ORIGINAL ARTICLE

Long-Term Survival Outcomes With First-Line Nivolumab Plus Ipilimumab–Based Treatment in Patients With Metastatic NSCLC and Tumor Programmed Death-Ligand 1 Lower Than 1%: A Pooled Analysis

Solange Peters, MD, PhD,[a,*] Luis G. Paz-Ares, MD, PhD,[b] Martin Reck, MD, PhD,[c] David P. Carbone, MD, PhD,[d] Julie R. Brahmer, MD,[e] Hossein Borghaei, DO, MS,[f] Shun Lu, MD, PhD,[g] Kenneth J. O'Byrne, MD, PhD,[h] Thomas John, MD, PhD,[i] Tudor-Eliade Ciuleanu, MD, PhD,[j] Michael Schenker, MD, PhD,[k] Reyes Bernabe Caro, MD, PhD,[l] Makoto Nishio, MD, PhD,[m] Manuel Cobo, MD, PhD,[n] Jong-Seok Lee, MD, PhD,[o] Bogdan Zurawski, MD, PhD,[p] Adam Pluzanski, MD, PhD,[q] Takekazu Aoyama, MD, PhD,[r] Marina Tschaika, MD, PhD, MSc, MBA,[s] Vipul Devas, PhD,[t] Diederik J. Grootendorst, PhD,[u] Suresh S. Ramalingam, MD[v]

[a]*Oncology Department, Lausanne University Hospital, Lausanne, Switzerland*
[b]*Medical Oncology Department, Hospital Universitario 12 de Octubre, Universidad Complutense de Madrid, Madrid, Spain*
[c]*Department of Thoracic Oncology, Airway Research Center North, German Center for Lung Research, LungenClinic Grosshansdorf, Grosshansdorf, Germany*
[d]*Department of Medical Oncology, The Ohio State University Comprehensive Cancer Center and the Pelotonia Institute for Immuno-Oncology, Columbus, Ohio*
[e]*Department of Oncology, The Bloomberg-Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Medicine, The Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland*
[f]*Hematology and Oncology Department, Fox Chase Cancer Center, Temple Health, Philadelphia, Pennsylvania*
[g]*Department of Medical Oncology, Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, People's Republic of China*
[h]*Department of Medical Oncology, Princess Alexandra Hospital, Translational Research Institute and Queensland University of Technology, Brisbane, Queensland, Australia*
[i]*Medical Oncology Department, Austin Hospital, Heidelberg, Victoria, Australia*
[j]*Department of Medical Oncology, Institutul Oncologic Prof Dr Ion Chiricuță and University of Medicine and Pharmacy Iuliu Haţieganu, Cluj-Napoca, Romania*
[k]*Department of Medical Oncology, SF Nectarie Oncology Center, Craiova, Romania*
[l]*Medical Oncology Department, Hospital Universitario Virgen Del Rocio, Instituto de Biomedicina de Seville, Seville, Spain*
[m]*Department of Thoracic Medical Oncology, Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan*
[n]*Department of Medical Oncology, Unidad de Gestión Clínica Intercentros de Oncología Médica, Hospitales Universitarios Regional y Virgen de la Victoria, Instituto de Investigación Biomédica de Málaga (IBIMA), Málaga, Spain*
[o]*Department of Hematology/Oncology, Seoul National University Bundang Hospital, Seongnam, Republic of Korea*
[p]*Chemotherapy Department, Ambulatorium Chemioterapii, Bydgoszcz, Poland*
[q]*Department of Lung Cancer and Chest Tumours, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland*
[r]*Clinical Development, Bristol Myers Squibb, Princeton, New Jersey*
[s]*Global Clinical Research Oncology, Bristol Myers Squibb, Princeton, New Jersey*
[t]*Global Biometrics and Data Sciences, Bristol Myers Squibb, Princeton, New Jersey*
[u]*Translational Sciences Oncology Imaging, Bristol Myers Squibb, Princeton, New Jersey*

***Corresponding author.**

Drs. Peters and Paz-Ares contributed equally to this work.

Address for correspondence: Solange Peters, MD, PhD, Oncology Department, Lausanne University Hospital (CHUV), Bugnon 46, 1011 Lausanne, Switzerland. E-mail: solange.peters@chuv.ch

Cite this article as: Peters S, Paz-Ares LG, Reck M, et al. Long-term survival outcomes with first-line nivolumab plus ipilimumab-based treatment in patients with metastatic NSCLC and tumor programmed death-ligand 1 lower than 1%: a pooled analysis. *J Thorac Oncol*. 2025;20:94-108.

ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2024.09.1439

[v]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, Georgia

Received 28 June 2024; revised 29 August 2024; accepted 27 September 2024
Available online - 4 October 2024

ABSTRACT

Introduction: Nivolumab plus ipilimumab–based treatment regimens have shown long-term, durable efficacy benefits in patients with metastatic NSCLC. Here we report clinical outcomes from a pooled analysis of patients with metastatic NSCLC and tumor programmed death-ligand 1 (PD-L1) lower than 1% treated with first-line nivolumab plus ipilimumab with or without two cycles of chemotherapy versus up to four cycles of chemotherapy in the randomized phase 3 CheckMate 227 and CheckMate 9LA studies.

Methods: Patients were aged 18 years or older and had stage IV or recurrent NSCLC with no sensitizing *EGFR*/*ALK* alterations. Assessments included overall survival (OS), progression-free survival (PFS), objective response rate, duration of response, and safety.

Results: In patients with tumor PD-L1 lower than 1% in the nivolumab plus ipilimumab with or without chemotherapy (n = 322) versus chemotherapy (n = 315) arms, median OS was 17.4 versus 11.3 months, respectively, (hazard ratio [HR] = 0.64, 95% confidence interval [CI]: 0.54–0.76; 5-y OS rate, 20% versus 7%) at a median follow-up of 73.7 months. The OS benefit was observed across key subgroups, including difficult-to-treat populations such as those with baseline brain metastases (HR = 0.44, 95% CI: 0.26–0.75) or squamous NSCLC (HR = 0.51, 95% CI: 0.36–0.72). In the overall pooled population, the median PFS was 5.4 versus 4.9 months (HR = 0.72, 95% CI: 0.60–0.87; 5-y PFS rate, 9% versus 2%), the objective response rate was 29% versus 22%, and the median duration of response was 18.0 versus 4.6 months. No new safety signals were observed.

Conclusion: Nivolumab plus ipilimumab with or without chemotherapy provides a long-term, durable clinical benefit in patients with metastatic NSCLC and tumor PD-L1 lower than 1%, supporting the use of this strategy as a first-line treatment option in this population with high unmet need. Clinical Trial Registrations: NCT02477826, NCT03215706

Keywords: Non–small cell lung cancer; PD-L1; Immunotherapy; Nivolumab; Ipilimumab

Introduction

Programmed death-ligand 1 (PD-L1) expression in tumors is a predictive biomarker for PD-L1 or programmed cell death protein-1 (PD-1) inhibitors in patients with metastatic NSCLC with no targetable genomic driver mutations, with increasing tumor PD-L1 expression associated with an enriched efficacy benefit.[1,2] Anti–PD-(L)1 immunotherapies, including pembrolizumab, atezolizumab, and cemiplimab, are currently recommended as first-line treatment options, as monotherapy or in combination with chemotherapy, in eligible patients with tumor PD-L1 equal to or higher than 1%.[3] However, patients with tumor PD-L1 lower than 1% experience suboptimal long-term clinical outcomes when treated with these regimens, indicating a patient population with a high unmet need.[1,4–9] Nivolumab, an anti–PD-1 immunotherapy, and ipilimumab, a CTLA-4 inhibitor, have distinct but complementary mechanisms of action to reactivate the immune system.[10,11] Ipilimumab may increase tumor PD-L1 expression, reinvigorate and maintain CD4 and CD8-positive T-cell responses, and inhibit regulatory T cells, even in tumors with PD-L1 lower than 1%, thereby increasing the potential therapeutic activity of the dual immunotherapy regimen of nivolumab in combination with ipilimumab relative to nivolumab-based regimens alone.[10,11]

Nivolumab plus ipilimumab, with or without two cycles of chemotherapy, is currently recommended as a first-line treatment option for patients with metastatic NSCLC without targetable genomic driver alterations and with tumor PD-L1 equal to or higher than 1% or lower than 1% in several treatment guidelines, including the National Comprehensive Cancer Network, the American Society of Clinical Oncology, and the European Society for Medical Oncology,[3,12,13] based on data from the randomized phase 3 CheckMate 227 and CheckMate 9LA studies. In CheckMate 227, first-line nivolumab plus ipilimumab improved overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and duration of response (DOR) versus up to four cycles of chemotherapy in patients with metastatic NSCLC and tumor PD-L1 higher than or equal to 1% or lower than 1%[14] Nivolumab plus ipilimumab was approved in the United States, Canada, and other countries based on improved OS in patients with metastatic NSCLC and tumor PD-L1 higher than or equal to 1% (primary end point population)[15,16] and regardless of tumor PD-L1 expression in Japan and Argentina.[17,18] Patients with tumor PD-L1 lower than 1% continued to derive long-term, durable clinical benefit from nivolumab plus ipilimumab versus chemotherapy at 6 years of follow-up in CheckMate 227, with a hazard ratio (HR) of 0.65 (95%

confidence interval [CI]: 0.52–0.81) for OS; 6-year OS rates of 16% versus 5%; ORRs of 27% versus 23%; and median DOR of 19.4 versus 4.8 months with 25% versus 0% of responders experiencing an ongoing response at 6 years.[19] Long-term clinical benefit with nivolumab plus ipilimumab was also observed in a large, pooled analysis of patients with metastatic NSCLC (including those with tumor PD-L1 lower than 1%) from the CheckMate 227, CheckMate 817, CheckMate 568, and CheckMate 012 studies.[20]

Similarly, in CheckMate 9LA, first-line nivolumab plus ipilimumab with two cycles of chemotherapy improved OS, PFS, ORR, and DOR versus four cycles of chemotherapy alone in patients with metastatic NSCLC, including both the tumor PD-L1 higher than or equal to 1% and lower than 1% subgroups.[21] Based on the primary results from CheckMate 9LA, nivolumab plus ipilimumab with chemotherapy was approved in the United States, European Union, and other countries for the treatment of patients with metastatic NSCLC, regardless of tumor PD-L1 expression.[15,17,22] At the 5-year follow-up of CheckMate 9LA, nivolumab plus ipilimumab with chemotherapy versus chemotherapy alone in patients with tumor PD-L1 lower than 1% had an HR of 0.63 (95% CI: 0.49–0.83) for OS; 5-year OS rates of 22% versus 8%; ORRs of 31% versus 20%; and median DOR of 17.5 versus 4.3 months with 25% versus 0% of responders experiencing an ongoing response at 5 years.[23]

Here, we present long-term efficacy and safety outcomes of nivolumab plus ipilimumab with or without chemotherapy versus chemotherapy alone in a large, pooled population of patients with metastatic NSCLC and tumor PD-L1 lower than 1% from CheckMate 227 and CheckMate 9LA, including subgroups by baseline brain metastases status and tumor type (squamous or nonsquamous NSCLC). In addition, we report long-term clinical outcomes in patients with tumor PD-L1 lower than 1% who discontinued nivolumab plus ipilimumab with or without chemotherapy due to treatment-related adverse events (TRAEs) or who completed the 2-year per-protocol immunotherapy regimen.

Materials and Methods

Study Designs and Patients

Study designs and eligibility criteria from CheckMate 227 Part 1 (NCT02477826) and CheckMate 9LA (NCT03215706) have been previously reported and are summarized in Supplementary Table 1.[14,19,21,23] Both CheckMate 227 and CheckMate 9LA are randomized, open-label, phase 3 studies. Briefly, adults with histologically confirmed stage IV or recurrent NSCLC (per the Seventh International Association for the Study of Lung Cancer classification), no prior systemic anticancer therapy, no known sensitizing *EGFR* or *ALK* alterations, and Eastern Cooperative Oncology Group performance status 1 and lower were enrolled.

In the CheckMate 227 study, patients with tumor PD-L1 equal to or higher than 1% were assigned to the Part 1a cohort, whereas patients with tumor PD-L1 lower than 1% were assigned to part 1b. In part 1b, patients were randomly assigned in a one-to-one-to-one ratio (1:1:1) to receive nivolumab (3 mg/kg every 2 wk) plus ipilimumab (1 mg/kg every 6 wk), nivolumab (360 mg every 3 wk) with chemotherapy (up to four cycles every 3 wk), or chemotherapy alone (up to four cycles every 3 wk). In the CheckMate 9LA study, patients were randomly assigned in a one-to-one ratio to receive nivolumab (360 mg every 3 wk) plus ipilimumab (1 mg/kg every 6 wk) with chemotherapy (two cycles every 3 wk) or chemotherapy alone (four cycles every 3 wk). Stratification factors included tumor PD-L1 expression (higher than or equal to 1% or lower than 1%). Optional pemetrexed maintenance was permitted for patients with nonsquamous NSCLC randomly assigned to chemotherapy. In both studies, treatment with nivolumab plus ipilimumab continued until disease progression, unacceptable toxicity, or for up to 2 years.

Both the CheckMate 227 and CheckMate 9LA studies were conducted in accordance with the Declaration of Helsinki and International Standards of Good Clinical Practice. The independent ethics committee or institutional review board of each participating study center approved the protocols and all amendments. All patients provided written informed consent.

End Points and Assessments

Primary outcomes for patients with tumor PD-L1 lower than 1% in the CheckMate 227 and CheckMate 9LA studies are shown in Supplementary Table 1. The current analysis includes a pooled population of patients with tumor PD-L1 lower than 1% treated with nivolumab plus ipilimumab (CheckMate 227 Part 1b) or nivolumab plus ipilimumab with chemotherapy (CheckMate 9LA) versus a pooled population with tumor PD-L1 lower than 1% treated with chemotherapy alone (both studies).

All assessments in this post hoc analysis were exploratory. OS was assessed in the pooled population overall and in patient subgroups, including those defined by baseline brain metastases status and tumor type (squamous or nonsquamous). PFS, best overall response, ORR, and DOR were analyzed in the pooled population overall and by tumor type based on data from Response Evaluation Criteria in Solid Tumors version 1.1 assessments per blinded independent central review in each of the individual studies. Efficacy was also assessed in the pooled population of patients who discontinued all

components of nivolumab plus ipilimumab with or without chemotherapy due to TRAEs and in patients who completed 2 years of immunotherapy. Safety was assessed in all patients who received one or more doses of the study drug; per the protocols of both studies, TRAEs included all events reported between the first dose to 30 days after the last dose of study therapy.

Statistical Analysis

Survival curves and rates for OS, PFS, and DOR were estimated using the Kaplan–Meier methodology. HRs and associated CIs were estimated using unstratified Cox proportional hazard models with the treatment arm as a single covariate. CIs for ORR were based on the Clopper–Pearson method.

Results

Patients and Treatment

The pooled cohort of patients with tumor PD-L1 lower than 1% included 322 patients in the nivolumab plus ipilimumab with or without chemotherapy arm (n = 187 with nivolumab plus ipilimumab from CheckMate 227 and n = 135 with nivolumab plus ipilimumab with chemotherapy from CheckMate 9LA) and 315 patients in the chemotherapy-alone arm (n = 186 from CheckMate 227 and n = 129 from CheckMate 9LA) (Supplementary Fig. 1). Baseline patient characteristics of the pooled population were generally balanced between treatment arms (Table 1) and were largely similar between the individual studies (Supplementary Table 2). Among patients with or without baseline brain metastases, baseline characteristics were generally similar with the exception of a higher proportion of patients with nonsquamous (versus squamous) NSCLC in those with brain metastases across both treatment arms, as expected, and a higher proportion of male patients among those without brain metastases in the chemotherapy arm (Supplementary Table 3). In addition, some differences in the presence of bone and liver metastases were observed between studies and between patient subgroups with or without baseline brain metastases (Supplementary Tables 2 and 3).

The database lock dates used for CheckMate 227 and CheckMate 9LA were February 21, 2023, and December 15, 2023, respectively. Median follow-up in the overall pooled population was 73.7 months (range: 57.3–86.2) (Supplementary Table 1). Patients received a median of eight doses of nivolumab (range: 1–55) and four doses of ipilimumab (range: 1–19); median treatment duration and treatment exposure are summarized in Supplementary Table 4. Subsequent immunotherapy was administered to 8% of patients in the nivolumab plus ipilimumab with or without the chemotherapy arm and 36% of patients in the chemotherapy arm (Supplementary Table 5).

Table 1. Demographics and Baseline Characteristics in the Pooled Tumor PD-L1 Lower Than 1% Population

Characteristics	Nivolumab Plus Ipilimumab With or Without Chemotherapy (n = 322)	Chemotherapy (n = 315)
Median age, y (range)	64.0 (34-87)	64.0 (30-80)
Sex, n (%)		
Male	234 (73)	216 (69)
Female	88 (27)	99 (31)
ECOG PS, n (%)[a]		
0	116 (36)	101 (32)
1	205 (64)	212 (67)
≥2	1 (<1)	1 (<1)
Smoking status, n (%)[b]		
Current or former	278 (86)	271 (86)
Never smoked	43 (13)	44 (14)
Tumor type, n (%)		
Squamous	82 (26)	82 (26)
Nonsquamous	240 (74)	233 (74)
Metastasis, n (%)		
Brain	36 (11)	33 (10)
Liver	64 (20)	56 (18)
Bone	63 (20)	53 (17)
Prior therapy, n (%)		
Platinum-based chemotherapy	25 (8)	17 (5)
Other chemotherapy	26 (8)	17 (5)

Note: Percentages may not total 100 due to rounding.
[a]ECOG PS not reported in 1 (<1%) patient in the chemotherapy arm.
[b]Smoking status unknown in 1 (<1%) patient in the nivolumab plus ipilimumab with or without chemotherapy arm.
ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death ligand 1.

Efficacy in the Overall Pooled Population With Tumor PD-L1 Lower Than 1% and by Tumor Type

Nivolumab plus ipilimumab with or without chemotherapy in the pooled population improved OS versus chemotherapy alone, with a median OS of 17.4 versus 11.3 months, respectively (HR = 0.64, 95% CI: 0.54–0.76) and 5-year OS rates of 20% versus 7% (Fig. 1*A*). This OS benefit remained consistent for all key patient subgroups, including those defined by age, sex, Eastern Cooperative Oncology Group performance status, smoking status, and tumor type (Fig. 1*B*). In patients with squamous NSCLC, median OS was 16.2 versus 8.2 months with nivolumab plus ipilimumab with or without chemotherapy versus chemotherapy alone, respectively (HR = 0.51, 95% CI: 0.36–0.72), and 5-year OS rates were 21% versus 5% (Fig. 1*C*). In those with nonsquamous NSCLC, median OS was 17.8 versus 12.6

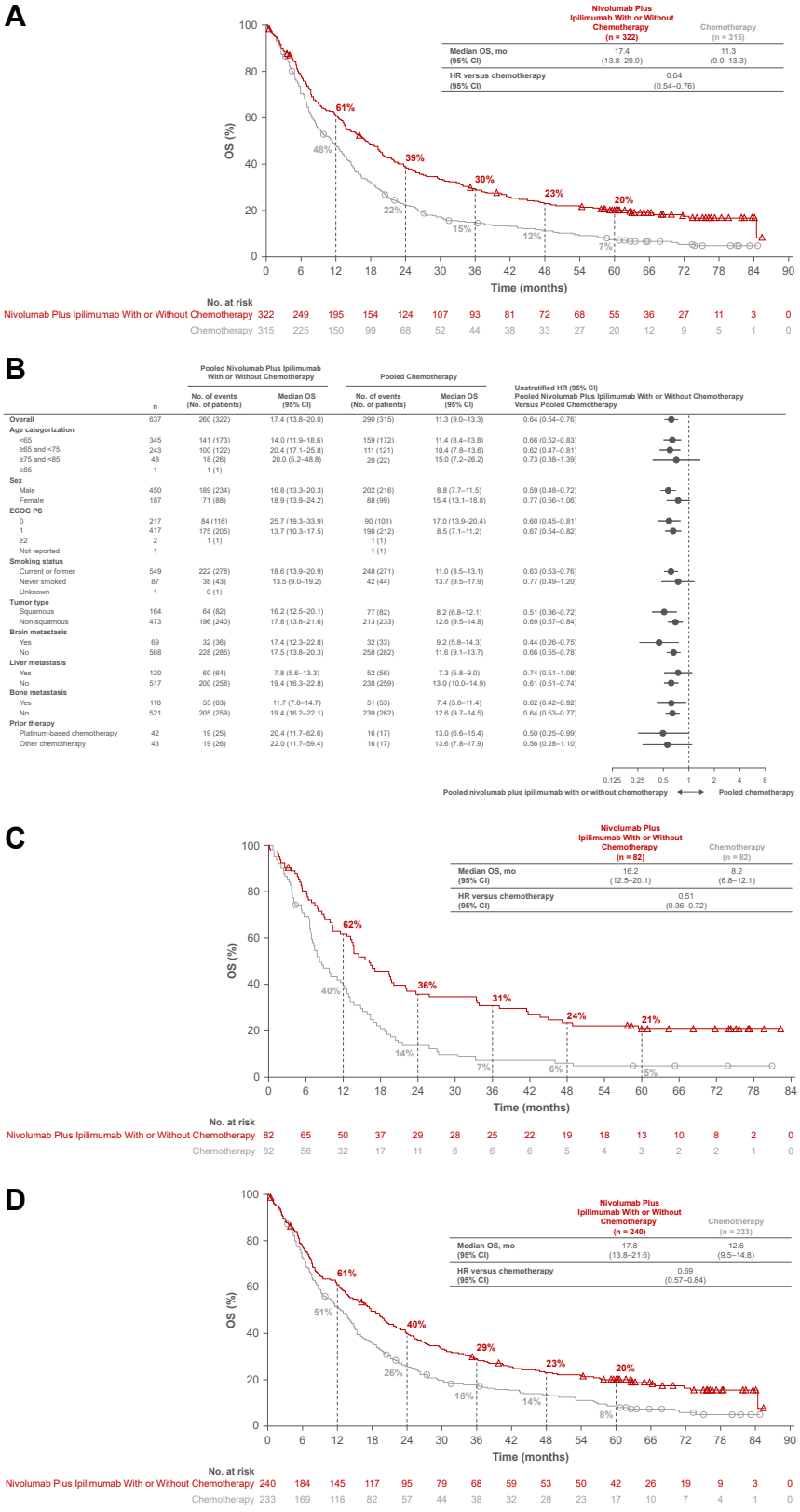

Figure 1. OS in the pooled tumor PD-L1 lower than 1% population for *(A)* all patients, *(B)* key patient subgroups, *(C)* patients with squamous NSCLC, and *(D)* patients with nonsquamous NSCLC. The 95% CIs for 5-year OS rates with nivolumab plus ipilimumab with or without chemotherapy and chemotherapy alone, respectively, were: *(A)* 16 to 25 and 5 to 11; *(C)* 13 to 30 and 2 to 11; *(D)* 15 to 25 and 5 to 12. CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand 1.

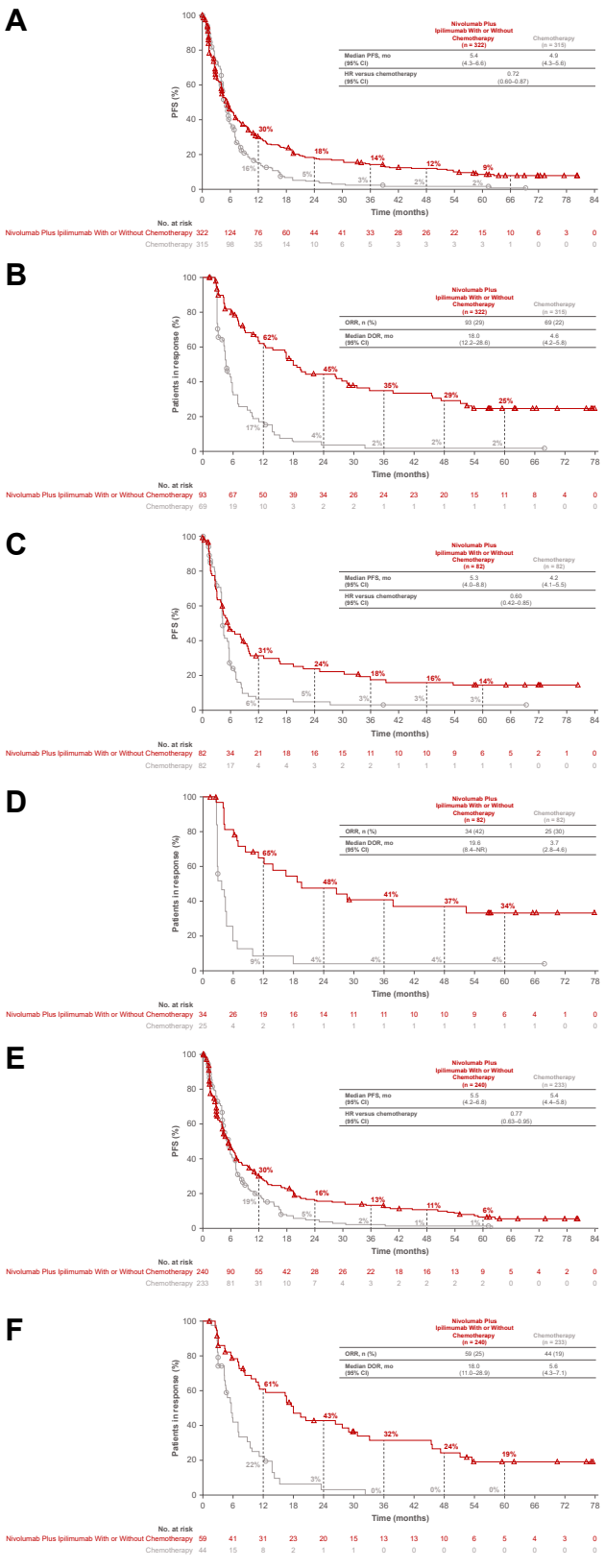

Figure 2. *(A)* PFS and *(B)* DOR in the pooled tumor PD-L1 lower than 1% population; *(C)* PFS and *(D)* DOR in patients with squamous NSCLC; and *(E)* PFS and *(F)* DOR in patients with nonsquamous NSCLC. The 95% CIs for 5-year landmark rates with nivolumab plus ipilimumab with or without chemotherapy and chemotherapy alone, respectively, were: *(A)* 6 to 13 and 1 to 5; *(B)* 16 to 35 and less than 1 to 9; *(C)* 7 to 24 and 1 to 10; *(D)* 18 to 50 and less than 1 to 18; *(E)* 3 to 11 and less than 1 to 5; *(F)* 9 to 32 and NA to NA[a]. [a]No patients alive at the time point. CI, confidence interval; DOR, duration of response; HR, hazard ratio; NA, not available; ORR, objective response rate; PD-L1, programmed death ligand 1; PFS, progression-free survival.

months (HR = 0.69, 95% CI: 0.57–0.84), and 5-year OS rates were 20% versus 8% (Fig. 1*D*).

Median PFS in the pooled population was 5.4 months in the nivolumab plus ipilimumab with or without chemotherapy arm versus 4.9 months with chemotherapy alone (HR = 0.72, 95% CI: 0.60–0.87), and 5-year PFS rates were 9% versus 2%, respectively (Fig. 2*A*). The ORR was 29% versus 22%, with median DOR of 18.0 versus 4.6 months and ongoing responses at 5 years observed in 25% versus 2% of responders, respectively (Fig. 2*B* and Supplementary Table 6). Similar PFS results were also observed with nivolumab plus ipilimumab with or without chemotherapy versus chemotherapy alone in patients with squamous (median PFS: 5.3 versus 4.2 mo, respectively; HR = 0.60, 95% CI: 0.42–0.85; 5-y PFS rate: 14% versus 3%) or nonsquamous NSCLC (median PFS: 5.5 versus 5.4 mo; HR = 0.77, 95% CI: 0.63–0.95; 5-y PFS rate: 6% versus 1%) (Figs. 2*C* and *E*). The ORRs in the respective arms among patients with squamous NSCLC were 42% versus 30%, and median DOR was 19.6 versus 3.7 months; ongoing responses at 5 years were observed in 34% versus 4% of responders (Fig. 2*D*). In patients with nonsquamous NSCLC, ORR was 25% with nivolumab plus ipilimumab with or without chemotherapy versus 19%, with chemotherapy alone and median DOR was 18.0 versus 5.6 months, respectively, with ongoing responses at 5 years observed in 19% versus 0% of responders (Fig. 2*F* and Supplementary Table 6).

Although no patient in CheckMate 9LA was treated with a regimen containing nivolumab without ipilimumab, CheckMate 227 Part 1b included patients (n = 177) randomly assigned to receive nivolumab plus chemotherapy. The 5-year OS rate in this arm was 10%, the 5-year PFS rate was 5%, the ORR was 38%, and ongoing response at 5 years was observed in 10% of responders[19] (Supplementary Table 7).

Efficacy in Patients With Tumor PD-L1 Lower Than 1% With or Without Brain Metastases

In patients with baseline brain metastases, median OS was 17.4 versus 9.2 months with nivolumab plus ipilimumab with or without chemotherapy versus chemotherapy, respectively (HR = 0.44, 95% CI: 0.26–0.75), and 5-year OS rates were 6% versus 0% (Fig. 3*A*). In

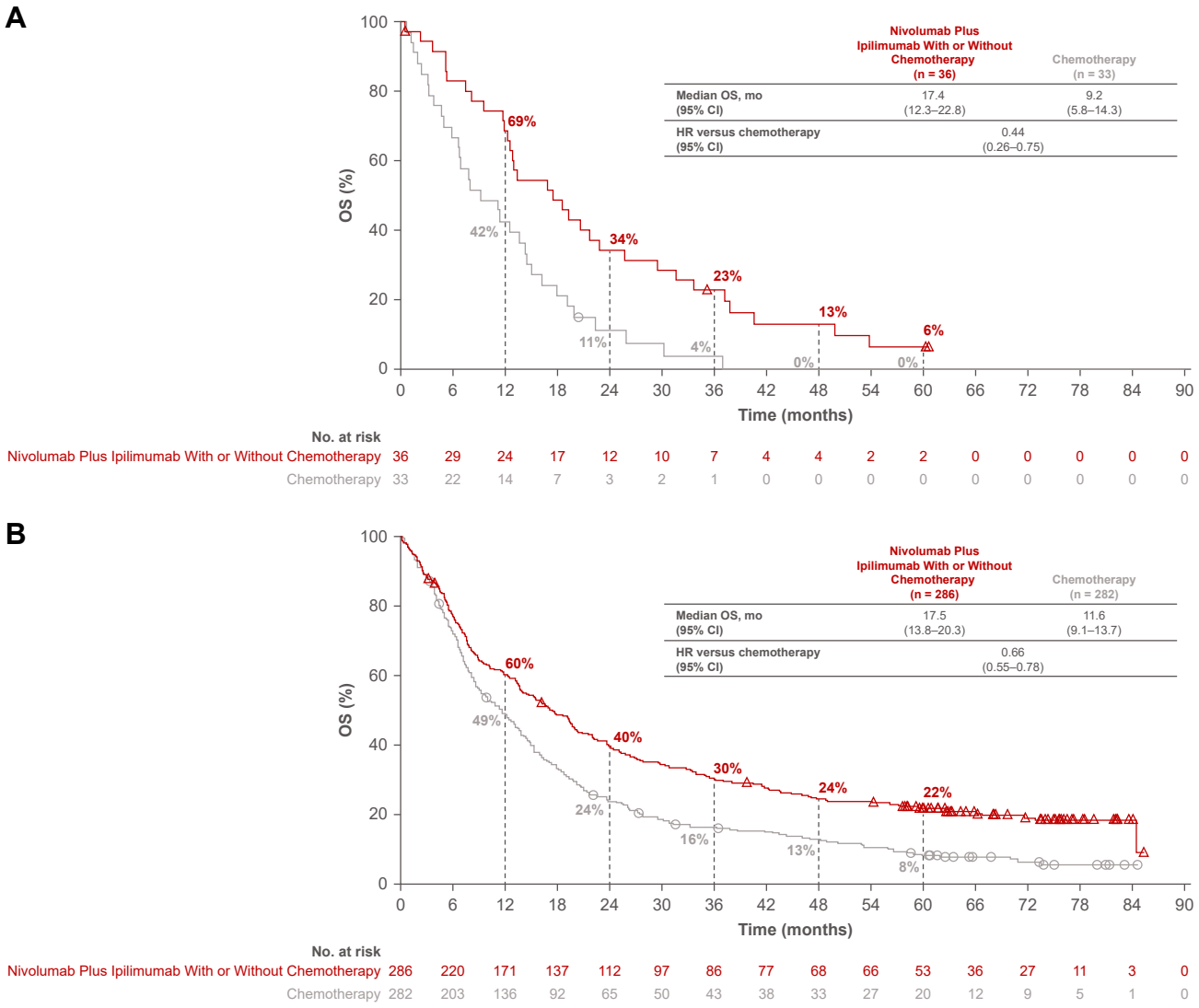

Figure 3. OS in the pooled tumor PD-L1 lower than 1% population for *(A)* patients with baseline brain metastases, and *(B)* patients without baseline brain metastases. The 95% CIs for 5-year OS rates with nivolumab plus ipilimumab with or without chemotherapy and chemotherapy alone, respectively, were: *(A)* 1 to 19 and NA to NA[a]; *(B)* 17 to 27 and 5 to 12. [a]No patients alive at the time point. CI, confidence interval; HR, hazard ratio; NA, not available; OS, overall survival; PD-L1, programmed death ligand 1.

those without baseline brain metastases, median OS was 17.5 versus 11.6 months (HR = 0.66, 95% CI: 0.55–0.78), and 5-year OS rates were 22% versus 8% (Fig. 3*B*), respectively.

Efficacy in the Pooled Population of Patients With Tumor PD-L1 Lower Than 1% and Who Discontinued Nivolumab Plus Ipilimumab With or Without Chemotherapy Due to TRAEs

Among patients treated with nivolumab plus ipilimumab with or without chemotherapy, 69 (21%) discontinued all components of the regimen due to TRAEs. Median OS was 35.4 months in this population, and the 5-year OS rate was 37% (Fig. 4*A*). By the data cutoff dates for CheckMate 227 and CheckMate 9LA, 26 patients in this subgroup of the pooled population had received subsequent therapy, of whom 10 were alive and 16 had died. Forty-three patients had not received subsequent therapy, of whom 14 were alive and 29 had died. Duration of treatment and response patterns among patients who discontinued nivolumab plus ipilimumab with or without chemotherapy due to TRAEs are shown in Figure 4*B*.

Efficacy in the Pooled Population of Patients With Tumor PD-L1 Lower Than 1% and Who Completed 2 Years of Immunotherapy Treatment

In the nivolumab plus ipilimumab with or without chemotherapy arm, 32 patients (10%) completed 2 years

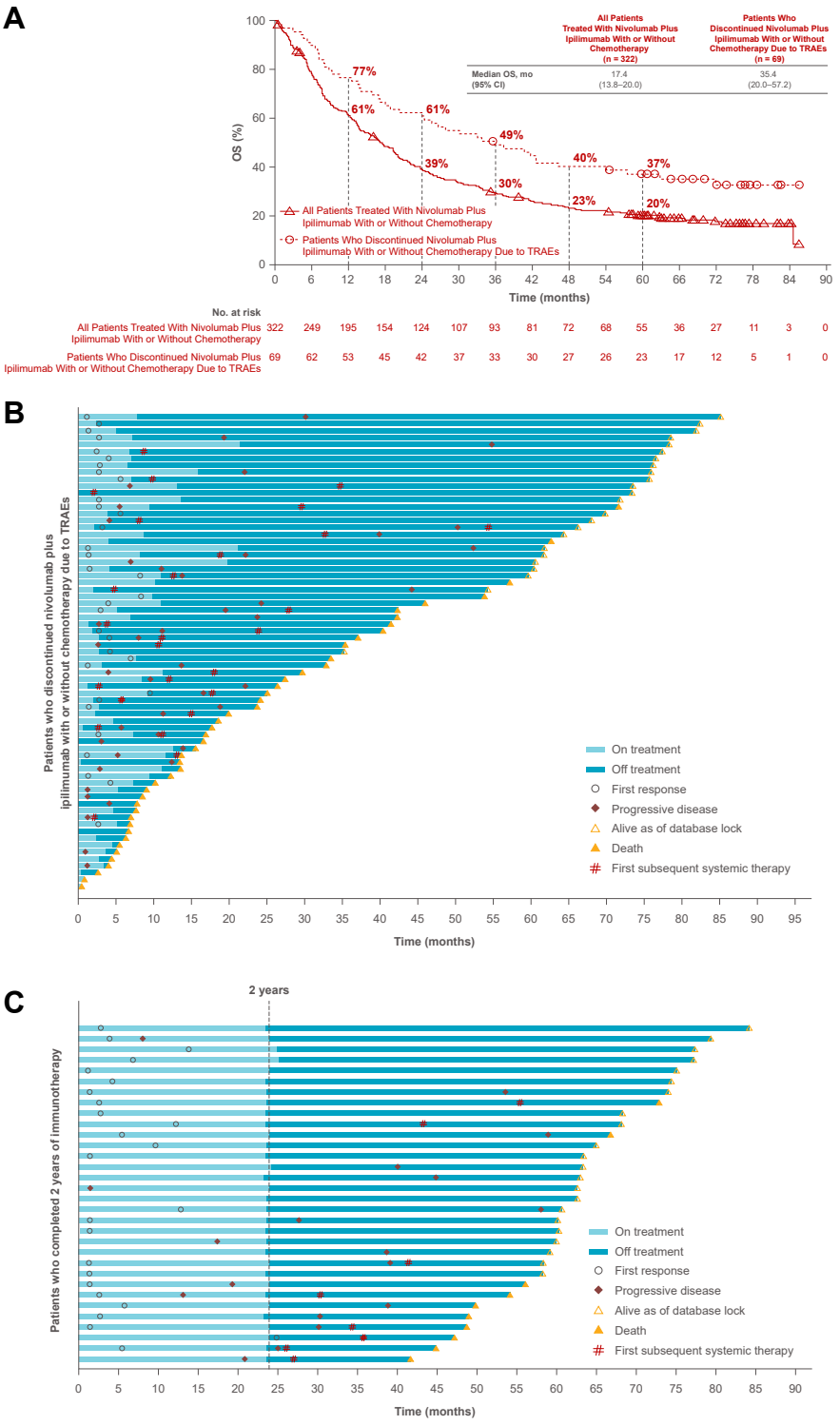

Figure 4. *(A)* OS and *(B)* response in individual patients with tumor PD-L1 lower than 1% who discontinued nivolumab plus ipilimumab with or without chemotherapy due to TRAEs; *(C)* response in individual patients who completed 2 years of immunotherapy in the pooled tumor PD-L1 lower than 1% population. The 95% CIs for 5-year OS rates with nivolumab plus ipilimumab with or without chemotherapy in panel A were: 16 to 25 (all patients with tumor PD-L1 lower than 1% treated with nivolumab plus ipilimumab with or without chemotherapy) and 26 to 48 (patients with tumor PD-L1 lower than 1% who discontinued nivolumab plus ipilimumab with or without chemotherapy due to TRAEs). CI, confidence interval; OS, overall survival; PD-L1, programmed death ligand 1; TRAEs, treatment-related adverse events.

of immunotherapy. By the data cutoff dates for CheckMate 227 and CheckMate 9LA, eight patients in this subgroup of the pooled population had received subsequent therapy, of whom two were alive and six had died. Twenty-four patients had not received subsequent therapy, of whom 20 were alive and four had died. Duration of treatment and response patterns among patients who completed 2 years of immunotherapy are shown in Figure 4*C*.

Safety

No new safety signals were identified among the patients in the pooled analysis. The most common TRAEs of any grade among patients treated with nivolumab plus ipilimumab with or without chemotherapy were diarrhea (19%), nausea (19%), and fatigue (17%), whereas the most common grade 3 to 4 TRAEs were increased lipase (7%), neutropenia (4%), and diarrhea (3%) (Table 2). Serious TRAEs were experienced by 28% of patients (21% with grade 3–4 serious TRAEs). Four patients (1%) in the nivolumab plus ipilimumab with or without chemotherapy arm and six patients (2%) in the chemotherapy arm died due to TRAEs. TRAEs occurring in equal to or higher than 10% of patients who discontinued all components of nivolumab plus ipilimumab from CheckMate 227 or nivolumab plus ipilimumab with chemotherapy from CheckMate 9LA are shown in Supplementary Table 8.

Discussion

To our knowledge, this is the largest pooled analysis of efficacy and safety outcomes in patients with metastatic NSCLC and tumor PD-L1 lower than 1% treated with a first-line dual immunotherapy–based regimen and the longest follow-up reported for this population across pooled studies. This analysis reported long-term, durable, and clinically meaningful benefits with nivolumab plus ipilimumab with or without chemotherapy versus chemotherapy alone, with 20% versus 7% of patients being alive at 5 years, and a median DOR of approximately 1.5 years with nearly one-fourth of responders maintaining their response at 5 years. OS benefit was also observed across all subgroups assessed, including in patients with squamous NSCLC and in patients with baseline brain metastases, which represent patient populations with high unmet need. No new safety signals were identified. Additional analyses reported that there was no negative impact on efficacy in patients who discontinued immunotherapy due to TRAEs or who completed 2 years of treatment.

Results from this pooled analysis are consistent with OS, PFS, and DOR data for patients with metastatic NSCLC and tumor PD-L1 lower than 1% from the individual CheckMate 227 and CheckMate 9LA studies, with a 5-year OS rate of 19% observed with nivolumab plus ipilimumab versus 7% with chemotherapy in CheckMate 227[19] and 22% with nivolumab plus ipilimumab with chemotherapy versus 8% with chemotherapy alone in CheckMate 9LA.[23] Outcomes from this pooled analysis were also similar to analyses of first-line nivolumab plus ipilimumab using pooled data from CheckMate 227, CheckMate 817, CheckMate 568, and CheckMate 012, reporting a 3-year OS rate of 30% for patients with tumor PD-L1 lower than 1%.[20] The separation of the Kaplan–Meier curves for nivolumab plus ipilimumab with or without chemotherapy versus chemotherapy alone was maintained over time, with a clear plateau for OS suggestive of long-term, durable survival benefit in patients with NSCLC and tumor PD-L1 lower than 1%. Safety outcomes in the current pooled analysis were also consistent with data from CheckMate 227, CheckMate 9LA, and a pooled analysis of patients treated with first-line nivolumab plus ipilimumab from CheckMate 227, CheckMate 817, and CheckMate 568, based on similar incidence and severity of TRAEs observed with nivolumab plus ipilimumab–based treatment in these analyses.[14,21,24] Overall, results from this pooled analysis reinforce previous efficacy and safety data for patients with PD-L1 lower than 1% treated with nivolumab plus ipilimumab with or without chemotherapy. Furthermore, median OS in the pooled nivolumab plus ipilimumab with or without chemotherapy arm with tumor PD-L1 lower than 1% was similar to median OS among patients with tumor PD-L1 equal to or higher than 1% treated with nivolumab plus ipilimumab from CheckMate 227 (17.1 mo; 5-y OS rate: 24%)[19] and patients with tumor PD-L1 equal to or higher than 1% treated with nivolumab plus ipilimumab with chemotherapy from CheckMate 9LA (15.8 mo; 5-y OS rate: 18%),[23] suggesting that consistent efficacy benefit was observed among patients treated with nivolumab plus ipilimumab–based treatments, regardless of tumor PD-L1 expression.

Long-term, durable clinical benefit, which is considered a hallmark of immunotherapy in advanced solid tumors, is critical for treatment selection for patients to derive maximal clinically meaningful benefit. In this pooled analysis, long-term survivorship and durability of the response benefit with the dual immunotherapy–based regimen containing nivolumab and ipilimumab seemed to be greater compared with first-line anti–PD-(L)1–based immunotherapy regimens lacking anti–CTLA-4 agents in patients with metastatic NSCLC and tumor PD-L1 lower than 1%,[6–9,25] although caution should be exercised when comparing outcomes from different clinical trials given differences in trial design and patient populations. In CheckMate 227, nivolumab plus chemotherapy was associated with only a moderate

Table 2. Safety Summary in the Pooled Tumor PD-L1 Lower Than 1% Population

	Nivolumab Plus Ipilimumab With or Without Chemotherapy (n = 319)		Chemotherapy (n = 308)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Any TRAEs[a]	261 (82)	114 (36)	253 (82)	110 (36)
TRAEs occurring in ≥10% of patients in either study[a,b]				
Diarrhea	60 (19)	11 (3)	38 (12)	4 (1)
Nausea	60 (19)	2 (1)	103 (33)	6 (2)
Fatigue	53 (17)	3 (1)	46 (15)	5 (2)
Pruritus	48 (15)	2 (1)	6 (2)	0
Asthenia	47 (15)	5 (2)	50 (16)	6 (2)
Decreased appetite	47 (15)	0	58 (19)	6 (2)
Rash	47 (15)	2 (1)	9 (3)	0
Hypothyroidism	44 (14)	1 (<1)	0	0
Anemia	35 (11)	6 (2)	111 (36)	43 (14)
Increased lipase	33 (10)	21 (7)	1 (<1)	0
Increased alanine aminotransferase	32 (10)	6 (2)	10 (3)	0
Vomiting	32 (10)	3 (1)	41 (13)	4 (1)
Constipation	27 (8)	0	44 (14)	2 (1)
Increased aspartate aminotransferase	26 (8)	7 (2)	8 (3)	0
Neutropenia	15 (5)	12 (4)	54 (18)	35 (11)
Thrombocytopenia	5 (2)	3 (1)	27 (9)	8 (3)
Decreased platelet count	3 (1)	0	30 (10)	10 (3)
Serious TRAEs[a]	88 (28)	67 (21)	50 (16)	39 (13)
TRAEs leading to discontinuation of any component of the study drug[a]	63 (20)	45 (14)	43 (14)	25 (8)
Treatment-related deaths	4[c] (1)		6[d] (2)	

Note: Data presented as n (%) of patients with an event.
[a]TRAEs include events reported between the first dose and 30 days after the last dose of study therapy.
[b]TRAEs occurring in equal to or higher than 10% of patients with tumor PD-L1 less than 1% in either CheckMate 227 or CheckMate 9LA are included here; some TRAEs shown occurred in less than 10% of patients in the pooled population overall.
[c]Includes three patients from CheckMate 227 (shock, pneumonitis, and cardiac tamponade) and one patient from CheckMate 9LA (sepsis and acute renal insufficiency).
[d]Includes one patient from CheckMate 227 (febrile neutropenia with sepsis) and five patients from CheckMate 9LA (sepsis, anemia, pancytopenia, respiratory failure, and pulmonary sepsis).
PD-L1, programmed death ligand 1; TRAE, treatment-related adverse event.

OS benefit versus chemotherapy alone in patients with tumor PD-L1 lower than 1% (HR = 0.79, 95% CI: 0.64–0.98; 5-y OS rate: 10% versus 5%).[19] Furthermore, in the phase 3 POSEIDON study, no improvement in OS was observed in patients with tumor PD-L1 lower than 1% treated with the PD-L1 inhibitor durvalumab plus chemotherapy versus chemotherapy alone (HR = 0.98, 95% CI: 0.75–1.27; 5-y OS rate: 6.5% versus 4.0%).[25] A pooled analysis of patients with tumor PD-L1 lower than 1% from the phase 3 KEYNOTE-189 and KEYNOTE-407 studies evaluating pembrolizumab plus chemotherapy versus chemotherapy alone reported 5-year OS rates of 12.5% versus 9.3%, respectively (HR = 0.64, 95% CI: 0.51–0.79).[9] In the phase 3 IMpower130 study of patients with nonsquamous advanced NSCLC, atezolizumab plus chemotherapy versus chemotherapy alone conferred a moderate improvement to OS (HR = 0.81, 95% CI: 0.61–1.08) in patients with tumor PD-L1 lower than 1%, although long-term data were not available.[4] A lack of OS benefit was also observed with cemiplimab plus chemotherapy versus placebo plus chemotherapy in the EMPOWER-Lung 3 phase 3 study in patients with tumor PD-L1 lower than 1% (HR = 1.01, 95% CI: 0.63–1.60)[6]; the European Medicines Agency subsequently approved cemiplimab plus chemotherapy for use in patients with tumor PD-L1 equal to or higher than 1%, but not in those with tumor PD-L1 lower than 1% based on these results.[26] In contrast with anti–PD-(L)1–based therapies with chemotherapy, the addition of agents inhibiting CTLA-4 to anti–PD-(L)1–based regimens shows a consistent trend in the long-term improvement of OS in patients with PD-L1 lower than 1%. In CheckMate 227, nivolumab plus ipilimumab was associated with numerically higher long-term OS benefits than nivolumab plus chemotherapy in this patient population.[19] In POSEIDON, the addition of tremelimumab, an anti–CTLA-4 agent, to durvalumab plus four cycles of chemotherapy conferred a slight improvement in OS at 5

years of follow-up relative to six cycles of chemotherapy alone in patients with tumor PD-L1 lower than 1% (HR = 0.81, 95% CI: 0.62–1.05; 5-y OS rate: 6.1% versus 4.0%).[25] Furthermore, a network meta-analysis found a long-term survival benefit with dual immunotherapy of nivolumab plus ipilimumab from CheckMate 227 versus anti–PD-(L)1 agents with chemotherapy from KEYNOTE-189, KEYNOTE-407, and IMpower150.[27] In addition to OS benefit, patients who responded to nivolumab plus ipilimumab with or without chemotherapy had a median DOR of 18.0 months in the present pooled analysis; previously reported values for anti–PD-(L)1–based therapies with chemotherapy (without CTLA-4 inhibition) in patients with tumor PD-L1 lower than 1% from CheckMate 227, KEYNOTE-189, KEYNOTE-407, IMpower130, POSEIDON, and EMPOWER-Lung 3 ranged from 6.7 to 10.8 months, whereas PFS and ORR from the pooled analysis of nivolumab plus ipilimumab with or without chemotherapy fell within previously reported ranges from these studies (median PFS: 4.6 to 6.3 mo versus 5.4 mo from the present study; ORR: 27% to 67% versus 29%).[4,7,8,19,28,29] Taken together, these findings suggest a long-term clinical benefit observed with dual anti–PD-(L)1 plus anti–CTLA-4 regimens in patients with tumor PD-L1 lower than 1%, particularly nivolumab plus ipilimumab–based treatments, compared with various anti–PD-(L)1 plus chemotherapy regimens lacking CTLA-4 inhibition. Future studies of additional biomarkers could potentially identify patients with tumor PD-L1 lower than 1% who could benefit most from combination immunotherapy.

Certain patient subgroups with NSCLC, including those with baseline brain metastases or squamous NSCLC, historically have a poor prognosis and derive limited long-term efficacy benefits from chemotherapy or PD-(L)1–based regimens,[30,31] underscoring high unmet need in these patient subgroups, especially among those with tumor PD-L1 lower than 1%. In patients with advanced squamous NSCLC and tumor PD-L1 lower than 1% treated with pembrolizumab plus chemotherapy in KEYNOTE-407, median PFS was 6.3 months, ORR was 67.4%, median DOR was 6.9 months, and the 5-year OS rate was 10.7%.[8] Among patients with brain metastases and tumor PD-L1 lower than 1% from the pooled KEYNOTE-189 and KEYNOTE-407 study, OS HR for pembrolizumab plus chemotherapy versus chemotherapy was 0.59 (95% CI: 0.35–0.99).[9] In the current analysis, nivolumab plus ipilimumab with or without chemotherapy demonstrated improvement in DOR and OS in patients with tumor PD-L1 lower than 1%, even in those with squamous NSCLC (median PFS: 5.3 mo; ORR, 42%; median DOR: 19.6 mo; 5-y OS rate: 21% [OS HR versus chemotherapy = 0.51, 95% CI: 0.36–0.72]) or baseline brain metastases (5-y OS rate: 6% [OS HR versus chemotherapy = 0.44, 95% CI: 0.26–0.75]), indicating clinical benefit over long-term follow-up. Notably, a higher magnitude of clinical benefit versus chemotherapy was observed in patients with baseline brain metastases or squamous NSCLC (compared with patients without brain metastases or nonsquamous NSCLC, respectively), likely due to poor efficacy from chemotherapy alone as expected in these subgroups. These findings are consistent with OS outcomes observed from the individual CheckMate 227 and CheckMate 9LA studies in patients with squamous NSCLC or baseline brain metastases, irrespective of tumor PD-L1 expression,[19,23,32,33] and further support the efficacy of dual immunotherapy–based treatment regimens in these subgroups with additional unmet need.

Patient survivorship is increasingly at the forefront when considering treatment choice, raising the question of whether efficacy benefit can be maintained, even after a drug regimen is discontinued, to preserve patient quality of life. Discontinuation of nivolumab plus ipilimumab with or without chemotherapy due to TRAEs did not seem to negatively impact OS relative to the entire pooled nivolumab plus ipilimumab with or without chemotherapy arm, although it should be noted that such analyses are limited by immortal time bias. Moreover, the results were consistent with outcomes in patients who completed 2 years of immunotherapy treatment, and who continued to experience prolonged clinical benefit even after discontinuation. Of note, patients who were alive at the time of the database lock dates had completed or discontinued study immunotherapy for a minimum of 3 years in this analysis. In the 5-year update of CheckMate 227, 14% of patients with tumor PD-L1 lower than 1% were alive and treatment-free for 3 years or longer in the nivolumab plus ipilimumab arm compared with 2% in the chemotherapy arm.[34] Consistent with prior exploratory data from CheckMate 227 and CheckMate 9LA,[34,35] results from this pooled analysis support the durable efficacy of nivolumab plus ipilimumab with or without chemotherapy, even in patients with tumor PD-L1 lower than 1% who discontinued treatment.

This analysis shares limitations inherent to pooled analyses, including differences in the study designs and patient populations of CheckMate 227 and CheckMate 9LA that may have introduced heterogeneity in the pooled treatment arms, particularly differences in the treatment regimens (e.g., the inclusion of two cycles of chemotherapy in the experimental arm of CheckMate 9LA but not in CheckMate 227) and dosing of nivolumab. Interpretation of these results should also be limited to long-term outcomes to avoid confounding effects from the inclusion of the limited chemotherapy course, which is thought to provide rapid initial disease control in the

experimental arm of CheckMate 9LA. Finally, as this was an exploratory post hoc analysis, it was not statistically powered, further limiting the interpretation of the results.

This analysis of a pooled patient population with tumor PD-L1 lower than 1% from CheckMate 227 and CheckMate 9LA shows that first-line treatment with nivolumab plus ipilimumab with or without chemotherapy is associated with long-term, durable survival benefit and a generally manageable safety profile in patients with metastatic NSCLC and tumor PD-L1 lower than 1%, including subgroups with brain metastases or squamous NSCLC. These results further support the use of nivolumab plus ipilimumab with or without chemotherapy in this patient population with high unmet need.

CRediT Authorship Contribution Statement

Solange Peters: Conceptualization, Methodology, Investigation, Supervision, Writing - original draft, Writing - review & editing.

Luis G. Paz-Ares: Conceptualization, Methodology, Investigation, Supervision, Writing - original draft, Writing - review & editing.

Martin Reck: Conceptualization, Methodology, Investigation, Writing - review & editing.

David P. Carbone: Conceptualization, Methodology, Writing - review & editing.

Julie R. Brahmer: Conceptualization, Methodology, Writing - review & editing.

Hossein Borghaei: Conceptualization, Methodology, Investigation, Writing - review & editing.

Shun Lu: Conceptualization, Methodology, Investigation, Writing - review & editing.

Kenneth J. O'Byrne: Conceptualization, Methodology, Investigation, Writing - review & editing.

Thomas John: Conceptualization, Methodology, Writing - review & editing.

Tudor-Eliade Ciuleanu: Investigation, Writing - review & editing.

Michael Schenker: Investigation, Writing - review & editing.

Reyes Bernabe Caro: Investigation, Writing - review & editing.

Makoto Nishio: Investigation, Writing - review & editing.

Manuel Cobo: Investigation, Writing - review & editing.

Jong-Seok Lee: Investigation, Writing - review & editing.

Bogdan Zurawski: Investigation, Writing - review & editing.

Adam Pluzanski: Investigation, Writing - review & editing.

Takekazu Aoyama: Formal analysis, Writing - review & editing.

Marina Tschaika: Formal analysis, Writing - review & editing.

Vipul Devas: Formal analysis, Writing - review & editing.

Diederik J. Grootendorst: Formal analysis, Writing - review & editing.

Suresh S. Ramalingam: Conceptualization, Methodology, Investigation, Supervision, Writing - original draft, Writing - review & editing.

Disclosure

Dr. Peters reports grants or contracts to her institution from Amgen, AstraZeneca, BeiGene, Bristol Myers Squibb, GlaxoSmithKline, Merck Sharp & Dohme, and Roche/Genentech; consulting fees to her institution from AbbVie, AiCME, Amgen, Arcus, AstraZeneca, Bayer, BeiGene, Biocartis, BioInvent, Blueprint Medicines, Boehringer Ingelheim, Bristol Myers Squibb, Clovis, Daiichi Sankyo, Debiopharm, ecancer, Eli Lilly, Elsevier, F-Star, Fishawack, Foundation Medicine, Genzyme, Gilead, GlaxoSmithKline, Illumina, Imedex, IQVIA, Incyte, Ipsen, iTeos, Janssen, Medscape, medtoday, Merck Sharp & Dohme, Merck Serono, Merrimack, Novartis, Novocure, OncologyEducation, PharmaMar, Phosplatin Therapeutics, PER, PeerView, Pfizer, PRIME, Regeneron, RMEI, Roche/Genentech, RTP, Sanofi, Seattle Genetics, Takeda, and Vaccibody; honoraria to her institution from AiCME, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, ecancer, Eli Lilly, Foundation Medicine, Illumina, Imedex, Medscape, Merck Sharp & Dohme, Mirati, Novartis, PeerView, PER, Pfizer, Prime, Roche/Genentech, RTP, Sanofi, and Takeda; support for attending meetings and/or travel paid to her institution from AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Roche/Genentech, and Takeda; and participation on a Data Safety Monitoring Board or Advisory Board for AbbVie, Amgen, Arcus, AstraZeneca, Bayer, BeiGene, Biocartis, BioInvent, Blueprint Medicines, Boehringer Ingelheim, Bristol Myers Squibb, Clovis, Daiichi Sankyo, Debiopharm, Eli Lilly, F-Star, Foundation Medicine, Genzyme, Gilead, GlaxoSmithKline, Illumina, Incyte, iTeos, Janssen, Merck Sharp & Dohme, Merck Serono, Merrimack, Novartis, Novocure, PharmaMar, Phosplatin Therapeutics, Pfizer, Regeneron, Roche/Genentech, Sanofi, Seattle Genetics, Takeda, and Vaccibody with fees paid to her institution. Dr. Paz-Ares reports grants or contracts from Merck Sharp & Dohme, AstraZeneca, Pfizer, and Bristol Myers Squibb; consulting fees from Eli Lilly, Merck Sharp & Dohme, Roche, PharmaMar, Merck KGaA (Darmstadt, Germany), AstraZeneca, Novartis, Servier, Amgen, Pfizer,

Sanofi, Bayer, Bristol Myers Squibb, Mirati, GlaxoSmithKline, Janssen, Takeda, and Daiichi Sankyo; honoraria from AstraZeneca, Janssen, Merck, and Mirati; and has participated on a Data Safety Monitoring Board or Advisory Board for Altum Sequencing and Genomica. Dr. Reck reports consulting fees from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, BeiGene, Eli Lilly, Mirati, Merck Sharp & Dohme, Merck, Novartis, Pfizer, Sanofi, Regeneron, Roche, Takeda, and Samsung Bioepis; honoraria from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, BeiGene, Eli Lilly, Mirati, Merck Sharp & Dohme, Merck, Novartis, Pfizer, Sanofi, Regeneron, Roche, Takeda, and Samsung Bioepis; meeting or travel support from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, BeiGene, Eli Lilly, Mirati, Merck Sharp & Dohme, Merck, Novartis, Pfizer, Sanofi, Regeneron, Roche, Takeda, and Samsung Bioepis; and has participated on a Data Safety Monitoring Board or Advisory Board for Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, BeiGene, Eli Lilly, Mirati, Merck Sharp & Dohme, Merck, Novartis, Pfizer, Sanofi, Regeneron, Roche, Takeda, and Samsung Bioepis. Dr. Carbone reports consulting fees from Arcus Biosciences, Bristol Myers Squibb, Bristol Myers Squibb KK, Boehringer Ingelheim, Curio Science, Daiichi Sankyo, Genentech/Roche, GI Therapeutics (Intellisphere), GlaxoSmithKline, Janssen, Merck, Mirati, Novartis, Novocure, OncoCyte, OncoHost, Roche China, and Seattle Genetics; and has participated on the Advisory Board of Amgen, Arcus Biosciences, AstraZeneca, Merck, Flame Biosciences, Gritstone Oncology, Cantargia (PPD), Daiichi Sankyo, EMD Serono GlaxoSmithKline, Eli Lilly, Regeneron, Sanofi, and Seattle Genetics and the Data Safety Monitoring Board of EORTC, AbbVie, and Eli Lilly. Dr. Brahmer reports grants or contracts to her institution from Bristol Myers Squibb and AstraZeneca; consulting fees from Bristol Myers Squibb, AstraZeneca, Merck, and Regeneron; honoraria from Bristol Myers Squibb; participation in Data Safety Monitoring Board or Advisory Board for Johnson & Johnson, Sanofi, and GlaxoSmithKline; board membership for Society for the Immunotherapy of Cancer (SITC), LUNGevity, Lung Cancer Research Foundation, and Lung Cancer Foundation of America; and medical writing support from Bristol Myers Squibb and Merck. Dr. Borghaei reports research support from Bristol Myers Squibb, Eli Lilly, and Amgen; participation as a consultant or advisory board member for Bristol Myers Squibb, Eli Lilly, Genentech, Pfizer, Merck, EMD Serono, Boehringer Ingelheim, AstraZeneca, Novartis, Genmab, Regeneron, BioNTech, Amgen, Axiom, PharmaMar, Takeda, Mirati, Daiichi Sankyo, Guardant, Natera, Oncocyte, BeiGene, iTEO, Jazz, Janssen, Puma, BerGenBio, Bayer, Iobiotech, Grid Therapeutics, and RAPT; participation in Data and Safety Monitoring Boards for the University of Pennsylvania CAR T Program, Takeda, Incyte, Novartis, and SpringWorks; employment with Fox Chase Cancer Center; stock options with Sonnet Bio, Inspirna (formerly Rgenix), and Nucleai; honoraria from Amgen, Pfizer, Daiichi Sankyo, and Regeneron; and travel support from Amgen, Bristol Myers Squibb, Merck, Eli Lilly, EMD Serono, Genentech, Regeneron, and Mirati. Dr. Lu reports research support from AstraZeneca, Hutchinson MediPharma, Bristol Myers Squibb, Hengrui Therapeutics, BeiGene, Roche, and Hansoh; consulting fees from AstraZeneca, Hutchinson MediPharma, Simcere Zaiming Pharmaceutical Co., Ltd., Yuhan Corporation, and Zai Lab; honoraria from AstraZeneca, Roche, Hansoh, and Hengrui Therapeutics; participation as an advisor and consultant of AstraZeneca, Yuhan Corporation, and InventisBio Co. Ltd.; participation as an independent director and board member of Innovent Biologics, Inc.; participated as a scientific advisory board member of Simcere Zaiming Pharmaceutical Co., Ltd., Shanghai Fosun Pharmaceutical, and Phanes Therapeutics, Inc.; and stock ownership and other financial or nonfinancial interests. Dr. O'Byrne reports consulting fees from TriStar; honoraria from Astellas, AstraZeneca, Bristol Myers Squibb, Janssen, Merck, Merck Sharp & Dohme, and Roche; travel support from Bayer; participation on a Data Safety Monitoring Board, Advisory Board, or other board or committee for AstraZeneca, BeiGene, Bristol Myers Squibb, Boehringer Ingelheim, Ipsen, Janssen, Merck Sharp & Dohme, Pfizer, Roche, Takeda, TriStar, and Yuhan; and stock or stock options for Carpe Vitae Pharmaceuticals, DGC Diagnostics, and RepLuca Pharmaceuticals. Dr. John reports consulting fees from Roche, Merck, Merck Sharp & Dohme, Puma, AstraZeneca, Bristol Myers Squibb, Amgen, Gilead, and Specialised Therapeutics; and honoraria from AstraZeneca. Dr. Ciuleanu reports honoraria from Astellas, Janssen, Merck Sharp & Dohme, Merck Serono, Amgen, Roche, Pfizer, Sanofi Genzyme, Servier, Ipsen, AstraZeneca, Eli Lilly, Novartis, Boehringer Ingelheim, and Bristol Myers Squibb; and has participated on a Data Safety Monitoring Board or Advisory Board of Astellas, Janssen, Merck Sharp & Dohme, Merck Serono, Amgen, Roche, Pfizer, Sanofi Genzyme, Servier, Ipsen, AstraZeneca, Eli Lilly, Novartis, Boehringer Ingelheim, and Bristol Myers Squibb. Dr. Schenker has received funding from Bristol Myers Squibb, Merck Sharp & Dohme, Merck Serono, Pfizer, GlaxoSmithKline, Roche, Bayer, Astellas, Amgen, Gilead, Tesaro, Clovis, Eli Lilly, Novartis, Regeneron, AbbVie, AstraZeneca, PharmaMar, Mylan, Samsung Pharmaceuticals, Bioven, BeiGene, and Daiichi Sankyo. Dr. Caro reports investigational grants from Roche; honoraria from Roche, Bristol Myers Squibb, Pfizer, Merck Sharp & Dohme, Amgen, Takeda, and AstraZeneca; and participation on a Data Safety Monitoring Board or Advisory Board for

Takeda, Roche, Bristol Myers Squibb, and AstraZeneca. Dr. Nishio reports honoraria from Ono Pharmaceuticals, Chugai Pharmaceutical, Taiho Pharmaceutical, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, AstraZeneca, Merck Sharp & Dohme, AbbVie, Takeda, Pfizer, Boehringer Ingelheim, Novartis, Nippon Kayaku, Merck, and Janssen. Dr. Zurawski reports honoraria from Amgen, AstraZeneca, Bristol Myers Squibb, GlaxoSmithKline, Janssen-Cilag, Merck Sharp & Dohme, and Roche. Dr. Pluzanski reports consulting fees from Roche and Amgen; honoraria from Bristol Myers Squibb, Roche, Merck Sharp & Dohme, Takeda, Amgen, Pfizer, and Astra; meeting or travel support from Bristol Myers Squibb, Takeda, Merck Sharp & Dohme, and Astra; and participation in Data Safety Monitoring Board or Advisory Board for Takeda, Sanofi, Bristol Myers Squibb, and Merck Sharp & Dohme. Dr. Aoyama is an employee and stockholder of Bristol Myers Squibb. Dr. Tschaika is an employee and stockholder of Bristol Myers Squibb. Dr. Devas is an employee and shareholder of Bristol Myers Squibb. Dr. Grootendorst is an employee and stockholder of Bristol Myers Squibb. The remaining authors declare no conflict of interest.

Acknowledgments

This work was supported by Bristol Myers Squibb. We thank the patients and families who made this trial possible; the investigators and clinical study teams who participated in the trial; Dako, an Agilent Technologies company, for collaborative development of the PD-L1 IHC 28-8 pharmDx assay; Javed Mahmood, DDS, PhD, and Judith Bushong, BS, for their contributions as clinical scientists; Rui Wang, MS, for her contribution as a statistician; and Bristol Myers Squibb (Princeton, NJ) and Ono Pharmaceutical Company, Ltd. (Osaka, Japan). Medical writing and editorial support for the development of this manuscript, under the direction of the authors, was provided by Sabrina Hom, PhD; Adel Chowdhury, PharmD, and Michele Salernitano of Ashfield MedComms, an Inizio company, funded by Bristol Myers Squibb.

Data Availability

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

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2024.09.1439.

References

1. Brody R, Zhang Y, Ballas M, et al. PD-L1 expression in advanced NSCLC: insights into risk stratification and treatment selection from a systematic literature review. *Lung Cancer*. 2017;112:200–215.
2. Xu Y, Wan B, Chen X, et al. The association of PD-L1 expression with the efficacy of anti-PD-1/PD-L1 immunotherapy and survival of non-small cell lung cancer patients: a meta-analysis of randomized controlled trials. *Transl Lung Cancer Res*. 2019;8:413–428.
3. Referenced With Permission From the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-small Cell Lung Cancer. V7.2024. © National Comprehensive Cancer Network, Inc; 2024. All rights reserved. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1450. Accessed August 7, 2024.
4. West H, McCleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (Impower130): a multicentre, randomized, open-label, phase 3 trial. *Lancet Oncol*. 2019;20:924–937.
5. Jotte R, Cappuzzo F, Vynnychenko I, et al. Atezolizumab in combination with carboplatin and nab-paclitaxel in advanced squamous NSCLC (IMpower131): results from a randomized phase III trial. *J Thorac Oncol*. 2020;15:1351–1360.
6. Gogishvili M, Melkadze T, Makharadze T, et al. Cemiplimab plus chemotherapy versus chemotherapy alone in non-small cell lung cancer: a randomized, controlled, double-blind phase 3 trial. *Nat Med*. 2022;28:2374–2380.
7. Garassino MC, Gadgeel S, Speranza G, et al. Pembrolizumab plus pemetrexed and platinum in non-squamous non-small-cell lung cancer: 5-year outcomes from the phase 3 KEYNOTE-189 study. *J Clin Oncol*. 2023;41:1992–1998.
8. Novello S, Kowalski DM, Luft A, et al. Pembrolizumab plus chemotherapy in squamous non-small-cell lung cancer: 5-year update of the phase III KEYNOTE-407 Study. *J Clin Oncol*. 2023;41:1999–2006.
9. Gadgeel S, Rodríguez-Abreu D, Halmos B, et al. Pembrolizumab plus chemotherapy for metastatic NSCLC with programmed cell death ligand 1 tumor proportion score less than 1%: pooled analysis of outcomes after five years of follow-up. *J Thorac Oncol*. 2024;19:1228–1241.
10. Rotte A. Combination of CTLA-4 and PD-1 blockers for treatment of cancer. *J Exp Clin Cancer Res*. 2019;38:255.
11. Michielin O, Lalani AK, Robert C, Sharma P, Peters S. Defining unique clinical hallmarks for immune checkpoint inhibitor-based therapies. *J Immunother Cancer*. 2022;10:e003024.
12. Singh N, Jaiyesimi IA, Ismaila N, et al. Therapy for stage IV non-small-cell lung cancer without driver alterations: ASCO living guideline, version 2023.1. *J Clin Oncol*. 2023;41:e51–e62.
13. Hendriks LE, Kerr KM, Menis J, et al. Non-oncogene-addicted metastatic non-small-cell lung cancer: ESMO

Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023;34:358–376.
14. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *N Engl J Med*. 2019;381:2020–2031.
15. OPDIVO (nivolumab) injection prescribing information. Princeton, NJ: Bristol-Myers Squibb; 2024. https://packageinserts.bms.com/pi/pi_opdivo.pdf. Accessed April 15, 2024.
16. OPDIVO (nivolumab) product monograph. Ontario, Canada: Bristol-Myers Squibb Canada; 2024. https://www.bms.com/assets/bms/ca/documents/productmonograph/OPDIVO_EN_PM.pdf. Accessed June 24, 2024.
17. OPDIVO (nivolumab) approval. Chuo-ku, Osaka, Japan: Ono Pharmaceutical Co, Ltd; 2020. https://www.ono-pharma.com/sites/default/files/en/news/press/sm_cn201127_1.pdf. Accessed April 15, 2024.
18. OPDIVO (nivolumab) solución inyectable para infusión intravenosa. Buenos Aires, Argentina: Bristol-Myers Squibb Argentina S.R.L; 2024. https://www.bms.com/assets/bms/argentina/documents/prospecto/Opdivo-Prospecto.pdf. Accessed October 15, 2024.
19. Ramalingam SS, Ciuleanu TE, Bernabe Caro R, et al. Six-year survival and health-related quality of life outcomes with first-line nivolumab plus ipilimumab in patients with metastatic NSCLC from CheckMate227. Oral presentation at the 2023 World Conference on Lung Cancer (WCLC); Singapore; 2023.
20. Borghaei H, Ciuleanu TE, Lee JS, et al. Long-term survival with first-line nivolumab plus ipilimumab in patients with advanced non-small-cell lung cancer: a pooled analysis. *Ann Oncol*. 2023;34:173–185.
21. Paz-Ares L, Ciuleanu TE, Cobo M, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22:198–211.
22. OPDIVO (nivolumab) European Commission summary of product characteristics. Dublin, Ireland: Bristol Myers Squibb Pharma EEIG; 2020. https://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf. Accessed June 25, 2024.
23. Reck M, Ciuleanu CE, Schenker M, et al. Five-year outcomes with first-line nivolumab plus ipilimumab with 2 cycles of chemotherapy versus 4 cycles of chemotherapy alone in patients with metastatic non-small cell lung cancer in the randomized CheckMate 9LA trial. *Eur J Cancer*. 2024;211:114296.
24. Paz-Ares LG, Ciuleanu TE, Pluzanski A, et al. Safety of first-line nivolumab plus ipilimumab in patients with metastatic NSCLC: a pooled analysis of CheckMate 227, CheckMate 568, and CheckMate 817. *J Thorac Oncol*. 2023;18:79–92.
25. Peters S, Chul Cho B, Luft A, et al. Durvalumab With or Without Tremelimumab in Combination With Chemotherapy in First-Line Metastatic NSCLC: Five-Year Overall Survival Outcomes From the Phase 3 POSEIDON Trial. *J Thorac Oncol*. 2025;20:76–93.
26. LIBTAYO (cemiplimab) Union Register of medicinal products for human use. European Commission; 2024. https://ec.europa.eu/health/documents/community-register/html/h1376.htm. Accessed June 14, 2024.
27. O'Byrne K, Popoff E, Badin F, et al. Efficacy of nivolumab + ipilimumab vs other immunotherapy-based first-line treatments for metastatic NSCLC with PD-L1 <1%: a network meta-analysis. Poster presentation at the 2023 World Conference on Lung Cancer (WCLC), September 9–12, 2023; Singapore.
28. Makharadze T, Gogishvili M, Melkadze T, et al. Cemiplimab plus chemotherapy versus chemotherapy alone in advanced NSCLC: 2-year follow-up from the phase 3 EMPOWER-Lung 3 part 2 trial. *J Thorac Oncol*. 2023;18:755–768.
29. Garon EB, Cho BC, Luft A, et al. A brief report of durvalumab with or without tremelimumab in combination with chemotherapy as first-line therapy for metastatic non-small-cell lung cancer: outcomes by tumor PD-L1 expression in the phase 3 POSEIDON study. *Clin Lung Cancer*. 2024;25:266–273.e5.
30. Ernani V, Stinchcombe TE. Management of brain metastases in non-small-cell lung cancer. *J Oncol Pract*. 2019;15:563–570.
31. Santos ES, Rodriguez E. Treatment considerations for patients with advanced squamous cell carcinoma of the lung. *Clin Lung Cancer*. 2022;23:457–466.
32. Paz-Ares L, Ciuleanu TE, Cobo M, et al. First-line nivolumab plus ipilimumab with chemotherapy versus chemotherapy alone for metastatic NSCLC in CheckMate 9LA: 3-year clinical update and outcomes in patients with brain metastases or select somatic mutations. *J Thorac Oncol*. 2022;18:204–222.
33. Reck M, Ciuleanu TE, Lee JS, et al. Systemic and intracranial outcomes with first-line nivolumab plus ipilimumab in patients with metastatic NSCLC and baseline brain metastases from CheckMate 227 Part 1. *J Thorac Oncol*. 2023;18:1055–1069.
34. Brahmer JR, Lee JS, Ciuleanu TE, et al. Five-year survival outcomes with nivolumab plus ipilimumab versus chemotherapy as first-line treatment for metastatic non-small-cell lung cancer in CheckMate 227. *J Clin Oncol*. 2023;41:1200–1212.
35. Carbone DP, Ciuleanu TE, Schenker M, et al. Four-year clinical update and treatment switching-adjusted outcomes with first-line nivolumab plus ipilimumab with chemotherapy for metastatic non-small cell lung cancer in the CheckMate 9LA randomized trial. *J Immunother Cancer*. 2024;12:e008189.