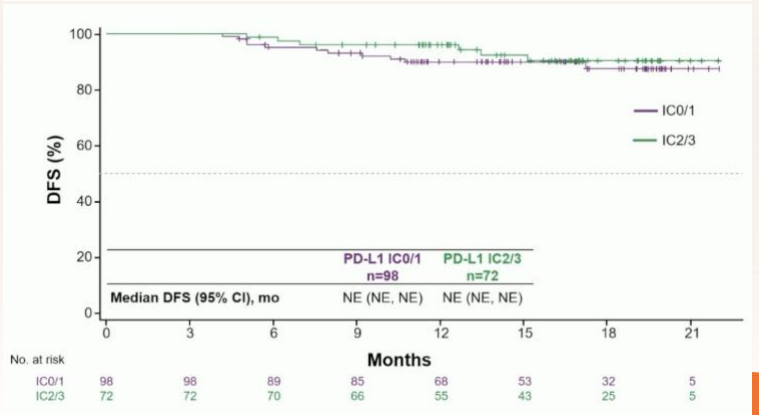

Powles T, et al. EAU 2024

IMVIGOR 011

n (%)	Patients with disease recurrence n=15	Patients without disease recurrence[a] n=156	All ctDNA− patients n=171
Tumour stage[b]			
<T2	2 (13.3)	16 (10.4)	18 (10.7)
T2	6 (40.0)	53 (34.4)	59 (34.9)
T3	6 (40.0)	68 (44.2)	74 (43.8)
T4	1 (6.7)	17 (11.0)	18 (10.7)
Nodal stage			
N0	11 (73.3)	124 (79.5)	135 (78.9)
N+	4 (26.7)	32 (20.5)	36 (21.1)
PD-L1 status[c]			
IC0/1	11 (73.3)	87 (56.1)	98 (57.6)
IC2/3	4 (26.7)	68 (43.9)	72 (42.4)
Lymph nodes removed			
<10	3 (20.0)	34 (22.4)	37 (22.2)
≥10	12 (80.0)	118 (77.6)	130 (77.8)
Lymph node density[d]			
<20	15 (100)	147 (96.7)	162 (97.0)
≥20	0	5 (3.3)	5 (3.0)
Site of recurrence			
Distant	11 (73.3)	–	–
Local	4 (26.7)	–	–
Prior neoadjuvant chemotherapy			
Yes	7 (46.7)	76 (48.7)	83 (48.5)
No	8 (53.3)	80 (51.3)	88 (51.5)

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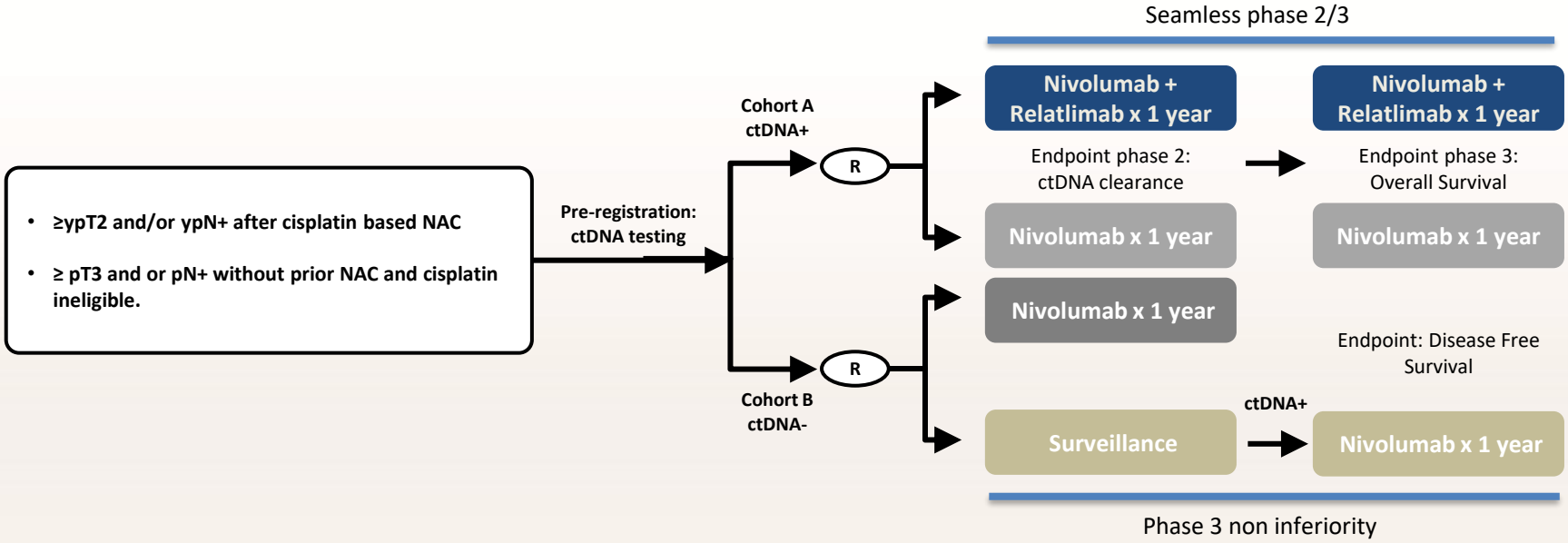
A032103 (MODERN) TRIAL

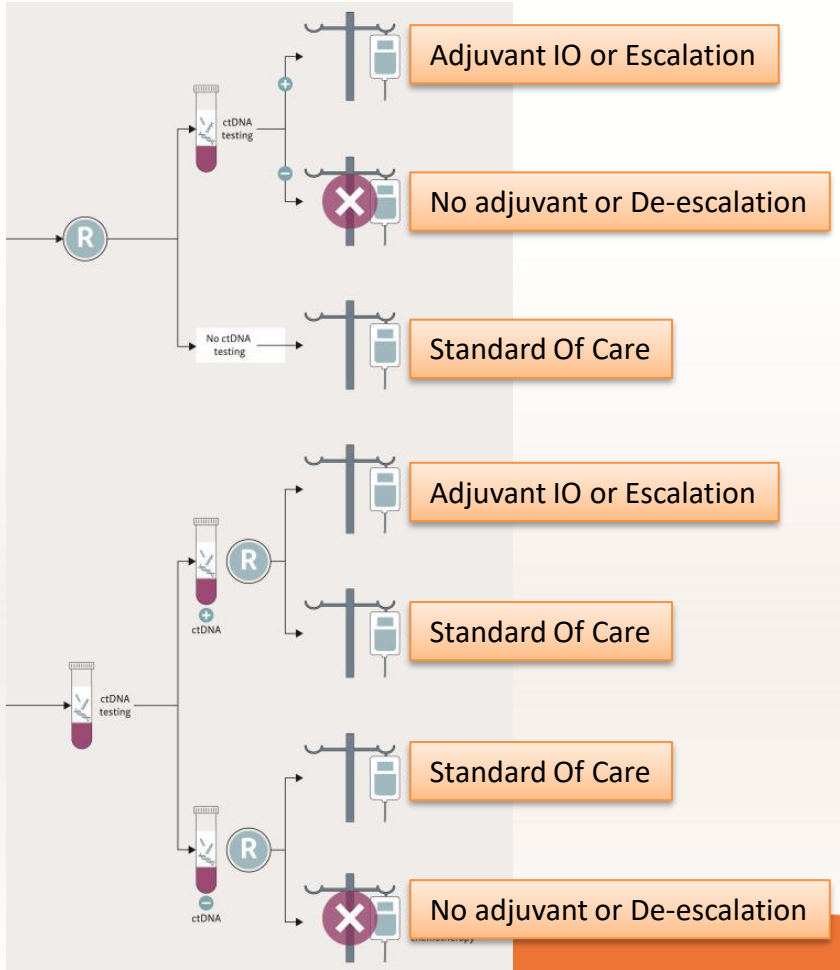


Surgery (+/-NAC+/-IO)

ctDNA baseline

Surgery (+/-NAC+/-IO)

ctDNA baseline



Genitourinary Cancer—Kidney and Bladder

Presenters summarize their novel research findings and provide background on their methodologies. Discussants analyze the significance of each abstract within the context of current knowledge, highlighting clinical application and implications for future research and practice. Abstract presenters and discussants answer questions during a moderated panel discussion.

Meeting 2025 ASCO Annual Meeting

Track Genitourinary Cancer—Kidney and Bladder

Type Oral Abstract Session

Location Hall D2 | Live Stream

Time 1 de junio de 2025
9:45 – 12:45 GMT-5

Chairs

Manuela Schmidinger, MD
Department of Urology, Comprehensive Cancer Center, Medical University of Vienna

Elizabeth Henry, MD
Loyola University Medical Center

CE Credit 3 Credits
Deadline to claim credit ends 4 de septiembre de 2025, 6:00 CEST

10:45 – 10:57 GMT-5

ABSTRACT PRESENTATION 4

Circulating tumor DNA (ctDNA) in patients with muscle-invasive bladder cancer (MIBC) who received perioperative durvalumab (D) in NIAGARA.

Abstract 4503

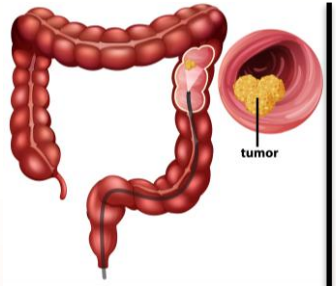
Thomas Powles, MD, PhD, FCRP
Barts Cancer Institute, Experimental Cancer Medicine Centre, Queen Mary University of London, St Bartholomew's Hospital

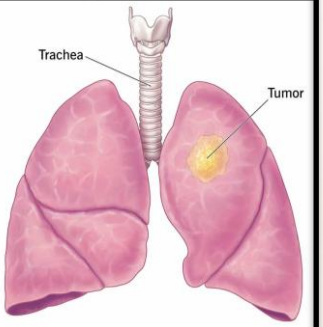
10:57 – 11:09 GMT-5

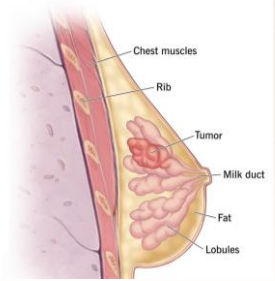
ABSTRACT PRESENTATION 5

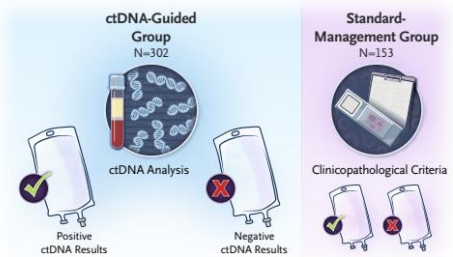
Mitomycin plus BCG as adjuvant intravesical

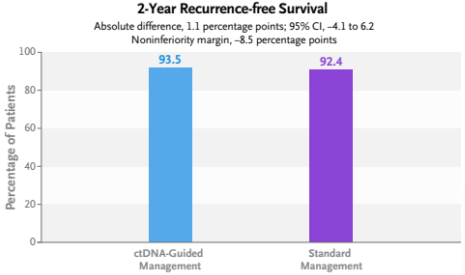
ctDNA IN OTHER SOLID TUMORS

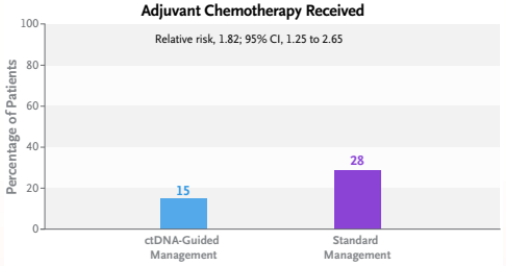


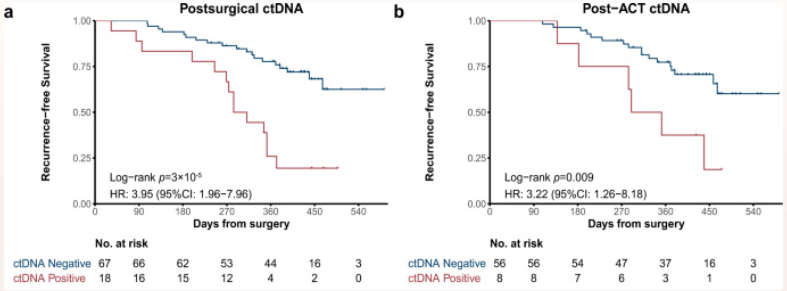


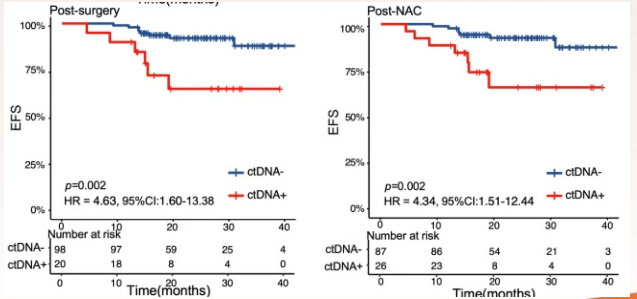




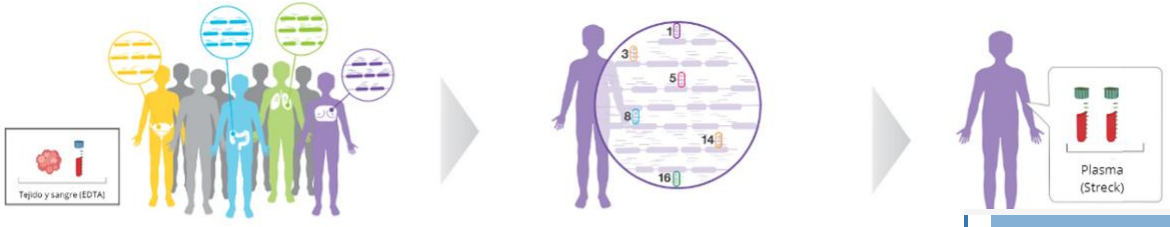




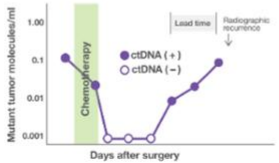




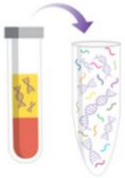
ctDNA IN CLINICAL PRACTICE



1. Secuenciación de tejido tumoral y sangre en el punto inicial
2. Selección de 16 mutaciones clonales especificas del paciente para el diseño de primers personalizados
3. a



5. Análisis ultraprofundo de los datos de la NGS para detectar la presencia de ctDNA



4. 1. Extracción del ADN libre
   2. Amplificación mediante l para las 16 mutaciones e
   3. NGS para la detección de

Tejido tumoral
- cirugía o biopsia (>25 mm2 (>30% tumor))
- tumor primario, nódulo o metástasis

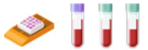
Tubo sangre **EDTA**

Tubos sangre **STRECK**

Selección de 16 **mutaciones clonales y *passenger*** + eliminación de **mutaciones germinales y CHIP** para el diseño de la prueba personalizada para cada paciente

Biopsia líquida para la **detección de MRD** mediante la detección de ctDNA

Primer punto



Resultado en 3-4 semanas

Puntos de seguimiento*

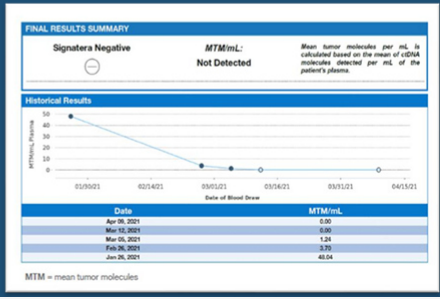
Resultado en 15 dias

La extracción de sangre debe hacerse:
- >2 semanas post-cirugía
- >2 semanas post-tratamiento con QT

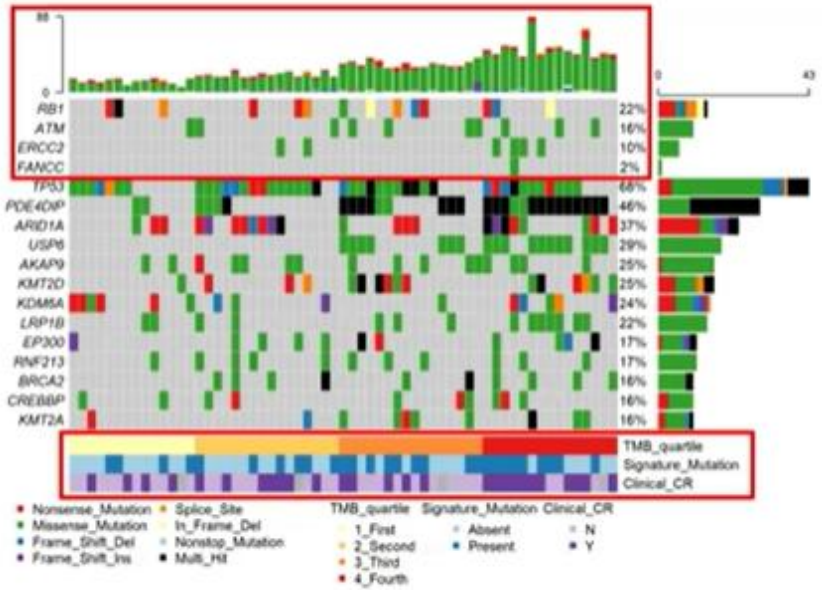
*El protocolo de seguimiento puede adaptarse a la realidad clínica de cada entidad tumoral, centro y paciente.

Informe resultados

- Resultados **cualitativos** (+/-)
- Resultados **cuantitativos** (MTM/mL)
- **Histórico de resultado**s → analisis de las dinàmicas del ctDNA



Can we orientate perioperative treatment by genomical features?



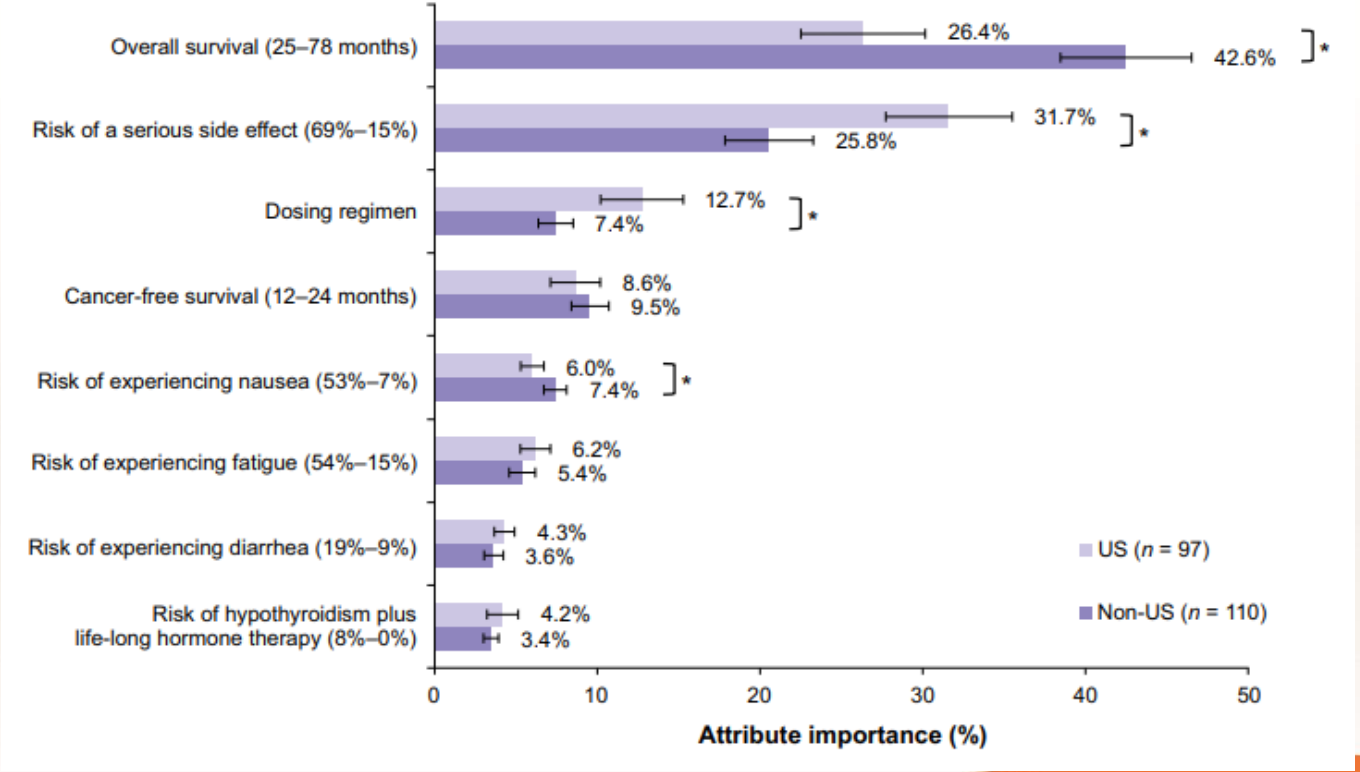
TMB ≥ 10 mut/Mb (p = 0.02) or mERCC2 (p = 0.02) were associated with cCR or pCR

ATM, FANCC, or RB1 alterations were not associated with cCR or pCR

Correlation of genomic alterations with more relevant endpoints (i.e., bladder intact long-term survival) requires longer follow-up

Galsky M et al. ASCO 2021

Adjuvant treatment: patients` preferences



King-Concialdi K, et al. Patient Preference and Adherence 2023 Sep 8:17:2237-2248.

Conclusions

- Adjuvant treatment based on PD-1 inhibitors, has demonstrated a statistical and clinically significant benefit in DFS with a trend to improve OS (nivolumab/Checkmate 274, limitations from pembrolizumab/AMBASSADOR trial).
- Candidate for adjuvant IO treatment are those patients:
  - ypT2-T4a/N+ after cisplatin-neoadjuvant treatment
  - pT3-4a/N+ (no NA or not candidate to cisplatin-based adjuvant treatment) → Waiting data on perioperative randomized studies directed to cis-ineligible patients.
  - PD-L1 expression
- ctDNA is a prognostic biomarker in MIBC.
- ctDNA detection and dynamics are important in this disease—currently informative but with many potential clinical applications in the future clinical context.

MUCHAS GRACIAS POR SU ATENCIÓN