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Avelumab vs chemotherapy for first-line treatment of advanced PD-L1+ NSCLC: primary analysis from JAVELIN Lung 100

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Disclosures

Commercial Interest	Relationship(s)
Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Daiichi Sankyo, GSK, Lilly, Merck, Mirati, MSD, Novartis, Pfizer, Roche, Sanofi	Advisory role
Amgen, AstraZeneca, BMS, Boehringer Ingelheim, GSK, Lilly, Merck, Mirati, MSD, Novartis, Pfizer, Roche, Sanofi	Speaker's bureau

- This trial was sponsored by Merck (CrossRef Funder ID: 10.13039/100009945) as part of an alliance between Merck and Pfizer
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Background

- Avelumab is an anti–PD-L1 antibody that is approved worldwide as monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma (1L maintenance) and metastatic Merkel cell carcinoma, as well as in combination with axitinib for advanced renal cell carcinoma[1,2]
- In the phase 1 JAVELIN Solid Tumor trial, avelumab showed antitumor activity and an acceptable safety profile in patients with NSCLC[3-5]
- While post hoc analyses in the phase 3 JAVELIN Lung 200 trial showed longer OS and PFS and higher ORRs in subgroups with higher levels of PD-L1 expression, avelumab did not statistically significantly prolong OS vs docetaxel in patients with platinum-treated PD-L1+ NSCLC[6,7]
- Here we report results from the primary analysis of the phase 3 JAVELIN Lung 100 trial, which compared avelumab (administered in 2 different dosing schedules) vs platinum-based doublet chemotherapy as 1L treatment for patients with PD-L1+ advanced NSCLC

1. Bavencio (avelumab). Prescribing information. EMD Serono, Inc., Rockland, MA, USA, an affiliate of Merck; 2020. **2.** Bavencio (avelumab). Summary of product characteristics. Merck Europe B.V., Amsterdam, Netherlands, an affiliate of Merck KGaA; 2022. **3.** Heery CR, et al. Lancet Oncol. 2017;18(5):587-98. **4.** Gulley JL, et al. Lancet Oncol. 2017;18(5):599-610. **5.** Verschraegen CF, et al. J Immunother Cancer. 2020;8(2):e001064. **6.** Barlesi F, et al. Lancet Oncol. 2018;19(11):1468-79. **7.** Park K, et al. J Thorac Oncol. 2021;16(8):1369-78.

1L, first-line; **NSCLC**, non-small cell lung cancer; **ORR**, objective response rate; **OS**, overall survival; **PFS**, progression-free survival.

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JAVELIN Lung 100: a multicenter, randomized, phase 3 trial

Before protocol amendment
Randomization 1:1
Stratified by histology

Post protocol amendment
Randomization 1:2:2
Stratified by histology and PD-L1 expression

Key eligibility criteria

- Metastatic or recurrent NSCLC (Stage IV)*
- No *EGFR* mutation or *ALK* rearrangement
- PD-L1 expression in ≥1% of tumor cells
- Measurable disease according to RECIST 1.1
- ECOG PS 0 or 1

Randomized patients: N=1214

Safety run-in: N=10

R1

Avelumab Q2W
10 mg/kg IV
n=205

Platinum-based doublet chemotherapy
Q3W
n=205

Avelumab QW
10 mg/kg IV
Safety run-in
N=10

R2

Avelumab Q2W
10 mg/kg IV
n=161

Platinum-based doublet chemotherapy
Q3W
n=321

Avelumab QW
first 12 weeks, then Q2W
10 mg/kg IV
n=322

Primary endpoints

- PFS† and OS‡ in patients with high-expression PD-L1+ tumors§

Key secondary endpoints

- PFS and OS in patients with moderate-to-high-expression PD L1+ tumors¶
- OS in patients with PD L1+ ≥1% tumors
- Best overall response†
- Duration of response†
- Safety

*Patients with pretreated and stable brain metastases were eligible for enrollment. †Per independent review committee. ‡OS was changed to a primary endpoint in the protocol amendment that added the avelumab QW arm. §PD-L1 expression on ≥80% of tumor cells determined by Dako PD-L1 IHC 73-10 pharmDx assay, which is comparable to the TPS ≥50% cutoff for the PD-L1 IHC 22C3 pharmDx (pembrolizumab) assay. ¶PD-L1 expression on ≥50% of tumor cells determined by Dako PD-L1 IHC 73-10 pharmDx assay.

Grote HJ, et al. J Thorac Oncol. 2020;15(8):1306-1316.

ECOG PS, Eastern Cooperative Oncology Group performance status; **IHC**, immunohistochemistry; **IV**, intravenous; **NSCLC**, non-small cell lung cancer; **OS**, overall survival; **PFS**, progression-free survival; **QW**, once weekly; **Q2W**, every 2 weeks; **Q3W**, every 3 weeks; **R1**, randomization before protocol amendment; **R2**, randomization after protocol amendment; **TPS**, tumor proportion score.

Rationale for protocol amendment and key design elements

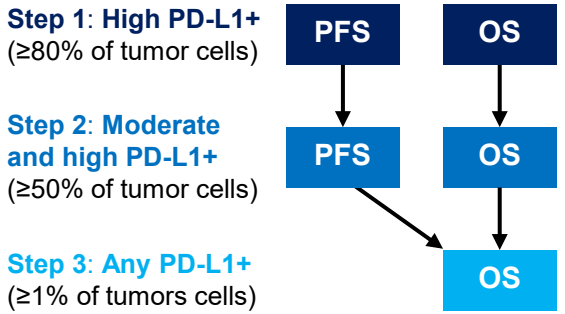
Avelumab QW arm

- Preliminary exposure-efficacy analyses from the phase 1 JAVELIN Solid Tumor trial suggested an association between greater exposure to avelumab and increased ORR in patients with NSCLC[1]
- More frequent dosing with 10 mg/kg QW dosing will result in increased exposure vs 10 mg/kg Q2W dosing[1]
- Avelumab QW was administered for the first 12 weeks, followed by Q2W from Week 13 onwards

Statistical methods

- Primary analysis population was defined as patients with high-expression PD-L1+ (≥80% of tumor cells)*
- The target HR for PFS and OS in the primary analysis populations was 0.6
- Statistical comparisons used a 1-sided stratified log-rank test
- The overall α was 0.025, split across PFS and OS endpoints (2:1) and the 2 treatment group comparisons vs control (3:1)

Hierarchical testing procedure
(Avelumab Q2W or QW vs chemotherapy)†



Steps 2 and 3 were tested only if the null hypothesis in step 1 was rejected

*PD-L1 level was determined using the Dako PD-L1 IHC 73-10 pharmDx assay; ≥80% of tumor cells is comparable to a TPS ≥50% in the PD-L1 IHC 22C3 pharmDx (pembrolizumab) assay.[2]
†Avelumab Q2W vs chemotherapy: patients randomized at any time; avelumab QW vs chemotherapy: patients randomized post protocol amendment.
1. Gulley JL, et al. J Clin Oncol. 2017;35(15_suppl):Abstract 9086. **2.** Grote HJ, et al. J Thorac Oncol. 2020;15(8):1306-1316.

HR, hazard ratio; **IHC**, immunohistochemistry; **NSCLC**, non-small cell lung cancer; **ORR**, objective response rate; **OS**, overall survival; **PFS**, progression-free survival; **PK**, pharmacokinetics; **QW**, once weekly; **Q2W**, every 2 weeks; **TPS**, tumor proportion score.

Baseline characteristics in the high PD-L1+ populations*

	Avelumab Q2W (n=151)	Chemotherapy (n=216)	Avelumab QW (n=130)	Chemotherapy (n=129)
Male, n (%)	112 (74.2)	158 (73.1)	100 (76.9)	93 (72.1)
Median age, years (range)	64.0 (35-82)	63.0 (29-85)	64.0 (25-80)	64.0 (36-81)
ECOG PS, n (%)†				
0	47 (31.1)	70 (32.4)	44 (33.8)	45 (34.9)
≥1	104 (68.9)	145 (67.1)	86 (66.2)	83 (64.3)
Race, n (%)				
Asian	38 (25.2)	48 (22.2)	28 (21.5)	29 (22.5)
Black or African American	0	1 (0.5)	1 (0.8)	0
White	98 (64.9)	154 (71.3)	96 (73.8)	92 (71.3)
Other	6 (4.0)	6 (2.8)	4 (3.1)	4 (3.1)
Stage at study entry, n (%)‡				
IV	150 (99.3)	215 (99.5)	130 (100.0)	129 (100.0)
History of smoking, n (%)	134 (88.7)	186 (86.1)	112 (86.2)	109 (84.5)
Non-squamous tumor histology, n (%)	104 (68.9)	150 (69.4)	84 (64.6)	86 (66.7)
Metastatic sites, n (%)				
Brain§	10 (6.6)	21 (9.7)	9 (6.9)	12 (9.3)
Visceral	59 (39.1)	70 (32.4)	55 (42.3)	44 (34.1)
Bone	28 (18.5)	49 (22.7)	40 (30.8)	30 (23.3)
Pleural effusion	41 (27.2)	61 (28.2)	34 (26.2)	41 (31.8)

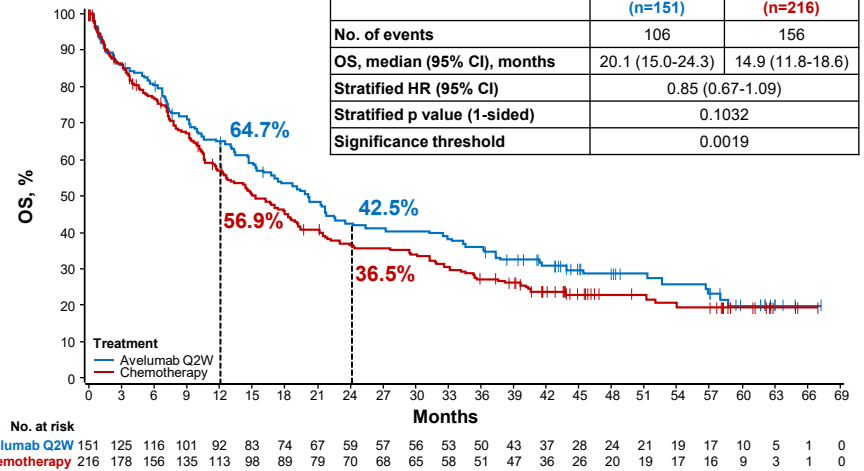
Patients with missing data are not shown.
*High-expression PD-L1+ (≥80% of tumor cells) determined by Dako PD-L1 IHC 73-10 pharmDx assay (avelumab QW vs chemotherapy: in patients randomized post protocol amendment).
†Patients had ECOG PS 0 or 1, except for one 1 patient in the avelumab QW arm with ECOG PS 2 (PS of this patient worsened from 1 at screening to 2 at the Week 1 Day 1 visit). ‡One patient in the chemotherapy arm had stage IIIB disease. §Patients with pretreated and stable brain metastases were eligible for enrollment.

ECOG PS, Eastern Cooperative Oncology Group performance status; **IHC**, immunohistochemistry; **QW**, once weekly; **Q2W**, every 2 weeks.

Primary endpoint: OS in the high PD-L1+ populations*

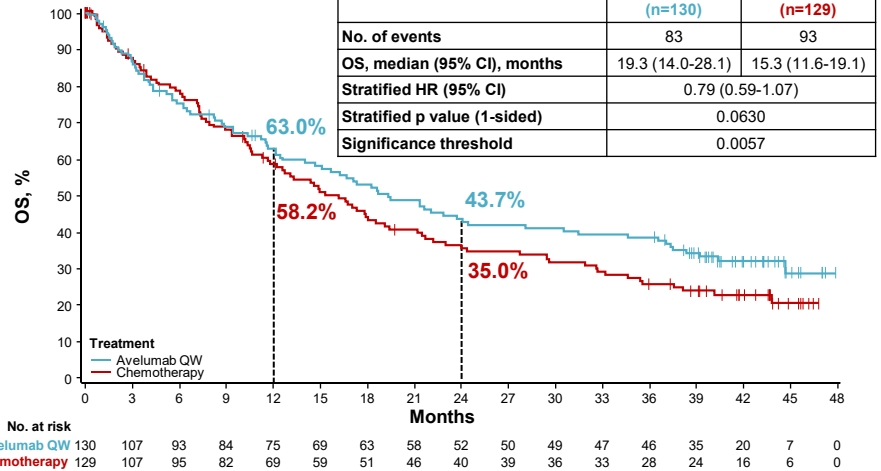
Avelumab Q2W vs chemotherapy

	Avelumab Q2W (n=151)	Chemotherapy (n=216)
No. of events	106	156
OS, median (95% CI), months	20.1 (15.0-24.3)	14.9 (11.8-18.6)
Stratified HR (95% CI)	0.85 (0.67-1.09)	
Stratified p value (1-sided)	0.1032	
Significance threshold	0.0019	



Avelumab QW vs chemotherapy

	Avelumab QW (n=130)	Chemotherapy (n=129)
No. of events	83	93
OS, median (95% CI), months	19.3 (14.0-28.1)	15.3 (11.6-19.1)
Stratified HR (95% CI)	0.79 (0.59-1.07)	
Stratified p value (1-sided)	0.0630	
Significance threshold	0.0057	



OS analyses favored avelumab vs chemotherapy but differences were not statistically significant

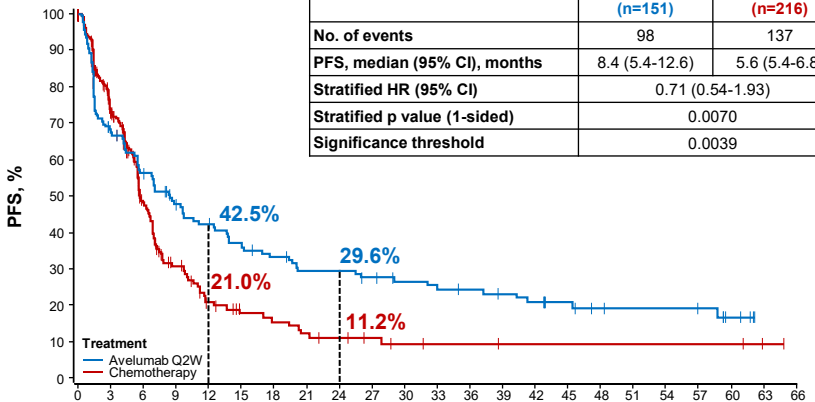
Median follow up in primary analysis populations across all arms was 41.7-48.8 months (data cutoff: October 15, 2021)
*High-expression PD-L1+ (≥80% of tumor cells) determined by Dako PD-L1 IHC 73-10 pharmDx assay (avelumab QW vs chemotherapy: in patients randomized post protocol amendment).

HR, hazard ratio; **IHC**, immunohistochemistry; **OS**, overall survival; **QW**, once weekly; **Q2W**, every 2 weeks.

Primary endpoint: PFS by IRC in the high PD-L1+ populations*

Avelumab Q2W vs chemotherapy

	Avelumab Q2W (n=151)	Chemotherapy (n=216)
No. of events	98	137
PFS, median (95% CI), months	8.4 (5.4-12.6)	5.6 (5.4-6.8)
Stratified HR (95% CI)	0.71 (0.54-1.93)	
Stratified p value (1-sided)	0.0070	
Significance threshold	0.0039	

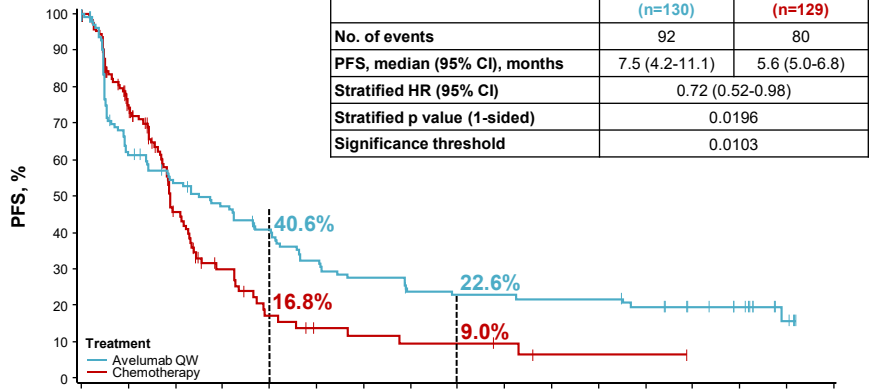


No. at risk

Avelumab Q2W	151	88	69	55	48	41	36	31	31	28	25	23	22	20	18	13	10	9	9	8	4	0	0
Chemotherapy	216	128	69	39	23	16	14	11	9	7	5	4	4	3	3	3	3	3	3	3	1	0

Avelumab QW vs chemotherapy

	Avelumab QW (n=130)	Chemotherapy (n=129)
No. of events	92	80
PFS, median (95% CI), months	7.5 (4.2-11.1)	5.6 (5.0-6.8)
Stratified HR (95% CI)	0.72 (0.52-0.98)	
Stratified p value (1-sided)	0.0196	
Significance threshold	0.0103	



No. at risk

Avelumab QW	130	72	60	52	43	34	29	24	23	23	22	22	19	15	12	4	0
Chemotherapy	129	74	36	19	10	6	5	4	4	3	1	1	1	0	0	0	0

PFS analyses also favored avelumab vs chemotherapy but differences were not statistically significant

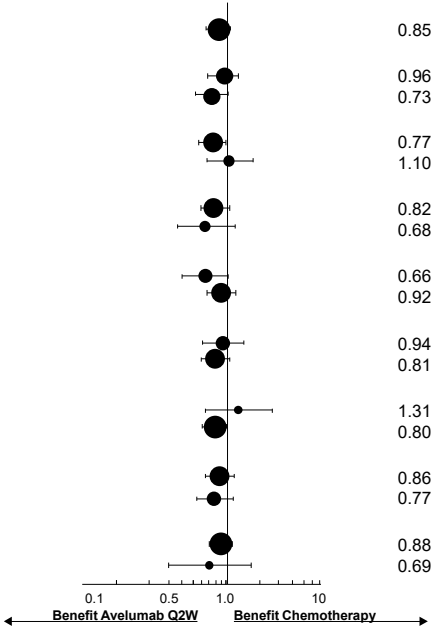
*High-expression PD-L1+ (≥80% of tumor cells) determined by Dako PD-L1 IHC 73-10 pharmDx assay (avelumab QW vs chemotherapy: in patients randomized post protocol amendment).

HR, hazard ratio; **IHC**, immunohistochemistry; **IRC**, independent review committee; **PFS**, progression-free survival; **QW**, once weekly; **Q2W**, every 2 weeks.

OS by subgroup in the high PD-L1+ populations*

Avelumab Q2W vs chemotherapy

Prognostic Factor	Subgroup (Number of patients chemotherapy vs avelumab Q2W)	HR (95% CI)
Overall	High PD-L1+ (n=216 vs 151)	0.85 (0.66 - 1.09)
Age group	Age < 65 years (n=118 vs 80)	0.96 (0.68 - 1.34)
	Age ≥ 65 years (n=98 vs 71)	0.73 (0.51 - 1.06)
Gender	Male (n=158 vs 112)	0.77 (0.58 - 1.03)
	Female (n=58 vs 39)	1.10 (0.69 - 1.75)
Race	White (n=154 vs 98)	0.82 (0.61 - 1.10)
	Asian (n=48 vs 38)	0.68 (0.38 - 1.22)
ECOG PS at baseline	0 (n=70 vs 47)	0.66 (0.41 - 1.06)
	≥1 (n=145 vs 104)	0.92 (0.68 - 1.23)
NSCLC histology	Squamous cell (n=66 vs 47)	0.94 (0.61 - 1.45)
	Non-squamous (n=150 vs 104)	0.81 (0.60 - 1.10)
Smoking status	Never smoker (n=30 vs 17)	1.31 (0.65 - 2.62)
	Ever smoker (n=186 vs 134)	0.80 (0.61 - 1.04)
Visceral metastasis at baseline	Absent (n=144 vs 91)	0.86 (0.62 - 1.19)
	Present (n=70 vs 59)	0.77 (0.52 - 1.14)
Brain metastasis at baseline	Absent (n=193 vs 140)	0.88 (0.68 - 1.14)
	Present (n=21 vs 10)	0.69 (0.27 - 1.74)



- OS analyses in subgroups favored avelumab Q2W vs chemotherapy
- Results were similar in the OS by subgroup analyses for avelumab QW vs chemotherapy

*High-expression PD-L1+ (≥80% of tumor cells) determined by Dako PD-L1 IHC 73-10 pharmDx assay (avelumab QW vs chemotherapy: in patients randomized post protocol amendment).
OS, overall survival; **QW**, every week; **Q2W**, every 2 weeks.

Tumor responses in the high PD-L1+ populations*

	Avelumab Q2W (n=151)	Chemotherapy (n=216)	Avelumab QW (n=130)	Chemotherapy (n=129)
ORR by IRC (95% CI), %	**37.7 (30.0-46.0)**	**30.1 (24.1-36.7)**	**34.6 (26.5-43.5)**	**30.2 (22.5-38.9)**
Confirmed best overall response, n (%)				
CR	5 (3.3)	1 (0.5)	4 (3.1)	1 (0.8)
PR	52 (34.4)	64 (29.6)	41 (31.5)	38 (29.5)
SD	36 (23.8)	89 (41.2)	30 (23.1)	54 (41.9)
PD	27 (17.9)	19 (8.8)	29 (22.3)	11 (8.5)
NE†	31 (20.5)	43 (19.9)	26 (20.0)	25 (19.4)
Median duration of response (95% CI), months	**35.9 (14.6-NR)**	**8.4 (5.0-15.1)**	**19.4 (10.8-NR)**	**8.4 (4.4-11.1)**

- ORR and median duration of response favored avelumab vs chemotherapy

*High-expression PD-L1+ (≥80% of tumor cells) determined by Dako PD-L1 IHC 73-10 pharmDx assay (avelumab QW vs chemotherapy: in patients randomized post protocol amendment).
†Includes patients with non-CR/non-PD, patients whose tumors were not measurable per IRC and who did not have CR or PD.

CR, complete response; **IHC**, immunohistochemistry; **IRC**, independent review committee; **NE**, not evaluable; **NR**, not reached; **ORR**, objective response rate; **PD**, progressive disease; **PR**, partial response; **QW**, once weekly; **Q2W**, every 2 weeks, **SD**, stable disease.

Subsequent anticancer drug therapies in the high PD-L1+ populations*

	Avelumab Q2W (n=151)	Chemotherapy (n=216)	Avelumab QW (n=130)	Chemotherapy (n=129)
Subsequent anticancer treatment, n (%)	**62 (41.1)**	**113 (52.3)**	**49 (37.7)**	**75 (58.1)**
Subsequent ICI, n (%)†	**8 (5.3)**	**66 (30.6)**	**2 (1.5)**	**45 (34.9)**
Nivolumab	2 (1.3)	32 (14.8)	0	19 (14.7)
Pembrolizumab	4 (2.6)	22 (10.2)	1 (0.8)	18 (14.0)
Atezolizumab	2 (1.3)	11 (5.1)	1 (0.8)	7 (5.4)
Durvalumab	0	2 (0.9)	0	1 (0.8)
Avelumab	0	1 (0.5)	0	1 (0.8)

*High-expression PD-L1+ (≥80% of tumor cells) determined by Dako PD-L1 IHC 73-10 pharmDx assay (avelumab QW vs chemotherapy: in patients randomized post protocol amendment).
†Patients who received >1 subsequent ICI are counted only once.

ICI, immune checkpoint inhibitor; **QW**, once weekly; **Q2W**, every 2 weeks.

Overview of safety in all treated patients*

	Avelumab Q2W (n=361)	Avelumab QW (n=318)	Chemotherapy (n=500)
AE, n (%)			
Any grade	346 (95.8)	308 (96.9)	484 (96.8)
Grade ≥3	217 (60.1)	181 (56.9)	324 (64.8)
Treatment-related AE, n (%)			
Any grade	243 (67.3)	224 (70.4)	430 (86.0)
Grade ≥3	60 (16.6)	44 (13.8)	230 (46.0)
Serious AE, n (%)	181 (50.1)	143 (45.0)	195 (39.0)
Serious treatment-related AE, n (%)	50 (13.9)	31 (9.7)	88 (17.6)
Immune-related AE, n (%)†	70 (19.4)	51 (16.0)	–
Grade ≥3	19 (5.3)	6 (1.9)	–
Infusion-related reaction, n (%)	104 (28.8)	81 (25.5)	6 (1.2)
AE leading to treatment discontinuation, n (%)	100 (27.7)	58 (18.2)	122 (24.4)
Treatment-related AE leading to treatment discontinuation, n (%)	44 (12.2)	27 (8.5)	76 (15.2)
AE leading to death, n (%)	63 (17.5)	51 (16.0)	63 (12.6)
Treatment-related AE leading to death, n (%)‡	3 (0.8)	1 (0.3)	6 (1.2)

*Patients who received ≥1 dose of study treatment. †Immune-related AEs assessed only for the avelumab treatment arms. ‡Avelumab Q2W, cytokine release syndrome, pneumonia, and pneumonitis (all n=1); avelumab QW, dyspnea; chemotherapy, febrile neutropenia (n=2), gastric hemorrhage/ulcer, hepatic cytolysis, pneumonia, and renal failure.

AE, adverse event; **QW**, once weekly; **Q2W**, every 2 weeks.

Conclusions

- Longer OS and PFS was observed with avelumab compared with platinum-based doublet chemotherapy although this did not achieve statistical significance
- Factors that may have contributed to these results were:
  - Significant changes to the study design, including changes to the primary analysis population, primary endpoints, and addition of the QW arm, that lead to multiple hypothesis testing and splitting of the α across endpoints
  - Evolution of the 2L treatment for advanced NSCLC during this study, and many patients in the chemotherapy arm received subsequent immune checkpoint inhibitor therapy
- Safety profile of avelumab was consistent with previous studies of avelumab monotherapy and no new safety signals were observed
- Efficacy and safety results were similar in the avelumab Q2W and QW arms

1L, first line; **ICI**, immune checkpoint inhibitor; **NSCLC**, non-small cell lung cancer; **OS**, overall survival; **PFS**, progression-free survival; **QW**, once weekly; **Q2W**, every 2 weeks.

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