XXIV Simposio de Revisiones en Cáncer

"Tratamiento médico del cáncer en el año 2022"

Mantenimiento en 1L de CU: un nuevo estándar de tratamiento

Aránzazu González del Alba
Servicio de Oncología Médica
Hospital Universitario Puerta de Hierro
Majadahonda, Madrid
7 de febrero de 2022

ARÁN

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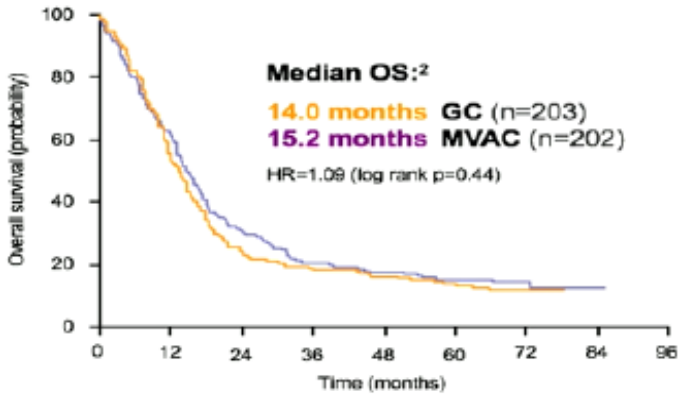
Conflictos de interes

- Consultant or Advisory Role: Astellas Pharma, Janssen, Bayer, Roche, Novartis, Pfizer, Bristol-Myers-Squibb, Astra Zeneca, Ipsen, Eisai Pierre-Fabre, Sanofi, MSD, EUSA Pharma
- Speaking honoraria: Sanofi, Ipsen, Roche, Astellas Pharma, Bayer, Merck
- Travel/Accommodations: Bristol-Myers-Squibb, Pfizer, Roche, Ipsen, Astellas

Treatment options in first-line mUC

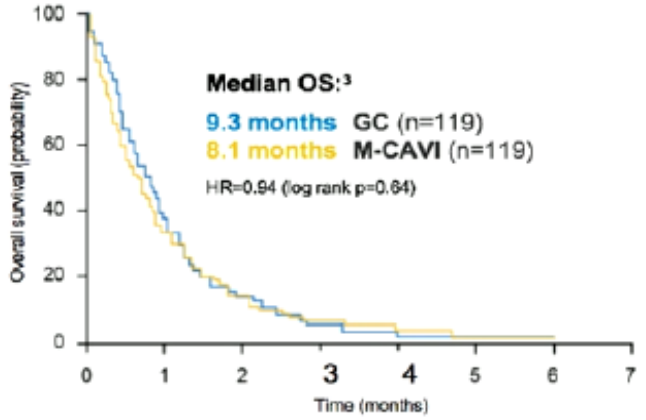
Fit patients

ORR 50% (12% CR)
ORR + SD: 83%
Median PFS 7.7 months
Median OS 15 months
1 y OS: 60%



Unfit patients

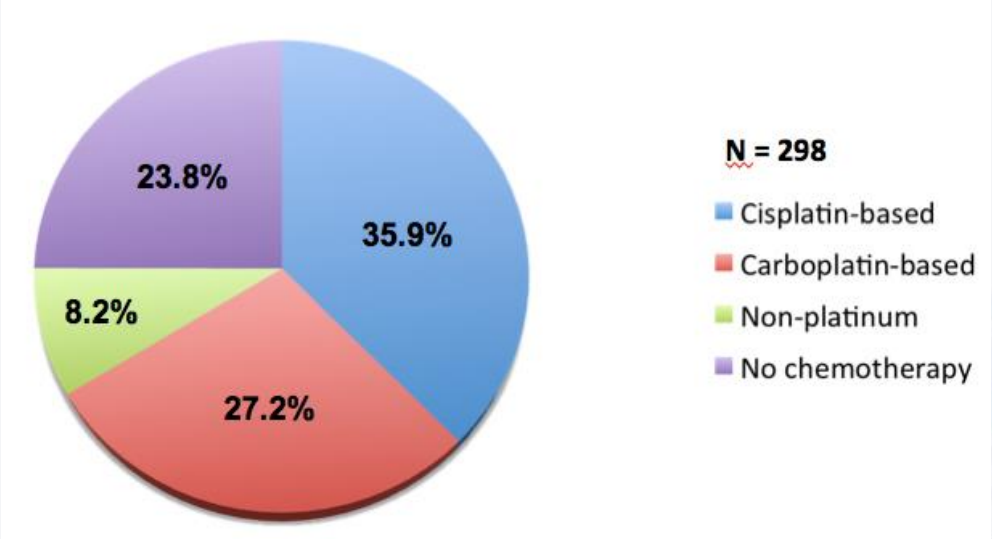
ORR 36% (3%)
ORR + SD: 73%
Median PFS 5.8 months
Median OS 9 months
1 y OS: 37%



von de Maase H et al, J Clin Oncol 2000; Von de Maase H et al J Clin Oncol 2005; de Santis M et al J Clin Oncol 2011

Primera línea: «unfit»

✓ Frecuencia administración de cisplatino



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

Table 4. Proposed Working Group Eligibility Criteria for Clinical Trials Enrolling Patients With Metastatic Urothelial Carcinoma "Unfit" for Cisplatin-Based Chemotherapy

Eligibility Criteria (at least one of the following)
WHO or ECOG PS of 2 or Karnofsky PS of 60%-70%
Creatinine clearance (calculated or measured) < 60 mL/min
CTCAE v4 grade ≥ 2 audiometric hearing loss
CTCAE v4 grade ≥ 2 peripheral neuropathy
NYHA Class III heart failure

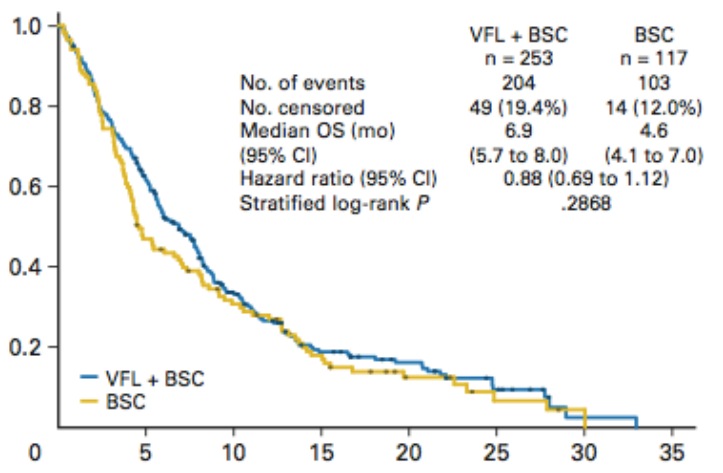
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; NYHA, New York Heart Association; PS, performance status.

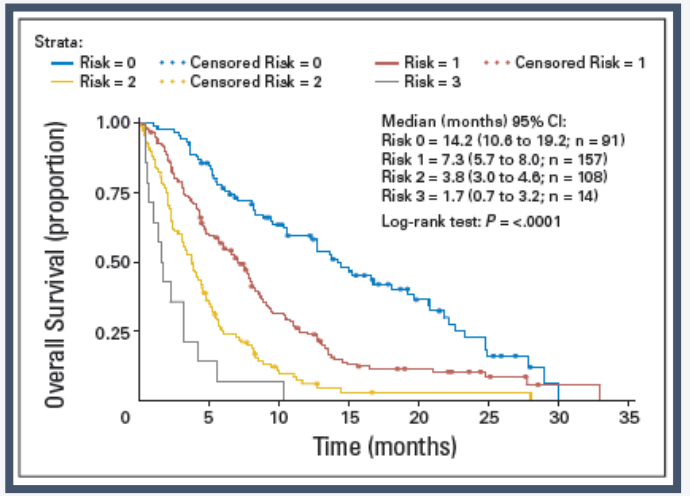
Sonpavde et al. Clin Genitourin Cancer. 2012; 10(1): 1.
Galsky et al. J Clin Oncol. 2011; 29(17): 2.432.

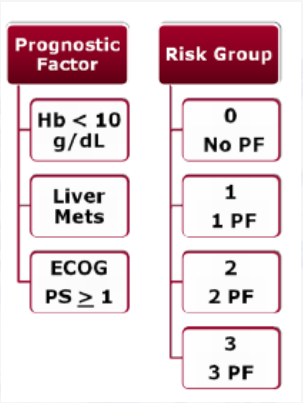
Cáncer de vejiga metastásico. Segunda línea. QT

- **Estudio en fase III: vinflunina**
  - ✓ n= 370

SG







Nº factores pronósticos	SGm
0	14.2 meses
1	7.3 meses
2	3.8 meses
3	1.7 meses

Bellmunt et al. J Clin Oncol. 2009; 27(27): 4.454.
Bellmunt et al. J Clin Oncol. 2010; 28(11): 1.850.

Cáncer de vejiga metastásico. Segunda línea

Ensayos fase III. Inmunoterapia

KEYNOTE-045 Study Design (NCT02256436)

- Urothelial cancer
- Progression or recurrence of urothelial cancer following a first-line platinum-containing regimen.
- No more than 2 prior lines of systemic chemotherapy.

Randomization
N = 542 patients

Estimated timelines
Estimated completion: Sept 2016 (Early termination)

IMvigor211 Study Design (NCT02302807)

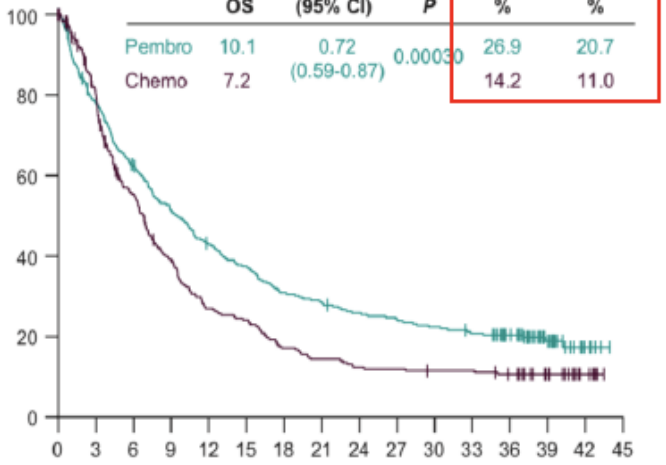
- Urothelial cancer
- Progression or recurrence of urothelial cancer following a first-line platinum-containing regimen.

Randomization
N = 932 patients

Estimated timelines
Estimated completion: Nov 2017

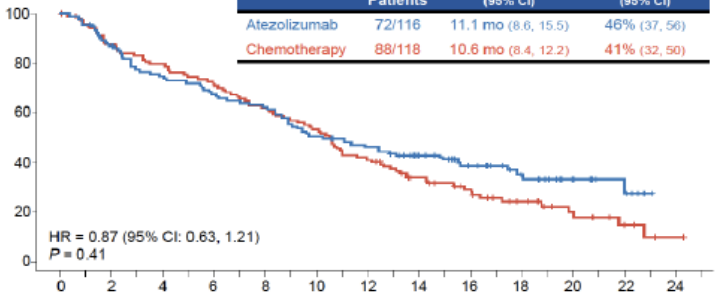
SG

	Median OS	HR (95% CI)	P	24-Month OS Rate, %	36-Month OS Rate %
Pembro	10.1	0.72 (0.59-0.87)	0.00030	26.9	20.7
Chemo	7.2			14.2	11.0



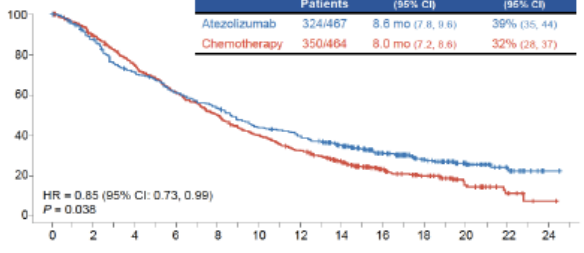
OS PD-L1+

	Events/ Patients	Median OS (95% CI)	12-mo OS Rate (95% CI)
Atezolizumab	72/116	11.1 mo (8.6, 15.5)	46% (37, 56)
Chemotherapy	88/118	10.6 mo (8.4, 12.2)	41% (32, 50)



OS ITT

	Events/ Patients	Median OS (95% CI)	12-mo OS Rate (95% CI)
Atezolizumab	324/467	8.6 mo (7.8, 9.6)	39% (35, 44)
Chemotherapy	350/464	8.0 mo (7.2, 8.6)	32% (28, 37)



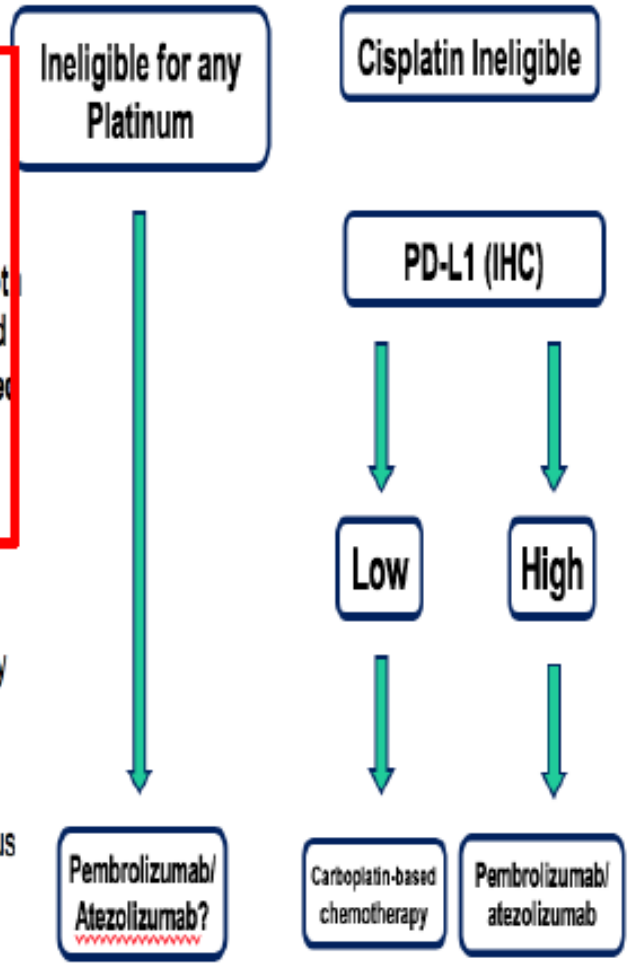
Unfit patients: IO monotherapy

	Atezolizumab	Pembrolizumab
Phase	Phase II	Phase II
Number of patients	119	370
ORR	24% (8%CR)	29% (7%CR)
Median OS	16.3 months	11.3 months
Median PFS	2.7 months	2.2 months

Table adapted from Grivas P, ASCO 2017

5/18/2018 - FDA Alert

- In 2 ongoing clinical trials (KEYNOTE-361 and IMVIGOR-130), the Data Monitoring Committees' (DMC) found patients in the **monotherapy (pembrolizumab/atezolizumab) arms of both trials with PD-L1 low status had decreased survival compared to patients who received cisplatin- or carboplatin-based chemotherapy**
- Both trials have stopped enrolling patients whose tumors have PD-L1 low status to the pembrolizumab or atezolizumab monotherapy arms
- The monotherapy arms remain open only to patients whose tumors have PD-L1 high status

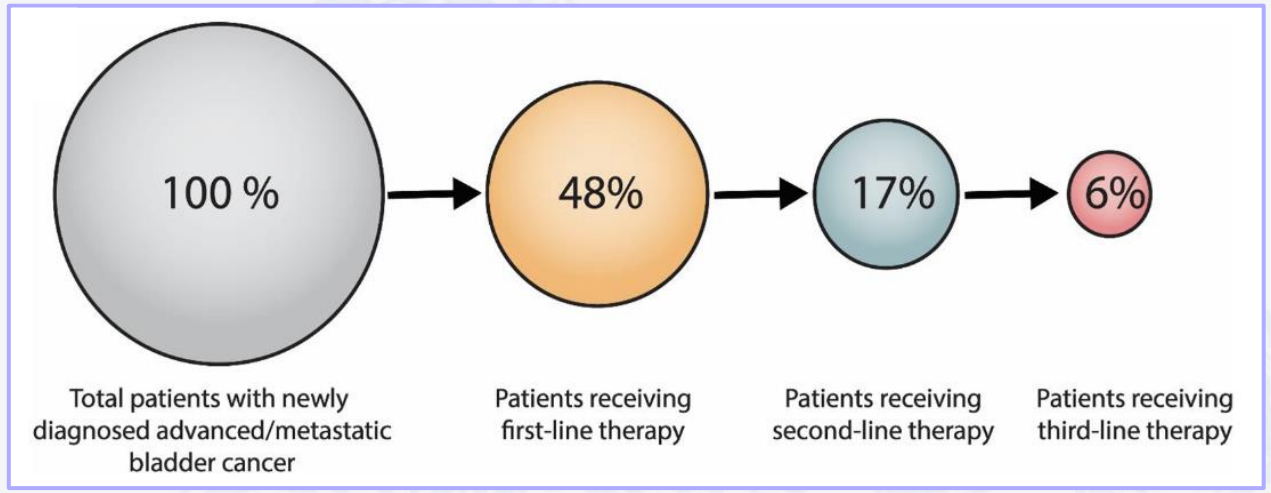


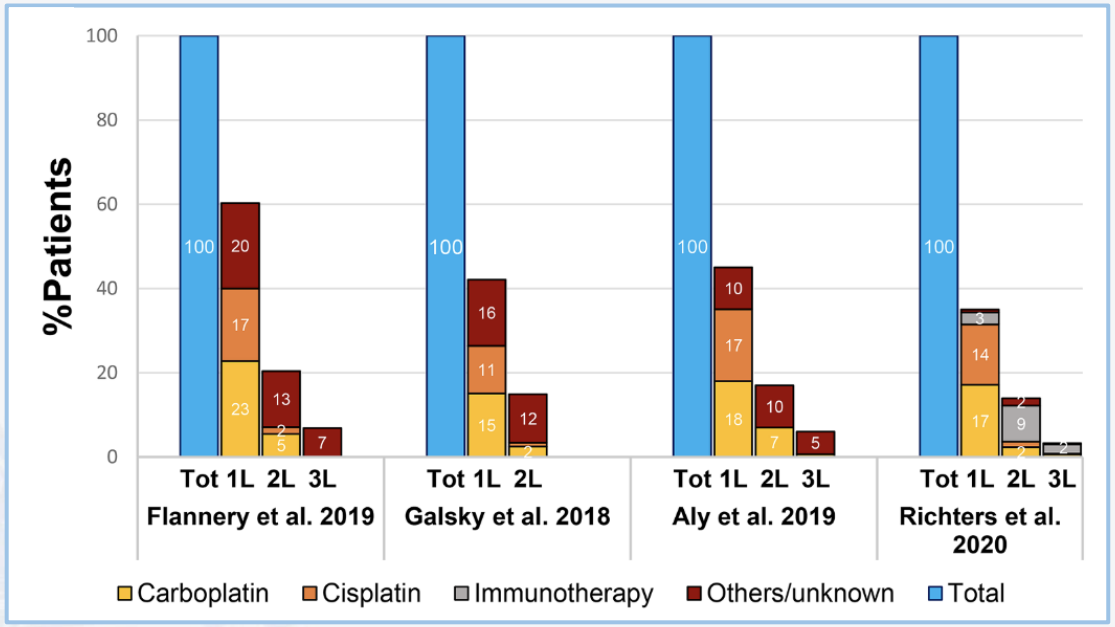
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

FDA. Https://www.fda.gov/DrugsSafety/ucm608075.htm. May 18,2018.
EMA Press release, 1 June 2018. Accedded 9 Jun 2018.

Metastatic Urotelial cancer

- ***Real-world***





Swami U, et al. Cancer Treat Res Commun 2021;27:100325.

Primera línea cáncer urotelial

Combinaciones IO-QT

N=1200

- Locally advanced or mUC
- No prior systemic therapy in the metastatic setting
- ECOG PS ≤ 2
- 1L platinum-eligible
- N = 1200
- Randomised 1:1:1

→ Arm A: Atezo + plt/gem
→ Arm B: Atezo monotherapy
→ Arm C: Placebo + plt/gem

Obj 1º: SLP (A vs. C) -> SG (A vs.C)

IMvigor130

N=990

Key Eligibility Criteria
- UC of renal pelvis, ureter, bladder or urethra
- Locally advanced unresectable or metastatic disease
- No prior systemic therapy for advanced disease
- ECOG PS 0, 1 or 2
- Tissue sample for PD-L1 assessment[a]

R (1:1:1)

→ Pembrolizumab 200 mg Q3W + Gemcitabine 1000 mg/m² + Cisplatin 70 mg/m² *OR* Carboplatin AUC 5 for ≤6 cycles → Pembrolizumab 200 mg Q3W for ≤29 cycles
→ Pembrolizumab 200 mg Q3W for ≤35 cycles
→ Gemcitabine 1000 mg/m² on days 1 and 8 Q3W + Cisplatin 70 mg/m² *OR* Carboplatin AUC 5 on day 1 Q3W for ≤6 cycles

Obj 1º: SLP -> SG (A VS C)

KEYNOTE-361

N=1032

Patients with untreated, unresectable, locally advanced or metastatic UC N=1032

1:1:1

R

→ **Durvalumab** 1500 mg q4w until progression (n=346)
→ **Durvalumab** 1500 mg q4w until progression + **Tremelimumab** 75 mg q4w for up to 4 doses (n=342)
→ **SoC Chemotherapy** (gemcitabine + cisplatin or carboplatin, up to 6 cycles) (n=344)

Obj 1º: SG (durva vs. QT en PD-L1+)
SG (durva + treme vs. QT)

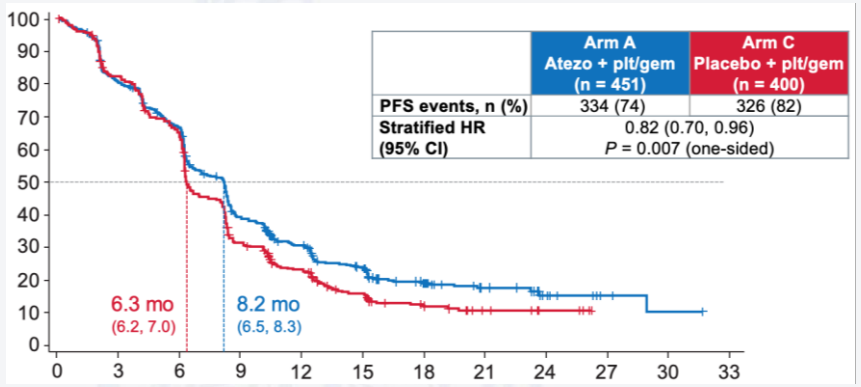
DANUBE

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.

Primera línea cáncer urotelial

Combinaciones IO-QT

SLP

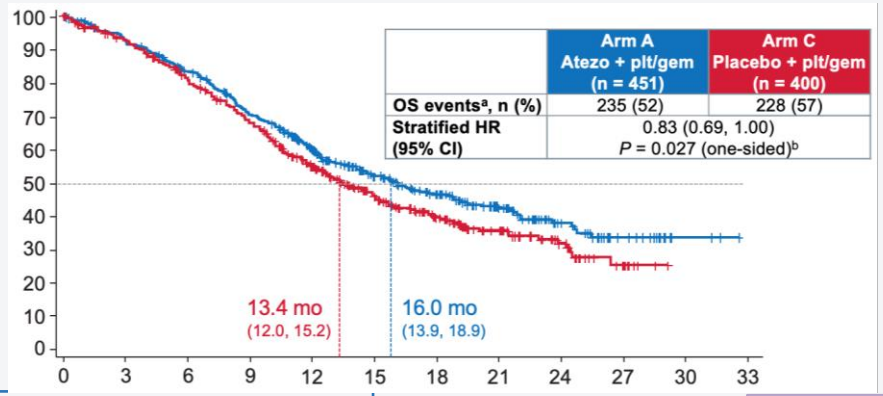


	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
PFS events, n (%)	334 (74)	326 (82)
Stratified HR (95% CI)	0.82 (0.70, 0.96) *P* = 0.007 (one-sided)	

Obj 1º: SLP (A vs. C) -> SG (A vs.C)

IMvigor130

SG

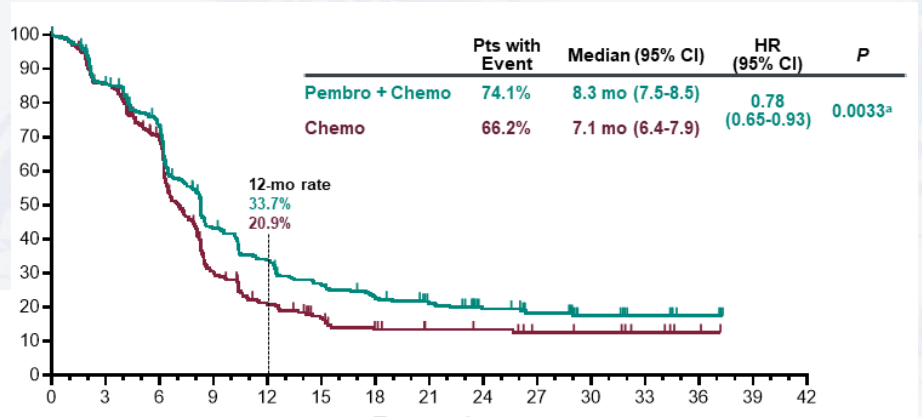


	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
OS events[a], n (%)	235 (52)	228 (57)
Stratified HR (95% CI)	0.83 (0.69, 1.00) *P* = 0.027 (one-sided)[b]	

Obj 1º: SLP (A vs. C) -> SG (A vs.C)

IMvigor130

SLP

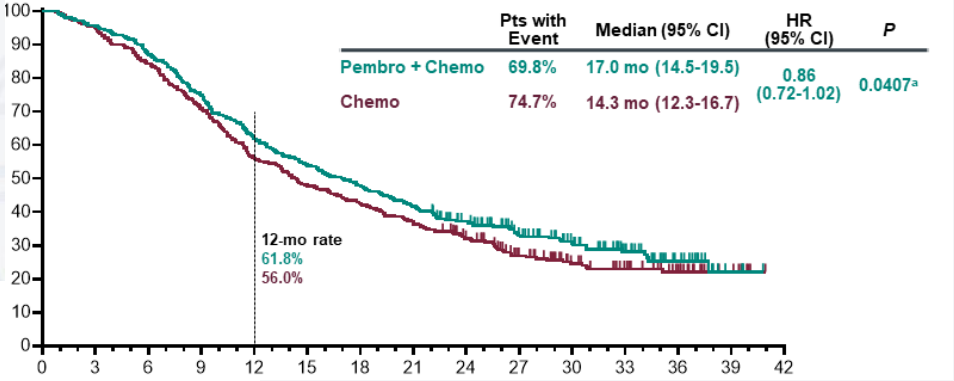


	Pts with Event	Median (95% CI)	HR (95% CI)	*P*
Pembro + Chemo	74.1%	8.3 mo (7.5-8.5)	0.78 (0.65-0.93)	0.0033[a]
Chemo	66.2%	7.1 mo (6.4-7.9)		

Obj 1º: SLP -> SG (A VS C)

KEYNOTE-361

SG



	Pts with Event	Median (95% CI)	HR (95% CI)	*P*
Pembro + Chemo	69.8%	17.0 mo (14.5-19.5)	0.86 (0.72-1.02)	0.0407[a]
Chemo	74.7%	14.3 mo (12.3-16.7)		

Obj 1º: SLP -> SG (A VS C)

KEYNOTE-361

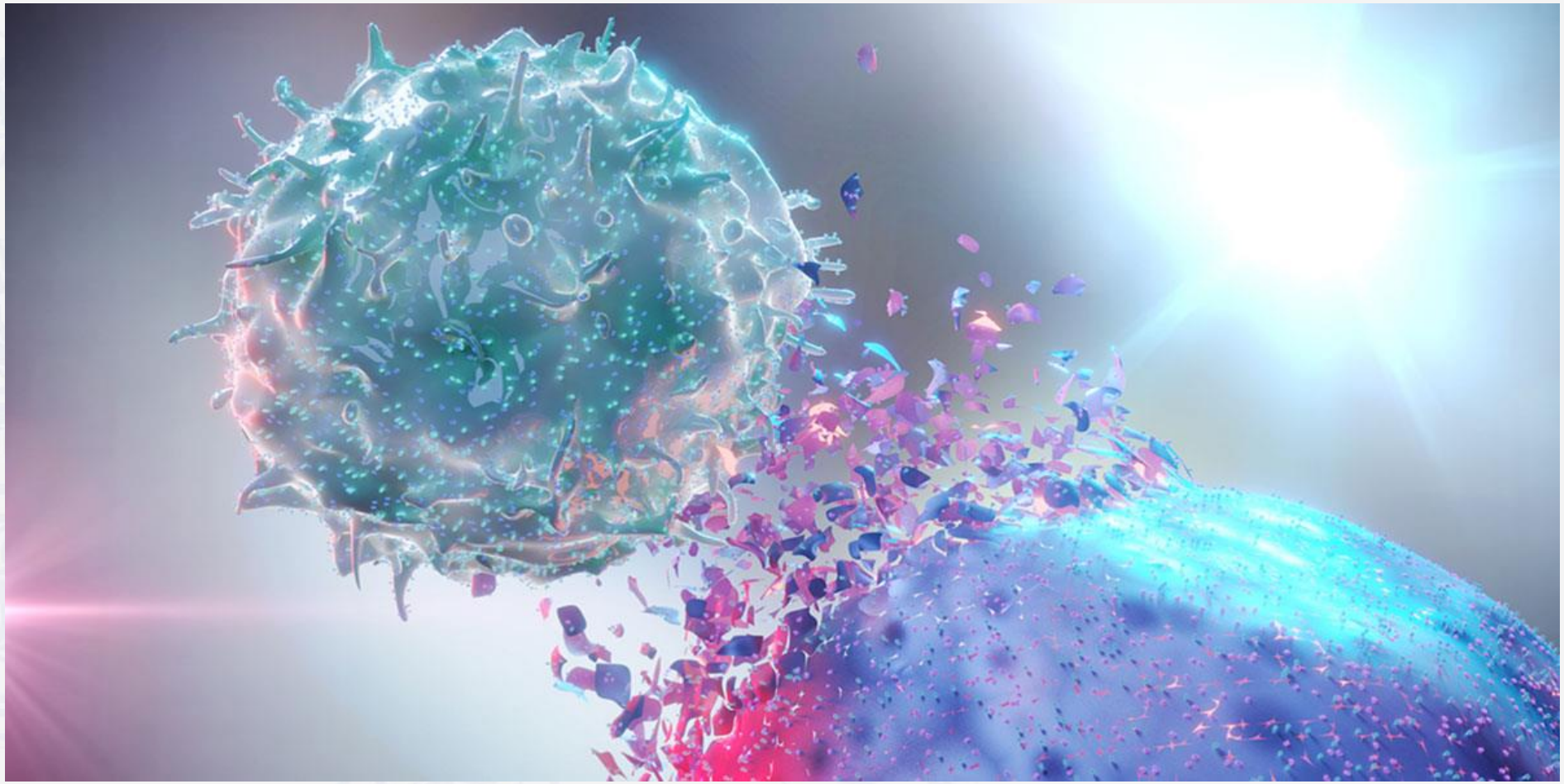
Galsky MD, et al. Lancet 2020;395(10236):1547
Alva A, et al. Ann Oncol 2020;31(suppl_4):S1142

Immune/chemotherapy combinations in front line UC.

	RR in ITT IO vs chemo	PFS in ITT (HR with 95%CI)	OS in ITT (HR with 95%CI)	OS in PD-L1 +ve (HR with 95%CI)	Subsequent IO therapy in control	mOS for chemo in ITT (months)
Atezolizumab & chemotherapy	**47 vs 44%**	**0.82** (0.70, 0.96)	**0.83** 0.69-1.00	**0.74** 0.49-1.12	**20%**	**13.4** **12.0-15.2**
Pembrolizumab & Chemotherapy	**55 vs 45%**	**0.78** (0.65-0.93)	**0.86** 0.72-1.02	**0.90** 0.69-1.18	**48%**	**14.3** **12.3-15.1**

1] Adding atezolizumab or pembrolizumab to chemo has similar, modest effects on efficacy. The positive atezo trial (IM130) and negative pembro trial (KN361) is likely due to differences in design rather than differences in drug. The same could be said about the 2nd line space where pembro was +ve (KN45) and atezo was –ve (IM211).
2] The benefit is not enough to change practice. Final OS atezo data is awaited.
3] More patients in the pembrolizumab trial received subsequent immune therapy (but OS HR 0.90)
4] The PD-L1 biomarker did not enrich for responders in either study.
6] Progression of disease as best response was the same in the chemotherapy and chemotherapy + IO arm. Therefore immune therapy is not rescuing any patients from progression.
5] The studies had a maintenance period of IO after the combination, which is likely to be responsible for part or all of the benefits seen. Sequencing therapy is preferable to combining.

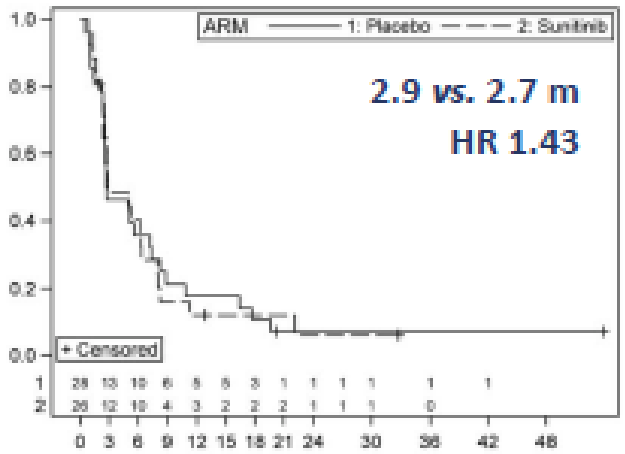
¿Como mejorar estos resultados?



Mantenimiento en cáncer de vejiga avanzado tras respuesta a platino

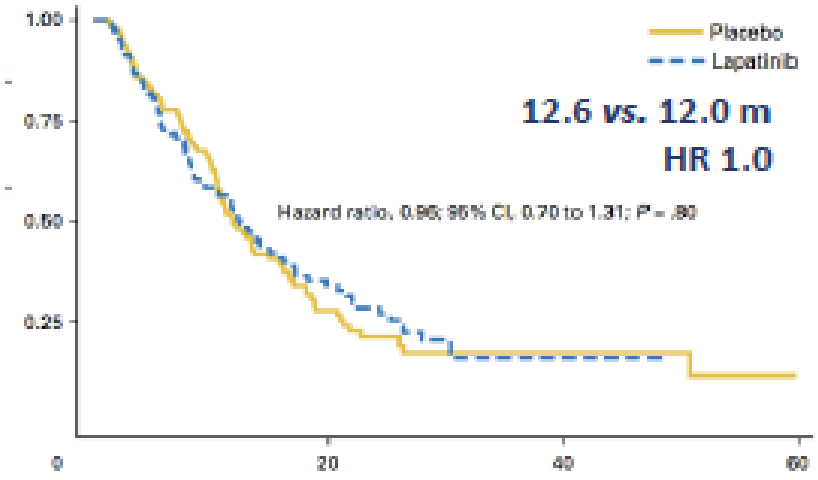
Sunitinib: fase IIR

- N=54



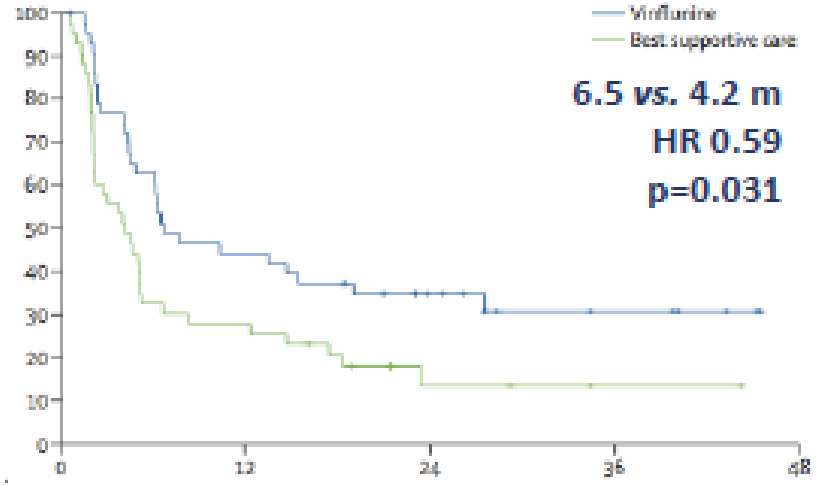
Lapatinib: fase IIR

- N=232



Vinflunina: fase IIR

- N=86



Grivas PD, et al. Cancer 2014;120:692.
Powles T, et al. J Clin Oncol 2017;35(1):48.
García Donas J, et al. Lancet Oncol 2017;18(5):672.

Mantenimiento en cáncer de vejiga avanzado tras respuesta a platino

HCRN GU14-182

RR 22%
PFS 2.7 months
OS 15.8 months

n= 108

QT-platino

≤8 ciclos.

Obj 1º: SLP (irRECIST)

- **Resp. Completa**
- **Resp. Parcial**
- **Enf. Estable**

Estratificación
- Tipo de respuesta a Qt
- Afectación ganglionar

RANDOMIZACIÓN

PEMBROLIZUMAB
200 mg/día
c/ 21d

Máx 24 meses

n= 52

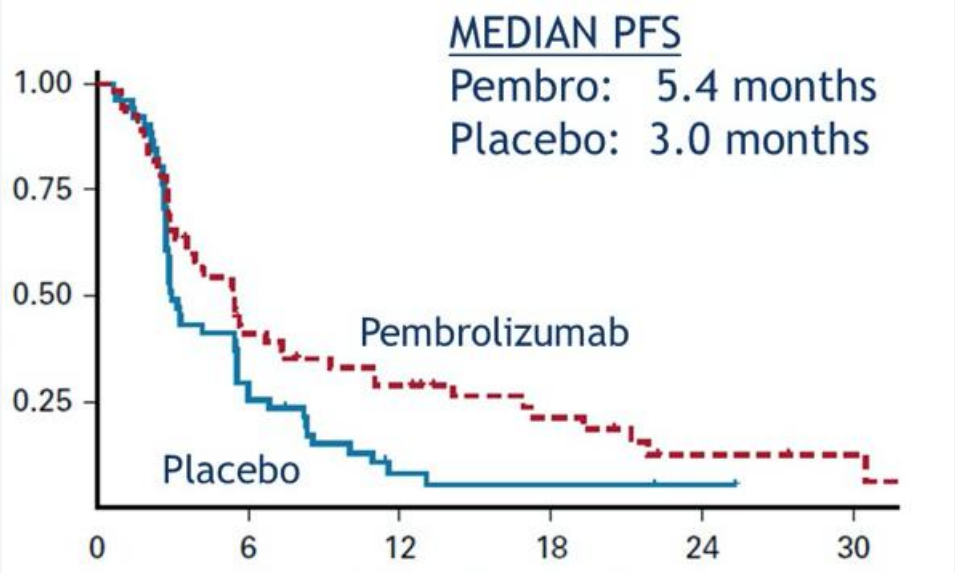
PLACEBO

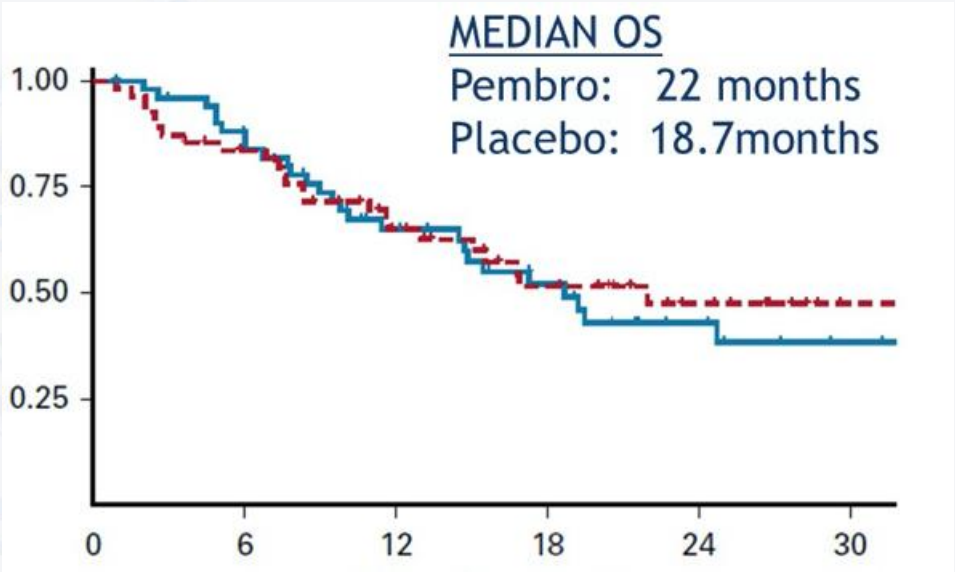
Máximo 24 meses

13% died

CRITERIOS DE INCLUSIÓN:
- Carcinoma urotelial localmente avanzado/ metastásico.
- Beneficio clínico con Qt de primera línea

Objetivo primario: SLP





Galsky et al. J Clin Oncol. 2020; 38(16): 1.797.

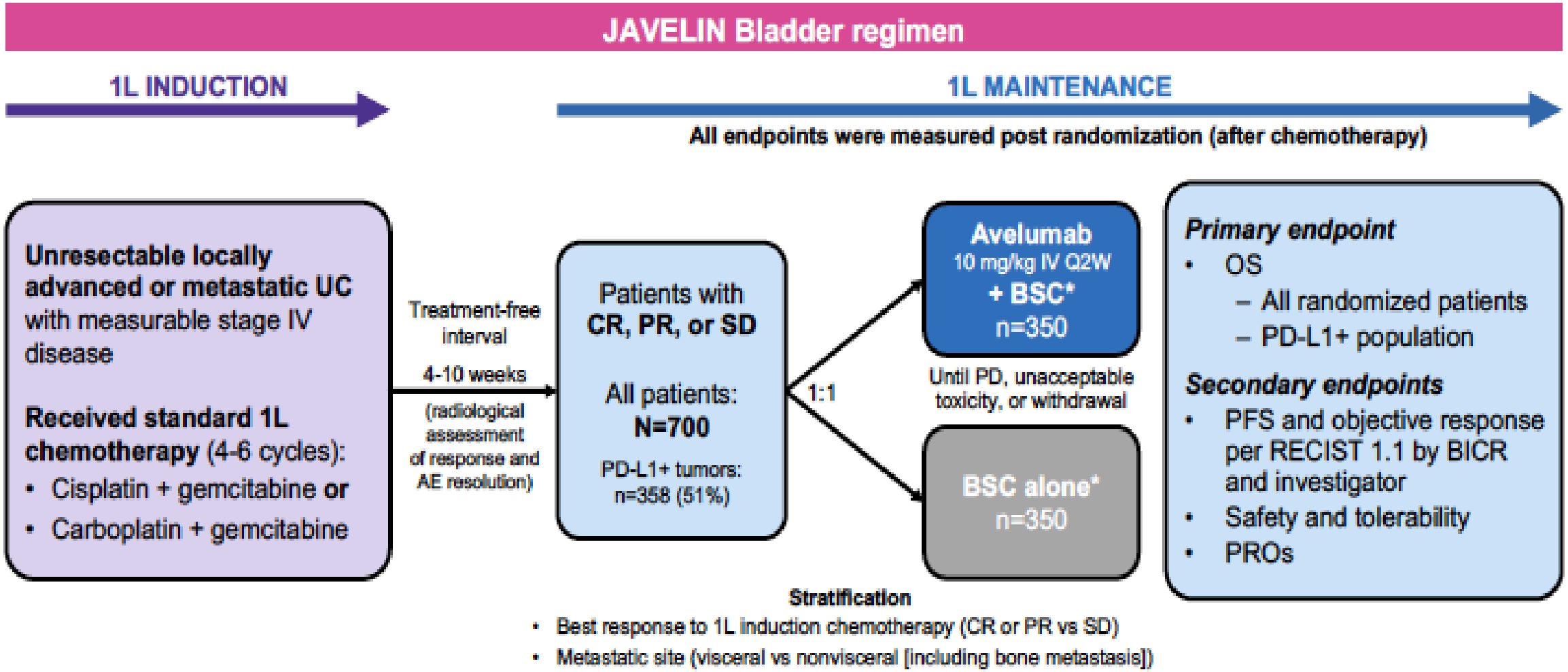
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma

T. Powles, S.H. Park, E. Voog, C. Caserta, B.P. Valderrama, H. Gurney, H. Kalofonos, S. Radulović, W. Demey, A. Ullén, Y. Loriot, S.S. Sridhar, N. Tsuchiya, E. Kopyltsov, C.N. Sternberg, J. Bellmunt, J.B. Aragon-Ching, D.P. Petrylak, R. Laliberte, J. Wang, B. Huang, C. Davis, C. Fowst, N. Costa, J.A. Blake-Haskins, A. di Pietro, and P. Grivas

The JAVELIN Bladder 100 international phase 3 trial evaluated avelumab 1L maintenance therapy[1]



Baseline characteristics were balanced between treatment arms

Selected baseline characteristics[1]

	Avelumab + BSC (N=350)	BSC alone (N=350)
Median age (range), years	68.0 (37.0-90.0)	69.0 (32.0-89.0)
Sex, %		
Male	76.0	78.6
Female	24.0	21.4
Race or ethnic group, %		
White	66.3	68.0
Asian	21.4	23.1
Black/African American	0.6	0
Other	6.0	4.3
Unknown	5.7	4.6
Pooled geographic region, %		
North America	3.4	6.3
Europe	61.1	58.0
Asia	20.9	21.1
Australia	9.7	10.6
Rest of the world	4.9	4.0
ECOG PS at randomization, %		
0	60.9	60.3
1	38.9	38.9
≥2	0.3	0.9
Site of primary tumor, %		
Upper tract	30.3	23.1
Lower tract	69.7	76.9
Site of baseline metastasis, %*		
Visceral	54.6	54.6
Nonvisceral*	45.4	45.4
PD-L1 status, %		
Positive†	54.0	48.3
Negative	39.7	37.4
Unknown	6.3	14.3
1L chemotherapy regimen, %		
Gemcitabine + cisplatin	52.3	58.9
Gemcitabine + carboplatin	42.0	34.9
Gemcitabine + cisplatin/carboplatin‡	5.7	5.7
Not reported	0	0.6
Best response to 1L chemotherapy, %		
CR/PR	72.3	72.0
SD	27.7	28.0

First line

Immunotherapy

JAVELIN Bladder 100

N=700

- 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

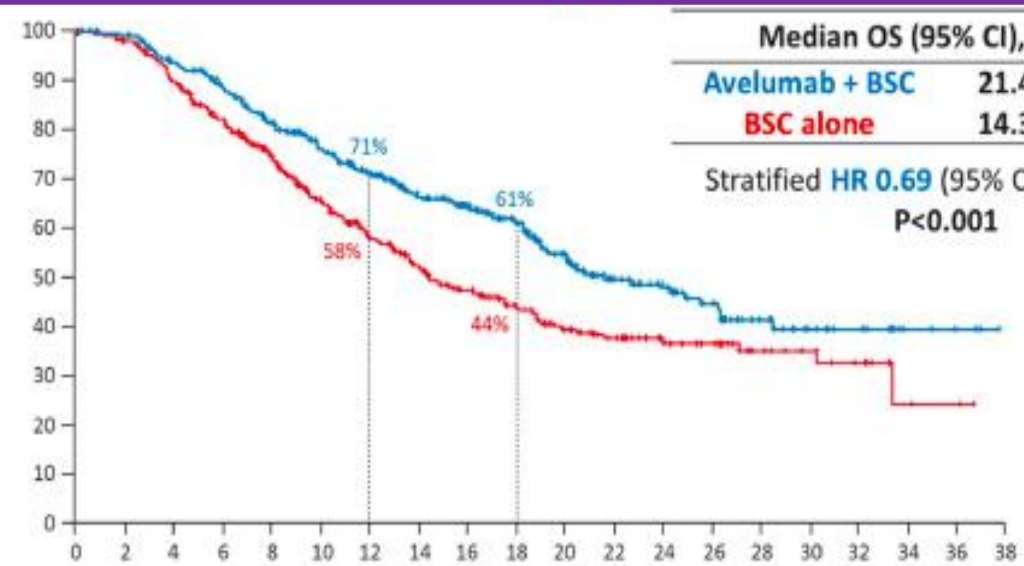
Stratification

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

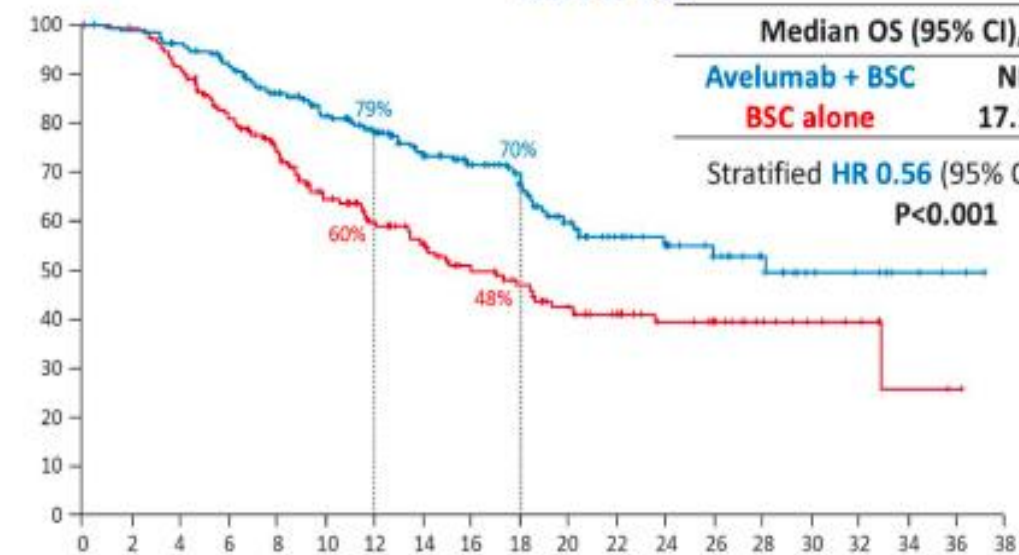
Primary endpoint: OS in ITT and PD-L1+

- Median follow-up -> 19.5 months

All endpoints measured post randomization (after chemotherapy)



OS PD-L1+



Powles T, et al. J Clin Oncol 38; 2020 (suppl; abstr LBA1).

Primera línea

Inmunoterapia

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

R 1:1

N=700

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

Until PD, unacceptable toxicity, or withdrawal

BSC alone* n=350

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

Primary endpoint
- OS

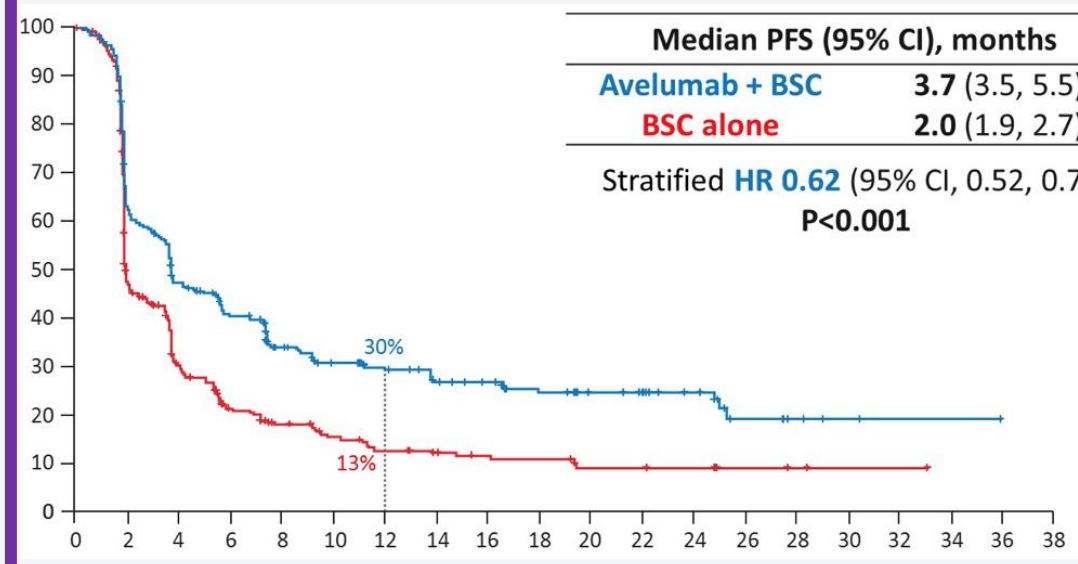
Primary analysis populations
- All randomized patients
- PD-L1+ population

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

All endpoints measured post randomization (after chemotherapy)

- Mediana seguimiento -> 19.5 meses

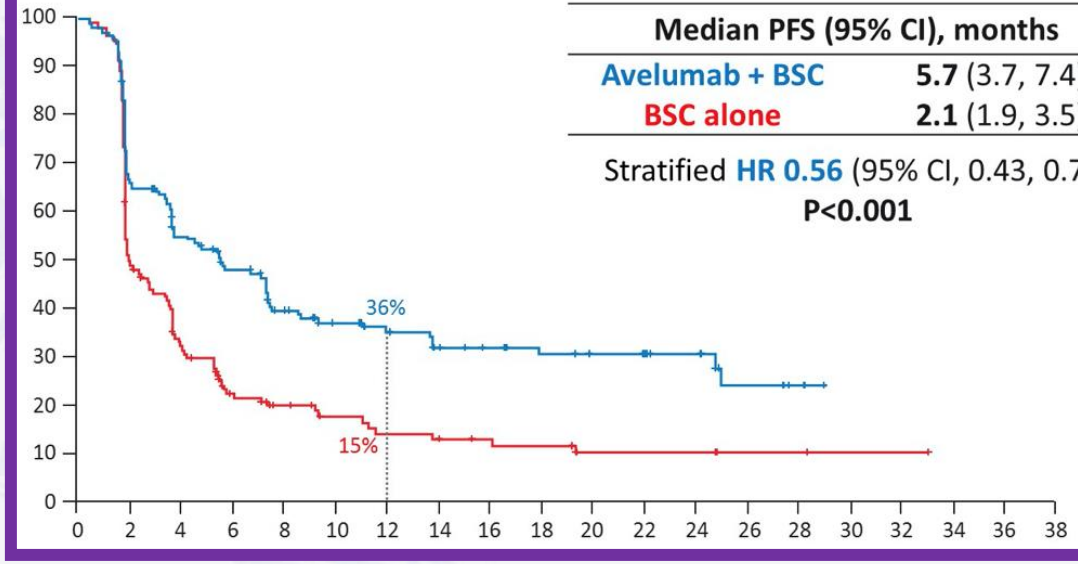
SLP ITT



Median PFS (95% CI), months	
Avelumab + BSC	**3.7** (3.5, 5.5)
BSC alone	**2.0** (1.9, 2.7)

Stratified **HR 0.62** (95% CI, 0.52, 0.75)
P<0.001

SLP PD-L1+



Median PFS (95% CI), months	
Avelumab + BSC	**5.7** (3.7, 7.4)
BSC alone	**2.1** (1.9, 3.5)

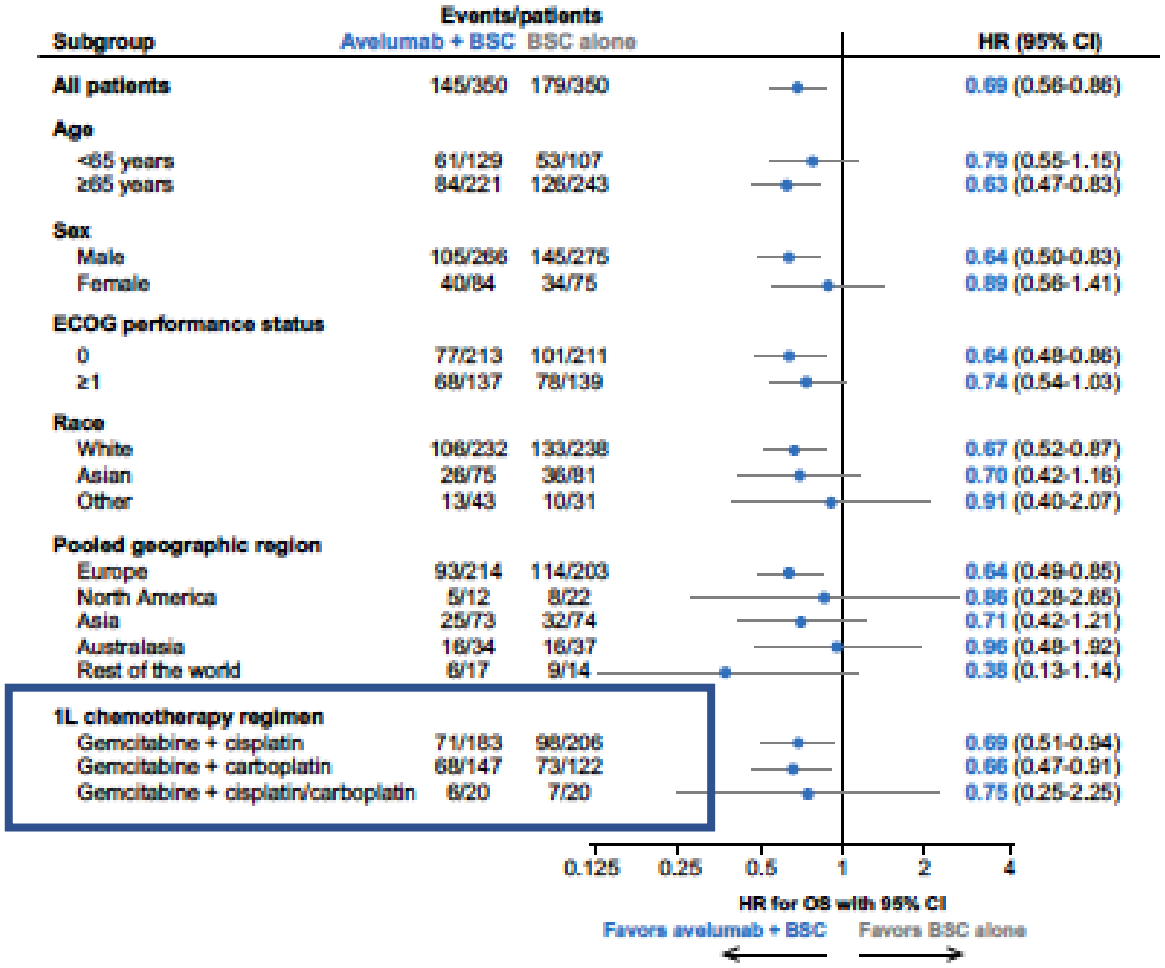
Stratified **HR 0.56** (95% CI, 0.43, 0.73)
P<0.001

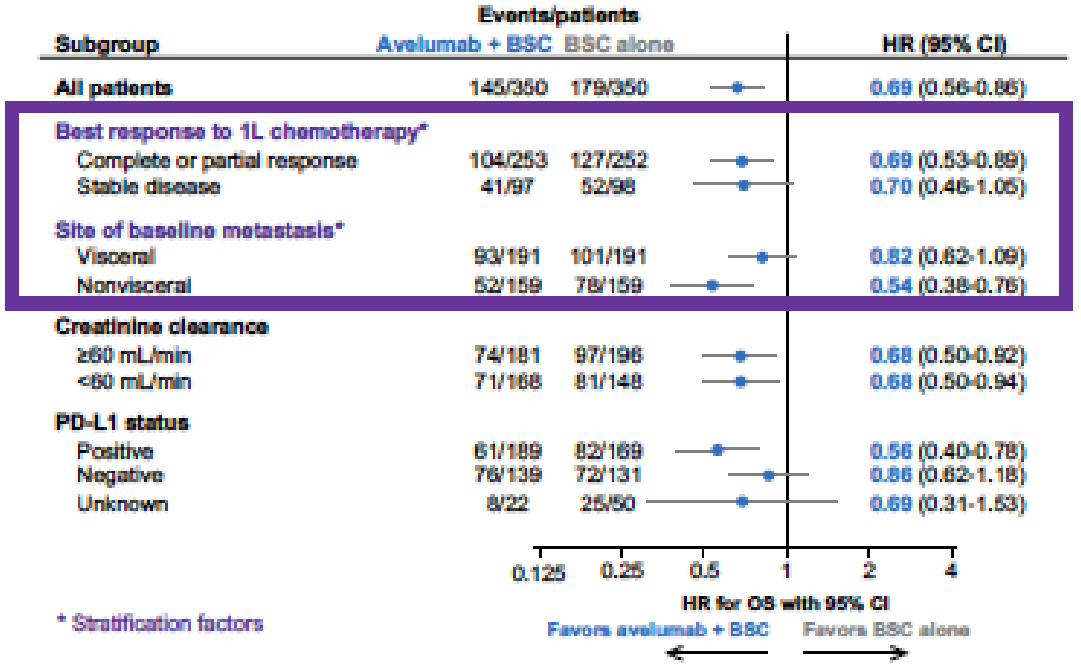
Powles T, et al. J Clin Oncol 38; 2020 (suppl; abstr LBA1).

Table 2. Responses in the Overall Population and the PD-L1–Positive Population.*

Variable	Overall Population			PD-L1–Positive Population		
	Avelumab Group (N=350)	Control Group (N=350)	Stratified Odds Ratio (95% CI)	Avelumab Group (N=189)	Control Group (N=169)	Stratified Odds Ratio (95% CI)
Confirmed objective response (95% CI) — %	9.7 (6.8–13.3)	1.4 (0.5–3.3)	7.46 (2.82–24.45)	13.8 (9.2–19.5)	1.2 (0.1–4.2)	12.70 (3.16–114.12)
Confirmed best overall response — no. (%)						
Complete response	21 (6.0)	3 (0.9)		18 (9.5)	1 (0.6)	
Partial response	13 (3.7)	2 (0.6)		8 (4.2)	1 (0.6)	
Stable disease	44 (12.6)	46 (13.1)		19 (10.1)	23 (13.6)	
Non–complete response or non–progressive disease†	66 (18.9)	45 (12.9)		38 (20.1)	22 (13.0)	
Progressive disease	130 (37.1)	169 (48.3)		59 (31.2)	82 (48.5)	
Could not be evaluated	76 (21.7)‡	85 (24.3)§		47 (24.9)¶	40 (23.7)‖	
Disease control — no. (%)**	144 (41.1)	96 (27.4)		83 (43.9)	47 (27.8)	
Median time to objective response (range) — mo	2.0 (1.7–16.4)	2.0 (1.8–7.0)		2.0 (1.7–16.4)	2.8 (1.8–3.8)	

OS benefits with avelumab 1L maintenance were seen across subgroups[1]

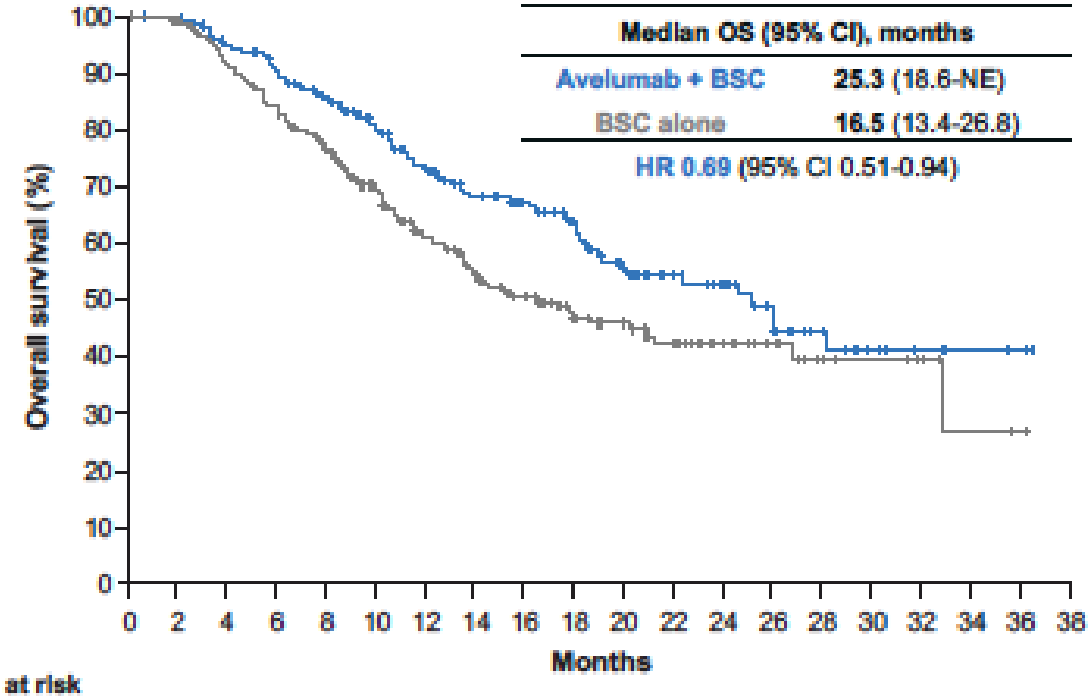




OS was longer for avelumab + BSC vs BSC alone (HR <1.0) in all protocol-specified subgroups[1]

OS benefits with avelumab 1L maintenance were similar in patients who received cisplatin + gemcitabine or carboplatin + gemcitabine as 1L chemotherapy

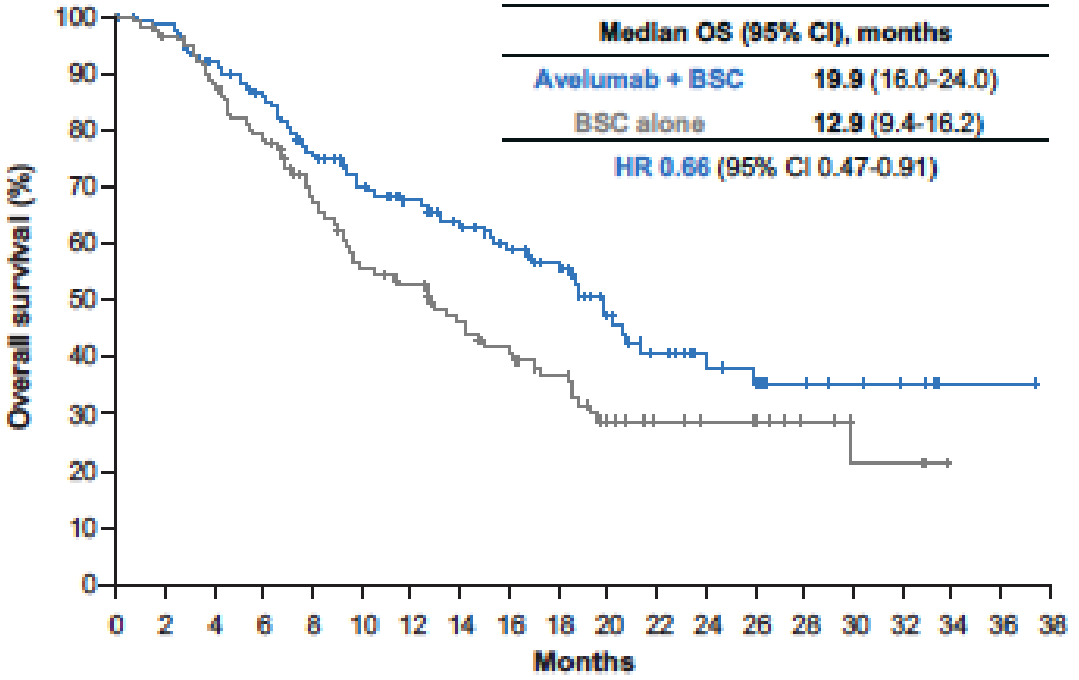
1L induction with cisplatin + gemcitabine



No. at risk

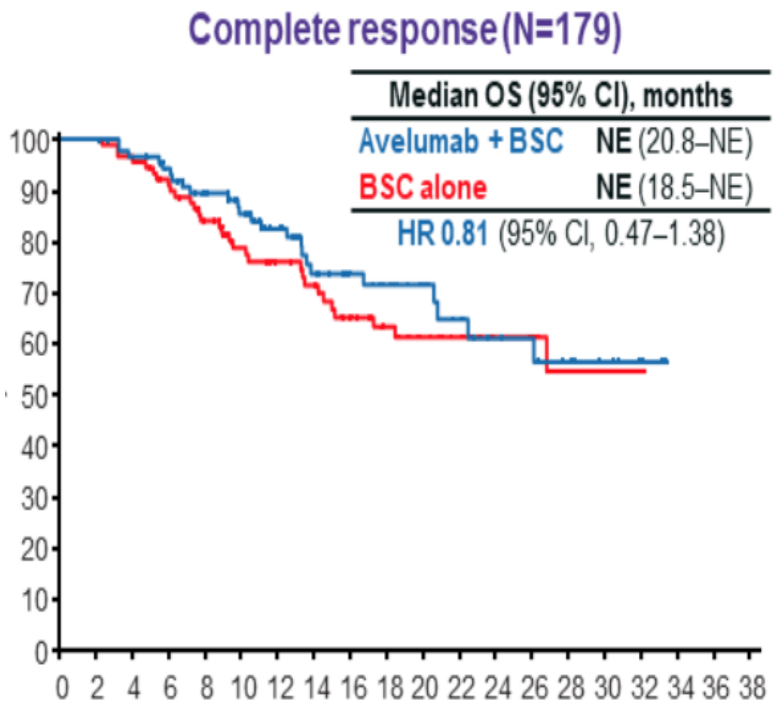
Avelumab + BSC	183	180	169	157	141	122	103	89	77	66	49	38	32	22	14	8	5	3	2	0
BSC	206	199	182	165	142	116	92	76	63	48	42	34	23	17	11	8	6	2	1	0

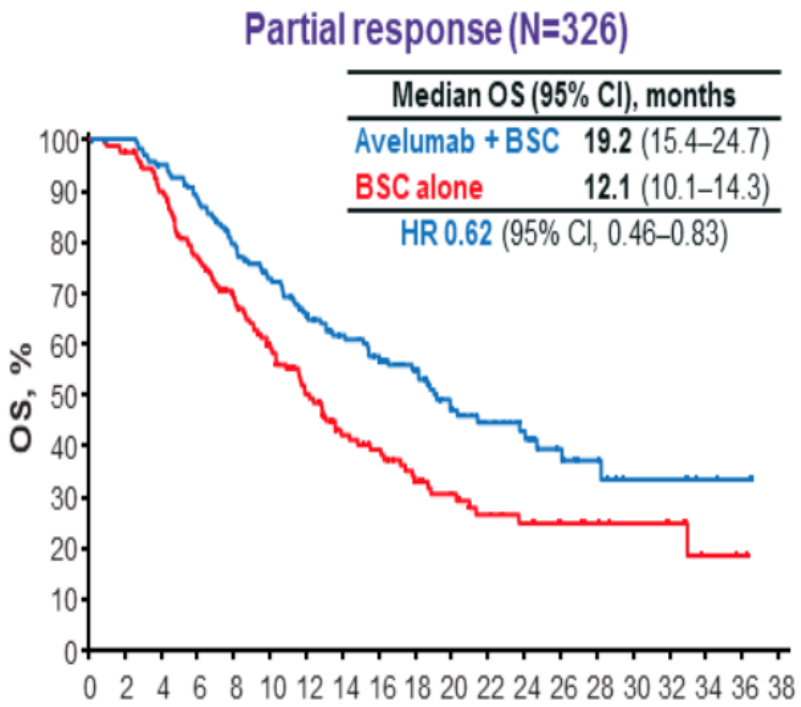
1L induction with carboplatin + gemcitabine

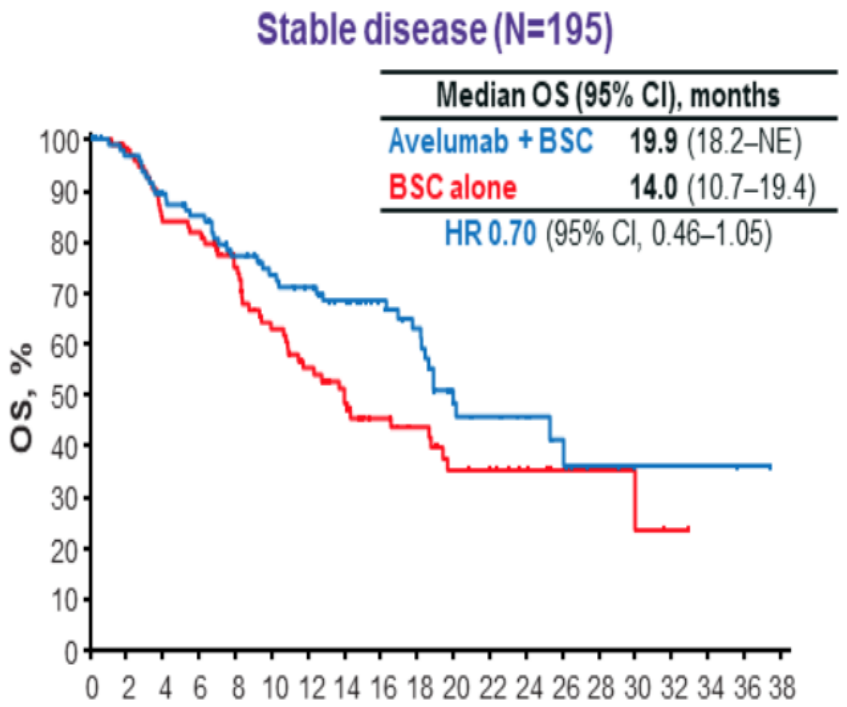


	147	142	130	119	102	88	78	68	59	46	32	21	16	14	9	6	5	1	1	0
	122	114	104	91	72	57	52	42	36	29	20	15	13	12	6	3	3	0		

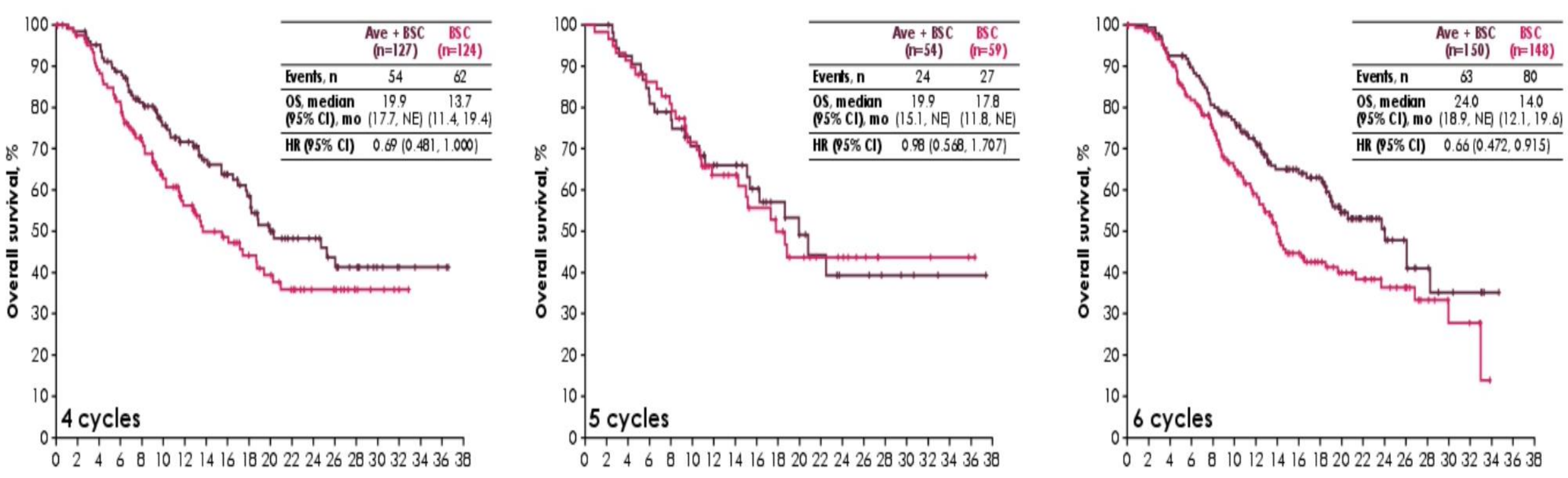
OS: Best response to 1L CT







OS: Cycles of 1L Chemotherapy



Loriot et al ASCO GU 2021

Subsequent anticancer therapy

	Overall population		Subgroup who discontinued study therapy due to PD	
	Avelumab + BSC (N=350)	BSC alone (N=350)	Avelumab + BSC (N=189)	BSC alone (N=263)
Discontinued and received subsequent drug therapy, %	**42.3**	**61.7**	**70.4**	**75.3**
PD-L1/PD-1 inhibitor	**6.3**	**43.7**	**9.0**	**52.9**
Fibroblast growth factor receptor inhibitor	2.6	2.3	4.8	3.0
Any other drug	40.0	34.0	67.2	41.8
Discontinued with no subsequent drug therapy, %	33.4	30.9	29.6	24.7
Study treatment ongoing, %	24.3	7.4	–	–

All percentages were calculated using the denominator of all patients in the treatment arm within each population; some patients received >1 category of subsequent therapy

Treatment-emergent AEs (any causality)

	Avelumab + BSC (N=344)		BSC alone (N=345)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TEAE, %	**98.0**	**47.4**	**77.7**	**25.2**
Fatigue	17.7	1.7	7.0	0.6
Pruritus	17.2	0.3	1.7	0
UTI	17.2	4.4	10.4	2.6
Diarrhea	16.6	0.6	4.9	0.3
Arthralgia	16.3	0.6	5.5	0
Asthenia	16.3	0	5.5	1.2
Constipation	16.3	0.6	9.0	0
Back pain	16.0	1.2	9.9	2.3
Nausea	15.7	0.3	6.4	0.6
Pyrexia	14.8	0.3	3.5	0
Decreased appetite	13.7	0.3	6.7	0.6
Cough	12.8	0.3	4.6	0
Vomiting	12.5	1.2	3.5	0.6
Hypothyroidism	11.6	0.3	0.6	0
Rash	11.6	0.3	1.2	0
Anemia	11.3	3.8	6.7	2.9
Hematuria	10.5	1.7	10.7	1.4
IRR	10.2	0.9	0	0

- TEAEs led to discontinuation of avelumab in 11.9%
- Death was attributed by the investigator to study treatment toxicity in 2 patients (0.6%) in the avelumab + BSC arm
  - Due to sepsis (in Cycle 10) and ischemic stroke (100 days after a single dose of avelumab)

Table shows TEAEs of any grade occurring in ≥10% or grade ≥3 TEAEs occurring in ≥5% in either arm

AE, adverse event; **IRR**, infusion-related reaction; **TEAE**, treatment-emergent adverse event; **UTI,** urinary tract infection
Safety was assessed in all patients who received ≥1 dose of avelumab in the avelumab arm, or who completed the cycle 1 day 1 visit in the BSC arm (N=689)

Immune-related AEs

	Avelumab + BSC (N=344)	
	Any grade	**Grade 3**
Any irAE, %	**29.4**	**7.0**
Hypothyroidism	10.2	0.3
Rash	4.9	0.3
Hyperthyroidism	4.7	0
Rash maculopapular	2.3	0.3
Pruritis	2.0	0
Pneumonitis	1.5	0.3
Colitis	0.9	0.6
Increased ALT	0.9	0.9
Increased AST	0.6	0.6
Hyperglycemia	0.9	0.9
Myositis	0.6	0.6

irAEs were identified according to a prespecified case definition
ALT, alanine aminotransferase; **AST**, aspartate aminotransferase; **irAE**, immune-related adverse event

- No grade 4/5 irAEs occurred
- High-dose corticosteroids (≥40 mg total daily prednisone or equivalent) were administered following irAE in 9.0% of avelumab-treated patients

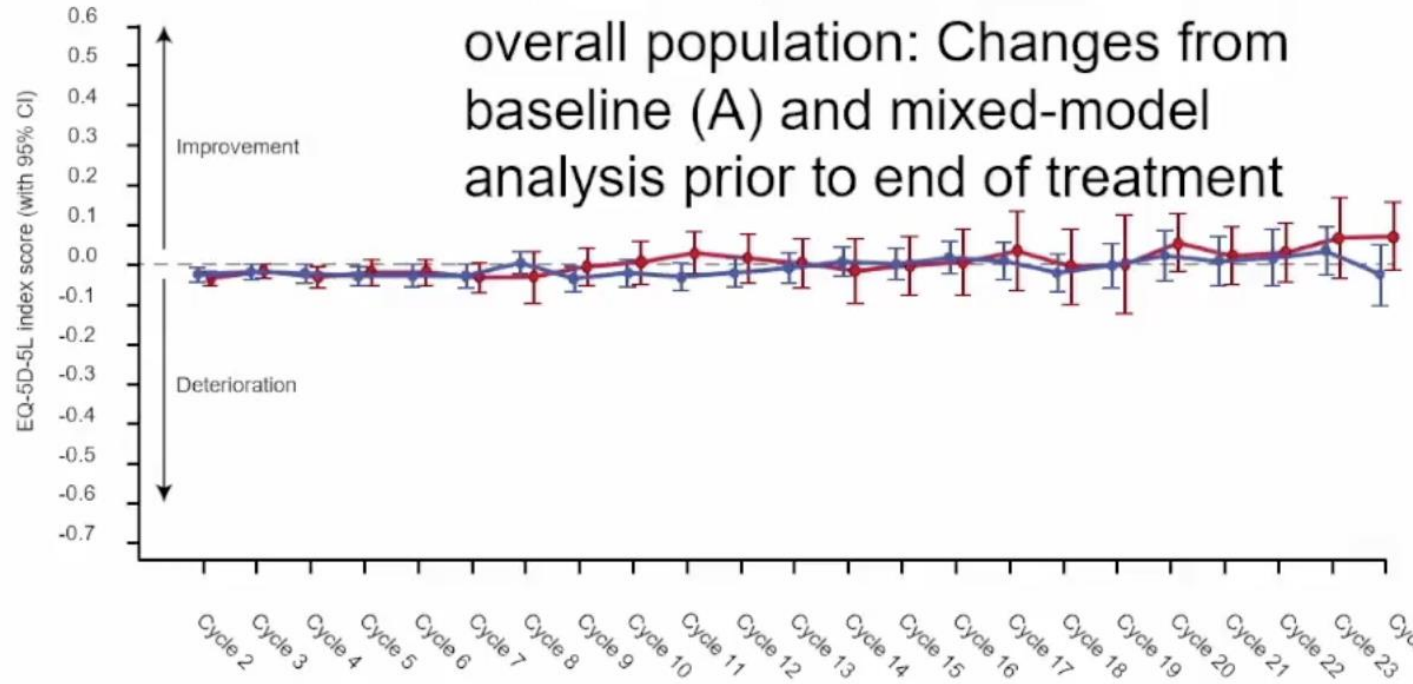
Table shows irAEs of any grade occurring in ≥1% or grade ≥3 irAEs occurring in ≥0.5% in either arm

Powles et al ESMO abstract2653

Maintenance avelumab in first line treatment for UC show similar quality of life data vs. best supportive care

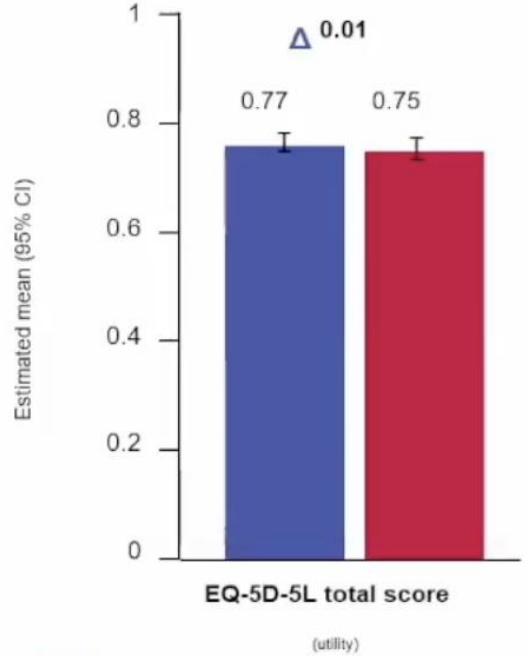
A

Method: EQ-5D-5L index score in overall population: Changes from baseline (A) and mixed-model analysis prior to end of treatment



No. of patients*																								
Avelumab + BSC	310	273	244	208	181	164	144	134	124	120	103	97	88	81	70	65	58	49	44	44	40	37	35
BSC	298	221	154	123	111	84	67	55	49	47	43	34	32	28	26	23	21	18	16	16	15	14	10

B



Best supportive care

avelumab

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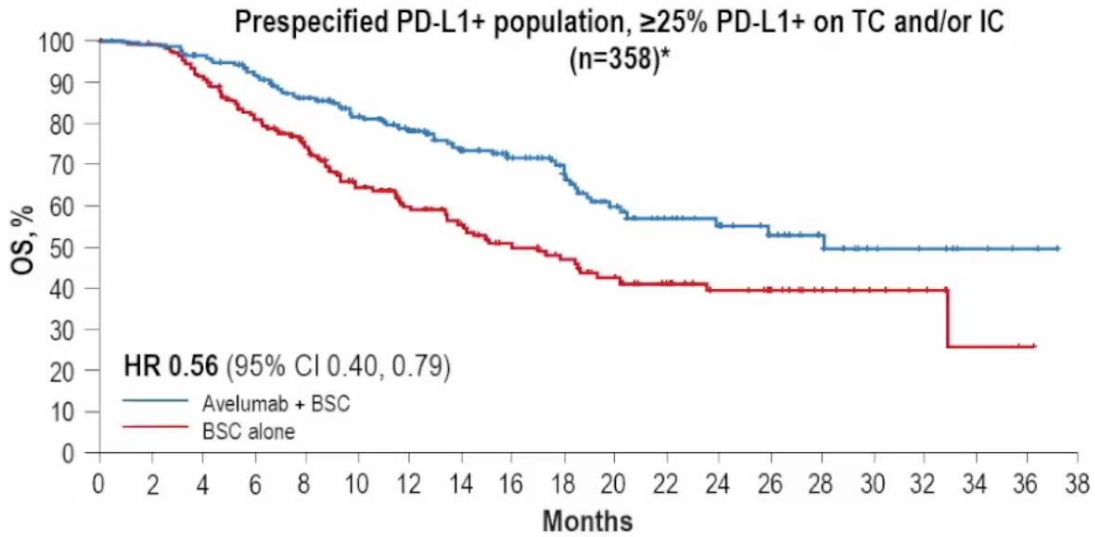
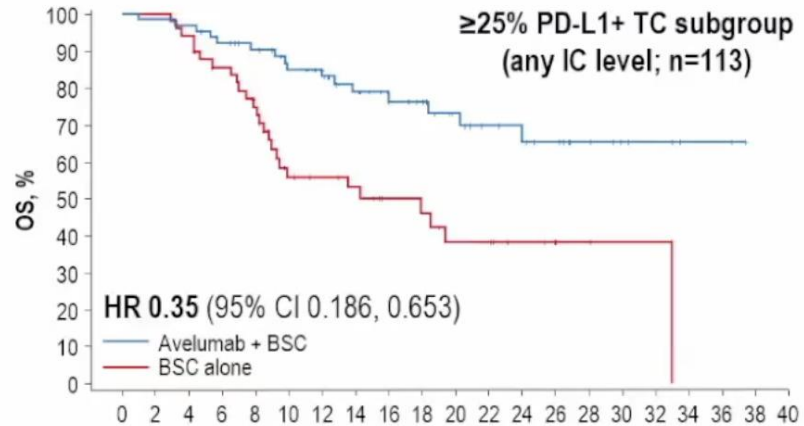
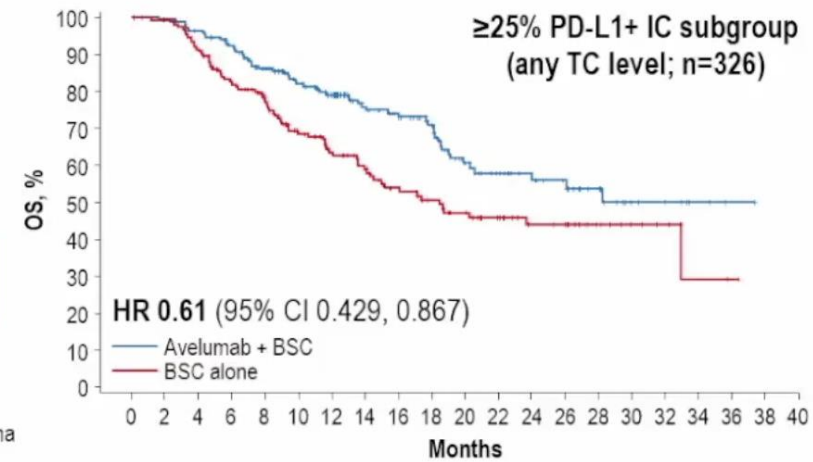
•OS benefit in subgroups defined by PD-L1 expression on TC and/or IC





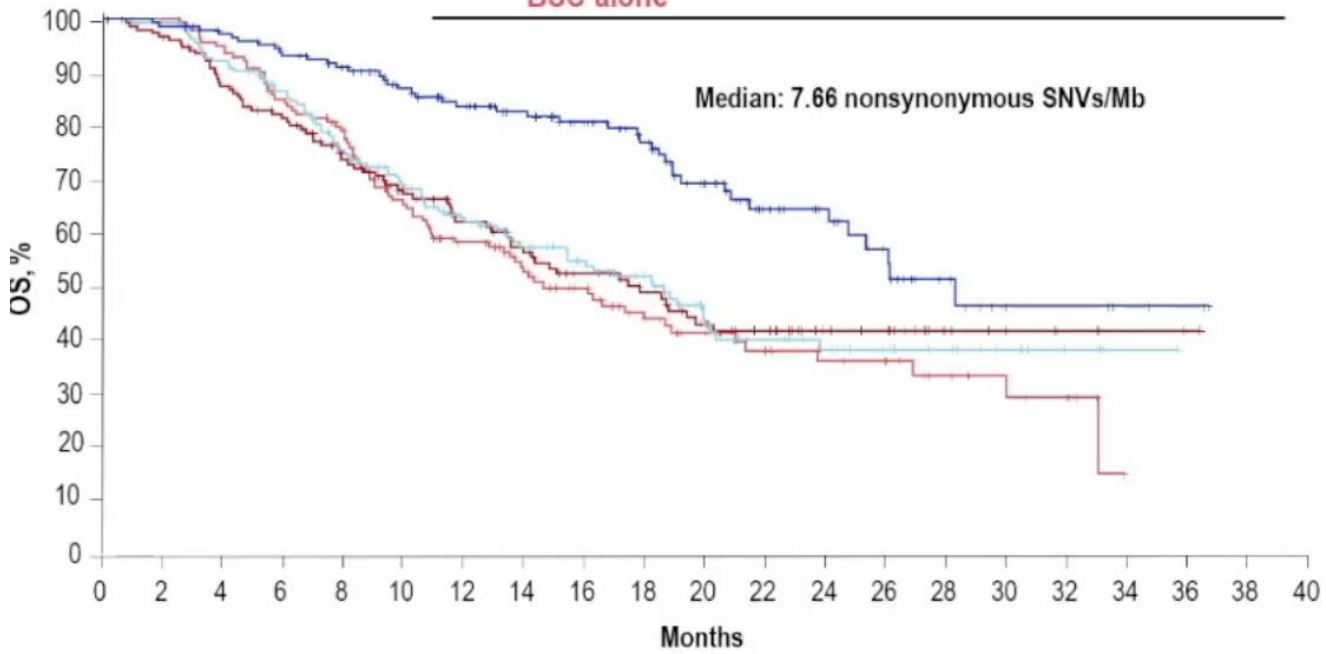


Neither PD-L1+ TC nor IC alone fully predicts OS benefit

- **TC**, tumor cell; **IC**, immune cell; **NE**, not evaluable.
- *PD-L1 expression in ≥25% of TC or in ≥25% or 100% of IC if the percentage of IC was >1% or ≤1%, respectively, using the Ventana SP263 assay.

•OS benefit in subgroups defined by Tumor Mutation Burden (TMB) and PD-L1 status

Arm	TMB	HR (95% CI)
Avelumab + BSC / BSC alone	>Median	**0.48** (0.332, 0.707)
Avelumab + BSC / BSC alone	≤Median	**0.88** (0.643, 1.197)



Subgroup	HR (95% CI) Avelumab + BSC vs BSC alone
PD-L1+	0.56 (0.400, 0.790)
PD-L1−	0.85 (0.616, 1.181)
TMB-high	0.46 (0.321, 0.673)
TMB-low	0.93 (0.665, 1.289)
TMB-high, PDL1+ (n=190)	0.49 (0.291, 0.812)
TMB-high PDL1− (n=105)	0.42 (0.247, 0.732)
TMB-low PDL1+ (n=148)	0.62 (0.389, 0.995)
TMB-low, PDL1− (n=140)	1.40 (0.871, 2.252)

Neither TMB nor PD-L1 status alone fully predict OS benefit

•Relationship between immune cell gene expression signatures and OS with avelumab

Multiple immune cell signatures may predict OS benefit with avelumab

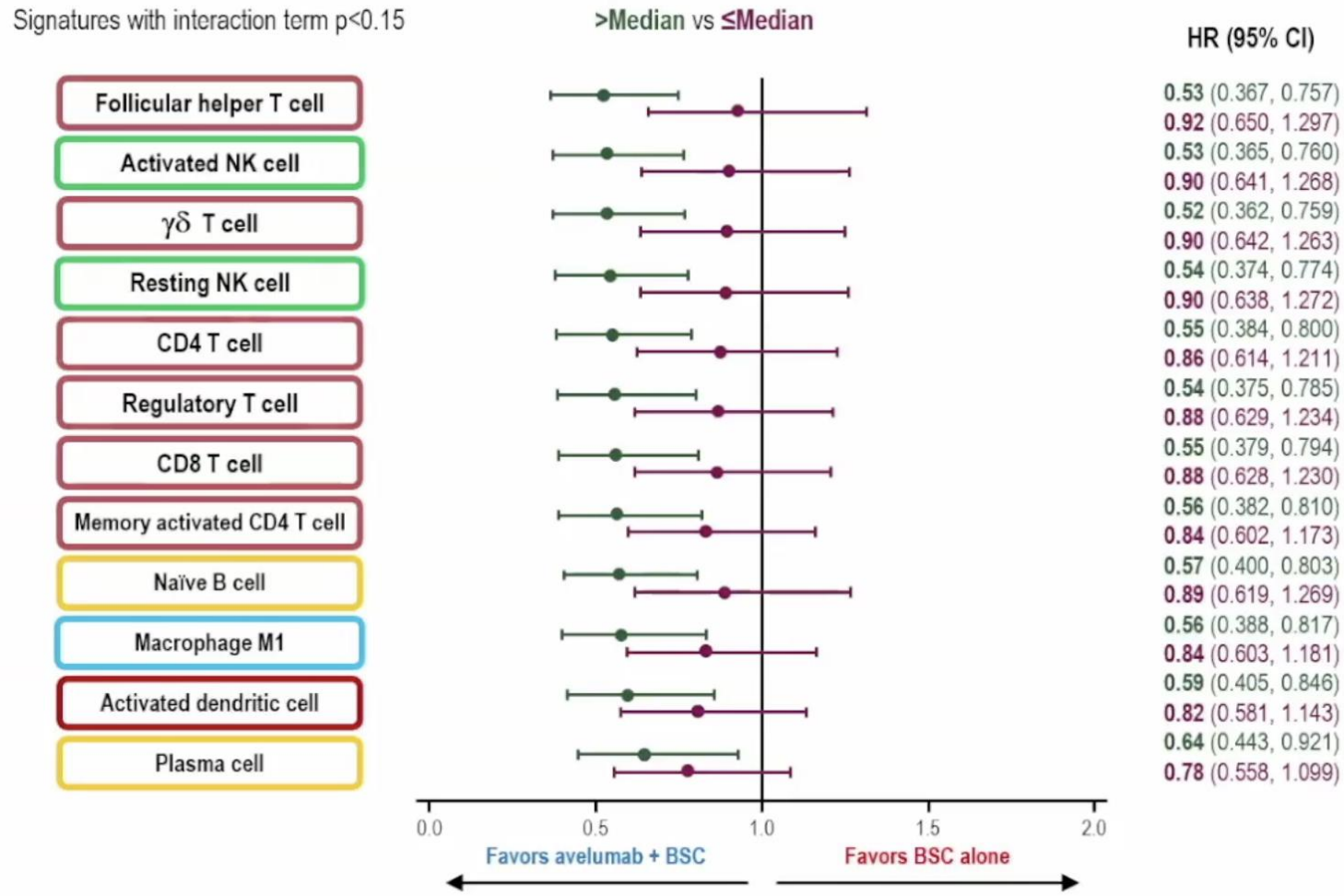
T cell

NK cell

Macrophage

Dendritic cell

B cell



Gene signatures are from the Leukocyte gene signature matrix (LM22), Newman et al (2015) Nature Methods, https://doi.org/10.1038/nmeth.3337

Journal Pre-proof

BLADDER CANCER: ESMO CLINICAL PRACTICE GUIDELINE FOR DIAGNOSIS, TREATMENT AND FOLLOW-UP†

T. Powles, J. Bellmunt, E. Comperat, M. De Santis, R. Huddart, Y. Loriot, A. Necchi, B.P. Valderrama, A. Ravaud, S.F. Shariat, B. Szabados, M.S. van der Heijden, S. Gillessen, on behalf of the ESMO Guidelines Committee

PII: S0923-7534(21)04827-4

DOI: https://doi.org/10.1016/j.annonc.2021.11.012

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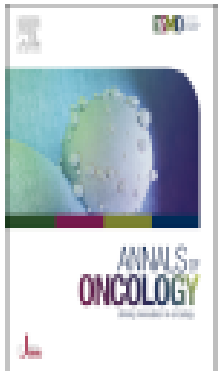

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- **Maintenance avelumab, started within 10 weeks of completion of first-line platinum based ChT,** is associated with an OS advantage compared with best supportive care in patients who did not have disease progression after four to six cycles of gemcitabine plus cisplatin or carboplatin, and is recommended (HR 0.69, 95% CI 0.56-0.86) [I, A; MCBS 4]. An increase in mOS from 14 to 21 months was observed with avelumab. **Treatment was given until progression.**

- **Platinum-based ChT followed by maintenance avelumab is preferential compared with upfront ICIs in PD-L1 biomarker-positive patients**.

1. https://doi.org/10.1016/j.annonc.2021.11.012

Consideraciones finales

- **Inmunoterapia tras fallo a platino** es una alternativa a la que un porcentaje importante de pacientes no llegarán
- **Inmunoterapia en 1L** no consigue unas tasas de control de enfermedad aceptables en un número suficiente de pacientes
- Los resultados de la **combinación inmuno-quimio** hasta la fecha han sido desalentadores
- **Avelumab en mantenimiento** en pacientes que no experimentan progresión a una primera línea de platino mejora la supervivencia global y es la mejor opción en cáncer urotelial metastásico.