

ORIGINAL RESEARCH

First-line nivolumab + ipilimumab in advanced NSCLC: CheckMate 227 subpopulation analyses in Asian patients[☆]

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Available online xxx

Background: Nivolumab plus ipilimumab demonstrated clinically meaningful improvement in efficacy versus chemotherapy with a manageable safety profile in patients with advanced non-small cell lung cancer (NSCLC) and tumor programmed death-ligand 1 (PD-L1) expression $\geq 1\%$ or $< 1\%$ in Part 1 of CheckMate 227. Here we report efficacy and safety results for the Asian subpopulation.

Methods: Patients with stage IV/recurrent NSCLC were randomized 1 : 1 : 1 to nivolumab plus ipilimumab, nivolumab monotherapy, or chemotherapy (PD-L1 $\geq 1\%$) or nivolumab plus ipilimumab, nivolumab plus chemotherapy, or chemotherapy (PD-L1 $< 1\%$). Overall survival (OS), progression-free survival, objective response rate, duration of response, and safety were evaluated among patients in Japan, South Korea, and Taiwan.

Results: In the Asian subpopulation with PD-L1 $\geq 1\%$, 81 patients received nivolumab plus ipilimumab and 81 received chemotherapy. Median OS was not reached with nivolumab plus ipilimumab versus 24.8 months with chemotherapy; 3-year OS rate was 53% versus 37% [hazard ratio (HR), 0.72; 95% confidence interval (CI) 0.47-1.11]. The 3-year progression-free survival rate was 26% versus 7% (HR, 0.65; 95% CI 0.45-0.96), objective response rate was 56% versus 37%, and median duration of response was 29.0 months (95% CI 15.0 months-not reached) versus 6.9 months (95% CI 3.9-11.1 months). Similar results were observed regardless of tumor PD-L1 expression and in Japanese patients. Grade 3-4 treatment-related adverse events occurred in 40% of patients receiving nivolumab plus ipilimumab and 36% receiving chemotherapy, in the overall Asian subpopulation (tumor PD-L1 expression $\geq 1\%$ and $< 1\%$); no new safety signals were identified.

Conclusions: At 3-year follow-up, nivolumab plus ipilimumab provided durable long-term efficacy benefits versus chemotherapy regardless of tumor PD-L1 expression in the Asian subpopulation, including Japanese patients. Consistent with findings for all randomized patients, these data support the use of nivolumab plus ipilimumab as first-line treatment of Asian patients with advanced NSCLC.

Key words: Asia, Japan, non-small cell lung cancer, nivolumab, ipilimumab

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[☆]Note: These data were presented in part at the European Society for Medical Oncology Virtual Congress 2020, 19-21 September (poster 1274P), and the 61st Annual Meeting of the Japan Lung Cancer Society, 12-14 November 2020 (oral presentation PS-3).

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INTRODUCTION

The immune checkpoint inhibitors nivolumab and ipilimumab have distinct but complementary mechanisms of action^{1,2}; nivolumab, a fully human immunoglobulin G4 (IgG4) programmed cell death protein 1 (PD-1) immune checkpoint inhibitor antibody, restores antitumor T-cell function,³⁻⁵ whereas ipilimumab, a fully human IgG1 cytotoxic T lymphocyte antigen-4 (CTLA-4) immune checkpoint inhibitor antibody, induces *de novo* antitumor T-cell responses,

including an increase in memory T cells.^{1,2,6} Clinically, the combination of nivolumab plus ipilimumab has improved long-term survival compared with standard therapies for advanced cancers such as melanoma,⁷ renal cell carcinoma,⁸ mesothelioma,⁹ and non-small cell lung cancer (NSCLC).¹⁰

In part 1 of the randomized, open-label, phase III trial CheckMate 227 (ClinicalTrials.gov identifier, NCT02477826), the combination of nivolumab plus ipilimumab as first-line treatment significantly prolonged overall survival (OS) compared with chemotherapy in patients with advanced NSCLC and tumor programmed death-ligand 1 (PD-L1) expression $\geq 1\%$ (co-primary endpoint) or $< 1\%$ (pre-specified descriptive analysis).¹¹ At 3 years' minimum follow-up (37.7 months), nivolumab plus ipilimumab continued to demonstrate a durable and long-term benefit versus chemotherapy, regardless of tumor PD-L1 expression; 3-year OS rates were 33% versus 22% in patients with PD-L1 $\geq 1\%$ and 34% versus 15% in patients with PD-L1 $< 1\%$.¹⁰ Based on data from this trial, nivolumab plus ipilimumab was approved in the USA as first-line treatment of adult patients with metastatic NSCLC and tumor PD-L1 expression $\geq 1\%$ (as determined by a Food and Drug Administration-approved test), with no *EGFR* or *ALK* tumor aberrations.^{12,13} Nivolumab plus ipilimumab has also been approved in Japan as first-line treatment for unresectable, advanced or recurrent NSCLC regardless of tumor PD-L1 expression, and in South Korea and Taiwan as first-line treatment for adult patients with advanced/recurrent NSCLC and tumor PD-L1 expression $\geq 1\%$.¹⁴⁻¹⁷

Differences in treatment outcomes between Asian and non-Asian patients with NSCLC have been observed with various therapies. Especially in countries with well-resourced healthcare systems like Japan, higher rates of subsequent therapy after disease progression have been reported in several clinical trials, which may have potentially contributed to differences in survival outcomes.¹⁸⁻²¹ Therefore, there is a need for studies that assess clinical benefit in regional versus global populations to better evaluate treatment options and inform clinical decisions.²²⁻²⁴ Here, we report the 3-year efficacy and safety results of nivolumab plus ipilimumab compared with chemotherapy in the Asian subpopulation, including Japanese patients, from CheckMate 227 part 1.

METHODS

Patients

Eligibility criteria for CheckMate 227 have been described previously.^{11,25} Briefly, adult patients were enrolled with histologically confirmed squamous or nonsquamous stage IV or recurrent NSCLC and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, who had not received previous systemic anticancer therapy for advanced or metastatic disease. Key exclusion criteria included the presence of *EGFR* mutations or known *ALK* translocations sensitive to targeted therapy, autoimmune disease, or untreated or symptomatic central nervous system metastases.

Study design and treatment

The CheckMate 227 trial is a multi-part phase III trial designed to evaluate different nivolumab-based regimens versus chemotherapy in distinct patient populations. Patients with tumor PD-L1 expression $\geq 1\%$ were randomly assigned in a 1 : 1 : 1 ratio to receive nivolumab (3 mg/kg every 2 weeks) plus ipilimumab (1 mg/kg every 6 weeks), nivolumab monotherapy (240 mg every 2 weeks), or platinum-doublet chemotherapy every 3 weeks for up to four cycles. Patients with tumor PD-L1 expression $< 1\%$ were randomly assigned in a 1 : 1 : 1 ratio to receive nivolumab plus ipilimumab, nivolumab (360 mg every 3 weeks) plus platinum-doublet chemotherapy (every 3 weeks for up to four cycles), or platinum-doublet chemotherapy alone (every 3 weeks for up to four cycles).

Treatment continued until disease progression or unacceptable toxicity or, for the immunotherapy regimens, for a maximum of 2 years of follow-up. Crossover between the treatment groups during the trial was not permitted. Subsequent therapy was determined at the physician's discretion.

Endpoints and assessments

The primary endpoints (including OS with nivolumab plus ipilimumab versus chemotherapy in patients with tumor PD-L1 expression $\geq 1\%$) and secondary endpoints for part 1 of the CheckMate 227 trial have been described previously.^{11,25} Here we assessed efficacy and safety in Asian patients, including the following endpoints: (i) OS, progression-free survival (PFS), objective response rate (ORR), and duration of response (DOR) in patients with tumor PD-L1 expression $\geq 1\%$; (ii) OS, PFS, ORR, and DOR in patients with tumor PD-L1 expression $< 1\%$; and (iii) OS, PFS, ORR, and DOR in all randomized patients (with tumor PD-L1 expression $\geq 1\%$ and $< 1\%$). PFS, ORR, and DOR were assessed by blinded independent central review (BICR). Tumor PD-L1 expression level was determined as described previously.²⁶ Safety was assessed in all treated patients. Treatment-related adverse events (TRAEs) and treatment-related select AEs (defined as AEs with potential immunological cause) were assessed by the investigator and collected between first dose and 30 days after last dose of study drug. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Statistical analyses

Efficacy and safety data analyses of nivolumab plus ipilimumab versus chemotherapy in the Asian subpopulation are exploratory; data are summarized using descriptive statistics. Although not powered for statistical testing, geographic region including Asia was a predefined subset of interest for descriptive analyses including survival and response assessments. OS, PFS, and DOR were estimated using Kaplan–Meier analysis. A Cox proportional hazards model, with the treatment group as a single covariate, was used to calculate hazard ratios (HRs) for death with

Table 1. Baseline characteristics of patients in the Asian subpopulation, including Japanese patients

n (%)	Asian ^a		Japanese	
	Nivolumab plus ipilimumab (n = 121)	Chemotherapy (n = 124)	Nivolumab plus ipilimumab (n = 66)	Chemotherapy (n = 77)
Age, years				
Median (range)	65 (34-81)	66 (30-87)	66 (42-81)	66 (30-78)
<65	60 (50)	58 (47)	30 (45)	33 (43)
≥65 to <75	49 (40)	55 (44)	32 (48)	38 (49)
≥75 years	12 (10)	11 (9)	4 (6)	6 (8)
Female	25 (21)	26 (21)	12 (18)	17 (22)
ECOG performance status				
0	43 (36)	44 (35)	26 (39)	35 (45)
1	78 (64)	80 (65)	40 (61)	42 (55)
Smoking status^b				
Current or former smoker	97 (80)	101 (81)	58 (88)	66 (86)
Never-smoker	23 (19)	23 (19)	8 (12)	11 (14)
Histology				
Squamous	31 (26)	25 (20)	18 (27)	14 (18)
Nonsquamous	90 (74)	99 (80)	48 (73)	63 (82)
Tumor PD-L1 expression				
<1	40 (33)	43 (35)	25 (38)	29 (38)
≥1	81 (67)	81 (65)	41 (62)	48 (62)
1-49	29 (24)	43 (35)	14 (21)	25 (32)
≥50	52 (43)	38 (31)	27 (41)	23 (30)

ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1.

^a Includes patients randomized in Asia: 143 patients from Japan (66 nivolumab plus ipilimumab, 77 chemotherapy), 86 patients from Republic of Korea (46 nivolumab plus ipilimumab, 40 chemotherapy), and 16 patients from Taiwan (9 nivolumab plus ipilimumab, 7 chemotherapy).

^b Smoking status was defined by patient self-report. Current and former smokers reported the number of cigarettes smoked per day, and former smokers also reported the date they permanently stopped smoking; status unknown for 1 Asian patient in the nivolumab plus ipilimumab arm.

associated two-sided confidence intervals (CIs). For ORR, the Clopper–Pearson method was used to calculate 95% exact two-sided CIs. Baseline demographics and safety were reported using descriptive statistics.

The trial was approved by the institutional review board or independent ethics committee at each center and was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. Informed consent was obtained from all patients. The trial protocol has been published previously.²⁵

RESULTS

Patients

This report is based on a database lock of 28 February 2020. Of a total of 347 randomized Asian patients with tumor PD-L1 expression $\geq 1\%$ or $< 1\%$ in part 1 of the CheckMate 227 study, 245 patients were randomized to nivolumab plus ipilimumab (n = 121) or chemotherapy (n = 124) (Supplementary Figure S1, available at <https://doi.org/10.1016/j.esmooop.2022.100394>). Patients were enrolled from 32 treatment centers in Japan (n = 143), 5 centers in the Republic of Korea (n = 86), and 5 centers in Taiwan (n = 16). Among Japanese patients, 66 were randomized to nivolumab plus ipilimumab and 77 to chemotherapy. Baseline characteristics were generally balanced between arms for the Asian subpopulation, including Japanese patients (Table 1). Among patients in the Asian subpopulation, however, the proportion of those with squamous histology was slightly higher in the nivolumab plus ipilimumab arm (26%) versus the chemotherapy arm (20%). Among Japanese patients, the proportion of those with ECOG performance status of 0 was slightly lower in the nivolumab plus ipilimumab

arm (39%) versus the chemotherapy arm (45%). The proportion of patients with tumor PD-L1 expression $\geq 1\%$ was similar for the two treatment arms among the Asian subpopulation (67% in the nivolumab plus ipilimumab arm and 65% in the chemotherapy arm), as well as among Japanese patients (62% in both arms).

Subsequent therapy

For patients with tumor PD-L1 expression $\geq 1\%$ in the Asian subpopulation, the median duration of therapy in the nivolumab plus ipilimumab arm was 6.0 months (95% CI 3.32-10.41 months) and 4.2 months (95% CI 3.38-5.75 months) in the chemotherapy arm. Subsequent systemic therapy was received by 41% of patients in the nivolumab plus ipilimumab arm and 72% of patients in the chemotherapy arm; subsequent immunotherapy by 11% and 58%; and subsequent chemotherapy by 38% and 43%, respectively. For all patients in the Asian subpopulation, the median duration of therapy in the nivolumab plus ipilimumab arm was 4.6 months (95% CI 3.25-6.51 months) and 3.7 months (95% CI 2.60-4.17 months) in the chemotherapy arm. Subsequent systemic therapy was received by 46% of patients in the nivolumab plus ipilimumab arm and 73% of patients in the chemotherapy arm; subsequent immunotherapy by 11% and 57%; and subsequent chemotherapy by 45% and 49%, respectively (Supplementary Table S1, available at <https://doi.org/10.1016/j.esmooop.2022.100394>).

The proportion of Japanese patients receiving subsequent therapy was numerically higher in both arms compared with that in the overall Asian subpopulation. For all Japanese patients, subsequent systemic therapy was

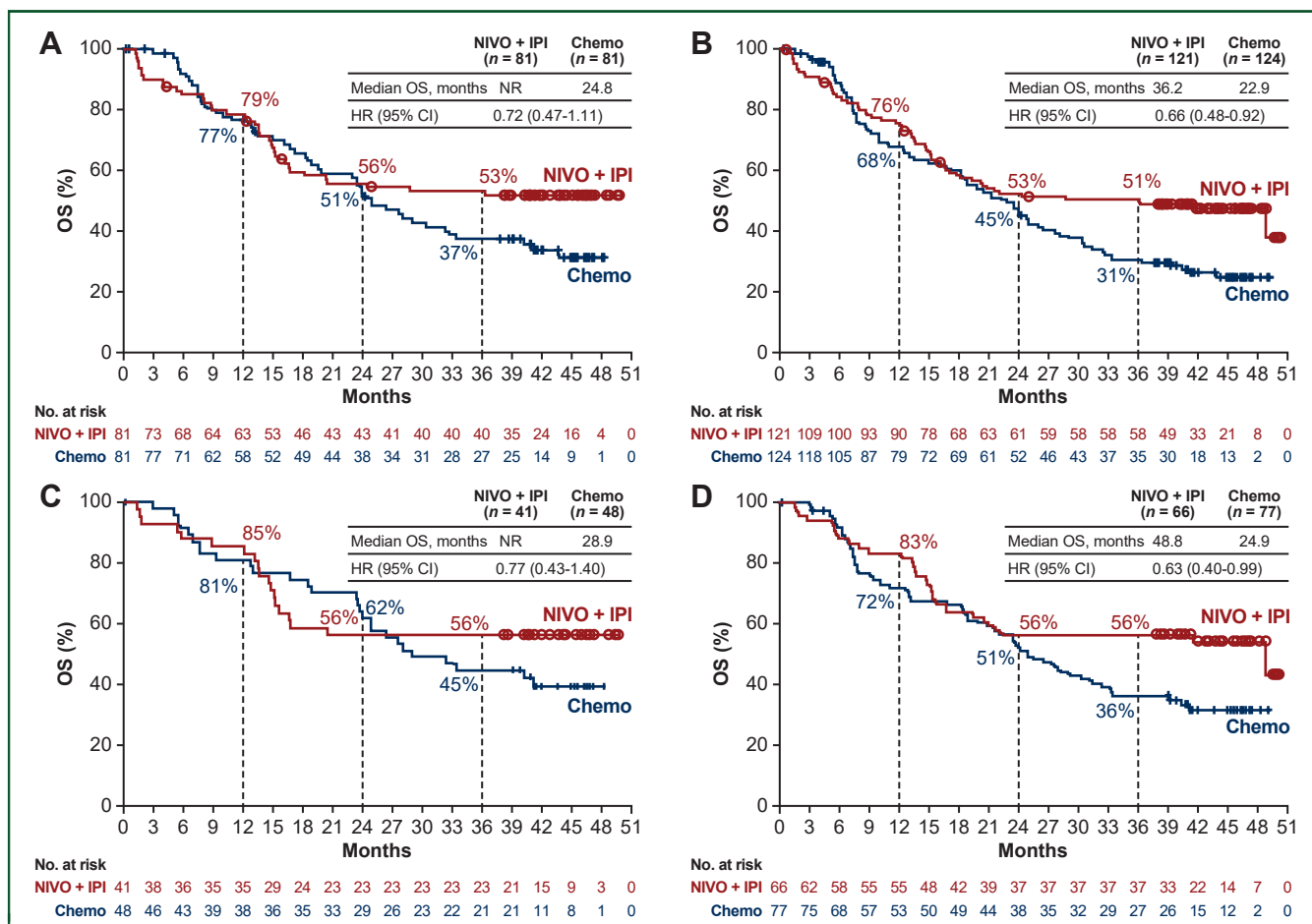


Figure 1. Overall survival in the Asian subpopulation, including Japanese patients, based on tumor programmed death-ligand 1 expression. (A) OS in the Asian subpopulation among patients with tumor PD-L1 expression $\geq 1\%$. (B) OS in the Asian subpopulation (tumor PD-L1 expression $\geq 1\%$ and $< 1\%$). (C) OS in Japanese patients with tumor PD-L1 expression $\geq 1\%$. (D) OS in Japanese patients (tumor PD-L1 expression $\geq 1\%$ and $< 1\%$). Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; NIVO + IPI, nivolumab plus ipilimumab; NR, not reached; OS, overall survival; PD-L1, programmed death-ligand 1.

received by 58% of patients in the nivolumab plus ipilimumab arm, and 83% of patients in the chemotherapy arm; subsequent immunotherapy was received by 14% and 75%, respectively; and subsequent chemotherapy by 55% in each arm (Supplementary Table S1, available at <https://doi.org/10.1016/j.esmoop.2022.100394>).

Efficacy

The minimum follow-up time for OS among all randomized patients in the Asian subpopulation was 38.1 months. Nivolumab plus ipilimumab improved OS versus chemotherapy in this subpopulation, regardless of tumor PD-L1 expression. Median OS among patients with tumor PD-L1 expression $\geq 1\%$ was not reached with nivolumab plus ipilimumab versus 24.8 months with chemotherapy (HR, 0.72; 95% CI 0.47-1.11); 3-year OS rates were 53% (95% CI 41.6% to 63.5%) versus 37% (95% CI 26.4% to 48.2%) (Figure 1A). For patients with tumor PD-L1 expression $< 1\%$, median OS was 21.6 months with nivolumab plus ipilimumab versus 13.0 months with chemotherapy (HR, 0.55; 95% CI 0.33-0.94); 3-year OS (95% CI) rates were 46% (30.2% to 60.7%) versus 20% (9.2% to 32.8%). Median OS among all patients

in the Asian subpopulation (tumor PD-L1 expression $\geq 1\%$ and $< 1\%$) was 36.2 months with nivolumab plus ipilimumab versus 22.9 months with chemotherapy (HR, 0.66; 95% CI 0.48-0.92); 3-year OS (95% CI) rates were 51% (41.5% to 59.5%) versus 31% (22.9% to 39.6%) (Figure 1B). OS was also improved with nivolumab plus ipilimumab compared with chemotherapy in Japanese patients both with tumor PD-L1 expression $\geq 1\%$ [3-year rate, 56% (95% CI 39.7% to 69.6%) versus 45% (95% CI 30.2% to 58.1%); HR, 0.77; 95% CI 0.43-1.40] and with tumor PD-L1 expression $\geq 1\%$ and $< 1\%$ [3-year rate, 56% (95% CI 43.3% to 67.0%) versus 36% (95% CI 25.7% to 47.3%); HR, 0.63; 95% CI 0.40% to 0.99%], at a minimum follow-up of 38.5 months for all randomized patients in Japan (Figure 1C and D).

Similarly, PFS per BICR favored nivolumab plus ipilimumab over chemotherapy regardless of tumor PD-L1 expression among patients in the Asian subpopulation. In those with tumor PD-L1 expression $\geq 1\%$, the median PFS was 11.0 and 6.7 months, respectively (HR 0.65; 95% CI 0.45-0.96); 3-year PFS (95% CI) rates were 26% (16.3% to 36.8%) versus 7% (1.7% to 19.1%) (Figure 2A). For patients with tumor PD-L1 expression $< 1\%$, median PFS was 5.5 months with nivolumab plus ipilimumab versus 5.6 months with chemotherapy;

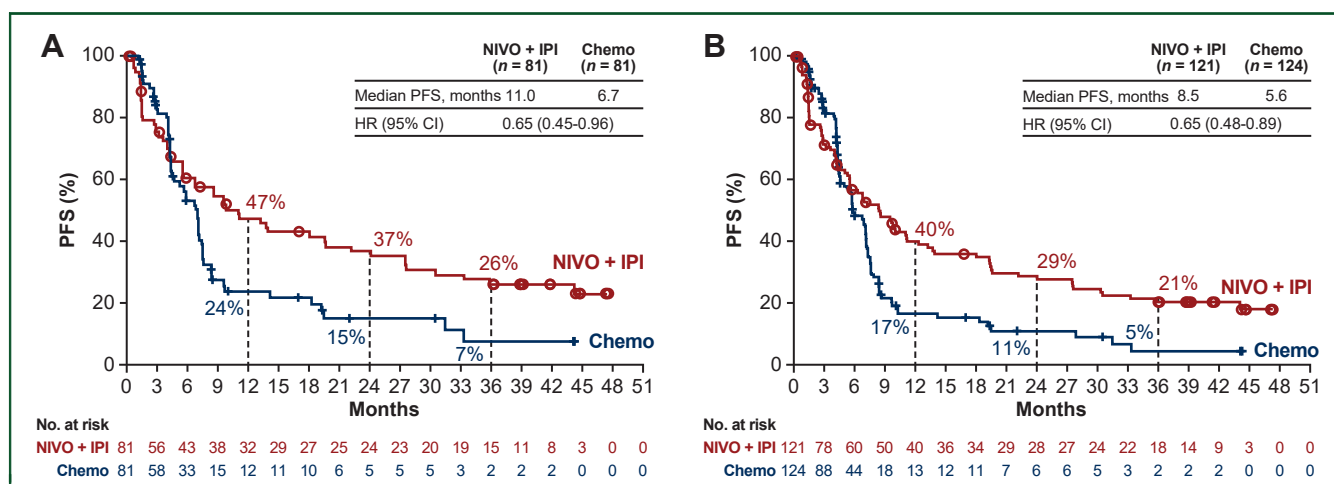


Figure 2. Progression-free survival in the Asian subpopulation based on tumor programmed death-ligand 1 expression.

(A) PFS in the Asian subpopulation among patients with tumor PD-L1 expression $\geq 1\%$. (B) PFS in the Asian subpopulation (tumor PD-L1 expression $\geq 1\%$ and $< 1\%$). Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; NIVO + IPI, nivolumab plus ipilimumab; NR, not reached; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

3-year PFS rates were 10% (95% CI 2.5% to 22.5%) versus 0%, respectively. In all Asian patients (tumor PD-L1 expression $\geq 1\%$ and $< 1\%$), median PFS was 8.5 and 5.6 months, respectively (HR, 0.65; 95% CI 0.48-0.89), with 3-year PFS (95% CI) rates of 21% (13.4% to 29.1%) versus 5% (1.0% to 12.6%), respectively (Figure 2B). PFS in Japanese patients (tumor PD-L1 expression $\geq 1\%$ and $< 1\%$) also favored nivolumab plus ipilimumab compared with chemotherapy (Supplementary Figure S2A and B, available at <https://doi.org/10.1016/j.esmooop.2022.100394>).

ORR per BICR was higher among patients treated with nivolumab plus ipilimumab as compared with chemotherapy in the Asian subpopulation (Table 2). For those with tumor PD-L1 expression $\geq 1\%$, the ORR was 56% with nivolumab plus ipilimumab and 37% with chemotherapy; 11 (14%) patients receiving nivolumab plus ipilimumab versus 2 (2%) patients receiving chemotherapy achieved complete responses. Median DOR was 29.0 months (95% CI 15.0 months-not reached) with nivolumab plus ipilimumab versus 6.9 months (95% CI 3.9-11.1 months) with chemotherapy; 43% versus 9% of patients, respectively, maintained their responses for 3 years. For patients with tumor PD-L1 expression $< 1\%$, the ORR was 32% with nivolumab plus ipilimumab and 26% with chemotherapy; two (5%) patients receiving nivolumab plus ipilimumab versus no patients receiving chemotherapy achieved complete responses. Median DOR was 16.6 months (95% CI 5.7 months-not reached) with nivolumab plus ipilimumab versus 3.7 months (95% CI 2.7-5.3 months) with chemotherapy. For all patients in the Asian subpopulation (tumor PD-L1 expression $\geq 1\%$ and $< 1\%$), the ORR was higher with nivolumab plus ipilimumab than with chemotherapy (48% versus 33%, respectively); 13 (11%) patients receiving nivolumab plus ipilimumab versus 2 (2%) patients receiving chemotherapy achieved complete responses. Median DOR was 24.9 months (95% CI 15.2-42.7 months) with nivolumab plus ipilimumab versus 5.6 months (95% CI 3.7-6.9 months) with chemotherapy; 3-year DOR rates were 39% versus 6%, respectively. The higher ORR and 3-year DOR rate

and longer median DOR with nivolumab plus ipilimumab versus chemotherapy were also observed among Japanese patients (Table 2).

Safety

For the Asian subpopulation, TRAEs of any grade occurred in 105 (87%) patients treated with nivolumab plus ipilimumab and 109 (89%) patients treated with chemotherapy (Table 3). The most common ($\geq 15\%$) any-grade TRAEs in patients treated with nivolumab plus ipilimumab were rash (22%), pyrexia (19%), pruritus (17%), diarrhea (17%), decreased appetite (17%), and fatigue (16%); the most common ($\geq 30\%$) any-grade TRAEs in patients treated with chemotherapy were nausea (42%), constipation (42%), decreased appetite (39%), and decreased neutrophil count (31%). Grade 3-4 TRAEs occurred in 49 (40%) and 44 (36%) patients treated with nivolumab plus ipilimumab and chemotherapy, respectively. The most common ($\geq 5\%$) grade 3-4 TRAEs in patients treated with nivolumab plus ipilimumab were increased amylase and hyponatremia (5% each); the most common ($\geq 15\%$) grade 3-4 TRAE in patients treated with chemotherapy was decreased neutrophil count (15%). Any-grade TRAEs leading to discontinuation of any component of the regimen occurred in 26 (21%) and 17 (14%) patients treated with nivolumab plus ipilimumab and chemotherapy, respectively. Two treatment-related deaths were reported in the nivolumab plus ipilimumab arm (one due to pneumonitis and one due to shock) versus one in the chemotherapy arm (due to interstitial lung disease).

The most common ($\geq 20\%$) select TRAEs of any grade observed with nivolumab plus ipilimumab were skin (54%), endocrine (27%), and gastrointestinal (20%) events. Most common ($\geq 5\%$) grade 3-4 select TRAEs were endocrine (9%) and hepatic (8%) events (Supplementary Table S2, available at <https://doi.org/10.1016/j.esmooop.2022.100394>).

The safety profile of nivolumab plus ipilimumab in Japanese patients was similar to that in the overall Asian subpopulation, and no new safety signals were identified

Table 2. Efficacy in the Asian subpopulation, including Japanese patients											
All patients (PD-L1 ≥1% and <1%)											
Patients with tumor PD-L1 expression ≥1%						Patients with tumor PD-L1 expression <1%					
Asian			Japanese			Asian			Japanese		
	Nivolumab plus ipilimumab (n = 81)	Chemotherapy (n = 81)	Nivolumab plus ipilimumab (n = 41)	Chemotherapy (n = 48)	Nivolumab plus ipilimumab (n = 121)	Chemotherapy (n = 124)	Nivolumab plus ipilimumab (n = 66)	Chemotherapy (n = 77)			
Confirmed ORR, ^a n (%)	56 (68)	37 (46)	63 (78)	40 (50)	48 (59)	33 (41)	53 (65)	36 (45)			
95% CI	44-67	27-48	47-78	26-55	39-57	25-42	40-65	26-48			
Best overall response, ^a n (%)	11 (14)	2 (2)	9 (22)	2 (4)	13 (11)	2 (2)	11 (17)	2 (3)			
Complete response	34 (42)	28 (35)	17 (41)	17 (35)	45 (37)	39 (31)	24 (36)	26 (34)			
Partial response	17 (21)	41 (51)	7 (17)	24 (50)	32 (26)	67 (54)	15 (23)	41 (53)			
Stable disease	12 (15)	7 (9)	7 (17)	4 (8)	20 (17)	12 (10)	13 (20)	6 (8)			
Progressive disease	7 (9)	3 (4)	1 (2)	1 (2)	11 (9)	4 (3)	3 (5)	2 (3)			
Not determined											
Median DOR, ^{a,b} months (95% CI)	29.0 (15.0-NR)	6.9 (3.9-11.1)	NR (18.0-NR)	7.1 (3.9-31.6)	24.9 (15.2-42.7)	5.6 (3.7-6.9)	28.6 (16.6-NR)	5.6 (3.1-7.1)			
3-year DOR rate, ^{a,b} % (95% CI)	43 (28-58)	9 (1-30)	51 (29-69)	14 (1-42)	39 (26-52)	6 (1-22)	44 (26-60)	9 (1-30)			

CI, confidence interval; DOR, duration of response; NR, not reached; ORR, objective response rate; PD-L1, programmed death-ligand 1.

^a ORR and DOR were assessed by blinded independent central review.

^b DOR evaluated for all responders.

(Table 3 and Supplementary Table S2, available at <https://doi.org/10.1016/j.esmooop.2022.100394>).

DISCUSSION

The primary results of part 1 of CheckMate 227 established the superior efficacy of first-line nivolumab plus ipilimumab versus chemotherapy in the treatment of patients with advanced NSCLC and tumor PD-L1 expression ≥1%.¹¹ With a 3-year follow-up, benefits in OS, BICR-assessed PFS, and DOR were durable with nivolumab plus ipilimumab versus chemotherapy in patients with tumor PD-L1 expression ≥1%, as well as those with tumor PD-L1 expression <1% and all randomized patients.¹⁰ The present analysis examined the efficacy and safety of nivolumab plus ipilimumab versus chemotherapy in the Asian subpopulation from part 1 of CheckMate 227. With 38.1 months of minimum follow-up, nivolumab plus ipilimumab provided durable long-term OS, PFS, and DOR benefit versus chemotherapy, regardless of tumor PD-L1 expression, in this subgroup of patients. Results were consistent with those of all randomized patients in the study.^{10,11} Similar results were also observed in the Japanese patients. Of note, although the sample size of Japanese patients was relatively small, the proportion of patients with ECOG performance status 0 in the chemotherapy arm was slightly higher than that in the nivolumab plus ipilimumab arm. Nonetheless, this did not appear to negatively impact efficacy results with nivolumab plus ipilimumab.

As differences in treatment outcomes for NSCLC between Asian and non-Asian populations have been observed with various therapies (possibly due to inherent genetic variations and/or varying standards of clinical care between countries),²² analyses of efficacy and safety in Asian subpopulations are important for evaluating optimal treatment options. The consistent findings across subgroups and all randomized patients in this study are in line with prior studies that compared clinical outcomes of first-line immunotherapy for NSCLC between Asian and global populations.²⁷⁻³³ In a subanalysis of Asian patients enrolled in CheckMate 9LA, first-line nivolumab plus ipilimumab in combination with two cycles of chemotherapy showed survival benefit over chemotherapy, consistent with results in all randomized patients.^{30,31} Subanalyses of the KEYNOTE-407 study in East Asian patients and the KEYNOTE-189 study in Japanese patients showed clinical benefits of first-line pembrolizumab plus chemotherapy over chemotherapy for metastatic squamous or nonsquamous NSCLC, respectively, consistent with results in the all randomized population of each study.^{27,28,32,33} Similarly, in a subgroup analysis of the KEYNOTE-024 study in Japanese patients with metastatic NSCLC and PD-L1 tumor proportion score ≥50%, pembrolizumab monotherapy showed survival benefit over platinum-based chemotherapy, consistent with the outcomes for all randomized patients in the study.^{34,35} Cross-study comparisons should be made with caution, however, due to differences in patient populations, study design, and other key elements.

No new safety signals were identified among patients in the Asian subpopulation. Notably, the frequencies of TRAEs

Table 3. TRAEs in the Asian subpopulation, including Japanese patients (tumor PD-L1 expression $\geq 1\%$ and $< 1\%$)

TRAEs, ^a n (%)	Asian				Japanese			
	Nivolumab plus ipilimumab (n = 121)		Chemotherapy (n = 123)		Nivolumab plus ipilimumab (n = 66)		Chemotherapy (n = 76)	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
All events	105 (87)	49 (40)	109 (89)	44 (36)	63 (96)	36 (55)	73 (96)	36 (47)
Reported in $\geq 15\%$ of patients								
Rash	27 (22)	1 (1)	9 (7)	0	7 (11)	0	4 (5)	0
Pyrexia	23 (19)	1 (1)	3 (2)	0	21 (32)	1 (2)	2 (3)	0
Pruritus	21 (17)	0	2 (2)	0	10 (15)	0	1 (1)	0
Diarrhea	20 (17)	0	11 (9)	0	14 (21)	0	8 (11)	0
Decreased appetite	20 (17)	1 (1)	48 (39)	3 (2)	12 (18)	1 (2)	35 (46)	3 (4)
Fatigue	19 (16)	1 (1)	17 (14)	0	8 (12)	1 (2)	10 (13)	0
Maculopapular rash	17 (14)	3 (2)	7 (6)	0	17 (26)	3 (5)	7 (9)	0
Hyponatremia	10 (8)	6 (5)	3 (2)	1 (1)	9 (14)	5 (8)	3 (4)	1 (1)
Malaise	8 (7)	0	19 (15)	0	7 (11)	0	18 (24)	0
Increased amylase	8 (7)	6 (5)	2 (2)	0	5 (8)	3 (5)	2 (3)	0
Nausea	7 (6)	1 (1)	52 (42)	3 (2)	4 (6)	1 (2)	39 (51)	1 (1)
Anemia	7 (6)	3 (2)	33 (27)	12 (10)	6 (9)	2 (3)	25 (33)	9 (12)
Constipation	6 (5)	0	52 (42)	1 (1)	5 (8)	0	45 (59)	1 (1)
Neutrophil count decreased	3 (2)	0	38 (31)	19 (15)	3 (5)	0	33 (43)	15 (20)
Platelet count decreased	1 (1)	0	22 (18)	4 (3)	1 (2)	0	19 (25)	4 (5)
TRAEs leading to treatment discontinuation	26 (21)	17 (14)	17 (14)	7 (6)	19 (29)	11 (17)	14 (18)	6 (8)
Reported in ≥ 2 patients								
Pneumonitis	5 (4)	4 (3)	2 (2)	0	3 (5)	2 (3)	1 (1)	0
Interstitial lung disease	2 (2)	0	1 (1)	1 (1)	2 (3)	0	1 (1)	1 (1)
Adrenal insufficiency	2 (2)	0	0	0	2 (3)	0	0	0
Hypopituitarism	2 (2)	2 (2)	0	0	2 (3)	2 (3)	0	0
Hepatitis	2 (2)	2 (2)	0	0	0	0	0	0
Blood creatinine increased	0	0	2 (2)	0	0	0	2 (3)	0
Neutrophil count decreased	0	0	2 (2)	2 (2)	0	0	2 (3)	2 (3)
Anemia	0	0	2 (2)	0	0	0	1 (1)	0
Treatment-related deaths	2 (2) ^b	—	1 (1) ^c	—	1 (2)	—	1 (1)	—

PD-L1, programmed death-ligand 1; TRAE, treatment-related adverse event.

^a Includes events reported between first dose and 30 days after last dose of study drug.

^b Treatment-related deaths in the nivolumab plus ipilimumab arm were pneumonitis (n = 1) and shock (n = 1, a Japanese patient).

^c Treatment-related death in the chemotherapy arm was due to interstitial lung disease (n = 1, a Japanese patient).

and those leading to treatment discontinuation in both treatment groups were somewhat higher among patients in the Asian subpopulation compared with all randomized patients, which may be due to regional differences in AE management, or differences in genetic or disease characteristics in Asian patients with NSCLC.^{22,23} Of select TRAEs with nivolumab plus ipilimumab, skin events were more frequent among patients in the Asian subpopulation than among all randomized patients¹¹; however, most were grade 1-2.

Among the Asian subpopulation, subsequent therapy was received by more than half of the patients in the nivolumab plus ipilimumab arm and by the majority of patients in the chemotherapy arm; this proportion was greater compared with those in the chemotherapy arm among all randomized patients. Of note, 75% of Japanese patients in the chemotherapy arm received subsequent immunotherapy, with 71% receiving PD-1 inhibitors. This proportion was higher compared with patients in the Asian subpopulation who received chemotherapy, with 57% receiving subsequent immunotherapy and 51% receiving PD-1 inhibitors.

This exploratory analysis was not powered to carry out statistical testing for differences between treatment arms. Additionally, this study was limited by small sample sizes for these subpopulations. The findings for the Asian subpopulation, however, were consistent with those in all

randomized patients and in line with what has been reported with other immunotherapy-based treatments.^{30,34} Future confirmatory studies should be conducted in larger cohorts to further evaluate the efficacy and safety of nivolumab plus ipilimumab in these patient groups.

In conclusion, first-line nivolumab plus ipilimumab provided efficacy benefits versus chemotherapy for patients with advanced NSCLC and tumor PD-L1 expression $\geq 1\%$ in the Asian subpopulation of CheckMate 227 part 1, as well as in patients regardless of tumor PD-L1 expression. Consistent with findings in all randomized patients, these data lend additional support to the use of nivolumab plus ipilimumab as first-line treatment of advanced NSCLC in Asian patients, including Japanese patients.

ACKNOWLEDGEMENTS

We thank the patients and their families for making this trial possible; the investigators and clinical trial teams who participated in the trial; Sridhar Rabindran and Ravi Kasinathan who served as clinical trial leads; Ang Li who served as protocol statistician; Arteid Memaj who conducted the statistical analysis for the Asian population; Suresh Alaparthi, Judith Bushong, and Dimple Kapadia-Carallo who served as protocol managers; Foundation Medicine for the collaborative development of the FoundationOne CDx

assay; Dako for the collaborative development of the PD-L1 IHC 28-8 pharmDx assay; and Bristol Myers Squibb (Princeton, NJ) and Ono Pharmaceutical Company Ltd. (Osaka, Japan). All authors contributed to and approved the presentation; writing and editorial assistance were provided by Thai Cao, MS, and Brooke Middlebrook, CMPP, of Evidence Scientific Solutions, Philadelphia, PA, funded by Bristol Myers Squibb. This trial was supported by Bristol Myers Squibb.

FUNDING

This work was supported by Bristol Myers Squibb (Princeton, NJ) (no grant number) and Ono Pharmaceutical Company Ltd (Osaka, Japan) (no grant number).

ROLE OF THE FUNDER

The study was designed by the steering committee and the funder. The funder contributed to data collection with the investigators, to data analysis and interpretation in collaboration with the authors, and to the writing of the report by funding professional medical writing assistance. All authors had full access to all the data in the study. Authors received no financial support or compensation for publication of this manuscript.

DISCLOSURE

KJO: advisory board and/or speaker bureau and/or meeting travel/registration support from Astellas, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Janssen-Cilag, Merck Sharp & Dohme (MSD), Mundipharma, Natera, Novartis, Pfizer, Roche-Genentech, Teva, and TriStar; board member and shareholder: Carpe Vitae Pharmaceuticals; shareholder: DGC Diagnostics and ReLuca Pharmaceuticals; holds patents for novel therapeutics and diagnostic tests. KHL: advisory board: AstraZeneca, Bristol Myers Squibb, Eli Lilly, MSD, and Pfizer. KP: advisor/consultant: Bristol Myers Squibb. MN: consulting/advisory and/or honoraria and/or research funding: Abbvie, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Chugai Pharmaceutical Co. Ltd., Daichi Sankyo, Janssen, Lilly, Merck, MSD, Nippon Kayaku, Novartis, Ono Pharmaceutical Co. Ltd, Pfizer, Taiho Pharmaceutical Co. Ltd, Takeda, and Teijin Pharma. HS: research funding and/or honoraria: AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Bristol Myers Squibb Japan, Chugai Pharmaceutical Co. Ltd., Merck KGaA, MSD K.K., Ono Pharmaceutical Co. Ltd, and Taiho Pharmaceutical Co. Ltd. YO: research funding and/or honoraria: Amgen, AstraZeneca, Boehringer Ingelheim, Celtrion, Chugai Pharmaceutical Co. Ltd, Eli Lilly, Janssen, Kissei, Kyorin, MSD, Nippon Kayaku, Novartis, Pfizer, Taiho Pharmaceutical Co. Ltd, and Takeda. TF: research funding: Bristol Myers Squibb. HD: honoraria: AstraZeneca, Chugai Pharmaceutical Co. Ltd, Eli Lilly Japan, and Ono Pharmaceutical Co. Ltd. KH: research funding and/or honoraria: AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Chugai Pharmaceutical Co. Ltd, Lilly, MSD, Nippon Kayaku, Ono Pharmaceutical Co. Ltd, Pfizer, Taiho Pharmaceutical Co. Ltd,

and Takeda. MT: honoraria: AstraZeneca, Bristol Myers Squibb, Chugai Pharmaceutical Co. Ltd, Novartis, and Ono Pharmaceutical Co. Ltd. TY: research funding and/or honoraria: AstraZeneca, Boehringer Ingelheim Japan, Bristol Myers Squibb, Chugai Pharmaceutical Co. Ltd, Delta-Fly Pharma, Eli Lilly Japan, MSD K.K., Nippon Kayaku, Novartis K.K., Ono Pharmaceutical Co. Ltd, Pfizer Japan, Taiho Pharmaceutical Co. Ltd, and Takeda. FEN: employee of Bristol Myers Squibb; ownership/stockholder: AstraZeneca, Bristol Myers Squibb, Eli Lilly, Gilead Sciences, and Johnson & Johnson. All other authors have declared no conflicts of interest.

DATA SHARING

Data are available upon reasonable request. Bristol Myers Squibb policy on data sharing may be found at <https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html>.

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