ORIGINAL ARTICLE

First-Line Nivolumab Plus Ipilimumab in Advanced NSCLC: 4-Year Outcomes From the Randomized, Open-Label, Phase 3 CheckMate 227 Part 1 Trial

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ABSTRACT

Introduction: In CheckMate 227, nivolumab plus ipilimumab prolonged overall survival (OS) versus chemotherapy in patients with tumor programmed death-ligand 1 (PD-L1) greater than or equal to 1% (primary end point) or less than 1% (prespecified descriptive analysis). We report results with minimum 4 years' follow-up.

Methods: Adults with previously untreated stage IV or recurrent NSCLC were randomized (1:1:1) to nivolumab plus ipilimumab, nivolumab, or chemotherapy (PD-L1 $\geq$1%); or to nivolumab plus ipilimumab, nivolumab plus chemotherapy, or chemotherapy (PD-L1 <1%). Efficacy included OS and other measures. Safety included timing and management of immune-mediated adverse events (AEs). A post hoc analysis evaluated efficacy in patients who discontinued nivolumab plus ipilimumab due to treatment-related AEs (TRAEs).

Results: After 54.8 months' median follow-up, OS remained longer with nivolumab plus ipilimumab versus chemotherapy in patients with PD-L1 greater than or equal to 1% (hazard ratio = 0.76; 95% confidence interval: 0.65–0.90) and PD-L1 less than 1% (0.64; 0.51–0.81); 4-year OS rate with nivolumab plus ipilimumab versus chemotherapy was 29% versus 18% (PD-L1 $\geq$1%); and 24% versus 10% (PD-L1 <1%). Benefits were observed in both squamous and nonsquamous histologies. In a descriptive analysis, efficacy was improved with nivolumab plus ipilimumab relative to nivolumab (PD-L1 $\geq$1%) and nivolumab plus chemotherapy (PD-L1 <1%). Safety was consistent with previous reports. The most common immune-mediated AE with nivolumab plus ipilimumab, nivolumab, and nivolumab plus chemotherapy was rash; most immune-mediated AEs (except endocrine events) occurred within 6 months from start of treatment and resolved within 3 months after, mainly with systemic corticosteroids. Patients who discontinued nivolumab plus ipilimumab due to TRAEs had long-term OS benefits, as seen in the all randomized population.

Conclusions: At more than 4 years' minimum follow-up, with all patients off immunotherapy treatment for at least 2 years, first-line nivolumab plus ipilimumab continued to demonstrate durable long-term efficacy in patients with advanced NSCLC. No new safety signals were identified. Immune-mediated AEs occurred early and resolved quickly with guideline-based management. Discontinuation of nivolumab plus ipilimumab due to TRAEs did not have a negative impact on the long-term benefits seen in all randomized patients.

Keywords: PD-1 checkpoint inhibitor; Immunotherapy; First-line; Metastatic non–small cell lung cancer; CTLA-4

Introduction

In recent years, immunotherapy-based regimens as first-line treatment for advanced NSCLC have significantly prolonged overall survival (OS) versus chemotherapy alone, and long-term data in this setting remain of clinical interest.[1–10] Nivolumab, a fully human PD-1 antibody, and ipilimumab, a fully human CTLA-4 antibody, are immune checkpoint inhibitors with distinct but complementary mechanisms of action. Nivolumab restores the antitumor function of T cells while ipilimumab induces de novo antitumor T-cell responses, including an increase in memory T cells.[11–13] Combination immunotherapy with nivolumab plus ipilimumab has improved long-term survival in multiple advanced cancers including melanoma, renal cell carcinoma, malignant pleural mesothelioma, and NSCLC.[6,14–19] In Part 1 of the randomized phase 3 CheckMate 227 study (NCT02477826), which met both of its independent primary end points, first-line treatment with nivolumab plus ipilimumab for advanced NSCLC significantly improved progression-free survival (PFS, $p < 0.001$) in patients with a high tumor mutational burden ($\geq$10 mutations per megabase),[20] and significantly prolonged OS in patients with tumor PD-L1 expression greater than or equal to 1% ($p = 0.007$, hazard ratio [HR] = 0.79) versus platinum-doublet chemotherapy.[6] In a prespecified descriptive analysis, OS was also improved with nivolumab plus ipilimumab over chemotherapy in patients with tumor PD-L1 expression less than 1% (HR = 0.62).[6] The safety profile of nivolumab plus

ipilimumab was manageable and consistent with prior reports for this dual immunotherapy regimen in NSCLC.[21,22] Furthermore, patients treated with nivolumab plus ipilimumab tended to have improved symptom burden and health-related quality of life with delayed deterioration of symptoms versus chemotherapy.[23]

Based on results from CheckMate 227, nivolumab plus ipilimumab was approved in the United States and other countries as first-line treatment for adult patients with metastatic NSCLC expressing PD-L1 greater than or equal to 1% with no *EGFR* or *ALK* genomic tumor aberrations, and in Japan and Argentina as first-line treatment regardless of tumor PD-L1 expression.[24–27] Nivolumab plus ipilimumab is also recommended by the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines) and the European Society for Medical Oncology guidelines as a first-line treatment option for eligible patients with metastatic NSCLC with either tumor PD-L1 greater than or equal to 1% or less than 1% but without actionable oncogenic driver mutations, regardless of tumor histology.[25,28,29] Long-term outcomes with nivolumab plus ipilimumab and the management of adverse events (AEs) remain of clinical interest. We report updated OS and other efficacy data from CheckMate 227 Part 1 in patients with tumor PD-L1 expression greater than or equal to 1% or less than 1% with a minimum follow-up of 4 years, and a comprehensive characterization of the safety profile of nivolumab plus ipilimumab, including a post hoc analysis of efficacy in patients who discontinued both nivolumab and ipilimumab due to treatment-related AEs (TRAEs).

Materials and Methods

Patients

Eligibility criteria for CheckMate 227 Part 1 have previously been described.[6,20] Eligible patients had stage IV or recurrent NSCLC, histologically confirmed squamous or nonsquamous disease, no *EGFR* or *ALK* genomic tumor aberrations, and an Eastern Cooperative Oncology Group performance status less than or equal to 1.[30]

Trial Design and Treatment

CheckMate 227 Part 1 was an open-label, randomized, phase 3 trial evaluating first-line nivolumab-based regimens for advanced NSCLC (Supplementary Fig. 1).

Patients with tumor PD-L1 expression greater than or equal to 1% were randomly assigned (1:1:1) to receive nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks, nivolumab monotherapy 240 mg every 2 weeks, or platinum-doublet chemotherapy. Those with tumor PD-L1 expression less than 1% were randomly assigned (1:1:1) to receive nivolumab plus ipilimumab, nivolumab 360 mg every 3 weeks plus platinum-doublet chemotherapy, or platinum-doublet chemotherapy alone. Platinum-doublet chemotherapy was administered every 3 weeks for up to four cycles. Optional pemetrexed maintenance (500 mg/m^2) was permitted for patients with nonsquamous histology in chemotherapy-containing arms. Randomization was stratified by tumor histology (squamous versus nonsquamous).

Treatment continued until disease progression or unacceptable toxicity, or for up to 2 years for immunotherapy. Immunotherapy treatment could continue beyond disease progression if patients met the prespecified criteria.[6] Crossover between treatment arms was not permitted per protocol.

This trial was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines. The study protocol and amendments were approved by an institutional review board or independent ethics committee at each site. 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 two independent primary end points, hierarchical secondary end points, and prespecified descriptive analyses were reported previously.[6,20] The current manuscript provides updates for the primary end point of OS in patients with tumor PD-L1 expression greater than or equal to 1% and other efficacy measures in the PD-L1 hierarchy (Supplementary Fig. 1).[6] Updated safety outcomes are also reported.

Immune-mediated AEs were defined as specific events (including endocrine events), regardless of causality. Nonendocrine events were reported for patients who received immunosuppressive medication as treatment; endocrine events were included regardless of treatment, since these are often managed without immunosuppression. Immune-mediated AEs were reported between first dose and 100 days after last dose of study treatment. Types, rates, time to onset, time to resolution of immune-mediated AEs, and the use of corticosteroids and other immune-modulating medications for the management of these events in immunotherapy-containing arms (nivolumab plus ipilimumab, nivolumab monotherapy, and nivolumab plus chemotherapy), were evaluated.

Post hoc analyses included assessment of efficacy in patients who discontinued nivolumab plus ipilimumab due to TRAEs. Patients included in this analysis had

TRAEs (reported between first dose and 30 days after last dose of study treatment) that led to the discontinuation of all components of study treatment. OS (from randomization), objective response rate (ORR), duration of response (DOR) from time of treatment discontinuation, and treatment-free interval (defined as time from last dose of study therapy to start of the first subsequent systemic therapy or death, whichever occurred first; set to zero for patients who received subsequent therapy prior to treatment discontinuation) were evaluated.

Statistical Analysis

Efficacy was evaluated in all randomized patients, and safety in all patients who received at least one dose of study treatment. OS, PFS, DOR, treatment-free interval, and other time-to-event end points were estimated using Kaplan–Meier methodology. HRs between randomized treatment arms with associated two-sided confidence intervals (CIs) were estimated using a stratified Cox proportional hazard model, with treatment arm as a single covariate. HRs between treatment arms in patient subgroups used an unstratified model. For ORRs, two-sided exact 95% CIs were calculated using the Clopper–Pearson method. Descriptive statistics were used to summarize safety results, where applicable.

Results

Patients and Treatment

As previously reported, 2876 patients were enrolled between August 5, 2015, and November 30, 2016, of whom 1739 were randomized; baseline characteristics were generally well balanced across treatment arms (Supplementary Table 1).[6] As of the February 18, 2021, database lock, the minimum follow-up was 49.4 months and median (range) follow-up was 54.8 (49.4–65.8) months for OS.

At the current database lock, all patients treated with nivolumab plus ipilimumab, nivolumab monotherapy, or nivolumab plus chemotherapy had completed or discontinued immunotherapy treatment for at least 2 years. One patient treated with chemotherapy alone remained on pemetrexed maintenance treatment. Patient disposition is summarized in Supplementary Figure 2.

Among those with a PFS event in the tumor PD-L1 expression greater than or equal to 1% and less than 1% combined patient population, 165 (38%) patients in the nivolumab plus ipilimumab arms and 215 (48%) in the chemotherapy arms received subsequent systemic anticancer therapies; 32 (7%) and 166 (38%), respectively, received subsequent immunotherapy. Among 81 patients who survived for at least 4 years in the chemotherapy arm, 59 (73%) received subsequent immunotherapy. Data regarding subsequent therapies among patients surviving for at least 4 years, all randomized patients, and all randomized patients with a PFS event are provided in Supplementary Table 2A–C.

Efficacy

With a minimum follow-up of 49.4 months, OS benefits with nivolumab plus ipilimumab versus chemotherapy were seen regardless of tumor PD-L1 expression level (Fig. 1) or tumor histology (Fig. 2). Patients with tumor PD-L1 expression greater than or equal to 1% receiving nivolumab plus ipilimumab continued to derive OS benefits versus chemotherapy (HR = 0.76; 95% CI: 0.65–0.90; Fig. 1*A*), consistent with the primary analysis[6]; 29% versus 18% of patients were alive at 4 years, respectively. The OS benefit of nivolumab plus ipilimumab versus chemotherapy was seen in both nonsquamous and squamous histologies (Fig. 2*A*–*B*) and across most patient subgroups (Supplementary Fig. 3). Among patients treated with nivolumab plus ipilimumab, 14% were progression-free at 4 years versus 4% with chemotherapy (Fig. 3*A*). ORRs (Supplementary Table 3A) were consistent with those previously reported[6,19]; median DOR was 23.2 months with nivolumab plus ipilimumab and 6.7 months with chemotherapy, and 34% and 7%, respectively, of confirmed responders had ongoing responses for at least 4 years since their first response (Fig. 3*C*). PFS rates and DOR at 4 years were improved in both nonsquamous and squamous histologies (Supplementary Table 3B–C).

In the subset of patients with tumor PD-L1 expression greater than or equal to 50%, median OS was 21.2 months with nivolumab plus ipilimumab versus 14.0 months with chemotherapy; 4-year OS rates were 37% versus 20%, respectively (Fig. 1*B*); OS benefit was seen in both nonsquamous and squamous histologies (Supplementary Fig. 4). PFS rates at 4 years were 20% versus 1%, respectively (Fig. 3*B*). ORR in patients with tumor PD-L1 expression greater than or equal to 50% was 45% with nivolumab plus ipilimumab and 35% with chemotherapy, with a median DOR of 31.8 months versus 5.8 months, respectively; 40% and 3% of responders, respectively, remained in response for at least 4 years (Fig. 3*D*).

Similarly, patients with tumor PD-L1 expression less than 1% continued to have improved OS with nivolumab plus ipilimumab versus chemotherapy (HR = 0.64 [95% CI: 0.51–0.81]; Fig. 1*C*), which was consistent with the previous reports[6,19]; 4-year OS rates were 24% versus 10%, respectively. OS benefit with nivolumab plus ipilimumab versus chemotherapy was seen in both nonsquamous and squamous histologies (Fig. 2*C* and *D*). PFS rate at 4 years was 12% with nivolumab plus ipilimumab, whereas no patient remained progression-free with chemotherapy (Fig. 4*A*). ORRs in each treatment arm (Supplementary Table 3A)

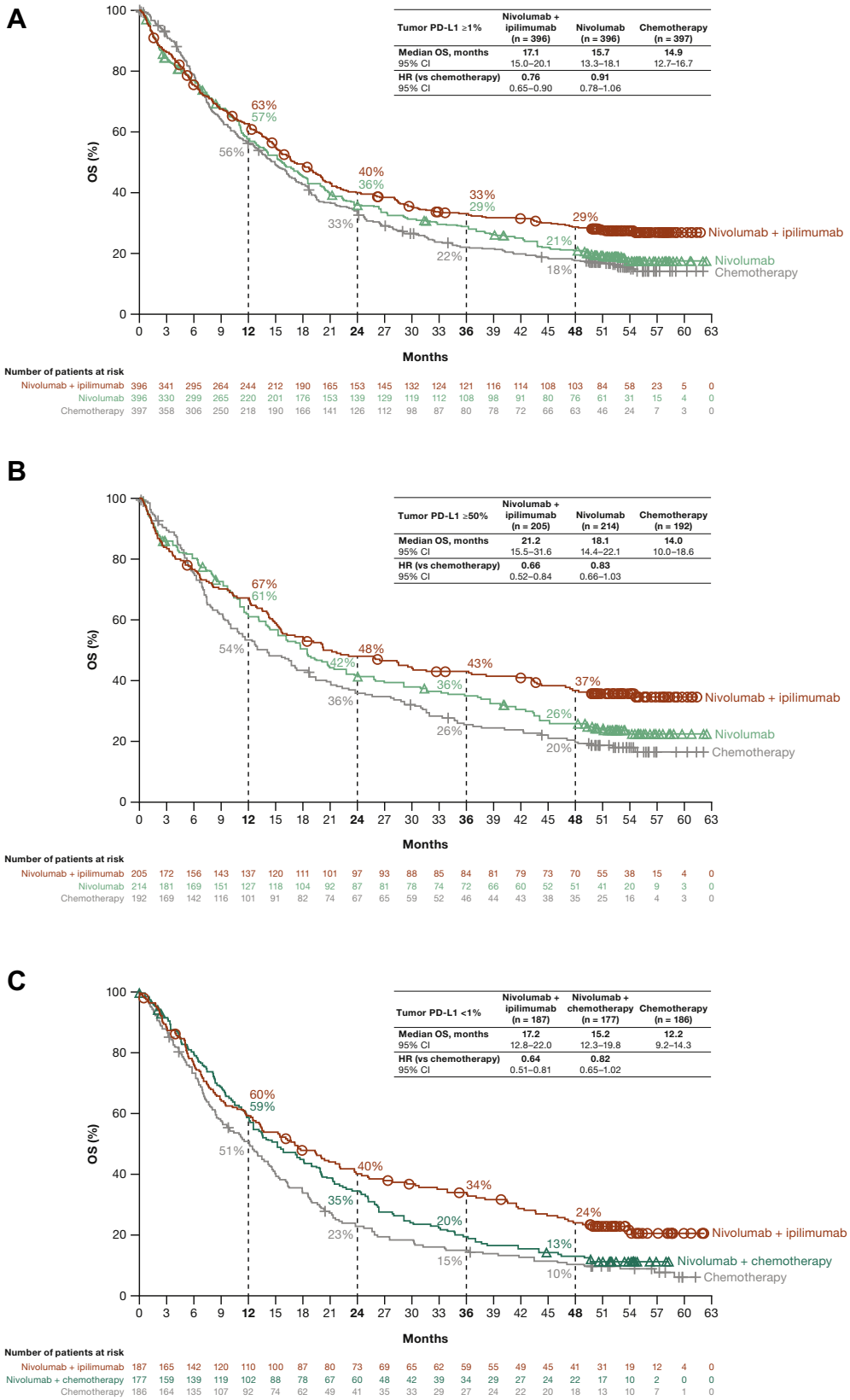


Figure 1. OS in patients with (*A*) tumor PD-L1 expression greater than or equal to 1%,[a] (*B*) tumor PD-L1 expression greater than or equal to 50%,[b] and (*C*) tumor PD-L1 expression less than 1%.[c] Minimum follow-up for all randomized patients was 49.4 months. [a]Nivolumab plus ipilimumab versus nivolumab OS HR (95% CI) = 0.84 (0.71–0.99). [b]Nivolumab plus ipilimumab versus nivolumab OS HR (95% CI) = 0.79 (0.63–1.00). [c]Nivolumab plus ipilimumab versus nivolumab plus chemotherapy OS HR (95% CI) = 0.77 (0.61–0.97). CI, confidence interval; HR, hazard ratio; OS, overall survival.

were unchanged since the primary database lock[6]; median DOR was 18.0 months with nivolumab plus ipilimumab versus 4.8 months with chemotherapy; 31% of confirmed responders who received nivolumab plus ipilimumab had ongoing responses for at least 4 years; no patient who received chemotherapy had an ongoing response (Fig. 4*B*).

Consistent with the previous report, clinical benefit was also observed with nivolumab plus ipilimumab in the tumor PD-L1 expression greater than or equal to 1% and less than 1% combined patient population (Supplementary Fig. 5*A* and Supplementary Fig. 6), regardless of tumor histology (Supplementary Fig. 5*B–C*, Supplementary Table 3). HR for OS with nivolumab plus ipilimumab versus chemotherapy was 0.72 (95% CI: 0.63–0.82), and 4-year OS rates were 27% versus 15%, respectively (Supplementary Fig. 5*A*). In tumor histology subgroups, 4-year OS rates were 30% (nivolumab plus ipilimumab) versus 19% (chemotherapy) among patients with nonsquamous histology and 20% versus 6%, respectively, among patients with squamous histology (Supplementary Fig. 5*B–C*). PFS and DOR also favored nivolumab plus ipilimumab over chemotherapy (Supplementary Fig. 6).[6,19]

Nivolumab plus ipilimumab showed numerically higher benefit across all efficacy end points compared with nivolumab monotherapy (descriptive analysis) in patients with tumor PD-L1 expression greater than or equal to 1% and in the subset with tumor PD-L1 expression greater than or equal to 50%. The OS curves of nivolumab plus ipilimumab and nivolumab monotherapy separated approximately 12 months (PD-L1 $\geq$1%) or 18 months (PD-L1 $\geq$50%) from randomization (Fig. 1*A* and *B*) and PFS curves separated approximately 6 months from randomization, favoring nivolumab plus ipilimumab over time (Fig. 3*A* and *B*). Nivolumab plus ipilimumab versus nivolumab monotherapy separations increased with time and were maintained at 4 years for both PD-L1 greater than or equal to 1% (OS rates, 29% and 21%; PFS rates, 14% and 10%) and PD-L1 greater than or equal to 50% populations (OS rates, 37% and 26%; PFS rates, 20% and 14%). Among patients with PD-L1 greater than or equal to 1%, ORRs were 36% with nivolumab plus ipilimumab and 28% with nivolumab monotherapy; median DOR was 23.2 months and 15.5 months, respectively. In the subset of patients with tumor PD-L1 expression greater than or equal to 50%, ORRs were 45% with nivolumab plus ipilimumab and 37% with nivolumab monotherapy; median DOR was 31.8 months and 16.8 months, respectively (Fig. 3*C* and *D*).

In patients with tumor PD-L1 expression less than 1%, OS improvements with nivolumab plus ipilimumab over nivolumab plus chemotherapy (4-year OS rate, 24% versus 13%) were increased from the primary database lock (Fig. 1*C*)[6]; PFS and DOR improvements were maintained at 4 years; PFS rates were 12% versus 7%; median DORs were 18.0 months versus 8.3 months, respectively (Fig. 4).

Safety

With all patients off immunotherapy treatment for 2 years or longer, no new TRAEs were reported in the nivolumab plus ipilimumab arm since the previous database lock; the incidence of any-grade and grade 3 or 4 TRAEs, serious TRAEs, and TRAEs leading to discontinuation in all treatment arms was largely unchanged from previous reports (Supplementary Table 4). Treatment exposure was 400.9 patient-years and 277.6 patient-years with nivolumab plus ipilimumab and chemotherapy, respectively (PD-L1 $\geq$1% and <1% combined patient population), 277.1 patient-years with nivolumab monotherapy (PD-L1 $\geq$1%), and 143.5 patient-years with nivolumab plus chemotherapy (PD-L1 <1%). Overall incidence rates of TRAEs per 100 patient-years were 607.7 (nivolumab plus ipilimumab), 1059.8 (chemotherapy), 351.8 (nivolumab monotherapy), and 933.7 (nivolumab plus chemotherapy) (Supplementary Table 4). TRAEs of any grade leading to discontinuation occurred in 18% and 9% of patients treated with nivolumab plus ipilimumab and chemotherapy, respectively (PD-L1 $\geq$1% and <1% combined patient population), 12% treated with nivolumab monotherapy (PD-L1 $\geq$1%), and 14% treated with nivolumab plus chemotherapy (PD-L1 <1%). The most common TRAE ($\geq$3%) leading to discontinuation in the nivolumab plus ipilimumab arms was pneumonitis (3.6%). No new treatment-related deaths were reported since the previous analysis.

The most common any-grade immune-mediated AE was rash, which occurred in 19% of patients treated with nivolumab plus ipilimumab (PD-L1 $\geq$1% and <1%), 8% of patients treated with nivolumab monotherapy (PD-L1 $\geq$1%), and 10% of patients treated with nivolumab plus chemotherapy (PD-L1 <1%; Supplementary Table 5); most events were grade 1 or 2 in all treatment arms. In the nivolumab plus ipilimumab arm, the most common ($\geq$2%) grade 3 or 4 immune-mediated AEs were increased alanine aminotransferase, increased aspartate aminotransferase and pneumonitis (3% each), adrenal insufficiency and diarrhea (2% each). The most common grade 3 or 4 event in the nivolumab monotherapy arm was increased alanine aminotransferase (2%) and in the nivolumab plus chemotherapy arm was pneumonitis (2%).

The immune-mediated AE with shortest time to onset was hypersensitivity, which generally occurred within the first month of nivolumab plus ipilimumab treatment;

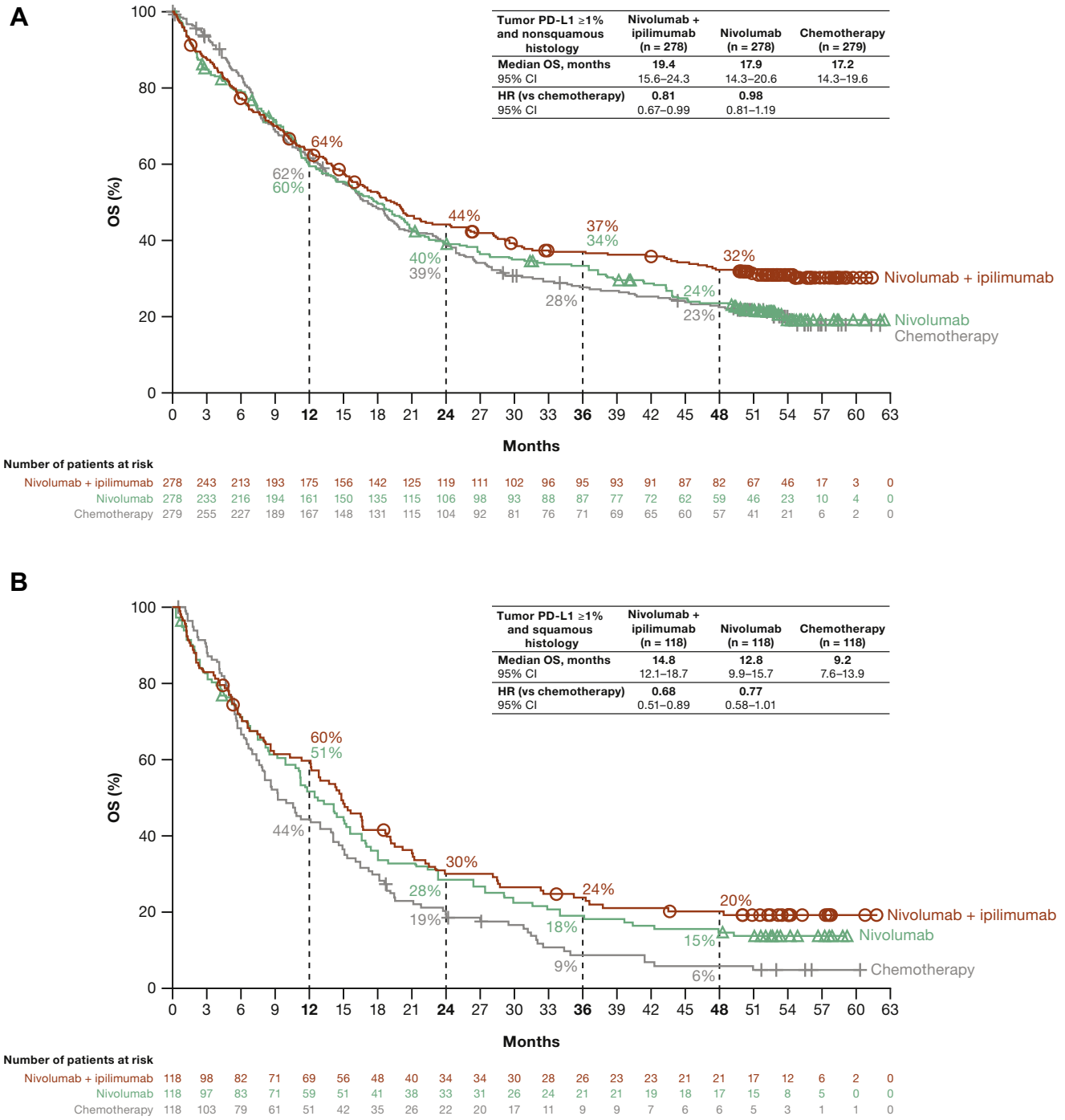


Figure 2. OS in patients with (*A*) tumor PD-L1 expression greater than or equal to 1% and nonsquamous histology, (*B*) tumor PD-L1 expression greater than or equal to 1% and squamous histology, (*C*) tumor PD-L1 expression less than 1% and nonsquamous histology, and (*D*) tumor PD-L1 expression less than 1% and squamous histology. Minimum follow-up for all randomized patients was 49.4 months. CI, confidence interval; HR, hazard ratio; OS, overall survival.

nephritis and renal dysfunction, rash, and hyperthyroidism generally occurred within the first 3 months (Fig. 5*A* and Supplementary Table 6). Fewer patients had new immune-mediated AEs after 6 to 12 months of treatment, and even fewer beyond 12 months (Supplementary Fig. 7). The majority (74%–100% across categories) of the events resolved after established safety management algorithms, with exceptions of endocrine-related events, which were not considered resolved if long-term hormone replacement therapy was needed. Median time to resolution for nonendocrine events ranged from less than 1 to 1.5 months (Fig. 5*B*, Supplementary Table 7). Similar times to onset and resolution of immune-mediated AEs were observed with

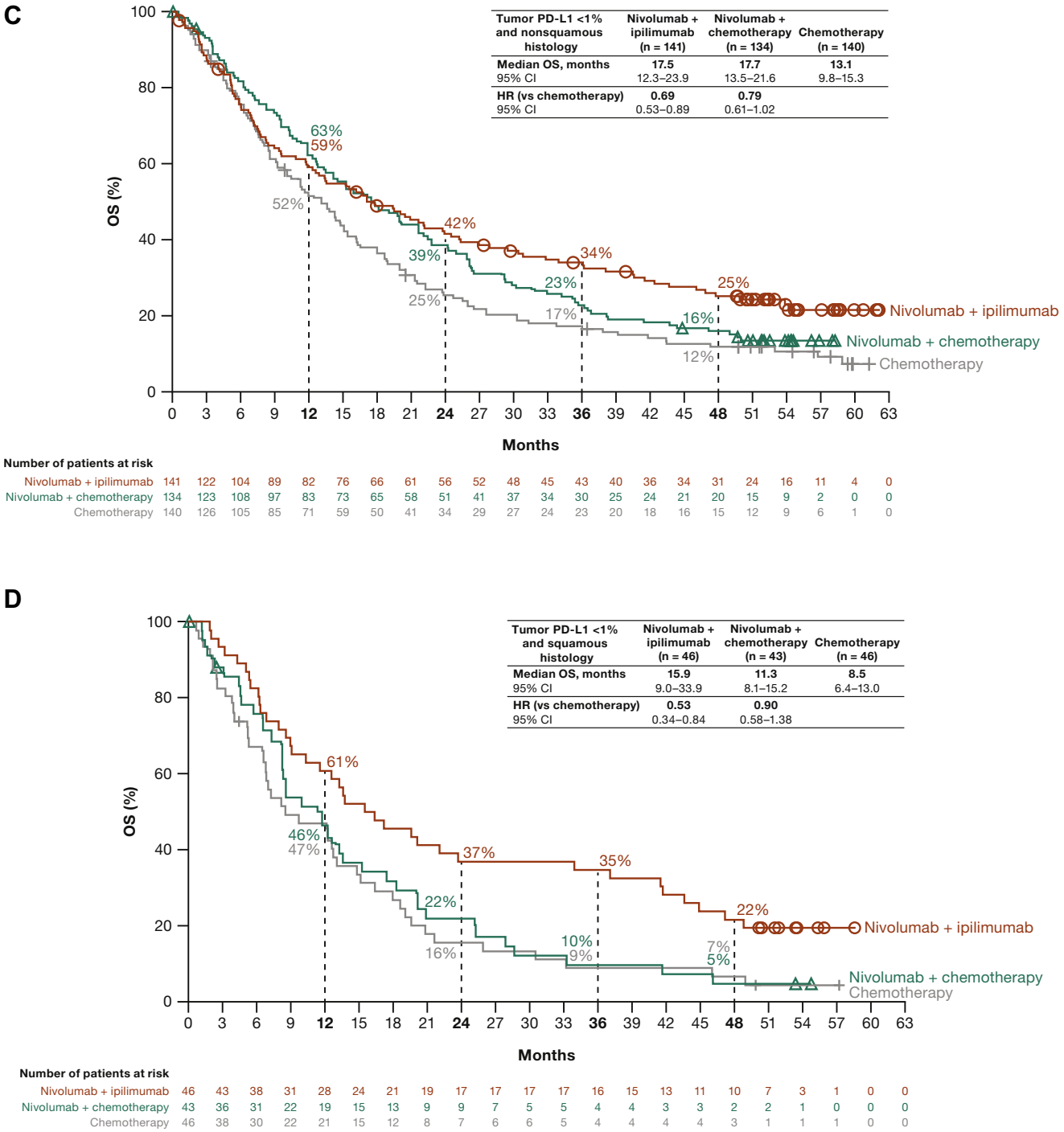


Figure 2. Continued.

nivolumab monotherapy and nivolumab plus chemotherapy (Supplementary Fig. 8 and Supplementary Table 6–7).

Systemic corticosteroids (≥40 mg prednisone or equivalent) were the most common immunosuppressive agents used for the management of immune-mediated AEs with nivolumab plus ipilimumab (Supplementary Table 8), ranging from 6% in patients with hypothyroidism or thyroiditis to 94% in patients with pneumonitis. Median duration of corticosteroid treatment for immune-mediated AEs ranged from 0.1 week for hypersensitivity to 5.0 weeks for hypothyroidism or thyroiditis, similar to corticosteroid treatment used in the nivolumab monotherapy or nivolumab plus chemotherapy arms (Supplementary Table 8). Very few patients required additional immunosuppressive treatment beyond corticosteroids to manage immune-mediated AEs: with nivolumab plus ipilimumab, three patients with pneumonitis and three patients with

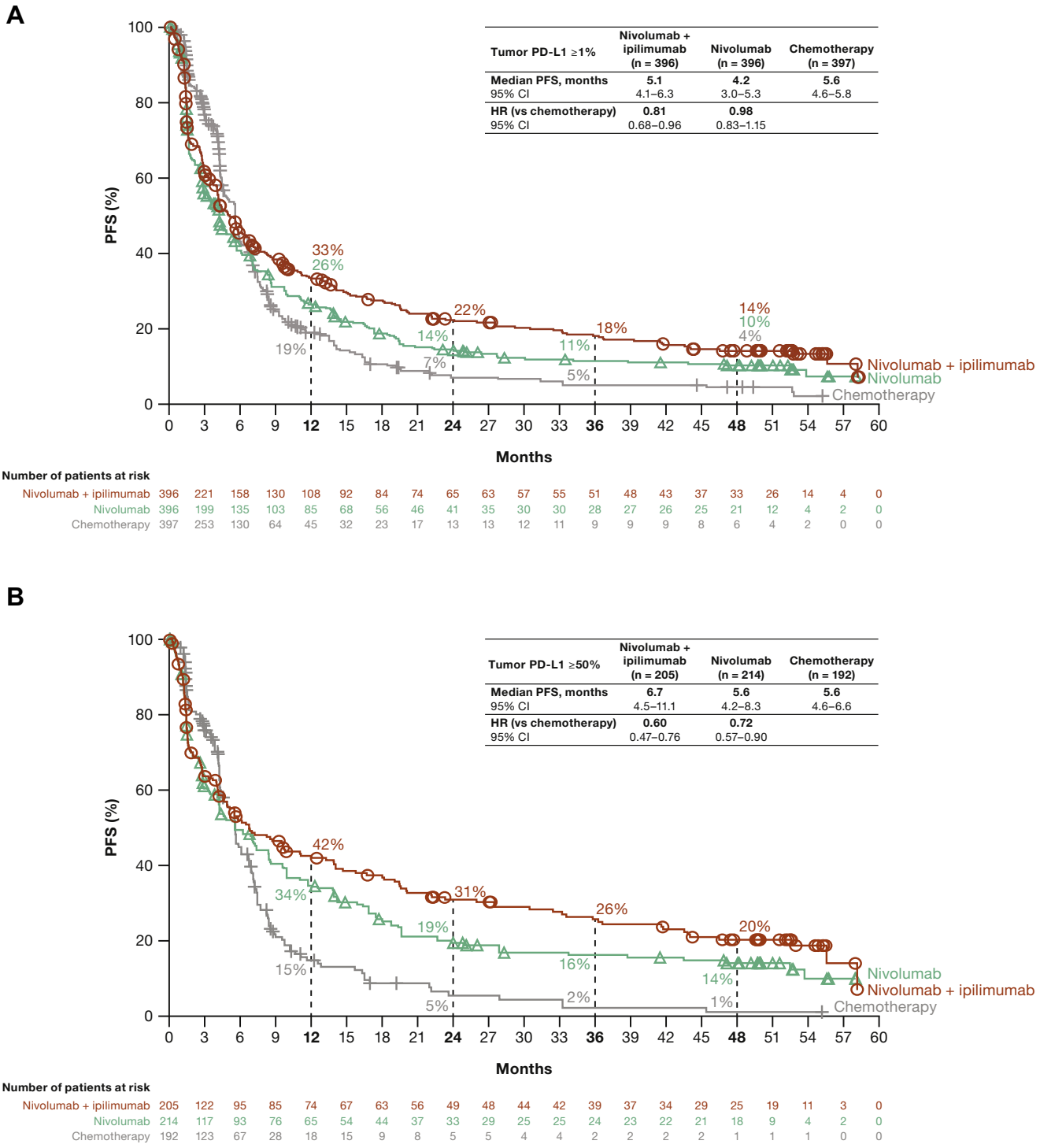
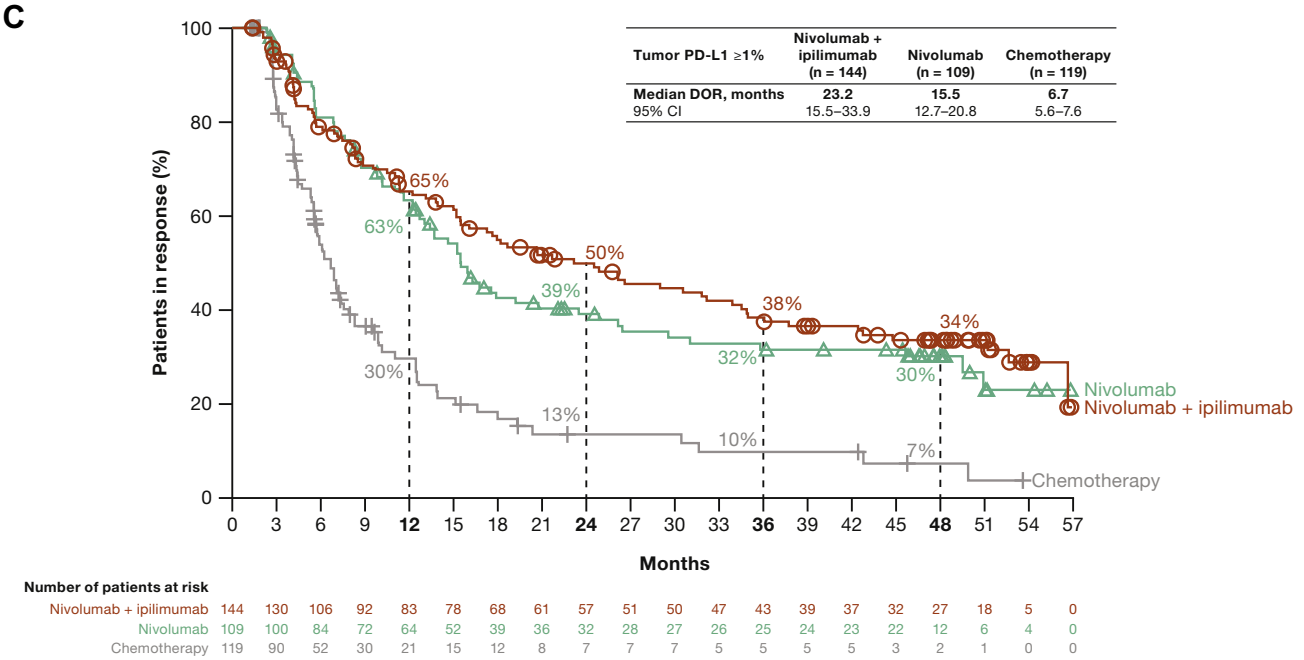


Figure 3. (*A*) PFS in patients with tumor PD-L1 expression greater than or equal to 1%, (*B*) PFS in patients with tumor PD-L1 expression greater than or equal to 50%, (*C*) DOR in patients with tumor PD-L1 expression greater than or equal to 1%, and (*D*) DOR in patients with tumor PD-L1 expression greater than or equal to 50% in patients treated with nivolumab plus ipilimumab, nivolumab, and tumor histology-based chemotherapy. Response was assessed according to the Response Evaluation Criteria in Solid Tumors, version 1.1, by blinded independent central review. CI, confidence interval; DOR, duration of response; HR, hazard ratio; ORR, overall response rate; PFS, progression-free survival.

diarrhea or colitis were treated with infliximab. Four patients with hepatitis were treated with mycophenolic mofetil. With nivolumab monotherapy, one patient with hepatitis was treated with one dose of infliximab (which is not recommended for inadequate hepatic function) and recovered, and one patient with hepatitis was treated with

C



Number of patients at risk

Nivolumab + ipilimumab	144	130	106	92	83	78	68	61	57	51	50	47	43	39	37	32	27	18	5	0
Nivolumab	109	100	84	72	64	52	39	36	32	28	27	26	25	24	23	22	12	6	4	0
Chemotherapy	119	90	52	30	21	15	12	8	7	7	7	5	5	5	5	3	2	1	0	0

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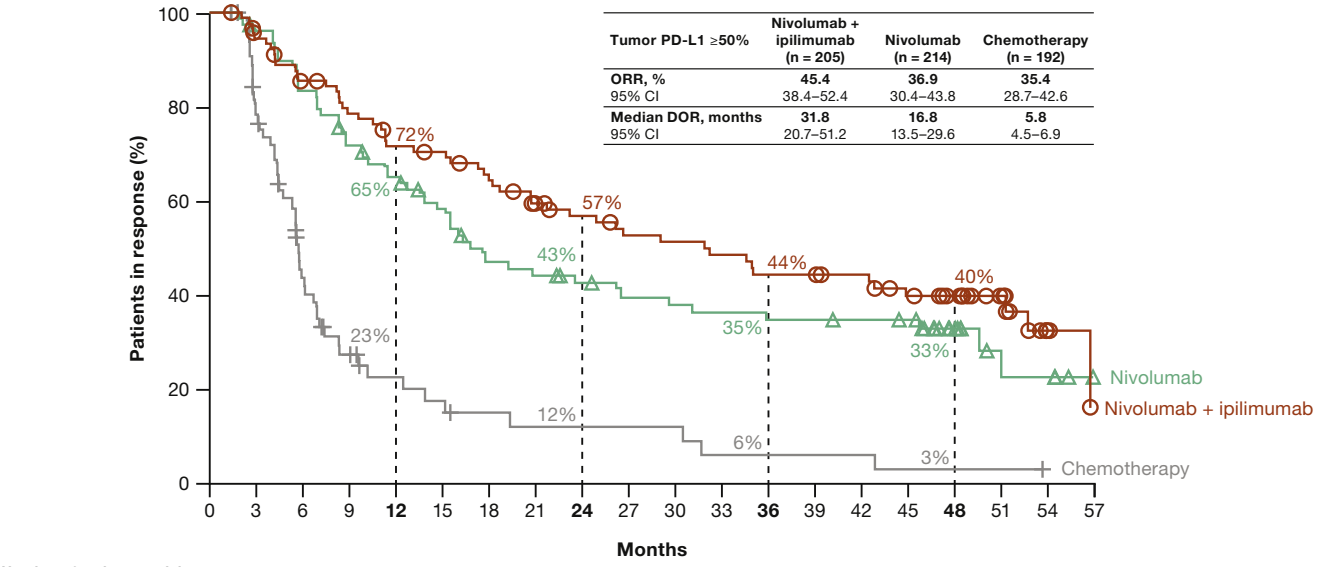

Number of patients at risk

Nivolumab + ipilimumab	93	85	75	68	61	59	53	46	42	38	37	35	32	32	30	25	21	14	3	0
Nivolumab	79	75	65	55	49	42	33	31	28	25	24	23	22	22	21	20	10	4	4	0
Chemotherapy	68	50	25	14	9	7	5	4	4	4	4	2	2	2	2	1	1	1	0	0

Figure 3. Continued.

mycophenolic mofetil; with nivolumab plus chemotherapy, one patient with hepatitis was treated with mycophenolic mofetil, and one patient with pneumonitis was treated with cyclosporin. Dose delays and treatment discontinuations due to immune-mediated AEs occurred in a limited proportion of patients (Supplementary Table 9).

Outcomes in Patients Who Discontinued Nivolumab Plus Ipilimumab Due to TRAEs

Among patients with tumor PD-L1 expression greater than or equal to 1%, 66 (16.9%) had TRAEs that led to discontinuation of both nivolumab and ipilimumab. Baseline characteristics of this subgroup were generally

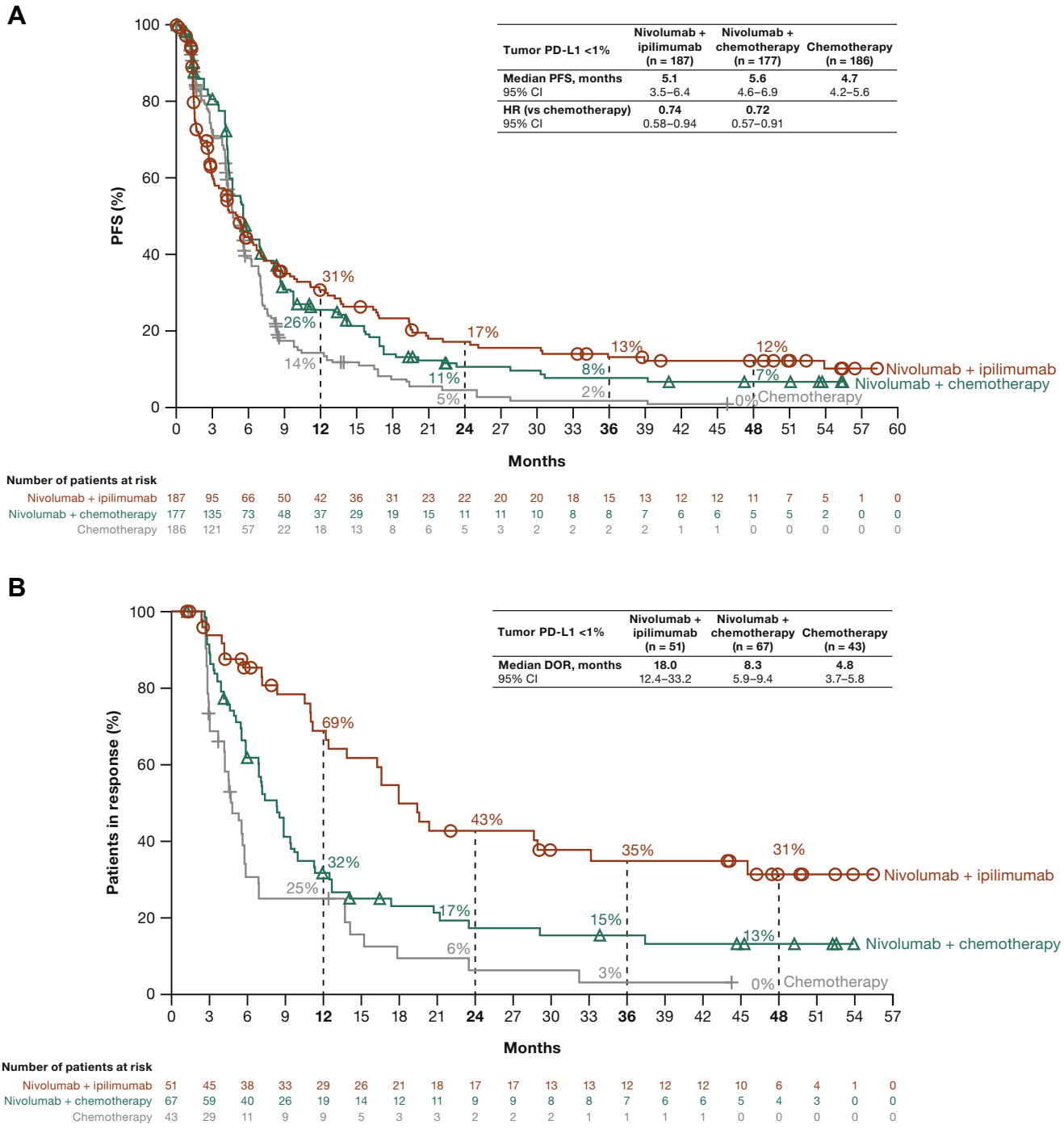

Figure 4. (*A*) PFS and (*B*) DOR with nivolumab plus ipilimumab, nivolumab plus chemotherapy, and tumor histology-based chemotherapy in patients with tumor PD-L1 expression less than 1%. Response was assessed according to the Response Evaluation Criteria in Solid Tumors, version 1.1, by blinded independent central review. CI, confidence interval; DOR, duration of response; HR, hazard ratio; PFS, progression-free survival.

consistent with the overall study population (Supplementary Table 10). These patients received a median (range) of 7.5 (1–49) doses of nivolumab and 3.0 (1–16) doses of ipilimumab; median (range) treatment duration was 3.2 (0.0–22.9) months. Patients who discontinued nivolumab plus ipilimumab due to TRAEs had a median OS of 30.6 months from randomization and 4-year OS rate of 44% (Fig. 6*A* and Supplementary Table 11); ORR was 53% (Supplementary Table 11); responders had a median DOR after treatment discontinuation of 52.6 months and 53% of responders maintained their responses for at least 3 years after discontinuation

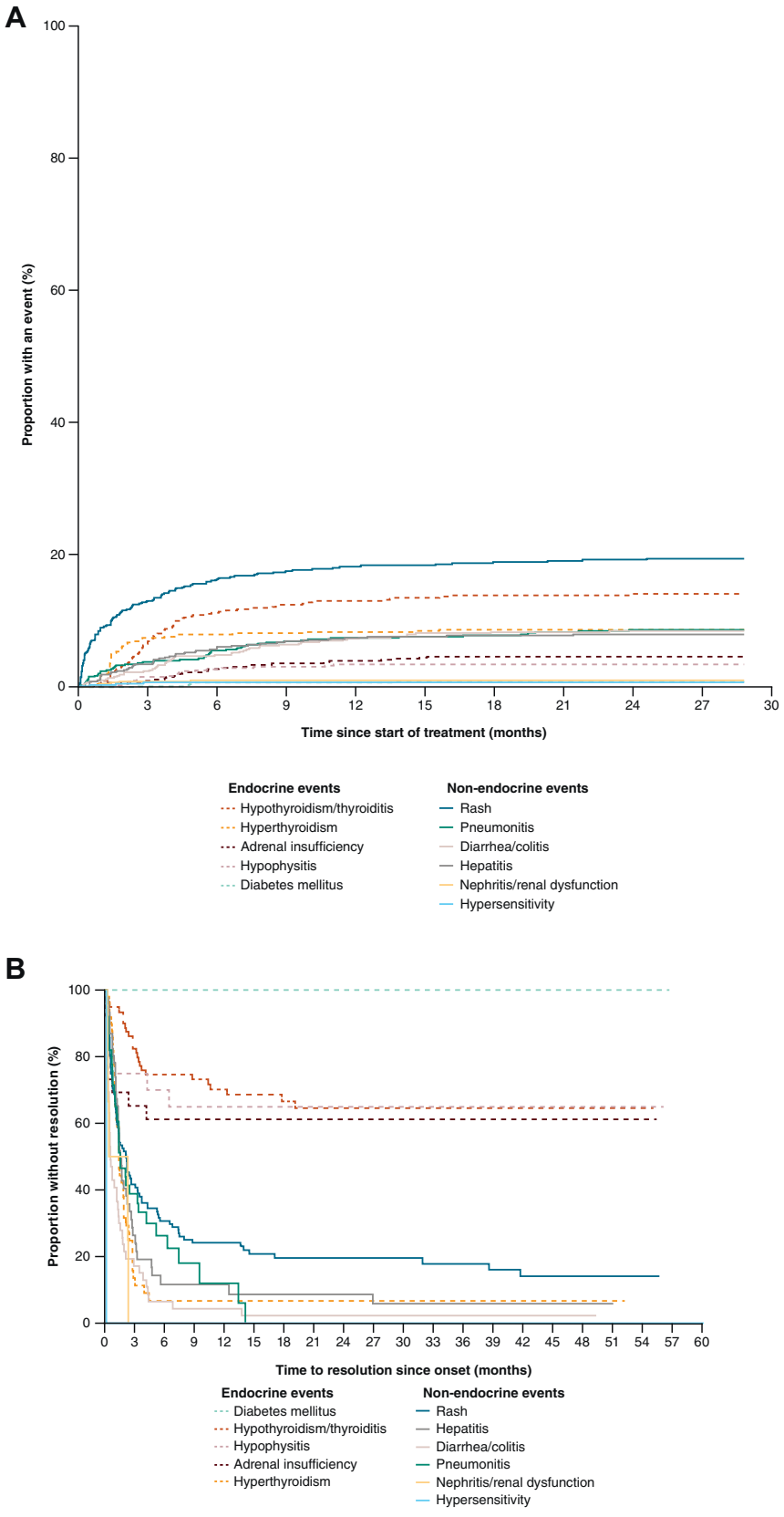

Figure 5. Time-to-onset (*A*) and time-to-resolution (*B*) of immune-mediated AEs in patients treated with nivolumab plus ipilimumab. Includes AEs considered as potential immune-mediated events by investigator occurring within 100 days of last dose of study drug regardless of causality and treated with immune-modulating medication, with the exception of endocrine events (adrenal insufficiency, hypophysitis, hypothyroidism or thyroiditis, hyperthyroidism, and diabetes mellitus), which were included in the analysis regardless of treatment since these events are often managed without immunosuppression. AE, adverse event.

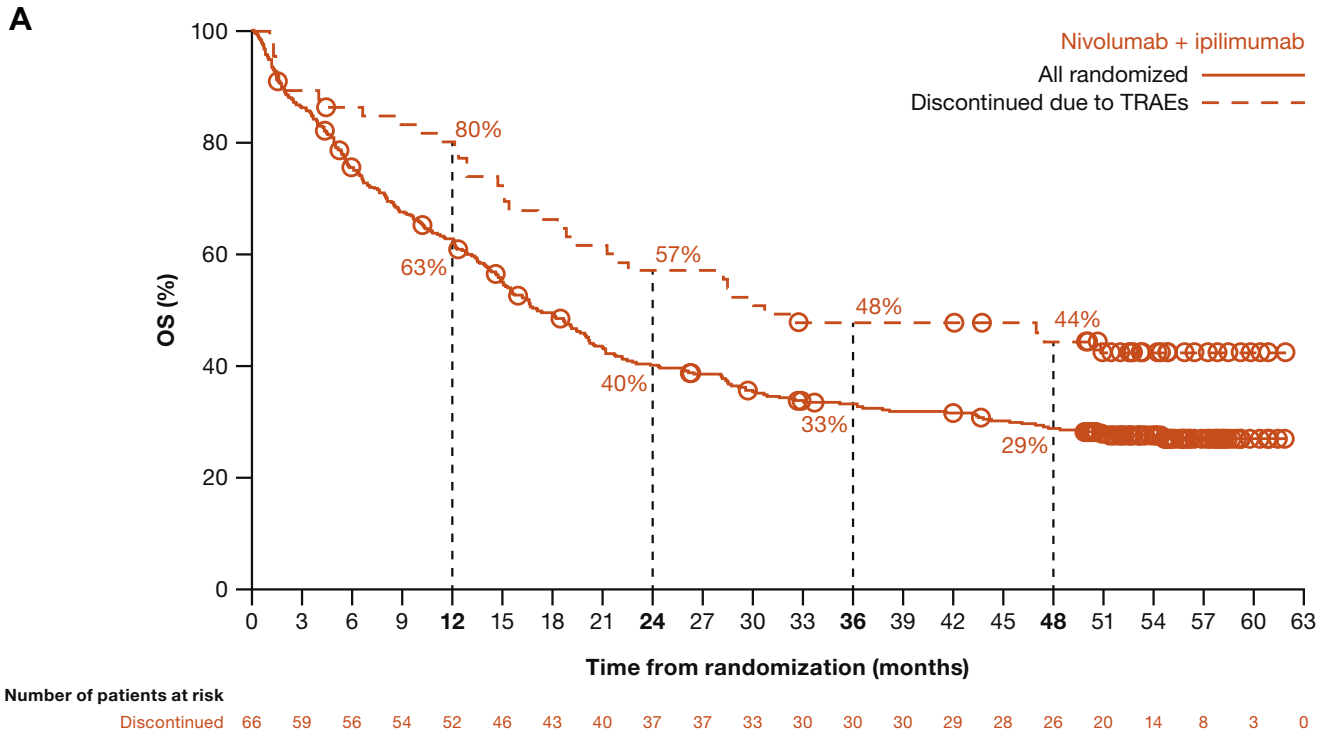

Figure 6. (*A*) OS[a] in patients with tumor PD-L1 expression greater than or equal to 1% who had a TRAE leading to discontinuation of all components of the study regimen and (*B*) treatment characteristics of individual patients with tumor PD-L1 expression greater than or equal to 1% who discontinued treatment due to TRAEs. Minimum follow-up for all randomized patients was 49.4 months. [a]Censored or ongoing response. CR, complete response; DBL, database lock; HR, hazard ratio; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease; TRAE, treatment-related adverse event; UTD, unable to determine.

(Supplementary Table 11). Patients remained free of treatment for median of 10.3 (95% CI: 5.5–21.2) months (Supplementary Table 11). In contrast, patients who discontinued chemotherapy due to TRAEs remained free of treatment for a median of 3.3 (95% CI: 2.3–4.3) months. One year after the last dose of study therapy, patients in the nivolumab plus ipilimumab arm had a 49.6% chance of being treatment free versus a 15.4% chance among patients in the chemotherapy arm. Subsequent systemic therapy was received by 25.8% of patients after discontinuation of nivolumab plus ipilimumab for TRAEs and subsequent immunotherapy by 12.1%. Among patients who discontinued chemotherapy for TRAEs, subsequent systemic therapy was received by 61.5%, subsequent immunotherapy by 42.3% (Supplementary Table 12). Treatment characteristics of individual patients who discontinued nivolumab plus ipilimumab due to TRAEs are shown (Fig. 6*B*). Similar outcomes in patients who discontinued nivolumab plus ipilimumab because of TRAEs were observed among the tumor PD-L1 expression greater than or equal to 1% and less than 1% combined patient population (Supplementary Fig. 9 and Supplementary Table 11).

Discussion

To our knowledge, these results from CheckMate 227 Part 1 represent the longest survival follow-up reported to date (minimum 49.4 months; median 54.8 months) among phase 3 studies evaluating first-line combination immunotherapy treatment for advanced NSCLC in both tumor PD-L1 greater than or equal to 1% and less than 1% patient populations.[5,7,8,31–36] In this planned exploratory long-term follow-up analysis (4 y minimum follow-up), nivolumab plus ipilimumab continued to demonstrate clinically meaningful and sustained efficacy improvements over chemotherapy in both patients with tumor PD-L1 expression greater than or equal to 1% (primary analysis population) and less than 1% (prespecified descriptive analysis population) and regardless of tumor histology; no new safety signals were identified.[6] The separation of nivolumab plus ipilimumab and chemotherapy OS curves increased over time, despite a relevant rate of subsequent immunotherapy treatment among patients alive at 4 years in the chemotherapy arm; notably, all patients have been off nivolumab plus ipilimumab study treatment for at least 2 years. Separations in the PFS and DOR curves were maintained with longer follow-up, further demonstrating the quality of

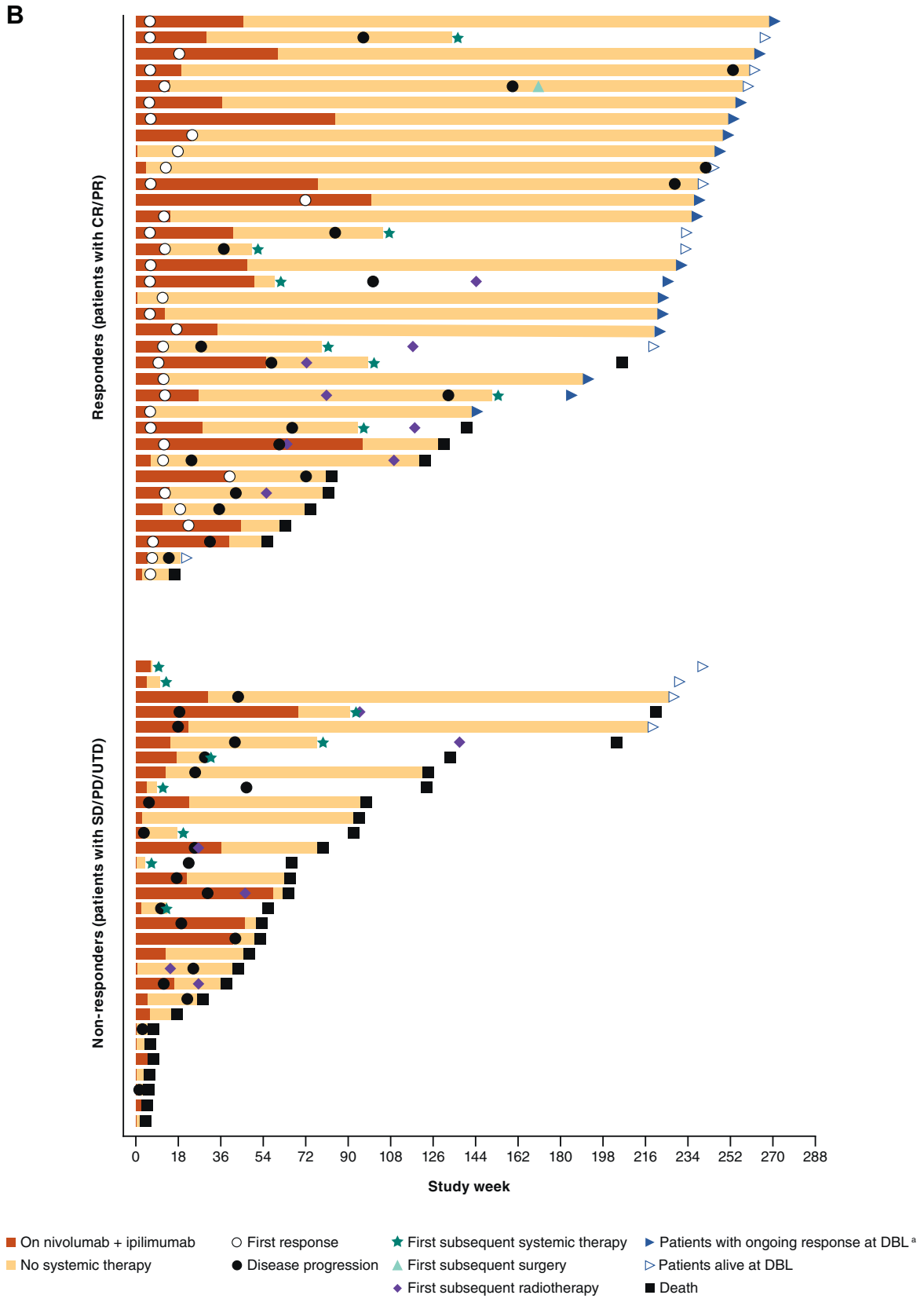

Figure 6. Continued.

responses and durable benefits of this dual immunotherapy regimen versus chemotherapy in the first-line setting. While continued follow-up is needed to better understand longer-term outcomes, the emerging plateau in the OS and PFS curves for patients treated with nivolumab plus ipilimumab (PD-L1 $\geq$1%) indicates the possibility of sustained long-term benefit in some patients, and elicits the hope for a potential cure in a subset of patients.

In recent years, the standard of care for first-line treatment of advanced NSCLC without targetable mutations has shifted from chemotherapy to immunotherapy-based regimens; in current clinical practice, immunotherapy selection with or without chemotherapy is generally based on tumor PD-L1 expression level. Among patients with tumors expressing PD-L1, those with expression greater than or equal to 50% are mostly treated with anti–PD-(L)1 monotherapy, whereas immunotherapy plus chemotherapy treatment is used in cases of high disease burden or tumor PD-L1 expression greater than or equal to 1%.[1–3,10] Immunotherapy plus chemotherapy is an approved regimen across tumor PD-L1 expression levels (PD-L1 $\geq$1% and PD-L1 <1%) for both nonsquamous and squamous tumor histologies.[2,3] Nivolumab plus ipilimumab has shown clinically meaningful efficacy improvements across tumor PD-L1 expression levels and tumor histologies; the 4-year outcomes reported here demonstrate the unprecedented durable benefit of dual immunotherapy in this setting, including in patients with typically higher unmet need for durable response (e.g., patients with squamous histology and those with tumor PD-L1 expression <1%). This durable efficacy with dual immunotherapy provided the clinical rationale for the randomized phase 3 CheckMate 9LA study, which evaluated the combination of nivolumab plus ipilimumab with two cycles of chemotherapy in advanced NSCLC.[37] This regimen could potentially provide rapid initial disease control while building on the reported durable survival benefits of dual immunotherapy.[37] In CheckMate 9LA, benefits with nivolumab plus ipilimumab combined with two cycles of chemotherapy versus chemotherapy alone were demonstrated regardless of tumor PD-L1 expression level or tumor histology; this combination has been approved in the United States, European Union, and several other countries.[27,38] With the recently reported 5-year OS results for single-agent pembrolizumab as first-line treatment in patients with advanced NSCLC and tumor PD-L1 expression greater than or equal to 50%,[39] continued follow-up from CheckMate 227 will be important to understand the potential long-term benefits of adding a CTLA-4 inhibitor to a PD-1 inhibitor. However, cross-trial comparisons are limited by various factors, including differences in patient populations and study designs, and should be interpreted with caution.

The design of CheckMate 227 provides the opportunity to compare different immunotherapy-based regimens within one study. While not powered to formally test the difference between nivolumab plus ipilimumab and nivolumab monotherapy in either patients with tumor PD-L1 expression greater than or equal to 1% (primary analysis population) or greater than or equal to 50% (prespecified descriptive analysis population), descriptive results showed improvement across all efficacy measures with nivolumab plus ipilimumab at 4 years. Despite the delayed separation of OS and PFS curves for patients with tumor PD-L1 expression greater than or equal to 1% and greater than or equal to 50%, nivolumab plus ipilimumab showed improved outcomes over nivolumab monotherapy starting from approximately 12 to 18 months, with the separations being sustained over time. These results were consistent with the long-term OS seen with minimum follow-up of 6.5 years in patients with untreated advanced melanoma, and highlight the contribution of memory T-cell induction by ipilimumab when combined with nivolumab.[40] Recent data from the phase 3 randomized KEYNOTE-598 study suggested no incremental clinical benefit from the addition of ipilimumab to pembrolizumab as a first-line therapy in patients with NSCLC and tumor PD-L1 expression greater than or equal to 50%, although, patient-reported outcomes in KEYNOTE-598 also showed no detriment with the addition of ipilimumab to pembrolizumab, despite a numerically higher rate of AEs.[41,42] Nevertheless, these data might not be mature yet with the short follow-up of a minimum of 12.4 months (with heavy censoring of the OS curves beyond that point) to sufficiently demonstrate the incremental long-term clinical benefit of CTLA-4 inhibitors when combined with a PD-1 inhibitor compared with PD-1 inhibitors only.[41]

In patients with tumor PD-L1 expression less than 1%, efficacy results with nivolumab plus chemotherapy were consistent with previously reported outcomes for immunotherapy plus chemotherapy according to tumor histology.[3,7] Patients with tumor PD-L1 expression less than 1% and those with squamous histology typically have a higher unmet need for durable response; in patients with tumor PD-L1 expression less than 1%, nivolumab plus ipilimumab demonstrated improved outcomes relative to nivolumab plus chemotherapy across tumor histologies, with benefit sustained at 4 years. With longer follow-up, the OS and PFS curves of nivolumab plus ipilimumab and nivolumab plus chemotherapy maintained separation, suggesting that dual immunotherapy is associated with more durable efficacy even when patients are off therapy

for at least 2 years. This is further supported by the marked difference in the durability of responses, with approximately one-third of all responses in the nivolumab plus ipilimumab arm still ongoing at 4 years relative to 13% in the nivolumab plus chemotherapy arm.

With longer follow-up, the safety profile of nivolumab plus ipilimumab was consistent with previous reports of this study.[6,19,20] In contrast to the similar incidence of TRAEs with nivolumab plus ipilimumab versus chemotherapy, the exposure-adjusted incidence rate of events (which accounts for the longer duration of nivolumab plus ipilimumab treatment versus chemotherapy) was numerically lower with dual immunotherapy versus chemotherapy. A modest increase in the frequency of all-cause immune-mediated AEs was reported with nivolumab plus ipilimumab treatment relative to nivolumab monotherapy or nivolumab plus chemotherapy; most events were low-grade and resolved (except endocrine events, which were not considered resolved if long-term hormone replacement therapy was needed). The onset and resolution kinetics of immune-mediated AEs were similar among all three nivolumab-based regimens; most importantly, very few patients required immune-modulating agents beyond systemic corticosteroids. Furthermore, a post hoc analysis suggests that discontinuation of nivolumab plus ipilimumab due to TRAEs did not have a negative impact on the long-term benefits in patients with tumor PD-L1 expression greater than or equal to 1% or in those with tumor PD-L1 expression greater than or equal to 1% and less than 1% combined. Approximately half of patients who discontinued nivolumab plus ipilimumab due to TRAEs were treatment free at least 1 year after treatment discontinuation, and nearly half of the responders remained in response for at least 3 years after treatment discontinuation. Additionally, patient-reported outcomes in KEYNOTE-598 showed no detriment with the addition of ipilimumab to PD-1 inhibition with pembrolizumab, despite a higher rate of toxicities.[41,42] These results, together with the previously reported patient-reported outcomes, which showed that patients treated with nivolumab plus ipilimumab tended to have improved symptom burden and health-related quality of life with delayed deterioration of symptoms versus chemotherapy, support a manageable safety and tolerability profile of this dual immunotherapy.[1–5,7,8,10]

In summary, with a minimum of 4 years of follow-up, the chemotherapy-free combination of nivolumab plus ipilimumab demonstrated durable long-term efficacy benefits over platinum-doublet chemotherapy in patients with advanced NSCLC and tumor PD-L1 expression greater than or equal to 1% or less than 1%, across nonsquamous and squamous histologies. The safety profile of nivolumab plus ipilimumab remained consistent with previous reports, and immune-mediated AEs were manageable with established algorithms. These results continue to support nivolumab plus ipilimumab as a first-line treatment option in patients with advanced NSCLC.

CRediT Authorship Contribution Statement

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

Suresh S. Ramalingam: Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing - review & editing, Supervision.

Tudor-Eliade Ciuleanu: Validation, Investigation, Resources, Data curation, Writing - review & editing.

Jong-Seok Lee: Validation, Investigation, Resources, Data curation, Writing - review & editing.

Laszlo Urban: Validation, Investigation, Resources, Data curation, Writing - review & editing.

Reyes Bernabe Caro: Validation, Investigation, Resources, Data curation, Writing - review & editing.

Keunchil Park: Validation, Investigation, Resources, Data curation, Writing - review & editing.

Hiroshi Sakai: Validation, Investigation, Resources, Data curation, Writing - review & editing.

Yuichiro Ohe: Validation, Investigation, Resources, Data curation, Writing - review & editing.

Makoto Nishio: Validation, Investigation, Resources, Data curation, Writing - review & editing.

Clarisse Audigier-Valette: Validation, Investigation, Resources, Data curation, Writing - review & editing.

Jacobus A. Burgers: Validation, Investigation, Resources, Data curation, Writing - review & editing.

Adam Pluzanski: Validation, Investigation, Resources, Data curation, Writing - review & editing.

Randeep Sangha: Validation, Investigation, Resources, Data curation, Writing - review & editing.

Carlos Gallardo: Validation, Investigation, Resources, Data curation, Writing - review & editing.

Masayuki Takeda: Validation, Investigation, Resources, Data curation, Writing - review & editing.

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Lorena Lupinacci: Validation, Investigation, Resources, Data curation, Writing - review & editing.

Ki Hyeong Lee: Validation, Investigation, Resources, Data curation, Writing - review & editing.

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Enric Carcereny: Validation, Investigation, Resources, Data curation, Writing - review & editing.

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Kynan Feeney: Validation, Investigation, Resources, Data curation, Writing - review & editing.

Sang-We Kim: Validation, Investigation, Resources, Data curation, Writing - review & editing.

Hossein Borghaei: Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing - review & editing, Supervision.

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Arteid Memaj: Software, Validation, Formal Analysis, Resources, Data curation, Writing - review & editing, Visualization.

Faith Ellen Nathan: Conceptualization, Methodology, Validation, Resources, Data curation, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition.

Judith Bushong: Validation, Resources, Data curation, Writing - review & 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.2021.09.010.

References

1. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med*. 2016;375:1823–1833.
2. Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378:2078–2092.
3. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med*. 2018;379:2040–2051.
4. Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet*. 2019;393:1819–1830.
5. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med*. 2018;378:2288–2301.
6. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *N Engl J Med*. 2019;381:2020–2031.
7. Gadgeel S, Rodriguez-Abreu D, Speranza G, et al. Updated analysis from KEYNOTE-189: pembrolizumab or placebo plus pemetrexed and platinum for previously untreated metastatic nonsquamous non-small-cell lung cancer. *J Clin Oncol*. 2020;38:1505–1517.
8. West H, McCleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019;20:924–937.
9. Spigel D, de Marinis F, Giaccone G, et al. IMPOWER110: Interim overall survival (OS) analysis of a phase III study of atezolizumab (atezo) vs platinum-based chemotherapy (chemo) as first-line (1L) treatment (TX) in PD-L1-selected NSCLC. Presented at: the European Society for Medical Oncology (ESMO) Congress. September 27-October 1, 2019; Barcelona, Spain. Abstract 6256.

10. Herbst RS, Giaccone G, de Marinis F, et al. Atezolizumab for first-line treatment of PD-L1-selected patients with NSCLC. *N Engl J Med*. 2020;383:1328–1339.
11. Das R, Verma R, Sznol M, et al. Combination therapy with anti-CTLA-4 and anti-PD-1 leads to distinct immunologic changes in vivo. *J Immunol*. 2015;194:950–959.
12. Wei SC, Duffy CR, Allison JP. Fundamental mechanisms of immune checkpoint blockade therapy. *Cancer Discov*. 2018;8:1069–1086.
13. Sharma P, Allison JP. Dissecting the mechanisms of immune checkpoint therapy. *Nat Rev Immunol*. 2020;20:75–76.
14. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med*. 2019;381:1535–1546.
15. Motzer RJ, Escudier B, McDermott DF, et al. Survival outcomes and independent response assessment with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma: 42-month follow-up of a randomized phase 3 clinical trial. *J Immunother Cancer*. 2020;8:e000891.
16. Motzer RJ, Rini BI, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2019;20:1370–1385.
17. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med*. 2018;378:1277–1290.
18. Baas P, Scherpereel A, Nowak AK, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. *Lancet*. 2021;397:375–386.
19. Ramalingam SS, Ciuleanu TE, Pluzanski A, et al. Nivolumab + ipilimumab versus platinum-doublet chemotherapy as first-line treatment for advanced non-small cell lung cancer: Three-year update from CheckMate 227 Part 1. Presented at: the American Society of Clinical Oncology (ASCO) Meeting. May 29–31, 2020; Virtual. Abstract 9500.
20. Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N Engl J Med*. 2018;378:2093–2104.
21. Hellmann MD, Rizvi NA, Goldman JW, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. *Lancet Oncol*. 2017;18:31–41.
22. Ready N, Hellmann MD, Awad MM, et al. First-line nivolumab plus ipilimumab in advanced non-small-cell lung cancer (CheckMate 568): outcomes by programmed death ligand 1 and tumor mutational burden as biomarkers. *J Clin Oncol*. 2019;37:992–1000.
23. Reck M, Ciuleanu TE, Lee JS, et al. First-line nivolumab plus ipilimumab versus chemotherapy in advanced NSCLC with 1% or greater tumor PD-L1 expression: patient-reported outcomes from CheckMate 227 Part 1. *J Thorac Oncol*. 2021;16:665–676.
24. Ono Pharmaceutical Co. Ltd. Combination therapy concerning Opdivo and Yervoy approved in Japan for first-line treatment of unresectable advanced or recurrent non-small cell lung cancer. https://www.ono-pharma.com/sites/default/files/en/news/press/sm_cn201127_1.pdf. Accessed August 11, 2021.
25. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology: (NCCN Guidelines®) for Non-Small Cell Lung Cancer. Version 5.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed August 6, 2021. See the NCCN Guidelines® for detailed recommendations including preferred treatment options. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
26. Bristol Myers Squibb Argentina S.R.L. OPDIVO® (nivolumab) prescribing information. https://www.bms.com/assets/bms/argentina/documents/medicine-prospecto/Opdivo%20-%20Disp%206551-17%20-%20Prescribing%20Information%20AR%20Feb17.pdf. Accessed August 11, 2021.
27. Bristol Myers Squibb. Opdivo® (nivolumab) prescribing information. https://packageinserts.bms.com/pi/pi_opdivo.pdf. Accessed August 30, 2021.
28. Planchard D, Popat S, Kerr K, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29:iv192–iv237.
29. Planchard D, Popat S, Kerr K, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. https://www.esmo.org/guidelines/lungandchesttumours/clinical-practice-livingguidelinesmetastatic-nonsmallcelllungcancer. Accessed April 23, 2021.
30. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5:649–655.
31. Rizvi NA, Cho BC, Reinmuth N, et al. Durvalumab with or without tremelimumab vs standard chemotherapy in first-line treatment of metastatic non-small cell lung cancer: the MYSTIC Phase 3 randomized clinical trial. *JAMA Oncol*. 2020;6:661–674.
32. Robinson A, Vicente D, Tafreshi A, et al. 97O First-line pembrolizumab plus chemotherapy for patients with advanced squamous NSCLC: 3-year follow-up from KEYNOTE-407. *J Thorac Oncol*. 2021;16:S748–S749.
33. Jotte R, Cappuzzo F, Vynnychenko I, et al. Atezolizumab in combination with carboplatin and Nab-paclitaxel in advanced squamous NSCLC (IMpower131): results from a randomized phase III trial. *J Thorac Oncol*. 2020;15:1351–1360.
34. Nishio M, Barlesi F, West H, et al. Atezolizumab plus chemotherapy for first-line treatment of nonsquamous NSCLC: results from the randomized Phase 3 IMpower132 trial. *J Thorac Oncol*. 2021;16:653–664.
35. Reck M, Mok TSK, Nishio M, et al. Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a

randomised, open-label phase 3 trial. *Lancet Respir Med*. 2019;7:387–401.
36. Rodríguez-Abreu D, Powell S, Hochmair M, et al. Pemetrexed plus platinum with or without pembrolizumab in patients with previously untreated metastatic non-squamous NSCLC: protocol-specified final analysis from KEYNOTE-189. *Ann Oncol*. 2021;32:881–895.
37. Paz-Ares L, Ciuleanu TE, Cobo M, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22:198–211.
38. ecancer. EU approves first-line treatment option for advanced non-small cell lung cancer. https://ecancer.org/en/news/19041-eu-approves-first-line-treatment-option-for-advanced-non-small-cell-lung-cancer. Accessed August 11, 2021.
39. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Five-year outcomes with pembrolizumab versus chemotherapy for metastatic non-small-cell lung cancer with PD-L1 tumor proportion score $\geq$ 50%. *J Clin Oncol*. 2021;39:2339–2349.
40. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. CheckMate 067: 6.5-year outcomes in patients (pts) with advanced melanoma. *J Clin Oncol*. 2021;39:9506.
41. Boyer M, Sendur MAN, Rodriguez-Abreu D, et al. Pembrolizumab plus ipilimumab or placebo for metastatic non-small-cell lung cancer with PD-L1 tumor proportion score $\geq$ 50%: randomized, double-blind Phase III KEYNOTE-598 study. *J Clin Oncol*. 2021;39:2327–2338.
42. Sendur MN, Reck M, Rodriguez-Abreu D, et al. Health-related quality of life for pembrolizumab (pembro) plus ipilimumab (ipi) versus pembro plus placebo in patients with metastatic NSCLC with PD-L1 tumor proportion score $\geq$ 50%: KEYNOTE-598. *J Clin Oncol*. 2021;39:9038.