

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

David P. Carbone ¹, Tudor-Eliade Ciuleanu,² Michael Schenker,³ Manuel Cobo,⁴ Stéphanie Bordenave,⁵ Oscar Juan-Vidal,⁶ Juliana Menezes,⁷ Niels Reinmuth,⁸ Eduardo Richardet,⁹ Ying Cheng,¹⁰ Hideaki Mizutani,¹¹ Enriqueta Felip,¹² Bogdan Zurawski,¹³ Aurelia Alexandru,¹⁴ Luis Paz-Ares,¹⁵ Shun Lu,¹⁶ Thomas John,¹⁷ Xiaoqing Zhang,¹⁸ Javed Mahmood,¹⁸ Nan Hu,¹⁹ Tuli De,²⁰ Irene Santi,²⁰ John R. Penrod,¹⁸ Yong Yuan,¹⁸ Adam Lee,¹⁸ Martin Reck²¹

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For numbered affiliations see end of article.

Correspondence to

Dr David P. Carbone;
david.carbone@osumc.edu

ABSTRACT

Background In CheckMate 9LA, nivolumab plus ipilimumab with chemotherapy prolonged overall survival (OS) versus chemotherapy regardless of tumor PD-L1 expression or histology. We report updated efficacy and safety in all randomized patients with a minimum 4-year follow-up and an exploratory treatment-switching adjustment analysis in all treated patients who received chemotherapy and subsequent immunotherapy.

Methods Adults with stage IV/recurrent non-small cell lung cancer (NSCLC), no sensitizing *EGFR/ALK* alterations, and ECOG performance status ≤ 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 (four cycles, with optional maintenance pemetrexed for the nonsquamous population). Assessments included OS, progression-free survival, and objective response rate. Exploratory analyses included efficacy by tumor PD-L1 expression and histology and in patients who discontinued nivolumab plus ipilimumab with chemotherapy due to treatment-related adverse events (TRAEs), and a treatment-switching adjustment analysis using inverse probability of censoring weighting.

Results With a 47.9-month minimum follow-up for OS, nivolumab plus ipilimumab with chemotherapy continued to prolong OS over chemotherapy in all randomized patients (HR 0.74, 95% CI 0.63 to 0.87; 4-year OS rate: 21% versus 16%), regardless of tumor PD-L1 expression (HR (95% CI): PD-L1 <1%, 0.66 (0.50 to 0.86) and $\geq 1\%$, 0.74 (0.60 to 0.92)) or histology (squamous, 0.64 (0.48 to 0.84) and non-squamous, 0.80 (0.66 to 0.97)). In patients who discontinued all components of nivolumab plus ipilimumab with

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Immunotherapies that target the programmed cell death (ligand) 1 (PD-(L)1) pathway, with or without other treatment modalities, have improved the overall survival of patients with metastatic non-small cell lung cancer (NSCLC) without targetable mutations. The CheckMate 9LA regimen of nivolumab plus ipilimumab with two cycles of chemotherapy was shown to provide long-term clinical benefit over chemotherapy as first-line treatment in patients with metastatic or recurrent NSCLC. However, unmet needs remain in patients with metastatic NSCLC.

chemotherapy due to TRAEs (n=61), the 4-year OS rate was 41%. With treatment-switching adjustment for the 36% of patients receiving subsequent immunotherapy in the chemotherapy arm, the estimated HR of nivolumab plus ipilimumab with chemotherapy versus chemotherapy was 0.66 (95% CI 0.55 to 0.80). No new safety signals were observed.

Conclusions In this 4-year update, patients treated with nivolumab plus ipilimumab with chemotherapy continued to have long-term, durable efficacy benefit over chemotherapy regardless of tumor PD-L1 expression and/or histology. A greater estimated relative OS benefit was observed after adjustment for subsequent immunotherapy use in the chemotherapy arm. These results further support nivolumab plus ipilimumab with chemotherapy as a first-line treatment for patients with metastatic/recurrent NSCLC, including those with tumor PD-L1 <1% or squamous histology, populations with high unmet needs.

WHAT THIS STUDY ADDS

⇒ With 4 years of follow-up data, this report indicates that nivolumab plus ipilimumab with two cycles of chemotherapy provides long-term, durable survival benefit over chemotherapy alone in patients with metastatic NSCLC, including those with tumor PD-L1 expression <1% or squamous histology. The survival benefit of nivolumab plus ipilimumab with chemotherapy versus chemotherapy was further proven by the results from exploratory treatment-switching adjustment analyses, which demonstrated greater estimated overall survival benefit after adjusting for the potential bias introduced by subsequent immunotherapy received by patients in the chemotherapy arm.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides additional support for the use of nivolumab plus ipilimumab with chemotherapy as a first-line treatment for patients with metastatic or recurrent NSCLC, regardless of tumor PD-L1 expression level or tumor histology, among which, tumor PD-L1 expression <1% and squamous histology populations represent a high unmet need.

INTRODUCTION

Over the past decade, immunotherapy-based regimens have transformed the treatment landscape for non-small cell lung cancer (NSCLC) and are currently first-line therapy options for eligible patients with metastatic NSCLC without targetable mutations.^{1–3} Nivolumab and ipilimumab are immune checkpoint inhibitors with distinct but complementary mechanisms of action targeting programmed death 1 (PD-1) and cytotoxic T lymphocyte antigen-4 (CTLA-4), respectively. Dual immunotherapy with first-line nivolumab plus ipilimumab, with or without concurrent chemotherapy, has shown long-term, durable overall survival (OS) benefit in patients with several advanced cancers, including metastatic NSCLC.^{4–8} Although multiple phase 3 randomized trials of immunotherapy alone⁹ or in combination with chemotherapy^{10,11} have reported clinical survival outcomes at the 5-year milestone, long-term survival in certain subpopulations, such as those with tumor programmed death ligand 1 (PD-L1) expression <1%^{12,13} or squamous histology,¹¹ remains suboptimal.

In the randomized, phase 3 CheckMate 9LA trial (NCT03215706), OS was significantly improved in patients with metastatic NSCLC treated with first-line nivolumab plus ipilimumab combined with two cycles of platinum-doublet chemotherapy versus four cycles of chemotherapy alone (median OS 14.1 versus 10.7 months, respectively; HR 0.69, 96.71% CI 0.55 to 0.87), meeting the primary endpoint.¹⁴ On the basis of these results, the combination regimen of nivolumab plus ipilimumab combined with two cycles of chemotherapy was approved in the USA, European Union, and several other countries for the first-line treatment of metastatic NSCLC.^{15,16} Treatment guidelines by the National Comprehensive Cancer Network, the American Society of Clinical Oncology, and the European Society for Medical Oncology currently recommend nivolumab plus

ipilimumab with chemotherapy as a first-line therapy option for patients with metastatic NSCLC, regardless of tumor PD-L1 expression level or tumor histology.^{1–3} At the 3-year follow-up from CheckMate 9LA, nivolumab plus ipilimumab with chemotherapy continued to prolong OS versus chemotherapy alone (HR 0.74, 95% CI 0.62 to 0.87; 3-year OS rate 27% versus 19%), despite the fact that 36% of patients in the chemotherapy arm received subsequent immunotherapy.⁴

With the approval of several immunotherapy agents in the second-line setting, there has been growing use of subsequent immunotherapy postprogression on first-line chemotherapy, which can confound OS analyses in clinical trials that compare first-line immunotherapies to chemotherapy control arms.^{17,18} Previous reports have demonstrated that adjusting for potential biases in the calculation of treatment effect introduced by patients switching from chemotherapy to immunotherapy increased the relative survival with immunotherapy-based treatment versus the adjusted chemotherapy arm.^{19,20}

Here, we present updated efficacy and safety data from CheckMate 9LA in patients with at least 4 years of follow-up. Additionally, we report exploratory efficacy outcomes from patients who discontinued nivolumab plus ipilimumab with chemotherapy due to treatment-related adverse events (TRAEs) and results from an exploratory treatment-switching adjustment analysis in patients who switched from chemotherapy to subsequent immunotherapy. See also the graphical abstract.

MATERIALS AND METHODS

The study design, patient eligibility criteria, and protocol of CheckMate 9LA have previously been described^{4,14,21} and are briefly summarized here.

Study design and patients

CheckMate 9LA is a randomized, open-label, international phase 3 trial.¹⁴ Enrolled patients were aged ≥18 years with squamous or non-squamous stage IV/recurrent NSCLC, Eastern Cooperative Oncology Group performance status 0 or 1, and no known sensitizing *EGFR/ALK* alterations. Patients were stratified by tumor histology (squamous versus non-squamous), sex (male versus female), and tumor PD-L1 expression (<1% versus ≥1%); patients without quantifiable tumor PD-L1 expression were stratified with the <1% population but were only included in analyses of the all-randomized population, as previously described.^{14,21}

Patients were randomized 1:1 to receive nivolumab (360 mg every 3 weeks) plus ipilimumab (1 mg/kg every 6 weeks) combined with platinum-doublet chemotherapy (every 3 weeks for two cycles) or chemotherapy alone (every 3 weeks for four cycles) (online supplemental figure S1). Treatment continued until disease progression (unless prespecified criteria were met for treatment beyond progression in the experimental arm), unacceptable toxicity, or until patients had received 2 years

of immunotherapy in the experimental arm. Optional pemetrexed maintenance therapy (500 mg/m² every 3 weeks), permitted for the non-squamous population of the control arm only, has been described previously.^{4 14 21} Per protocol, no crossover between treatment arms was allowed; however, patients could receive subsequent immunotherapy at the physician's discretion if study treatment was discontinued in either group.

Endpoints and assessments

The primary, secondary, and other protocol-specified and exploratory endpoints have been reported previously (online supplemental figure S1).^{4 14 21} With a 4-year minimum follow-up, exploratory analyses of updated OS, progression-free survival (PFS), objective response rate (ORR), and duration of response (DOR) were conducted in all randomized patients, in patients by tumor PD-L1 expression (<1%, ≥1%, 1%–49%, or ≥50%), tumor histology (squamous or non-squamous), and by both tumor PD-L1 expression and histology. Other exploratory analyses included efficacy assessments in patients who discontinued all components of nivolumab plus ipilimumab with chemotherapy due to TRAEs (OS from randomization; PFS and DOR from time of treatment discontinuation)²¹ and treatment-switching adjustment analyses, which were conducted to account for potential bias in the estimation of OS due to subsequent immunotherapy treatment in the chemotherapy-alone arm. The subsequent use of immunotherapy in patients after chemotherapy can introduce bias in the calculation of treatment effect, potentially leading to an underestimation of the survival benefit of the experimental treatment regimen. Thus, these analyses were performed to better

clarify the efficacy difference between nivolumab plus ipilimumab with chemotherapy and chemotherapy alone.

Safety outcomes were reported as adverse events observed between the first dose and 30 days after the last dose of study therapy and graded per National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0), with the exception of immune-mediated adverse events (IMAEs), which were recorded between the first dose and within 100 days after the last dose of study therapy. Additional details of the study endpoints were previously reported.^{4 14 21}

Statistical analysis

Efficacy and safety outcomes were evaluated in all randomized patients and in all patients who received ≥1 dose of study drug (all treated patients), respectively. Kaplan-Meier methodology was used to estimate OS and PFS curves. HRs and associated 95% CIs were estimated using stratified (all randomized patients) or unstratified (patient subgroups) Cox proportional hazards models with treatment arm as a single covariate. The Clopper-Pearson method was used to estimate response rates and exact two-sided 95% CIs.

Treatment-switching adjustment analyses were conducted in all-treated patients using four statistical methods as recommended by NICE Decision Support Unit Technical Support Document 16,²² similar to previously described analyses²⁰: inverse probability of censoring weighting (IPCW),²³ rank-preserving structural failure time (RPSFT),²⁴ iterative parameter estimation (IPE),²⁵ and simplified two-stage estimation (TSE).¹⁸ The primary treatment-switching analysis was conducted using IPCW because of its ability to handle informative censoring and not require a common treatment effect assumption.^{26 27}

Sensitivity analyses to test the robustness of the IPCW methodology were conducted using RPSFT, IPE, and TSE methods. Details on these analyses can be found in the online supplemental methods.

Baseline and time-varying covariates for the IPCW, RPSFT, IPE, and TSE analyses were selected using clinical knowledge and hypotheses (online supplemental table S1). SAS (V.9.4) and R (V.4.2.3) software were used for all treatment-switching adjustment analyses.

RESULTS

Patient disposition and treatment summary

As previously reported,^{4 14 21} 719 patients were randomly assigned to receive nivolumab plus ipilimumab with chemotherapy (n=361) or chemotherapy alone (n=358); 358 (99%) patients and 349 (97%) patients received at least one dose of the study treatment, respectively (online supplemental figure S2). Baseline characteristics for the overall population have been previously reported and were generally well balanced between treatment arms.^{4 14 21} Of all randomized patients, 227 (32%) had squamous and 492 (68%) had non-squamous NSCLC. At the current database lock (February 13, 2023), the

Table 1 Subsequent systemic therapy for all randomized patients

	Nivolumab plus ipilimumab with chemotherapy (n=361)	Chemotherapy (n=358)
Received subsequent systemic therapy, n (%)	135 (37)	174 (49)
Any immunotherapy	26 (7)	130* (36)
Anti-PD-1	15 (4)	107 (30)
Nivolumab	11 (3)	72 (20)
Pembrolizumab	4 (1)	36 (10)
Anti-PD-L1	8 (2)	24 (7)
Anti-CTLA-4	2 (1)	2 (1)
Other immunotherapy	5 (1)	6 (2)
Targeted therapy	26 (7)	30 (8)
Chemotherapy	126 (35)	99 (28)
Platinum-doublet chemotherapy	71 (20)	22 (6)

Percentages based on all randomized patients. Patients may have received more than one type of subsequent therapy. Subsequent therapy was defined as therapy that started on or after the first dosing date (randomization date if the patient was never treated).

*Includes one patient who was randomized to the chemotherapy arm but did not receive treatment.

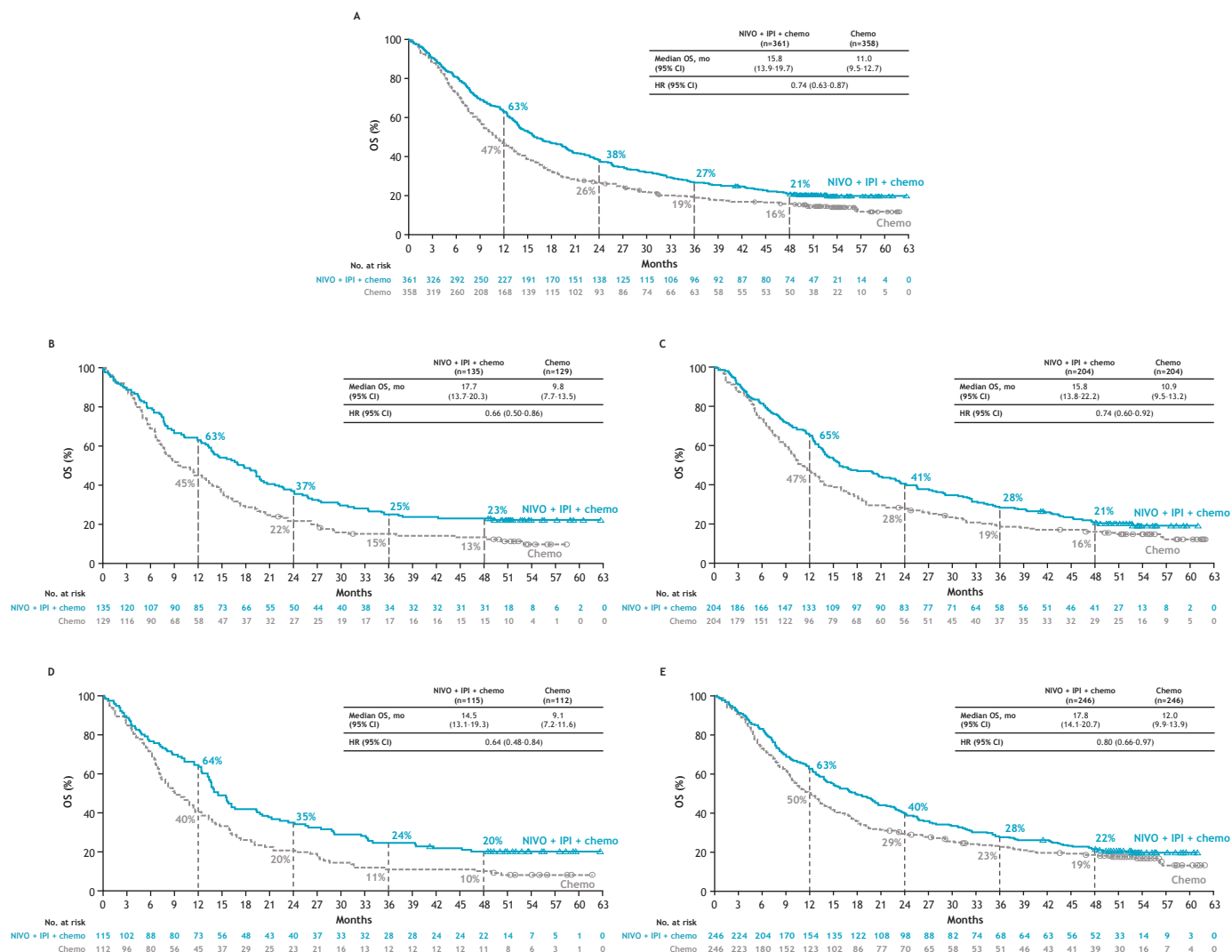


Figure 1 OS in (A) all randomized patients, (B) patients with tumor PD-L1 expression $\geq 1\%$, (C) patients with tumor PD-L1 expression $< 1\%$, (D) patients with squamous histology, and (E) patients with non-squamous histology. Minimum follow-up for OS was 47.9 months. 95% CIs for 4-year OS rates with nivolumab (NIVO) plus ipilimumab (IPI) with chemotherapy (Chemo) and chemotherapy alone, respectively, were: (A) 17–25 and 12–20; (B) 16–30 and 8–20; (C) 16–27 and 11–22; (D) 13–28 and 5–16; and (E) 17–27 and 14–24. OS, overall survival; PD-L1, programmed death ligand 1.

median follow-up was 54.5 months (range, 49.1–64.4), and the minimum follow-up for OS was 47.9.

Patients in the nivolumab plus ipilimumab with chemotherapy and chemotherapy-alone arms received study treatment for a median of 6.1 months (range, 0–24.4) and 2.5 months (range, 0–58.2), respectively (online supplemental table S2). Most patients in the nivolumab plus ipilimumab with chemotherapy arm (93%) received two cycles of chemotherapy, and 14% ($n=50$) completed the protocol-defined 2-year treatment period. Patients in the nivolumab plus ipilimumab with chemotherapy arm received a median of 9 (range, 1–36) nivolumab doses and 4 (range, 1–18) ipilimumab doses. In the chemotherapy-alone arm, 261 patients (75%) received at least four cycles of chemotherapy, and 159 patients (67%) with non-squamous NSCLC received pemetrexed maintenance (online supplemental table S2); 4 patients (1%) continued to receive pemetrexed maintenance therapy at

the 4-year follow-up. Among all randomized patients, 135 (37%) in the nivolumab plus ipilimumab with chemotherapy arm and 174 (49%) in the chemotherapy-alone arm received subsequent systemic therapy (table 1). Subsequent immunotherapy was administered to 26 (7%) patients and 130 (36%) patients, respectively, while 71 (20%) and 22 (6%) received subsequent platinum-doublet chemotherapy (table 1).

Efficacy

Overall survival

At a minimum follow-up of 47.9 months for OS, nivolumab plus ipilimumab with chemotherapy continued to provide sustained OS benefit versus chemotherapy alone. In the all-randomized population, median OS was 15.8 months (95% CI 13.9 to 19.7) in the nivolumab plus ipilimumab with chemotherapy arm versus 11.0 months (95% CI 9.5 to 12.7) in the chemotherapy-alone arm (HR 0.74,

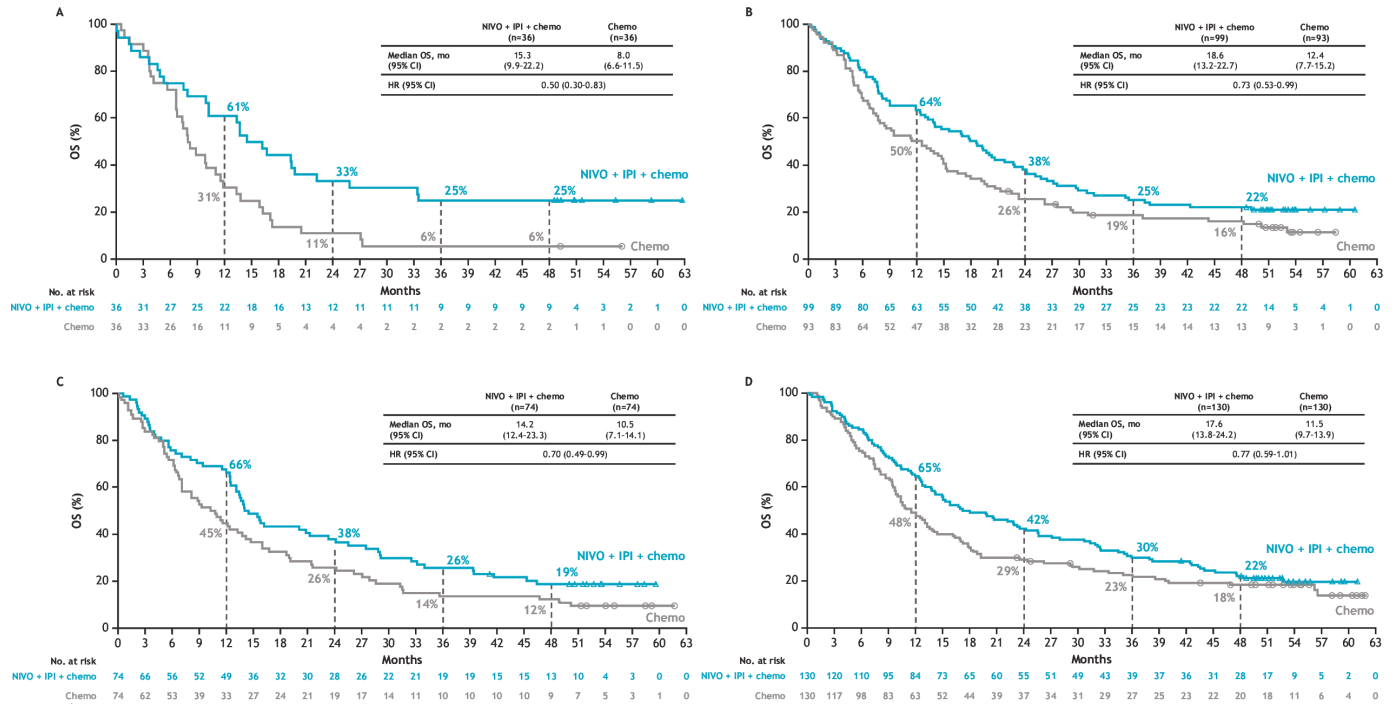


Figure 2 OS in patients with (A) tumor PD-L1 expression <1% and squamous histology, (B) tumor PD-L1 expression <1% and non-squamous histology, (C) tumor PD-L1 expression ≥1% and squamous histology, and (D) tumor PD-L1 expression ≥1% and non-squamous histology. Subgroups defined on the basis of baseline tumor PD-L1 expression level in the clinical database and histology per interactive response technology. The 95% CIs for 4-year rates for nivolumab (NIVO) plus ipilimumab (IPI) with chemotherapy (chemo) and chemo alone, respectively, were: (A) 12–40 and 1–16; (B) 15–31 and 10–25; (C) 11–28 and 6–21; (D) 15–30 and 12–26. OS, overall survival; PD-L1, programmed death ligand 1.

95% CI 0.63 to 0.87); 4-year OS rates were 21% versus 16%, respectively (figure 1A).

Consistent with previous reports, nivolumab plus ipilimumab with chemotherapy improved OS versus chemotherapy alone across most subgroups (online supplemental figure S3), including by tumor PD-L1 expression (<1%, ≥1% (figure 1B,C), 1%–49%, and ≥50% (online supplemental figure S4A,B)) and histology (figure 1D,E). In patients with tumor PD-L1 expression <1% or ≥1%, 4-year OS rates in the nivolumab plus ipilimumab with chemotherapy arm versus the chemotherapy-alone arm were 23% versus 13% and 21% versus 16%, respectively (figure 1B,C); in patients

with squamous or non-squamous NSCLC, 4-year OS rates were 20% versus 10% and 22% versus 19%, respectively (figure 1D,E).

Similar to all randomized CheckMate 9LA patients and subgroups by tumor PD-L1 expression or histology, an OS benefit of nivolumab plus ipilimumab with chemotherapy versus chemotherapy alone was also observed in smaller subgroups by both tumor PD-L1 expression and tumor histology combined. In the tumor PD-L1 expression <1% and squamous NSCLC subgroups (n=36 per arm), median OS was 15.3 months (95% CI 9.9 to 22.2) versus 8.0 months (95% CI 6.6 to 11.5) (HR 0.50, 95% CI 0.30 to 0.83), whereas in the tumor PD-L1 expression

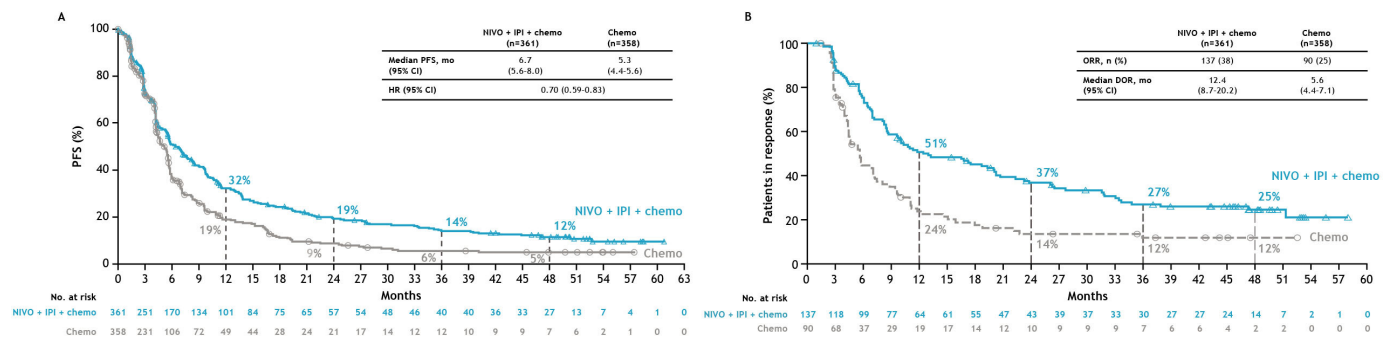


Figure 3 (A) PFS and (B) DOR in the all-randomized population. PFS and DOR were per blinded independent central review. Minimum follow-up for PFS was 47.1 months. The 95% CIs for 4-year rates for nivolumab (NIVO) plus ipilimumab (IPI) with chemotherapy (Chemo) and chemotherapy alone, respectively, were: (A) 8–15 and 3–8; (B) 17–33 and 6–20. DOR, duration of response; ORR, objective response rate; OS, overall survival. PFS, progression-free survival.

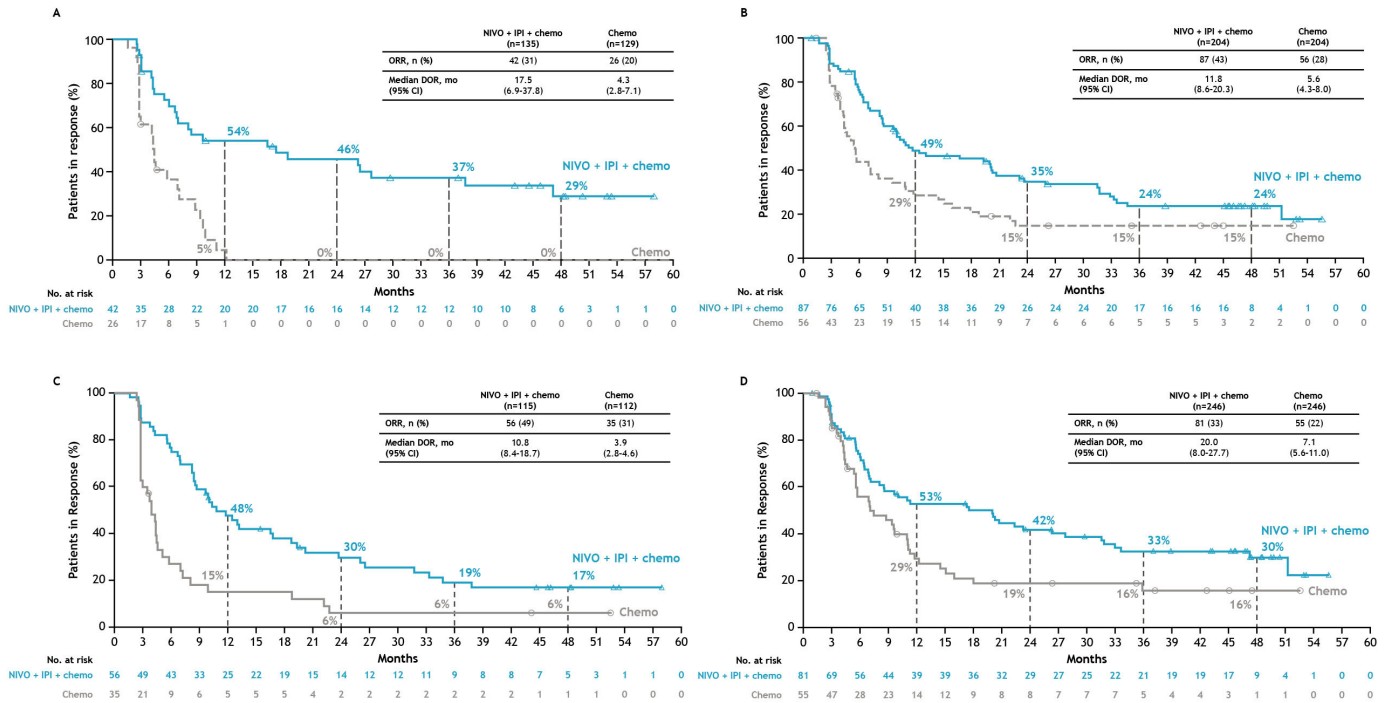


Figure 4 DOR for patients with (A) tumor PD-L1 expression <1%, (B) tumor PD-L1 expression ≥1%, (C) squamous histology, and (D) non-squamous histology. The 95% CIs for 4-year rates for nivolumab (NIVO) plus ipilimumab (IPI) with chemotherapy (chemo) and chemotherapy alone are: (A) 15–45 and not applicable (NA); (B) 15–34 and 7–26; (C) 8–29 and 1–17; and (D) 19–41 and 7–28. DOR, duration of response; ORR, objective response rate; PD-L1, programmed death ligand 1.

<1% and non-squamous NSCLC subgroups (n=99 and n=93, respectively), median OS was 18.6 months (95% CI 13.2 to 22.7) versus 12.4 months (95% CI 7.7 to 15.2) (HR 0.73, 95% CI 0.53 to 0.99) (figure 2A,B); respective 4-year OS rates were 25% versus 6% and 22% versus 16%. In the tumor PD-L1 expression ≥1% and squamous subgroups (n=74 per arm), the HR and 4-year OS rates of nivolumab plus ipilimumab with chemotherapy versus chemotherapy alone were 0.70 (95% CI 0.49 to 0.99) and 19% versus 12%, whereas in the tumor PD-L1 expression

≥1% and non-squamous NSCLC subgroups (n=130 per arm), the HR and 4-year OS rates were 0.77 (95% CI 0.59 to 1.01) and 22% versus 18%, respectively (figure 2C,D).

PFS and tumor response

Nivolumab plus ipilimumab with chemotherapy continued to improve PFS compared with chemotherapy alone in all randomized patients (HR 0.70; 95% CI 0.59 to 0.83) with 4-year PFS rates of 12% versus 5% (figure 3A) and across all tumor PD-L1 expression or histology

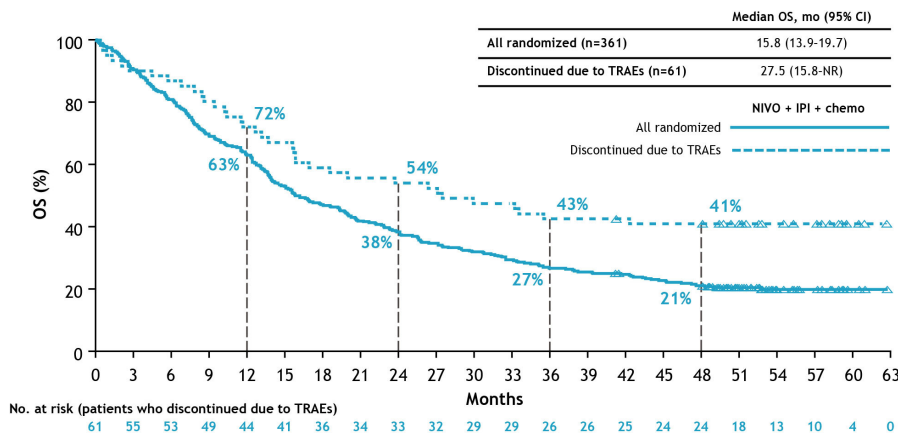


Figure 5 OS in patients who discontinued nivolumab plus ipilimumab with chemotherapy due to TRAEs. Minimum follow-up for OS was 47.9 months. An exploratory analysis was conducted in patients with TRAEs (reported between first dose and 30 days after the last dose of study treatment) leading to the discontinuation of all components of study treatment. The 95% CIs for the 4-year OS rates for patients who discontinued due to TRAEs and for the all-randomized population, respectively, were 29–53 and 17–25. IPI, ipilimumab; NIVO, nivolumab; NR, not reached; OS, overall survival; TRAEs, treatment-related adverse events.

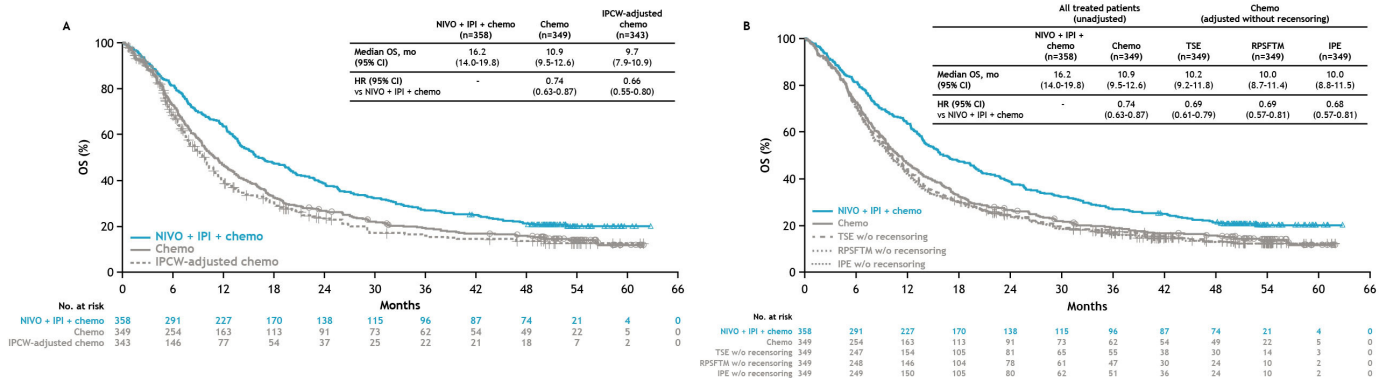


Figure 6 OS in patients in the all-treated population after adjustments using (A) IPCW (primary analysis) and (B) TSE, RPSFT, and IPE (sensitivity analyses) methodologies. Chemo, chemotherapy; IPCW, inverse probability of censoring weighting; IPE, iterative parameter estimation; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; RPSFT, rank-preserving structural failure time; TSE, two-stage estimation; w/o, without.

subgroups (online supplemental table S3), as well as subgroups of both tumor PD-L1 expression and histology combined (online supplemental table S4).

The ORR among all randomized patients was 38% in the nivolumab plus ipilimumab with chemotherapy arm versus 25% in the chemotherapy-alone arm; the complete response rate was 4% versus 1%, respectively (online supplemental table S5). Median DOR in the nivolumab plus ipilimumab with chemotherapy arm was 12.4 months (95% CI 8.7 to 20.2) versus 5.6 months (95% CI 4.4 to 7.1) in the chemotherapy-alone arm, and responses were ongoing at 4 years in 25% versus 12% of patients, respectively (figure 3B). Similar prolonged DOR rates were observed with nivolumab plus ipilimumab with chemotherapy versus chemotherapy alone in subgroups by tumor PD-L1 expression (figure 4A,B) and by histology (figure 4C,D). Median DOR for the tumor PD-L1 expression <1% subgroup was 17.5 months (95% CI 6.9 to 37.8) versus 4.3 months (95% CI 2.8 to 7.1) and 11.8 months (95% CI 8.6 to 20.3) versus 5.6 months (95% CI 4.3 to 8.0) in the tumor PD-L1 expression ≥1% subgroup, respectively (figure 4A,B), with ongoing responses at 4 years in 29% versus 0% (PD-L1 <1%) and 24% versus 15% (PD-L1 ≥1%), respectively (figure 4A,B). Median DOR in patients with squamous histology was 10.8 months (95% CI 8.4 to 18.7) versus 3.9 months (95% CI 2.8 to 4.6) and 20.0 months (95% CI 8.0 to 27.7) versus 7.1 months (95% CI 5.6 to 11.0) in the non-squamous subgroup (figure 4C,D), respectively, with ongoing responses at 4 years in 17% versus 6% (squamous histology) and 30% versus 16% (non-squamous histology), respectively (figure 4C,D). It is notable that a numerically greater magnitude of DOR benefit was seen in patients with tumor PD-L1 expression <1% (figure 4A) compared with tumor PD-L1 ≥1% (figure 4B) or with squamous histology (figure 4C) compared with non-squamous histology (figure 4D) at the 4-year follow-up. DOR results in patients with other tumor PD-L1 expression (1%–49% and ≥50%) subgroups are shown in online supplemental table S6.

Efficacy in patients who discontinued nivolumab plus ipilimumab with chemotherapy due to TRAEs

As described previously, an exploratory analysis was performed in patients who discontinued all components of nivolumab plus ipilimumab with chemotherapy because of TRAEs; baseline characteristics of this subgroup were generally similar to those of the all-randomized population.²¹ TRAEs led to discontinuation of all study drugs in 61 (17%) patients treated with nivolumab plus ipilimumab with chemotherapy; these patients received treatment for a median of 4.4 months (95% CI 2.9 to 6.9). The most common toxicities (≥3% of patients) reported in patients who discontinued all study drugs were gastrointestinal disorders (n=14; 4%) and hepatobiliary disorders (n=11; 3%). Consistent with results from the 2-year update,²¹ at the 4-year analysis, median OS was 27.5 months (95% CI 15.8 to not reached (NR)), and the 4-year OS rate was 41% (95% CI 29 to 53) (figure 5). Median PFS was 5.1 months (95% CI 2.6 to 14.5), with a 4-year PFS rate of 17%; median DOR was 14.5 months (95% CI 2.9 to 35.3), with 23% of patients having an ongoing response at 4 years (online supplemental table S7).

Treatment-switching adjustment analysis

Patients in the chemotherapy-alone arm who switch to subsequent immunotherapy can introduce bias in the calculation of treatment effect, making treatment outcomes in the chemotherapy-alone arm appear more favorable than they would be in the absence of subsequent immunotherapy treatment. Thus, a treatment-switching adjustment analysis was conducted. The baseline demographics and disease characteristics of patients who switched treatment from chemotherapy alone to immunotherapy are shown in online supplemental table S8 and were generally similar to those of the all-treated population (data not shown).

All-treated and IPCW-adjusted analysis

After adjustment for treatment switching using the IPCW model, the estimated median OS for all treated patients

in the chemotherapy-alone arm was revised from 10.9 months (95% CI 9.5 to 12.6) to 9.7 months (95% CI 7.9 to 10.9) (figure 6A). The adjusted HR for nivolumab plus ipilimumab with chemotherapy versus chemotherapy alone was 0.66 (95% CI 0.55 to 0.80), compared with an unadjusted HR of 0.74 (95% CI 0.63 to 0.87) from the all-treated population.

Sensitivity analyses

Results from sensitivity analyses using other treatment-switching adjustment methods were generally consistent with the IPCW analysis. Median OS for all treated patients in the chemotherapy-alone arm after adjustment without recensoring using the TSE, RPSFT, and IPE models was 10.2 months (95% CI 9.2 to 11.8), 10.0 months (95% CI 8.7 to 11.4), and 10.0 months (95% CI 8.8 to 11.5), respectively (figure 6B). The respective adjusted HR values were 0.69 (95% CI 0.61 to 0.79), 0.69 (95% CI 0.57 to 0.81), and 0.68 (95% CI 0.57 to 0.81). Adjustment analyses were also performed using the RPSFT and IPE models with recensoring, and similar results were obtained (data not shown).

Safety

With a minimum follow-up of 49.1 months, safety in all treated patients was consistent with prior reports,^{4,14,21} and no new safety signals were identified (online supplemental table S9). Per protocol, patients discontinued nivolumab plus ipilimumab with chemotherapy after a maximum of 2 years of treatment; thus, no new safety signals were identified in this 4-year analysis. The summary of TRAEs in all treated patients is provided in online supplemental table S9, and the incidence of IMAEs in the nivolumab plus ipilimumab with chemotherapy arm is summarized in online supplemental table S10.

DISCUSSION

In CheckMate 9LA, with a minimum of 4 years of follow-up, patients with metastatic NSCLC continued to derive long-term, durable OS benefit from first-line nivolumab plus ipilimumab with two cycles of chemotherapy versus four cycles of chemotherapy alone (HR 0.74), regardless of tumor PD-L1 expression level or histology. PFS and DOR continued to favor nivolumab plus ipilimumab with chemotherapy compared with chemotherapy alone; durable responses were seen in all randomized patients and across all subgroups, including patients with limited efficacious treatment options (tumor PD-L1 expression <1% or squamous histology). The clinical benefit of nivolumab plus ipilimumab with chemotherapy was further supported by exploratory analyses of efficacy in patients who discontinued treatment due to TRAEs and in patients who switched from chemotherapy to subsequent immunotherapy treatment, which revealed a greater estimated relative OS benefit for nivolumab plus ipilimumab with chemotherapy versus chemotherapy alone (OS HR 0.66) than in the unadjusted population of

all-treated patients (OS HR 0.74). No new safety signals were identified at the 4-year follow-up.

In this clinical update from CheckMate 9LA, although patients have been off of immunotherapy treatment for at least 2 years per protocol, the long-term survival benefit of nivolumab plus ipilimumab with chemotherapy versus chemotherapy alone was clearly evident with the continued separation of the Kaplan-Meier OS curves; 21% of patients in the nivolumab plus ipilimumab with chemotherapy arm were still alive at 4 years versus 16% of patients in the chemotherapy-alone arm. Sustained PFS benefit and durable responses were also demonstrated at 4 years; the difference in the proportion of responders with an ongoing response between treatment arms appeared to be nearly twofold in all randomized patients and threefold or more in certain subgroups, such as tumor PD-L1 expression <1% and squamous histology.

Recently, several phase 3 clinical trials of first-line immunotherapy in patients with metastatic NSCLC have reported milestone 5-year clinical outcomes, including trials with immunotherapy alone,^{9, 28} in combination with chemotherapy,^{10, 11} or dual-immunotherapy combination regimens.⁸ Although patients with NSCLC with high tumor PD-L1 expression ($\geq 50\%$) consistently have improved long-term survival benefit from all immunotherapy regimens,^{8–11} clinical outcomes with immunotherapy plus chemotherapy in certain patient populations, such as those with tumor PD-L1 expression <1% and/or squamous histology, remain suboptimal.^{10–12, 29–31} No incremental benefit was evident with pembrolizumab plus chemotherapy versus chemotherapy alone at 5 years in patients with tumor PD-L1 expression <1% and squamous histology (OS rates, 11% versus 13%).¹¹ Furthermore, the survival curves appeared to be converging between the treatment arms for patients with tumor PD-L1 expression <1% and non-squamous histology with extended follow-up.¹⁰ In contrast, data from the CheckMate 9LA 4-year update showed sustained long-term OS benefit with nivolumab plus ipilimumab with chemotherapy versus chemotherapy alone in patients with either tumor PD-L1 expression <1% or $\geq 1\%$; in addition, the magnitude of survival benefit was apparently greater in patients with tumor PD-L1 expression <1% (HR 0.66) or squamous histology (HR 0.64) than in those with tumor PD-L1 expression $\geq 1\%$ (HR 0.74) or non-squamous histology (HR 0.80). In addition to the survival benefit, the durability of response with nivolumab plus ipilimumab with chemotherapy was more notable in CheckMate 9LA in both tumor PD-L1 expression and histology subgroups than in the pembrolizumab plus chemotherapy profile in these subgroups,^{10, 11} although caution is needed when performing cross-trial comparisons. Similar to the results from the 4-year analysis of CheckMate 9LA, long-term durable clinical benefit has been reported with nivolumab plus ipilimumab in CheckMate 227,³² underscoring the potential contribution of ipilimumab to a sustained response through enhanced memory

T cell induction.^{33–35} Furthermore, a recent systematic review of first-line therapies for advanced NSCLC also demonstrated the long-term benefit of nivolumab plus ipilimumab compared with immunotherapy-based combinations.^{13 36} As long-term data with first-line immunotherapy-based regimens continue to mature, the 4-year update from CheckMate 9LA supports first-line nivolumab plus ipilimumab-based regimens as efficacious treatment options for patients with metastatic NSCLC, including those with tumor PD-L1 expression <1% or squamous histology who have high unmet needs.

No new safety signals were observed with nivolumab plus ipilimumab with chemotherapy in our updated analysis. Discontinuation of nivolumab plus ipilimumab with chemotherapy due to TRAEs did not negatively impact the long-term clinical or efficacy benefit, with a 4-year OS rate of 41%. These results are consistent with previous reports in patients who discontinued dual nivolumab plus ipilimumab due to TRAEs, including data from CheckMate 227 and from patients with advanced sarcomatoid renal cell carcinoma in CheckMate 214.^{8 37} Similar findings have been reported recently from a real-world data analysis in melanoma³⁸ and NSCLC,^{39 40} which showed that patients may experience a durable response even after discontinuing immunotherapy for any reason or due to adverse events.

With the availability of second-line immunotherapy options for patients with NSCLC, treatment switching to subsequent immunotherapy in the chemotherapy arm can potentially impact the calculation of the OS benefit observed in the study by making the survival benefit from chemotherapy appear larger than it would be if second-line immunotherapy were unavailable. At the time of this analysis, 36% of patients in the chemotherapy arm of CheckMate 9LA had switched to subsequent immunotherapy. A treatment-switching adjustment analysis substituting these patients with “like” patients who did not receive subsequent immunotherapy lowered the calculated median OS in the chemotherapy arm from 10.9 to 9.7 months, improving the estimated relative OS benefit from nivolumab plus ipilimumab with chemotherapy (adjusted HR 0.66). Recent reports of treatment-switching adjustment analyses conducted for clinical trials of immunotherapy regimens versus chemotherapy, such as KEYNOTE-024 and CheckMate 227, have found similar improvements in relative survival outcomes compared with chemotherapy.^{19 20} Of note, although only 7% of the patients in the nivolumab plus ipilimumab with chemotherapy arm received subsequent immunotherapy, any potential impact of this on the OS benefit is undetermined. This adjustment for treatment switching supports the evidence for the efficacy of nivolumab plus ipilimumab with chemotherapy versus chemotherapy alone and can also inform other analyses, such as indirect treatment comparisons, meta-analyses, and assessments of cost-effectiveness.

In conclusion, this 4-year update from CheckMate 9LA showed that patients with metastatic or recurrent

NSCLC continued to derive long-term, durable efficacy benefit from first-line nivolumab plus ipilimumab with chemotherapy versus chemotherapy alone regardless of tumor PD-L1 expression or histology. These findings, taken together with exploratory analyses in patients who discontinued nivolumab plus ipilimumab with chemotherapy due to TRAEs and treatment-switching adjustment analysis, further support the use of nivolumab plus ipilimumab with chemotherapy as an efficacious first-line treatment option for metastatic NSCLC, particularly for patients with tumor PD-L1 expression <1% or squamous histology, populations with high unmet needs.

Author affiliations

- ¹Division of Medical Oncology and the Pelotonia Institute for Immuno-Oncology, The Ohio State University Comprehensive Cancer Center, Columbus, Ohio, USA
- ²Department of Medical Oncology, Institutul Oncologic Prof Dr Ion Chiricută and University of Medicine and Pharmacy Iuliu Hațieganu, Cluj-Napoca, Romania
- ³Department of Medical Oncology, SF Nectarie Oncology Center, Craiova, Romania
- ⁴Department of Medical Oncology, Unidad de Gestión Clínica Intercentros de Oncología Médica, Hospitales Universitarios Regional y Virgen de la Victoria, IBIMA, Málaga, Spain
- ⁵L'institut du Thorax, Nantes, France
- ⁶Department of Medical Oncology, Hospital Universitario La Fe, Valencia, Spain
- ⁷Department of Oncology, Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil
- ⁸Department of Oncology, Asklepios Lung Clinic, German Center for Lung Research, Munich-Gauting, Germany
- ⁹Department of Clinical Oncology, IONC Instituto Oncológico de Córdoba, Córdoba, Argentina
- ¹⁰Department of Oncology, Jilin Cancer Hospital, Changchun, Jilin, China
- ¹¹Department of Thoracic Oncology, Saitama Cancer Center, Saitama, Japan
- ¹²Medical Oncology Service, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain
- ¹³Chemotherapy Department, Ambulatorium Chemioterapii, Bydgoszcz, Poland
- ¹⁴Department of Oncology, Institute of Oncology Prof Dr Alexandru Trestioreanu Bucha, Bucharest, Romania
- ¹⁵Medical Oncology Department, Hospital Universitario 12 de Octubre, Universidad Complutense de Madrid, Madrid, Spain
- ¹⁶Department of Medical Oncology, Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai JiaoTong University, Shanghai, China
- ¹⁷Medical Oncology Department, Austin Hospital, Heidelberg, Victoria, Australia
- ¹⁸Global Drug Development, Oncology Clinical Development, Bristol Myers Squibb, Princeton, New Jersey, USA
- ¹⁹Global Biometrics and Data Sciences, Bristol Myers Squibb, Princeton, New Jersey, USA
- ²⁰Parexel, Billerica, Massachusetts, USA
- ²¹Department of Thoracic Oncology, Airway Research Center North, German Center for Lung Research, Lung Clinic, Grosshansdorf, Germany

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Patient consent for publication Not applicable.

Ethics approval

This study was conducted according to 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 protocol and all amendments. All patients provided written informed consent.

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ORCID iD

David P. Carbone <http://orcid.org/0000-0003-3002-1921>

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