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Pembrolizumab and platinum-based chemotherapy as first-line therapy for advanced non–small-cell lung cancer: Phase 1 cohorts from the KEYNOTE-021 study☆

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2018.08.019.

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Abstract

Objectives: Platinum-based chemotherapy for advanced non–small-cell lung cancer (NSCLC) has modest benefit overall, but has the potential to amplify immune responses. In cohorts A-C of the multicohort phase 1/2 study KEYNOTE-021 (Clinicaltrials.gov,), we evaluated combinations of platinum-doublet chemotherapy with the anti–programmed death 1 monocloncal antibody pembrolizumab.

Materials and methods: Patients with previously untreated, advanced NSCLC without *EGFR*/*ALK* aberrations were randomized to pembrolizumab 2 or 10 mg/kg Q3W plus carboplatin area under the serum concentration-time curve (AUC) 6 mg/mL/min plus paclitaxel 200 mg/m^2 (cohort A, any histology), carboplatin AUC 6 mg/mL/min plus paclitaxel 200 mg/m^2 plus bevacizumab 15 mg/kg (cohort B, non-squamous), or carboplatin AUC 5 mg/mL/min plus pemetrexed 500 mg/m^2 (cohort C, non-squamous) for 4 cycles followed by maintenance pembrolizumab (cohort A), pembrolizumab plus bevacizumab (cohort B), or pembrolizumab plus pemetrexed (cohort C). Response was assessed by blinded independent central review.

Results: Overall, 74 patients were randomized; median follow-up was 21.4, 16.4, and 17.4 months in cohorts A, B, and C, respectively. No dose-limiting toxicities occurred in any cohort at either pembrolizumab dose. Most frequent treatment-related adverse events (AEs) were alopecia, fatigue, and nausea. Treatment-related grade 3/4 AEs occurred in 40%, 42%, and 46% of patients in cohorts A, B, and C, respectively; AEs with possible immune etiology occurred in 24%, 50%, and 38% of patients, respectively. Objective response rates were 48%, 56%, and 75% in cohorts A, B, and C, respectively.

Conclusion: Pembrolizumab in combination with carboplatin-paclitaxel and with pemetrexed-carboplatin yielded encouraging antitumor activity and toxicity consistent with known toxicities of platinum-based chemotherapy or pembrolizumab monotherapy.

Keywords

Carcinoma; Non–small-cell lung; Pembrolizumab; Drug therapy; Combination; Antineoplastic agents; Bevacizumab

1. Introduction

Standard-of-care first-line therapy for advanced non–small-cell lung cancer (NSCLC) without sensitizing *EGFR* mutations or *ALK* translocations has historically been platinum-doublet chemotherapy with or without maintenance therapy [1]. Adding bevacizumab may improve outcomes in eligible patients with non-squamous histology albeit with added toxicity [1–4]; otherwise there has been limited evidence that addition of a third agent provides clinical benefit.

Immunotherapy targeting the programmed death 1 (PD-1) pathway has recently emerged as an effective treatment strategy for patients with advanced NSCLC [5]. Pembrolizumab, a monoclonal anti–PD-1 antibody, has demonstrated efficacy as monotherapy in patients with PD-L1–expressing NSCLC in first-line and second-line settings [6,7]. In KEYNOTE-024, first-line pembrolizumab 200 mg every 3 weeks (Q3W) significantly improved progression-free survival (PFS) and overall survival (OS) compared with investigator's choice of platinum-based chemotherapy in patients with advanced NSCLC with PD-L1 tumor proportion score (TPS) ≥50% and without *EGFR*/*ALK* aberrations [7]. In the phase 2/3 KEYNOTE-010 study, pembrolizumab, 2 or 10 mg/kg Q3W, significantly improved OS compared with docetaxel 75 mg/m^2 Q3W in patients with previously treated advanced NSCLC with PD-L1 TPS ≥1% (hazard ratio [HR], 0.71 and 0.61, respectively) [6].

Recent evidence indicates that, in addition to its cytotoxic effects, platinum-based chemotherapy mediates immunologic effects, including reducing the number and activity of immune suppressor cells, enhancing antigen presentation, and enhancing T-cell cytotoxicity [8,9]. This evidence suggests that combining anti-PD-1 therapy with chemotherapy has the potential for synergistic antitumor activity.

KEYNOTE-021 () is a multicohort, phase 1/2 study of pembrolizumab combination therapy in patients with advanced NSCLC. We describe results from 3 cohorts from the phase 1b part of the study that evaluated the safety and antitumor activity of pembrolizumab 2 or 10 mg/kg Q3W with carboplatin-paclitaxel in patients with any NSCLC histology, carboplatin-paclitaxel-bevacizumab in patients with non-squamous NSCLC, or pemetrexed-carboplatin in patients with non-squamous NSCLC. The primary objective was to identify a recommended dose for evaluation in phase 2. Positive results from the phase 2 cohort G of KEYNOTE-021 comparing the efficacy and safety of pembrolizumab 200 mg Q3W plus carboplatin-pemetrexed with carboplatin-pemetrexed alone in non-squamous NSCLC were previously published [10].

2. Methods

2.1. Study population

Patients diagnosed with NSCLC without targetable *EGFR* mutations/*ALK* translocations were eligible if they were ≥18 years of age and had histologically/cytologically confirmed stage IIIB/IV disease (cohort A, any histology; cohorts B and C, non-squamous histology); no prior systemic therapy for advanced NSCLC; ≥1 measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 [11] by investigator assessment; Eastern Cooperative Oncology Group (ECOG) performance status 0/1; life expectancy ≥3 months; and adequate organ function. Patients were excluded if they had received > 30 Gy of radiation to the lungs during the previous 6 months, had active central nervous system metastases (stable, treated metastases were permitted), autoimmune disease requiring systemic treatment (disease-modifying agents/corticosteroids/other immunosuppressive drugs) within the previous 2 years, or active interstitial lung disease/history of pneumonitis requiring management with oral-intravenous glucocorticoids. Patients were required to provide a tumor tissue sample adequate for evaluation of PD-L1 status before being considered eligible for enrollment.

Study procedures (current protocol number: 021–03; available via the *Lung Cancer* website) were approved by institutional review boards/ethics committees at each participating institution. Good Clinical Practice guidelines, Declaration of Helsinki ethical standards, and all local and national regulations were followed. All patients provided written informed consent prior to participation.

2.2. Study design

Patients from 11 healthcare institutions in the United States and 1 in Taiwan were assigned by investigators to one of three chemotherapy regimens and then randomly assigned (1:1) to either pembrolizumab 2 or 10 mg/kg Q3W administered intravenously over 30 min using an interactive voice response system. Those in cohort A (any histology) received carboplatin area under the serum concentration-time curve (AUC) 6 mg/mL/min and paclitaxel 200 or 175 mg/m^2 Q3W; those in cohort B (non-squamous histology) received carboplatin AUC 6 mg/mL/min, paclitaxel 200 or 175 mg/m^2, and bevacizumab 15 mg/kg Q3W; and those in cohort C (non-squamous histology) received carboplatin AUC 5 mg/mL/min and pemetrexed 500 mg/m^2 Q3W with appropriate vitamin supplementation. All study treatments were administered on day 1 of each cycle; pembrolizumab was administered first, followed by chemotherapy. Treatment continued every 3 weeks for four cycles, followed by 2 years of maintenance pembrolizumab and optional bevacizumab (cohort B) or pemetrexed (cohort C) at the doses described above, or until disease progression, unacceptable toxicity, or withdrawal of consent.

The primary objective was determination of the recommended dose for investigation in the phase 2 portion of the study. In each cohort, 24 patients were to be randomized to either pembrolizumab dose (12 per dose). If ≤2 of 12 patients at the pembrolizumab 10-mg/kg dose experienced a dose-limiting toxicity (DLT; defined below), this dose level was considered acceptable and the maximum tolerated dose. If the pembrolizumab 10-mg/kg

dose was considered unacceptable, the 2-mg/kg dose would be considered acceptable if ≤2 of 12 patients at that dose experienced a DLT. DLTs were defined as treatment-related adverse events (AEs) occurring during the first treatment cycle and meeting ≥1 of the following criteria: any grade 4 nonhematologic toxicity, grade 4 hematologic toxicity lasting ≥7 days, grade 3 nonhematologic nonlaboratory toxicity lasting > 3 days despite best supportive care, grade 3/4 nonhematologic laboratory toxicity lasting > 1 week or requiring medical intervention or hospitalization, grade 3/4 febrile neutropenia, thrombocytopenia < 25,000/mm^3 (if associated with a life-threatening bleeding event or bleeding event requiring platelet transfusion), any toxicity delaying treatment cycle 2 by > 2 weeks, or grade 5 toxicity.

Secondary objectives included evaluation of antitumor activity (objective response rate; ORR) per RECIST version 1.1, PFS, OS, and the correlation between PD-L1 expression levels and antitumor activity of pembrolizumab.

2.3. Assessments

Adverse events occurring during the study and up to 30 days after the last dose of study treatment (90 days for serious AEs) were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Radiographic imaging by computed tomography/magnetic resonance imaging was conducted at baseline, every 6 weeks through the first 18 weeks, every 9 weeks for the remainder of year 1, and every 12 weeks during year 2 of treatment. Response was assessed per RECIST, version 1.1. Treatment decisions were based on assessment by investigators; efficacy analyses were based on assessment by blinded independent central review. Patients with progressive disease (PD) who were clinically stable could remain on therapy until confirmation of PD ≥4 weeks later. PD-L1 expression was assessed in formalin-fixed tumor tissue obtained from core needle biopsy, excisional biopsy, or resected tissue collected at the time of diagnosis of metastatic disease by a central laboratory using the commercially available PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA, USA) prior to initiation of treatment. Treating physicians were masked to the outcome of PD-L1 assessment.

2.4. Statistical analysis

Safety analyses included all patients who received ≥1 dose of study treatment. Those who completed cycle 1 of study treatment or discontinued due to a treatment-related AE were included in the DLT-evaluable population. Efficacy analyses were conducted in the intent-to-treat population, which comprised all randomized patients. Duration of follow up was defined as time from randomization to data cutoff or death. ORR and PFS were based on RECIST version 1.1 by blinded independent central review. The 95% CI for ORR was estimated using the Clopper-Pearson method. Patients without a response assessment were considered nonresponders. Duration of response was defined as time from documented objective response until disease progression/death, whichever occurred earlier; PFS as time from randomization to disease progression/death, whichever occurred earlier; and OS as time from randomization to death. Patients without PFS events were censored on the date of last disease assessment or the last disease assessment before initiation of new anticancer

treatment if new treatment was initiated before PD occurred. Those with OS events were censored on the date they were last known to be alive or at data cutoff, if a survival update was available after that date. PFS and OS were estimated using the Kaplan-Meier method.

3. Results

3.1. Patients

Between March 4, 2014, and August 7, 2015, 74 patients were enrolled and randomized. Twenty-five patients were enrolled in cohort A, 25 in cohort B, and 24 in cohort C. At the time of data cutoff (November 7, 2016), 1 patient in cohort A and 5 in cohort B were still receiving study treatment (Fig. 1). Median (range) follow-up was 21.4 (2.0–31.9) months in cohort A, 16.4 (0.9–27.5) months in cohort B, and 17.4 (4.6–29.2) months in cohort C. Most patients had stage IV disease and were current or former smokers. Baseline demographics are shown by cohort in Table 1 and by cohort and dose group in Supplemental Table 1.

Across both doses, median number of pembrolizumab doses administered for cohorts A, B, and C was 10 (range, 2–35), 11 (range, 1–33), and 12.5 (range, 1–35), respectively. Median (range) number of pembrolizumab 10 mg/kg doses was 6 (2–35), 9 (1–33), and 14 (1–35), respectively. Median (range) number of pembrolizumab 2 mg/kg doses was 18 (2–35), 16 (2–31), and 11 (3–33), respectively. Eleven patients (46%) in cohort B received maintenance bevacizumab; 14 patients (58%) in cohort C received maintenance pemetrexed. Five patients in cohort A and 2 in cohort C completed 2 years of therapy.

3.2. Dose-limiting toxicities

No study-defined DLTs occurred in any cohort at either pembrolizumab dose. Consequently, the incidence of DLTs was below the prespecified threshold for unacceptability and the combination of either pembrolizumab 10 mg/kg Q3W or pembrolizumab 2 mg/kg Q3W with the evaluated platinum-based chemotherapy regimens was considered acceptable.

3.3. Safety

Consistent with the finding that both pembrolizumab dose levels yielded acceptable safety profiles across all 3 cohorts, there was no evidence of a relationship between pembrolizumab dose and incidence of AEs (Supplemental Tables 2–4).

After pooling doses, treatment-related AEs occurred in 25 patients (100%) in cohort A, in 23 patients (96%) in cohort B, and in 24 patients (100%) in cohort C. The most frequent treatment-related AEs were alopecia (cohort A, 48%; cohort B, 67%; cohort C, 8%), fatigue (44%; 50%; 46%), and nausea (32%, 38%, 29%; Table 2). Most events were of mild-to-moderate severity. Treatment-related grade 3/4 AEs occurred in 10 (40%), 10 (42%), and 11 (46%) patients in cohorts A, B, and C, respectively (Table 2). The most frequent treatment-related grade 3/4 AEs were anemia, febrile neutropenia, neutropenia, and fatigue in cohort A (each n = 2; 8%); febrile neutropenia, neutropenia, white blood cell count decreased, and drug hypersensitivity in cohort B (each n = 2; 8%); and elevated aspartate aminotransferase (n = 3; 13%), elevated alanine aminotransferase, and anemia (both n = 2; 8%) in cohort C. No other grade 3/4 treatment-related AEs occurred in more than 1 patient. No treatment-

related fatal AEs occurred. Treatment-related AEs resulted in discontinuation of study treatment in 1 patient in cohort A (rash), 5 in cohort B (neutropenia, autoimmune colitis, diarrhea, drug hypersensitivity, and pneumonitis [all n = 1]), and 6 in cohort C (rash [n = 2], increased blood creatinine, colitis, acute pyelonephritis, and renal disorder [all n = 1]).

Adverse events with possible immune etiology (regardless of attribution to study treatment or immune relatedness by the investigator) occurred in 6 (24%), 12 (50%), and 9 (38%) patients in cohorts A, B, and C, respectively (Table 2). Immune-mediated AEs and infusion reactions occurring in ≥2 patients were colitis, hypothyroidism, and infusion reactions in cohort A (each n = 2); hypothyroidism (n = 5) and infusion reactions (n = 4) in cohort B; and hypothyroidism (n = 4) and colitis (n = 3) in cohort C. The only grade 3 immune-mediated AEs and infusion reactions were severe skin reaction (cohort A; n = 1); colitis, pneumonitis, and pancreatitis (cohort B; each n = 1); and colitis and severe skin reaction (cohort C; each n = 1). There were no grade 4/5 immune-mediated AEs and infusion reactions.

3.4. Antitumor activity

ORR was 48% (12/25), 56% (14/25), and 75% (18/24) in cohorts A, B, and C, respectively (Table 3). One patient in each cohort achieved a complete response; all remaining patients achieved partial responses. Sixty-five of 71 evaluable patients had a decrease from baseline in target lesion size (Supplemental Fig. 1). Across all 3 cohorts, response rates were similar across all PD-L1 TPS groups, defined by PD-L1 TPS ≥50%, 1–49%, and < 1% (Table 3).

At the time of this analysis, 20 of 25 (80%), 17 of 25 (68%), and 19 of 24 (79%) patients in cohorts A, B, and C, respectively had disease progression or had died. Median PFS was 10.3 months (95% CI, 6.1–14.6 months), 7.1 months (95% CI, 4.2–14.3), and 10.2 months (95% CI, 6.5–13.9), respectively (Fig. 2). Six-month PFS rates were 72.0%, 65.8%, and 78.4%, respectively.

Thirteen of 25 (52%), 12 of 25 (48%), and 16 of 24 (67%) patients in cohorts A, B, and C had died. Median OS was 21.4 (95% CI, 10.5–not reached), 16.7 (95% CI, 8.5–not reached), and 16.7 (95% CI, 13.9–29.2) months, respectively (Fig. 2); 6-month OS rates were 87.7%, 79.2%, and 87.5%.

4. Discussion

In this phase 1 study, pembrolizumab plus either carboplatin-paclitaxel or pemetrexed-carboplatin proved tolerable and yielded encouraging antitumor activity in patients with previously untreated advanced NSCLC. The combination of pembrolizumab with carboplatinpaclitaxel-bevacizumab was associated with increased rates of particular AEs compared with the other regimens evaluated. No prespecified DLTs were observed at either dose level (pembrolizumab 2 and 10 mg/kg Q3W) in any of the cohorts. Because findings from a phase 1 trial of pembrolizumab in patients with advanced head and neck squamous cell carcinoma provided evidence that a fixed pembrolizumab dose of 200 mg Q3W was tolerable and provided comparable antitumor activity to weight-based dosing (2 mg/kg Q3W, 10 mg/kg Q3W, and 10 mg/kg Q2W) [12], and since no DLTs were observed in this

study, a pembrolizumab dose of 200 mg Q3W was selected for further evaluation in phase 2 and later studies. This decision is further supported by a study that compared weight-based versus fixed dosing across multiple pembrolizumab trials [13]. The pharmacokinetics of pembrolizumab with 200 mg Q3W administration were similar to those with 2 mg/kg Q3W administration and fell within the range observed with all previously tested regimens [13].

Toxicity with the combination of pembrolizumab and either carboplatin-paclitaxel or pemetrexed-carboplatin appeared consistent with known toxicities of platinum-based chemotherapy or pembrolizumab monotherapy. The most frequently occurring treatment-related AEs were alopecia, fatigue, and nausea. However, most events were mild-to-moderate in severity, few patients discontinued therapy due to treatment-related AEs, and there were no fatal AEs considered related to treatment by investigators. There was no evidence of a relationship between dose and toxicity. Incidence of immune-mediated AEs and infusion reactions in cohorts A (24%) and C (38%) was consistent with that reported with pembrolizumab monotherapy in the KEYNOTE-010 study (20%) in patients with previously treated NSCLC [6] and in the KEYNOTE-024 study in patients with treatment-naive NSCLC (29%) [7]. Few events rose to grade 3 severity, and there were no grade 4/5 immune-mediated AEs and infusion reactions.

Combining pembrolizumab with carboplatin-paclitaxel-bevacizumab was more toxic when compared with the other regimens evaluated, leading to higher rates of alopecia, fatigue, nausea, neutrophil count decreased, white blood cell count decreased, hypothyroidism, constipation, stomatitis, and epistaxis. Bevacizumab has a well-established toxicity profile and has been associated with increased toxicity when combined with carboplatin-paclitaxel in patients with previously untreated non-squamous NSCLC, in particular toxicities associated with its anti–vascular endothelial growth factor mechanism of action [2]. A recent meta-analysis also suggested that bevacizumab treatment may increase the risk of high-grade neutropenia and febrile neutropenia [14]. Thus, the finding of increased toxicity in this cohort was not unanticipated. Although the rate of immune-mediated AEs and infusion reactions in this cohort was higher than the other cohorts, much of this increase appeared to be attributable to the incidence of hypothyroidism (21%) and infusion reactions (17%); both events have previously been reported in patients receiving bevacizumab [15,16] and may have increased in incidence due to administration in combination with pembrolizumab.

Although the population size in this phase 1 study was small, the efficacy outcomes were encouraging. ORR across all 3 cohorts appeared to be greater than those observed with these chemotherapy combinations alone [2,17,18]. Objective responses were noted in all subsets, independent of PD-L1 status, although there were a limited number of patients in each PD-L1 group. Median PFS and OS appeared favorable compared with previous studies that have evaluated the respective chemotherapy backbones [2,17,18]. Patients treated with pembrolizumab plus carboplatin-paclitaxel-bevacizumab appeared to have shorter PFS and OS compared with those treated with pembrolizumab plus carboplatin-paclitaxel or pembrolizumab plus carboplatin-pemetrexed.

Notwithstanding the small sample size (a limitation of the phase 1 cohorts of this study), pembrolizumab plus carboplatin-paclitaxel and pemetrexed-carboplatin yielded manageable

toxicity profiles and promising antitumor activity in patients with treatment-naive advanced NSCLC. Based on results from cohort C, the efficacy and safety of pembrolizumab and pemetrexed-carboplatin was further explored in a randomized phase 2 cohort (cohort G1) in the KEYNOTE-021 study [10]. Results from cohort G1, which enrolled 123 patients with non-squamous NSCLC, showed ORR (the primary endpoint) to be nearly doubled in the pembrolizumab plus pemetrexed-carboplatin arm (ORR, 55% vs 29%; estimated treatment difference, 26%; 95% CI, 9%–42%; $P = 0.0016$), and the risk of progression or death was reduced by nearly half (PFS HR, 0.53; 95% CI, 0.31–0.91; $P = 0.010$). These results led the United States Food and Drug Administration to grant accelerated approval for this combination [19]. An updated analysis demonstrated ongoing improvements in ORR and PFS and a trend toward improved OS (median OS, NR vs 20.9 months; HR, 0.59; nominal $P = 0.03$ [one-sided nominal $P < 0.025$]) [20]. The randomized, placebo-controlled, phase 3 KEYNOTE-189 study (ClinicalTrials.gov,) further investigated pembrolizumab 200 mg Q3W combined with pemetrexed and either carboplatin or cisplatin, similar to the pemetrexed-carboplatin regimen used in cohort C in this study, in patients with metastatic non-squamous NSCLC. The KEYNOTE-189 study demonstrated significantly improved OS (HR, 0.49; 95% CI, 0.38−0.64; $P < 0.001$), PFS (HR, 0.52; 95% CI, 0.43−0.64; $P < 0.001$), and response rates (47.6% vs 18.9%, $P < 0.001$) with a slight increase in renal dysfunction with pembrolizumab plus pemetrexed-carboplatin/cisplatin versus placebo plus chemotherapy [21]. The randomized, placebo-controlled, phase 3 KEYNOTE-407 study (ClinicalTrials.gov,) further investigated pembrolizumab 200 mg Q3W combined with carboplatin and either paclitaxel or nab-paclitaxel, in metastatic squamous NSCLC, similar to the carboplatin-paclitaxel regimen used in cohort A. The KEYNOTE-407 study showed significantly longer OS (HR, 0.64; 95% CI, 0.49−0.85; $P = 0.0008$) and PFS (HR, 0.56; 95% CI, 0.45−0.70; $P < 0.0001$) with pembrolizumab plus carboplatinpaclitaxel/nab-paclitaxel versus placebo plus chemotherapy [22]. More patients experienced confirmed responses with pembrolizumab versus without (58% vs 35%; $P = 0.0004$). The frequency and severity of AEs were mostly similar between the treatment arms. Pembrolizumab plus chemotherapy was associated with somewhat higher rates of AEs leading to discontinuation, although these were generally low overall. Immune-mediated AEs and infusion reactions were also more frequent with pembrolizumab plus chemotherapy, but were consistent with those observed with pembrolizumab monotherapy [22].

Other anti-PD-(L)1 antibodies have also been shown to improve PFS when used in combination with these chemotherapy regimens. The randomized, phase 3 IMpower131 study, which analyzed a regimen similar to that used in cohort A, showed that atezolizumab with carboplatin and nab-paclitaxel improved median PFS (HR, 0.71; 95% CI, 0.60−0.85; $P = 0.0001$) but not OS (HR, 0.96; 95% CI, 0.78–1.18; $P = 0.6931$) versus carboplatin plus nab-paclitaxel alone in patients with advanced squamous NSCLC [23]. The randomized, phase 3 CheckMate 227 study, which evaluated a regimen similar to that in cohort C, demonstrated that nivolumab with pemetrexed and cisplatin or carboplatin improved PFS (HR, 0.68) versus chemotherapy alone in patients with advanced non-squamous NSCLC with < 1% PD-L1 expression [24]. The randomized, phase 3 IMpower150 study demonstrated that atezolizumab with bevacizumab, carboplatin, and paclitaxel, a regimen similar to that used in cohort B, improved PFS (HR, 0.62; 95% CI, 0.52−0.74; $P < 0.001$) in

patients with metastatic nonsquamous NSCLC and wild-type genotype (no *EGFR* or *ALK* genomic alterations) [25].

Our analysis of cohorts A and C in KEYNOTE-021 strongly suggests that combination therapy with standard platinum-based chemotherapy regimens and pembrolizumab is a feasible treatment strategy in the front-line setting in patients with treatment-naive advanced NSCLC. The efficacy and safety of these combinations are further supported by the randomized, placebo-controlled phase 3 KEYNOTE-189 and KEYNOTE-407 studies, and are now recommended as first-line therapy for patients with advanced non-squamous (pembrolizumab with pemetrexed and carboplatin/cisplatin) or metastatic squamous (pembrolizumab with carboplatin and paclitaxel/nab-paclitaxel) NSCLC [1].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

AUC	area under the serum concentration-time curve
DLT	dose-limiting toxicity
PD-1	programmed death 1
PD-L1	programmed death ligand 1
SLD	sum of longest diameters
TPS	tumor proportion score

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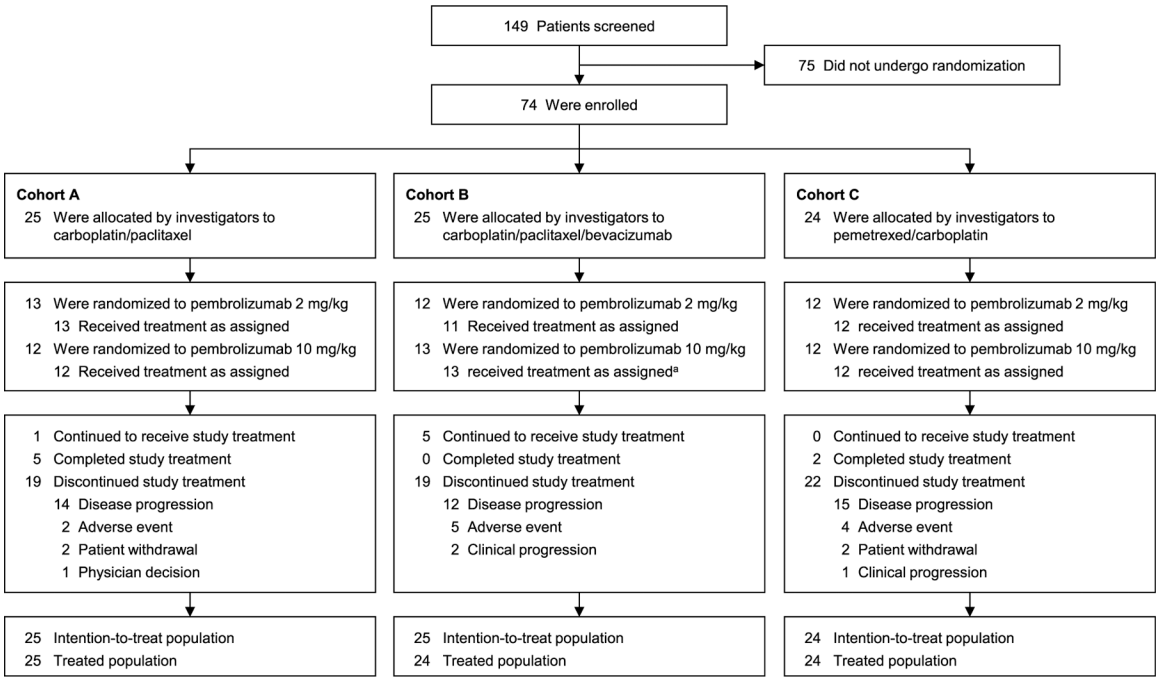

Fig. 1.

Disposition of patients in the study. [a]One patient in cohort B withdrew before receiving study treatment.

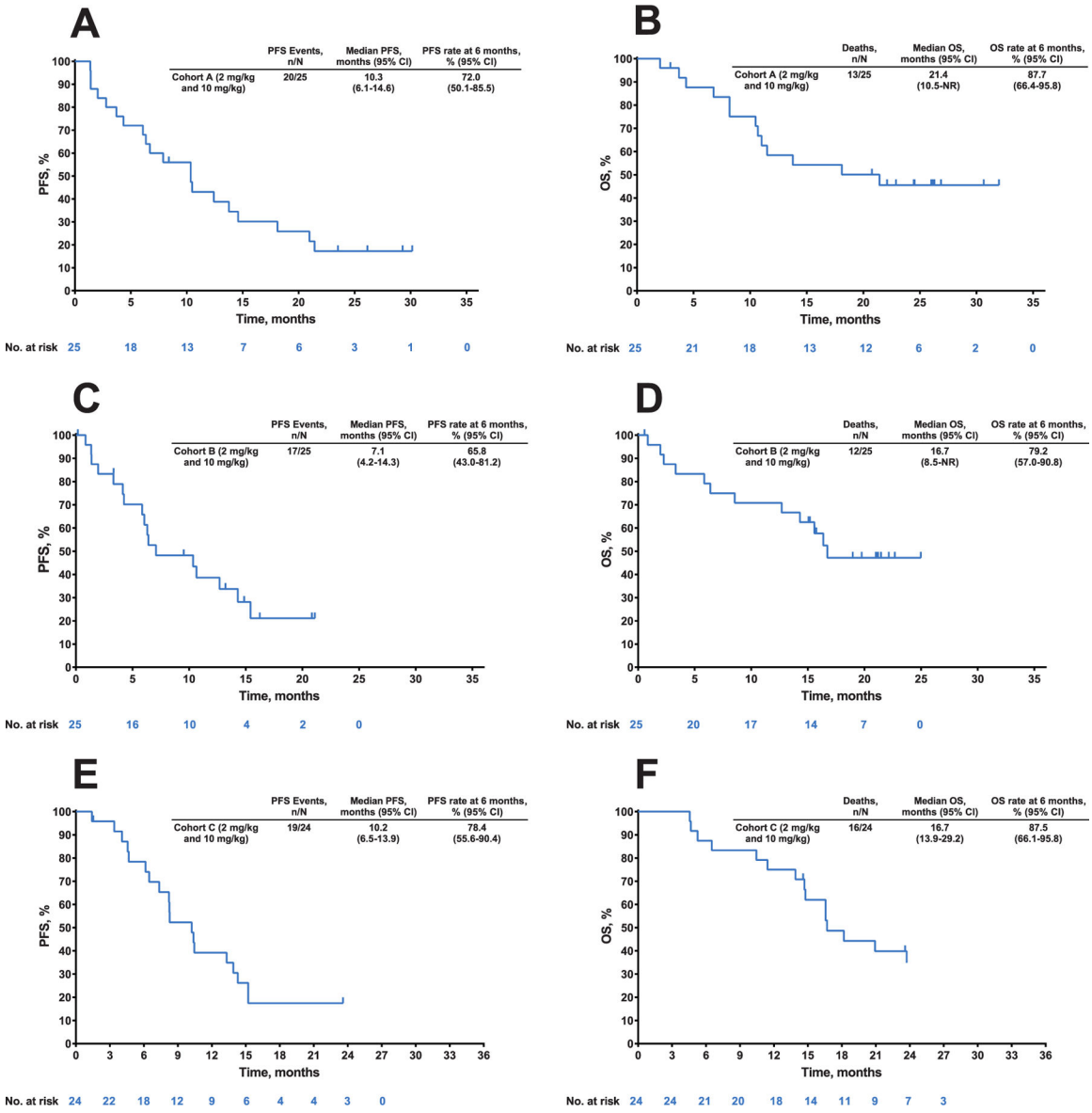

Fig. 2.

Kaplan-Meier analysis of progression-free survival by blinded independent central review and overall survival in patients enrolled the pembrolizumab and carboplatin-paclitaxel cohort (**A**) and (**B**), the pembrolizumab and carboplatin-paclitaxel-bevacizumab cohort (**C**) and (**D**), and the pembrolizumab and carboplatin-pemetrexed cohort (**E**) and (**F**). Outcomes are pooled for the pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W dose groups within each cohort. PFS, progression-free survival. NR, not reached. OS, overall survival.

Table 1

Baseline Demographic and Disease Characteristics.

Characteristic	Cohort A Pembrolizumab 2 or 10 mg/kg Q3W Plus Carboplatin-Paclitaxel N = 25	Cohort B Pembrolizumab 2 or 10 mg/kg Q3W Plus Carboplatin-Paclitaxel-Bevacizumab N = 25	Cohort C Pembrolizumab 2 or 10 mg/Kg Q3W Plus Pemetrexed-Carboplatin N = 24
Age, median (range), years	66 (45–75)	62 (44–74)	59.5 (36–75)
Sex, n (%)			
Male	12 (48)	13 (52)	12 (50)
Female	13 (52)	12 (48)	12 (50)
Ethnic origin			
White	19 (76)	24 (96)	16 (67)
Black or African American	4 (16)	0	8 (33)
Asian	2 (8)	1 (4)	0
ECOG performance status, n (%)			
0	11 (44)	11 (44)	7 (29)
1	14 (56)	14 (56)	17 (71)
Histology, n (%)			
Adenocarcinoma	13 (52)	21 (84)	19 (79)
Squamous	9 (36)	0	0
NSCLC not otherwise specified/other	3 (12)	4 (16)	5 (21)
Disease stage, n (%)			
IIIB	0	1 (4)	1 (4)
IV	25 (100)	24 (96)	23 (96)
Smoking status, n (%)			
Current or former smoker	23 (92)	24 (96)	20 (83)
Never	2 (8)	1 (4)	4 (17)
Brain metastases, n (%)	2 (8)	4 (16)	2 (8)
PD-L1 TPS			
≥50%	9 (36)	8 (32)	8 (33)
1%–49%	6 (24)	12 (48)	8 (33)
<1%	9 (36)	5 (20)	8 (33)
Missing	1 (4)	0	0

Characteristic	Cohort A Pembrolizumab 2 or 10 mg/kg Q3W Plus Carboplatin-Paclitaxel N = 25	Cohort B Pembrolizumab 2 or 10 mg/kg Q3W Plus Carboplatin-Paclitaxel-Bevacizumab N = 25	Cohort C Pembrolizumab 2 or 10 mg/Kg Q3W Plus Pemetrexed-Carboplatin N = 24
Prior systemic (neo)adjuvant therapy, n (%)	1 (4)	1 (4)	1 (4)

NSCLC, non–small-cell lung cancer; PD-L1, programmed death ligand 1; Q3W, every 3 weeks; TPS, tumor proportion score.

Table 2

Summary of Adverse Events.

	Cohort A Pembrolizumab 2 or 10 mg/kg Q3W Plus Carboplatin-Paclitaxel N = 25		**Cohort B Pembrolizumab 2 or 10mg/Kg Q3W plus Carboplatin-Paclitaxel-Bevacizumab N = 24[a]**		**Cohort C Pembrolizumab 2 or 10 mg/Kg Q3W Plus Pemetrexed-Carboplatin N= 24**	
Treatment-related AEs, n (%)						
Any grade	25 (100)		23 (96)		24 (100)	
Grade 3–4	10 (40)		10 (42)		11 (46)	
Leading to discontinuation	1 (4)		5 (21)		6 (25)	
Leading to death[b]	0		0		0	
Treatment-related AEs occurring in ≥15% of patients in any cohort, n (%)	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3[c]
Alopecia	12 (48)	0	16 (67)	0	2 (8)	0
Fatigue	11 (44)	2 (8)	12 (50)	0	11 (46)	0
Nausea	8 (32)	0	9 (38)	0	7 (29)	0
Anemia	7 (28)	2 (8)	5 (21)	0	8 (33)	2 (8)
Peripheral sensory neuropathy	6 (24)	0	8 (33)	0	1 (4)	0
Peripheral neuropathy	6 (24)	0	2 (8)	0	0	0
Arthralgia	6 (24)	0	8 (33)	0	1 (4)	0
Rash	6 (24)	0	6 (25)	0	5 (21)	1 (4)
Dysgeusia	5 (20)	0	5 (21)	0	1 (4)	0
Diarrhea	4 (16)	0	6 (25)	0	6 (25)	1 (4)
Thrombocytopenia	4 (16)	0	3 (13)	1 (4)	0	0
Pain in extremity	4 (16)	0	4 (17)	0	2 (8)	0
Decreased appetite	3 (12)	0	5 (21)	0	4 (17)	1 (4)
Neutrophil count decreased	3 (12)	0	5 (21)	1 (4)	0	0
White blood cell count decreased	3 (12)	1 (4)	4 (17)	2 (8)	1 (4)	0
Hypothyroidism	2 (8)	0	5 (21)	0	2 (8)	0
Constipation	1 (4)	0	9 (38)	0	4 (17)	0
Stomatitis	0	0	4 (17)	0	2 (8)	0
Epistaxis	1 (4)	0	6 (25)	0	1 (4)	0
Aspartate aminotransferase increased	1 (4)	0	0	0	7 (29)	3 (13)

	Cohort A Pembrolizumab 2 or 10 mg/kg Q3W Plus Carboplatin-Paclitaxel N = 25		Cohort B Pembrolizumab 2 or 10mg/Kg Q3W plus Carboplatin-Paclitaxel-Bevacizumab N = 24[a]		Cohort C Pembrolizumab 2 or 10 mg/Kg Q3W Plus Pemetrexed-Carboplatin N= 24	
Alanine aminotransferase increased	0	0	0	0	7 (29)	2 (8)
Maculopapular rash	0	0	2 (8)	0	5 (21)	0
Dry skin	1 (4)	0	2 (8)	0	4 (17)	0
Peripheral edema	2 (8)	0	1 (4)	0	4 (17)	0
Pruritus	1 (4)	0	2 (8)	0	4 (17)	0
Immune-mediated AEs and infusion reactions[d]	Any grade	Grade 3[e]	Any grade	Grade 3[e]	Any grade	Grade 3[e]
Colitis	2 (8)	0	1 (4)	1 (4)	3 (13)	1 (4)
Hypothyroidism	2 (8)	0	5 (21)	0	4 (17)	0
Hyperthyroidism	0	0	1 (4)	0	0	0
Infusion reactions	2 (8)	0	4 (17)	0	1 (4)	0
Pneumonitis	1 (4)	0	1 (4)	1 (4)	0	0
Severe skin reaction	1 (4)	1 (4)	0	0	1 (4)	1 (4)
Pancreatitis	0	0	1 (4)	1 (4)	0	0
Thyroiditis	0	0	1 (4)	0	0	0
Uveitis	0	0	1 (4)	0	0	0
Adrenal insufficiency	0	0	0	0	1 (4)	0

AE, adverse event; Q3W, every 3 weeks.

[a] One patient in cohort B withdrew before receiving therapy and is not included in safety analyses.

[b] No treatment-related fatal AEs occurred. Two patients in cohort B (including one patient with a grade 5 pericardial effusion) and two patients in cohort C had fatal AEs that were not considered treatment-related.

[c] No grade 4 treatment-related adverse events were recorded in cohort C.

[d] Adverse events with a possible immune etiology regardless of attribution to study treatment or immune-relatedness by the investigator.

[e] No grade 4 or 5 immune-mediated events and infusion reactions were recorded.

Table 3

Confirmed Objective Response Rate per RECIST v1.1 by Blinded, Independent Central Review.

	Cohort A Pembrolizumab 2 or 10 mg/kg Q3W Plus Carboplatin-Paclitaxel N = 25		Cohort B Pembrolizumab 2 or 10 mg/Kg Q3W Plus Carboplatin-Paclitaxel-Bevacizumab N = 25		Cohort C Pembrolizumab 2 or 10 mg/Kg Q3W Plus Pemetrexed-Carboplatin N = 24	
Best overall response, n (%)						
Complete response	1 (4)		1 (4)		1 (4)	
Partial response	11 (44)		13 (52)		17 (71)	
Stable disease	9 (36)		5 (20)		5 (21)	
Progressive disease	4 (16)		2 (8)		1 (4)	
Not evaluable[a]	0		4 (16)		0	
Objective response rate, % (95% CI)	48 (28–69)		56 (35–76)		75 (53–90)	
Time to response, median (range), months	2.7 (1.3–4.1)		2.8 (1.3–4.2)		2.4 (1.3–6.2)	
Duration of response, median (range), months	18.3 (4.4–28.6+)		9.9 (2.9–18.2+)		8.3 (2.7–24.2+)	
Objective response rate by PD-L1 status	n/N[b]	ORR, %	n/N	ORR, %	n/N	ORR, %
PD-L1 TPS ≥ 50%	5/9	56	6/8	75	5/8	63
PD-L1 TPS 1–49%	3/6	50	5/12	42	6/8	75
PD-L1 TPS < 1%	3/9	33	3/5	60	7/8	88

+, ongoing response (no progressive disease at last assessment); ORR, objective response rate; PD-L1, programmed death ligand 1; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TPS, tumor proportion score.

[a]Includes patients who were not evaluated in cohort B because they discontinued before the first scheduled imaging due to the following reasons: grade 3 hypersensitivity to paclitaxel (received 1 cycle of study therapy), grade 5 sepsis (never received study therapy), grade 5 pericardial effusion (received 1 cycle of study therapy), and malignant neoplasm progression.

[b]One patient in cohort A did not have a PD-L1 assessment.