Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial

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Lancet 2016; 387: 1540–50

Published Online December 19, 2015 http://dx.doi.org/10.1016/S0140-6736(15)01281-7

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Summary

Background Despite recent advances in the treatment of advanced non-small-cell lung cancer, there remains a need for effective treatments for progressive disease. We assessed the efficacy of pembrolizumab for patients with previously treated, PD-L1-positive, advanced non-small-cell lung cancer.

Methods We did this randomised, open-label, phase 2/3 study at 202 academic medical centres in 24 countries. Patients with previously treated non-small-cell lung cancer with PD-L1 expression on at least 1% of tumour cells were randomly assigned (1:1:1) in blocks of six per stratum with an interactive voice-response system to receive pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg, or docetaxel 75 mg/m² every 3 weeks. The primary endpoints were overall survival and progression-free survival both in the total population and in patients with PD-L1 expression on at least 50% of tumour cells. We used a threshold for significance of p<0·00825 (one-sided) for the analysis of overall survival and a threshold of p<0·001 for progression-free survival. This trial is registered at ClinicalTrials.gov, number NCT01905657.

Findings Between Aug 28, 2013, and Feb 27, 2015, we enrolled 1034 patients: 345 allocated to pembrolizumab 2 mg/kg, 346 allocated to pembrolizumab 10 mg/kg, and 343 allocated to docetaxel. By Sept 30, 2015, 521 patients had died. In the total population, median overall survival was 10·4 months with pembrolizumab 2 mg/kg, 12·7 months with pembrolizumab 10 mg/kg, and 8·5 months with docetaxel. Overall survival was significantly longer for pembrolizumab 2 mg/kg versus docetaxel (hazard ratio [HR] 0·71, 95% CI 0·58–0·88; p=0·0008) and for pembrolizumab 10 mg/kg versus docetaxel (0·61, 0·49–0·75; p<0·0001). Median progression-free survival was 3·9 months with pembrolizumab 2 mg/kg, 4·0 months with pembrolizumab 10 mg/kg, and 4·0 months with docetaxel, with no significant difference for pembrolizumab 2 mg/kg versus docetaxel (0·88, 0·74–1·05; p=0·07) or for pembrolizumab 10 mg/kg versus docetaxel (HR 0·79, 95% CI 0·66–0·94; p=0·004). Among patients with at least 50% of tumour cells expressing PD-L1, overall survival was significantly longer with pembrolizumab 2 mg/kg than with docetaxel (median 14·9 months *vs* 8·2 months; HR 0·54, 95% CI 0·38–0·77; p=0·0002) and with pembrolizumab 10 mg/kg than with docetaxel (17·3 months *vs* 8·2 months; 0·50, 0·36–0·70; p<0·0001). Likewise, for this patient population, progression-free survival was significantly longer with pembrolizumab 2 mg/kg than with docetaxel (median 5·0 months *vs* 4·1 months; HR 0·59, 95% CI 0·44–0·78; p=0·0001) and with pembrolizumab 10 mg/kg than with docetaxel (5·2 months *vs* 4·1 months; 0·59, 0·45–0·78; p<0·0001). Grade 3–5 treatment-related adverse events were less common with pembrolizumab than with docetaxel (43 [13%] of 339 patients given 2 mg/kg, 55 [16%] of 343 given 10 mg/kg, and 109 [35%] of 309 given docetaxel).

Interpretation Pembrolizumab prolongs overall survival and has a favourable benefit-to-risk profile in patients with previously treated, PD-L1-positive, advanced non-small-cell lung cancer. These data establish pembrolizumab as a new treatment option for this population and validate the use of PD-L1 selection.

Funding Merck & Co.

Introduction

Although treatment for non-small-cell lung cancer has improved in recent years with the development of targeted drugs for patients with amenable mutations,[1–5] only a small proportion of patients have these mutations, and most tumours become resistant to targeted treatment.[6] Immunotherapy is a new paradigm for the treatment of non-small-cell lung cancer, and targeting the PD-1 pathway is a promising therapeutic option.[7–11] The PD-1 receptor is an immune checkpoint inhibitor expressed on activated B and T cells that normally down-modulates excessive immune responses.[12,13] Binding of PD-1 to its ligands (PD-L1 and PD-L2) on tumour cells suppresses T cells through a negative feedback loop, leading to evasion of the immune response.[14–17]

Pembrolizumab (MK-3475) is a highly selective, humanised, IgG4 monoclonal antibody against PD-1. Pembrolizumab 2 mg/kg given once every 3 weeks was granted accelerated approval in the USA for the treatment of patients with metastatic non-small-cell lung cancer

Panel: Research in context

Evidence before this study

We searched PubMed on Nov 2, 2015, using the following terms: "PD-1 OR PD-L1 OR MK-3475 OR pembrolizumab OR lambrolizumab OR Keytruda OR nivolumab OR BMS-936558 OR Opdivo OR atezolizumab OR MPDL3280A OR BMS-936559 OR durvalumab OR MEDI4736 OR avelumab OR MSB0010718C OR docetaxel" AND "non-small-cell lung cancer OR NSCLC". The search was not limited by date. We also searched the abstracts for the 2014 and 2015 American Society of Clinical Oncology Annual Meetings, the 2014 European Society for Medical Oncology Congress, and the 2015 European Cancer Congress using the same search terms. We identified three randomised trials of anti-PD-1 or anti-PD-L1 treatment versus docetaxel for non-small-cell lung cancer: the CheckMate 017 study of nivolumab for squamous non-small-cell lung cancer, the CheckMate 057 study of nivolumab for non-squamous non-small-cell lung cancer, and the POPLAR study of atezolizumab for squamous and non-squamous non-small-cell lung cancer. We focused on the CheckMate studies because they are published in peer-reviewed journals.

Added value of this study

Results of KEYNOTE-010 confirm the efficacy and safety of PD-1 inhibition with pembrolizumab in patients with previously treated non-small-cell lung cancer. These data are the first published report of a randomised, controlled clinical trial of non-small-cell lung cancer that prospectively shows the utility of PD-L1 as a biomarker. This study is also the first of a PD-1 inhibitor for non-small-cell lung cancer to include patients who received more than one line of previous treatment. Both pembrolizumab 2 mg/kg and pembrolizumab 10 mg/kg every 3 weeks provided superior overall survival compared with docetaxel, with similar outcomes for each pembrolizumab dose. Pembrolizumab was also associated with fewer high-grade toxic effects than was docetaxel.

Implications of all the available evidence

Our data support pembrolizumab 2 mg/kg given every 3 weeks as a new treatment option for patients with non-small-cell lung cancer with a PD-L1 tumour proportion score of at least 1% that progressed after platinum-based chemotherapy and, in those with an *EGFR* sensitising mutation or an *ALK* translocation, an appropriate tyrosine kinase inhibitor. These data also validate the use of PD-L1 on tumour cells as a biomarker to identify patients most likely to obtain a benefit from pembrolizumab.

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whose tumours express PD-L1 (as determined by test approved by the US Food and Drug Administration) with disease progression during or after platinum-containing chemotherapy. This approval was based on data from 550 patients with non-small-cell lung cancer enrolled in the large, multicohort, phase 1b KEYNOTE-001 study.[9,18] In KEYNOTE-001, a PD-L1 tumour proportion score of 50% or greater, defined as PD-L1 expression on at least 50% of tumour cells (appendix p 5), was associated with better outcomes.[9]

We present results of KEYNOTE-010, the first randomised comparison of pembrolizumab 2 mg/kg or 10 mg/kg every 3 weeks versus standard-of-care treatment for PD-L1-positive non-small-cell lung cancer that progressed after at least platinum-based chemotherapy. This study is the first active-control trial that enrolled patients on the basis of prospective assessment of tumour PD-L1 expression based on the association between higher PD-L1 expression and greater clinical benefit from pembrolizumab.

Methods

Study design and participants

We did this randomised, controlled, phase 2/3 clinical trial at 202 academic medical centres in 24 countries (Argentina, Australia, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Japan, Lithuania, Netherlands, Portugal, Russia, South Africa, South Korea, Spain, Taiwan, UK, and USA). We included patients aged at least 18 years, with progression as per Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1)[19] after two or more cycles of platinum-doublet chemotherapy, as well as an appropriate tyrosine kinase inhibitor for those with an *EGFR*-sensitising mutation or *ALK* gene rearrangement; measurable disease as per investigator-assessed RECIST; an Eastern Cooperative Oncology Group performance status of 0 or 1; provision of a tumour sample; and PD-L1 expression on at least 1% of tumour cells (ie, a tumour proportion score ≥1%). Initially, any tumour sample was permitted for PD-L1 testing. The study protocol was later amended to require a new tumour sample for PD-L1 testing except when attempting to take a biopsy would be too risky. To be considered a new sample, no intervening treatment was permitted between the time the sample was taken and initiation of study treatment. The only exception was that patients receiving tyrosine kinase inhibitors before the biopsy was taken were permitted to resume them after sample collection. 456 patients were enrolled on the basis of archival samples.

See Online for appendix

Key exclusion criteria were previous treatment with PD-1 checkpoint inhibitors or docetaxel, known active brain metastases or carcinomatous meningitis, active autoimmune disease requiring systemic steroids, and interstitial lung disease or history of pneumonitis requiring systemic steroids. The appendix shows all the inclusion and exclusion criteria.

The study protocol and all amendments were approved by the appropriate institutional review boards and ethics committees at each institution. The study was done in accordance with the protocol, Good Clinical Practice

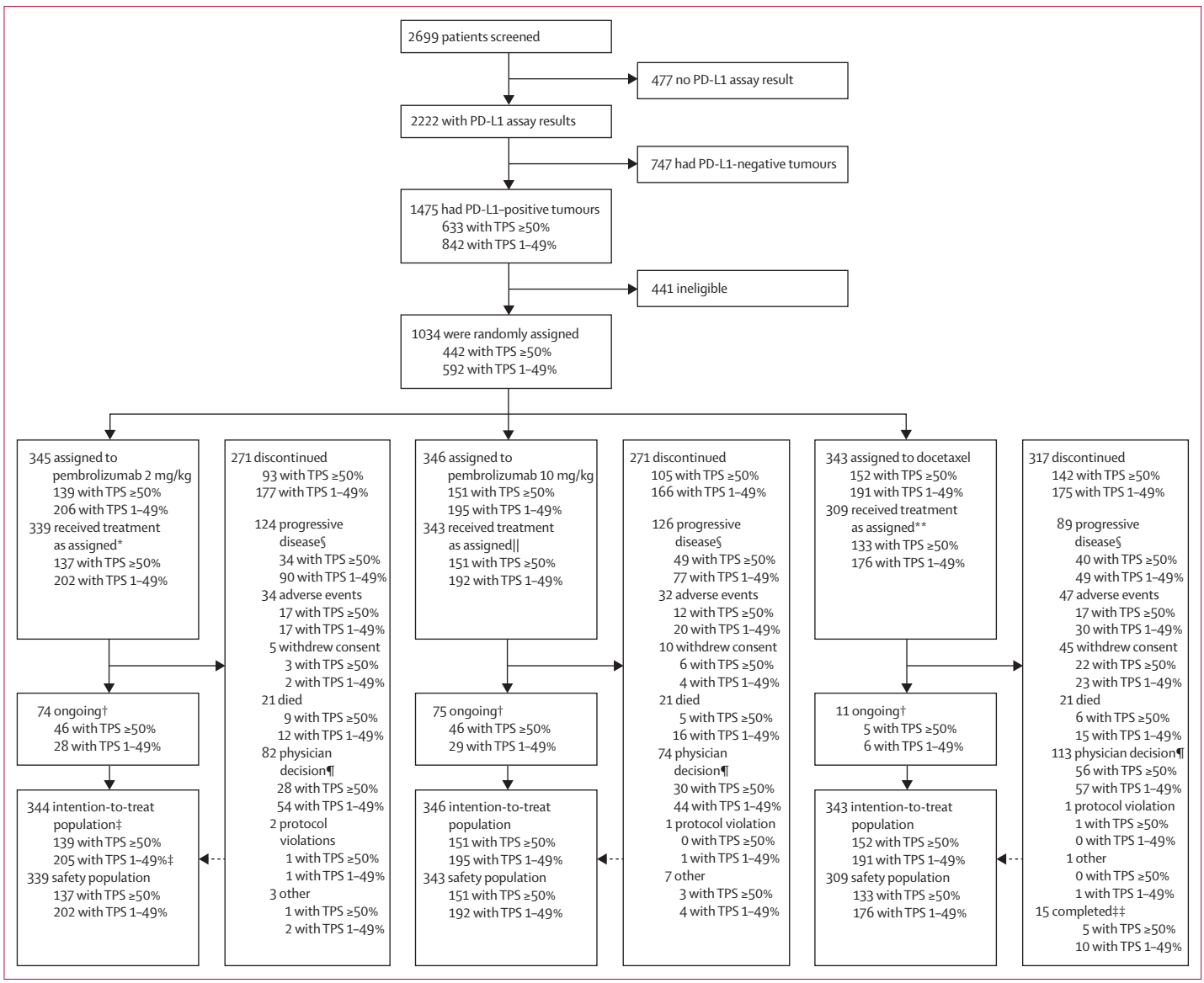

Figure 1: **Trial profile**

TPS=tumour proportion score. *Three patients had clinical progression that rendered them ineligible before treatment could be started, two patients did not meet all eligibility criteria but were incorrectly allocated to study treatment, and one patient was not treated because of physician decision. †Patients without a completed study medication discontinuation form. ‡One patient was permitted to remain on treatment and was included in the safety analysis population, but because it would not be possible to adequately assess tumour response, the patient was excluded from the efficacy analysis population. §Includes only disease progression observed on radiological imaging. ¶Mainly clinical disease progression: for 80 (98%) of 82 patients in the pembrolizumab 2 mg/kg group, 72 (97%) of 74 patients in the pembrolizumab 10 mg/kg group, and 84 (74%) of 113 in the docetaxel group. ||Two patients had adverse events (one had myocardial infarction, one had anaemia with blood transfusion) that rendered them ineligible for study treatment, and one patient did not meet all eligibility criteria but was incorrectly allocated to study treatment. **34 patients withdrew consent after learning they were allocated to the docetaxel group. ††Patients who discontinued docetaxel after receiving the maximum number of cycles approved by the local authorities were considered to have completed study treatment.

guidelines, and the Declaration of Helsinki. All patients provided written informed consent.

Randomisation and masking

Patients were randomly assigned (1:1:1) with a central interactive voice-response system to receive pembrolizumab 2 mg/kg intravenously over 30 min every 3 weeks, 10 mg/kg intravenously over 30 min every 3 weeks, or docetaxel 75 mg/m² intravenously over 1 h every 3 weeks. The allocation schedule was generated by the system vendor using a computerised randomised list generator. Patients were stratified by Eastern Oncology Cooperative Group performance status (0 *vs* 1) and region (east Asia *vs* not east Asia). A third stratification variable, extent of PD-L1 expression (tumour proportion score ≥50% *vs* 1–49%), was added after 441 patients were allocated and the PD-L1 immunohistochemistry assay cutpoint was established.[9] Treatment was allocated in blocks of six in each stratum.

	All patients			Patients with tumour proportion score ≥50%		
	Pembrolizumab 2 mg/kg (n=344)	Pembrolizumab 10 mg/kg (n=346)	Docetaxel (n=343)	Pembrolizumab 2 mg/kg (n=139)	Pembrolizumab 10 mg/kg (n=151)	Docetaxel (n=152)
Age (years)	63·0 (56·0–69·0)	63·0 (56·0–69·0)	62·0 (56·0–69·0)	62·0 (56·0–69·0)	64·0 (58·0–70·0)	60·0 (54·0–69·5)
Men	212 (62%)	213 (62%)	209 (61%)	81 (58%)	89 (59%)	93 (61%)
Race						
White	246 (72%)	250 (72%)	251 (73%)	102 (73%)	111 (74%)	117 (77%)
Asian	73 (21%)	72 (21%)	72 (21%)	27 (19%)	28 (19%)	29 (19%)
Black or African American	13 (4%)	8 (2%)	7 (2%)	5 (4%)	5 (3%)	1 (1%)
Other	5 (1%)	5 (1%)	2 (1%)	2 (1%)	0 (0%)	1 (1%)
Unknown	7 (2%)	11 (3%)	11 (3%)	3 (2%)	7 (5%)	4 (3%)
Region						
East Asia	64 (19%)	64 (18%)	62 (18%)	21 (15%)	25 (17%)	26 (17%)
Not east Asia	280 (81%)	282 (82%)	281 (82%)	118 (85%)	126 (83%)	126 (83%)
ECOG performance status*						
0	112 (33%)	120 (35%)	116 (34%)	47 (34%)	47 (31%)	49 (32%)
1	229 (67%)	225 (65%)	224 (65%)	91 (65%)	104 (69%)	102 (67%)
2	3 (1%)	1 (<1%)	1 (<1%)	1 (1%)	0 (0%)	1 (1%)
3	0 (0%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Unknown	0 (0%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Histology						
Squamous	76 (22%)	80 (23%)	66 (19%)	29 (21%)	41 (27%)	26 (17%)
Non-squamous	240 (70%)	244 (71%)	240 (70%)	95 (68%)	98 (65%)	111 (73%)
Other	9 (3%)	6 (2%)	10 (3%)	4 (3%)	5 (3%)	5 (3%)
Unknown	19 (6%)	16 (5%)	27 (8%)	11 (8%)	7 (5%)	10 (7%)
PD-L1 TPS						
≥50%	139 (40%)	151 (44%)	152 (44%)	139 (100%)	151 (100%)	152 (100%)
1–49%	205 (60%)	195 (56%)	191 (56%)	0 (0%)	0 (0%)	0 (0%)
Smoking status						
Former or current	279 (81%)	285 (82%)	269 (78%)	112 (81%)	122 (81%)	113 (74%)
Never	63 (18%)	60 (17%)	67 (20%)	26 (19%)	29 (19%)	34 (22%)
Unknown	2 (1%)	1 (<1%)	7 (2%)	1 (1%)	0 (0%)	5 (3%)
Stable brain metastases	56 (16%)	48 (14%)	48 (14%)	32 (23%)	23 (15%)	23 (15%)
EGFR status						
Wild-type	293 (85%)	288 (83%)	294 (86%)	119 (86%)	127 (84%)	131 (86%)
Mutant	28 (8%)	32 (9%)	26 (8%)	8 (6%)	13 (9%)	12 (8%)
Unknown	23 (7%)	26 (8%)	23 (7%)	12 (9%)	11 (7%)	9 (6%)
ALK translocation						
No	307 (89%)	305 (88%)	310 (90%)	120 (86%)	131 (87%)	137 (90%)
Yes	2 (1%)	4 (1%)	2 (1%)	2 (1%)	2 (1%)	1 (1%)
Unknown	35 (10%)	37 (11%)	31 (9%)	17 (12%)	18 (12%)	14 (9%)
Previous systemic therapies						
Adjuvant	6 (2%)	7 (2%)	3 (1%)	2 (1%)	4 (3%)	3 (2%)
Neo-adjuvant	1 (<1%)	1 (<1%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)

(Table 1 continues on next page)

Patients, treating physicians, and the external data monitoring committee were not masked to treatment assignment. Personnel of the funder were not masked to individual treatment assignment but were masked to the PD-L1 tumour proportion score and aggregate data by treatment group during the study; the study statistician remained masked to treatment assignment until the final analysis was completed.

Procedures

Corticosteroid premedication was permitted for the docetaxel group. Treatment was continued for 24 months or until disease progression, intolerable toxic effects, physician decision, patient withdrawal, or other reasons. Patients who progressed according to investigator-assessed immune-related response criteria[20] could remain on treatment until a confirmatory scan done

	All patients			Patients with tumour proportion score ≥50%		
	Pembrolizumab 2 mg/kg (n=344)	Pembrolizumab 10 mg/kg (n=346)	Docetaxel (n=343)	Pembrolizumab 2 mg/kg (n=139)	Pembrolizumab 10 mg/kg (n=151)	Docetaxel (n=152)
(Continued from previous page)						
Number of lines for advanced disease						
1	243 (71%)	235 (68%)	235 (69%)	97 (70%)	104 (69%)	109 (72%)
2	66 (19%)	69 (20%)	75 (22%)	30 (22%)	26 (17%)	25 (16%)
≥3	27 (8%)	34 (10%)	29 (8%)	10 (7%)	16 (11%)	15 (10%)
Unknown	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Previous systemic treatment for advanced disease						
Chemotherapy†	335 (97%)	337 (97%)	339 (99%)	137 (99%)	146 (97%)	149 (98%)
Immunotherapy	2 (1%)	1 (<1%)	1 (<1%)	1 (1%)	1 (1%)	0 (0%)
EGFR tyrosine kinase inhibitor	40 (12%)	56 (16%)	47 (14%)	14 (10%)	20 (13%)	21 (14%)
ALK inhibitor	3 (1%)	5 (1%)	2 (1%)	3 (2%)	3 (2%)	1 (1%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. TPS=tumour proportion score. *For five of the six patients who had and ECOG performance status ≥2 during screening, the score improved to 1 by the time the patients were randomly allocated to treatment. †Patients whose disease progressed within 1 year of completing platinum-based adjuvant therapy were also eligible.

Table 1: **Baseline characteristics**

4–6 weeks later. Per protocol, patients in the docetaxel group were not permitted to cross over to receive pembrolizumab.

Radiographic imaging was done every 9 weeks. Response was assessed as per RECIST version 1.1 by independent central review (for efficacy) and as per immune-related response criteria by investigator (to inform treatment decisions). Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). PD-L1 expression was assessed at a central laboratory with an immunohistochemistry assay (Dako; Carpinteria, CA, USA) with the murine 22C3 anti-human PD-L1 antibody (Merck; Kenilworth, NJ, USA), as previously described (appendix p 5).[9]

Outcomes

The primary endpoints were overall survival (time from randomisation to death due to any cause) and progression-free survival (time from randomisation to radiologically confirmed progressive disease or death due to any cause) both in the total population (ie, tumour proportion score of 1% or greater) and in patients with tumour proportion score of 50% or greater. Secondary endpoints were safety, response rate (percentage of patients with complete or partial response as per RECIST version 1.1), and duration of response (time from first evidence of response until disease progression or death).

We did prespecified subgroup analyses of age, sex, Eastern Oncology Cooperative Group performance status, *EGFR* mutation status, and age of tumour sample. We also did post-hoc exploratory subgroup analyses of tumour histology.

We analysed overall survival, progression-free survival, and response rate in the intention-to-treat population and we analysed duration of response for all patients who had a best overall response of complete or partial response according to RECIST (version 1.1) by central review; we assessed safety in all patients who received at least one dose of study treatment. After one patient was allocated to and received pembrolizumab 2 mg/kg, it was found that their pre-baseline scans were not compliant with the protocol. The patient was permitted to remain on treatment and was included in the safety analysis population, but because it would not be possible to adequately assess tumour response, the patient was excluded from the efficacy analysis population.

Statistical analysis

Because the lowest effective dose and the relative merit of progression-free survival versus overall survival were unknown and the importance of PD-L1 staining was being validated when this study was designed, we assessed four primary outcomes at two doses. The two doses were selected on the basis of pharmacological models, and the statistical analysis plan appropriately accounted for the multiple endpoints. Two prespecified interim analyses were done by an unmasked statistician (appendix p 4). The data monitoring committee recommended continuing the study as planned after both interim analyses. This study was designed to show a difference in overall survival in patients with a tumour proportion score of 50% or greater. Because we assumed that half of the total sample would have a tumour proportion score of 50% or greater, we believed that an overall survival benefit in this group would provide enough power to show a benefit for all primary endpoints. The final analysis was planned for when roughly 200 deaths occurred across all treatment groups in patients with a tumour proportion score of 50% or greater. Assuming that overall survival

follows an exponential distribution with an expected median of 9 months in the docetaxel group (based on previous studies), a hazard ratio (HR) of 0·60 between pembrolizumab and docetaxel, an enrolment period of 16 months, a minimum of 8 months of follow-up after enrolment was complete to observe the required number of events, and a dropout rate of 2% over 12 months, we calculated that we would need to enrol 460 patients with a tumour proportion score of 50% or greater to provide at least 81% power to detect an HR of 0·55 for overall survival, with a one-sided α of 0·00825 using the Hochberg procedure. We expected that roughly 920 patients would be enrolled in total and that 550 patients would die by the final analysis, giving the study at least 80% power to detect an HR of 0·70 for overall survival in the total population. For the analysis of progression-free survival, we used a threshold of p<0·001 for significance. The appendix (p 6) shows the multiplicity strategy we applied to the stratum of patients with a tumour proportion score of 50% or greater and to the overall population.

For overall survival, data for patients who were alive or lost to follow-up were censored at the time of last confirmed contact. For progression-free survival, data for patients who had not progressed or were lost to follow-up were censored at the time of last tumour assessment. For duration of response, data for patients whose response was ongoing at the time of the analysis or who discontinued the study without radiological evidence of progression were censored at the time of the last radiological assessment showing response, data for patients who had radiological disease progression after missing two radiological assessments were censored at the time of the last radiological assessment showing response, and data for patients who initiated new cancer treatment without radiological evidence of disease progression were censored at the time of starting their new treatment.

We did the statistical analyses using SAS (version 9.3). We used the Kaplan-Meier method to estimate overall survival, progression-free survival, and duration of response. We used the stratified log-rank test to assess treatment differences in progression-free survival and overall survival; we used stratified Cox proportional hazard models with Efron's method of tie handling to calculate HRs and associated 95% CIs.[21] We compared response rate between treatment groups with the Miettinen and Nurminen method.[22] All primary and subgroup analyses were stratified with the randomisation stratification factors.

This study is registered with ClinicalTrials.gov, NCT01905657.

Role of the funding source

The funder had a role in study design, analysis and interpretation of data, and the writing of the report. The funder maintained the study database. All authors had full access to the data and had responsibility for the decision to submit for publication.

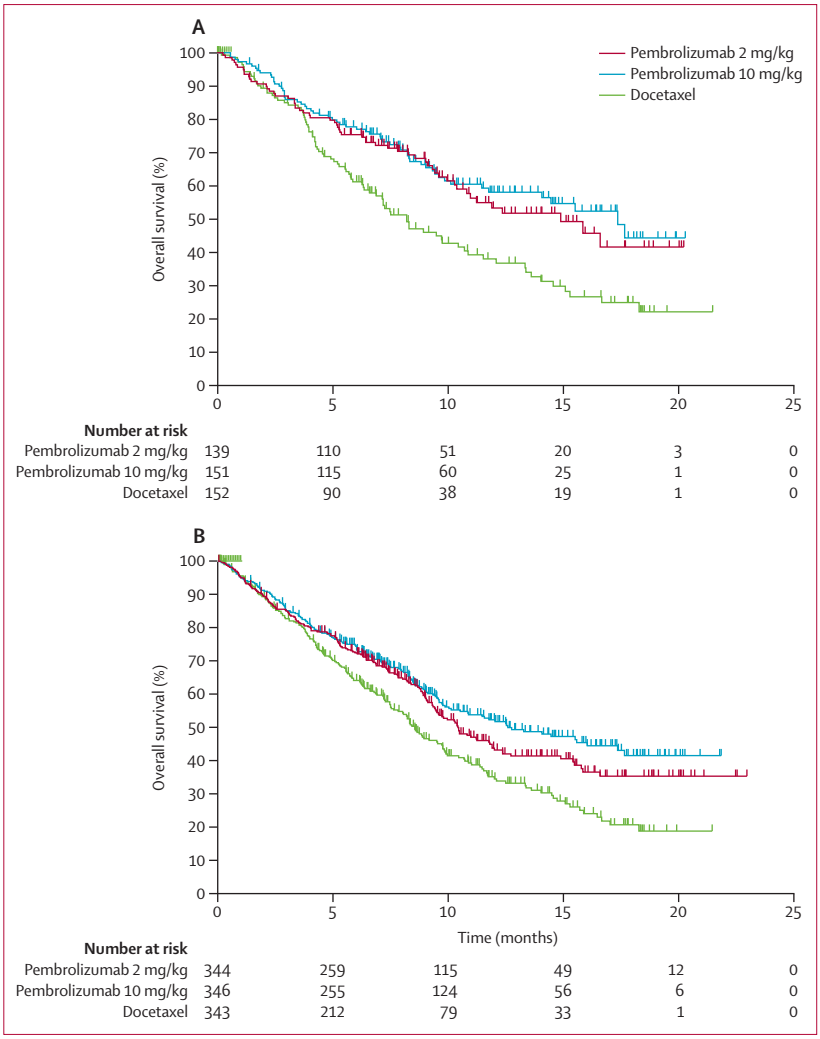

Figure 2: **Kaplan-Meier analysis of overall survival**
(A) For patients with a PD-L1 tumour proportion score of 50% or greater. (B) For all patients.

Results

Between Aug 28, 2013, and Feb 27, 2015, we screened 2699 patients for enrolment. Of the 2222 patients whose tumour samples were assessable for PD-L1 expression, 1475 (66%) had PD-L1 expression on at least 1% of tumour cells, including 633 (28%) with PD-L1 expression on at least 50% of tumour cells. 1034 (70%) of 1475 patients met the eligibility criteria and were enrolled in the study: 345 allocated to pembrolizumab 2 mg/kg, 346 to pembrolizumab 10 mg/kg, and 343 to docetaxel (figure 1). 991 patients received at least one dose of assigned study drug: 339 in the 2 mg/kg group, 343 in the 10 mg/kg group, and 309 in the docetaxel group (figure 1). At the cutoff date of Sept 30, 2015, median follow-up was 13·1 months (IQR 8·6–17·7).

Baseline characteristics were as expected for patients with advanced non-small-cell lung cancer and were balanced between groups (table 1). Most patients were current or former smokers, had tumours of non-

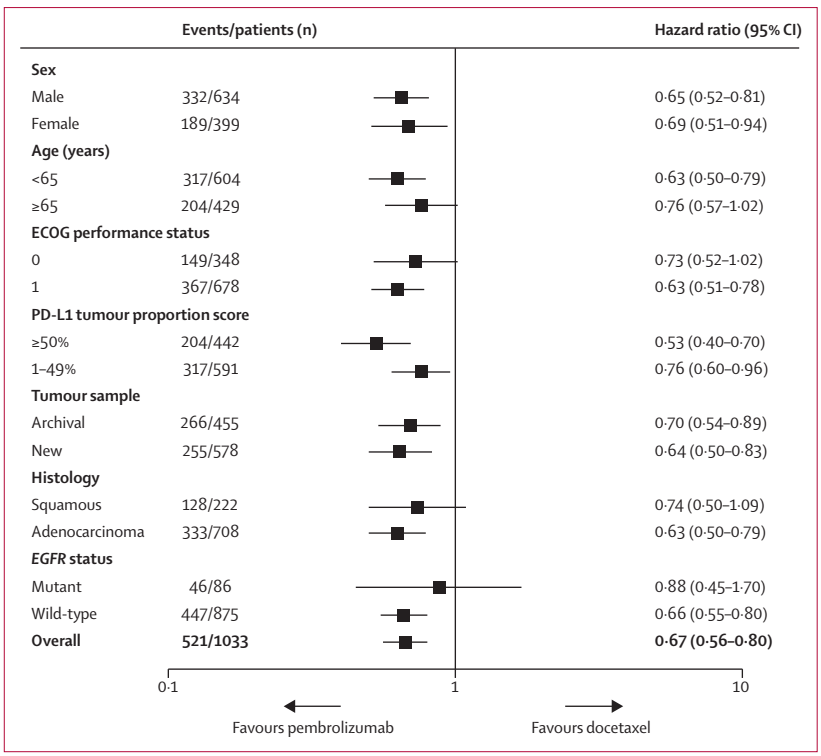

Figure 3: **Subgroup analysis of overall survival**
Shows the comparison of the pooled pembrolizumab doses versus docetaxel. ECOG=Eastern Cooperative Oncology Group.

squamous histology, and had received one line of previous systemic treatment (table 1). Few patients had *EGFR*-mutant or *ALK*-translocated tumours. Baseline characteristics were similar in the 442 patients who had a PD-L1 tumour proportion score of 50% or greater (table 1).

At the time of data cutoff, 521 patients had died: 172 (50%) of 344 in the pembrolizumab 2 mg/kg group, 156 (45%) of 346 in the pembrolizumab 10 mg/kg group, and 193 (56%) of 343 in the docetaxel group. 204 patents with a PD-L1 tumour proportion score of 50% or greater died: 58 (42%) of 139 in the pembrolizumab 2 mg/kg group, 60 (40%) of 151 in the pembrolizumab 10 mg/kg group, and 86 (57%) of 152 in the docetaxel group. After discontinuation of study treatment, additional anti-neoplastic treatment was received by 138 (40%) of 344 patients in the pembrolizumab 2 mg/kg group, 133 (38%) of 346 patients in the pembrolizumab 10 mg/kg group, and 151 (44%) of 343 patients in the docetaxel group, including two (1%), six (2%), and 45 (13%), respectively, who received other immunotherapies (appendix pp 8–9).

In patients with a PD-L1 tumour proportion score of 50% or greater, the HR for overall survival for pembrolizumab 2 mg/kg versus docetaxel was 0·54 (95% CI 0·38–0·77; p=0·0002), and for pembrolizumab 10 mg/kg versus docetaxel it was 0·50 (0·36–0·70; p<0·0001). Median overall survival was 14·9 months (95% CI 10·4–not reached) for the pembrolizumab 2 mg/kg group, 17·3 months (11·8–not reached) for the pembrolizumab 10 mg/kg group, and 8·2 months (6·4–10·7) for the docetaxel group (figure 2A).

In the total population, the HR for pembrolizumab 2 mg/kg versus docetaxel was 0·71 (95% CI 0·58–0·88; p=0·0008) and the HR for pembrolizumab 10 mg/kg versus docetaxel was 0·61 (0·49–0·75; p<0·0001). Median overall survival was 10·4 months (95% CI 9·4–11·9) for the pembrolizumab 2 mg/kg group, 12·7 months (10·0–17·3) for the pembrolizumab 10 mg/kg group, and 8·5 months (95% CI, 7·5–9·8) for the docetaxel group (figure 2B). 1-year overall survival was 43·2% versus 52·3% versus 34·6%. Overall survival was similar in the two pembrolizumab groups both in patients with a PD-L1 tumour proportion score of 50% or greater (HR for 2 mg/kg *vs* 10 mg/kg 1·12, 95% CI 0·77–1·62) and in the total population (1·17, 0·94–1·45). Pembrolizumab provided benefit compared with docetaxel irrespective of whether archival or new tumour samples were used to assess PD-L1 expression. There was a significant benefit for patients with non-squamous disease. For those with squamous disease, the difference was not statistically significant, but the data suggest a clinical benefit in this group also (figure 3).

776 patients had died or had disease progression, including 266 (77%) of 344 in the pembrolizumab 2 mg/kg group, 254 (73%) of 346 in the pembrolizumab 10 mg/kg group, and 256 (75%) of 343 in the docetaxel group. In patients with a tumour proportion score of 50% or greater, 304 patients had a progression-free survival event (89 [64%] of 139, 97 [64%] of 151, and 118 [78%] of 152, respectively). Progression-free survival was significantly longer with pembrolizumab than with docetaxel in patients with a tumour proportion score of 50% or greater (figure 4A), with an HR of 0·59 (95% CI 0·44–0·78; p=0·0001) for pembrolizumab 2 mg/kg versus doxetaxel and 0·59 (0·45–0·78; p<0·0001) for pembrolizumab 10 mg/kg versus docetaxel. Median progression-free survival was 5·0 months (95% CI 4·0–6·5) in the pembrolizumab 2 mg/kg group, 5·2 months (4·1–8·1) in the pembrolizumab 10 mg/kg group, and 4·1 months (3·6–4·3) in the docetaxel group.

For the total population, progression-free survival did not meet the prespecified criterion for declaring statistical significance between pembrolizumab 2 mg/kg and doxetaxel (HR 0·88, 95% CI 0·74–1·05; p=0·07) or between pembrolizumab 10 mg/kg and doxetaxel (HR 0·79, 0·66–0·94; p=0·004). Median progression-free survival was 3·9 months (95% CI 3·1–4·1) in the pembrolizumab 2 mg/kg group, 4·0 months (2·7–4·3) in the pembrolizumab 10 mg/kg group, and 4·0 months (3·1–4·2) in the docetaxel group (figure 4B). Progression-free survival was similar for each pembrolizumab dose in patients with a tumour proportion score of 50% or greater (HR 1·01, 95% CI 0·75–1·36) and in the total population (1·09, 0·92–1·30). The effect on progression-free survival did not differ by tumour histology (figure 5).

Among patients with a tumour proportion score of 50% or greater, responses occurred in 42 (30%) of 139 patients in the pembrolizumab 2 mg/kg group, 44 (29%) of 151 in the pembrolizumab 10 mg/kg group, and 12 (8%) of 152 in the docetaxel group (p<0·0001 for each pembrolizumab group *vs* docetaxel; appendix p 10). In the total population, 62 (18%) of 344 patients versus 64 (18%) of 346 patients versus 32 (9%) of 343 had responses (p=0·0005 for 2 mg/kg *vs* docetaxel and p=0·0002 for 10 mg/kg *vs* docetaxel; appendix p 10). All responses were partial responses. Median time to response was 9 weeks in each treatment group (appendix p 10). Responses were longer in the pembrolizumab groups than in the docetaxel group (appendix p 7), with a median duration of response not reached for either pembrolizumab group compared with 8 months in the docetaxel group for patients with a tumour proportion score of ≥50% or greater and 6 months in the docetaxel group for all patients (appendix p 10).

In the safety population, the median duration of treatment was 3·5 months (IQR 1·4–7·2) in the pembrolizumab 2 mg/kg group, 3·5 months (1·4–7·0) in the pembrolizumab 10 mg/kg group, and 2·0 months (0·8–3·6) in the docetaxel group. Grade 3–5 adverse events attributed to study treatment occurred in 43 (13%) of 339 patients in the pembrolizumab 2 mg/kg group, 55 (16%) of 343 patients in the pembrolizumab 10 mg/kg group, and 109 (35%) of 309 patients in the docetaxel group (table 2). 15 (4%) of 339 patients, 17 (5%) of 343 patients, and 31 (10%) of 309 patients, respectively, permanently discontinued study drug because of treatment-related adverse events. Deaths attributed to study treatment occurred in three patients in the pembrolizumab 2 mg/kg group (two cases of pneumonitis and one of pneumonia), three patients in the pembrolizumab 10 mg/kg group (one case each of myocardial infarction, pneumonia, and pneumonitis), and five patients in the docetaxel group (one case each of acute cardiac failure, dehydration, febrile neutropenia, interstitial lung disease, and respiratory tract infection).

Adverse events were as expected for pembrolizumab and docetaxel (table 2, appendix pp 11–12). Adverse events of special interest based on their likely immune aetiology, irrespective of attribution to study treatment, occurred in 69 (20%) of 339 patients in the pembrolizumab 2 mg/kg group and 64 (19%) of 343 patients in the pembrolizumab 10 mg/kg group. The most common of these events were hypothyroidism, hyperthyroidism, and pneumonitis (table 2). The only adverse events of special interest of grade 3–5 severity that occurred in 1% or more of patients were pneumonitis and severe skin reactions (table 2).

Discussion

Pembrolizumab 2 mg/kg and 10 mg/kg every 3 weeks met the prespecified criteria for improved overall survival in all patients (ie, PD-L1 tumour proportion score of 1% or greater) and in those with a tumour proportion score of 50% or greater—patients with high PD-L1 expression had an unprecedented benefit for refractory non-small-cell lung cancer. Both pembrolizumab groups had significantly improved progression-free survival in patients with a tumour proportion score of 50% or greater, and although the prespecified criterion for declaring statistical significance was not met, progression-free survival was longer with pembrolizumab than with docetaxel for the total population. Responses to pembrolizumab were durable, regardless of PD-L1 expression level. Pembrolizumab was associated with fewer high-grade treatment-related adverse events than was docetaxel, despite a longer exposure. Immune-mediated adverse events, including pneumonitis, occurred at manageable rates, although three (<1%) of 682 patients treated with pembrolizumab died because of pneumonitis.

Median overall survival with docetaxel seemed to be consistent with that previously reported (9 months),[23] and there was no difference in survival with docetaxel

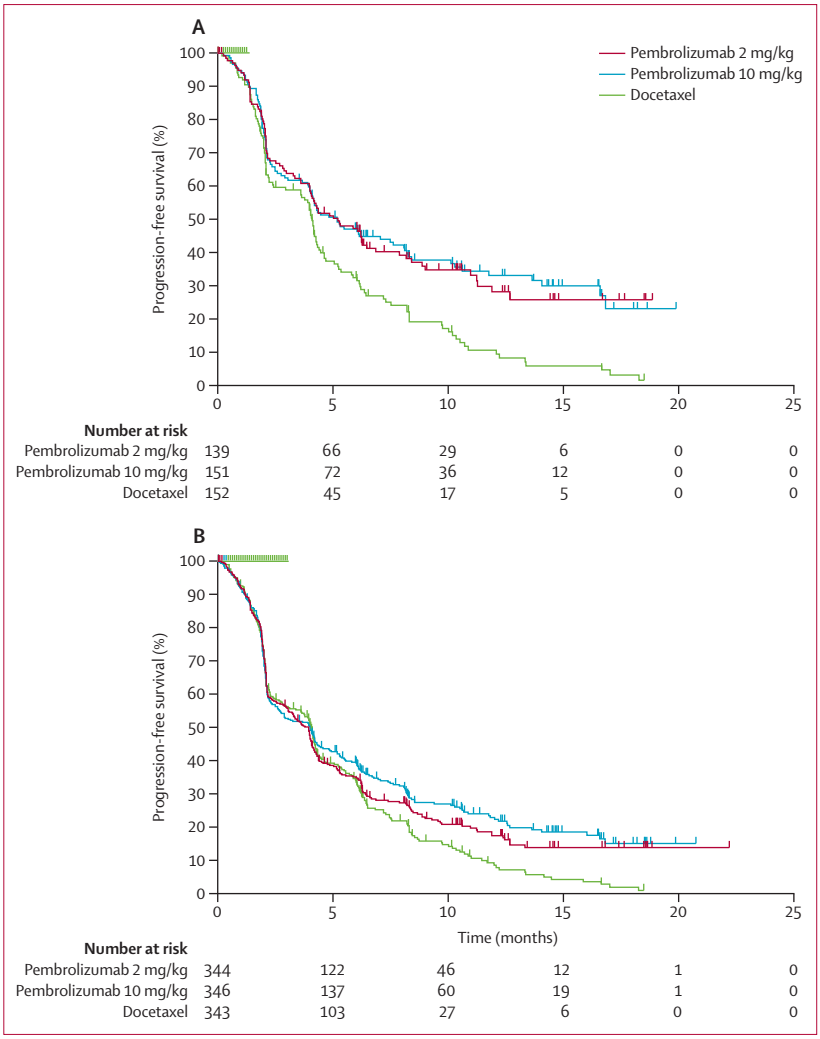

Figure 4: **Kaplan-Meier analysis of progression-free survival**
(A) For patients with a PD-L1 tumour proportion score of 50% or greater. (B) For all patients.

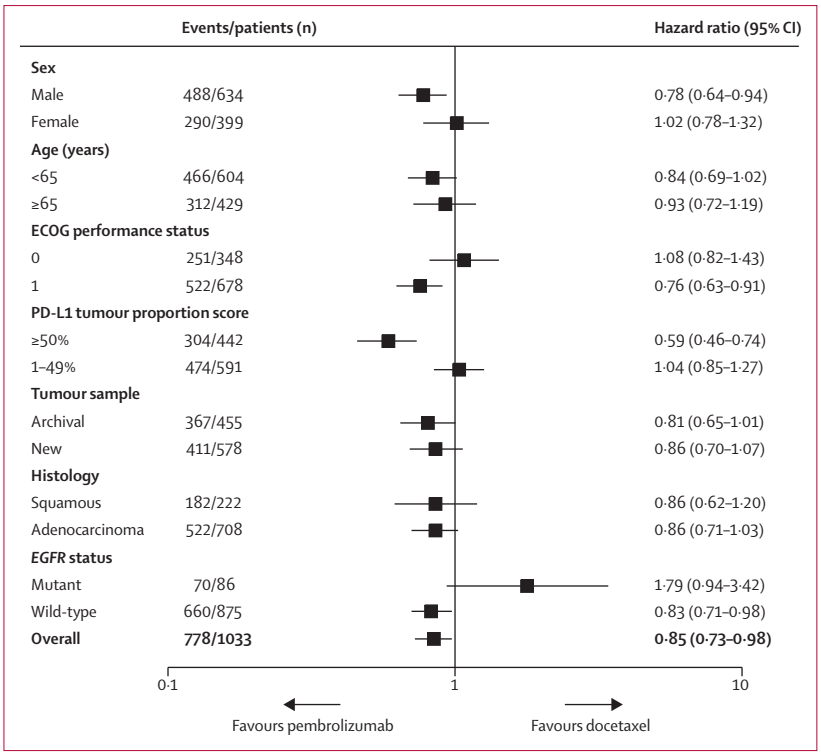

Figure 5: **Subgroup analysis of progression-free survival**
Shows the comparison of the pooled pembrolizumab doses versus docetaxel. ECOG=Eastern Cooperative Oncology Group.

among patients with a PD-L1 tumour proportion score of 50% or greater or in the total population. Consistent with KEYNOTE-001,[9] pembrolizumab efficacy was greater in patients with a tumour proportion score of 50% or greater than in the overall population. Progression-free survival with pembrolizumab was superior to that of docetaxel in patients with a tumour proportion score of 50% or greater, but not in the total population. However, overall survival with pembrolizumab was superior to that of docetaxel in both tumour proportion score strata, suggesting that progression-free survival might not appropriately capture the true benefit of pembrolizumab. The lack of a benefit for progression-free survival despite a significant overall survival benefit was also reported in the CheckMate 057 study of nivolumab versus docetaxel for non-squamous non-small-cell lung cancer.[8]

Few patients assigned to pembrolizumab withdrew consent, whereas the incidence in the docetaxel group was higher than what is typical in a phase 3 trial. Many of the patients allocated to docetaxel who withdrew consent probably did so to seek anti-PD-1 treatment. A similarly high percentage of patients in the CheckMate 057 trial who were assigned to docetaxel did not receive it (22 [8%] of 290).[8] This finding is not surprising given the many other studies of PD-1 inhibitors for non-small-cell lung cancer that were ongoing during KEYNOTE-010. Patients who withdrew and subsequently received another immunotherapy could affect overall survival. However, any bias of this unplanned crossover would likely favour the docetaxel group. Therefore, the high dropout rate in the docetaxel group does not diminish our confidence in the significant survival benefit for pembrolizumab. Another limitation of this study is the incidence of *EGFR* mutation or *ALK* translocation, which was lower than would be expected in the general non-small-cell lung cancer population. Finally, because we excluded patients with no PD-L1 tumour expression, we could not do statistically meaningful analyses of the interaction between PD-L1 expression and outcome by treatment allocation.

Our results contribute to the growing evidence that supports PD-1 pathway inhibition in non-small-cell lung cancer.[7,8,10,11,24] Although reports of treatment with pembrolizumab and nivolumab have shown a survival benefit for PD-1 inhibition, several aspects of KEYNOTE-010 differentiate it from the CheckMate 017 and CheckMate 057 studies of nivolumab.[7,8] Whereas there were separate nivolumab studies for squamous[7] and non-squamous[8] histology, KEYNOTE-010 enrolled patients regardless of histology. Our data suggest that, like nivolumab, pembrolizumab provides benefit for squamous and non-squamous non-small-cell lung cancer (although the difference for squamous cell disease was not statistically significant, probably partly because of the small population size). In addition, whereas both CheckMate studies limited enrolment to patients who received only one line of previous treatment for metastatic disease, almost one-third of patients in KEYNOTE-010 received at least two lines of previous treatment.

Our data are the first reported for lung cancer prospectively showing the utility of PD-L1 as a biomarker; all patients derived a survival benefit from pembrolizumab. This finding contrasts with the findings of studies of unselected populations. The assay used in KEYNOTE-010 was rigorously evaluated and validated before the study began[9] and has been approved by the Food and Drug Administration as a companion diagnostic test. Our data indicate that assessment of PD-L1 in archival samples with this assay is appropriate because pembrolizumab provided superior overall survival regardless of the age of the sample. Among patients with evaluable samples screened for enrolment in our study, two-thirds had a PD-L1 tumour proportion score of 1% or greater, and more than a quarter had a score of 50% or greater. The higher proportion of patients with a score of 50% or greater in the enrolled population (43%) was a result of the exclusion of patients with PD-L1-negative tumours. Whether the benefit of pembrolizumab extends to patients with a tumour proportion score of less than 1% will require additional study. Ongoing studies are assessing pembrolizumab as first-line therapy (KEYNOTE-024, ClinicalTrials.gov number NCT02142738; and KEYNOTE-042, ClinicalTrials.gov number NCT02220894) and as

	Pembrolizumab 2 mg/kg (n=339)		Pembrolizumab 10 mg/kg (n=343)		Docetaxel (n=309)	
	Any grade	Grade 3–5	Any grade	Grade 3–5	Any grade	Grade 3–5
Related to treatment*						
Any	215 (63%)	43 (13%)	226 (66%)	55 (16%)	251 (81%)	109 (35%)
Occurring in ≥10% of patients in any group						
Decreased appetite	46 (14%)	3 (1%)	33 (10%)	1 (<1%)	49 (16%)	3 (1%)
Fatigue	46 (14%)	4 (1%)	49 (14%)	6 (2%)	76 (25%)	11 (4%)
Nausea	37 (11%)	1 (<1%)	31 (9%)	2 (1%)	45 (15%)	1 (<1%)
Rash	29 (9%)	1 (<1%)	44 (13%)	1 (<1%)	14 (5%)	0 (0%)
Diarrhoea	24 (7%)	2 (1%)	22 (6%)	0 (0%)	56 (18%)	7 (2%)
Asthenia	20 (6%)	1 (<1%)	19 (6%)	2 (1%)	35 (11%)	6 (2%)
Stomatitis	13 (4%)	0 (0%)	7 (2%)	1 (<1%)	43 (14%)	3 (1%)
Anaemia	10 (3%)	3 (1%)	14 (4%)	1 (<1%)	40 (13%)	5 (2%)
Alopecia	3 (1%)	0 (0%)	2 (1%)	0 (0%)	101 (33%)	2 (1%)
Neutropenia	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	44 (14%)	38 (12%)
Of special interest occurring in ≥2 patients in the pembrolizumab groups†						
Hypothyroidism	28 (8%)	0 (0%)	28 (8%)	0 (0%)	1 (<1%)	0 (0%)
Pneumonitis‡	16 (5%)	7 (2%)	15 (4%)	7 (2%)	6 (2%)	2 (1%)
Hyperthyroidism	12 (4%)	0 (0%)	20 (6%)	1 (<1%)	3 (1%)	0 (0%)
Colitis	4 (1%)	3 (1%)	2 (1%)	1 (<1%)	0 (0%)	0 (0%)
Severe skin reactions	4 (1%)	3 (1%)	7 (2%)	6 (2%)	2 (1%)	2 (1%)
Pancreatitis§	3 (1%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Adrenal insufficiency	2 (1%)	0 (0%)	3 (1%)	1 (<1%)	0 (0%)	0 (0%)
Myositis	2 (1%)	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)
Thyroiditis	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Autoimmune hepatitis	1 (<1%)	1 (<1%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)
Hypophysitis	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	0 (0%)	0 (0%)
Type 1 diabetes	1 (<1%)	1 (<1%)	2 (1%)	1 (<1%)	0 (0%)	0 (0%)

*Decided by the investigator. Events are listed in descending frequency in the pembrolizumab 2 mg/kg group. †Irrespective of attribution to study drug. Events are listed in descending order of frequency in the pembrolizumab 2 mg/kg group. ‡Includes patients with interstitial lung disease (one in the pembrolizumab 2 mg/kg group, two in the pembrolizumab 10 mg/kg group, and two in the docetaxel group). §Includes one patient with acute pancreatitis.

Table 2: **Adverse events in the safety population**

adjuvant therapy (PEARLS, ClinicalTrials.gov number NCT02504372). These studies are enrolling patients using different biomarker cutpoints, and we await the final analyses to determine which cutpoint best predicts the effectiveness of pembrolizumab monotherapy in these earlier lines of therapy. For those patients for whom pembrolizumab monotherapy is not as effective as cytotoxic chemotherapy, combinations with chemotherapy[25] or other immunotherapies[26] might be needed. To augment patient identification based on PD-L1 expression, which may be limited by tumour heterogeneity and the dynamic nature of the immune microenvironment,[27,28] other checkpoint molecules,[29] tumour infiltrating cells,[30] mutational load,[31] blood-based immune biomarkers,[10] and inflammatory gene signatures[32,33] could be explored. Additional studies will also be needed to determine the optimal duration of therapy for pembrolizumab and other anti-PD-1 drugs.

Our findings validate pembrolizumab as a new treatment option for patients with advanced non-small cell lung cancer who have received one or more previous treatment regimen and who have a tumour proportion score of at least 1%. These data also support the use of a dose of 2 mg/kg every 3 weeks and validate the use of PD-L1 selection in this population.

Contributors

RSH, GML, MD-F, and EBG designed the study. RSH, PB, D-WK, EF, JPL-G, J-YH, JM, J-HK, CDA, M-JA, MM, MJF, GdC, MG, and EBG collected data. RSH, M-JA, JLP-G, EI, and EBG analysed data. RSH, PB, D-WK, EF, JLP-G, J-YH, JM, M-JA, MM, MJF, GdC, GML, YS, EI, and EBG interpreted the data. RSH and EI wrote the first draft. All authors revised the report and approved the final version.

Declaration of interests

RSH has received funding from Merck and served as an advisory board member for AstraZeneca, Bristol-Myers Squibb, Genentech, and Roche. PB has received grants from and served as an adviser for Merck. EF has received consultation fees from Boehringer Ingelheim, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Pfizer, and Roche, and participated in company-sponsored speaker's bureaux for Bristol-Myers Squibb, Eli Lilly, and Novartis. JLP-G has received grants from Merck. GdC has received personal fees from Merck Sharp & Dohme. GML, YS, EI, and MD-F are employees of and hold stock options in Merck & Co. EBG has received grants from Merck, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Genentech, Novartis, and Pfizer. The other authors declare no competing interests.

Acknowledgments

This study was funded by Merck & Co. We thank the patients and their families and caregivers for participating in the study; LabCorp Clinical Trials (Los Angeles, CA, USA) for performing the PD-L1 screening; Dako (Carpinteria, CA, USA) for contributing to the development of the PD-L1 immunohistochemistry assay; Dean Harvey (LabCorp Clinical Trials) for providing the PD-L1 immunohistochemistry images shown in the appendix; James C Knowles, Ann Marie Mantz, Andrea J Rybak-Feiglin, and Diane M Zawada (Merck & Co, Kenilworth, NJ, USA) for study support; and Roger Dansey (Merck & Co, Kenilworth, NJ, USA) for critical review of the report and study support. Medical writing support in the preparation of this report was provided by Tricia Brown and Melanie Leiby (The ApotheCom Merck oncology team, Yardley, PA, USA); this assistance was funded by Merck & Co.

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