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ORIGINAL ARTICLE

Nivolumab plus ipilimumab with chemotherapy as first-line treatment of patients with metastatic non-small-cell lung cancer: final, 6-year outcomes from CheckMate 9LA

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Background: The phase III CheckMate 9LA study demonstrated durable overall survival (OS) benefit with nivolumab plus ipilimumab with chemotherapy versus chemotherapy in patients with metastatic non-small-cell lung cancer (NSCLC). Here, we report final, 6-year efficacy and safety outcomes.

Patients and methods: Treatment-naive adults with stage IV/recurrent NSCLC and no sensitizing *EGFR/ALK* alterations were randomized to nivolumab plus ipilimumab with chemotherapy ($n = 361$) or chemotherapy ($n = 358$). Assessments included OS, progression-free survival, objective response rate, and duration of response (DOR) in all randomized patients and subgroups, and OS by select somatic mutation status (*KRAS*, *STK11*, *KEAP1*, and *TP53*).

Results: With 68.6 months' minimum follow-up, nivolumab plus ipilimumab with chemotherapy demonstrated continued OS benefit versus chemotherapy (hazard ratio 0.74, 95% confidence interval 0.63-0.87, 6-year OS rates 16% versus 10%), regardless of tumor programmed death ligand 1 (PD-L1) expression (PD-L1 $<1\%$, 20% versus 7%; PD-L1 $\geq 1\%$, 15% versus 10%) and histology (squamous, 14% versus 5%; non-squamous, 17% versus 12%). The 6-year DOR rate was 19% with nivolumab plus ipilimumab with chemotherapy; all patients in the chemotherapy arm were censored or stopped responding before this timepoint. Trends toward improved OS were observed with nivolumab plus ipilimumab with chemotherapy over chemotherapy regardless of *KRAS*, *STK11*, *KEAP1*, or *TP53* mutation status. No new safety signals were observed.

Conclusions: These final analyses demonstrate the durable, long-term OS and response benefit with first-line nivolumab plus ipilimumab with chemotherapy over chemotherapy in patients with metastatic NSCLC, regardless of tumor PD-L1 expression, histology, or select somatic mutation status, further supporting this regimen as a standard-of-care treatment option.

Key words: non-small-cell lung cancer, nivolumab, ipilimumab, chemotherapy, first-line

INTRODUCTION

Regimens containing immune checkpoint inhibitors have demonstrated sustained improvements in survival and response outcomes compared with chemotherapy alone and are now standard-of-care first-line treatment options for patients with metastatic non-small-cell lung cancer (NSCLC).[1-9] The immune checkpoint inhibitors nivolumab,

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which inhibits programmed death 1 activity, and ipilimumab, which inhibits cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) activity, have distinct but complementary mechanisms of action.[10,11] The combination of nivolumab and ipilimumab has demonstrated durable, long-term clinical benefit as first-line therapy for metastatic NSCLC.[5]

The addition of chemotherapy to immune checkpoint inhibitor-based regimens may stimulate antitumor immunity, potentially increasing immunotherapy activity and providing early disease control while building on the durable survival benefit provided by nivolumab and ipilimumab.[12,13] The global, randomized, open-label phase III CheckMate 9LA study (NCT03215706) demonstrated that first-line nivolumab plus ipilimumab (until disease progression, unacceptable toxicity, or for 2 years) with two cycles of platinum-doublet chemotherapy significantly improved overall survival (OS) versus chemotherapy in patients with metastatic NSCLC [hazard ratio (HR) 0.69, 96.71% confidence interval (CI) 0.55-0.87],[14] resulting in the regimen's approval in several countries, including the USA and European Union.[15-19] Treatment guidelines by the European Society for Medical Oncology, the American Society of Clinical Oncology, and the National Comprehensive Cancer Network also recommend nivolumab plus ipilimumab with chemotherapy as a first-line therapy option for patients with metastatic NSCLC.[7-9,20]

The 5-year follow-up for CheckMate 9LA demonstrated continued survival and response benefit and increased 5-year survivorship with nivolumab plus ipilimumab with chemotherapy compared with chemotherapy.[21] We now report the final, 6-year efficacy and safety outcomes from CheckMate 9LA, which, to our knowledge, represents the longest follow-up for a clinical trial evaluating patients with metastatic NSCLC treated with a regimen consisting of single or dual immune checkpoint inhibition plus chemotherapy.

METHODS

Patients and study design

Detailed information on the study design has been previously reported.[14] Briefly, adults with histologically confirmed stage IV or recurrent NSCLC and no known sensitizing *EGFR*/*ALK* alterations were eligible for enrollment (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.105123). Stratification factors included tumor histology (squamous versus non-squamous), sex (male versus female), and tumor programmed death ligand 1 (PD-L1) expression (<1% versus ≥1%). Patients were randomized 1 : 1 to receive either nivolumab 360 mg every 3 weeks plus ipilimumab 1 mg/kg every 6 weeks with platinum-doublet chemotherapy every 3 weeks for two cycles, or chemotherapy alone every 3 weeks for four cycles. In addition, patients with non-squamous NSCLC in the chemotherapy arm were eligible to receive optional maintenance treatment with pemetrexed 500 mg/m^2. Patients received treatment until disease progression, unacceptable toxicity, or until patients had received 2 years of immunotherapy; patients in the nivolumab plus ipilimumab with chemotherapy arm may have continued treatment beyond disease progression based on prespecified criteria, as previously reported.[14]

This study was carried out in accordance with the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines. Independent ethics committee or institutional review boards at each study site approved the protocol and all amendments. All patients provided written informed consent.

Endpoints

The primary endpoint (OS) and other protocol-specified secondary and exploratory endpoints have been previously reported.[14,21-24] Assessments for this 6-year follow-up analysis included OS; progression-free survival (PFS), objective response rate (ORR), and duration of response (DOR) per blinded independent central review according to Response Evaluation Criteria in Solid Tumors version 1.1; and safety. Efficacy assessments were carried out in all randomized patients and prespecified subgroups, including those defined by tumor PD-L1 expression (<1%, ≥1%, 1%-49%, or ≥50%) and histology (squamous or non-squamous). *Post hoc* exploratory analyses included OS in patients who discontinued treatment due to treatment-related adverse events (TRAEs) and OS by select somatic mutation status (*KRAS* and *STK11* in patients with non-squamous NSCLC, in whom they are more prevalent; *KEAP1* and *TP53* in patients with squamous or non-squamous NSCLC, due to their prevalence across both histologies[25]). As described previously,[23] genes were identified in baseline tumor samples among patients with mutation-evaluable tissue using the FoundationOne CDx assay. Safety outcomes included the incidence of adverse events occurring between the first dose and 30 days after the last dose of study treatment [or 100 days after the last dose of study treatment of immune-mediated adverse events (IMAEs)], categorized per the Medical Dictionary for Regulatory Activities version 27.1 and graded per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Statistical analyses

Detailed statistical methods have been reported previously.[14] Efficacy was evaluated in the intent-to-treat population (i.e. all randomized patients) and prespecified subgroups. Safety was evaluated in the all-treated population (i.e. all patients who received one or more doses of study treatment). Survival curves and rates were estimated using the Kaplan–Meier method, with HRs and associated CIs estimated using stratified (for all randomized patients) or unstratified (for all subgroups) Cox proportional hazards models with treatment as a single covariate. Response rates and associated CIs were estimated using the Clopper–Pearson method.

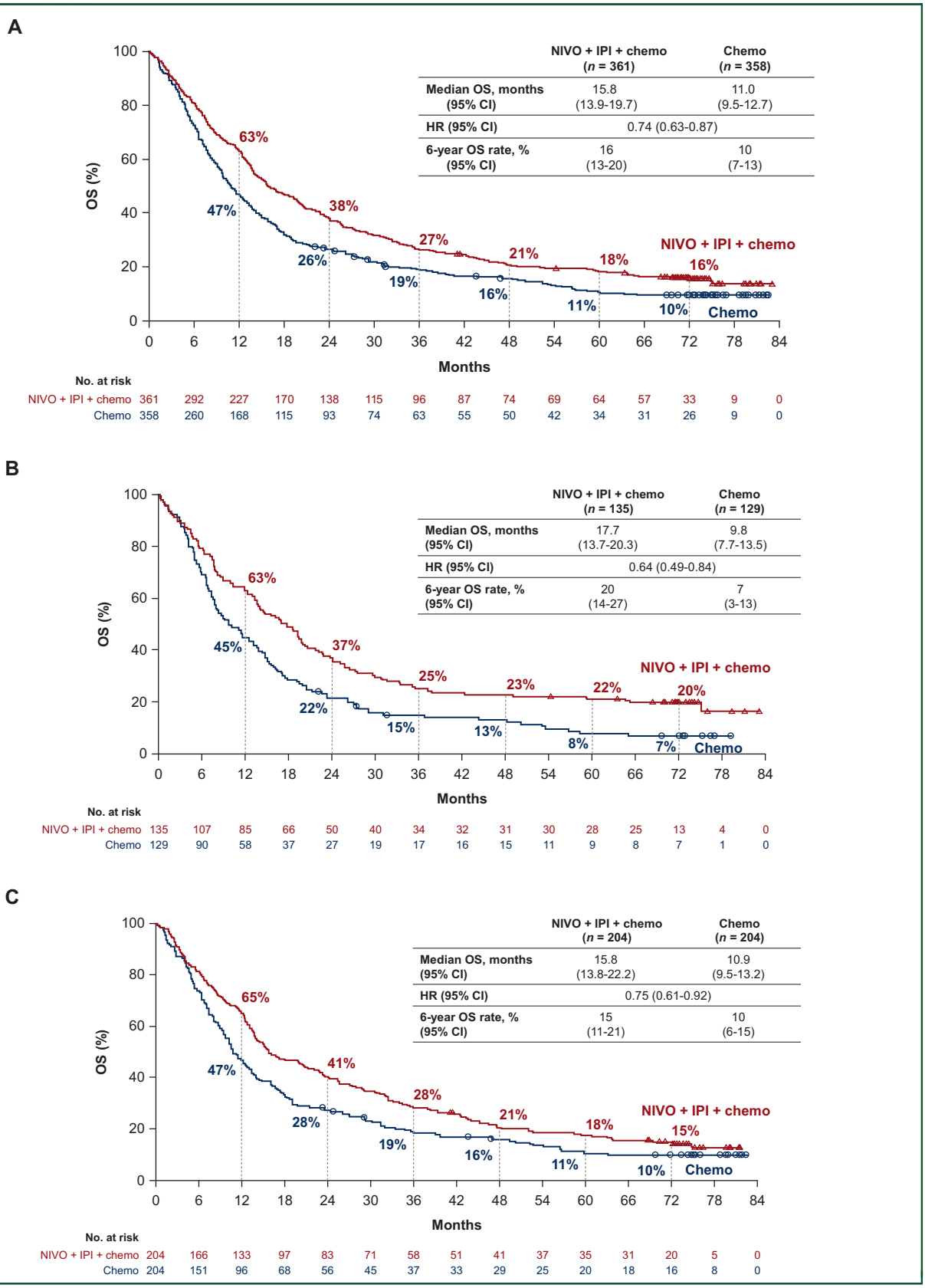

Figure 1. OS in (A) all randomized patients, and in patients with (B) tumor PD-L1 <1%, (C) tumor PD-L1 ≥1%, (D) squamous tumor histology, and (E) non-squamous tumor histology. Minimum follow-up for OS was 68.6 months.
Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; PD-L1, programmed death ligand 1.

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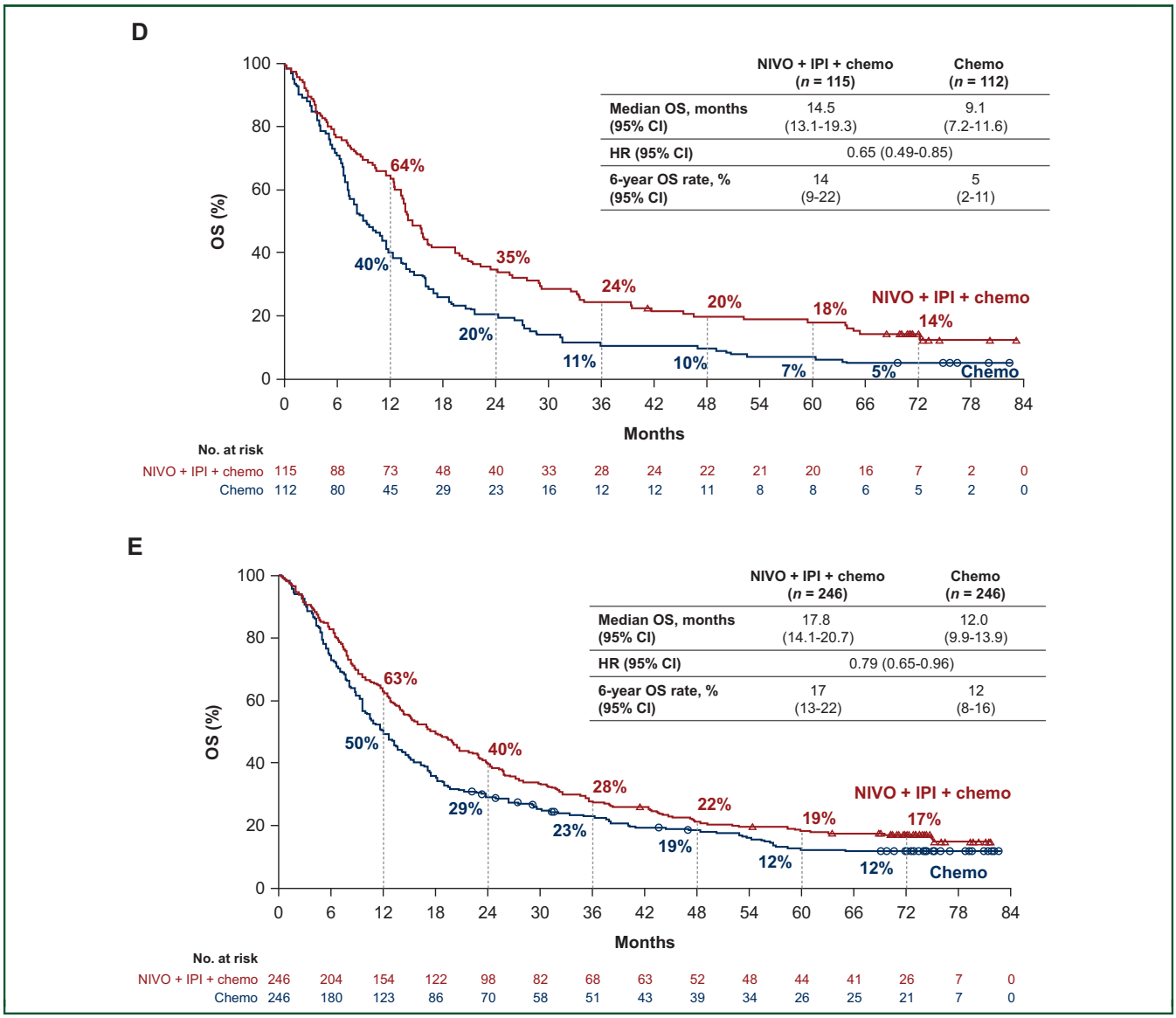

Figure 1. Continued.

RESULTS

Patients

As reported previously,[14] 361 patients were randomized to nivolumab plus ipilimumab with chemotherapy and 358 patients to chemotherapy; 358 and 349 patients, respectively, received one or more doses of treatment. Baseline characteristics were generally similar between treatment arms.[14] As of the 22 November 2024, database lock, the minimum follow-up for OS was 68.6 months and median follow-up (time between the randomization date and database lock date) was 75.8 months; all patients had discontinued study treatment (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105123). Among all treated patients, median duration of treatment (range) was 6.1 months (0-24.4 months) with nivolumab plus ipilimumab with chemotherapy and 2.5 months (0-72.0 months) with chemotherapy alone. In the nivolumab plus ipilimumab with chemotherapy arm, the median number of nivolumab doses received was 9 (range, 1-36) and the median number of ipilimumab doses received was 4 (range, 1-18); 333 patients (93%) received two cycles of chemotherapy. In the chemotherapy arm, 261 patients (75%) received at least four cycles of chemotherapy, and 159 patients (46%) with non-squamous NSCLC received pemetrexed maintenance. Among all treated patients who were alive at least 6 years after randomization (nivolumab plus ipilimumab with chemotherapy, $n = 33$; chemotherapy, $n = 25$), median duration of treatment (range) was 23.3 months (1.4-24.3 months) with nivolumab plus ipilimumab with chemotherapy and 8.7 months (0.7-72.0 months) with chemotherapy (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.105123). Subsequent therapy was received by 38% of patients in the nivolumab plus ipilimumab with chemotherapy arm and 50% of patients in the chemotherapy arm; 8% and 37% received

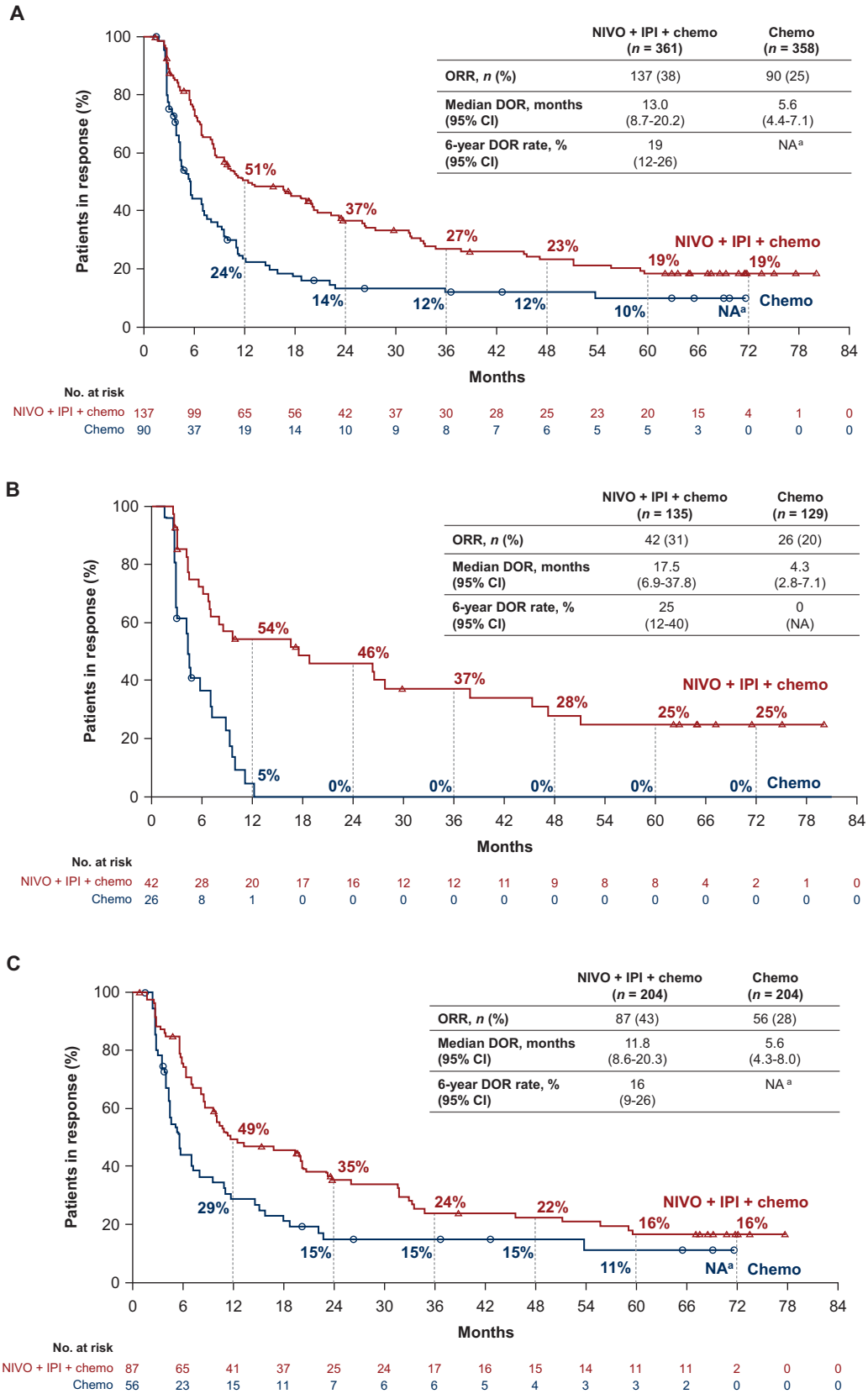

Figure 2. DOR in (A) all randomized patients, and in patients with (B) tumor PD-L1 <1%, (C) tumor PD-L1 ≥1%, (D) squamous tumor histology, and (E) non-squamous tumor histology. DOR was per blinded independent central review according to Response Evaluation Criteria in Solid Tumors v1.1.
Chemo, chemotherapy; CI, confidence interval; DOR, duration of response; IPI, ipilimumab; NA, not available; NIVO, nivolumab; ORR, objective response rate; PD-L1, programmed death ligand 1. [a]Rate is reported as NA because all patients with continuing response in the chemo arm were censored before 72 months.

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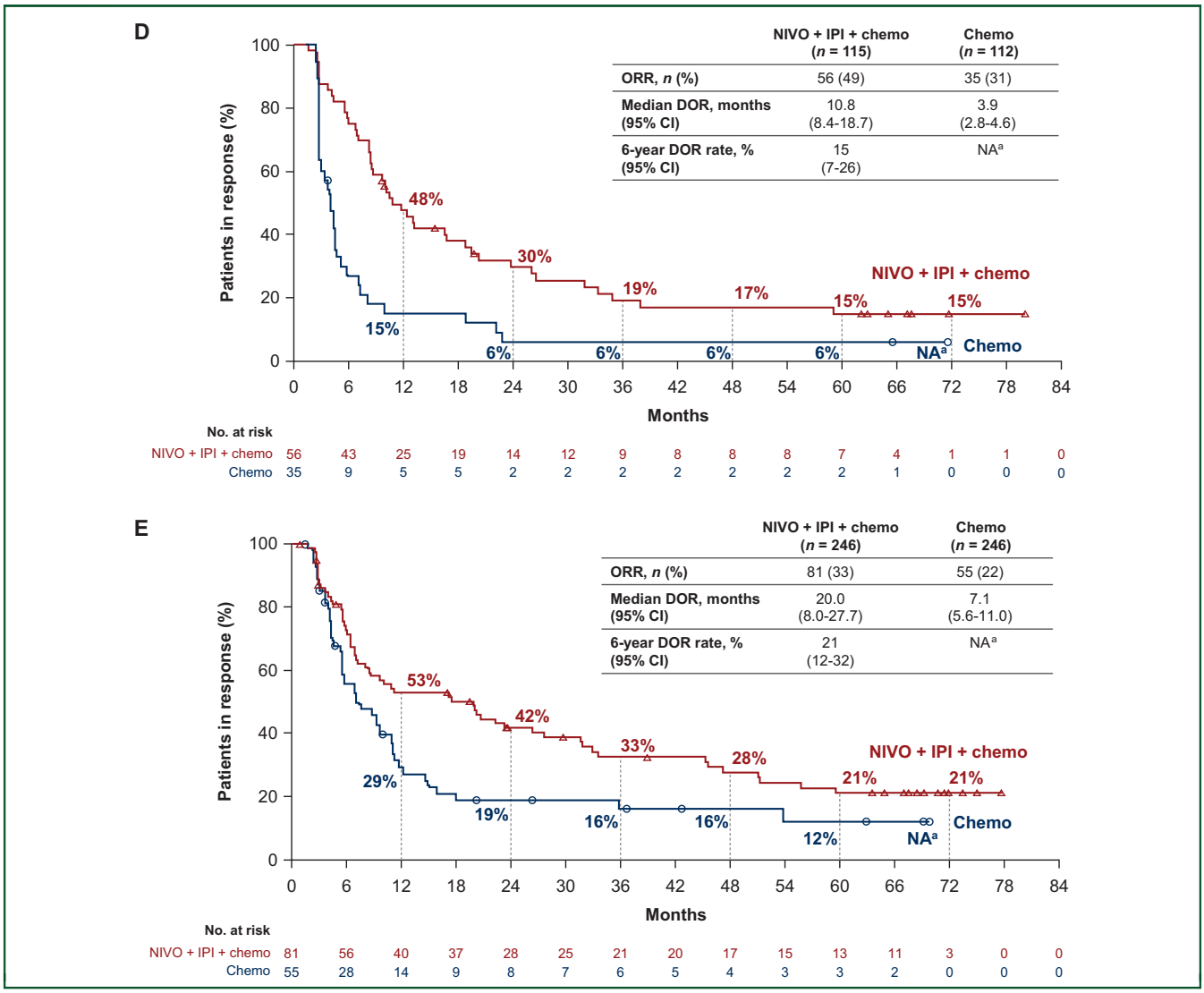


Figure 2. **Continued.**

subsequent immunotherapy, and 36% and 28% received subsequent chemotherapy, respectively (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2025.105123). Subsequent platinum-doublet chemotherapy was received by 73 patients (20%) in the nivolumab plus ipilimumab with chemotherapy arm and 23 patients (6%) in the chemotherapy arm.

Efficacy

At this 6-year follow-up, continued OS benefit was observed in all randomized patients with nivolumab plus ipilimumab with chemotherapy versus chemotherapy (HR 0.74, 95% CI 0.63-0.87; Figure 1A); 6-year OS rates were 16% and 10%, respectively. Consistent OS benefit with nivolumab plus ipilimumab with chemotherapy versus chemotherapy was observed across most prespecified subgroups (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2025.105123), including by tumor PD-L1 expression (Figure 1B and C; Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2025.105123) and histology (Figure 1D and E). In patients with tumor PD-L1 <1% or ≥1%, 6-year OS rates with nivolumab plus ipilimumab with chemotherapy versus chemotherapy were 20% versus 7% and 15% versus 10%, respectively (Figure 1B and C). Six-year OS rates in patients with squamous or non-squamous NSCLC were 14% versus 5% and 17% versus 12%, respectively (Figure 1D and E). Higher 6-year OS rates were also observed with nivolumab plus ipilimumab with chemotherapy versus chemotherapy in patients with tumor PD-L1 <1% or ≥1%, regardless of tumor histology (Supplementary Figure S4, available at https://doi.org/10.1016/j.esmoop.2025.105123).

Continued PFS benefit with nivolumab plus ipilimumab with chemotherapy versus chemotherapy was observed in all randomized patients (6-year PFS rates, 9% versus 3%; HR 0.70; 95% CI 0.59-0.82) and across most prespecified subgroups; higher 6-year PFS rates were also observed with nivolumab plus ipilimumab with chemotherapy than with chemotherapy regardless of tumor PD-L1 expression or histology (Supplementary Figures S5 and S6, available at https://doi.org/10.1016/j.esmoop.2025.105123). PFS in

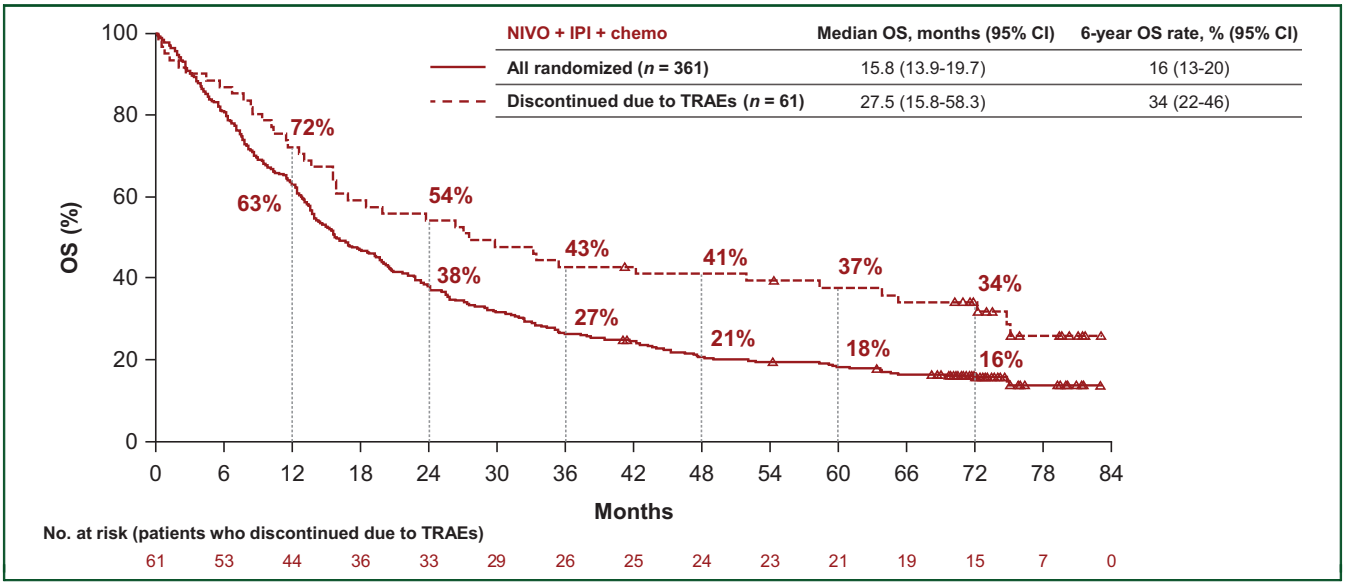


Figure 3. OS in patients who discontinued due to TRAEs. Adverse events were reported between the first dose and 30 days after the last dose of study treatment and led to discontinuation of all components of study treatment. Minimum follow-up for OS was 68.6 months.
Chemo, chemotherapy; CI, confidence interval; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; TRAE, treatment-related adverse event.

patients with tumor PD-L1 <1% or ≥1% by tumor histology is shown in Supplementary Figure S7, available at https://doi.org/10.1016/j.esmoop.2025.105123.

ORRs in all randomized patients and most prespecified subgroups (Supplementary Figure S8 and Supplementary Tables S4-S6, available at https://doi.org/10.1016/j.esmoop.2025.105123) were higher with nivolumab plus ipilimumab with chemotherapy versus chemotherapy. Among all responders, rates of ongoing responses at 6 years were 19% with nivolumab plus ipilimumab with chemotherapy and not available with chemotherapy because all patients in this treatment arm were censored or stopped responding to treatment before this timepoint (Figure 2A). In responders with tumor PD-L1 <1%, rates of ongoing response at 6 years were 25% with nivolumab plus ipilimumab with chemotherapy versus 0% with chemotherapy; rates were 16% versus not available, respectively, in responders with tumor PD-L1 ≥1% (Figure 2B and C). DOR in patients with tumor PD-L1 1%-49% and ≥50% is reported in Supplementary Figure S9, available at https://doi.org/10.1016/j.esmoop.2025.105123. Rates of ongoing response at 6 years were 15% with nivolumab plus ipilimumab with chemotherapy versus not available with chemotherapy in responders with squamous NSCLC, and 21% versus not available, respectively, in responders with non-squamous NSCLC (Figure 2D and E).

An exploratory OS analysis was carried out in 61 patients who discontinued all components of the nivolumab plus ipilimumab with chemotherapy regimen due to TRAEs. The 6-year OS rate in this subgroup (34%) suggests that discontinuation of nivolumab plus ipilimumab with chemotherapy due to TRAEs did not adversely affect clinical outcomes (Figure 3). Additional information on these patients has been reported previously.[21]

Of randomized patients, 463 (64%) had mutation-evaluable tissue, of whom 313 had non-squamous NSCLC. Baseline characteristics of patients with mutation-evaluable tissue were consistent with all randomized patients (Supplementary Table S7, available at https://doi.org/10.1016/j.esmoop.2025.105123). *KRAS* and *STK11* mutations were detected in 39% and 27% of patients with mutation-evaluable tissue and non-squamous NSCLC, respectively, and *KEAP1* and *TP53* mutations were detected in 8% and 69% of all patients with mutation-evaluable tissue, respectively (Supplementary Figure S10, available at https://doi.org/10.1016/j.esmoop.2025.105123). Among analyzed patients, 6-year OS rates were 21% with nivolumab plus ipilimumab with chemotherapy versus 10% with chemotherapy and 19% versus 17%, respectively, in patients with *KRAS* mutation and wild-type *KRAS* (Figure 4A and B); 6-year OS rates were 19% versus 16% and 20% versus 13% in patients with *STK11* mutation and wild-type *STK11*, respectively (Figure 4C and D). Median OS was 13.2 months with nivolumab plus ipilimumab with chemotherapy versus 6.9 months with chemotherapy in patients with *KEAP1* mutation (HR 0.63, 95% CI 0.32-1.24) and 15.8 months versus 13.1 months (HR 0.81, 95% CI 0.66-0.99), respectively, in patients without *KEAP1* mutation (Supplementary Table S8, available at https://doi.org/10.1016/j.esmoop.2025.105123). Six-year OS rates were 16% versus 12% and 22% versus 11% in patients with *TP53* mutation and wild-type *TP53*, respectively (Figure 4E and F). Among 6-year survivors, the proportions of patients with these select somatic mutations were similar between treatment arms (Figure 5).

Safety

Consistent with previous reports of long-term follow-up analyses from this study,[21-23] no new TRAEs or treatment-related deaths were identified at 6 years (Supplementary Table S9, available at https://doi.org/10.1016/j.esmoop.

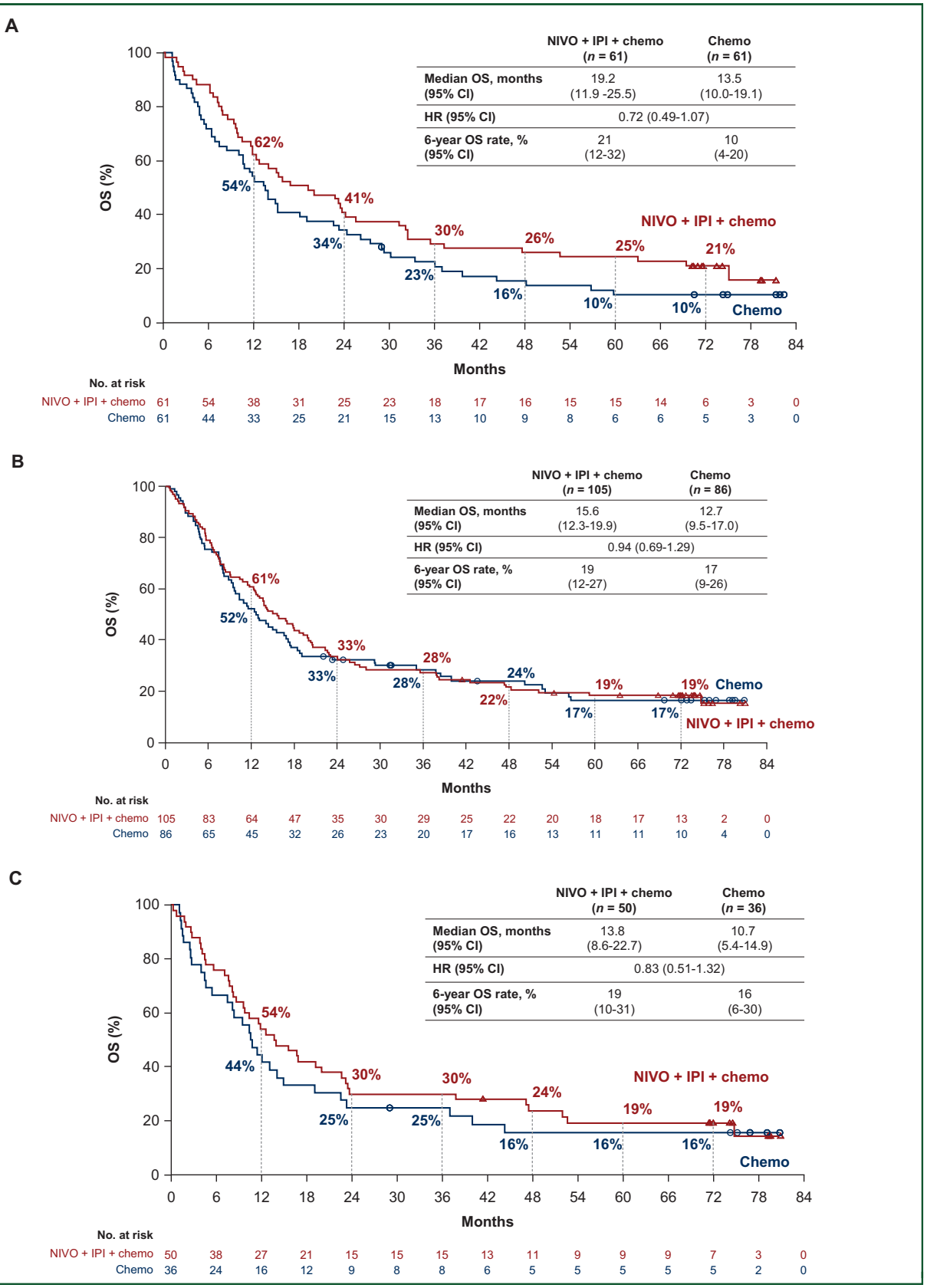
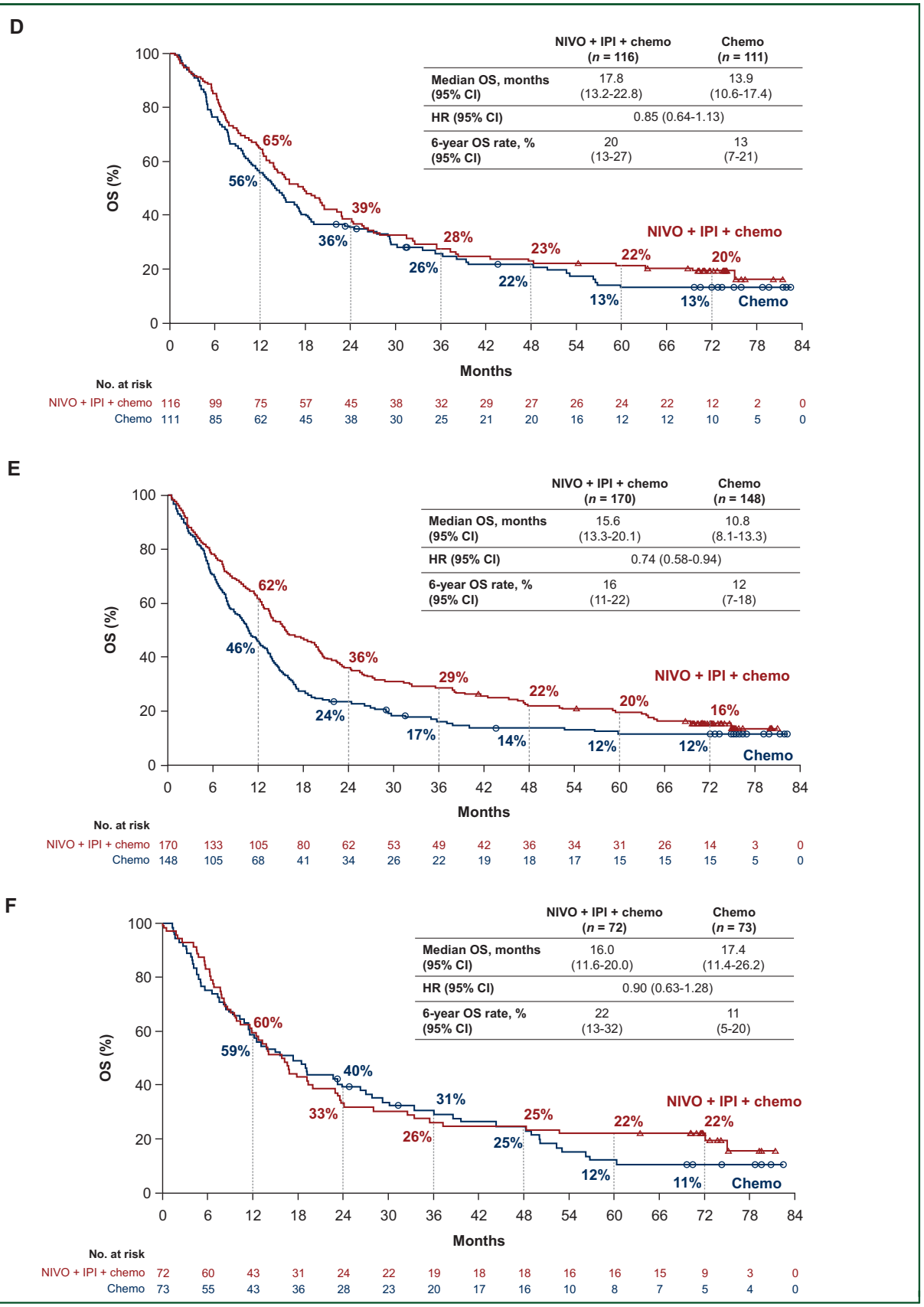


Figure 4. OS by select mutation status: (A) *KRAS* mutant (non-squamous only), (B) *KRAS* wild-type (non-squamous only), (C) *STK11* mutant (non-squamous only), (D) *STK11* wild-type (non-squamous only), (E) *TP53* mutant, and (F) *TP53* wild-type. Minimum follow-up for OS was 68.6 months.
Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival.



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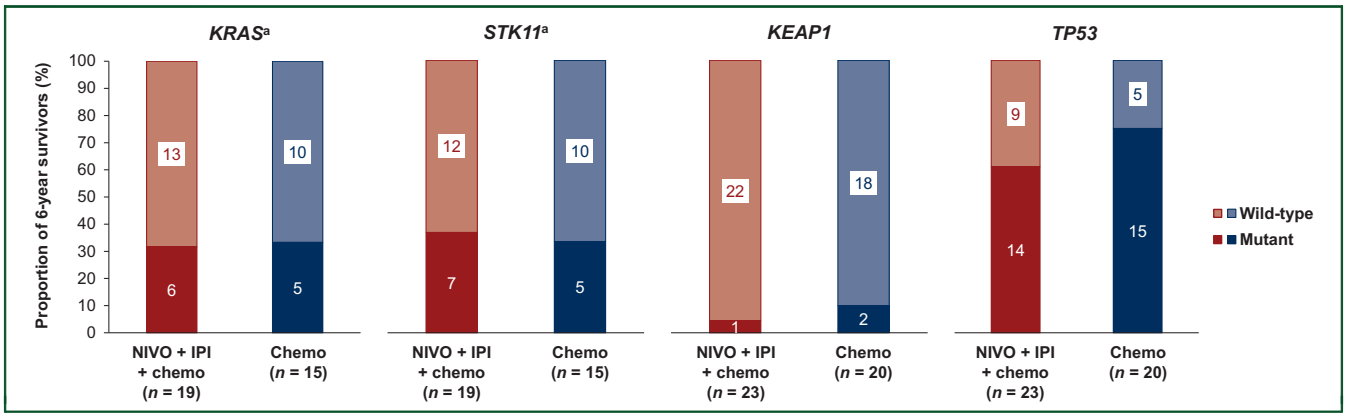

Figure 5. Genomic mutation status in long-term (≥6-year) survivors. Data within the bars represent the number of patients with wild-type or mutant tumors. Chemo, chemotherapy; IPI, ipilimumab; NIVO, nivolumab; NSCLC, non-small-cell lung cancer.
[a]Non-squamous NSCLC only.

2025.105123). Additionally, no new IMAEs occurred following the database lock for the 5-year analysis.[21] Per protocol, all patients had discontinued nivolumab plus ipilimumab with chemotherapy after a maximum of 2 years.

DISCUSSION

In CheckMate 9LA, with a median follow-up of 75.8 months, nivolumab plus ipilimumab with chemotherapy continued to provide durable, long-term survival benefit versus chemotherapy in all randomized patients. Moreover, nivolumab plus ipilimumab with chemotherapy demonstrated durable, long-term response benefit over chemotherapy, with 19% of responders in the nivolumab plus ipilimumab with chemotherapy arm maintaining response at 6 years despite protocol-mandated treatment cessation at 2 years. Consistent survival and response benefit with nivolumab plus ipilimumab with chemotherapy was observed across subgroups, including patients with either tumor PD-L1 <1% or ≥1% and patients with either squamous or non-squamous NSCLC. Exploratory analyses also suggested that discontinuing treatment due to TRAEs or harboring select somatic mutations did not negatively impact 6-year OS outcomes with nivolumab plus ipilimumab with chemotherapy. No new safety signals with nivolumab plus ipilimumab with chemotherapy were identified.

The addition of a short course of chemotherapy to nivolumab plus ipilimumab appeared to provide greater response benefit compared with nivolumab plus ipilimumab. In the phase III CheckMate 227 study, ORRs with nivolumab plus ipilimumab were 27% in patients with tumor PD-L1 <1% and 36% in patients with tumor PD-L1 ≥1%[5] compared with 31% and 43% with nivolumab plus ipilimumab with chemotherapy in the respective tumor PD-L1 expression subgroups in CheckMate 9LA. Long-term survival outcomes were similar between the two immunotherapy-based regimens, however, with 6-year OS rates of 16% and 22% with nivolumab plus ipilimumab in the tumor PD-L1 <1% and ≥1% subgroups groups of CheckMate 227, respectively,[5] compared with 20% and 15%, respectively, with nivolumab plus ipilimumab with chemotherapy in the current study. Notably, the current study demonstrated a high long-term DOR rate in the chemotherapy arm (10% at 5 years), which is consistent with some clinical studies also evaluating first-line treatments in patients with metastatic NSCLC (e.g. 13% at 5 years in KEYNOTE-042),[1] but not others (e.g. 3% at 5 years in CheckMate 227; none reached at 5 years in KEYNOTE-189),[2,26] suggesting potential differences in the enrolled populations that may limit cross-trial comparisons.

Long-term results in the overall population of CheckMate 9LA were generally comparable with those from other studies evaluating chemoimmunotherapy regimens versus chemotherapy alone[2-4,27]; however, nivolumab plus ipilimumab with chemotherapy appeared to provide a greater magnitude of clinical benefit in patients with tumor PD-L1 expression <1% or squamous NSCLC, patient populations that typically have poor prognoses.[3,28] Although cross-trial comparisons should be made with caution due to differences in study design and patient populations, an approximately threefold difference in 6-year OS rates favoring nivolumab plus ipilimumab with chemotherapy (20%) over chemotherapy (7%) was observed in patients with tumor PD-L1 <1% in CheckMate 9LA, which was numerically greater than the difference in 5-year OS rates observed with durvalumab plus tremelimumab with chemotherapy in the phase III POSEIDON study (5-year OS rates, 6% versus 4%) and pembrolizumab plus chemotherapy in the phase III KEYNOTE-407 study (5-year OS rates, 11% versus 13%; squamous NSCLC only), the phase III KEYNOTE-189 study (5-year OS rates, 10% versus 5%; non-squamous NSCLC only), and a pooled analysis of KEYNOTE-407 and KEYNOTE-189 (5-year OS rates, 12% versus 9%).[2-4,29] Similarly, median DOR (95% CI) with nivolumab plus ipilimumab with chemotherapy in this subgroup from CheckMate 9LA [17.5 months (6.9-37.8 months)] was numerically greater than that observed with durvalumab plus tremelimumab with chemotherapy in POSEIDON [7.8 months (5.1-12.5 months)] and pembrolizumab plus chemotherapy in KEYNOTE-407 [6.9 months (1.4+ to 58.9+ months); squamous NSCLC only], KEYNOTE-189 [10.8 months (1.1+ to 59.4+ months); non-squamous NSCLC only], and a pooled analysis of

KEYNOTE-407 and KEYNOTE-189 [7.6 months (1.1+ to 59.4+ months)].[2,3,27,29] OS and DOR results from the present analysis were also consistent with those in the pooled population of patients with tumor PD-L1 <1% who received nivolumab plus ipilimumab with or without chemotherapy in CheckMate 227 and CheckMate 9LA.[30] Nivolumab plus ipilimumab with chemotherapy also improved clinical outcomes versus chemotherapy regardless of tumor histology in CheckMate 9LA, with a greater magnitude of OS benefit versus chemotherapy in CheckMate 9LA among patients with squamous histology (HR 0.65, 95% CI 0.49-0.85) than with non-squamous histology (HR 0.79, 95% CI 0.65-0.96). In contrast, other chemoimmunotherapy regimens, such as durvalumab plus tremelimumab with chemotherapy in POSEIDON and pembrolizumab plus chemotherapy in KEYNOTE-189 and KEYNOTE-407, demonstrated numerically lower or non-meaningful benefit in patients with squamous NSCLC (HR 0.85, 95% CI 0.65-1.10 in POSEIDON; HR 0.71, 95% CI 0.59-0.85 in KEYNOTE-407) compared with patients with non-squamous NSCLC (HR 0.69, 95% CI 0.56-0.85 in POSEIDON; HR 0.60, 95% CI 0.50-0.72 in KEYNOTE-189).[2-4] However, some subgroups (e.g. patients aged ≥75 years and patients who never smoked) did not appear to benefit from nivolumab plus ipilimumab with chemotherapy compared with chemotherapy alone based on OS HRs that were >1, although the small sample sizes of these subgroups limit the interpretability of these findings. Notably, subsequent immunotherapy, which has been demonstrated to improve OS in patients who experienced disease progression on first-line treatment across several phase III trials,[31-34] was available to patients in CheckMate 9LA and was administered to 37% of patients in the chemotherapy arm. Use of subsequent immunotherapy may have impacted time-to-event OS analyses,[35,36] as suggested by treatment switching—adjusted analyses previously carried out in CheckMate 9LA.[22] Based on these findings, nivolumab plus ipilimumab with chemotherapy may be particularly useful in the management of certain patient populations that are historically difficult to treat.

Previous studies have suggested that somatic mutations in *KRAS*, *STK11*, *KEAP1*, and *TP53* are prognostic factors for clinical outcomes in patients with metastatic NSCLC.[37-40] Consistent with previous analyses from CheckMate 227 and CheckMate 9LA,[23,41] patients receiving nivolumab plus ipilimumab with chemotherapy in the current analysis appeared to have improved OS outcomes compared with patients receiving chemotherapy regardless of select somatic mutation status. Furthermore, patients with mutations were generally associated with shorter OS across treatment arms, with the exception of *KRAS*. Harboring these mutations, however, did not negatively impact long-term OS in patients receiving nivolumab plus ipilimumab with chemotherapy given that 32%, 37%, and 61% of 6-year survivors with mutation-evaluable tissue had *KRAS*-, *STK11*-, or *TP53*-mutant NSCLC, respectively. These results were similar to those in POSEIDON, which found that durvalumab plus tremelimumab with chemotherapy appeared to provide OS benefit versus chemotherapy among patients with *KRAS*-mutant (non-squamous; HR 0.55, 95% CI 0.36-0.83), *STK11*-mutant (non-squamous; HR 0.57, 95% CI 0.32-1.04), and *KEAP1*-mutant (squamous and non-squamous; HR 0.43, 95% CI 0.16-1.25) NSCLC.[4] Given the small number of patients in some subgroups, results should be interpreted with caution. Further prospective investigations, such as the phase III TRITON study evaluating anti-PD-L1 plus anti-CTLA-4 inhibition with chemotherapy in patients with *KRAS*-, *STK11*-, and/or *KEAP1*-mutant metastatic NSCLC,[42] will help determine the prognostic value of these biomarkers in patients with metastatic NSCLC treated with immunotherapy.

Consistent with the 5-year analysis,[21] no new long-term treatment-related complications were observed with nivolumab plus ipilimumab with chemotherapy. Additionally, discontinuation of nivolumab plus ipilimumab with chemotherapy due to TRAEs did not negatively impact long-term OS benefit (6-year OS rate, 34%), thereby highlighting the durable survival benefit of this regimen, even if patients discontinued treatment early.

In conclusion, this final, 6-year analysis of CheckMate 9LA demonstrated durable, long-term clinical benefit with nivolumab plus ipilimumab with two cycles of chemotherapy for patients with metastatic NSCLC. OS, PFS, and DOR all continued to favor nivolumab plus ipilimumab with chemotherapy over chemotherapy alone in all randomized patients and across patient subgroups, including patient populations with high unmet need such as those with tumor PD-L1 <1% or squamous histology, and OS was not negatively impacted by discontinuation due to TRAEs. In particular, the long-term DOR associated with this regimen highlights the durability of the clinical benefit gained by using this combination regimen of dual immune checkpoint inhibition and chemotherapy. These results further support nivolumab plus ipilimumab with chemotherapy as an efficacious standard-of-care first-line treatment option for patients with metastatic NSCLC.

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DATA SHARING

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.

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