Title

Avelumab for patients with previously treated metastatic or recurrent non-small-cell lung cancer (JAVELIN Solid Tumor): dose-expansion cohort of a multicentre, open-label, phase 1b trial

Permalink

Journal

ISSN

Authors

Gulley, James L
Rajan, Arun
Spigel, David R
et al.

Publication Date

DOI

Peer reviewed

Avelumab for patients with previously treated metastatic or recurrent non-small-cell lung cancer (JAVELIN Solid Tumor): dose-expansion cohort of a multicentre, open-label, phase 1b trial

James L Gulley, Arun Rajan, David R Spigel, Nicholas Iannotti, Jason Chandler, Deborah J L Wong, Joseph Leach, W Jeff Edenfield, Ding Wang, Hans Juergen Grote, Anja von Heydebreck, Kevin Chin, Jean-Marie Cuillerot, Karen Kelly

Summary

Background Avelumab, a human Ig-G1 monoclonal antibody targeting PD-L1 and approved in the USA for the treatment of metastatic Merkel cell carcinoma, has shown antitumour activity and an acceptable safety profile in patients with advanced solid tumours in a dose-escalation phase 1a trial. In this dose-expansion cohort of that trial, we assess avelumab treatment in a cohort of patients with advanced, platinum-treated non-small-cell lung cancer (NSCLC).

Methods In this dose-expansion cohort of a multicentre, open-label, phase 1 study, patients with progressive or platinum-resistant metastatic or recurrent NSCLC were enrolled at 58 cancer treatment centres and academic hospitals in the USA. Eligible patients had confirmed stage IIIB or IV NSCLC with squamous or non-squamous histology, measurable disease by Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1), tumour biopsy or archival sample for biomarker assessment, and Eastern Cooperative Oncology Group performance status 0 or 1, among other criteria. Patient selection was not based on PD-L1 expression or expression of other biomarkers, including *EGFR* or *KRAS* mutation or *ALK* translocation status. Patients received infusional avelumab monotherapy 10 mg/kg every 2 weeks until disease progression or toxicity. The primary objective was to assess safety and tolerability. This trial is registered with ClinicalTrials.gov, number NCT01772004; enrolment in this cohort is closed and the trial is ongoing.

Findings Between Sept 10, 2013, and June 24, 2014, 184 patients were enrolled and initiated treatment with avelumab. Median follow-up duration was 8·8 months (IQR 7·2–11·9). The most common treatment-related adverse events of any grade were fatigue (46 [25%] of 184 patients), infusion-related reaction (38 [21%]), and nausea (23 [13%]). Grade 3 or worse treatment-related adverse events occurred in 23 (13%) of 184 patients; the most common (occurring in more than two patients) were infusion-related reaction (four [2%] patients) and increased lipase level (three [2%]). 16 (9%) of 184 patients had a serious adverse event related to treatment with avelumab, with infusion-related reaction (in four [2%] patients) and dyspnoea (in two [1%]) occurring in more than one patient. Serious adverse events irrespective of cause occurred in 80 (44%) of 184 patients. Those occurring in more than five patients (≥3%) were dyspnoea (ten patients [5%]), pneumonia (nine [5%]), and chronic obstructive pulmonary disease (six [3%]). Immune-related treatment-related events occurred in 22 patients (12%). Of 184 patients, 22 (12% [95% CI 8–18]) achieved a confirmed objective response, including one complete response and 21 partial responses. 70 (38%) had stable disease. Overall, 92 (50%) of 184 patients achieved disease control (they had a confirmed response or stable disease as their best overall response). One patient was initially thought to have died from grade 5 radiation pneumonitis during the study; however, this adverse event was subsequently regraded to grade 3 and the death was attributed to disease progression.

Interpretation Avelumab showed an acceptable safety profile and antitumour activity in patients with progressive or treatment-resistant NSCLC, providing a rationale for further studies of avelumab in this disease setting.

Funding Merck KGaA and Pfizer.

Introduction

Lung cancer is the leading cause of cancer deaths worldwide.[1] Most patients present with stage IV disease, which has a median overall survival of 8–10 months and a 5-year relative survival of about 4%.[2–4] First-line treatment for patients with non-small-cell lung cancer (NSCLC) without any actionable mutation is generally based on platinum-doublet chemotherapy. Until recently, eligible patients with progressive disease following first-line therapy typically received chemotherapy with docetaxel or pemetrexed, which has been associated with a 1-year survival of about 30%.[5] In eligible subsets of patients with specific tumour biomarkers, such as *EGFR* mutations or *ALK* or protein kinase *ROS1* rearrangements, targeted therapy with tyrosine kinase inhibitors has shown clinical efficacy, but resistance eventually develops.[6,7]

Correspondence to:
Dr James L Gulley, Laboratory of
Tumor Immunology and Biology,
Center for Cancer Research,
National Cancer Institute,
National Institutes of Health,
Bethesda, MD 20892-1750, USA
gulleyj@mail.nih.gov

Research in context

Evidence before this study

Because the field of immunotherapy with anti-PD-L1 or anti-PD-1 immune checkpoint inhibitors has expanded rapidly in recent years, we did a 5-year systematic search of the English language literature using both PubMed and selected annual congresses (American Society of Clinical Oncology, European Society for Medical Oncology, European Cancer Congress, and World Conference on Lung Cancer). Search dates were between Jan 1, 2011, and Aug 22, 2016, and terms included "PD-1" and "PD-L1," in addition to relevant generic and investigational drug names of immune checkpoint inhibitors ("nivolumab", "BMS-936558", "pembrolizumab", "lambrolizumab", "MK-3475", "atezolizumab", "MPDL3280A", "durvalumab", "MEDI4736", "avelumab", and "MSB0010718A"). Most clinical studies were published after 2013. Additional search terms were used to identify literature about patients with advanced non-small-cell lung cancer (NSCLC). Recent evidence from phase 2 and phase 3 trials indicates that anti-PD-L1 and anti-PD-1 antibodies have efficacy and are well tolerated in patients with squamous and non-squamous histological subtypes of NSCLC. Tumour PD-L1 expression might have predictive value for efficacy of anti-PD-1 antibodies in non-squamous NSCLC. Avelumab is a human anti-PD-L1 IgG1 antibody that is approved in the USA for the treatment of metastatic Merkel cell carcinoma and has shown promising antitumour activity and a manageable safety profile in several other tumour types. Unlike other anti-PD-L1 or anti-PD-1 antibodies approved or in advanced clinical development, avelumab has been shown to mediate antibody-dependent cellular cytotoxicity in vitro. Based on safety, pharmacokinetic, target occupancy, and preliminary efficacy data obtained during a dose-escalation study of avelumab, the dose of 10 mg/kg given as a 1-h intravenous infusion every 2 weeks was selected for phase 1 dose expansion in various tumours.

Added value of this study

We report the safety and antitumour activity of avelumab monotherapy in a large phase 1 cohort of patients with progressive or platinum-resistant metastatic or recurrent NSCLC. Eligible patients in this cohort were not preselected based on NSCLC histology, PD-L1 expression status, or *EGFR* or *ALK* status. Clinical activity was recorded independent of PD-L1 expression, or squamous versus non-squamous histology. This is the largest cohort of patients studied in a phase 1 trial of avelumab and further characterises its clinical attributes.

Implications of all the available evidence

Avelumab had a manageable safety profile and promising clinical activity in a population of patients with progressive, platinum-treated, metastatic, or recurrent NSCLC. Responses occurred irrespective of PD-L1 expression status and in squamous and non-squamous tumours. These findings support the therapeutic benefit of anti-PD-L1 antibodies in patients with previously treated NSCLC. These results with avelumab have provided the rationale for an ongoing phase 3 trial in the second-line NSCLC population and underscore the potential benefits of immunotherapy for patients with this difficult-to-treat disease.

NSCLC tumours can evade immune activity through several mechanisms, including the expression of molecules (immune checkpoints) that inhibit T-cell activation. In particular, PD-L1 expression is often up-regulated in immunogenic tumours, including NSCLC,[8,9] and binding of PD-L1 to its receptor on T cells, PD-1, inhibits tumour immunity by suppressing T-cell activation,[8,10,11] enabling tumours to escape T-cell surveillance. PD-L1–PD-1 axis blockade might stimulate a patient's antitumour immune response by promoting T-cell reactivity against tumour neoantigens.[12] Patients with recurrent or metastatic NSCLC have few therapeutic options. However, recently, PD-L1–PD-1-targeted immune checkpoint inhibitors have been shown to increase overall survival versus docetaxel in patients with previously treated advanced NSCLC, leading to regulatory approval of three anti-PD-L1–PD-1 therapies (atezolizumab, nivolumab, and pembrolizumab) in this setting.[13–16] These agents might therefore be able to address a major unmet need. Correlative and translational studies in NSCLC and other tumour types suggest that the clinical benefits of immune checkpoint inhibition might be affected by tumour histology, mutational load, molecular drivers of disease, and expression of PD-L1 by tumours, although responses have been achieved independently of these factors.[9,17,18] However, patient selection and stratification based on such factors are important characteristics to consider in clinical study design and prespecified subgroup analyses.

Avelumab (MSB0010718C) is a human anti-PD-L1 IgG1 antibody that has been approved in the USA for the treatment of metastatic Merkel cell carcinoma. Avelumab inhibits PD-L1–PD-1 interactions but leaves the PD-L2–PD-1 pathway intact. By contrast with other PD-L1–PD-1 drugs assessed in clinical trials so far, avelumab binding to the surface of tumour cells via PD-L1 has the potential to induce natural killer cell-mediated antibody-dependent cellular cytotoxicity (ADCC) of tumour cells, as shown by preclinical models, which might contribute to its clinical activity.[19,20] A large, multicohort, phase 1 dose-escalation and dose-expansion trial is being done[21] to assess the safety and activity of avelumab in patients with a range of advanced solid tumours. In the phase 1a dose-escalation part of the study, avelumab was safely given by intravenous infusion every 2 weeks, had a predictable pharmacokinetic profile at doses up to 20 mg/kg, and showed preliminary evidence of antitumour activity, including durable responses and stable disease.[21,22] The 10 mg/kg dose, which has a half-life of about 4 days, was selected for further study in dose-expansion cohorts in a range of

tumour types. Here, we present phase 1b results from this study in a cohort of patients with advanced NSCLC whose disease has progressed after platinum-based chemotherapy and are unselected for PD-L1 expression.

Methods

Study design and participants

JAVELIN Solid Tumor is an ongoing, international, multicentre, phase 1, open-label trial that includes several expansion cohorts. This trial included a dose-escalation part (phase 1a), the results of which are reported separately, and a dose-expansion part (phase 1b) comprising 16 different cohorts. In the dose-expansion cohort reported here, eligible patients had histologically or cytologically confirmed stage IIIB or IV NSCLC, with squamous or non-squamous histology, which had progressed after treatment with platinum-based doublet chemotherapy for metastatic disease. Eligible patients were aged 18 years or older and had an Eastern Co-operative Oncology Group (ECOG) performance status of 0–1, a life expectancy of at least 3 months, no active or history of CNS metastases, and adequate haematological, hepatic, and renal function (defined by the following laboratory values: white blood cell count ≥3×10⁹ cells per L with an absolute neutrophil count ≥1·5×10⁹ cells per L, lymphocyte count ≥0·5×10⁹ cells per L, platelet count ≥100×10⁹ platelets per L, haemoglobin ≥9 g/dL, total bilirubin concentration of ≤1·5×the upper limit of normal [ULN] range, aspartate aminotransferase and alanine aminotransferase concentrations of ≤2·5×ULN, and an estimated creatinine clearance >50 mL/min according to the Cockcroft-Gault formula). Patients had to have measurable disease by CT or MRI scan and Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1[23] and available fresh biopsy or tumour archival material for biomarker analyses (see appendix pp 16–18 for full eligibility criteria). Patient selection was not based on PD-L1 expression or other biomarkers, including *EGFR* or *KRAS* mutation or *ALK* translocation status. Previous use of a T-cell-targeting immune checkpoint inhibitor was not permitted and no other anticancer therapies could be continued on study. Patients could not have had another cancer diagnosis within 5 years before study entry, rapidly progressing disease, CNS metastases, previous stem-cell or organ transplant, known hyper-sensitivity to monoclonal antibodies, or known auto-immune disease. Pregnant or lactating patients were excluded because of the unknown effects of avelumab on a foetus or infant. Steroid use within 30 days of enrolment was not allowed, and steroids were not allowed on study except to manage immune-related adverse events. Patients were enrolled in accordance with an approved protocol, which was approved by the principal and coordinating investigator of the trial (JLG), individuals employed by the sponsor with responsibility for the trial, and relevant regulatory authorities—international standards of good clinical practice in accordance with the ethics principles of the Declaration of Helsinki and the International Council on Harmonisation Guidelines on Good Clinical Practice, and institutional safety monitoring, and written informed consent was provided by patients or their representatives. Ethics committees at all of the participating institutions approved the protocol. The appendix lists participating institutions (appendix pp 6, 7).

Procedures

Avelumab was supplied as a 10 mg/mL solution. Patients received avelumab 10 mg/kg by 1-h intravenous infusion once every 2 weeks until confirmed disease progression, unacceptable toxicity, or any other criterion for withdrawal occurred. Treatment was discontinued permanently in the event of any grade 3 or worse adverse event (with the exception of transient [≤6 h] influenza-like symptoms or pyrexia controlled with medical management; fatigue, local infusion-related reaction, headache, nausea, or emesis that resolved to grade ≤1 within 24 h; single laboratory values out of the normal range that were unrelated to study treatment and without clinical correlate [except for increase in liver enzyme concentrations] that resolved to grade ≤1 within 7 days; and tumour flare, defined as local pain, irritation, or rash localised at sites of known or suspected malignant tissue) or recurring grade 2 treatment-related adverse events. Grade 2 adverse drug reactions were managed by dose modifications (changes in the infusion rate) and dose delays, and those that did not resolve to grade 1 or less severity by the end of the next cycle led to permanent discontinuation of avelumab. Dose modifications were not recommended; however, interruptions in delivery of the planned dose that resulted in an actual dose that was less than 90% of the planned dose were defined as dose reductions. Detailed guidelines were provided for delaying or discontinuing treatment following specified adverse events of different grades (appendix pp 18, 19).

Safety was assessed at each biweekly trial visit and included assessment of performance status, physical examination, clinical laboratory tests (haematology, serum chemistry, and hepatic panels), and documentation of concurrent medications and adverse events. Adverse events and laboratory abnormalities were classified and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Adverse events that had an immune-related cause were identified using a prespecified list of Medical Dictionary for Regulatory Activities (MedDRA) terms. Infusion-related reaction was classified as an adverse event of special interest, and signs and symptoms such as fever, chills, or rigors reported on the same day or next day following treatment were queried with investigators to ascertain whether an adverse event of infusion-related reaction should be recorded. A premedication regimen of diphenhydramine and paracetamol, implemented as mandatory on Jan 29, 2014, was required 30–60 min

See **Online** for appendix

288 patients assessed for eligibility

104 excluded before treatment
    81 did not meet all eligibility criteria
    8 withdrew informed consent
    4 died before study treatment
    11 other reasons

184 enrolled and treated with ≥1 dose of avelumab

143 discontinued study treatment
    93 had disease progression
    18 had an adverse event
    10 died
    6 withdrew informed consent
    2 not compliant with protocol
    1 lost to follow-up
    13 other reasons
44 discontinued treatment and still in follow-up

41 treatment ongoing

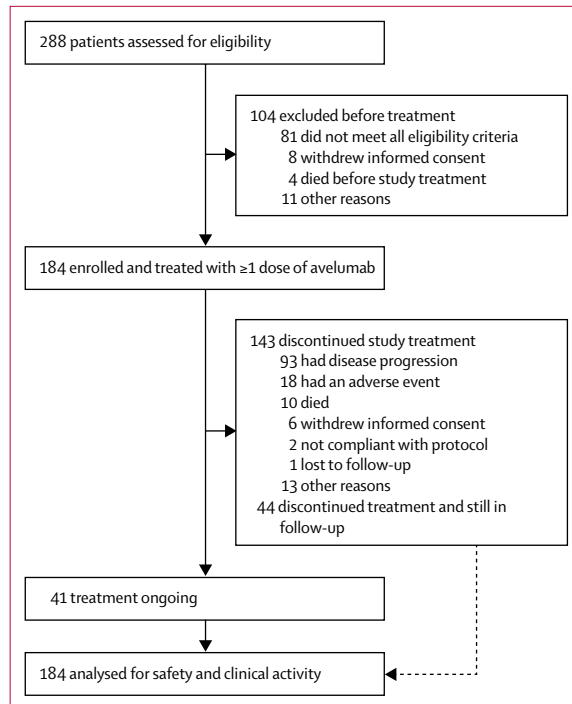**184 analysed for safety and clinical activity**

Figure 1: Trial profile

before all infusions of avelumab. Patients enrolled before this date might not have received premedication.

Clinical activity was assessed by investigators using RECIST version 1.1 to determine best overall response, defined as the best response obtained among all tumour assessments after the start of treatment with avelumab until documented disease progression, and duration of response. Radiographic tumour assessments were done at baseline and then every 6 weeks. Change in the sum of target lesion diameters from baseline over time was evaluated in patients with baseline tumour assessments and at least one post-baseline assessment. Modified immune-related response criteria, derived from RECIST version 1.1, were used to assess response patterns related to immunotherapeutic agents that might not have been adequately captured by RECIST or modified WHO criteria (appendix p 20).[24]

Levels of PD-L1 protein expressed by tumour cells and immune cells within the tumour microenvironment were measured in a central laboratory by immunohisto-chemistry staining of formalin-fixed, paraffin-embedded blocks (preferred) or slides of the most recent suitable biopsy or surgical specimen with a proprietary assay (Dako, Carpinteria, CA, USA) on the basis of an anti-PD-L1 rabbit monoclonal antibody clone 73–10 under licence from Merck KGaA (Darmstadt, Germany). PD-L1 positivity in tumour cells was scored on the basis of the proportion of tumour cells showing membranous PD-L1 staining. Three thresholds were prospectively defined, based on preliminary assessments of PD-L1 expression

and tumour response: 1% and 5% tumour cells PD-L1 positive with any staining intensity, and 25% of tumour cells positive with moderate-to-high staining intensity (2+ to 3+). PD-L1 positivity in tumour-associated immune cells (identified as non-malignant cells based on conventional morphological features) was determined with the use of a prospectively defined threshold of 10% of immune cells showing PD-L1 staining of any intensity within hotspots (dense aggregates of tumour-associated immune cells adjacent to tumour cells showing PD-L1 staining in immune cells). Tumour assessment for *EGFR* or *KRAS* mutation or *ALK* translocation was done at individual centres based on local protocols.

Outcomes

The primary endpoint of the trial was occurrence of dose-limiting toxicities during the first 3 weeks of treatment in the dose-escalation part of the study; these data are reported elsewhere.[21] Secondary endpoints included best overall response (defined as complete response, partial response, stable disease, or progressive disease), unconfirmed response at week 13 according to RECIST version 1.1 per investigator assessment, duration of response (defined as the time from first documented complete or partial response until documented progressive disease or death, whichever occurred first) and progression-free survival (defined as time from the first administration of avelumab until documented progressive disease or death, whichever occurred first) by RECIST version 1.1 and by modified immune-related response criteria per investigator assessment; overall survival (defined as the time from first administration of avelumab until the date of death); safety (number, severity, and duration of treatment-emergent or treatment-related adverse events); and activity according to PD-L1 expression on tumour and tumour-associated immune cells. Other secondary endpoints (pharmacokinetic and pharmacodynamic profile and immunogenicity of avelumab) will be analysed across several cohorts of this phase 1 study of patients with different tumour types and will be reported elsewhere. Exploratory subgroup analyses based on patient and disease characteristics at baseline were done post hoc.

Statistical analysis

Enrolment of 150 patients was planned in this cohort. The sample size was chosen to explore safety and antitumour activity of avelumab in the overall cohort in addition to subgroups defined by prespecified PD-L1 tumour expression status and to provide data to help in future study design. Safety and activity were analysed in all patients who received at least one dose of avelumab. Patients with no post-baseline assessments due to discontinuation or death within the first 6 weeks were not evaluable for a confirmed best overall response and were categorised as non-responders. The specified

	Patients (n=184)
Age (years)	65·0 (58·0–69·5)
Sex	
Men	100 (54%)
Women	84 (46%)
ECOG performance status	
0	55 (30%)
1	128 (70%)
2	0
3*	1 (1%)
Disease stage†	
IIIB	13 (7%)
IV	170 (92%)
Unknown	1 (1%)
Time since first diagnosis (months)	11·5 (6·8–21·7)
Time since diagnosis of metastatic disease (months)	8·5 (5·5–16·2)
Histology	
Adenocarcinoma	114 (62%)
Large cell	5 (3%)
Squamous cell carcinoma	53 (29%)
Other‡	12 (7%)
Smoking history	
Never smoked	24 (13%)
Ever smoked	159 (86%)
Unknown	1 (1%)
EGFR mutation status	
Wild type	101 (55%)
Mutant	9 (5%)
Unknown	74 (40%)
KRAS mutation status	
Wild type	38 (21%)
Mutant	21 (11%)
Unknown	125 (68%)
ALK translocation status	
Negative	103 (56%)
Positive	1 (1%)
Unknown	80 (44%)
(Table 1 continues in next column)	

	Patients (n=184)
(Continued from previous column)	
Number of previous lines of anticancer therapy for advanced disease	
0§	1 (1%)
1	122 (66%)
2	44 (24%)
≥3	17 (9%)
Number of previous lines of anticancer therapy for advanced disease	1 (1–2)
PD-L1 expression status¶	
≥1% tumour cells	
PD-L1-positive	122 (86%)
PD-L1-negative	20 (14%)
≥5% tumour cells	
PD-L1-positive	84 (59%)
PD-L1-negative	58 (41%)
≥25% tumour cells	
PD-L1-positive	53 (37%)
PD-L1-negative	89 (63%)
≥10% tumour-associated immune cells in hotspots	
PD-L1-positive	27 (19%)
PD-L1-negative	115 (81%)

Data are n (%) or median (IQR). Some percentages do not sum to 100 because of rounding. ECOG=Eastern Cooperative Oncology Group. *The patient had an ECOG performance status of 1 at screening, which had increased to 3 at start of treatment. †Data for disease stage was missing for one patient. ‡Other category includes poorly differentiated carcinoma (n=3), poorly differentiated adenocarcinoma (n=2), poorly differentiated non-squamous (n=1), poorly differentiated sarcomatoid carcinoma (n=1), moderately differentiated adenocarcinoma (n=1), adenosquamous (n=2), neuroendocrine (n=1), and carcinoma not further defined (n=1). §One patient with stage IV disease at study entry was enrolled without having received previous systemic therapy for advanced disease. This patient had been treated with two lines of previous systemic therapy in the adjuvant setting (pemetrexed plus carboplatin and paclitaxel, followed by erlotinib) and a protocol deviation was noted by the investigator. ¶PD-L1 expression was evaluable in 142 (77%) of 184 patients. Non-evaluable specimens (n=42) included those that were missing (n=8), of poor quality or quantity (insufficient tissue on slide [n=8] or insufficient tumour sample [n=9]), or otherwise not available to provide results (n=17). Thresholds for positive PD-L1 status were based on any intensity of staining except for ≥25% tumour cells, for which moderate-to-high intensity staining was required.

Table 1: Baseline characteristics

timeframe for the primary analysis was 6 months after the date of the first dose in the last patient enrolled. Objective response—defined as the proportion of patients with a confirmed best overall response of complete or partial response—was calculated with corresponding Clopper-Pearson CI; if at least 10% of patients (95% CI 6–16) achieved an objective response, this was regarded as indicative of clinical benefit (ie, 15 patients with a response of 150 patients planned for enrolment). Time-to-event endpoints were estimated with Kaplan-Meier methods; median values were calculated with corresponding 95% CIs using Brookmeyer-Crowley methods. Data were analysed with SAS (version 9.2), and R software package (version 2.15.0) was used for the sample size calculations.

This trial is registered with ClinicalTrials.gov, number NCT01772004.

Role of the funding source

	Grade 1–2	Grade 3	Grade 4	Grade 5
Treatment-related adverse events occurring at any grade in ≥5% of patients or any grade ≥3				
Any event	119 (65%)	16 (9%)	6 (3%)	1 (1%)
Fatigue	46 (25%)	0	0	0
Infusion-related reaction*	34 (19%)	2 (1%)	2 (1%)	0
Nausea	23 (13%)	0	0	0
Decreased appetite	13 (7%)	0	0	0
Diarrhoea	13 (7%)	0	0	0
Chills	12 (7%)	0	0	0
Hypothyroidism	11 (6%)	0	0	0
Arthralgia	9 (5%)	0	0	0
Vomiting	9 (5%)	0	0	0
Anaemia	6 (3%)	1 (1%)	0	0
Dyspnoea	4 (2%)	1 (1%)	1 (1%)	0
Constipation	3 (2%)	2 (1%)	0	0
Increased lipase	1 (1%)	3 (2%)	0	0
Increased amylase	2 (1%)	0	1 (1%)	0
Increased γ glutamyltransferase	1 (1%)	1 (1%)	0	0
Radiation pneumonitis†	1 (1%)	0	0	1 (1%)
Anaphylactic reaction	0	1 (1%)	0	0
Autoimmune neutropenia	0	0	1 (1%)	0
Chronic obstructive pulmonary disease	0	1 (1%)	0	0
Increased transaminases	0	1 (1%)	0	0
Embolic stroke	0	0	1 (1%)	0
Fall	0	1 (1%)	0	0
Hypertension	0	1 (1%)	0	0
Hyponatraemia	0	1 (1%)	0	0
Hypovolaemia	0	1 (1%)	0	0
Hypoxia	0	1 (1%)	0	0
Lung abscess	0	1 (1%)	0	0
Monoplegia	0	0	1 (1%)	0
Musculoskeletal pain	0	1 (1%)	0	0
Pneumonitis	0	0	1 (1%)	0
Syncope	0	0	1 (1%)	0
Systemic inflammatory response syndrome	0	1 (1%)	0	0
Urosepsis	0	1 (1%)	0	0
(Table 2 continues in next column)				

	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous column)				
Treatment-related adverse events classified as immune-related occurring at any frequency				
Any event	18 (10%)	1 (1%)	2 (1%)	1 (1%)
Hypothyroidism	11 (6%)	0	0	0
Adrenal insufficiency	2 (1%)	0	0	0
Radiation pneumonitis†	1 (1%)	0	0	1 (1%)
Arthritis	1 (1%)	0	0	0
Autoimmune neutropenia	0	0	1 (1%)	0
Dry eye	1 (1%)	0	0	0
Iritis	1 (1%)	0	0	0
Pneumonitis	0	0	1 (1%)	0
Psoriasis	1 (1%)	0	0	0
Increased rheumatoid factor	1 (1%)	0	0	0
Systemic inflammatory response syndrome	0	1 (1%)	0	0

Data are n (%). *Signs and symptoms of a potential infusion-related reaction (eg, fever, chills, or rigors) reported on the day of infusion were queried with investigators to ascertain whether an adverse event of infusion-related reaction should be recorded. †Grade 5 radiation pneumonitis was reported in one patient, which was later regraded to a grade 3 event of radiation pneumonitis that had not resolved at the time of death. The primary cause of death in this patient was ultimately attributed to disease progression.

Table 2: Treatment-related adverse events (worst grade per patient)

Results

Between Sept 10, 2013, and June 24, 2014, 288 patients were screened and 184 eligible patients with locally advanced or metastatic measurable disease that had relapsed following treatment with a platinum-based doublet therapy were enrolled at 58 cancer treatment centres and academic hospitals in the USA (appendix pp 6, 7) and received avelumab (figure 1). Because of high interest in the study and subsequent acceleration of recruitment by investigators at the end of the enrolment period, planned enrolment (of 150 patients) was exceeded by 34 patients. The median age of the participants was 65·0 years (IQR 58·0–69·5) and just over half were men

(table 1). Of 184 treated patients, most had an ECOG performance status of 1, had stage IV disease, were current or former smokers, and had received only one previous line of chemotherapy for metastatic disease (table 1). One patient with stage IV disease at study entry was enrolled without having received previous systemic therapy for advanced disease. This patient had been treated with two lines of prior systemic therapy in the adjuvant setting (pemetrexed plus carboplatin and paclitaxel, followed by erlotinib) and a protocol deviation was noted by the investigator. Tumours had squamous cell histology in approximately a third of patients. *EGFR* mutational status was assessed in 110 (60%) of 184 patients, and a mutation was found in nine (5%). *ALK* translocation status was determined in 104 (57%) of 184 patients, and one tumour (1%) was positive. PD-L1 expression was evaluable in 142 (77%) of 184 patients; 122 (86%) of 142 had PD-L1-positive tumours based on a 1% threshold. Additional patient demographic and disease characteristics and previous anticancer therapies are provided in the appendix (pp 8, 9).

Patients received a median of six doses of avelumab (IQR 3–15) given every 2 weeks for a median of 12·2 weeks (IQR 6·1–30·0). At data cutoff on Jan 15, 2015, median follow-up was 8·8 months (IQR 7·2–11·9; all patients were followed up for a minimum of 6 months), and 41 (22%) of 184 patients were still on treatment. Among 143 patients who discontinued avelumab, the most common reason was

disease progression (figure 1). Dosing was modified (the planned dose was not administered in full) in nine (5%) of 184 patients, due to infusion-related reaction in seven patients (4%; five grade 1–2, one grade 3, and one grade 4), treatment-related grade 2 chest discomfort in one (1%) patient, and unrelated grade 1 erythema in one (1%) patient. Dosing was delayed for 3–6 days in 34 (19%) patients and for 7 days or longer in 42 (23%) patients; these delays were due to an adverse event (related or unrelated to treatment) in 28 (15%) of 184 patients, most commonly diarrhoea and upper respiratory tract infection (three patients [2%] each).

Of 184 treated patients, 182 (99%) had an adverse event of any grade (appendix pp 10–13); 142 (77%) had a treatment-related adverse event (table 2), of which fatigue (46 [25%]), infusion-related reaction (38 [21%]), and nausea (23 [13%]) were the most common. Grade 3 or worse treatment-related adverse events occurred in 23 (13%) of 184 patients, of which only infusion-related reaction (four [2%] patients) and increased lipase level (three [2%] patients) occurred in more than two patients. Avelumab was permanently discontinued because of a treatment-related adverse event in 17 (9%) patients: infusion-related reaction in eight (4%) patients, increased lipase level in two (2%), dyspnoea in two (2%), and syncope, increased gamma-glutamyltransferase, auto-immune neutropenia, adrenal insufficiency, stomatitis, anaphylactic reaction, and radiation pneumonitis occurring in one (1%) patient each.

The incidence of infusion-related reactions was analysed post hoc in more detail using a composite definition including three MedDRA-preferred terms (infusion-related reaction, drug hypersensitivity, and anaphylactic reaction) occurring within 1 day or related symptoms (eg, chills, pyrexia, and flushing) that resolved within 2 days of infusion. Of 39 patients who had an event using this expanded definition, 34 (87%) were grade 1–2, and five (13%) were grade 3–4. Most infusion-related reactions (35 [90%] of 39 cases) occurred during the first or second administration of avelumab (appendix p 2). Of 166 patients who received premedication before at least one dose of avelumab, 26 (16%) had an infusion-related reaction, which reached grade 3 in one (1%) patient and grade 4 in one (1%) patient.

Immune-related adverse events of any grade occurred in 36 (20%) of 184 patients and were considered treatment-related by the investigator in 22 (12%) patients, of which hypothyroidism (11 [6%]), adrenal insufficiency (two [1%]), and radiation pneumonitis (two [1%]) were the most common. Four (2%) patients had a grade 3 or worse immune-related treatment-related adverse event (one radiation pneumonitis, one autoimmune neutro-penia, one pneumonitis, and one systemic inflammatory response syndrome). Three (2%) patients permanently discontinued avelumab treatment following immune-related events, all of which were judged to be treatment related (grade 5 radiation pneumonitis that was

	Patients (n=184)
Complete response	1 (1%)
Partial response	21 (11%)
Stable disease	70 (38%)
Progressive disease	69 (38%)
Non-evaluable*	23 (13%)
Objective responses	22 (12%; 8–18)
Disease control	92 (50%)
Progression-free survival	
Progression-free survival, weeks	11·6 (8·4–13·7)
Progression-free survival at 24 weeks	26% (20–33)
Progression-free survival at 48 weeks	18% (12–26)
Overall survival	
Overall survival, months	8·4 (7·3–10·6)
Overall survival at 12 months	36% (26–46)

Data are n (%) or n (%; 95% CI), % (95% CI), or median (95% CI). Response rates are based on confirmed responses. *Patients with missing or no assessable information included 19 patients without post-baseline tumour assessments (12 patients died within 6 weeks, one patient had an unevaluable post-baseline target lesion, four patients withdrew consent, and two patients discontinued because of disease progression) and four patients with stable disease who did not meet minimum duration requirement and for whom no further tumour assessments were available during follow-up.

***Table 3:* Clinical activity of avelumab**

subsequently regraded to grade 3, grade 3 autoimmune neutropenia, and grade 2 adrenal insufficiency.

Serious adverse events irrespective of cause occurred in 80 (44%) of 184 patients (appendix pp 10–13). Those occurring in more than five (≥3%) patients were dyspnoea (ten [5%] patients), pneumonia (nine [5%]), and chronic obstructive pulmonary disease (six [3%]). 16 (9%) of 184 patients had a serious adverse event related to treatment with avelumab (six patients had two events each), with infusion-related reaction (four [2%]) and dyspnoea (two [1%]) occurring in more than one patient, and abdominal pain, anaphylactic reaction, autoimmune neutropenia, chronic obstructive pulmonary disease, embolic stroke, hyponatraemia, hypovolaemia, mono-plegia, pneumonitis, pleural effusion, radiation pneu-monitis, generalised rash, syncope, systemic inflammatory response syndrome, and urosepsis occurring in one (1%) patient each. Of these treatment-related events judged to be serious, grade 3 systemic inflammatory response syndrome, grade 4 autoimmune neutropenia, grade 4 pneumonitis, and grade 5 radiation pneumonitis (which occurred in one patient each) were classified as immune-related. One (1%) death was reported that was initially assessed by the investigator as being related to trial treatment and attributed to radiation pneumonitis. The patient had a history of dyspnoea and had received radiotherapy to the chest and right lung 4 months before treatment with avelumab. After further assessment, the event of radiation pneumonitis was reclassified as a grade 3 event that had not resolved at the time of death, and disease progression was recorded as the primary cause of death.
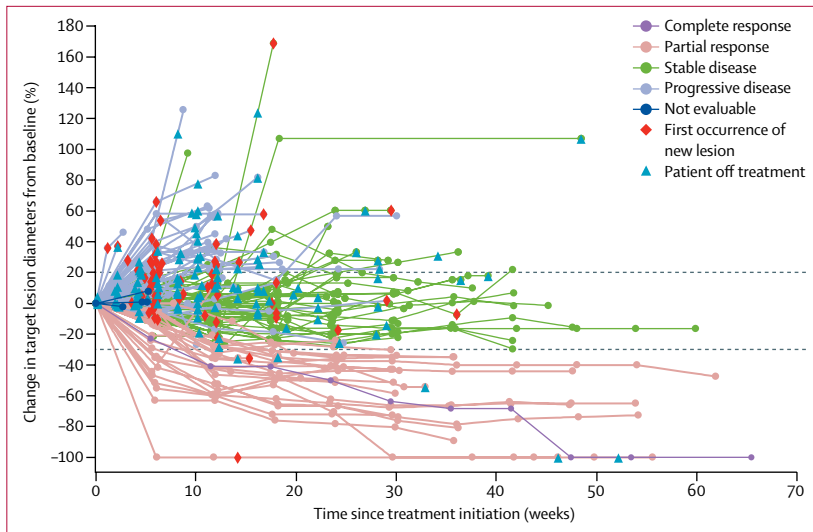
Figure 2: Change from baseline in target lesion diameters over time
Spider plot of the change in sum of target lesion diameters from baseline over time for all evaluable patients (n=158), defined as those with baseline tumour assessments and at least one post-baseline assessment. Lines are colour coded based on best overall response (confirmed and unconfirmed). Horizontal dashed lines represent Response Evaluation Criteria In Solid Tumors version 1.1 guideline for partial response (≥30% decrease in target lesion) and progressive disease (≥20% increase in target lesion).
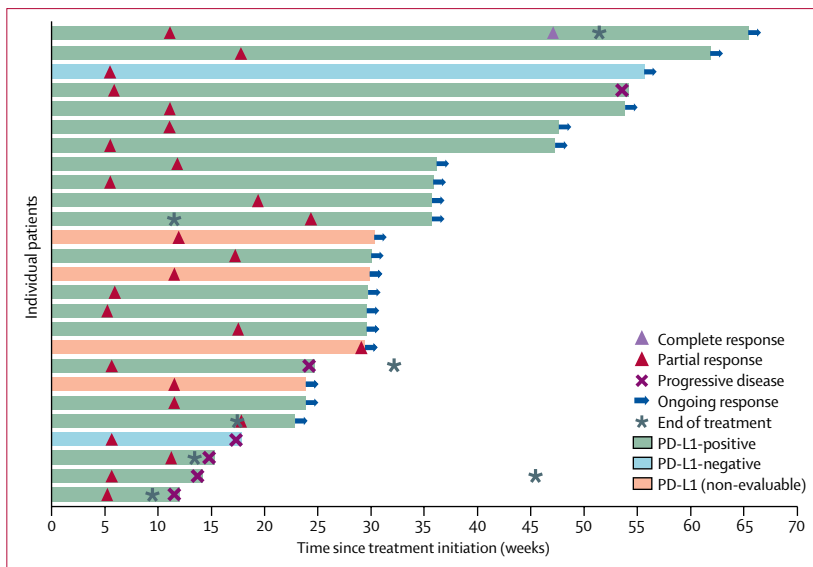
Figure 3: Time to and duration of response in patients with a complete or partial response
Bars represent individual patients with partial response or complete response (confirmed and unconfirmed) and are colour coded on the basis of PD-L1 status at the ≥1% tumour cell staining cutoff. Responses were ongoing in 20 patients at the time of data cutoff. 26 patients achieved a response (two PD-L1-negative patients, 20 PD-L1-positive patients, and four patients not evaluable for PD-L1 staining).

Of 184 patients, 22 (12% [95% CI 8–18]; table 3) achieved a confirmed objective response, including one complete response and 21 partial responses. 26 (14%; 95% CI 9–20) patients achieved an unconfirmed objective response, including one complete response and 25 partial responses. 22 patients (12% [95% CI 8–18]) achieved a confirmed objective response by immune-related response criteria. 26 (14%) of 184 patients had a reduction in size of target lesions by 30% or more from baseline (appendix p 3), including four patients not classified as achieving a confirmed response because of absence of response confirmation or new lesion developing. 92 (50%) of 184 patients achieved disease control (they had a confirmed response or stable disease as their best overall response) and 70 (38%) had stable disease. Figure 2 shows change in target lesion diameters over time in 158 evaluable patients. Based on confirmed or unconfirmed responses by RECIST version 1.1, ten (39%) of 26 responding patients had responded by the first assessment at 6 weeks, and 19 (73%) of 26 had responded by 12 weeks (figure 3); median duration of response was not reached (95% CI 48·1–not evaluable), with response durations ranging from 0·1 weeks to ongoing at 54·1 weeks (figure 3). In 22 patients with a confirmed response, response was maintained for 24 weeks or longer in 83% of patients (95% CI 54–94) by Kaplan-Meier estimates. Median progression-free survival according to RECIST version 1.1 was 11·6 weeks (95% CI 8·4–13·7), and progression-free survival was 26% (20–33) at 24 weeks and 18% (12–26) at 48 weeks (table 3). At the time of analysis, 139 (76%) of 184 patients had experienced an event, which was disease progression in 116 (63%) or death in 23 (13%). Based on immune-related response criteria, median progression-free survival was 17·6 weeks (95% CI 12·1–22·9), and progression-free survival at 24 weeks was 39% (95% CI 31–46) and at 48 weeks was 33% (25–42). Median overall survival was 8·4 months (95% CI 7·3–10·6), and overall survival at 12 months was 36% (26–46; table 3), based on 90 (49%) of 184 patients who had died. 38 (21%) of 184 patients received anticancer therapy after discontinuing avelumab, including drug therapy in 33 (18%) and radiotherapy in 16 (9%); drugs given were cytotoxic chemotherapy in 28 (15%) patients and targeted therapy in 13 (7%) patients.

Antitumour activity was seen in tumours defined as PD-L1-positive or PD-L1-negative using prespecified PD-L1 expression levels on tumour cells (≥1%, ≥5%, and ≥25%) and tumour-associated immune cells (table 4). The proportion of patients who achieved an objective response or overall survival outcomes did not differ between patients with PD-L1-positive versus PD-L1-negative tumours at any prespecified PD-L1 expression level (table 4, figure 4A). Progression-free survival outcomes also did not differ between patients with PD-L1-positive versus PD-L1-negative tumours at most cutoff levels used (table 4); however, progression-free survival was longer in those patients with PD-L1-positive tumours than in those with PD-L1-negative tumours in an analysis based on a 1% cutoff for tumour cell staining (hazard ratio for progressive disease 0·45 [95% CI 0·27–0·75]; figure 4B, table 4, appendix pp 4, 5).

In an exploratory post-hoc analysis, responses were observed independently of patient and disease characteristics, including tumour histology, previous lines of therapy, and smoking status (appendix pp 14, 15). No responses were recorded among the few patients with

known *EGFR*-mutant (n=9) or *ALK*-translocation-positive (n=1) tumours, and there was one responder among 21 patients with known KRAS-mutant tumours (appendix pp 14, 15).

Discussion

In this large cohort of patients with metastatic NSCLC that had progressed following chemotherapy with a platinum-containing doublet, avelumab monotherapy showed an acceptable safety profile and encouraging clinical activity. Confirmed responses, which generally occurred early and were durable, were recorded in some patients, and more than a third of patients achieved stable disease. The time to response observed with avelumab is similar to median time to response reported for chemotherapy administered in the second-line setting;[5] assessment of early responses was enabled by the prespecified schedule for radiological tumour assessments. Subgroup analyses done post hoc were generally consistent with overall findings and included responses in tumours with squamous and non-squamous histology.

Recently, the proportion of patients achieving disease response who have been given other anti-PD-L1–anti-PD-1 monotherapy in the second-line setting has been reported at 15–21%, although data cannot be compared directly because of differences in study designs and eligibility criteria, including reporting of unconfirmed responses and differences in eligibility based on previous treatment (drugs given and number of previous lines of therapy) or PD-L1 status using different assays.[16,25–28] Additionally, head-to-head comparisons of the various anti-PD-L1–anti-PD-1 antibodies in randomised trials have not been done. Thus, the data reported here do not enable us to draw more detailed conclusions about the efficacy of avelumab compared with other drugs in the same therapeutic class. 1-year progression-free survival and overall survival with avelumab were 18% and 36%, respectively. However, based on immune-related response criteria, the 1-year progression-free survival with avelumab was higher at 33%. These data support previous suggestions that the standard endpoints measured by RECIST might underestimate the benefit of treatment with anti-PD-L1 or anti-PD-1 antibodies.[16,29]

In some studies of anti-PD-L1–PD-1 therapy in NSCLC, better response rates and improved progression-free and overall survival with anti-PD-L1–PD-1 treatment have been associated with PD-L1-positive tumour cells or tumour-associated lymphocytes.[15,16,25,30] In our study, patients with PD-L1-positive tumour cells using the 1% cutoff had longer progression-free survival with avelumab than did patients with PD-L1-negative tumours, based on tumour classification using the novel anti-PD-L1 rabbit monoclonal antibody clone 73-10, although this finding should be interpreted with caution. Work is ongoing to further investigate the use of PD-L1 as a potential

	PD-L1-positive tumours	PD-L1-negative tumours	p value*	Hazard ratio (95% CI)
≥1% tumour cells, any intensity				
Patients	122	20	..	..
Objective response	17/122 (14% [8–21])	2/20 (10% [1–32])	>0·99	..
Median progression-free survival (weeks)	12·0 (10·4–17·7)	5·9 (5·6–7·1)	..	0·45 (0·27–0·75)
Progression-free survival at 48 weeks	21% (13–30)	5% (0–21)	..	..
Median overall survival (months)	8·9 (8·0–NE)	4·6 (2·8–NE)	..	0·64 (0·34–1·20)
Overall survival at 12 months	39% (26–52)	36% (14–58)	..	..
≥5% tumour cells, any intensity				
Patients	84	58	..	..
Objective response	12/84 (14% [8–24])	7/58 (12% [5–23])	0·81	..
Progression-free survival (weeks)	11·9 (6·7–18·3)	7·8 (6·0–12·0)	..	..
Progression-free survival at 48 weeks	25% (16–36)	10% (3–21)	..	0·70 (0·48–1·02)
Overall survival (months)	10·6 (7·9–NE)	8·4 (5·6–NE)	..	..
Overall survival at 12 months	39% (22–55)	37% (22–52)	..	
≥25% tumour cells, moderate-to-high intensity				
Patients	53	89	..	..
Objective response	9/53 (17% [8–30])	10/89 (11% [6–20])	0·45	..
Progression-free survival (weeks)	11·9 (6·1–22·9)	10·79 (6·0–13·7)	..	0·79 (0·53–1·18)
Progression-free survival at 48 weeks	28% (16–41)	15% (8–24)	..	..
Overall survival (months)	8·44 (6·0–11·1)	8·57 (7·16–NE)	..	1·14 (0·70–1·85)
Overall survival at 12 months	28% (12–47)	48% (35–60)	..	..
≥10% tumour-associated immune cells in hotspots, any intensity				
Patients	27	115	..	..
Objective response	4/27 (15% [4–34])	15/115 (13% [8–21])	0·76	..
Progression-free survival (weeks)	8·4 (5·7–15·1)	11·3 (6·7–15·3)	..	1·19 (0·74–1·92)
Progression-free survival at 48 weeks	NE	19% (11–28)	..	..
Overall survival (months)	8·5 (3·9–NE)	8·9 (7·9–NE)	..	1·20 (0·68–2·14)
Overall survival at 12 months	30% (10–53)	41% (28–54)	..	..

Data are n, n/number of patients with tumours evaluable for PD-L1 expression (%; 95% CI), or median (95% CI). NE=non-evaluable. *Fisher's exact test; p values were calculated on the basis of the binary comparison of positive versus negative.

Table 4: Confirmed responses, progression-free survival, and overall survival associated with PD-L1 expression (n=142)

biomarker for avelumab in NSCLC and other tumour types (NCT02576574, NCT0215564, NCT02603432, NCT02952586, NCT02493751, NCT02684006, NCT02625610, NCT02625623, NCT02718417, and NCT02580058). Direct comparisons of clinical activity based on PD-L1 status with different drugs is hampered by differences in PD-L1 assays in terms of sensitivity and staining properties between antibody clones; criteria for evaluating PD-L1 expression on tumour cell membranes, stroma, or immune cells within the
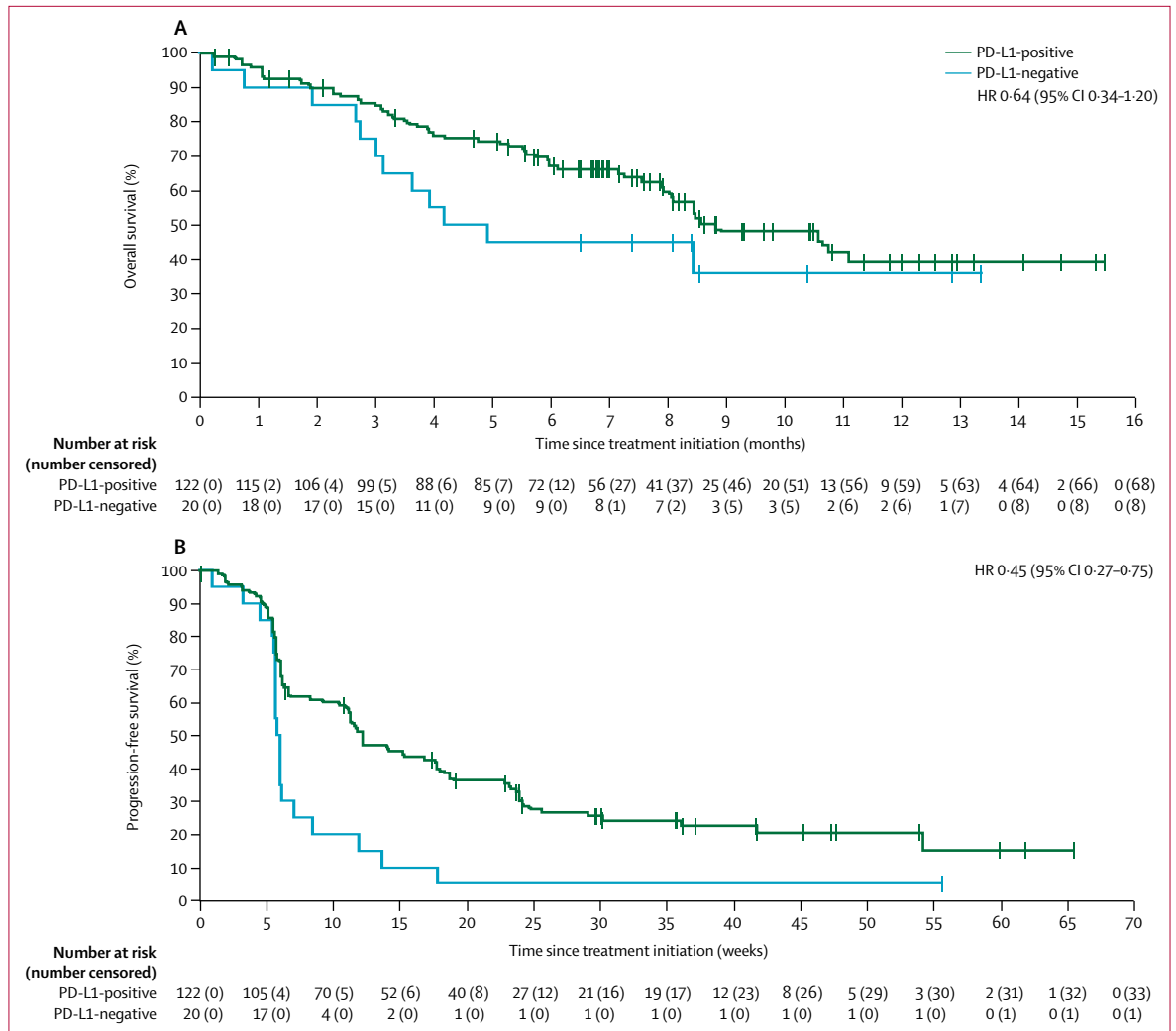
Figure 4: **Survival outcomes by PD-L1 expression status (≥1% tumour cell cutoff)**
(A) Overall survival. (B) Progression-free survival.

tumour microenvironment; testing platforms; and scoring algorithms. PD-L1 positivity was defined in this study at three prespecified levels for frequency and intensity of staining on tumour cell membranes and one prespecified level on tumour-associated immune cells. At the staining cutoffs defined for this study, the proportion of tumours expressing PD-L1 was higher than levels reported by other investigators using different assays—eg, Dako immunohistochemistry assay using murine clone 22C3 and VENTANA immunohistochemistry SP142 assay.[15,16,25] However, preliminary data using commercially procured NSCLC samples suggest that our assay is highly sensitive across a broad dynamic range; these data will be reported elsewhere (Grote HJ, Merck KGaA, Darmstadt, Germany, personal communication). Efforts to develop standardised approaches to PD-L1 expression diagnostics are underway, including the BLUEPRINT

proposal initiated by the US Food and Drug Administration, American Association for Cancer Research, American Society of Clinical Oncology, and the International Association for the Study of Lung Cancer.[31,32] No data have been reported so far comparing the novel PD-L1 assay used in this study with other assays, although studies are ongoing and will hopefully be published in the future (Grote HJ, Merck KGaA, Darmstadt, Germany, personal communication). Clinical data for other potential predictive biomarkers of response to anti-PD-L1 or anti-PD-1 antibodies have also been reported, including an association between longer overall survival with atezolizumab (anti-PD-L1) and pre-existing immunity based on high T-effector-interferon γ-associated gene expression.[16] Exploratory analyses of potential correlates of response to avelumab are ongoing using data from this trial, including analyses of cytokines, CD8+ T cells in tumour specimens,

pharmacokinetic parameters, and expanded scoring algorithms for PD-L1 expression.

The occurrence of adverse events related to avelumab treatment in this trial was low and generally consistent with adverse events reported for other anti-PD-L1 or anti-PD-1 agents.[9,13–18,25,26] One patient had treatment-related pneumonitis (grade 4); in studies of other anti-PD-L1 or anti-PD-1 antibodies given as monotherapy in patients with metastatic NSCLC, rates of treatment-related pneumonitis were 1–5% for all grades and 1–3% for grade 3 or worse events.[13,14,25,26] Immune-related adverse events (in 12% of patients) were mostly grade 1 or 2, and led to treatment discontinuation in very few patients (2%). In this study, infusion-related reaction was monitored as an adverse event of special interest and occurred in approximately a fifth of patients. However, most infusion-related reactions with avelumab were mild to moderate in severity, occurred after the first or second infusion, and did not lead to treatment discontinuation. The frequency and management of infusion-related reactions will be further characterised in ongoing clinical trials of avelumab.

Enrolment in this cohort exceeded our prespecified target of 150 patients because of an acceleration in investigator recruitment towards the end of the enrolment process. Consequently, quite a large number of patients were screened and signed informed consent forms within a short period. We decided to include all patients who met eligibility criteria rather than exclude these patients once the planned total had been exceeded.

Preclinical studies suggest that avelumab can mediate tumour lysis through ADCC, which contrasts with other anti-PD-L1 or anti-PD-1 antibodies that are based on a non-active Ig-G subtype (IgG4) or contain engineered mutations in the Fc region designed to exclude ADCC.[19,33] Although ADCC could theoretically provide a secondary mechanism of action for avelumab in addition to PD-L1–PD-1 blockade, currently no clinical data show whether or not ADCC contributes to the clinical activity of avelumab. However, clinical studies have shown that avelumab treatment does not lead to any reduction in the frequency of various circulating immune cell subsets, suggesting that avelumab does not have ADCC activity against PD-L1-positive immune cells.[21,33]

In conclusion, the results of this study show that avelumab has acceptable safety and promising activity in patients with NSCLC that has progressed after platinum doublet therapy. Although interpretation of these results is restricted by the early phase and single-arm study design, our findings provided the rationale for an ongoing phase 3 head-to-head trial of avelumab versus docetaxel in patients with recurrent NSCLC, in which patients are stratified according to PD-L1 expression status and NSCLC histology (NCT02395172). Studies of avelumab monotherapy in first-line NSCLC are also ongoing, including a separate cohort in the JAVELIN Solid Tumor phase 1 trial (NCT01772004) and a randomised phase 3 trial comparing avelumab with platinum-based doublet therapy in patients with squamous and non-squamous PD-L1-positive NSCLC (NCT02576574).

References
1 Global Burden of Disease Cancer Collaboration, Fitzmaurice C1, Dicker D, Pain A, et al. The global burden of cancer 2013. *JAMA Oncol* 2015; **1**: 505–27.
2 Dela Cruz CS, Tanoue LT, Matthay RA. Lung cancer: epidemiology, etiology, and prevention. *Clin Chest Med* 2011; **32**: 605–44.
3 Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002; **346**: 92–98.
4 Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. *J Clin Oncol* 2003; **21**: 3016–24.
5 Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004; **22**: 1589–97.
6 Jackman D, Pao W, Riely GJ, et al. Clinical definition of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer. *J Clin Oncol* 2010; **28**: 357–60.
7 Isozaki H, Takigawa N, Kiura K. Mechanisms of acquired resistance to *ALK* inhibitors and the rationale for treating *ALK*-positive lung cancer. *Cancers* 2015; **7**: 763–83.
8 Dong H, Strome SE, Salomao DR, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. *Nat Med* 2002; **8**: 793–800.
9 Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012; **366**: 2443–54.
10 Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. *Proc Natl Acad Sci USA* 2002; **99**: 12293–97.
11 Hirano F, Kaneko K, Tamura H, et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. *Cancer Res* 2005; **65**: 1089–96.
12 Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science* 2015; **348**: 124–28.

13 Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* 2015; **373:** 1627–39.

14 Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med* 2015; **373:** 123–35.

15 Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016; **387:** 1540–50.

16 Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet* 2016; **387:** 1837–46.

17 Gettinger SN, Horn L, Gandhi L, et al. Overall survival and long-term safety of nivolumab (anti-programmed death 1 antibody, BMS-936558, ONO-4538) in patients with previously treated advanced non-small-cell lung cancer. *J Clin Oncol* 2015; **33:** 2004–12.

18 Antonia S, Goldberg SB, Balmanoukian A, et al. Safety and antitumour activity of durvalumab plus tremelimumab in non-small cell lung cancer: a multicentre, phase 1b study. *Lancet Oncol* 2016; **17:** 299–308.

19 Boyerinas B, Jochems C, Fantini M, et al. Antibody-dependent cellular cytotoxicity activity of a novel anti-PD-L1 antibody avelumab (MSB0010718C) on human tumor cells. *Cancer Immunol Res* 2015; **3:** 1148–57.

20 Fujii R, Friedman ER, Richards J, et al. Enhanced killing of chordoma cells by antibody-dependent cell-mediated cytotoxicity employing the novel anti-PD-L1 antibody avelumab. *Oncotarget* 2016; **7:** 33498–511.

21 Heery CR, O'Sullivan-Coyne G, Madan RA, et al. Avelumab for metastatic or locally advanced previously treated solid tumours (JAVELIN Solid Tumor): a phase 1a, multicohort, dose-escalation trial. *Lancet Oncol* 2017; published online March 31. http://dx.doi.org/10.1016/S1470-2045(17)30239-5.

22 Heery CR, O'Sullivan Coyne G, Marte JL, et al. Pharmacokinetic profile and receptor occupancy of avelumab (MSB00110718C), an anti-PD-L1 monoclonal antibody, in a phase I, open-label, dose escalation trial in patients with advanced solid tumors. *Proc Am Soc Clin Oncol* 2015; **33:** abstr 3055.

23 Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45:** 228–47.

24 Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res* 2009; **15:** 7412–20.

25 Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med* 2015; **372:** 2018–28.

26 Rizvi NA, Mazieres J, Planchard D, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. *Lancet Oncol* 2015; **16:** 257–65.

27 Rizvi NA, Brahmer JR, Ou S-I, et al. Safety and clinical activity of MEDI4736, an anti-programmed cell death-ligand (PD-L1) antibody, in patients with non-small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol* 2015; **33:** abstr 8032.

28 Horn L, Spigel DR, Gettinger SN, et al. Clinical activity, safety, and predictive biomarkers of the engineered antibody MPDL3280A (anti-PDL1) in non-small cell lung cancer (NSCLC): update from a phase Ia study. *Proc Am Soc Clin Oncol* 2015; **33:** abstr 8029.

29 Pilotto S, Carbognin L, Karachaliou N, et al. Moving towards a customized approach for drug development: Lessons from clinical trials with immune checkpoint inhibitors in lung cancer. *Transl Lung Cancer Res* 2015; **4:** 704–12.

30 Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature* 2014; **515:** 563–67.

31 Hirsch FR, Suda K, Wiens J, Bunn PA Jr. New and emerging targeted treatments in advanced non-small-cell lung cancer. *Lancet* 2016; **388:** 1012–24.

32 Scheel AH, Dietel M, Heukamp LC, et al. Harmonized PD-L1 immunohistochemistry for pulmonary squamous-cell and adenocarcinomas. *Mod Pathol* 2016; **29:** 1165–72.

33 Grenga I, Donahue RN, Lepone LM, Richards J, Schlom J. A fully human IgG1 anti-PD-L1 MAb in an in vitro assay enhances antigen-specific T-cell responses. *Clin Transl Immunology* 2016; **5:** e83.