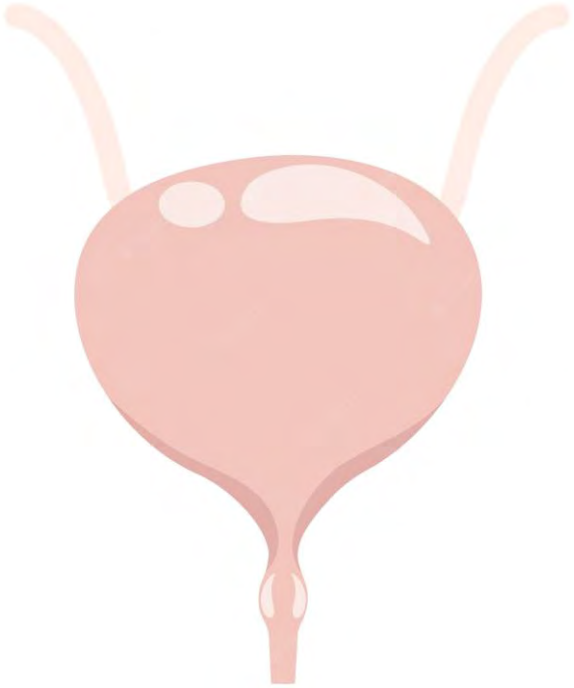
Grupo Português
Génito - Urinário

XXVII Workshop
Urologia Oncológica

Avelumab maintenance in bladder cancer



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Disclosures

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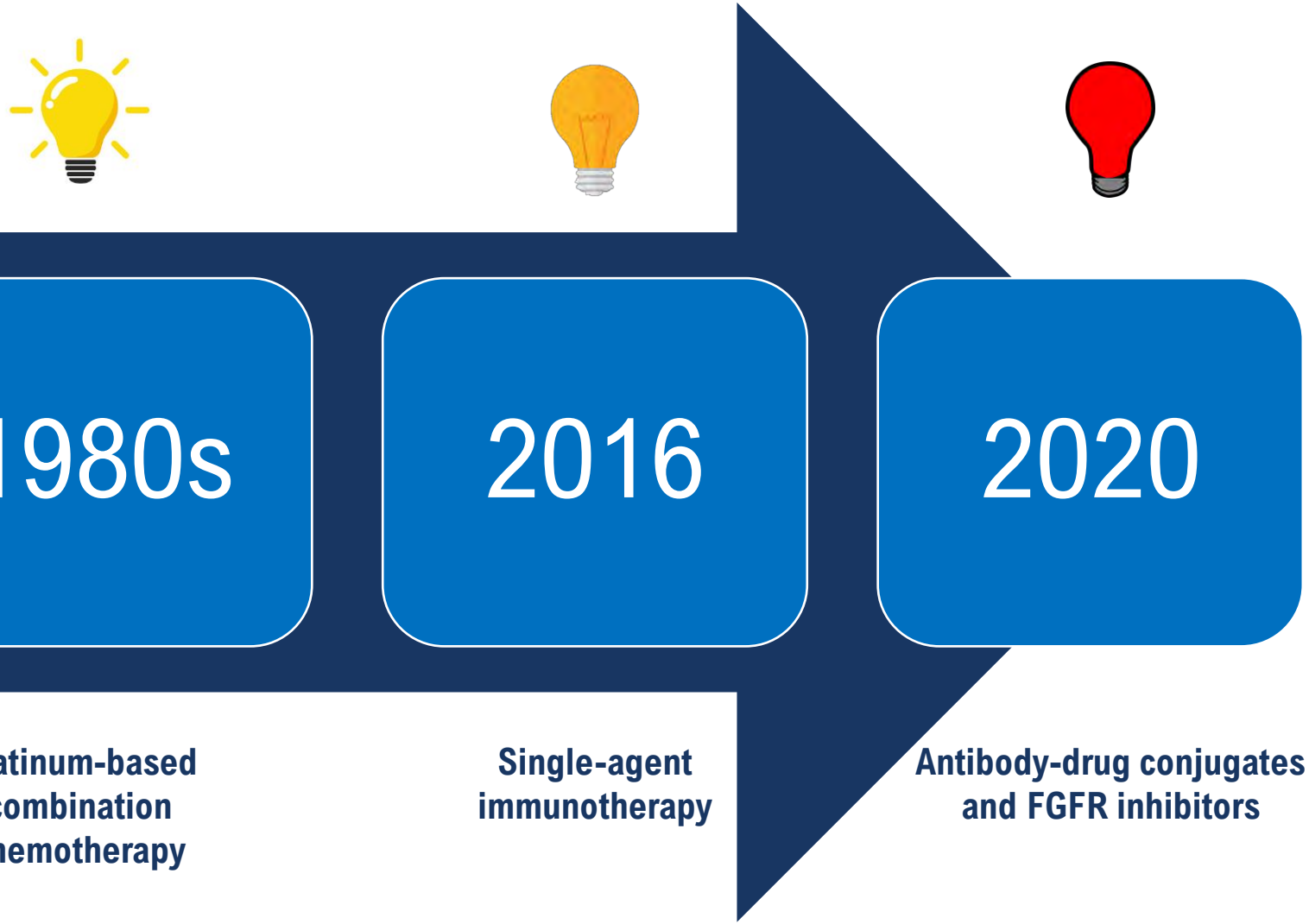
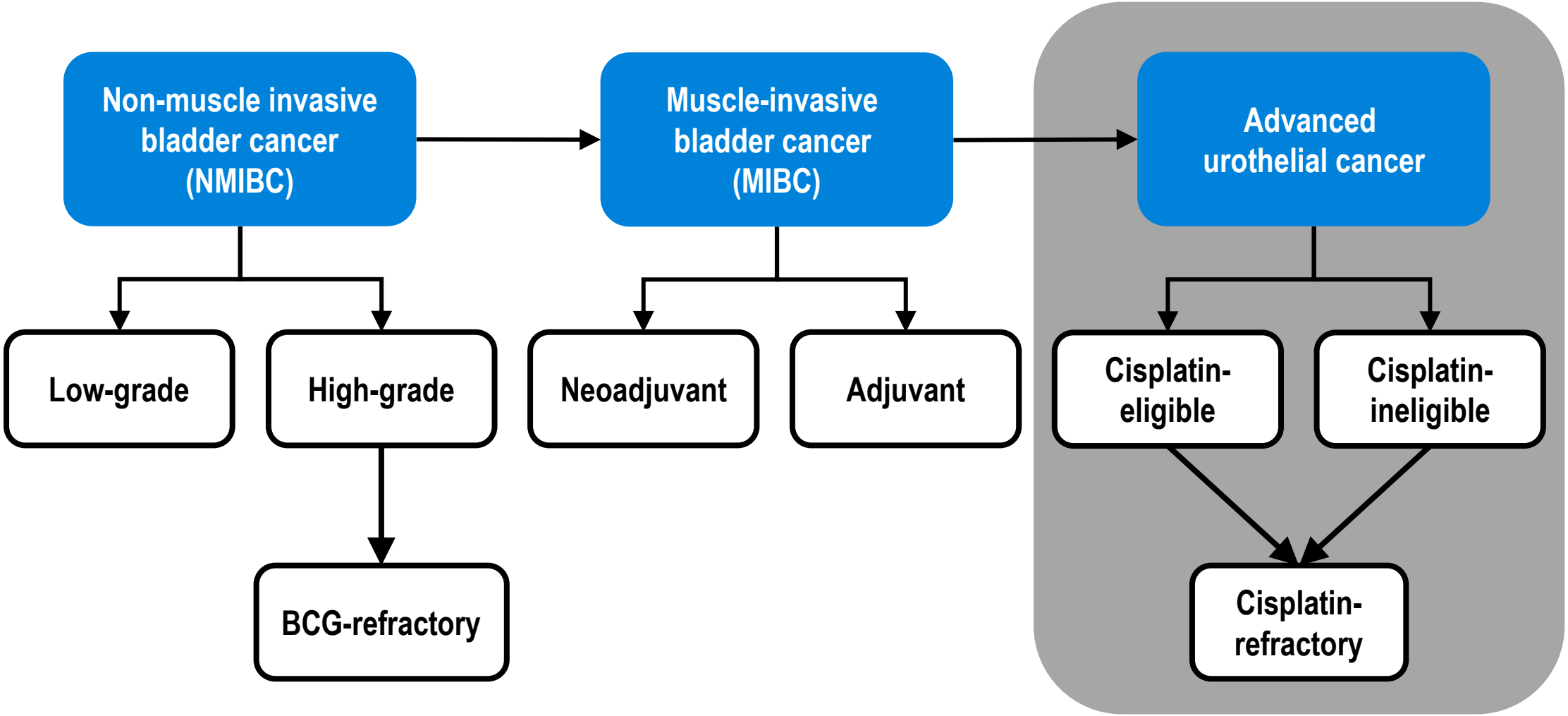
The opinions expressed in this presentation represent those of the speaker(s).

This scientific discussion may include data on investigational uses of compounds/drugs that have not yet been approved by regulatory authorities.

Chronology of aUC treatment



Focus on aUC


Non-muscle invasive bladder cancer (NMIBC)
Muscle-invasive bladder cancer (MIBC)
Advanced urothelial cancer
Low-grade
High-grade
BCG-refractory
Neoadjuvant
Adjuvant
Cisplatin-eligible
Cisplatin-ineligible
Cisplatin-refractory

aUC - Definitions

Advanced urothelial cancer

Platinum eligible

Fit for cisplatin-based chemotherapy

- ECOG PS 0-1
- GFR > 50-60 ml/min
- Audiometric hearing loss grade <2
- Peripheral neuropathy grade <2
- Cardiac insufficiency NYHA class <III

Fit for carboplatin-based chemotherapy (but unfit for cisplatin)

- ECOG PS 2
- GFR 30-60 ml/min
- Not fulfilling other cisplatin-eligibility criteria

Platinum ineligible

Unfit for any platinum-based chemotherapy

- ECOG PS > 2
- GFR < 30 ml/min
- ECOG PS 2 and GFR < 60 ml/min
- Comorbidities grade > 2

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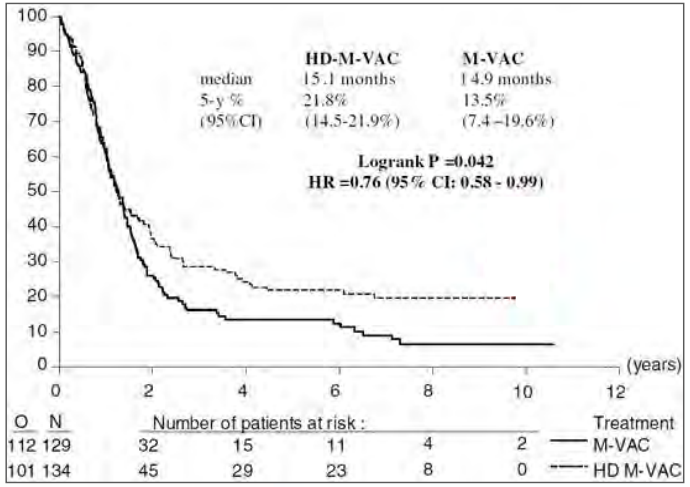
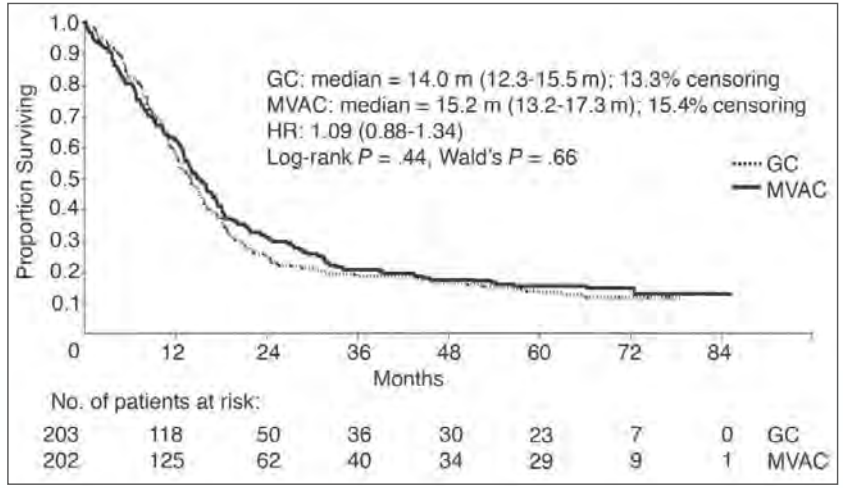
aUC - Chemotherapy is standard of care

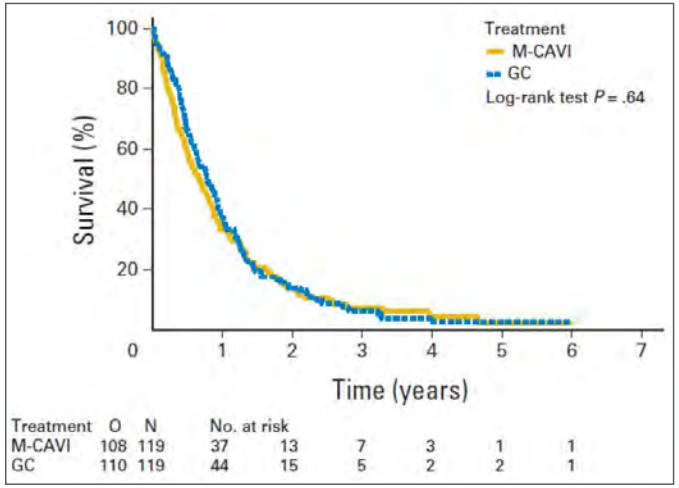
Cisplatin-eligible[1]
Dose Dense MVAC
ORR 72%
CR 25%
mOS 15.1 mo

Cisplatin-eligible[2]
Gemcitabine Cisplatin
ORR 49%
CR 12%
mOS 14 mo

Cisplatin-ineligible[3]
Gemcitabine Carboplatin
ORR 36%
CR 3%
mOS 9.3 mo







HD, high dose; HR, hazard ratio; MVAC, methotrexate, vinblastine, adriamycin and cisplatin (C)

1. Sternberg CN et al., *Eur J Cancer* 2006;42(1):50–4; 2. Von der Maase H et al., *J Clin Oncol* 2005;23:4602–4608;
3. De Santis M et al., *J Clin Oncol* 2012; 30: 191–199.

aUC – First-line ChT in patients fit for cisplatin

Cisplatin-containing combination chemotherapy

OS 12-14 mo

Standard of care since the late 1980s
> Higher CR and OS rates versus carboplatin-containing regimens

GC

Similar OS (13.8% vs. 14.8%) and ORR (49% vs. 46%) of MVAC
Lower toxicity than MVAC

dd MVAC

Less toxic and more efficacious (CR and 2-yr OS) than MVAC
No significant difference in median survival versus MVAC

4-6 cycles

Sustained benefit in 10-15% patients

aUC – First-line ChT in patients fit for carboplatin

Carboplatin-containing combination chemotherapy

Up to 50% of patients are not fit for cisplatin-containing chemotherapy, but most are candidates for carboplatin

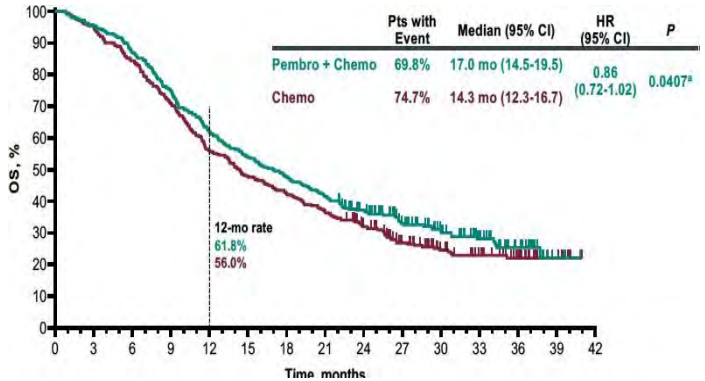
GemCarbo

Less several acute toxicity (13.6% vs. 23%) and higher ORR (42% vs. 30%) than M-CAVI

4-6 cycles

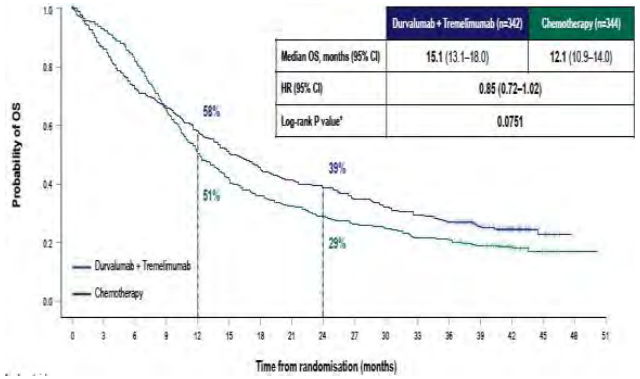
aUC – Integration of IO in first-line ChT in patients fit for platinum-based ChT

Immunotherapy



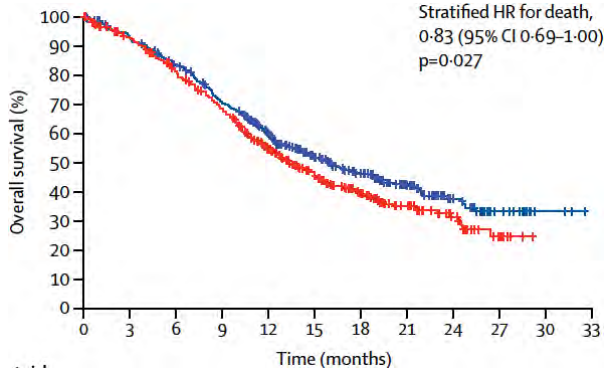
CT + Pembrolizumab (KEYNOTE-361)

Powles et al. Lancet Oncol 2021



Durvalumab + Tremelimumab (DANUBE)

Powles et al. Lancet Oncol 2020



CT + Atezolizumab (IMvigor130)

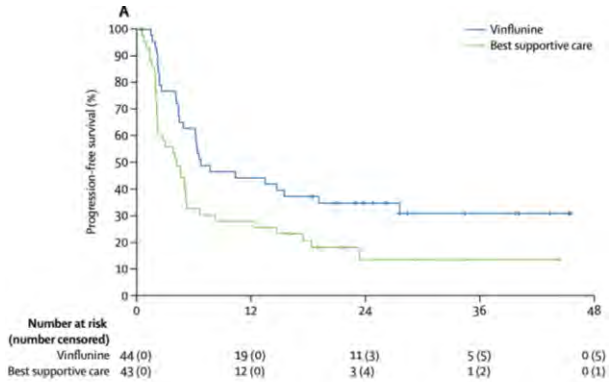
Galsky et al. Lancet 2020

No OS benefit

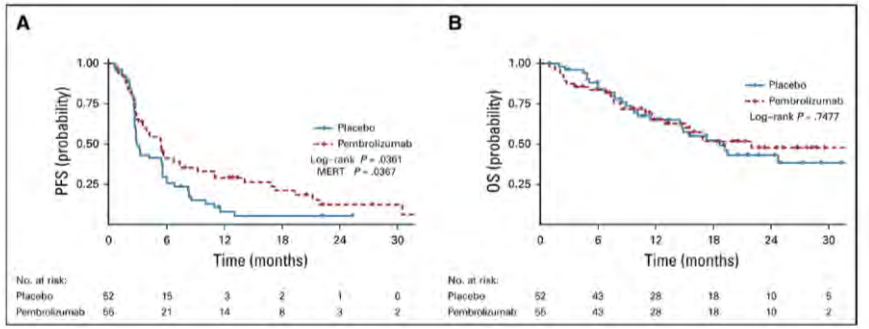
aUC – CR, PR or SD with standard 1 L ChT (4-6 cycles)

LA or mUC – CR, PR or SD with standard 1L platinum-chemotherapy

Maintenance Strategies



MAJA Study **(Vinflunine)**



Hoosier Study **(Pembrolizumab)**

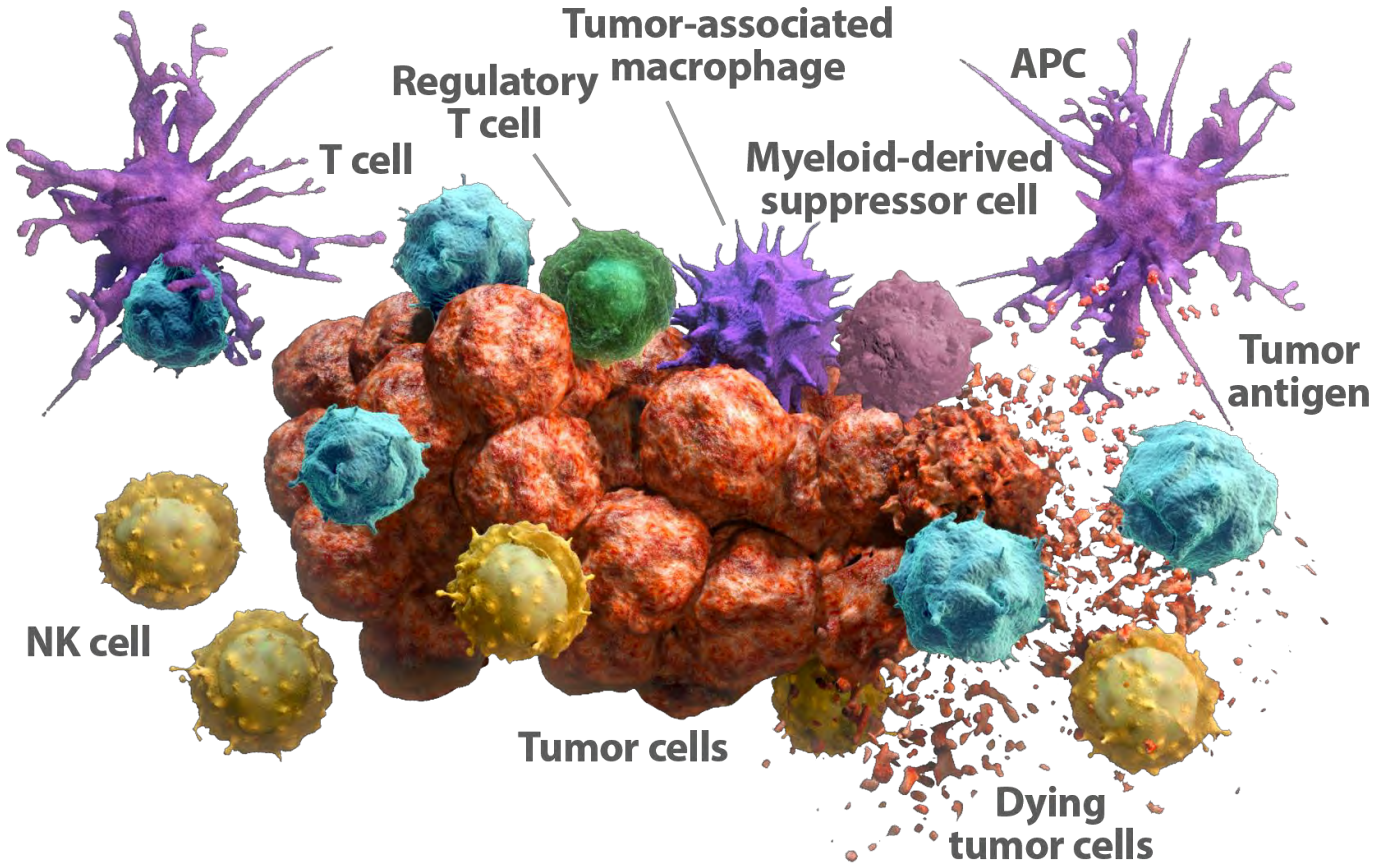
aUC – CR, PR or SD with standard 1 L ChT (4-6 cycles)

LA or mUC – CR, PR or SD with standard 1L platinum-chemotherapy

JAVELIN Bladder 100

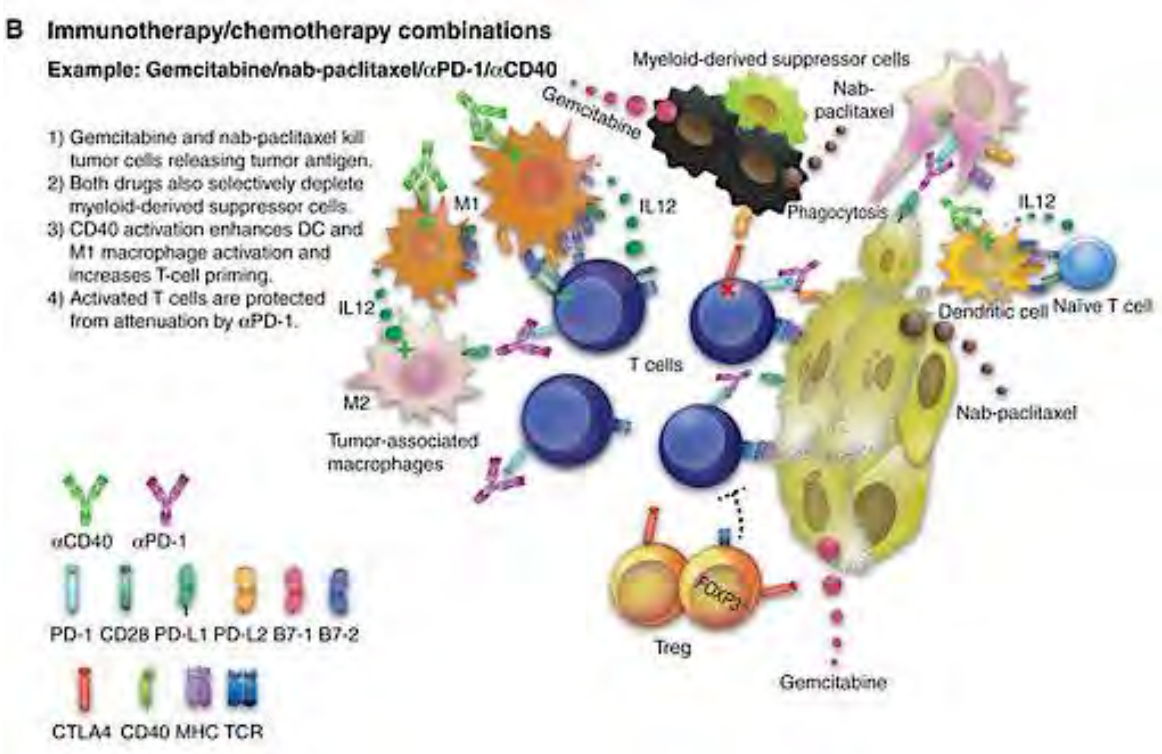
Maintenance Avelumab

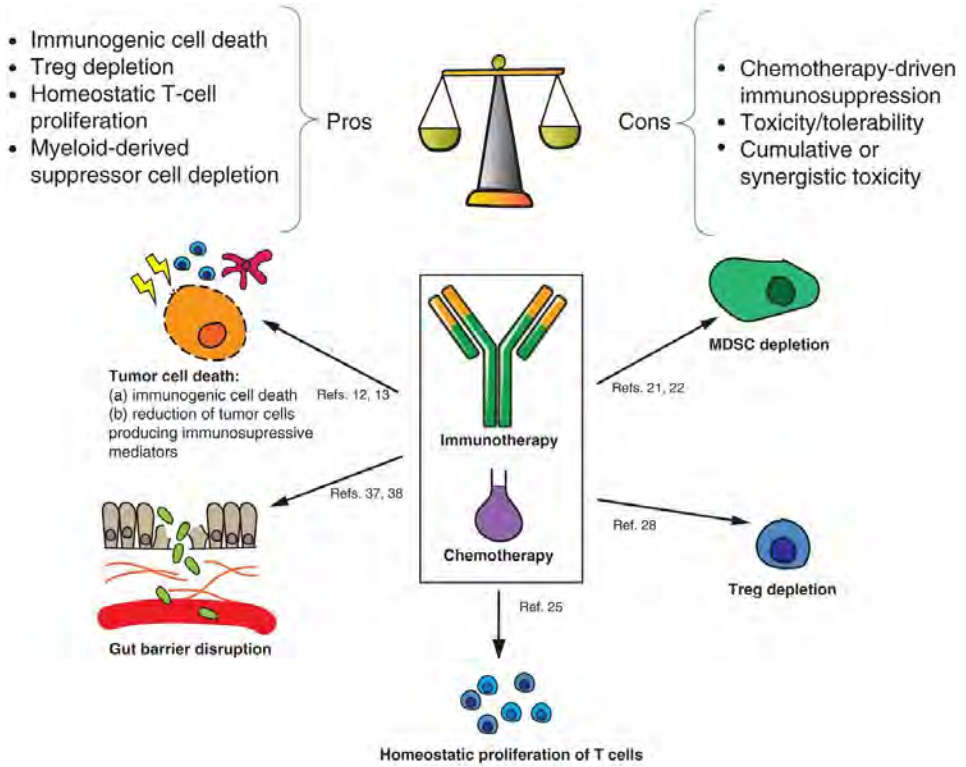
Tumor microenvironment



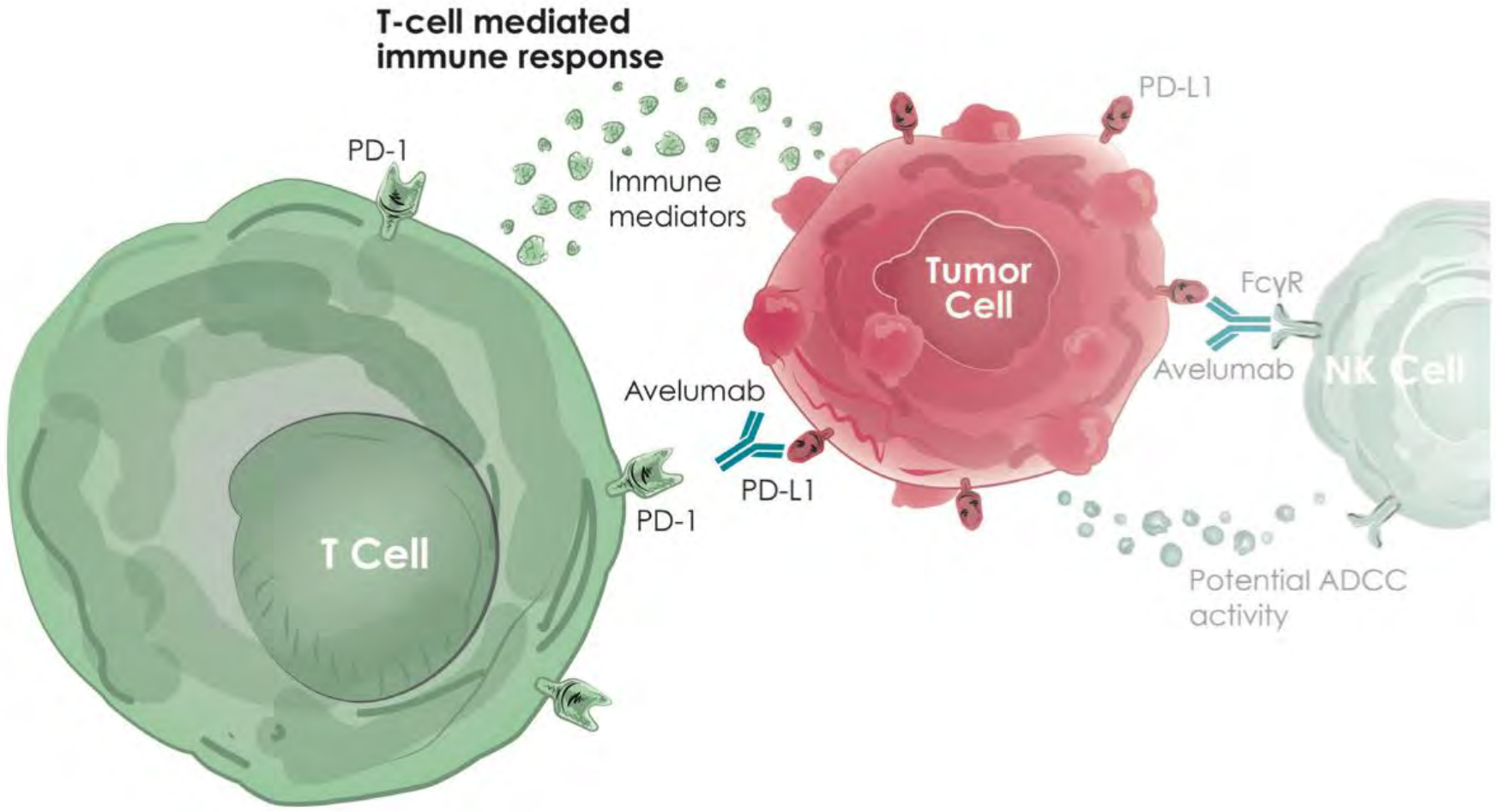
Rationale behind ChT/IO combos

AACR American Association for Cancer Research®

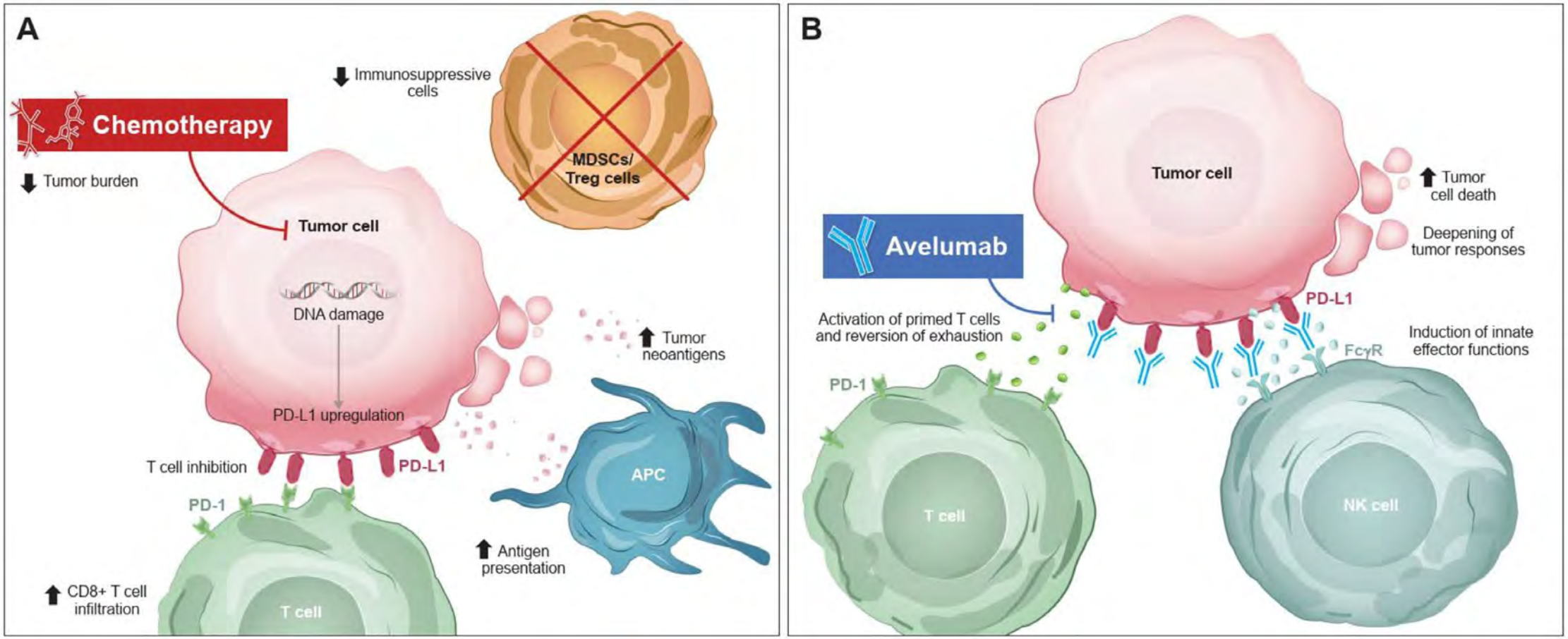




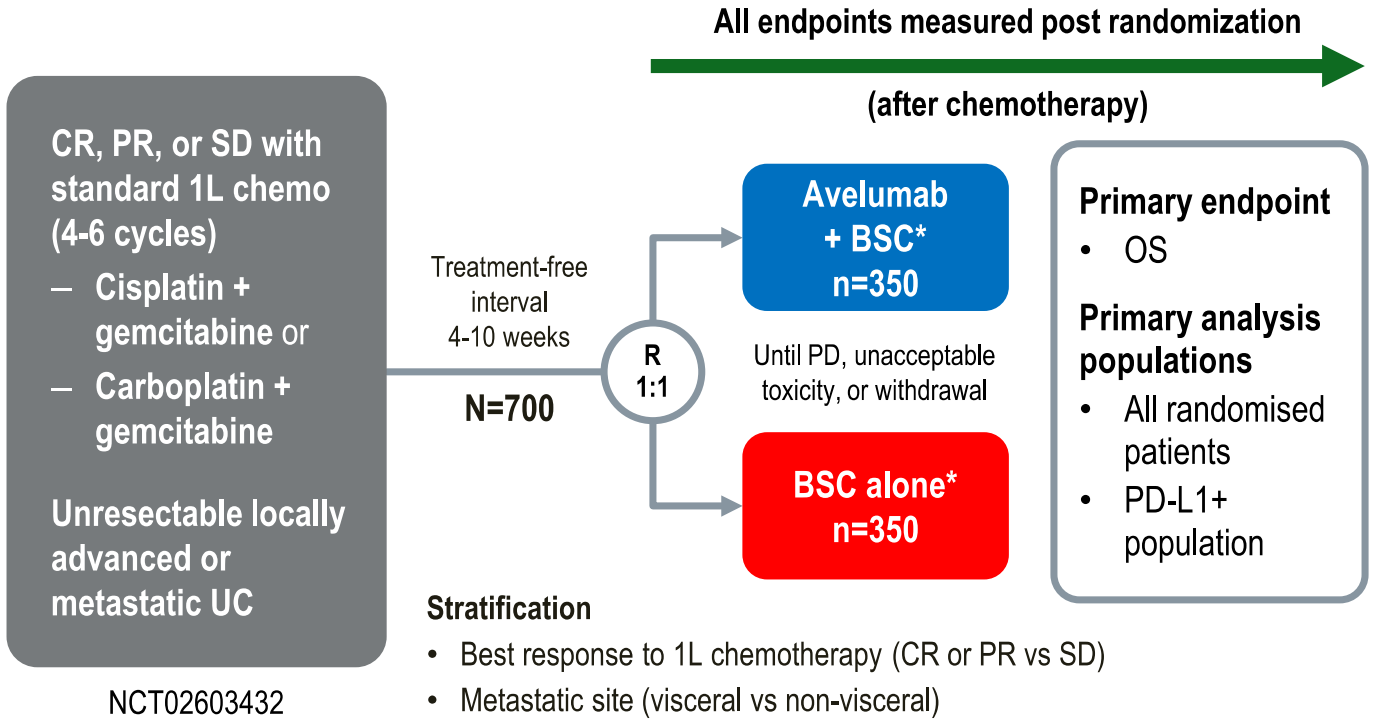
Avelumab mechanism of action



Avelumab mechanism of action



Avelumab 1L maintenance + BSC significantly prolonged OS vs. BSC alone in the JAVELIN Bladder 100 phase 3 trial[1]



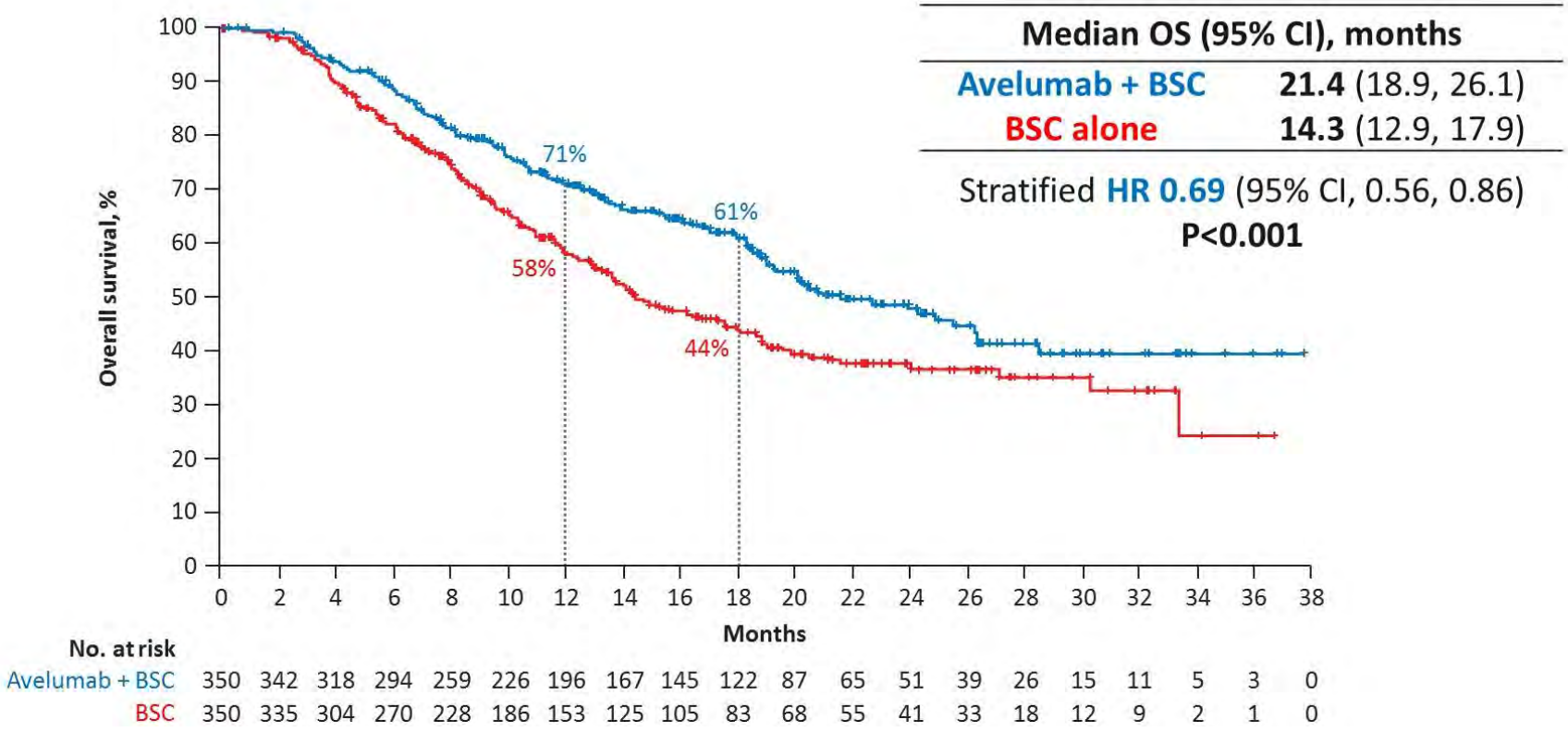
- Median OS in all randomised patients[1]
  - **Avelumab 1L maintenance + BSC**: **21.4 months** (95% CI, 18.9, 26.1)
  - **BSC alone: 14.3 months** (95% CI, 12.9, 17.9)
  - **HR 0.69** (95% CI, 0.56, 0.86); P<0.001
- The safety profile of avelumab 1L maintenance was manageable and consistent with previous studies of avelumab monotherapy[1,2]

OS benefit with avelumab + BSC vs BSC alone were analysed in patient subgroups

1L, first line; BSC, best supportive care; CR, complete response; HR, hazard ratio; OS, overall survival; PR, partial response; R, randomisation; SD, stable disease; UC, urothelial carcinoma
*BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other systemic antitumour therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable. 1. Powles T, et al. *New Engl J Med* 2020.

JAVELIN BLADDER 100

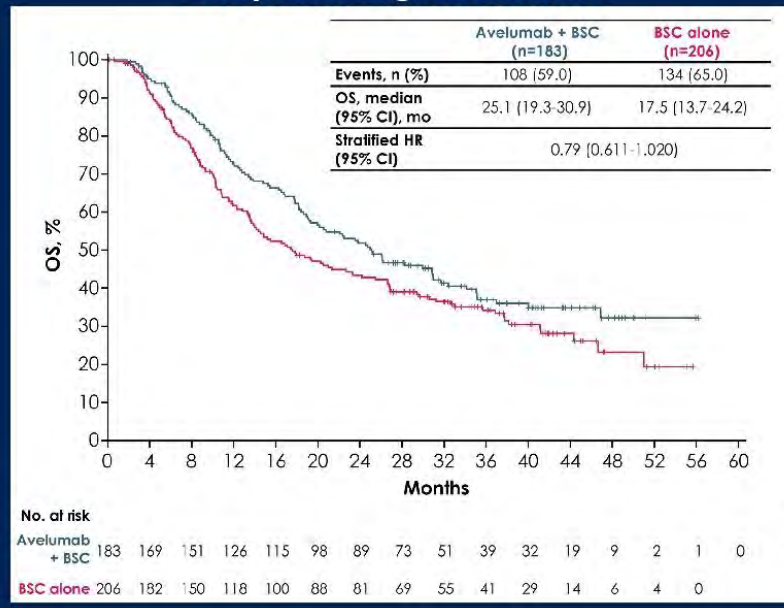
Maintenance avelumab lead to an OS benefit



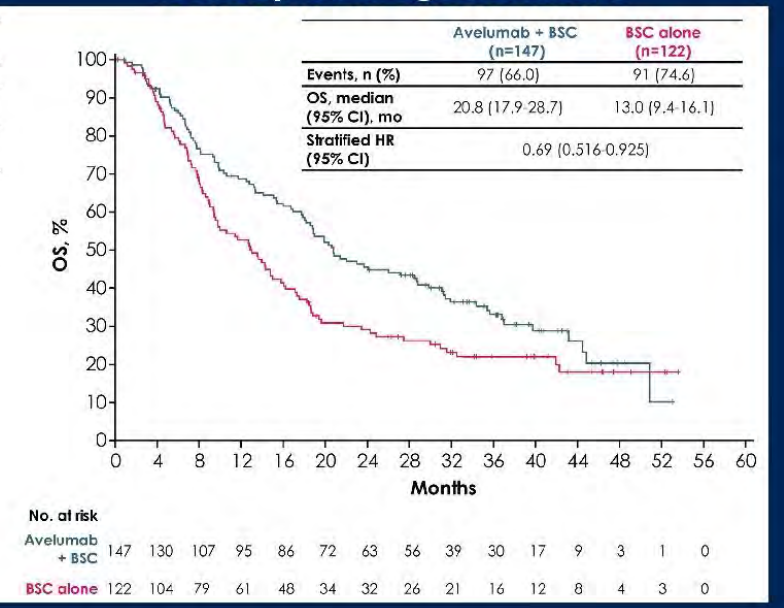
JAVELIN BLADDER 100 – Resultados após ≥ 2 anos FU

OS from start of maintenance (randomization)

Cisplatin + gemcitabine



Carboplatin + gemcitabine



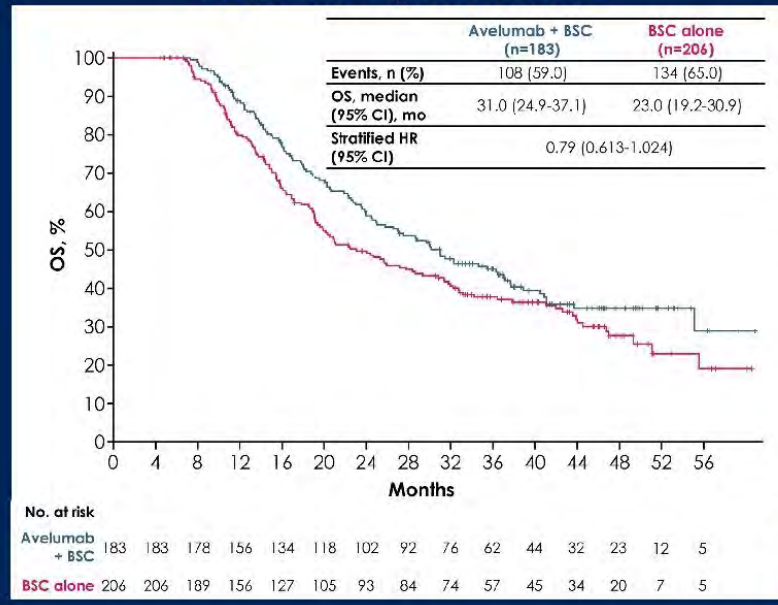
- OS* was longer with avelumab + BSC vs BSC alone in both the cisplatin and carboplatin subgroups
- In both subgroups, investigator-assessed PFS* was also longer with avelumab + BSC vs BSC alone

1L, first line; **BSC,** best supportive care; **HR,** hazard ratio; **OS,** overall survival; **PFS,** progression-free survival.
*Measured from the start of maintenance (randomization).

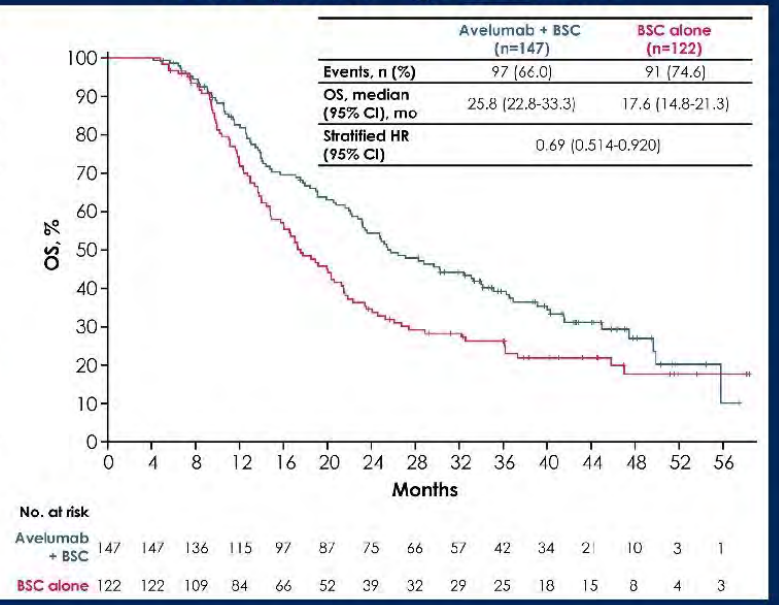
JAVELIN BLADDER 100 – Resultados após ≥ 2 anos FU

OS from start of 1L chemotherapy

Cisplatin + gemcitabine



Carboplatin + gemcitabine

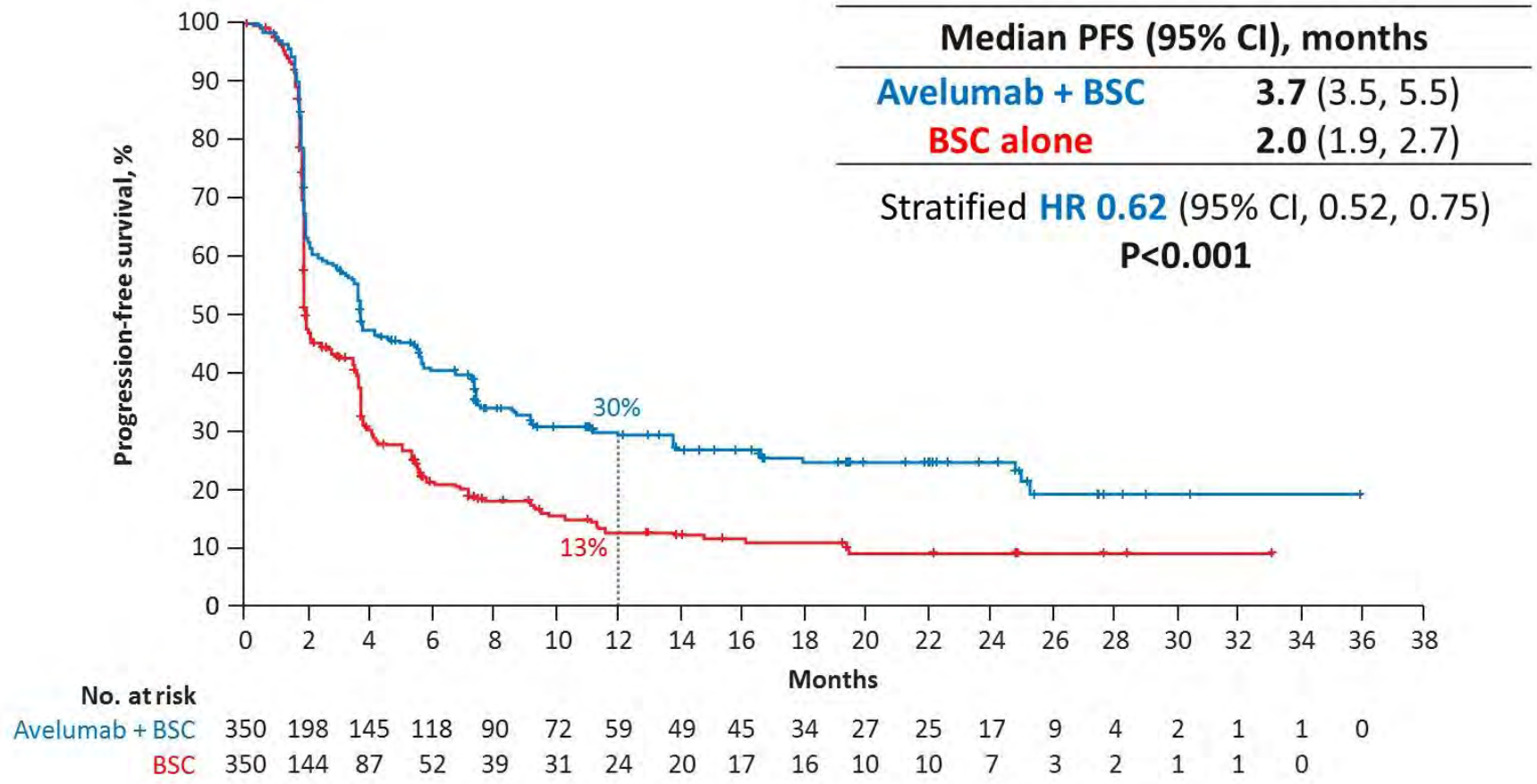


- In the overall population, median OS measured from the start of 1L chemotherapy was 29.7 months with avelumab + BSC and 20.5 months with BSC alone
- OS measured from the start of 1L chemotherapy was also longer with avelumab + BSC vs BSC alone irrespective of 1L chemotherapy regimen

1L, first line; **BSC**, best supportive care; **HR**, hazard ratio; **OS**, overall survival.

JAVELIN BLADDER 100

Maintenance avelumab lead to a PFS benefit



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

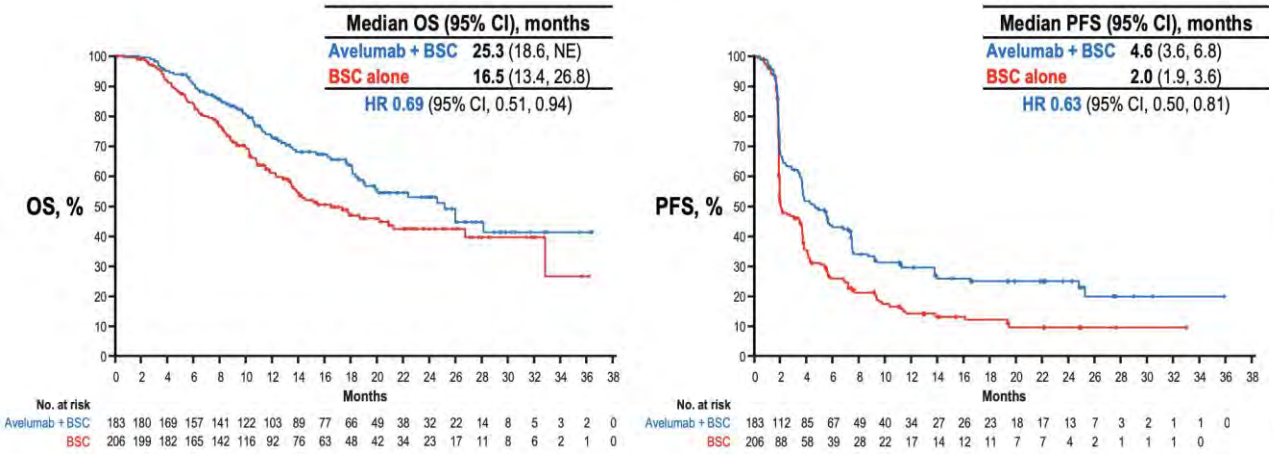
Stratified **HR 0.62** (95% CI, 0.52, 0.75)

P<0.001

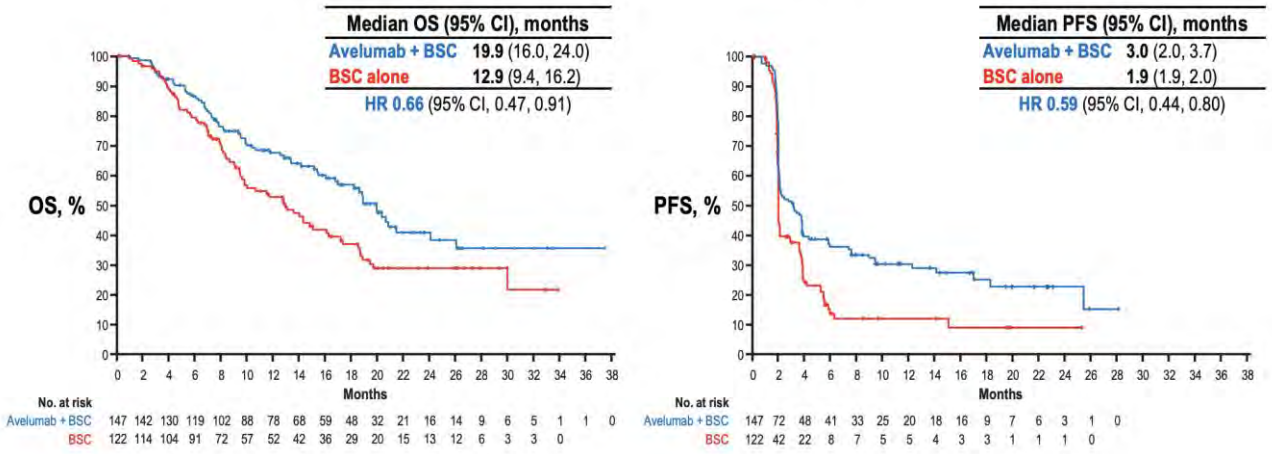
JAVELIN BLADDER 100

PFS/OS benefit is independent of induction CT

Gemcitabine + cisplatin (N=389)



Gemcitabine + carboplatin (N=269)



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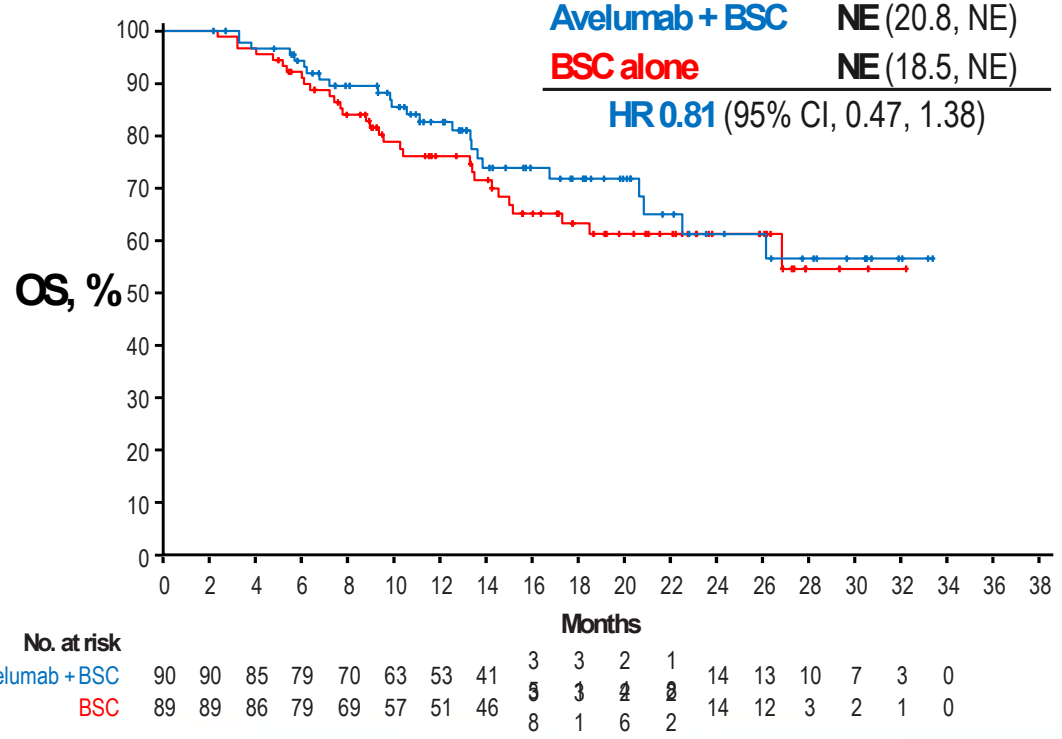
JAVELIN BLADDER 100

OS and PFS benefit with avelumab 1L maintenance was observed irrespective of best response to 1L chemotherapy

Complete response (n=179)

Median OS (95% CI), months	
Avelumab + BSC	**NE** (20.8, NE)
BSC alone	**NE** (18.5, NE)

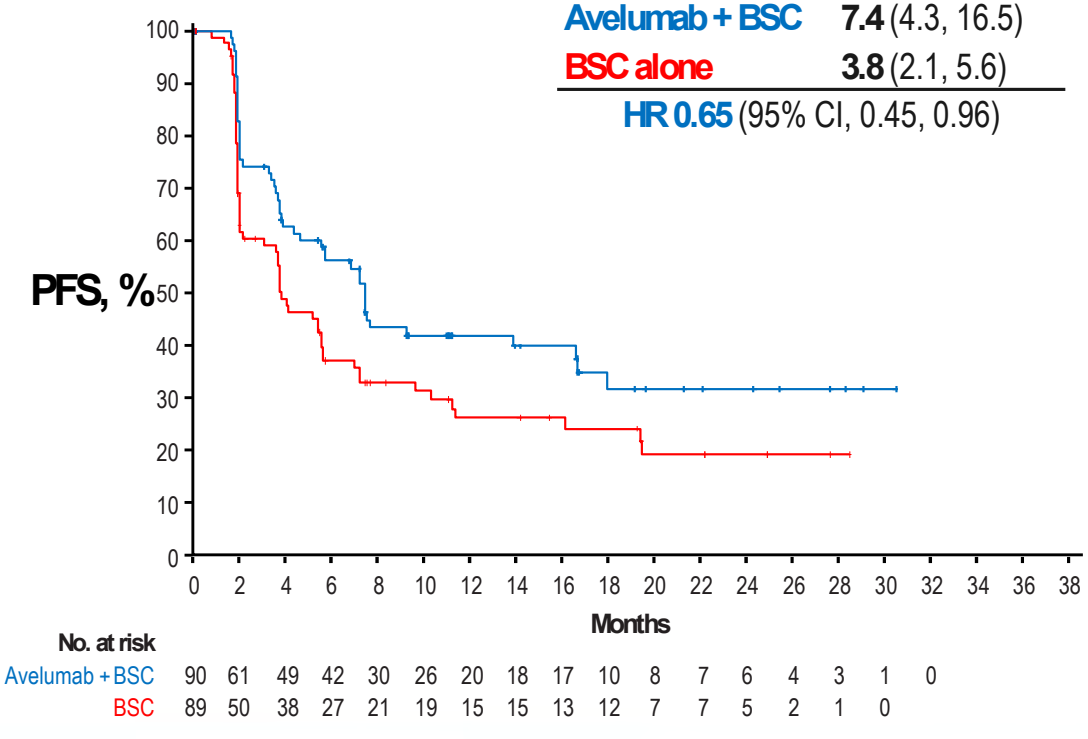
HR 0.81 (95% CI, 0.47, 1.38)



No. at risk																	
Avelumab + BSC	90	90	85	79	70	63	53	41	35	33	22	12	14	13	10	7	3	0
BSC	89	89	86	79	69	57	51	46	38	31	16	12	14	12	3	2	1	0

Median PFS (95% CI), months	
Avelumab + BSC	**7.4** (4.3, 16.5)
BSC alone	**3.8** (2.1, 5.6)

HR 0.65 (95% CI, 0.45, 0.96)



No. at risk																	
Avelumab + BSC	90	61	49	42	30	26	20	18	17	10	8	7	6	4	3	1	0
BSC	89	50	38	27	21	19	15	15	13	12	7	7	5	2	1	0	

BSC, best supportive care; CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival; PFS, progression-free survival. OS and PFS were measured post randomisation (after chemotherapy); CR (i.e., no evidence of disease at baseline). PR, and SD at baseline was based on either BICR or investigator assessment up to protocol amendment 3, or investigator assessment only from protocol amendment 3 (19 Dec 2016) onward. Powles T et al., Oral 699O presented at virtual ESMO congress 2020.

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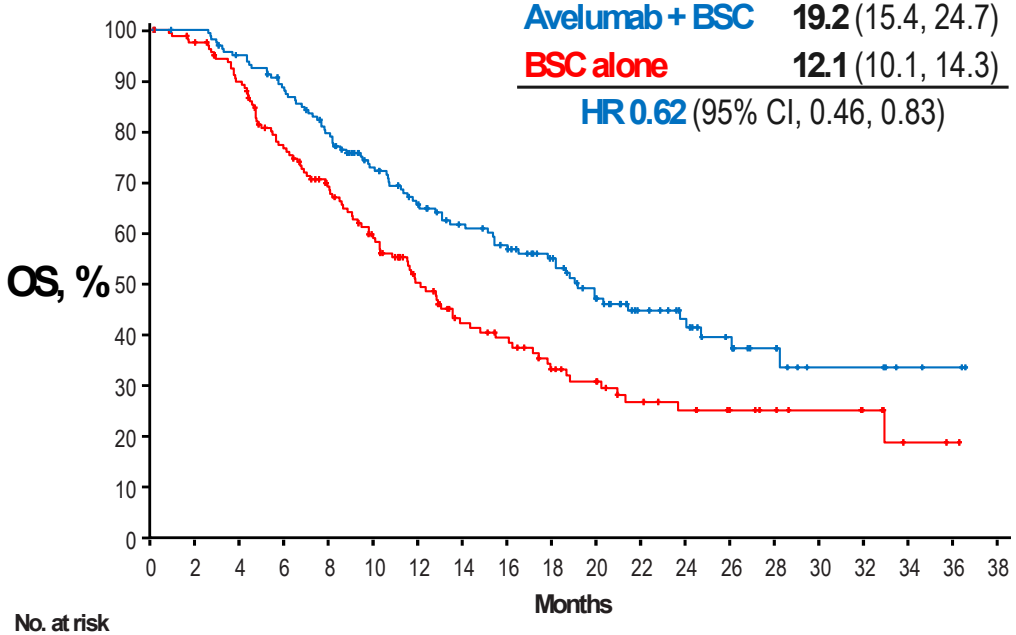
JAVELIN BLADDER 100

OS and PFS benefit with avelumab 1L maintenance was observed irrespective of best response to 1L chemotherapy

Partial response (n=326)

Median OS (95% CI), months	
Avelumab + BSC	**19.2** (15.4, 24.7)
BSC alone	**12.1** (10.1, 14.3)

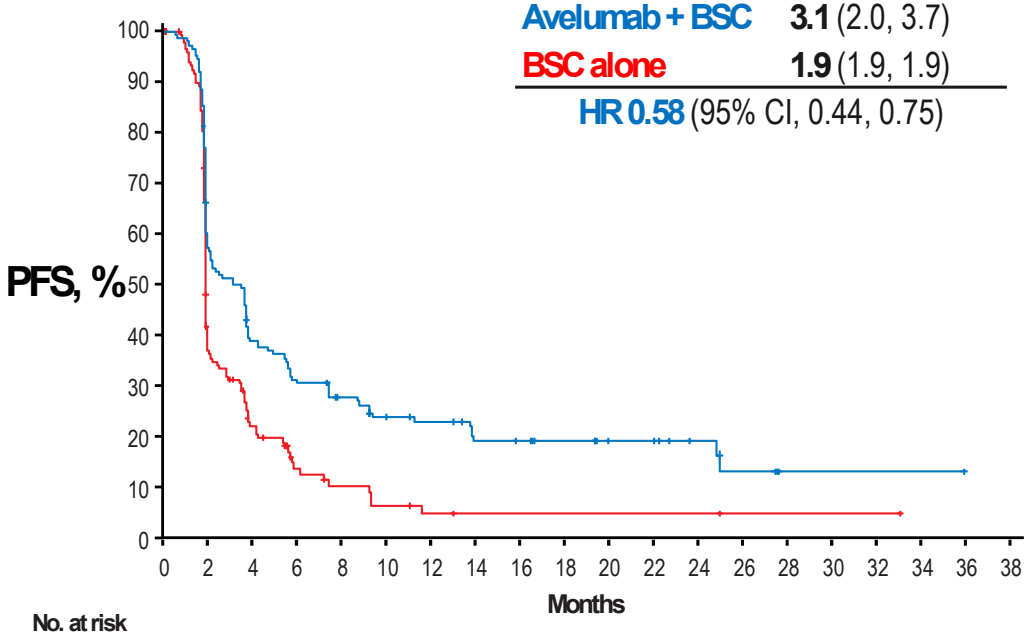
HR **0.62** (95% CI, 0.46, 0.83)



No. at risk																				
Avelumab + BSC	163	161	151	138	123	103	87	77	70	59	45	32	26	18	12	6	6	3	2	0
BSC	163	155	140	115	96	79	60	45	40	30	26	19	16	13	10	8	7	2	1	0

Median PFS (95% CI), months	
Avelumab + BSC	**3.1** (2.0, 3.7)
BSC alone	**1.9** (1.9, 1.9)

HR **0.58** (95% CI, 0.44, 0.75)



No. at risk																				
Avelumab + BSC	163	84	56	44	36	28	26	20	19	16	11	11	7	4	1	1	1	1	0	
BSC	163	52	28	12	8	5	3	2	2	2	2	2	2	1	1	1	1	0		

OS and PFS were measured post randomisation (after chemotherapy); CR (i.e., no evidence of disease at baseline), PR, and SD at baseline was based on either BICR or investigator assessment up to protocol amendment 3, or investigator assessment only from protocol amendment 3 (19 Dec 2016) onward

Powles T et al., Oral 699O presented at virtual ESMO Congress 2020.

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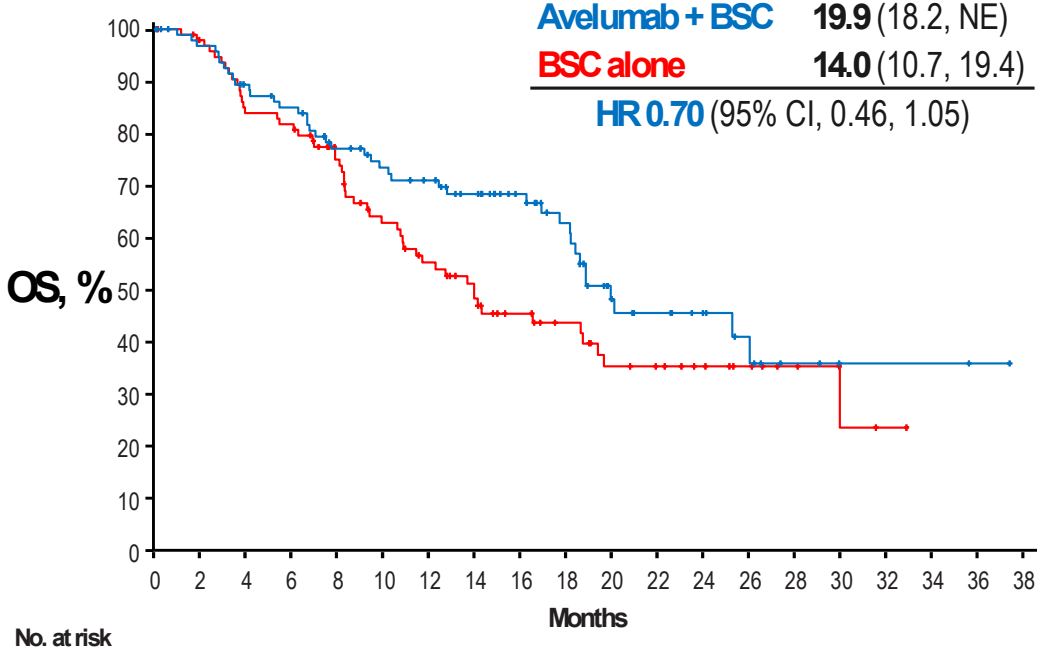
JAVELIN BLADDER 100

OS and PFS benefit with avelumab 1L maintenance was observed irrespective of best response to 1L chemotherapy

Stable disease (n=195)

Median OS (95% CI), months	
Avelumab + BSC	**19.9** (18.2, NE)
BSC alone	**14.0** (10.7, 19.4)

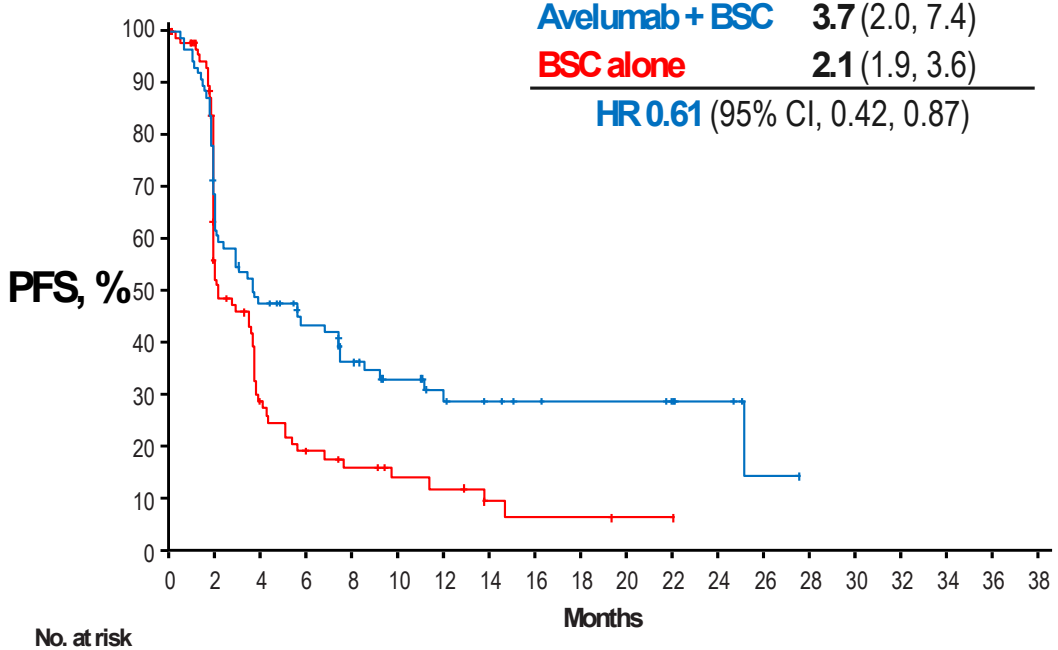
HR 0.70 (95% CI, 0.46, 1.05)



No. at risk																				
Avelumab + BSC	97	91	82	77	66	60	56	49	40	32	18	15	11	8	4	2	2	2	1	0
BSC	98	91	78	76	63	50	42	34	27	22	16	14	11	8	5	2	1	0		

Median PFS (95% CI), months	
Avelumab + BSC	**3.7** (2.0, 7.4)
BSC alone	**2.1** (1.9, 3.6)

HR 0.61 (95% CI, 0.42, 0.87)



No. at risk																				
Avelumab + BSC	97	53	40	32	24	18	13	11	9	8	8	7	4	1	0					
BSC	98	42	21	13	10	7	6	3	2	2	1	1	0							

OS and PFS were measured post randomisation (after chemotherapy); CR (i.e., no evidence of disease at baseline), PR, and SD at baseline was based on either BICR or investigator assessment up to protocol amendment 3, or investigator assessment only from protocol amendment 3 (19 Dec 2016) onward

Powles T et al. *New Engl J Med* 2020.

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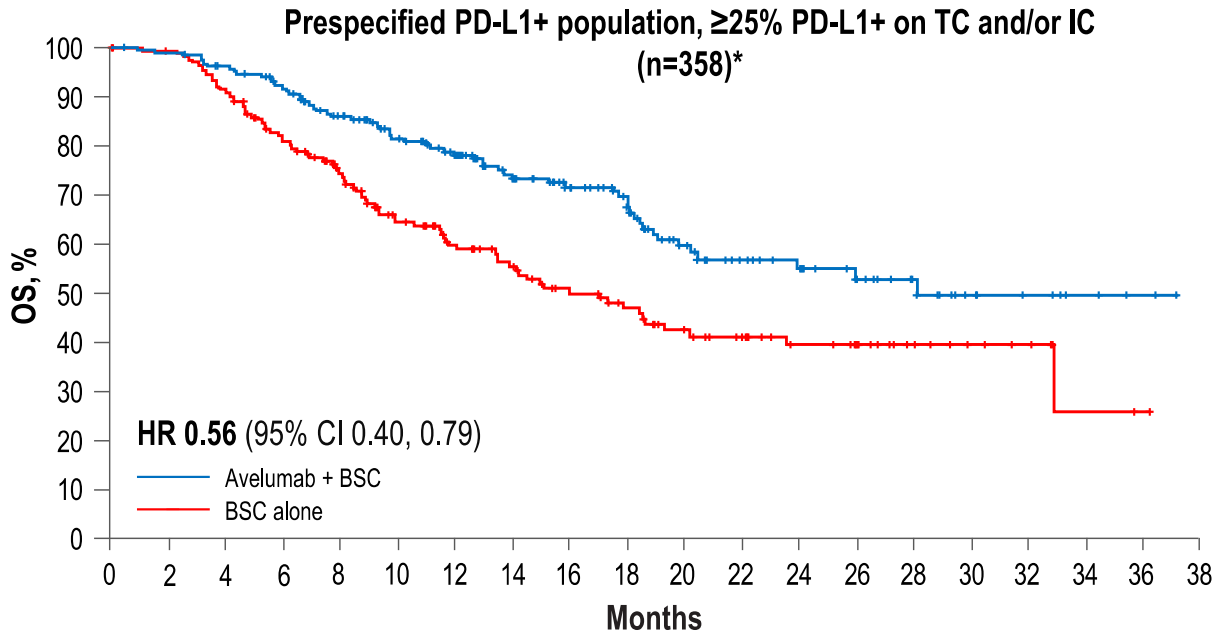
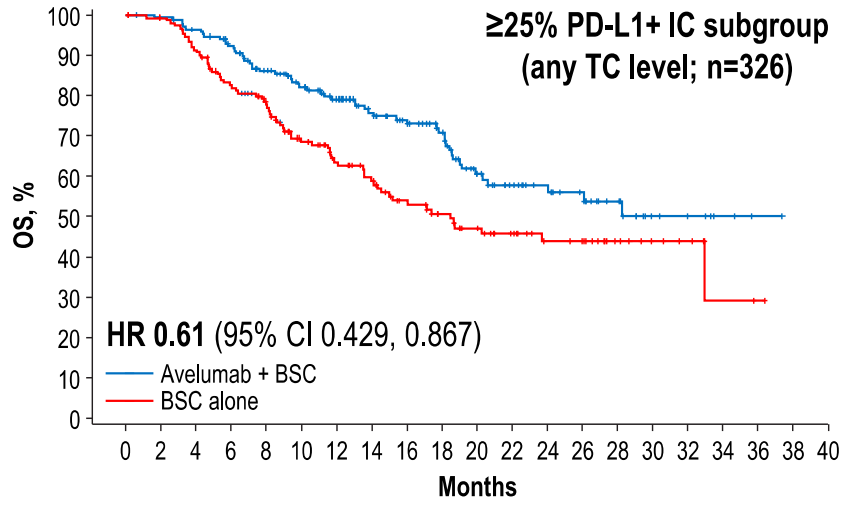
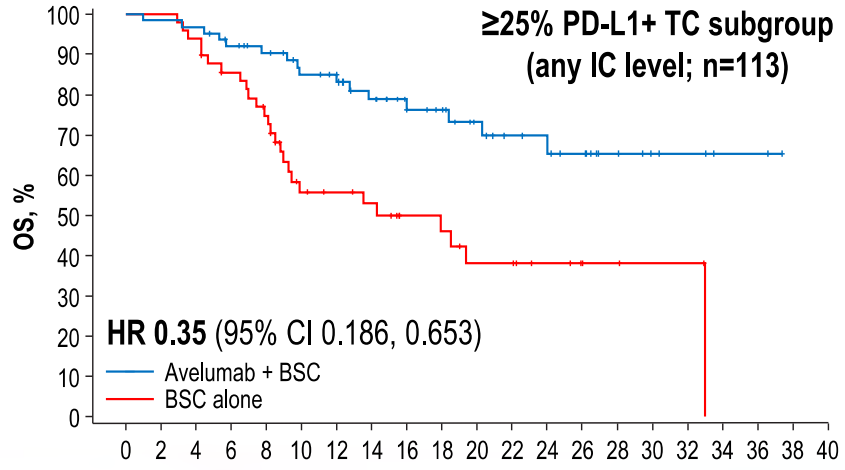
OS benefit in subgroups defined by PD-L1 expression on TC and/or IC

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







* PD-L1 expression in ≥25% of tumour cells or in ≥25% or 100% of tumour-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively, using the Ventana SP263 assay.

BSC, best supportive care; CI, confidence interval; HR, hazard ratio; OS, overall survival; TC, tumour cell; IC, immune cell; NE, not evaluable.; PD-L1, programmed cell death ligand 1

Powles T et al., Oral 699O presented at Virtual ESMO Congress 2020.

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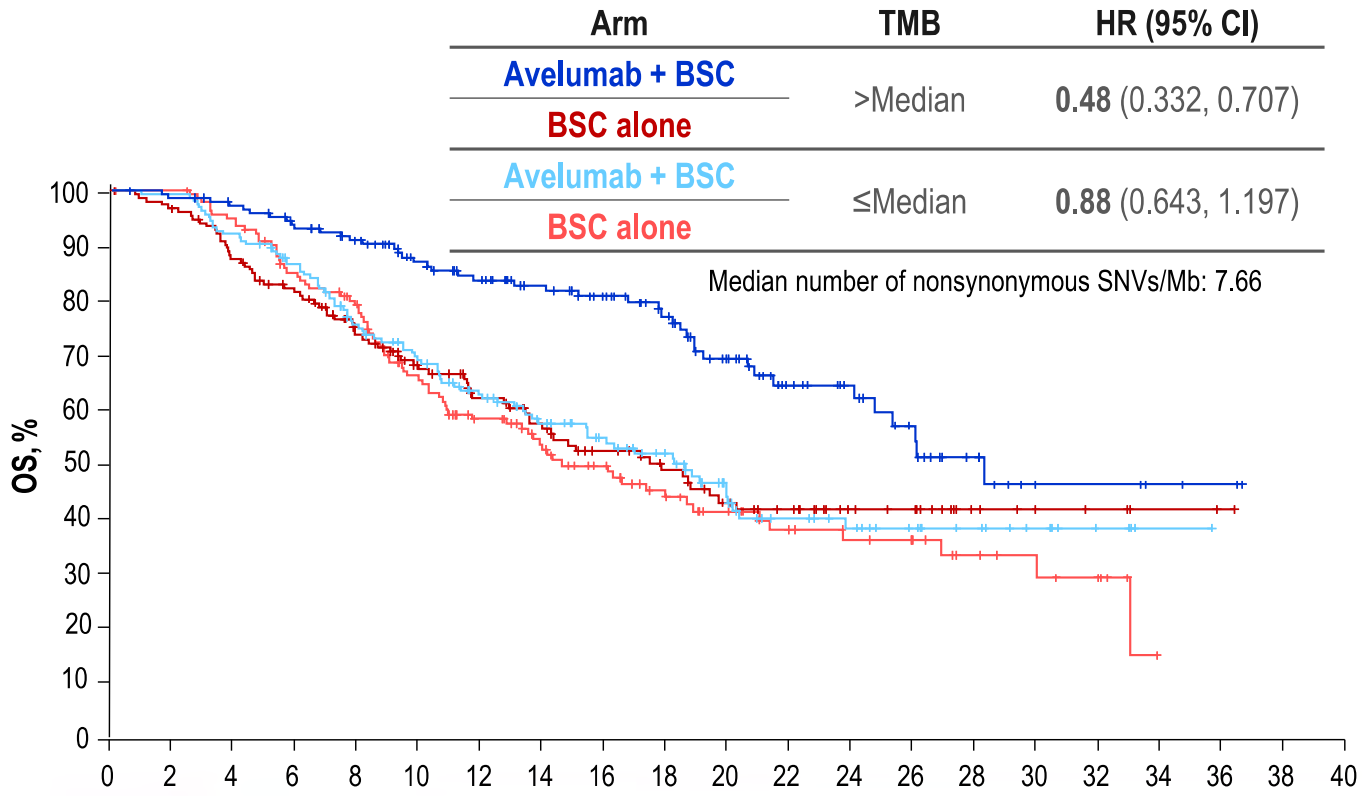
OS benefit in subgroups defined by tumor mutational burden and PD-L1 status

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



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	0.48 (0.332, 0.707)
TMB-low	0.88 (0.643, 1.197)
PDL1+ TMB-high (n=190)	0.51 (0.305, 0.868)
PDL1+ TMB-low (n=148)	0.60 (0.382, 0.955)
PDL1− TMB-high (n=105)	0.44 (0.251, 0.768)
PDL1− TMB-low (n=140)	1.27 (0.799, 2.006)

BSC, best supportive care; OS, overall survival; TMB, tumour mutational burden

Powles T et al., Oral 699O presented at Virtual ESMO Congress 2020.

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Safety of maintenance avelumab

	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)

Safety of maintenance avelumab

Long-term safety for maintenance treatment by prior 1L chemotherapy regimen

Events, n (%)	Cisplatin + gemcitabine		Carboplatin + gemcitabine	
	Avelumab + BSC (n=182)	BSC alone (n=204)	Avelumab + BSC (n=142)	BSC alone (n=119)
AE of any grade	182 (100)	160 (78.4)	136 (95.8)	90 (75.6)
Grade ≥3 AE	92 (50.5)	51 (25.0)	82 (57.7)	34 (28.6)
TRAE of any grade	147 (80.8)	5 (2.5)	107 (75.4)	1 (0.8)
Grade ≥3 TRAE	30 (16.5)	0	32 (22.5)	0
Serious AE	47 (25.8)	36 (17.6)	51 (35.9)	31 (26.1)
Serious TRAE	15 (8.2)	0	15 (10.6)	0
AE leading to interruption of avelumab	80 (44.0)	NA	69 (48.6)	NA
AE leading to discontinuation	19 (10.4)	0	27 (19.0)	0
TRAE leading to discontinuation	16 (8.8)	0	21 (14.8)	0
AE leading to death	3 (1.6)	9 (4.4)	4 (2.8)	12 (10.1)
TRAE leading to death	1 (0.5)	0	1 (0.7)	0
IRR of any grade	41 (22.5)	0	27 (19.0)	0

- Long-term safety was similar in both the cisplatin and carboplatin subgroups
  - No new safety concerns were identified

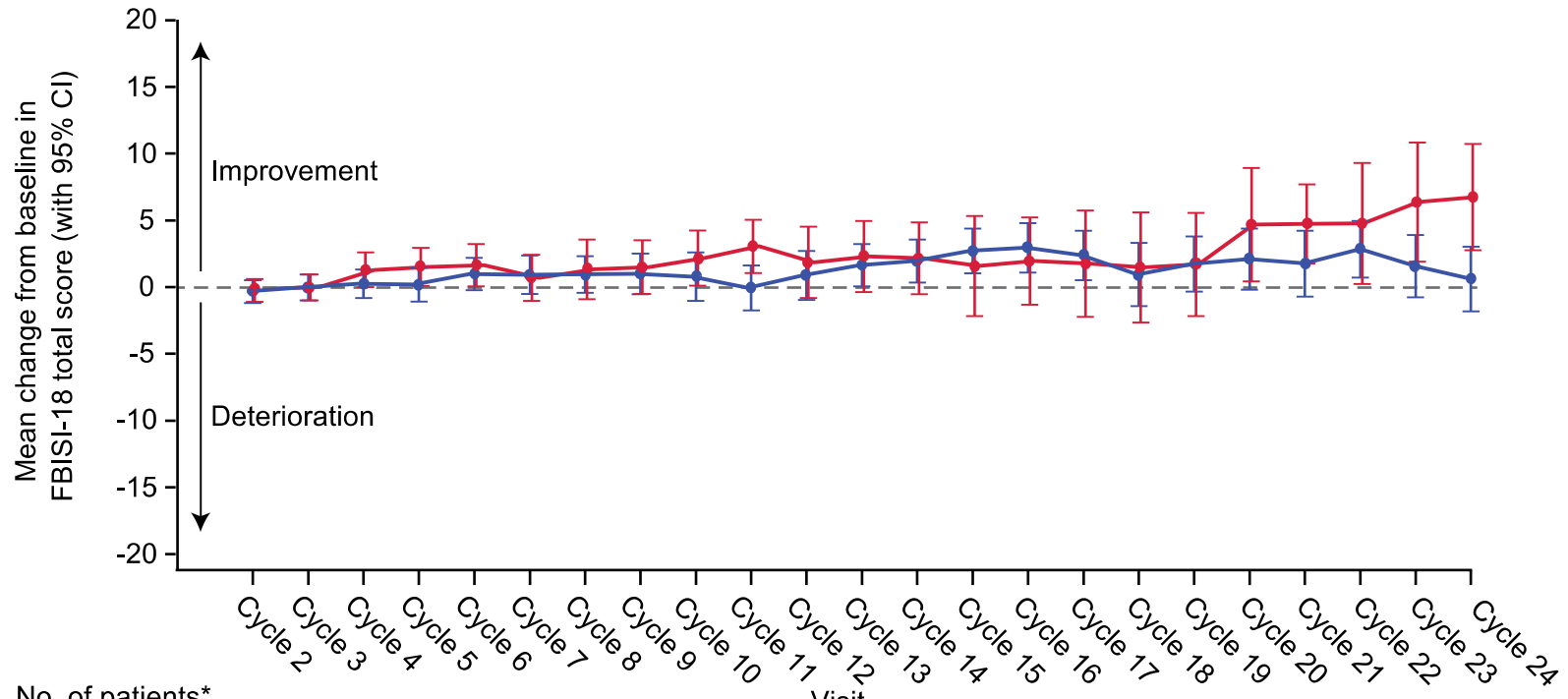
1L, first line; **AE**, adverse event; **BSC**, best supportive care; **IRR**, infusion-related reaction; **NA**, not applicable; **TRAE**, treatment-related adverse event.

Grupo Português Génito - Urinário

FBISI-18 total score in overall population: Changes from baseline (A) and mixed-model analysis prior to end of treatment (B)

A

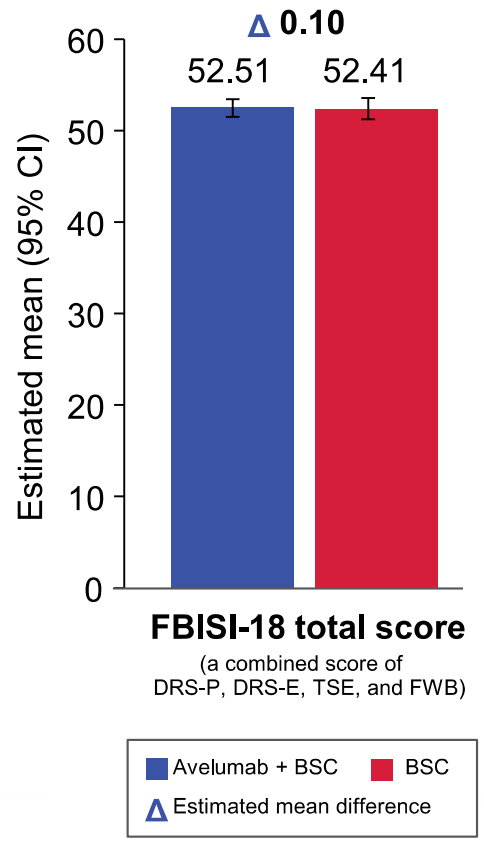
Figure A includes data for on-treatment visits that had ≥10 patients in each arm



No. of patients*																							
Avelumab + BSC	310	269	240	202	178	160	144	132	123	120	103	96	87	80	67	63	57	47	42	43	38	35	33
BSC	297	223	155	120	109	85	68	55	49	47	43	36	32	28	26	23	21	18	16	16	15	14	10

* Number of patients who completed the baseline assessment and the assessment at the respective cycle

B



Note: The FBISI-18 measures symptoms and quality of life (QOL) in patients with UC in the past 7 days. FBISI-18 total score range, 0–72; disease-related symptoms–physical (DRS-P) score range, 0–36; disease-related symptoms–emotional (DRS-E) score range, 0–8; treatment side effects (TSE) score range, 0–20; general function/functional and well-being (FWB) score range, 0—8. An estimate of clinically important difference for a within-patient change is one-third of standard deviation (SD); total score, 3–4; DRS-P, 2-3; DRS-E, 1; TSE, 1; FWB, 1.[1]

1. Yost KJ, Eton DT. Eval Health Prof. 2005;28(2):172-91; 2. Powles, T. et al., *New Engl J Med* 2020; 3. Powles T et al., Poster 745P presented at virtual ESMO 2020.

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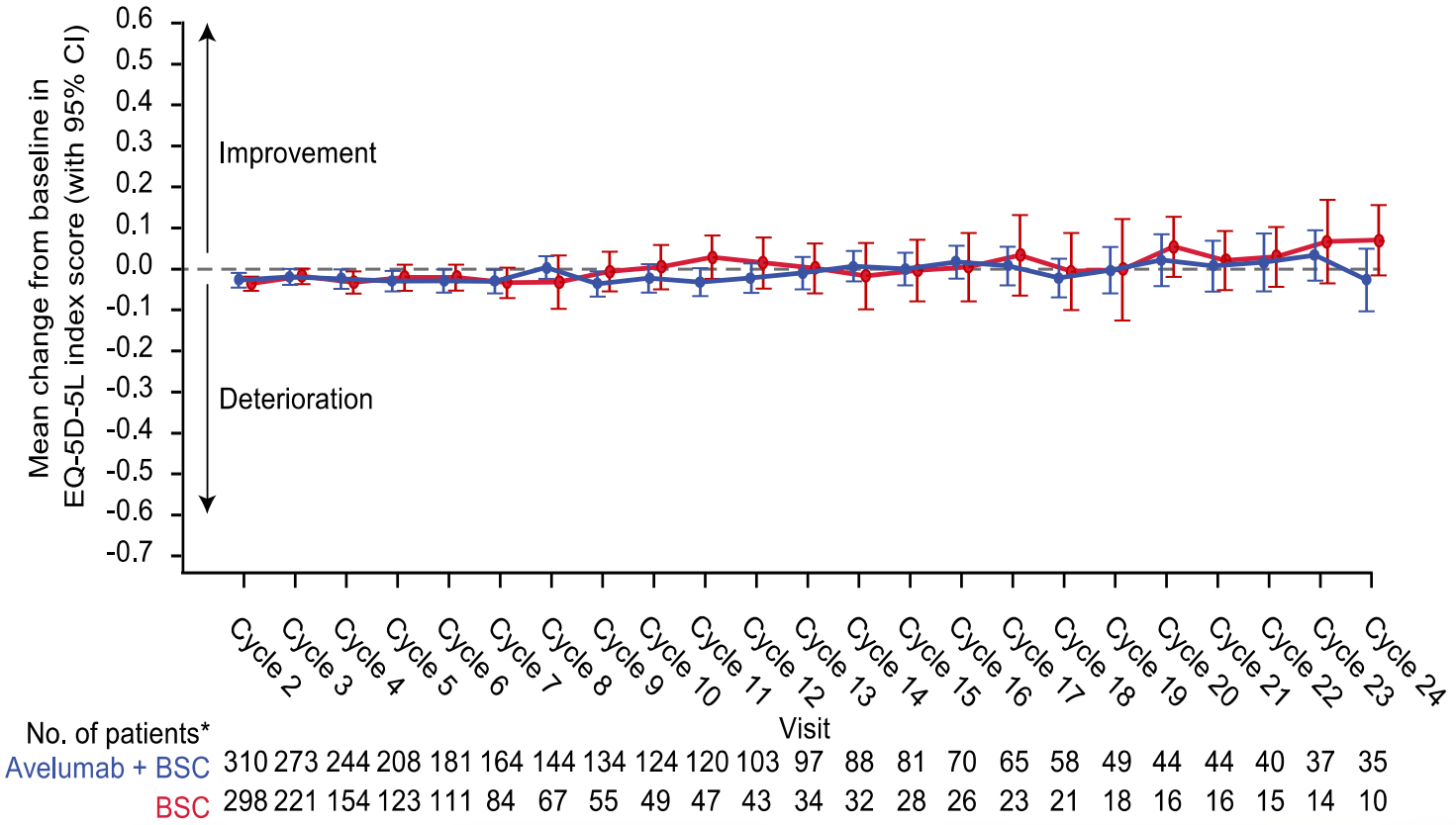
EQ-5D-5L index score in overall population: Changes from baseline (A) and mixed-model analysis prior to end of treatment (B)

A

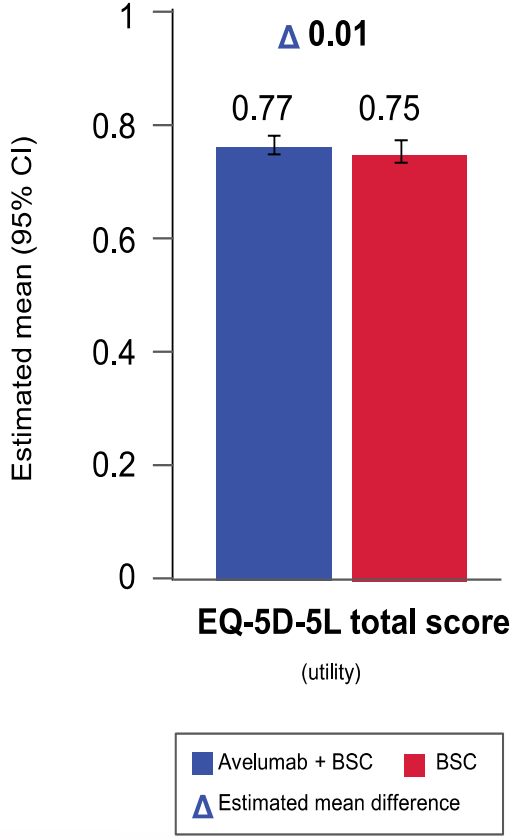
Figure A includes data for on-treatment visits that had ≥10 patients in each arm



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

* Number of patients who completed the baseline assessment and the assessment at the respective cycle

B



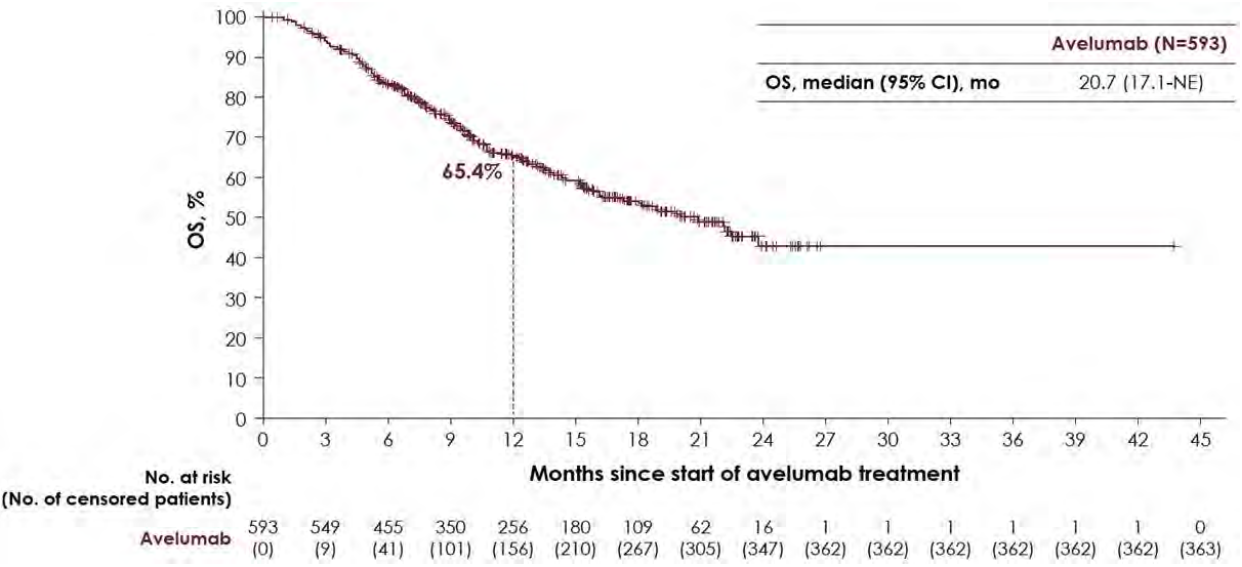
Note: The EQ-5D-5L index measures general health status based on mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-5L index is calculated based on UK weights, and scores range from −0.594 to 1; the EQ-5D-5L visual analogue scale (EQ-VAS) range is 0-100. A minimally important difference is 0.09-0.012 for the EQ-5D-5L index score and 7-12 for the EQ-VAS based on UK weights.[1]

1. Pickard AS, et al. *Health Qual Life Outcomes*. 2007;5:70; 2. Powles T et al., *New Engl J Med* 2020; 3. Powles T et al., Poster 745P presented at virtual ESMO 2020.

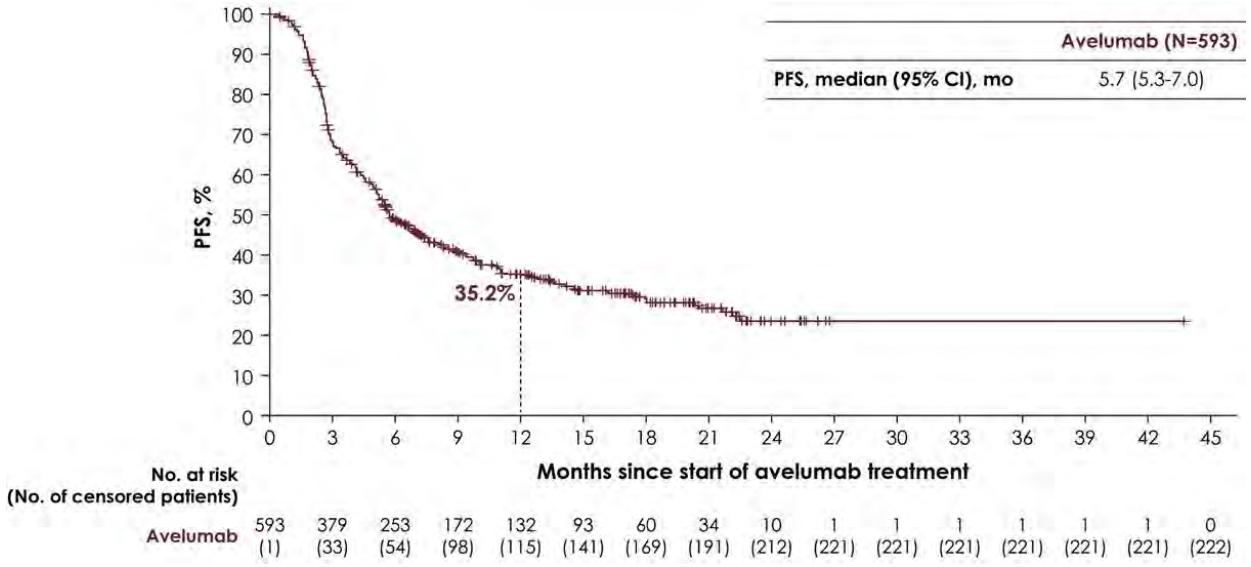
AVENANCE: A real-world study of avelumab 1L maintenance treatment in patients with aUC

- AVENANCE (NCT04822350) is an ongoing, real-world, ambispective study evaluating the effectiveness and safety of avelumab 1L maintenance in patients with aUC that has not progressed with platinum-based chemotherapy in France
  - Preliminary results from this study in the first 267 patients enrolled who had started avelumab treatment ≥6 months prior to January 31, 2022 (data cutoff) have been published previously[7]
    - The 12-month OS rate from the start of avelumab treatment was 66.9%, and median PFS was 5.7 months

OS from the start of avelumab treatment



PFS from the start of avelumab treatment



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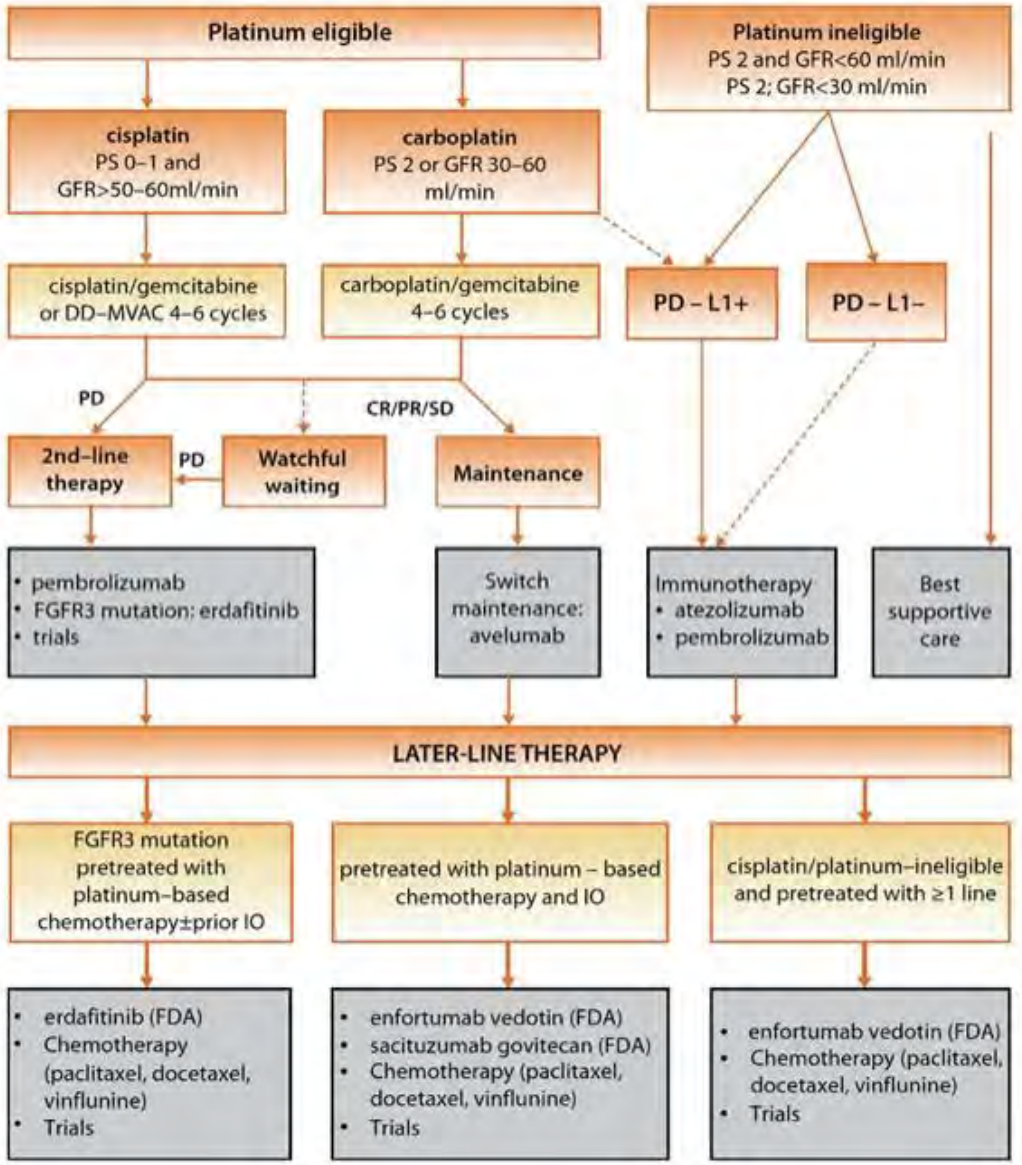
Summary of AEs

Events, n (%)	N=593
TEAE*	428 (72.2)
Serious TEAE	200 (33.7)
TEAE leading to temporary/permanent discontinuation	171 (28.8)
TEAE leading to death	99 (16.7)
TRAE	254 (42.8)
Serious TRAE	31 (5.2)
TRAE leading to temporary/permanent discontinuation	78 (13.2)
TRAE leading to death	5 (0.8)

aUC – Treatment algorithm



Conclusions

- With ≥2 years of follow-up in all patients, long-term outcomes from JAVELIN Bladder 100 confirm that avelumab 1L maintenance provides similar OS and PFS benefits in patients with advanced UC who are progression free following standard-of-care 1L cisplatin- or carboplatin-based chemotherapy, with an acceptable safety profile
  - Long-term safety of avelumab 1L maintenance was similar in patients who had received 1L cisplatin or carboplatin + gemcitabine
- In the overall population, median OS with the full JAVELIN Bladder regimen (1L cisplatin- or carboplatin-based chemotherapy followed by avelumab 1L maintenance) was 29.7 months
  - This result further supports avelumab 1L maintenance as standard of care in patients with advanced UC who are progression free following 1L platinum-based chemotherapy and provides a benchmark for ongoing and future clinical trial outcomes

1L, first line; **BSC**, best supportive care; **OS**, overall survival; **PFS**, progression-free survival; **UC**, urothelial carcinoma.