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ABSTRACT

Objectives: The JAVELIN Lung 200 phase 3 trial did not meet its primary endpoint of improving overall survival (OS) with avelumab vs docetaxel in patients with platinum-treated PD-L1+ NSCLC. We report post hoc analyses assessing the effects of subsequent immune checkpoint inhibitor (ICI) treatment on OS.

Material and methods: Patients with stage IIIB/IV NSCLC progressed following platinum-doublet therapy were randomized to receive avelumab or docetaxel. OS was analyzed in the PD-L1+ population (≥1% of tumor cells) and full analysis set (PD-L1+ or PD-L1−). Effects of subsequent ICI (after permanent discontinuation of study treatment) on OS were analyzed using a preplanned naive sensitivity analysis and post hoc inverse probability of censoring weighting (IPCW) analysis. Subgroups with or without subsequent ICI treatment were analyzed using descriptive statistics.

Results: In the avelumab and docetaxel arms, a subsequent ICI was received by 16/396 (4.0 %) and 104/396 (26.3 %) after a median of 10.5 months (range, 3.9–20.4) and 5.7 months (range, 0.1–24.4), respectively. Some subgroups showed trends for higher subsequent ICI treatment, including patients with non-squamous NSCLC (avelumab arm, 4.3 % vs docetaxel arm, 32.1 %) or with a baseline ECOG performance status of 0 (6.3 % vs 31.3 %); those enrolled in the early recruitment wave (11.6 % vs 54.3 %), or enrolled in the US/Western Europe (2.8 % vs 45.5 %) or Asia (11.0 % vs 35.4 %); and non-white patients (10.1 % vs 35.0 %). The hazard ratio for OS with avelumab vs docetaxel was lower in the IPCW analysis than in the naive sensitivity analysis (PD-L1+ population: 0.80 [95 % CI, 0.62−1.04] vs 0.86 [95 % CI, 0.68−1.09], respectively).

Conclusion: In the JAVELIN Lung 200 trial, avelumab showed clinical activity as second-line treatment for patients with advanced NSCLC. Post hoc analyses suggest that the primary OS analysis may have been confounded by subsequent ICI use in the docetaxel arm. ClinicalTrials.gov identifier: NCT02395172.

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HR, hazard ratio; ICI, immune checkpoint inhibitor; Ig, immunoglobulin; IHC, immunohistochemistry; IPCW, inverse probability of censoring weighting; IRC, independent review committee; KEAP1, kelch-like ECH associated protein 1; NR, not reached; NSCLC, non-small cell lung cancer; OS, overall survival; PD-1, programmed cell death 1 protein; PD-L1, programmed cell death 1 ligand 1; PFS, progression-free survival; STK11, serine/threonine kinase 11.

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1. Introduction

Avelumab is a human anti–programmed cell death 1 ligand 1 (PD-L1) IgG1 antibody that has shown durable antitumor activity and an acceptable safety profile in patients with a range of tumor types [1–7]. Avelumab has been approved as monotherapy for the treatment of Merkel cell carcinoma and for urothelial carcinoma that has not progressed (first-line maintenance therapy) or progressed (second-line therapy) with platinum-containing chemotherapy, as well as in combination with axitinib as first-line treatment for renal cell carcinoma [8,9]. In addition to stimulating adaptive immunity by blocking the interaction between PD-L1 and PD-L1, avelumab also has a wild-type Fc region, which has been shown in preclinical models to induce antitumor activity via innate effector cells [10,11].

In the phase 3 JAVELIN Lung 200 trial, overall survival (OS; primary endpoint) was not improved with avelumab vs docetaxel in patients with platinum-treated advanced PD-L1+ non-small cell lung cancer (NSCLC; defined as PD-L1 expression on ≥1% of tumor cells) [12]. The JAVELIN Lung 200 trial enrolled patients between March 2015 and January 2017; during this period, several immune checkpoint inhibitors (ICIs; nivolumab, pembrolizumab, and atezolizumab) gained regulatory approval for second-line or later treatment of NSCLC following positive results from randomized phase 2 and 3 trials [13–20]. Consequently, more ICI options for subsequent therapy were available for patients who were enrolled in the docetaxel arm of JAVELIN Lung 200 compared with earlier trials, resulting in greater subsequent ICI use (Table 1) [12–20]. OS as a study endpoint in oncology trials may be affected by agents with a known survival benefit administered after study treatment has been discontinued, as exemplified by studies of targeted therapies in NSCLC [21–23]. Given the larger proportion of JAVELIN Lung 200 patients who received subsequent ICI in the docetaxel arm compared with the avelumab arm, it is possible that OS analyses were affected by subsequent ICI treatment.

Here, we report post hoc analyses evaluating the potential effect of subsequent ICI treatment on the primary endpoint of OS in the JAVELIN Lung 200 trial.

2. Materials and methods

2.1. Study design and treatment

JAVELIN Lung 200 (NCT02395172) was an open-label, multicenter, randomized, phase 3 trial. The study design, methodology, and primary analyses have been previously reported in detail [12]. Briefly, the trial enrolled adult patients with histologically confirmed stage IIIB, IV, or recurrent NSCLC with disease progression after prior platinum-doublet chemotherapy. Patients were excluded from the trial if they had non-squamous cell NSCLC harboring an *EGFR* or *ALK* mutation or prior treatment with an antibody or drug targeting a T-cell coregulatory protein (eg, ICI). The primary analysis population was patients with PD-L1 expression in ≥1% of tumor cells (PD-L1+ population), whereas the secondary analysis population (full analysis set) included patients with PD-L1+ and PD-L1− tumors. Patients were randomly assigned (1:1) to either avelumab 10 mg/kg intravenously every 2 weeks or docetaxel 75 mg/m^2 intravenously every 3 weeks. Allocation was stratified by PD-L1 expression (≥1% vs <1% of tumor cells) and NSCLC histology (squamous vs nonsquamous). Treatment was continued in both groups until unacceptable toxicity, progressive disease, clinical deterioration, or any other protocol-specified withdrawal criteria occurred. Crossover from docetaxel to avelumab was not permitted per protocol. The trial was conducted in accordance with the ethics principles of the Declaration of Helsinki and the International Council on Harmonization Guidelines on Good Clinical Practice. The protocol was approved by the institutional review board or independent ethics committee of each center, and all patients provided written informed consent before enrollment.

2.2. Assessments and outcomes

The primary study endpoint was OS, defined as time from randomization to death (irrespective of cause). Secondary endpoints included progression-free survival (PFS; defined as time from randomization until the first documentation of objective progressive disease or death from any cause, whichever occurred first) according to Response Evaluation Criteria in Solid Tumors version 1.1 [24] and adjudicated by an independent review committee (IRC). PD-L1 expression in tumor tissue was assessed centrally at baseline using the PD-L1 IHC 73−10 assay (Agilent Technologies/Dako, Carpinteria, CA). Various prespecified analyses have been reported previously [12].

2.3. Statistical analyses

To estimate the treatment difference between avelumab and docetaxel adjusted for patients who received subsequent ICI, statistical analyses were conducted in both the full analysis set and PD-L1+ population. Preplanned analyses included the primary confirmatory analysis, which measured the treatment effect of avelumab on OS compared with docetaxel in the PD-L1+ population (reported previously [12]). A limitation of this analysis with respect to assessing OS is that all patients were analyzed, including those who potentially benefited from subsequent ICI; therefore, the analysis may have been confounded in favor of the chemotherapy arm.

Based on previously published recommendations [25], various post hoc descriptive analyses were performed, including (a) the proportion of patients that had received ≥1 dose of subsequent ICI per arm; (b) timing of subsequent treatment relative to randomization, disease progression, decision to discontinue treatment, and time from subsequent ICI to death; (c) Kaplan-Meier analysis of PFS in patients who did or did not receive subsequent ICI, where PFS was assessed as a surrogate for OS that was not affected by subsequent treatment; and (d) covariates that influenced switch (ie, baseline characteristics split by subsequent ICI status in pooled patients and separated by treatment arm).

To explore the robustness of the primary analysis with regards to subsequent ICI treatment, a preplanned naive sensitivity analysis was performed in which patients were censored at the start of subsequent ICI therapy. This analysis assessed all data and included patients censored at

Table 1
Proportions of patients receiving a subsequent ICI in previous randomized studies of ICIs vs docetaxel.

Study drug	Study	Accrual period	Patients receiving subsequent ICI, %		Date of US approval
			Docetaxel arm	ICI arm	
Nivolumab [13]	CheckMate 017 (squamous)	Oct 2012-Dec 2013	2 (8 % in 3-year update)	– (5 % in 3-year update)	March 2015 [18]
Nivolumab [14]	CheckMate 057 (nonsquamous)	Nov 2012-Dec 2013	2 (11 % in 3-year update)	- (3 % in 3-year update)	October 2015 [18]
Atezolizumab [15]	POPLAR	Aug 2013-Mar 2014	5	0	October 2016 [20]
Pembrolizumab [16]	KEYNOTE-010	Aug 2013-Feb 2015	13	1	October 2015 [19]
Atezolizumab [17]	OAK	Mar 2014-Nov 2014	17	4	October 2016 [20]
Avelumab [12]	JAVELIN Lung 200	Mar 2015-Jan 2017	26	4 (full analysis set) 6 (PD-L1+)	–

Abbreviations: ICI, immune checkpoint inhibitor; PD-L1, programmed cell death 1 ligand 1.

the time of switch to subsequent ICI using standard survival analysis techniques; however, the naive sensitivity analysis assumed that the switch was not influenced by any patient characteristics or covariates that influence OS, creating the potential for bias due to informative censoring [25]. To address this potential bias, a post hoc inverse probability of censoring weighting (IPCW) analysis was performed [26,27]. IPCW analysis is an established method that was used, for example, to adjust for treatment crossover in the phase 3 BIG 1-98 study of adjuvant letrozole vs tamoxifen in patients with breast cancer [26]; this method has also been used in other ICI studies to adjust for potential bias introduced by subsequent treatments [27]. The IPCW method uses patient data to create an artificial hypothetical analysis set, within which subsequent ICI therapy was not possible. To adjust for censored patients, remaining patients who are not censored but have similar characteristics are reweighted according to inverse probability of treatment switching. To implement the IPCW analysis, a data-driven, stepwise variable selection procedure (based on the Akaike information criterion) was performed on the full analysis set to identify the most relevant covariates from a list of variables, including baseline demographics, disease-related characteristics, time-varying indicators of disease progression, response, and occurrence of adverse events. Models of time to treatment switch were fitted independently by treatment arm. Based on this model, IPCW weights were calculated for observations before subsequent ICI. Estimated weights that are extreme in value or in aggregate and that do not have mean values close to 1 indicate misspecification of the model; weights for the model are shown in Supplementary Fig. 1. IPCW weight values were used in a weighted Cox proportional hazards model. Treatment effects were estimated with a weighted Cox proportional hazards model to calculate hazard ratios (HRs) and 95 % confidence intervals (CIs).

3. Results

3.1. Subsequent ICI use in JAVELIN Lung 200

Of 792 patients randomized to avelumab or docetaxel in the full analysis set, 120 received ≥1 subsequent ICI (anti–PD-1 [nivolumab, pembrolizumab, tislelizumab, or cemiplimab; n = 117], anti–PD-L1 [durvalumab, avelumab, or bintrafusp alfa; n = 5], or anti–CTLA-4 [tremelimumab; n = 3]), including 16 (4.0 %) in the avelumab arm and 104 (26.3 %) in the docetaxel arm. In the PD-L1+ population (n = 529; primary analysis population), subsequent ICI treatment was received by 15 of 264 (5.7 %) in the avelumab arm and 70 of 265 (26.4 %) in the docetaxel arm [12].

In all subgroups defined by PD-L1 expression, the proportion of patients receiving subsequent ICI in the docetaxel arm was consistently greater compared with the avelumab arm. Some subgroups had a higher proportion of subsequent ICI use (Table 2), specifically patients with nonsquamous tumors or Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 at baseline; patients enrolled in the early recruitment wave (wave 1) or in the United States, Western Europe, and Asia; and non-white patients. Because few patients had activating *EGFR* mutations or *ALK* translocations (24 [3.0 %] and 2 [0.3 %], respectively), associated subgroups were not analyzed. Patients who received a subsequent ICI also had a smaller median tumor size at baseline compared with those who did not; median values were 50.5 mm (range, 0.0–164.0 mm) vs 65.0 mm (range, 0–347.0 mm) in the avelumab arm and 50.0 mm (range, 0–217.0 mm) vs 77.0 mm (range, 0–338.0 mm) in the docetaxel arm. In the full analysis set, median time to subsequent ICI was shorter in the docetaxel arm than in the avelumab arm (5.7 months [range, 0.1–24.4 months] vs 10.5 months [range, 3.9–20.4 months], respectively). Median time to subsequent ICI after disease progression (by IRC) was also shorter in the docetaxel arm than in the avelumab arm

Table 2
Subgroup analysis of subsequent ICI use in the full analysis set.

	Avelumab (n = 396)			Docetaxel (n = 396)		
	Total, N	Subsequent ICI, n (%)	No subsequent ICI, n (%)	Total	Subsequent ICI, n (%)	No subsequent ICI, n (%)
Sex						
Male	269	12 (4.5)	257 (95.5)	273	66 (24.2)	207 (75.8)
Female	127	4 (3.1)	123 (96.9)	123	38 (30.9)	85 (69.1)
Histology						
Squamous	119	4 (3.4)	115 (96.6)	119	15 (12.6)	104 (87.4)
Nonsquamous	277	12 (4.3)	265 (95.7)	277	89 (32.1)	188 (67.9)
ECOG PS						
0	144	9 (6.3)	135 (93.8)	134	42 (31.3)	92 (68.7)
1	252	7 (2.8)	245 (97.2)	262	62 (23.7)	200 (76.3)
Recruitment wave[a]						
Early	121	14 (11.6)	107 (88.4)	129	70 (54.3)	59 (45.7)
Late	275	2 (0.7)	273 (99.3)	267	34 (12.7)	233 (87.3)
Race						
White	273	4 (1.5)	269 (98.5)	262	52 (19.8)	210 (80.2)
Nonwhite	109	11 (10.1)	98 (89.9)	120	42 (35.0)	78 (65.0)
Not reported	14	1 (7.1)	13 (92.9)	14	10 (71.4)	4 (28.6)
Smoking status						
Ever smoker	324	13 (4.0)	311 (96.0)	333	85 (25.5)	248 (74.5)
Never smoker	70	3 (4.3)	67 (95.7)	63	19 (30.2)	44 (69.8)
Not reported	2	0	2 (100)		0	0
Region						
Asia	100	11 (11.0)	89 (89.0)	113	40 (35.4)	73 (64.6)
Eastern Europe	79	0	79 (100.0)	75	6 (8.0)	69 (92.0)
USA or Western Europe	106	3 (2.8)	103 (97.2)	110	50 (45.5)	60 (54.5)
Rest of the world	111	2 (1.8)	109 (98.2)	98	8 (8.2)	90 (91.8)
PD-L1 expression in tumor cells						
<1 %	100	2 (2.0)	98 (98.0)	102	29 (28.4)	73 (71.6)
≥1 % to <50 %	116	3 (2.6)	113 (97.4)	138	36 (26.1)	102 (73.9)
≥50 % to <80 %	49	2 (4.1)	47 (95.9)	43	12 (27.9)	31 (72.1)
≥80 %	122	8 (6.6)	114 (93.4)	108	25 (23.1)	83 (76.9)
Not evaluable	9	1 (11.1)	8 (88.9)	5	2 (40.0)	3 (60.0)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ICI, immune checkpoint inhibitor; PD-L1, programmed cell death 1 ligand 1. [a] Recruitment waves were subdivided as either early or late and were based on geographical region.

(1.3 months [range, -2.4–10.2 months] vs 5.1 months [range, 2.3–8.1 months], respectively). A similar trend was seen in the PD-L1+ population, although sample sizes were smaller.

3.2. Descriptive efficacy outcomes according to subsequent ICI use

Among all patients who received a subsequent ICI, median OS from the start of study treatment was 23.9 months (95 % CI, 14.9–29.2 months) in the avelumab arm and 19.4 months (95 % CI, 15.3–21.4 months) in the docetaxel arm. For patients who did not receive a subsequent ICI from start of study treatment, median OS was 9.9 months (95 % CI, 8.6–11.7 months) in the avelumab arm and 6.8 months (95 % CI, 5.6–8.5 months) in the docetaxel arm (Fig. 1A). Results were similar in the PD-L1+ population (Fig. 1B). In the full analysis set, median OS from the start of subsequent ICI treatment (ie, start of third-line treatment) was 10.9 months (95 % CI, 5.3–14.7 months) with avelumab and 10.7 months (95 % CI, 7.4–14.9 months) with docetaxel. In the PD-L1+ population, median OS from the start of subsequent (third-line) ICI treatment was 10.9 months (95 % CI, 7.2–14.7 months) with avelumab and 12.6 months (95 % CI, 7.5 months-not estimable) with docetaxel.

Patients who received a subsequent ICI as third-line treatment tended to have longer PFS during study treatment (ie, second-line treatment) than those who did not. In the full analysis set, median PFS by IRC in patients with or without a subsequent ICI was 6.9 months (95 % CI, 2.9–11.0 months) and 2.8 months (95 % CI, 2.5–3.2 months) in the avelumab arm and 5.6 months (95 % CI, 4.3–6.9 months) and 3.2 months (95 % CI, 2.7–4.2 months) in the docetaxel arm, respectively. Trends were similar for median PFS by investigator assessment; however, PFS was shorter by investigator assessment compared with IRC assessment. That is, patients with or without subsequent ICI treatment in the avelumab arm had PFS of 4.0 months (95 % CI, 2.6–4.4 months) and 2.7 months (95 % CI, 1.9–2.8 months), respectively; in the docetaxel arm, PFS was 4.1 months (95 % CI, 2.9–4.8 months) and 2.8 months (95 % CI, 2.6–3.1 months), respectively. PFS data were similar in the PD-L1+ population.

Furthermore, discordance was observed between investigator and IRC assessment in the classification of progressive disease. Specifically, the proportion of patients who had progressive disease based on investigator assessment but no progression event based on IRC assessment was higher in the docetaxel arm (28.3 %) than in the avelumab arm (16.7 %; Table 3).

3.3. IPCW analysis outcomes

Covariates selected from baseline characteristics for the final IPCW model were smoking status, recruitment wave, PD-L1 status (≥80 % expression cutoff), histology, and ECOG PS at baseline (Supplementary Table 1). Covariates from time-dependent assessments were first indication of progressive disease and objective response by investigator assessment. Because of the small proportion of patients who received subsequent treatment in the avelumab arm, the list of covariates for the avelumab model was reduced to recruitment wave and PD-L1 status.

HRs for OS with avelumab vs docetaxel were lower in the IPCW model than in the naive sensitivity analysis in both the full analysis set and PD-L1+ population (Table 4 and **Supplementary Fig. 2**).

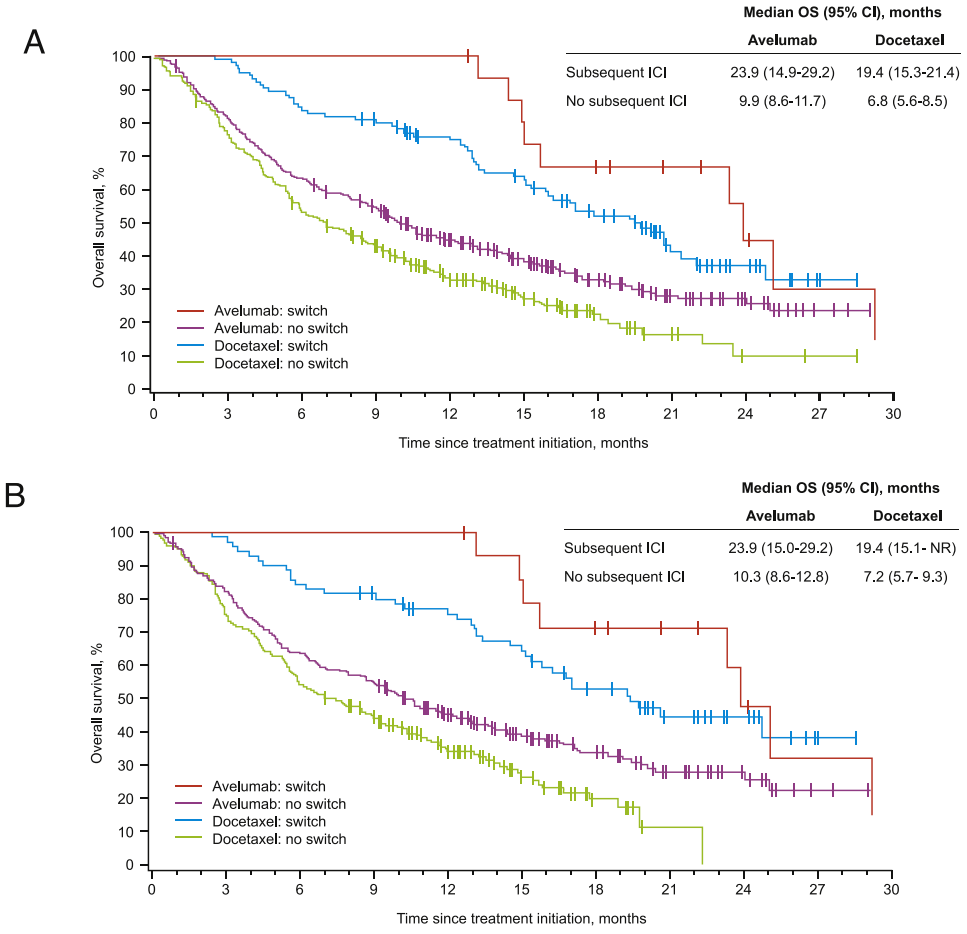

Fig. 1. Median OS in patients with and without subsequent ICI by treatment arm in the (A) full analysis set and (B) PD-L1+ population. Abbreviations: CI, confidence interval; ICI, immune checkpoint inhibitor; NR, not reached; OS, overall survival; PD-L1, programmed cell death 1 ligand 1.

Table 3
Discordance of disease progression classification between IRC and investigator assessment in the full analysis set.

Investigator assessment	IRC assessment		
	No progression event	Progressive disease or death	Total
Avelumab, n (%)			
No progression event	44 (11.1)	13 (3.3)	57 (14.4)
Progressive disease or death	66 (16.7)	273 (68.9)	339 (85.6)
Total	110 (27.8)	286 (72.2)	396 (100.0)
Docetaxel, n (%)			
No progression event	73 (18.4)	6 (1.5)	79 (19.9)
Progressive disease or death	112 (28.3)	205 (51.8)	317 (80.1)
Total	185 (46.7)	211 (53.3)	396 (100.0)

Abbreviation: IRC, independent review committee.

Table 4
OS based on the primary analysis, naive sensitivity analysis, and IPCW model.

	Full analysis set		PD-L1+ population (primary analysis population)	
	Avelumab (n = 396)	Docetaxel (n = 396)	Avelumab (n = 264)	Docetaxel (n = 265)
Deaths, n	257	263	169	173
Subsequent ICI, n	16	104	15	70
Primary confirmatory analysis (intent to treat)				
Median OS (95 % CI), months	10.5 (9.2–12.9)	9.9 (8.1–11.8)	11.4 (9.4–13.9)	10.3 (8.5–13.0)
HR (96 % CI)	0.90 (0.76–1.07)		0.90 (0.73–1.11)	
Naive sensitivity analysis (patients censored at subsequent ICI)				
Median OS (95 % CI), months	10.5 (9.1–12.8)	9.5 (8.4–11.3)	10.8 (9.4–13.8)	10.3 (8.5–13.0)
HR (95 % CI)	0.89 (0.74–1.07)		0.86 (0.68–1.09)	
IPCW adjusted model				
HR (95 % CI)	0.85 (0.70–1.05)		0.80 (0.62–1.04)	

Abbreviations: CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor; IPCW, inverse probability of censoring weighting; OS, overall survival; PD-L1, programmed cell death 1 ligand 1.

4. Discussion

In the phase 3 JAVELIN Lung 200 trial, OS was not improved for avelumab vs docetaxel in the primary analysis. However, 26 % of patients received subsequent ICI treatment in the docetaxel arm, which is a larger proportion compared with earlier trials of similar agents in the second-line NSCLC setting, and this may have confounded the primary OS analysis in favor of the docetaxel arm. The phenomenon of post-study therapy confounding OS analyses has been reported previously in NSCLC [21–23], and in the phase 3 KEYNOTE-024 study of first-line pembrolizumab vs platinum-based chemotherapy, post hoc analyses showed that crossover from chemotherapy to pembrolizumab attenuated the observed OS benefit [27]. In JAVELIN Lung 200, the proportion of patients who received a subsequent ICI in the docetaxel arm in this study was higher than in previous studies of ICIs as second-line treatment for NSCLC [12–17], with the proportions between trials reflecting the periods of enrollment and increasing availability of ICIs in different countries.

As planned before study readout, a naive sensitivity analysis was performed to provide an initial assessment of the effects of subsequent ICI on OS. This method would have yielded unbiased estimates if use of subsequent ICIs was not influenced by covariates that affect survival. Because these assumptions were violated, it can be assumed that informative censoring was introduced. Consistent with this assumption, patients who received a subsequent ICI tended to have more favorable prognostic factors at baseline, eg, ECOG PS of 0 or smaller baseline tumor size. Furthermore, these patients had a longer PFS with study treatment than those who did not receive a subsequent ICI. In both treatment arms, patients who received a subsequent ICI tended to survive longer than comparable patients who did not receive subsequent ICI. Additionally, OS from the start of subsequent ICI in the docetaxel arm (ie, from start of third-line therapy) appeared to be longer in the PD-L1+ population than in the overall population (median 12.6 and 10.7 months, respectively), supporting the suggestion that subsequent ICI treatment affected OS. However, these descriptive analyses of efficacy outcomes based on use of subsequent ICIs are affected by various limitations, including immortal-time bias (ie, patients needed to live long enough to receive subsequent ICI).

Given the limitations, we performed an IPCW analysis to account for factors that may confound OS and to adjust for possible bias due to informative censoring in the naive sensitivity analysis. Potential covariates were selected based on differences in frequencies of subsequent treatment between arms and observed differences in OS, and additional time-dependent variables were also considered. Relevant covariates were selected via a data-driven stepwise procedure. The HR for OS for avelumab vs docetaxel was lower in the IPCW model than in the naive sensitivity analysis, emphasizing that the OS benefit for avelumab would have been more pronounced if subsequent ICI had not been available. Comparisons between the IPCW analysis and the primary confirmatory analysis are not appropriate because of differences in the data, introduced by censoring at treatment switch. In addition, only 16 patients in the avelumab arm received a subsequent ICI, limiting the number of covariates that could be considered in the model for time to subsequent ICI model for avelumab and limiting the associated conclusions that could be drawn in the avelumab arm. IPCW analysis assumes a sufficient number of patients are in follow-up at all times, and that no unmeasured confounders and no deterministic or nearly deterministic predictors are present. Although the assumption of no unmeasured confounders cannot be verified statistically, a comprehensive model-selection procedure was implemented to ensure its validity. Furthermore, it is possible that factors other than subsequent ICI use may have contributed to the different result of the JAVELIN Lung 200 trial compared with trials of other ICIs vs docetaxel, such as an imbalance in tumor mutational burden, an imbalance in unmeasured tumor mutations associated with ICI resistance (eg, *STK11/KEAP1*) [28], presence of actionable mutations, or differences in activity between different ICI agents at established

dosages; however, it is not possible to assess these factors using currently available data.

Because JAVELIN Lung 200 was an open-label study and patient management decisions were based on investigator assessments, patients randomized to docetaxel may have permanently discontinued study treatment due to "borderline" cases of progression so that they could receive ICI therapy. This suggestion is supported by the discordance between IRC and investigator assessments of the incidence of disease progression. Specifically, the proportion of patients classified as having disease progression by investigator assessment but no disease progression by IRC assessment was 28.3 % in the docetaxel arm vs 16.7 % in the avelumab arm, suggesting a potential subconscious bias between arms when assessing the need to permanently discontinue study treatment in order to initiate subsequent treatment. Notably, median time to subsequent ICI after disease progression was shorter in the docetaxel arm than in the avelumab arm.

5. Conclusions

In conclusion, the IPCW analysis and other exploratory analyses support the hypothesis that the relatively high proportion of patients who received subsequent ICI in the docetaxel arm of JAVELIN Lung 200 may have confounded the OS outcomes in the study. These analyses further highlight the potential impact of subsequent treatment in oncology trials, which has implications for study designs, and provide an illustration of methods that can be used to analyze this scenario.

Availability of data and materials

Data are available upon reasonable request. For all new products or new indications approved in both the European Union and the USA after January 1, 2014, Merck KGaA, Darmstadt, Germany will share patient-level and study-level data after deidentification, as well as redacted study protocols and clinical study reports from clinical trials in patients. These data will be shared with qualified scientific and medical researchers, upon researchers' request, as necessary for conducting legitimate research. Such requests must be submitted in writing to the company's data sharing portal. More information can be found at https://www.merckgroup.com/en/research/our-approach-to-research-anddevelopment/healthcare/clinical-trials/commitment-responsible-data-sharing.html. Where Merck KGaA has a coresearch, codevelopment or comarketing/copromotion agreement or where the product has been out-licensed, it is recognized that the responsibility for disclosure may be dependent on the agreement between parties. Under these circumstances, Merck KGaA will endeavor to gain agreement to share data in response to requests.

Consent for publication

Not applicable.

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Ethics approval and consent to participate

The study protocol was approved by institutional review boards and ethics committees at each institution. The study was done in accordance with the trial protocol, Good Clinical Practice guidelines, and the Declaration of Helsinki. All patients provided written informed consent.

Competing interests

F. Barlesi: honoraria, advisory/consultancy, research funding: AstraZeneca, Bristol Myers Squibb, Roche, Merck KGaA, Merck & Co./MSD, Pierre Fabre; honoraria, advisory/consultancy: Boehringer Ingelheim, Eli Lilly, Mirati, Novartis; Pfizer; Seattle Genetics, Takeda; honoraria (institution): AbbVie; ACEA; Amgen; Bayer; Eisai; Genentech; Ipsen; Ignyta; Innate Pharma; Loxo; Sanofi-Aventis. *M. Özgüroğlu*: honoraria, advisory/consultancy, travel/accommodation/expenses: Janssen; honoraria, advisory/consultancy: Astellas; travel/accommodation/expenses: Bristol Myers Squibb. *J. Vansteenkiste*: advisory/consultancy, research funding: Merck & Co./MSD; advisory/consultancy: AstraZeneca, Boehringer Ingelheim, Eli Lilly, Roche, Apotex. *D. Spigel*: advisory/consultancy, research funding, travel/accommodation/expenses: AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, EMD Serono/Merck KGaA, Pfizer, Roche/Genentech; advisory/consultancy, research funding: AbbVie, Amgen, Foundation Medicine, GSK, Nektar, Novartis, Takeda; advisory/consultancy: Evelo Therapeutics, Illumina, Moderna Therapeutics, PharmaMar, Precision Oncology, TRM Oncology; research funding: Acerta Pharma, OncoGenex, Aeglea BioTherapeutics, ARMO Biosciences, Astellas Pharma, Celldex, Clovis Oncology, Daiichi Sankyo, G1 Therapeutics, GRAIL, Ipsen, Millennium, Neon Therapeutics, Tesaro, Transgene, University of Texas Southwestern Medical Center - Simmons Cancer Center; travel/accommodation/expenses: Genzyme, Intuitive Surgical, Purdue Pharma, Spectrum Pharmaceuticals, Sysmex. *J.C.-H. Yang*: honoraria, advisory/consultancy: AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Chugai Pharmaceutical, Eli Lilly, Merck & Co./MSD, Novartis, Ono Pharmaceuticals, Roche/Genentech, Pfizer; advisory/consultancy: Blueprint Medicines, Celgene, Daiichi Sankyo, G1 Therapeutics, Hansoh Pharmaceuticals, Merck KGaA, Merrimack, Takeda Pharmaceuticals, Yuhan Pharmaceuticals; *M. Bajars*: full/part-time employment: EMD Serono Research & Development Institute, Inc., Billerica, MA, USA (an affiliate of Merck KGaA, Darmstadt, Germany); *M. Ruisi*: full/part-time employment: EMD Serono Research & Development Institute, Inc., Billerica, MA, USA (an affiliate of Merck KGaA, Darmstadt, Germany); *J. Manitz*: full/part-time employment: EMD Serono Research & Development Institute, Inc., Billerica, MA, USA (an affiliate of Merck KGaA, Darmstadt, Germany); *K. Park*: advisory/consultancy, speaker bureau, research funding: AstraZeneca; advisory/consultancy, speaker bureau: Boehringer Ingelheim; advisory/consultancy, research funding: Merck & Co./MSD; advisory/consultancy: Amgen, Astellas Pharma, BluePrint, Bristol Myers Squibb, Clovis Oncology, Eli Lilly, GSK, Hanmi, Kyowa Hakko Kirin, Merck KGaA, Novartis, Ono Pharmaceuticals, Roche.

CRediT authorship contribution statement

Keunchil Park: Conceptualization, Investigation, Resources, Writing - review & editing. **Mustafa Özgüroğlu:** Investigation, Resources, Writing - review & editing. **Johan Vansteenkiste:** Investigation, Resources, Writing - review & editing. **David Spigel:** Investigation, Resources, Writing - review & editing. **James C.-H. Yang:** Investigation, Resources, Writing - review & editing. **Marcis Bajars:** Conceptualization, Investigation, Writing - review & editing. **Mary Ruisi:** Conceptualization, Investigation, Writing - review & editing. **Juliane Manitz:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing - original draft, Writing - review & editing. **Fabrice Barlesi:** Conceptualization, Investigation, Resources, Writing - review & editing.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2021.01.026.

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