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MAINTENANCE THERAPY FOR METASTATIC UROTHELIAL CANCER

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BACKGROUND

- **Platinum-based chemotherapy (CT) is the standard of care for patients** with metastatic urothelial carcinoma in the first-line (1L) setting[1,2]
  - However, progression-free survival (PFS) and overall survival (OS) benefits are limited due to emergence of CT resistance[2]
- **Most patients have disease progression within approximately 9 months of CT treatment**, and median OS is 14-15 months with cisplatin-based regimens and 9-10 months with carboplatin-based regimens among patients who are not suitable candidates for cisplatin-based therapy[2]
- **Attempts at improving OS through the addition of other chemotherapeutics and/or immunotherapies have been disappointing**

1. Flaig TW, et al. J Natl Compr Canc Netw. 2020;18:329-54; 2. Powles T, et al. N Engl J Med. 2020;383:1218-30

FIRST-LINE PHASE 3 TRIALS IN METASTATIC UROTHELIAL CANCER

Trial	Arms	No. enrolled	ORR (%)	PFS	OS	HR OS[f]	HR OS PD-L1+,[f]	Comment
IMvigor130[1,2]	Atezo/CT Atezo CT	451 362 400	47 23 44	8.2 NA 6.3	16.0 15.7 13.4[a]/13.1[b]	0.83 1.02	0.74 0.68	IMvigor130 trial was the first immune checkpoint inhibitor study to show a PFS benefit for 1L treatment of locally advanced and metastatic urothelial cancer. Atezo monotherapy may have benefit relative to CT, but this may be limited to PD-L1 high-expressing tumours.
KEYNOTE-361[3]	Pembro/CT Pembro CT	351 307 352	55 30 45	8.3 3.9 7.1	17.9 16.1 14.3	0.86 0.92	0.9 1.0	The addition of pembro to platinum-based CT for 1L treatment of advanced urothelial carcinoma did not provide a statistically significant benefit for PFS or OS. Patients who did respond to 1L immunotherapy had more durable responses, suggesting a subset of patients who may not require aggressive therapy to induce disease regression may benefit longer from immunotherapy.
DANUBE[4,5]	Durva/Treme Durva CT	342 346 344	36[c] 26[c] 49[c]	3.7[c] 2.3[c] 6.7[c]	15.1[c] 14.4[d] 12.1[c,d]	0.85[e] 0.99	0.74 0.89[e]	The DANUBE trial was negative for its co-primary endpoints of OS in 1.) durva monotherapy vs CT in the PD-L1-high patient population and 2.) combination durva and treme vs CT in the ITT population. Results from the secondary endpoint analysis of combination immunotherapy in the PD-L1-high population warrants further investigation.

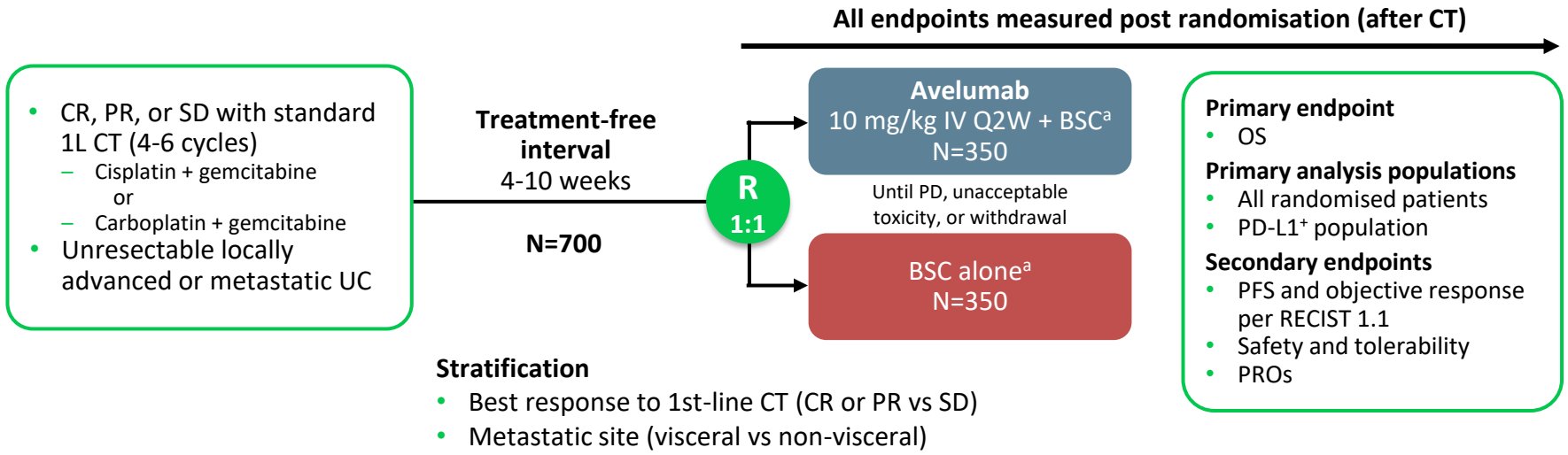
[a] Comparison of atezo/CT vs CT; [b] Comparison of atezo vs CT; [c] ITT population results; [d] High PD-L1-expression results; [e] DANUBE trial co-primary endpoints: OS comparison between durva and CT for high PD-L1 expression tumours and OS comparison between durva/treme and CT for ITT population; [f]hazard ratios represent comparison between respective treatment and CT

1L, first line; Atezo, atezolizumab; CT, chemotherapy; Durva, durvalumab; HR, hazard ratio; ITT, intent-to-treat; NA, not available; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; Treme, tremelimumab

1. Grande E, et al. ESMO 2019. Abstract #LBA14_PR (oral presentation); 2. Galsky M, et al. Lancet. 2020;395:1547-57; 3. Alva A, et al. ESMO 2020. Abstract #LBA23 (oral presentation); 4. Powles T, et al. ESMO 2020; Abstract #6970 (oral presentation); 5. Powles T, et al. Lancet. 2020;21:1574-88

JAVELIN BLADDER 100 STUDY DESIGN (NCT02603432)

- **JAVELIN Bladder 100** assessed patients with locally advanced or metastatic urothelial cancer that did not progress following 1st-line CT and who were randomised to either standard of care or avelumab (anti-PD-L1)



[a] BSC was administered per local practice based on patient needs and clinical judgement; other systemic antitumour therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable

PD-L1+ status was defined as 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; 358 patients (51%) had a PD-L1+ tumour

BSC, best supportive care; CR, complete response; CT, chemotherapy; IV, intravenous; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; PR, partial response; PRO, patient reported outcome; Q2W, every 2 weeks; R, randomisation; RECIST 1.1; Response Evaluation Criteria in Solid Tumours version 1.1; SD, stable disease; UC, urothelial carcinoma

Powles T, et al. N Engl J Med. 2020;383:1218-30

JAVELIN BLADDER 100 STUDY

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SELECT BASELINE CHARACTERISTICS

	Overall population (N=700)		PD-L1⁺ population (N=358)	
	Avelumab + BSC (N=350)	BSC alone (N=350)	Avelumab + BSC (N=189)	BSC alone (N=169)
Median age, years	68	69	70	70
Site of primary tumour, %				
Upper tract (renal pelvis, ureter)	30	23	23	21
Lower tract (bladder, urethra, prostate gland)	70	77	77	79
Site of baseline metastasis, %				
Visceral	55	55	47	47
Non-visceral[a]	45	45	53	53
PD-L1 status, %[b]				
Positive	54	48	100	100
Negative	40	38	0	0
Unknown	6	14	0	0
1st-line CT regimen, %				
Gemcitabine + cisplatin	52	59	53	58
Gemcitabine + carboplatin	42	35	39	32
Gemcitabine + cisplatin/carboplatin[c]	6	6	7	9
Not reported	0	1	0	1
Baseline response to 1st-line CT, %				
CR or PR	72	72	74	76
SD	28	28	26	24

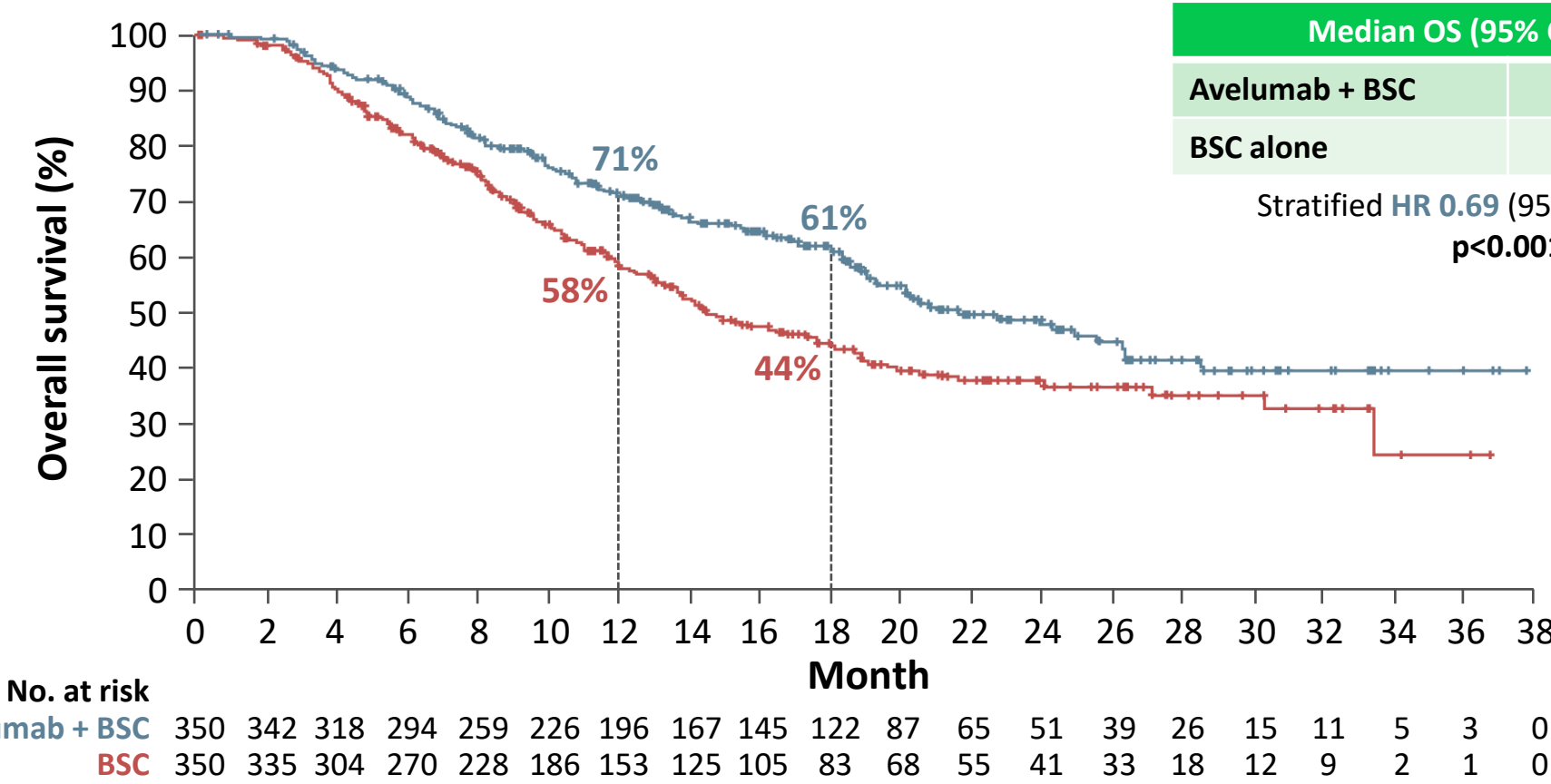
[a] Non-visceral includes patients with locally advanced disease or only non-visceral disease, including bone metastasis
[b] PD-L1⁺ status was defined as PD-L1 expression in ≥25% or 100% of tumour-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively (SP263 assay); among patients evaluable for PD-L1 status in the avelumab and control arms, 58% and 56% had a PD-L1⁺ tumour, respectively
[c] Patients who switched platinum-based regimens while receiving 1st-line CT

BSC, best supportive care; CR, complete response; PD-L1, programmed death ligand-1; PR, partial response; SD, stable disease

Powles T, et al. N Engl J Med. 2020;383:1218-30

JAVELIN BLADDER 100 STUDY

OS IN THE OVERALL POPULATION



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

Stratified **HR 0.69** (95% CI 0.56-0.86)
p<0.001

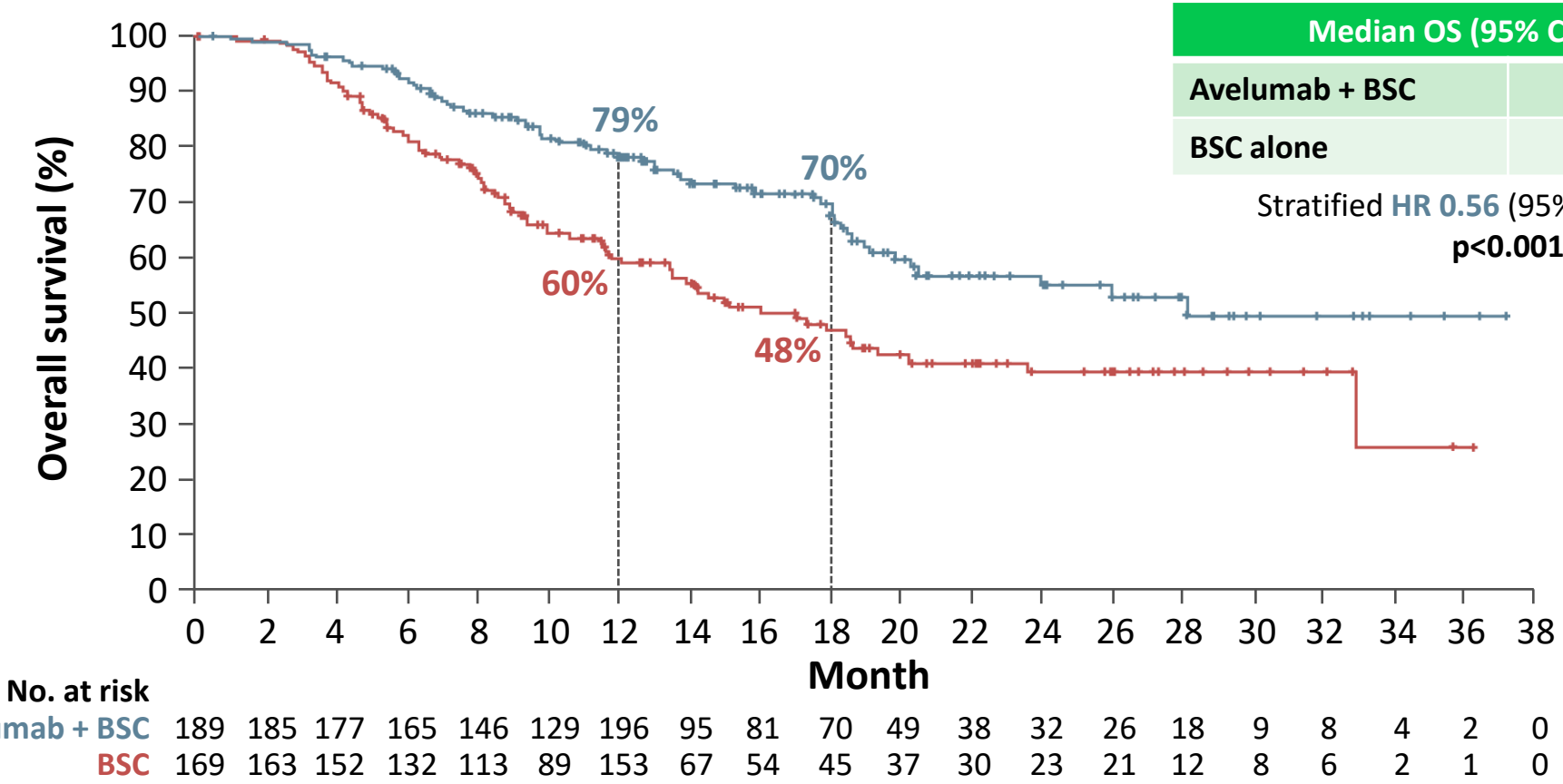
OS was measured post randomisation (after CT); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (p<0.0053)

BSC, best supportive care; CI, confidence interval; HR, hazard ratio; OS, overall survival

Powles T, et al. N Engl J Med. 2020;383:1218-30; Powles T, et al. Oral presentation ASCO 2020: LBA1

JAVELIN BLADDER 100 STUDY

OS IN THE PD-L1^{+} POPULATION



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

Stratified **HR 0.56** (95% CI 0.40-0.79)
p<0.001

OS was measured post randomisation (after CT); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (p<0.0014)

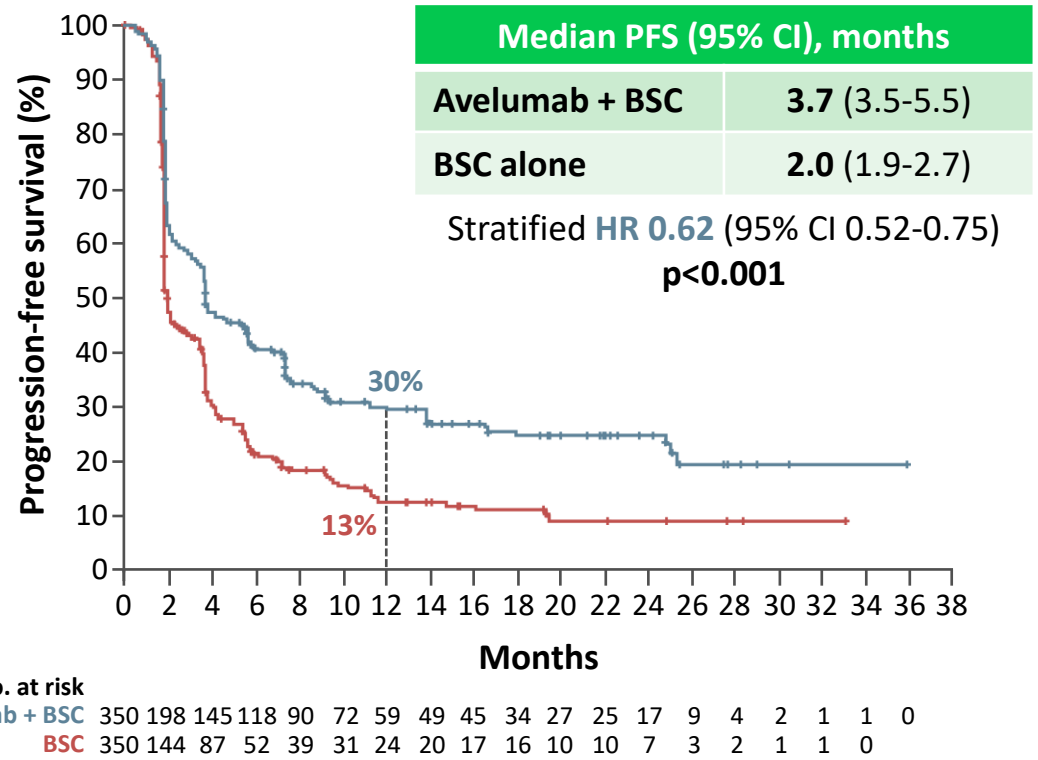
BSC, best supportive care; CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival; PD-L1, programmed death ligand-1

Powles T, et al. N Engl J Med. 2020;383:1218-30; Powles T, et al. Oral presentation ASCO 2020: LBA1

JAVELIN BLADDER 100 STUDY

PFS RESULTS

PFS by independent radiology review in the overall population



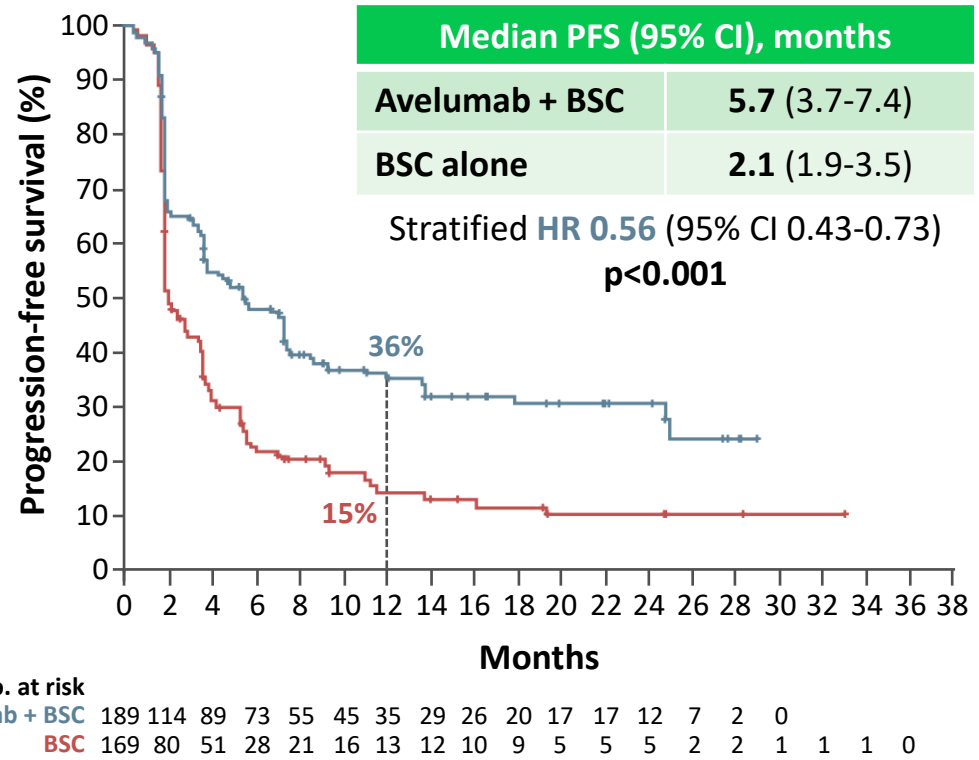
Median PFS (95% CI), months	
Avelumab + BSC	**3.7** (3.5-5.5)
BSC alone	**2.0** (1.9-2.7)

Stratified **HR 0.62** (95% CI 0.52-0.75)
p<0.001

No. at risk																			
Avelumab + BSC	350	198	145	118	90	72	59	49	45	34	27	25	17	9	4	2	1	1	0
BSC	350	144	87	52	39	31	24	20	17	16	10	10	7	3	2	1	1	0	

PFS was measured post randomisation (from end of CT)

PFS by independent radiology review in the PD-L1^{+} population



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

No. at risk																			
Avelumab + BSC	189	114	89	73	55	45	35	29	26	20	17	17	12	7	2	0			
BSC	169	80	51	28	21	16	13	12	10	9	5	5	5	2	2	1	1	1	0

PFS was measured post randomisation (from end of CT)

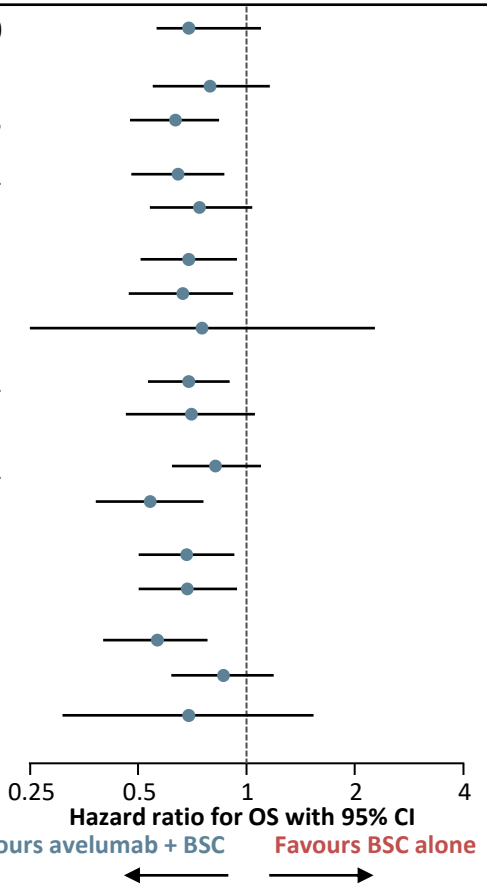
BSC, best supportive care; CI, confidence interval; HR, hazard ratio; PD-L1, programmed death ligand-1; PFS, progression-free survival

Powles T, et al. N Engl J Med. 2020;383:1218-30; Powles T, et al. Oral presentation ASCO 2020: LBA1

JAVELIN BLADDER 100 STUDY

SUBGROUP ANALYSIS OF OS IN THE OVERALL POPULATION

Subgroup		Events/patients, N: Avelumab + BSC	BSC alone	Hazard ratio (95% CI)
All patients		145/350	179/350	**0.69** (0.56-0.86)[a]
Age	<65 years	61/129	53/107	**0.79** (0.55-1.15)
	≥65 years	84/221	126/243	**0.63** (0.47-0.83)
ECOG PS score	0	77/123	101/211	**0.64** (0.48-0.86)
	≥1	68/137	78/139	**0.74** (0.54-1.03)
1st-line CT regimen	Gemcitabine + cisplatin	71/183	98/206	**0.69** (0.51-0.94)
	Gemcitabine + carboplatin	68/147	73/122	**0.66** (0.47-0.91)
	Gemcitabine + cisplatin/carboplatin	6/20	7/20	**0.75** (0.25-2.25)
Best response to 1st-line CT	CR or PR	104/253	127/252	**0.69** (0.53-0.89)
	SD	41/97	52/98	**0.70** (0.46-1.05)
Site of baseline metastasis	Visceral	93/191	101/191	**0.82** (0.62-1.09)
	Non-visceral	52/159	78/159	**0.54** (0.38-0.76)
Creatinine clearance	≥60 mL/min	74/181	97/196	**0.68** (0.50-0.92)
	<60 mL/min	71/168	81/148	**0.68** (0.50-0.94)
PD-L1 status	Positive	61/189	82/169	**0.56** (0.40-0.78)
	Negative	76/139	72/132	**0.86** (0.62-1.18)
	Unknown	8/22	25/49	**0.69** (0.31-1.53)



Error bars show 95% CI

[a] Stratified (all other analyses are unstratified)

BSC, best supportive care; CI, confidence interval; CR, complete response; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival; PD-L1, programmed death ligand-1; PR, partial response; SD, stable disease

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JAVELIN BLADDER 100 STUDY

TREATMENT EMERGENT ADVERSE EVENTS (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
Urinary tract infection	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
Infusion-related reaction	10.2	0.9	0	0

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)

- 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 avelumab + BSC arm
  - 1 due to sepsis (in cycle 10)
  - 1 due to ischaemic 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

BSC, best supportive care

Powles T, et al. N Engl J Med. 2020;383:1218-30

SUMMARY

- Checkpoint inhibitors have altered the treatment landscape in metastatic urothelial cancer
- **Immunotherapy as monotherapy does not appear to prolong OS** in platinum-based CT-eligible patients, regardless of PD-L1 expression
- **Combination treatment** (either immuno-oncology [IO]–CT or IO–IO) **does not appear to offer a survival benefit** across all platinum-based CT-eligible patients
  - Further investigation is warranted to understand if combining PD-(L)1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors in the PD-L1^{+} patient population improves survival
- In the **JAVELIN Bladder 100 trial**, maintenance avelumab after CT in patients whose disease has not progressed results in improvement in OS
  - Higher magnitude of benefit in PD-L1-high tumours
  - Benefit seen irrespective of type of CT, no. of cycles of CT, and prior response to CT
  - **Maintenance immunotherapy with avelumab is the new standard of care in patients with advanced urothelial cancer** whose disease has not progressed with platinum-based CT

CT, chemotherapy; OS, overall survival; PD-L1, programmed death (ligand)-1

Powles T, et al. N Engl J Med. 2020;383:1218-30

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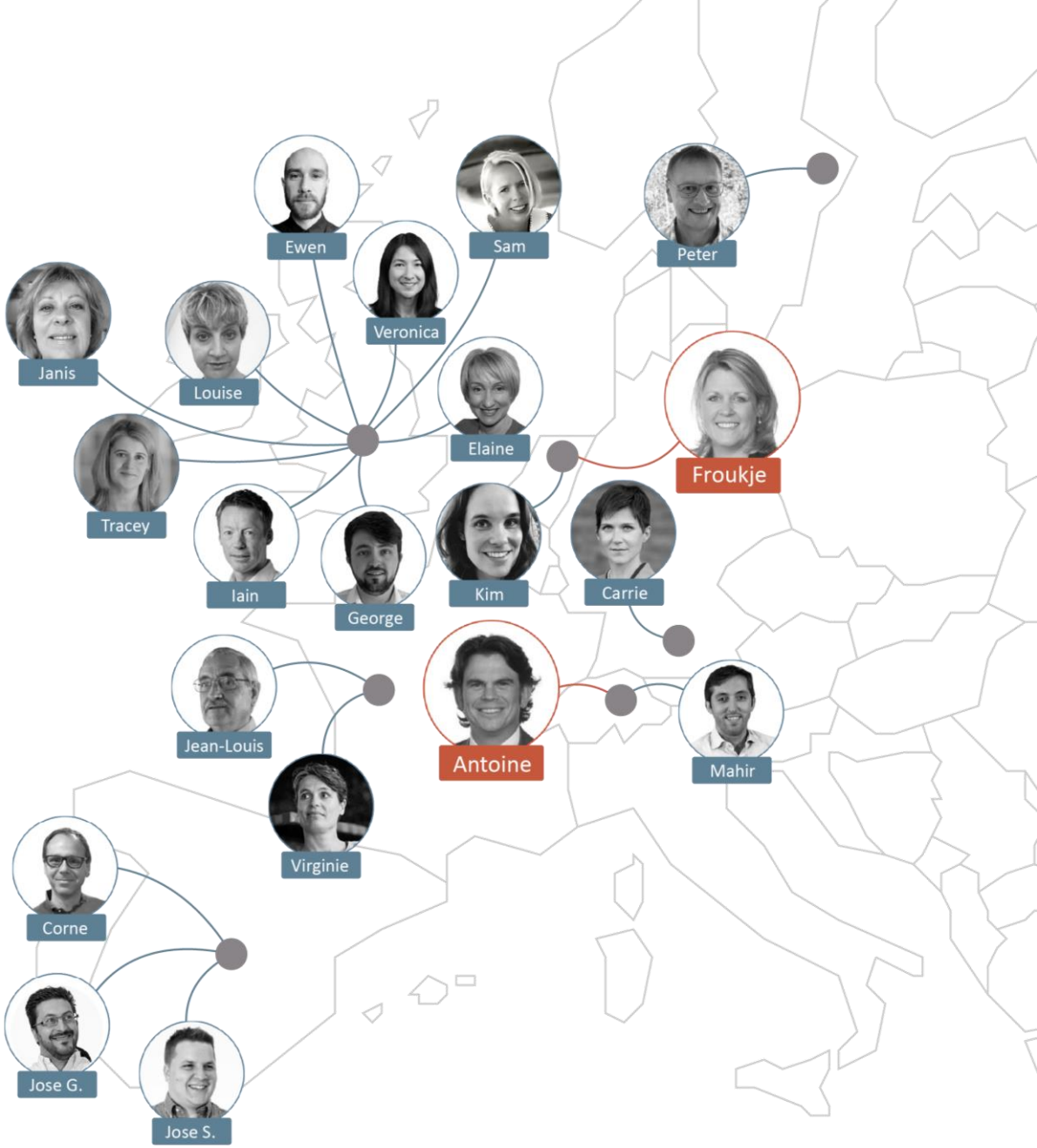

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