CAMPUS SEOM

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Cáncer de vejiga

Dra. Begoña Pérez-Valderrama
Hospital Universitario Virgen del Rocío. Sevilla

SEOM Sociedad Española de Oncología Médica

CONFLICTOS DE INTERÉS

- ✓ *Consultant or Advisory Role: Astellas Pharma, AAA, Pfizer, Bristol-Myers-Squibb, Ipsen, Sanofi, MSD, Recordati, Bayer, Merck*
- ✓ *Speaking honoraria: Bristol-Myers-Squibb, Ipsen, Astellas Pharma, Bayer; Pfizer-Merck Alliance, Astra Zeneca*
- ✓ *Travel/Accommodations: Bristol-Myers-Squibb, Merck*

Cáncer de vejiga músculo-infiltrante

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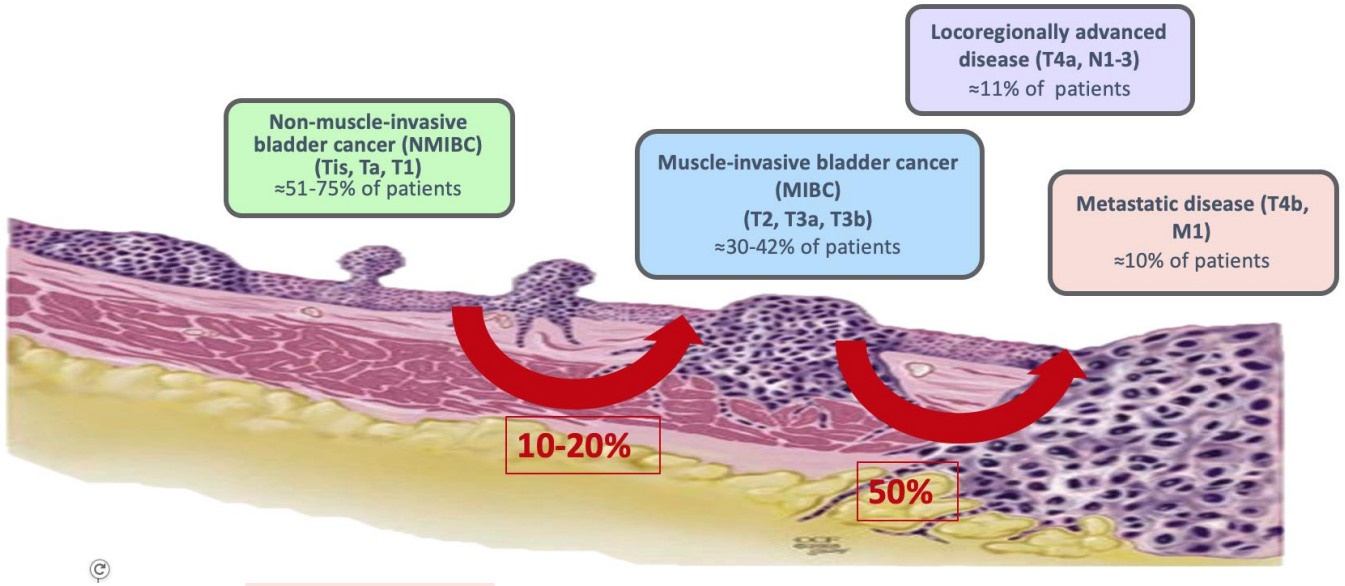
Tratamiento peri-operatorio

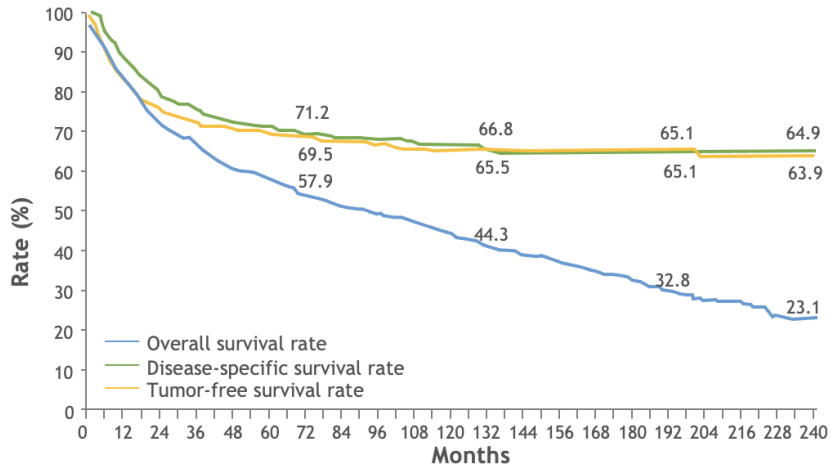
- Cistectomía radical



Cistectomía radical + linfadectomía pélvica es el tratamiento estándar del carcinoma de vejiga músculo-invasivo cT2-T4a N0 M0
(IA)

Control pélvico a 5 años del 80%.
Supervivencia Global a 5 años del 40-60%.
Complicaciones postoperatorias: 50-60%.
Mortalidad a 90 días: ~5%.
Impacto en calidad de vida e imagen corporal.

Overall, disease-specific, and recurrence-free survival rate for the complete series of 1100 patients



Adapted from Knowles & Hurst. Nature Rev Cancer 2015.
Howlader N, et al. (eds). SEER Cancer Statistics Review 1975–2013.
Powles T, et al. Ann Oncol 2021;33(3):244.
Lee RK, et al. BJU Int 2014;113(1):11.
Hautmann RE, et al. Eur Urol 2012;61:1039.

Cáncer de vejiga músculo-infiltrante

Tratamiento peri-operatorio

Quimioterapia

Neoadjuvant treatment

- Tto precoz de met. subclínicas
  - Menor masa tumoral
- QT llega al tumor y linfáticos
- Mejor PS del paciente (?)
- Testa quimiosensibilidad in vivo
  - Probar nuevas drogas
- Podría ↑ conservación vesical
  - Valor pronóstico de pT0

→ **Radical cystectomy** →

Adjuvant treatment

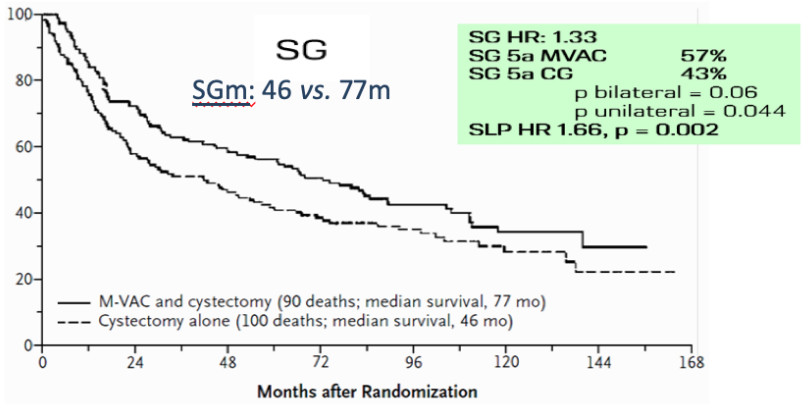
- No se demora el tratamiento quirúrgico estándar
  - Tpo diagnóstico - CG < 3 m.
  - RG a QT no es del 100%
- Tratamiento precoz de las metástasis subclínicas
- Mejor selección de pacientes de riesgo
  - Informe AP de cistectomía
  - MK moleculares
- Mejor PS del paciente (?)

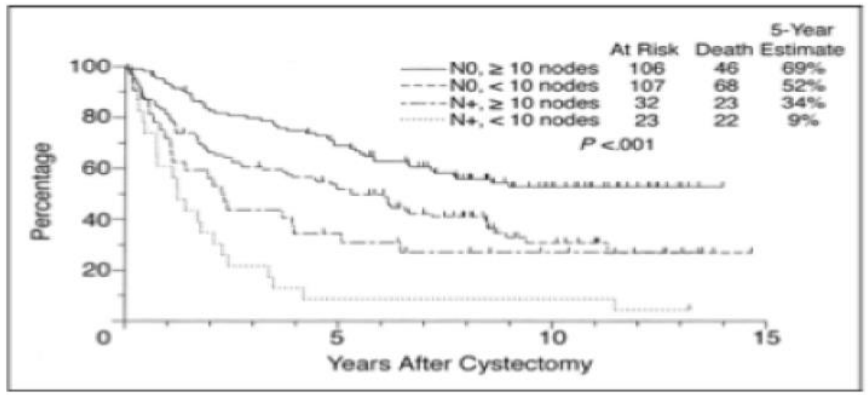
QT basada en cisplatino

Neoadyuvancia

SWOG 8710

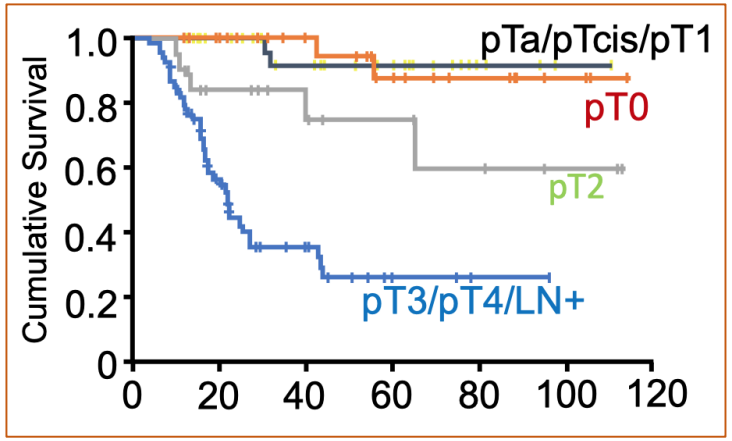
- ✓ MVAC x 3 -> CR *vs.* CR
- ✓ N=317 cT2-T4aN0M0





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

pT0=24%



Grossman HB, et al. N Engl J Med 2003;349:859.
Herr HW, et al. J Clin Oncol 2004;22:2781.

Cáncer de vejiga músculo-infiltrante

Tratamiento peri-operatorio

Quimioterapia

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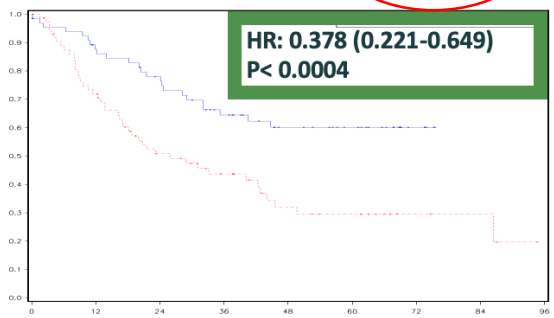
  - MK moleculares
- Mejor PS del paciente (?)

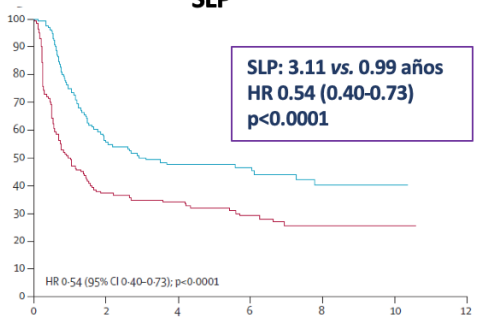
Adyuvancia

SOWG	pT1-2N0 (p53+)	CG ± 3 MVAC
Grupo Italiano:	G3pT2-4, N+	CG ± 4 Cis-Gem
SOGUG	pT3-4, N+	CG ± 4 Taxol-Cis-Gem
EORTC 30994 :	pT3-4 ó N+	CG +/-± HDMVAC o Cis-Gem

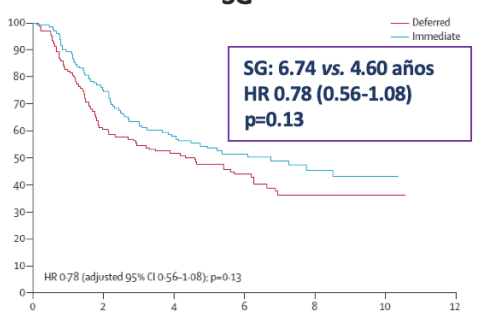
SG



SLP



SG

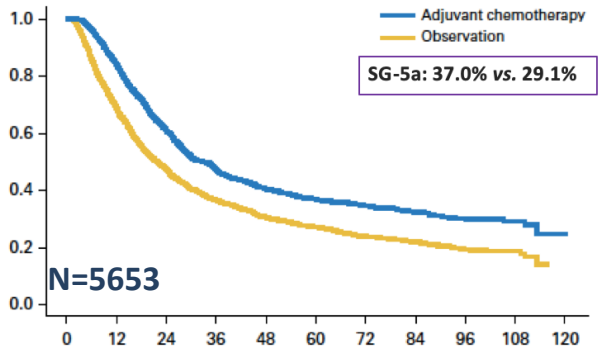


QT basada en cisplatino

Table 2. Effect of Adjuvant Chemotherapy on OS in Patients With ≥ pT3 and/or pN+ Bladder Cancer Postcystectomy

Model	Adjuvant Chemotherapy Versus Observation: Sample Size	HR (95% CI)
Unadjusted	1,293 *v* 4,360	0.72 (0.67 to 0.78)
Propensity score–based models*		
Adjusted	1,293 *v* 4,360	0.70 (0.65 to 0.76)
Stratified	1,293 *v* 4,360	0.70 (0.64 to 0.76)
Weighted (IPTW)	1,293 *v* 4,360	0.72 (0.69 to 0.76)
Matched†	1,293 *v* 2,080	0.61 (0.55 to 0.68)

SG



Paz-Ares LG, et al. J Clin Oncol 2010;28:18s (LBA4518).
Sternberg C, et al. Lancet Oncol 2015;16:76.
Galsky MD, et al. J Clin Oncol 2016;34(8):825.

Cáncer de vejiga músculo-infiltrante

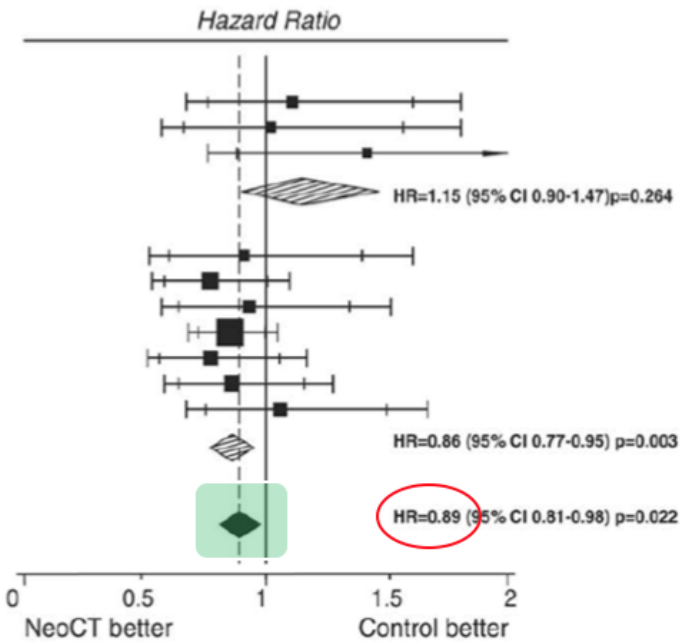
Tratamiento peri-operatorio

- Quimioterapia

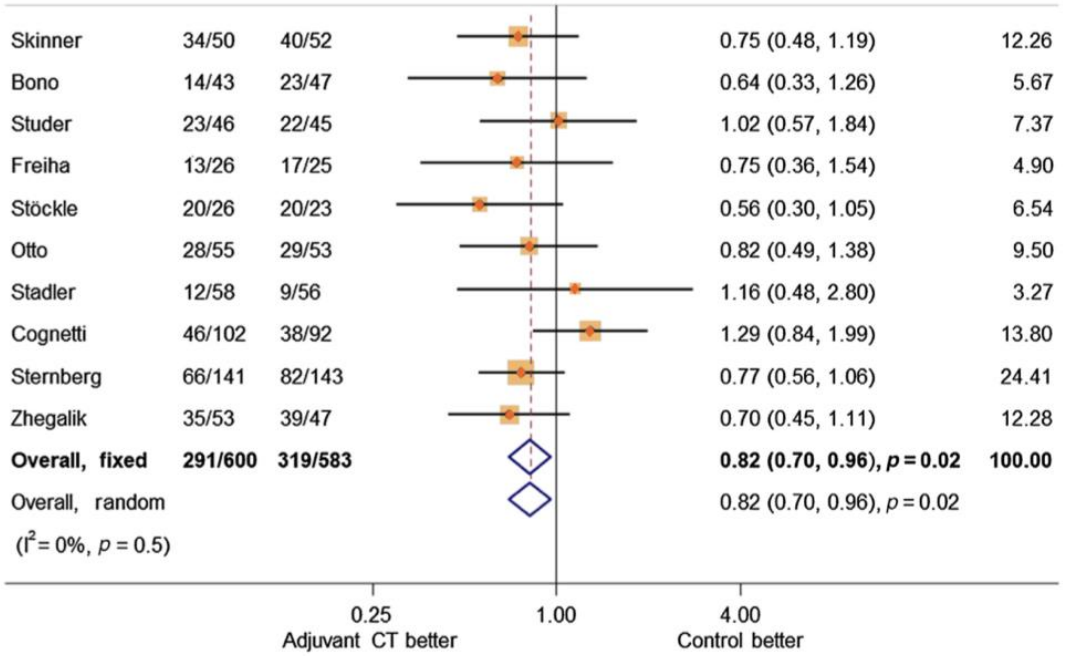
Neoadyuvancia

	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%



Adyuvancia



HR 0.82; 95%IC 0.70-0.96; p=0.02

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

Cáncer de vejiga músculo-infiltrante

Tratamiento peri-operatorio

Quimioterapia

GETUF/AFO V05 VESPER

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)

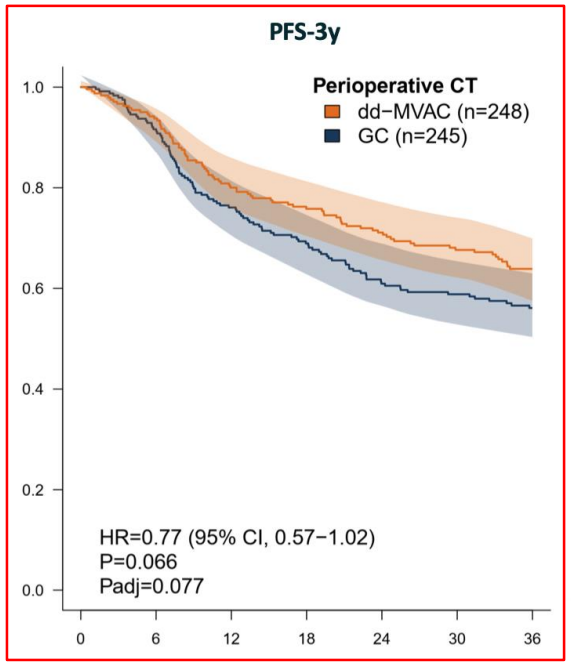
Primary Endpoint: PFS-3y

Radical cystectomy

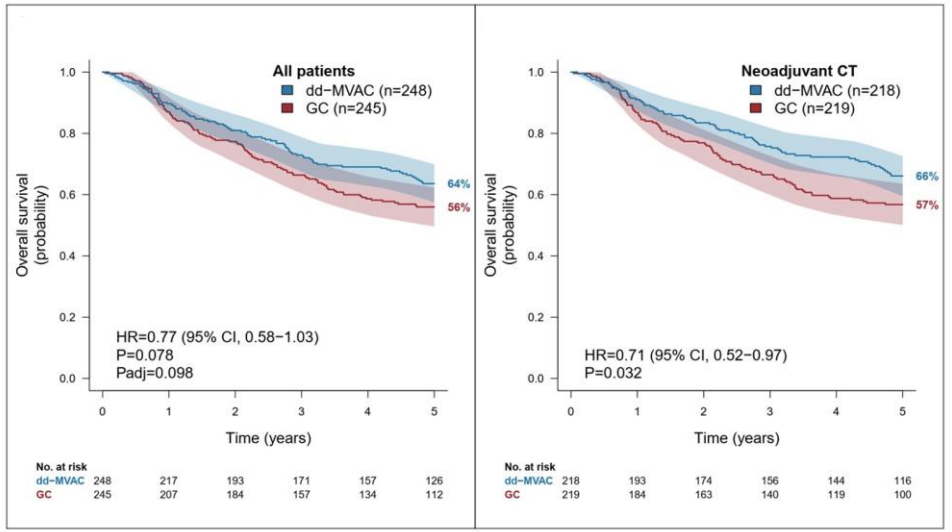
Median follow-up -> 40 months

Neoadjuvant N=437 (89%)

Adjuvant N=56 (11%)



OS-5y



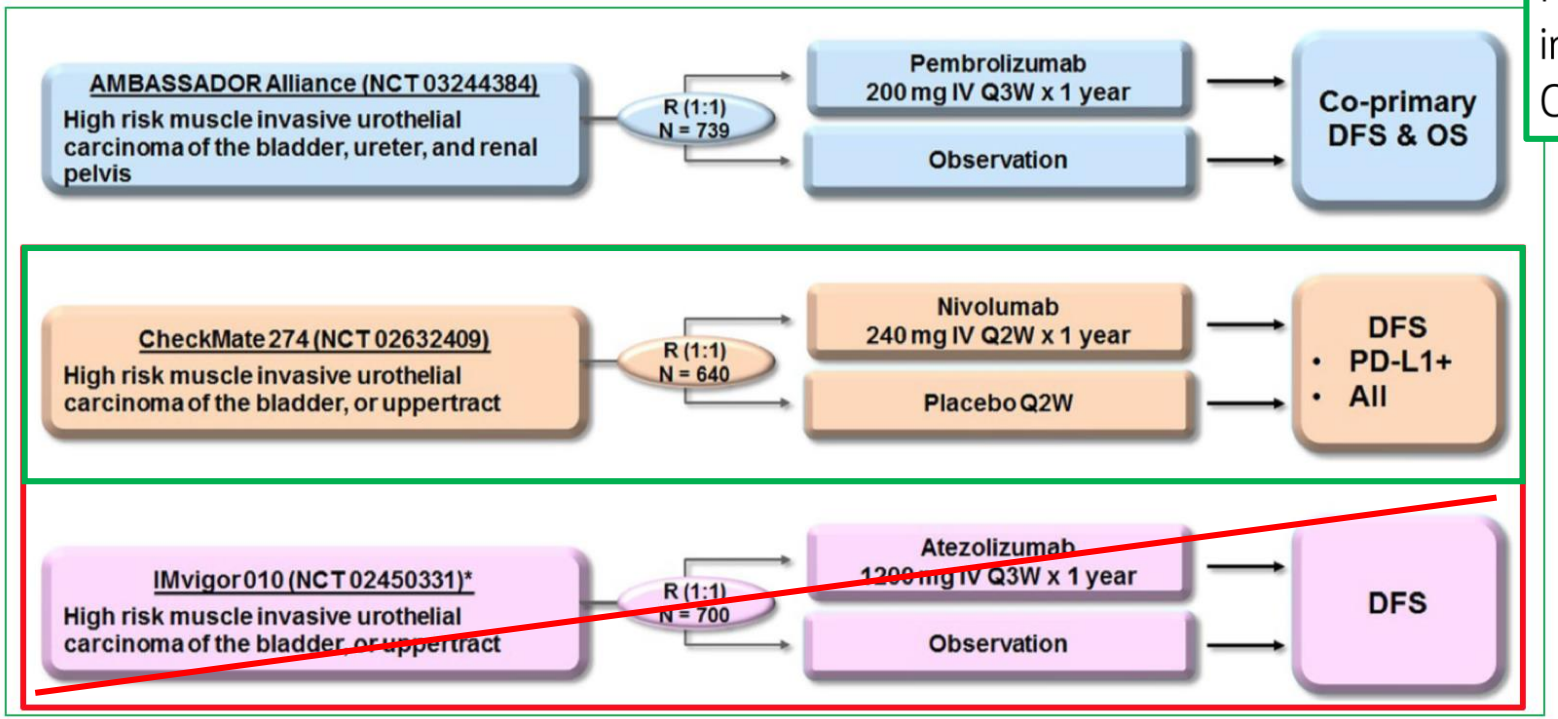
	GC (n = 198)	dd-MVAC (n = 199)		p value
Complete response				
ypT0 pN0	71 (36%)	84 (42%)	*p=0.2*	0.021
ypTis or ypTa or ypT1 and ypN0		42 (21%)		
≥ypT2 and ypN0	63 (32%)	51 (26%)		
ypN+	35 (18%)	20 (10%)		
Uncertain staging	2	2		
Non-muscle invasive				
<ypT2 pN0	98 (49%)	126 (63%)		0.007
≥ypT2 or ypN+	99 (50%)	72 (36%)		
Uncertain staging	1	1		
Organ-confined disease				
<ypT3 pN0	124 (63%)	154 (77%)		0.001
≥ypT3 or ypN+	73 (37%)	43 (22%)		
Uncertain staging	1	2		

Pfister C, et al. Ann Oncol 2021;32(suppl_5):S678-S724.
Pfister C, et al. J Clin Oncol 2023;41 (suppl 6; abstr 4507).

Cáncer de vejiga músculo-infiltrante

Adyuvancia

Inmunoterapia



Merck's KEYTRUDA® (pembrolizumab) Met Primary Endpoint of Disease-Free Survival (DFS) in Certain Patients With Muscle-Invasive Urothelial Carcinoma (MIUC) After Surgery

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.
https://www.merck.com/news/mercks-keytruda-pembrolizumab-met-primary-endpoint-of-disease-free-survival-dfs-in-certain-patients-with-muscle-invasive-urothelial-carcinoma-miuc-after-surgery.

Cáncer de vejiga músculo-infiltrante

Adyuvancia

Inmunoterapia

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

R 1:1 → PBO IV Q2W

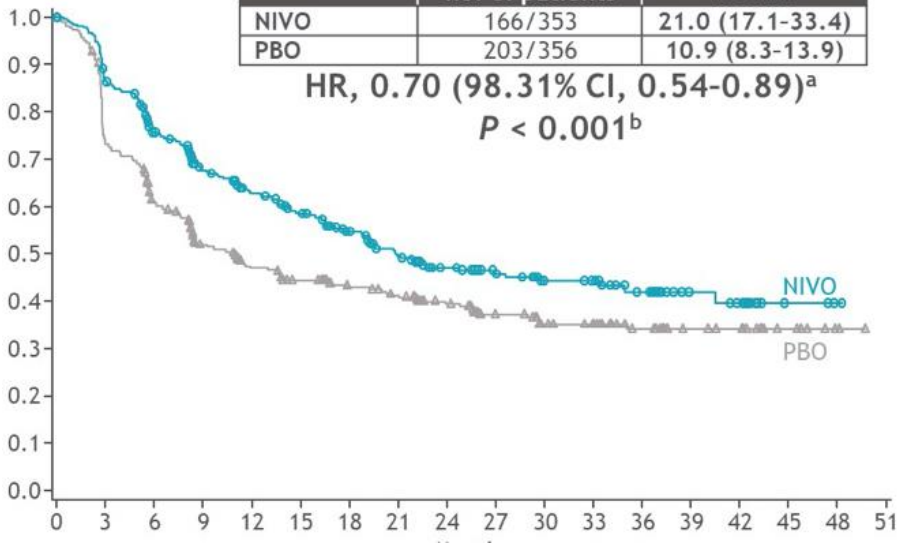
- Two primary objectives
  - To compare **DFS** for NIVO versus PBO in all randomized patients (ITT)
  - To compare **DFS** for NIVO versus PBO in all randomized patients with PD-L1 ≥ 1%

Median follow-up -> 20.9 (NIVO) and 19.5 (PLACEBO)

DFS ITT

	No. of events/ no. of patients	Median (95% CI), months
NIVO	166/353	21.0 (17.1-33.4)
PBO	203/356	10.9 (8.3-13.9)

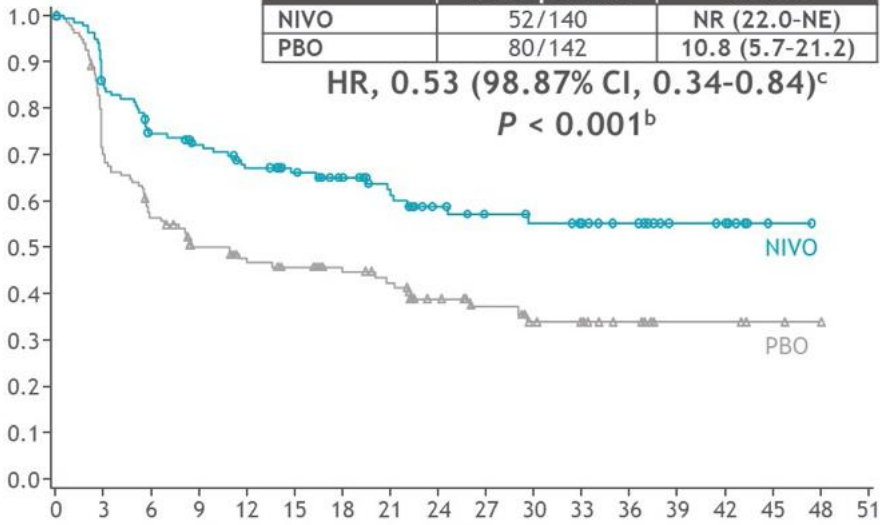
HR, 0.70 (98.31% CI, 0.54-0.89)[a]
P < 0.001[b]



DFS PDL1+

	No. of events/ no. of patients	Median (95% CI), months
NIVO	52/140	NR (22.0-NE)
PBO	80/142	10.8 (5.7-21.2)

HR, 0.53 (98.87% CI, 0.34-0.84)[c]
P < 0.001[b]



Bajorin DF, et al. N Engl J Med 2021;384(22):2102.

Cáncer de vejiga músculo-infiltrante

Tratamiento peri-operatorio

- Nuevos esquemas y combos

RE-DESIGNING NEOADJUVANT TRIALS

NEOADJUVANT → ADJUVANT

NCT03732677
NCT03661320
NCT03924856

NIAGARA
A Phase III study of Neodjuvant Durvalumab & Gemcitabine+Cisplatin vs Gemcitabine+Cisplatin **Followed by Adjuvant** Durvalumab Alone in MIBC

CA017-078
Phase III Study of Neoadjuvant Chemotherapy vs Neoadjuvant Chemotherapy & Nivolumab or Nivolumab & IDO inhibitor, **Followed by Adjuvant** Nivolumab or Nivolumab & IDO inhibitor in MIBC

KEYNOTE 866
A Phase III study of Neodjuvant Pembrolizumab & Gemcitabine+Cisplatin vs Placebo & Gemcitabine+Cisplatin **Followed by Adjuvant** Pembrolizumab Alone in MIBC

Primary endpoints: pRC and DFS

From Drakaki A. ASCO 2019.

Cáncer de vejiga músculo-infiltrante

Tratamiento peri-operatorio

- Nuevos esquemas y combos

RE-DESIGNING NEOADJUVANT TRIALS

NEOADJUVANT

ADJUVANT

KEYNOTE-B15/EV-304
Phase 3, Randomized, Open-label Study to Evaluate Perioperative Enfortumab Vedotin Plus Pembrolizumab versus neoadjuvant gemcitabine and cisplatin in cisplatin-eligible participants with muscle-invasive bladder cancer

KEYNOTE-905/EV-303
Perioperative pembrolizumab plus cystectomy or perioperative pembrolizumab plus enfortumab vedotin in cisplatin-inelegible participants with muscle-invasive bladder cancer

CA045-009
A study of nivolumab plus bepegaldesleukin (Bempeg/NKTR-214) vs nivolumab alone vs standard of care in participants with bladder cancer that has invaded the muscle wall of the Bladder and who cannot get cisplatin, a type of medicine given to treat Bladder cancer

NCT04700124
NCT03924895
NCT04209114

Cáncer de vejiga músculo-infiltrante

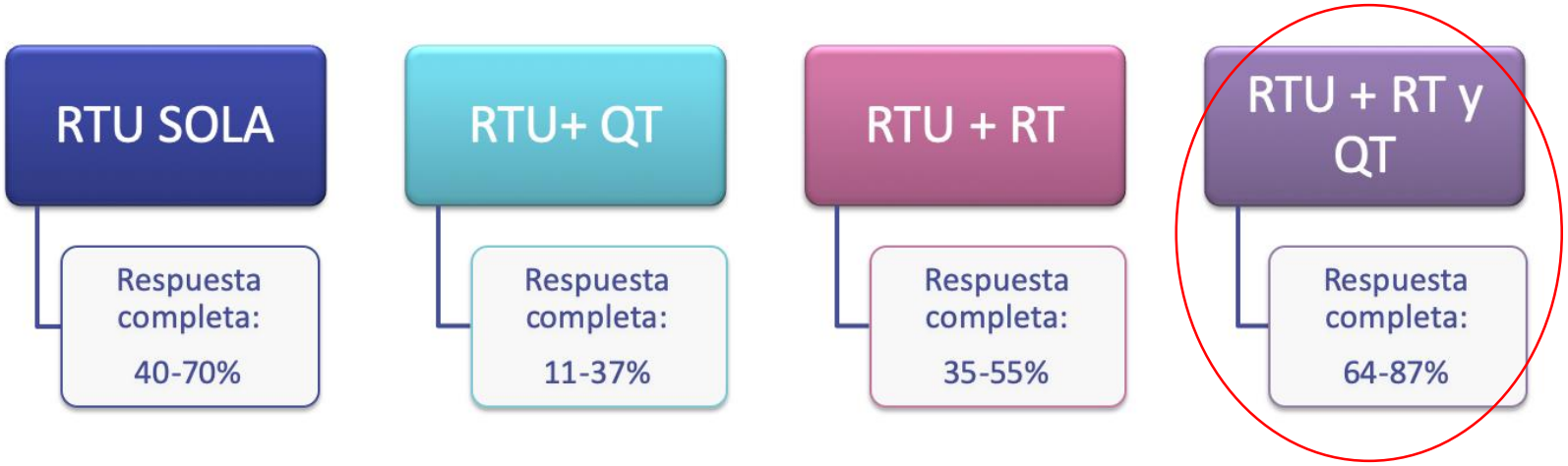
Preservación vesical

- **Estrategias**

  - ✓ **Cirugía**
    - ✓ RTU completa
    - ✓ Cistectomía parcial.

  - ✓ **Radioterapia**
    - ✓ RT externa
    - ✓ Braquiterapia

  - ✓ **Terapia combinada**
    - ✓ RTU + RT
    - ✓ RTU + QT
    - ✓ RTU + RT + QT -> **terapia trimodal**

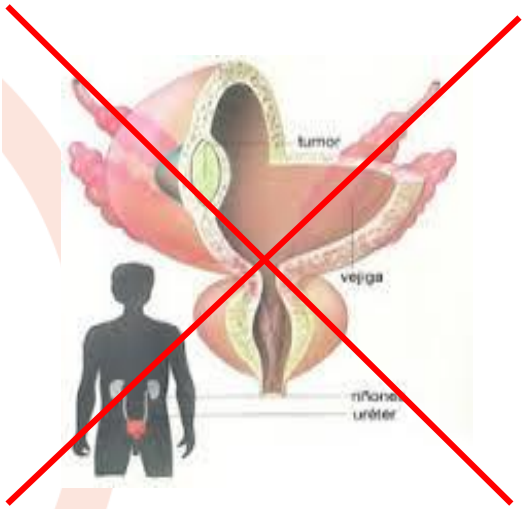


Adaptada de Dra. Calvo.

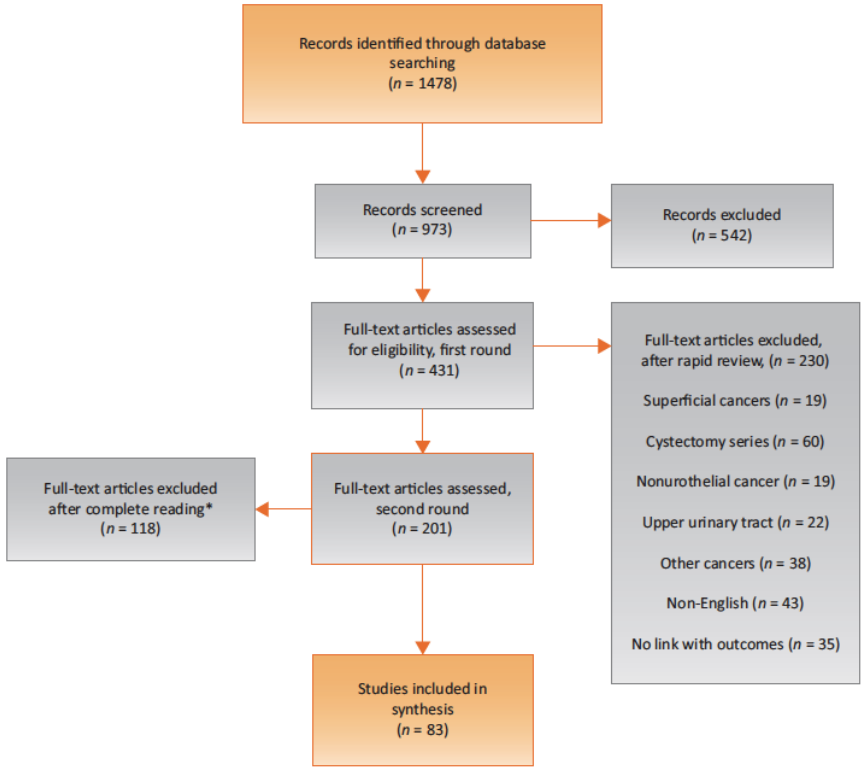
Cáncer de vejiga músculo-infiltrante

Preservación vesical

- Selección de pacientes



Preservación obligada *vs.* electiva



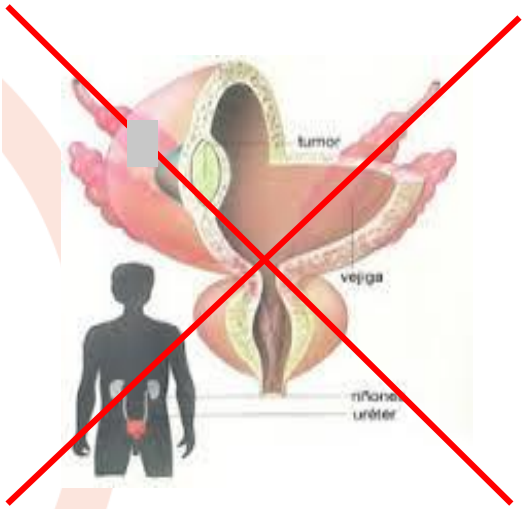
	Médicamente operables	Médicamente inoperables
TRC	73%	49%
SCE	50-82%	
SG 5a	36-74%	30-42%

Ploussard G, et al. Eur Urol 2014;66:120.

Cáncer de vejiga músculo-infiltrante

Preservación vesical

- Selección de pacientes



Preservación obligada *vs. ELECTIVA*

Patient selection for bladder preservation

Preferred or Ideal	Less than Ideal	Relative Contraindications	Absolute Contraindications
T2 No hydronephrosis No CIS Visibly complete TURBT Unifocal tumor Good bladder function and capacity	T3a Incomplete TURBT Multifocal tumor Poor bladder function or capacity	T3b-T4a Diffuse CIS Lymph node positive disease	T4b Tumor-Related Hydronephrosis Prior pelvic radiation therapy Not a candidate for chemotherapy Prostatic stromal invasion

20% - 30%

Del total de pacientes con TVMI

CONDICIONANTES

- Correcta función vesical.
- No estenosis de uretra.
- < cT3

Premo C, et al. Urol Clin North Am 2015;42(2):169.

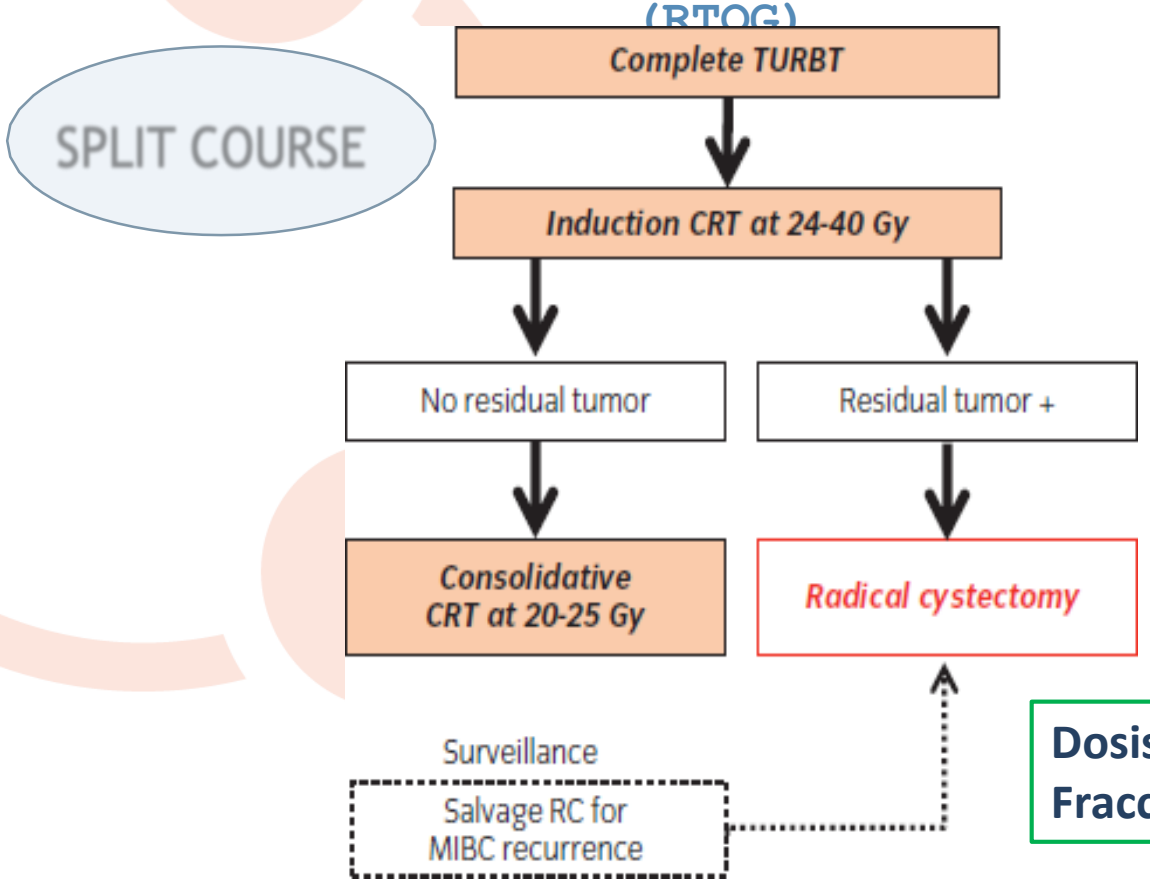
Cáncer de vejiga músculo-infiltrante

Preservación vesical

- RT: fraccionamiento estándar

Massachusetts General Hospital (MGH)

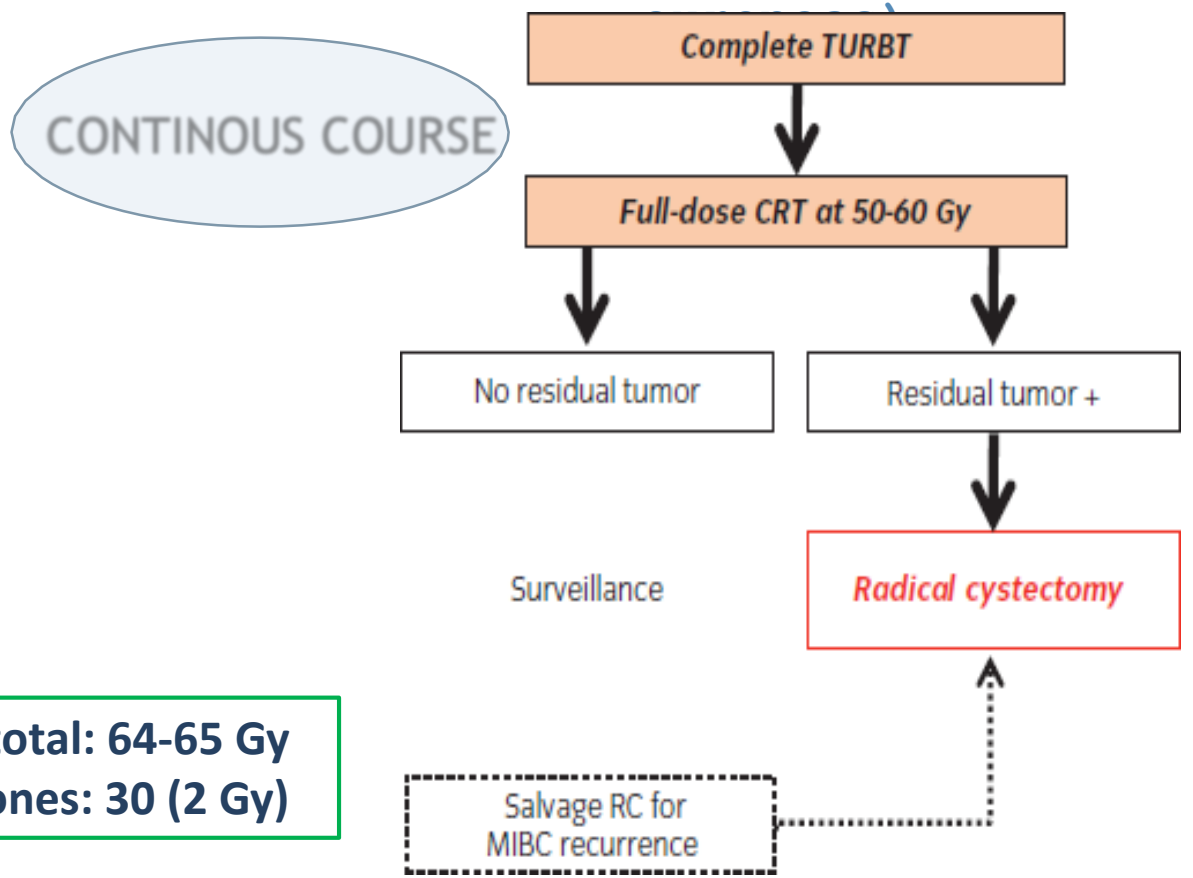
Radiation Therapy Oncology Group (RTOG)



Dosis total: 64-65 Gy
Fracciones: 30 (2 Gy)

University of Erlangen

(adoptado por muchas instituciones



Amestoy F, et al. Crit Rev Oncol Hematol 2019;142:72.

Cáncer de vejiga músculo-infiltrante

Preservación vesical

RT: hipofraccionamiento

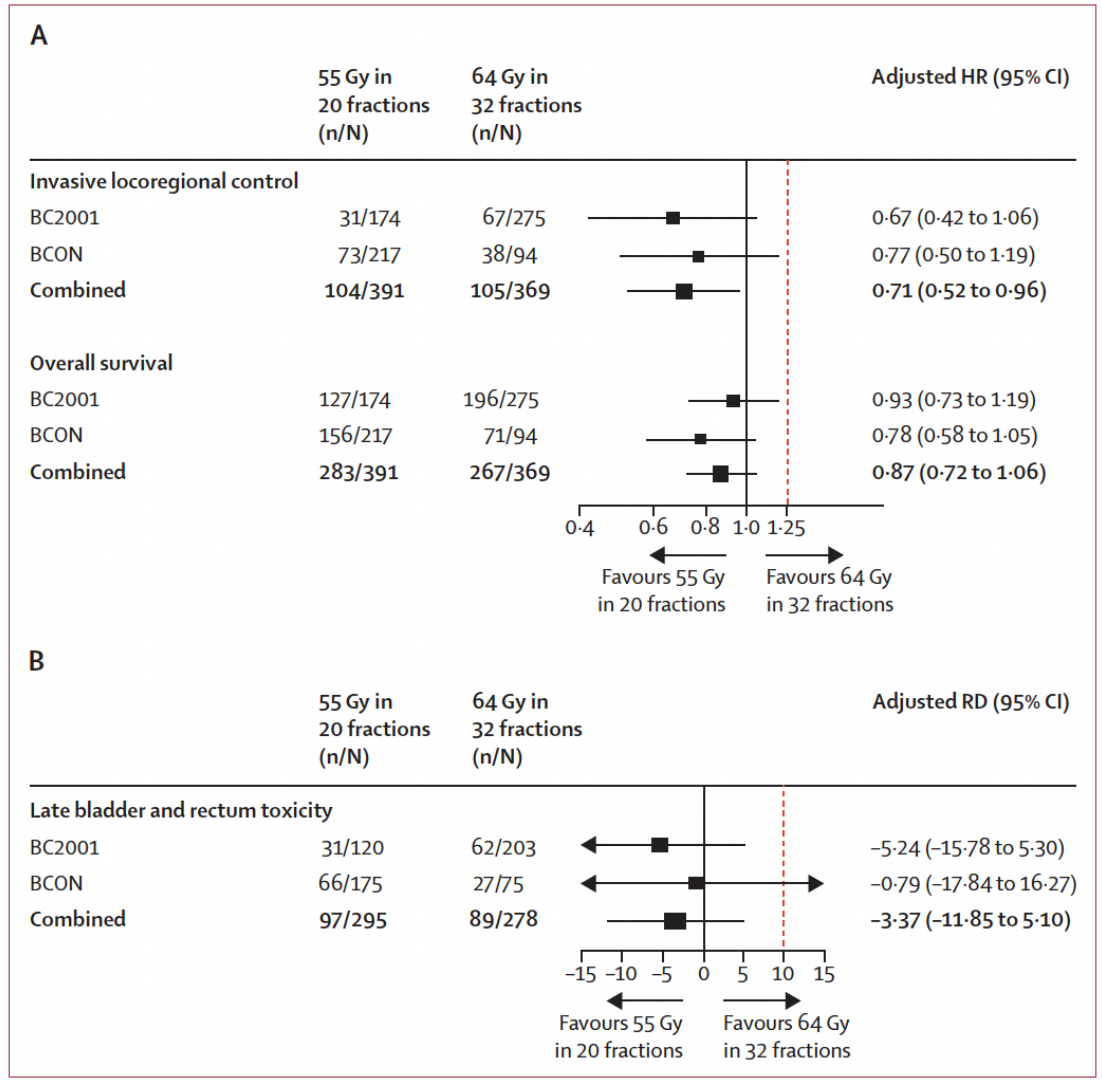
Hypofractionated radiotherapy in locally advanced bladder cancer: an individual patient data meta-analysis of the BC2001 and BCON trials

Ananya Choudhury, Nuria Porta*, Emma Hall, Yee Pei Song, Ruth Owen, Ranald MacKay, Catharine M L West, Rebecca Lewis, Syed A Hussain, Nicholas D James†, Robert Huddart†, Peter Hoskin†, on behalf of the BC2001 and BCON investigators*

Summary

Background Two radiotherapy fractionation schedules are used to treat locally advanced bladder cancer: 64 Gy in 32 fractions over 6·5 weeks and a hypofractionated schedule of 55 Gy in 20 fractions over 4 weeks. Long-term outcomes of these schedules in several cohort studies and case series suggest that response, survival, and toxicity are similar, but no direct comparison has been published. The present study aimed to assess the non-inferiority of 55 Gy in 20 fractions to 64 Gy in 32 fractions in terms of invasive locoregional control and late toxicity in patients with locally advanced bladder cancer.

Dosis total: 55 Gy
Fracciones: 20 (2 Gy)

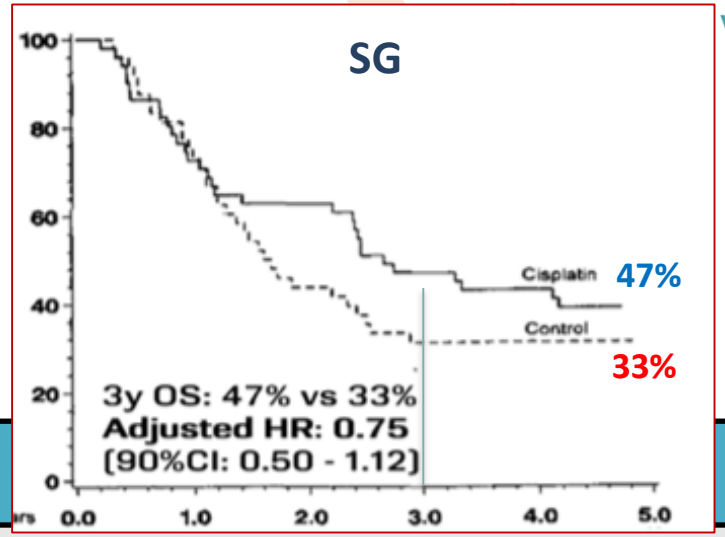


Choudhury A, et al. Lancet Oncol 2021;22:246.

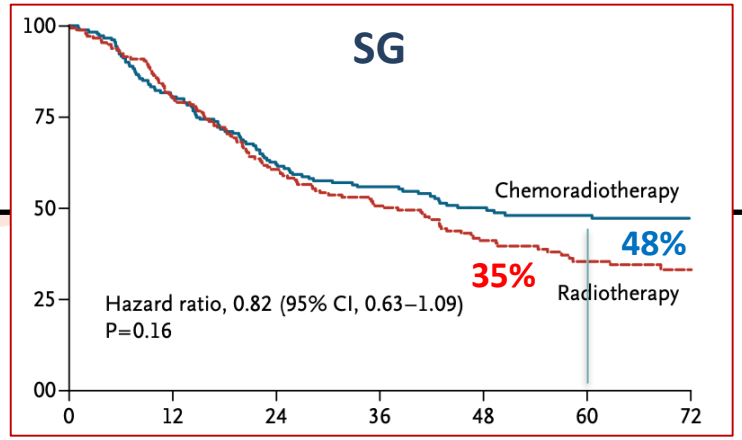
Cáncer de vejiga músculo-infiltrante

Preservación vesical

- QT: estudios fase III



Estudio	Diseño	Estadio	N	QT concomitante			SG
Coppin C. **Fase III**	RT vs. RQT	T2-4 N0-3 M0	99	CDDP 100 mg/m^2/2s x 3 ciclos	40 Gy (pélvica)	SLE Pélvica: A 2 años: 67% vs. 47% A 5 años: 60% vs. 41% p=0.038	NS
James N. **Fase III**	RT vs.RQT	T2-4a N0 M0	360	5-FU 500 mg/m^2 ic d1-5,16-20 Mitomicina C 12 mg/m^2 iv d1	55 Gy (en 20 fr) 64 Gy (en 32 fr)	SLE locorregional: A 2 años: 67% vs. 54% p=0.03 SLE locorregional inv: A 2 años: 82% vs. 68% p=0.1	NS



Coppin C, et al. J Clin Oncol 1996;14:2901.
James N, et al. N Engl G Med 2012;366:1477.

Cáncer de vejiga músculo-infiltrante

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Preservación vesical

QT: esquemas de tratamiento

Long-term Outcomes After Bladder-preserving Tri-modality Therapy for Patients with Muscle-invasive Bladder Cancer: An Updated Analysis of the Massachusetts General Hospital Experience

Protocol	Neoadjuvant chemotherapy	Induction	Response	Consolidation or cystectomy	Maximum RT dose to tumor (Gy)	Adjuvant chemotherapy	Pts., *n* (%)
MGH 180	MCV 2 cycles	CP + QD RT	CR	CP + RT	64.8	None	52 (11)
MGH 880, RTOG 8903 Arm 1	MCV 2 cycles	CP + QD RT	IR CR	Cystectomy CP + RT	64.8	None	56 (12)
MGH 880, RTOG 8903 Arm 2	None	CP + QD RT	IR CR	Cystectomy CP + RT	64.8	None	50 (11)
MGH 930A	None	CP + 5-FU + BID RT	IR CR	Cystectomy CP + 5-FU + BID RT	64.8	MCV 3 cycles	21 (4.4)
RTOG 9506	None	CP + 5-FU + BID RT	IR CR	Cystectomy CP + 5-FU + BID RT	44	None	15 (3.2)
RTOG 9706	None	CP + BID RT	IR CR	Cystectomy CP + BID RT	64.8	MCV 3 cycles	23 (4.8)
RTOG 9906	None	CP + pacl + BID RT	IR CR	Cystectomy CP + Pacl + BID RT	64.3	CP + gem 4 cycles	44 (9.3)
RTOG 0233 Arm 1	None	CP + 5-FU + BID RT	IR CR	Cystectomy CP + 5-FU + BID RT	64.3	CP + Pacl + gem 4 cycles	28 (5.9)
RTOG 0233 Arm 2	None	CP + Pacl + BID RT	IR CR	Cystectomy CP + Pacl + BID RT	64.3	CP + Pacl + gem 4 cycles	33 (6.9)
RTOG 0524 Group 2	None	Pacl + QD RT	CR	CP + RT	64.8	None	3 (0.6)
RTOG 0712 Arm 1	None	CP + 5-FU + BID RT	IR CR	Cystectomy CP + 5-FU + BID RT	64.3	CP + gem 4 cycles	18 (3.8)
RTOG 0712 Arm 2	None	Gem + QD RT	IR CR	Cystectomy Gem + RT	64	CP + gem 4 cycles	14 (2.9)
Per protocol	Varied[a]	Varied[b]	IR CR	Cystectomy Varied[b]	64–66	Varied[c]	118 (25)

Radiosensitizing Chemotherapy Regimens for Organ-Preserving Chemoradiation
Preferred regimens • 5-FU and mitomycin[33] • Cisplatin[h] alone[34]
Other recommended regimen • Cisplatin and 5-FU[30,31] • Cisplatin and paclitaxel[30,32] • Low-dose gemcitabine[31,35,36]

- 475 pts con T2-T4 MIBC entre 1986 y 2013.
- RTU seguida de QRT.
- A los pacientes sin remisión completa o con recidiva infiltrante se les recomendó realizar cistectomía radical
- Seguimiento medio de 7,2 años.
- Supervivencia cáncer-específica a los 5 años → 66 %.
- Supervivencia global a los 5 años → 57 %.
- Frecuencia de cistectomía de rescate → 16%.

Giacalone NJ, et al. Eur Urol 2017;71:952.

Cáncer de vejiga músculo-infiltrante

Preservación vesical

Meta-análisis

A systematic review and meta-analysis on the oncological long-term outcomes after trimodality therapy and radical cystectomy with or without neoadjuvant chemotherapy for muscle-invasive bladder cancer
Urol Oncol. 2018 Feb;36(2):43-53. doi: 10.1016/j.urolonc.2017.10.002.

→ 57 estudios. (TMT vs. RC)
OS 10y. 30.9% vs. 35.1%, p=0.32.
DSS 10y. 50.9% vs. 57.8%, p=0.26.
NAC 13.3% vs. 3%, p<0.001.
cCR TMT: 75.3%

Muscle-invasive bladder cancer organ-preserving therapy: systematic review and meta-analysis
World J Urol. 2018 Dec;36(12):1997-2008. doi: 10.1007/s00345-018-2384-6.

→ 11 estudios. (TMT vs. RC)
OS HR 1.06 (0.85-1.31)
PFS 1.11 (0.63-1.95)
CSS HR 1.23 (1.04-1.46)

Systematic review and meta-analysis on trimodal therapy versus radical cystectomy for muscle-invasive bladder cancer: Does the current quality of evidence justify definitive conclusions?
PLoS One. 2019 Apr 29;14(4):e0216255. doi: 10.1371/journal.pone.0216255.

→ 12 estudios. (TMT vs. RC)
OS HR 1.39 (1.2-1.59)
Elevado riesgo de sesgo

Trimodal Therapy vs. Radical Cystectomy for Muscle-Invasive Bladder Cancer: A Meta-Analysis
Front Oncol. 2020 Oct 14;10:564779. doi: 10.3389/fonc.2020.564779.

→ 9 estudios. (TMT vs. RC)
OS <10y HR 1.26 (0.92-1.73),p=0.14
OS >10y HR 1.50 (1.29-1.76),p<0.001
CSS HR 1.34 (1.18.1-54), p<0.001

PROBLEMAS

No existen RCT

(SPARE y NCT02716896 abortados)

Comparación difícil

CONCLUSIONES

Los resultados entre TMT vs. RC son comparables, aunque existen ciertos parámetros que dan cierta ventaja a la cistectomía.

15-30% acabarán con CR de rescate.

Cortesía de Dr. Arturo Domínguez.

Cáncer de vejiga músculo-infiltrante

Preservación vesical

Inmunoterapia

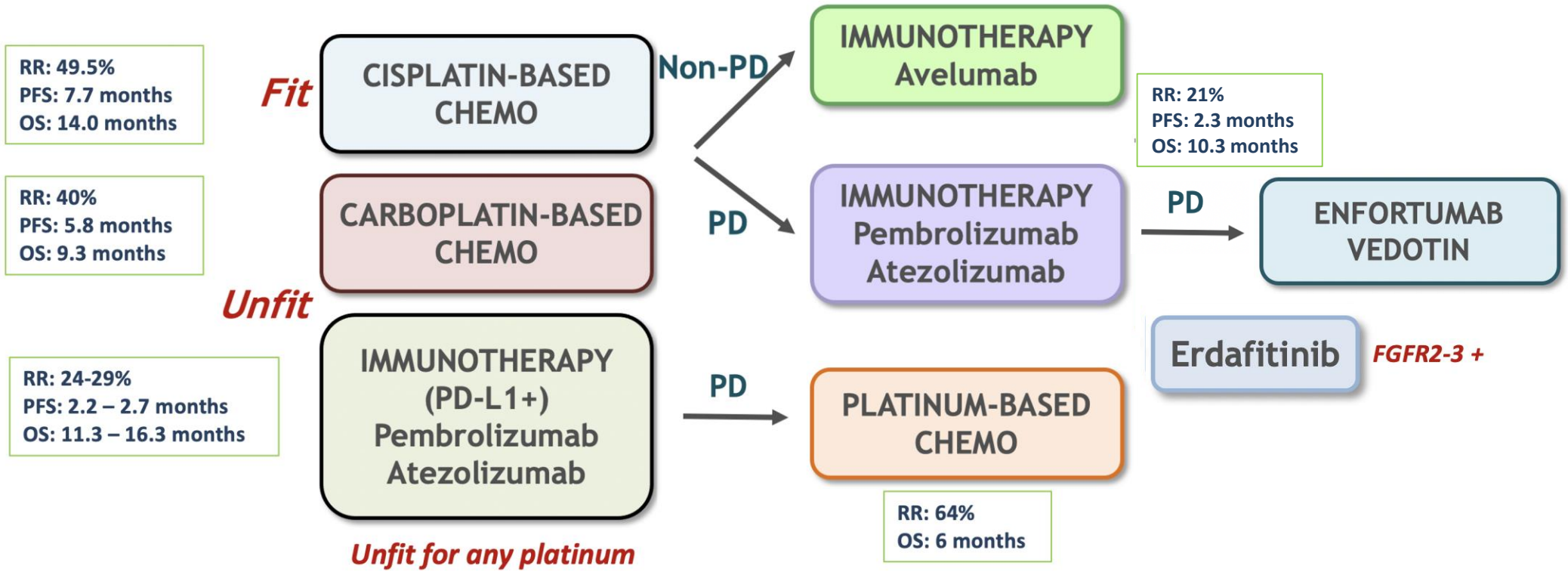
Trial Name	Treatments	Estimated Enrollment	Sponsor	Primary Endpoints
NCT03747419	Avelumab Q2W x6 + RT	24	DFCI	CR at 3M
IMMUNOPRESERVE NCT03702179	Durvalumab + Tremelimumab Q4W x3 + RT	32	Spanish Oncology GU Group	≤cT1 at 12W
NCT03617913	Avelumab + Cis/5FU or 5FU/Mitomycin + RT	?	Mayo	CR
NCT02621151	Pembrolizumab Q3W x4 + Gemcitabine BIW x 4W + Hypofractionated RT	54	NYU	BIDFS
BladderSpar NCT03697850	Atezolizumab Q3W x12M beginning 30 days after completion of chemo RT	77	UNICANCER	DFS
DUART NCT02891161	Concurrent/adjuvant durvalumab + RT (cis-ineligible, unresectable, unfit for surgery, locally advanced or node positive)	26	Big Ten Consortium	PFS DCR
PCR-MIB NCT02662062	Concurrent/adjuvant pembrolizumab + Cis + RT		ANZUP	
NEXT NCT03171025	ChemoRT followed by adjuvant nivolumab		University of Utah	
NCT03419130	Concurrent pembrolizumab + RT (conventional vs hypofractionated), no chemo		UCSF	
NCT03601455	RT + durvalumab +/- tremelimumab (M0-M1, cis-ineligible)		UCLA	

Dr. Bellmunt. ESMO2022.

Cáncer de vejiga avanzado

Tratamiento sistémico

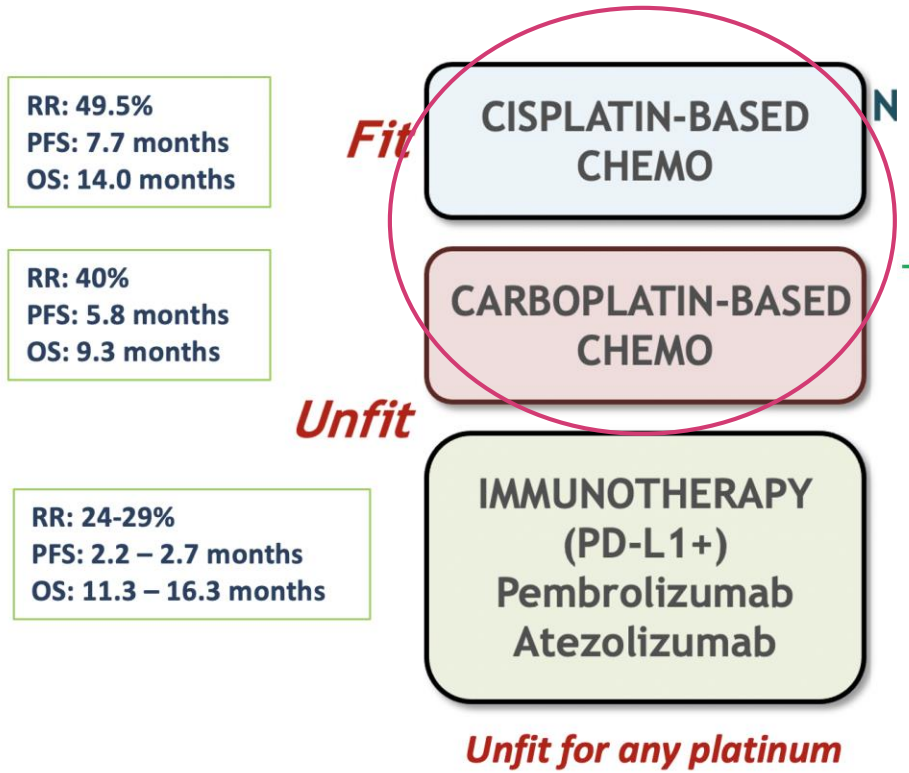
- Aproximación actual



Cáncer de vejiga avanzado

Tratamiento sistémico

- 1L QT +/- Inmunoterapia



Clinical Trial	Phase	Control arm	Experimental arm	n	Status
IMvigor130	III	CDDP + GMZ CBDCA + GMZ	Atezolizumab + Platinum + GMZ Atezolizumab	1200	Completed
KEYNOTE-361	III	CDDP + GMZ CBDCA + GMZ	Pembrolizumab + Platinum + GMZ Pembrolizumab	990	Completed
DANUBE	III	CDDP + GMZ CBDCA + GMZ	Durvalumab + tremelimumab Durvalumab	1032	Completed
CheckMate 901	III	CDDP + GMZ CBDCA + GMZ	Nivolumab + Ipilimumab Nivolumab + Cisplatin + GMZ	1045	Recruiting
NILE	III	CDDP + GMZ CBDCA + GMZ	Durvalumab + Platinum + GMZ Durvalumab + Tremelimumab + Platinum + GMZ	885	Closed
JAVELIN Bladder 100 (maintenance)	III	BSC	Avelumab + BSC	700	Completed

Galsky MD, et al. Lancet 2020;395(10236):1547.
Alva A, et al. Ann Oncol 2020;31(suppl_4):S1142.
Powles T, et al. Ann Oncol 2020;31(suppl_4):S550.
Grande E, et al. J Clin Oncol 2023;41(suppl 6; abstrLBA440).
https://news.bms.com/news/details/2022/Bristol-Myers-Squibb-Provides-Update-on-CheckMate--901-Trial-Evaluating-Opdivo-nivolumab-Plus-Yervoy-ipilimumab-as-First-Line-Treatment-for-Patients-with-Unresectable-or-Metastatic-Urothelial-Carcinoma/default.aspx.

Cáncer de vejiga avanzado

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Tratamiento sistémico

1L QT +/- Inmunoterapia

CheckMate-901

N=608

Key inclusion criteria
- Age ≥ 18 years
- Previously untreated unresectable or mUC involving the renal pelvis, ureter, bladder, or urethra
- Cisplatin eligible
- ECOG PS of 0-1

Stratification factors:
- Tumor PD-L1 expression (≥ 1% vs < 1%)
- Liver metastases (yes vs no)

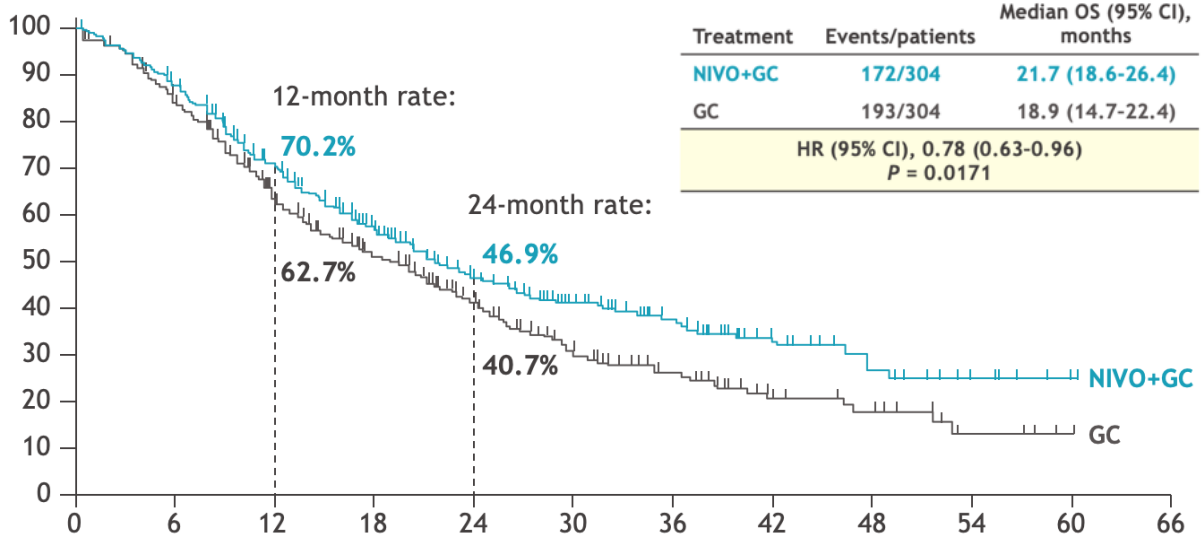
R 1:1

	Combination phase	Monotherapy phase
N = 304	**NIVO** 360 mg on D1 + **Gemcitabine** 1000 mg/m² on D1/D8 + **Cisplatin** 70 mg/m² on D1 Q3W (up to 6 cycles)[b]	3 weeks → **NIVO** 480 mg Q4W (until progression, unacceptable toxicity, withdrawal, or up to 24 months[c])
N = 304	**Gemcitabine** 1000 mg/m² on D1/D8 + **Cisplatin** 70 mg/m² on D1 Q3W (up to 6 cycles)[b]	

Primary endpoint: OS and PFS by BIRC

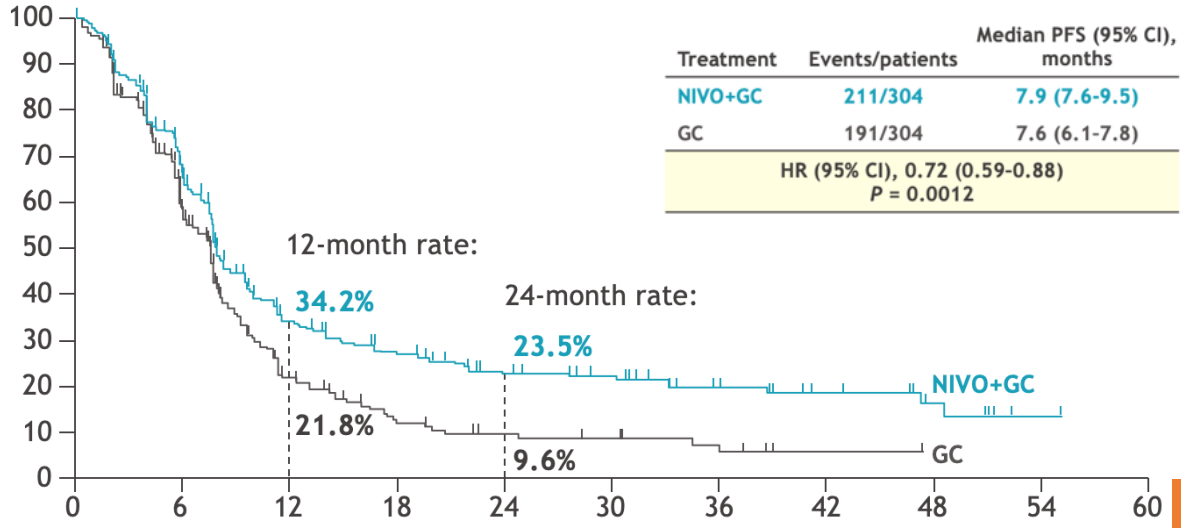
Median follow-up -> 33.6 months

OS



Treatment	Events/patients	Median OS (95% CI), months
NIVO+GC	172/304	21.7 (18.6-26.4)
GC	193/304	18.9 (14.7-22.4)
HR (95% CI), 0.78 (0.63-0.96) *P* = 0.0171		

PFS by BIRC



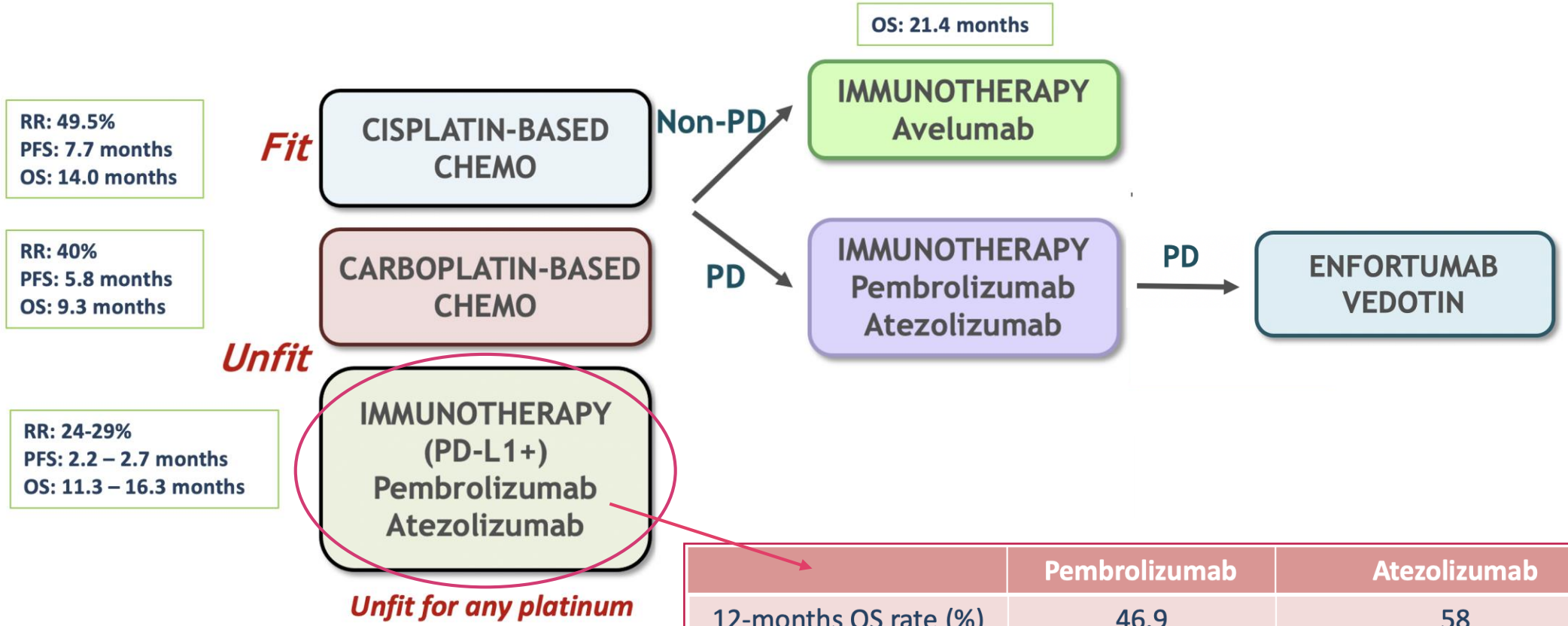
Treatment	Events/patients	Median PFS (95% CI), months
NIVO+GC	211/304	7.9 (7.6-9.5)
GC	191/304	7.6 (6.1-7.8)
HR (95% CI), 0.72 (0.59-0.88) *P* = 0.0012		

van der Heijden MS, et al. N Engl J Med 2023;389(19):1778.

Cáncer de vejiga avanzado

Tratamiento sistémico

- 1L Inmunoterapia



	Pembrolizumab	Atezolizumab
12-months OS rate (%)	46.9	58
24-months OS rate (%)	31.2	41
60-months OS rate (%)	19	21.6

O'Donnell PH, et al. J Clin Oncol 2021;39(suppl 15; abstr 4508).
Rosenbeg JE, et al. Ann Oncol 2021;32(suppl_5):S678-S24.

Cáncer de vejiga avanzado

Tratamiento sistémico

1L Inmunoterapia

RR: 49.5%
PFS: 7.7 months
OS: 14.0 months

Fit → CISPLATIN-BASED CHEMO

RR: 40%
PFS: 5.8 months
OS: 9.3 months

CARBOPLATIN-BASED CHEMO

Unfit →

RR: 24-29%
PFS: 2.2 – 2.7 months
OS: 11.3 – 16.3 months

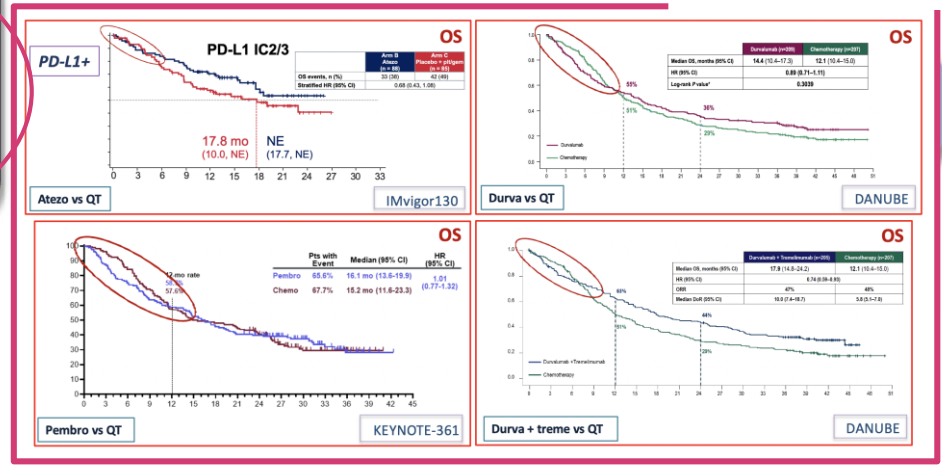
IMMUNOTHERAPY (PD-L1+) Pembrolizumab Atezolizumab

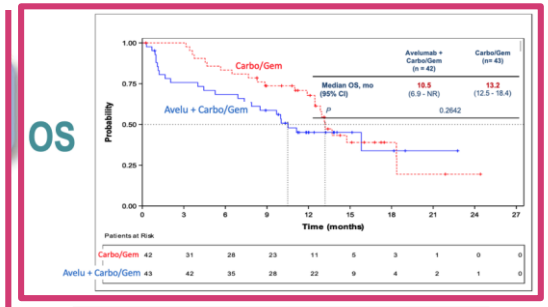
Unfit for any platinum

Non-PD → OS: 21.4 months → IMMUNOTHERAPY Avelumab

PD → IMMUNOTHERAPY Pembrolizumab Atezolizumab

PD → ENFORTUMAB VEDOTIN





* 13 p (31%) in avelumab arm progressed or died before or in the 1st planned response assessment *vs.* 4 (9.3%) in CT arm.

Bálar AV, et al. Lancet 2017;289(10064):67.
O´Donell PH, et al. J Clin Oncol 35,2017 (suppl;4502).
O'Donnell PH, et al. J Clin Oncol 2021;39(suppl 15; abstr 4508).
Rosenbeg JE, et al. Ann Oncol 2021;32(suppl_5):S678-S24.
Valderrama BP, et al. Ann Oncol 2020;31(suppl_4):S1142.

Cáncer de vejiga avanzado

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Tratamiento sistémico

1L Inmunoterapia

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Systematic or Meta-analysis Studies

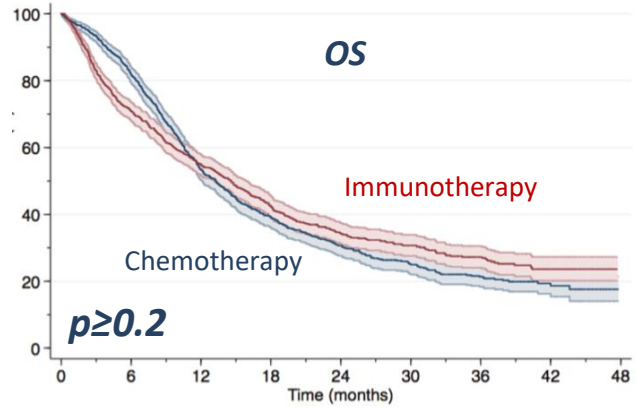
Immunotherapy versus chemotherapy as first-line treatment for advanced urothelial cancer: A systematic review and meta-analysis

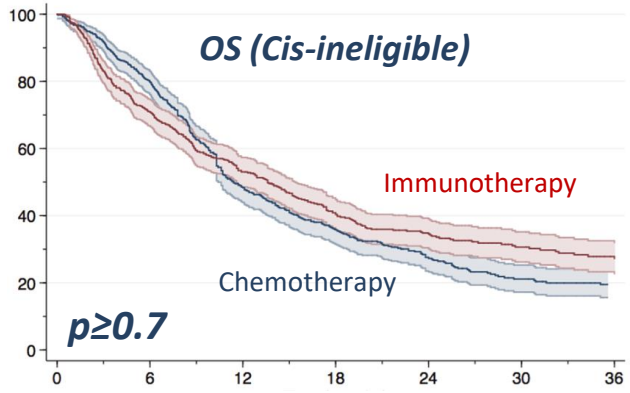
Alberto Martini [a,*,1], Daniele Raggi [a,1], Giuseppe Fallara [a,1], Luigi Nocera [a], Julianne G. Schultz [b], Federico Belladelli [a], Laura Marandino [c], Andrea Salonia [a,d], Alberto Briganti [a,d], Francesco Montorsi [a,d], Thomas Powles [e,2], Andrea Necchi [a,d,2]

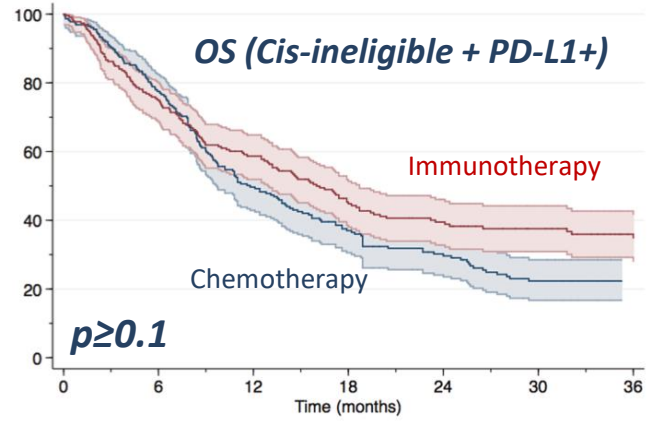
N=2068

Clinical Trial	Phase	Control arm	Experimental arm	n	Status
IMvigor130	III	CDDP + GMZ CBDCA + GMZ	Atezolizumab + Platinum + GMZ Atezolizumab	1200	Completed
KEYNOTE-361	III	CDDP + GMZ CBDCA + GMZ	Pembrolizumab + Platinum + GMZ Pembrolizumab	990	Completed
DANUBE	III	CDDP + GMZ CBDCA + GMZ	Durvalumab + tremelimumab Durvalumab	1032	Completed
CheckMate 901	III	CDDP + GMZ CBDCA + GMZ	Nivolumab + Ipilimumab Nivolumab + Cisplatin + GMZ	1045	Recruiting
NILE	III	CDDP + GMZ CBDCA + GMZ	Durvalumab + Platinum + GMZ Durvalumab + Tremelimumab + Platinum + GMZ	885	Closed
JAVELIN Bladder 100 (maintenance)	III	BSC	Avelumab + BSC	700	Completed

	ΔRMST up to 18 months of follow-up (95% CI)	ΔRMST up to 24 months of follow-up (95% CI)
	Overall survival	
Immuno- vs chemo-therapy	−0.6 (−1.1 to −0.04)	−0.4 (−1.1 to 0.4)
	Overall survival among cisplatin ineligible patients	
Immuno- vs chemo-therapy	−0.2 (−0.9 to 0.6)	0.1 (−0.9 to 1.2)
	Overall survival among cisplatin ineligible patients with high PDL1 expression	
Immuno- vs chemo-therapy	0.6 (−0.6 to 1.7)	1.1 (−0.5to– 2.7)







Martini A , et al. Cancer Treat Rev 2022;104:102360.

Cáncer de vejiga avanzado

Tratamiento sistémico

2L Inmunoterapia

RR: 49.5%
PFS: 7.7 months
OS: 14.0 months

RR: 40%
PFS: 5.8 months
OS: 9.3 months

RR: 24-29%
PFS: 2.2 – 2.7 months
OS: 11.3 – 16.3 months

Fit

CISPLATIN-BASED CHEMO

CARBOPLATIN-BASED CHEMO

Unfit

IMMUNOTHERAPY (PD-L1+) Pembrolizumab Atezolizumab

Unfit for any platinum

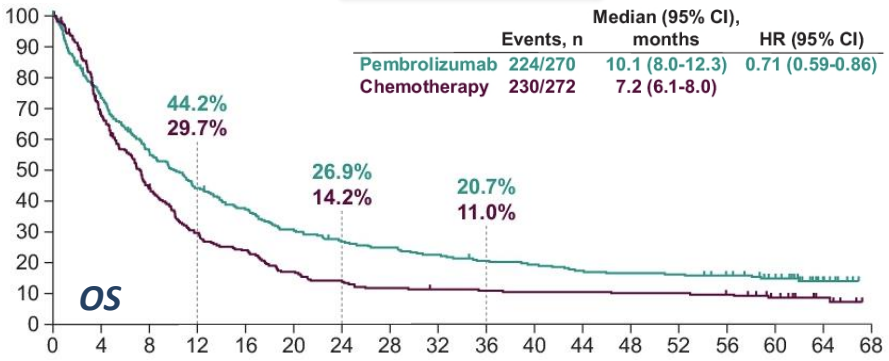
Non-PD → IMMUNOTHERAPY Avelumab

PD → IMMUNOTHERAPY Pembrolizumab Atezolizumab

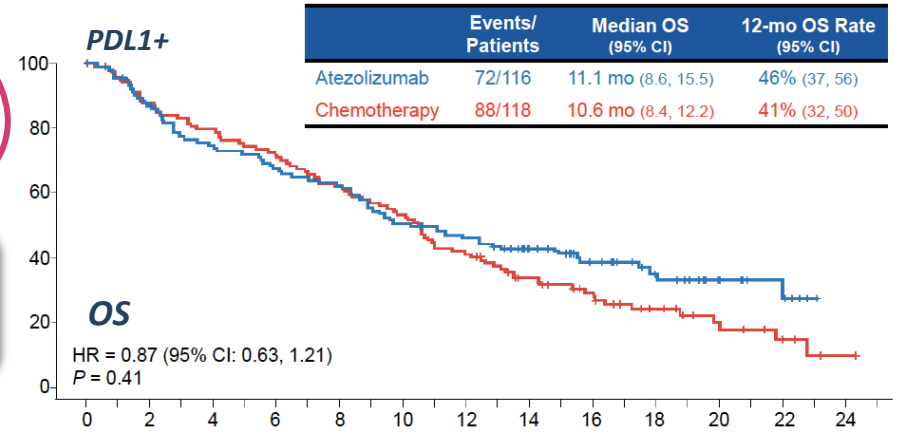
PD → PLATINUM-BASED CHEMO

ENFORTUMAB VEDOTIN

Keynote-045



IMvigor211



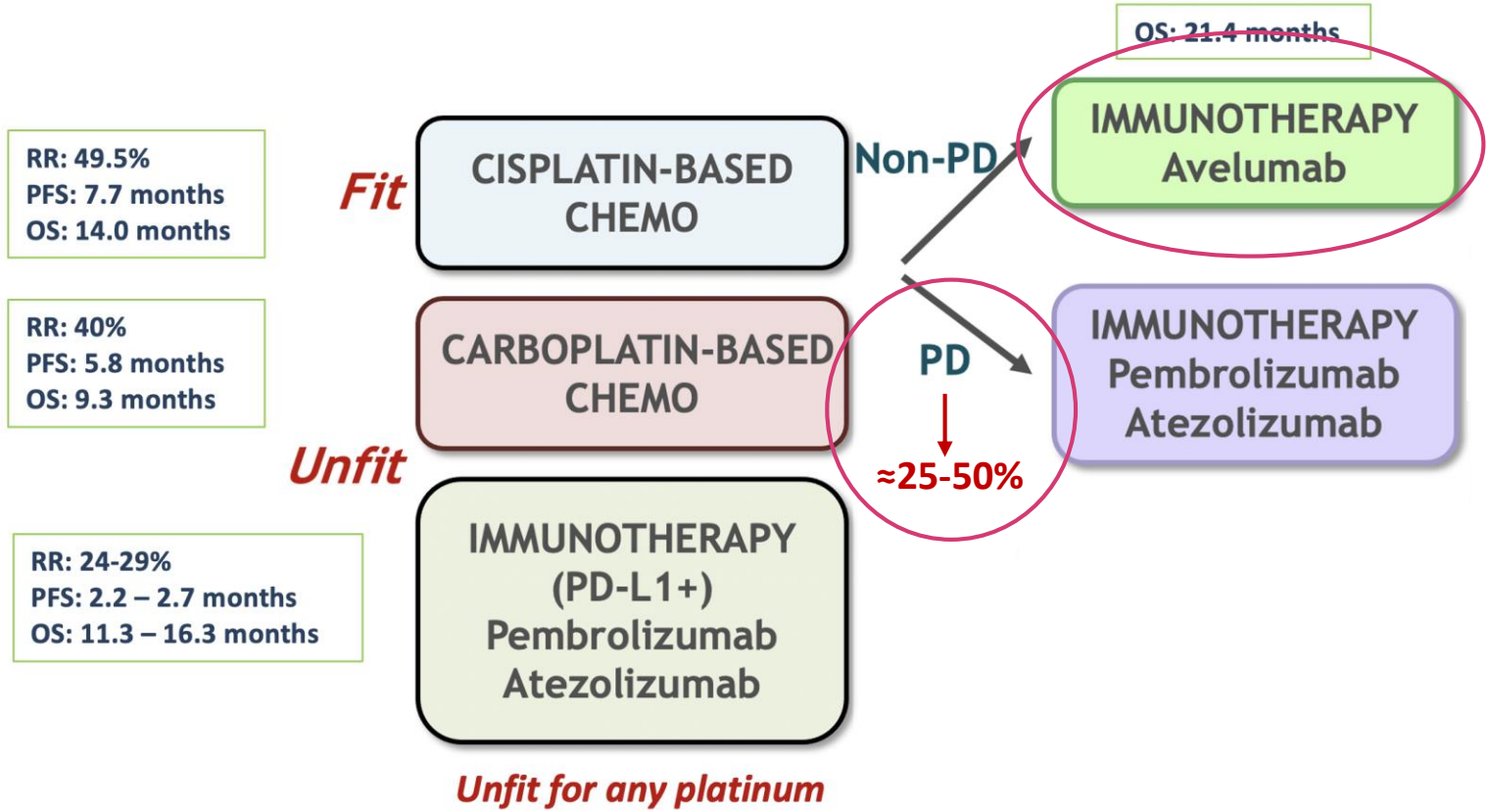
	KN-045 (*vs. CT*) n=272	IMvigor211 (*vs. CT*) n=467
36-month OS rate (%)	20.7 (*vs 11*)	18 (*vs 10*)

Powles T, et al. Lancet 2018;391(10122):748.
Bellmunt J, et al. N Engl J Med. 2017; 376(11): 1.015.

Cáncer de vejiga avanzado

Tratamiento sistémico

- 2L Inmunoterapia



Cáncer de vejiga avanzado

Tratamiento sistémico

1L Inmunoterapia mantenimiento

JAVELIN Bladder 100

- CR, PR, or SD with standard 1st-line chemotherapy (4-6 cycles)
  - Cisplatin + gemcitabine or
  - Carboplatin + gemcitabine
- Unresectable locally advanced or metastatic UC

Treatment-free interval 4-10 weeks

N=700

R 1:1

Avelumab 10 mg/kg IV Q2W + BSC* n=350

BSC alone* n=350

Until PD, unacceptable toxicity, or withdrawal

Stratification
- Best response to 1st-line chemo (CR or PR vs SD)
- Metastatic site (visceral vs non-visceral)

Primary endpoint
- OS

Primary analysis populations
- All randomized patients
- PD-L1+ population

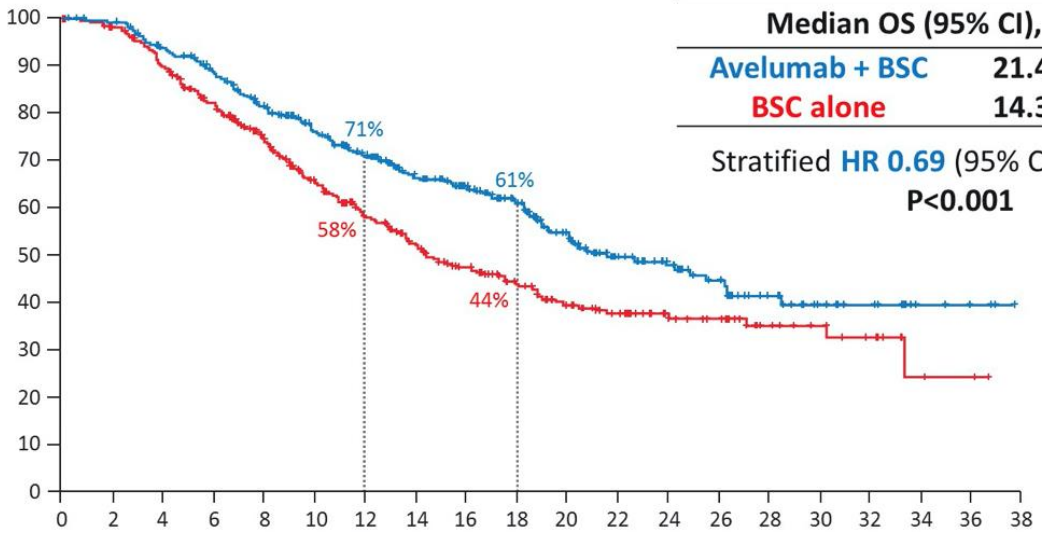
Secondary endpoints
- PFS and objective response per RECIST 1.1
- Safety and tolerability
- PROs

PD-L1 + (VENTANA SP263)
- PD-L1+ ≥ 25% en TC
- PD-L1+ ≥ 25% en IC (si > 1% del área tumoral contiene IC)
- PD-L1+ 100% en IC (si ≤ 1% contiene IC)

All endpoints measured post randomization (after chemotherapy)

- **Median follow-up: 19.5 months**

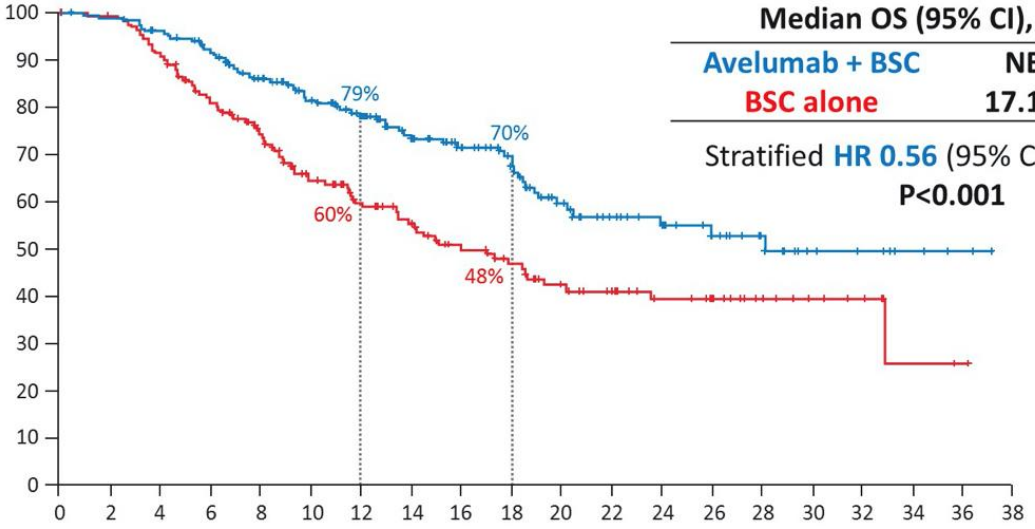
OS ITT



Median OS (95% CI), months	
Avelumab + BSC	**21.4** (18.9, 26.1)
BSC alone	**14.3** (12.9, 17.9)

Stratified **HR 0.69** (95% CI, 0.56, 0.86)
P<0.001

OS PD-L1+



Median OS (95% CI), months	
Avelumab + BSC	**NE** (20.3, NE)
BSC alone	**17.1** (13.5, 23.7)

Stratified **HR 0.56** (95% CI, 0.40, 0.79)
P<0.001

Powles T, et al. N Engl J Med 2020;383(13):1218.

Cáncer de vejiga avanzado

Tratamiento sistémico

1L Inmunoterapia mantenimiento

JAVELIN Bladder 100

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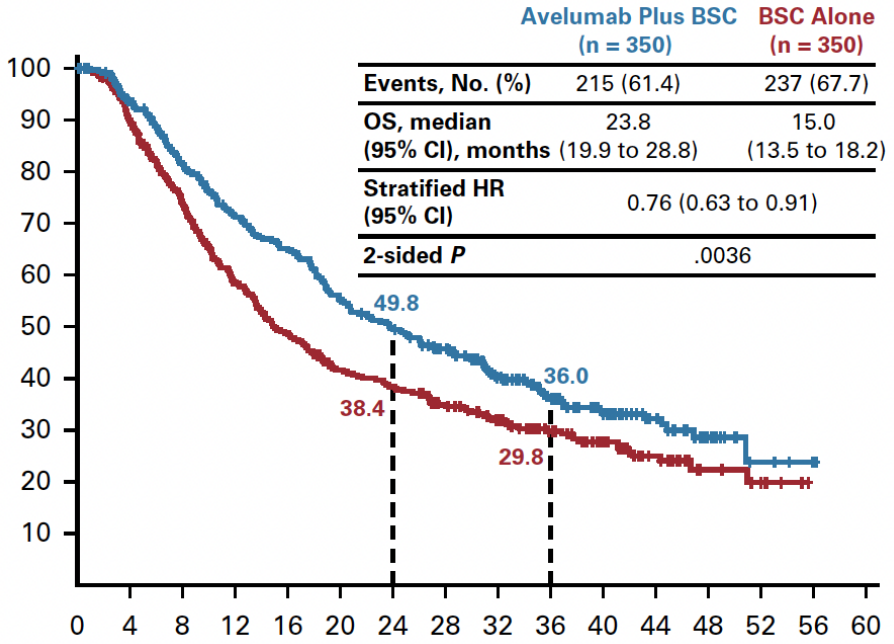
- PD-L1+ ≥ 25% en TC
- PD-L1+ ≥ 25% en IC (si > 1% del área tumoral contiene IC)
- PD-L1+ 100% en IC (si ≤ 1% contiene IC)

All endpoints measured post randomization (after chemotherapy)

- **Median follow-up: 38 months**

OS ITT



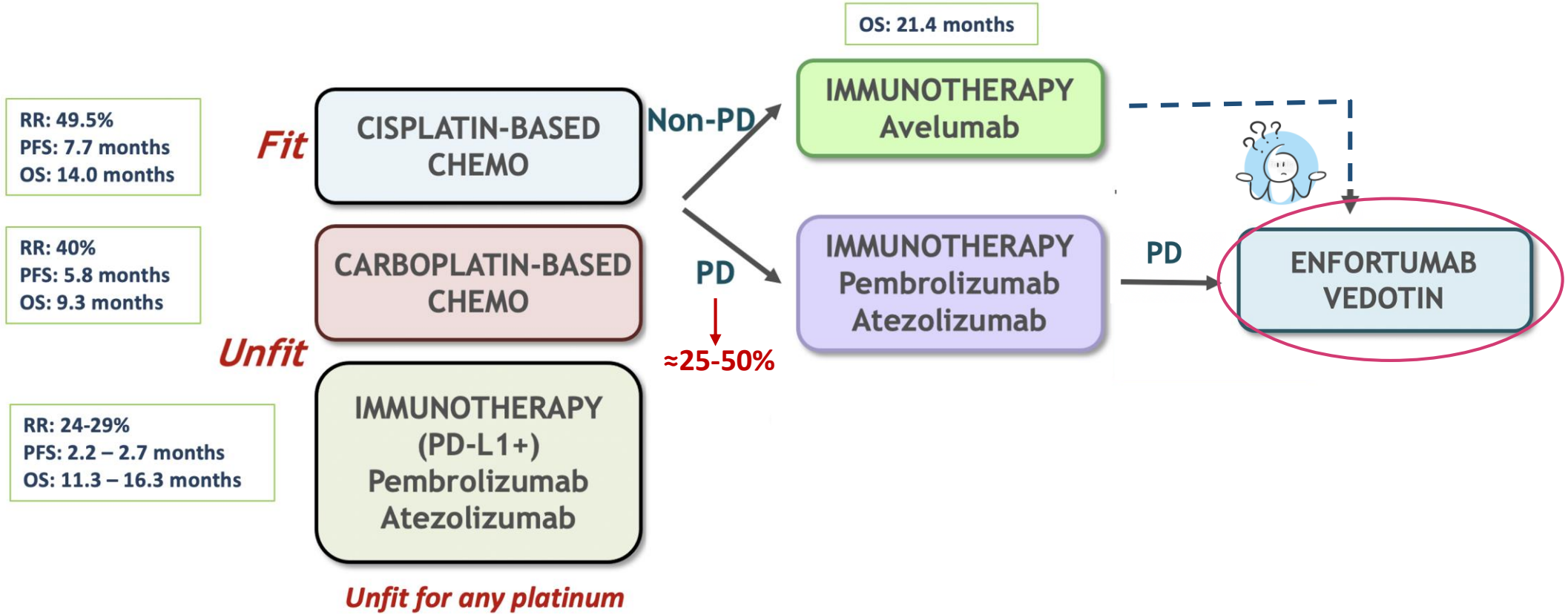
Independent of:
- ✓ 1L Chemo regimen (cis *vs.* carbo)
- ✓ Number of cycles and 1L chemo duration
- ✓ Best response to 1L chemo (CR *vs.* PR *vs.* SD)
- ✓ Time from last chemo cycle to start of maintenance
- ✓ Tumour location
- ✓ Tumour extension
- ✓ TCGA subgroups

Powles T, et al. J Clin Oncol 2023;41(19):3486.

Cáncer de vejiga avanzado

Tratamiento sistémico

- 2L Inmunoterapia



Cáncer de vejiga avanzado

N Engl J Med. 2021 Mar 25;384(12):1125-1135

CAMPUS SEOM
Área de formación virtual SEOM

Tratamiento sistémico

3L Enfortumab vedotin

EV-301

N=608
- Advanced or metastatic transitional cell carcinoma of the urothelium
- Progressive disease following 1L platinum based chemotherapy
- Prior PD-1/L1 inhibitor

RANDOMIZED

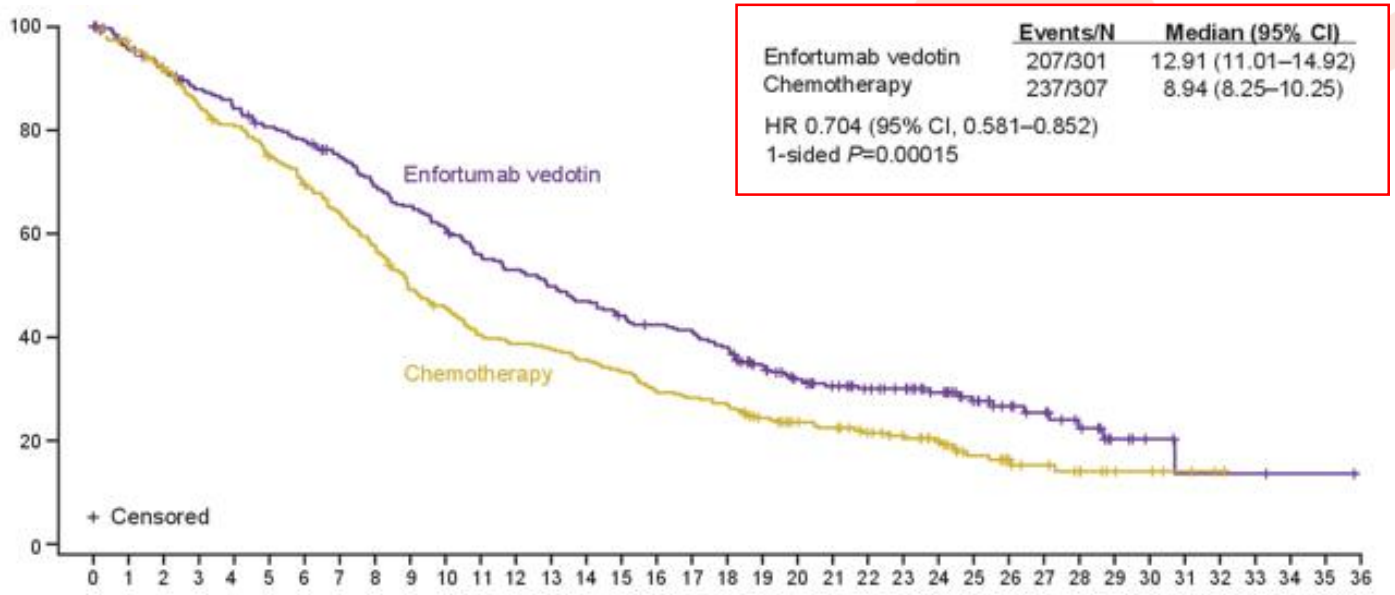
Enfortumab vedotin
1.25 mg/kg iv
On days 1,8 and 15 of each 28-day cycle

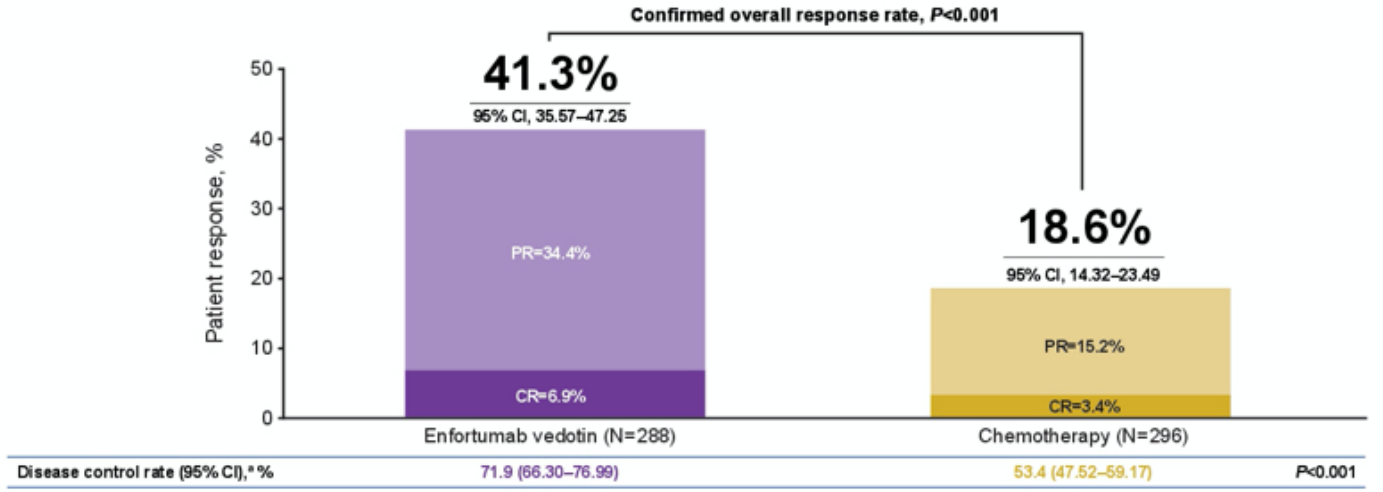
Chemotherapy
Vinflunine 35%
Taxanes

Primary endpoint: OS

Median follow-up -> 24 months

OS





Powles T, et al. N Engl J Med 2021;384(12):1125.
Rosenberg JE, et al. J Clin Oncol 2022;40(suppl 16; abstr 4516).

Cáncer de vejiga avanzado

Tratamiento sistémico

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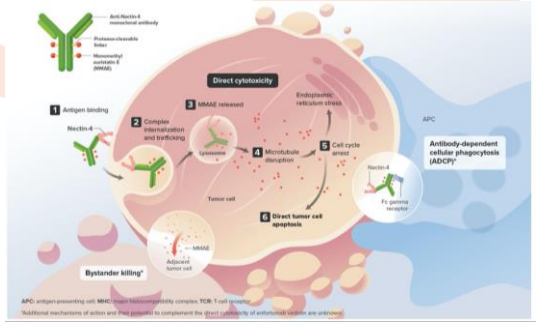
Chemotherapy
Vinflunine 35%
Taxanes

Primary endpoint: OS



Adverse Events of special interest

Skin Reactions: 61% any grade, 17% ≥Grade 3
- No Grade 5 events, 1 Grade 4 event
- 13 severe cutaneous adverse reactions[2] occurred
  - Most ≤Grade 2, no Grade 4 or 5 events
  - 4 Grade 3 events: stomatitis, skin exfoliation, dermatitis bullous, dermatitis exfoliative generalised
  - 1 discontinuation due to severe cutaneous adverse reaction

Median Onset	0.5 months[3]
% resolution/ improvement[4]	80%

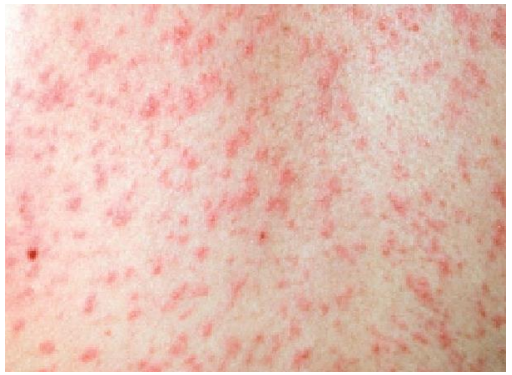
Peripheral neuropathy (PN): 54% any grade, 8% ≥Grade 3
- PN rate was similar in patients with and without pre-existing PN (53% vs 54%)

Median Onset	2.4 months
% resolution/ improvement[4]	56%

Hyperglycemia (HG): 10% any grade, 6% ≥Grade 3
- Higher rate of HG in patients with pre-existing HG than those without (20% vs. 7%)
- Higher rate of HG in patients with BMI ≥30 kg/m^2 than those with BMI ≤30 kg/m^2 (23% vs. 8%)

Median Onset	0.5 months[3]
% resolution/ improvement[4]	89%

[1]Medical Dictionary for Regulatory Activities
[2]A range of skin reaction preferred terms, irrespective of grade
[3]Most occurred in Cycle 1
[4]Resolution/Improvement was evaluated at last follow-up



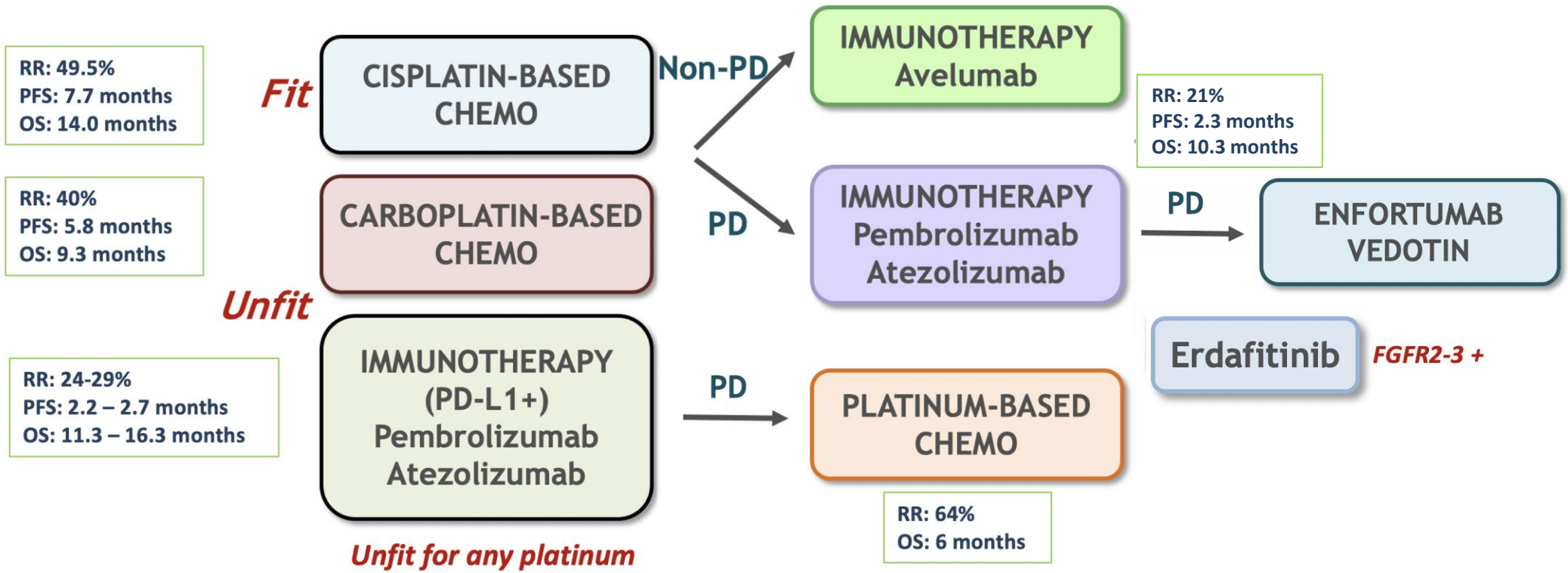
WARNING: SERIOUS SKIN REACTIONS
See full prescribing information for complete boxed warning.
- **PADCEV can cause severe and fatal cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN).**
- **Immediately withhold PADCEV and consider referral for specialized care for suspected SJS or TEN or severe skin reactions.**
- **Permanently discontinue PADCEV in patients with confirmed SJS or TEN; or Grade 4 or recurrent Grade 3 skin reactions. (2.2), (5.1) (6.1)**

Balar AV, et al. J Clin Oncol 2021;39 (suppl 6; abstr394).
https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761137s006s008lbl.pdf.

Cáncer de vejiga avanzado

Tratamiento sistémico

- 3L Erdafitinib

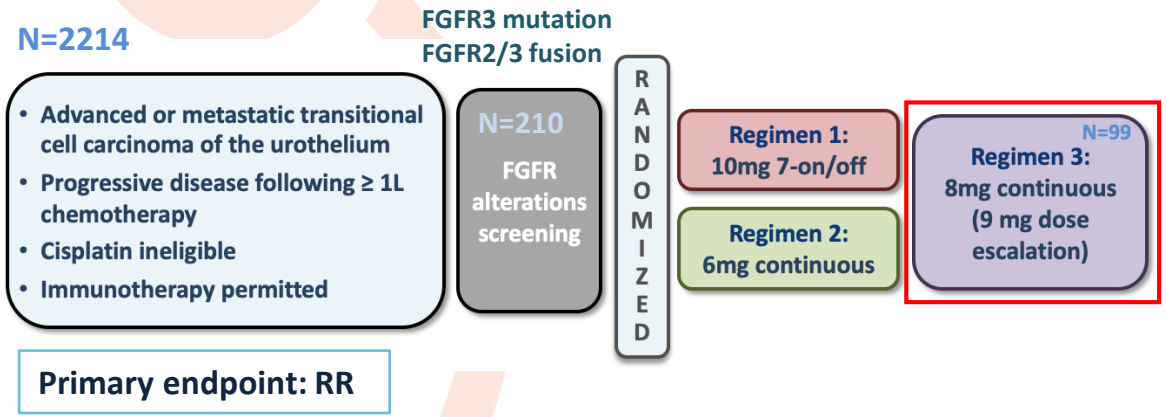


Cáncer de vejiga avanzado

Tratamiento sistémico

3L Erdafitinib

BLC2001



Primary endpoint: RR

Median follow-up -> 11 months

		RR
Response per investigator assessment — no. of patients†		
Any objective response	40	40 (31–50)
Complete response	3	3
Partial response	37	37
Stable disease	39	39
Progressive disease	18	18
Could not be evaluated or unknown	2	2
Median time to response — mo	1.4	
Median duration of response (95% CI) — mo	5.6 (4.2–7.2)	
Response per independent radiologic assessment — no. of patients†		
Objective response	34	34 (25–44)
Complete response	3	3
Partial response	31	31
Response according to previous treatment — no./total no.		
No chemotherapy	5/12	42
Progression or relapse after chemotherapy	35/87	40
Immunotherapy	13/22	59

21 not IO response

Loriot Y, et al. N Engl J Med 2019;381:338.

Cáncer de vejiga avanzado

Tratamiento sistémico

3L Erdafitinib

THOR

N=280

- Advanced or metastatic transitional cell carcinoma of the urothelium
- Progressive disease following 1L platinum based chemotherapy

Primary endpoint: OS

FGFR alterations screening

Prior treatment with PD-(L)1 inhibitor?

YES

Cohorte 1

- **Erdafitinib**
- **Chemotherapy**

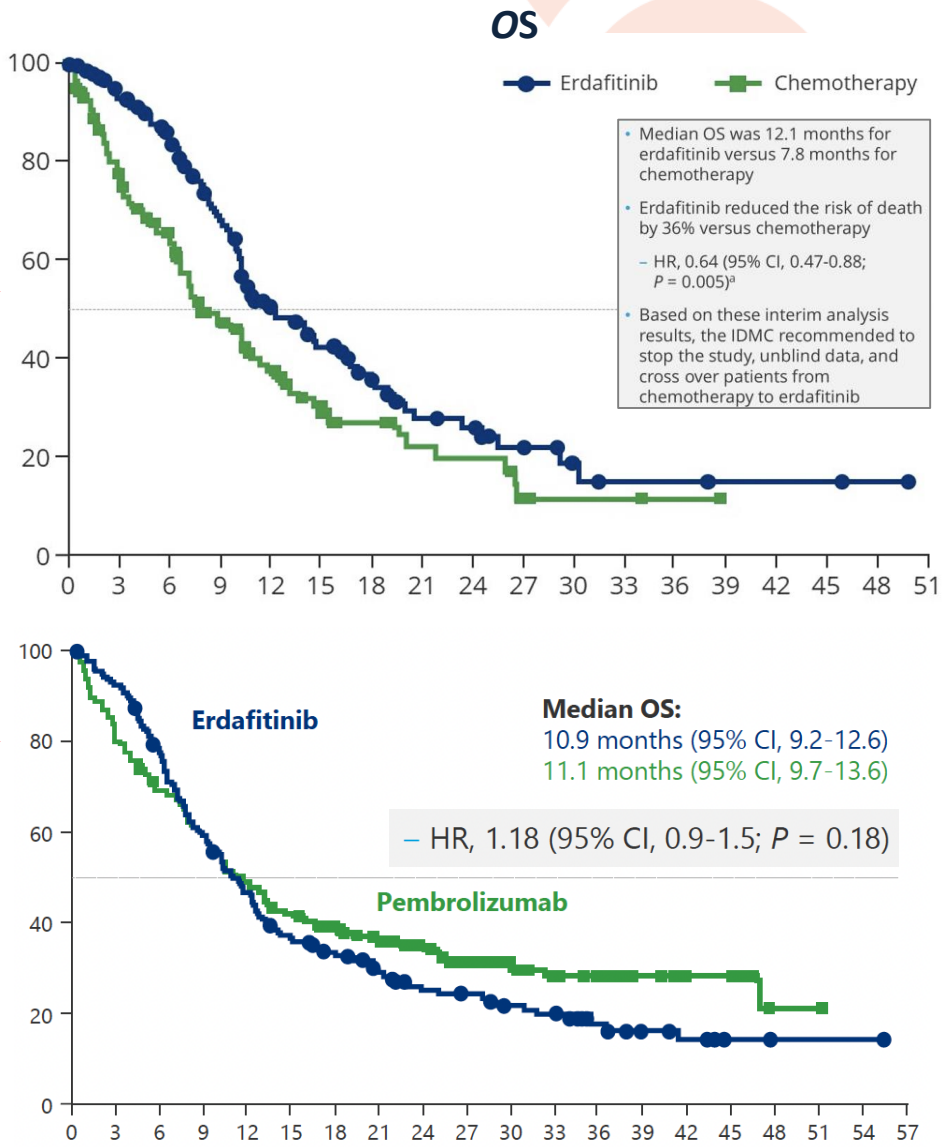
NO

N=266

Cohorte 2

- **Erdafitinib**
- **Pembrolizumab**

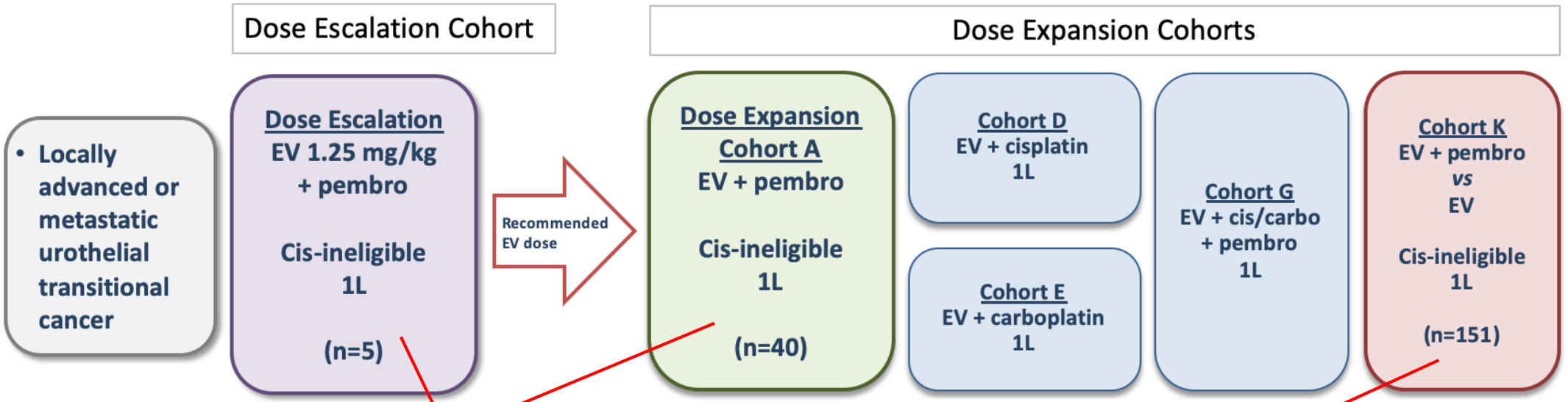
Median follow-up -> 15.9 months



Loriot Y, et al. N Engl J Med 2023;389(21):1961.
Siefker-Radtke O, et al. Ann Oncol 2023;34(suppl_2):S1202-S1228.

Tratamiento sistémico

Nueva estrategia: EV + pembrolizumab



Confirmed ORR 95% CI	73.3% (33/45) (58.1, 85.4)
Complete response	15.6% (7/45)
Partial response	57.8% (26/45)

	EV+P (N=76)	EV Mono (N=73)
Confirmed ORR, n (%) (95% CI)	49 (64.5) (52.7, 75.1)	33 (45.2) (33.5, 57.3)
Best overall response, n (%)		
Complete Response	8 (10.5)	3 (4.1)
Partial Response	41 (53.9)	30 (41.1)
Stable Disease	17 (22.4)	25 (34.2)
Progressive Disease	6 (7.9)	7 (9.6)
Not Evaluable	3 (3.9)	5 (6.8)
No Assessment	1 (1.3)	3 (4.1)
Median time to objective response (range), mos	2.07 (1.1, 6.6)	2.07 (1.9, 15.4)
Median number of treatment cycles (range)	11.0 (1, 29)	8.0 (1, 33)

Friedlander TW, et al. J Clin Oncol 2021;39(suppl 15; abstr 4528).
Rosenberg JE, et al. Ann Oncol 2022;abstr2895.

Cáncer de vejiga avanzado

Tratamiento sistémico

Nueva estrategia: 1L EV + pembrolizumab

EV-302

N=860

- Locally advanced or metastatic urothelial carcinoma
- No prior chemotherapy for metastatic disease
- ECOG PS 0-1
- GFR ≥ 30 ml/min

RANDOMIZED

→ Enfortumab vedotin 1.25 mg
Pembrolizumab 200 mg
Máx 35 cycles

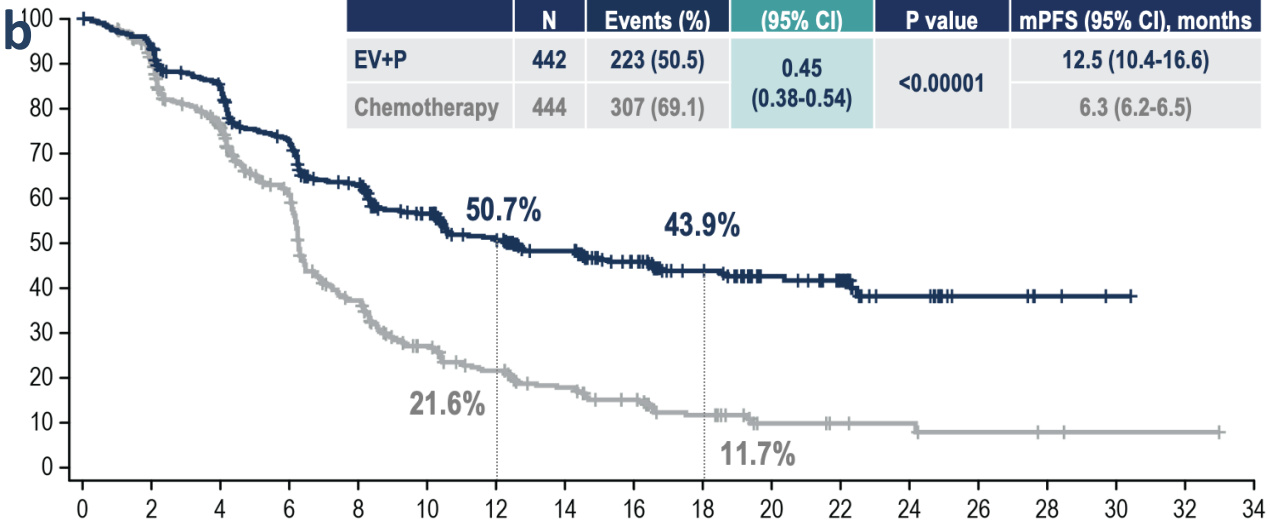
→ Gemcitabine 1000 mg/m²
Cisplatin 70 mg/m²
or
Gemcitabine 1000 mg/m²
Carboplatin AUV 4.5-5
Máx 6 cycles

Primary endpoint: OS and PFS by BIRC

Median follow-up -> 17.2 months

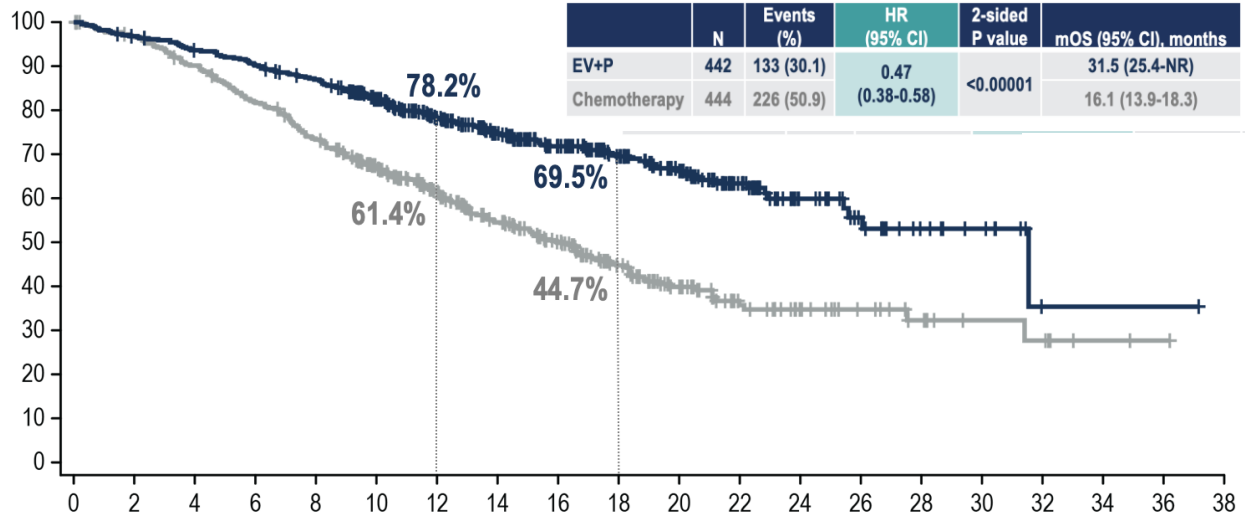
PFS by BIRC

	N	Events (%)	HR (95% CI)	2-sided P value	mPFS (95% CI), months
EV+P	442	223 (50.5)	0.45 (0.38-0.54)	<0.00001	12.5 (10.4-16.6)
Chemotherapy	444	307 (69.1)			6.3 (6.2-6.5)



OS

	N	Events (%)	HR (95% CI)	2-sided P value	mOS (95% CI), months
EV+P	442	133 (30.1)	0.47 (0.38-0.58)	<0.00001	31.5 (25.4-NR)
Chemotherapy	444	226 (50.9)			16.1 (13.9-18.3)



Powles T, et al. Ann Oncol 2023;34(suppl_2):S1254-S1335.

Cáncer de vejiga avanzado

Tratamiento sistémico

Nueva estrategia: 1L EV + pembrolizumab

EV-302

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- No prior chemotherapy for metastatic disease
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Máx 35 cycles

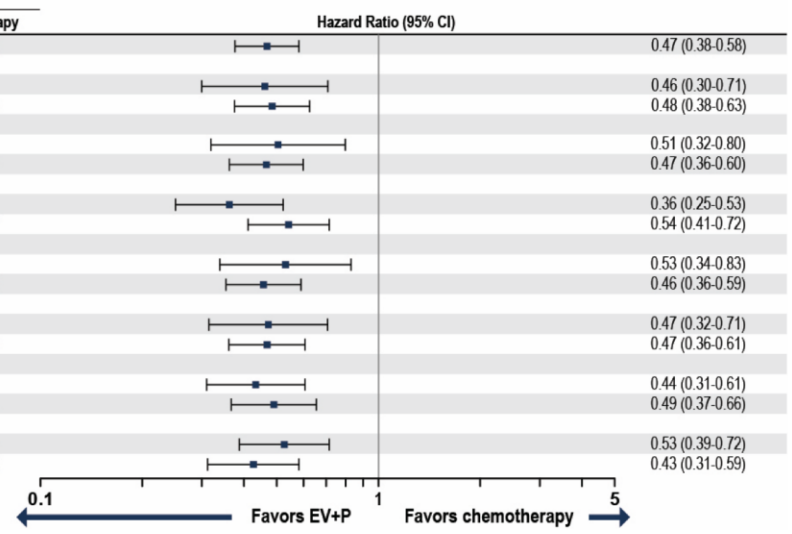
→ **Gemcitabine 1000 mg/m²**
Cisplatin 70 mg/m²
or
Gemcitabine 1000 mg/m²
Carboplatin AUV 4.5-5
Máx 6 cycles

Primary endpoint: OS and PFS by BIRC

Median follow-up -> 17.2 months

OS in pre-specified supgroups

Subgroup	Events/N EV+P	Events/N Chemotherapy	Hazard Ratio (95% CI)
Overall	133/442	226/444	0.47 (0.38-0.58)
Age			
<65 years	39/144	58/135	0.46 (0.30-0.71)
≥65 years	94/298	168/309	0.48 (0.38-0.63)
Sex			
Female	32/98	54/108	0.51 (0.32-0.80)
Male	101/344	172/336	0.47 (0.36-0.60)
ECOG PS			
0	44/223	94/215	0.36 (0.25-0.53)
1-2	89/219	131/227	0.54 (0.41-0.72)
Primary disease site of origin			
Upper tract	38/135	45/104	0.53 (0.34-0.83)
Lower tract	94/305	180/339	0.46 (0.36-0.59)
Liver metastases			
Present	43/100	67/99	0.47 (0.32-0.71)
Absent	90/342	159/345	0.47 (0.36-0.61)
PD-L1 expression			
Low (CPS <10)	53/184	99/185	0.44 (0.31-0.61)
High (CPS ≥10)	79/254	125/254	0.49 (0.37-0.66)
Cisplatin eligibility			
Eligible	69/244	106/234	0.53 (0.39-0.72)
Ineligible	64/198	120/210	0.43 (0.31-0.59)



OS

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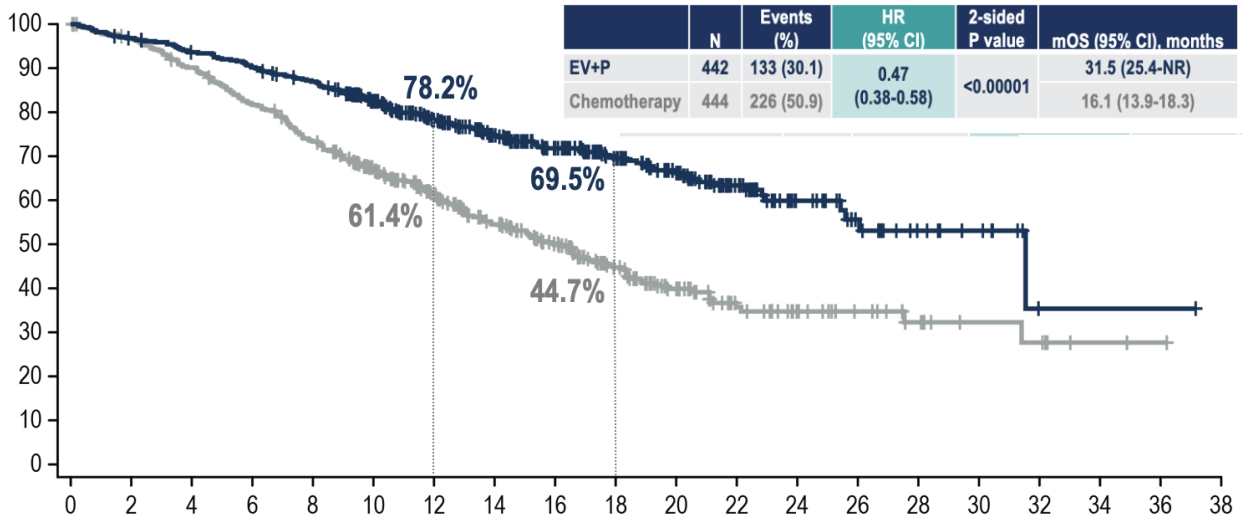
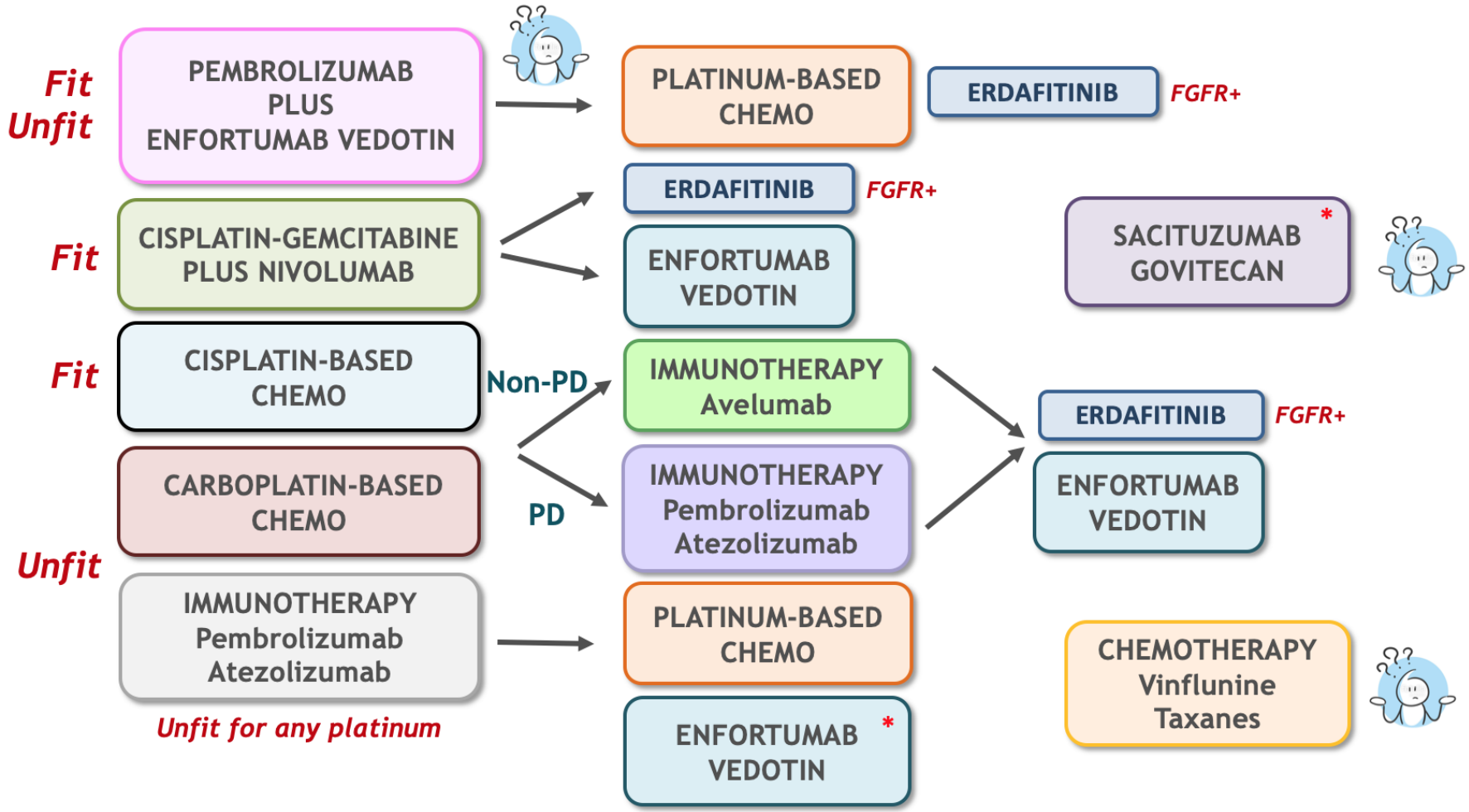


Powles T, et al. Ann Oncol 2023;34(suppl_2):S1254-S1335.

Tratamiento sistémico

¿Cómo cambiará el estándar?



Guía de prática clínica

Clinical and Translational Oncology (2022) 24:613–624
https://doi.org/10.1007/s12094-022-02815-w

CLINICAL GUIDES IN ONCOLOGY

Check for updates

SEOM-SOGUG clinical guideline for localized muscle invasive and advanced bladder cancer (2021)

Begoña P. Valderrama[1] · Aránzazu González-del-Alba[2] · Rafael Morales-Barrera[3] · Ignacio Peláez Fernández[4] · Sergio Vázquez[5] · Cristina Caballero Díaz[6] · Montserrat Domènech[7] · Ovidio Fernández Calvo[8] · Alfonso Gómez de Liaño Lista[9] · José Ángel Arranz Arija[10]

Muchas gracias por vuestra atención

SEOM
Sociedad Española de Oncología Médica