ORIGINAL ARTICLE

# 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

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**ABSTRACT**

**Introduction:** In the phase 3 CheckMate 9LA study, nivolumab plus ipilimumab with chemotherapy prolonged overall survival (OS) versus chemotherapy alone. We report updated efficacy and safety (≥3 y of follow-up), clinical outcomes in patients with baseline brain metastases, and exploratory somatic mutation analyses.

**Methods:** Adults with stage IV or recurrent NSCLC, no known sensitizing *EGFR or ALK* alterations, and Eastern Cooperative Oncology Group performance status less than or equal to 1 were randomized 1:1 to nivolumab 360 mg every 3 weeks plus ipilimumab 1 mg/kg every 6 weeks with chemotherapy (two cycles) or chemotherapy alone (four cycles). Assessments included OS, progression-free survival (PFS), and objective response rate. Exploratory analyses included systemic and intracranial efficacy in patients with or without baseline brain metastases, in addition to OS and PFS by *KRAS*, *TP53*, *STK11*, and *KEAP1* somatic mutation status in patients with nonsquamous NSCLC.

**Results:** With a minimum follow-up of 36.1 months, nivolumab plus ipilimumab with chemotherapy continued to prolong OS versus chemotherapy alone in the intent-to-treat population (median [hazard ratio; 95% confidence interval] OS: 15.8 versus 11.0 mo [0.74; 0.62–0.87]; 3-y OS: 27% versus 19%). Efficacy outcomes were improved in patients with pretreated baseline brain metastases (median [hazard ratio; 95% confidence interval] OS: 19.3 versus 6.8 mo [0.45; 0.29–0.70]; systemic PFS: 9.7 versus 4.1 mo [0.44; 0.28–0.69]; intracranial PFS: 11.4 versus 4.6 mo [0.42; 0.26–0.68]). A trend of OS benefit was observed in patients treated with nivolumab plus ipilimumab with chemotherapy versus chemotherapy alone, despite *KRAS*, *TP53*, and *STK11* tumor mutations. Extended follow-up revealed no new safety signals.

**Conclusions:** With a 3-year minimum follow-up, nivolumab plus ipilimumab with two cycles of chemotherapy continued to have long-term, durable efficacy versus chemotherapy alone; a manageable safety profile; and survival benefit in patients with or without baseline brain metastases or select somatic mutations, further supporting the regimen as first-line treatment for patients with metastatic NSCLC.

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*Keywords:* PD-1 checkpoint inhibitor; Metastatic non–small cell lung cancer; First-line; Brain metastases; Somatic mutations

## Introduction

Immune checkpoint inhibitors targeting the programmed death-ligand 1 (PD-L1)–programmed cell death protein 1 (PD-1) pathway alone or combined with other treatment modalities have substantially prolonged overall survival (OS) versus chemotherapy alone in previously untreated patients with NSCLC without targetable mutations.[1–6] Nivolumab, a fully human anti–PD-1 antibody, and ipilimumab, a fully human anti–CTLA-4 antibody, are immune checkpoint inhibitors with distinct but complementary mechanisms of action.[7,8] Nivolumab restores the function of existing antitumor T cells, whereas ipilimumab induces de novo antitumor T-cell responses, including an increase in memory T cells.[7,8] Dual immunotherapy with first-line nivolumab plus ipilimumab was found to have long-term, durable survival benefit in several metastatic solid tumors, including NSCLC,[9,10] melanoma,[11] renal cell carcinoma,[12] and malignant pleural mesothelioma.[13]

Up to 26% of patients with metastatic NSCLC present with brain metastases at diagnosis, representing a population with considerable unmet need.[14,15] In several phase 1 or 2 studies, immune checkpoint inhibitors (with or without chemotherapy) were found to have activity in patients with untreated or progressive brain metastases and cancers, such as NSCLC, melanoma, and renal cell carcinoma.[16–20] Clinical benefit with immune checkpoint inhibitors has also been reported from pooled and exploratory analyses of treated brain metastases in patients with NSCLC.[21–25] Nevertheless, limited evidence exists for intracranial efficacy of immunotherapy in patients with NSCLC, particularly from phase 3 clinical trials.[24,25] In addition, reliable biomarkers predicting a benefit from immunotherapy are of high clinical interest.

CheckMate 9LA (NCT03215706) is a randomized phase 3 study evaluating nivolumab plus ipilimumab combined with platinum-doublet chemotherapy (two cycles) as a first-line treatment in patients with metastatic NSCLC versus chemotherapy alone (four cycles).[4] The study met its primary end point with a statistically significant improvement in OS (hazard ratio [HR], 0.69; $p = 0.00065$).[4] On the basis of results from CheckMate 9LA, the combination of nivolumab plus ipilimumab with chemotherapy has received regulatory approvals in the USA, European Union, and several other countries for first-line treatment of adults with metastatic or recurrent NSCLC with no *EGFR* or *ALK* genomic tumor aberrations.[26–31] In addition, guidelines from both the National Comprehensive Cancer Network® (NCCN®) and the European Society for Medical Oncology recommend the combination of nivolumab plus ipilimumab (with or without chemotherapy) as a first-line treatment option for patients with metastatic NSCLC regardless of tumor PD-L1 expression or histology (see the National Comprehensive Cancer Network Guidelines for detailed recommendations, including preferred treatment options).[32,33]

In the 2-year follow-up of CheckMate 9LA, first-line nivolumab plus ipilimumab with chemotherapy continued to have prolonged OS compared with chemotherapy alone.[10] Here, we report updated efficacy and safety results from CheckMate 9LA with a minimum follow-up of 3 years. We also report the systemic and intracranial efficacy of this combination in patients with pretreated baseline brain metastases and describe results of an exploratory analysis of efficacy by somatic mutation status.

## Materials and Methods

CheckMate 9LA methodology has been previously described[4,10] and is briefly summarized here.

### *Patients*

Eligibility criteria for CheckMate 9LA have been previously described.[4,10] Eligible patients were adults aged 18 years or more with histologically confirmed squamous

or nonsquamous stage IV or recurrent NSCLC, Eastern Cooperative Oncology Group performance status of 0 to 1, and no known sensitizing *EGFR* or *ALK* alterations. Patients with brain metastases were eligible if they were asymptomatic for 2 weeks or more before the first study treatment and the metastases were adequately treated; corticosteroids were permitted if the dose ($\leq$10 mg daily prednisone or equivalent) was stable or decreasing for 2 weeks or more before starting the study treatment.

## Trial Design and Treatment

CheckMate 9LA was an international, randomized, open-label, phase 3 trial.[4] Enrolled patients were stratified according to tumor histology (squamous versus nonsquamous), sex (male versus female), and PD-L1 expression ($<$1% versus $\geq$1%). Patients without quantifiable PD-L1 expression were stratified with the less than 1% population but only included in the analyses of all randomized patients, as previously described.[4,10] Patients were randomized 1:1 to receive nivolumab (360 mg every 3 wk) plus ipilimumab (1 mg/kg every 6 wk) combined with squamous or nonsquamous histology-based platinum-doublet chemotherapy (every 3 wk for 2 cycles) or chemotherapy alone (every 3 wk for 4 cycles) (Supplementary Fig. 1).

Patients received treatment until disease progression (unless prespecified criteria were met for treatment beyond progression in the experimental arm), unacceptable toxicity, or 2 years of immunotherapy. Use of optional pemetrexed maintenance therapy (500 mg/m$^2$) has been described previously.[4,10] No crossover between treatment arms was allowed per protocol; however, at the physician's discretion, patients could receive subsequent immunotherapy if the study treatment was discontinued in either group.

This study was conducted in accordance with the Declaration of Helsinki and international standards of Good Clinical Practice. The institutional review board or independent ethics committee of each participating study center approved the protocol and all amendments. All patients provided written informed consent. 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.

## Outcomes

The primary end point of OS and hierarchical secondary end points of progression-free survival (PFS) and objective response rate (ORR) have been reported previously.[4,10] At the 3-year minimum follow-up, exploratory analyses included updated efficacy and safety outcomes in all randomized patients, patients with or without baseline brain metastases, and patients with mutation-evaluable tissue in the nonsquamous NSCLC subgroup.

Brain magnetic resonance imaging (or computed tomography in case of contraindication), with and without contrast, was performed at baseline in all patients and approximately every 12 weeks until disease progression or treatment discontinuation in patients with a history or symptoms of brain metastases. Radiographic assessment of systemic tumor response in patients with or without brain metastases at baseline was assessed by blinded independent central review (BICR) per modified Response Evaluation Criteria in Solid Tumors version 1.1 on the basis of all lesions; post hoc exploratory systemic and intracranial tumor responses including development of new brain lesions were assessed in patients with baseline brain metastases per modified Response Evaluation Criteria in Solid Tumors (adapted for brain metastases) by BICR.[34,35]

Safety outcomes were reported between the first dose and 30 days after the last dose of the study therapy, with the exception of immune-mediated adverse events (IMAEs) graded per the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). The IMAEs were defined as specific events for which participants received immunosuppressive medication as treatment. Endocrine events were included regardless of treatment, as these events are often managed without immunosuppression. IMAEs, regardless of causality, were reported between the first dose and 100 days after the last dose of the study treatment. Time to onset and resolution of IMAEs were evaluated, along with the use of corticosteroids and other immune-modulating medications for the management of these events.

Further details on end points and assessments were previously reported.[4,10]

## Mutation Analysis

Exploratory analyses were conducted on baseline tumor samples to evaluate select somatic mutations. Mutations in *KRAS*, *TP53*, *STK11*, and *KEAP1* genes were identified in patients with mutation-evaluable tissue among the nonsquamous NSCLC subgroup using Foundation Medicine's FoundationOne CDx assay; deleterious mutations were defined as single nucleotide variants, insertions, and deletions or copy number alterations with likely or known deleterious effect on protein function. Furthermore, OS and PFS were assessed by mutation status with no adjustments for baseline factors.

## Statistical Analysis

Efficacy outcomes were evaluated in all randomized patients. Survival curves and rates were estimated using Kaplan–Meier methodology. HRs and associated

confidence intervals (CIs) were estimated using a stratified (all randomized patients) or unstratified (patient subgroups) Cox proportional hazard model with treatment arm as a single covariate. Estimates of response rate and exact two-sided 95% CIs were summarized using the Clopper–Pearson method. Safety was assessed in all patients who received at least 1 dose of the study drug.

## Results

### *Patient Disposition and Treatment Summary*

In total, 361 patients were randomized to the nivolumab plus ipilimumab with chemotherapy arm and 358 were randomized to the chemotherapy-alone arm; 358 (99%) and 349 (97%) patients, respectively, received at least 1 dose of the study treatment.[4,10] At the database lock (February 15, 2022), minimum follow-up was 36.1 months (median follow-up: 42.6 mo) for OS and 35.2 months for all other analyses. Baseline characteristics for the overall population have been previously reported and were generally well balanced between the treatment arms (Supplementary Table 1).[4,10] Of all randomized patients, 227 (32%) had squamous and 492 (68%) had nonsquamous NSCLC.

No patients in the nivolumab plus ipilimumab with chemotherapy arm remained on the study treatment, per the protocol-defined maximum immunotherapy treatment duration of 2 years. The patients received the study treatment for a median (range) of 6.1 (0–24.4) months in the nivolumab plus ipilimumab with chemotherapy arm and 2.5 (0–46.1) months in the chemotherapy-alone arm (Supplementary Table 2). Most of the patients in the nivolumab plus ipilimumab with chemotherapy arm (93%) received 2 cycles of chemotherapy, and 14% completed the 2-year treatment period. Patients in the nivolumab plus ipilimumab with chemotherapy arm received a median (range) of 9.0 (1–36) nivolumab doses and 4.0 (1–18) ipilimumab doses. In the chemotherapy arm, 261 patients (75%) received 4 cycles of chemotherapy, and 159 patients (67%) with nonsquamous NSCLC received pemetrexed maintenance. In total, five patients (1%) continued to receive pemetrexed maintenance therapy at the 3-year follow-up (Supplementary Table 2).

Among all randomized patients, 37% in the nivolumab plus ipilimumab with chemotherapy arm and 49% in the chemotherapy-alone arm received subsequent systemic therapy; 8% and 36% received subsequent immunotherapy; and 19% and 6% received subsequent platinum-doublet chemotherapy, respectively (Supplementary Table 3). Among patients who were alive at 3 years in the nivolumab plus ipilimumab with chemotherapy arm (n = 96) and chemotherapy-alone arm (n = 63), 25% and 54% received subsequent systemic therapy, 12% and 51% received subsequent immunotherapy, and 15% and 11% received platinum-doublet chemotherapy, respectively (Supplementary Table 3).

### *Efficacy*

**Overall survival.** At a minimum follow-up of 36.1 months, nivolumab plus ipilimumab with chemotherapy continued to have sustained OS benefit versus chemotherapy alone (Fig. 1*A*). In the nivolumab plus ipilimumab with chemotherapy arm, median OS was 15.8 months (95% CI: 13.9–19.7) versus 11.0 months (95% CI: 9.5–12.7) in the chemotherapy-alone arm (HR 0.74; 95% CI: 0.62–0.87); 3-year OS rates were 27% versus 19%, respectively.

Consistent with previously reported results from the study,[4,10] improved OS was observed across most key subgroups (Fig. 2), including by tumor histology (Supplementary Fig. 2) and PD-L1 expression (<1%, ≥1%, 1%–49%, and ≥50%; Fig. 1*B*–*E*). In patients with tumor PD-L1 expression less than 1%, median OS was 17.7 versus 9.8 months in the nivolumab plus ipilimumab with chemotherapy arm versus the chemotherapy-alone arm, respectively (HR: 0.67; 95% CI: 0.51–0.88); 3-year OS rates were 25% versus 15% (Fig. 1*B*). In patients with tumor PD-L1 expression greater than or equal to 1%, median OS was 15.8 versus 10.9 months, respectively (HR: 0.74; 95% CI: 0.60–0.93); 3-year OS rates were 28% versus 19% (Fig. 1*C*). Among all patients with tumor PD-L1 expression greater than or equal to 1%, consistent OS benefit was found with nivolumab plus ipilimumab with chemotherapy versus chemotherapy alone in patients with PD-L1 expression 1% to 49% and greater than or equal to 50%; 3-year OS rates were 26% versus 15% in patients with PD-L1 expression 1% to 49% (Fig. 1*D*) and 33% versus 24% in patients with PD-L1 expression greater than or equal to 50% (Fig. 1*E*).

**PFS and tumor response.** PFS continued to be prolonged in the nivolumab plus ipilimumab with chemotherapy arm versus the chemotherapy-alone arm, with an HR of 0.70 (95% CI: 0.59–0.83) and 3-year PFS rate of 13% versus 5% (Fig. 3*A*). ORR was 38% in the nivolumab plus ipilimumab with chemotherapy arm versus 25% in the chemotherapy-alone arm (Supplementary Table 4). The complete response rate was 4% in the nivolumab plus ipilimumab with chemotherapy arm versus 1% in the chemotherapy-alone arm; median duration of response (DOR) in the nivolumab plus ipilimumab with chemotherapy arm was 12.4 months (95% CI: 8.7–20.1) versus 5.6 months (95% CI: 4.4–7.2) in the chemotherapy-alone arm, and responses were

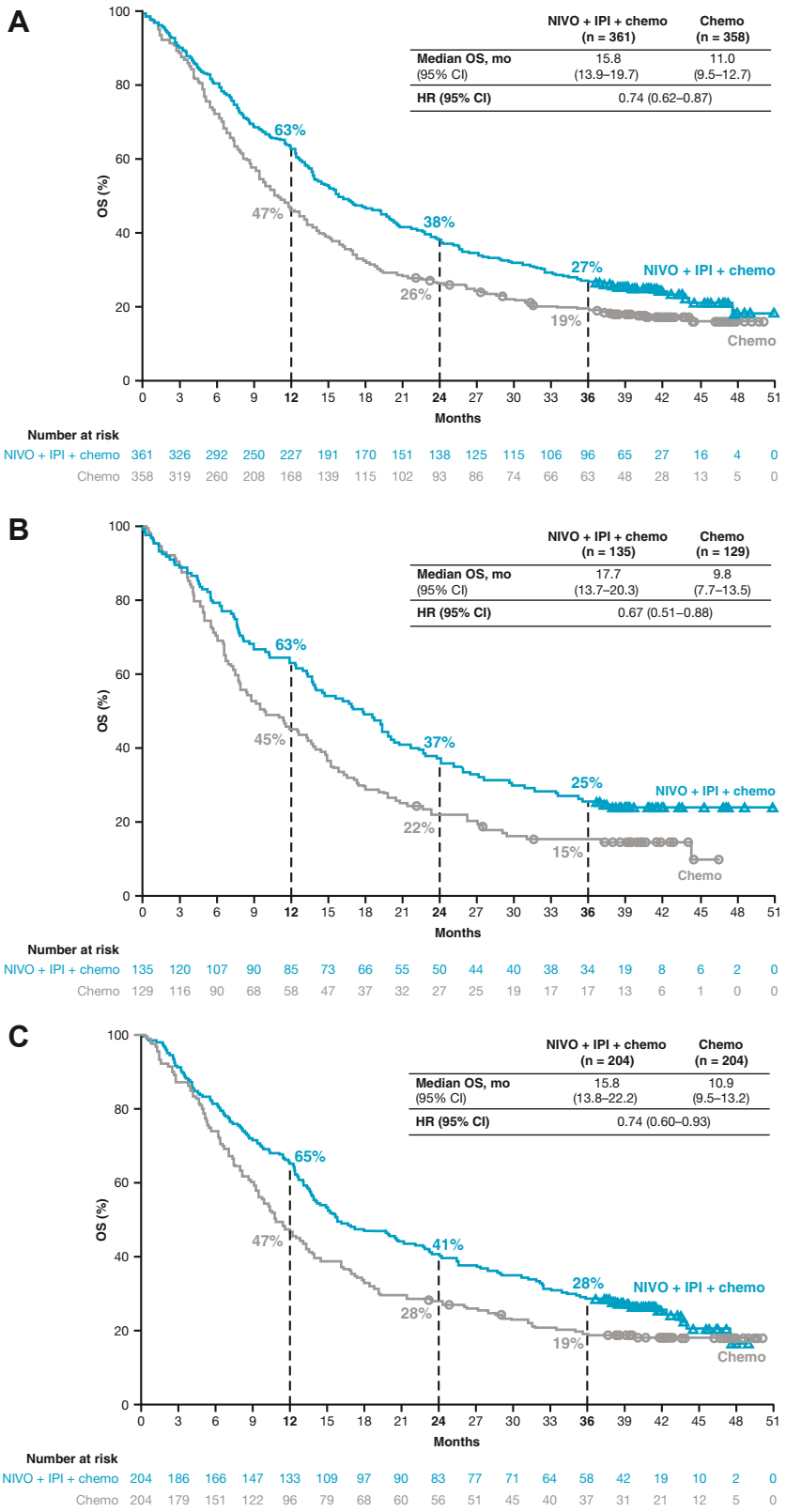


**Figure 1.** OS in (*A*) all randomized patients and in patients with tumor PD-L1 expression levels (*B*) less than 1%, (*C*) greater than or equal to 1%, (*D*) 1% to 49%, and (*E*) greater than or equal to 50%. Minimum follow-up of 36.1 months. The 95% CIs for 3-year OS rates with NIVO plus IPI plus chemo and chemo were (*A*) 22.1 to 31.2 and 15.2 to 23.5, (*B*) 18.2 to 32.7 and 9.5 to 21.9, (*C*) 22.4 to 34.7 and 14.1 to 24.9, (*D*) 18.6 to 33.6 and 8.9 to 22.7, and (*E*) 22.7 to 43.5 and 15.6 to 32.2, respectively. Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; PD-L1, programmed death-ligand 1.

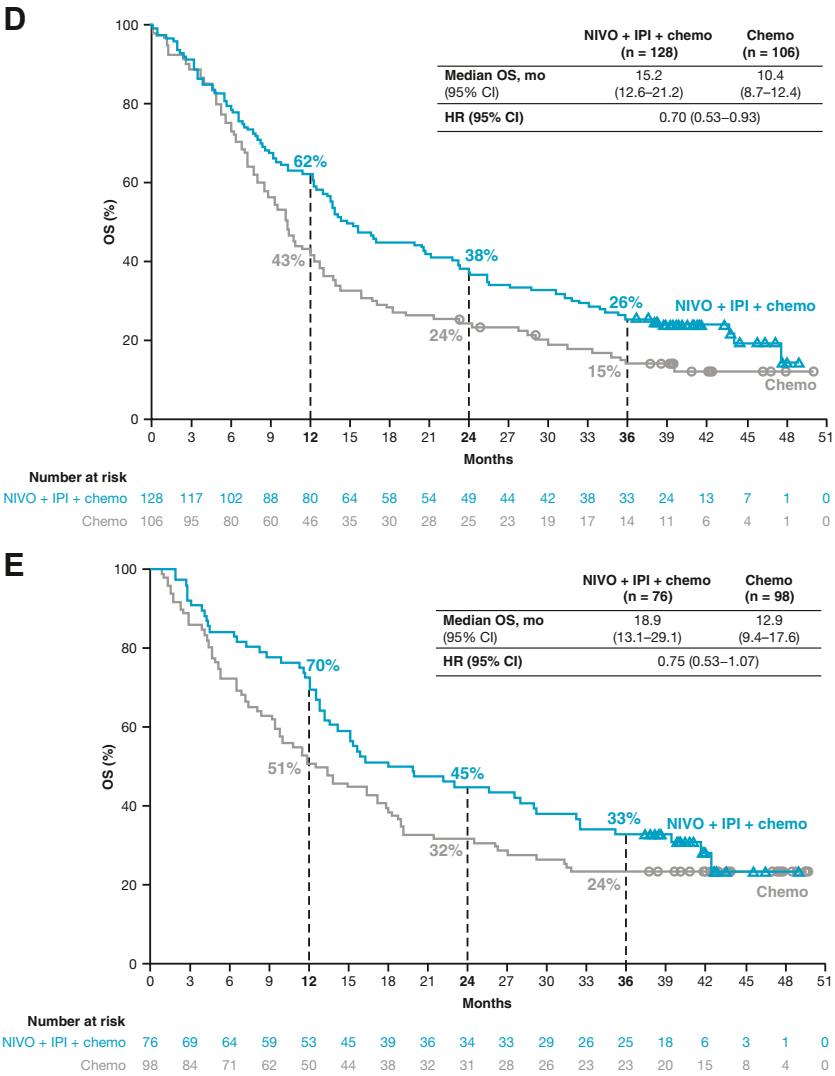


**Figure 1.** Continued.

ongoing at 3 years in 23% versus 14% of patients, respectively (Fig. 3*B*). A PFS and DOR benefit continued to be observed in the nivolumab plus ipilimumab with chemotherapy arm versus the chemotherapy-alone arm in patients with nonsquamous and squamous NSCLC (Supplementary Fig. 3) and in patients with PD-L1 expression less than 1% or greater than or equal to 1% (Supplementary Fig. 4). In an analysis of patients who were alive at 3 years, PFS was prolonged in the nivolumab plus ipilimumab with chemotherapy arm versus the chemotherapy-alone arm (Supplementary Table 5); ORR was 69% versus 57%, respectively (Supplementary Table 4). Median DOR was 34.7 months (95% CI: 31.5–not reached [NR]) in the nivolumab plus ipilimumab with chemotherapy arm versus 12.2 months (95% CI: 9.6–NR) in the chemotherapy-alone arm, and responses were ongoing in 48% versus 36% of patients, respectively (Supplementary Table 5).

### *Clinical Outcomes in Patients With or Without Baseline Brain Metastases*

Of 719 patients randomized, 101 (14%) patients had pretreated baseline brain metastases as assessed by BICR. In patients with baseline brain metastases, 51 received nivolumab plus ipilimumab with chemotherapy and 50 received chemotherapy alone. In patients without baseline brain metastases, 310 received nivolumab plus ipilimumab with chemotherapy and 308 received chemotherapy alone. Baseline characteristics were generally similar in patients with and without baseline brain metastases and between the treatment arms. Nevertheless, among patients with baseline brain metastases, a greater proportion had never smoked (22% versus 8%) and fewer had baseline liver metastases (16% versus 40%) in the nivolumab plus ipilimumab with chemotherapy versus the chemotherapy-alone arm (Supplementary Table 6). In addition, among patients

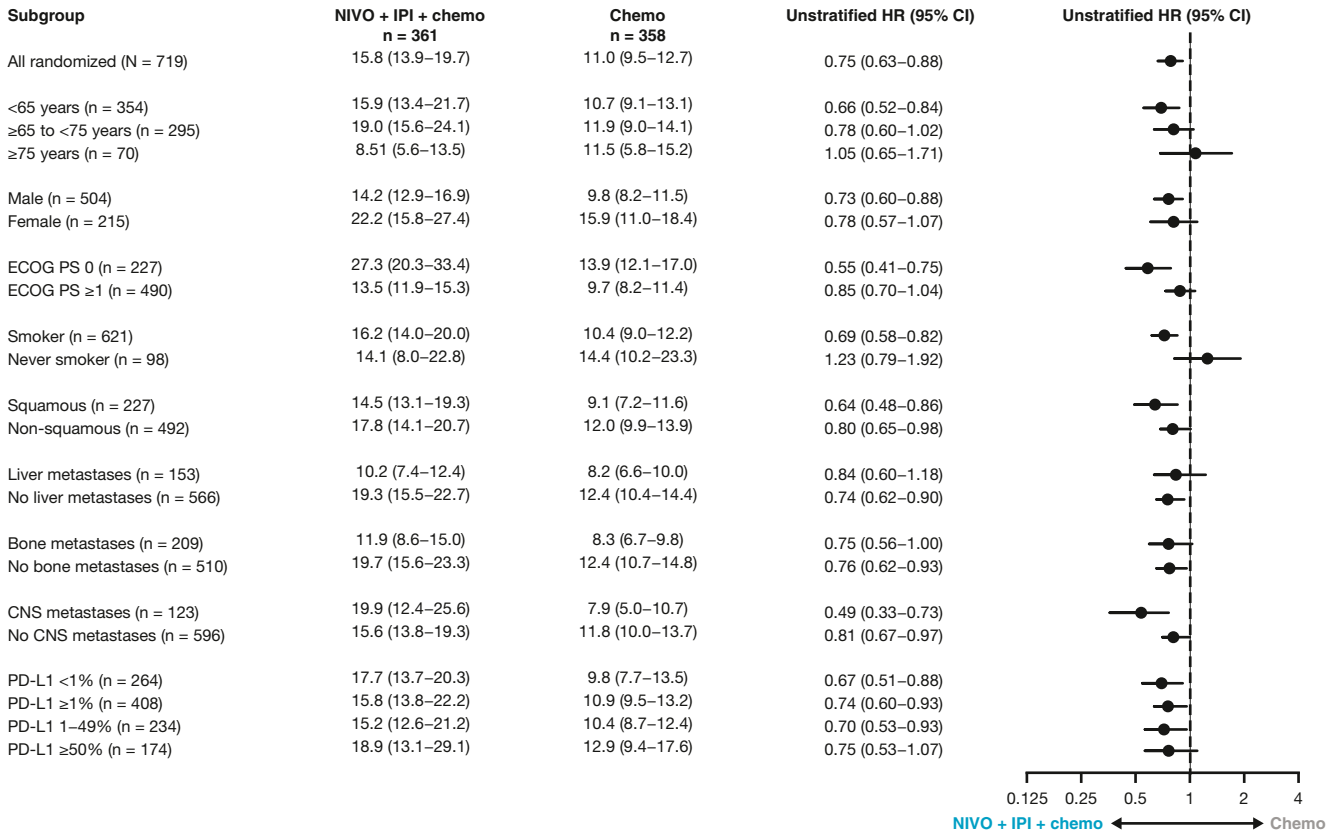


**Figure 2.** OS by prespecified subgroups. Chemo, chemotherapy; CI, confidence interval; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; PD-L1, programmed death-ligand 1.

with baseline brain metastases, 88% in the nivolumab plus ipilimumab with chemotherapy arm versus 88% in the chemotherapy-alone arm had prior brain radiotherapy, 37% versus 40% of whom received whole brain radiation (Supplementary Table 6). In patients with brain metastases at baseline, the median (range) baseline brain tumor burden was 20.0 (10−113) mm in the nivolumab plus ipilimumab with chemotherapy arm versus 29.5 (12−71) mm in the chemotherapy-alone arm (Supplementary Table 6).

Among the patients with baseline brain metastases, 29% in the nivolumab plus ipilimumab with chemotherapy arm and 34% in the chemotherapy-alone arm received subsequent systemic therapy; 4% and 26% received subsequent immunotherapy, and 18% and 2% received subsequent platinum-doublet chemotherapy, respectively (Supplementary Table 7). Among the patients without baseline brain metastases in the nivolumab plus ipilimumab with chemotherapy arm and chemotherapy-alone arm, 38% and 51% received subsequent systemic therapy, 9% and 38% received subsequent immunotherapy, and 19% and 6% received platinum-doublet chemotherapy, respectively (Supplementary Table 7).

**OS, systemic PFS, and tumor response.** Nivolumab plus ipilimumab with chemotherapy provided OS benefit versus chemotherapy alone in patients with or without baseline brain metastases (Fig. 4*A* and *B*). In the nivolumab plus ipilimumab with chemotherapy arm, patients with baseline brain metastases had a median (95% CI) OS of 19.3 (12.3–23.9) versus 6.8 (95% CI: 4.7–9.7) months in the chemotherapy-alone arm (HR: 0.45; 95% CI: 0.29–0.70); 3-year OS rates were 28% versus 12%, respectively. Patients without baseline brain metastases in the nivolumab plus ipilimumab with chemotherapy arm had a median (95% CI) OS of 15.6 (13.8–19.4) versus 12.1 (10.2–13.7) months in the chemotherapy-alone arm (HR: 0.80; 95% CI: 0.67–0.96); 3-year OS rates were 26% versus 20%, respectively. Similarly, systemic PFS and systemic DOR were improved with nivolumab plus ipilimumab with chemotherapy versus chemotherapy alone in patients with or without baseline brain metastases (Fig. 4*C* and *D* and Supplementary Fig. 5).

**Intracranial PFS and tumor response.** Consistent with systemic PFS, intracranial PFS favored the nivolumab

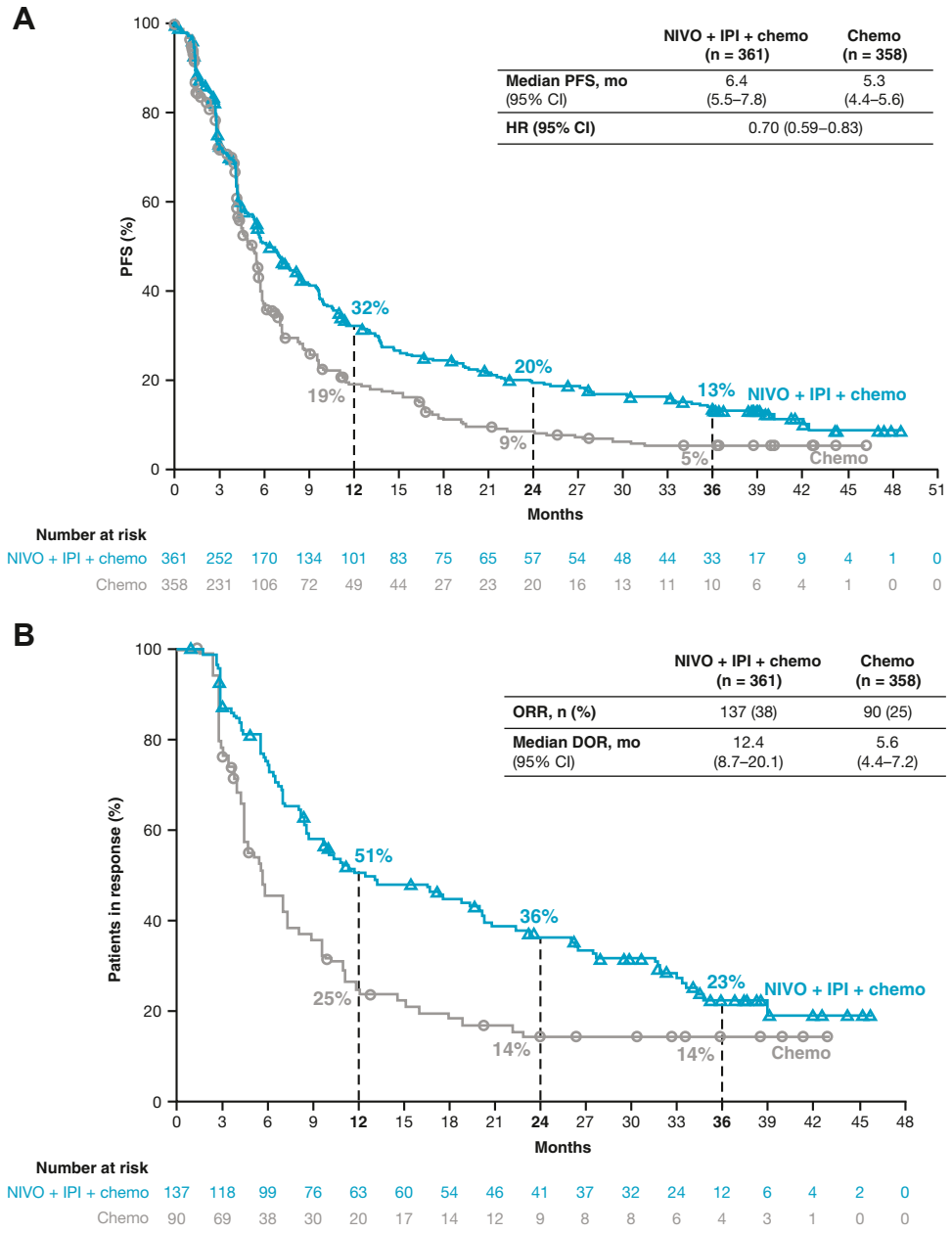


**Figure 3.** (*A*) PFS and (*B*) DOR in all randomized patients. Minimum follow-up of 35.2 months. The 95% CIs for 3-year PFS rates with NIVO plus IPI plus chemo and chemo were (*A*) 9.7 to 17.4 and 3.0 to 8.7 and (*B*) 15.0 to 31.0 and 8.0 to 23.0, respectively. Chemo, chemotherapy; CI, confidence interval; DOR, duration of response; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; ORR, objective response rate; PFS, progression-free survival.

plus ipilimumab with chemotherapy arm over the chemotherapy-alone arm, with a median (95% CI) intracranial PFS of 11.4 (8.4–18.6) versus 4.6 (3.2–5.7) months (HR: 0.42; 95% CI: 0.26–0.68; Supplementary Fig. 6) and 3-year intracranial PFS rates of 14% and 6%, respectively. Intracranial DOR, ORR, best overall response, tumor response, and development of new brain lesions in the patients with baseline brain metastases are described in Table 1. Intracranial ORR was 39% for the nivolumab plus ipilimumab with chemotherapy arm versus 20% for the chemotherapy-alone arm; median intracranial DOR (95% CI) was 15.8 (7.8–NR) versus 18.9 (1.8–NR) months, respectively, and responses were ongoing in 29% versus 30% of the patients. Intracranial tumor burden reduction in patients with baseline brain lesions was greater for the nivolumab plus ipilimumab with chemotherapy arm versus the chemotherapy-alone arm, with a median reduction from baseline of 45% versus 28%, respectively (Supplementary Fig. 7).

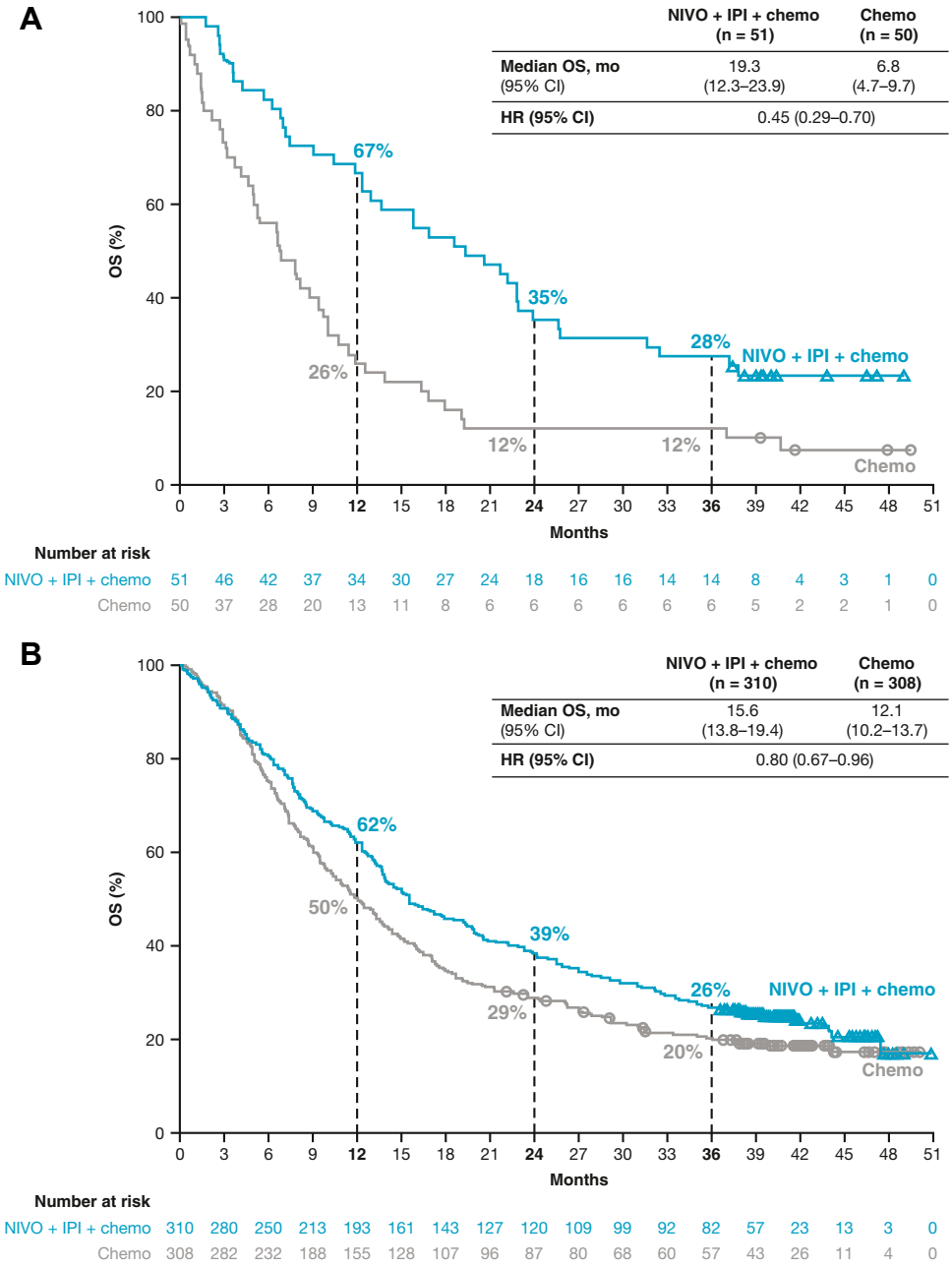


**Figure 4.** OS and systemic PFS in the patients with or without baseline brain metastases: OS (*A*) with and (*B*) without brain metastases; PFS (*C*) with and (*D*) without brain metastases. The 95% CIs for 3-year OS rates with NIVO plus IPI plus chemo and chemo were (*A*) 16.1 to 40.0 and 4.9 to 22.6, (*B*) 21.7 to 31.5 and 16.0 to 25.0, (*C*) 6.9 to 27.7 and 1.0 to 15.9, and (*D*) 9.0 to 17.2 and 2.9 to 9.1, respectively. Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; PFS, progression-free survival.

### *Development of New Brain Lesions*

Among the patients with baseline brain metastases, fewer of those treated with nivolumab plus ipilimumab with chemotherapy developed new brain lesions compared with chemotherapy alone (20% versus 30%, respectively; Table 1); similar results were observed in the patients without baseline brain metastases (3.2% versus 3.6%, respectively) (Supplementary Table 8). Median time to development of new brain lesions was also prolonged in the nivolumab plus ipilimumab with chemotherapy arm versus the chemotherapy-alone arm: 10.9 versus 4.6 months in the patients with baseline brain metastases (Table 1) and 6.9 versus 5.3 months in the patients without baseline brain metastases, respectively (Supplementary Table 8).

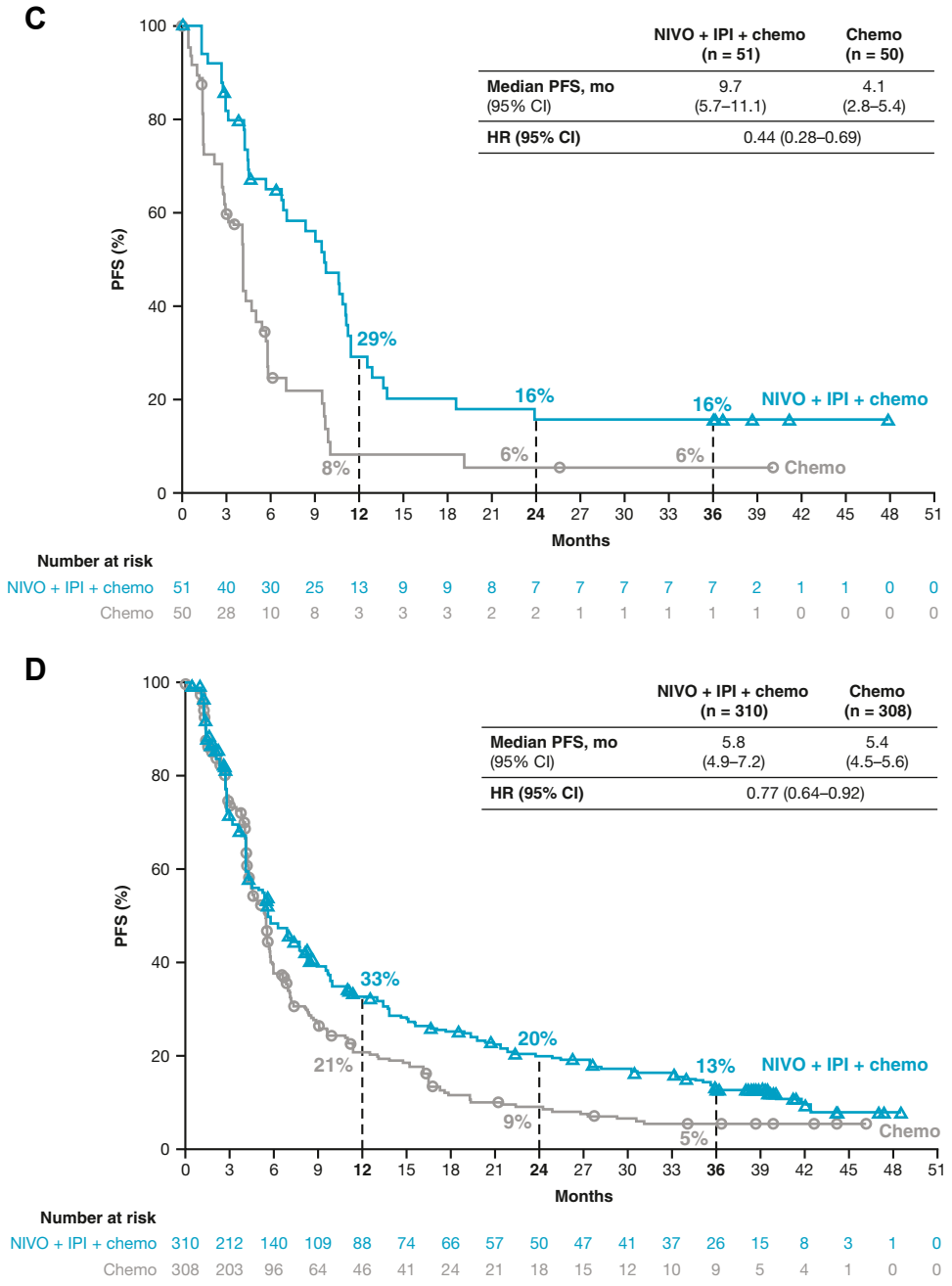


**Figure 4.** Continued.

### *Mutation Analysis*

In total, 492 (68%) of all randomized patients had nonsquamous NSCLC, of whom 313 (64%) had mutation-evaluable tissue. Baseline characteristics of the patients with mutation-evaluable tissue were consistent with all randomized patients and patients with nonsquamous NSCLC (Supplementary Table 9). Of the patients with mutation-evaluable tissue, *KRAS*, *TP53*, *STK11*, and *KEAP1* mutations were found in 39%, 60%, 27%, and 10%, respectively (Supplementary Fig. 8).

Consistent with results from all randomized patients, OS was improved with nivolumab plus ipilimumab with chemotherapy versus chemotherapy alone in all mutation-evaluable patients; median (95% CI) OS was 16.3 (12.7–20.3) months versus 13.1 (10.6–15.4) months, respectively. A numerical trend of prolonged OS with nivolumab plus ipilimumab with chemotherapy versus chemotherapy alone was observed in patients with or without select somatic mutations. Median OS was 19.2 months (nivolumab plus ipilimumab with chemotherapy) versus 13.5 months (chemotherapy

**Table 1.** Intracranial Efficacy, Tumor Response, and Development of New Brain Lesions in the Patients With Baseline Brain Metastases

| | Brain Metastases at Baseline[a] | |
|---|---|---|
| Intracranial Outcomes | Nivolumab Plus Ipilimumab With Chemotherapy (2 Cycles) (n = 51) | Chemotherapy (n = 50) |
| ORR, n (%) | 20 (39.2) | 10 (20.0) |
| 95% CI | 25.8-53.9 | 10.0-33.7 |
| BOR, n (%) | | |
| Complete response | 5 (9.8) | 4 (8.0) |
| Partial response | 15 (29.4) | 6 (12.0) |
| Stable disease | 19 (37.3) | 18 (36.0) |
| Progressive disease | 1 (2.0) | 3 (6.0) |
| Unable to determine | 1 (2.0) | 5 (10.0) |
| Not reported | 10 (19.6) | 14 (28.0) |
| Disease control rate, n (%) | 39 (76.5) | 28 (56.0) |
| Time to response, median (range), mo | 2.8 (1.3-11.4) | 2.2 (1.3-5.8) |
| PFS, mo (95% CI) | 11.4 (8.4-18.6) | 4.6 (3.2-5.7) |
| DOR, median (range), mo | 15.8 (7.8-NR) | 18.9 (1.8-NR) |
| New brain lesions developed, n (%) | 10 (19.6) | 15 (30.0) |
| Time to development of new brain lesions, median (range), mo | 10.9 (2.3-19.6) | 4.6 (1.9-9.5) |
| Tumor burden in patients who developed new brain lesions,[b,c] range, mm | 13-19 | 10-38 |

[a]Brain metastases were assessed by modified RECIST (adapted for brain metastases analysis).
[b]Sum of longest diameter from all new brain tumors at the same visit.
[c]Nivolumab plus ipilimumab with chemotherapy, n = 2; chemotherapy, n = 5.
BOR, best overall response; CI, confidence interval; DOR, duration of response; NR, not reached; ORR, objective response rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

alone) and 15.6 versus 12.7 months, respectively, in patients with or without *KRAS* mutation (Fig. 5*A* and *B*); 16.9 versus 12.9 months and 15.8 versus 13.5 months, respectively, in patients with or without *TP53* mutation (Fig. 5*C* and *D*); and 13.8 versus 10.7 months and 17.8 versus 13.9 months, respectively, in patients with or without *STK11* mutation (Fig. 5*E* and *F*). Similar trends of prolonged OS with nivolumab plus ipilimumab with chemotherapy versus chemotherapy alone were observed in the patients with or without *KRAS* G12C and *KEAP1* mutations (Supplementary Table 10).

Consistent with all randomized patients, PFS appeared to improve with nivolumab plus ipilimumab with chemotherapy (median PFS, 6.7 mo [95% CI: 4.5–8.4]) versus chemotherapy alone (5.6 mo [95% CI: 4.5–6.2]) in patients with mutation-evaluable tissue. Similar trends of prolonged PFS with nivolumab plus ipilimumab with chemotherapy versus chemotherapy alone were also observed, regardless of mutation status (Supplementary Table 11).

## *Safety*

With a minimum follow-up of 35.2 months, safety data were consistent with the prior report at 2 years of follow-up,[10] and no new safety signals were identified. TRAEs of any grade and of grade 3 or 4, respectively, occurred in 92% and 48% of the patients in the nivolumab plus ipilimumab with chemotherapy arm compared with 88% and 38% in the chemotherapy-alone arm (Supplementary Table 12). The onset of grade 1 or 2 TRAEs by treatment cycle was generally comparable between the treatment arms. TRAEs of any grade leading to treatment discontinuation of any component of the regimen were reported in 79 (22%) versus 30 (9%) patients in the nivolumab plus ipilimumab with chemotherapy versus the chemotherapy-alone arm, respectively (Supplementary Table 12). Treatment-related deaths occurred in eight (2%) versus six (2%) patients, respectively. In the combination arm, the most frequently reported any-grade IMAE and grade 3 or 4 IMAE were rash (18%) and hepatitis (4%), respectively (Supplementary Table 13). Median time to onset and time to resolution of IMAEs of any grade and grades 3 or 4 are found in Supplementary Table 13.

Among the patients with baseline brain metastases, any-grade and grade 3 or 4 TRAEs, respectively, occurred in 90% and 43% of patients in the nivolumab plus ipilimumab with chemotherapy arm compared with 82% and 46% in the chemotherapy-alone arm (Supplementary Table 14). Serious TRAEs, TRAEs leading to treatment discontinuation, and treatment-related deaths are reported in Supplementary Table 14. The

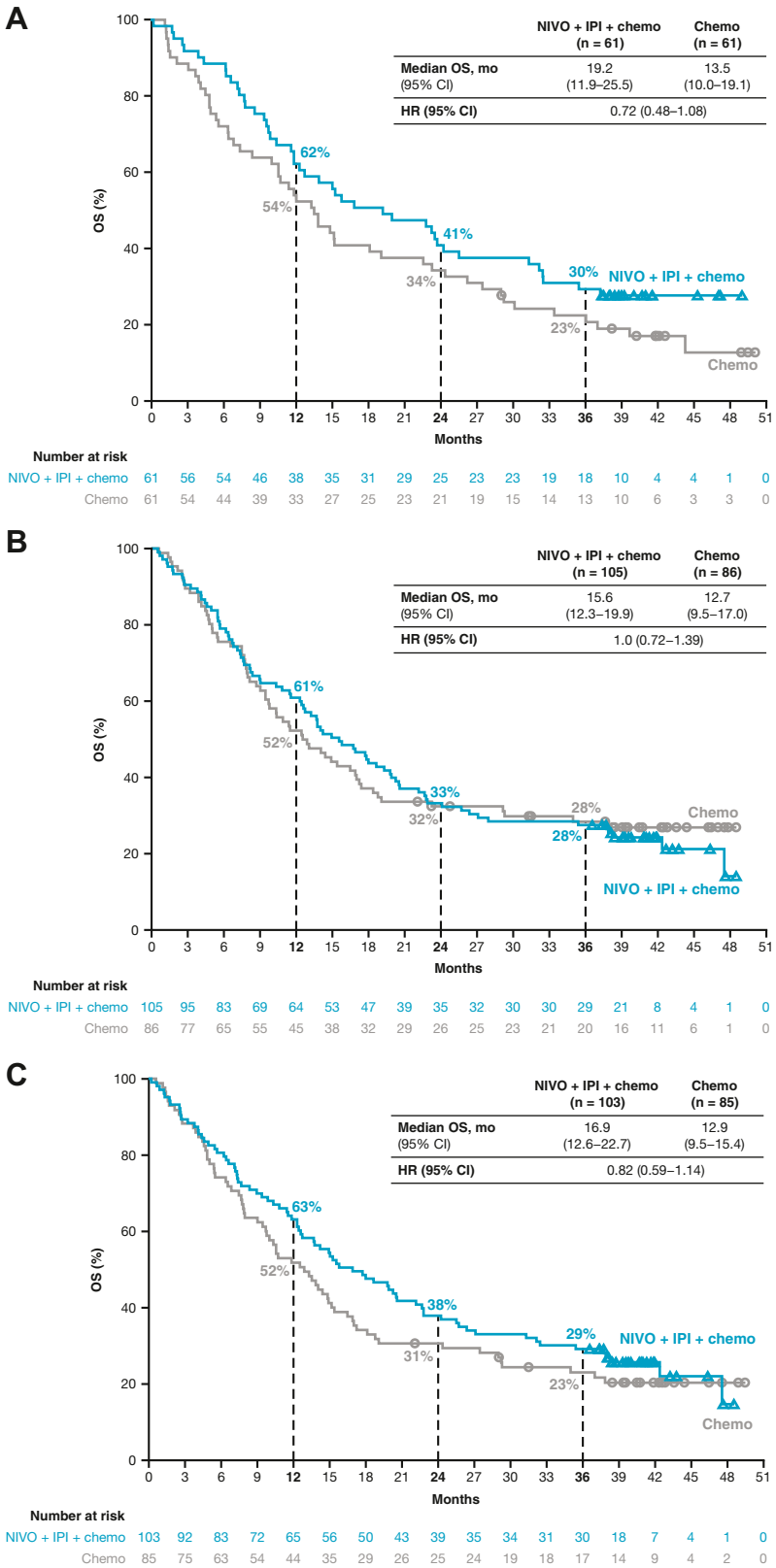


**Figure 5.** OS in patients by select somatic mutation status: (*A*) *KRAS* mutant, (*B*) *KRAS* wild-type, (*C*) *TP53* mutant, (*D*) *TP53* wild-type, (*E*) *STK11* mutant, and (*F*) *STK11* wild-type. The 95% CIs for 3-year OS rates with NIVO plus IPI plus chemo and chemo were (*A*) 20.0 to 43.5 and 14.2 to 36.1, (*B*) 20.3 to 37.6 and 20.3 to 40.0, (*C*) 21.6 to 39.4 and 15.5 to 34.1, (*D*) 18.0 to 40.5 and 20.3 to 44.0, (*E*) 19.6 to 45.8 and 14.2 to 44.0, and (*F*) 20.5 to 37.0 and 19.0 to 36.0. Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival.

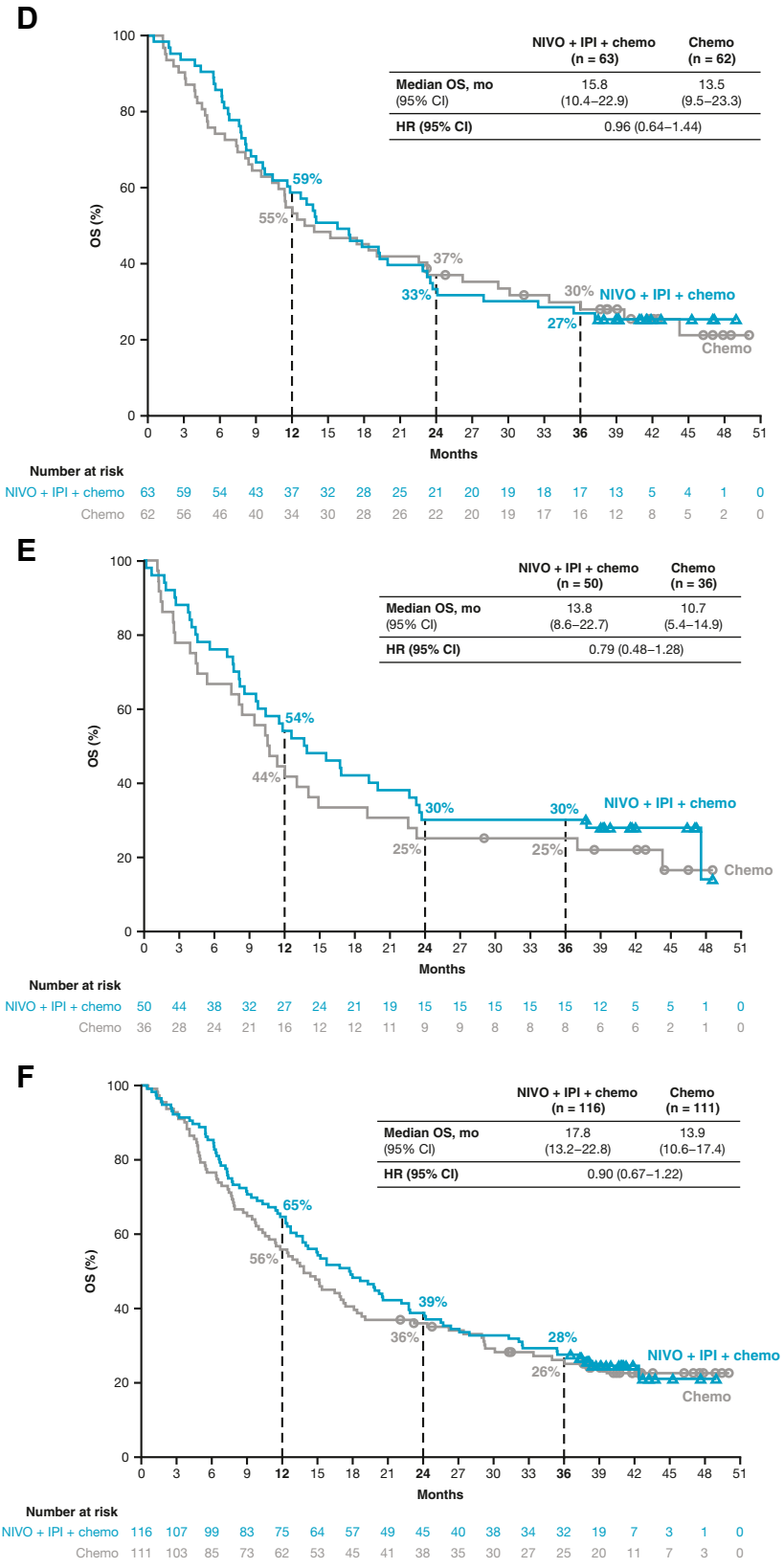


**Figure 5.** Continued.

most frequently reported IMAEs of any grade in the nivolumab plus ipilimumab with chemotherapy arm are found in Supplementary Table 15. Any-grade and grade 3 or 4 nervous system TRAEs, respectively, occurred in 20% and 2% of the patients in the nivolumab plus ipilimumab with chemotherapy arm, respectively, compared with 10% and 0% in the chemotherapy-alone arm (Supplementary Table 16).

## Discussion

In CheckMate 9LA, with a minimum follow-up of 3 years, first-line nivolumab plus ipilimumab with 2 cycles of chemotherapy versus 4 cycles of chemotherapy alone continued to provide prolonged survival (HR: 0.74) and improved clinical benefits (PFS, ORR, and DOR) in patients with metastatic NSCLC, regardless of tumor PD-L1 expression level or squamous or nonsquamous histology. At 3 years, 27% of the patients treated with nivolumab plus ipilimumab with chemotherapy were alive versus 19% in the chemotherapy-alone arm, PFS benefit was sustained, and responses continued to be durable in the nivolumab plus ipilimumab with chemotherapy arm compared with the chemotherapy-alone arm. In addition, nivolumab plus ipilimumab with chemotherapy had OS benefit versus chemotherapy alone in the patients with baseline brain metastases, a population with known poor prognosis; other systemic efficacy outcomes also favored nivolumab plus ipilimumab with chemotherapy, consistent with the efficacy benefit in the patients without brain metastases. Notably, intracranial PFS was improved with nivolumab plus ipilimumab with chemotherapy in the patients with brain metastases. In this exploratory analysis in the patients with nonsquamous NSCLC, a trend toward OS benefit was observed with nivolumab plus ipilimumab with chemotherapy versus chemotherapy alone, regardless of *KRAS*, *TP53*, or *STK11* mutations. No new safety signals were identified with the extended follow-up.

PD-(L)1 inhibitors have become the standard of care for the patients with metastatic NSCLC with high tumor PD-L1 expression, including immunotherapy plus chemotherapy, dual immunotherapy, or dual immunotherapy with chemotherapy. Although the addition of ipilimumab to pembrolizumab monotherapy did not improve efficacy in the KEYNOTE-598 study in the patients with PD-L1 greater than or equal to 50%, this may have been due to the relatively short follow-up (12.4 mo minimum) at the time of the prespecified interim analysis.[36] In contrast to patients with NSCLC and high tumor PD-L1 expression, however, immunotherapy-based regimens were found to have limited efficacy in patients with low tumor PD-L1 expression.[37,38] Therefore, an unmet need remains for patients with metastatic NSCLC, particularly those with PD-L1 expression less than 1% or squamous NSCLC.[39,40] In CheckMate 9LA, nivolumab plus ipilimumab with chemotherapy continued to provide consistent survival benefit versus chemotherapy alone, regardless of PD-L1 expression levels; OS was improved in the patients with PD-L1 expression less than 1% (HR: 0.67) and PD-L1 greater than or equal to 1% (HR: 0.74). Similarly, the benefit of nivolumab plus ipilimumab with chemotherapy versus chemotherapy alone was found in both the squamous (HR: 0.64) and nonsquamous (HR: 0.80) NSCLC subgroups. These results are consistent with previous reports from the study, revealing improved OS with nivolumab plus ipilimumab with chemotherapy compared with chemotherapy alone across most subgroups, including PD-L1 expression and squamous or nonsquamous NSCLC subtypes.[4,10]

Patients with NSCLC and brain metastases have a poor prognosis and represent a population with an ongoing unmet need.[41] Although the blood–brain barrier can limit the effectiveness of systemic therapies in patients with brain metastases owing to heterogeneous permeability on the basis of the size of drug molecules,[41] activated immune cells can infiltrate the brain, thus providing a potential mechanism for intracranial efficacy of immunotherapy.[42] As treatment options for this population continue to evolve, an increasing body of evidence, including data from CheckMate 9LA, supports a role for immunotherapy in patients with brain metastases.

In this 3-year update, data from a post hoc analysis revealed a benefit of nivolumab plus ipilimumab with chemotherapy versus chemotherapy alone in patients with or without baseline brain metastases. To our knowledge, this is the first phase 3 trial of immunotherapy in metastatic NSCLC to report intracranial analyses of patients with baseline brain metastases. Importantly, intracranial efficacy was improved in the nivolumab plus ipilimumab with chemotherapy arm, as revealed by the depth of best tumor reduction for intracranial lesions from baseline. In addition, fewer patients developed new brain lesions and time to development of new brain lesions was longer in the nivolumab plus ipilimumab with chemotherapy arm compared with the chemotherapy-alone arm. The results from these analyses are consistent with the improved survival benefit found with immunotherapy-based regimens in patients with treated baseline brain metastases associated with NSCLC[21,22,43] and other cancers such as melanoma and renal cell carcinoma.[16–19] Although the clinical benefit of nivolumab plus ipilimumab with chemotherapy versus chemotherapy alone was observed regardless of baseline brain metastases, numerical differences in median OS were found between patients with or without brain metastases. For example, median OS

with chemotherapy was shorter in patients with brain metastases compared with those without, as expected given previous studies indicating that the presence of brain metastases is a negative prognostic marker.[41] In contrast, median OS with nivolumab plus ipilimumab with chemotherapy was longer in the patients with versus without baseline brain metastases. Nevertheless, these data should be interpreted with caution owing to the small size of the subgroups and potential imbalances in other confounders such as baseline characteristics or subsequent therapies in this exploratory analysis. In addition to studies in the patients with NSCLC and treated brain metastases,[21,22,43] results from the phase 3b CheckMate 817 and the phase 2 ATEZO-BRAIN studies suggest that dual immunotherapy or immunotherapy combined with chemotherapy is efficacious in patients with NSCLC and untreated brain metastases.[20,44] Future clinical research is needed to understand the role of radiotherapy versus systemic immunotherapy in patients with NSCLC and brain metastases and prospectively identify optimal treatment options for this patient population.

PD-L1 expression is a validated, well-established predictive biomarker for response to immunotherapy in NSCLC and other tumor types, though there are biological limitations to its use in informing treatment decisions.[45] Therefore, biomarkers that can further predict efficacy benefits continue to be of high clinical interest.[46–48] Several studies have suggested that somatic mutations such as *KRAS*, *TP53*, *STK11*, or *KEAP1* are associated with clinical benefit with immunotherapies in metastatic NSCLC.[49–55] At this 3-year update, data from an exploratory analysis from CheckMate 9LA assessing survival outcomes by select somatic mutation status revealed that the survival benefit observed in the patients treated with nivolumab plus ipilimumab with chemotherapy versus chemotherapy alone was maintained regardless of *KRAS*, *TP53*, or *STK11* mutation status; however, the number of patients with *KEAP1* mutations was small, limiting data interpretation. This is consistent with an exploratory analysis of CheckMate 227, in which survival benefit with nivolumab plus ipilimumab versus chemotherapy was observed, regardless of the mutation status of these select genes.[56] It should be noted that in these univariate exploratory analyses, the subgroups were small and not statistically powered. Therefore, these results should be interpreted with caution, owing to potential differences in baseline factors or other genomic mutations, and should be considered as hypothesis-generating. Future studies are warranted to prospectively assess applicability of mutation status to guide clinical practice.

With the 3-year minimum follow-up, the safety profile of nivolumab plus ipilimumab combined with chemotherapy was consistent with prior reports, and no new safety signals were identified.[4,10] Similarly, no new safety signals were identified in the post hoc analyses of safety in patients with or without baseline brain metastases, and the results are consistent with other reports of immunotherapy-based regimens in this patient population.[24] Importantly, the incidence of nervous system TRAEs was comparable in patients with or without baseline brain metastases.

In conclusion, first-line nivolumab plus ipilimumab with chemotherapy had long-term, durable efficacy benefit versus chemotherapy alone in patients with metastatic NSCLC, regardless of tumor PD-L1 expression or squamous or nonsquamous histology. The survival curves separated early, and this separation was maintained at 3 years, reinforcing the clinical rationale of adding a limited course of chemotherapy to dual immunotherapy with nivolumab plus ipilimumab to control rapid disease progression. In addition, survival benefit of nivolumab plus ipilimumab with chemotherapy versus chemotherapy alone was observed across patient subgroups typically associated with poor prognosis, such as those with squamous NSCLC, brain metastases at baseline, or select somatic mutations. These results support the use of nivolumab plus ipilimumab with 2 cycles of chemotherapy as an efficacious first-line treatment option for patients with metastatic NSCLC, including those with brain metastases.

## CRediT Authorship Contribution Statement

**Luis G. Paz-Ares:** Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing—review and editing, Supervision.

**Tudor-Eliade Ciuleanu:** Validation, Investigation, Resources, Data curation, Writing—review and editing.

**Manuel Cobo:** Validation, Investigation, Resources, Data curation, Writing—review and editing.

**Jaafar Bennouna:** Validation, Investigation, Resources, Data curation, Writing—review and editing.

**Michael Schenker:** Validation, Investigation, Resources, Data curation, Writing—review and editing.

**Ying Cheng:** Validation, Investigation, Resources, Data curation, Writing—review and editing.

**Oscar Juan-Vidal:** Validation, Investigation, Resources, Data curation, Writing—review and editing.

**Hideaki Mizutani:** Validation, Investigation, Resources, Data curation, Writing—review and editing.

**Alejo Lingua:** Validation, Investigation, Resources, Data curation, Writing—review and editing.

**Felipe Reyes-Cosmelli:** Validation, Investigation, Resources, Data curation, Writing—review and editing.

**Niels Reinmuth:** Validation, Investigation, Resources, Data curation, Writing—review and editing.

**Juliana Menezes:** Validation, Investigation, Resources, Data curation, Writing—review and editing.

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**Aurelia Alexandru:** Validation, Investigation, Resources, Data curation, Writing—review and editing.

**Emmanuel de la Mora Jimenez:** Validation, Investigation, Resources, Data curation, Writing—review and editing.

**Shaker Dakhil:** Validation, Investigation, Resources, Data curation, Writing—review and editing.

**Shun Lu:** Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing—review and editing, Supervision.

**Martin Reck:** Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing—review and editing, Supervision.

**Thomas John:** Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing—review and editing, Supervision.

**David Balli:** Software, Validation, Formal analysis, Data curation, Writing—review and editing, Visualization.

**David P. Carbone:** Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing—review and editing, Supervision.

**Ashvanti Valji (acknowledged contributor):** Writing—original draft.

**Laura J. Eccles:** Writing—review and editing, Visualization.

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**Nan Hu:** Software, Formal analysis, Data curation, Writing—review and editing, Visualization.

**Jaclyn Neely:** Software, Validation, Formal analysis, Data curation, Writing—review and editing, Visualization.

**Judi Sylvester:** Validation, Data curation, Writing—review and editing, Visualization, Supervision, Project administration, Funding acquisition.

**Xiaoqing Zhang:** Validation, Data curation, Writing—review and editing, Visualization, Supervision, Project administration, Funding acquisition.

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## 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.2022.10.014.

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