Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS2): a multicentre, open-label, randomised, non-comparative, phase 2 trial

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Summary

Background There is no recommended therapy for malignant pleural mesothelioma that has progressed after first-line pemetrexed and platinum-based chemotherapy. Disease control has been less than 30% in all previous studies of second-line drugs. Preliminary results have suggested that anti-programmed cell death 1 (PD-1) monoclonal antibody could be efficacious in these patients. We thus aimed to prospectively assess the anti-PD-1 monoclonal antibody alone or in combination with anti-cytotoxic T-lymphocyte protein 4 (CTLA-4) antibody in patients with malignant pleural mesothelioma.

Methods This multicentre randomised, non-comparative, open-label, phase 2 trial was done at 21 hospitals in France. Eligible patients were aged 18 years or older with an Eastern Cooperative Oncology Group performance status of 0–1, histologically proven malignant pleural mesothelioma progressing after first-line or second-line pemetrexed and platinum-based treatments, measurable disease by CT, and life expectancy greater than 12 weeks. Patients were randomly allocated (1:1) to receive intravenous nivolumab (3 mg/kg bodyweight) every 2 weeks, or intravenous nivolumab (3 mg/kg every 2 weeks) plus intravenous ipilimumab (1 mg/kg every 6 weeks), given until progression or unacceptable toxicity. Central randomisation was stratified by histology (epithelioid *vs* non-epithelioid), treatment line (second line *vs* third line), and chemosensitivity to previous treatment (progression ≥3 months *vs* <3 months after pemetrexed treatment) and used a minimisation method with a 0·8 random factor. The primary outcome was the proportion of patients who achieved 12-week disease control, assessed by masked independent central review; the primary endpoint would be met if disease control was achieved in at least 40% of patients. The primary endpoint was assessed in the first 108 eligible patients. Efficacy analyses were also done in the intention-to-treat population and safety analyses were done in all patients who received at least one dose of their assigned treatment. This trial is registered at ClinicalTrials.gov, number NCT02716272.

Findings Between March 24 and August 25, 2016, 125 eligible patients were recruited and assigned to either nivolumab (n=63) or nivolumab plus ipilimumab (n=62). In the first 108 eligible patients, 12-week disease control was achieved by 24 (44%; 95% CI 31–58) of 54 patients in the nivolumab group and 27 (50%; 37–63) of 54 patients in the nivolumab plus ipilimumab group. In the intention-to-treat population, 12-week disease control was achieved by 25 (40%; 28–52) of 63 patients in the nivolumab group and 32 (52%; 39–64) of 62 patients in the combination group. Nine (14%) of 63 patients in the nivolumab group and 16 (26%) of 61 patients in the combination group had grade 3–4 toxicities. The most frequent grade 3 adverse events were asthenia (one [2%] in the nivolumab group *vs* three [5%] in the combination group), asymptomatic increase in aspartate aminotransferase or alanine aminotransferase (none *vs* four [7%] of each), and asymptomatic lipase increase (two [3%] *vs* one [2%]). No patients had toxicities leading to death in the nivolumab group, whereas three (5%) of 62 in the combination group did (one fulminant hepatitis, one encephalitis, and one acute kidney failure).

Interpretation Anti-PD-1 nivolumab monotherapy or nivolumab plus anti-CTLA-4 ipilimumab combination therapy both showed promising activity in relapsed patients with malignant pleural mesothelioma, without unexpected toxicity. These regimens require confirmation in larger clinical trials.

Funding French Cooperative Thoracic Intergroup.

Introduction

Malignant pleural mesothelioma is a rare but aggressive malignancy of the pleural surface, commonly associated with occupational asbestos exposure, and its incidence is increasing worldwide.[1] Patients with malignant pleural mesothelioma usually have a very poor prognosis, with a

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Research in context

Evidence before this study

On Nov 15, 2015, we searched PubMed for studies assessing immunotherapeutic antibody use of anti-programmed cell death 1 (PD-1) or anti-cytotoxic T-lymphocyte protein 4 (CTLA-4) antibodies in patients with mesothelioma using the following search terms: "mesothelioma" and "nivolumab" OR "pembrolizumab" OR "atezolizumab" OR "avelumab" OR "durvalumab" OR "ipilimumab" OR "tremelimumab" OR "PD-1" OR "PD-L1", OR "CTLA-4". Additionally, we examined abstracts from the 2015, 2016, and 2017 editions of the American Society of Clinical Oncology annual meeting. Although several studies confirmed that mesothelioma tumour cells do express immune checkpoint proteins, including programmed cell death ligand 1 (PD-L1), and that mesothelioma specimens at times show high stromal infiltration by immune cells such as lymphocytes or monomacrophage and dendritic cells, we found no published clinical studies investigating the safety or efficacy of the anti-PD-1 nivolumab and anti-CTLA-4 ipilimumab combination or anti-PD-1 nivolumab monotherapy in patients with malignant pleural mesothelioma. One large randomised phase 2b trial (DETERMINE; NCT01843374) assessed tremelimumab, an anti-CTLA-4 antibody, administered alone versus placebo as second-line or third-line treatment in 564 patients with malignant pleural mesothelioma, but no survival gain was recorded compared with placebo. Also, a phase 1b trial in 25 patients with PD-L1-expressing malignant pleural mesothelioma (>1% positive tumour cells) treated with the anti-PD-1 antibody pembrolizumab, mostly as second-line treatment, reported five (20%) patients with an overall response and 13 (52%) patients with stable disease, along with a median duration of response of 12 months (95% CI 3·7–not reached), without any safety concerns. Last, a single-arm phase 2 trial (NIBIT-MESO-1; NCT02588131) assessed the combination of 1 mg/kg anti-CTLA-4 tremelimumab and 20 mg/kg anti-PDL-1 durvalumab intravenously injected every 4 weeks in four doses and followed by maintenance durvalumab, as first-line or second-line treatment in patients with unresectable malignant mesothelioma. The authors reported evidence of clinical activity, with 11 (28%) of 40 patients having an immune-related partial response (median duration of response 16·1 months) and another 26 (65%) with immune-related disease control, resulting in a median immune-related progression-free survival of 8 months and median overall survival of 16·6 months.

Added value of this study

On Nov 15, 2015, no second-line or third-line treatment had as yet shown efficacy in patients with malignant pleural mesothelioma who had received first-line pemetrexed and platinum-based chemotherapy with or without bevacizumab (ie, the standard first-line treatment strategy in patients with unresectable malignant pleural mesothelioma). Furthermore, no PD-1-directed or PD-L1-directed antibodies, non-PD-1-directed targeted immunotherapies, or dual immunotherapies had been approved for malignant pleural mesothelioma indications. There is thus a substantial unmet need for new therapeutic strategies assessing immunotherapies in patients with relapsed malignant pleural mesothelioma. Our study achieved its statistical endpoint and is, to the best of our knowledge, the first to assess the safety and efficacy of anti-PD-1 nivolumab monotherapy or anti-PD-1 nivolumab and anti-CTLA-4 ipilimumab combination therapy in patients with malignant pleural mesothelioma as second-line or third-line treatment following first-line pemetrexed and platinum-based chemotherapy. These findings provide supporting evidence that both monotherapy with nivolumab and combination therapy with both nivolumab and ipilimumab are effective in this setting.

Implications of all the available evidence

Our findings, in 125 randomly assigned patients, clearly show that immune checkpoint inhibitors achieve notable clinical activity in relapsed malignant pleural mesothelioma, either as monotherapy or combination therapy, at standard doses. The data showed that immune checkpoint inhibitors are capable of inducing antitumour objective responses according to Response Evaluation Criteria in Solid Tumours criteria for mesothelioma, as well as significant median progression-free and overall survival, with a tolerable safety profile, in this orphan-disease population. Although these results require further confirmation in larger trials, they could now justify the use of immune checkpoint inhibitors in patients with relapsed malignant pleural mesothelioma who have no other efficient therapeutic options available.

median overall survival of approximately 12 months, despite some patients having surprisingly long tumour doubling time, indicative of a slow-growing tumour, specifically in the second-line or third-line setting. Moreover, patients often exhibit strong resistance to chemotherapy, and few patients are suitable candidates for multimodal treatment, including radical surgery.[2] In 2015, we initiated a phase 3 open-label randomised controlled trial, the IFCT-GFPC-0701 Mesothelioma Avastin plus Pemetrexed-cisplatin Study (MAPS), which showed an overall survival benefit when adding bevacizumab to standard cisplatin plus pemetrexed chemotherapy (median overall survival 18·8 months [95% CI 15·9–22·6] with bevacizumab *vs* 16·1 months [14·0–17·9] without bevacizumab; hazard ratio [HR] 0·77 [95% CI 0·62–0·95]; p=0·017).[3] However, an optimal second-line treatment for malignant pleural mesothelioma has not yet been defined by the most recent guidelines.[2,4–7]

Understanding of malignant pleural mesothelioma pathogenesis has substantially improved during the past few years, leading to innovative drugs and strategies,[8,9]

with targeted therapies and immunotherapies sparking new hope for patients with this disease.[3,9–11] By instigating chronic inflammation and localised tumour immunosuppression, the immune system plays a crucial part in malignant pleural mesothelioma pathogenesis, with improved outcomes correlated with higher intra-tumour infiltration by CD8+ cytotoxic T cells.[12] Conversely, high tumour expression of programmed cell death ligand 1 (PD-L1), which inhibits T-cell function via binding programmed cell death 1 (PD-1), has been associated with poor prognosis in mesothelioma (median overall survival 5·0 months (IQR 2·0–9·5) in PD-L1-positive patients *vs* 14·5 months (9·0–19·0) in PD-L1-negative patients).[9,13,14]

Among the different immunotherapies evaluated so far to restore antitumour immune response in malignant pleural mesothelioma, immune checkpoint inhibitors (ICIs) have garnered the most attention on the basis of their efficacy, particularly in melanoma and non-small-cell lung cancer (NSCLC).[9,10] Cytotoxic T-lymphocyte protein 4 (CTLA-4) is an immune checkpoint that blocks interactions between antigen-presenting cells, such as dendritic and naive T cells, occurring early in the antitumour cycle. After encouraging phase 2 trial results, tremelimumab, an anti-CTLA-4 antibody, was tested alone versus placebo in second-line or third-line treatment of patients with malignant pleural mesothelioma in a large randomised phase 2b trial (DETERMINE),[15] but survival was not improved compared with placebo. By contrast, several studies assessing ICIs targeting the PD-1 or PD-L1 pathway have generated promising results.[9,16] In a phase 1b trial, five (20%) of 25 patients with PD-L1-expressing malignant pleural mesothelioma (≥1% positive tumour cells) treated with the anti-PD-1 monoclonal antibody pembrolizumab, mostly as a second-line treatment, had an overall response, and 13 (52%) achieved stable disease. The median duration of response was 12 months (95% CI 3·7–not reached), with no safety concerns.[16] Other trials assessing anti-PD-1 or anti-PD-L1 antibodies in malignant pleural mesothelioma have reported similar proportions of patients with responses.[9,10] Another anti-PD-1 monoclonal antibody, nivolumab, is being assessed as third-line monotherapy versus placebo in the UK in a randomised phase 3 trial (CONFIRM; Cancer Research UK trial number CRUK/16/022).

Checkpoint antibody combination trials are another area of great interest in malignant pleural mesothelioma research. Combined 1 mg/kg tremelimumab and 20 mg/kg durvalumab given in four intravenous doses every 4 weeks, followed by maintenance durvalumab at the same dose and schedule for nine doses, was tested in a single-arm phase 2 trial (NIBIT-MESO-1) as first-line or second-line treatment in patients with unresectable malignant mesothelioma.[17] The trial met its primary endpoint with 11 (28%) of 40 patients exhibiting immune-related partial responses (median duration of response 16·1 months [IQR 11·5–20·5]); 26 (65%) of 40 had immune-related disease control, leading to a median immune-related progression-free survival of 8·0 months (95% CI 6·7–9·3) and a median overall survival of 16·6 months (13·1–20·1).[17] Baseline tumour PD-L1 expression had no predictive or prognostic value.

Based on this rationale, we aimed to assess, in patients with malignant pleural mesothelioma, the value of nivolumab as a single drug or in combination with the anti-CTLA-4 monoclonal antibody ipilimumab in a second-line or third-line setting by means of a randomised, non-comparative phase 2 trial.

Methods

Study design and participants

This multicentre, randomised, controlled non-comparative, open-label phase 2 trial was done at 21 hospitals in France. We recruited patients aged at least 18 years with malignant pleural mesothelioma that was histologically proven by pleural biopsy (thoracoscopy recommended), irrespective of PD-L1 tumour status. Eligible patients had disease progression according to modified Response Evaluation Criteria in Solid Tumours (RECIST) criteria for mesothelioma, version 1.0[18] (centrally assessed with CT by three radiologists experienced in malignant pleural mesothelioma) and had already received one or two systemic chemotherapy lines, at least one involving a pemetrexed–platinum salt doublet line (triplet including bevacizumab also accepted), without a mandatory washout period. Eligible patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, had not lost more than 10% bodyweight over the previous 3 months, and were not candidates for curative surgery (according to a malignant pleural mesothelioma-dedicated multidisciplinary board, including a thoracic surgeon), with at least one lesion (pleural tumour, solid thickening) measurable on CT and life expectancy greater than 12 weeks. Patients had to have recovered from toxicities associated with previous treatment to an acceptable baseline status or grade 0 or 1, except for toxicities not considered a safety risk. They also had to have had adequate haematological, hepatic, and renal function (creatinine clearance ≥60 mL/min) within 7 days of enrolment and available tumour tissue (fresh or archived) for PD-L1 immunohistochemistry analysis.

Exclusion criteria comprised active or history of inflammatory bowel disease (eg, haemorrhagic rectocolitis or Crohn's disease); central nervous system metastases; a recent history of other malignancies except adequately treated non-melanoma skin cancer; peritoneal or pericardial mesothelioma without any pleural involvement at the time of diagnosis; live attenuated vaccination administered in the 30 days before randomisation; active, known, or suspected autoimmune disease; active or uncontrolled infections or serious illnesses or medical conditions that would not permit management according to the protocol; known primary immunodeficiency or immunosuppressive treatment within 28 days preceding inclusion; corticosteroid treatment of more than 10 mg/day

prednisone or equivalent within 14 days preceding inclusion; and known history of lung interstitial disease. Other previous treatments that were not permitted were anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways. The last dose of previous chemotherapy or radiotherapy must have been received at least 3 weeks before randomisation.

The research protocol was approved by the Nord-Ouest III ethics committee (Comité de Protection des Personnes) of the University Hospital of Caen, France, and the trial was conducted in line with the Declaration of Helsinki and Good Clinical Practice guidelines. Before inclusion, all patients provided written informed consent to participate in the trial.

Randomisation and masking

We used an interactive web-response system to generate random, non-masked treatment allocation. We randomly assigned patients enrolled by investigators (1:1) to receive nivolumab or nivolumab plus ipilimumab. We did randomisation centrally using a minimisation method (random factor of 0·8) and stratified patients by histology (epithelioid *vs* sarcomatoid or mixed-histological subtypes), treatment line (second line *vs* third line), and chemosensitivity to pemetrexed–platinum doublet (progression ≥3 months after completing pemetrexed–platinum doublet *vs* <3 months).

Procedures

Patients received intravenous nivolumab at 3 mg/kg of their bodyweight (60 min infusion) every 2 weeks, or 3 mg/kg nivolumab every 2 weeks given first (60 min infusion) followed by 1 mg/kg ipilimumab (90 min infusion) every 6 weeks. Patients received open-label treatment until progression or unacceptable toxicity for a maximum of 2 years. No dose reduction or modifications were permitted for nivolumab or ipilimumab. Treatment was interrupted for immune toxicities of at least grade 3 until recovery of event back to less than grade 2. Any nivolumab dose delay associated with treatment interruption of more than 6 weeks required treatment discontinuation. Ipilimumab treatment interruption for more than 12 weeks also required treatment discontinuation, except for delays due to drug-related adverse events needing slow steroid tapering off until less than 10 mg daily steroid dose was required for full recovery from an immunotherapy-related adverse event. Criteria for permanent treatment discontinuation were grade 3 non-skin events lasting 7 days or more, grade 3 laboratory abnormalities of thrombocytopenia or liver function test, and all grade 4 events, as well as laboratory abnormalities, except for asymptomatic amylase or lipase increases. Other potential reasons for treatment termination included tumour progression, death, intercurrent illness, protocol violation, non-compliance, and withdrawal of patient consent.

After disease progression or unacceptable toxicity, further treatment with different drugs could be initiated at the discretion of the investigators, although crossover and further ipilimumab or ipilimumab plus nivolumab were not permitted in the nivolumab group.

Baseline laboratory tests required to assess eligibility were white blood cell counts, neutrophils, platelets, haemoglobin, serum creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, albumin, and lipase. These tests were done at baseline and at every treatment infusion. Thyroid-stimulating hormone was measured at baseline and monitored every 12 weeks.

Adverse event monitoring was performed before each treatment infusion (ie, every 2 weeks until the end of protocol treatment) and for 3 months after discontinuation.

At baseline, we assessed disease using chest CT scans, including abdominal exploration and brain MRI or CT. Tumour–node–metastasis (TNM) classification was centrally assessed post hoc by expert thoracic radiologists masked to allocation group, on thoracic CT scans at diagnosis, and by reviewing the pathological and surgical reports in cases involving initial diagnostic thoracoscopy, according to the eighth TNM classification for malignant pleural mesothelioma.[19] We performed CT scans every 12 weeks from randomisation, at the same timepoints in both groups, with response assessed at 12 weeks by modified RECIST criteria for mesothelioma.[18] CT scans were centrally reviewed by three masked independent radiologists experienced in malignant pleural mesothelioma. Patients were followed up every 12 weeks to assess survival. Adverse events and laboratory abnormalities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

We assessed quality of life using the Lung Cancer Symptom Score (LCSS)[20] at baseline, treatment initiation, and every 12 weeks. For each scale or item in LCSS, a linear transformation was applied to standardise the raw score to a 0–100 range (100 being best possible function or quality of life for functional scales and highest symptom burden for symptom scales and symptom items). A ten-point change in an item or domain was considered clinically meaningful.[3] Quality of life was defined as improved when at least a ten-point increase was recorded for functioning scales and at least a ten-point reduction was recorded for symptom domains or items between baseline and 12-week assessments. We deemed quality of life stable when variations of less than ten points were recorded for functioning scales and symptom domains and items, and as worsened with a ten-point or greater decrease for functioning scales and a ten-point or greater increase for symptom domains or items. To compute treatment exposure, we calculated the ratio of the dose intensity measured as a proportion of the theoretical dose intensity.

Formalin-fixed tumour samples were collected and PD-L1 expression was assessed by immunohistochemistry at a central laboratory (Léon Bérard Cancer Center, Lyon, France) by PD-L1 immunohistochemistry: 28-8 pharmDx and SP-263 monoclonal antibody clones on an Autostainer Link 48 platform (Agilent, Santa Clara, CA, USA) were used according to previously described laboratory-developed tests for SP-263 clones on this platform[21] with formalin-fixed tumour samples obtained by thoracoscopy or CT-guided core-needle biopsies by the MESOPATH National Reference Center (Cancer Center Institut Léon Bérard, Lyon, France) for malignant pleural mesothelioma pathological diagnosis certification.[22] The pathologist in charge of analysing the specimens was masked to treatment and patient response. Expression was categorised according to tumour proportion scores (ie, percentage of tumour cells with membranous PD-L1 staining, regardless of intensity). Typically, the same two cutoffs are used in the literature to define patients with high PD-L1 tumour expression—ie, 25% or more tumour cells expressing PD-L1 regardless of the intensity[21,22] or 50% or more tmour cells expressing PD-L1.[23] We defined an exploratory cutoff threshold of tumour cells presenting membranous PD-L1 staining on the basis of data resulting from a post-hoc analysis to ensure there were sufficient numbers of patients in each subset.

Outcomes

The primary outcome was the proportion of patients achieving disease control, defined as the proportion of patients with complete response, partial response, or stable disease at 12 weeks after randomisation, assessed by independent central review involving three radiologists masked to treatment using modified RECIST criteria for mesothelioma.[18]

Secondary outcomes were overall survival (time from randomisation to death from any cause), progression-free survival (time from randomisation to documented disease progression or death, whichever occurred first), quality of life as assessed by LCSS questionnaires at each infusion, and safety.

Statistical analysis

The primary study endpoint (disease control) was assessed in the first 108 eligible patients, whereas efficacy (progression-free survival and overall survival) was assessed in the intention-to-treat population of all randomly assigned patients; the safety population was all patients who received at least one cycle of their assigned study treatment. Quality of life was assessed in all patients who were assessable for response or survival at 12 weeks.

Patients were considered as assessable for response or survival if they had the 12-week tumour evaluation (for response) or if they progressed before the 12-week evaluation (either clinically or by CT scan).

We assumed 20% or lower disease control at 12 weeks (null hypothesis), a level at which the treatment is of no therapeutic interest (ie, disease control below which the treatment would be deemed inactive), validated by a masked independent central review by one of three radiologists, and a target of at least 40% disease control (alternative hypothesis), indicating clinical activity, along with a one-sided α error of 0·05. We thus calculated that a total of 54 eligible patients in each group (108 in total) would allow detection of an effect on the primary outcome with 95% power. Assuming 5% of patients would be ineligible, we had to recruit 57 patients to each group. Based on these assumptions, at least 17 patients without treatment failure had to be independently recorded at 12 weeks in either group, using a one-step Fleming procedure, to enable conclusions to be made about the activity of the corresponding regimen. No interim analysis was planned.

For patients with no events, the cutoff point was final contact. We plotted progression-free survival and overall survival by means of Kaplan-Meier curves, with follow-up censored on Dec 28, 2017. In subgroup analyses, HRs and 95% CIs were estimated using a Cox model adjusted for stratification factors. For statistical analyses, we used SAS software version 9.4, with all p values and CIs two sided.

We did a post-hoc anlaysis to analyse the correlation between PD-L1 tumour expression and proportion of patients with an overall response, disease control, progression-free survival, and overall survival. We also did an exploratory post-hoc analysis to establish the effect of known prognostic factors for malignant pleural mesothelioma on overall survival.

We tested the prognostic effect of PD-L1 tumour expression (28-8 PharmDX or SP-263 assays) using a non-adjusted Cox model. We assessed the prognostic factors for malignant pleural mesothelioma using an adjusted Cox model for the stratification variables, represented as a forest plot for each treatment group.

This trial is registered with the European Union Clinical Trials Register (2015-004475-75) and ClinicalTrials.gov (NCT02716272). The study protocol is in the appendix (pp 10–84).

See Online for appendix

Role of the funding source

The study funder designed the trial and collected and interpreted the data. Investigators and staff of the funder participated in study design and data analysis. The corresponding author (AS) and co-principal investigator (GZ) had full access to all study data and took final responsibility for the decision to submit for publication.

Results

Between March 24 and Aug 25, 2016, we recruited 132 patients and randomly assigned 68 patients to nivolumab and 64 patients to nivolumab plus ipilimumab. After group assignment, five patients in the nivolumab group and two in the combination group were found to be ineligible and excluded from the intention-to-treat

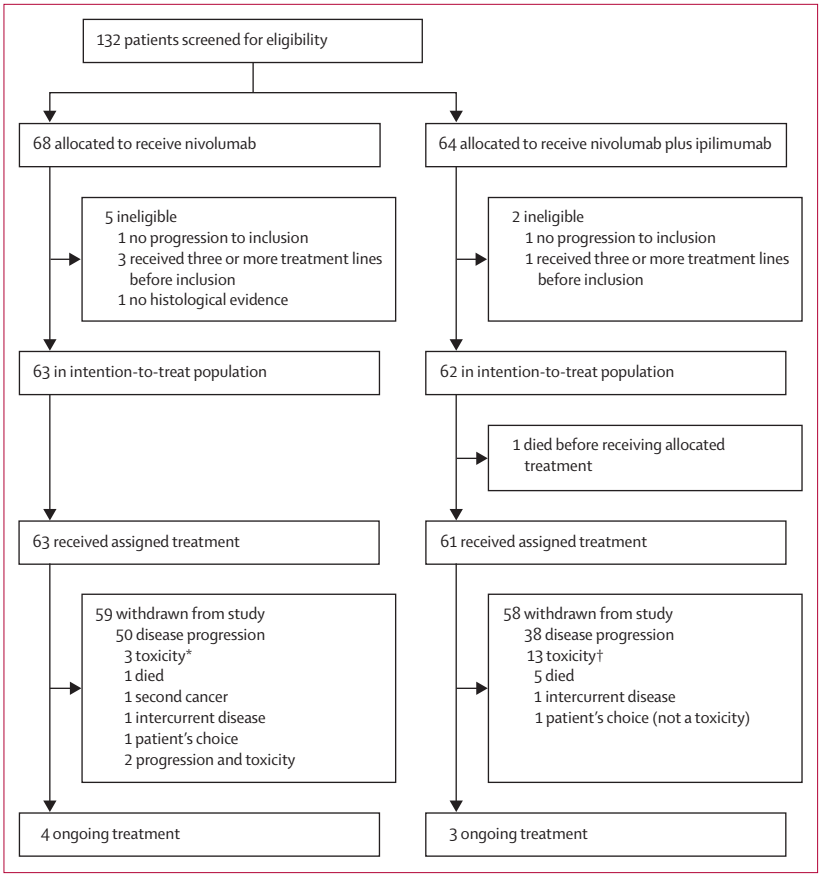

Figure 1: **Trial profile**
Eligibility was systematically centrally reviewed by the steering committee based on the patients' individual charts, after central allocation of treatments. *Toxicities leading to study discontinuation in the nivolumab group were renal failure, pericardial effusion, and keratitis, in one patient each. †Toxicities leading to study discontinuation in the nivolumab plus ipilimumab group were cardiac failure, lipase increased, pneumopathy, gastritis, dermatitis bullous, pneumonitis, atrioventricular block, hepatitis, colitis, atrial fibrillation, polyneuropathy, diarrhoea, in one patient each except hepatitis, which led to discontinuation in two patients.

	Nivolumab group (n=63)	Nivolumab plus ipilimumab group (n=62)
Sex		
Female	16 (25%)	9 (15%)
Male	47 (75%)	53 (85%)
Age, years		
Mean (SD)	71·2 (9·5)	70·4 (9·0)
Median (IQR)	72·3 (32·5–87·2)	71·2 (48·1–88·1)
Histological subtype		
Epithelioid	52 (83%)	53 (85%)
Sarcomatoid or biphasic	11 (17%)	9 (15%)
ECOG performance status*		
0	19 (30%)	25 (40%)
1	42 (67%)	36 (58%)
2	0	1 (2%)
Pemetrexed chemosensitivity		
Progression before 3 months	26 (41%)	21 (34%)
Progression after 3 months	37 (59%)	41 (66%)
Smoking status		
Smoker	34 (54%)	36 (58%)
Never smoker	29 (46%)	26 (42%)
Number of previous lines of treatment		
One (second-line patients)	44 (70%)	42 (68%)
Two (third-line patients)	17 (27%)	19 (31%)
More than two	2 (3%)	1 (2%)
Tumour–node–metastasis classification		
Stages I–II	7 (11%)	11 (18%)
Stages III–IV	56 (89%)	51 (82%)
Leucocytes		
<8·3 × 10⁹ per L	43 (68%)	41 (66%)
≥8·3 × 10⁹ per L	20 (32%)	21 (34%)
Haemoglobin		
≤12 g/L	30 (48%)	25 (40%)
>12 g/L	33 (52%)	37 (60%)
Platelets		
<350 × 10⁹ per L	46 (73%)	43 (69%)
≥350 × 10⁹ per L	17 (27%)	19 (31%)
PD-L1 status available (28-8 monoclonal antibody, Dako PharmDx)		
Negative	31 (49%)	27 (44%)
≥1%	19 (30%)	22 (35%)
≥25%	2 (3%)	5 (8%)
≥50%	0	3 (5%)
Data not available	13 (21%)	13 (21%)

Data are n (%) unless otherwise stated. ECOG=Eastern Cooperative Oncology Group. PD-L1=programmed cell death ligand 1. *Performance status was not available for two patients in the nivolumab group.

Table 1: **Baseline patient characteristics**

population. The intention-to-treat population therefore included 125 patients (63 in the nivolumab group and 62 in the nivolumab plus ipilimumab group) Because accrual was faster than anticipated, 11 patients who provided consent on the final day of accrual were enrolled in the intention-to-treat population in addition to the 114 initially planned (figure 1). All 63 patients in the nivolumab group and 61 (98%) of 62 patients in the nivolumab plus ipilimumab group received at least one dose of their assigned treatment, and were thus included in the safety population.

Median age was 72·3 years (IQR 32·5–87·2) in the nivolumab group and 71·2 years (48·1–88·1) in the nivolumab plus ipilimumab group (table 1). 16 (25%) of 63 patients in the nivolumab group were women, compared with nine (15%) of 62 patients in the nivolumab plus ipilimumab group. 56 (89%) patients in the nivolumab group and 51 (82%) patients in the nivolumab plus ipilimumab group had stage III–IV disease; 19 (30%) patients in the nivolumab group and 25 (40%) in the nivolumab plus ipilimumab group had an ECOG performance status of 0.

Malignant pleural mesothelioma histology, as assessed by central review of the MESOPATH National Reference Center, was epithelioid in 52 (83%) patients in the nivolumab group versus 53 (85%) in the combination

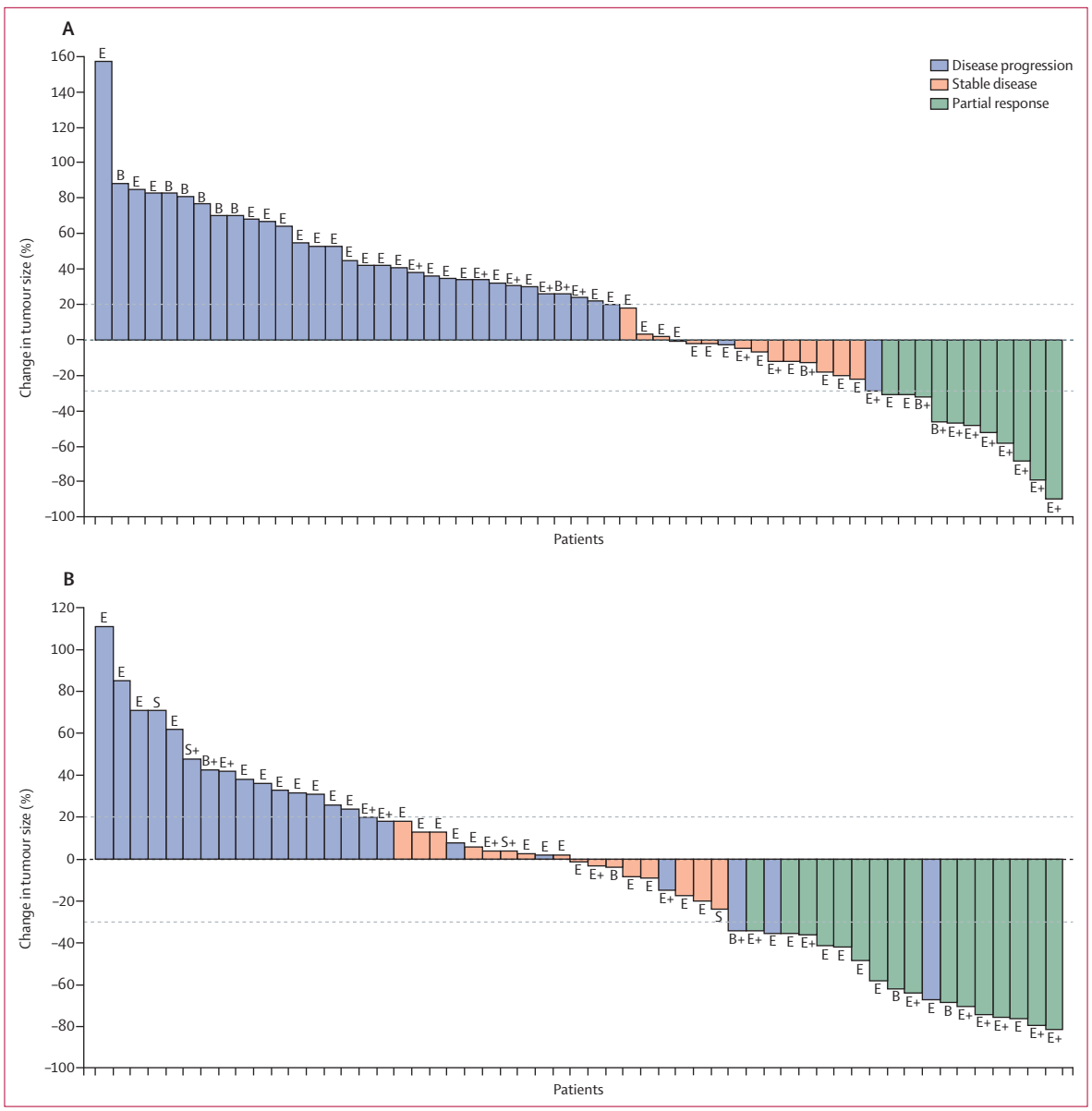

Figure 2: **Percentage changes in tumour size, baseline to week 12**
(A) Nivolumab group. Four patients were not evaluable at 12 weeks. (B) Nivolumab plus ipilimumab group. Six patients were not evaluable at 12 weeks. Positive symbol indicates patients with PD-L1 ≥1%. Negative symbol indicates patients with PD-L1 <1%. E=epithelioid. B=biphasic. S=sarcomatoid. Horizontal dashed line at –30% shows cutoff for partial response and horizontal dashed line at 20% shows cutoff for progressive disease. PD-L1=programmed cell death ligand 1.

therapy group; histology was biphasic or sarcomatoid in 11 (17%) patients versus nine (15%) patients. Most patients had progression more than 3 months after receiving first-line pemetrexed and platinum-based chemotherapy and most patients had received only one previous therapy. Blood counts (leucocytes, red cells estimated by haemoglobin concentration, and platelets) were balanced between the groups (table 1).

Drug delivery was quite successful: about 70% of patients received the first six infusions (nivolumab or nivolumab plus ipilimumab) as initially planned, at 100% of the planned drug dose; 31 (49%) of 63 nivolumab patients and 24 (39%) of 62 nivolumab plus ipilimumab patients received ten planned infusions (both drugs injected by infusion on weeks 1, 6, 12, and every 6 weeks thereafter in the nivolumab plus ipilimumab group).

At data cutoff on Dec 28, 2017, after a median follow-up of 20·1 months (IQR 19·6–20·3), 59 (94%) of 63 patients had discontinued treatment in the nivolumab group, 50 of whom discontinued because they had disease progression, three because of toxicities, one patient died without toxicity or progression, another had a second unrelated cancer, one patient had an intercurrent disease, one patient decided to stop treatment by their own

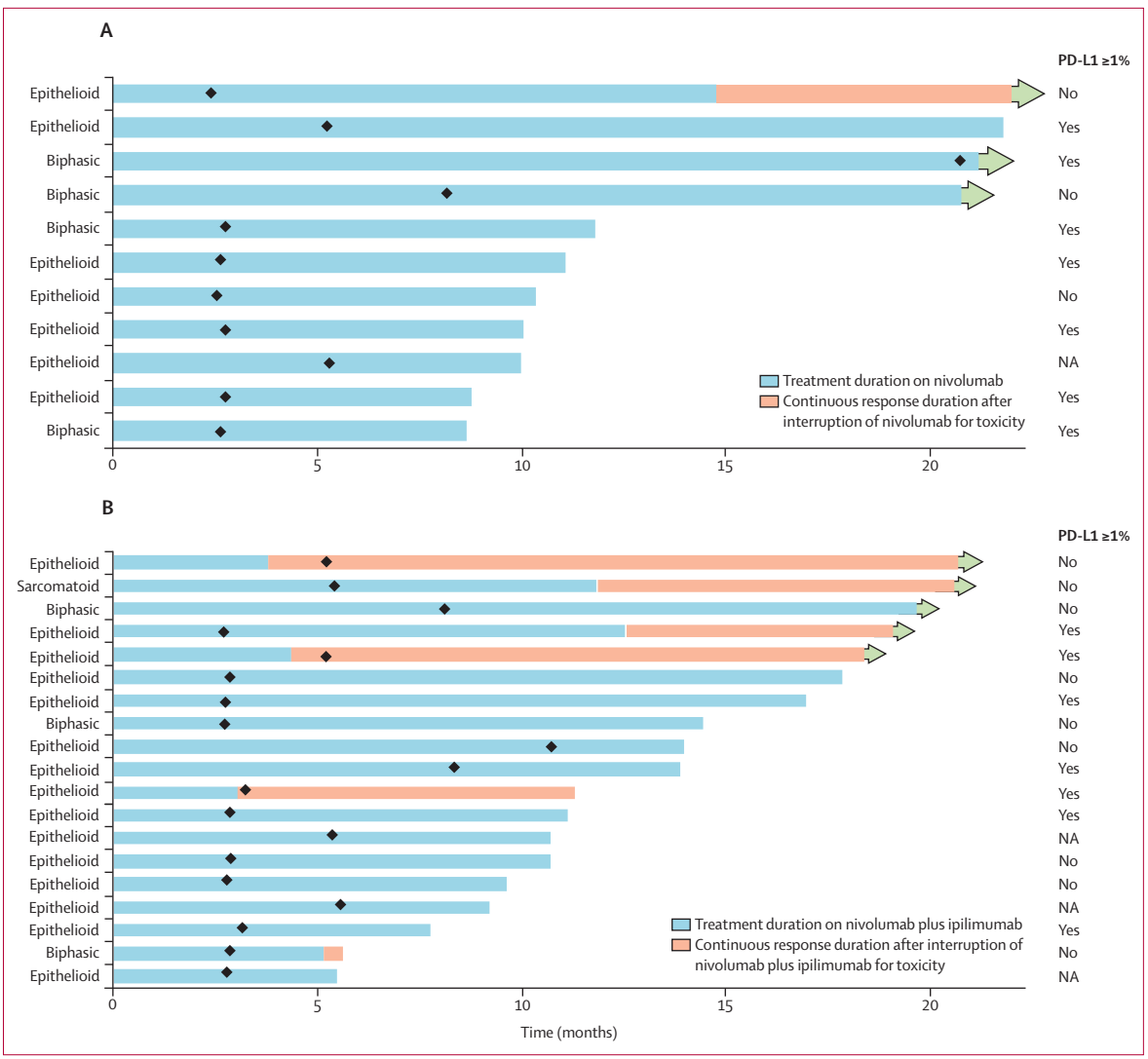

Figure 3: **Treatment duration, time to response, and treatment response duration in patients with an objective response**
Results are at data cutoff. (A) Nivolumab group. (B) Nivolumab plus ipilimumab group. Black diamonds show time of response. Arrows show ongoing response at data cutoff. PD-L1=programmed cell death ligand 1. NA=not available.

choice, and two patients had both toxicity and progression; only four patients were receiving ongoing treatment (figure 1). In the nivolumab plus ipilimumab group, 58 patients had discontinued treatment, 38 of whom discontinued because they had disease progression, 13 because of toxicities, five patients died without toxicity or progression, one patient had an intercurrent disease, and one patient was removed by the decision of the investigator; only three patients were still on treatment (figure 1).

The primary endpoint of disease control at 12 weeks after randomisation in the first 108 patients was met in both groups: 24 (44%; 95% CI 31–58) of 54 patients in the nivolumab group and 27 (50%; 37–63) of 54 in the nivolumab plus ipilimumab group achieved disease control at 12 weeks, as centrally assessed by an independent masked radiological expert panel. Objective responses were achieved by ten (19%; 8–29) of 54 patients in the nivolumab group and 15 (28%; 16–40) of 54 in the nivolumab plus ipilimumab group. In the intention-to-treat population of 125 patients, 12-week disease control was achieved by 25 (40%; 28–52) of 63 patients in the nivolumab group and 32 (52%; 39–64) of 62 patients in the nivolumab plus ipilimumab group (appendix p 3). At the 12th week of treatment at the first tumour response evaluation, six (10%) of 59 patients treated with nivolumab and two (4%) of 55 assessable patients treated with nivolumab plus ipilimumab had a greater than 80% increase in the size of their target lesions, suggesting hyperprogression, with no obvious correlation with the subtype (figure 2). In the patients who achieved an objective response at data cutoff (Dec 28, 2017; 11 in the

nivolumab group and 19 in the combination therapy group), median duration of responses were 7·4 months (95% CI 4·1–11·9) in the nivolumab group and 8·3 months (3·0–14·0) in the nivolumab plus ipilimumab group, with four patients (one still on nivolumab) still responding at 15 months in the nivolumab group and seven patients (two still on the combination) still responding at 15 months in the nivolumab and nivolumab plus ipilimumab group (figure 3).

After a median follow-up of 20·1 months (IQR 19·6–20·3), median progression-free survival was 4·0 months (95% CI 2·8–5·7) in the nivolumab group and 5·6 months (3·1–8·3) in the nivolumab plus ipilimumab group; 58 (92%) of 63 patients in the nivolumab group and 53 (85%) of 62 patients in the nivolumab plus ipilimumab group had disease progression or had died by study cutoff (figure 4A). 1-year progression-free survival estimates were 15·9% (95% CI 6·8–24·9) in the nivolumab group and 22·6% (12·2–33·0) in the nivolumab plus ipilimumab group.

Median overall survival was 11·9 months (95% CI 6·7–17·7) in the nivolumab group and 15·9 months (10·7–not reached) in the nivolumab plus ipilimumab group; 41 (65%) of 63 patients in the nivolumab group and 32 (52%) of 62 patients in the nivolumab plus ipilimumab group had died by data cutoff (figure 4B). 1-year survival estimates were 49·2% (36·9–61·6) in the nivolumab group and 58·1% (45·8–70·3) in the nivolumab plus ipilimumab group. Treatments received by patients after discontinuation were not notably different between the groups (appendix p 4).

All-grade drug-related adverse events occurred in 56 (89%) of 63 patients in the nivolumab group and 57 (93%; including three deaths) of 61 in the combination group (table 2). Grade 3–4 drug-related adverse events were less common in the nivolumab group (nine [14%] of 63 patients) than in the nivolumab plus ipilimumab group (16 [26%] of 61). The most frequent grade 3–4 adverse events were asthenia (one [2%] in the nivolumab group *vs* three [5%] in the combination group), asymptomatic increase in aspartate aminotransferase or alanine aminotransferase (none *vs* four [7%] of each), and asymptomatic lipase increase (three [5%] *vs* two [3%]). All-grade serious drug-related adverse events occurred in three (5%) of 63 patients in the nivolumab group and in 17 (28%; three of which were deaths) of 61 patients in the combination groups. Three (5%) of 63 patients in the nivolumab group and 13 (21%) of 61 patients in the combination group had drug-related adverse events that led to treatment discontinuation. There were three (5%) treatment-related deaths reported in the combination group: one fulminant hepatitis, one encephalitis (normal cerebrospinal fluid cellular and biochemical composition, normal brain MRI, and no blood cerebrospinal fluid neuronal self-antibodies found), and one acute kidney failure in a patient with (end of life) disease progression exhibiting recurrent pleural and peritoneal effusions needing daily punctures. These three grade 5 events occurred within the first 4 months of the study, with no other toxic deaths reported later in the trial. No treatment-related deaths were reported in the nivolumab group. The incidence of grade 4 adverse events was low in both groups (one [2%] case of lipase increase for nivolumab and two [3%] for nivolumab plus ipilimumab [one lipase increase and one acute kidney failure]).

No differences in drug-related haematological adverse events were noted (none of grades 3–4 in either group; data not shown).

Any-grade immune-related adverse events had frequencies of none up to four (6%) of 63 in the nivolumab group and none to seven (11%) of 61 in the nivolumab plus ipilimumab group (table 2). The only grade 4

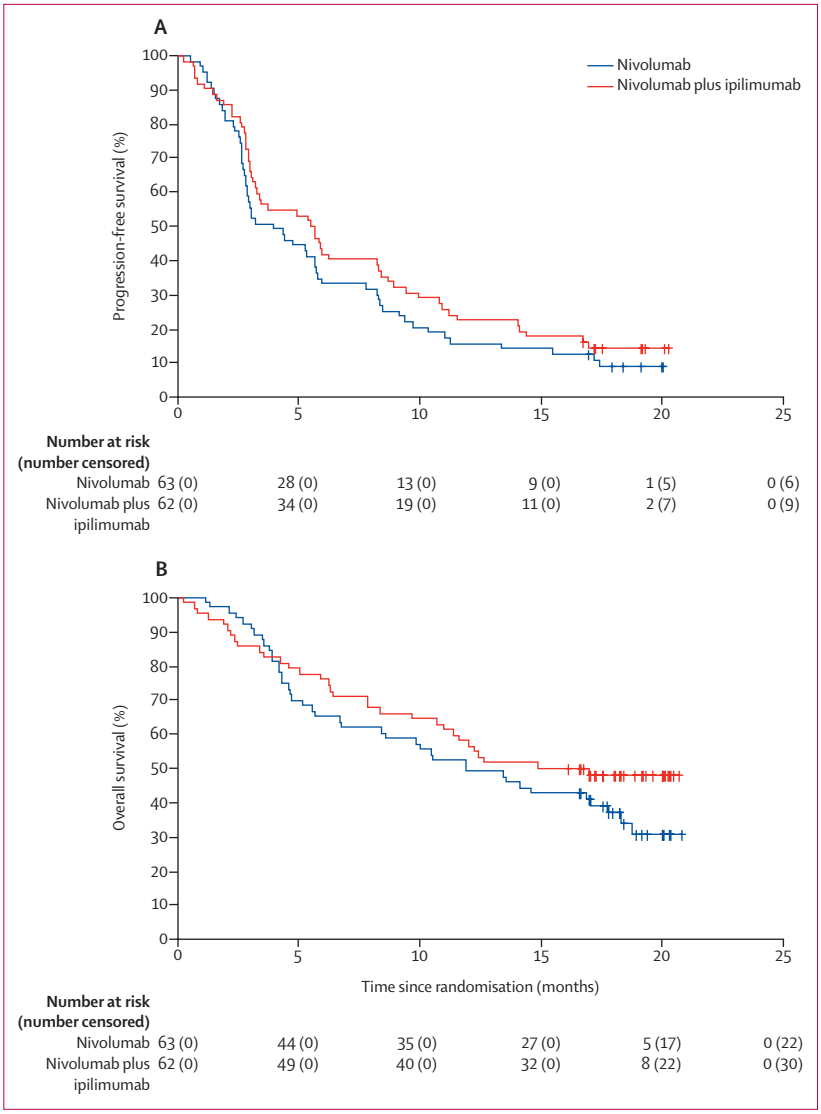

Figure 4: **Progression-free survival and overall survival in all patients at data cutoff**
(A) Progression-free survival. (B) Overall survival. Crosses represent censored patients.

	Nivolumab group (n=63)			Nivolumab plus ipilimumab group (n=61)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any adverse event	47 (75%)	8 (13%)	1 (2%)	38 (62%)	14 (23%)	2 (3%)
Serious adverse event	1 (2%)	2 (3%)	0	7 (11%)	6 (10%)	1 (2%)
Led to discontinuation	2 (3%)	1 (2%)	0	4 (7%)	7 (11%)	2 (3%)
Led to death	0	0	0	0	0	0
Immune-related adverse events						
Stomatitis	4 (6%)	1 (2%)	0	4 (7%)	0	0
Arthritis	3 (5%)	0	0	7 (11%)	0	0
Aspartate aminotransferase increase	2 (3%)	0	0	3 (5%)	4 (7%)	0
Alanine aminotransferase increase	1 (2%)	0	0	4 (7%)	4 (7%)	0
Lipase increase	1 (2%)	2 (3%)	1 (2%)	2 (3%)	1 (2%)	1 (2%)
Oedema peripheral	4 (6%)	0	0	3 (5%)	1 (2%)	0
γ-Glutamyltransferase increased	1 (2%)	0	0	3 (5%)	3 (5%)	0
Amylase increased	1 (2%)	1 (2%)	0	3 (5%)	0	0
General physical health deterioration	3 (5%)	0	0	0	2 (3%)	0
Acute kidney failure	0	0	0	0	0	1 (2%)
Blood alkaline phosphatase increased	0	0	0	2 (3%)	2 (3%)	0
Colitis	1 (2%)	0	0	1 (2%)	1 (2%)	0
Pneumonitis	1 (2%)	0	0	1 (2%)	1 (2%)	0
Polyneuropathy	0	0	0	0	1 (2%)	0
Acute respiratory distress syndrome	0	0	0	0	1 (2%)	0
Cardiac failure	0	0	0	0	1 (2%)	0
Dermatitis bullous	0	0	0	0	1 (2%)	0
Encephalitis	0	0	0	0	0	0
Hepatitis	0	0	0	0	2 (3%)	0
Hyperbilirubinaemia	0	0	0	0	1 (2%)	0
Hyponatraemia	0	0	0	0	1 (2%)	0
Hypophysitis	0	0	0	0	1 (2%)	0
Interstitial lung disease	0	0	0	0	1 (2%)	0
Pericardial effusion	0	1 (2%)	0	0	0	0
Pleural effusion	0	1 (2%)	0	0	0	0

All grade 3 and 4 events are shown as well as grade 1 and 2 occurrences of these events. For other grade 1–2 events, only events occurring in more than ten people are included. Three serious grade 5 events (deaths) occurred in the nivolumab plus ipilimumab group: one acute kidney failure, one fulminant hepatitis, and one encephalitis.

Table 2: **Drug-related adverse events**

immune-related adverse events reported were one (2%) patient exhibiting grade 4 increased lipase concentrations in each group and one (2%) patient with grade 4 acute kidney failure and creatinine increase. Most all-grade immune-related toxicities were biological, causing neither relevant clinical consequences nor treatment interruption. All-grade asymptomatic increases in alanine aminotransferase concentrations also occurred in both groups (one [2%] of 63 in the nivolumab group *vs* eight [13%] of 61 in the nivolumab plus ipilimumab group). The incidence of grade 3–5 and all-grade adverse events is summarised in the appendix (p 5).

No patients in the nivolumab group versus one (2%) of 61 patients in the nivolumab plus ipilimumab group had a drug-related grade 4 non-haematological adverse event and two (3%) of 63 versus five (8%) of 61 patients had grade 3 events (table 3). All-grade diarrhoea events were frequent in both groups (nine [14%] of 63 for nivolumab and 18 [30%] of 61 for nivolumab plus ipilimumab), as were all-grade pruritus events (six [10%] of 63 and 15 [25%] of 61).

Patient-reported outcomes were collected using the LCSS questionnaire, expressed as the percentage of patients who reported deteriorating quality of life between the baseline and 12-week questionnaires. A graphical representation of the rate of decline for ten items on the questionnaire is depicted in the appendix (p 2). No notable differences were detected between the groups in the proportions of patients reporting score decline at 12 weeks in each item, taking into account the exploratory nature of such unpowered analyses precluding any formal statistical test. Longitudinal quality of life studies, using time until definitive deterioration, and thus long-term quality of life data, will be published separately.

We did an exploratory analysis of PD-L1 expression in 104 of the 125 patients for SP-263 antibodies and 99 patients for 28-8 antibodies; there was insufficient tissue remaining for analysis for the other patients. For this analysis, results were not recorded by treatment group but patients were combined and then grouped by PD-L1 expression. 28-8 PD-L1 expression in at least 1% of cells was found to be significantly associated with objective response to immunotherapy (16 [39%] of 41 PD-L1-positive patients *vs* seven [12%] of 58 PD-L1-negative patients had an objective response; p=0·002), but not with 12-week disease control (22 [54%] *vs* 24 [41%]; p=0·23; appendix p 6). SP-263 PD-L1 expression in at least 1% of cells was significantly associated with objective response to immunotherapy (15 [32%] of 47 PD-L1-positive patients *vs* eight [14%] of 57 PD-L1-negative patients; p=0·038) but not with 12-week disease control (22 [47%] *vs* 24 [42%]; p=0·70). We did a post-hoc analysis with a 25% cutoff as the threshold for high tumour PD-L1 expression because there were not enough patients with 50% cells or more expressing PD-L1 in this cohort (none in the nivolumab group and three in the combination group). Seven patients with the 28-8 assay and 16 with the SP-263 assay had high PD-L1 tumour expression of at least 25%, whereas 92 and 88 patients, respectively, did not have high expression. Proportions of patients with overall responses and 12-week disease control were significantly greater in the high-expression subgroups than in PD-L1-negative patients (appendix p 6). Overall responses were achieved by five (71%) PD-L1-positive patients versus 18 (20%; p=0·007) PD-L1-negative patients with the 28-8 assay and by ten (63%) versus 13 (15%; p<0·001) with the SP-263 assay; disease control was achieved by six (86%) versus 40 (44%; p=0·047) patients with the 28-8 assay and by 12 (75%)

versus 34 (39%; p=0·003) patients with the SP-263 assay. Thus, although the concordance κ index was low (κ=0·56), reflecting differences in sensitivity of the two assays, analyses of responses or disease control were similar whether using the 28-8 or SP-263 assay. This observation further supports how consistently valuable PD-L1 expression is in predicting responses to ICIs and survival.

We did an exploratory post-hoc subgroup analysis of overall survival for known prognostic factors in malignant pleural mesothelioma using an adjusted Cox model for the stratification variables, represented as a forest plot, in both groups, separately (appendix p 8). Patients in the nivolumab group with progression 3 months or later after pemetrexed had a slight overall survival benefit versus those with more aggressive cancers that progressed before 3 months (adjusted HR 0·35 [95% CI 0·19–0·67]).

	Nivolumab group (n=63)			Nivolumab plus ipilimumab group (n=61)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Asthenia or fatigue	25 (40%)	1 (2%)	0	31 (51%)	3 (5%)	0
Diarrhoea	9 (14%)	0	0	16 (26%)	1 (2%)	1 (2%)
Decreased appetite	14 (22%)	0	0	11 (18%)	0	0
Nausea or vomiting	11 (17%)	1 (2%)	0	12 (20%)	0	0
Pruritus	6 (10%)	0	0	15 (25%)	0	0
Constipation	7 (11%)	0	0	9 (15%)	0	0
Weight loss	6 (10%)	0	0	7 (11%)	1 (2%)	0
Dry skin	3 (5%)	0	0	9 (15%)	0	0

Grade 1 or 2 events occurring in at least 10% of patients and all grade 3 and 4 events are reported. No grade 5 drug-related non-haematological events occurred.

Table 3: **Drug-related non-haematological adverse events**

Discussion

Our findings show that nivolumab monotherapy and nivolumab plus ipilimumab combination therapy provide clinically meaningful response and survival benefits for patients with pretreated malignant pleural mesothelioma who progressed after one or two lines of treatment, including pemetrexed–platinum doublet chemotherapy. The combination group had a slightly greater proportion of all-grade drug-related adverse events (93% with combination *vs* 89% with monotherapy) and three toxicity-related deaths (*vs* none in the monotherapy group). After the publication of a few small trials suggesting that anti-PD-1 and anti-PD-L1 antibodies are efficacious in relapsed or refractory malignant pleural mesothelioma,[16,24,25] our trial of 125 patients reached its disease control primary endpoint in both groups, with promising median overall survival in both groups (11·9 months in the nivolumab group and 15·9 months in the combination group).

The nivolumab plus ipilimumab combination has similarly been assessed at several different doses and schedules as first-line therapy in patients with advanced NSCLC, such as in the CheckMate 012 phase 1 study.[23] Early cohorts assessed two different dosing schedules, of which nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks resulted in notable toxicity, with 37% of patients discontinuing treatment because of treatment-related adverse events. Therefore, four other combination cohorts were studied, including nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks, which was selected for the first-line NSCLC phase 3 trial, CheckMate 227,[26] and then for our trial in patients with malignant pleural mesothelioma.

The stratified, randomised nature of our trial ensured that both groups were well balanced. Another strength of this study was its very fast accrual for such a disease that, given its rare incidence, could have been limited to an overly restrictive selection of patients. However, we acknowledge that our patient population could still be a group of patients with good prognosis, taking into account the favourable performance status selection (performance status 0–1), which is usual for a clinical trial but not necessarily representative of a wider population of patients with second-line or third-line malignant pleural mesothelioma.

We made a pragmatic choice to select 12-week disease control as the primary endpoint rather than overall response because patients with long-term control without any formal objective response criteria could also drive an essential part of the survival effect. This method choice should be considered in the time context in which the trial was designed—namely, in mid-2015. At that time, only scarce data were available on the efficacy of immunotherapy in or the ICI tolerance of patients with malignant pleural mesothelioma, who are slightly older than patients with NSCLC or melanoma—the typical cancer types analysed in most trials assessing ICIs. We also did not know the best regimen to choose, either single anti-PD-1 monoclonal antibody or dual immunotherapy combination, and thus were undecided about the optimal statistical comparative hypothesis to propose with survival (progression-free survival or overall survival) as primary endpoint, supposing a preconceived idea about the best ICI regimen. Such considerations led us to choose a classic non-comparative design for a randomised phase 2 trial, not powered for face-to-face comparisons, but instead allowing the study of two ICI regimens simultaneously. The phase 2 nature of this trial was a conservative choice aimed solely to detect early efficacy (and tolerance) signals of two different immunotherapy regimens at the same time, with no preconceptions, and to select at least one of these regimens for a future comparative phase 3 trial.

An impressive response was achieved with both drug regimens, considering they were given as second-line or third-line treatments. Additionally, overall responses as assessed by central review were clinically meaningful and median overall survival was also noteworthy compared with previously reported results with standard chemotherapies or investigational targeted therapies. Thus, the MAPS2 study was able by its randomised design

to ascertain that both regimens were effective with distinct safety profiles, providing clear data for selecting adequate experimental groups in future prospective comparative trials of these regimens. The MAPS2 results already support a decision by a National Comprehensive Cancer Network (NCCN) panel to recommend nivolumab or nivolumab plus ipilimumab as options for second-line or third-line therapy in patients with malignant pleural mesothelioma.[7] Notably, a small non-randomised trial by Disselhorst and colleagues[24] was presented at the 2018 International Mesothelioma Interest Group meeting, similarly assessing the usefulness of nivolumab (240 mg every 2 weeks) plus ipilimumab (1 mg/kg every 6 weeks) as second-line or third-line treatment in 34 patients with either malignant pleural mesothelioma (85% of patients) or peritoneal mesothelioma. The tolerance and efficacy results of their study were similar to those of our trial. However, these exciting data now require confirmation in a comparative randomised phase 3 trial that could establish whether or not the nivolumab plus ipilimumab combination is superior to nivolumab alone or another single chemotherapy drug, such as vinorelbine or gemcitabine, which are commonly used as second-line or third-line therapy in patients with malignant pleural mesothelioma, despite the absence of any data from prospective randomised trials. Larger randomised trials are also needed to assess the reproducibility of the survival results and their external validity—ie, whether the MAPS2 patients are wholly representative of patients with standard pretreated malignant pleural mesothelioma. This information would also be valuable in that it would exclude the possibility that our patients who exhibited good general status after one or two treatment lines might have had more indolent tumour biology than most patients with malignant pleural mesothelioma.

Some large randomised phase 3 trials are already ongoing in patients with mesothelioma, testing ICIs alone or in combination with chemotherapy or targeted therapies, as first-line or second-line or third-line treatment.[9] Taking into account the increased toxicity in the combination group, with 22% of withdrawals due to toxicity and three toxicity-related deaths, we recognise that this regimen could be debatable in such second-line and third-line settings, despite the appealing 15·9-month median overall survival. Only a phase 3 trial would be able to provide definitive conclusions on that issue. One large ongoing randomised phase 3 trial (CheckMate 743; NCT02899299; n=600) is assessing the benefit of nivolumab plus ipilimumab versus standard first-line chemotherapy in patients with malignant pleural mesothelioma, with progression-free survival and overall survival as co-primary endpoints. Another ongoing phase 3 trial (Canadian Cancer Trials Group; NCT02784171) is analysing pembrolizumab plus cisplatin and pemetrexed versus cisplatin and pemetrexed as second-line or third-line therapy in patients with malignant pleural mesothelioma. Two single-arm phase 2 trials are assessing durvalumab plus cisplatin and pemetrexed in the USA (NCT02899195; n=55) and Australia (DREAM trial;[27] n=54). The response results for the first 31 patients of this last trial were presented at the 2018 American Society of Clinical Oncology meeting, reporting an excellent dose intensity of both chemotherapy (95%) and durvalumab (94%), a median progression-free survival of 7·3 months (95% CI 5·8–11·0), a 65% 6-month progression-free survival and a remarkable 84% disease control.[27]

Although patients with malignant pleural mesothelioma have low tumour mutational burden,[8] which is a potential predictive biomarker for the effectiveness of ICIs in other tumour types, the pathogenesis of malignant pleural mesothelioma seems to be mostly driven by inflammation. Accordingly, the MAPS2 results suggest that nivolumab or nivolumab plus ipilimumab efficacy might be strongest in patients with PD-L1-positive malignant pleural mesothelioma, and particularly in patients with high PD-L1 expression (≥25% positive tumour cells). In our trial, 71% of patients with high PD-L1 expression had an overall response with the 28-8 assay and 63% did with the SP-263 assay, suggesting that the 28-8 assay is less sensitive than the SP-263 assay. However, the post-hoc data-driven choice of a 25% cutoff point is a weakness. Consistent with previously reported data,[14,28] only a small proportion of tumours in our patients had very high PD-L1 expression (ie, on more than 50% of positive tumour cells), compared with patients with NSCLC.[13,14,29] Another weakness of our trial is that the biomarker analysis was only possible in roughly 80% of patients because the other patients did not have enough tumour tissue remaining for analysis. The 25% cutoff point was therefore a pragmatic choice taken from among all the different thresholds used in the literature to ensure a sufficient patient number in each subset to allow for statistical comparison. Similarly, because the non-comparative nature of our trial did not enable analysis of PD-L1 prognostic value between the groups, we simply observed that the two groups of patients were well balanced in terms of high PD-L1 expression.

In an Australian cohort, 50% of patients with PD-L1 expression in at least 50% of cells had an overall response versus 22% in patients with PD-L1 expression less than 5%,[25] with a similar trend observed in a US cohort.[29] A subgroup of patients with mesothelioma thus seemingly benefit from ICIs, as already described in patients with melanoma or NSCLC. Nevertheless, it is still unclear how to accurately select the patients best suited for such immunotherapy.[29] The complex interplay of tumour-infiltrating lymphocytes and immune checkpoints probably affects response to ICIs in malignant pleural mesothelioma. More in-depth studies of immunohistochemistry markers and tumour infiltration by immune cells in our MAPS2 patients are thus ongoing. Therefore, it is of paramount importance that patient clinical characteristics (histological subtype, previous chemosensitivity, and performance status) and biomarkers (tumour PD-L1 immunohistochemistry status, CD8 or

myelomonocytic infiltration extent, tumour mutational burden, genomic signatures,[8] expression of multiple checkpoint inhibitors, and specific mutations[30–35]) be prospectively investigated in all future immunotherapy trials for patients with malignant pleural mesothelioma.[22]

We reported quite high proportions of patients with drug-related adverse events (almost 90% in both groups) and more grade 3 adverse events in the combination group than the nivolumab group. However, it should be noted that all the three treatment-related deaths (all in the combination group) occurred in the first 4 months of the trial, with no other toxic deaths subsequently occurring over 20 months. This observation might suggest that our investigators had to work through a learning curve of identifying immune-related adverse events and optimising treatment for these patients, as well as simultaneously optimising care for the patients with NSCLC who they started to treat routinely with anti-PD-1 at that time. It should also be noted that the safety profiles of nivolumab alone or combined with ipilimumab compared favourably with what has already been posited in the literature for platinum-based chemotherapy, and that the adverse events observed in our trial were similar in type to those reported for immunotherapy drugs used in other settings and in numerous previous trials.

This adverse event incidence could raise questions about the dosing schedule in the combination group. We chose what was considered to be the most tolerable of six schemes previously tested in the Checkmate 012 phase 1 trial,[23] and this scheme was subsequently selected for the NSCLC phase 3 Checkmate 227 trial[26] and the ongoing first-line phase 3 Checkmate 743 trial in patients with malignant pleural mesothelioma (NCT02899299). Furthermore, most adverse events were classed as grade 1–2, including a substantial number that were purely biological or asymptomatic, rapidly resolving either spontaneously or once treatment was interrupted. Moreover, our preliminary quality-of-life analysis did not detect any obvious consequences on patient-reported outcome items at week 12. Considering potential immunotherapy-induced harm, it was crucial to report some quality-of-life data early (ie, at 12 weeks of treatment)in our study, even if these data were underpowered and incomplete (appendix p 2). We are aware that the scientific considerations about estimating a minimally clinically important difference are challenging and that our choice of a ten-point change in the scores as a cutoff point has not been prospectively validated for patients with malignant pleural meso thelioma. To resolve this issue, additional studies of health-related quality of life data from the MAPS2 trial are underway, which are modelling longitudinal quality of life on the basis of the time until definitive deterioration, the results of which will be reported in a separate paper dedicated to this outcome. Additionally, the study's open-label design could have influenced the quality of life analysis.

We provide an exploratory subgroup analysis of overall survival, although carefully avoiding direct comparison of the two groups of patients because the trial was not powered for such comparisons. Our results for the nivolumab group show that PD-1 inhibition in more indolent tumours (ie, patients relapsing at least 3 months after pemetrexed-based chemotherapy was stopped) provided a minor survival benefit versus those with more aggressive cancers that progressed before 3 months. However, such exploratory analyses should be considered as purely hypothesis-generating and must thus not be overinterpreted, taking into account the wide-ranging 95% CIs observed, reflecting the low patient numbers in each subset, and considering, although these analyses were adjusted for stratification factors, that some biases could have been introduced by the prognosis influence of other variables. Hence, the optimal strategy in view of a better efficacy to safety (and cost) ratio remains to be defined for all patients. Of note, we suspected in our trial that a few patients would exhibit hyperprogression under ICIs, as previously described in some patients with NSCLC.[36] Hyperprogression has been defined as tumour growth rate greater than 50%, and additional studies for patients with hyperprogression are aiming to establish the still-debated criteria for hyperprogressive disease,[37] which requires analysis of two CT scans before ICI treatment is initiated.

In conclusion, as previously observed in patients with melanoma and NSCLC, immunotherapy appears to offer hope for patients with malignant pleural mesothelioma, a cancer which, until now, has had very few therapeutic options. Thus, ICIs are likely to change our standard of care in malignant pleural mesothelioma, as already emphasised for nivolumab alone or combined with ipilimumab in the NCCN guidelines.[7] Yet many questions remain unanswered, and more data are required from randomised phase 2 or 3 trials to select the best-suited patients for ICIs (pretreated *vs* frontline patients, biomarkers, and tolerance) and to define the long-term survival benefit, as well as the optimal treatment regimen (anti-PD-1 monotherapy *vs* combination with ICIs, chemotherapy or targeted therapy, or even surgery or radiotherapy). Malignant pleural mesothelioma experts from all over the world must collaborate to speed up the recruitment of patients with this rare type of cancer into large randomised trials and translational studies, to bring new hope and progress to the future of mesothelioma patient care.

Contributors

AS and GZ were the principal investigators of the trial and were involved in conception and design of the study. All investigators were involved in data collection. SL contributed to pathological review, diagnostic certification, and immunohistochemistry analysis. All authors contributed to data analysis, data interpretation, and the writing of and approval of the final manuscript.

Declaration of interests

AS reports personal fees and non-financial support from Bristol-Myers Squibb (BMS), Roche, and Merck Sharp & Dohme (MSD) and personal

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Data sharing

The data sharing statement is in the appendix (p 9).

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References

1 Robinson BW, Musk AW, Lake RA. Malignant mesothelioma. *Lancet* 2005; **366**: 397–408.

2 Scherpereel A, Astoul P, Baas P, et al. Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma. *Eur Respir J* 2010; **35:** 479–95.

3 Zalcman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. *Lancet* 2016; **387:** 1405–14.

4 Baas P, Fennell D, Kerr KM, Van Schil PE, Haas RL, Peters S. Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015; **26:** v31–39.

5 Woolhouse I, Bishop L, Darlison L, et al. British Thoracic Society Guideline for the investigation and management of malignant pleural mesothelioma. *Thorax* 2018; **73:** i1–30.

6 Kindler HL, Ismaila N, Armato SG 3rd, et al. Treatment of malignant pleural mesothelioma: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2018; **36:** 1343–73.

7 National Comprehensive Cancer Network. NCCN malignant pleural mesothelioma guidelines, version 2.2018. Feb 26, 2018. https://www.nccn.org/professionals/physician_gls/pdf/mpm_blocks.pdf (accessed Sept 9, 2018).

8 Bueno R, Stawiski EW, Goldstein LD, et al. Comprehensive genomic analysis of malignant pleural mesothelioma identifies recurrent mutations, gene fusions and splicing alterations. *Nat Genet* 2016; **48:** 407–16.

9 Scherpereel A, Wallyn F, Albelda SM, Munck C. Novel therapies for malignant pleural mesothelioma. *Lancet Oncol* 2018; **19:** e161–72.

10 Yap TA, Aerts JG, Popat S, Fennell DA. Novel insights into mesothelioma biology and implications for therapy. *Nat Rev Cancer* 2017; **17:** 475–88.

11 Grosso F, Steele N, Novello S, et al. Nintedanib plus pemetrexed/cisplatin in patients with malignant pleural mesothelioma: phase II results from the randomised, placebo-controlled LUME-Meso trial. *J Clin Oncol* 2017; **35:** 3591–600.

12 Yamada N, Oizumi S, Kikuchi E, et al. CD8+ tumor-infiltrating lymphocytes predict favorable prognosis in malignant pleural mesothelioma after resection. *Cancer Immunol Immunother* 2010; **59:** 1543–49.

13 Mansfield AS, Roden AC, Peikert T, et al. B7-H1 expression in malignant pleural mesothelioma is associated with sarcomatoid histology and poor prognosis. *J Thorac Oncol* 2014; **9:** 1036–40.

14 Cedrés S, Ponce-Aix S, Zugazagoitia J, et al. Analysis of expression of programmed cell death 1 ligand 1 (PD-L1) in malignant pleural mesothelioma (MPM). *PLoS One* 2015; **10:** e0121071.

15 Maio M, Scherpereel A, Calabrò L, et al. Tremelimumab as second-line or third-line treatment in relapsed malignant mesothelioma (DETERMINE): a multicentre, international, randomised, double-blind, placebo-controlled phase 2b trial. *Lancet Oncol* 2017; **18**: 1261–73.

16 Alley EW, Lopez J, Santoro A, et al. Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): preliminary results from a non-randomised, open-label, phase 1b trial. *Lancet Oncol* 2017; **18**: 623–30.

17 Calabrò L, Morra A, Giannarelli D, et al. Tremelimumab combined with durvalumab in patients with mesothelioma (NIBIT-MESO-1): an open-label, non-randomised, phase 2 study. *Lancet Respir Med* 2018; **6:** 451–60.

18 Byrne MJ, Nowak AK. Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. *Ann Oncol* 2004; **15:** 257–60.

19 Rusch VW, Chansky K, Kindler HL, et al. The IASLC mesothelioma staging project: proposals for the M descriptors and for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for mesothelioma. *J Thorac Oncol* 2016; **11:** 2112–19.

20 Hollen PJ, Gralla RJ, Kris MG, Potanovich LM. Quality of life assessment in individuals with lung cancer: testing the Lung Cancer Symptom Scale (LCSS). *Eur J Cancer* 1993; **29A** (suppl 1)**:** S51–58.

21 Adam J, Le Stang N, Rouquette I, et al. Multicenter harmonization study for PD-L1 IHC testing in non-small-cell lung cancer. *Ann Oncol* 2018; **29:** 953–58.

22 Lantuejoul S, Le Stang N, Damiola F, Scherpereel A, Galateau-Sallé F. PD-L1 testing for immune checkpoint inhibitors in mesothelioma: for want of anything better? *J Thorac Oncol* 2017; **12:** 778–81.

23 Hellmann MD, Rizvi NA, Goldman JW, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. *Lancet Oncol* 2017; **18:** 31–41.

24 Disselhorst M, Quispel-Janssen J, Harms E, et al. Ipilimumab and nivolumab in the treatment of recurrent malignant pleural mesothelioma (INITIATE): results of a prospective, single-arm, phase 2 trial. *Lancet Respir Med* 2019; published online Jan 16. http://dx.doi.org/10.1016/S2213-2600(18)30420-X.

25 Rivalland G, Chuan-Hao Kao S, Pavlakis N, et al. Outcomes of anti-PD-1 therapy in mesothelioma and correlation with PD-L1 expression. *Proc Am Soc Clin Oncol* 2017; **35:** 8514 (abstr).

26 Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N Engl J Med* 2018; **378:** 2093–104.

27 Nowak AK, Lesterhuis WJ, Maxwell Hughes BG, et al. DREAM: a phase II trial of durvalumab with first line chemotherapy in mesothelioma—final result. *J Thorac Oncol* 2018; **13** (suppl)**:** S338–39.

28 Antonia SJ, Villegas A, Daniell D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med* 2017; **377:** 1919–29.

29 Kindler HL, Karrison TG, Rose B, et al. Biomarkers of pembrolizumab (P) activity in mesothelioma (MM): results from a phase II trial. *Proc Am Soc Clin Oncol* 2017; **35:** 8557 (abstr).

30 Reck M, Rodríguez-Abreu D, Robinson AG et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med* 2016; **375:** 1823–33.

31 Thapa B, Salcedo A, Lin X, et al. The immune microenvironment, genome-wide copy number aberrations, and survival in mesothelioma. *J Thorac Oncol* 2017; **12:** 850–59.

32 Suzuki K, Kadota K, Sima CS, et al. Chronic inflammation in tumor stroma is an independent predictor of prolonged survival in epithelioid malignant pleural mesothelioma patients. *Cancer Immunol Immunother* 2011; **60:** 1721–28.

33 Ujiie H, Kadota K, Nitadori JI, et al. The tumoral and stromal immune microenvironment in malignant pleural mesothelioma: a comprehensive analysis reveals prognostic immune markers. *Oncoimmunol* 2015; **4**: e1009285.

34 Awad MM, Jones RE, Liu H, et al. Cytotoxic T cells in PD-L1-positive malignant pleural mesotheliomas are counterbalanced by distinct immunosuppressive factors. *Cancer Immunol Res* 2016; **4:** 1038–48.

35 Ayers M, Lunceford J, Nebozhyn M, et al. IFN-γ-related mRNA profile predicts clinical response to PD-1 blockade. *J Clin Invest* 2017; **127:** 2930–40.

36 Champiat S, Dercle L, Ammari S, et al. Hyperprogressive disease is a new pattern of progression in cancer patients treated by anti-PD-1/PD-L1. *Clin Cancer Res* 2017; **23:** 1920–28.

37 Ferrara R, Mezquita L, Texier M, et al. Hyperprogressive disease in patients with advanced non-small cell lung cancer treated with PD-1/PD-L1 inhibitors or with single-agent chemotherapy. *JAMA Oncol* 2018; **4:** 1543–52.