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ORIGINAL ARTICLE

Safety and efficacy of quavonlimab, a novel anti-CTLA-4 antibody (MK-1308), in combination with pembrolizumab in first-line advanced non-small-cell lung cancer

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Available online 2 December 2020

Background: Quavonlimab (MK-1308), a novel anti-CTLA-4 antibody, in combination with pembrolizumab was investigated in a phase I study.

Patients and methods: Dose-escalation (DE) phase: patients with advanced/metastatic solid tumors received an initial flat dose of quavonlimab as monotherapy [25 mg (cohort 1), 75 mg (cohort 2), or 200 mg (cohort 3)] followed by four treatments of the same quavonlimab dose plus pembrolizumab every 3 weeks (Q3W). Dose-confirmation phase (DC): patients with stage IIIB/IV non-small-cell lung cancer (NSCLC) received first-line quavonlimab [25 mg Q3W (arm A), 25 mg Q6W (arm B), 75 mg Q6W (arm C), or 75 mg Q3W (arm E)] plus pembrolizumab. Primary objectives were safety and tolerability and establishment of the recommended phase II dose (RP2D) of quavonlimab when used with pembrolizumab. Objective response rate (ORR) was a secondary endpoint. Efficacy based on PD-L1 expression, tumor mutational burden (TMB), and changes in circulating CD4+/CD8+ cells were exploratory endpoints.

Results: Thirty-nine patients were enrolled in DE [$n = 14$ (cohort 1); $n = 17$ (cohort 2); $n = 8$ (cohort 3)] and 134 in DC [$n = 40$ (arm A); $n = 40$ (arm B); $n = 40$ (arm C); $n = 14$ (arm E)]. Maximum-tolerated dose was not reached. Grade 3-5 treatment-related adverse events (AEs; graded according to NCI CTCAE v4.03) occurred in 0%, 23.5%, and 75.0% of patients in DE cohorts 1, 2, and 3, respectively, and 35.0%, 30.0%, 35.0%, and 57.1% of patients in DC arms A, B, C, and E, respectively. Efficacy was observed at all dose levels/schedules in patients with NSCLC. ORRs were 40.0% [95% confidence interval (CI), 24.9-56.7; arm A], 37.5% (95% CI, 22.7-54.2; arm B), 27.5% (95% CI, 14.6-43.9; arm C), and 35.7% (95% CI, 12.8-64.9; arm E). PD-L1 expression and total number of circulating CD4+ cells correlated with ORR.

Conclusions: Quavonlimab 25 mg Q6W plus pembrolizumab demonstrated similar efficacy and a better safety profile among all quavonlimab doses/schedules evaluated; this regimen was the chosen RP2D.

Key words: non-small-cell lung cancer, quavonlimab, MK-1308, CTLA-4, pembrolizumab, immunotherapy

INTRODUCTION

Tumor cells commonly evade host immune surveillance through activation of immune checkpoint pathways.[1,2] Monoclonal antibodies targeting cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed death 1 (PD-1) or its ligand, PD-L1, restore T-cell-mediated anti-tumor immunity and have conferred improved outcomes in

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multiple cancer types.[2] CTLA-4 and PD-1 suppress antitumor immune activity through distinct, non-redundant mechanisms.[1,3,4] Several clinical studies have reported antitumor activity with the combination of a CTLA-4 inhibitor and a PD-1/PD-L1 inhibitor in multiple tumor types, including non-small-cell lung cancer (NSCLC).[5-12]

Quavonlimab (MK-1308) is a novel humanized immunoglobulin G1 monoclonal antibody that binds to CTLA-4 and blocks interaction with its ligands, CD80 and CD86.

We report safety results for dose-escalation (DE) and dose-confirmation (DC) phases of a phase I study of quavonlimab plus pembrolizumab in patients with advanced solid tumors and antitumor activity and biomarker analyses in patients with advanced NSCLC receiving first-line treatment.

PATIENTS AND METHODS

Preclinical and first-in-human studies

The methodology for these experiments can be found in the supplementary data, available at https://doi.org/10.1016/j.annonc.2020.11.020.

Study design and treatment

This first-in-human (FIH), multicenter, open-label, non-randomized, phase I study (ClinicalTrials.gov, NCT03179436) was designed to evaluate various doses and schedules of intravenous quavonlimab combined with intravenous pembrolizumab in patients with advanced solid tumors and was conducted in two parts: DE (part 1) and DC (part 2). During DE, eligible patients with advanced solid tumors (cohort 1, any subtype; cohorts 2 and 3, any subtype except NSCLC) received an initial flat dose of quavonlimab monotherapy at 25 mg (cohort 1), 75 mg (cohort 2), or 200 mg (cohort 3), followed by four treatments of the same quavonlimab dose plus pembrolizumab 200 mg every 3 weeks (Q3W). Pembrolizumab was then continued Q3W as monotherapy for up to 2 years. During DC, patients with advanced/metastatic NSCLC were treated in the first-line setting with quavonlimab at 25 mg Q3W (arm A), 25 mg Q6W (arm B), 75 mg Q6W (arm C), or 75 mg Q3W (arm E) in combination with 200 mg pembrolizumab Q3W, with combination dosing continuing for up to 2 years. Enrollment alternated among all open arms during dose-confirmation. The alternation of patient enrollment mimics randomization. Specifically, treatment allocation occurred centrally using an interactive voice response system/integrated web response system. Because this was an open-label study, investigators and the sponsor were aware of all patient assignments; enrollment alternated among all open arms with different dose levels and frequencies to reduce bias. This alternating enrollment among all open arms is similar to the traditional blocked randomized enrollment in terms of balancing patient baseline characteristics.

Herein, we report results for the DE (cohorts 1, 2, 3) and DC (arms A, B, C, E) phases. Arm D of the DC phase enrolled patients with small-cell lung cancer; those results will be reported separately.

The study was conducted in accordance with International Conference on Harmonisation guidelines for Good Clinical Practice and principles of the Declaration of Helsinki. The protocol was approved by the Institutional Review Boards/Independent Ethics Committees of all participating institutions. All patients provided written informed consent before participating.

Patients

The DE phase included adults with any histologically/cytologically confirmed advanced/metastatic solid tumors (excluding NSCLC for cohorts 2 and 3) who had received, been intolerant of, been ineligible for, or refused all treatment known to confer clinical benefit. The DC phase (arms A, B, C, and E) included patients with newly diagnosed, histologically/cytologically confirmed, stage IIIB/IV NSCLC, no previous systemic treatment for advanced-stage disease, absence of tumor-activating (sensitizing) *EGFR* mutations or *ALK* gene rearrangements, no (neo)adjuvant chemotherapy within 6 months before study drug administration, and any tumor PD-L1 expression level. All patients were required to have disease measurable by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, Eastern Cooperative Oncology Group performance status 0 or 1, adequate organ function, and no previous anti-CTLA-4 treatment. Previous treatment with anti-PD-1, PD-L1, or PD-L2 agents was permitted in the DE but not the DC phase.

Outcomes and assessments

Primary objectives were to determine the safety and tolerability of quavonlimab plus pembrolizumab and establish a recommended phase II dose (RP2D) of quavonlimab when used with pembrolizumab. The dose-limiting toxicity (DLT) observation period was defined as the first two treatment cycles (3 weeks/cycle) in the DE phase, allowing for 3 weeks of observation for quavonlimab monotherapy and 3 weeks for combination treatment, and the first treatment cycle in the DC phase, allowing for 3 weeks of observation for the combination treatment. DLTs were defined as grade $\geq$3 non-hematologic adverse events (AEs); grade 3-4 non-hematologic laboratory value abnormalities necessitating clinically significant medical intervention, leading to hospitalization, persisting for $>$1 week, or resulting in drug-induced liver injury; grade 4 thrombocytopenia of any duration or grade 3 thrombocytopenia associated with bleeding necessitating platelet transfusion; grade 4 hematologic AE lasting $\geq$7 days; grade 3-4 febrile neutropenia; delay of $>$2 weeks in initiating the next treatment cycle because of treatment-related AE (TRAE); any TRAE leading to discontinuation during the DLT observation period; and any grade 5 AE.

Secondary endpoints included objective response rate (ORR) per RECIST v1.1 by investigator assessment. Progression-free survival (PFS) per RECIST v1.1 and overall survival (OS) were evaluated as exploratory endpoints.

Exploratory biomarker analyses were performed to evaluate associations between efficacy outcomes, baseline PD-L1 tumor proportion score (TPS), baseline tumor mutational burden (TMB), or change in Ki67-positive CD4+ and CD8+ cells, and changes in CD4+ counts from baseline to cycle 1 day 8 (C1D8) in peripheral blood samples.

Safety and tolerability assessments included AEs, serious AEs, laboratory tests, vital signs, electrocardiogram measurements, and physical examinations. AEs were monitored throughout treatment until 30 days after the last dose of study treatment and were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. Immune-mediated AEs (imAEs), defined for the safety profile of pembrolizumab as events with potentially treatment-related immunological causes, were also reported.

Tumor assessments for response and progression were performed using computed tomography every 9 weeks until week 54 and every 12 weeks thereafter. Partial or complete response was confirmed by repeat tumor imaging $\geq$4 weeks after the first documentation of response. Response assessments were reviewed by blinded independent central review (BICR).

Details for biomarker analyses are provided in the supplementary data, available at https://doi.org/10.1016/j.annonc.2020.11.020.

Statistical analysis

AEs were summarized descriptively by counts and frequencies for each arm. ORR was summarized for each arm, with 95% confidence intervals (CIs) calculated according to the Clopper—Pearson method for binomial data. PFS, OS, duration of response, and time to first grade 3-5 AE were estimated using the Kaplan—Meier method.

Safety was evaluated in all patients who received $\geq$1 dose of study treatment. The DLT-evaluable population included patients who received $\geq$90% of planned dose administration and completed the DLT observation period, including patients who experienced a DLT during the observation period. Efficacy outcomes were evaluated for patients with NSCLC (arms A, B, C, E) who received $\geq$1 dose of study treatment and had measurable disease at baseline per the investigator. All patients were monitored for safety and efficacy until they discontinued from study. The data cutoff date for analysis was 3 January 2020.

RESULTS

Antibody properties

CTLA-4 is an inhibitory molecule expressed on activated T cells that competes with the costimulatory molecule CD28 for binding with CD80 and CD86, effectively shutting down T-cell activation. Quavonlimab, a humanized monoclonal immunoglobulin G1 (IgG1) antibody, demonstrates low nanomolar binding affinity for CTLA-4 in biochemical and cell-based binding assays and blocks the interaction of CD80 and CD86 to cells expressing CTLA-4 (supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2020.11.020). In mixed lymphocyte reactions using human T cells and monocyte-derived dendritic cells, quavonlimab increases the production of interferon-γ by an average of $\sim$3-fold alone and $\sim$13-fold with the addition of pembrolizumab (supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2020.11.020). In a humanized mouse tumor model implanted with the Panc 08.13 pancreatic adenocarcinoma cell line, quavonlimab showed single-agent expansion and activation of T cells, reduction of tumor T-regulatory cells, and suppression of tumor growth (supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2020.11.020).

FIH dose selection

The FIH dose projection for quavonlimab was developed using an integrated approach based on the experimental no-observed-adverse-effect-level (NOAEL) from non-clinical Good Laboratory Practice safety studies in cynomolgus monkeys, data from *in vitro* experiments, pharmacokinetic studies in cynomolgus monkeys, and FDA guidelines for antibody-based immunotherapies.[13] Predicted human quavonlimab exposure following administration of doses ranging from 0.1 to 10 mg/kg Q3W are shown in supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2020.11.020. It was anticipated that the maximum concentration at steady state ($C_{max,ss}$) after administration of 0.3 mg/kg Q3W would not exceed $\sim$8 μg/mL, excluding intrapatient and interpatient variability. This predicted steady state concentration provided a $\sim$15-fold safety margin relative to the observed $C_{max,ss}$ of $\sim$120 μg/mL at NOAEL at 3 mg/kg quavonlimab Q1W. Based on these assessments, the FIH starting dose of 0.3 mg/kg quavonlimab (equivalent to a flat dose of 25 mg for an 85-kg patient) was selected. Different dosing frequencies were tested with 25 mg given Q3W and Q6W in combination with pembrolizumab. The maximum dose studied in the clinical trial was determined based on the DLT rate observed during the DE and DC phases as well as the total AE rate and the time of onset of AEs during these phases.

Patients

Thirty-nine patients with advanced solid tumors were enrolled in the DE phase; 134 patients with advanced/metastatic NSCLC were enrolled in the DC phase (supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2020.11.020). At data cutoff, 21 patients remained on treatment [cohort 3, 12.5% (1/8); arm A, 10.0% (4/40); arm B, 20.0% (8/40); arm C, 12.5% (5/40); arm E, 21.4% (3/14)]; median efficacy follow-up [interquartile range (IQR)] was 12.8 months (5.3-26.3) in cohort 1, 5.9 months (3.0-12.7) in cohort 2, 5.8 months (2.3-15.9) in cohort 3, 17.8 months (6.6-21.5) in arm A, 17.6 months (10.4-21.8) in arm B, 16.9 months (4.5-21.2) in arm C, and 13.9 months (4.8-18.7) in arm E. Clinical characteristics in the DE phase were typical of those in patients with advanced/metastatic solid tumors in a phase I study. Clinical

characteristics in those with advanced NSCLC receiving first-line therapy in the DC phase are summarized in supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2020.11.020.

Safety

DLT rates ranged from 0% to 13.3% in the DE cohorts and 5.0% to 10.0% in the DC arms (Table 1; supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2020.11.020). The only DLT observed in ≥1 patient across all treatment arms was pneumonitis, which occurred in 1/40 patients (2.5%) in arm A, 2/40 patients (5.0%) in arm B, and 1/40 patients (2.5%) in arm C. Maximum-tolerated dose (MTD) was not reached for quavonlimab administered in combination with pembrolizumab.

Median treatment duration was 43 days in the DE phase and 127 days in the DC phase. AEs of any cause occurred in 100% of patients in the DE phase and 98% of patients in the DC phase. Median time to onset of first grade 3-5 AE was not reached (cohort 1), 1.5 months (cohort 2), 1.2 months (cohort 3), 6.5 months (arm A), 9.7 months (arm B), 5.6 months (arm C), and 1.1 months (arm E).

Most patients experienced TRAEs. In both phases, the most common TRAEs were rash, pruritus, fatigue, diarrhea, and transaminitis (Table 1; supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2020.11.020). Grade 3-5 TRAEs and TRAEs leading to discontinuation occurred more often with higher (75 mg and 200 mg) and more frequent (Q3W) quavonlimab dosing than with lower (25 mg) and less frequent (Q6W) quavonlimab dosing (Table 1). No TRAEs leading to death were reported during the DE phase. In the DC phase, two patients (5.0%) in arm A and one (2.5%) in arm C experienced treatment-related pneumonitis that led to death. Serious AEs were reported in 14.3% of patients in cohort 1, 58.8% cohort 2, 50.0% cohort 3, 50.0% arm A, 35.0% arm B, 55.0% arm C, and 71.4% arm E. Serious TRAEs were reported in ≤30.0% of patients (Table 1). imAEs were reported in 35.7% of patients in cohort 1, 47.1% cohort 2, 87.5% cohort 3, 62.5% arm A, 55.0% arm B, 62.5% arm C, and 85.7% arm E. The most common imAEs (≥5%) were hyperthyroidism (17.9%), transaminitis (17.9%), hypothyroidism (15.4%), pneumonitis (5.1%), and severe skin reactions (5.1%) in the DE phase; transaminitis (50.7%), hypothyroidism (17.9%), pneumonitis (14.9%), adrenal insufficiency (10.4%), and hyperthyroidism (8.2%) in the DC phase. Infusion reactions were reported in 2/39 patients (5.1%) in the DE phase and 4/134 patients (3.0%) in the DC phase. Myocarditis was not reported in this study.

Efficacy

Among the 39 patients in the DE phase, two patients achieved confirmed objective responses (5.1%; both partial responses); one patient with pancreatic cancer (cohort 1) had a response duration of 64 days and one patient with liver/hepatobiliary cancer (cohort 3) had a response duration of 480 days. Both responses were ongoing at the time of this analysis.

In patients with NSCLC treated in the first-line setting, confirmed ORRs were 35.1% overall (40.0% arm A; 37.5% arm B; 27.5% arm C; 35.7% arm E) (supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2020.11.020). Reduction in target lesion size occurred in most patients in each treatment arm (25/36 arm A; 26/37 arm B; 26/34 arm C; 8/11 arm E) (Figure 1). Most responses were evident at the first tumor assessment (week 9) (supplementary Figures S3 and S4, available at https://doi.org/10.1016/j.annonc.2020.11.020). Response duration ranged from 7.9 months (ongoing) to not reached (ongoing); 58% of responding patients had responses lasting ≥12 months based on Kaplan–Meier estimates (supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2020.11.020).

In patients with NSCLC treated in the first-line setting, median PFS was 6.1 months (supplementary Figure S5A, available at https://doi.org/10.1016/j.annonc.2020.11.020) and the 6-month PFS rate was 54% (supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2020.11.020). Median OS was 16.5 months (supplementary Figure S5B, available at https://doi.org/10.1016/j.annonc.2020.11.020) and the 12-month OS rate was 67% (supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2020.11.020).

Biomarkers

Biomarker analyses were performed in 134 patients in the DC phase only. Among patients with NSCLC treated in the first-line setting, 110 (82.1%) had available tumor PD-L1 expression data. Twenty-seven of these 110 patients (27.0%) had tumors with PD-L1 TPS <1% (PD-L1 negative) and 83 of 110 (75.5%) had tumors with TPS ≥1% (PD-L1 positive) (supplementary Table S8, available at https://doi.org/10.1016/j.annonc.2020.11.020). When evaluating PD-L1 using TPS as a continuous variable, the increase of PD-L1 TPS was significantly associated with better best overall response (BOR; one-sided $P = 0.015$). Tumor PD-L1 expression was generally higher in responders than non-responders (supplementary Figure S6A, available at https://doi.org/10.1016/j.annonc.2020.11.020). However, responses were observed regardless of tumor PD-L1 status: 39% for PD-L1-positive tumors and 33% for PD-L1-negative tumors (supplementary Table S8, available at https://doi.org/10.1016/j.annonc.2020.11.020). PD-L1 TPS was significantly associated with PFS (one-sided $P = 0.037$) but not OS (one-sided $P = 0.134$).

TMB data were available in 82.8% (111/134) of patients. The association between TMB and BOR was not significant (one-sided $P = 0.074$); however, TMB was numerically higher in responders than in non-responders (supplementary Figure S6B, available at https://doi.org/10.1016/j.annonc.2020.11.020). TMB was significantly associated with PFS (one-sided $P = 0.028$) but not OS (one-sided $P = 0.054$). The association between PD-L1 and TMB confirmed that they were independent (supplementary

Table 1. Dose-limiting toxicity (DLT) in the DLT-evaluable population[a] and treatment-related adverse events in the safety population

	Dose-escalation phase			Dose-confirmation phase			
	Cohort 1 quavonlimab 25 mg Q3W + pembrolizumab	Cohort 2 quavonlimab 75 mg Q3W + pembrolizumab	Cohort 3 quavonlimab 200 mg Q3W + pembrolizumab	Arm A quavonlimab 25 mg Q3W + pembrolizumab	Arm B quavonlimab 25 mg Q6W + pembrolizumab	Arm C quavonlimab 75 mg Q6W + pembrolizumab	Arm E quavonlimab 75 mg Q3W + pembrolizumab
DLT-evaluable population	*n* = 13	*n* = 15	*n* = 7	*n* = 40	*n* = 40	*n* = 40	*n* = 14
Any DLT, no. of DLT (%) (80% CI)	0 (0) (0-10.9)	2 (13.3) (4.9-26.6)	0 (0) (0-18.2)	3 (7.5) (3.3-14.0)	2 (5.0) (1.7-10.8)	4 (10.0) (5.0-17.1)	1 (7.1) (1.4-19.4)
Safety population	*n* = 14	*n* = 17	*n* = 8	*n* = 40	*n* = 40	*n* = 40	*n* = 14
Any TRAE, *n* (%)	12 (85.7)	15 (88.2)	8 (100.0)	31 (77.5)	34 (85.0)	36 (90.0)	13 (92.9)
Grade 3-5 TRAE	0	4 (23.5)	6 (75.0)	14 (35.0)	12 (30.0)	14 (35.0)	8 (57.1)
Serious TRAE	0	4 (23.5)	2 (25.0)	10 (25.0)	5 (12.5)	12 (30.0)	2 (14.3)
Death due to TRAE[b]	0	0	0	2 (5.0)	0	1 (2.5)	0
Discontinued due to TRAE	1 (7.1)	3 (17.6)	3 (37.5)	6 (15.0)	8 (20.0)	9 (22.5)	2 (14.3)
Quavonlimab	1 (7.1)	3 (17.6)	3 (37.5)	6 (15.0)	7 (17.5)	9 (22.5)	2 (14.3)
Pembrolizumab	0	3 (17.6)	3 (37.5)	6 (15.0)	7 (17.5)	7 (17.5)	0
Most common TRAEs, *n* (%)[c]							
Rash	0	4 (23.5)	1 (12.5)	10 (25.0)	12 (30.0)	12 (30.0)	6 (42.9)
Pruritus	2 (14.3)	6 (35.3)	0	12 (30.0)	7 (17.5)	11 (27.5)	4 (28.6)
Hypothyroidism	3 (21.4)	3 (17.6)	0	5 (12.5)	8 (20.0)	8 (20.0)	2 (14.3)
Fatigue	6 (42.9)	3 (17.6)	2 (25.0)	6 (15.0)	3 (7.5)	4 (10.0)	2 (14.3)
AST increased	0	1 (5.9)	0	5 (12.5)	4 (10.0)	10 (25.0)	5 (35.7)
ALT increased	0	0	0	5 (12.5)	4 (10.0)	9 (22.5)	5 (35.7)
Pneumonitis	1 (7.1)	0	1 (12.5)	6 (15.0)	8 (20.0)	5 (12.5)	1 (7.1)
Maculopapular rash	3 (21.4)	2 (11.8)	0	5 (12.5)	4 (10.0)	6 (15.0)	1 (7.1)
Diarrhea	2 (14.3)	1 (5.9)	2 (25.0)	6 (15.0)	3 (7.5)	5 (12.5)	3 (21.4)

TRAEs were determined by the investigator to be related to the study drug.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; DLT, dose-limiting toxicity; Q3W, every 3 weeks; Q6W, every 6 weeks; TRAE, treatment-related adverse event.

[a] Patients may have experienced more than one dose-limiting toxicity.

[b] There were three pneumonitis-related deaths. The adverse events occurred at 39, 52, and 72 days after the first dose, respectively. All patients were treated with steroids.

[c] Occurring in ≥10% of patients overall in the dose-confirmation phase.

https://doi.org/10.1016/j.annonc.2020.11.020

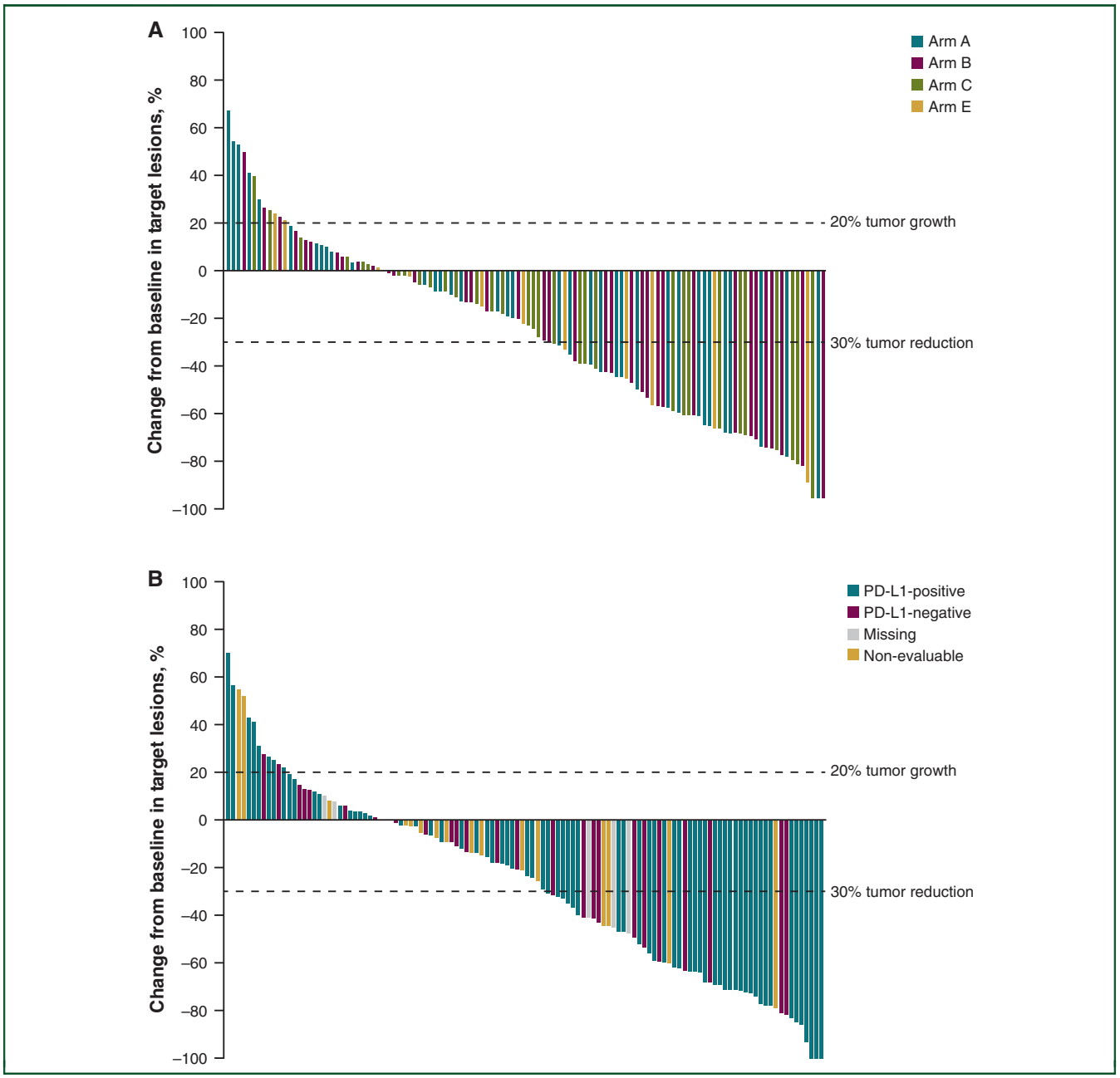

Figure 1. Maximum percentage change from baseline in target lesion size in patients with advanced non-small-cell lung cancer treated by (A) treatment arm and (B) PD-L1 status.
PD-L1, programmed death ligand 1.

Figure S7, available at https://doi.org/10.1016/j.annonc.2020.11.020).

Overall, 121 of 134 total patients (90.3%) had evaluable peripheral blood CD4 and CD8 cell count data. An increase (200-fold to >1000-fold) in the number of proliferating (Ki67-positive) CD4+ and CD8+ cells was observed following treatment with quavonlimab that correlated directly with dose level (supplementary Figure S8A and B, available at https://doi.org/10.1016/j.annonc.2020.11.020). An increase was also observed in patients in the DE phase treated with one cycle of quavonlimab monotherapy (supplementary Figure S8C. available at https://doi.org/10.1016/j.annonc.2020.11.020), supporting the mechanism of anti-CTLA-4 in stimulating T-cell proliferation. The increases of Ki67-positive T cells did not correlate with response; however, an increase in total CD4 count (baseline to C1D8) was significantly associated with BOR (one-sided $P = 0.044$; supplementary Figure S6C, available at https://doi.org/10.1016/j.annonc.2020.11.020).

DISCUSSION

In this FIH phase I study, quavonlimab plus pembrolizumab showed encouraging antitumor activity in patients with advanced NSCLC receiving first-line treatment at all dose levels and treatment intervals, including at the lowest quavonlimab dose of 25 mg when administered Q6W in

combination with 200 mg pembrolizumab Q3W. The target DLT rate was not reached in any of the DE cohorts and MTD was not reached; however, a numerically higher rate of any-grade and grade 3-5 TRAEs was observed with a higher quavonlimab dose in the DE and the DC phases. In patients with NSCLC, the 25-mg quavonlimab dose and the Q6W treatment interval had a more favorable toxicity profile than 25 mg Q3W, 75 mg Q6W, and 75 mg Q3W. Time to onset of the first grade 3-5 AE also occurred more rapidly at the 75-mg and 200-mg quavonlimab doses and at the Q3W dosing interval than at the 25-mg dose and Q6W interval in the DE and DC phases. With regard to antitumor activity, no considerable differences were observed at any dose level or dosing interval evaluated in patients with NSCLC receiving first-line treatment. Although not statistically different, combination treatment with 25 mg quavonlimab Q6W plus pembrolizumab produced the greatest numerical tumor size changes and numerically better PFS and OS across all four arms (Figure 1; supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2020.11.020). Based on these combined results showing increasing toxicity at higher doses with no improvement in efficacy at these dose levels, higher doses were not investigated.

Given the numerical trend of worsening toxicity with higher doses and shorter dosing intervals (75% of patients developed grade 3-5 TRAEs with 200 mg quavonlimab Q3W compared with 0% with 25 mg Q3W during DE) and similar efficacy in patients with NSCLC receiving first-line treatment at the higher doses and shorter intervals, the RP2D was determined based on the favorable safety profile observed with 25 mg quavonlimab Q6W. Improved tolerability of this dosing regimen may allow patients to receive these agents for longer periods of time, which could ultimately improve the depth and durability of responses in patients with advanced malignancies.

The safety profile for quavonlimab plus pembrolizumab was consistent with that observed with other anti-CTLA-4 and anti-PD-1 combination therapies in patients with advanced NSCLC.[10-12] Commonly reported TRAEs for this drug class include pruritus, diarrhea, rash, fatigue, and decreased appetite,[11,14] which were also observed with quavonlimab plus pembrolizumab. In addition, the frequency of grade 3-5 TRAEs in the DE and DC phases in the present study (0%-75% and 30%-57%, respectively) were similar to those previously reported with this drug class (33%-37%)[11,14]; similar trends were observed with the incidence of serious TRAEs and TRAEs leading to discontinuation. It is notable that a higher incidence of transaminitis in the studied patient population was observed following treatment with quavonlimab plus pembrolizumab (arm B, 10.0%) than were reported from pembrolizumab monotherapy trials (Table 1). Furthermore, patients who received quavonlimab plus pembrolizumab had a higher incidence of imAEs (∼63%) compared with those found in patients in studies of pembrolizumab monotherapy in NSCLC (17%-29%).[15-18] However, the types of events, most commonly hypothyroidism, pneumonitis, hyperthyroidism, and severe skin reactions, observed in the combination study and in pembrolizumab monotherapy studies were comparable. Overall, no new unexpected AEs were observed with quavonlimab plus pembrolizumab.

Among patients with advanced NSCLC receiving first-line quavonlimab plus pembrolizumab, encouraging antitumor activity was observed at all dose levels, with ORRs of 28%-40% across treatment arms. Comparisons with other pembrolizumab trials are limited by differences in study populations. ORRs appeared higher than those observed with pembrolizumab monotherapy in NSCLC, especially in patients with lower PD-L1 expression.[18,19] ORRs were within the range expected based on previous studies of combined anti-CTLA-4 and anti-PD-1/PD-L1 therapy in patients with advanced NSCLC.[10-12,14,17]

Although cross-trial comparisons should be interpreted with caution and the data for PFS and OS in the current trial are immature, the clinical outcomes observed with quavonlimab plus pembrolizumab as first-line treatment for advanced NSCLC (ORR, 35.1%; median PFS, 6.1 months; median OS, 16.5 months) appear comparable with those previously reported. In the phase I CheckMate 012 study, ORR was 47% and median PFS was 8.1 months (95% CI, 5.6-13.6) with nivolumab 3 mg/kg Q2W plus ipilimumab 1 mg/kg Q12W while ORR was 38% and median PFS was 3.9 months (95% CI, 2.6-13.2) with nivolumab 3 mg/kg Q12W plus ipilimumab 1 mg/kg Q6W.[11] In the phase III CheckMate 227 study of nivolumab 3 mg/kg Q2W plus ipilimumab 1 mg/kg Q6W, ORR was 36%, median PFS was 5.1 months (95% CI, 4.1-6.3), and median OS was 17.1 months (95% CI, 15.2-19.9).[14]

PD-L1 expression has been identified as a predictor of response to anti-PD-1/PD-L1 therapies in NSCLC.[19-21] Consistent with ORRs observed in pembrolizumab monotherapy studies,[18,19] the ORR with quavonlimab plus pembrolizumab was highest in patients with PD-L1-positive tumors (39%). Interestingly, ORRs in patients with PD-L1-negative tumors (33%) were much higher than might have been expected in patients receiving pembrolizumab monotherapy based on historical comparisons with an earlier KEYNOTE study.[19] Although TMB was associated with response to anti-PD-1 monotherapy treatment in prior studies,[22] the association between TMB and response was not significant in the present study population using combination treatment. Interestingly, the majority of patients enrolled in the current study with a diagnosis of NSCLC were Asian, and although the PD-L1 expression rate has been reported to be numerically higher in NSCLC tumors of Asian patients compared with those of Caucasian patients,[23] mutational burden has been reported to be lower.[24] As this was a phase I study with relatively small sample sizes and no comparator arms, all biomarker results should be interpreted with caution until data from larger studies are available.

Several FDA-approved immunotherapy options are now available to patients with previously untreated advanced NSCLC. Pembrolizumab is currently indicated in combination with pemetrexed and platinum chemotherapy as first-line treatment of patients with metastatic non-squamous NSCLC, with no *EGFR* or *ALK* genomic tumor aberrations,

regardless of PD-L1 status (based on KEYNOTE-189); in combination with carboplatin and paclitaxel, as first-line treatment of patients with metastatic squamous NSCLC (based on KEYNOTE-407); and as a single agent for the first-line treatment of patients with metastatic NSCLC that express PD-L1 (TPS $\geq$1%) and have no *EGFR* or *ALK* genomic tumor aberrations (based on KEYNOTE-042).[25] Nivolumab is indicated for patients with metastatic NSCLC that express PD-L1 ($\geq$1%) and have no *EGFR* or *ALK* genomic tumor aberrations, as first-line treatment in combination with ipilimumab (based on CheckMate-227); and for patients with metastatic or recurrent NSCLC with no *EGFR* or *ALK* genomic tumor aberrations as first-line treatment in combination with ipilimumab and two cycles of platinum-doublet chemotherapy (based on CheckMate-9LA).[19] Atezolizumab is indicated as first-line treatment for patients with metastatic NSCLC whose tumors have high PD-L1 expression [PD-L1 stained $\geq$50% of tumor cells (TC) (TC $\geq$50%) or PD-L1 stained tumor-infiltrating immune cells (IC) covering $\geq$10% of the tumor area (IC $\geq$10%)] with no *EGFR* or *ALK* genomic tumor aberrations; in combination with bevacizumab, paclitaxel, or carboplatin, for the first-line treatment of patients with metastatic non-squamous NSCLC with no *EGFR* or *ALK* genomic tumor aberrations; and in combination with paclitaxel protein-bound and carboplatin for the first-line treatment of patients with metastatic non-squamous NSCLC with no *EGFR* or *ALK* genomic tumor aberrations.[26] Whether the data will support the addition of quavonlimab to pembrolizumab in a defined patient cohort with NSCLC will have to be evaluated in larger phase III trials.

Based on the favorable findings in this study, the efficacy of quavonlimab in combination with pembrolizumab is now being explored in additional tumor types. These include a phase I/II open-label study in patients with PD-1-refractory melanoma (NCT04305041) and a phase II study in treatment-naive patients with advanced NSCLC stratified by gene expression profile and TMB (KEYNOTE-495; NCT03516981). A phase III study in NSCLC is also planned.

In summary, quavonlimab plus pembrolizumab demonstrated antitumor activity in patients with advanced NSCLC receiving first-line treatment at all dose levels, including the lowest dose of quavonlimab, and was generally well tolerated with no unexpected toxicities. The RP2D for quavonlimab was chosen as 25 mg Q6W when used in combination with pembrolizumab because this dosing regimen conferred the lowest toxicity while preserving efficacy similar to that of the other dosing regimens examined.

ACKNOWLEDGEMENTS

The authors thank Brent Butts, Jane Guo, Dewan Hossain, Mohini Rajasagi, and Yiwei Zhang from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. Medical writing and/or editorial assistance were provided by Melanie Sweetlove, MSc, Holly C. Cappelli, PhD, CMPP, and Dana Francis, PhD, of ApotheCom (Yardley, PA). This assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

FUNDING

This work was supported by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (grant number: not applicable).

DISCLOSURE

RP reports a consultant role for Karyopharm Therapeutics and BioLineRx. JB reports an advisory board role for Roche, AstraZeneca, Pfizer, Takeda, Boehringer Ingelheim, and Bayer; and a consultant role for MSD, BMS, Novartis, and AbbVie. DWR reports research grants from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. M-JA reports an advisory board role for AstraZeneca, Lilly, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, ONO, BMS, Takeda, Amgen, Novartis, and Roche; and a consultant role for Alpha Pharmaceutical Company, AstraZeneca, Lilly, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, ONO, BMS, Takeda, Amgen, Novartis, and Roche. KY reports honorarium received from promotional activities from Chugai Pharma, AstraZeneca, Lilly Japan, Novartis, Kirin, Bristol Myers Squibb Japan, and Taiho. D-WK reports travel and accommodation support for advisory board meeting attendance from Amgen and Daiichi Sankyo. AN reports an advisory board role for MSD, BMS, Roche, and AstraZeneca. MS reports honoraria received from promotional activities from AstraZeneca, MSD, Chugai, Taiho, Pfizer, Nippon Kayaku, Boehringer Ingelheim, Bristol Myers Squibb, ONO, Novartis, and Eli Lilly; and research grants from Chugai, AstraZeneca, MSD, Pfizer, Boehringer Ingelheim, Bristol Myers Squibb, ONO, Novartis, Eli Lilly, AbbVie, Ignyta, and Takeda. DHL reports honoraria for lecturing or consulting from AbbVie, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, ChongKunDang, CJ Healthcare, Eli Lilly, Janssen, Menarini, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, Mundipharma, Novartis, Roche, ST Cube, and Takeda; and travel accommodations from Takeda and Blueprint Medicines. DRS reports leadership for Centennial Medical Center; consulting or advisory role for Genentech/Roche, Novartis, Celgene, Bristol Myers Squibb, AstraZeneca, Pfizer, Boehringer Ingelheim, AbbVie, Foundation Medicine, GlaxoSmithKline, Lilly, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, Moderna Therapeutics, Nektar, Takeda, Amgen, TRM Oncology, Precision Oncology, Evelo Therapeutics, Illumina, and PharmaMar; research funding (institution) from Genentech/Roche, Novartis, Celgene, Bristol Myers Squibb, Lilly, AstraZeneca, Pfizer, Boehringer Ingelheim, University of Texas Southwestern Medical Center — Simmons Cancer Center, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, AbbVie, GlaxoSmithKline, G1 Therapeutics, Neon Therapeutics, Takeda, Foundation Medicine, Nektar, Celldex, Clovis Oncology, Daiichi Sankyo,

EMD Serono, Acerta Pharma, OncoGenex, Astellas Pharm, GRAIL, Transgene, Ipsen, ARMO BioSciences, Amgen, and Millennium; and travel, accommodation, and expenses from AstraZeneca, Boehringer Ingelheim, Celgene, Lilly, EMD Serono, Bristol Myers Squibb, Genentech, Genzyme, Intuitive Surgical, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, Pfizer, Purdue Pharma, Spectrum Pharmaceuticals, and Sysmex. SS is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. XL is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. JC is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and has stock ownership interests in Merck & Co., Inc., Kenilworth, NJ, USA. AC is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and has stock ownership interests in Merck & Co., Inc., Kenilworth, NJ, USA. AC is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. RAA is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. BCC reports a speakers bureau role for Novartis; an advisory board role for Novartis, Bayer, AstraZeneca, MOGAM Institute, Dong-A ST, Champions Oncology, Janssen, Yuhan, ONO, Dizal Pharma, and MSD; a consultant role for Novartis, AstraZeneca, Boehringer Ingelheim, Roche, BMS, ONO, Yuhan, Pfizer, Eli Lilly, Janssen, Takeda, and MSD; stock ownership interests in TheraCanVac Inc., Gencurix Inc., and BridgeBio Therapeutics; honoraria from promotional activities for Novartis, Bayer, AstraZeneca, MOGAM Institute, Dong-A ST, Champions Oncology, Janssen, Yuhan, ONO, Dizal Pharma, and MSD; research grants from Novartis, Bayer, AstraZeneca, MOGAM Institute, Dong-A ST, Champions Oncology, Janssen, Yuhan, Ono, Dizal Pharma, MSD; and royalties, intellectual property or patents with Champions Oncology. All other authors declare no conflicts of interest.

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