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Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study

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Summary

Background—Limited evidence exists to show that adding a third agent to platinum-doublet chemotherapy improves efficacy in the first-line advanced non-small-cell lung cancer (NSCLC) setting. The anti-PD-1 antibody pembrolizumab has shown efficacy as monotherapy in patients with advanced NSCLC and has a non-overlapping toxicity profile with chemotherapy. We assessed whether the addition of pembrolizumab to platinum-doublet chemotherapy improves efficacy in patients with advanced non-squamous NSCLC.

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Contributors

CJL, SMG, JF, YG, and HR designed or planned the study. CJL, SMG, HB, YG, and HR analysed the data. JF acquired the data. CJL, HR, and YJG wrote the first draft. All authors interpreted the results, critically reviewed and revised the report, and approved the final version.

Methods—In this randomised, open-label, phase 2 cohort of a multicohort study (KEYNOTE-021), patients were enrolled at 26 medical centres in the USA and Taiwan. Patients with chemotherapy-naive, stage IIIB or IV, non-squamous NSCLC without targetable *EGFR* or *ALK* genetic aberrations were randomly assigned (1:1) in blocks of four stratified by PD-L1 tumour proportion score (<1% *vs* ≥1%) using an interactive voice-response system to 4 cycles of pembrolizumab 200 mg plus carboplatin area under curve 5 mg/mL per min and pemetrexed 500 mg/m^2 every 3 weeks followed by pembrolizumab for 24 months and indefinite pemetrexed maintenance therapy or to 4 cycles of carboplatin and pemetrexed alone followed by indefinite pemetrexed maintenance therapy. The primary endpoint was the proportion of patients who achieved an objective response, defined as the percentage of patients with radiologically confirmed complete or partial response according to Response Evaluation Criteria in Solid Tumors version 1.1 assessed by masked, independent central review, in the intention-to-treat population, defined as all patients who were allocated to study treatment. Significance threshold was p<0·025 (one sided). Safety was assessed in the as-treated population, defined as all patients who received at least one dose of the assigned study treatment. This trial, which is closed for enrolment but continuing for follow-up, is registered with ClinicalTrials.gov, number .

Findings—Between Nov 25, 2014, and Jan 25, 2016, 123 patients were enrolled; 60 were randomly assigned to the pembrolizumab plus chemotherapy group and 63 to the chemotherapy alone group. 33 (55%; 95% CI 42–68) of 60 patients in the pembrolizumab plus chemotherapy group achieved an objective response compared with 18 (29%; 18–41) of 63 patients in the chemotherapy alone group (estimated treatment difference 26% [95% CI 9–42%]; p=0·0016). The incidence of grade 3 or worse treatment-related adverse events was similar between groups (23 [39%] of 59 patients in the pembrolizumab plus chemotherapy group and 16 [26%] of 62 in the chemotherapy alone group). The most common grade 3 or worse treatment-related adverse events in the pembrolizumab plus chemotherapy group were anaemia (seven [12%] of 59) and decreased neutrophil count (three [5%]); an additional six events each occurred in two (3%) for acute kidney injury, decreased lymphocyte count, fatigue, neutropenia, and sepsis, and thrombocytopenia. In the chemotherapy alone group, the most common grade 3 or worse events were anaemia (nine [15%] of 62) and decreased neutrophil count, pancytopenia, and thrombocytopenia (two [3%] each). One (2%) of 59 patients in the pembrolizumab plus chemotherapy group experienced treatment-related death because of sepsis compared with two (3%) of 62 patients in the chemotherapy group: one because of sepsis and one because of pancytopenia.

Interpretation—Combination of pembrolizumab, carboplatin, and pemetrexed could be an effective and tolerable first-line treatment option for patients with advanced non-squamous NSCLC. This finding is being further explored in an ongoing international, randomised, double-blind, phase 3 study.

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Introduction

Currently, the standard first-line therapy for patients with advanced non-squamous non-small-cell lung cancer (NSCLC) without targetable genetic aberrations is platinum-doublet chemotherapy. With the exception of bevacizumab,[1,2] and despite extensive study of multiple targeted and cytotoxic agents, the addition of a third agent to platinum-doublet

chemotherapy has not been shown to improve progression-free or overall survival over platinum-doublet chemotherapy alone in randomised studies.

When used as monotherapy in patients with advanced NSCLC, drugs targeting programmed death 1 (PD-1) and its ligand, PD-L1, have shown a manageable safety profile and robust efficacy, including a significant prolongation of overall survival compared with docetaxel in patients whose disease progressed on platinum-based chemotherapy.[3–10] One of these therapies is pembrolizumab, a humanised, monoclonal antibody against PD-1 that prevents PD-1 from binding to its ligands, PD-L1 and PD-L2. Evidence for the efficacy and safety of pembrolizumab in both treatment-naive and previously treated advanced NSCLC initially came from the large, multicohort KEYNOTE-001 study, which showed a correlation between PD-L1 expression on tumour cells and response to pembrolizumab.[3,4] The efficacy and safety of pembrolizumab monotherapy was confirmed in the international, randomised KEYNOTE-010 study, in which pembrolizumab yielded superior overall survival compared with docetaxel in patients with previously treated, PD-L1-expressing (ie, PD-L1 tumour proportion score ≥1%), advanced NSCLC.[5]

Increasing evidence suggests that the antitumour activity of chemotherapy is mediated not only though cytotoxic effects, but also through immunological effects, including reducing T-regulatory cell activity and enhancing cross-presentation of tumour antigens.[11–13] Chemotherapy has also been shown to induce PD-L1 expression on tumour cells.[14–16] Combining immunotherapy and chemotherapy could thus synergistically improve the anticancer activity of anti-PD-1 and anti-PD-L1 monotherapy.[11–13] Early clinical data for combinations of chemotherapy with PD-1[17,18] and PD-L1[19] inhibitors have suggested that these regimens have manageable toxicity and promising antitumour activity as first-line therapy for advanced NSCLC with non-overlapping toxicity profiles. In the international, multi-cohort, phase 1/2 KEYNOTE-021 study (ClinicalTrials.gov number), the safety and anti-tumour activity of pembrolizumab added to either carboplatin and paclitaxel (cohort A), carboplatin, paclitaxel, and bevacizumab (cohort B), or pemetrexed and carboplatin (cohort C) were assessed.[18] All three combinations showed promising antitumour activity irrespective of tumour PD-L1 expression, with manageable safety profiles observed in cohorts A and C. The greatest antitumour activity was observed in cohort C (N=24), where the combination of pembrolizumab, carboplatin, and pemetrexed resulted in 17 (71%) of 24 patients achieving an overall response and a median progression-free survival of 10·2 months (95% CI 6·2–15·2).[18]

Based on these results and to further explore the potential synergy of combining chemotherapy with immunotherapy, we aimed to compare the efficacy and safety of pembrolizumab at a fixed intravenous dose of 200 mg plus carboplatin and pemetrexed versus those of carboplatin and pemetrexed alone as first-line therapy for patients with advanced NSCLC of non-squamous histology as part of KEYNOTE-021.

Methods

Study design and participants

This randomised, controlled, phase 2 study was done at 26 academic medical centres in the USA and Taiwan (appendix p 2). Eligibility criteria stipulated no previous systemic treatment for histologically or cytologically confirmed non-squamous, stage IIIB or IV NSCLC and the absence of targetable *EGFR* mutations or *ALK* translocations. Other eligibility criteria included Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (a 5-point scale where higher numbers indicate greater disability), at least one measurable lesion assessed per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1[20] by the investigator, life expectancy 3 months or longer, and provision of a tumour biopsy sample for assessment of PD-L1 expression (for full inclusion criteria, see the protocol [appendix p 5]). Exclusions from enrolment included receiving more than 30 Gy of radiation to the lungs in the previous 6 months, ongoing use of systemic corticosteroids or other immunosuppressive treatment, active autoimmune disease requiring systemic treatment in the previous 2 years (excluding replacement therapy), untreated brain metastases (stable, treated metastases allowed), or active interstitial lung disease or a history of pneumonitis that required intravenous glucocorticoids (for full exclusion criteria, see appendix).

The protocol and all subsequent amendments were approved by the appropriate institutional review board or independent ethics committee at each study centre. The study was done in accordance with the protocol and all amendments, Good Clinical Practice guidelines, and the provisions of the Declaration of Helsinki. All patients provided written informed consent before enrolment.

Randomisation and masking

Using an interactive voice-response system, patients were randomly assigned (1:1) to treatment with pembrolizumab (Merck Sharp & Dohme Corp, a subsidiary of Merck & Co Inc, Whitehouse Station, NJ, USA) plus carboplatin and pemetrexed (Eli Lilly and Company, Indianapolis, IN, USA) or to carboplatin and pemetrexed alone. Randomisation was stratified by PD-L1 tumour proportion score (less than 1% *vs* 1% or greater), necessitating adequate tumour tissue for PD-L1 assessment. Treatment was allocated in blocks of four in each stratum via a schedule generated by Almac Clinical Technologies (Souderton, PA, USA) using a computerised randomised list generator. Patients, treating physicians, and representatives of the study funder were not masked to study treatment assignment but were masked to PD-L1 expression level. The funder was masked to aggregate data by treatment group during the study.

Procedures

In the pembrolizumab plus chemotherapy group, 4 cycles of pembrolizumab 200 mg administered over 30 min, pemetrexed 500 mg/m^2 administered over 10 min, and carboplatin area under curve 5 mg/mL per min administered over 15–60 min were given intravenously every 3 weeks in the order listed, followed by pembrolizumab for 24 months and optional indefinite pemetrexed maintenance therapy. In the chemotherapy alone group,

pemetrexed 500 mg/m^2 and carboplatin AUC 5 mg/mL per min were given for 4 cycles followed by optional indefinite pemetrexed maintenance therapy. Premedication with folic acid, vitamin B12, and corticosteroids was administered according to local guidelines. In the pembrolizumab group, pembrolizumab was given at least 30 min before chemotherapy. Patients in the carboplatin and pemetrexed alone group who experienced radiological disease progression could cross over to receive pembrolizumab monotherapy after a washout period of 21 days if protocol-specified safety criteria were met. Treatment was continued for the maximum number of cycles allowed or until disease progression, intolerable toxicity, physician decision, or patient withdrawal of consent, whichever occurred first. Clinically stable patients who were considered to be deriving clinical benefit by the investigator despite radiological evidence of disease progression could continue therapy until progression was confirmed on imaging done at least 4 weeks later. As outlined in the protocol (appendix p 5), pembrolizumab treatment was withheld for severe or life-threatening treatment-related toxicities; pembrolizumab dose reduction was not allowed. Modification of carboplatin and pemetrexed doses was done according to the locally approved product information.

Tumour imaging by CT (preferred) or MRI was done at baseline, every 6 weeks for the first 18 weeks, then every 9 weeks through the first 12 months and every 12 weeks thereafter. Response was assessed per RECIST version 1.1. Treatment decisions were based on investigator review, whereas efficacy was based on masked, independent central radiology review. During the treatment phase, adverse events were reviewed, physical examination and vital signs were obtained, a complete blood count with differential, and a comprehensive serum chemistry panel were assessed every 3 weeks; tri-iodothyronine, free thyroxine, and thyroid-stimulating hormone were assessed at baseline, week 3, and every 12 weeks thereafter. During the follow-up phase, patient survival was assessed every 8 weeks. All adverse events and laboratory abnormalities were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. PD-L1 expression was assessed in formalin-fixed tumour samples obtained from core needle biopsies, excisional biopsies, or resected tissue collected at the time of diagnosis of metastatic disease. Assessment of PD-L1 expression was done during the screening period at a central laboratory using the commercially available IHC 22C3 pharmDx assay (Dako North America, Carpinteria, CA, USA).[21,22]

Outcomes

The primary endpoint was the proportion of patients who achieved an objective response, defined as the percentage of patients with radiologically confirmed complete or partial response according to RECIST version 1.1 assessed by masked, independent central review. The key secondary endpoint was progression-free survival, defined as the time from randomisation to RECIST-defined progression based on masked, independent central review or death from any cause. Other secondary endpoints included duration of response, defined as the time from first documentation of complete or partial response to radiological disease progression, overall survival, defined as the time from randomisation to death from any cause, safety, and the correlation between PD-L1 expression levels and antitumour activity. Response and progression-free survival were assessed in the intention-to-treat population, defined as all patients randomly allocated to treatment. Safety was assessed in the as-treated

population, which included all patients who received at least one dose of assigned study treatment.

Statistical analysis

The analysis was planned to occur at least 6 months after the last patient enrolled. As calculated based on an asymptotic method[23] and with a planned enrolment of about 108 patients, the study had at least 89% power to detect a 30% difference in the proportion of patients achieving an objective response at a one-sided α of 0·025. Assuming 68 progression-free survival events, the study had roughly 81·5% power to detect a hazard ratio of 0·5 for progression-free survival at a one-sided α of 0·025. The sample size and power calculations were done with East 6 (Cytel, Cambridge, MA, USA). The overall type I error rate was strictly controlled at a one-sided α of 0·025 by a fixed-sequence, closed testing procedure[24] that was first applied to the primary endpoint of response rate in the total population. If pembrolizumab plus chemotherapy showed superiority over chemotherapy alone at a one-sided α of 0·025, the testing procedure was then applied to the key secondary endpoint of progression-free survival in the total population. No α was allocated to analyses of overall survival or to subgroups based on PD-L1 tumour proportion score.

The difference in the proportion of patients achieving an objective response between treatment groups was assessed with the stratified Miettinen and Nurminen method with weighting by sample size. Patients with unknown best overall response were considered non-responders. The Kaplan-Meier method was used to estimate progression-free survival, overall survival, and duration of response. For progression-free survival, patients who were alive and without disease progression or who were lost to follow-up were censored at the time of last radiological imaging. For overall survival, patients who were alive or who were lost to follow-up were censored at the time of last known survival. For duration of response, patients with confirmed response who were without subsequent radiological disease progression were censored at the time of last radiological imaging. Treatment differences in progression-free and overall survival were assessed with a stratified log-rank test. Hazard ratios and associated 95% CIs were assessed with a stratified Cox proportional hazard model with Efron's method of tie handling. The same stratification factor used for randomisation was applied to all stratified statistical analyses. Data were analysed with SAS, version 9.3.

This study is registered with ClinicalTrials.gov, number .

Role of the funding source

The study was funded by Merck & Co. Representatives of the funder, including JF, YG, and HR, contributed to various aspects of the study design, data analysis and interpretation, and preparation of the report. The study database was maintained by the funder. All authors had access to the data and had responsibility for the decision to submit the article for publication.

Results

Between Nov 25, 2014, and Jan 25, 2016, 219 patients were screened for enrolment at 23 sites in the USA and three sites in Taiwan (figure 1). 123 (56%) of these patients met all eligibility criteria and were randomly assigned; 60 (49%) were allocated to pembrolizumab

plus carboplatin and pemetrexed and 63 (51%) to carboplatin and pemetrexed alone (figure 1). One patient in the pembrolizumab plus chemotherapy group had deterioration in their ECOG performance status to a score of 2 after randomisation but before treatment started and therefore did not receive study therapy. One patient in the chemotherapy group withdrew consent before receiving treatment. Pemetrexed maintenance therapy was received by 50 (85%) of 59 treated patients in the pembrolizumab plus chemotherapy group and 43 (69%) of 62 patients in the chemotherapy group.

Baseline demographics and disease characteristics were mostly as expected for an advanced NSCLC population (table 1), except that proportionally, more women were enrolled than men (38 [63%] of 60 patients in the pembrolizumab plus chemotherapy group and 37 [59%] of 63 patients in the chemotherapy group were women). Demographics and disease characteristics were generally balanced between groups (table 1). Most patients had stage IV adenocarcinoma and were current or former smokers. Although absolute differences were small, there were more patients in the pembrolizumab plus chemotherapy group who were of non-white ethnic origin (11 [18%] of 60 *vs* five [8%] of 63 in the chemotherapy group), never smoked (15 [25%] of 60 *vs* nine [14%] of 63), and had a tumour histology of adenocarcinoma (58 [97%] of 60 *vs* 55 [87%] of 63).

As of the cutoff date of Aug 8, 2016, median follow-up was 10·6 months (IQR 8·2–13·3). 28 (47%) of 59 patients in the as-treated pembrolizumab plus chemotherapy group and 19 (31%) of 62 patients in the as-treated chemotherapy group remained on assigned study treatment (figure 1). The most common reason for treatment discontinuation in the as-treated population was progressive disease (17 [29%] of 59 patients in the pembrolizumab plus chemotherapy group and 31 [50%] of 62 patients in the chemotherapy group). 20 (32%) of 62 patients in the as-treated chemotherapy group crossed over to receive pembrolizumab monotherapy as allowed by the study protocol. Beyond the in-study crossover, at least one line of subsequent systemic anticancer therapy in the as-treated population was received by 13 (22%) of 59 patients in the pembrolizumab plus chemotherapy group and 17 (27%) of 62 patients in the chemotherapy alone group (appendix p 3). Including the in-study crossover, 32 (74%) of the 43 patients in the chemotherapy alone group who discontinued assigned study treatment received subsequent anti-PD-1 or anti-PD-L1 therapy compared with no patients in the pembrolizumab plus chemotherapy group.

33 (55%; 95% CI 42–68) of 60 patients in the pembrolizumab plus chemotherapy group achieved an objective responses compared with 18 (29%; 18–41) of 63 patients in the chemotherapy alone group; all responses were partial (table 2). Pembrolizumab plus chemotherapy significantly improved the proportion of patients who achieved an objective response compared with chemotherapy alone (estimated treatment difference 26% [95% CI 9–42%]; p=0·0016). Median time to response was 1·5 months (IQR 1·4–2·8) with pembrolizumab plus chemotherapy versus 2·7 months (1·4–2·8) with chemotherapy alone. Responses in both groups were durable: 29 (88%) of 33 responders in the pembrolizumab plus chemotherapy group and 14 (78%) of 18 responders in the chemotherapy alone group remained alive and progression free at the time of data cutoff. Kaplan-Meier estimates of response duration of at least 6 months were 92% (95% CI 73–98) for responses to pembrolizumab plus chemotherapy and 81% (51–93) for responses to chemotherapy alone.

Only two (3%) of 60 patients in the pembrolizumab plus chemotherapy group had a best overall response of progressive disease compared with 11 (17%) of 63 patients in the chemotherapy alone group. Overall, 55 (98%) of 56 patients in the pembrolizumab plus chemotherapy group and 45 (82%) of 55 patients in the chemotherapy alone group who had measurable disease per masked, independent central review at baseline and at least one post-baseline tumour assessment experienced a decrease from baseline in the sum of their target lesions (figure 2). Median change from baseline was −44% (IQR −62 to −27) for the pembrolizumab plus chemotherapy group and −28% (−50 to −10) for the chemotherapy alone group. In the pembrolizumab plus chemotherapy group, 12 of 21 patients who had a PD-L1 tumour proportion score of less than 1% achieved a response (response rate 57%; 95% CI 34–79), as did 21 of 39 patients who had a tumour proportion score of 1% or greater (response rate 54%; 37–70; appendix p 4). In the pembrolizumab plus chemotherapy group, within the tumour proportion score 1% or greater population, five (26%) of 19 patients who had a tumour proportion score of 1–49% and 16 (80%) of 20 patients who had a score of 50% or greater achieved an objective response (appendix p 4). In the chemotherapy alone group, three of 23 patients who had a tumour proportion score of less than 1% achieved a response (response rate 13%; 95% CI 3–34), as did nine of 23 patients who had a score of 1–49% (39%; 20–61) and six of 17 patients who had a score of 50% or greater (35%; 14–62; appendix p 4).

56 patients died or experienced disease progression, including 23 (38%) of 60 in the pembrolizumab plus chemotherapy group and 33 (52%) of 63 in the chemotherapy alone group. Progression-free survival was significantly longer with pembrolizumab plus chemotherapy compared with chemotherapy alone (HR 0·53 [95% CI 0·31–0·91]; p=0·010; figure 3A). Median progression-free survival was 13·0 months (95% CI 8·3 to not reached) for pembrolizumab plus chemotherapy and 8·9 months (4·4–10·3) for chemotherapy alone. Estimated 6-month progression-free survival was 77% (95% CI 64–86) for pembrolizumab plus chemotherapy and 63% (49–74) for chemotherapy alone.

At the time of data cutoff, 27 patients had died, including 13 (22%) of 60 in the pembrolizumab plus chemotherapy group and 14 (22%) of 63 in the chemotherapy alone group. No difference in survival was noted between treatment groups (HR 0·90 [95% CI 0·42–1·91]; nominal p=0·39; figure 3B). Estimated 6-month survival was 92% in both treatment groups (95% CI 81–96 for the pembrolizumab plus chemotherapy group; 95% CI 82–97 for the chemotherapy group alone group); after 6 months, there is a high degree of censoring.

In the as-treated population, median duration of treatment was 8·0 months (IQR 4·7–11·2) for the pembrolizumab plus chemotherapy group and 4·9 months (2·1–7·4) for the chemotherapy alone group. Six (10%) of 59 treated patients in the pembrolizumab plus chemotherapy group and eight (13%) of 62 treated patients in the chemotherapy alone group discontinued study treatment because of treatment-related events. The protocol did not provide specific dose reductions for pemetrexed and carboplatin but rather relied on investigators to reduce the dose based on their local regulations and treatment guidelines, data for chemotherapy dose reductions were not captured in this analysis. Deaths attributed to study treatment occurred in one patient (1%) in the pembrolizumab plus chemotherapy

group (sepsis) and two patients (3%) in the chemotherapy alone group (one case each of pancytopenia and sepsis). No additional adverse events led to death. Without adjustment for the difference in exposure, treatment-related adverse events occurred in 55 (93%) of 59 patients in the as-treated pembrolizumab plus chemotherapy group and 56 (90%) of 62 patients in the as-treated chemotherapy alone group, including 23 (39%) and 16 (26%), respectively, who had events of grade 3 or worse severity (table 3).

Treatment-related adverse events were as expected in both treatment groups of the as-treated population (table 3). The most common treatment-related events of any grade were fatigue (38 [64%] of 59 in the pembrolizumab plus chemotherapy group *vs* 25 [40%] of 62 in the chemotherapy alone group), nausea (34 [58%] *vs* 27 [44%]), and anaemia (19 [32%] *vs* 33 [53%]). In addition to fatigue, nausea, and anaemia, other events for which there was a greater than 10% difference in incidence between groups were rash (16 [27%] in the pembrolizumab plus chemotherapy group *vs* nine [15%] in the chemotherapy alone group) and alopecia (eight [14%] *vs* two [3%]). Treatment-related adverse events of grade 3 or worse severity that occurred in three or more patients in either treatment group were anaemia (seven [12%] in the pembrolizumab plus chemotherapy group *vs* nine (15%) in the chemotherapy alone group), decreased neutrophil count (three [5%] *vs* two [3%]), thrombocytopenia (two [3%] *vs* two [3%]), and decreased lymphocyte count, neutropenia, and sepsis (two [3%] *vs* one [2%] each).

The incidence of adverse events of interest based on a presumed immunological mechanism of action, regardless of attribution to study treatment or immune relatedness by the investigator, in the as-treated population was 13 (22%) of 59 in the pembrolizumab plus chemotherapy group and seven (11%) of 62 in the chemotherapy group (table 3). The only events of grade 3 or worse severity were grade 4 infusion reaction (one [2%] of 59 in the pembrolizumab plus chemotherapy group *vs* none in the chemotherapy alone group), grade 3 skin reaction (one [2%] in the pembrolizumab plus chemotherapy group *vs* one [2%] of 62 in the chemotherapy group), and grade 3 pneumonitis (one [2%] in the pembrolizumab plus chemotherapy group). The most common immune-mediated adverse events of any grade in the pembrolizumab plus chemotherapy group were hypothyroidism (nine [15%] of 59), hyperthyroidism (five [8%]), and pneumonitis (three [5%]).

Discussion

The addition of pembrolizumab to standard-of-care carboplatin and pemetrexed followed by pembrolizumab for 2 years and indefinite pemetrexed maintenance therapy significantly improved the proportion of patients who achieved an objective response compared with carboplatin and pemetrexed alone in patients with chemotherapy-naive, advanced non-squamous NSCLC. In addition, this combination also significantly prolonged progression-free survival in this non-squamous NSCLC population. These data constitute, to the best of our knowledge, the first published report of a randomised, controlled clinical trial in NSCLC to prospectively show the benefit of combination therapy with a PD-1 pathway inhibitor and chemotherapy in the treatment-naive setting. The rate of treatment discontinuation because of treatment-related adverse events was similar between groups, despite a greater incidence

of treatment-related adverse events of grade 3 or worse severity in the pembrolizumab plus chemotherapy treatment group.

The proportion of patients who achieved an objective response in the pembrolizumab plus carboplatin and pemetrexed group (55%) in this randomised, controlled cohort was somewhat lower than the preliminary proportion who achieved an objective response (71%) in the phase 1 cohort of this study, although the confidence intervals for these response rates overlap.[18] The proportion of patients who achieved an objective response was also similar to that noted in other phase 1 studies of anti-PD-1 and anti-PD-L1 therapy added to platinum-doublet chemotherapy.[17–19] Notably, the median time to response was around the time of the first radiological assessment at 6 weeks in the pembrolizumab plus chemotherapy group, whereas the median time to response was around the time of the second assessment at 12 weeks in the chemotherapy alone group. As previously reported with pembrolizumab monotherapy, responses in the pembrolizumab plus chemotherapy group were durable. Together, these data suggest that addition of pembrolizumab to platinum-doublet chemotherapy could help a greater number of patients experience durable response more rapidly compared with standard platinum-based combination chemotherapy alone.

Median progression-free survival in the pembrolizumab plus chemotherapy group was 13·0 months (95% CI 8·3 to not reached). Although caution must be used in view of the relatively short follow-up duration and the amount of censoring noted after 6 months, to the best of our knowledge, this makes KEYNOTE-021 one of the first randomised, controlled studies of first-line chemotherapy for advanced NSCLC in which median progression-free survival exceeded 1 year. Similarly, although the 8·9 month (95% CI 4·4–10·3) median progression-free survival noted in the chemotherapy alone group seems to exceed the 5–7 months observed in recent randomised studies of carboplatin and pemetrexed induction followed by maintenance pemetrexed,[25,26] there is a large amount of censoring around the time the median was reached. If the longer than expected progression-free survival is confirmed with additional follow-up, contributing factors might include the enrolment of more women than men because women have better outcomes with chemotherapy[27,28] and the greater use of pemetrexed maintenance therapy compared with that observed in the phase 3 PARAMOUNT study.[29] Because any benefit provided by these factors would probably extend to both treatment groups, they would not be expected to affect the relative benefit of pembrolizumab plus chemotherapy over chemotherapy alone.

No difference in overall survival was noted over the median follow-up of 10·6 months. With only 27 deaths and estimated 6-month survival of more than 90% in both treatment groups, it is likely that survival will be longer than that which has been observed historically for platinum-doublet chemotherapy. Additional follow-up is planned to further assess overall survival, although the interpretability of these results will probably be restricted by the crossover design of the study and the fact that including the crossover phase, 32 (52%) of 62 patients in the chemotherapy alone as-treated group (ie, 74% of the 43 patients who discontinued chemotherapy) received subsequent PD-1-pathway-directed therapy, whereas no patients in the pembrolizumab plus chemotherapy group did so.

The large, multicohort, phase 1 KEYNOTE-001 study not only established the safety and antitumour activity of pembrolizumab monotherapy for advanced NSCLC, but also showed an association between tumour PD-L1 expression and improved response to pembrolizumab.[3] In cohort C of KEYNOTE-021, the dose-finding cohort for the combination of pembrolizumab plus carboplatin and pemetrexed, there was no apparent relationship between PD-L1 expression and response, with more than 60% of patients achieving a response across the PD-L1 tumour proportion score subgroups.[18] In this randomised cohort of KEYNOTE-021, the proportion of patients who achieved an objective response was similar in patients with a PD-L1 tumour proportion score of less than 1% and those with a score of 1% or greater, with a possibly higher proportion of responses in patients with a tumour proportion score of 50% or greater. In view of the small sample sizes of the individual PD-L1 subgroups, it is not possible to conclusively determine whether there is a relationship between PD-L1 expression and efficacy in patients treated with pembrolizumab plus chemotherapy. Results of the ongoing double-blind, phase 3 KEYNOTE-189 study of carboplatin or cisplatin and pemetrexed with or without pembrolizumab for non-squamous NSCLC (ClinicalTrials.gov, number) might provide a better opportunity to assess the relationship between PD-L1 expression and efficacy of pembrolizumab plus chemotherapy in view that the planned enrolment is 570 patients.

The adverse event profile noted for pembrolizumab plus chemotherapy was manageable. With a 1·6-times longer exposure in the pembrolizumab plus chemotherapy group, there was a higher incidence of chemotherapy-associated adverse events such as fatigue and nausea in the pembrolizumab plus chemotherapy versus the chemotherapy alone group. However, most of the treatment-related adverse events were mild and of grade 1 or 2 severity, and rate of death or treatment discontinuation did not increase in the pembrolizumab plus chemotherapy group. The incidence of potentially immune-mediated adverse events in the pembrolizumab plus chemotherapy group of the as-treated population (13 [22%] of 59) was comparable to that noted for pembrolizumab monotherapy in KEYNOTE-010 (69 [20%] of 339 patients in the pembrolizumab 2 mg/kg group and 64 [19%] of 343 patients in the pembrolizumab 10 mg/kg group).[5] As previously reported for pembrolizumab monotherapy in patients with NSCLC,[3–5] most immune-mediated adverse events were of grade 1 or 2 severity and were manageable without treatment discontinuation.

Limitations of our study include the relatively short duration of follow-up at the current analysis and the open-label design. Although the open-label design could have affected the reporting of adverse events, we do not believe it affected the reported efficacy because the number of objective responses and progression-free survival were assessed according to RECIST version 1.1 by independent, blinded central review. Therefore, although the treating physician, patient, and funder were aware of the treatment assignment for a given patient, the radiologists who assessed the tumour images were not.

Data from KEYNOTE-021, along with those from studies of nivolumab and atezolizumab added to platinum-doublet chemotherapy, support the continued exploration of the efficacy and safety of addition of anti-PD-1/anti-PD-L1 therapy to standard of care platinum-doublet chemotherapy as first-line therapy for advanced NSCLC. Ongoing randomised, double-blind, phase 3 studies exploring the addition of pembrolizumab to chemotherapy in the

chemotherapy-naive setting include the aforementioned KEYNOTE-189 study and the KEYNOTE-407 study of carboplatin and paclitaxel or nab-paclitaxel with or without pembrolizumab for squamous histology (ClinicalTrials.gov, number).

Our data suggest that the combination of pembrolizumab, carboplatin, and pemetrexed provides a significant and clinically relevant improvement in antitumour activity compared with chemotherapy alone. Combined with the manageable safety profile, these data suggest that pembrolizumab plus platinum-doublet chemotherapy might be an effective treatment option for patients with chemotherapy-naive, advanced, non-squamous NSCLC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Declaration of interests

CJL has received research support to the institution from Advantagene, Clovis, Genentech/Roche, GlaxoSmithKline, Inovio, and Merck; has served as an advisory board member for AstraZeneca, Bristol-Myers Squibb, Clovis, and Genentech/Roche; and has served as a Data and Safety Monitoring Committee member for AbbVie, Amgen, Lilly, and Synta. SMG has served as an advisory board member for Ariad, AstraZeneca, Bristol-Myers Squibb, Genentech, and Pfizer. HB has received research support to the institution from Merck and has served as a consultant or advisory board member for Bristol-Myers Squibb, Celgene, EMD-Serono, Genentech, Lilly, Merck, Pfizer, and Trovogene. VAP has received research support from and served as a consultant for Merck. APat has received research funding from Merck. SFP has received research funding from Bristol-Myers Squibb, Genentech, Incyte Corporation, Merck Sharp & Dohme, and Novartis. RDG has received research support from Bristol-Myers Squibb, Celgene, Clovis Oncology, and Merck and has served as a consultant for Ariad and Clovis Oncology. RGM has received research support to the institution from Merck. JPS has received research support to the institution from Bayer, Merck & Co, and Verastem. JC-HY has served as an adviser for Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Clovis Oncology, Eli Lilly, Merck Serono, Merrimack, MSD, Novartis, Ono Pharmaceutical, Pfizer, Roche/Genentech/Chugai, and Yuhan Pharmaceutical. MG has received research support to the institution from AbbVie, Celgene, Genentech/Roche, Merck, and OncoMed and served as a consultant or advisory board member for Ariad, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Calithera Biosciences, Clovis Oncolocy, Genentech/Roche, Nektar, Novartis, and Pfizer. LVS has served as a consultant for Ariad, AstraZeneca, Boehringer Ingelheim, Clovis Oncology, Genentech/Roche, Merrimack, Novartis, and Taiho. MMA has served as a consultant for Bristol-Myers Squibb, Genentech, and Merck. JF, YG, and HR are employed by Merck Sharp & Dohme Corp, a subsidiary of Merck & Co (Kenilworth, NJ, USA). YG has stock options in Merck & Co. LG has received a grant from the Bristol-Myers Squibb IION Foundation and has served on scientific advisory boards for AbbVie, AstraZeneca, Genentech/Roche, Merck, and Pfizer. APan and SIJ declare no competing interests.

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Research in context

Evidence before this study

We searched PubMed on Sept 4, 2016, using the following terms: “PD-1 OR PD-L1 OR MK-3475 OR pembrolizumab OR lambrolizumab OR Keytruda OR nivolumab OR BMS-936558 OR Opdivo OR atezolizumab OR MPDL3280A OR Tecentriq OR durvalumab OR MEDI4736 OR avelumab” AND “platinum-doublet chemotherapy OR triple chemotherapy OR triple therapy OR maintenance therapy OR carboplatin and pemetrexed OR cisplatin AND pemetrexed” AND “advanced non–small-cell lung cancer OR NSCLC”. The search was not limited by date, but was limited to articles and abstracts published in English only. We also searched the abstracts for the 2015 and 2016 American Society of Clinical Oncology Annual Meetings, the 2015 European Cancer Congress, and the 2015 World Conference for Lung Cancer using the same search terms. Similar to the phase 1 cohorts of KEYNOTE-021, these two studies suggested that addition of anti-PD-1 or anti-PD-L1 therapy to platinum-doublet chemotherapy had a manageable safety profile and promising antitumour activity. A thorough review of the literature showed that most large, randomised, controlled clinical studies did not show superior efficacy or a favourable benefit-risk profile for the addition of a third agent to platinum-doublet chemotherapy in the first-line advanced non-small-cell lung cancer setting. One notable exception is the addition of bevacizumab to platinum-doublet chemotherapy, which showed superior efficacy to platinum-doublet chemotherapy alone and a manageable safety profile in randomised, controlled clinical studies.

Added value of this study

Results of this cohort of KEYNOTE-021 show that addition of pembrolizumab to carboplatin and pemetrexed improves efficacy and has a favourable benefit-to-risk profile in patients with chemotherapy-naive, advanced non-squamous NSCLC. Not only do these data represent, to the best of our knowledge, the first published report of a randomised, controlled clinical trial in NSCLC to prospectively show a benefit of addition of a PD-1 pathway inhibitor to chemotherapy, they are also among the only randomised data to show a benefit of adding a third agent to platinum-doublet chemotherapy.

Implications of all the available evidence

Our data suggest that the addition of pembrolizumab to platinum-doublet chemotherapy is an effective treatment option with a manageable, predictable safety profile for patients with chemotherapy-naive, advanced, non-squamous NSCLC. The efficacy and safety of addition of pembrolizumab to platinum-doublet chemotherapy as first-line therapy for advanced NSCLC is being further explored in two ongoing international, randomised, double-blind, phase 3 studies: the KEYNOTE-189 study of platinum and pemetrexed with or without pembrolizumab in patients with non-squamous non–small-cell lung cancer () and the KEYNOTE-407 study of carboplatin and paclitaxel or nab-paclitaxel with or without pembrolizumab in patients with squamous NSCLC ().

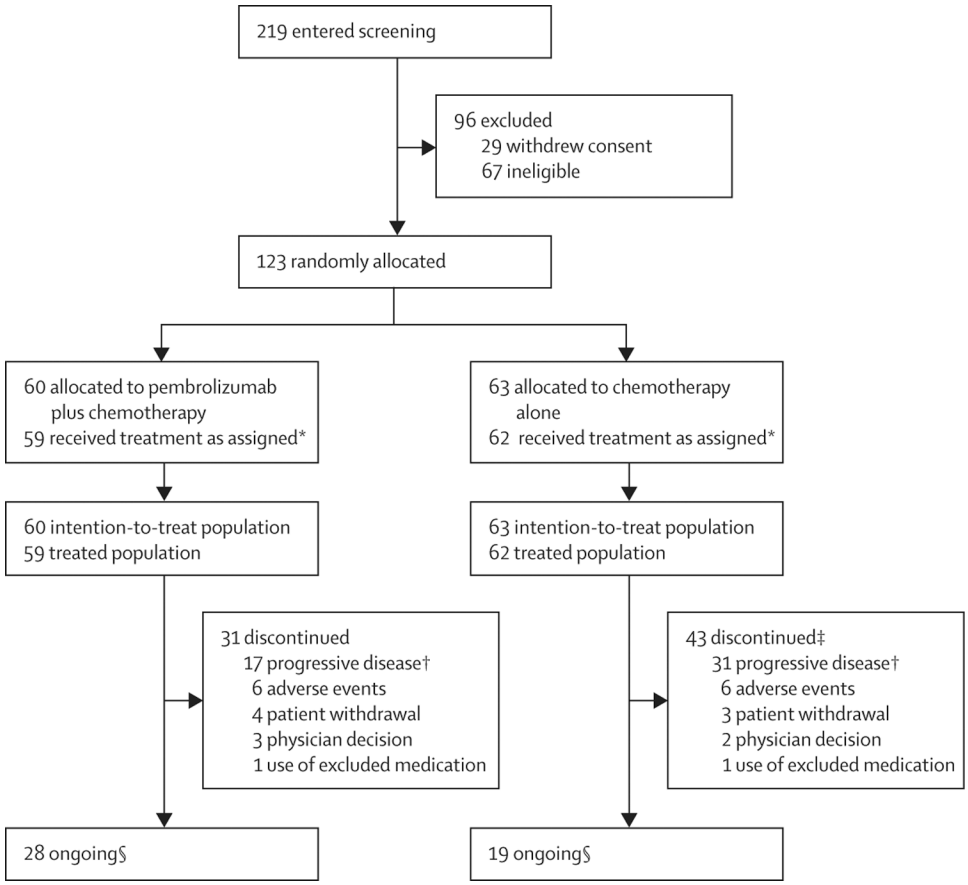

Figure 1: Trial profile

*One patient allocated to pembrolizumab plus chemotherapy experienced deterioration in Eastern Cooperative Oncology Group performance status to a score of 2 after screening but before receiving the first dose of treatment. One patient allocated to chemotherapy alone withdrew consent before receiving the first dose of study treatment. †Includes clinical disease progression. ‡Includes 20 patients who crossed over to receive pembrolizumab monotherapy as part of the study. §Patients without a completed study medication discontinuation form.

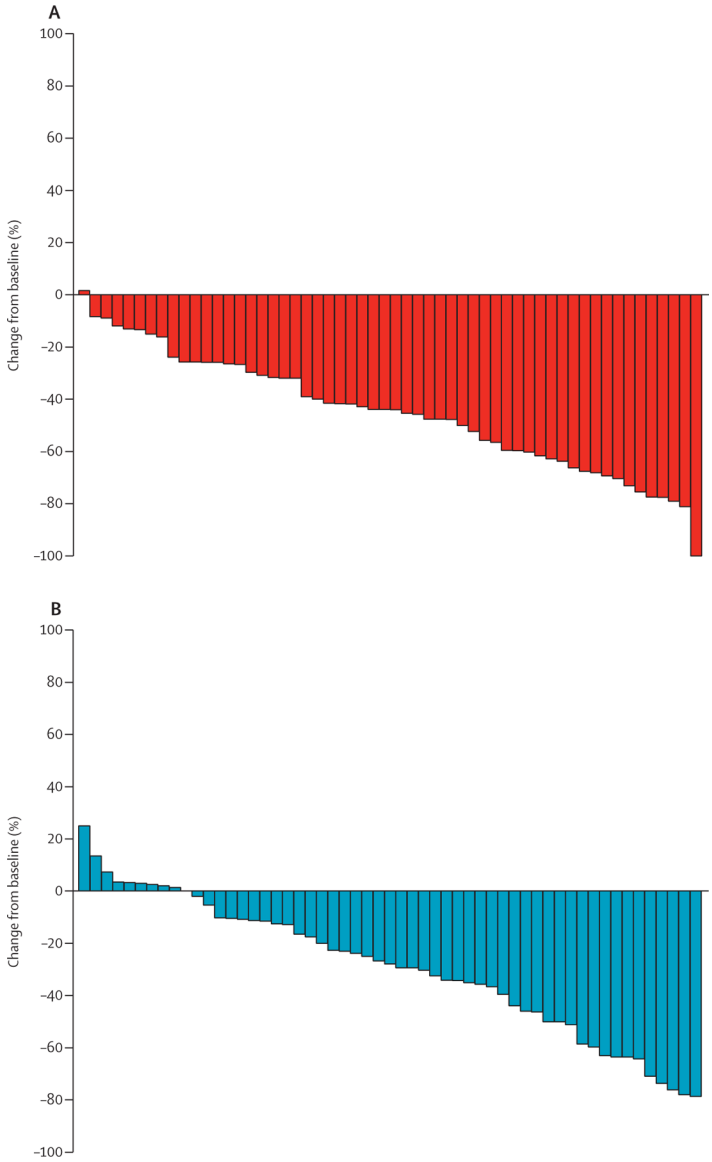

Figure 2: Best percentage change from baseline in tumour size in the pembrolizumab plus chemotherapy group (n=56; A) and the chemotherapy alone group (n=55; B)

Tumour size was defined as the sum of the longest diameters of target lesions. Evaluable patients were those who had both measurable disease per Response Evaluation Criteria In Solid Tumors version 1.1 by masked, independent central radiology review at baseline and at least one post-baseline radiological assessment.

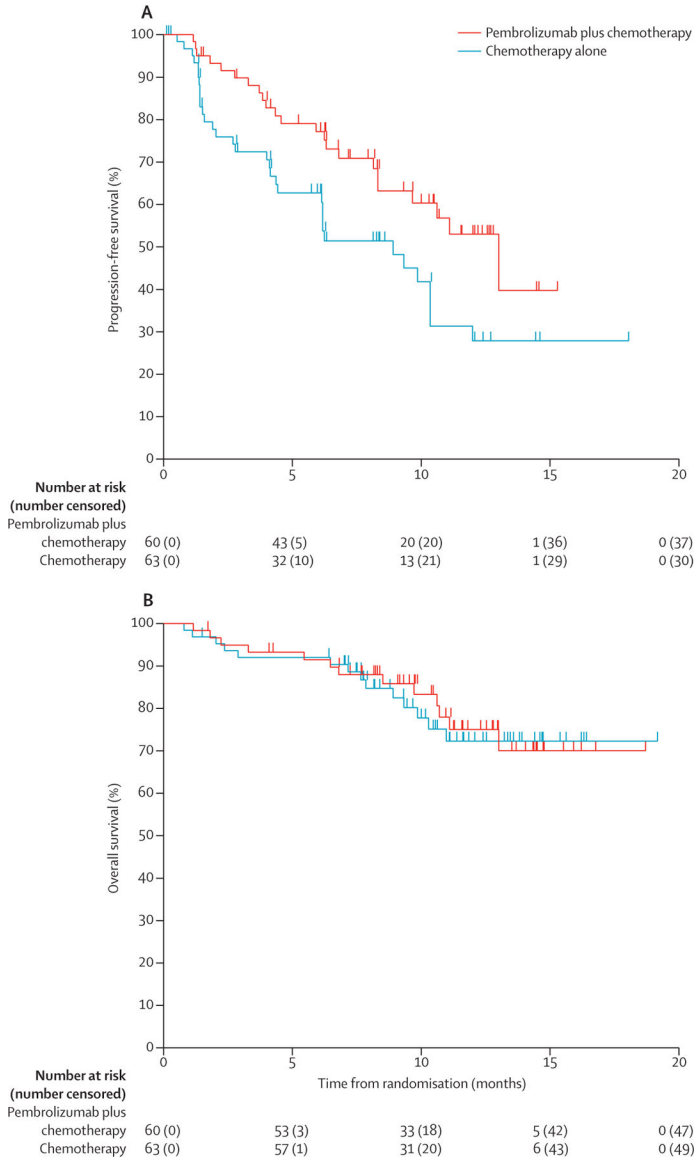

Figure 3: Kaplan-Meier estimates of progression-free survival (A) and overall survival (B)
Progression-free survival assessed per Response Evaluation Criteria In Solid Tumors version 1.1 by masked, independent central radiology review in the intention-to-treat population.

Table 1:

Baseline demographics and disease characteristics in the intention-to-treat population

	Pembrolizumab plus chemotherapy (N=60)	Chemotherapy (N=63)
Age, years	62·5 (54–70)	63·2 (58–70)
Sex		
Male	22 (37%)	26 (41%)
Female	38 (63%)	37 (59%)
Ethnic origin		
White	49 (82%)	58 (92%)
Asian	5 (8%)	5 (8%)
Black or African American	4 (7%)	0
Other*	2 (3%)	0
ECOG performance status†		
0	24 (40%)	29 (46%)
1	35 (58%)	34 (54%)
Tumour histology		
Adenocarcinoma	58 (97%)	55 (87%)
NSCLC not otherwise specified	2 (3%)	7 (11%)
Large cell carcinoma	0	1 (2%)
Disease stage		
IIIA	0	1 (2%)
IIIB	1 (2%)	2 (3%)
IV	59 (98%)	60 (95%)
Smoking status		
Current or former smoker	45 (75%)	54 (86%)
Never smoker	15 (25%)	9 (14%)
Stable brain metastases	9 (15%)	6 (10%)
PD-L1 TPS		
<1%	21 (35%)	23 (37%)
1–49%	19 (32%)	23 (37%)
≥50%	20 (33)	17 (27%)
Previous systemic (neo)adjuvant therapy	4 (7%)	5 (8%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. NSCLC=non-small-cell lung cancer. TPS=tumour proportion score.

*Other ethnic origins in the pembrolizumab plus chemotherapy group included one patient (2%) who was American Indian or Alaska Native and one patient (2%) who did not define their ethnic origin.

†One patient (2%) in the pembrolizumab plus chemotherapy group had an ECOG performance status of 2; this patient did not receive study treatment.

Table 2:

Responses assessed per RECIST version 1.1 by masked, independent central review in the intention-to-treat population

	Pembrolizumab plus chemotherapy (N=60)	Chemotherapy (N=63)
Objective response		
n (%; 95% CI)	33 (55%; 42–68)	18 (29%; 18–41)
Estimated difference, % (95% CI)	26% (9–42)	..
p value	0·0016	..
Median time to response (IQR), months *	1·5 (1·4–2·8)	2·7 (1·4–2·8)
Median duration of response (IQR), months *†	Not reached (4·2–9·0)	Not reached (3·5–10·4)
Best overall response, n (%)		
Complete response	0	0
Partial response	33 (55%)	18 (29%)
Stable disease	20 (33%)	26 (41%)
Progressive disease	2 (3%)	11 (17%)
Not assessable	5 (8%)	8 (13%)

RECIST=Response Evaluation Criteria in Solid Tumors.

*Assessed in patients who had a best overall response of complete or partial response (n=33 in the pembrolizumab plus chemotherapy group and n=18 in the chemotherapy group).

†Median duration of response calculated with the Kaplan-Meier method for censored data.

Table 3:

Adverse events in the as-treated population

	Pembrolizumab plus chemotherapy (N=59)				Chemotherapy (N=62)			
	Grade 1–2	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 5**
Related to treatment *								
Any	32 (54%)	18 (31%)	4 (7%)	1 (2%)	40 (65%)	12 (19%)	2 (3%)	2 (3%)
Serious	2 (3%)	10 (17%)	3 (5%)	1 (2%)	1 (2%)	2 (3%)	1 (2%)	2 (3%)
Led to discontinuation	1 (2%)	4 (7%)	0	1 (2%)	5 (8%)	1 (2%)	0	2 (3%)
Led to death	0	0	0	1 (2%)	0	0	0	2 (3%)
Occurring in ≥10% of patients in either group or of grade 3, 4, or 5 severity †								
Fatigue	36 (61%)	2 (3%)	0	0	25 (40%)	0	0	0
Nausea	33 (56%)	1 (2%)	0	0	27 (44%)	0	0	0
Anaemia	12 (20%)	7 (12%)	0	0	24 (39%)	9 (15%)	0	0
Vomiting	15 (25%)	1 (2%)	0	0	11 (18%)	0	0	0
Rash	15 (25%)	1 (2%)	0	0	9 (15%)	0	0	0
Decreased appetite	11 (19%)	0	0	0	11 (18%)	0	0	0
Diarrhoea	12 (20%)	0	0	0	6 (10%)	1 (2%)	0	0
Increased aspartate aminotransferase	10 (17%)	1 (2%)	0	0	6 (10%)	1 (2%)	0	0
Decreased neutrophil count	7 (12%)	2 (3%)	1 (2%)	0	6 (10%)	2 (3%)	0	0
Increased alanine aminotransferase	9 (15%)	1 (2%)	0	0	6 (10%)	1 (2%)	0	0
Constipation	11 (19%)	0	0	0	6 (10%)	0	0	0
Dysgeusia	10 (17%)	0	0	0	6 (10%)	0	0	0
Increased lacrimation	7 (12%)	0	0	0	6 (10%)	0	0	0
Alopecia	8 (14%)	0	0	0	2 (3%)	0	0	0
Increased blood creatinine	6 (10%)	0	0	0	4 (6%)	0	0	0
Dizziness	6 (10%)	0	0	0	4 (6%)	0	0	0
Neutropenia	3 (5%)	2 (3%)	0	0	4 (6%)	1 (2%)	0	0
Decreased white blood cell count	4 (7%)	1 (2%)	0	0	4 (6%)	1 (2%)	0	0
Peripheral oedema	7 (12%)	0	0	0	2 (3%)	0	0	0
Decreased platelet count	1 (2%)	0	1 (2%)	0	6 (10%)	0	1 (2%)	0
Pruritus	7 (12%)	0	0	0	2 (3%)	0	0	0

	Pembrolizumab plus chemotherapy (N=59)				Chemotherapy (N=62)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Hypokalaemia	5 (8%)	1 (2%)	0	0	2 (3%)	0	0	0
Decreased lymphocyte count	3 (5%)	2 (3%)	0	0	2 (3%)	1 (2%)	0	0
Thrombocytopenia	1 (2%)	1 (2%)	1 (2%)	0	2 (3%)	0	2 (3%)	0
Stomatitis	3 (5%)	0	0	0	2 (3%)	1 (2%)	0	0
Dehydration	1 (2%)	1 (2%)	0	0	2 (3%)	1 (2%)	0	0
Acute kidney injury	0	2 (3%)	0	0	1 (2%)	0	0	0
Hypocalcaemia	2 (3%)	1 (2%)	0	0	0	0	0	0
Leukopenia	0	1 (2%)	0	0	2 (3%)	0	0	0
Sepsis	0	0	1 (2%)	1 (2%)	0	0	0	1 (2%)
Pancytopenia	0	0	0	0	0	1 (2%)	0	1 (2%)
Cellulitis	1 (2%)	1 (2%)	0	0	0	0	0	0
Anaphylactic reaction	0	0	1 (2%)	0	0	0	0	0
Febrile neutropenia	0	1 (2%)	0	0	0	0	0	0
Myocardial infarction	0	1 (2%)	0	0	0	0	0	0
Pneumonia	0	1 (2%)	0	0	0	0	0	0
Rash macular	0	0	0	0	0	1 (2%)	0	0
Increased transaminases	0	1 (2%)	0	0	0	0	0	0
Of interest based on a presumed immunological mechanism of action[†‡]								
Any	11 (19%)	1 (2%)	1 (2%)	0	6 (10%)	1 (2%)	0	0
Hypothyroidism	9 (15%)	0	0	0	3 (5%)	0	0	0
Hyperthyroidism	5 (8%)	0	0	0	1 (2%)	0	0	0
Pneumonitis	2 (3%)	1 (2%)	0	0	0	0	0	0
Infusion reactions	1 (2%)	0	1 (2%)	0	2 (3%)	0	0	0
Severe skin reactions	0	1 (2%)	0	0	0	1 (2%)	0	0

Data are presented as n (%).

[*] As attributed by the investigator. Events are listed in order of descending frequency in the pembrolizumab plus chemotherapy group.

[†] Listed in order of descending frequency in the total population.

[‡] Events include related terms, are provided regardless of attribution to study treatment by the investigator, and are listed in order of descending frequency in the pembrolizumab group.