First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743) a multicentre, randomised, open-label, phase 3 trial

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First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma: results from the global, randomised, open-label phase 3 CheckMate 743 trial

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ABSTRACT

BACKGROUND: Approved systemic treatments for malignant pleural mesothelioma (MPM) were limited to chemotherapy regimens that have moderate survival benefit with poor outcomes. Nivolumab plus ipilimumab showed clinical benefit in other tumour types, including first-line non-small cell lung cancer. We hypothesised that this regimen would improve overall survival in MPM.

METHODS: This open-label phase 3 study was conducted at 103 hospitals across 21 countries. Adults with previously untreated, histologically confirmed unresectable MPM were randomised (1:1) to nivolumab (3 mg/kg intravenously Q2W) plus ipilimumab (1 mg/kg intravenously Q6W) for ≤2 years, or platinum plus pemetrexed chemotherapy (pemetrexed [500 mg/m^2 intravenously] plus cisplatin [75 mg/m^2 intravenously] or carboplatin [AUC 5 mg/mL/min intravenously]) Q3W for up to 6 cycles. The primary endpoint was overall survival (all randomised patients); safety was assessed in all treated patients. This study is registered with ClinicalTrials.gov, NCT02899299.

FINDINGS: Between November 29, 2016 and April 18, 2018, 713 patients were enrolled; 303 were randomised to nivolumab plus ipilimumab and 302 to chemotherapy. At the prespecified interim analysis (median follow-up 29·7 months [IQR, 26·7–32·9]), nivolumab plus ipilimumab significantly prolonged overall survival versus chemotherapy. Median overall survival was 18·1 months (95% CI 16·8–21·4) versus 14·1 months (95% CI 12·4–16·2), with a hazard ratio of 0·74 (96·6% CI 0·60–0·91; p=0·0020); 2-year overall survival rates were 41% (95% CI 35·1–46·5) and 27% (95% CI 21·9–32·4), respectively. Grade 3–4 treatment-related adverse events were reported in 91 (30%) of 300 patients treated with nivolumab plus ipilimumab and 91 (32%) of 284 treated with chemotherapy. There were three (1%) and one (<1%) treatment-related deaths, respectively.

INTERPRETATION: Nivolumab plus ipilimumab provided statistically significant and clinically meaningful improvements in overall survival versus standard-of-care chemotherapy, supporting the use of this first-in-class approved (United States) regimen for previously untreated unresectable MPM.

Funding: Bristol Myers Squibb.

Research in context

A literature search was conducted for studies relevant to unresectable malignant pleural mesothelioma (MPM) and cancer immunotherapy regimens with a focus primarily on first-line phase 3 trials. Articles were obtained using PubMed and abstracts obtained from major oncology congresses; search terms included, but were not limited to, “mesothelioma” and “nivolumab” OR “chemotherapy” OR “pembrolizumab” OR “atezolizumab” OR “avelumab” OR “durvalumab” OR “ipilimumab” OR “tremelimumab” OR “PD-1” OR “PD-L1” OR “CTLA-4” (full names and abbreviations), and relevant articles published from database inception to October 2, 2020 were identified. Although there were several studies evaluating immunotherapy in MPM, we found no published randomised phase 3 studies investigating the efficacy or safety of immunotherapy regimens in the first-line setting. Various phase 1 and 2 studies in previously treated MPM have suggested that immunotherapy regimens may provide clinical benefit. Of note, the multicentre, open-label, single-arm, phase 2 MERIT study led to the approval of nivolumab monotherapy for unresectable recurrent MPM in Japan. However, with recommended first-line systemic treatments limited to chemotherapy since 2004, with or without bevacizumab, there remains a need for new and effective therapeutic options. In the phase 2 single-arm DREAM study (ACTRN12616001170415) first-line durvalumab plus chemotherapy exhibited promising activity in 54 patients with MPM; the objective response rate was 48% and the progression-free survival rate at 6 months was 57% but the combination requires evaluation in a larger, randomised phase 3 study. CheckMate 743 was designed to investigate the efficacy and safety of nivolumab plus ipilimumab versus chemotherapy. A previous non-comparative phase 2 trial (MAPS2; NCT02716272) and single-arm phase 2 study (INITIATE; NCT03048474) evaluating nivolumab plus ipilimumab in MPM showed that this regimen was tolerable and exhibited encouraging clinical activity.

Added value of this study

In this paper we provide results from the randomised CheckMate 743 study, which is the first phase 3 study to demonstrate statistically significant and clinically meaningful improvements in overall survival

with immunotherapy versus standard-of-care platinum plus pemetrexed chemotherapy for first-line treatment of unresectable MPM. Data presented here demonstrate the clinical benefit and tolerability of this regimen thus providing patients with a new first-line chemotherapy-free treatment option. Notably, survival with nivolumab plus ipilimumab was similar in patients with both non-epithelioid and epithelioid histologies suggesting that the regimen could be considered for all patients with unresectable MPM; responses were durable, with 32% of immunotherapy-treated patients still in response at 2 years. The safety profile of nivolumab plus ipilimumab was consistent with that observed in first-line non-small-cell lung cancer at this dosage and schedule and no new safety signals were reported.

Implications of all the available evidence

Overall, our results demonstrate that nivolumab plus ipilimumab can provide notable and clinically meaningful improvements in overall survival versus the current standard of care. Data from CheckMate 743 support a favourable clinical benefit–risk profile for nivolumab plus ipilimumab. Nivolumab plus ipilimumab is now indicated in the United States as a first-line treatment for unresectable malignant pleural mesothelioma.

INTRODUCTION

Malignant pleural mesothelioma (MPM) is a highly aggressive cancer and typically unresectable at diagnosis, with less than 10% of patients surviving 5 years or beyond.[1-3] Historically, age, gender, tumour grade and stage, and histology have been shown to be independent prognostic factors. Notably, worse prognosis has been reported for non-epithelioid histology versus the epithelioid subtype.[2-4] Until recently, platinum agents plus folate antimetabolites, such as pemetrexed, had been the only approved first-line treatment regimens for MPM since 2004.[1,5,6] However, long-term survival outcomes remain poor with chemotherapy[7-10]; bevacizumab has been added to these regimens[1,11] but its use varies across regions. As such, there is an urgent need for new and effective therapeutic options.

Nivolumab, a fully human anti-programmed cell death protein 1 (PD-1) antibody, and ipilimumab, a fully human anti-cytotoxic T-lymphocyte protein 4 (CTLA-4) antibody are immune checkpoint inhibitors with distinct but complementary mechanisms of action. Ipilimumab induces T-cell proliferation and de novo anti-tumour T-cell responses, including in memory T cells, while nivolumab restores the function of existing anti-tumour T cells.[12] Nivolumab plus ipilimumab is approved in various tumours[13] and has demonstrated durable overall survival benefit in melanoma,[14] renal cell carcinoma,[15] and in non-small-cell lung cancer (NSCLC).[16] Furthermore, current National Comprehensive Cancer Network (NCCN) guidelines include nivolumab with or without ipilimumab in second-line or later MPM settings[1] based on results from three phase 2 trials,[17-19] including the multicentre, open-label, randomised, non-comparative, IFCT-1501 MAPS2 trial that showed encouraging clinical activity of the combination therapy.[17]

CheckMate 743 is a randomised, global, open-label, phase 3 study designed to assess efficacy and safety of first-line nivolumab plus ipilimumab versus platinum plus pemetrexed chemotherapy in unresectable MPM. We present results from the prespecified interim analysis, which recently led to nivolumab plus ipilimumab gaining approval in the United States, as well as being recommended in the NCCN guidelines, for the first-line treatment of unresectable MPM.[1,13]

METHODS

Study design and patients

CheckMate 743 is a global, open-label, phase 3 study conducted at 103 hospitals across 21 countries (appendix p 18). Eligible patients were aged ≥18 years with histologically confirmed unresectable MPM that was not amenable to curative therapy (surgery with or without chemotherapy), and an Eastern Cooperative Oncology Group performance status of 0 or 1.[20] Irresectability of the disease was determined by the investigator at individual sites using local standards. Patients must have completed any prior palliative radiotherapy ≥2 weeks before initiating treatment, with no residual signs of toxicity, and have measurable disease according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST)[21] for pleural mesothelioma; patients without measurable pleural lesions but with metastatic non-pleural lesions measurable per RECIST 1.1 could be considered for inclusion after consultation with the medical monitor. Patients were required to have tumour samples available for programmed cell death 1 ligand 1 (PD-L1) testing. Baseline laboratory tests required to assess eligibility included white blood cell counts, neutrophils, platelets, haemoglobin, serum creatinine, alanine aminotransferase, aspartate aminotransferase, and total bilirubin (appendix p 6).

Exclusion criteria included brain metastases (unless resected or treated with stereotactic radiotherapy and asymptomatic with no evolution within 3 months before study inclusion), autoimmune disease, and previous treatment with drugs targeting T-cell co-stimulation or checkpoint pathways. Patients were excluded if they presented with primitive peritoneal, pericardial, tunica vaginalis, or testis mesotheliomas. Other exclusion criteria included inadequate haematologic, renal, or hepatic function, known HIV infection, or interstitial lung disease that was either symptomatic or might influence the detection or management of suspected drug-related pulmonary toxicity. Patients with current or prior malignancy with <3 years of complete remission (except for non-melanoma skin cancers and in situ cancers) requiring or likely to require concurrent intervention during the study period were ineligible, as were patients requiring systemic corticosteroids (>10 mg daily prednisone or equivalent) or immunosuppressive

medication within 14 days of the first dose of study drug. Additional detail on eligibility criteria are provided in the appendix p 5, and study protocol (appendix p 23).

An institutional review board or independent ethics committee at each centre approved all versions of the protocol. An independent Data Monitoring Committee (IDMC) provided general oversight of efficacy and safety for the trial. The trial was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent.

Randomisation and masking

Patients were enrolled and randomised using an Interactive Web Response System. Eligible patients were randomly assigned (1:1) to nivolumab plus ipilimumab or platinum plus pemetrexed chemotherapy (appendix p 18), and stratified by gender and histology (epithelioid vs non-epithelioid [including sarcomatoid and mixed subtypes]). The trial was open label; patients and investigators were not masked to treatment assignment.

Procedures

Patients received nivolumab (3 mg/kg intravenous infusion once every 2 weeks) plus ipilimumab (1 mg/kg intravenous infusion once every 6 weeks); nivolumab was administered first, followed by ipilimumab. The chemotherapy regimens consisted of an intravenous infusion of cisplatin (75 mg/m^2) or carboplatin (AUC 5 mg/mL/min) plus pemetrexed (500 mg/m^2) every 3 weeks for a maximum of 6 cycles (appendix p 18). Pretreatment with folic acid (350–1000 µg orally daily) and vitamin B12 (1000 µg intramuscularly) was given to patients in both treatment groups 1 week prior to the administration of the first dose of study drug (see appendix p 5 for further details). Treatment was continued until disease progression, unacceptable toxicity, or for two years for immunotherapy; treatment with nivolumab plus

ipilimumab was permitted beyond disease progression if prespecified requirements were met (see appendix p 7).

Tumour assessments were performed 6 weeks after the first dose date and then every 6 weeks for the first 12 months; after 12 months tumours were assessed every 12 weeks until blinded independent central review (BICR)-confirmed disease progression per mRECIST and/or RECIST 1.1 criteria. At the time of investigator-assessed initial radiographic progression, the site had to request the blinded independent central review of progression from the third-party radiology vendor; if progression was not confirmed, treatment could continue.

Adverse event assessments were performed at baseline and continuously throughout the study and during follow-up; adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Histology was determined by individual sites using local protocols. Archival or fresh formalin-fixed paraffin-embedded tumour samples were collected prior to randomisation; optional on-treatment fresh tumour samples were collected at week 7 (±7 days) and at disease progression, at the discretion of the investigator. Samples were sent to a central laboratory to determine the percentage of tumour cells demonstrating plasma membrane PD-L1 staining of any intensity using the validated immunohistochemical 28-8 pharmDx assay (Dako).[22]

Outcomes

The primary endpoint was overall survival in all randomised patients. Overall survival was defined as the time from randomisation to the date of death due to any cause. Secondary endpoints were progression-free survival, objective response rate, and disease control rate (radiographic tumour assessments per adapted mRECIST for pleural mesothelioma and/or RECIST v1.1 conducted by BICR) in all randomised patients, as well as overall survival, progression-free survival, and objective response rate by PD-L1 expression. Progression-free survival was defined as the time from randomisation to the date of the first documented tumour progression or death due to any cause; patients who died or received subsequent

therapy without prior reported progression were considered to have progressed on the date of death or were censored at date of the last evaluable tumour assessment prior to or on initiation of subsequent therapy, respectively. Objective response rate was defined as the proportion of patients with a best overall response of partial response or complete response and disease control rate was defined as the proportion of patients with a best overall response of complete response, partial response, or stable disease. Exploratory endpoints included safety and tolerability in all treated patients. Analysis of other exploratory endpoints that are ongoing but not reported here include pharmacokinetics, biomarkers, and patient-reported outcomes.

Statistical Analysis

For the primary endpoint of overall survival, a sample of approximately 600 randomised patients with 473 deaths would provide 90% power to detect a target hazard ratio (HR) of 0·72 with a two-sided type 1 error of 0·05, by means of a log-rank test. There was one prespecified interim analysis of overall survival for superiority at approximately 403 deaths (85% of total events). At the time of interim analysis, 419 patients had died (89% of total events); the boundary for declaring superiority for overall survival was a p-value of <0·0345, based on the Lan–DeMets alpha spending function with O'Brien–Fleming boundaries. None of the secondary endpoints were included in the testing procedure; as a result, no formal statistical testing or allocation of alpha values were performed for progression-free survival and objective response rate. Demographic and efficacy analyses included all randomised patients. Analyses for overall survival and progression-free survival were stratified by gender and histology. HRs and CIs were estimated with a stratified Cox proportional-hazards model with treatment group as a single covariate. The proportional-hazards assumption was checked only for the primary endpoint of overall survival by adding a time-dependent covariate, defined by treatment-by-time interaction, into the stratified Cox regression model of overall survival. Survival curves and rates were estimated using Kaplan–Meier methodology. Exact two-sided 95% CIs for objective response and disease control rates were calculated using the Clopper–Pearson method. Prespecified descriptive subgroup analyses were performed for

overall survival and were summarised using HRs (with 95% CIs) calculated using an unstratified Cox proportional-hazards model. Safety analyses included all patients who received ≥1 dose of study drug (see Supplementary Methods for additional details). Statistical analyses were carried out using Statistical Analysis System software (version 9.2). An independent data monitoring committee reviewed efficacy and safety data on a periodic basis and at the time of the pre-planned interim analysis. This trial is registered with ClinicalTrials.gov, number NCT02899299.

Role of the Funding Source

The study was designed by the sponsor (Bristol Myers Squibb) and study steering committee. The sponsor contributed to data collection with the investigators, and to data analysis and interpretation in collaboration with the authors. All the authors attest that the trial was conducted in accordance with the protocol (appendix p 23), vouch for the accuracy and completeness of the data and analyses, and approved the manuscript for submission. All authors had full access to the data reported from the study. The corresponding author had final responsibility for the decision to submit for publication. The manuscript was developed with medical writing support funded by the sponsor.

RESULTS

From November 29, 2016, through April 18, 2018, 713 patients were enrolled. Of these, 605 patients were randomised to nivolumab plus ipilimumab (n=303) or chemotherapy (n=302); 300 and 284, respectively, were treated (appendix p 18–19). The median follow-up for overall survival was 29·7 months (IQR, 26·7–32·9), with a minimum of 22·1 months. The minimum follow-up for progression-free survival was 19·8 months. Baseline characteristics were well-balanced between treatment groups (Table 1); overall, 456 (75%) of 605 patients had epithelioid tumour histology.

At the April 3, 2020, database lock, 5 (2%) of 300 patients in the nivolumab plus ipilimumab group remained on treatment and no patients remained on treatment in the chemotherapy group. The main

reasons for treatment discontinuation in the nivolumab plus ipilimumab group were disease progression (182 [61%] of 300 patients) and study drug toxicity (59 [20%] patients) (appendix p 19); 25 (8%) of 300 patients completed 2 years of immunotherapy. During the study, one patient in the nivolumab plus ipilimumab group discontinued study drug but received subsequent therapy from the investigator prior to BICR confirmation of disease progression. In the chemotherapy group, 176 (62%) of 284 patients completed the 6 cycles; 44 (16%) discontinued due to disease progression and 24 (8%) due to study drug toxicity. Median duration of treatment was 5·6 months (IQR, 2·0–11·4) in the nivolumab plus ipilimumab group and 3·5 months (IQR, 2·7–3·7) in the chemotherapy group (appendix p 9). The median number of nivolumab and ipilimumab doses received was 12·0 (IQR, 5·0–23·5) and 4·0 (IQR, 2·0–7·0), respectively. Following randomisation, 104 (34%) of 302 patients in the chemotherapy group received cisplatin and 180 (60%) received carboplatin; 29 (28%) of the 104 patients who received cisplatin switched to carboplatin after first dose. The median numbers of cisplatin, carboplatin, and pemetrexed doses received were 5·0 (IQR, 3·0–6·0), 6·0 (IQR, 4·0–6·0), and 6·0 (IQR, 4·0–6·0), respectively. Further information on treatment exposure is available in the appendix (pp 9–10).

Subsequent systemic therapy was received by 134 (44%) of 303 patients treated with nivolumab plus ipilimumab and 123 (41%) of 302 of patients treated with chemotherapy (appendix p 11); subsequent immunotherapy was received by 10 (3%) of 303 patients and 61 (20%) of 302 patients, and subsequent chemotherapy by 131 (43%) and 95 (32%) patients, respectively.

The study met its primary endpoint at the prespecified interim analysis according to the recommendation of the IDMC. Given that the study was able to reject the null hypothesis at the interim analysis, this analysis is considered final. Median overall survival was 18·1 months (95% CI 16·8–21·4) with nivolumab plus ipilimumab versus 14·1 months (95% CI 12·4–16·2) with chemotherapy, with a stratified HR of 0·74 (96·6% CI 0·60–0·91; p=0·0020) (Figure 1A). The p-value for the time-dependent covariate was 0·9646 (>0·1), indicating that there was no evidence of non-constant treatment effect over time. Overall survival rates at 1 year were 68% (95% CI 62·3–72·8) versus 58% (95% CI 51·7–63·2) and at 2

years were 41% (95% CI 35·1–46·5) versus 27% (95% CI 21·9–32·4), respectively. Overall survival favoured nivolumab plus ipilimumab across most subgroups, although survival in patients aged ≥75 years (n=157) was similar between treatments (Figure 1B). Notably, overall survival was improved with nivolumab plus ipilimumab versus chemotherapy regardless of histology (study stratification factor; Figure 1C and D); the magnitude of benefit was greater in patients with non-epithelioid histology (HR, 0·46 [95% CI 0·31–0·68]) than with the epithelioid subtype (HR, 0·86 [95% CI 0·69–1·08]). Median overall survival with nivolumab plus ipilimumab was similar between non-epithelioid and epithelioid subtypes (18·1 months [95% CI 12·2–22·8] and 18·7 months [95% CI 16·9–22·0], respectively), as were 2-year survival rates (38% [95% CI 27·0–49·5] and 42% [95% CI 35·0–48·1], respectively). In contrast, median overall survival with chemotherapy differed strikingly between non-epithelioid and epithelioid subtypes (8·8 months [95% CI 7·4–10·2] and 16·5 months [95% CI 14·9–20·5], respectively), as did 2-year survival rates (8% [95% CI 3·3–16·7] and 33% [95% CI 26·8–39·5], respectively). Overall survival benefit by tumour PD-L1 expression level for nivolumab plus ipilimumab versus chemotherapy was greater in patients with tumour PD-L1 ≥1% (HR, 0·69; 95% CI 0·55–0·87) compared with patients with tumour PD-L1 <1% (HR, 0·94; 95% CI 0·62–1·40). Nonetheless, median overall survival with nivolumab plus ipilimumab was similar in patients with tumour PD-L1 ≥1% (18·0 months [95% CI 16·8–21·5]) and tumour PD-L1 <1% (17·3 months [95% CI 10·1–24·3]); 2-year survival rates were 41% (95% CI 34·3–47·2) and 39% (95% CI 25·9–51·3), respectively. Conversely, median overall survival with chemotherapy differed between patients with PD-L1 ≥1% (13·3 months [95% CI 11·6–15·4]) and PD-L1 <1% (16·5 months [95% CI 13·4–20·5]); 2-year survival rates were 28% (95% CI 22·1–34·7) and 25% (95% CI 15·5–35·0), respectively (appendix pp 20–21).

Median progression-free survival was similar between treatment groups: 6·8 months (95% CI 5·6–7·4) with nivolumab plus ipilimumab and 7·2 months (95% CI 6·9–8·0) with chemotherapy (HR, 1·00; 95% CI 0·82–1·21). However, progression-free survival rates at 2 years were numerically greater with

nivolumab plus ipilimumab (16% [95% CI 11·7–21·5]) versus chemotherapy (7% [95% CI 4·0–11·7]), (Figure 2A).

An objective response was reported in 120 of 303 patients (40%; 95% CI 34·1–45·4) with nivolumab plus ipilimumab versus 129 of 302 patients (43%; 95% CI 37·1–48·5) with chemotherapy (Table 2); complete responses were only observed in the nivolumab plus ipilimumab group (5 [2%] of 303 patients). The disease control rate was 77% (95% CI 71·4–81·2) versus 85% (95% CI 80·6–88·9), respectively. Median duration of response in all confirmed responders was 11·0 months (95% CI 8·1–16·5) with nivolumab plus ipilimumab versus 6·7 months (95% CI 5·3–7·1) with chemotherapy (Figure 2B). At 2 years, there were ongoing responses in 32% (95% CI 23–41) of patients in the nivolumab plus ipilimumab group versus 8% (95% CI 3–15) in the chemotherapy group.

Safety is summarised in Table 3, and all reported grade 3 and 4 treatment-related adverse events are listed in the appendix (pp 13–15). Of the 300 patients treated with nivolumab plus ipilimumab, 28 patients (9%) discontinued ipilimumab early; of these, 18 (64%) of 300 discontinued ipilimumab due to adverse event and 10 (36%) of 300 discontinued for "other" reasons. In the chemotherapy group, dose reductions occurred in 89 (31%) of 284 patients who received pemetrexed, 18 (17%) of 104 patients who received cisplatin, and 85 (41%) of 209 patients who received carboplatin, whereas dose reductions were not permitted for the nivolumab plus ipilimumab group. Grade 3–4 treatment-related adverse events were reported in 91 (30%) of 300 patients treated with nivolumab plus ipilimumab and 91 (32%) of 284 patients with chemotherapy. Any-grade serious treatment-related adverse events were reported in 64 (21%) of 300 patients treated with nivolumab plus ipilimumab versus 22 (8%) of 284 patients treated with chemotherapy; grade 3–4 treatment-related serious events were reported in 46 (15%) of 300 patients versus 17 (6%) of 284 patients, respectively. Any-grade treatment-related adverse events that led to discontinuation (due to either component of the regimen) were reported in 69 (23%) of 300 patients treated with nivolumab plus ipilimumab and 45 (16%) of 284 patients treated with chemotherapy; 45 (15%) of 300 patients and 21 (7%) of 284 patients, respectively, had grade 3–4 (appendix p 16).

The most frequent any-grade treatment-related adverse events were diarrhoea (62 [21%] of 300 patients) in the nivolumab plus ipilimumab group and nausea (104 [37%] of 284 patients) in the chemotherapy group. The most frequently reported any-grade serious treatment-related adverse events were colitis (9 [3%] of 300 patients) in the nivolumab plus ipilimumab and anaemia (6 [2%] of 284 patients) in the chemotherapy group. Treatment exposure was 220·3 person-years with nivolumab plus ipilimumab, and 94·5 person-years with chemotherapy. The overall exposure-adjusted incidence rate of treatment-related adverse events per 100 patient-years was 502·1 with nivolumab plus ipilimumab versus 1355·3 with chemotherapy.

The most commonly reported any-grade treatment-related select adverse events (those with potential immunologic aetiology) with nivolumab plus ipilimumab were skin (108 [36%] of 300 patients) and gastrointestinal (66 [22%] of 300 patients) events. A summary of treatment-related select adverse events, time to onset and resolution of treatment-related select adverse events, the proportion of patients requiring immune-modulating concomitant medication (mostly corticosteroids), and the duration of use of immune-modulating concomitant medication are shown in appendix p 17. Overall, 198 (66%) of 300 patients in the nivolumab plus ipilimumab group died, the majority of deaths were due to disease progression (183 [61%] of 300 patients); a total of 212 (75%) of 284 patients in the chemotherapy arm died, also primarily due to disease progression (199 [70%] of 284 patients). There were 3 (1%) treatment-related deaths in the nivolumab plus ipilimumab group due to pneumonitis, encephalitis, and heart failure (in 1 patient each). There was 1 (<1%) treatment-related death in the chemotherapy group due to myelosuppression (Table 3).

DISCUSSION

CheckMate 743 is the first large, randomised, phase 3 study to demonstrate statistically significant and clinically meaningful improvement in overall survival with immunotherapy versus standard-of-care platinum plus pemetrexed chemotherapy for first-line treatment of unresectable MPM. Based on these

results, the United States Food and Drug Administration recently approved nivolumab plus ipilimumab for this patient population.[13] With a median follow-up of 29·7 months, nivolumab plus ipilimumab provided durable survival benefit versus chemotherapy, with a 50% improvement in the 2-year overall survival rate. Furthermore, estimated rates of patients still in response at 2 years increased from 8% (chemotherapy) to 32% (nivolumab plus ipilimumab); overall more than one-third of responders had a durable response with nivolumab plus ipilimumab. The safety profile of nivolumab plus ipilimumab in this study was consistent with that seen previously in NSCLC at this dosage and schedule[16] and no new safety signals were reported.

The frequencies of grade 3 or 4 serious treatment-related adverse events and those leading to discontinuation were higher with nivolumab plus ipilimumab versus chemotherapy, however most were manageable and resolved with steroids or supportive treatment. Moreover, when treatment-related adverse events were adjusted for exposure, the overall incidence rate of treatment-related adverse events was lower with nivolumab plus ipilimumab compared with chemotherapy.

Benefit with nivolumab plus ipilimumab was observed in most subgroups assessed with the exception of patients who were aged ≥75 years. However, these subgroups were small and lacked statistical power. As such, results from these subgroup analyses should be interpreted with caution. Importantly, benefit was observed across histologies, albeit with different magnitudes of benefit; median overall survival with nivolumab plus ipilimumab was consistent between patients with epithelioid histology (median overall survival, 18·7 months; HR 0·86 [95% CI 0·69–1·08]) and non-epithelioid histology (median overall survival, 18·1 months; HR 0·46 [95% CI 0·31–0·68]), showing clinically meaningful survival improvements across both groups; 1-year and 2-year survival rates were also similar between the two histologies. Of note, in the epithelioid subgroup, nivolumab plus ipilimumab showed an improvement of 2 months in median overall survival with a HR favouring nivolumab plus ipilimumab. Further, the 2-year overall survival rate in the epithelioid subgroup demonstrated a long-term benefit of nivolumab plus ipilimumab with a 9% absolute difference versus chemotherapy. The larger magnitude of benefit

observed in the non-epithelioid subgroup was primarily driven by the inferior effect of chemotherapy in the non-epithelioid subtype, as previously reported.[4] This difference in the performance of the chemotherapy group could not be attributed to the type of chemotherapy received as exploratory data from CheckMate 743 suggest that patients derive a similar overall survival benefit regardless of platinum backbone; median overall survival was similar between pemetrexed plus cisplatin and pemetrexed plus carboplatin.

Median progression-free survival and objective response rates were each numerically similar for nivolumab plus ipilimumab and chemotherapy. Median progression-free survival was similar to results from previously reported clinical trials in recurrent MPM.[17,19] The progression-free survival Kaplan–Meier curves crossed at approximately 8 months, reflecting more rapid although not durable disease control with chemotherapy. However, radiographic assessments in MPM can be challenging because of the lack of distinguishable tumour margins over time and successive CT evaluations.[23] Thus, overall survival is considered to be a more objective and reliable endpoint in this tumour type. Notably, nivolumab plus ipilimumab provided long-term overall survival benefit, while the slight early survival benefit observed with chemotherapy was not durable.

The duration of response and durable survival benefit observed with nivolumab plus ipilimumab in patients with MPM in CheckMate 743 builds on the existing body of evidence that shows prolonged survival benefit with this dual immunotherapy across a number of other tumour types, including NSCLC.[14-16,24] Ipilimumab is hypothesised to drive memory T-cell production leading to durable responses when combined with nivolumab.[12] Results of the current study also corroborate the promising activity seen with anti-PD-1/PD-L1 and anti-CTLA-4 combination therapies in phase 2 studies in second-line or later settings of MPM,[17,19,25] and support the use of dual immunotherapy over single-agent anti-PD-1 or anti-CTLA-4 inhibitors, which have shown limited benefit over chemotherapy.[26,27]

Some treatment guidelines include the optional addition of the anti-angiogenic agent bevacizumab to platinum plus pemetrexed chemotherapy for first-line treatment of MPM in select patients, based on the

survival benefit seen in a phase 3 trial[1,6,11]; however, this regimen is not approved. Nonetheless, given the durable survival benefit seen in CheckMate 743, combining nivolumab plus ipilimumab with other therapies, including anti-angiogenic agents or, as recently approved for NSCLC, a limited course of chemotherapy,[13] merits investigation to determine whether survival outcomes can be further enhanced. Similarly, future trials assessing benefit with second-line targeted therapies, such as bevacizumab and ramucirumab, following nivolumab plus ipilimumab treatment are also warranted.

Reliable biomarkers to predict the benefit of dual-agent immunotherapy in the treatment of MPM have not yet been identified. While PD-L1 expression is an established biomarker for single-agent immunotherapy in NSCLC[28], its role in predicting treatment outcomes with dual immunotherapy regimens has not been established. More specifically, in MPM trials investigating immunotherapies, the association between PD-L1 expression and efficacy is inconsistent.[18,19,25] In CheckMate 743, survival outcomes with nivolumab plus ipilimumab were similar in the PD-L1 <1% and ≥1% subgroups and outperformed chemotherapy at 24 months (39% vs 25% and 41% vs 28%, respectively). Whereas survival with chemotherapy was better in patients with tumour PD-L1 <1% and outperformed nivolumab plus ipilimumab at 12 months (64% vs 59%), this suggests that absence of PD-L1 expression may be indicative of better prognosis with chemotherapy. However, these descriptive and exploratory data should be interpreted with caution given the potential limitations; PD-L1 expression was not a stratification factor in the study and the sample size of the PD-L1 <1% group was small. As such, the potential for imbalances in known or unknown prognostic factors does not allow for drawing of definitive conclusions. Better characterisation of this heterogeneous disease using transcriptomic and epigenetic profiling should guide future patient selection and therapeutic strategies, and aid in the identification of novel biomarkers.[29,30]

In summary, first-line nivolumab plus ipilimumab provided a statistically significant and clinically meaningful improvement in overall survival versus platinum plus pemetrexed chemotherapy. Nivolumab plus ipilimumab has a favourable clinical benefit–risk profile which led to approval in the United States

and should be considered as a new standard of care for previously untreated patients with unresectable malignant pleural mesothelioma, regardless of histological subtype.

CONTRIBUTIONS

PB, AS, AKN, NF, SP, AST, ASM, SP, TJ, PA, AO, CB, and GZ provided substantial contributions to the conception and design of the study. PB, AS, AKN, NF, SP, AST, ASM, SA, YO, YB, RC, LG, FG, DZ, JRC, and GZ enrolled and treated patients. CB wrote the study statistical analysis plan, conducted all statistical analyses, and generated data. PB, AKN, NF, SP, AST, ASM, SP, TJ, PA, AO, CB, and GZ analysed and interpreted the data. PA and CB verified the data from the study. All authors reviewed the data, contributed to the development of the manuscript, and approved the final version for publication.

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DECLARATION OF INTEREST

Conflict of interest disclosure forms for all authors will be submitted separately.

PB has received institutional grant funding from Bristol Myers Squibb and Merck Sharp Dohme and has a consultancy/advisory role for Bristol Myers Squibb, Merck Sharp Dohme, Roche, Beigene, Epizyme, Takeda, Trizell, and Daichii-Sankyo (honoraria to institute).

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DATA SHARING STATEMENT

Bristol Myers Squibb policy on data sharing may be found at https://www.bms.com/researchers-and-partners/clinical-trials-and-research/disclosure-commitment.html.

REFERENCES

1 National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Malignant Pleural Mesothelioma. Version 2.2020. 2020. https://www.nccn.org/professionals/physician_gls/pdf/mpm.pdf (accessed Nov 11, 2020).

2 Van Gerwen M, Alpert N, Wolf A, et al. Prognostic factors of survival in patients with malignant pleural mesothelioma: an analysis of the National Cancer Database. *Carcinogenesis* 2019; **40**: 529-36.

3 Milano MT, Zhang H. Malignant pleural mesothelioma: a population-based study of survival. *J Thorac Oncol* 2010; **5**: 1841-8.

4 Bille A, Krug LM, Woo KM, Rusch VW, Zauderer MG. Contemporary analysis of prognostic factors in patients with unresectable malignant pleural mesothelioma. *J Thorac Oncol* 2016; **11**: 249-55.

5 Baas P, Fennell D, Kerr KM, et al. Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015; **26 Suppl 5**: v31-9.

6 Scherpereel A, Opitz I, Berghmans T, et al. ERS/ESTS/EACTS/ESTRO guidelines for the management of malignant pleural mesothelioma. *Eur Respir J* 2020; published online May 25. DOI:10.1183/13993003.00953-2019.

7 Santoro A, O'Brien ME, Stahel RA, et al. Pemetrexed plus cisplatin or pemetrexed plus carboplatin for chemonaive patients with malignant pleural mesothelioma: results of the International Expanded Access Program. *J Thorac Oncol* 2008; **3**: 756-63.

8 Taylor P, Castagneto B, Dark G, et al. Single-agent pemetrexed for chemonaive and pretreated patients with malignant pleural mesothelioma: results of an International Expanded Access Program. *J Thorac Oncol* 2008; **3**: 764-71.

9 Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol* 2003; **21**: 2636-44.

10 van Meerbeeck JP, Gaafar R, Manegold C, et al. Randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an intergroup study of the European Organisation for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute of Canada. *J Clin Oncol* 2005; **23**: 6881-9.

11 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.

12 Wei SC, Duffy CR, Allison JP. Fundamental mechanisms of immune checkpoint blockade therapy. *Cancer Discov* 2018; **8**: 1069-86.

13 Bristol Myers Squibb. OPDIVO® (nivolumab) Prescribing information. US FDA. October, 2020. https://packageinserts.bms.com/pi/pi_opdivo.pdf (accessed Aug 1, 2020).

14 Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med* 2019; **381**: 1535-46.

15 Motzer RJ, Rini BI, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. *Lancet Oncol* 2019; **20**: 1370-85.

16 Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *N Engl J Med* 2019; **381**: 2020-31.

17 Scherpereel A, Mazieres J, Greillier L, et al. 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. *Lancet Oncol* 2019; **20**: 239-53.

18 Quispel-Janssen J, van der Noort V, de Vries JF, et al. Programmed death 1 blockade with nivolumab in patients with recurrent malignant pleural mesothelioma. *J Thorac Oncol* 2018; **13**: 1569-76.
19 Disselhorst MJ, Quispel-Janssen J, Lalezari F, 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; **7**: 260-70.
20 Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; **5**: 649-55.
21 Byrne MJ, Nowak AK. Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. *Ann Oncol* 2004; **15**: 257-60.
22 Dako. PD-L1 IHC 28-8 pharmDx [product information]. Carpinteria, CA: Dako North America Inc; 2016.
23 U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Clinical trial endpoints for the approval of cancer drugs and biologics: Guidance for industry. 2018. https://www.fda.gov/media/71195/download (accessed July 24, 2020).
24 Ramalingam SS, Ciuleanu TE, Pluzanski A, et al. Nivolumab + ipilimumab versus platinum-doublet chemotherapy as first-line treatment for advanced non-small cell lung cancer: Three-year update from CheckMate 227 Part 1 American Society of Clinical Oncology (ASCO). 2020 May 29-31, 2020:Abstract 9500.
25 Calabro 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.
26 Popat S, Curioni-Fontecedro A, Polydoropoulou V, et al. A multicentre randomized phase III trial comparing pembrolizumab (P) vs single agent chemotherapy (CT) for advanced pre-treated malignant pleural mesothelioma (MPM): Results from the European Thoracic Oncology Platform (ETOP 9-15) PROMISE-meso trial. *Ann Oncol* 2019; **30**: Abstract LBA15_PR.
27 Maio M, Scherpereel A, Calabro 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.
28 Reck M, Rodriguez-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.
29 Blum Y, Meiller C, Quetel L, et al. Dissecting heterogeneity in malignant pleural mesothelioma through histo-molecular gradients for clinical applications. *Nat Commun* 2019; **10**: 1333.
30 Mansfield AS, Peikert T, Smadbeck JB, et al. Neoantigenic Potential of Complex Chromosomal Rearrangements in Mesothelioma. *J Thorac Oncol* 2019; **14**: 276-87.

627 **TABLES**

628 **Table 1:** Baseline characteristics

	Nivolumab plus ipilimumab (n=303)	Chemotherapy (n=302)
Age, years	69 (65–75)	69 (62–75)
<65	71 (23%)	96 (32%)
≥65 to <75	154 (51%)	127 (42%)
≥75	78 (26%)	79 (26%)
Gender		
Male	234 (77%)	233 (77%)
Region		
North America	32 (11%)	27 (9%)
Europe	177 (58%)	175 (58%)
Asia	26 (9%)	39 (13%)
Rest of world*	68 (22%)	61 (20%)
Eastern Cooperative Oncology Group performance status†		
0	114 (38%)	128 (42%)
1	189 (62%)	173 (57%)
Smoking status		
Current/former	173 (57%)	171 (57%)
Never	127 (42%)	122 (40%)
Unknown	3 (1%)	9 (3%)
Histology		
Epithelioid	229 (76%)	227 (75%)
Non-epithelioid	74 (24%)	75 (25%)
Sarcomatoid	35 (12%)	36 (12%)
Mixed/Other	39 (13%)	39 (13%)
Stage		
I	12 (4%)	20 (7%)
II	23 (8%)	22 (7%)
III	103 (34%)	106 (35%)

IV	160 (53%)	149 (49%)
Not reported	5 (2%)	5 (2%)
Prior cancer therapy		
Prior radiotherapy‡	29 (10%)	28 (9%)
Prior systemic therapy¶	1 (<1%)	0
PD-L1 status§		
Quantifiable	289 (95%)	297 (98%)
<1%**	57 (20%)	78 (26%)
≥1%**	232 (80%)	219 (74%)

Data are median (IQR) or n (%).

* Includes Australia, Brazil, Chile, and South Africa.

† On a score of 0 to 5, with higher scores indicating greater disability.[20] One patient in the chemotherapy arm had a baseline Eastern Cooperative Oncology Group performance status of 2 (protocol deviation).

‡ Prior radiotherapy was provided for palliative support, pain management, or prophylactic track irradiation for tumour biopsy.

¶ Due to incorrect data entry 1 patient was reported as having previous systemic cancer therapy.

§ The status of PD-L1 expression was determined with the use of the PD-L1 IHC 28–8 pharmDx assay (Dako).

** Calculated as a percentage of quantifiable patients.

Table 2: Tumour response* in all randomised patients

	Nivolumab plus ipilimumab (n=303)	Chemotherapy (n=302)
Objective response rate	120 (40%)	129 (43%)
95% CI	34·1–45·4	37·1–48·5
Best overall response		
Complete response	5 (2%)	0
Partial response	115 (38%)	129 (43%)
Stable disease	112 (37%)	125 (41%)
Non-complete response/non-progressive disease	0	3 (1%)
Progressive disease	55 (18%)	14 (5%)
Unable to determine	4 (1%)	5 (2%)
Not reported	12 (4%)	26 (9%)
Disease control rate	232 (77%)	257 (85%)
95% CI	71·4–81·2	80·6–88·9
Time to response, months		
Median	2·7	2·5
IQR	1·45–3·27	1·41–3·02
Duration of response, months		
Median	11·0	6·7
95% CI	8·1–16·5	5·3–7·1
Patients with a response who had ongoing responses		
At 1 year	47%	26%
95% CI	37–56	18–34
At 2 years	32%	8%
95% CI	23–41	3–15

Data are n (%) unless indicated otherwise. Minimum follow-up for objective response rate was 19·8 months.

* Per blinded independent central review.

Table 3: Summary of treatment-related adverse events in all treated patients*

	Nivolumab plus ipilimumab (n=300)			Chemotherapy (n=284)		
Treatment-related adverse events	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any	148 (49%)	79 (26%)	12 (4%)	141 (50%)	73 (26%)	18 (6%)
Diarrhoea	52 (17%)	10 (3%)	0	19 (7%)	2 (1%)	0
Pruritus	46 (15%)	3 (1%)	0	1 (<1%)	0	0
Rash	40 (13%)	3 (1%)	0	15 (5%)	0	0
Fatigue	38 (13%)	3 (1%)	0	50 (18%)	5 (2%)	0
Hypothyroidism	32 (11%)	0	0	0	0	0
Nausea	29 (10%)	1 (<1%)	0	97 (34%)	7 (2%)	0
Anaemia	5 (2%)	1 (<1%)	0	70 (25%)	32 (11%)	0
Decreased appetite	27 (9%)	2 (1%)	0	48 (17%)	2 (1%)	0
Constipation	12 (4%)	0	0	41 (14%)	1 (<1%)	0
Vomiting	8 (3%)	0	0	35 (12%)	6 (2%)	0
Asthenia	25 (8%)	0	0	32 (11%)	12 (4%)	0
Increased lipase	7 (2%)	11 (4%)	2 (1%)	0	1 (<1%)	0
Colitis	3 (1%)	7 (2%)	0	1 (<1%)	1 (<1%)	0
Increased amylase	10 (3%)	6 (2%)	1 (<1%)	1 (<1%)	0	0
Thrombocytopenia	0	2 (1%)	0	16 (6%)	4 (1%)	6 (2%)
Neutropenia	0	1 (<1%)	1 (<1%)	28 (10%)	31 (11%)	12 (4%)

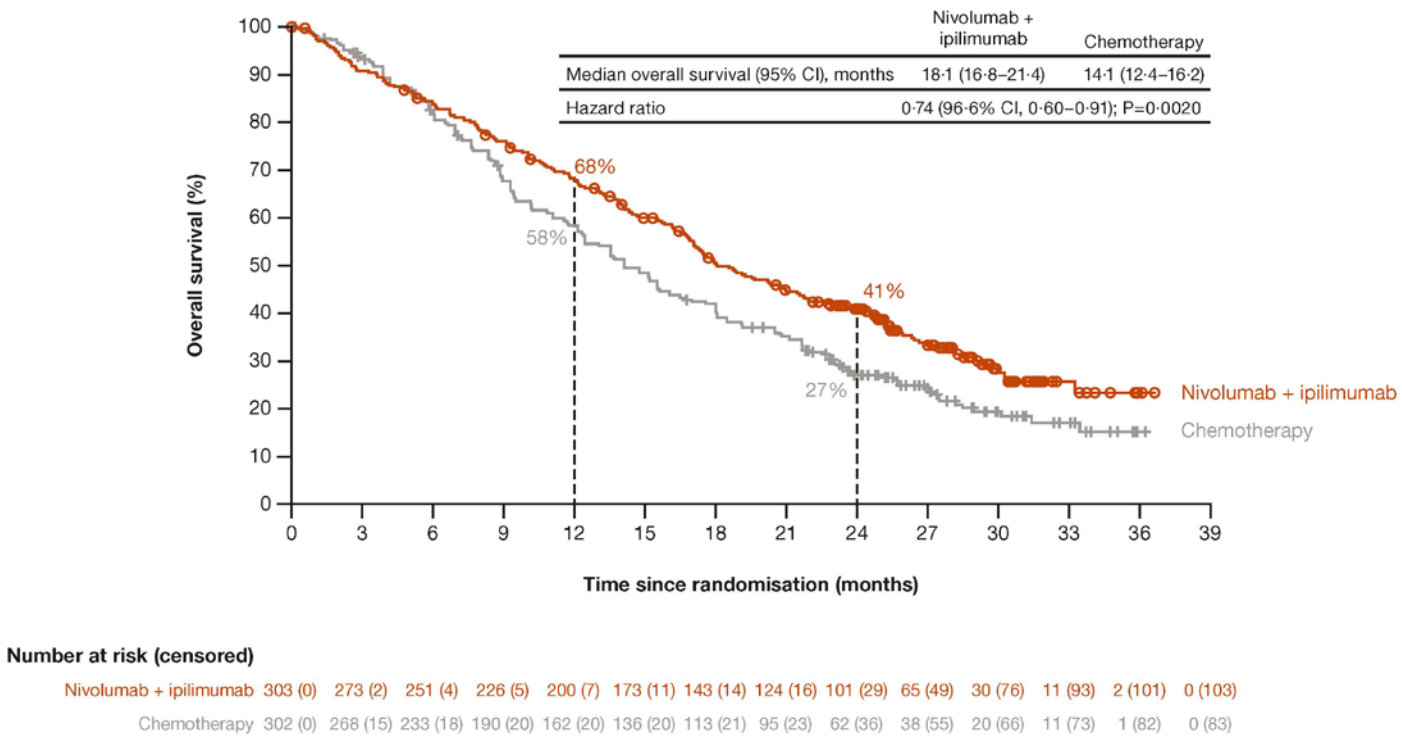
Data are n (%). Treatment-related adverse events with an incidence of ≥10% in any group or grade 3 or 4 severity with an incidence of ≥2% in any group are shown. All grade 3 and 4 events are listed in the appendix pp 13–15. Treatment-related adverse events included those reported between the first dose of study drug and 30 days after the last dose of study drug.

* According to the study sponsor practice, only events that led to death within 24 hours were documented as grade 5 and reported as deaths in the manuscript. Events leading to death >24 hours after onset are reported with the worst grade before death.

FIGURES

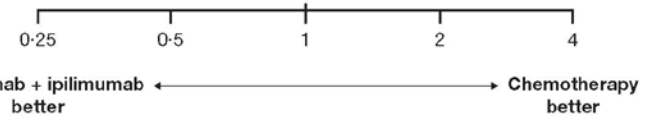
Figure 1. Overall survival in all randomised patients (A), in pre-defined patient subgroups (B), and in patients with epithelioid tumour histology (C) and non-epithelioid tumour histology (D). For all randomised patients, the stratified hazard ratio (96·6% CI) is reported in Panel A and the unstratified hazard ratio (95% CI) in Panel B; the stratified hazard ratio was 0·74 (95% CI 0·61–0·89). *One patient in the chemotherapy arm had a baseline Eastern Cooperative Oncology Group performance status of 2 (protocol deviation). Minimum and median follow-up for overall survival were 22·1 months and 29·7 months (IQR, 26·7–32·9), respectively.

A

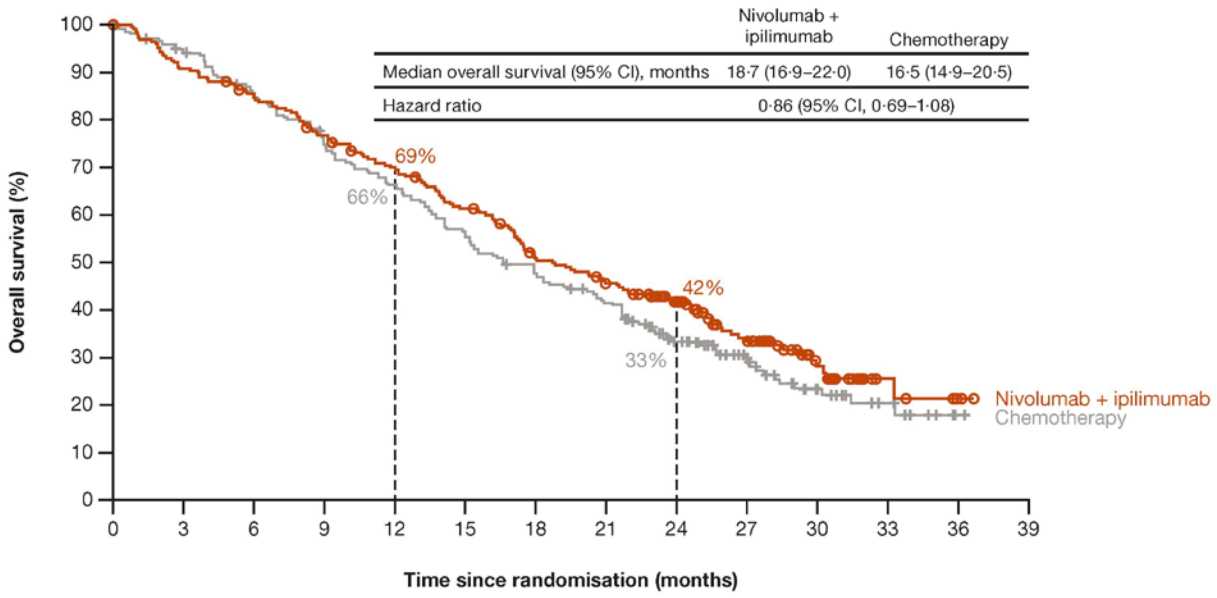


B

Subgroup	No. of Patients	Median Overall Survival (months)		Unstratified Hazard Ratio for Death (95% CI)
		Nivolumab + ipilimumab (N=303)	Chemotherapy (N=302)	
All randomised	605	18·1	14·1	0·75 (0·62–0·91)
Age				
<65 yrs	167	17·2	13·3	0·76 (0·52–1·11)
65 to <75 yrs	281	20·3	14·9	0·63 (0·48–0·83)
⩾75 yrs	157	16·9	15·4	1·02 (0·70–1·48)
Gender				
Male	467	17·5	13·7	0·74 (0·60–0·92)
Female	138	21·4	18·0	0·76 (0·50–1·16)
ECOG performance status*				
0	242	20·7	19·5	0·87 (0·64–1·19)
1	363	17·0	11·6	0·66 (0·52–0·85)
Tumor histologic type				
Epithelioid	456	18·7	16·5	0·86 (0·69–1·08)
Non-epithelioid	149	18·1	8·8	0·46 (0·31–0·68)
Stage				
III	209	23·9	16·3	0·61 (0·44–0·86)
IV	309	16·7	10·8	0·67 (0.52–0·87)
PD-L1 expression subgroups				
PD-L1 <1%	135	17·3	16·5	0·94 (0·62–1·40)
PD-L1 ⩾1%	451	18·0	13·3	0·69 (0·55–0·87)



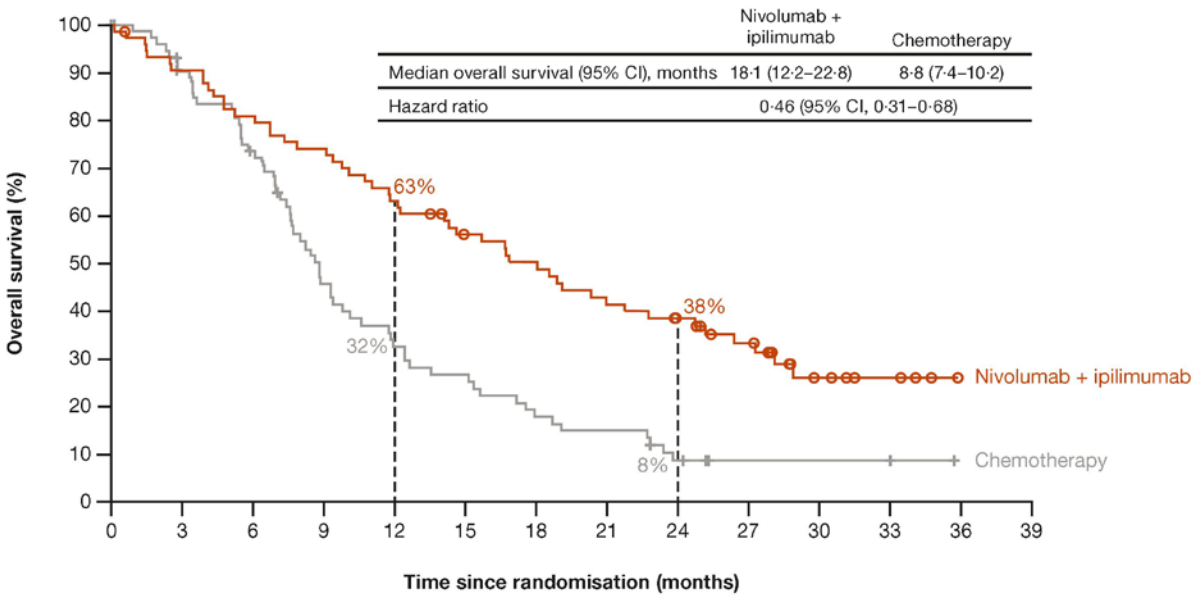
C



Number at risk (censored)

Nivolumab + ipilimumab	229 (0)	207 (1)	192 (3)	172 (4)	154 (6)	135 (7)	109 (10)	96 (12)	77 (23)	47 (40)	22 (60)	6 (74)	2 (77)	0 (79)
Chemotherapy	227 (0)	204 (11)	182 (13)	159 (14)	140 (14)	118 (14)	101 (15)	85 (17)	57 (29)	36 (45)	18 (56)	9 (63)	1 (70)	0 (71)

D



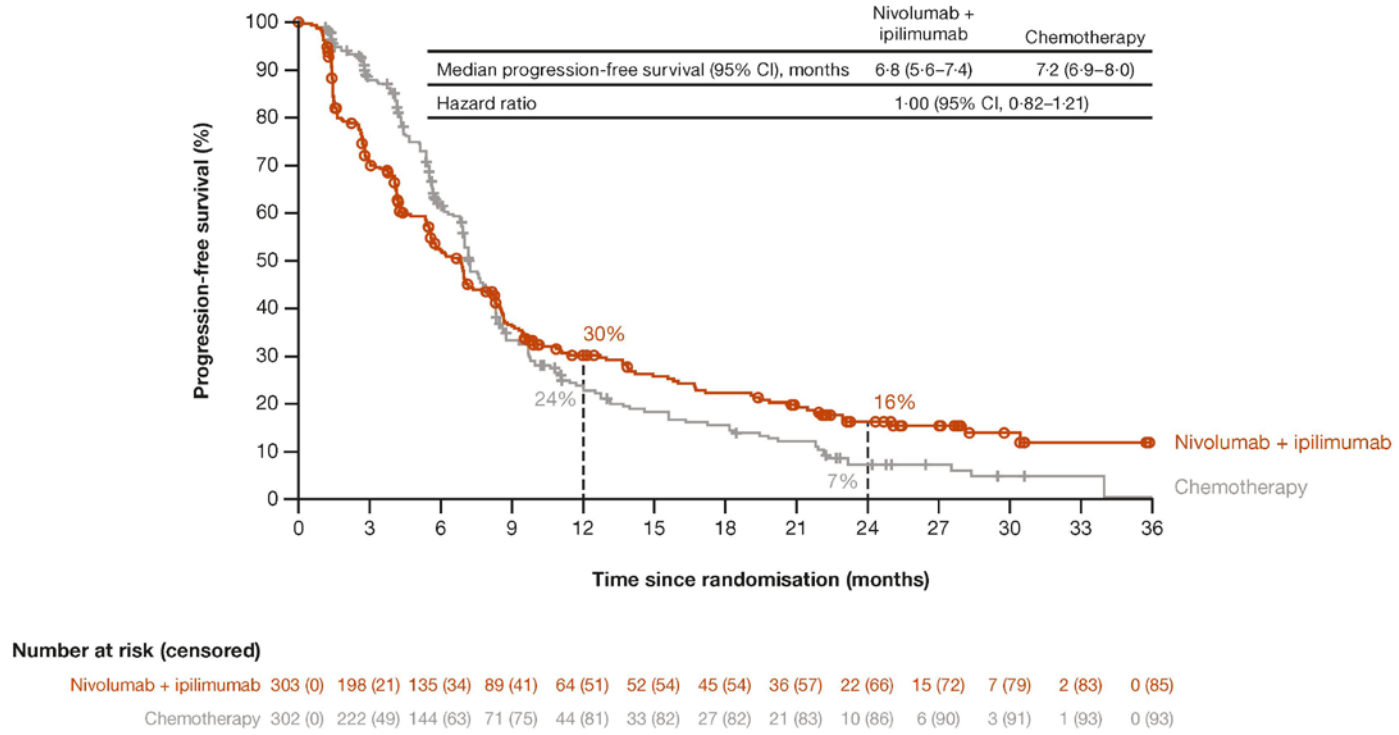
Number at risk (censored)

Nivolumab + ipilimumab	74 (0)	66 (1)	59 (1)	54 (1)	46 (1)	38 (4)	34 (4)	28 (4)	24 (6)	18 (9)	8 (16)	5 (19)	0 (24)	0 (24)
Chemotherapy	75 (0)	64 (4)	51 (5)	31 (6)	22 (6)	18 (6)	12 (6)	10 (6)	5 (7)	2 (10)	2 (10)	2 (10)	0 (12)	0 (12)

Figure 2. Progression-free survival* (A) and duration of response* (B) in all randomised patients.

* Per blinded independent central review. Minimum follow-up for progession-free survival was 19·8 months.

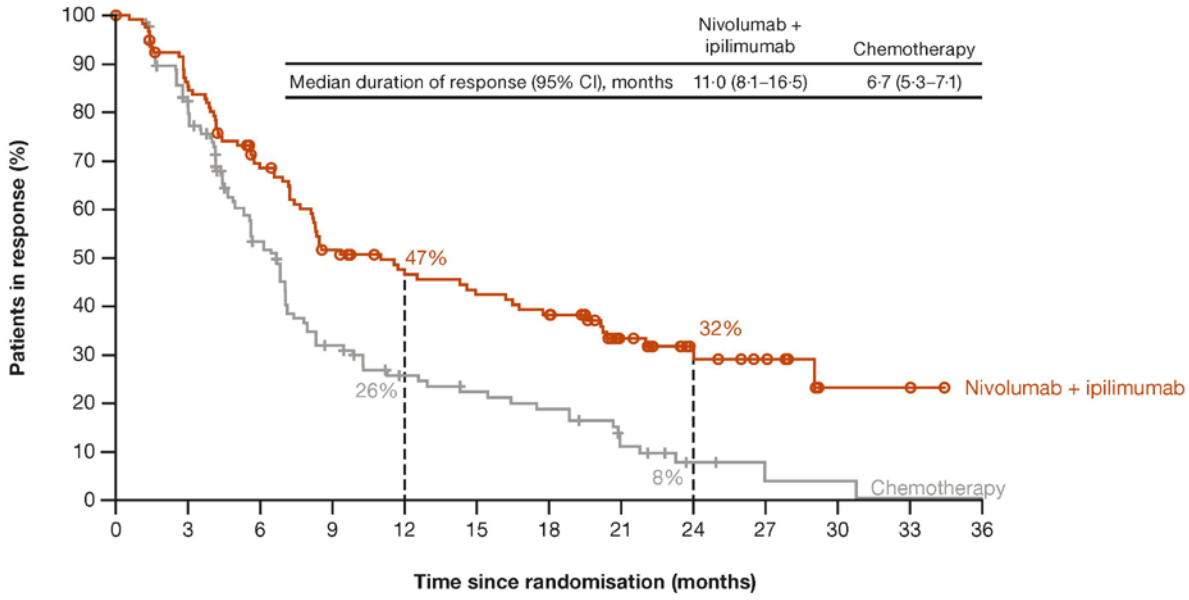
A



Number at risk (censored)

Nivolumab + ipilimumab	303 (0)	198 (21)	135 (34)	89 (41)	64 (51)	52 (54)	45 (54)	36 (57)	22 (66)	15 (72)	7 (79)	2 (83)	0 (85)
Chemotherapy	302 (0)	222 (49)	144 (63)	71 (75)	44 (81)	33 (82)	27 (82)	21 (83)	10 (86)	6 (90)	3 (91)	1 (93)	0 (93)

B



Number at risk (censored)

Nivolumab + ipilimumab	120 (0)	98 (5)	74 (10)	54 (12)	45 (16)	41 (16)	37 (16)	21 (28)	12 (36)	8 (39)	2 (44)	2 (44)	0 (46)
Chemotherapy	129 (0)	99 (8)	57 (16)	33 (18)	23 (22)	19 (23)	16 (23)	8 (25)	3 (28)	1 (29)	1 (29)	0 (29)	0 (29)