7th ANNUAL UC COURSE

Emerging personalized therapies for the management of urothelial carcinomas

7th MAY 2026
MADRID

El papel del ctDNA en la decisión del tratamiento postoperatorio del CVMI.

Begoña Pérez Valderrama
Oncología Médica. Hospital Universitario Virgen del Rocío, Sevilla.

CONFLICTOS DE INTERÉS

- ✓ *Employment: none*
- ✓ *Consultant or Advisory Role: Astellas Pharma, Novartis AAA, Astra-Zeneca, Bayer, Bristol-Myers-Squibb, Recordati, Ipsen, Merck, Pfizer, MSD, Janssen*
- ✓ *Stock Ownership: none*
- ✓ *Research Funding: none*
- ✓ *Speaking honoraria: Novartis AAA, Almirall Pharma, Astellas Pharma, Astra-Zeneca, Bayer, Bristol-Myers-Squibb, Merck, MSD, Roche, Pfizer; Janssen*
- ✓ *Travel/Accommodations: Bristol-Myers-Squibb, Pfizer, Roche, Astellas Pharma, MSD, Merck*

CVMI

- **Tratamiento perioperatorio: QT**

Neoadjuvant treatment

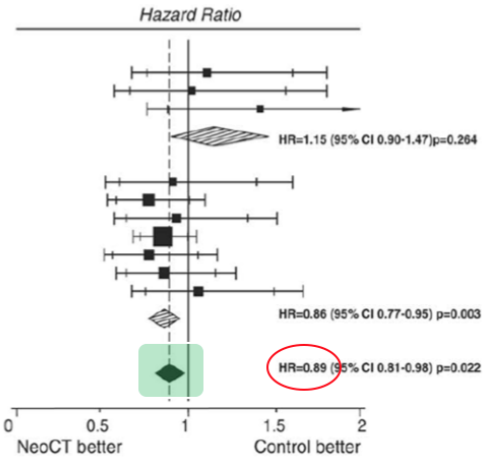
Adjuvant treatment

Neoadjuvant

Radical cystectomy

Adjuvant

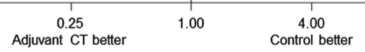
	CT	Control	O-E	Variance
Single agent platinum				
Wallace [2]	59/83	50/76	2.74	27.18
Martinez-Pineiro [3]	43/62	38/59	0.33	20.11
Raghavan [2]	34/41	37/55	5.85	16.51
Sub-total	136/186	125/190	8.92	63.80
Platinum-based combinations				
Cortesi unpublished	43/82	41/71	-1.87	20.84
Grossman [9]	98/158	108/159	-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



OS ABSOLUTE BENEFIT: 5%

Trial identifier	Adj. CT n/N	Control n/N	Haz. ratio (95% CI)	% Weight (Fixed)
Skinner	34/50	40/52	0.75 (0.48, 1.19)	12.26
Bono	14/43	23/47	0.64 (0.33, 1.26)	5.67
Studer	23/46	22/45	1.02 (0.57, 1.84)	7.37
Freiha	13/26	17/25	0.75 (0.36, 1.54)	4.90
Stöckle	20/26	20/23	0.56 (0.30, 1.05)	6.54
Otto	28/55	29/53	0.82 (0.49, 1.38)	9.50
Stadler	12/58	9/56	1.16 (0.48, 2.80)	3.27
Cognetti	46/102	38/92	1.29 (0.84, 1.99)	13.80
Sternberg	66/141	82/143	0.77 (0.56, 1.06)	24.41
Zhegalik	35/53	39/47	0.70 (0.45, 1.11)	12.28
Overall, fixed	**291/600**	**319/583**	**0.82 (0.70, 0.96), $p = 0.02$**	**100.00**
Overall, random			0.82 (0.70, 0.96), $p = 0.02$	
($I^2 = 0\%$, $p = 0.5$)				

N=1183 (10 RCTs)

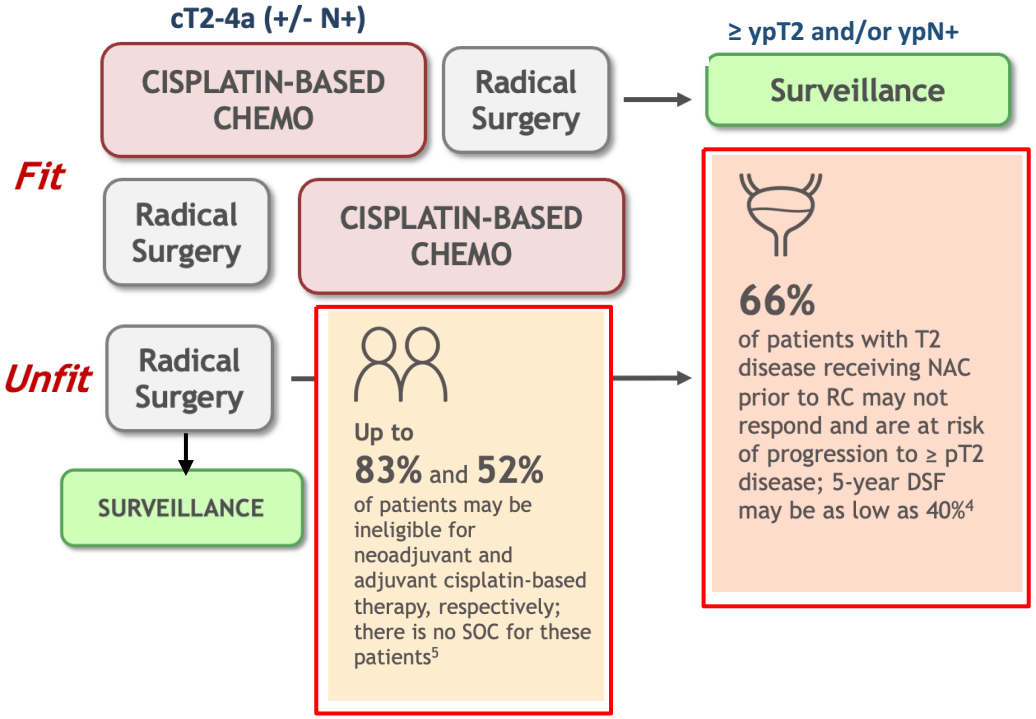


5y-OS ABSOLUTE BENEFIT: 6%

ABC Meta-analysis. Eur Urol 2005.
ABC Meta-analysis Collaborators Group. Eur Urol 2022.

CVMI

- **Tratamiento perioperatorio: QT**



- ✓ Any option for cisplatin-ineligible patients?
- ✓ Any option for patients with residual disease?

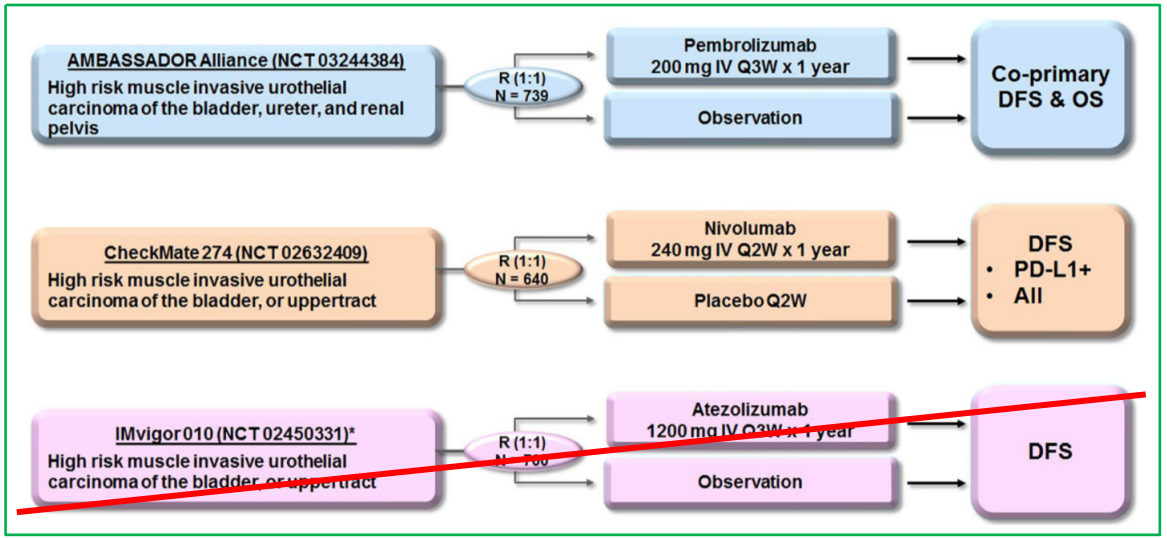
CVMI

- **Tratamiento perioperatorio: inmunoterapia**

High-risk MIUC (including UTUC)
Radical cystectomy/nephrouretectomy

Neoadjuvant:
≥ ypT2 or pN+ if prior NAC
Adjuvant:
≥ pT3 or pN+ if ineligible or decline cisplatin-based AC

- PD1/PD-L1 blockade
- Placebo or observation



Nadal R. Curr Treat Opin Oncol 2018.

CVMI

- **Tratamiento perioperatorio: inmunoterapia**

CheckMate-274

N = 709

Key inclusion criteria

- Patients with ypT2-ypT4a or ypN+ MIUC who had neoadjuvant cisplatin chemotherapy
- Patients with pT3-pT4a or pN+ MIUC without prior neoadjuvant cisplatin chemotherapy and not eligible/refuse adjuvant cisplatin chemotherapy
- Radical surgery within the past 120 days
- Disease-free status within 4 weeks of dosing

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

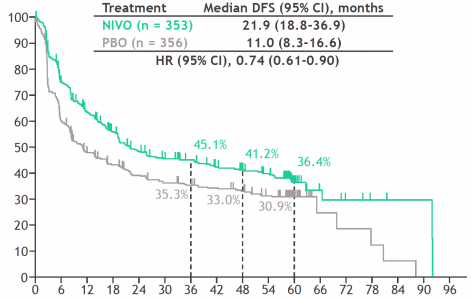
R 1:1 → NIVO IV 240 mg Q2W / PBO IV Q2W

Median follow-up -> 60 months

DFS ITT

All randomized patients[a]

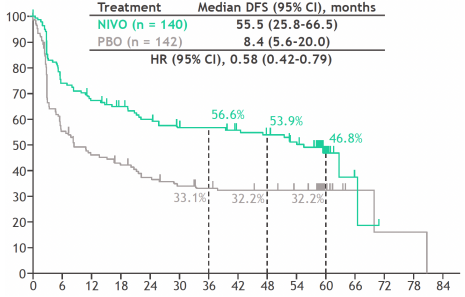
Treatment	Median DFS (95% CI), months
NIVO (n = 353)	21.9 (18.8-36.9)
PBO (n = 356)	11.0 (8.3-16.6)
HR (95% CI), 0.74 (0.61-0.90)	



DFS PD-L1 positive

Patients with PD-L1 ≥ 1%[b]

Treatment	Median DFS (95% CI), months
NIVO (n = 140)	55.5 (25.8-66.5)
PBO (n = 142)	8.4 (5.6-20.0)
HR (95% CI), 0.58 (0.42-0.79)	



AMBASSADOR

Key Eligibility

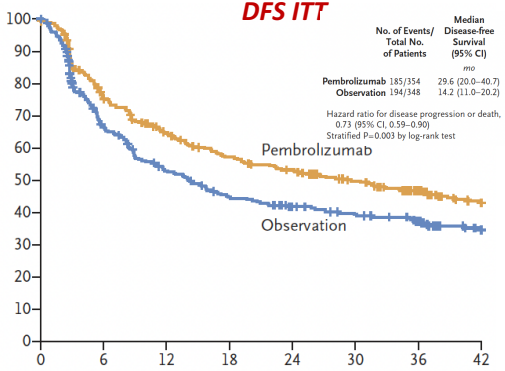
- Muscle-invasive urothelial carcinoma: bladder, urethra, renal pelvis, ureter
- Post-radical surgery (cystectomy, nephrectomy, nephroureterectomy, or ureterectomy) ≥ 4 but ≤ 16 weeks
- Post-neoadjuvant chemotherapy and ≥ pT2 and/or N+/+margins
  OR
- cisplatin-ineligible or refusing and ≥ pT3 and/or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

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

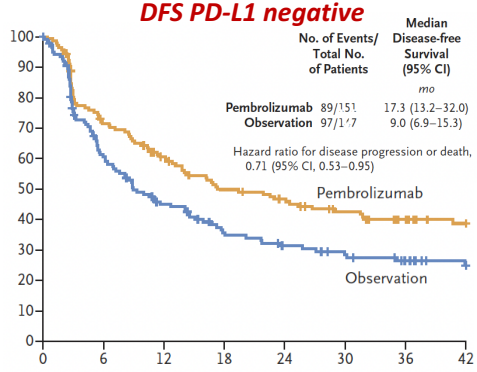
N=739 → R 1:1 → Pembrolizumab 200 mg q3W 1 year (18 cycles) / Observation

Median follow-up -> 44.8 months

DFS ITT



DFS PD-L1 negative



Galsky MD, et al. Ann Oncol 2026;37:69.
Apolo AB, et al. N Engl J Med 2025;392: 45.

CVMI

- **Tratamiento perioperatorio: inmunoterapia**

CheckMate-274

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- Patients with ypT2-ypT4a or ypN+ MIUC who had neoadjuvant cisplatin chemotherapy
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- Prior neoadjuvant cisplatin-based chemotherapy
- Nodal status

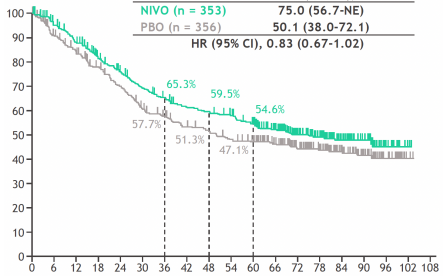
R 1:1 → NIVO IV 240 mg Q2W / PBO IV Q2W

Median follow-up -> 60 months

OS ITT

All randomized patients[a]

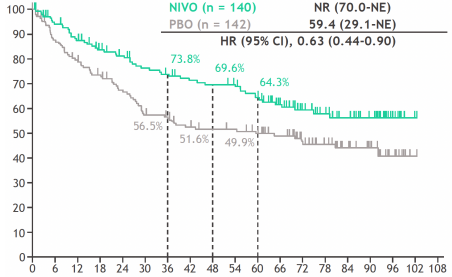
Treatment	Median OS (95% CI), months
NIVO (n = 353)	75.0 (56.7-NE)
PBO (n = 356)	50.1 (38.0-72.1)
HR (95% CI), 0.83 (0.67-1.02)	



OS PD-L1 positive

Patients with PD-L1 ≥ 1%[b]

Treatment	Median OS (95% CI), months
NIVO (n = 140)	NR (70.0-NE)
PBO (n = 142)	59.4 (29.1-NE)
HR (95% CI), 0.63 (0.44-0.90)	



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Key Eligibility

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Stratify

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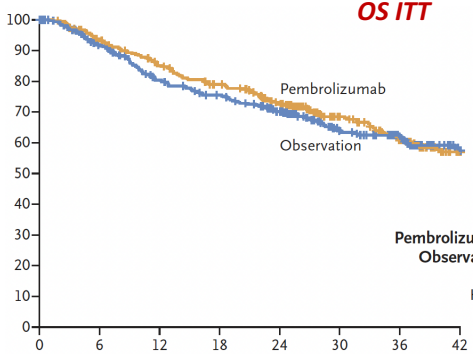
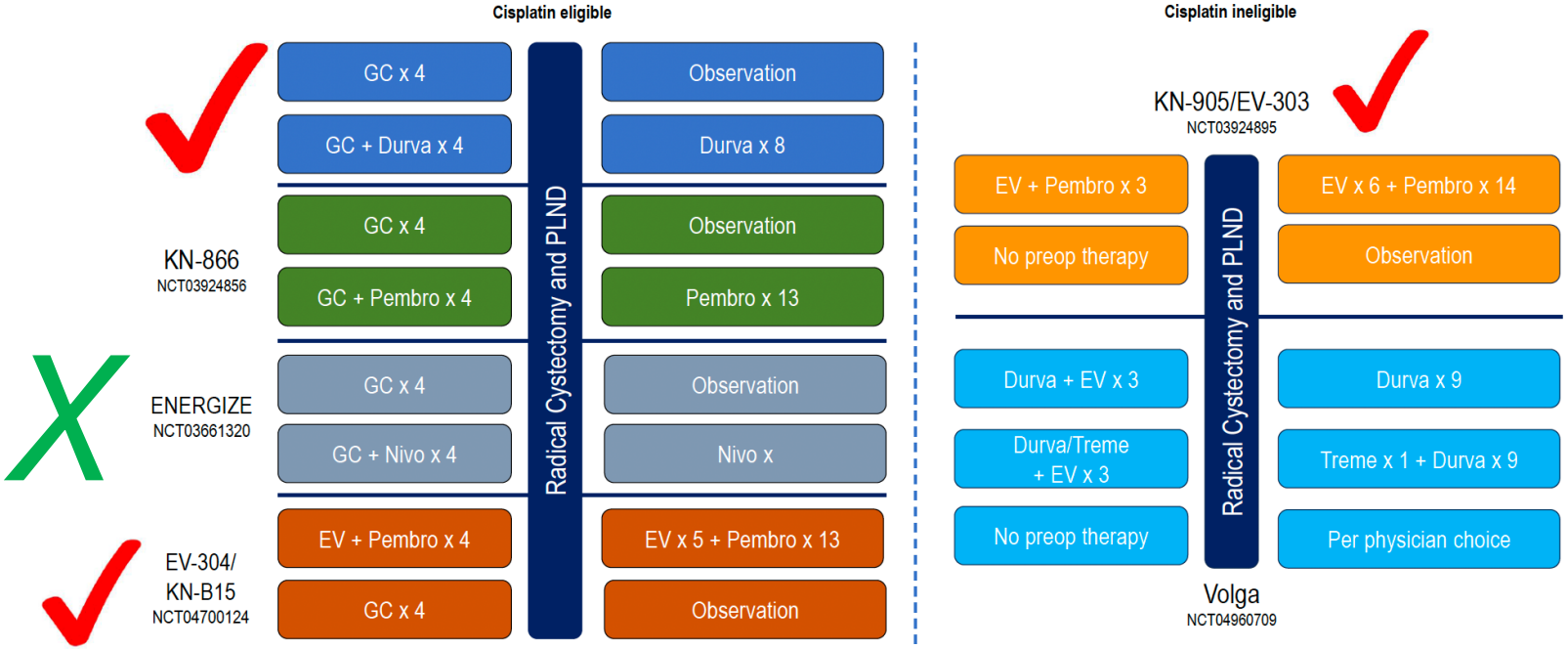


	No. of Events/ Total No. of Patients	3-Yr Survival (95% CI)
		percent
Pembrolizumab	131/354	60.8 (95% CI, 55.3 to 66.9)
Observation	126/348	61.9 (95% CI, 56.5 to 67.9)

Hazard ratio for death, 0.98 (95% CI, 0.76–1.26)

Galsky MD, et al. Ann Oncol 2026;37:69.
Apolo AB, et al. N Engl J Med 2025;392: 45.

- **Tratamiento perioperatorio: estudios en marcha**



- **Tratamiento perioperatorio: estudios en marcha**

✓ **NIAGARA (fit), EV-303 (unfit), EV-304 (fit) aumentan SG** -> ¿qué aporta cada parte?

Ventajas

- ✓ Tratamiento precoz de las metástasis subclínicas
- ✓ Testa sensibilidad al tratamiento "in vivo"
- ✓ Podría aumentar la preservación vesical (quimioselección)
  - Valor pronóstico de pT0

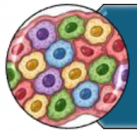
Ventajas

- ✓ Tratamiento quirúrgico estándar no se retrasa
- ✓ Tratamiento precoz de las metástasis subclínicas
- ✓ Tratamiento de enfermedad resistente / residual (si neoadyuvancia previa)
- ✓ Mejora la selección del paciente según riesgo (estadio patológico).

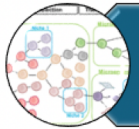
- ✓ ¿Debemos tratar a todos con todo? -> Toxicidad y acceso
- ✓ ¿Qué aporta la fase adyuvante en el tratamiento peri-operatorio (pT0 ¿?)
- ✓ ¿Cuánto tiempo debe durar la adyuvancia?

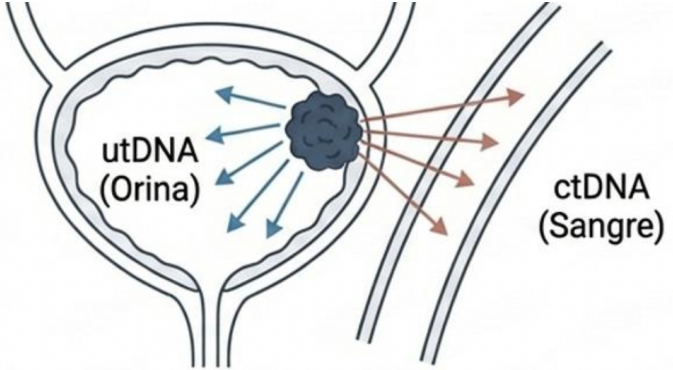
CVMI

- **Biopsia líquida: ctDNA y utDNA**


Captura heterogeneidad tumoral


Menos invasivas


Permite seguir la evolución tumoral (monitorización genómica)



Biopsia de Tejido	ctDNA (Sangre)	utDNA (Orina)
· Fotografía estática del tumor · Captura heterogeneidad espacial limitada · Altamente invasiva	· Monitorización sistémica dinámica · Captura MRD y micrometástasis globales · Permite seguimientos seriados en tiempo real	· Detección ultra-localizada · Alta sensibilidad para recurrencia local (NMIBC) · Totalmente no invasiva

CVMI

- **ctDNA: aplicaciones clínicas**

LOCAL

Improve cancer screening

Detect minimal residual disease

Monitor for response to therapy

Estimate cancer aggression

Predict treatment efficacy

Identify resistance mechanisms

Characterize biology and evolution

METASTATIC

- Enfermedad mínima residual
- Monitorización postquirúrgica

TUMOR-INFORMED

- Uses information about the individual cancer from tissue
- Pros: specific and established
- Cons: time and cost

TUMOR-NAÏVE

Relies on *de novo* detection of ctDNA features (e.g. mutations)

Pros: quick; can also screen

Cons: lower specificity

- Selección de terapias dirigidas
- Perfiles iniciales en enf. metastásica

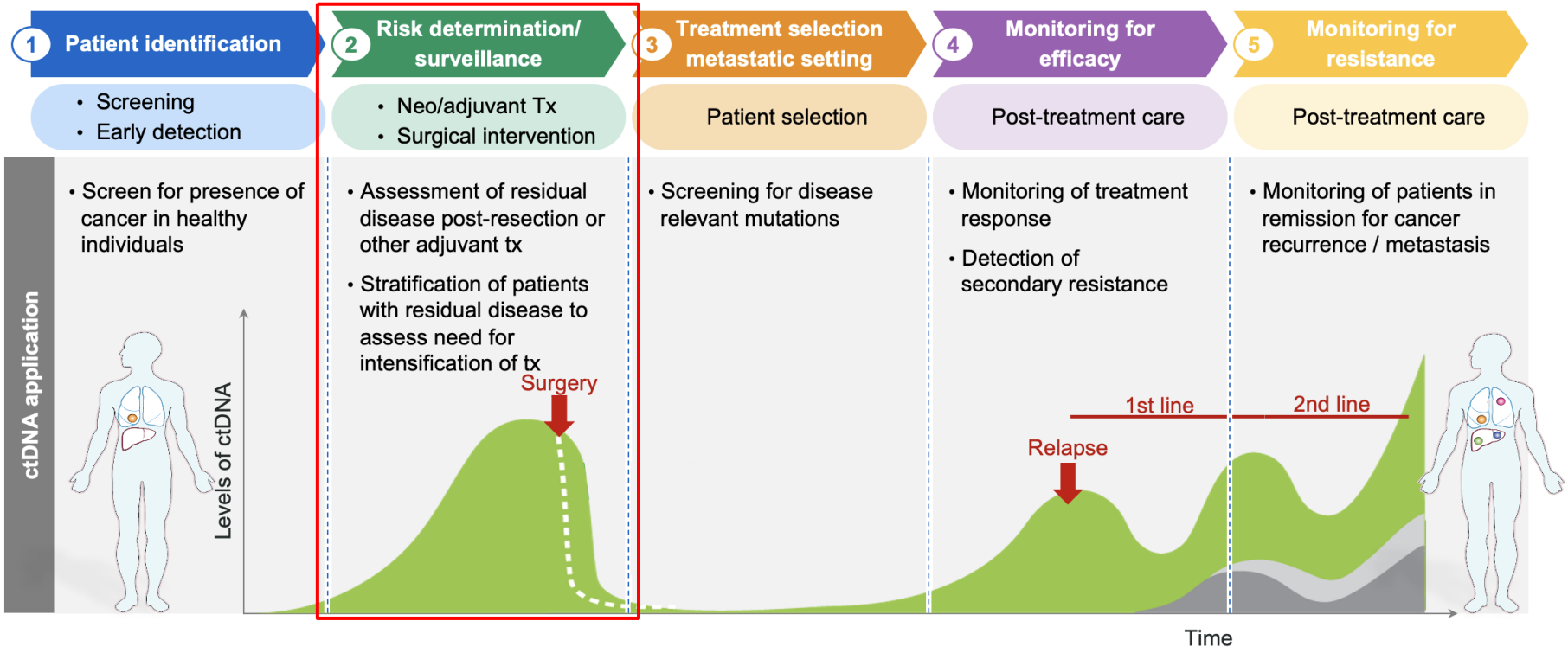
Adaptado de Wyatt A, et al. ASCO GU 2025.

- **ctDNA: plataformas**

Plataforma	Tipo	Tecnología	Genes / Variantes	Alteraciones detectadas
Guardant360 CDx	Tumor-agnostic	Captura híbrida + UMI	74–83 genes	SNV, indels, fusiones (ALK/ROS1/RET/NTRK/FGFR), CNV (ERBB2, MET, EGFR), MSI, bTMB
Guardant Reveal	Tumor-naïve MRD	Mut + metilación + UMI	Panel epigenético + 60 genes	MRD sin tejido tumoral; mejor en CRC y mama; en evaluación en urotelial
FoundationOne Liquid CDx	Tumor-agnostic	Captura híbrida	324 genes	SNV, indels, fusiones, CNV, MSI, bTMB, LOH, BRCA1/2 germinal y somática; CDx erdafitinib en urotelial
Tempus xF / xF+	Tumor-agnostic	Captura híbrida	105 / 523 genes	SNV, indels, fusiones, CNV, MSI, bTMB; integración con tejido y RNA
Caris Assure	Tumor-agnostic	WES + WTS + WBC pareado	Exoma completo	SNV, indels, CNV, fusiones, cfRNA, firmas funcionales
OncoBEAM (Sysmex)	Tumor-agnostic	BEAMing	Hotspots (KRAS, BRAF, EGFR, PIK3CA)	SNV puntuales en variantes hotspot
Signatera (Natera)	Tumor-informed MRD	WES tumor → mPCR + NGS	16 variantes personalizadas	SNV/indels personalizadas; LOD ~0,01%; usado en IMvigor010/011, MODERN, TOMBOLA
RaDaR (Inivata/NeoGenomics)	Tumor-informed MRD	WES tumor → captura híbrida	48 variantes personalizadas	SNV/indels; LOD ≤50 ppm; datos en MIBC (Christensen 2019)
NeXT Personal (Personalis)	Tumor-informed MRD	WES tumor → panel masivo	Hasta 1.800 variantes personalizadas	Ultra-sensibilidad (LOD ~1 ppm); en evaluación en urotelial
Haystack MRD / SAGA / PCM	Tumor-informed MRD	mPCR / AMP	16–50 variantes	Equivalentes funcionales a Signatera; uso creciente
Galleri (Grail)	MCED / cribado	Metilación dirigida	100.000+ regiones metiladas	Detección multicáncer; señal de origen tisular

Adaptado de Pascual J, et al., Ann Oncol 2022;33(8):750, con datos de fabricantes.

- **ctDNA: aplicaciones clínicas**



Adapted from Manolitsis I, et al. Expert Rev Anticancer Ther 2025;25(7):787.

Adaptado de Pascual et al., Ann Oncol 2022; con datos de fabricantes

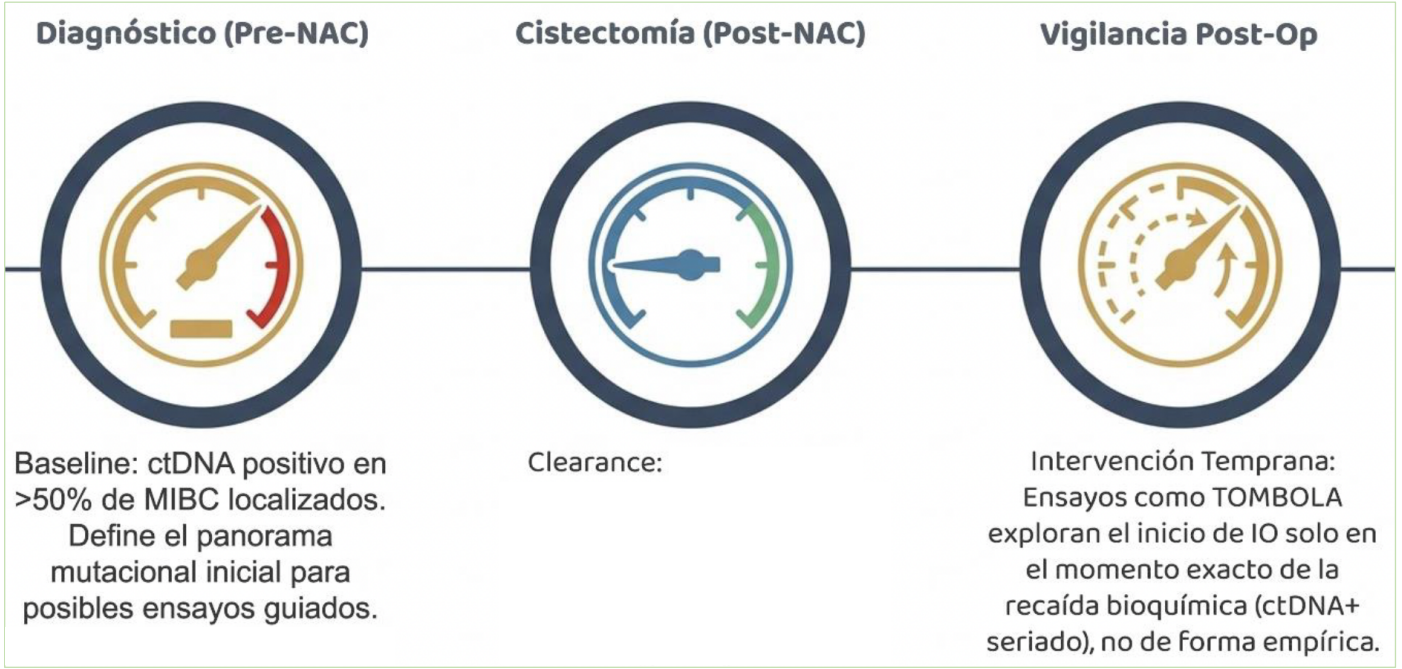
- ## ctDNA: Estudios clave en CVMI

Estudio	Diseño	Setting	Población	Resultados clave
Christensen et al. *[28,29]*	Prospective cohort study	Quimioterapia neoadyuvante con regímenes basados en cisplatino; ctDNA medido pre- y post-NAC	MIBC localizado en NAC (n = 68); estudio observacional prospectivo	Aclaramiento de ctDNA durante NAC asociado a RFS a 3 años del 88% vs. 46% en ctDNA persistente; predictivo de outcomes a largo plazo
ABACUS *NCT02662309*	Phase II, single-arm	Inmunoterapia con atezolizumab antes de cistectomía; ctDNA como endpoint exploratorio	MIBC no candidato a cisplatino (T2–T4aN0M0) con 2 ciclos de atezolizumab (n = 95)	Tasa de pCR del 37% en pacientes ctDNA-negativos; positividad de ctDNA correlacionada con riesgo de recurrencia
NABUCCO *NCT03387761*	Phase I/II	Doble bloqueo immune checkpoint (ipilimumab + nivolumab) prequirúrgico en cohorte de alto riesgo	MIBC localmente avanzado, operable (T3–T4aN0–1M0); sin terapia sistémica previa (n = 24)	Negatividad de ctDNA en cirugía predijo PFS a 12 meses del 88%; ctDNA-positivos con recurrencia significativamente mayor
IMvigor010 *NCT02450331*	Phase III RCT	Inmunoterapia postoperatoria (atezolizumab) vs. observación tras cistectomía radical	MIBC alto riesgo postcistectomía (pT2–T4a o pN+) randomizados a tratamiento adyuvante (n = 809)	Ensayo globalmente negativo, pero ctDNA+ obtuvieron beneficio en DFS con atezolizumab (HR 0,58); ctDNA– no
IMvigor011 *NCT04660344*	Phase III RCT (ongoing)	Diseño guiado por ctDNA: solo ctDNA+ randomizados a atezolizumab vs. placebo tras cistectomía	ctDNA detectable 4–16 semanas postcistectomía; randomización 1:1 atezolizumab vs. placebo (n = 809)	En curso; valida ctDNA como herramienta de selección para IO adyuvante; endpoint primario DFS en ctDNA+
TOMBOLA *NCT04138628*	Phase II RCT (ongoing)	Pacientes postcistectomía con monitorización seriada de ctDNA; tratamiento desencadenado por positivización	MIBC postoperatorio en programa de vigilancia con ctDNA; tratamiento al emerger ctDNA (n ≈ 100)	Resultados preliminares: solo 2 recaídas entre 66 ctDNA-negativos (~3%); apoya estrategia guiada por ctDNA
MODERN *NCT05987241*	Phase III RCT (ongoing)	Inmunoterapia adyuvante con nivolumab ± relatlimab guiada por estado de ctDNA postquirúrgico	MIBC postcistectomía estratificado por ctDNA; ctDNA+ recibe nivolumab ± relatlimab (en marcha)	Evalúa eficacia de la escalada de checkpoint (nivolumab + relatlimab) en pacientes ctDNA+
VOLGA *NCT04960709*	Phase III RCT (ongoing)	Esquema neoadyuvante multimodal (gem/cis + durvalumab + tremelimumab); incluye monitorización MRD por ctDNA	MIBC candidato a cisplatino: GC neoadyuvante + durvalumab + tremelimumab; MRD vía ctDNA como endpoint	Evaluará si el aclaramiento de ctDNA correlaciona con pCR y outcomes a largo plazo; podría definir respondedores moleculares

Adaptado de Manolitsis I, et al. Expert Rev Anticancer Ther 2025;25(7):787.

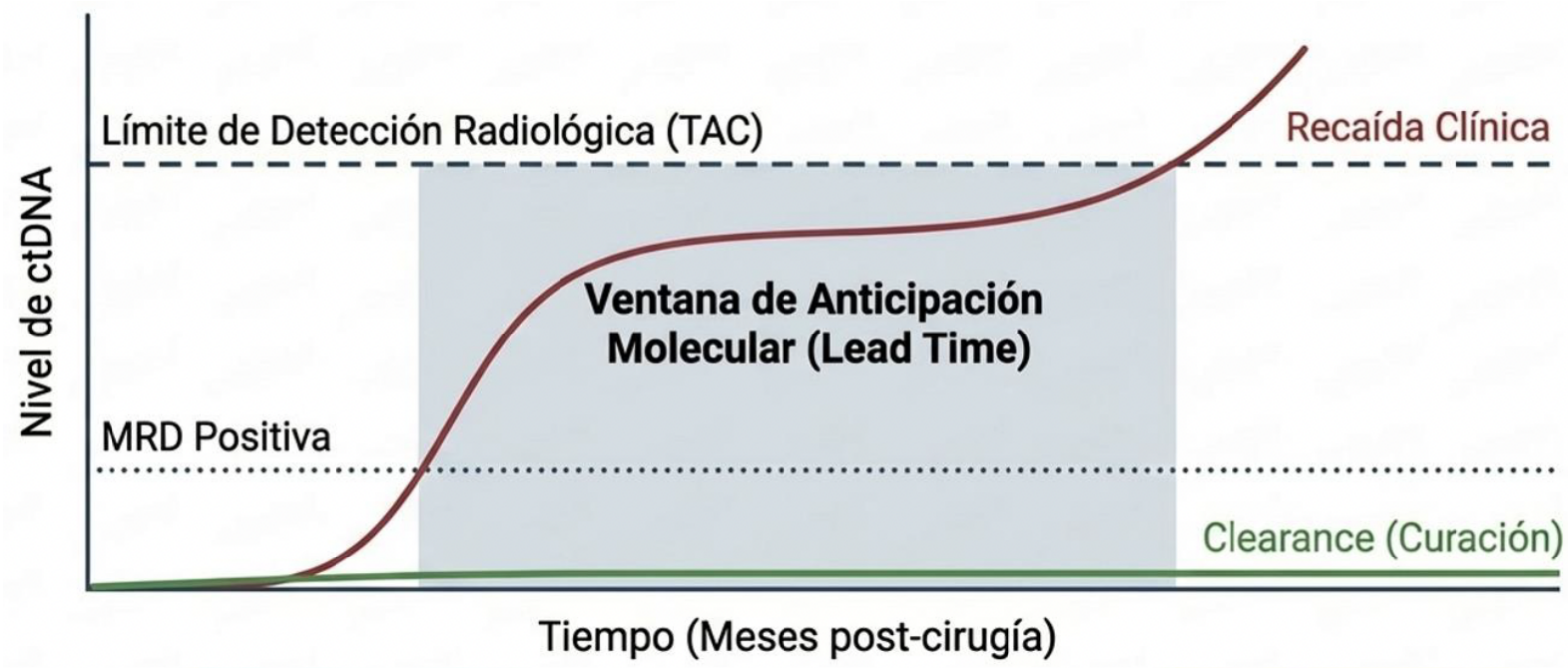
CVMI

- **ctDNA: aplicaciones clínicas en CVMI**



CVMI

- **ctDNA: Enfermedad Mínima Residual**



CVMI

- **ctDNA: tratamiento adyuvante**

IMvigor010

N=809

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

R 1:1

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

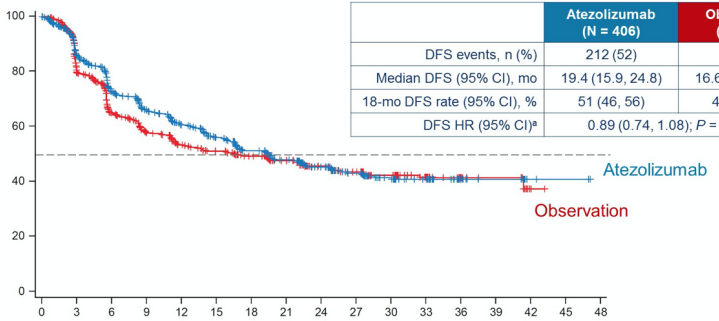
No crossover allowed

Observation[c] **q3w**

Primary endpoint: DFS

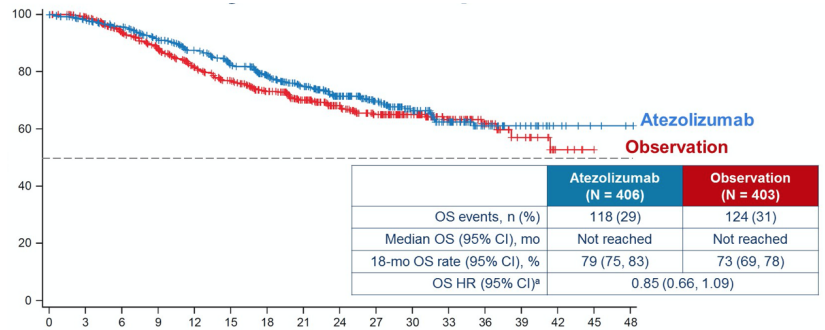
Median follow-up -> 21.8 months

DFS



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

OS

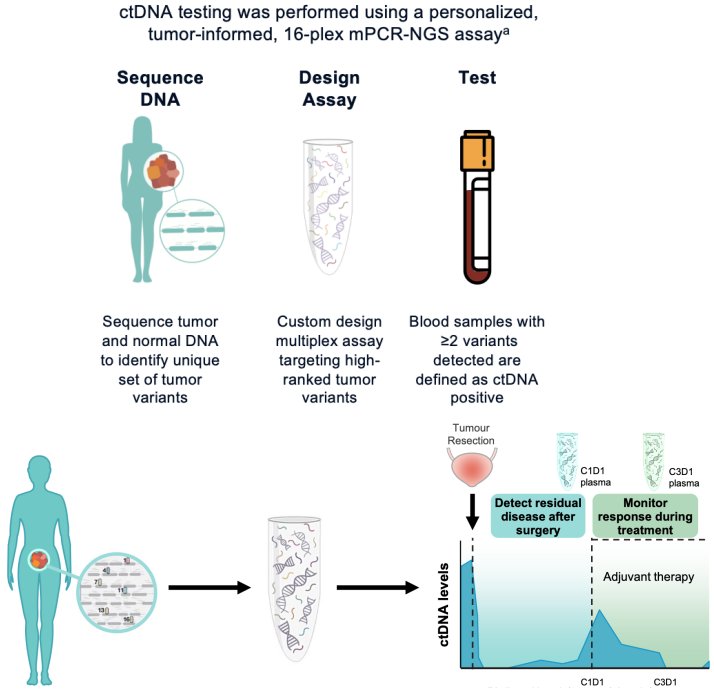


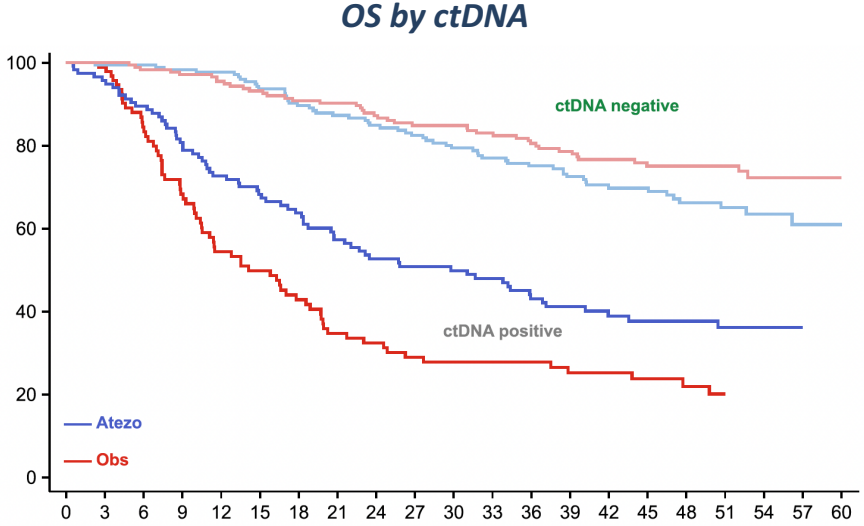
	Atezolizumab (N = 406)	Observation (N = 403)
OS events, n (%)	118 (29)	124 (31)
Median OS (95% CI), mo	Not reached	Not reached
18-mo OS rate (95% CI), %	79 (75, 83)	73 (69, 78)
OS HR (95% CI)[a]	0.85 (0.66, 1.09)	

Bellmunt J, et al. Lancet Oncol 2021 Mar 12:S1470.

- **ctDNA: tratamiento adyuvante**

IMvigor010





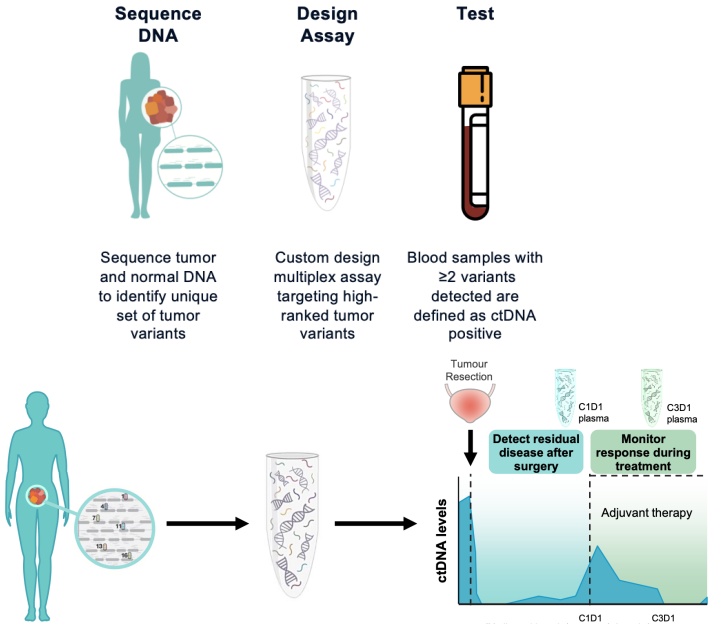
Powles T, et al. Eur Urol 2024;85:114.

CVMI

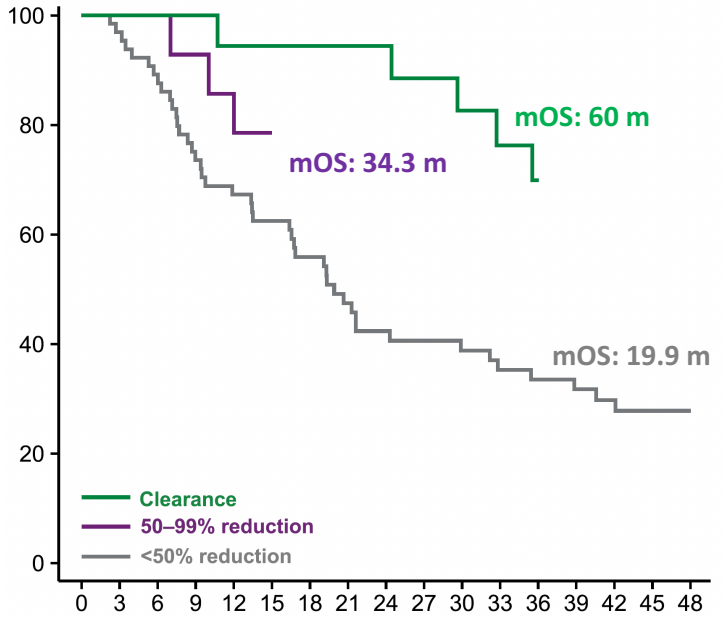
- **ctDNA: tratamiento adyuvante**

IMvigor010

ctDNA testing was performed using a personalized, tumor-informed, 16-plex mPCR-NGS assay[a]



OS by ctDNA clearance status



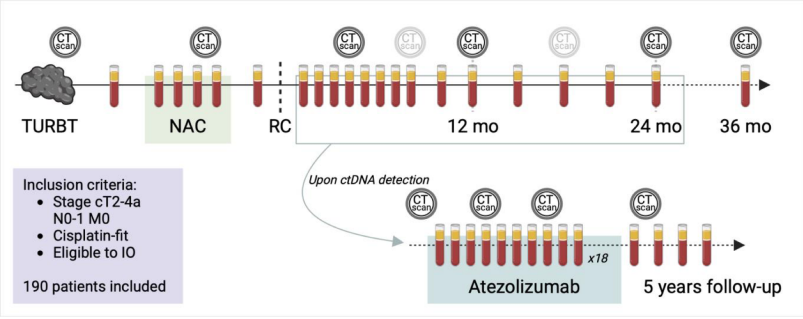
Powles T, et al. Eur Urol 2024;85:114.

CVMI

- **ctDNA: tratamiento adyuvante**

TOMBOLA

N=178



Primary endpoint: CR after treatment with immunotherapy initiated by ctDNA positive status after radical cystectomy
CR: negative ctDNA and no visible metastasis on CT

Median follow-up -> 34 months

Low-risk: ≤ ypT1 and N0
High-risk: ≥ ypT2 and/or N+

ctDNA-

70% Low-risk
30% High-risk

15% High-risk & PD-L1+

ctDNA+

50% Low-risk
50% High-risk

24% High-risk & PD-L1+

- Post-radical cystectomy -> 58% ctDNA+ (within 2 years)
- 63% were detected < 4 months post radical cystectomy
- ctDNA- patients -> only 3% developed metastases on CT-scan during follow-up
- Median lead time from ctDNA+ to imaging-confirmed recurrence: 90 days (61-961 days)

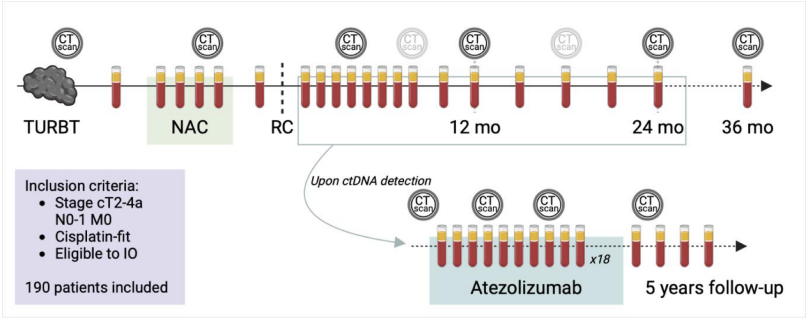
L. Dyrskjø L, et al. Ann Oncol 2026;37(5):712.

CVMI

- **ctDNA: tratamiento adyuvante**

TOMBOLA

N=178

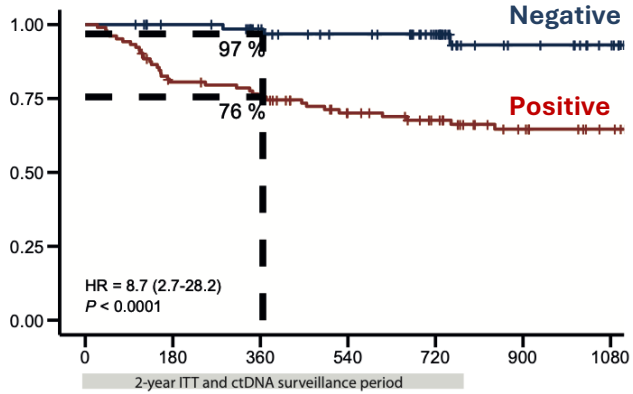


Primary endpoint: CR after treatment with immunotherapy initiated by ctDNA positive status after radical cystectomy

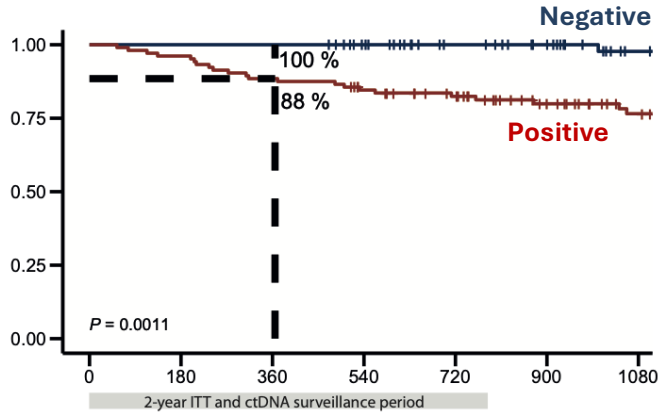
CR: negative ctDNA and no visible metastasis on CT

Median follow-up -> 34 months

RFS



OS



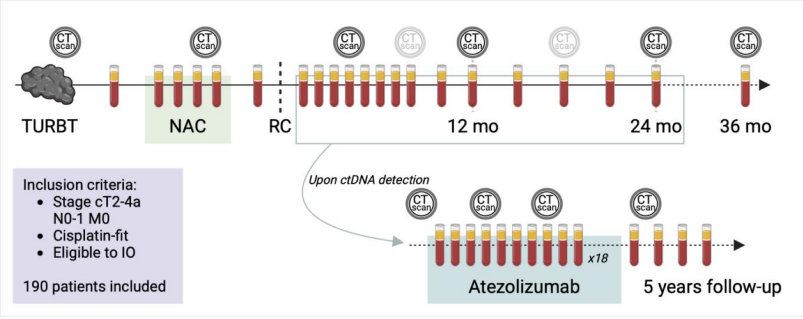
L. Dyrskjø L, et al. Ann Oncol 2026;37(5):712.

CVMI

- **ctDNA: tratamiento adyuvante**

TOMBOLA

N=178



Primary endpoint: CR after treatment with immunotherapy initiated by ctDNA positive status after radical cystectomy

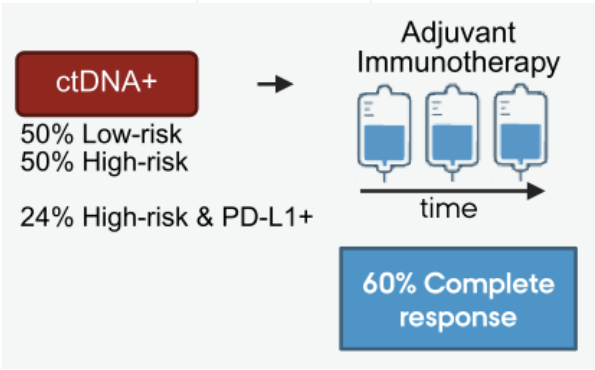
CR: negative ctDNA and no visible metastasis on CT

Median follow-up -> 34 months

Primary endpoint

NED (No evidense of disease) (CT and ctDNA-) following immunotherapy

N=84



- **ctDNA+ → treatment with atezolizumab**
  - 60% converted to ***ctDNA-*** with no evidence of disease on imaging

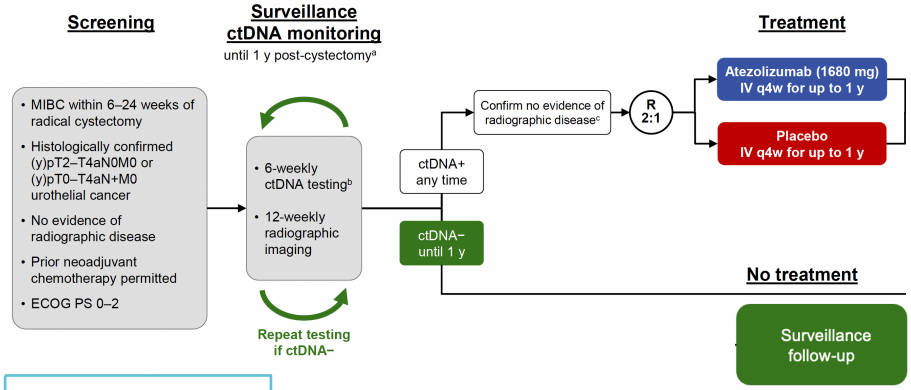
L. Dyrskjø L, et al. Ann Oncol 2026;37(5):712.

CVMI

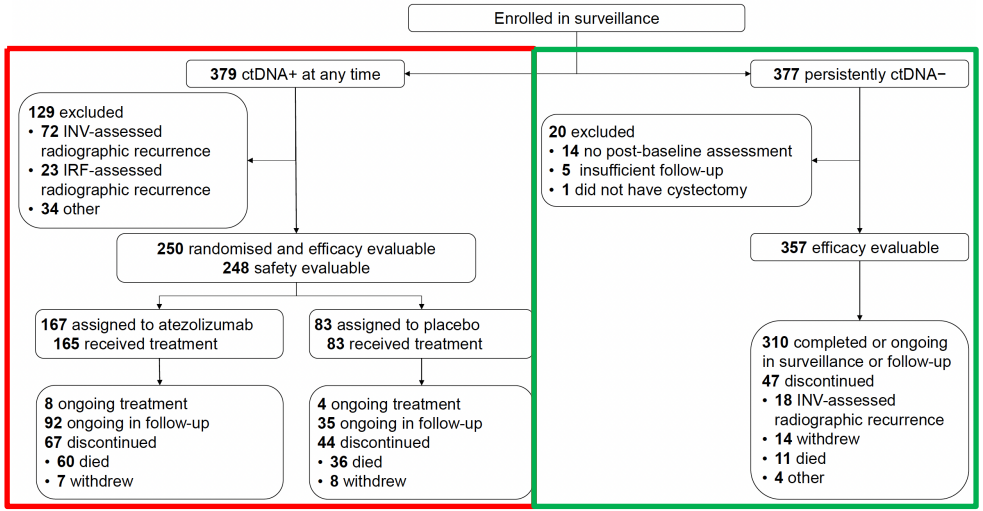
- **ctDNA: tratamiento adyuvante**

IMvigor011

N=761



Primary endpoint: DFS



All ctDNA+ (n=379)

ctDNA+ untreated (screen failed or placebo treated; n=212)

ctDNA+ randomized with ≥1 post-baseline ctDNA result (n=228)

Persistent ctDNA− (n=357)

Powles T, et al. N Engl J Med 2025;393:2395
Bellmunt J, et al. ASCO GU 2026

CVMI

- **ctDNA: tratamiento adyuvante**

IMvigor011

Characteristic		Randomised ctDNA+		Persistently ctDNA−
		Atezolizumab (n=167)	Placebo (n=83)	No treatment (n=357)
Age, median (range), y		69 (42–87)	67 (44–84)	69 (36–90)
Male, n (%)		141 (84.4)	67 (80.7)	278 (77.9)
Region, n (%)	Asia–Pacific	51 (30.5)	27 (32.5)	137 (38.4)
	Central and South America	14 (8.4)	6 (7.2)	25 (7.0)
	Europe	101 (60.5)	49 (59.0)	191 (53.5)
	North America	1 (0.6)	1 (1.2)	4 (1.1)
ECOG PS, n (%)	0	113 (67.7)	53 (63.9)	232 (65.7)
	1	52 (31.1)	29 (34.9)	110 (31.2)
	2	2 (1.2)	1 (1.2)	11 (3.1)
PD-L1 status, n (%)	IC0/1 (<5%)	108 (64.7)	53 (63.9)	189 (53.1)
	IC2/3 (≥5%)	59 (35.3)	30 (36.1)	167 (46.9)
Histological variants present, n (%)		18 (10.8)	8 (9.6)	56 (15.7)
Prior neoadjuvant chemotherapy, n (%)	Yes	80 (47.9)	33 (39.8)	168 (47.1)
	No	87 (52.1)	50 (60.2)	189 (52.9)
Tumour stage post-cystectomy, n (%)	≤T2	46 (27.5)	24 (28.9)	166 (46.8)
	T3/4	121 (72.5)	59 (71.1)	189 (53.2)
Nodal status, n (%)	Negative	71 (42.5)	35 (42.2)	285 (79.8)
	Positive	96 (57.5)	48 (57.8)	72 (20.2)
Pathological staging at cystectomy, n (%)[a]	pT2N0	8 (4.8)	3 (3.7)	62 (17.5)
	ypT2N0	15 (9.0)	5 (6.1)	61 (17.2)
	(y)pT2N+	30 (18.0)	18 (22.0)	43 (12.1)
	(y)pT3–4N0	49 (29.3)	26 (31.7)	160 (45.1)
	(y)pT3–4N+	65 (38.9)	30 (36.6)	29 (8.2)
Time from cystectomy to first ctDNA+ sample, n (%)	≤20 weeks	117 (70.1)	59 (71.1)	NA
	>20 weeks	50 (29.9)	24 (28.9)	NA
Achieved ctDNA+ status, n (%)	At initial test	99 (59.3)	49 (59.0)	NA
	At subsequent tests	68 (40.7)	34 (41.0)	NA

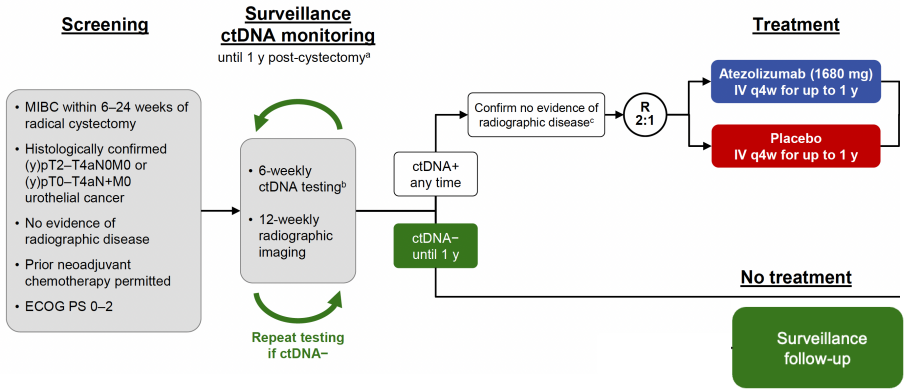
Powles T, et al. N Engl J Med 2025;393:2395.

CVMI

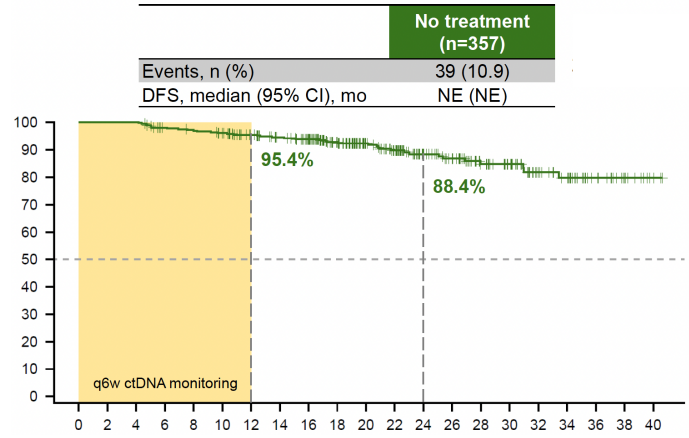
- **ctDNA: tratamiento adyuvante**

IMvigor011

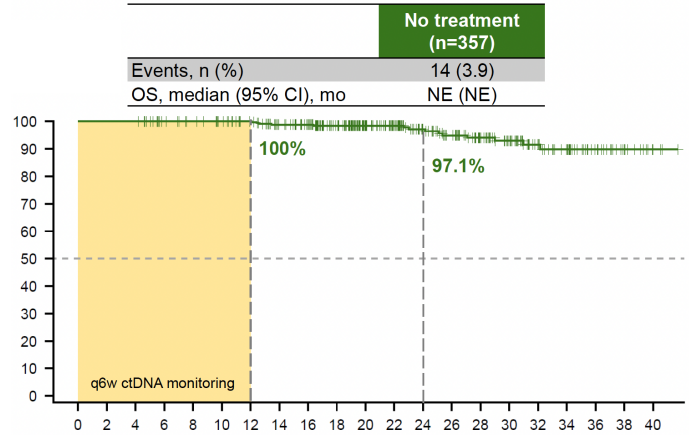
N=761



DFS



OS



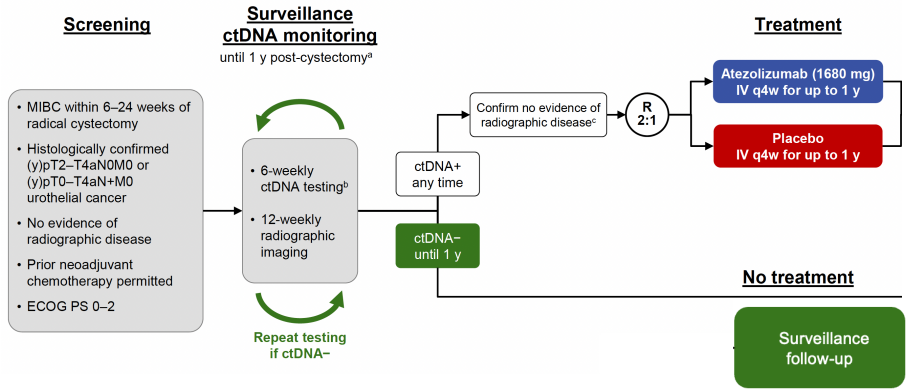
Powles T, et al. N Engl J Med 2025;393:2395.

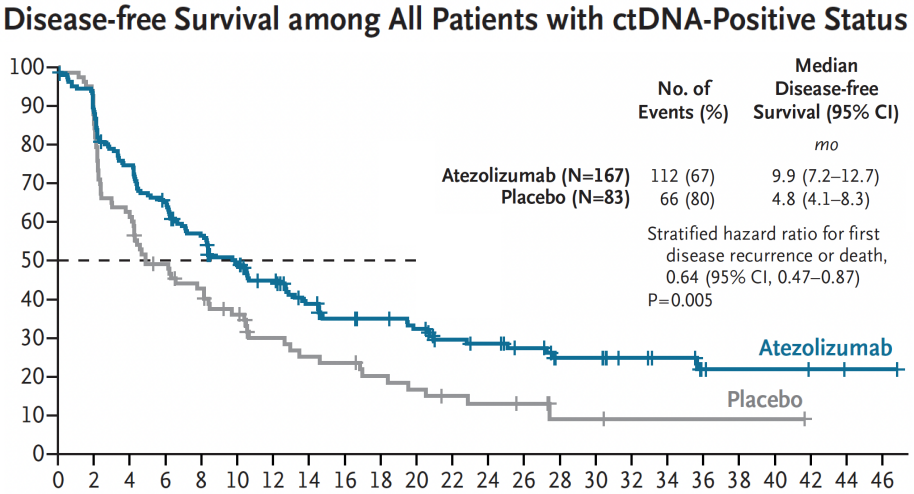
CVMI

- **ctDNA: tratamiento adyuvante**

IMvigor011

N=761





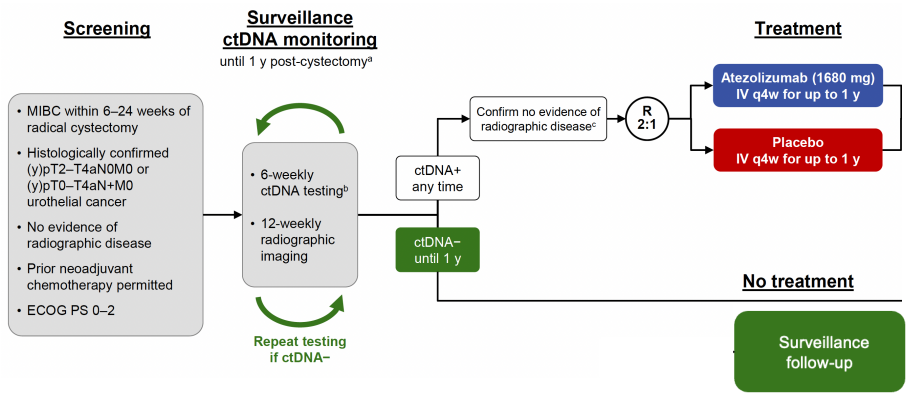
Powles T, et al. N Engl J Med 2025;393:2395.

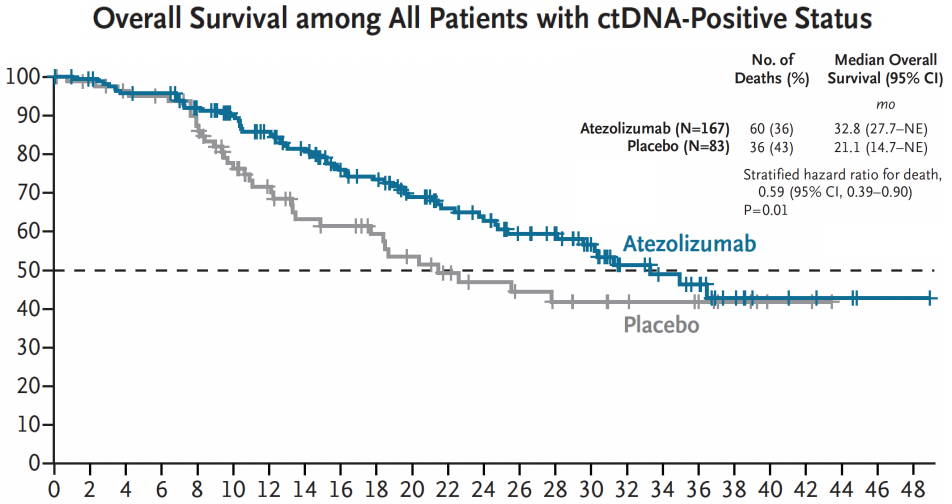
CVMI

- **ctDNA: tratamiento adyuvante**

IMvigor011

N=761





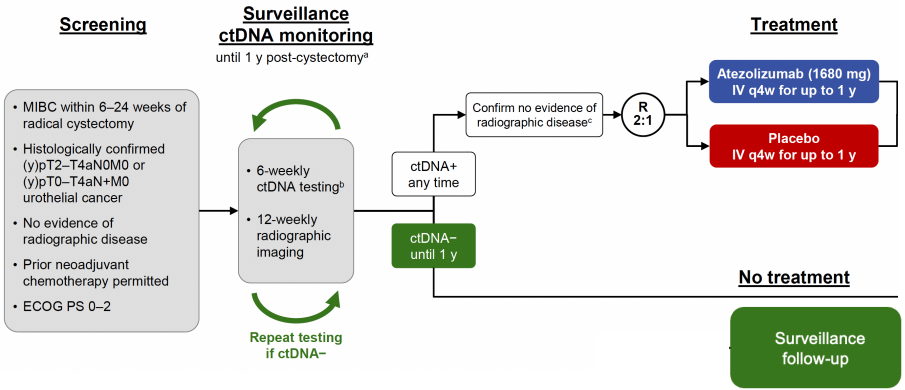
Powles T, et al. N Engl J Med 2025;393:2395.

CVMI

- **ctDNA: tratamiento adyuvante**

IMvigor011

N=761



Follow-up systemic anticancer treatments in ctDNA+

	Atezolizumab (N=167)	Placebo (N=83)
	number (percent)	
Patients with disease recurrence	106 (63)	65 (78)
Patients receiving follow-up therapy	86 (51)	45 (54)
Line of therapy completed		
First line	81 (49)	43 (52)
Second line	29 (17)	18 (22)
Third line	7 (4)	4 (5)
Fourth line	2 (1)	1 (1)
Therapy type		
Chemotherapy	61 (37)	26 (31)
Cancer immunotherapy	26 (16)	26 (31)
Antibody-drug conjugate	32 (19)	16 (19)
Other	10 (6)	4 (5)

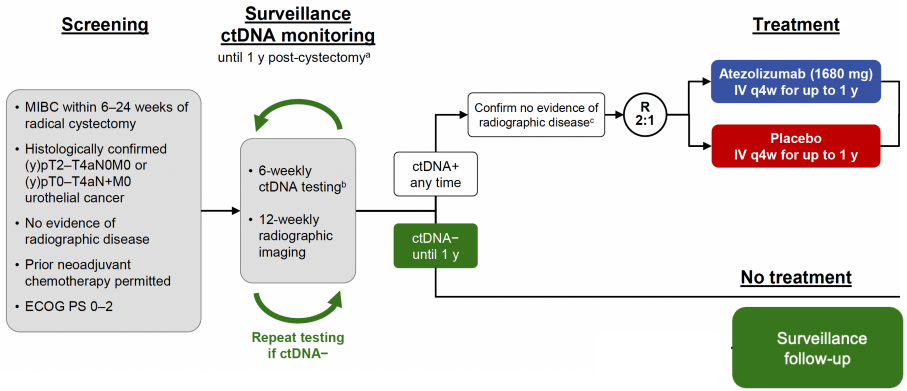
Powles T, et al. N Engl J Med 2025;393:2395.

CVMI

- **ctDNA: tratamiento adyuvante**

IMvigor011

N=761



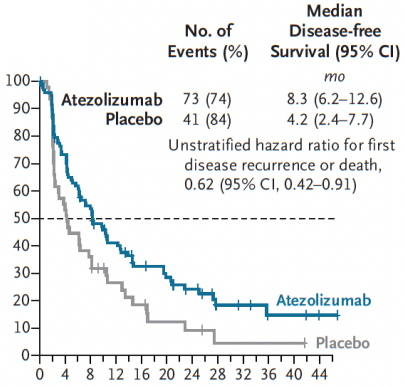
ctDNA+ at initial test

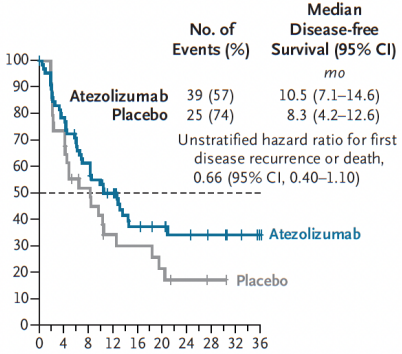
(148/250; 59.2%)

ctDNA+ at subsequent test

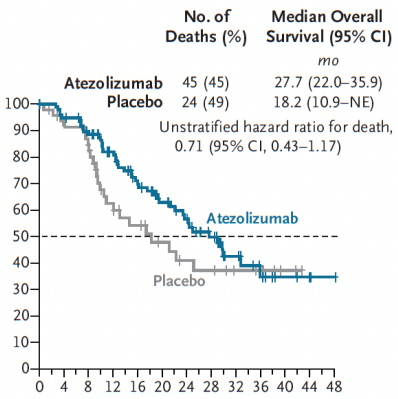
(102/250; 40.8%)

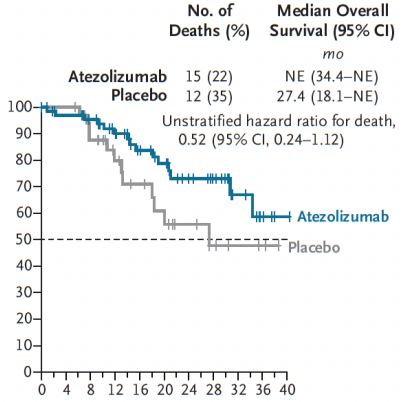
DFS





OS





Powles T, et al. N Engl J Med 2025;393:2395.

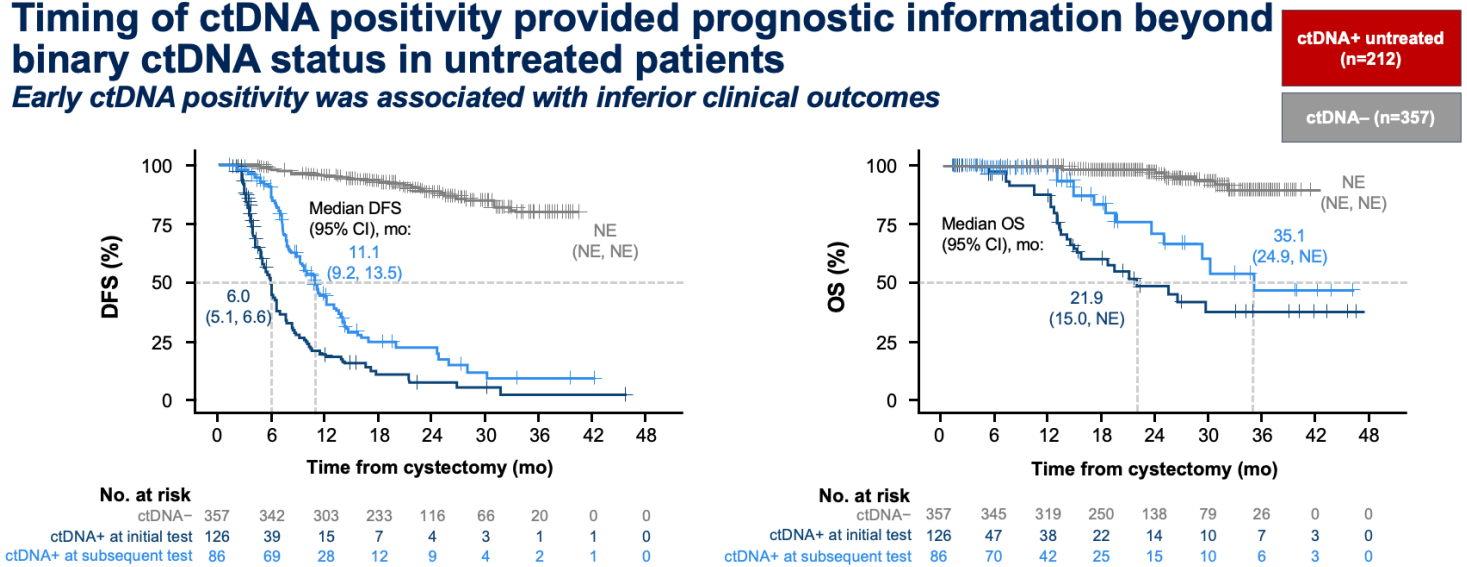
CVMI

- **ctDNA: tratamiento adyuvante**

IMvigor011

Timing of ctDNA positivity provided prognostic information beyond binary ctDNA status in untreated patients

Early ctDNA positivity was associated with inferior clinical outcomes



	DFS rate, % (no. at risk)		
Mo	ctDNA–	ctDNA+ at initial test	ctDNA+ at subsequent test
6	98.0 (342)	49.9 (39)	89.1 (69)
12	95.4 (303)	19.2 (15)	43.8 (28)
24	88.4 (116)	8.2 (4)	22.3 (9)

	OS rate, % (no. at risk)		
Mo	ctDNA–	ctDNA+ at initial test	ctDNA+ at subsequent test
6	100 (345)	96.4 (47)	98.8 (70)
12	100 (319)	87.4 (38)	98.8 (42)
24	97.1 (138)	48.5 (14)	71.8 (15)

Bellmunt J, et al. ASCO GU 2026.

CVMI

- **ctDNA: tratamiento adyuvante**

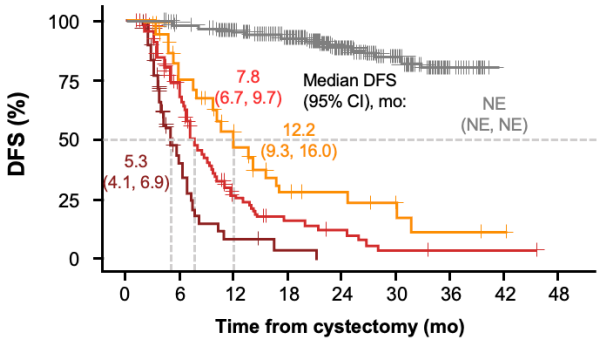
IMvigor011

ctDNA concentration provided prognostic information beyond binary ctDNA status in untreated patients

High ctDNA concentration was associated with inferior clinical outcomes

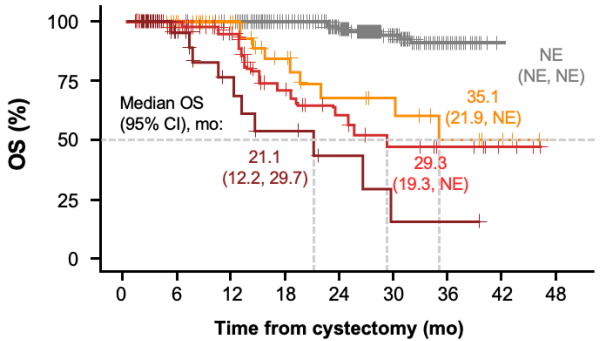
ctDNA+ untreated (n=212)

ctDNA– (n=357)



No. at risk

ctDNA–	357	342	303	233	116	66	20	0	0
≤0.1 MTM/mL	56	39	22	9	7	5	2	1	0
>0.1–≤3 MTM/mL	99	55	18	9	6	2	1	1	0
>3 MTM/mL	57	14	3	1	0	0	0	0	0



No. at risk

ctDNA–	357	345	319	250	138	79	26	0	0
≤0.1 MTM/mL	56	40	30	18	11	9	5	3	0
>0.1–≤3 MTM/mL	99	59	40	23	15	10	7	3	0
>3 MTM/mL	57	18	10	6	3	1	1	0	0

DFS rate, % (no. at risk)

Mo	ctDNA–	≤0.1 MTM/mL	>0.1–≤3 MTM/mL	>3 MTM/mL
6	98.0 (342)	82.1 (39)	71.2 (55)	44.0 (14)
12	95.4 (303)	53.4 (22)	26.6 (18)	9.4 (3)
24	88.4 (116)	28.4 (7)	13.2 (6)	0 (0)

OS rate, % (no. at risk)

Mo	ctDNA–	≤0.1 MTM/mL	>0.1–≤3 MTM/mL	>3 MTM/mL
6	100 (345)	100 (40)	97.2 (59)	95.2 (18)
12	100 (319)	100 (30)	95.0 (40)	76.0 (10)
24	97.1 (138)	67.4 (11)	60.1 (15)	42.6 (3)

Bellmunt J, et al. ASCO GU 2026.

CVMI

- **ctDNA: tratamiento adyuvante**

IMvigor011

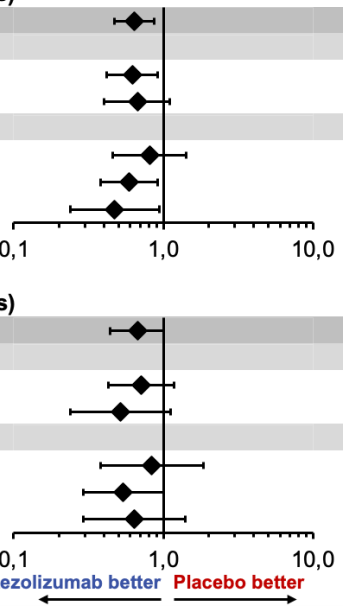
Atezolizumab had similar efficacy regardless of ctDNA+ timing or concentration

DFS

	Atezolizumab n	Atezolizumab Median (months)	Placebo n	Placebo Median (months)	DFS HR (95% CI)[a]
All patients	167	9.9	83	4.8	0.64 (0.47, 0.87)
Timing of ctDNA+ status					
ctDNA+ at initial test	99	8.3	49	4.2	0.62 (0.42, 0.91)
ctDNA+ at subsequent test	68	10.5	34	8.3	0.67 (0.40, 1.10)
ctDNA concentration (MTM/mL)					
≤0.1	59	12.6	28	10.5	0.81 (0.46, 1.42)
>0.1–≤3	77	8.5	39	4.5	0.59 (0.38, 0.91)
>3	31	8.1	16	2.3	0.47 (0.24, 0.94)

OS

	Atezolizumab n	Atezolizumab Median (months)	Placebo n	Placebo Median (months)	OS HR (95% CI)[a]
All patients	167	32.8	83	21.1	0.67 (0.44, 1.01)
Timing of ctDNA+ status					
ctDNA+ at initial test	99	27.7	49	18.2	0.71 (0.43, 1.17)
ctDNA+ at subsequent test	68	NA	34	27.4	0.52 (0.24, 1.12)
ctDNA concentration (MTM/mL)					
≤0.1	59	34.4	28	NA	0.83 (0.38, 1.85)
>0.1–≤3	77	35.9	39	21.1	0.54 (0.29, 1.01)
>3	31	24.3	16	10.9	0.64 (0.29, 1.40)



[a]All analyses shown in the forest plots are unstratified. The subgroup HRs are shown relative to an unstratified analysis of all randomized patients who tested ctDNA+. NA, not available.

Bellmunt J, et al. ASCO GU 2026.

CVMI

- **ctDNA: tratamiento adyuvante**

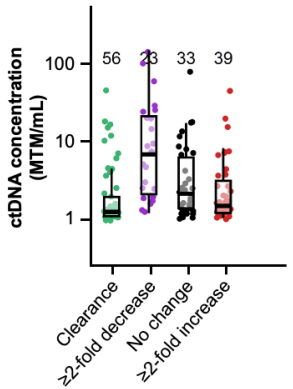
IMvigor011

Atezolizumab: ctDNA reduction or clearance was associated with improved DFS

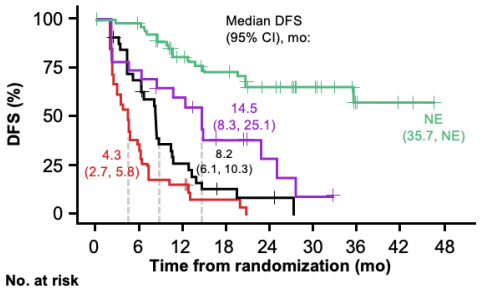
Many patients reduced or cleared ctDNA from high pre-treatment concentration

ctDNA+ randomized (n=228)

Maximum pre-treatment ctDNA concentration



DFS



No. at risk									
Clearance	56	53	37	29	21	15	4	2	0
≥2-fold decrease	23	17	12	6	3	1	0	0	0
No change	33	22	8	3	2	0	0	0	0
≥2-fold increase	39	13	6	2	0	0	0	0	0

DFS rate, % (no. at risk)				
Mo	Clearance	≥2-fold decrease	No change	≥2-fold increase
6	98.2 (53)	73.9 (17)	69.0 (22)	33.3 (13)
12	80.7 (37)	59.9 (12)	26.4 (8)	15.4 (6)
24	65.5 (21)	28.8 (3)	8.8 (2)	0

Pre-treatment ctDNA concentration was defined as the maximum ctDNA concentration measured during surveillance or at C1D1. ctDNA dynamic categories are defined as the maximum observed change from pre-treatment to any single time point during C2–C11 (best ctDNA change). No change was defined as any fluctuation in ctDNA concentration that did not meet criteria for >2-fold increase or >2-fold decrease.

Bellmunt J, et al. ASCO GU 2026.

CVMI

- **ctDNA: tratamiento adyuvante**

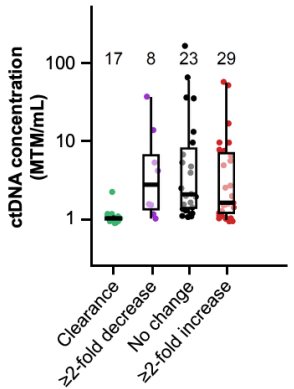
IMvigor011

Placebo: ctDNA clearance was associated with improved DFS

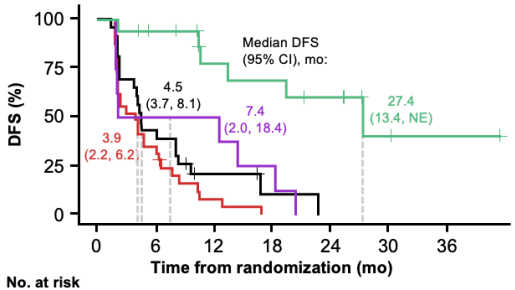
Patients who cleared ctDNA represent a prognostically favorable subgroup with low pre-treatment ctDNA concentration

ctDNA+ randomized (n=228)

Maximum pre-treatment ctDNA concentration



DFS



No. at risk							
Clearance	17	14	9	8	6	2	1
≥2-fold decrease	8	4	4	2	0	0	0
No change	23	10	3	1	0	0	0
≥2-fold increase	29	10	2	0	0	0	0

DFS rate, % (no. at risk)

Mo	Clearance	≥2-fold decrease	No change	≥2-fold increase
6	94.1 (14)	50.0 (4)	43.5 (10)	34.5 (10)
12	77.6 (9)	50.0 (4)	20.9 (3)	7.9 (2)
24	60.4 (6)	0	0	0

Pre-treatment ctDNA concentration was defined as the maximum ctDNA concentration measured during surveillance or at C1D1. ctDNA dynamic categories are defined as the maximum observed change from pre-treatment to any single time point during C2–C11 (best ctDNA change). No change was defined as any fluctuation in ctDNA concentration that did not meet criteria for >2-fold increase or >2-fold decrease.

Bellmunt J, et al. ASCO GU 2026.

CVMI

- **ctDNA: tratamiento adyuvante**

CheckMate274

N=709

Key inclusion criteria

- Patients with ypT2-ypT4a or ypN+ MIUC who had neoadjuvant cisplatin chemotherapy
- Patients with pT3-pT4a or pN+ MIUC without prior neoadjuvant cisplatin chemotherapy and not eligible/refuse adjuvant cisplatin chemotherapy
- Radical surgery within the past 120 days
- Disease-free status within 4 weeks of dosing

Stratification factors

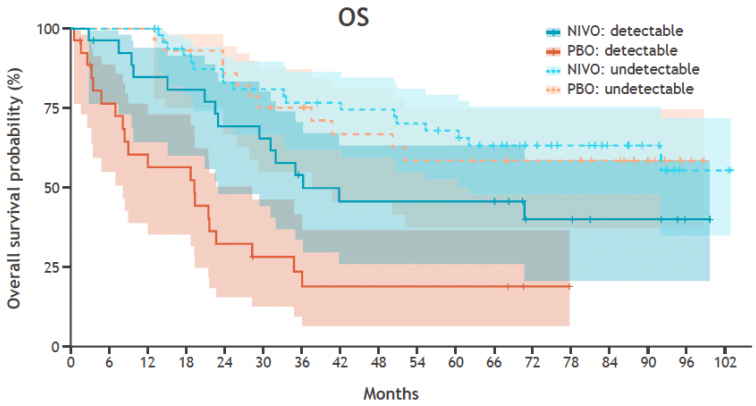
- PD-L1 status (<1% vs ≥ 1%)[a]
- Prior neoadjuvant cisplatin-based chemotherapy
- Nodal status

R 1:1 → NIVO IV 240 mg Q2W / PBO IV Q2W

- Two primary objectives
  - To compare **DFS for NIVO versus PBO in all randomized patients (ITT)**
  - To compare **DFS for NIVO versus PBO in all randomized patients with PD-L1 ≥ 1%**

Median follow-up -> 60 months

- ctDNA analysis was performed on 133 of 709 randomized patients (18.8%)
  54 of 133 patients (40.6%) had detectable ctDNA



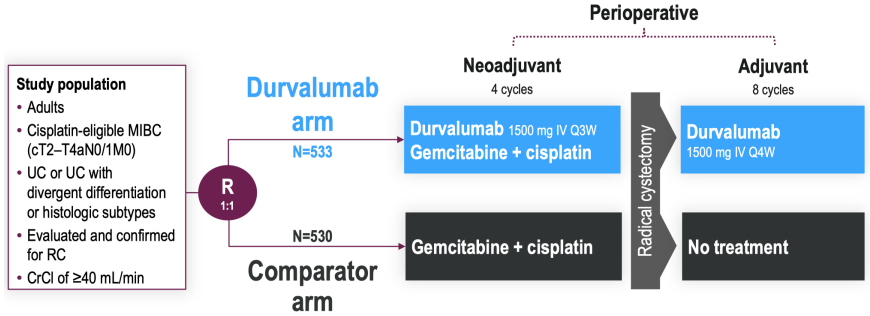
ctDNA detectable	NIVO (n = 27)	PBO (n = 27)
Median OS (95% CI), months	36.2 (23.0-NE)	19.3 (8.1-28.2)
OS HR (95% CI)	0.41 (0.20-0.83)	
ctDNA undetectable	**NIVO (n = 50)**	**PBO (n = 29)**
Median OS (95% CI), months	NR (62.0-NE)	NR (40.7-NE)
OS HR (95% CI)	0.87 (0.41-1.84)	

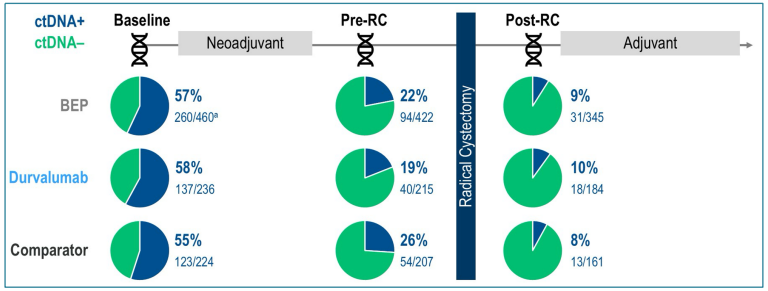
Galsky MD, et al. Ann Oncol 2026;37:69.

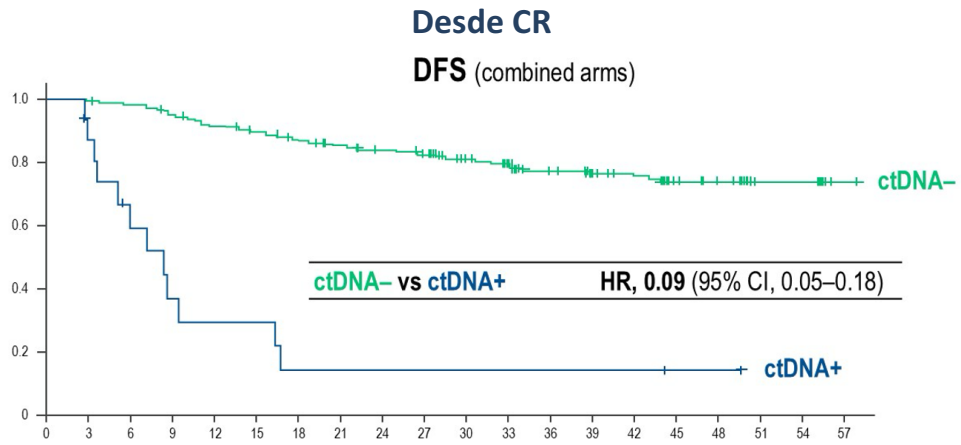
CVMI

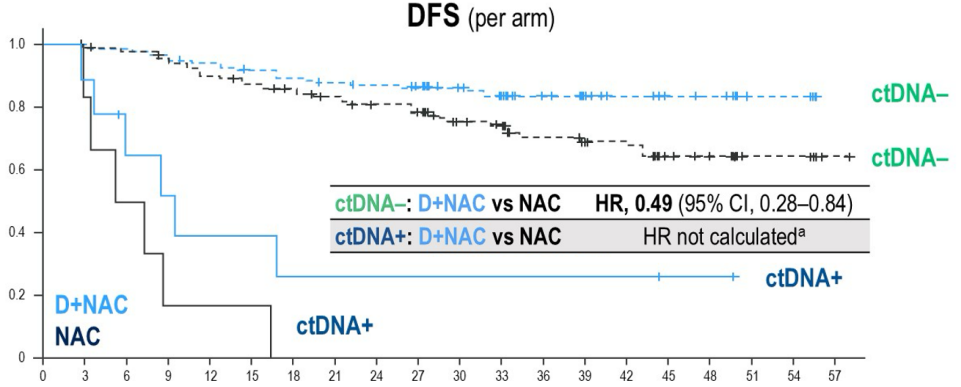
- **ctDNA: tratamiento adyuvante**

NIAGARA









Powles T, et al. ASCO 2025.

CVMI

- **ctDNA: tratamiento adyuvante**

✓ **OBJETIVO** tratamiento del CVMI -> **CURACIÓN** (+ mantener vejiga funcionante)

✓ 50% ya tendrán micrometástasis al diagnóstico.

✓ Tratamiento peri-operatorio -> aumenta SG ¿Debemos tratar a todos con todo?

✓ Selección de pacientes en adyuvancia determinada por:
- Riesgo patológico
- Enfermedad mínima residual medida con ctDNA

ESTRATEGIAS ADAPTADAS AL RIESGO

- **ctDNA: tratamiento adyuvante**

✓ **ctDNA** (SIGNATERA):

- Factor pronóstico en tratamiento post-operatorio con inmunoterapia
  ¡OJO! ≈ 12% de pacientes ctDNA- recaen a los 2 años (IMvigor011)

- ¿Factor predictivo?
  - IMvigor011 -> sí en los ctDNA+
  - NIAGARA no; CM-274 sí (exploratorios y n muy pequeña)
  - Tratamiento de la recidiva de forma precoz antes de imagen -> ¿nuevas terapias en 1L?
  - Aclaramiento de ctDNA -> ¿duración del tratamiento adyuvante? ¿cambio?
  - ¿Costo-efectivo?
  - ¿Cómo incorporarlo a las nuevas terapias peri-operatorias? -> EVP
  - ¿Válido para la preservación vesical tras neoadyuvancia?

7th ANNUAL UC COURSE

Emerging personalized therapies for the management of urothelial carcinomas

7th MAY 2026
MADRID

El papel del ctDNA en la decisión del tratamiento postoperatorio del CVMI.

Begoña Pérez Valderrama
Oncología Médica. Hospital Universitario Virgen del Rocío, Sevilla.