Overall survival at its core: The new ABC (Avelumab in Bladder Cancer)

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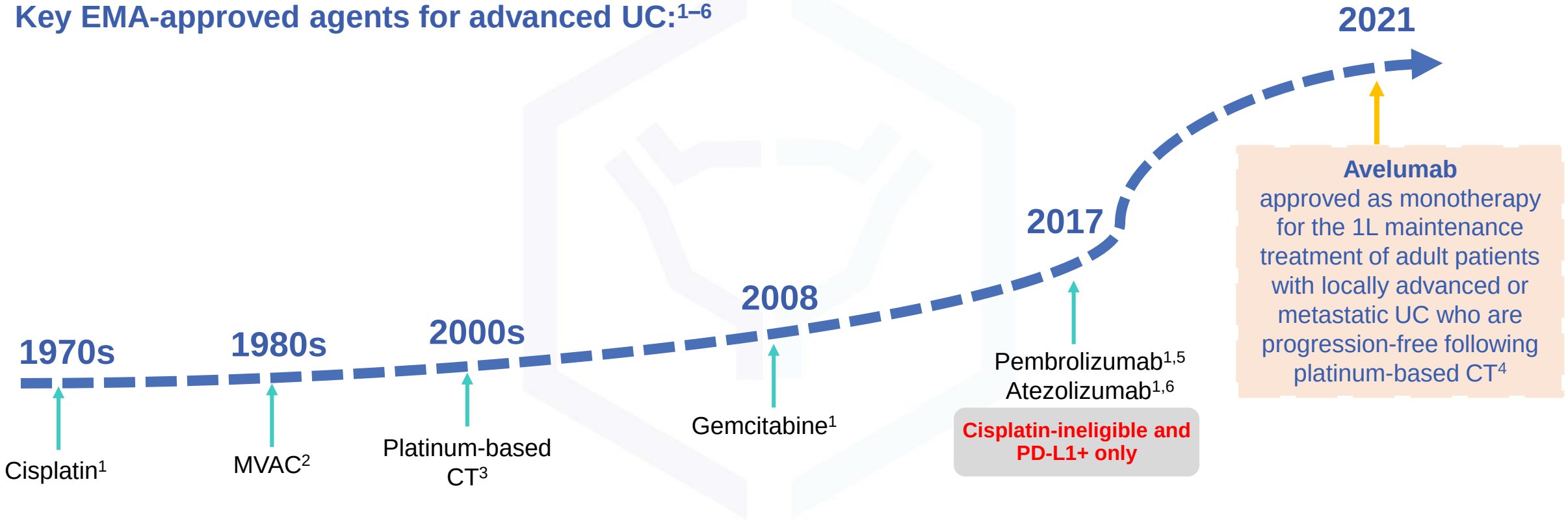
Fortis Hospital, Delhi

Timeline: Approved 1L therapies for advanced UC

Platinum-based CT has been the 1L SOC for eligible patients for two decades[1–3]
After platinum-based CT, BAVENCIO® (avelumab) can now be given as 1L maintenance treatment[4]

Key EMA-approved agents for advanced UC:[1–6]



1L, first-line; CT, chemotherapy; EMA, European Medicines Agency; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; PD-L1, programmed death-ligand 1; SOC, standard of care; UC, urothelial carcinoma.

1. Pichler R, et al. *memo - Magazine of European Medical Oncology*;2021:14:70–5; 2.Sternberg CN, et al. *Cancer;*1989:64:2448–58; 3. Koufopoulou M, et al. *Cancer Treat Rev*;2020;89:102072; 4. BAVENCIO® Summary of Product Characteristics, 2021; 5. KEYTRUDA® Summary of Product Characteristics, 2021; 6. TECENTRIQ® Summary of Product Characteristics, 2021.

Patient segments in 1L mUC

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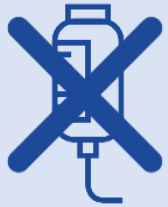
Patient

Cisplatin eligible

Cisplatin ineligible

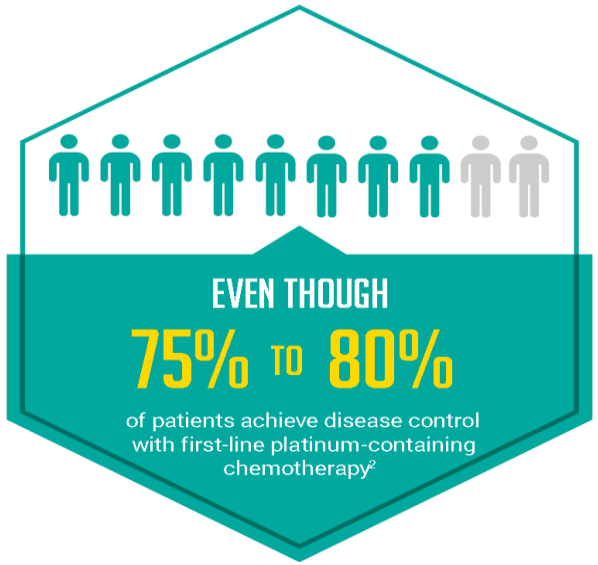


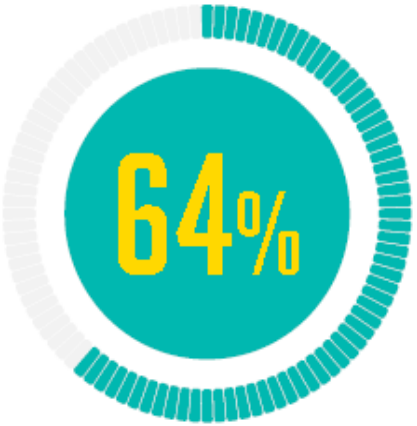
Platinum ineligible

Majority of the patients receive platinum-based therapy

Urothelial Cancer - For over 20 years, platinum-containing chemotherapy has been the standard of care because of its high initial response rate, but with limitations.

BAVENCIO® avelumab Injection





of patients progress within[2,5-6]
9 MONTHS

of patients do not receive second-line therapy [4,7-9]

2. Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. N Engl J Med. 2020;383(13):1218-1230. doi:10.1056/ NEJMoa2002788.; 3. Powles T, Park SH, Voog E, et al. Maintenance avelumab + best supportive care (BSC) versus BSC alone after platinum-based first-line chemotherapy in advanced urothelial carcinoma: JAVELIN Bladder 100 phase III results [Abstract LBA1]. Presented at: American Society of Clinical Oncology (ASCO) 2020 Virtual Annual Meeting; May 29 to June 2, 2020.;4. Niegisch G, Gerullis H, Lin S-W, et al. A real-world data study to evaluate treatment patterns, clinical characteristics and survival outcomes for first- and second-line treatment in locally advanced and metastatic urothelial cancer patients in Germany. J Cancer. 2018;9(8):1337-1348.; 5. Bukhari N, Al-Shamsi HO, Azam F. Update on the treatment of metastatic urothelial carcinoma. Hindawi Sci World J. 2018;5682078:1-7. doi.org/10.1155/2018/5682078.; 6. Von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol. 2000;17(17):3068-3077.; 7. Cheeseman S, Thompson M, Sopwith W, et al. Current treatment and outcomes benchmark for locally advanced or metastatic urothelial cancer from a large UK-based ingle centre. Front Oncol. 2020;10:167. doi:10.3389/fonc.2020.00167.; 8. Galsky MD, Pal SK, Lin S-W, et al. Real-world effectiveness of chemotherapy in elderly patients with metastatic bladder cancer in the United States. Bladder Cancer. 2018;4(2):227-238.;
9. Aly A, Johnson C, Yang S, Botteman MF, Rao S, Hussain A. Overall survival, costs, and healthcare resource use by line of therapy in Medicare patients with newly diagnosed metastatic urothelial carcinoma. J Med Econ. 2019 Jul;22(7):662-670.

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Patient attrition between first-line therapy and later lines of therapy in real-world studies in mUC

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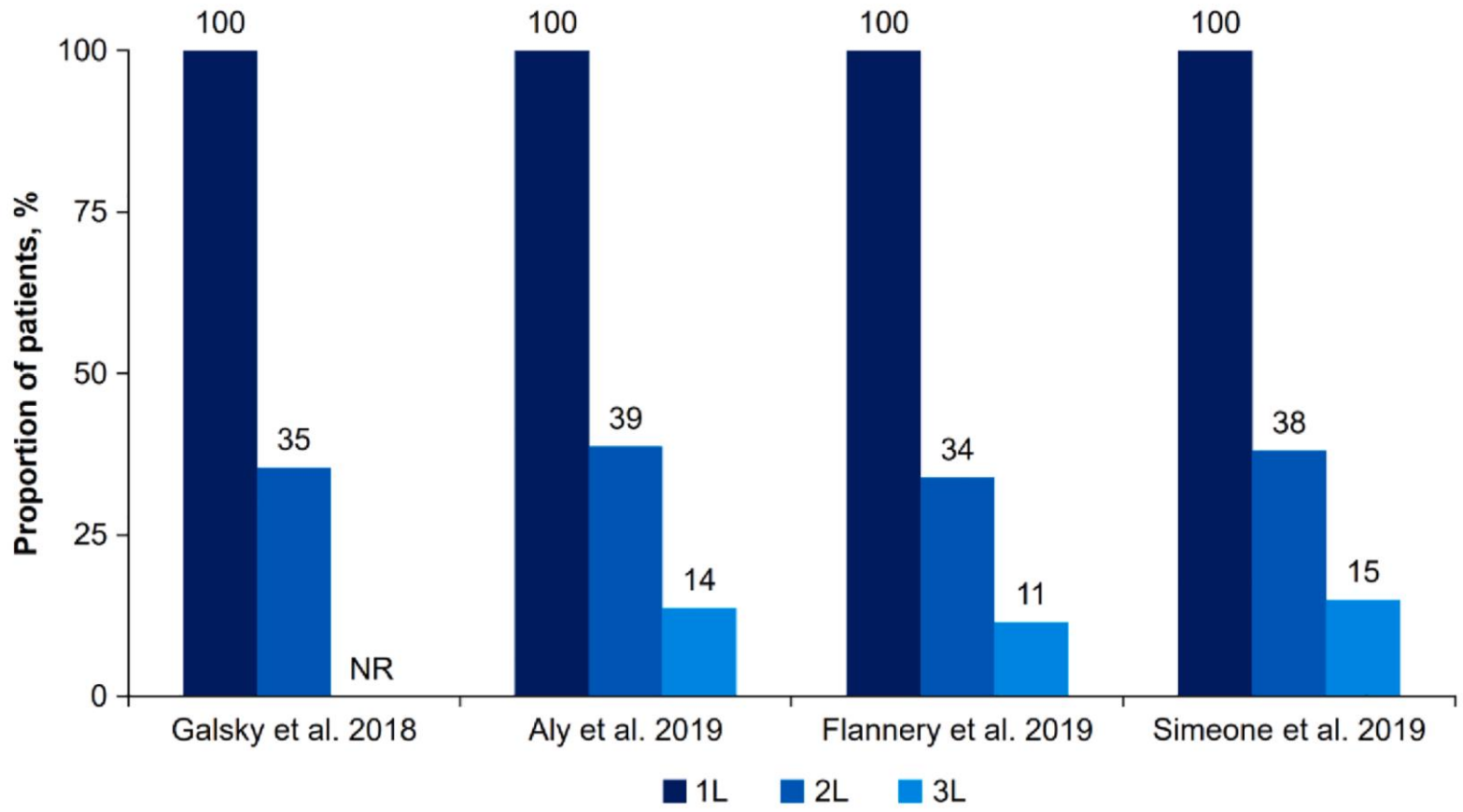

Optimizing 1L therapy is very important in aggressive disease like mUC

Grivas P, et al. Avelumab first-line maintenance in locally advanced or metastatic urothelial carcinoma: applying clinical trial findings to clinical practice. *Cancer Treat Rev*. 2021. [Epub ahead of print]. doi: 10.1016/j.ctrv.2021.102187.

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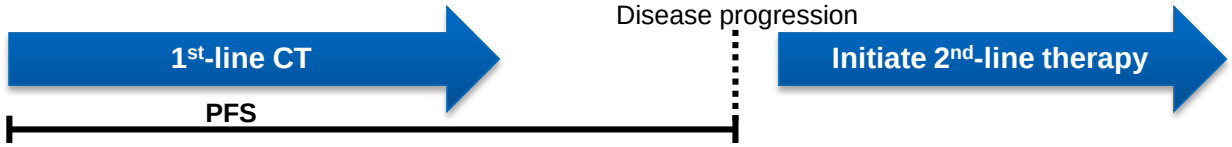
Treatment approaches to maximize OS

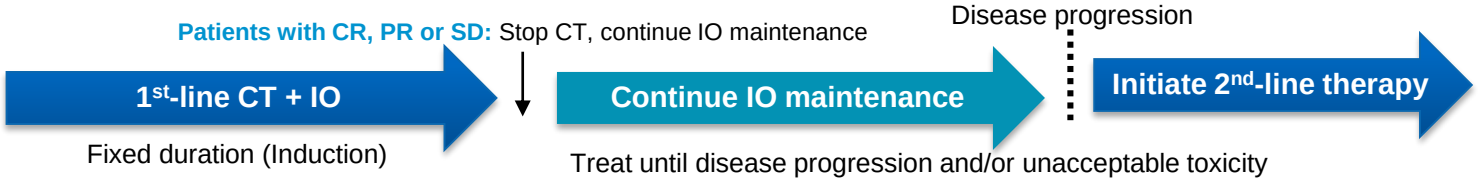
BAVENCIO® avelumab Injection

Cisplatin eligible **and** **Carboplatin eligible**

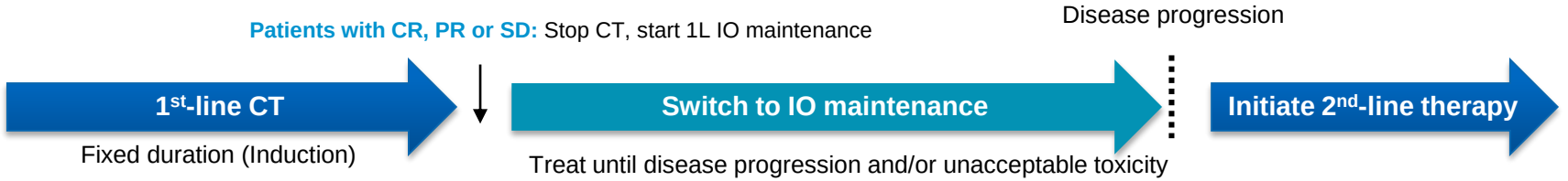
Wait and watch



Continuation maintenance



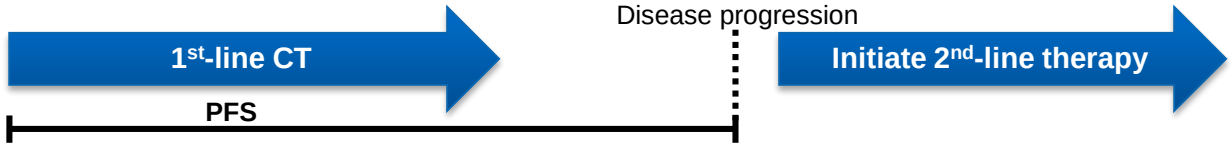
Switch maintenance



Wait and watch approach-

1L platinum-based CT (ORR: ~40–50%; DCR: ~50–80%) but mOS remains around 15 months

Wait and watch



50 to 80%

of patients achieve disease control with 1L platinum-based CT[3,4]

However, OS is limited by CT resistance[2]

Median OS

Cisplatin-based CT: **14 to 15 months**[3,5]

Carboplatin-based CT: **13 to 14 months**[6,7]

1L, first-line; CT, chemotherapy; OS, overall survival; SOC, standard of care; UC, urothelial carcinoma.

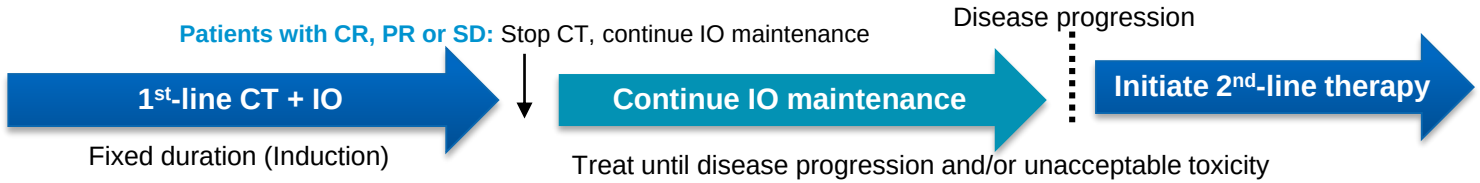
1. Niegisch G, et al. *J Cancer*;2018:9(8):1337–48; 2. Grivas P, et al. *Target Oncol*;2019:14(5):505–25;
3. von der Maase H, et al. *J Clin Oncol*;2000;17(17):3068–77; 4. De Santis M, et al. *J Clin Oncol*;2012;30(2):191–199;
5. von der Maase H, et al. *J Clin Oncol*;2005:23(21):4602–8; 6. Powles T, et al. *Lancet Oncol*. 2021 Jul;22(7):931-945;
7. Galsky MD, et al. *Lancet*. 2020 May 16;395(10236):1547-1557

Cross-trial comparisons should not be made due to differences in trial design

Continuation maintenance approach-

None of the IO+CT or IO+IO studies provides mOS benefits in these difficult to treat patients

Continuation maintenance



	IMvigor130[1]	KEYNOTE-361[2]	DANUBE[3]
Treatment strategy	CT + IO	CT + IO	IO doublet
Experimental agents	Atezolizumab + platinum-based CT	Pembrolizumab + platinum-based CT	Durvalumab + tremelimumab
Status	Awaiting final results	Negative trial	Negative trial
Outcome	No significant difference in OS at 2nd interim analysis (AACR 2021)	Did not meet OS or PFS primary endpoints (ESMO 2020)	Did not meet OS endpoints (ESMO 2020)

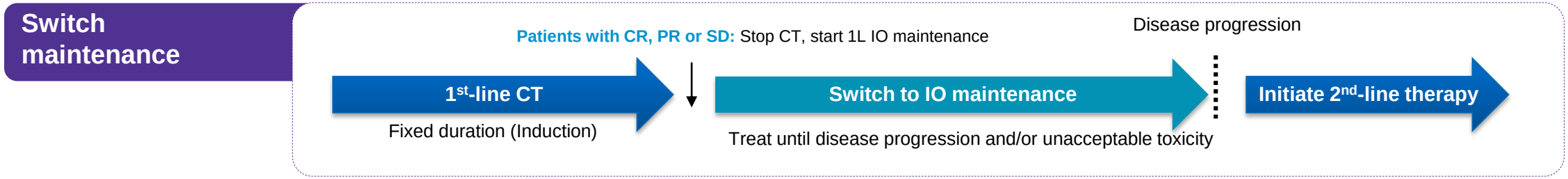
CT, chemotherapy; IO, immunotherapy; CR, complete remission; PR, partial remission; SD, stable disease; PFS, progression free survival

1. Galsky MD, et al. Lancet Oncol;2021;395;1547-57
2. Powles T, et al. Lancet Oncol; 2021; 22(7), 931-945
3. Powles T, et al. Lancet Oncol; 2020; 21; 1574-1588

Cross-trial comparisons should not be made due to differences in trial design

Switch Maintenance-

JAVELIN Bladder 100 the only phase III study demonstrates significant overall survival in UC maintenance setting



	JAVELIN Bladder 100 (Ph III)[1]	GU14-182 (Ph II)[2]
Treatment strategy	CT >> IO maintenance	CT >> IO maintenance
Experimental agents	Avelumab	Pembrolizumab
mOS benefit	Significant benefit vs no maintenance	Non-significant benefit vs no maintenance

CT, chemotherapy; IO, immunotherapy; CR, complete remission; PR, partial remission; SD, stable disease; PFS, progression free survival

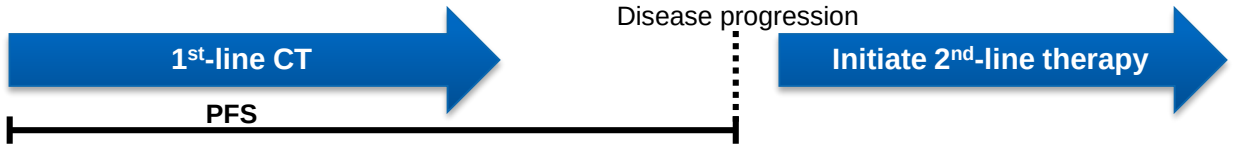
1. Powles T, et al. N Engl J Med 2020;383:1218–30
2. Galsky MD, et al. J Clin Oncol; 2020; 38(16):1797-1806

Cross-trial comparisons should not be made due to differences in trial design

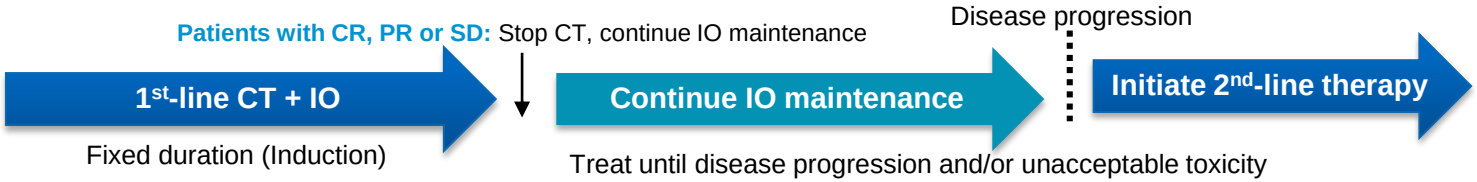
In unresectable LA or mUC platinum eligible patients

Cisplatin eligible **OR** **Carboplatin eligible**

Wait and watch

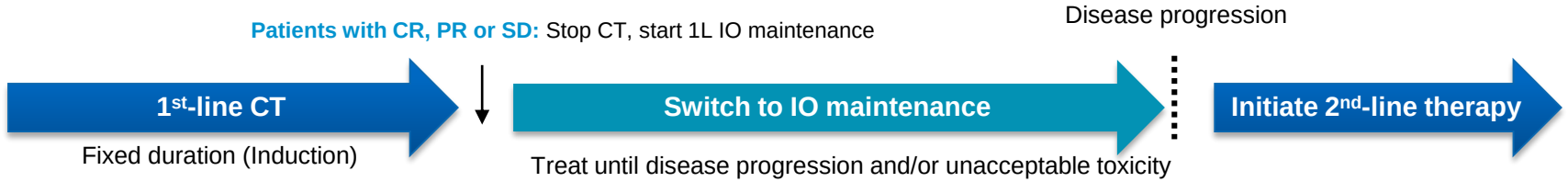


Continuation maintenance



NEXT

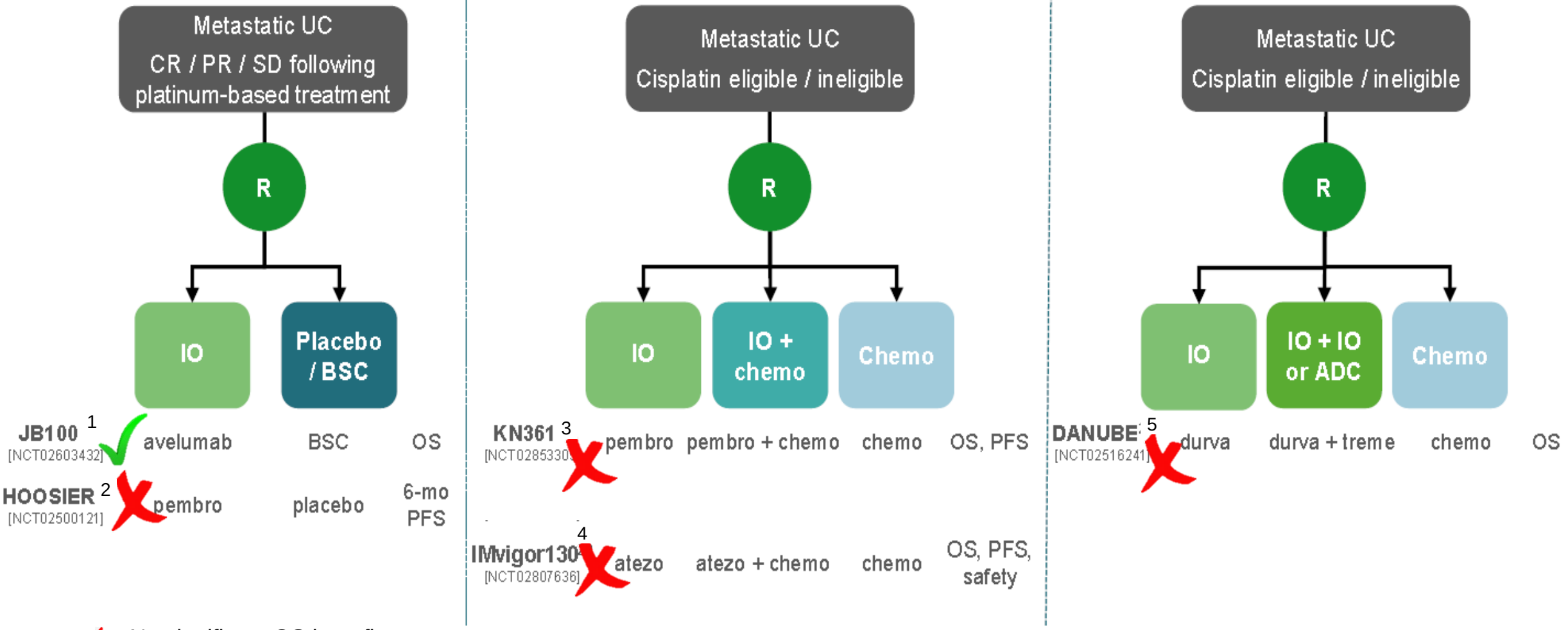
Switch maintenance



Only approach that has translated into maximizing mOS

CT, chemotherapy; IO, immunotherapy; CR, complete remission; PR, partial remission; SD, stable disease; PFS, progression free survival; mOS, median Overall survival; LA, locally advanced; mUC, metastatic urothelial carcninoma

Summary: Different strategies for Cisplatin/Carboplatin eligible mUC



No significant OS benefit

IO, immunotherapy; CR, complete remission; PR, partial remission; SD, stable disease; PFS, progression free survival; OS, overall survival

1. Powles T, et al. N Engl J Med 2020;383:1218–30. 2. Galsky MD, et al. J Clin Oncol; 2020; 38(16):1797-1806
3. Powles T, et al. Lancet Oncol; 2021; 22(7), 931-945. 4. Galsky MD, et al. Lancet Oncol;2021;395;1547-57
5. Powles T, et al. Lancet Oncol; 2020; 21; 1574-1588

Cross-trial comparisons should not be made due to differences in trial design

Maintenance therapy introduces a treatment approach for patients who have a response or stable disease after first-line platinum-based chemotherapy[1,2]

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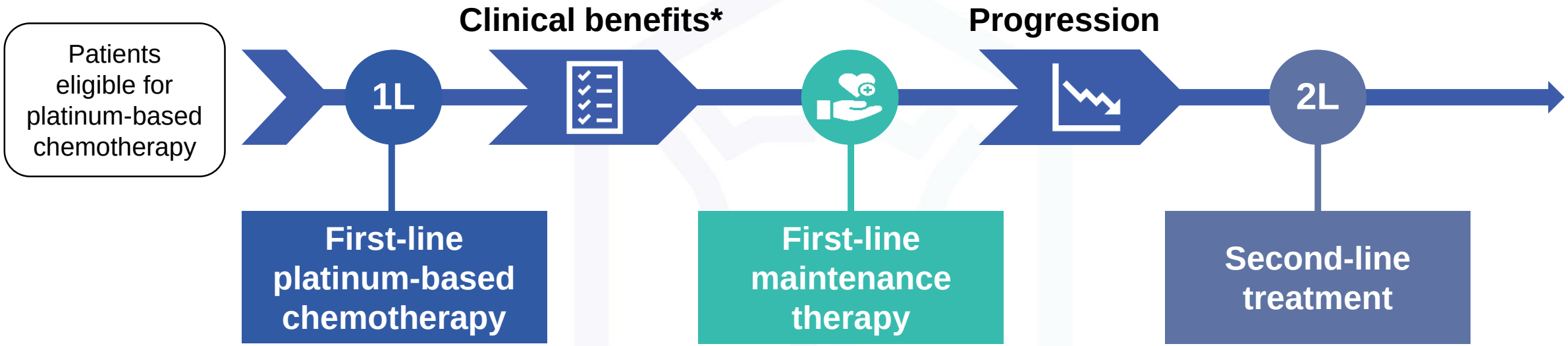
- Maintenance therapy can be given shortly after completion of the induction therapy in patients whose disease is not progressing and until disease progression or unacceptable toxicity, or for a fixed time period[1,2]
- Unlike existing approved PD-L1 inhibitors for advanced UC, patients may be treated with first-line maintenance BAVENCIO® (avelumab) regardless of PD-L1 status; PD-L1 testing is not a requirement[3]



First-line maintenance with BAVENCIO® (avelumab) offers an alternative option to the 'watch and wait' approach in patients who are progression-free after first-line platinum-based chemotherapy[3]

*Clinical benefit includes complete response, partial response and stable disease.
1L, first line; 2L, second line; PD-L1, programmed cell death ligand 1; UC, urothelial carcinoma.
1. Freidlin B et al. *J Natl Cancer Inst* 2015;107:djv225; 2. Grivas P et al. *Target Oncol* 2019;14:505–525; 3. BAVENCIO India PI, June 2021

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Maintenance therapy introduces a treatment approach that aims to prolong clinical responses and maintain the patient's quality of life[1]

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Work with the previous treatments[1]

Preclinical data showed that IO therapy has a MoA that complements the MoA of chemotherapy.[1,2] In addition, IO maintenance therapy may reinforce and sustain the clinical benefit of chemotherapy[1]

Prolong the response[1]

Clinical data demonstrated improved efficacy (prolonged OS and/or PFS) in patients treated with IO maintenance therapy compared with those not receiving maintenance therapy[3–5]

Maintain QoL[1]

Prolonged chemotherapy can result in cumulative toxicity, which may affect an individual's QoL. An optimal maintenance therapy will maintain QoL[1]

IO, immuno-oncology; MoA, mechanism of action; OS, overall survival; PFS, progression-free survival; QoL, quality of life.

1. Grivas P et al. *Target Oncol* 2019;14:505–525; 2. Kyi C, Postow MA. *Immunotherapy* 2016;8:821–837; 3. Galsky MD et al. *J Clin Oncol* 2020;38:1797–1806; 4. Antonia SJ et al. *N Engl J Med* 2017;377:1919–1929; 5. Moore K et al. *N Engl J Med* 2018;379:2495–2505.

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JAVELIN BLADDER 100 TRIAL

Overall efficacy and safety data

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JAVELIN Bladder 100

BAVENCIO® avelumab Injection

- Phase 3
- Randomized
- Open Label
- Parallel Arm
- 370 Locations
- 700 Patients
- Locally Advanced or Metastatic Urothelial Carcinoma
- Avelumab +BSC vs BSC As 1L Maintenance Treatment After 1L PBCT

JAVELIN Bladder 100

BAVENCIO® avelumab Injection

Phase III, randomized, open-label study[1,2]

INDUCTION

CHEMOTHERAPY

MAINTENANCE

All endpoints were measured post-randomization
(after CT and the treatment-free interval)

Unresectable locally advanced or metastatic UC with measurable Stage IV disease

Received standard 1st-line CT (4 to 6 cycles):

- Cisplatin + gemcitabine, or
- Carboplatin + gemcitabine

Treatment-free interval (4–10 weeks)

(Radiological assessment of response)

Patients with **CR, PR, or SD**

All patients: **N=700**

PD-L1+: n=358 (51%)

1:1

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 induction CT (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*
- OR*
- Time to response*
- Response duration*
- Disease control*
- Safety and tolerability
- PROs

*Supportive care was administered per local practice based on patient needs and clinical judgment and included antibiotics, nutritional support, hydration, and pain management; other systemic antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable. †Defined as response + stable disease for ≥6 weeks.

AE, adverse event; BICR, blinded independent central review; BSC, best supportive care; CR, complete response; CT, chemotherapy; IV, intravenous; OR, objective response; OS, overall survival; PD, progressive disease; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response; PRO, patient-reported outcomes; Q2W, every 2 weeks; RECIST, response evaluation criteria in solid tumors; SD, stable disease; UC, urothelial carcinoma.

1. Powles T, et al. N Engl J Med 2020;383:1218–30; 2. Powles T, et al. Oral presentation at ASCO 2020.

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Scientific rationale

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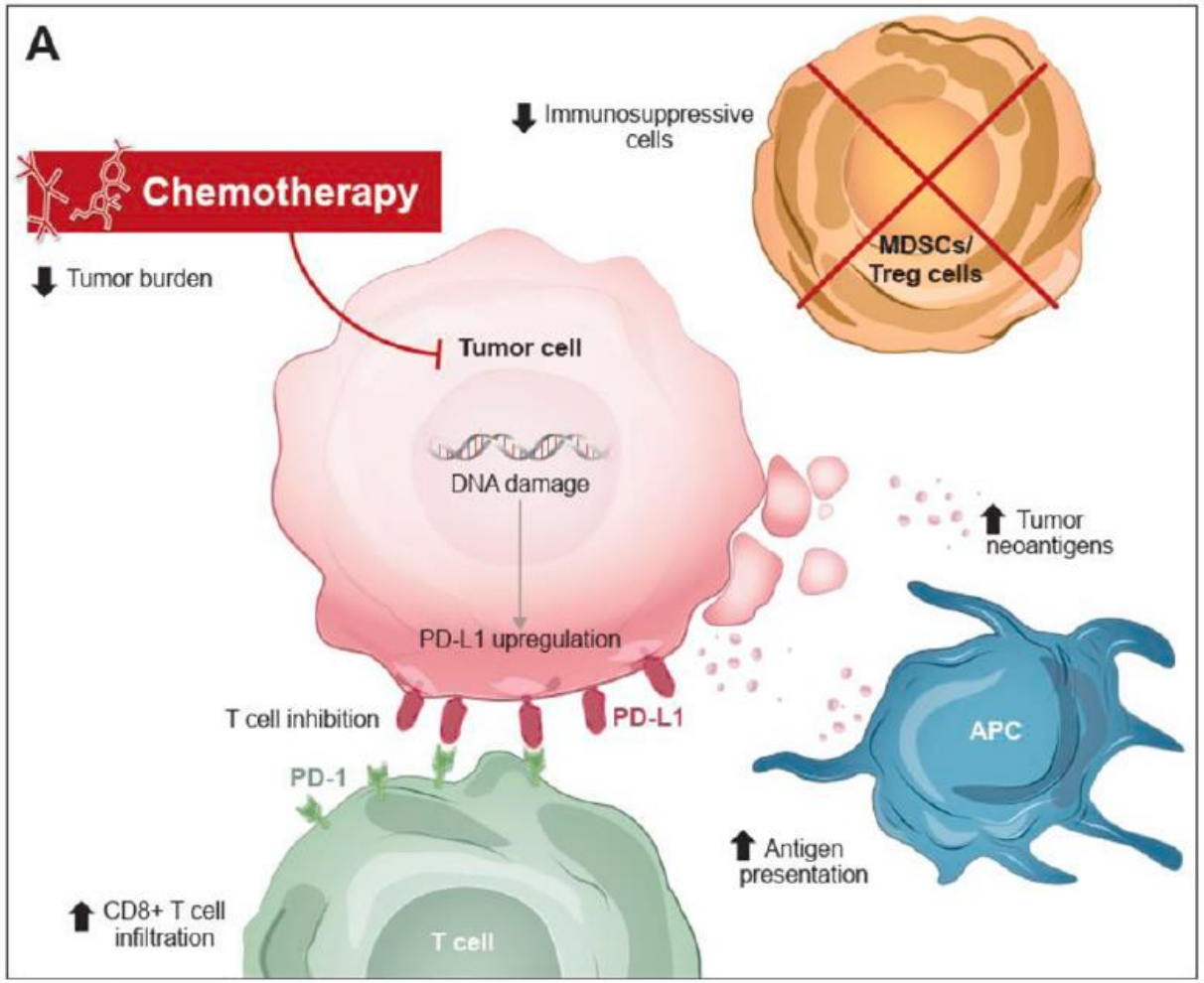

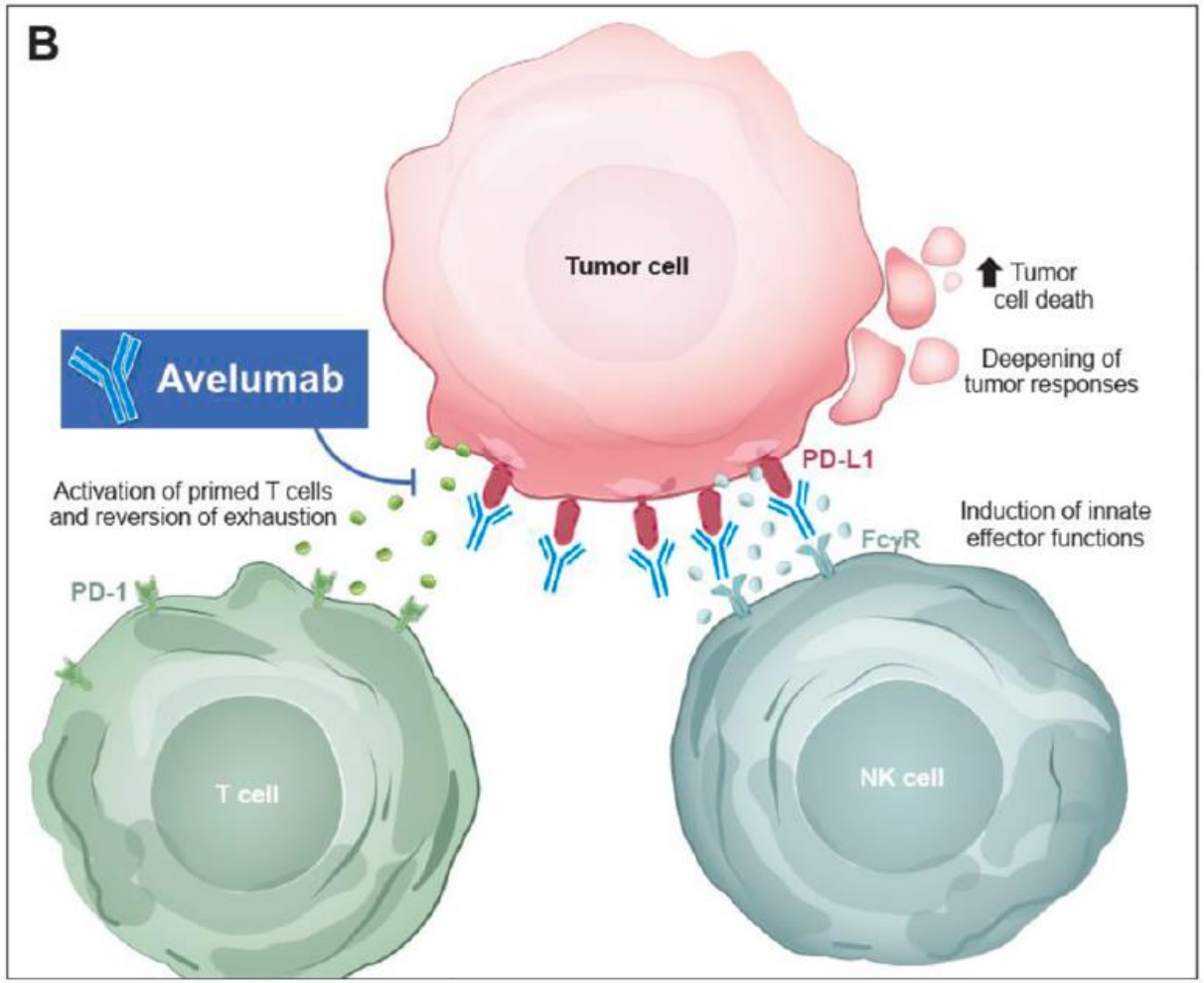

Baseline characteristics

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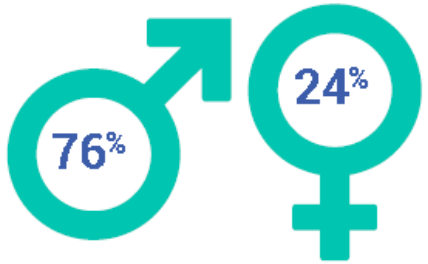
Median age

Gender



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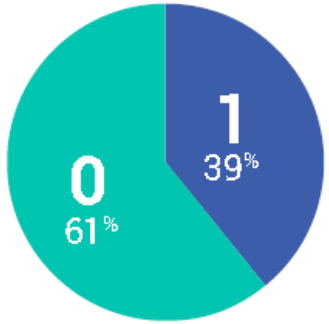
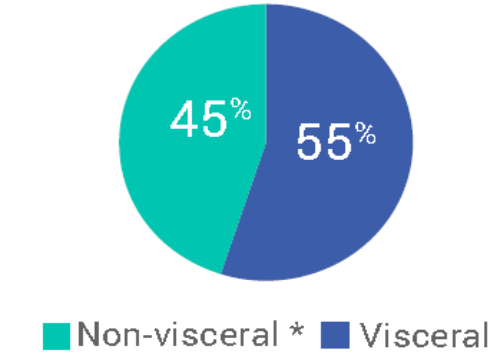
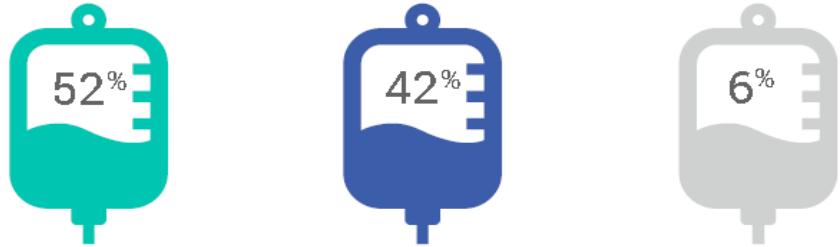


Location of Metastasis



First-line chemotherapy regimen:



1. Powles T, et al. N Engl J Med 2020;383:1218–30; 2. Powles T, et al. Oral presentation at ASCO 2020.

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Unprecedented OS benefit in overall population

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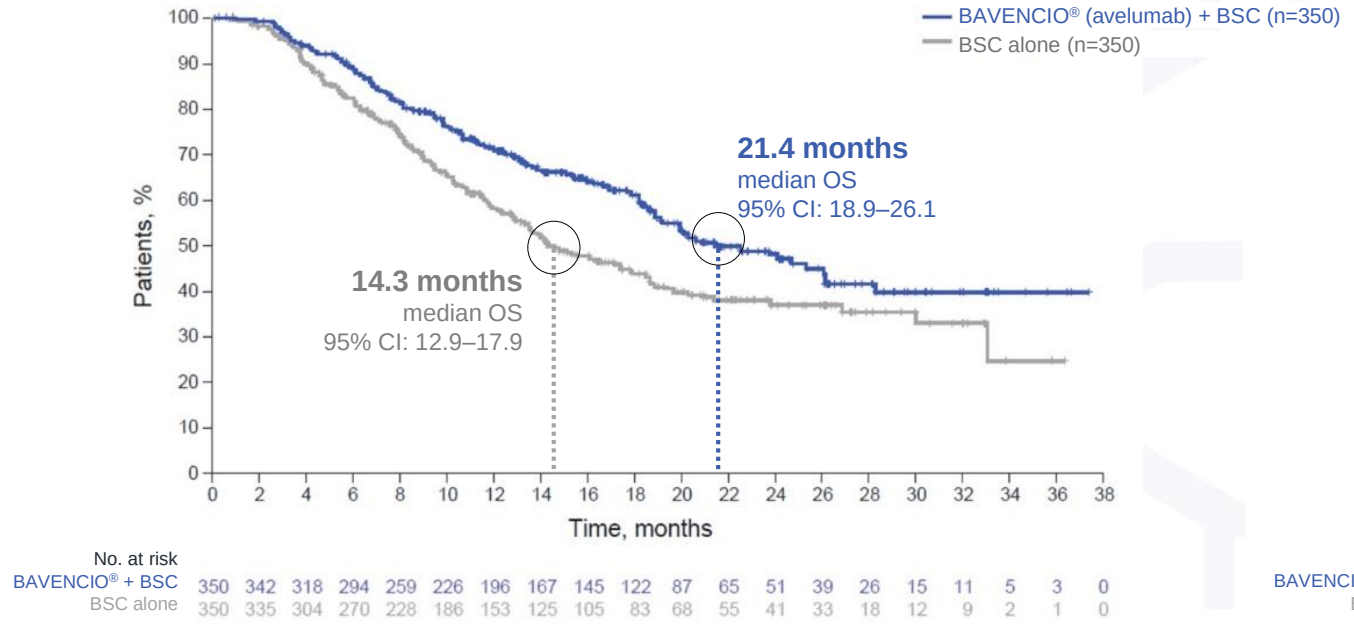
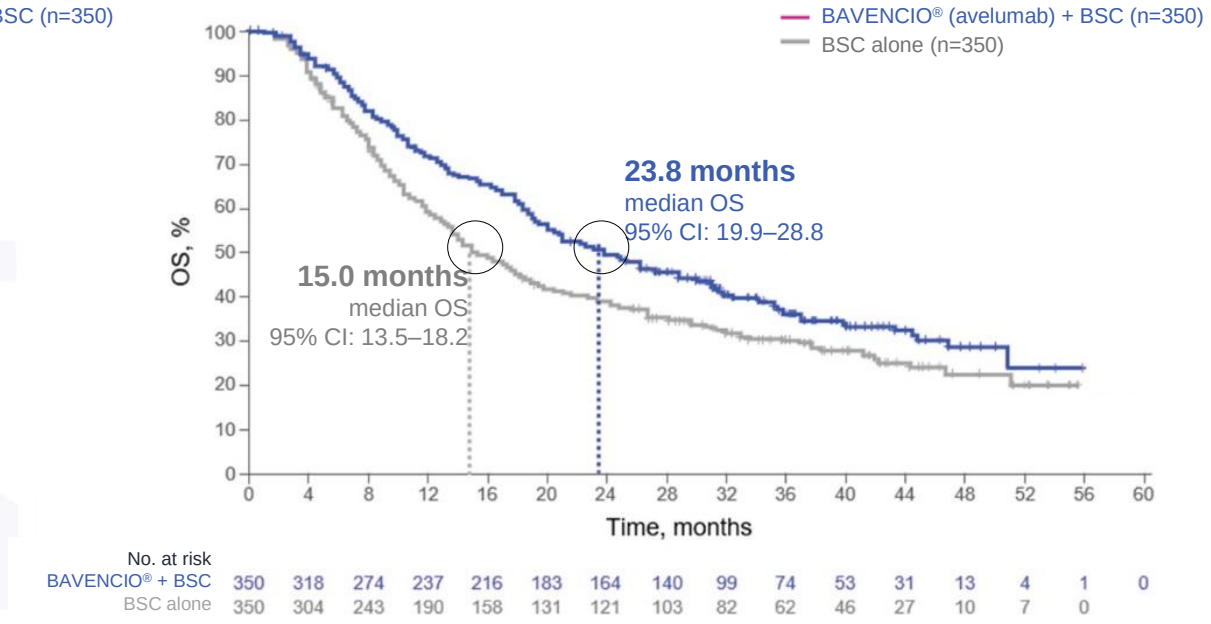
Primary Analysis
Primary endpoint. Data cut-off date: 21 October 2019*[1]



Stratified HR for death: 0.69[1]
(95% CI: 0.56–0.86)
p=0.001

7.1 months[1]
improvement in median OS in patients receiving BAVENCIO® (avelumab) + BSC vs BSC alone

Long Term Analysis
Primary endpoint. Data cut-off date: 4 June 2021†[2]



Stratified HR for death: 0.76[2]
(95% CI: 0.631–0.915)
p=0.0036

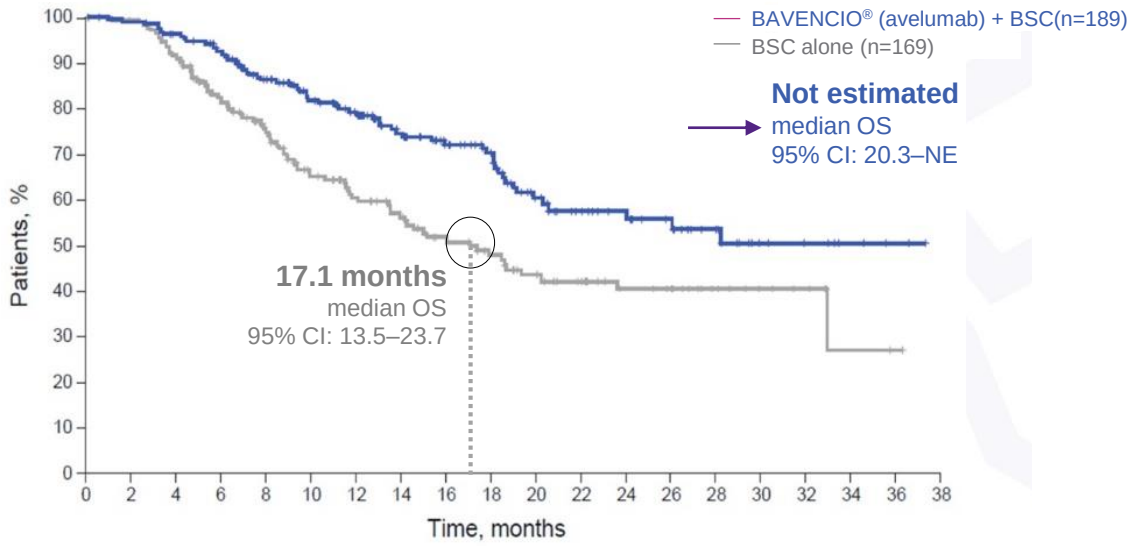
8.8 months[2]
improvement in median OS in patients receiving BAVENCIO® (avelumab) + BSC vs BSC alone

*Data cut-off date 21 October 2021. Median duration of treatment in the BAVENCIO® (avelumab) + BSC group was 24.9 weeks (range: 2.0–159.9); in the BSC alone group, it was 13.1 weeks (range: 0.1–155.6); †Data cut-off date: 4 June 2021. Median duration of treatment in the BAVENCIO® (avelumab) + BSC group was 25.3 weeks (range: 2.0–216.0). Median duration of treatment in the BSC alone arm was 13.1 weeks (range 0.1–231.7). BSC, best supportive care; CI, confidence interval; HR, hazard ratio; OS, overall survival. 1. Powles T et al. *N Engl J Med* 2020;383:1218–1230; 2. Powles T et al. *J Clin Oncol* 2022;40(Suppl 6):abstract 487

Unprecedented OS benefit in PD-L1+ population

BAVENCIO® avelumab Injection

Primary Analysis
Primary endpoint. Data cut-off date: 21 October 2019*[1]

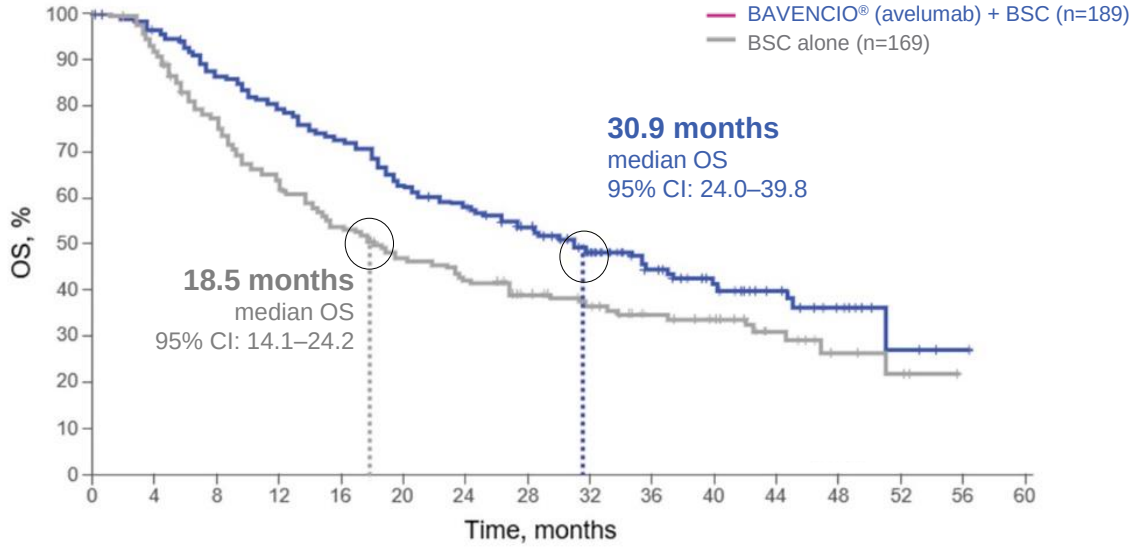


No. at risk

BAVENCIO® + BSC	189	185	177	165	146	129	114	95	81	70	49	38	32	26	18	9	8	4	2	0
BSC alone	169	165	152	132	113	89	76	67	54	45	37	30	23	21	12	8	6	2	1	0

Stratified HR for death: 0.56[1]
(95% CI: 0.40–0.79)
p<0.001

Long Term Analysis
Primary endpoint. Data cut-off date: 4 June 2021†[2]



No. at risk

BAVENCIO® + BSC	189	177	157	142	130	112	103	87	61	48	34	22	10	3	1	0
BSC alone	169	152	121	98	86	73	66	55	44	35	28	19	7	5	0	

Stratified HR for death: 0.69[2]
(95% CI: 0.521–0.901)
p=0.0064

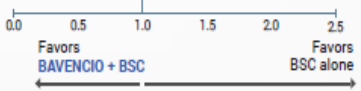
* Data cut-off date 21 October 2021. Median duration of treatment in the BAVENCIO® (avelumab) + BSC group was 24.9 weeks (range: 2.0–159.9); in the BSC alone group, it was 13.1 weeks (range: 0.1–155.6);[3] †Data cut-off date: 4 June 2021. Median duration of treatment in the BAVENCIO® (avelumab) + BSC group was 25.3 weeks (range: 2.0–216.0).[2] Median duration of treatment in the BSC alone arm was 13.1 weeks (range 0.1– 31.7).[4] BSC, best supportive care; CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival; PD-L1, programmed cell death ligand 1. 1. Powles T et al. *N Engl J Med* 2020;383:1218–1230; 2. Powles T et al. *J Clin Oncol* 2022;40(Suppl 6):abstract 487

OS benefit across subgroups - Type of 1L CT regimen, response to CT, PDL1 status and overall population

BAVENCIO® avelumab Injection

Long Term Analysis
Primary endpoint. Data cut-off date: 4 June 2021†1

Subgroup	Number of Events/Number of Patients: BAVENCIO + BSC	Number of Events/Number of Patients: BSC alone	Hazard Ratio (95% CI)
All patients (stratified)	215/350	237/350	0.76 (0.631-0.915)
All patients (unstratified)	215/350	237/350	0.75 (0.627-0.908)
Age:			
< 65 years	85/129	71/107	0.89 (0.651-1.224)
≥ 65 years	130/221	166/243	0.68 (0.544-0.862)
Sex:			
Male	163/266	189/275	0.74 (0.596-0.908)
Female	52/84	48/75	0.84 (0.568-1.250)
ECOG PS score:			
0	125/213	141/211	0.72 (0.563-0.913)
≥1	90/137	96/139	0.81 (0.605-1.078)
Race or ethnic group:			
White/Caucasian	151/232	162/238	0.78 (0.625-0.975)
Asian	41/75	55/81	0.70 (0.464-1.044)
Other	23/43	20/31	0.80 (0.435-1.470)
Pooled geographic region:			
Europe	136/214	146/203	0.71 (0.558-0.892)
North America	7/12	14/22	0.82 (0.330-2.035)
Asia	40/73	49/74	0.73 (0.479-1.108)
Australasia	23/34	18/37	1.29 (0.697-2.398)
Rest of the world	9/17	10/14	0.42 (0.163-1.061)
First-line chemotherapy regimen:			
Gemcitabine + cisplatin	108/183	134/206	0.78 (0.607-1.008)
Gemcitabine + carboplatin	97/147	91/122	0.70 (0.523-0.929)
Gemcitabine + cisplatin/carboplatin*	10/20	11/20	0.69 (0.294-1.639)
Best response to first-line risk chemotherapy:			
CR or PR	108/163	117/163	0.70 (0.541-0.914)
SD	64/97	66/98	0.84 (0.596-1.188)
Site of baseline metastasis:			
Visceral	130/191	130/191	0.91 (0.713-1.162)
Nonvisceral	85/159	107/159	0.60 (0.451-0.798)
Creatinine clearance:			
≥ 60mL/min	113/181	125/196	0.84 (0.652-1.085)
< 60mL/min	101/168	109/148	0.64 (0.491-0.845)
PD-L1 status:			
Positive	102/189	108/169	0.69 (0.530-0.912)
Negative	101/139	100/131	0.83 (0.630-1.096)
Unknown	12/22	29/50	0.82 (0.418-1.614)



* Includes patients who switched platinum regimens while receiving first-line chemotherapy.

†Data cut-off date: 4 June 2021. Median duration of treatment in the BAVENCIO® (avelumab) + BSC group was 25.3 weeks (range: 2.0–216.0). Median duration of treatment in the BSC alone arm was 13.1 weeks (range 0.1–231.7);[4] ‡This category includes patients who switched platinum-based regimens while receiving first-line chemotherapy.

1L, first line; BSC, best supportive care; CI, confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, overall survival; PD-L1, programmed cell death ligand 1; PR, partial response; SD, stable disease.

1. Powles T et al. *J Clin Oncol* 2022;40(Suppl 6):abstract 487

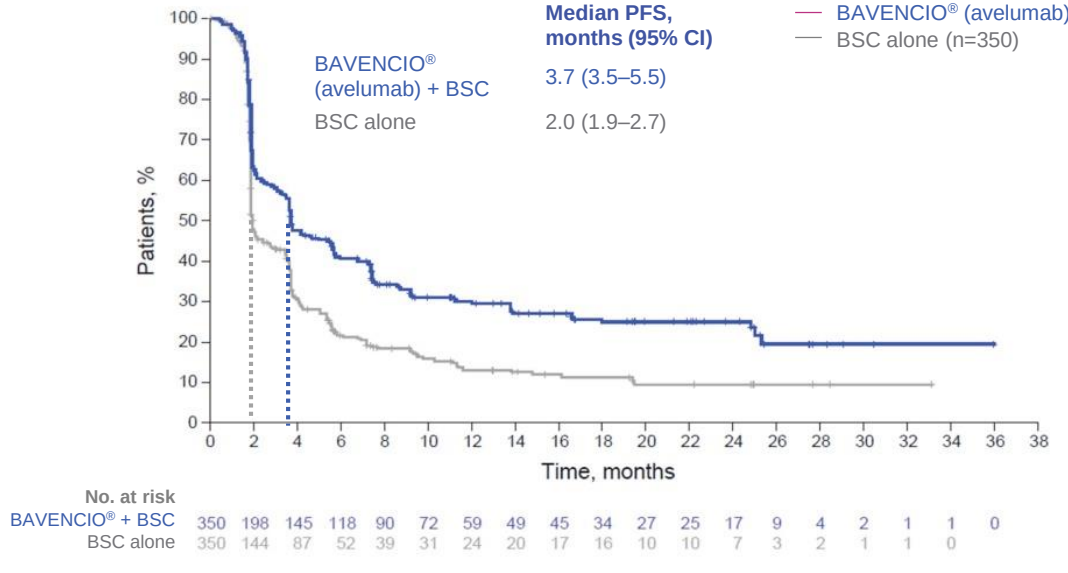
MERCK Pfizer

This message is intended for registered healthcare practitioners

In the overall population, patients treated with BAVENCIO® (avelumab) + BSC continued to achieve a longer median PFS compared with those treated with BSC alone*

BAVENCIO® avelumab Injection

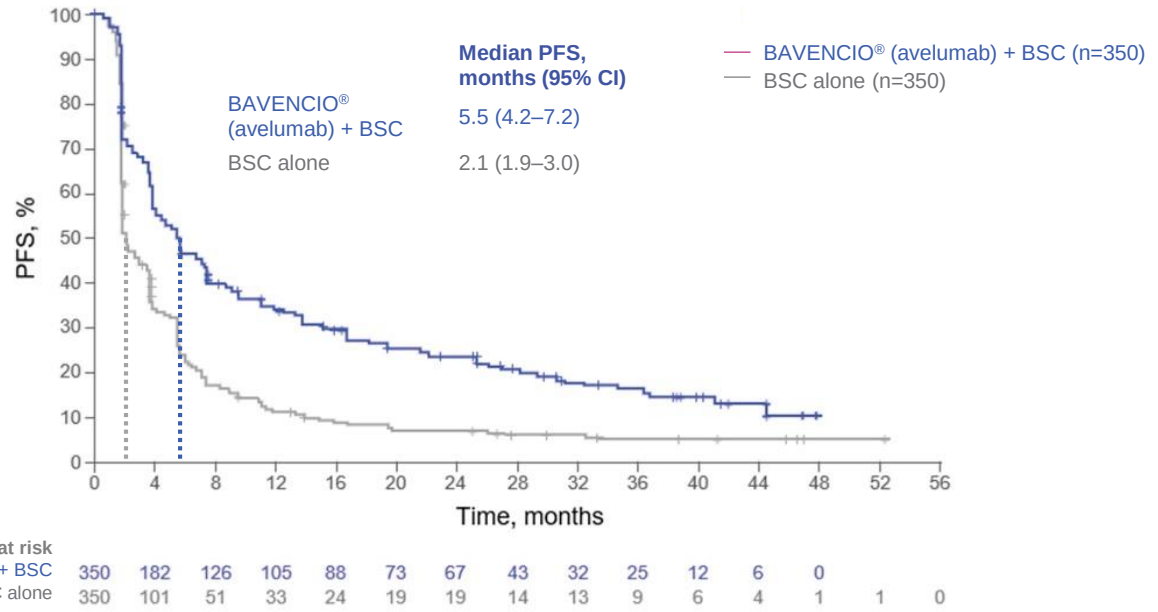
Primary Analysis
Data cut-off date: 21 October 2019*[1]



1.7-month improvement in median PFS in patients receiving BAVENCIO® (avelumab) + BSC vs BSC alone*[1]

Stratified HR for disease progression of death: 0.62[1] (95% CI: 0.52–0.75)*

Long Term Analysis
Data cut-off date: 4 June 2021†[2]



3.4-month improvement in median PFS in patients receiving BAVENCIO® (avelumab) + BSC vs BSC alone*[2]

Stratified HR for disease progression of death: 0.54[2] (95% CI: 0.457–0.645), 2-sided p-value=<0.0001*

*PFS was a secondary endpoint of the study; as such, median PFS data may not be defined as statistically significant; ˚Data cut-off date: 21 October 2019. Median duration of treatment in the BAVENCIO® (avelumab) + BSC group was 24.9 weeks (range: 2.0–159.9); in the BSC alone group, it was 13.1 weeks (range: 0.1–155.6); ‡Data cut-off date: 4 June 2021. Median duration of treatment in the BAVENCIO® (avelumab) + BSC group was 25.3 weeks (range: 2.0–216.0). Median duration of treatment in the BSC alone arm was 13.1 weeks (range 0.1–231.7). BSC, best supportive care; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

1. Powles T et al. *N Engl J Med* 2020;383:1218–1230; 2. Powles T et al. *J Clin Oncol* 2022;40(Suppl 6):abstract 487

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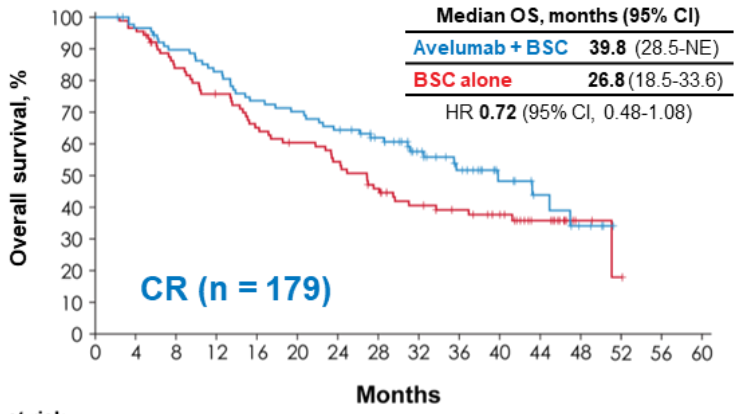
JAVELIN Bladder 100: mOS improvement irrespective of prior response to chemo

BAVENCIO® avelumab Injection

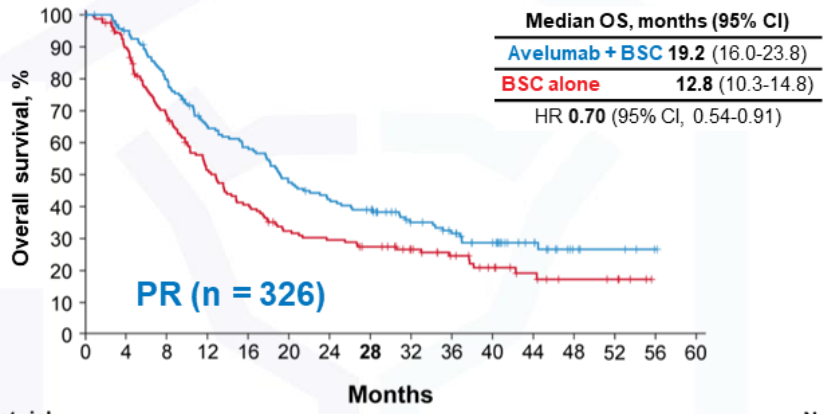
Long Term Analysis
Data cut-off date: 4 June 2021†1

Complete response



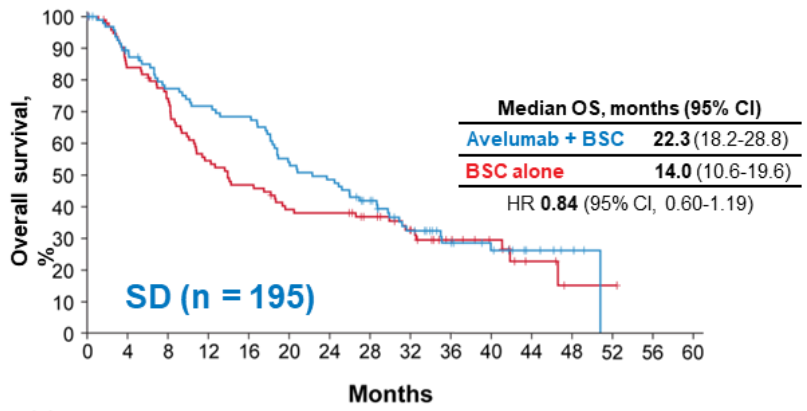
No. at risk														
Avelumab + BSC	90	85	78	72	64	61	56	47	34	24	14	9	4	0
BSC	89	86	72	64	55	50	45	37	30	26	21	13	3	1	0

Partial response



No. at risk															
Avelumab + BSC	163	151	126	100	90	73	64	58	42	35	27	16	6	4	1	0
BSC	163	140	103	76	60	46	42	37	29	22	15	10	6	5	0

Stable disease



No. at risk														
Avelumab + BSC	97	82	70	65	62	49	44	35	23	15	12	6	3	0
BSC	98	78	68	50	43	35	34	29	23	14	10	4	1	1	0

‡Data cut-off date: 4 June 2021. Median duration of treatment in the BAVENCIO® (avelumab) + BSC group was 25.3 weeks (range: 2.0–216.0). Median duration of treatment in the BSC alone arm was 13.1 weeks (range 0.1–231.7). BSC, best supportive care; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

1. Powles T et al. *J Clin Oncol* 2022;40(Suppl 6):abstract 487

MERCK Pfizer

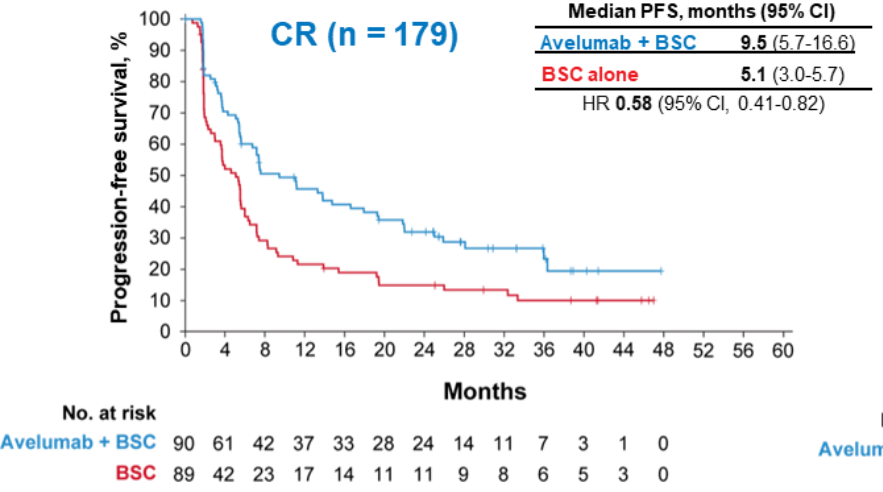
This message is intended for registered healthcare practitioners

JAVELIN Bladder 100: PFS improvement irrespective of prior response to chemo

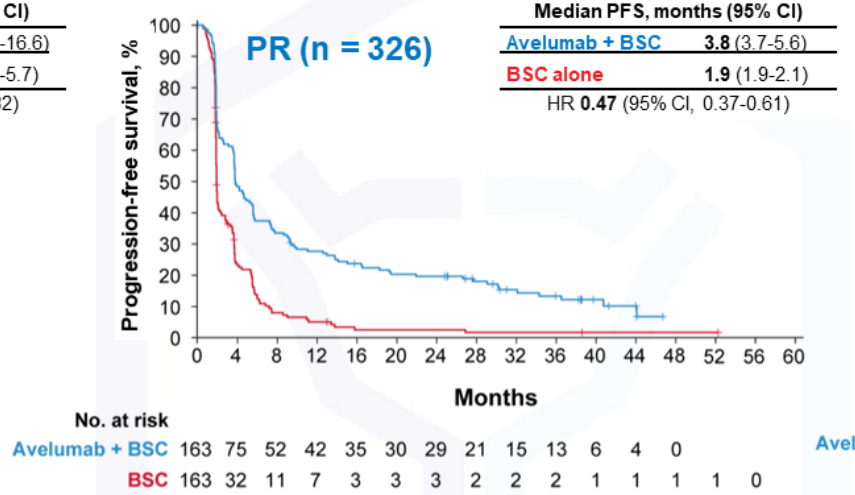
BAVENCIO® avelumab Injection

Long Term Analysis
Data cut-off date: 4 June 2021†1

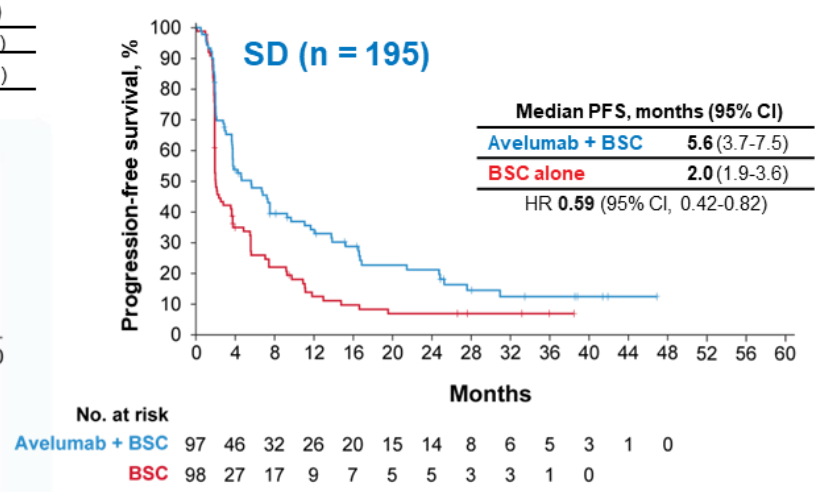
Complete response



Partial response



Stable disease



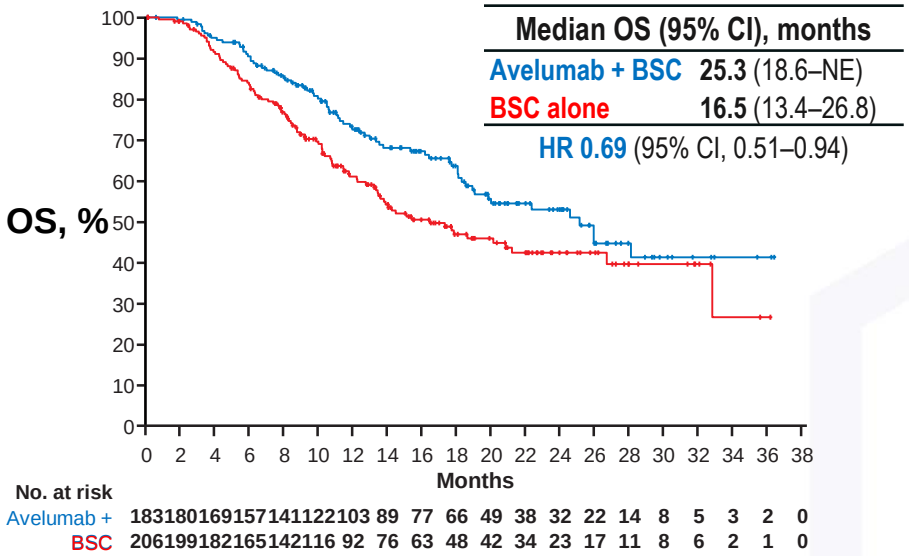
‡Data cut-off date: 4 June 2021. Median duration of treatment in the BAVENCIO® (avelumab) + BSC group was 25.3 weeks (range: 2.0–216.0). Median duration of treatment in the BSC alone arm was 13.1 weeks (range 0.1–231.7). BSC, best supportive care; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

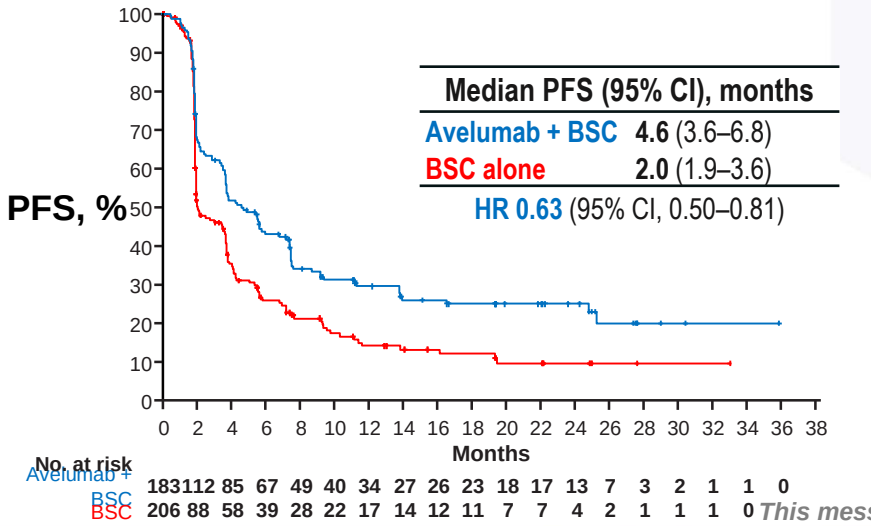
1. Powles T et al. *J Clin Oncol* 2022;40(Suppl 6):abstract 487

JAVELIN Bladder 100: OS and PFS benefit by 1L chemo

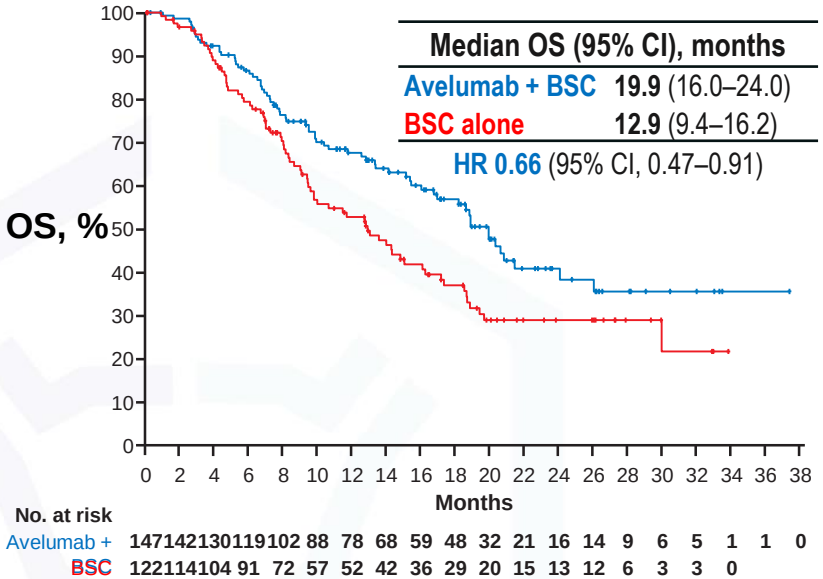
BAVENCIO® avelumab Injection

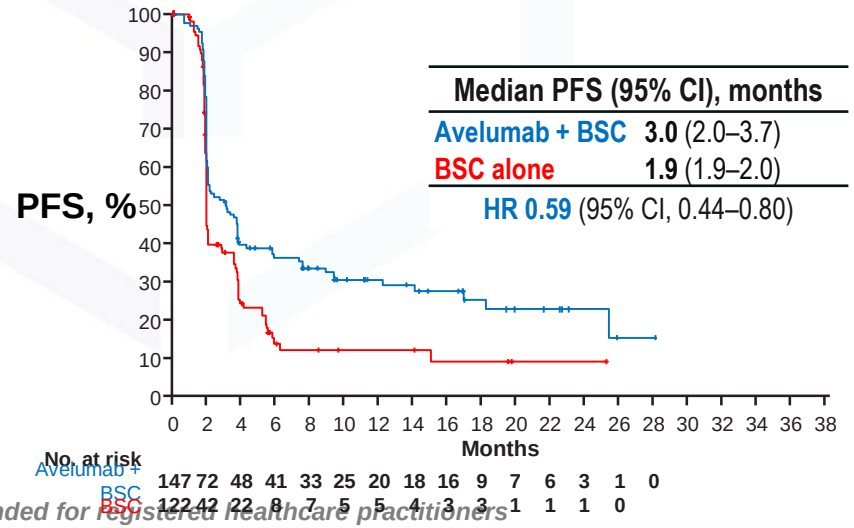
Gemcitabine + cisplatin (n=389)





Gemcitabine + carboplatin (n=269)





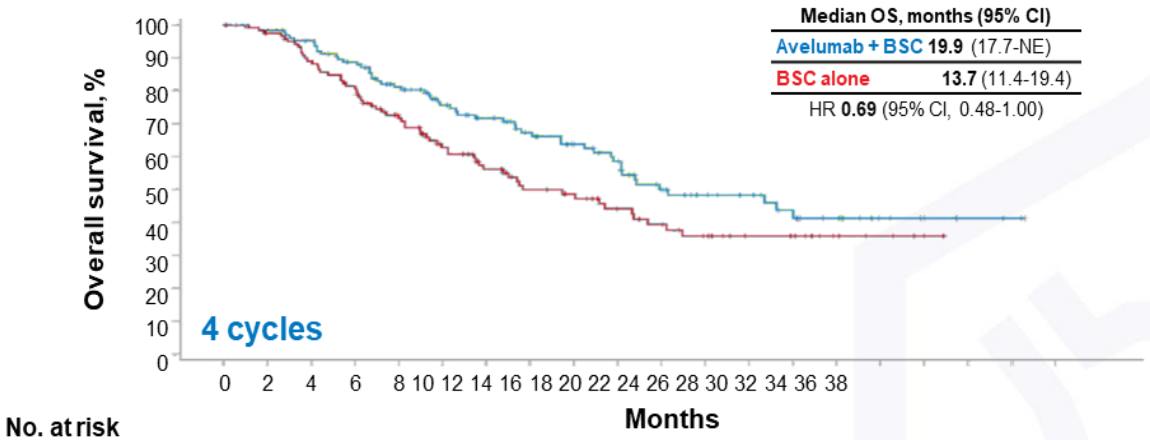
OS and PFS benefit with avelumab 1L maintenance occurred irrespective of 1st-line CT regimen

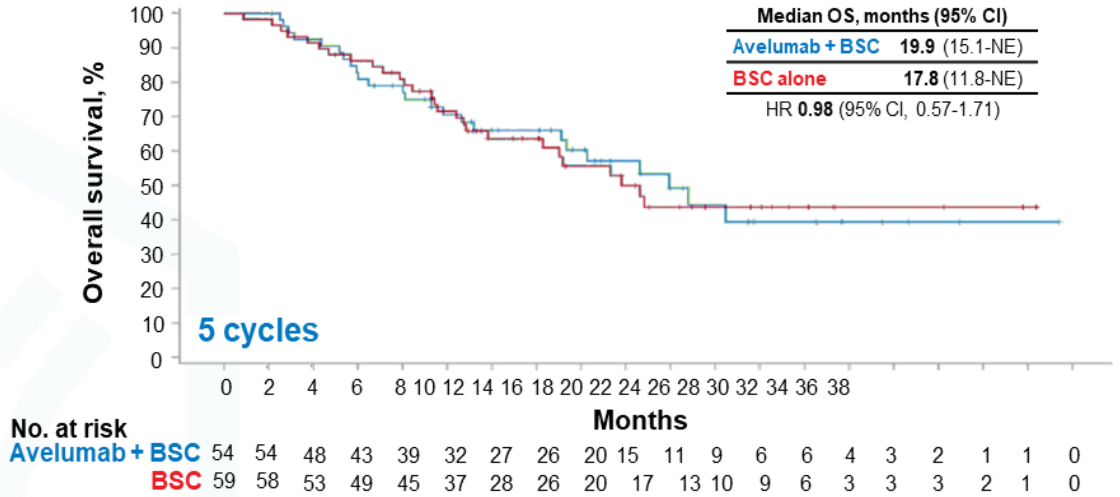
BSC, best supportive care; CI, confidence interval; CT, chemotherapy; HR, hazard ratio; NE, not estimable; OS, overall survival.
Grivas P, et al. Virtual ESMO 2020

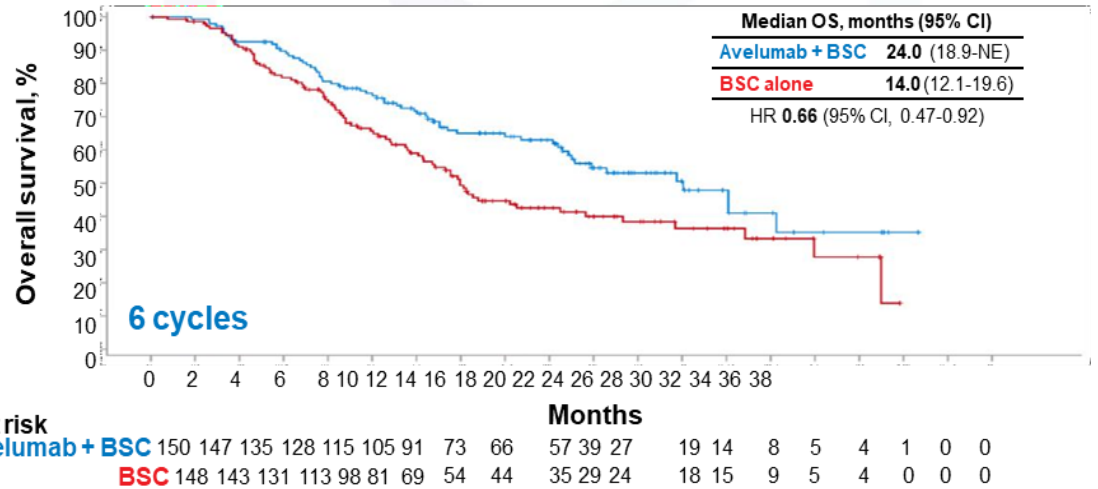
Overall Survival is not affected by number of CT cycles

BAVENCIO® avelumab Injection

Primary Analysis
Data cut-off date: 21 October 2019*[1]







*Data cut-off date: 21 October 2019. Median duration of treatment in the BAVENCIO® (avelumab) + BSC group was 24.9 weeks (range: 2.0–159.9); in the BSC alone group, it was 13.1 weeks (range: 0.1–155.6); BSC, best supportive care; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival. 1. Powles T et al. *N Engl J Med* 2020;383:1218–1230

Loriot Y, et al. ASCO GU 2021 Abstract #438

MERCK Pfizer

Avelumab first-line maintenance + best supportive care (BSC) vs BSC alone in Asian patients with advanced urothelial carcinoma: JAVELIN Bladder 100 subgroup analysis

M. Eto,[1] J.-L. Lee,[2] S. H. Park,[3] N. Tsuchiya,[4] P.-J. Su,[5] T. T. W. Chan,[6] C. Desai,[7]
A. di Pietro,[8] J. Wang,[9] R. Laliberte,[9] S. Gao,[10] H. Gurney[11]

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Abstract No. 486. Presented at the 2022 ASCO Genitourinary Cancers Symposium, February 17-19, 2022; San Francisco, CA; Hybrid.

The Asian subgroup represents 21% of the overall population of the JAVELIN Bladder 100 trial

BAVENCIO® avelumab Injection

INDUCTION CHEMOTHERAPY

Unresectable locally advanced or metastatic UC

CR, PR, or SD with standard 1L CT (4–6 cycles):

- Cisplatin + gemcitabine, OR
- Carboplatin + gemcitabine

MAINTENANCE

Asian subgroup:
(n=147)

1:1

BAVENCIO® (10 mg/kg IV Q2W) **+ BSC***
(n=73)

BSC alone*
(n=74)

Treatment-free interval (4–10 weeks) followed by radiological assessment of response

Until PD, unacceptable toxicity, or withdrawal

Stratification

- Best response to 1L induction CT (CR/PR vs SD)
- Metastatic site at the start of CT (visceral vs non-visceral)

Primary endpoint†

- OS

Primary analysis populations

- All randomized patients
- PD-L1+ patients‡

Secondary endpoints†:

- PFS§
- OR§
- Safety and tolerability

Data cutoff date: Oct 21, 2019.

* BSC (e.g., antibiotics, nutritional support, hydration, or pain management) was administered as per local practice, based on patient needs and clinical judgment; other antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable. † All endpoints were measured post-randomization (after CT). ‡ Assessed using the Ventana SP263 assay. § Determined by BICR and as per RECIST 1.1.

BSC, best standard of care; BICR, blinded independent central review; CR, complete response; CT, chemotherapy; OR, objective response; OS, overall survival; PD, progression of disease; PD-L1, programed-death ligand 1; PFS, progression-free survival; PR, partial response; SD, stable disease; UC, urothelial carcinoma.

Eto M, et al. Presented at the ASCO Genitourinary Cancers Symposium 2022, February 17–19, 2022 (Abstract 486).

MERCK Pfizer

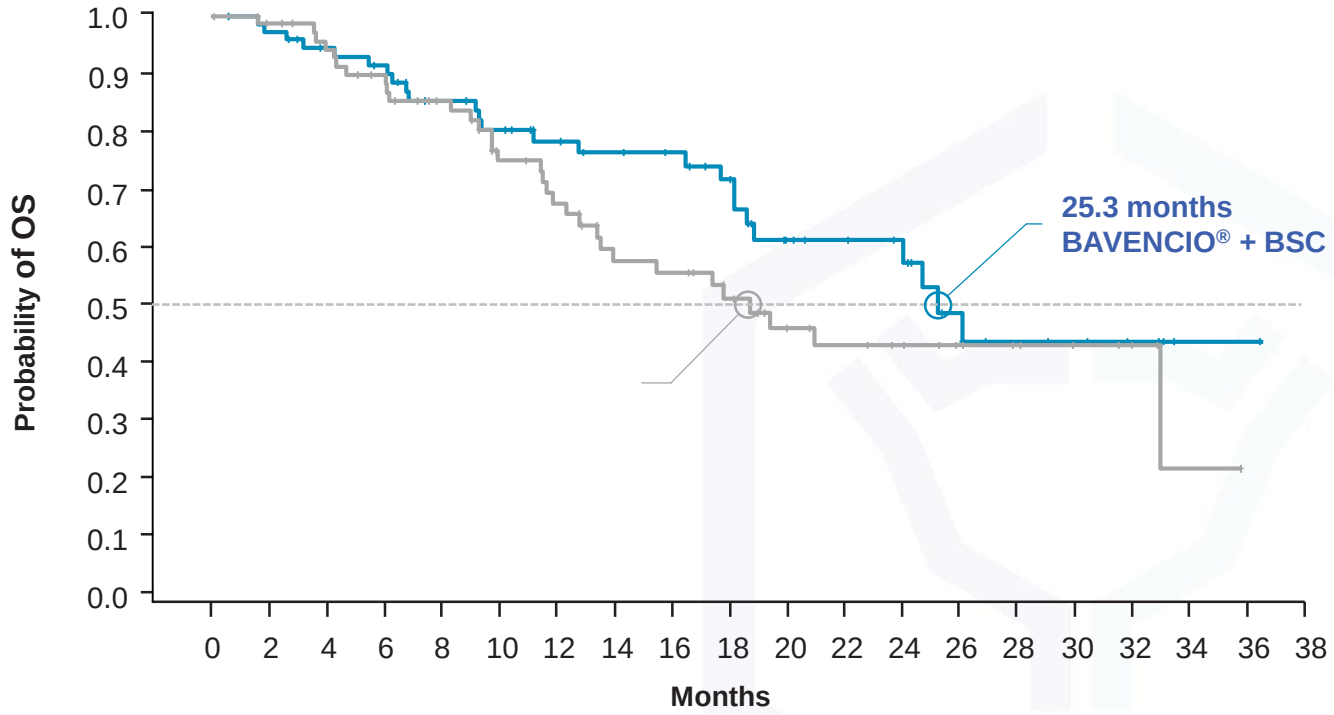
Patient baseline characteristics were similar between treatment arms and consistent with the overall population[1,2]

BAVENCIO® avelumab Injection

		Asian population (n=147)		PD-L1+ population (n=71)	
		BAVENCIO® + BSC (n=73)	BSC alone (n=74)	BAVENCIO® + BSC (n=40)	BSC alone (n=31)
Median age, years		69.0	70.0	70.0	70.0
ECOG PS, n (%)	0	51 (69.9)	49 (66.2)	27(67.5)	23 (74.2)
	≥1	22 (30.1)	25 (33.8)	13 (32.5)	8 (25.8)
Creatinine clearance at baseline, n (%)	≥60 mL/min	31 (42.5)	29 (39.2)	16 (40.0)	15 (48.4)
	<60 mL/min	42 (57.5)	43 (58.1)	24 (60.0)	14 (45.2)
	Unknown	0	2 (2.7)	0	2 (6.5)
Site of metastasis at start of CT, n (%)	Visceral	34 (46.6)	37 (50.0)	12 (30.0)	16 (51.6)
	Non-visceral	39 (53.4)	37 (50.0)	28 (70.0)	15 (48.4)
PD-L1 status, n (%)	Positive	40 (54.8)	31 (41.9)	40 (100.0)	31 (100.0)
	Negative	27 (37.0)	27 (36.5)	0	0
	Unknown	6 (8.2)	16 (21.6)	0	0
1L CT regimen, n (%)	GEM + CIS	51 (69.9)	53 (71.6)	29 (72.5)	25 (80.6)
	GEM + CAR	19 (26.0)	20 (27.0)	9 (22.5)	6 (19.4)
	GEM + CAR + CIS*	3 (4.1)	1 (1.4)	2 (5.0)	0
Best response to 1L CT, n (%)	CR or PR	50 (68.5)	51 (68.9)	27 (67.5)	23 (74.2)
	SD	23 (31.5)	23 (31.1)	13 (32.5)	8 (25.8)

1L, first line; **BSC**, best supportive care; **CR**, complete response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **PR**, partial response; **SD**, stable disease.
*Patients who switched platinum regimens while receiving 1L chemotherapy.
Eto M, et al. Presented at the ASCO Genitourinary Cancers Symposium 2022, February 17–19, 2022 (Abstract 486).

BAVENCIO® 1L maintenance treatment demonstrated prolonged survival compared with BSC alone



No. at risk

BAVENCIO® + BSC	73	70	64	61	52	48	39	36	34	29	20	18	16	10	7	6	4	1	1	0
BSC	74	69	64	59	52	41	36	28	27	22	17	14	12	9	7	5	4	1	0	

ASIAN POPULATION Median OS, months (95% CI)	
BAVENCIO® + BSC (n=73)	25.3 (18.6–NE)
BSC alone (n=74)	18.7 (12.8–NE)
Stratified HR (95% CI)	0.74 (0.434–1.260)

PD-L1+ POPULATION Median OS, months (95% CI)	
BAVENCIO® + BSC (n=40)	26.1 (18.2–NE)
BSC alone (n=31)	19.4 (11.9–NE)
Stratified HR (95% CI)	0.66 (0.279–1.541)

1L, first-line; BSC, best supportive care; HR, hazard ratio; NE, not estimable; OS, overall survival; PD-L1, programed-death ligand 1.

Eto, M et al. Presented at the ASCO Genitourinary Cancers Symposium 2022, February 17–19, 2022 (Abstract 486).

Summary: Asian Subgroup Data

BAVENCIO® 1L maintenance treatment is a new standard of care in Asian patients with advanced UC whose disease has not progressed with 1L platinum-based CT

- **Primary endpoint:** The mOS was 25.3 months (95% CI 18.6–NE) from the start of maintenance therapy versus 18.7 months (95% CI 12.8–NE) with BSC alone among all Asian patients
- 26% reduction in the risk of death vs BSC alone among all Asian patients HR: 0.74 (95% CI 0.434–1.260)
- BAVENCIO® 1L maintenance treatment led to a numerically longer time to **end of next-line therapy*** in the Asian subgroup compared with BSC alone
- **Safety and tolerability:** The safety profile of BAVENCIO® 1L maintenance treatment in Asian patients was consistent with the overall population

1L, first-line; BSC, best supportive care; HR, hazard ratio; NE, not estimable; OS, overall survival; PD-L1, programed-death ligand 1.
Eto, M et al. Presented at the ASCO Genitourinary Cancers Symposium 2022, February 17–19, 2022 (Abstract 486).

JAVELIN Bladder 100: A well-characterized safety and tolerability profile

BAVENCIO® avelumab Injection

TEAE	BAVENCIO® (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
Diarrhoea	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
Anaemia	11.3	3.8	6.7	2.9
Haematuria	10.5	1.7	10.7	1.4
IRR	10.2	0.9	0	0

- **TEAEs led to discontinuation of avelumab in 11.9% of patients**
- **Death was attributed by the investigator to study treatment toxicity in 2 patients (0.6%) in the BAVENCIO® (avelumab) + BSC arm**
- **One death occurred due to sepsis (after 11 infusions of BAVENCIO® [avelumab]) and the other due to ischaemic stroke (100 days after a single dose of BAVENCIO® [avelumab])**

Data cut-off date: 21 October 2019

The table shows TEAEs of any grade occurring in ≥10% or Grade ≥3 TEAEs occurring in ≥5% in either arm. Safety was assessed in all patients who received ≥1 dose of BAVENCIO® (avelumab) in the BAVENCIO® (avelumab) arm, or who completed the Cycle 1 Day 1 visit in the BSC arm (N=689). Data cut-off date: 21 October 2019. Median duration of treatment in the BAVENCIO® (avelumab) + BSC group was 24.9 weeks (range: 2.0–159.9); in the BSC alone group, it was 13.1 weeks (range: 0.1–155.6). Median follow-up for each group was more than 19 months.

BSC, best supportive care; IRR, infusion-related reaction; TEAE, treatment-emergent adverse event; UTI, urinary tract infection.

1. Powles T et al. *N Engl J Med* 2020;383:1218–1230.

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A well-characterized safety and tolerability profile

BAVENCIO® avelumab Injection

Immune-related AEs, %[2]	BAVENCIO® (avelumab) + BSC (n=344)	
	Any grade	Grade 3
Any immune-related AE	**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
Hyperglycaemia	0.9	0.9
Myositis	0.6	0.6

- **No grade 4/5 irAEs occurred**
- **High-dose corticosteroids (≥40 mg total daily prednisone or equivalent) were administered following immune-related AEs in 9.0% of BAVENCIO® (avelumab)-treated patients[1]**

Data cut-off date: 21 October 2019

The table shows immune-related AEs of any grade occurring in ≥1% or Grade ≥3 immune-related AEs occurring in ≥0.5% in the BAVENCIO® (avelumab) + BSC arm. Immune-related AEs were identified according to a prespecified case definition. Data cut-off date: 21 October 2019. Median duration of treatment in the BAVENCIO® (avelumab) + BSC group was 24.9 weeks (range: 2.0–159.9); in the BSC alone group, it was 13.1 weeks (range: 0.1–155.6).[1] Median follow-up for each group was more than 19 months.[1]

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSC, best supportive care.

1. Powles T et al. *N Engl J Med* 2020;383:1218–1230; 2. Powles T et al. *N Engl J Med* 2020;383:1218–1230 (supplementary appendix).

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Adverse events after ≥12 months of treatment in the BAVENCIO® (avelumab) + BSC arm

BAVENCIO® avelumab Injection

Summary of AEs overall and with onset after ≥12 months of treatment with BAVENCIO® (avelumab) + BSC[1]

Events, n (%)	BAVENCIO® (avelumab) + BSC	
	Onset after ≥12 months of treatment (n=118)*	Onset at any time (n=344)†
TEAE of any grade	102 (86.4)	338 (98.3)
Grade ≥3 TEAE	56 (47.5)	185 (53.8)
TRAE of any grade	59 (50.0)	269 (78.2)
Grade ≥3 TRAE	14 (11.9)	67 (19.5)
Serious TEAE	28 (23.7)	105 (30.5)
Serious TRAE	6 (5.1)	35 (10.2)
TEAE leading to interruption of BAVENCIO® (avelumab)	43 (36.4)	156 (45.3)
TEAE leading to discontinuation	13 (11.0)	49 (14.2)
TRAE leading to discontinuation	12 (10.2)	40 (11.6)
TEAE leading to death	3 (2.5)	7 (2.0)
TRAE leading to death	1 (0.8)	2 (0.6)
Infusion-related reaction of any grade	4 (3.4)	75 (21.8)

Most common TEAEs with onset after ≥12 months of treatment with BAVENCIO® (avelumab) + BSC‡[1]

Events, n (%)	BAVENCIO® (avelumab) + BSC (n=118)	
	Any grade	Grade ≥3
Any TEAE	102 (86.4)	56 (47.5)
Urinary tract infection	15 (12.7)	3 (2.5)
Diarrhoea	15 (12.7)	1 (0.8)
Arthralgia	14 (11.9)	1 (0.8)
Back pain	14 (11.9)	0
Cough	14 (11.9)	0
Pruritus	14 (11.9)	0
Nasopharyngitis	12 (10.2)	0

1 patient (0.8%) had a TRAE after ≥12 months of treatment with BAVENCIO® (avelumab) + BSC that led to death (attributed to immune-mediated nephritis by the treating investigator)[1]

Data cut-off date: 4 June 2021§

*Patients with ≥12 months of treatment; †All treated patients; ‡Table shows TEAEs of any grade occurring in ≥10% of patients with ≥12 months of treatment;[1] §Median duration of treatment in the BAVENCIO® (avelumab) + BSC arm was 25.3 weeks (range: 2.0–216.0). Median duration of treatment in the BSC alone arm was 13.1 weeks (range 0.1–231.7).
AE, adverse event; BSC, best supportive care; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.
1. Powles T et al. *J Clin Oncol* 2022;40(Suppl 6):abstract 487

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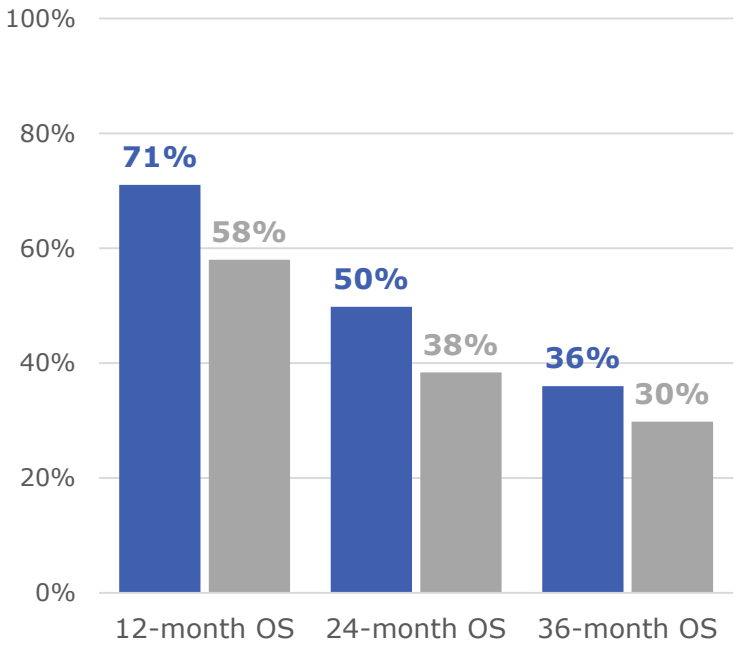
Continuation of Avelumab maintenance

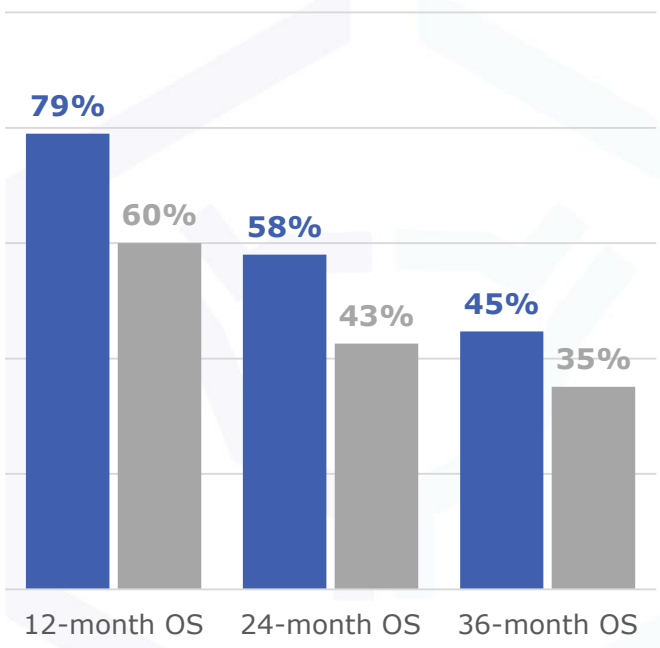
BAVENCIO® avelumab Injection

Long Term Analysis
Data cut-off date: 4 June 2021†[1]

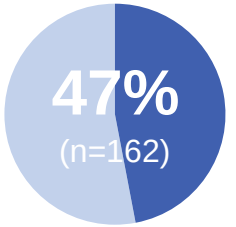
Overall population*



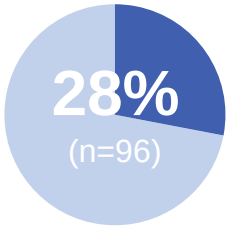
PD-L1+ population†



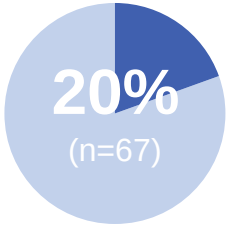
BAVENCIO® + BSC BSC alone



Patients were exposed to BAVENCIO® for **>6 months**



Patients were exposed to BAVENCIO® for **>12 months**



Patients were exposed to BAVENCIO® for **≥24 months**[2]

(Median duration of treatment was 25.3 weeks)[2]

* OS was measured post-randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0053)
† OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0014).
1. Powles T, et al. Presented at ASCO Genitourinary Cancers Symposium 2022, Feb 17–19, 2022 (Abstract 487).

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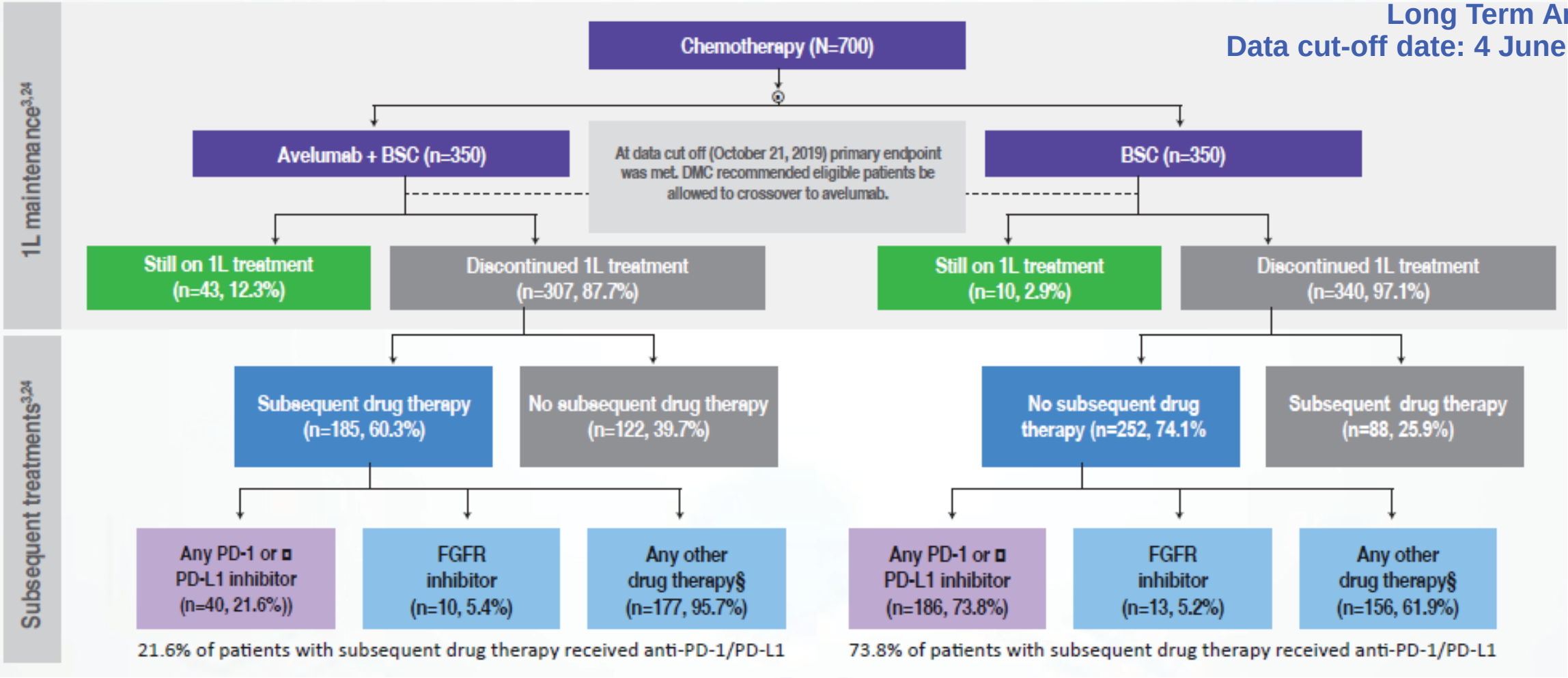
Subsequent therapy: 53.1% patients in BSC arm received PD-L1/PD-1 inhibitor in subsequent line

BAVENCIO® avelumab Injection

Long Term Analysis
Data cut-off date: 4 June 2021†1



§Other drug therapies included single agent or combination chemotherapies, TKI, anti-body drug conjugates, IDO1 inhibitors, PARP inhibitors, mTOR inhibitors, monoclonal antibodies, immunie-stimulating vaccines or investigational agents.
‡Data cut-off date: 4 June 2021. Median duration of treatment in the BAVENCIO® (avelumab) + BSC group was 25.3 weeks (range: 2.0–216.0). Median duration of treatment in the BSC alone arm was 13.1 weeks (range 0.1–231.7). DMC, Data Monitoring Committee; FGFR, fibroblast growth factor receptor; BSC, best supportive care; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

1. Powles T et al. *J Clin Oncol* 2022;40(Suppl 6):abstract 487

Survival goes further with the right IO at the right time

BAVENCIO® avelumab Injection

JAVELIN Bladder 100: 1L platinum-containing chemotherapy --> avelumab 1L maintenance in patients without PD

4-6 cycles (x3 weeks) | No PD

1L chemotherapy: 3-5 months	TFI: 4-10 weeks	Median 0S with avelumab 1L maintenance (Overall population): 23.8 months[1,2]

Estimated median 0S from start of 1L therapy

30 months

ICI as 2L therapy after 1L platinum-containing chemotherapy

Median PFS with 1L chemotherapy: 6-8 months	Median 0S with 2L pembrolizumab: 10.1 months

16-18 months

ICI in combination with 1L platinum-containing chemotherapy

Median OS with 1L chemotherapy + atezolizumab or pembrolizumab: 16.0-17.0 months

16.0-17.0 months

ICI as 1L monotherapy (for cisplatin-ineligible patients with a PD-L1+ tumor only)

Median 0S with 1L atezolizumab pembrolizumab: 12.3-18.5 months

12.3-18.5 months

ICI + ICI as 1L therapy (anti-PD-L1 + anti-CTLA-4)

Median OS with 1L durvalumab tremelimumab: 15.1 months

15.1 months

1. Grivas P, et al. Avelumab first-line maintenance in locally advanced or metastatic urothelial carcinoma: applying clinical trial findings to clinical practice. *Cancer Treat Rev*. 2021. [Epub ahead of print]. doi: 10.1016/j.ctrv.2021.102187. 2. Powles T et al. *J Clin Oncol* 2022;40(Suppl 6):abstract 487

JAVELIN Bladder 100 Summary

BAVENCIO® avelumab Injection

- Long-term follow-up from JAVELIN Bladder 100 trial (≥2 years in all patients) continues to show prolongation of OS and PFS with avelumab + BSC vs BSC alone, both among all randomized patients and those with PD-L1–positive tumors[1]
- OS rates at 2 years were 49.8% in the avelumab + BSC arm vs 38.4% in the BSC alone arm[1]
- 2-year PFS rates were 23.4% vs 7.1%, respectively
- The long-term safety profile of avelumab was consistent with previous monotherapy studies[3] and no new safety signals were identified
- OS was prolonged with avelumab 1L maintenance despite a high proportion of patients treated with BSC alone receiving a subsequent anticancer drug therapy (avelumab + BSC, 52.9%; BSC, 72.0%)
- These results further support the recommendation of avelumab 1L maintenance as standard of care for patients with advanced UC that has not progressed with 1L platinum-containing chemotherapy.[1] Long-term safety data and the high percentage of patients on treatment at 2 years indicate the good tolerability and feasibility of the regimen as treatment until progression

1L, first-line; BSC, best supportive care; CR, complete response; mOS, median overall survival; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response; SD, stable disease; UC, urothelial carcinoma.

1. Powles T, et al. Poster E7. Presented at: ASCO GU Symposium; February 17-19, 2022; San Francisco, CA

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Guideline Updates have followed the latest insights

BAVENCIO® avelumab Injection

Avelumab 1L maintenance is recommended with the **highest level of evidence** in major global guidelines

	NCCN[1]	ESMO[2]		EAU[3]
Cisplatin-ELIGIBLE	• Gemcitabine/cisplatin (Category 1) followed by **avelumab maintenance therapy (Category 1)** • DDMVAC with growth factor (Category 1) support followed by **avelumab maintenance therapy (Category 1)**	Cisplatin-based CT [I, A] followed by **maintenance avelumab for tumors which have not progressed on CT [I, A]**		Gemcitabine/cisplatin or DDMVAC, followed by **avelumab maintenance for tumors which have not progressed on CT (Strong)**
Cisplatin-INELIGIBLE	• Gemcitabine/carboplatin (Category 2A) followed by **avelumab maintenance therapy (Category 1)** • Atezolizumab (Category 2A) • Pembrolizumab (Category 2A)	PD-L1-unknown or -negative	PD-L1-positive	• Gemcitabine/carboplatin, followed by **avelumab maintenance for tumors which have not progressed on CT (Strong)** • Pembrolizumab or atezolizumab (Weak)
		Gemcitabine/ carboplatin [II, B] followed **by maintenance avelumab for tumors which have not progressed on CT [I, A]**	• Gemcitabine/ carboplatin [II, B] followed by maintenance **avelumab for tumors which have not progressed on CT [I, A]** • Atezolizumab or pembrolizumab [III, B]	

Also recommended by NICE[4] National Institute for Health and Care Excellence

CT, chemotherapy; EAU, European Association of Urology; ESMO, European Society for Medical Oncology; EV, enfortumab vedotin; FGFR, fibroblast growth factor receptor; ICI, immune checkpoint inhibitory; NCCN, National Comprehensive Cancer Network; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand

1. NCCN Clinical Practice Guidelines in Oncology. Bladder Cancer. V2. 2021; 2. Bladder cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up 2014. eUpdate – Bladder Cancer Treatment Recommendations. July 2020. Available at: https://www.esmo.org/guidelines/genitourinary-cancers/bladder-cancer/eupdate-bladder-cancer-treatment-recommendations4 (accessed July 2020); 3. EAU guidelines on muscle-invasive and metastatic bladder cancer March 2021. Available at https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Muscle-Invasive-and-Metastatic-Bladder-Cancer-2021.pdf (accessed May 2021). 4. Nice guidelines recommendations 11 May 2022, https://www.nice.org.uk/guidance/ta788/chapter/1-Recommendations

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Patient segment and new SoC in 1L mUC

BAVENCIO® avelumab Injection

Patient

 Cisplatin eligible	Cisplatin-based CT >> Avelumab maintenance
 Cisplatin ineligible	Carboplatin-based CT >> Avelumab maintenance
 Platinum ineligible	IO monotherapy

Platinum ineligibility based on Gupta criteria: Any mUC pt meeting one the following 5 parameters should be considered "platinum-ineligible": ECOG PS > / = 3; Cr Cl < 30 ml/min; peripheral neuropathy > / =Grade 2; NYHA Heart Failure Class > 3; ECOG PS 2 AND Cr Cl < 30 ml/min

Gupta S, et al. Journal of Clinical Oncology 40, no. 16_suppl (June 01, 2022) 4577-4577

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THANK YOU