Avelumab versus docetaxel in patients with platinum-treated advanced non-small-cell lung cancer (JAVELIN Lung 200): an open-label, randomised, phase 3 study

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Summary

Background Antibodies targeting the immune checkpoint molecules PD-1 or PD-L1 have demonstrated clinical efficacy in patients with metastatic non-small-cell lung cancer (NSCLC). In this trial we investigated the efficacy and safety of avelumab, an anti-PD-L1 antibody, in patients with NSCLC who had already received platinum-based therapy.

Methods JAVELIN Lung 200 was a multicentre, open-label, randomised, phase 3 trial at 173 hospitals and cancer treatment centres in 31 countries. Eligible patients were aged 18 years or older and had stage IIIB or IV or recurrent NSCLC and disease progression after treatment with a platinum-containing doublet, an Eastern Cooperative Oncology Group performance status score of 0 or 1, an estimated life expectancy of more than 12 weeks, and adequate haematological, renal, and hepatic function. Participants were randomly assigned (1:1), via an interactive voice-response system with a stratified permuted block method with variable block length, to receive either avelumab 10 mg/kg every 2 weeks or docetaxel 75 mg/m² every 3 weeks. Randomisation was stratified by PD-L1 expression (≥1% *vs* <1% of tumour cells), which was measured with the 73–10 assay, and histology (squamous *vs* non-squamous). The primary endpoint was overall survival, analysed when roughly 337 events (deaths) had occurred in the PD-L1-positive population. Efficacy was analysed in all PD-L1-positive patients (ie, PD-L1 expression in ≥1% of tumour cells) randomly assigned to study treatment (the primary analysis population) and then in all randomly assigned patients through a hierarchical testing procedure. Safety was analysed in all patients who received at least one dose of study treatment. This trial is registered with ClinicalTrials.gov, number NCT02395172. Enrolment is complete, but the trial is ongoing.

Findings Between March 24, 2015, and Jan 23, 2017, 792 patients were enrolled and randomly assigned to receive avelumab (n=396) or docetaxel (n=396). 264 participants in the avelumab group and 265 in the docetaxel group had PD-L1-positive tumours. In patients with PD-L1-positive tumours, median overall survival did not differ significantly between the avelumab and docetaxel groups (11·4 months [95% CI 9·4–13·9] *vs* 10·3 months [8·5–13·0]; hazard ratio 0·90 [96% CI 0·72–1·12]; one-sided p=0·16). Treatment-related adverse events occurred in 251 (64%) of 393 avelumab-treated patients and 313 (86%) of 365 docetaxel-treated patients, including grade 3–5 events in 39 (10%) and 180 (49%) patients, respectively. The most common grade 3–5 treatment-related adverse events were infusion-related reaction (six patients [2%]) and increased lipase (four [1%]) in the avelumab group and neutropenia (51 [14%]), febrile neutropenia (37 [10%]), and decreased neutrophil counts (36 [10%]) in the docetaxel group. Serious treatment-related adverse events occurred in 34 (9%) patients in the avelumab group and 75 (21%) in the docetaxel group. Treatment-related deaths occurred in four (1%) participants in the avelumab group, two due to interstitial lung disease, one due to acute kidney injury, and one due to a combination of autoimmune myocarditis, acute cardiac failure, and respiratory failure. Treatment-related deaths occurred in 14 (4%) patients in the docetaxel group, three due to pneumonia, and one each due to febrile neutropenia, septic shock, febrile neutropenia with septic shock, acute respiratory failure, cardiovascular insufficiency, renal impairment, leucopenia with mucosal inflammation and pyrexia, infection, neutropenic infection, dehydration, and unknown causes.

Interpretation Compared with docetaxel, avelumab did not improve overall survival in patients with platinum-treated PD-L1-positive NSCLC, but had a favourable safety profile.

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Introduction

Antibodies targeting the immune checkpoint molecules PD-1 or PD-L1 improve overall survival compared with standard-of-care chemotherapy in patients with metastatic non-small-cell lung cancer (NSCLC), and several of these drugs have received regulatory approvals.[1–3] Nivolumab and pembrolizumab (anti-PD-1 antibodies) were first approved in 2015 on the basis of data from randomised

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Research in context

Evidence before this study

Before the approval of anti-PD-1 and anti-PD-L1 immune checkpoint inhibitor antibodies, docetaxel was the mainstay of treatment for patients with non-small-cell lung cancer (NSCLC) and disease progression after platinum-based chemotherapy. We searched PubMed with the terms ("non-small cell lung cancer" OR "NSCLC") AND ("PD-1" OR "PD-L1" OR "checkpoint inhibitor") for clinical trials of checkpoint inhibitors in NSCLC published in English from database inception up to May 11, 2018. We identified 29 trials in patients with NSCLC, 11 of which exclusively enrolled or enrolled a specified cohort of patients who had received previous platinum treatment—including trials of atezolizumab, avelumab, durvalumab, nivolumab, and pembrolizumab. Of these trials, five were randomised trials of anti-PD-1 or anti-PD-L1 monotherapy compared with docetaxel (one phase 2 trial, one phase 2–3 trial, and three phase 3 trials); all were international and open label. In all randomised phase 3 trials, overall survival with anti-PD-1 antibodies (nivolumab and pembrolizumab) and an anti-PD-L1 antibody (atezolizumab) was significantly longer than that with docetaxel, including in trials specifically done in patients with squamous tumours, non-squamous tumours, or PD-L1-positive tumours, or all subpopulations. All reports of randomised trials identified were published after enrolment had begun for our trial of avelumab.

Added value of this study

To our knowledge, JAVELIN Lung 200 is the second phase 3, randomised clinical trial of an anti-PD-L1 antibody in patients with NSCLC and disease progression after platinum-based chemotherapy. It differs from earlier phase 3 trials of anti-PD-1 or anti-PD-L1 monotherapy because patients were enrolled at a time when an increasing proportion of patients had access to an approved agent of these classes. In our study, avelumab was not associated with increased overall survival compared with docetaxel in patients with PD-L1-positive tumours (defined as PD-L1 expression in ≥1% of tumour cells based on the 73-10 assay). However, exploratory analyses showed that avelumab was associated with improved overall survival relative to docetaxel in patients whose tumours had higher levels of PD-L1 expression (ie, at ≥50% and ≥80% cutoffs). The overall safety profile of avelumab was better than that of docetaxel.

Implications of all the available evidence

Although avelumab had clinical activity in patients with NSCLC who had disease progression after platinum-based chemotherapy, it did not significantly improve overall survival compared with docetaxel. Furthermore, the improved efficacy of avelumab relative to docetaxel in patients whose tumours had higher levels of PD-L1 expression could support the use of tumour-cell PD-L1 expression as a biomarker to identify patients more likely to obtain a clinical benefit with agents of this class.

trials—two trials[4,5] of nivolumab in patients unselected for PD-L1 expression, and a trial[6] of pembrolizumab in patients with PD-L1-positive disease (defined as PD-L1 expression in ≥1% of tumour cells based on the PD-L1 IHC 22C3 pharmDx assay; Dako, Carpinteria,CA, USA)—showing significantly longer overall survival with each drug than with docetaxel in patients with advanced squamous or non-squamous NSCLC and disease progression after platinum treatment. In 2016, atezolizumab became the first anti-PD-L1 antibody approved for treatment of metastatic NSCLC after platinum therapy on the basis of the results of the phase 3 OAK trial,[7] in which overall survival was significantly longer with atezolizumab than with docetaxel in patients with squamous or non-squamous tumours, irrespective of PD-L1 status. In the trials[4–6] of nivolumab and pembrolizumab, the relative treatment benefit of each drug compared with docetaxel was greater in patients with squamous tumours than in those with non-squamous disease. However, across all trials,[4–7] median overall survival in patients with non-squamous tumours was still significantly longer in the experimental groups than in the docetaxel groups. Since these trials, positive outcomes from phase 3 trials of anti-PD-1 and anti-PD-L1 antibodies in the context of earlier NSCLC have led to additional regulatory approvals, further changing the treatment landscape in NSCLC and improving patient outcomes.[8,9]

Avelumab is a human anti-PD-L1 IgG1 antibody that has durable antitumour activity and a tolerable safety profile in a range of solid tumours.[10–13] In a large phase 1 study of avelumab in patients with various solid tumours (n=1758), a cohort of patients with NSCLC who had already received platinum-based therapy (n=184) received avelumab as second-line or later treatment.[14] In this cohort, the proportion of patients who achieved an objective response was 14%, which increased with increasing levels of PD-L1 expression. Here, we report the results of a phase 3 trial of avelumab versus docetaxel in patients with advanced NSCLC and disease progression after platinum-based chemotherapy. To our knowledge, ours is the second randomised trial of an anti-PD-L1 antibody in this setting.

Methods

Study design and participants

JAVELIN Lung 200 (EMR 100070-004) is an open-label, multicentre, randomised phase 3 trial at 173 hosptials and cancer treatment centres in 31 countries (Argentina, Australia, Belgium, Brazil, Bulgaria, Chile, Colombia, Croatia, Czech Republic, Denmark, Estonia, France, Hungary, Israel, Italy, Japan, Latvia, Mexico, Peru, Poland, Romania, Russia, Slovakia, South Africa, South Korea, Spain, Switzerland, Taiwan, Turkey, UK, and USA). Eligible patients were aged 18 years or older and had

histologically confirmed stage IIIB, IV, or recurrent NSCLC with disease progression after previous platinum doublet treatment, available fresh biopsy or tumour archival material for biomarker assessment, an Eastern Cooperative Oncology Group performance status score of 0 or 1, an estimated life expectancy of more than 12 weeks, and adequate haematological (white blood cell count $\geq 2{\cdot}5\times10^9$ per L, absolute neutrophil count $\geq 1{\cdot}5\times10^9$ per L, lymphocyte count $\geq 0{\cdot}5\times10^9$/L, platelet count $>100\times10^9$ per L, and haemoglobin ≥90 g/L [transfused blood permitted]), renal (estimated creatine clearance >30 mL/min according to the Cockcroft-Gault formula or local institutional standard method), and hepatic (total bilirubin concentration $\leq 1{\cdot}5\times$ upper limit of normal, and aspartate aminotransferase and alanine aminotransferase concentrations $\leq 2{\cdot}5\times$ upper limit of normal) function. The presence of measurable disease was not an inclusion criterion. Patients were not eligible if they had non-squamous cell NSCLC harbouring an *EGFR* or *ALK* mutation (before the second protocol amendment on July 10, 2015, patients with tumours with *EGFR* mutations were eligible if they had also received previous treatment with a tyrosine kinase inhibitor) or if they had previously received a drug targeting a T-cell regulatory protein or systemic anticancer treatment after disease progression with platinum-based combination therapy. Other exclusion criteria included brain metastases (unless treated locally and not associated with ongoing neurological symptoms related to brain localisation of disease), persisting toxicity after previous treatment, or other clinically significant diseases. Full eligibility criteria are in the appendix (p 6).

The study protocol (appendix p 23) 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.

Randomisation and masking

Patients were enrolled by study investigators and were randomly assigned (1:1) via an interactive voice-response system to either avelumab or docetaxel. The system was used by study investigators, who were potentially assisted by colleagues and study coordinators. We used stratified permuted block randomisation with variable block length. Allocation was stratified by PD-L1 status (expression in ≥1% *vs* <1% of tumour cells) and NSCLC histology (squamous *vs* non-squamous). The trial was open label, so neither investigators nor patients were masked to assigned study treatments.

Procedures

PD-L1 expression in tumour tissue was assessed centrally at baseline with the PD-L1 IHC 73-10 pharmDx assay, which identifies a higher proportion of PD-L1-positive tumour cells than do other PD-L1 assays.[15,16] The primary analysis population (ie, the PD-L1-positive population) was defined as patients with PD-L1 expression in 1% or more of tumour cells. Tumour samples stained with the 73-10 assay were subsequently rescored to identify subgroups with PD-L1 expression in 50% or more and 80% or more of tumour cells.

Participants in the avelumab group received 10 mg/kg avelumab intravenously over 1 h once every 2 weeks. An antihistamine and paracetamol (eg, oral diphenhydramine 25–50 mg and oral or intravenous paracetamol 500–600 mg, or equivalent) were given 30–60 min before each infusion of avelumab. Participants in the docetaxel group received 75 mg/m² docetaxel intravenously over 1 h every 3 weeks according to label instructions and local guidelines. Dexamethasone was given before each infusion of docetaxel according to local standard of care. Treatment was continued in both groups until unacceptable toxicity, progressive disease, substantial clinical deterioration, or any other protocol-specified criterion for withdrawal occurred, including occurrence of an exclusion criterion, withdrawal of consent, non-compliance, or use of an unpermitted concomitant drug (appendix p 7). For patients in the avelumab group, treatment could continue beyond initial disease progression according to the Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1)[17] if their performance status remained stable, they were tolerating treatment, and if investigators decided that treatment beyond progression would not delay interventions to prevent serious complications of disease progression. Dose modification of avelumab was not permitted. However, in patients in whom infusion was stopped early because of an adverse event during the infusion, a dose reduction was defined as a patient receiving a non-zero dose of <90% of the planned dose. Dose modifications and discontinuations of docetaxel were made in accordance with label instructions and local guidelines. No crossover to avelumab was permitted. Treatment was discontinued permanently in both groups in the event of any grade 3 or worse treatment-related adverse events (with the exception of protocol-specified transient events). Treatment was delayed in patients with grade 2 treatment-related adverse events that had not resolved to grade 1 or less by the time of the next scheduled infusion. Guidance for delaying or discontinuing treatment after adverse events is in the appendix (p 8).

See Online for appendix

Tumours were assessed by radiographic imaging at baseline, every 6 weeks for the first 12 months, then every 12 weeks thereafter. Objective tumour response was assessed according to RECIST (version 1.1) by blinded independent endpoint review committee (IERC). Treatment decisions were based on investigator assessments. Safety assessments were done at each treatment visit. Adverse events were coded in accordance with MedDRA and graded according to the US National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.03). Infusion-related reactions

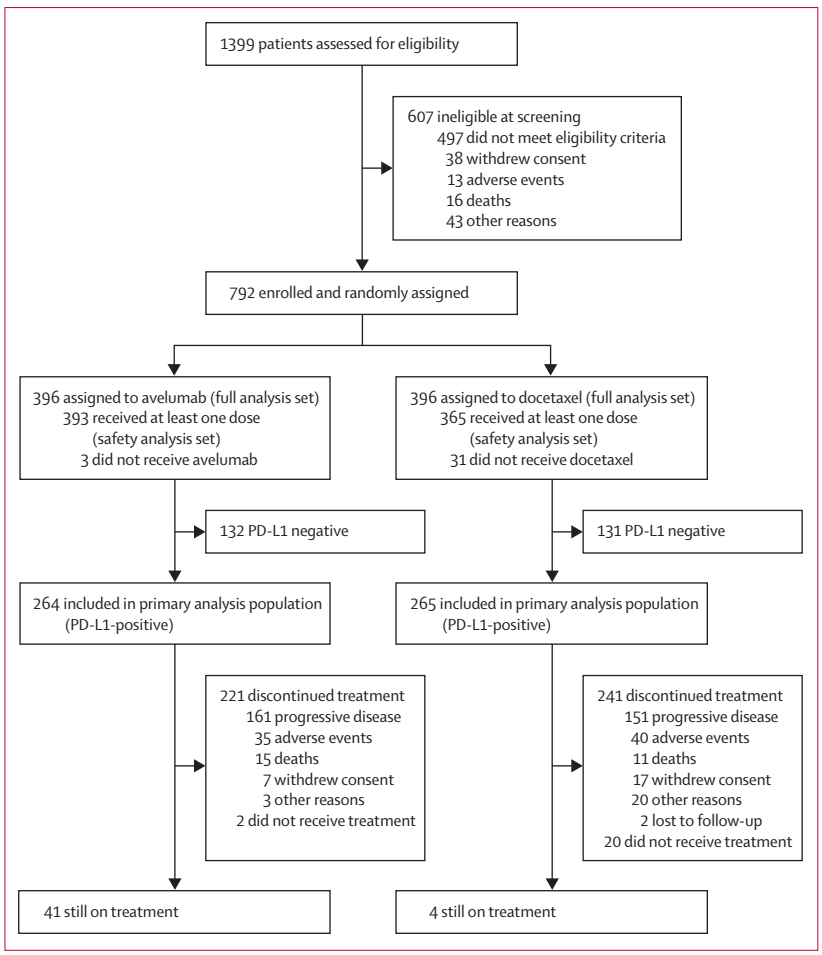

Figure 1: **Trial profile**

with avelumab were also assessed with a composite definition that comprised infusion-related reaction, drug hypersensitivity, or hypersensitivity reaction occurring on the day of or the day after the infusion, or various signs and symptoms of infusion-related reaction (including chills, pyrexia, back pain, hypersensitivity, drug hypersensitivity, type I hypersensitivity, dyspnoea, hypotension, and flushing) occurring on the day of the infusion and resolving within 2 days. Immune-related adverse events were identified with a prespecified list of adverse events followed by a comprehensive medical review. Blood and urine samples were taken from non-fasted patients at each trial visit for routine laboratory analyses, including core serum chemistry, haematology, haemostaseology, and urinalysis. Full serum chemistry was assessed at weeks 3, 5, and 13 in the avelumab group and at weeks 4, 7, and 13 in the docetaxel group. Thereafter, serum chemistry was assessed every 6 weeks in both groups. Free thyroxine and thyroid-stimulating hormone concentrations were tested every 6 weeks in the avelumab group, and at week 13 and week 25 in the docetaxel group; concentrations of all other hormones were tested in both groups when clinically indicated.

Outcomes

The primary endpoint was overall survival, which was defined as time from randomisation to death (irrespective of cause). Secondary endpoints were progression-free survival (defined as time from randomisation until the first documentation of objective progressive disease according to RECIST and adjudicated by the IERC or death from any cause, whichever occurred first), best overall response (defined as the best response obtained among all tumour assessments after the date of randomisation until documented disease progression, according to RECIST (version 1.1) and adjudicated by the IERC), changes in patient-reported outcomes or quality of life (assessed by the EQ-5D, the European Organisation for Research and Treatment of Cancer's QLQ-C30, and module QLQ-LC13 instruments), and safety. Prespecified exploratory endpoints were duration of response (time from complete or partial response until disease progression or death), tumour shrinkage in target lesions, serum titres of anti-avelumab antibodies, the pharmacokinetic profile of avelumab, the relationship between PD-L1 expression and clinical response parameters, and assessment of potential biomarkers. Quality of life assessments, tumour shrinkage, pharmacokinetic data, and biomarker assessments are not reported in this paper.

Statistical analysis

We planned to enrol around 750 patients, which we estimated would include 522 patients with PD-L1-positive tumours and 337 events (deaths) in the primary analysis population at the primary analysis. An interim analysis was planned after approximately 253 events had occurred in the PD-L1-positive population. Efficacy was analysed in all patients randomly assigned to study treatment (intention-to-treat analysis) and in the PD-L1-positive population (primary analysis set). Safety was analysed in all patients who received at least one dose of study treatment. Overall survival was analysed with a one-sided log-rank test (overall α 2·5%) stratified for PD-L1 status and tumour histology. A hierarchical test procedure was applied in the following order to control the overall significance level at 0·025 (one sided): overall survival in the PD-L1-positive population, overall survival in the full analysis set, best overall response in the PD-L1-positive population, progression-free survival in the PD-L1-positive population, best overall response in the full analysis set, and progression-free survival in the full analysis set. The α value in the primary analysis was 0·02041. Adjustment for multiple testing because of the interim analysis was done according to the O'Brien-Fleming approach and based on the observed number of overall survival events according to the Lan-DeMets method. Accordingly, CIs were adjusted to 96%. Treatment effects were estimated with a Cox proportional hazards model stratified by the randomisation strata (PD-L1 status and tumour histology) to calculate hazard ratios (HRs) and

adjusted 96% CIs. The proportional hazards assumption was checked visually for the primary analysis by plotting log(–log(overall survival)) versus log(time) within each randomisation stratum. Additionally, Schoenfeld residuals, including a locally weighted smoothing (LOESS) curve, were plotted to investigate graphically violations of the proportional hazards assumption. We analysed progression-free survival with the same log-rank test used for overall survival. The proportion of patients with an objective response (ie, a confirmed best overall response of complete or partial response) was calculated with corresponding two-sided exact Clopper-Pearson 95% CIs and compared with the Cochran-Mantel-Haenszel test, accounting for stratification factors. Exploratory analysis of PD-L1-positive subgroups (ie, ≥50% and ≥80% cutoffs) was prespecified in the statistical plan (statistical tests within subgroups were two sided and unstratified). To explore the interaction between treatment and subgroup factors, we did likelihood ratio tests. Time-to-event endpoints were estimated via the Kaplan-Meier method, and two-sided CIs for the median were calculated with the Brookmeyer-Crowley method. Follow-up times for overall and progression-free survival were estimated with the inverse Kaplan-Meier method. A Cox model based on an inverse probability of censoring weighting technique was used for a post-hoc analysis of the effect of post-study treatment.[18] Statistical analyses were done in SAS (version 9.4).

This study is registered with ClinicalTrials.gov, number NCT02395172.

Role of the funding source

Merck provided the study drug and worked with a study steering committee and investigators on the trial design and plan, collection and analysis of data, and interpretation of results. Funding for a professional medical writer with access to the data was provided by Merck and Pfizer. FB and the corresponding author had full access to all the study data and had final responsibility for the decision to submit for publication.

Results

Between March 24, 2015, and Jan 23, 2017, 792 patients were enrolled and randomly assigned: 396 to the avelumab group and 396 to the docetaxel group. 264 (67%) participants in the avelumab group and 265 (67%) in the docetaxel group had PD-L1-positive tumours (figure 1). The data cutoff date was Nov 22, 2017. Baseline characteristics were similar between the PD-L1-positive population and the full analysis set (table 1). In the PD-L1-positive population, 262 (99%) patients in the avelumab group and 245 (92%) in the docetaxel group received at least one dose of study treatment. 18 (90%) of the 20 PD-L1-positive participants in the docetaxel group who did not receive at least one dose withdrew consent, and thus information about subsequent treatment was scarce. Median duration of treatment in the PD-L1-positive population was 3·4 months (IQR 1·6–9·7) in the avelumab group and 2·8 months (1·4–4·4) in the

	PD-L1-positive population		Full analysis set	
	Avelumab group (n=264)	Docetaxel group (n=265)	Avelumab group (n=396)	Docetaxel group (n=396)
Age, years	64 (59–70)	63 (56–69)	64 (58–69)	63 (57–69)
Sex				
Male	182 (69%)	185 (70%)	269 (68%)	273 (69%)
Female	82 (31%)	80 (30%)	127 (32%)	123 (31%)
Country or region				
USA	9 (3%)	8 (3%)	10 (3%)	8 (2%)
Latin America	35 (13%)	28 (11%)	56 (14%)	44 (11%)
Western Europe	62 (23%)	62 (23%)	96 (24%)	102 (26%)
Eastern Europe	55 (21%)	52 (20%)	79 (20%)	75 (19%)
Australia	2 (1%)	3 (1%)	2 (1%)	3 (1%)
Asia*	69 (26%)	80 (30%)	100 (25%)	113 (29%)
South Africa	3 (1%)	0	3 (1%)	0
Middle East	29 (11%)	32 (12%)	50 (13%)	51 (13%)
Race				
White	182 (69%)	170 (64%)	273 (69%)	262 (66%)
Black	3 (1%)	1 (<1%)	5 (1%)	1 (<1%)
Asian	71 (27%)	81 (31%)	102 (26%)	114 (29%)
Native American or Alaskan	0	1 (<1%)	0	1 (<1%)
Native Hawaiian or other Pacific Islander	1 (<1%)	0	1 (<1%)	0
Other	7 (3%)	12 (5%)	15 (4%)	18 (5%)
Eastern Cooperative Oncology Group performance status				
0	96 (36%)	91 (34%)	144 (36%)	134 (34%)
1	168 (64%)	174 (66%)	252 (64%)	262 (66%)
Months since diagnosis of metastatic disease	11 (2–124)	10 (3–157)	12 (2–126)	10 (3–157)
Histology				
Squamous	88 (33%)	92 (35%)	120 (30%)	122 (31%)
Non-squamous	176 (67%)	173 (65%)	276 (70%)	274 (69%)
M category at study entry				
M0	15 (6%)	17 (6%)	22 (6%)	25 (6%)
M1, M1a, or M1b	248 (94%)	247 (93%)	373 (94%)	370 (93%)
Missing	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
CNS metastasis at baseline	27 (10%)	22 (8%)	46 (12%)	33 (8%)
Activating *EGFR* mutation	5 (2%)	7 (3%)	11 (3%)	13 (3%)
ALK rearrangement	1 (<1%)	0	1 (<1%)	1 (<1%)
Smoking status				
Current or former smoker	220 (83%)	224 (85%)	324 (82%)	333 (84%)
Never smoker	43 (16%)	41 (15%)	70 (18%)	63 (16%)
PD-L1 status (≥1% cutoff)†				
Positive	..	..	264 (67%)	263 (66%)
Negative	..	..	129 (33%)	132 (33%)
Not assessable	..	..	3 (1%)	1 (<1%)
PD-L1 status (≥50% cutoff)				
Positive	..	..	168 (42%)	147 (37%)
Negative	..	..	218 (55%)	243 (61%)
Not assessable	..	..	10 (3%)	6 (2%)
PD-L1 status (≥80% cutoff)				
Positive	..	..	120 (30%)	106 (27%)
Negative	..	..	266 (67%)	284 (72%)
Not assessable	..	..	10 (3%)	6 (2%)

(Table 1 continues on next page)

	PD-L1-positive population		Full analysis set	
	Avelumab group (n=264)	Docetaxel group (n=265)	Avelumab group (n=396)	Docetaxel group (n=396)
(Continued from previous page)				
Previous lines of therapy				
One	233 (88%)	238 (90%)	351 (89%)	353 (89%)
Two	30 (11%)	26 (10%)	43 (11%)	40 (10%)
Three	1 (<1%)	1 (<1%)	2 (1%)	3 (1%)
Previous lines of therapy for locally advanced or metastatic disease				
One	255 (97%)	257 (97%)	382 (96%)	381 (96%)
Two	9 (3%)	7 (3%)	14 (4%)	14 (4%)
Three	0	1 (<1%)	0	1 (<1%)

Data are n (%) or median (IQR). *Includes Japan (36 [14%] *vs* 38 [14%] in the PD-L1-positive population and 48 [12%] *vs* 53 [13%] in the full analysis set), South Korea (31 [12%] *vs* 39 [15%] in the PD-L1-positive population and 47 [12%] *vs* 53 [13%] in the full analysis set), and Taiwan (two [<1%] *vs* three [1%] in the PD-L1-positive population and five [1%] *vs* seven [2%] in the full analysis set). †The number of patients with PD-L1-positive tumours based on a ≥1% cutoff in the full analysis set is slightly different from that in the primary analysis population because of minor differences in PD-L1 status reporting in the randomisation system.

Table 1: **Baseline characteristics**

docetaxel group. The median number of infusions received was seven (IQR 3–21) in the avelumab group and four (2–6) in the docetaxel group. In the PD-L1-positive population, 41 (16%) participants in the avelumab group and four (2%) in the docetaxel group remained on treatment at data cutoff (figure 1). Figure 1 shows the reasons for treatment discontinuation in each treatment group.

In the PD-L1-positive population, anticancer treatment after the study was received by 105 (40%) of 264 patients in the avelumab group and 126 (48%) of 265 in the docetaxel group, and proportions were similar in the full analysis set (157 [40%] of 396 *vs* 185 [47%] of 396). Post-study therapy in the PD-L1-positive population included an immune checkpoint inhibitor (anti-PD-1, anti-PD-L1, or anti-CTLA-4 inhibitor) in 15 (6%) patients in the avelumab group and 70 (26%) in the docetaxel group (16 [4%] *vs* 104 [26%] in the full analysis set). In the docetaxel group, post-study immune checkpoint inhibitor treatment was more frequently received by patients with non-squamous (58 [34%] of 173) than with squamous (12 [13%] of 92) tumours. At data cutoff, 342 of 529 participants in the PD-L1-positive population had died: 169 (64%) patients in the avelumab group and 173 (65%) in the docetaxel group. At data cutoff, in the full analysis set, 520 of 792 patients had died: 257 (65%) of 396 participants in the avelumab group and 263 (66%) of 396 in the docetaxel group.

Median follow-up for overall survival in the PD-L1-positive population was 18·9 months (IQR 13·5–23·1) in the avelumab group, 17·8 months (12·6–22·4) in the docetaxel group, and 18·3 months (13·2–22·7) in the overall PD-L1 population. Median follow-up for overall survival was similar in the full analysis set (18·9 months [IQR 13·2–23·0] in the avelumab group, 17·8 months [12·5–22·4] in the docetaxel group, and 18·3 months [12·9–22·9] in the whole population). Overall survival in the PD-L1-positive population did not differ between the two treatment groups. Median overall survival was 11·4 months (95% CI 9·4–13·9) in the avelumab group versus 10·3 months (8·5–13·0) in the docetaxel group (stratified HR 0·90 [96% CI 0·72–1·12], p=0·16; figure 2A). No major violations of the proportional hazards assumption for overall survival were identified.

In our subsequent efficacy analyses, which were now rendered exploratory in nature, median overall survival in the full analysis set was 10·5 months (95% CI 9·2–12·9) in the avelumab group and 9·9 months (8·1–11·8) in the docetaxel group (stratified HR 0·90 [96% CI 0·75–1·08]; nominal p=0·12; appendix p 15). The overall survival results in the PD-L1-positive population were consistent across most subgroups examined (figure 3). However, prespecified exploratory analysis of overall survival at higher PD-L1 cutoffs showed improved overall survival with avelumab compared with docetaxel in patients whose tumours had PD-L1 expression in 50% or more of tumour cells (figure 2B) or 80% or more of tumour cells (figure 2C). Prespecified exploratory analyses of overall survival by tumour histology in the PD-L1-positive population and post-hoc analyses of overall survival by tumour histology in patients with PD-L1 expression in 80% or more of tumour cells are shown in the appendix (pp 16–17).

In the PD-L1-positive population, 323 of 529 patients had a progression event (disease progression or death) at data cutoff, including 180 (68%) of 264 participants in the avelumab group and 143 (54%) of 265 in the docetaxel group. In the full analysis set, 497 of 792 patients had a progression event, including 286 (72%) of 396 participants in the avelumab group and 211 (53%) of 396 in the docetaxel group. In the PD-L1-positive population, median progression-free survival according to IERC judgment was 3·4 months (95% CI 2·7–4·9) in the avelumab group and 4·1 months (3·0–5·3) in the docetaxel group (stratified HR 1·01 [96% CI 0·80–1·28]; nominal p=0·53; appendix p 18). In the full analysis set, median progression-free survival was 2·8 months (95% CI 2·7–3·5) in the avelumab group and 4·2 months (3·3–5·2) in the docetaxel group (unstratified HR 1·16 [95% CI 0·97–1·40]; nominal p=0·95). In the subgroup of patients with PD-L1 expression in 50% or more of tumour cells, median progression-free survival in the avelumab group was significantly longer than that in the docetaxel group (appendix p 19). Median progression-free survival was also longer in the avelumab group than in the docetaxel group in the subgroup of patients with PD-L1 expression in 80% or more of tumour cells (appendix p 19). Prespecified exploratory analyses of progression-free survival based on different PD-L1 cutoffs and post-hoc analyses of progression-free survival by histology based on different PD-L1 cutoffs are in the appendix (pp 18–19 and p 20, respectively).

There was some discordance between investigator and IERC assessments, whereby progressive disease was

diagnosed by the investigator but not the IERC. This discordance was noted more frequently in the docetaxel group than in the avelumab group (appendix p 9).

In the PD-L1-positive population, a higher proportion of participants had objective responses in the avelumab group than in the docetaxel group (50 [19%] of 264 *vs* 31 [12%] of 265; odds ratio [OR] 1·76 [95% CI 1·08–2·86]; nominal p=0·011; table 2). In prespecified analyses, objective responses were recorded significantly more frequently with avelumab than with docetaxel in the subgroups of patients with PD-L1 expression in 50% or more cells and in 80% or more cells (table 2). Median duration of response was not reached in the avelumab group (95% CI 9·9 to not estimable) and was 6·9 months (3·5 to not estimable) in the docetaxel group. Reasons for patients in the PD-L1-positive population not being assessable for best overall response are in the appendix (p 10). In the full analysis set, 59 (15%) of 396 patients in the avelumab group and 44 (11%) of 396 in the docetaxel group had an objective response (OR 1·40 [95% CI 0·92–2·13]; nominal p=0·055): five (1%) versus two (1%) had complete responses, 54 (14%) versus 42 (11%) had partial responses, and 129 (33%) versus 158 (40%) had stable disease.

Exploratory post-hoc analyses of the effect of treatment with an immune checkpoint inhibitor after discontinuation of study treatment on overall survival resulted in an adjusted HR for avelumab versus docetaxel in an inverse probability of censoring weighting model of the PD-L1-positive population of 0·80 (95% CI 0·62–1·04). In a naive sensitivity analysis in which patients were censored at the date of subsequent anticancer therapy, the adjusted HR was 0·86 (95% CI 0·68–1·09; appendix pp 11, 22).

Avelumab was associated with fewer treatment-related adverse events than was docetaxel, and most adverse events associated with avelumab were low grade (table 3). Treatment-related adverse events of any grade occurred in 251 (64%) of 393 avelumab-treated patients and 313 (86%) of 365 docetaxel-treated patients. The proportion of patients with a grade 3 or worse (39 [10%] of 393 *vs* 180 [49%] of 365) or grade 4 or worse (eight [2%] *vs* 79 [22%]) treatment-related adverse event was lower in the avelumab group than in the docetaxel group (appendix pp 12–13). In the avelumab group, the most common treatment-related adverse events of any grade were infusion-related reaction (65 [17%] of 393) and decreased appetite (34 [9%]; table 3, appendix pp 12–13), and the most common grade 3 or worse treatment-related adverse events were infusion-related reaction (six [2%]) and increased lipase (four [1%]; table 3, appendix pp 12–13). In the docetaxel group, the most common treatment-related adverse events of any grade were alopecia (97 [27%] of 365), anaemia (69 [19%]), and decreased appetite (66 [18%]), and the most common grade 3 or worse treatment-related adverse events were neutropenia (51 [14%]), febrile neutropenia (37 [10%]), and decreased neutrophil count (36 [10%]; table 3; appendix pp 12–13).

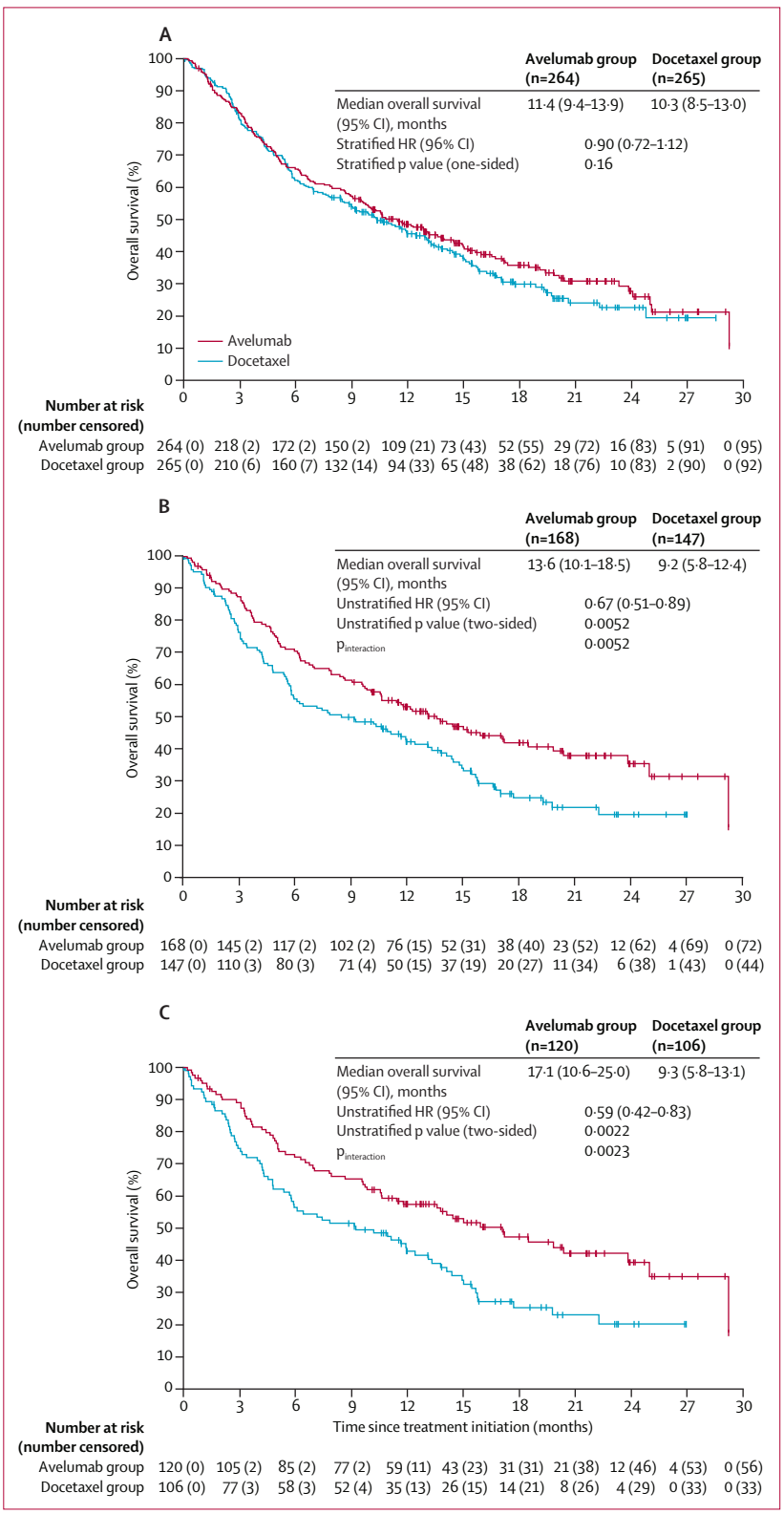

Figure 2: **Overall survival in the PD-L1-positive population at the ≥1% (A), ≥50% (B), and ≥80% (C) cutoffs**
HR=hazard ratio.
Figure 2A was adjusted for multiple comparisons.

	Events/patients (n/N)		Median overall survival (95% CI), months		Hazard ratio (95% CI)
	Avelumab group	Docetaxel group	Avelumab group	Docetaxel group	
Age (years)					
<65	87/134	98/145	10·5 (8·8–13·6)	9·2 (6·4–11·9)	0·84 (0·63–1·13)
≥65	82/130	75/120	12·9 (6·6–15·6)	12·9 (8·5–17·0)	0·98 (0·71–1·34)
<75	152/235	162/244	10·6 (9·0–13·8)	10·2 (7·5–13·0)	0·89 (0·71–1·11)
≥75	17/29	11/21	14·5 (5·1–NE)	18·9 (8·8–NE)	1·16 (0·54–2·47)
Sex					
Male	112/182	122/185	11·4 (9·0–14·9)	8·8 (6·2–11·9)	0·83 (0·64–1·08)
Female	57/82	51/80	10·8 (7·0–15·0)	13·1 (10·2–15·7)	1·08 (0·74–1·59)
Pooled region					
USA and western Europe	44/71	47/70	9·1 (6·5–17·3)	10·3 (5·8–15·0)	0·87 (0·58–1·32)
Eastern Europe	36/55	33/52	10·5 (5·5–12·9)	8·8 (5·9–13·0)	0·92 (0·57–1·49)
Asia	48/69	56/80	14·5 (9·4–19·8)	12·9 (6·2–15·7)	0·84 (0·57–1·25)
Rest of the world	41/69	37/63	10·6 (7·0–15·3)	11·1 (5·6–16·8)	0·99 (0·63–1·54)
ECOG performance status					
0	49/96	53/91	15·3 (12·8–24·0)	11·6 (9·1–15·3)	0·73 (0·50–1·08)
1	120/168	120/174	8·7 (6·1–11·4)	9·0 (6·1–13·1)	0·99 (0·77–1·28)
Histology					
Squamous	52/88	64/92	10·6 (8·8–18·5)	7·5 (5·9–10·6)	0·70 (0·48–1·01)
Non-squamous	117/176	109/173	11·5 (8·0–14·5)	12·9 (9·3–15·0)	1·02 (0·79–1·33)
Smoking status					
Never smoker	30/43	22/41	13·9 (8·6–15·0)	17·7 (12·0–19·8)	1·69 (0·97–2·95)
Ever smoker	139/220	151/224	10·6 (8·7–13·6)	8·6 (6·2–11·6)	0·83 (0·66–1·04)
Ethnicity					
Non-Hispanic or Latino	125/197	130/201	10·6 (8·8–14·5)	9·9 (7·0–12·4)	0·87 (0·68–1·11)
Hispanic or Latino	24/38	18/29	8·6 (5·1–15·3)	8·6 (3·1–NE)	0·96 (0·52–1·77)
All other patients	141/228	144/227	10·5 (8·6–13·8)	9·3 (7·0–11·9)	0·89 (0·71–1·13)
Japanese living in Japan	28/36	29/38	14·7 (10·1–23·9)	15·4 (9·9–19·7)	0·95 (0·56–1·61)
PD–L1 status (≥50% cutoff)					
Positive	96/168	103/147	13·6 (10·1–18·5)	9·2 (5·8–12·4)	0·67 (0·51–0·89)
Negative	153/218	158/243	9·4 (7·5–10·8)	9·9 (8·4–12·5)	1·11 (0·89–1·39)
PD–L1 status (≥80% cutoff)					
Positive	64/120	73/106	17·1 (10·6–25·0)	9·3 (5·8–13·1)	0·59 (0·42–0·83)
Negative	185/266	188/284	9·4 (7·9–10·7)	9·8 (8·1–11·9)	1·08 (0·88–1·32)
All participants	**169/264**	**173/265**	**11·4 (9·4–13·9)**	**10·3 (8·5–13·0)**	**0·90 (0·73–1·12)**

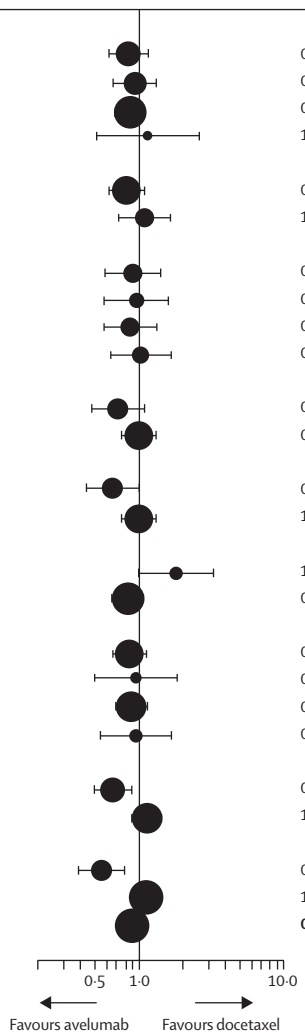

Figure 3: **Subgroup analysis of overall survival within the PD-L1-positive population**
ECOG=Eastern Cooperative Oncology Group. NE=not estimable.

In an expanded analysis of infusion-related reaction as an adverse event of special interest in the avelumab group, events of any grade occurred in 107 (27%) patients—including adverse events of grade 3 or worse in six (2%) participants—and led to avelumab discontinuation in six (2%) participants. First onset was within the first three infusions in 104 (26%) participants, and at infusion four or later in three (1%). Immune-related adverse events of any grade occurred in 65 (17%) of 393 avelumab-treated patients, and grade 3 or higher immune-related events occurred in 11 (3%) participants. The most common immune-related adverse events of any grade in the avelumab group that occurred in at least 2% of patients were rash and related terms (25 [6%]), hypothyroidism (19 [5%]), and pneumonitis (nine [2%]; appendix p 14).

28 (7%) of 393 patients in the avelumab group and 51 (14%) of 365 in the docetaxel group discontinued treatment because of a treatment-related adverse event. Dose reductions occurred in 16 (4%) participants in the avelumab group and 72 (20%) in the docetaxel group. Serious treatment-related adverse events occurred in 34 (9%) patients in the avelumab group and 75 (21%) in the docetaxel group. The most common serious treatment-related adverse events in the avelumab group were pneumonitis (five [1%]) and interstitial lung disease (three [1%]), whereas in the docetaxel group they were febrile neutropenia (21 [6%]), neutropenia (ten [3%]), pneumonia (nine [2%]), diarrhoea (five [1%]), decreased neutrophil count (four [1%]), asthenia (three [1%]), interstitial lung disease (three [1%]), leucopenia (three [1%]), and septic shock (three [1%]). Deaths

	PD-L1 positive (≥1% cutoff)*		PD-L1 positive (≥50% cutoff)		PD-L1 positive (≥80% cutoff)	
	Avelumab group (n=264)	Docetaxel group (n=265)	Avelumab group (n=168)	Docetaxel group (n=147)	Avelumab group (n=120)	Docetaxel group (n=106)
Complete response	4 (2%)	1 (<1%)	4 (2%)	0	4 (3%)	0
Partial response	46 (17%)	30 (11%)	38 (23%)	15 (10%)	33 (28%)	11 (10%)
Stable disease	86 (33%)	104 (39%)	56 (33%)	48 (33%)	33 (28%)	32 (30%)
Non-complete response or non-progressive disease	4 (2%)	12 (5%)	4 (2%)	7 (5%)	4 (3%)	6 (6%)
Progressive disease	93 (35%)	57 (22%)	47 (28%)	39 (27%)	33 (28%)	29 (27%)
Non-assessable†	31 (12%)	61 (23%)	19 (11%)	38 (26%)	13 (11%)	28 (26%)
Proportion of patients with objective responses (95% CI)	19% (14–24)	12% (8–16)	25% (19–32)	10% (6–16)	31% (23–40)	10% (5–18)
Odds ratio (95% CI)	1·76 (1·08–2·86)	..	2·93 (1·55–5·55)	..	3·85 (1·85–8·03)	..
p value‡	0·011	..	0·0007	..	0·0002	..
Disease control %§	140 (53%)	147 (55%)	102 (61%)	70 (48%)	74 (62%)	49 (46%)

Objective responses were assessed by the independent efficacy review committee. *PD-L1-positive population based on randomisation. †Includes missing and not assessable participants (reasons in appendix p 10). ‡One-sided p values for the primary analysis population (≥1% cutoff) and two-sided p values for the ≥50% and ≥80% subgroups (Cochran-Mantel-Haenszel test). §Complete response, partial response, and stable disease (including non-complete response or non-progressive disease).

Table 2: **Objective responses in the PD-L1-positive population and subgroups**

because of treatment-related adverse events occurred in four (1%) patients in the avelumab group (three on study and one 4 months after the last avelumab dose): two due to interstitial lung disease, one due to acute kidney injury, and one due to autoimmune myocarditis, acute cardiac failure, and respiratory failure. Deaths due to treatment-related adverse events occurred in 14 (4%) patients in the docetaxel group: three due to pneumonia, and one each due to febrile neutropenia, septic shock, febrile neutropenia with septic shock, acute respiratory failure, cardiovascular insufficiency, renal impairment, leucopenia with mucosal inflammation and pyrexia, infection, neutropenic infection, dehydration, and unknown causes. The total number of deaths in treated patients in the safety analysis set irrespective of relationship to study treatment was 255 (65%) of 393 patients in the avelumab group and 241 (66%) of 365 in the docetaxel group.

In the avelumab group, serum anti-drug antibodies to avelumab were detected in 51 (14%) of 368 assessable patients. Antibodies were treatment emergent in 46 patients (13%) and pre-existing in five (1%). No associations between efficacy or safety outcomes and serum anti-drug antibodies were identified (data not shown).

Discussion

In this randomised, phase 3 trial in patients with advanced or metastatic NSCLC and disease progression after platinum doublet therapy, avelumab was not associated with improved overall survival compared with docetaxel in the PD-L1-positive population (≥1% cutoff). Thus, the JAVELIN Lung 200 trial did not meet its primary endpoint. However, avelumab did show clinical activity and acceptable safety in these patients.

The high frequency of post-study use of checkpoint inhibitors in our study is indicative of the increasing use of checkpoint inhibitors in the treatment of NSCLC, and might have affected overall survival findings in our study. The frequency of use of checkpoint inhibitors after docetaxel treatment in this study (26% in the docetaxel group *vs* 6% in the avelumab group) is higher than that in previous trials in a similar setting, including a trial[7] of docetaxel versus atezolizumab (17% *vs* 4%) and a trial of docetaxel versus pembrolizumab (13% *vs* 1%).[6] Furthermore, the proportion of randomly assigned patients who did not receive any study treatment was higher in the docetaxel group than in the avelumab group (8% *vs* 1%), which is one of the limitations of a non-blinded randomised study and is suggestive of selective discontinuation after treatment assignment. Other potential factors that might have affected trial outcomes include methods of biomarker assessment, patient characteristics, or drug characteristics.

Treatment outcomes after chemotherapy in patients with NSCLC tend to be better in Asian patients than in patients from other regions.[19,20] Our trial included a high proportion of Asian patients in the PD-L1-positive population (71 [27%] in the docetaxel group *vs* 81 [31%] in the docetaxel group), including a high proportion of Japanese patients living in Japan (14% in both groups). By comparison, in both the KEYNOTE-010 and OAK trials, 21% of patients were Asian (217 of 1033 patients in KEYNOTE-010, and 180 of 850 in OAK).[6,7] Cross-study comparisons should be interpreted with caution because of differences in study designs, patient populations, and dates of enrolment. However, the median overall survival in the avelumab group in patients with PD-L1-positive tumours in our trial was similar to that in the pembrolizumab group of a phase 2–3 trial

	Avelumab group (n=393)				Docetaxel group (n=365)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Alopecia	0	0	0	0	97 (27%)	0	0	0
Decreased appetite	34 (9%)	0	0	0	59 (16%)	7 (2%)	0	0
Diarrhoea	24 (6%)	0	0	0	51 (14%)	4 (1%)	1 (<1%)	0
Anaemia	5 (1%)	0	0	0	51 (14%)	17 (5%)	1 (<1%)	0
Nausea	20 (5%)	0	0	0	49 (13%)	3 (1%)	0	0
Fatigue	29 (7%)	1 (<1%)	0	0	45 (12%)	10 (3%)	0	0
Stomatitis	3 (1%)	0	0	0	38 (10%)	3 (1%)	0	0
Asthenia	29 (7%)	1 (<1%)	0	0	37 (10%)	14 (4%)	0	0
Myalgia	6 (2%)	0	0	0	37 (10%)	3 (1%)	0	0
Mucosal inflammation	2 (1%)	0	0	0	19 (5%)	4 (1%)	0	1 (<1%)
Leucopenia	1 (<1%)	0	0	0	7 (2%)	8 (2%)	2 (1%)	1 (<1%)
Pneumonia	2 (1%)	0	0	0	6 (2%)	5 (1%)	0	3 (1%)
Infusion-related reaction	59 (15%)	5 (1%)	1 (<1%)	0	6 (2%)	1 (<1%)	0	0
Neutropenia	1 (<1%)	0	0	0	5 (1%)	21 (6%)	30 (8%)	0
Decreased white blood cell count	1 (<1%)	0	0	0	4 (1%)	13 (4%)	4 (1%)	0
Decreased neutrophil count	0	0	0	0	2 (1%)	8 (2%)	28 (8%)	0
Febrile neutropenia	0	0	0	0	0	34 (9%)	1 (<1%)	2 (1%)
Lipase increased	1 (<1%)	3 (1%)	1 (<1%)	0	0	1 (<1%)	0	0

Data are n (%). The table include grade 1–2 adverse events that occurred in ≥10% of patients, and grade 3–5 events that occurred in ≥1% of patients. All grade 3–5 adverse events are provided in the appendix (pp 12–13).

Table 3: **Treatment-related adverse events**

(KEYNOTE-010) in patients with PD-L1-positive tumours (based on tumour cell PD-L1 expression).[6] Across trials of other drugs, median overall survival with docetaxel (pooled for patients with squamous and non-squamous tumours) has ranged from 8·1 months to 9·6 months.[6,7,21]

Our prespecified exploratory analyses suggested that in subgroups of patients with higher PD-L1 expression, overall and progression-free survival were significantly longer, and objective responses were more common, with avelumab than with docetaxel—a finding consistent with those from other trials.[6,21,22] Studies of the analytic performance of different PD-L1 assays have shown that the 73-10 assay used in this trial has higher sensitivity to detect PD-L1-positive tumour cells than other assays used in trials of other drugs, including the 22C3 (pembrolizumab; Dako, Carpinteria, CA, USA) and SP142 (atezolizumab; Ventana, Tucson, AZ, USA) assays.[15,16] In a direct comparison[16] of PD-L1 staining with the 73-10 and 22C3 assays in NSCLC samples, 73-10 detected a higher proportion of PD-L1-positive tumours with a 1% or greater cutoff (80% *vs* 59%), and the 80% or greater cutoff for 73-10 was highly concordant with the 50% or greater cutoff for 22C3 (identifying 24% *vs* 20% of samples, respectively; overall percentage agreement 94%). Additionally, according to prevalence data, the 80% or greater cutoff with the 73-10 assay identified a similarly sized proportion of patients in this trial (226 [29%] of 792) to the 50% or greater cutoff with the 22C3 assay in the KEYNOTE-010 trial (28%).[6] By contrast, in the OAK trial of atezolizumab, in which PD-L1 expression by tumour or immune cells was measured with the SP142 assay, the proportion of patients with PD-L1-positive tumours above a minimum threshold (≥1% expression in tumour or immune cells) was only 54%, which emphasises the differences between PD-L1 assays.[7]

In this trial, the frequency of treatment with immune checkpoint inhibitors after docetaxel discontinuation was higher in patients with non-squamous NSCLC than in those with squamous NSCLC (34% *vs* 13%). In previous randomised trials[4–6,21] of similar drugs, greater treatment effects relative to docetaxel have been reported in patients with squamous tumours compared with those with non-squamous tumours, including a progression-free survival benefit in the trial[4] of nivolumab in squamous NSCLC, but not in the trial[5] of nivolumab in non-squamous NSCLC.[21] Additionally, the improved overall survival noted in patients with tumours with higher PD-L1 expression during nivolumab treatment compared with docetaxel was more pronounced in patients with non-squamous tumours than in those with squamous tumours, but signifigance testing was not reported.[21] These findings might be because of biological differences between histological subtypes that could affect responses to immunotherapy, such as immunological characteristics of the tumour microenvironment or viral integration,[23–25] although further studies are needed to clarify the effects

of these factors during checkpoint inhibitor treatment of NSCLC. Notably, in the high PD-L1 expression subgroup (≥80% cutoff) in our study, avelumab showed clinical activity (in terms of effects on overall survival, progression-free survival, and objective response) irrespective of NSCLC histology, suggesting that checkpoint inhibition has an increased likelihood of clinical benefit in both squamous and non-squamous tumours that are immunologically active. Analyses are underway to establish whether tumour mutational burden or other biomarkers could have contributed to the overall efficacy results in this trial.

In safety analyses, avelumab was associated with a lower frequency of treatment-related adverse events of any grade and of grade 3 or worse adverse events than docetaxel. However, consistent with previous trials of avelumab,[10–13,26] the frequency of infusion-related reactions was higher in the avelumab group than in the docetaxel group. Infusion-related reactions were mostly mild, rarely led to treatment discontinuation, and typically occurred within the first three infusions (99% of cases). Other treatment-related adverse events occurred at a similar frequency in our trial to those in previous studies of anti-PD-1 or anti-PD-L1 antibodies compared with docetaxel.[4,5,7,27] Avelumab was associated with a low frequency of grade 3 or worse immune-related treatment-related adverse events.

Overall, although this trial did not meet its primary endpoint, the clinical activity and safety noted in this study support further studies of avelumab in patients with NSCLC, and several trials are underway in different treatment settings. Findings from JAVELIN Lung 200 will help to inform the analyses of these trials, which could help to define a future role for avelumab in the treatment of NSCLC.

Contributors

FB, MB, and KP designed the study. All authors contributed to data collection, analysis, and interpretation, and writing of the Article, and approved the final version.

Declaration of interests

FB has provided advisory or consultancy services and received personal fees from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Clovis, Eli Lilly, Merck, Merck Sharp & Dohme, Novartis, Pierre Fabre, Pfizer, Roche, and Takeda. JV has received institutional research funding from Merck Sharp & Dohme, provided advisory or consultancy services for Apotex, AstraZeneca, Boehringer Ingelheim, Merck Sharp & Dohme, Novartis, and Roche, and provided speaker services for AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, and Roche. MG has received personal fees from AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, and Roche. FdM has received personal fees from AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, and Roche. MÖ has provided advisory or consultancy services to Astellas and received personal fees from Janssen. AP has received personal fees from Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme, and Roche. OAF has provided advisory or consultancy services for AstraZeneca, Bristol-Myers Squibb, Novartis, Regeneron, and Roche, and received honoraria from Bristol-Myers Squibb, Novartis, and Roche. BE-L is an employee of Merck. MB and MR are employees of EMD Serono Research & Development Institute, a biopharmaceutical business of Merck. KP has provided advisory or consultancy services and received personal fees from Astellas, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Clovis, Eli Lilly, GlaxoSmithKline, Hanmi, KHK, Merck Sharp & Dohme, Novartis, ONO Pharmaceutical, and Roche. All other authors declare no competing interests.

Data sharing

For all new products or new indications approved in both the European Union and the USA after Jan 1, 2014, Merck shares patient-level and study-level data after deidentification, and redacted study protocols and clinical study reports from clinical trials in patients. These data will be shared with qualified scientific and medical researchers, upon researcher's request, as necessary for legitimate research. Such requests should be submitted in writing to Merck's data sharing portal. When Merck has a co-research, co-development, or co-marketing or co-promotion agreement, or when the product has been out-licensed, the responsibility for disclosure might be dependent on the agreement between parties. Under these circumstances, Merck will endeavour to gain agreement to share data in response to requests.

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