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

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Background

- UC is the 6th most common cancer in the US and was responsible for 200,000 deaths globally in 2018[1,2]
- Although most patients with advanced UC have disease control with 1st-line platinum-based chemotherapy (DCR ~65-75%), PFS and OS are short because of chemotherapy resistance[3-6]
- After 1st-line chemotherapy, only ~25-55% of patients receive 2nd-line treatment[7-12]
- Outcomes with 2nd-line therapy remain suboptimal because of rapid disease progression[7-12]

DCR, disease control rate; **OS**, overall survival; **PFS**, progression-free survival; **UC**, urothelial carcinoma

1. Bray F, et al. CA Cancer J Clin 2018;68:394-424. **2.** Siegel RL, et al. CA Cancer J Clin 2019;69:7-34. **3.** von der Maase H, et al. J Clin Oncol 2000;18:3068-3077. **4.** von der Maase H, et al. J Clin Oncol 2005; 23:4602-4608. **5.** De Santis M, et al. J Clin Oncol 2012; 30:191-199. **6.** Dogliotti L, et al. Eur Urol 2007;52:134-141. **7.** Cheeseman S, et al. Front Oncol 2020;10:167. **8.** Aly A, et al. J Med Econ 2019;22:662-670. **9.** Galsky MD, et al. Bladder Cancer 2018;4:227-238. **10.** Fisher MD, et al. Clin Genitourin Cancer 2018;16:e1171-e1179. **11.** Niegisch G, et al. J Cancer 2018;9:1337-1348. **12.** Flannery K, et al. Future Oncol 2019;15:1323-1334.

Background

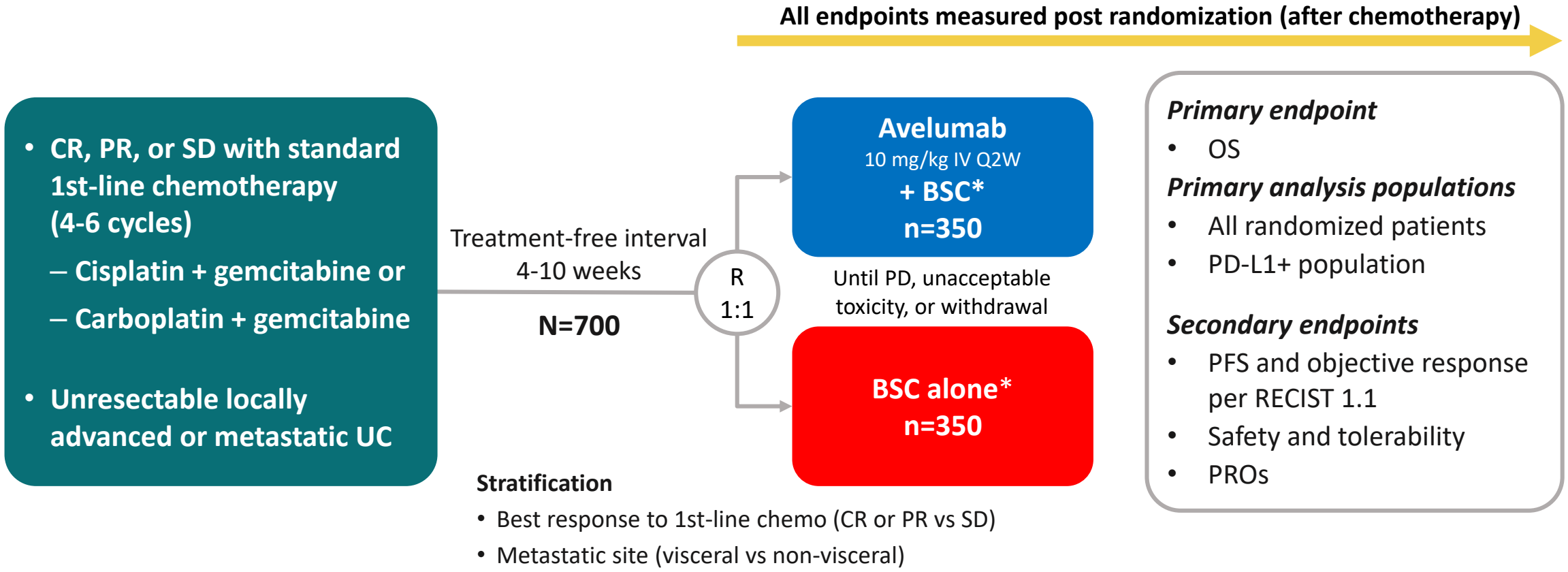
- PD-L1/PD-1 inhibitors are standard 2nd-line treatment for patients with disease progression after platinum-based chemotherapy[1]
  - This includes the PD-L1 inhibitor avelumab[2]

- Although PD-L1/PD-1 inhibitors have antitumor activity in UC, only a minority of patients obtain a durable clinical benefit with 2nd-line treatment[2-6]

- Avelumab maintenance therapy in patients whose disease has not progressed with 1st-line platinum-based induction chemotherapy is an attractive treatment strategy[7]
  - Disease control achieved with chemotherapy may provide time for immunotherapy to have an antitumor effect
  - Initiating immunotherapy before disease progression occurs may result in more patients receiving treatment

1. NCCN Clinical Practice Guidelines in Oncology: Bladder Cancer, V3.2020. **2.** Patel MR, et al. Lancet Oncol 2018;19:51-64. **3.** Bellmunt J, et al. N Engl J Med 2017;376:1015-26. **4.** Powles, T, et al. Lancet 2018;391:748-57. **5.** Powles T, et al. JAMA Oncol 2017;3:e172411. **6.** Sharma P, et al. Lancet Oncol 2017;18:312-22. **7.** Grivas P, et al. Target Oncol 2019;14:505-525.

JAVELIN Bladder 100 study design (NCT02603432)



PD-L1+ status was defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-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–positive tumor

BSC, best supportive care; **CR,** complete response; **IV,** intravenous; **PR**, partial response; **PRO**, patient reported outcome; **Q2W,** every 2 weeks; **R**, randomization; **RECIST 1.1,** Response Evaluation Criteria in Solid Tumors version 1.1; **SD**, stable disease

*BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other systemic antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable

Statistical design

- The type I-error rate was maintained at or below 1-sided 0.025 by allocating 0.015 and 0.01 alpha to OS comparisons, respectively
  - In the overall population, it was estimated that 425 events would provide 93% power to detect a hazard ratio (HR) of 0.7 at significance level of 0.015
  - In the PD-L1+ population, it was estimated that 219 events would provide 80% power to detect a HR of 0.65 at significance level of 0.01
- A planned interim analysis was performed after 324 events (76.2% information fraction) in the overall population and 143 events (65.3% information fraction) in the PD-L1+ population
  - Efficacy boundaries for OS in the overall population and PD-L1+ population were P<0.0053 and P<0.0014, respectively

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 tumor, %				
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
Nonvisceral*	45	45	53	53
PD-L1 status, %†				
Positive	54	48	100	100
Negative	40	38	0	0
Unknown	6	14	0	0
1st-line chemotherapy regimen, %				
Gemcitabine + cisplatin	52	59	53	58
Gemcitabine + carboplatin	42	35	39	32
Gemcitabine + cisplatin/carboplatin‡	6	6	7	9
Not reported	0	1	0	1
Best response to 1st-line chemotherapy, %				
CR or PR	72	72	74	76
SD	28	28	26	24

*Nonvisceral includes patients with locally advanced disease or only nonvisceral disease, including bone metastasis

†PD-L1+ status was defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-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+ tumor, respectively

‡Patients who switched platinum regimens while receiving 1st-line chemotherapy

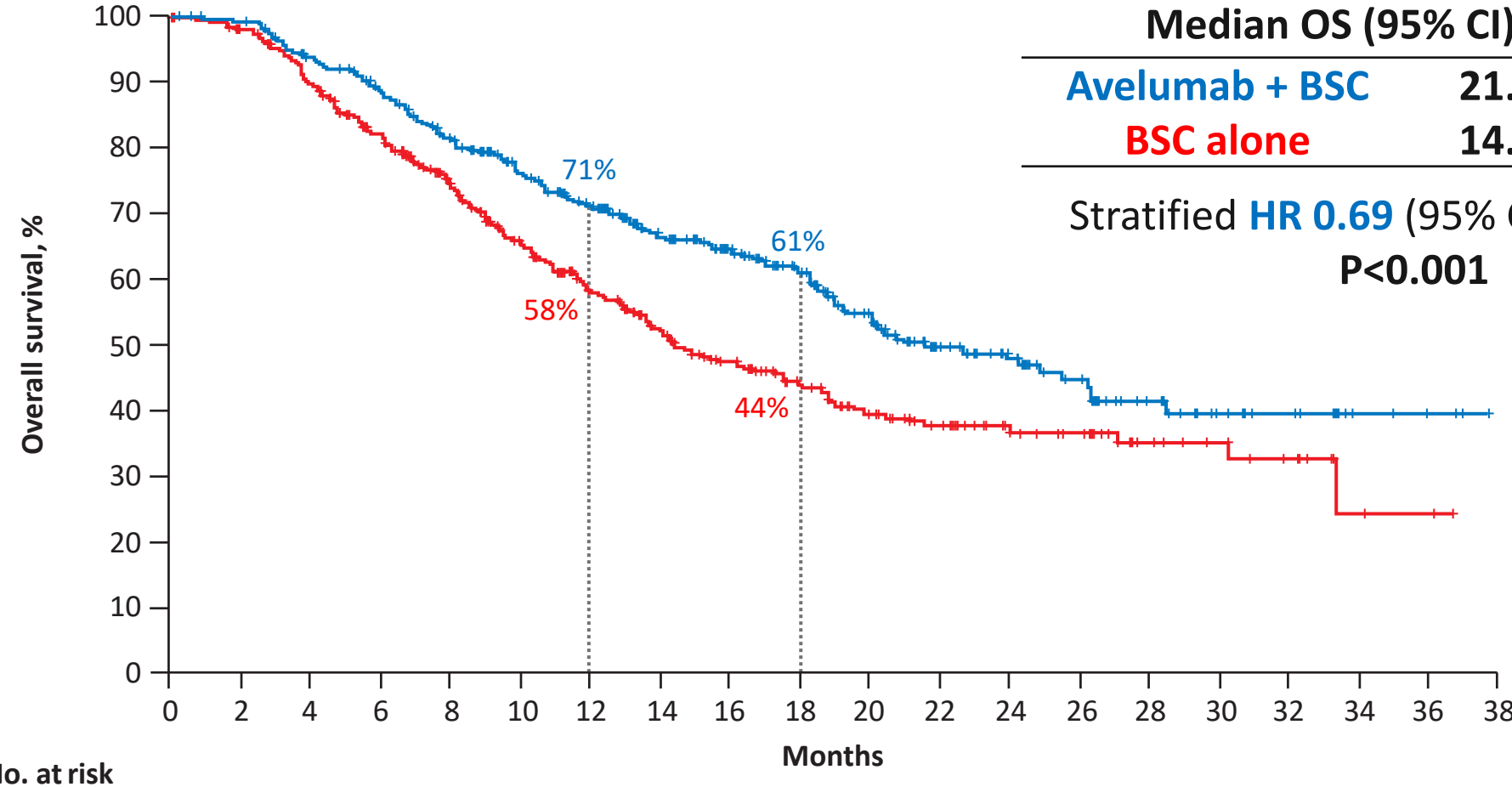
Patient disposition at the time of analysis

	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)
Treatment ongoing, %	**24**	**7**	**31**	**8**
Discontinued, %	**76**	**93**	**69**	**92**
Progressive disease	54	75	44	75
Adverse event	11	1	14	1
Withdrew consent	5	8	4	7
Death	1	4	2	5
Physician decision	1	2	2	4
Global health deterioration	1	2	1	1
Other reason*	2	1	3	1

*Includes no longer meets eligibility criteria, lost to follow-up, noncompliance with study drug, and other

- At data cutoff (October 21, 2019) the median follow-up in all randomized patients was 19.6 months for avelumab + BSC and 19.2 months for BSC alone
- Median duration of treatment (range):
  - Avelumab + BSC arm: 24.9 weeks (2.0-159.9); BSC alone arm, 13.1 weeks (0.1-155.6)

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)

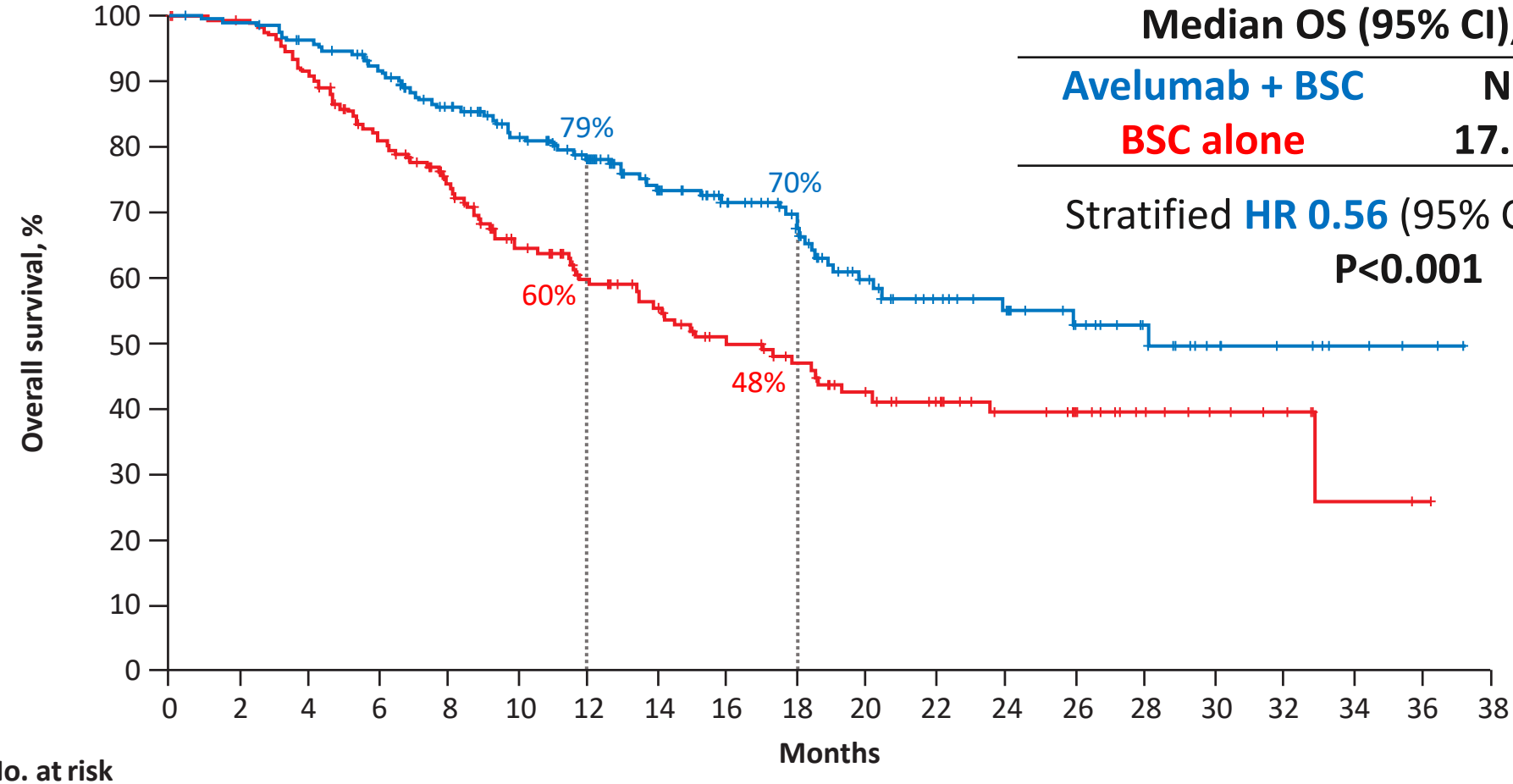
Stratified **HR 0.69** (95% CI, 0.56, 0.86)

P<0.001

No. at risk																			
Avelumab + BSC	350	342	318	294	259	226	196	167	145	122	87	65	51	39	26	15	11	5	3	0
BSC	350	335	304	270	228	186	153	125	105	83	68	55	41	33	18	12	9	2	1	0

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 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)

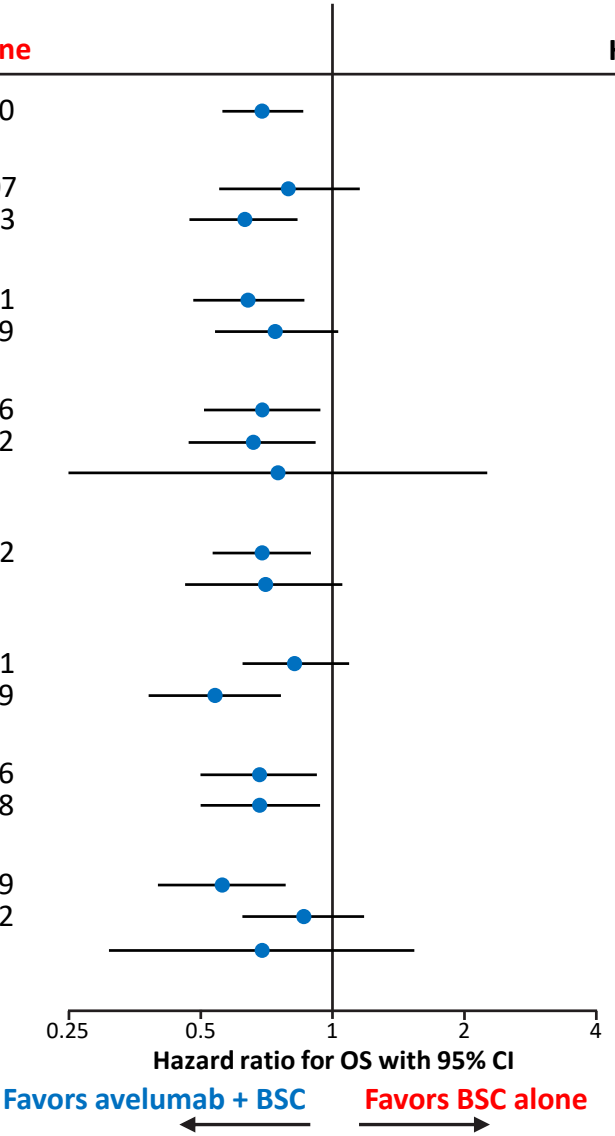
P<0.001

No. at risk																				
Avelumab + BSC	189	185	177	165	146	129	114	95	81	70	49	38	32	26	18	9	8	4	2	0
BSC	169	165	152	132	113	89	76	67	54	45	37	30	23	21	12	8	6	2	1	0

OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0014). **NE**, not estimable

Subgroup analysis of OS in the overall population

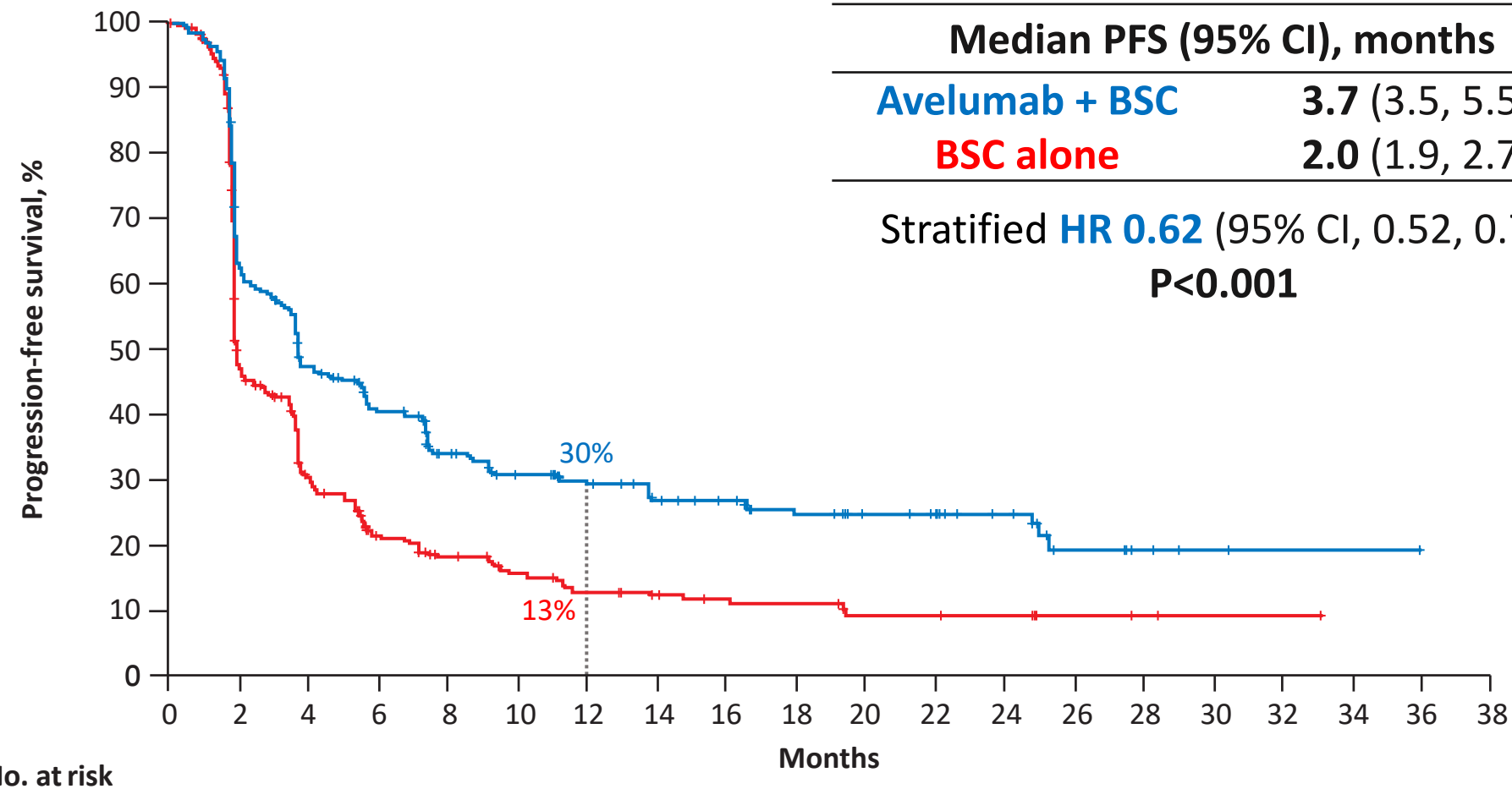
Subgroup		Events/patients, n: Avelumab + BSC	Events/patients, n: BSC alone	Hazard ratio (95% CI)
All patients		145/350	179/350	**0.69** (0.56, 0.86)*
Age	<65 years	61/129	53/107	**0.79** (0.55, 1.15)
	≥65 years	84/221	126/243	**0.63** (0.47, 0.83)
ECOG PS score	0	77/213	101/211	**0.64** (0.48, 0.86)
	≥1	68/137	78/139	**0.74** (0.54, 1.03)
1st-line chemotherapy 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 chemotherapy	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)
	Nonvisceral	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

*Stratified (all other analyses are unstratified)

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)

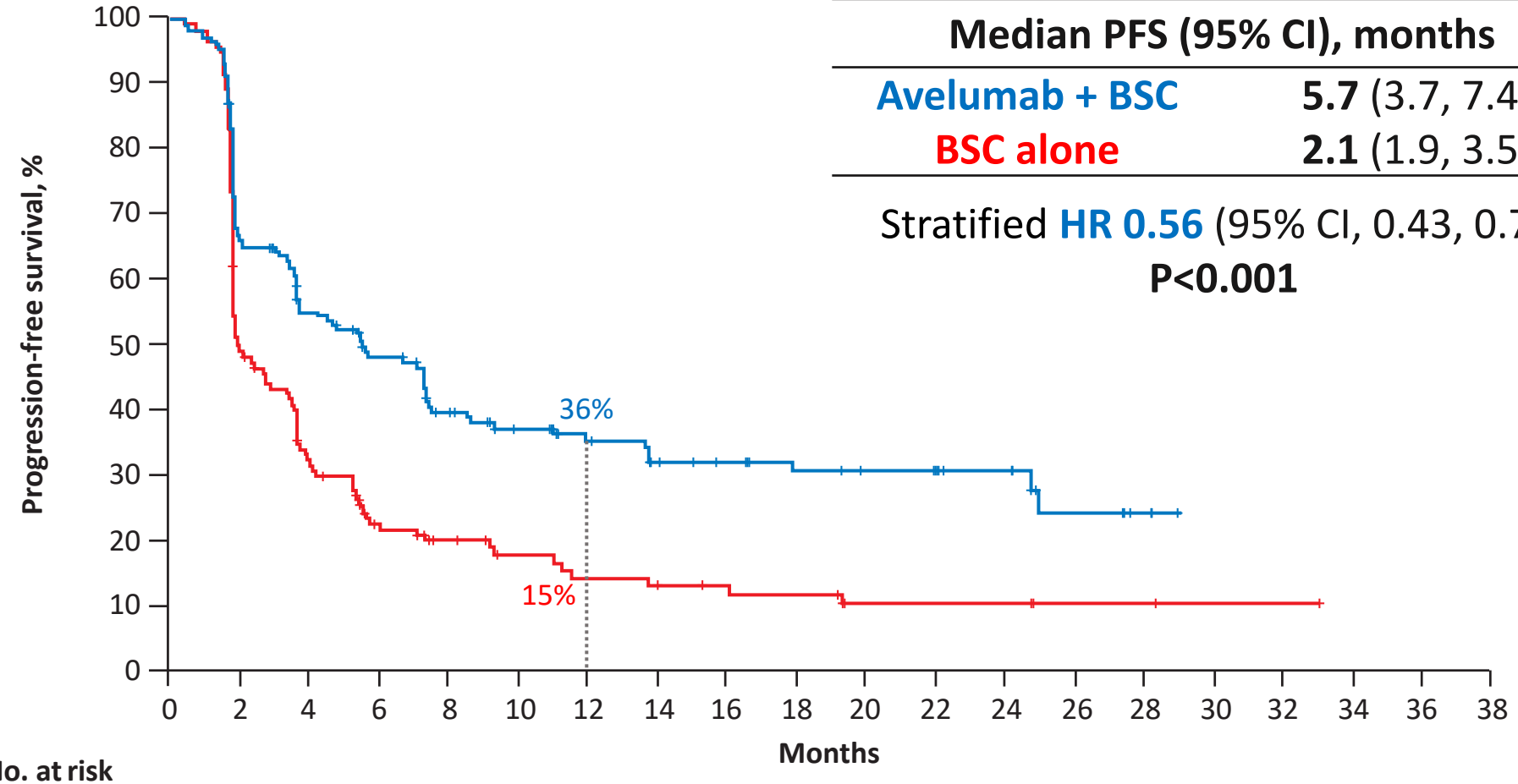
Stratified **HR 0.62** (95% CI, 0.52, 0.75)

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 randomization (from end of chemotherapy)

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	0

PFS was measured post randomization (from end of chemotherapy)

Confirmed objective response

Response to maintenance therapy post randomization

	Overall population		PD-L1+ population	
	Avelumab + BSC (N=350)	BSC alone (N=350)	Avelumab + BSC (N=189)	BSC alone (N=169)
ORR, %	**9.7**	**1.4**	**13.8**	**1.2**
(95% CI)	(6.8, 13.3)	(0.5, 3.3)	(9.2, 19.5)	(0.1, 4.2)
Stratified odds ratio (95% CI)	7.464 (2.824, 24.445)		12.699 (3.160, 114.115)	
Best overall response, %				
Complete response	6.0	0.9	9.5	0.6
Partial response	3.7	0.6	4.2	0.6
Stable disease	12.6	13.1	10.1	13.6
Non-CR/non-PD	18.9	12.9	20.1	13.0
Progressive disease	37.1	48.3	31.2	48.5
Not evaluable*	21.7	24.3	24.9	23.7
Disease control, %†	41.1	27.4	43.9	27.8

PD, progressive disease
Objective response was assessed by independent radiology review; in patients with a CR after chemotherapy, best overall response was not evaluable if no evidence of disease at baseline was maintained after randomization, or PD if disease progression occurred after randomization
*Reasons for not evaluable included no evidence of disease at baseline; no post-baseline assessments; SD <6 weeks after randomization; PD >12 weeks after randomization; new anticancer therapy started before first post-baseline assessment; or all post-baseline assessments have objective response of not evaluable
†Patients with a best overall response of CR, PR, SD, or non-CR/non-PD

Subsequent anticancer therapy

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

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

Treatment-emergent AEs (any causality)

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

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

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

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

Immune-related AEs

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

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

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

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

Conclusions

- JAVELIN Bladder 100 met its primary endpoint by showing significantly longer OS with avelumab 1st-line maintenance vs control, both in the overall population and PD-L1+ population
- OS was longer with avelumab vs control across all prespecified subgroups
  - Includes subgroups defined by cisplatin-based or carboplatin-based chemotherapy, or response or SD with 1st-line induction chemotherapy
- The safety profile of avelumab as 1st-line maintenance was manageable and consistent with previous studies of avelumab monotherapy[1]
- Avelumab 1st-line maintenance in patients whose disease has not progressed with platinum-based induction chemotherapy represents a new 1st-line standard of care for advanced UC

1. Kelly K, et al. Cancer. 2018;124:2010-17.

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