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JAVELIN Bladder Medley phase 2 trial of avelumab + sacituzumab govitecan vs avelumab monotherapy as first-line maintenance treatment for advanced urothelial carcinoma: subgroup analyses based on metastatic sites

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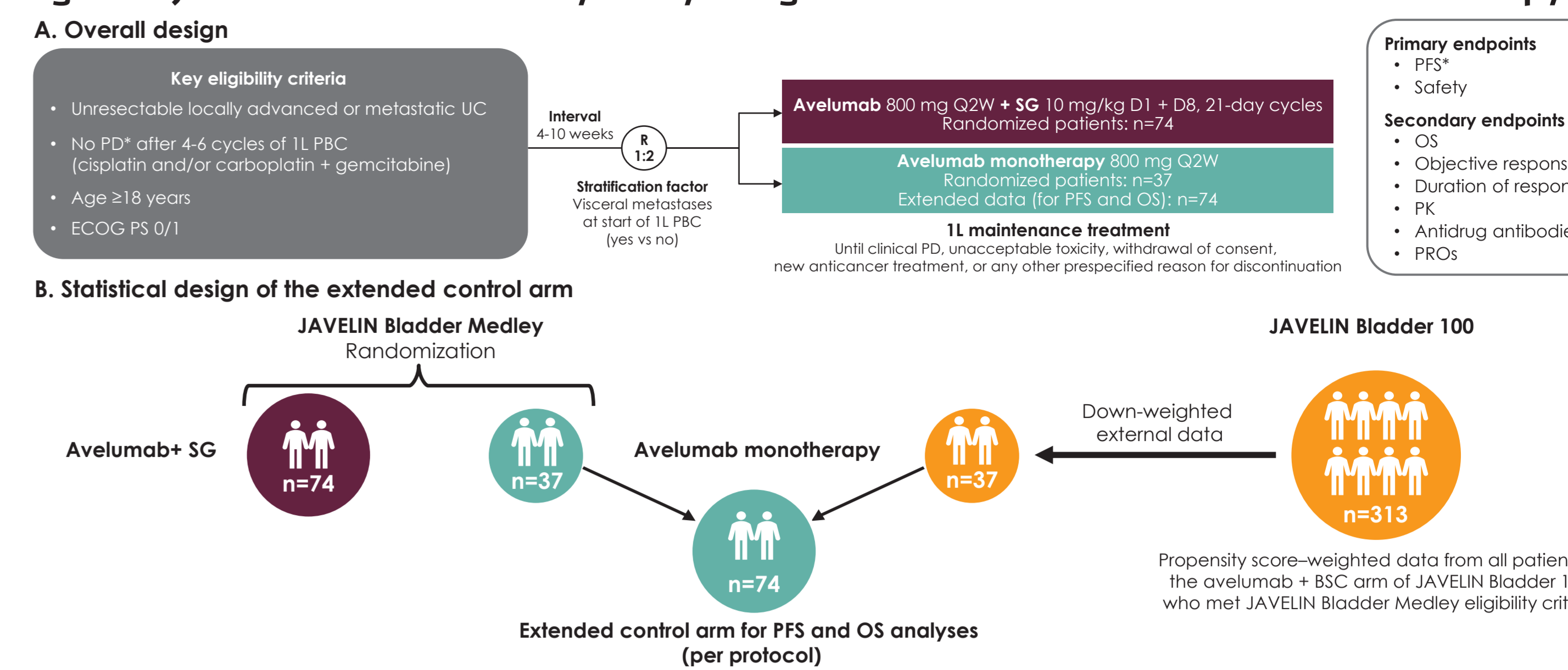
BACKGROUND

- Avelumab 1L maintenance is a recommended treatment for patients with advanced UC without progression after 1L PBC based on results from the JAVELIN Bladder 100 phase 3 trial, which showed significantly improved efficacy with avelumab 1L maintenance + best supportive care (BSC) vs BSC alone^{2,3}
 - After ≥2 years of follow-up (data cutoff: 4 June 2021), median OS (from randomization) was 23.8 vs 15.0 months (hazard ratio [HR], 0.74 [95% CI, 0.63-0.91]; p=0.0034), and median investigator-assessed PFS was 5.5 vs 2.1 months (HR, 0.54 [95% CI, 0.46-0.64]; p<0.0001), respectively³
 - The long-term safety of avelumab 1L maintenance was demonstrated, and health-related quality of life was preserved during treatment⁴
- SG is a Trop-2-targeted antibody-drug conjugate approved in various countries for specific populations of patients with previously treated advanced breast cancer⁵⁻⁶
 - SG has shown clinical activity in patients with advanced UC following PBC and anti-PD-L1 inhibitor treatment^{7,8}
 - However, accelerated approval in advanced UC was voluntarily withdrawn by the manufacturer in October 2024 because the TROPICS-04 phase 3 trial did not show a significant improvement in OS with SG monotherapy vs physician's choice of single-agent chemotherapy⁹; the authors concluded that early toxicity-related complications with SG may have impacted efficacy outcomes⁸
- In a phase 2 cohort, SG + pembrolizumab showed encouraging efficacy and a manageable safety profile in patients with advanced UC that progressed after PBC with no prior anti-PD-L1 treatment¹⁰
- JAVELIN Bladder Medley is a randomized phase 2 trial investigating avelumab in combination with other anticancer agents as 1L maintenance treatment for advanced UC¹
 - In the interim analysis, avelumab + SG showed improved PFS vs avelumab monotherapy (median, 11.17 vs 3.75 months; HR, 0.49 [95% CI, 0.31-0.76])
 - OS data were immature at data cutoff
 - Treatment-related adverse events were more frequent in the avelumab + SG arm and were consistent with the known safety profiles of each drug
- Previous studies have shown that the presence of visceral metastases in the liver or lung is a negative prognostic factor in patients with advanced UC receiving 1L treatment¹¹⁻¹⁴
- Here, we report efficacy and safety data from the interim analysis of the JAVELIN Bladder Medley trial in subgroups with or without visceral metastases at start of 1L PBC or liver/lung lesions at randomization

METHODS

- JAVELIN Bladder Medley (NCT05327530) is an ongoing international, randomized, open-label, parallel-arm, phase 2 trial (Figure 1A)
- Patients with unresectable locally advanced or metastatic UC without progression after 4-6 cycles of 1L PBC were randomized 2:1 to receive avelumab + SG or avelumab monotherapy, stratified by the presence of visceral metastases at the start of 1L PBC
 - In this study, nonvisceral metastasis was defined as locally advanced disease or nonvisceral metastases only, including lymph node-only disease; bone metastases were considered nonvisceral
- Primary endpoints were investigator-assessed PFS from randomization and safety
 - Secondary endpoints included OS and objective response from randomization
- Per protocol, PFS and OS data in the avelumab monotherapy arm were extended using propensity score-weighted data from the JAVELIN Bladder 100 phase 3 trial (Figure 1B)¹
 - All patients who met JAVELIN Bladder Medley eligibility criteria were included (n=313/350)
 - To account for population differences, external patients were propensity score weighted using predefined prognostic factors (age, visceral metastases, liver or lung lesions, Eastern Cooperative Oncology Group performance status [ECOG PS], and PD-L1 status)
 - The sum of external patients in the overall arm was down-weighted to 37 to be equal to the number of randomized patients
 - Applied weights resulted in decimal values for patient numbers and events

Figure 1. JAVELIN Bladder Medley study design: avelumab + SG vs avelumab monotherapy¹



1L first line; BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival; PBC, platinum-based chemotherapy; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; PRO, patient-reported outcome; Q2W, every 2 weeks; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; SG, sacituzumab govitecan; UC, urothelial carcinoma; *Per RECIST 1.1 as assessed by the investigator.

RESULTS

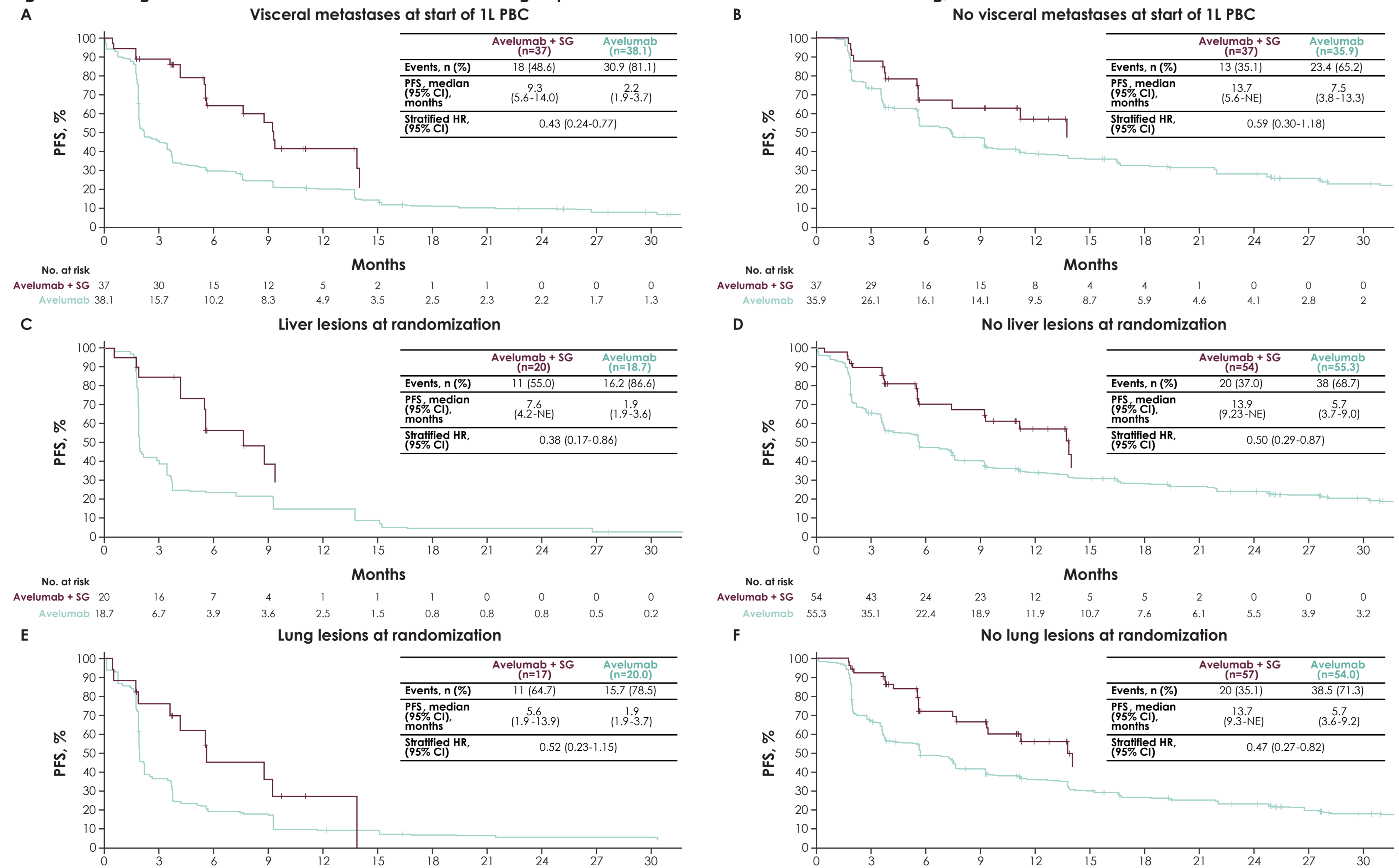
- Of 74 and 37 patients randomized to the avelumab + SG and avelumab monotherapy arms, respectively:
 - 37 (50.0%) and 19 (51.4%) had visceral metastases at start of 1L PBC
 - 20 (27.0%) and 9 (24.3%) had liver lesions at randomization
 - 17 (23.0%) and 11 (29.7%) had lung lesions at randomization
- Baseline characteristics in subgroups with and without visceral metastases or lung/liver lesions are shown in Table 1
 - Across all subgroups, the avelumab monotherapy arm had a higher proportion of patients with ECOG PS of 1 than the avelumab + SG arm
 - PFS was prolonged with avelumab + SG vs avelumab monotherapy across all subgroups defined by metastatic site (Figure 2)
- Median PFS (HR [95% CI]) with avelumab + SG vs avelumab monotherapy, respectively, was:
 - 9.3 vs 2.2 months (0.43 [0.24-0.77]) in patients with visceral metastases and 13.7 vs 7.5 months (0.59 [0.30-1.18]) in patients without visceral metastases (Figure 2A-B)
 - 7.6 vs 1.9 months (0.38 [0.17-0.86]) in patients with liver lesions and 13.9 vs 5.7 months (0.50 [0.29-0.87]) in patients without liver lesions (Figure 2C-D)
 - 5.6 vs 1.9 months (0.52 [0.23-1.15]) in patients with lung lesions and 13.7 vs 5.7 months (0.47 [0.27-0.82]) in patients without lung lesions (Figure 2E-F)
- At data cutoff (16 September 2024), OS analyses remained immature (Table 2)
- ORR results favored avelumab + SG vs avelumab monotherapy across all subgroups (Figure 3)
- A summary of safety by subgroup is shown in Table 3

Table 1. Baseline characteristics

	Visceral metastases at start of 1L PBC		No visceral metastases at start of 1L PBC		Liver lesions at randomization		No liver lesions at randomization		Lung lesions at randomization		No lung lesions at randomization	
	Avelumab + SG (n=37)	Avelumab (n=19)	Avelumab + SG (n=37)	Avelumab (n=18)	Avelumab + SG (n=20)	Avelumab (n=9)	Avelumab + SG (n=54)	Avelumab (n=28)	Avelumab + SG (n=17)	Avelumab (n=11)	Avelumab + SG (n=57)	Avelumab (n=26)
Age, median (range), years	69 (42-83)	69 (53-89)	72 (48-85)	67 (55-77)	67 (42-77)	65 (53-89)	70 (48-85)	68 (55-83)	70 (59-82)	66 (56-89)	69 (42-85)	68 (53-83)
Sex, n (%)												
Female	7 (18.9)	6 (31.6)	6 (16.2)	3 (16.7)	4 (20.0)	3 (33.3)	9 (16.7)	6 (21.4)	4 (23.5)	5 (45.5)	9 (15.8)	4 (15.4)
Male	30 (81.1)	13 (68.4)	31 (83.8)	15 (83.3)	16 (80.0)	6 (66.7)	45 (83.3)	22 (78.6)	13 (76.5)	6 (54.5)	48 (84.2)	22 (84.6)
ECOG PS, n (%)												
0	23 (62.2)	5 (26.3)	28 (75.7)	12 (66.7)	15 (75.0)	3 (33.3)	36 (66.7)	14 (50.0)	11 (64.7)	3 (27.3)	40 (70.2)	14 (53.8)
1	14 (37.8)	14 (73.7)	9 (24.3)	6 (33.3)	5 (25.0)	6 (66.7)	18 (33.3)	14 (50.0)	6 (35.3)	8 (72.7)	17 (29.8)	12 (46.2)
PD-L1 status, n (%)												
Positive	9 (24.3)	5 (26.3)	11 (29.7)	8 (44.4)	2 (10.0)	3 (33.3)	18 (33.3)	10 (35.7)	4 (23.5)	3 (27.3)	16 (28.1)	10 (38.5)
Negative	25 (67.6)	14 (73.7)	26 (70.3)	8 (44.4)	16 (80.0)	6 (66.7)	35 (64.8)	16 (57.1)	12 (70.6)	8 (72.7)	39 (68.4)	14 (53.8)
Primary tumor location, n (%)												
Bladder	24 (64.9)	11 (57.9)	32 (86.5)	15 (83.3)	14 (70.0)	5 (55.6)	42 (77.8)	21 (75.0)	12 (70.6)	6 (54.5)	44 (77.2)	20 (76.9)
Renal pelvis	6 (16.2)	4 (21.1)	4 (10.8)	0	3 (15.0)	2 (22.2)	7 (13.0)	2 (7.1)	4 (23.5)	3 (27.3)	6 (10.5)	1 (3.8)
Ureter/urethra	7 (18.9)	4 (21.1)	1 (2.7)	3 (16.7)	3 (15.0)	2 (22.2)	5 (9.3)	1 (5.9)	2 (18.2)	7 (12.3)	5 (19.2)	5 (19.2)
1L PBC, n (%)												
Cis + gem	24 (64.9)	12 (63.2)	17 (45.9)	13 (72.2)	12 (60.0)	5 (55.6)	29 (53.7)	20 (71.4)	12 (70.6)	6 (54.5)	29 (50.9)	19 (73.1)
Carbo + gem	13 (35.1)	7 (36.8)	20 (54.1)	5 (27.8)	8 (40.0)	4 (44.4)	25 (46.3)	8 (28.6)	5 (29.4)	5 (45.5)	28 (49.1)	7 (26.9)
BOR to 1L PBC, n (%)												
CR or PR	27 (73.0)	16 (84.2)	27 (73.0)	13 (72.2)	12 (60.0)	9 (100.0)	42 (77.8)	20 (71.4)	12 (70.6)	8 (72.7)	42 (73.7)	21 (80.8)
SD	10 (27.0)	3 (15.8)	9 (24.3)	5 (27.8)	8 (40.0)	0	11 (20.4)	8 (28.6)	5 (29.4)	3 (27.3)	14 (24.6)	5 (19.2)

Patients with unknown or missing data are not shown. 1L first line; BOR, best overall response; carbo, carboplatin; cis, cisplatin; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; gem, gemcitabine; PBC, platinum-based chemotherapy; PR, partial response; SD, stable disease; SG, sacituzumab govitecan.

Figure 2. Investigator-assessed PFS from randomization in subgroups with and without visceral metastases or lung/liver lesions



The sum of external patients in the overall arm was down-weighted to 37 to be equal to the number of randomized patients in the JAVELIN Bladder 100 trial; consequently, patient numbers in subgroups may include decimals. 1L first line; BOR, best overall response; carbo, carboplatin; cis, cisplatin; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; gem, gemcitabine; PBC, platinum-based chemotherapy; PR, partial response; SD, stable disease; SG, sacituzumab govitecan.

CONCLUSIONS

- The interim analysis of the JAVELIN Bladder Medley phase 2 trial showed that first-line (1L) maintenance with avelumab + sacituzumab govitecan (SG) improved progression-free survival (PFS) vs avelumab monotherapy in patients with advanced urothelial carcinoma (UC) without progression following 1L platinum-based chemotherapy (PBC)¹
 - Adverse events were consistent with the known safety profiles of each drug¹
- Here, we report interim subgroup analyses from JAVELIN Bladder Medley in patients with or without visceral metastases at start of 1L PBC or liver/lung lesions at randomization
 - Investigator-assessed PFS and objective response rate (ORR) results favored avelumab + SG vs avelumab monotherapy across all subgroups
 - Overall survival (OS) results were immature at data cutoff
 - Safety profiles were generally consistent with those observed in the overall population¹
- Overall, these results suggest that combining avelumab with anti-Trop-2 antibody-drug conjugates may be a promising strategy to improve patient outcomes in advanced UC, irrespective of the presence of visceral metastases

PLAIN LANGUAGE SUMMARY

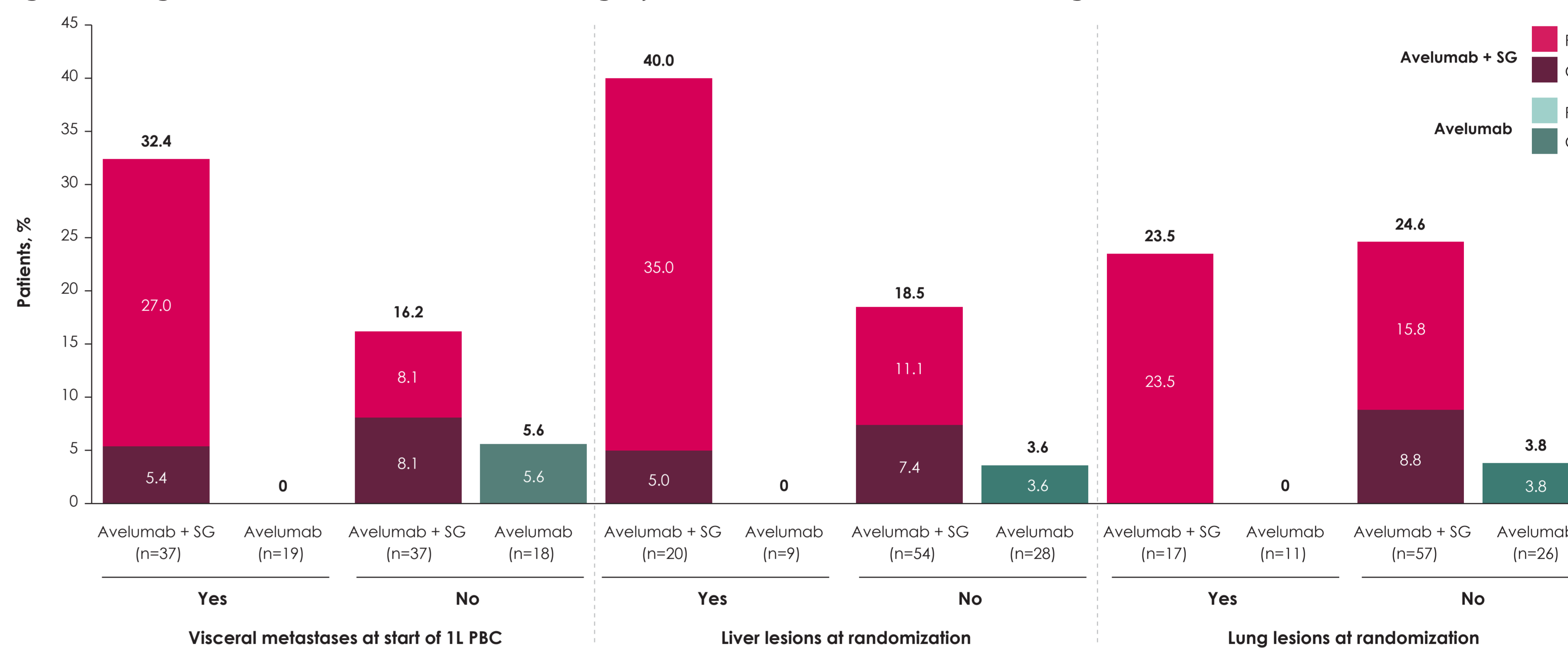
- Based on clinical study results, avelumab maintenance is a standard treatment for people with advanced urothelial cancer
 - Maintenance treatment means treating people whose cancer disappeared, shrank, or stopped growing after chemotherapy
- In a study called JAVELIN Bladder Medley, people with advanced urothelial cancer treated with avelumab together with another drug called sacituzumab govitecan as maintenance treatment lived longer without their cancer getting worse than people treated with avelumab alone
 - People treated with both drugs had more side effects than people treated with avelumab alone
- In this new analysis from JAVELIN Bladder Medley, researchers looked at results in people depending on whether the cancer had spread to their internal organs, including the liver or lungs, before starting study treatment
- Researchers found that on average, people treated with avelumab and sacituzumab govitecan lived longer without their cancer getting worse than people treated with avelumab alone, regardless of whether the cancer had spread to their internal organs
 - Findings about side effects were similar to the previous analysis that included all people in the study
- Overall, these results provide more evidence to suggest that avelumab together with sacituzumab govitecan or similar drugs might be a promising treatment for people with advanced urothelial cancer, but more studies are needed

Table 2. OS from randomization in subgroups with and without visceral metastases or lung/liver lesions

	Visceral metastases at start of 1L PBC		No visceral metastases at start of 1L PBC	
	Avelumab + SG (n=37)	Avelumab (n=38.1)	Avelumab + SG (n=37)	Avelumab (n=35.9)
Events, n (%)	10 (27.0)	19.1 (50.1)	6 (16.2)	12.1 (33.7)
OS, median (95% CI), months	NE (12.0-NE)	17.7 (10.7-21.4)	NE (15.5-NE)	31.7 (23.8-43.1)
Stratified HR (95% CI)	0.69 [0.31-1.52]		1.03 [0.36-2.96]	
Liver lesions at randomization				
Events, n (%)	9 (45.0)	10.9 (58.3)	7 (13.0)	20.3 (36.7)
OS, median (95% CI), months	14.1 (8.8-NE)	15.3 (6.5-19.2)	NE (NE-NE)	30.8 (20.9-34.4)
Stratified HR (95% CI)	0.85 [0.31-2.39]		0.61 [0.25-1.50]	
Lung lesions at randomization				
Events, n (%)	6 (35.3)	11 (55.0)	10 (17.5)	20.2 (37.4)
OS, median (95% CI), months	NE (5.8-NE)	13.4 (8.2-18.2)	NE (15.5-NE)	30.8 (20.9-35.2)
Stratified HR (95% CI)	0.83 [0.28-2.43]		0.77 [0.35-1.73]	

The sum of external patients in the overall arm was down-weighted to 37 to be equal to the number of randomized patients in the JAVELIN Bladder 100 trial; consequently, patient numbers in subgroups may include decimals. 1L first line; HR, hazard ratio; NE, not estimable; OS, overall survival; PBC, platinum-based chemotherapy; SG, sacituzumab govitecan.

Figure 3. Investigator-assessed ORR from randomization in subgroups with and without visceral metastases or lung/liver lesions



Change compared with baseline post 1L PBC. In patients with a CR to 1L PBC, the best overall response was noted as "not evaluable" if no evidence of disease was detected after randomization or "progressive disease" if disease progression occurred after randomization; these patients could not have had a best overall response of CR, PR, or SD after randomization. 1L first line; CR, complete response; ORR, objective response rate; PBC, platinum-based chemotherapy; PR, partial response; SD, stable disease; SG, sacituzumab govitecan.

Table 3. Summary of safety

Patients, n (%)	Visceral metastases at start of 1L PBC		No visceral metastases at start of 1L PBC		Liver lesions at randomization		No liver lesions at randomization		Lung lesions at randomization		No lung lesions at randomization	
	Avelumab + SG (n=36)	Avelumab (n=18)	Avelumab + SG (n=37)	Avelumab (n=18)	Avelumab + SG (n=20)	Avelumab (n=9)	Avelumab + SG (n=53)	Avelumab (n=27)	Avelumab + SG (n=17)	Avelumab (n=11)	Avelumab + SG (n=56)	Avelumab (n=25)
Any-grade AE	36 (100.0)	15 (83.3)	37 (100.0)	18 (100.0)	20 (100.0)	8 (88.9)	53 (100.0)	25 (92.6)	17 (100.0)	9 (81.8)	56 (100.0)	24 (96.0)
Grade ≥3	30 (83.3)	8 (44.4)	28 (75.7)	5 (27.8)	16 (80.0)	5 (55.6)	42 (79.2)	8 (29.6)	12 (70.6)	5 (45.5)	46 (82.0)	8 (32.0)
Any-grade TRAE	35 (97.2)	10 (55.6)	36 (97.3)	13 (72.2)	20 (100.0)	5 (55.6)	51 (96.2)	18 (66.7)	16 (94.1)	5 (45.5)	55 (98.2)	18 (72.0)
Grade ≥3	25 (69.4)	0	26 (70.3)	0	14 (70.0)	0	37 (69.8)	0	9 (52.9)	0	42 (75.0)	0
Avelumab related	4 (16.7)	0	10 (27.0)	0	7 (35.0)	0	9 (17.0)	0	2 (11.8)	0	14 (25.0)	0
SG related	25 (69.4)	0	24 (64.0)	0	14 (70.0)	0	35 (66.0)	0	9 (52.9)	0	40 (71.4)	0
TRAE leading to SG dose reduction	18 (50.0)	0	21 (56.8)	0	10 (50.0)	0	29 (54.7)	0	6 (35.3)	0	33 (58.9)	0
TRAE leading to drug discontinuation												
Avelumab	1 (2.8)	1 (5.6)	2 (5.4)	0	1 (5.0)	0	2 (3.8)	1 (3.7)	0	0	3 (5.4)	1 (4.0)
SG	2 (5.6)	0	7 (18.9)	0	3 (15.0)	0	6 (11.3)	0	1 (5.9)	0	8 (14.3)	0
Both avelumab and SG	2 (5.6)	0	1 (2.7)	0	1 (5.0)	0	2 (3.8)	0	1 (5.9)	0	2 (3.6)	0
Serious AE	16 (44.4)	5 (27.8)	11 (29.7)	3 (16.7)	11 (55.0)	2 (22.2)	16 (30.2)	6 (22.2)	7 (41.2)	2 (18.2)	20 (35.7)	6 (24.0)
Avelumab related	3 (8.3)	0	3 (8.1)	0	3 (15.0)	0	3 (5.7)	0	2 (11.8)	0	4 (7.1)	0
SG related	8 (22.2)	0	7 (18.9)	0	6 (30.0)	0	9 (17.0)	0	3 (17.6)	0	12 (21.4)	0
TRAE leading to death	1 (2.8)*	0	0	0	0	0	0	0	1 (5.9)*	0	0	0
Any-grade IRR	5 (13.9)	2 (11.1)	9 (24.3)	3 (16.7)	5 (25.0)	0	9 (17.0)	5 (18.5)	3 (17.6)	0	11 (19.6)	5 (20.0)
Any-grade IRR	6 (16.7)	2 (11.1)	1 (2.7)	2 (11.1)	2 (10.0)	1 (11.1)	5 (9.4)	3 (11.1)	4 (23.5)	2 (18.2)	3 (5.4)	2 (8.0)

1L first line; AE, adverse event; IAE, immune-related adverse event; IRR