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ORIGINAL RESEARCH

# First-line nivolumab plus ipilimumab with two cycles of chemotherapy versus chemotherapy alone (four cycles) in advanced non-small-cell lung cancer: CheckMate 9LA 2-year update

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**Background:** To further characterize survival benefit with first-line nivolumab plus ipilimumab with two cycles of chemotherapy versus chemotherapy alone, we report updated data from the phase III CheckMate 9LA trial with a 2-year minimum follow-up.

**Patients and methods:** Adult patients were treatment naïve, with stage IV/recurrent non-small-cell lung cancer, no known sensitizing *EGFR/ALK* alterations, and an Eastern Cooperative Oncology Group performance status  $\leq 1$ . Patients were randomized 1 : 1 to nivolumab 360 mg every 3 weeks plus ipilimumab 1 mg/kg every 6 weeks with two cycles of chemotherapy, or four cycles of chemotherapy. Updated efficacy and safety outcomes are reported, along with progression-free survival (PFS) after next line of treatment (PFS2), treatment-related adverse events (TRAEs) by treatment cycle, and efficacy outcomes in patients who discontinued all treatment components in the experimental arm due to TRAEs.

**Results:** With a median follow-up of 30.7 months, nivolumab plus ipilimumab with chemotherapy continued to prolong overall survival (OS) versus chemotherapy. Median OS was 15.8 versus 11.0 months [hazard ratio 0.72 (95% confidence interval 0.61-0.86)]; 2-year OS rate was 38% versus 26%. Two-year PFS rate was 20% versus 8%. ORR was 38% versus 25%, respectively; 34% versus 12% of all responses were ongoing at 2 years. Median PFS2 was 13.9 versus 8.7 months. Improved efficacy outcomes in the experimental versus control arm were observed across most subgroups, including by programmed death-ligand 1 and histology. No new safety signals were observed; onset of grade 3/4 TRAEs was mostly observed during the first two treatment cycles in the experimental arm. In patients who discontinued all components of nivolumab plus ipilimumab with chemotherapy treatment due to TRAEs ( $n = 61$ ) median OS was 27.5 months; 56% of responders had an ongoing response  $\geq 1$  year after discontinuation.

**Conclusions:** With a 2-year minimum follow-up, nivolumab plus ipilimumab with two cycles of chemotherapy provided durable efficacy benefits over chemotherapy with a manageable safety profile and remains an efficacious first-line treatment of advanced non-small-cell lung cancer.

**Key words:** nivolumab, ipilimumab, NSCLC, first-line, dual immunotherapy

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## INTRODUCTION

In recent years, immunotherapies that target the programmed death-ligand 1 (PD-L1)/programmed cell death protein 1 (PD-1) pathway have shown significant survival improvement versus chemotherapy and transformed the first-line treatment landscape for patients with advanced non-small-cell lung cancer (NSCLC) with no targetable driver alterations.<sup>1-10</sup>

Nivolumab, a fully human anti-PD-1 antibody, and ipilimumab, a fully human anti-cytotoxic T-lymphocyte antigen-4 antibody, are immune checkpoint inhibitors with distinct but complementary mechanisms of action.<sup>11-13</sup> Ipilimumab induces *de novo* antitumor T-cell responses, including an increase in memory T cells, whereas nivolumab restores the function of existing antitumor T cells.<sup>11-13</sup> The combination of nivolumab and ipilimumab in the first-line setting has improved long-term overall survival (OS) in multiple advanced cancers, including melanoma, renal cell carcinoma, mesothelioma, and NSCLC.<sup>1,14-18</sup> Guidelines from both the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) recommend nivolumab plus ipilimumab as a first-line treatment option for patients with advanced NSCLC with tumor PD-L1 expression either  $\geq 1\%$  or  $< 1\%$ , regardless of histology.<sup>19-21</sup>

CheckMate 9LA (NCT03215706) is a randomized phase III study evaluating nivolumab plus ipilimumab combined with a limited course of chemotherapy (two cycles) versus chemotherapy alone (four cycles) as a first-line treatment of patients with advanced NSCLC. The clinical rationale was that adding a limited course of chemotherapy to nivolumab plus ipilimumab would provide rapid initial disease control, potentially building on the durable response and survival observed with this dual immunotherapy,<sup>1,16,17</sup> while minimizing the side-effects associated with a full course of chemotherapy. The study met its primary and secondary endpoints at the pre-planned interim analysis (minimum follow-up 8.1 months), showing statistically significant improvements in OS, progression-free survival (PFS), and objective response rate (ORR), as well as a manageable safety profile with nivolumab plus ipilimumab with chemotherapy versus chemotherapy alone.<sup>8</sup> Clinical benefit was maintained with an additional 4.6-month follow-up and was also shown across tumor PD-L1 expression levels and histologies. Early and continued separation of the survival curves between the experimental and control arms, along with lower rates of progressive disease as best overall response in the experimental arm, confirmed the clinical rationale of the study. Subsequently, regulatory approvals of this combination treatment were granted in the European Union, USA, Australia, Japan, and several other countries for first-line treatment of patients with metastatic/recurrent NSCLC with no epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations.<sup>22,23</sup> Nivolumab plus ipilimumab combined with a limited course of chemotherapy (two cycles) is

also recommended by the ESMO guidelines and NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines<sup>®</sup>) as first-line treatment of advanced NSCLC regardless of PD-L1 expression or histology.<sup>19-21</sup>

To address key questions around the continued benefit of treatment with nivolumab plus ipilimumab with two cycles of chemotherapy in CheckMate 9LA, we characterize clinical outcomes with this regimen with a minimum follow-up of 2 years, report PFS after next line of treatment (PFS2), and describe *post hoc* analyses of the onset of treatment-related adverse events (TRAEs) by treatment cycle, and in the experimental arm, outcomes in patients who discontinued all components of treatment due to TRAEs.

## PATIENTS AND METHODS

The methodology for the study has been described previously<sup>8</sup> and is summarized below, with additional detail provided in the [Supplementary Methods](https://doi.org/10.1016/j.esmooop.2021.100273), available at <https://doi.org/10.1016/j.esmooop.2021.100273>.

### Patients

Patients were aged  $\geq 18$  years with histologically confirmed squamous or non-squamous stage IV or recurrent NSCLC, an Eastern Cooperative Oncology Group performance status of 0-1, and no previous systemic anticancer therapy as primary treatment of advanced/metastatic disease. Key exclusion criteria included known *EGFR* mutations or *ALK* translocations sensitive to targeted therapy and unknown or undetermined *EGFR* status in patients with non-squamous histology. All patients were required to have tumor tissue available to assess PD-L1 expression levels before treatment.

### Study design

CheckMate 9LA was an international, randomized, open-label phase III study. Patients were stratified by tumor histology (squamous versus non-squamous), sex (male versus female), and PD-L1 expression ( $< 1\%$  versus  $\geq 1\%$ ); patients who could not be assessed for tumor PD-L1 expression (maximum of 10% of all randomized patients) were stratified with the PD-L1 expression  $< 1\%$  population; however, these patients were only included in analyses of all randomized patients and were excluded from PD-L1 expression  $< 1\%$  subgroup analyses. Patients were randomized 1 : 1 to nivolumab (360 mg every 3 weeks) plus ipilimumab (1 mg/kg every 6 weeks) combined with histology-based platinum-doublet chemotherapy (every 3 weeks for two cycles) or chemotherapy alone (every 3 weeks for four cycles) ([Supplementary Figure S1](https://doi.org/10.1016/j.esmooop.2021.100273), available at <https://doi.org/10.1016/j.esmooop.2021.100273>). Histology-based chemotherapy regimens used in both treatment arms are summarized in the [Supplementary Methods](https://doi.org/10.1016/j.esmooop.2021.100273), available at <https://doi.org/10.1016/j.esmooop.2021.100273>.

Treatment continued until disease progression (unless prespecified criteria were met for treatment beyond

progression in the experimental arm; see [Supplementary Methods](https://doi.org/10.1016/j.esmoop.2021.100273), available at <https://doi.org/10.1016/j.esmoop.2021.100273>), unacceptable toxicity, or for 2 years for immunotherapy. In the control arm only, patients with non-squamous histology could receive optional pemetrexed maintenance therapy (500 mg/m<sup>2</sup>) until disease progression or unacceptable toxicity. Pemetrexed maintenance was not allowed in the experimental arm. Crossover between treatment groups was not permitted per protocol; however, at physician discretion, patients could receive subsequent immunotherapy upon discontinuation of study treatment in either group.

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

### Endpoints and assessments

The primary endpoint of OS and hierarchical secondary endpoints of PFS and ORR, as well as efficacy by PD-L1 expression levels and histology, have been reported previously.<sup>8</sup> At 2-year minimum follow-up, exploratory analyses included updated efficacy and safety outcomes. PFS2 was a pre-specified exploratory endpoint and was defined as time from randomization to objectively documented progression after the next line of therapy, per investigator assessment, or to death from any cause, whichever occurred first. Patients who were alive and without progression after the next line of therapy were censored at the last known alive date. Immune-mediated adverse events (IMAEs) were defined as specific events (or groups of preferred terms describing specific events) that included pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, endocrine (adrenal insufficiency, hypothyroidism/thyroiditis, hypothyroidism, thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis), and other specific events, considered as potential immune-mediated events by the investigator, regardless of causality, that occurred within 100 days of the last dose, with no clear alternate etiology based on investigator assessment, or with an immune-mediated component, that were treated with immune-modulating medication. Endocrine adverse events were considered IMAEs regardless of immune-modulating medication use, since endocrine drug reactions are often managed without immune-modulating medication. *Post hoc* analyses included assessment of onset of grade 1/2 or grade 3/4 TRAEs (reported between first dose and 30 days after last dose of study treatment) by treatment cycle in each arm, assessment of efficacy in patients who discontinued all components of treatment due to TRAEs [OS (from randomization), ORR, PFS, and duration of response (DOR) from time of treatment discontinuation], and assessment of treatment-free interval (time from last dose of study treatment to start of

subsequent systemic treatment or death) in the experimental arm. Further details on endpoints and assessments can be found in the [Supplementary Methods](https://doi.org/10.1016/j.esmoop.2021.100273), available at <https://doi.org/10.1016/j.esmoop.2021.100273>.

### Statistical analyses

Efficacy was assessed in all randomized patients. Survival curves and rates were estimated using Kaplan–Meier methodology. Hazard ratios (HRs) and confidence intervals (CIs) were estimated using a stratified Cox proportional hazard model with treatment arm as a single covariate. Estimates of response rate and exact two-sided 95% CIs were summarized using the Clopper–Pearson method. Estimates of difference in response rates between treatment groups and corresponding two-sided 95% CIs were computed using the Cochran–Mantel–Haenszel method. Efficacy analyses of OS, PFS, ORR, and DOR, and subgroup analyses for each, were descriptive and summarized using 95% CIs. Safety was assessed in all patients who received  $\geq 1$  dose of study drug.

## RESULTS

### Patient disposition and treatment summary

As previously reported,<sup>8</sup> 361 patients were randomized to the nivolumab plus ipilimumab with chemotherapy arm and 358 patients to the chemotherapy arm; 358 (99%) and 349 (97%) patients received  $\geq 1$  dose of treatment, respectively. Baseline characteristics were generally well balanced between treatment arms ([Supplementary Table S1](https://doi.org/10.1016/j.esmoop.2021.100273), available at <https://doi.org/10.1016/j.esmoop.2021.100273>).

At the database lock (DBL; 18 February 2021), minimum follow-up for OS was 24.4 months (median, 30.7 months). Minimum follow-up for all other analyses was 23.3 months. In the experimental arm, consistent with the duration of therapy per protocol, no patients remained on study treatment. The majority (93%) of patients received two cycles of chemotherapy and 13% completed the maximum 2 years of immunotherapy treatment ([Supplementary Figure S2](https://doi.org/10.1016/j.esmoop.2021.100273), available at <https://doi.org/10.1016/j.esmoop.2021.100273>). The median (range) number of doses was 9.0 (1-36) for nivolumab and 4.0 (1-18) for ipilimumab. In the control arm, 75% of patients received four cycles of chemotherapy with 159 of 238 (67%) patients with non-squamous tumor histology receiving pemetrexed maintenance. At the DBL, 11 of 349 (3%) treated patients were still receiving pemetrexed maintenance therapy and those patients had non-squamous tumor histology. Of note, a total of 100 (29%) patients in the control arm had completed the full four cycles of chemotherapy without optional pemetrexed maintenance therapy ([Supplementary Table S2](https://doi.org/10.1016/j.esmoop.2021.100273), available at <https://doi.org/10.1016/j.esmoop.2021.100273>). Median (range) duration of therapy was 6.1 (0-24.4) months in the experimental arm and 2.5 (0-34.5) months in the control arm.

Among patients with a PFS event in the experimental ( $n = 307$ ) and control arms ( $n = 334$ ), 122 (40%) and 158 (47%), respectively, received any subsequent systemic therapy. In the experimental arm, chemotherapy was the most common subsequent systemic therapy, received by 114 (37%) patients, and 66 (22%) patients received platinum-doublet chemotherapy. Immunotherapy was the most common subsequent systemic therapy in the control arm, received by 125 (37%) patients (Supplementary Table S3, available at <https://doi.org/10.1016/j.esmoop.2021.100273>). Subsequent treatment in all randomized patients and in patients who survived  $\geq 2$  years is also reported (Supplementary Table S3, available at <https://doi.org/10.1016/j.esmoop.2021.100273>).

In the experimental arm, among the 114 patients who received subsequent chemotherapy, 34 (30%) patients received the same subsequent platinum-doublet chemotherapy as they did during the study treatment and 56 (49%) had received at least one of the same chemotherapies as subsequent treatment.

### Efficacy

**OS, PFS, and tumor responses.** Nivolumab plus ipilimumab with chemotherapy continued to show OS improvement versus chemotherapy alone with a minimum follow-up of 24.4 months. Median OS was 15.8 months (95% CI 13.9–19.7 months) in the experimental arm versus 11.0 months (95% CI 9.5–12.7 months) in the control arm (HR 0.72; 95% CI 0.61–0.86; Figure 1A); 2-year OS rates were 38% versus 26%. Consistent with results from the previous DBL,<sup>8</sup> OS improvement was observed across most key subgroups (Figure 2), including by PD-L1 expression levels ( $<1\%$ ,  $\geq 1\%$ , 1%–49%, and  $\geq 50\%$ ) and by histology (Supplementary Figure S3, available at <https://doi.org/10.1016/j.esmoop.2021.100273>). Notably, patients with pretreated central nervous system (CNS) metastases at baseline had a median OS of 19.9 versus 7.9 months in the experimental versus control arm, respectively [HR 0.47 (95% CI 0.31–0.71); Figure 2].

PFS continued to be prolonged in the experimental versus control arm, with an HR of 0.67 (95% CI 0.56–0.79) and 2-year PFS rates of 20% versus 8%, respectively (Supplementary Figure S4A, available at <https://doi.org/10.1016/j.esmoop.2021.100273>). ORR was 38.0% versus 25.4% (complete response rate was 3.3% versus 1.1%; Supplementary Table S4, available at <https://doi.org/10.1016/j.esmoop.2021.100273>), respectively. Of note, four patients who had partial responses in the experimental arm at the previous DBL improved to complete responses at this 2-year follow-up. Median DOR was improved from the previous DBL for the experimental arm and remained longer versus the control arm (13.0 versus 5.6 months); 34% versus 12% of responses were ongoing at 2 years (Supplementary Figure S4B, available at <https://doi.org/10.1016/j.esmoop.2021.100273>). PFS, ORR, and DOR

remained higher in the experimental versus control arm in patients with non-squamous and squamous tumor histologies (Supplementary Figures S5 and S6, and Supplementary Table S5, available at <https://doi.org/10.1016/j.esmoop.2021.100273>).

In patients with PD-L1 expression  $<1\%$ , efficacy results were consistent with all randomized patients. Median OS was 17.7 versus 9.8 months in the experimental versus control arm, respectively (HR 0.67; 95% CI 0.51–0.88); 2-year OS rates were 37% versus 22% (Figure 1B); 20% versus 5% were progression free (Supplementary Figure S5C, available at <https://doi.org/10.1016/j.esmoop.2021.100273>). ORR was 31% in the experimental arm and 20% in the control arm (Supplementary Table S6, available at <https://doi.org/10.1016/j.esmoop.2021.100273>); median DOR was 17.5 versus 4.3 months, with 45% versus 0% of responses ongoing at 2 years (Supplementary Figure S6C, available at <https://doi.org/10.1016/j.esmoop.2021.100273>). Efficacy improvements in the experimental versus control arm in patients with PD-L1 expression  $<1\%$  were observed across non-squamous and squamous histologies; OS HRs were 0.75 (95% CI 0.54–1.04) and 0.48 (95% CI 0.28–0.81), respectively (Supplementary Figure S7A and C, available at <https://doi.org/10.1016/j.esmoop.2021.100273>). PFS and DOR were also improved with the experimental treatment versus control for both histologies (Supplementary Figures S8 and S9, available at <https://doi.org/10.1016/j.esmoop.2021.100273>).

In patients with PD-L1 expression  $\geq 1\%$ , efficacy results were consistent with those with PD-L1 expression  $<1\%$  and with all randomized patients. OS, PFS, ORR, and DOR were improved in the experimental versus control arm. Median OS was 15.8 versus 10.9 months, respectively (HR 0.70; 95% CI 0.56–0.89); 2-year OS rates were 41% versus 28% (Figure 1C), and 20% versus 9% were progression free (Supplementary Figure S5D, available at <https://doi.org/10.1016/j.esmoop.2021.100273>). ORR was 43% in the experimental arm and 28% in the control arm (Supplementary Table S6, available at <https://doi.org/10.1016/j.esmoop.2021.100273>); median DOR was 11.8 versus 5.6 months and 33% versus 13% of responses were ongoing (Supplementary Figure S6D, available at <https://doi.org/10.1016/j.esmoop.2021.100273>). Efficacy improvements in the experimental versus control arm in patients with PD-L1 expression  $\geq 1\%$  were observed across non-squamous and squamous histologies; OS HRs were 0.71 (95% CI 0.53–0.95) and 0.70 (95% CI 0.48–1.01), respectively (Supplementary Figure S7B and D, available at <https://doi.org/10.1016/j.esmoop.2021.100273>). PFS and DOR also improved in the experimental versus control arm in patients with PD-L1 expression  $\geq 1\%$  across histology subgroups (Supplementary Figures S8 and S9, available at <https://doi.org/10.1016/j.esmoop.2021.100273>).

Results in patients with PD-L1 expression  $\geq 50\%$  also favored the experimental arm over the control arm. Median OS was 18.9 versus 12.9 months, respectively (HR

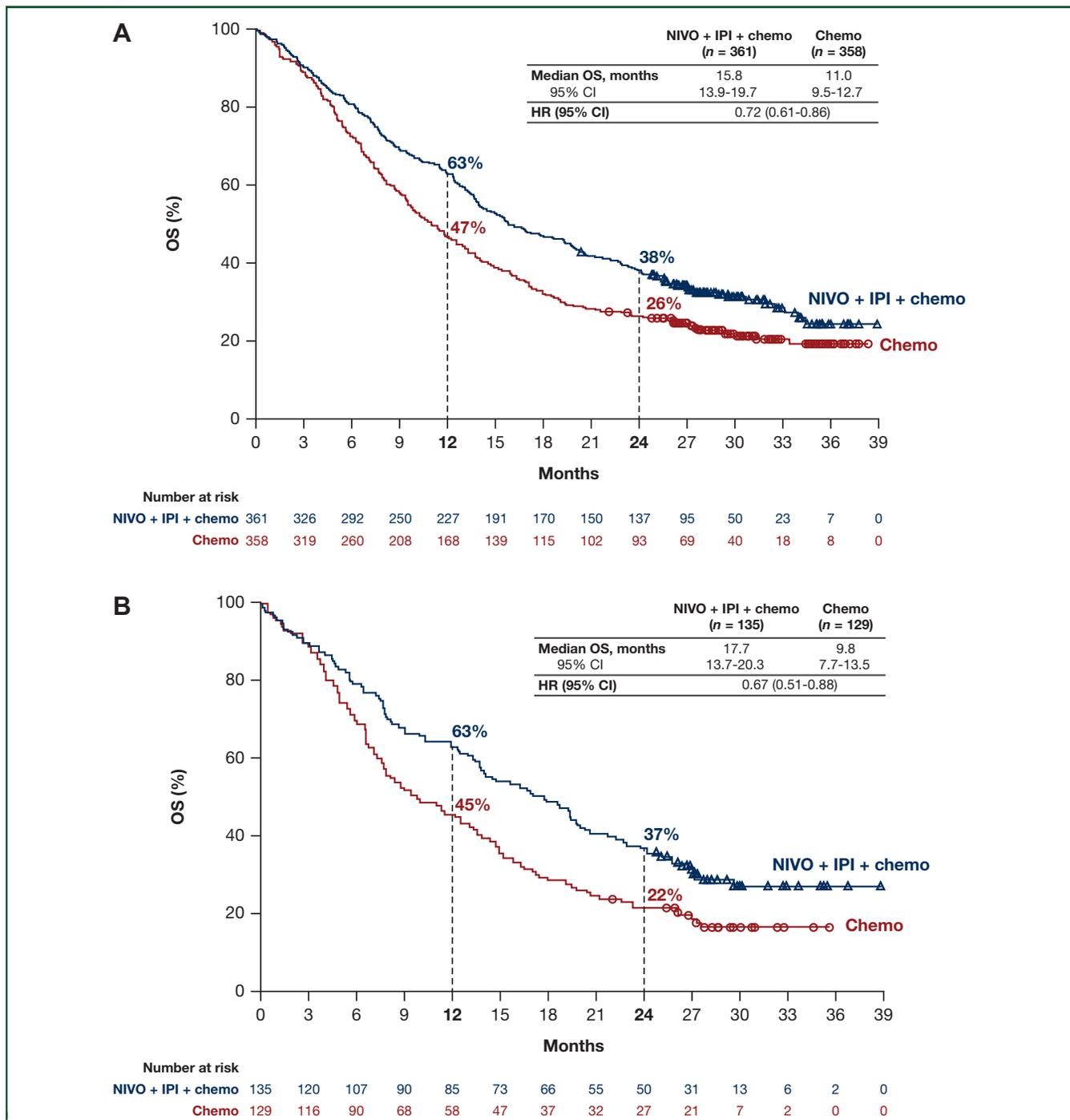


Figure 1. OS in all randomized patients (A), and in patients with tumor PD-L1 expression <1% (B), ≥1% (C), and ≥50% (D). Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; PD-L1, programmed death-ligand 1.

0.67; 95% CI 0.46-0.97); 2-year OS rates were 45% versus 32% (Figure 1D) and 28% versus 10% were progression free (Supplementary Figure S10A, available at <https://doi.org/10.1016/j.esmooop.2021.100273>). ORR was 50% in the experimental arm and 32% in the control arm (Supplementary Table S6, available at <https://doi.org/10.1016/j.esmooop.2021.100273>); median DOR was 26.0 versus 5.4 months and 52% versus 16% of responses were ongoing (Supplementary Figure S10B, available at <https://doi.org/10.1016/j.esmooop.2021.100273>).

**PFS2.** To determine the impact of next line of treatment, PFS2 was assessed. Median PFS2 in all randomized patients was 13.9 and 8.7 months in the experimental and control arms, respectively (HR 0.66; 95% CI 0.56-0.78; Figure 3). The 1- and 2-year PFS2 rates were 55% versus 37% and 35% versus 21%, respectively. PFS2 also favored the experimental arm over the control arm in subgroups by PD-L1 expression, and by histology (Supplementary Figure S11, available at <https://doi.org/10.1016/j.esmooop.2021.100273>).

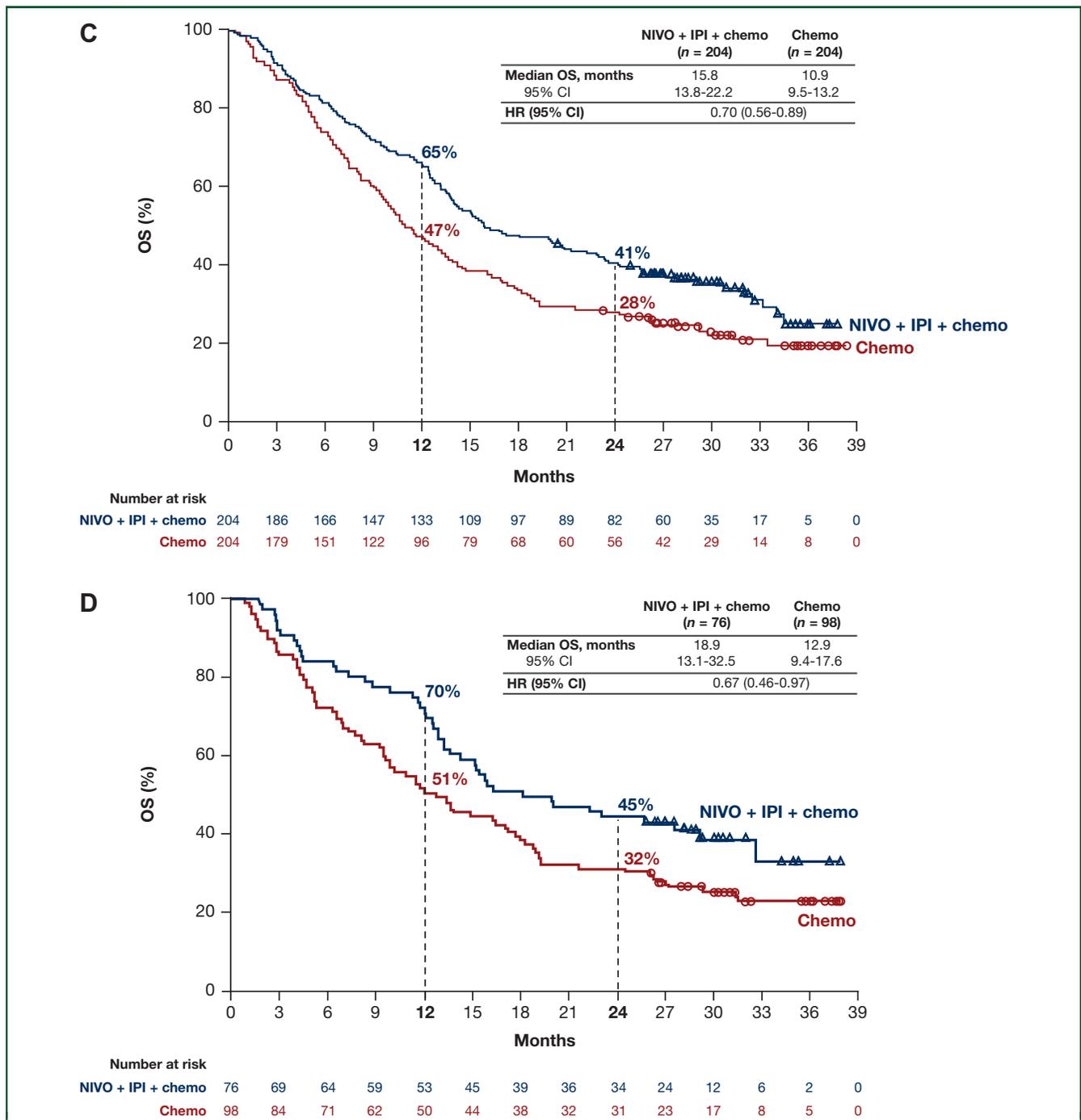
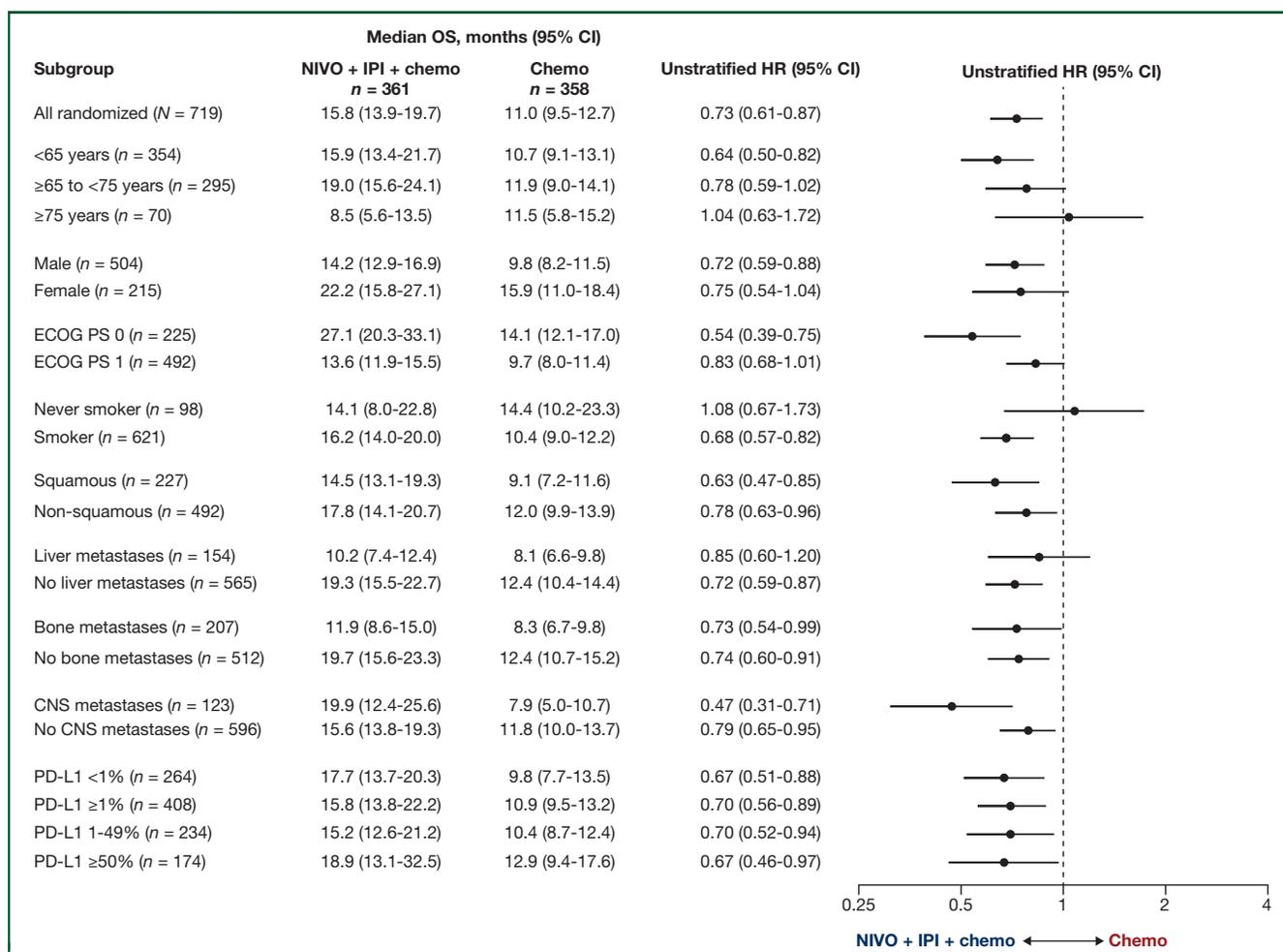


Figure 1. Continued.

**Safety**

With a minimum follow-up of 23.3 months, safety data remained consistent with the prior report.<sup>8</sup> TRAEs of any grade occurred in 92% of patients in the nivolumab plus ipilimumab with chemotherapy arm and 88% of patients in the chemotherapy arm; grade 3/4 TRAEs were reported in 48% and 38%, respectively (Supplementary Table S7, available at <https://doi.org/10.1016/j.esmooop.2021.100273>). When adjusted for the different treatment exposure in each arm, the incidence of TRAEs per 100 patient-years was 714.8 versus 880.0. A *post hoc* analysis of the onset of

TRAEs by treatment cycle showed that the onset of grade 1/2 TRAEs was generally similar between the two treatment arms in respective cycles (Supplementary Figure S12, available at <https://doi.org/10.1016/j.esmooop.2021.100273>). The onset of the majority of grade 3/4 TRAEs in the experimental arm occurred during the first two cycles, corresponding to the duration of the limited course of platinum-doublet chemotherapy in this arm; the majority of grade 3/4 TRAEs in the control arm occurred until cycles 7-8 (Figure 4). In the experimental versus control arms, respectively, TRAEs of any grade leading to treatment



**Figure 2. OS by prespecified subgroups.**

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

discontinuation of any component of the regimen were reported in 79 (22%) versus 29 (8%) patients, and those leading to treatment discontinuation of all components of the regimen were reported in 61 (17%) versus 21 (6%) patients. Treatment-related deaths occurred in eight (2%) versus six (2%) patients, respectively. The most commonly reported IMAEs of any grade were rash (17%), hypothyroidism/thyroiditis (16%), and hyperthyroidism (8%); the most common grade 3/4 IMAEs were hepatitis, rash, and colitis (each 4%). Median time to onset and time to resolution for IMAEs of any grade and grades 3/4 are shown in [Supplementary Table S8](https://doi.org/10.1016/j.esmooop.2021.100273), available at <https://doi.org/10.1016/j.esmooop.2021.100273>.

### Outcomes in patients who discontinued due to TRAEs

A *post hoc* analysis of patients who discontinued all components of the nivolumab plus ipilimumab with chemotherapy treatment regimen due to TRAEs ( $n = 61$ ) was conducted. Baseline characteristics of this subgroup were generally consistent with the overall study population ([Supplementary Table S9](https://doi.org/10.1016/j.esmooop.2021.100273), available at <https://doi.org/10.1016/j.esmooop.2021.100273>). These patients received a

median of 7 (range, 1-33) doses of nivolumab, and 3 (range, 1-17) doses of ipilimumab; median treatment duration was 4.4 months. Median OS was 27.5 months with a 2-year OS rate of 54% ([Figure 5](https://doi.org/10.1016/j.esmooop.2021.100273)). Median PFS was 5.1 months with a 1-year PFS rate of 44% and ORR ( $n = 31$ ) was 51%, with responses being maintained for a median of 14.5 months (95% CI 2.86 months to not reached) after treatment discontinuation ([Supplementary Table S10](https://doi.org/10.1016/j.esmooop.2021.100273), available at <https://doi.org/10.1016/j.esmooop.2021.100273>). Furthermore, of the 29 responders who were included in the DOR analysis, 56% maintained their response for at least 12 months after treatment discontinuation ([Supplementary Table S10](https://doi.org/10.1016/j.esmooop.2021.100273), available at <https://doi.org/10.1016/j.esmooop.2021.100273>). After discontinuing nivolumab plus ipilimumab combined with chemotherapy, patients remained treatment-free for a median of 11.9 months (95% CI 3.8-21.0 months) and had a 48% chance of being treatment-free at 1 year ([Supplementary Table S10](https://doi.org/10.1016/j.esmooop.2021.100273), available at <https://doi.org/10.1016/j.esmooop.2021.100273>). Patients who discontinued nivolumab plus ipilimumab with chemotherapy due to TRAEs had similar subsequent treatment patterns as all randomized patients; the most frequent

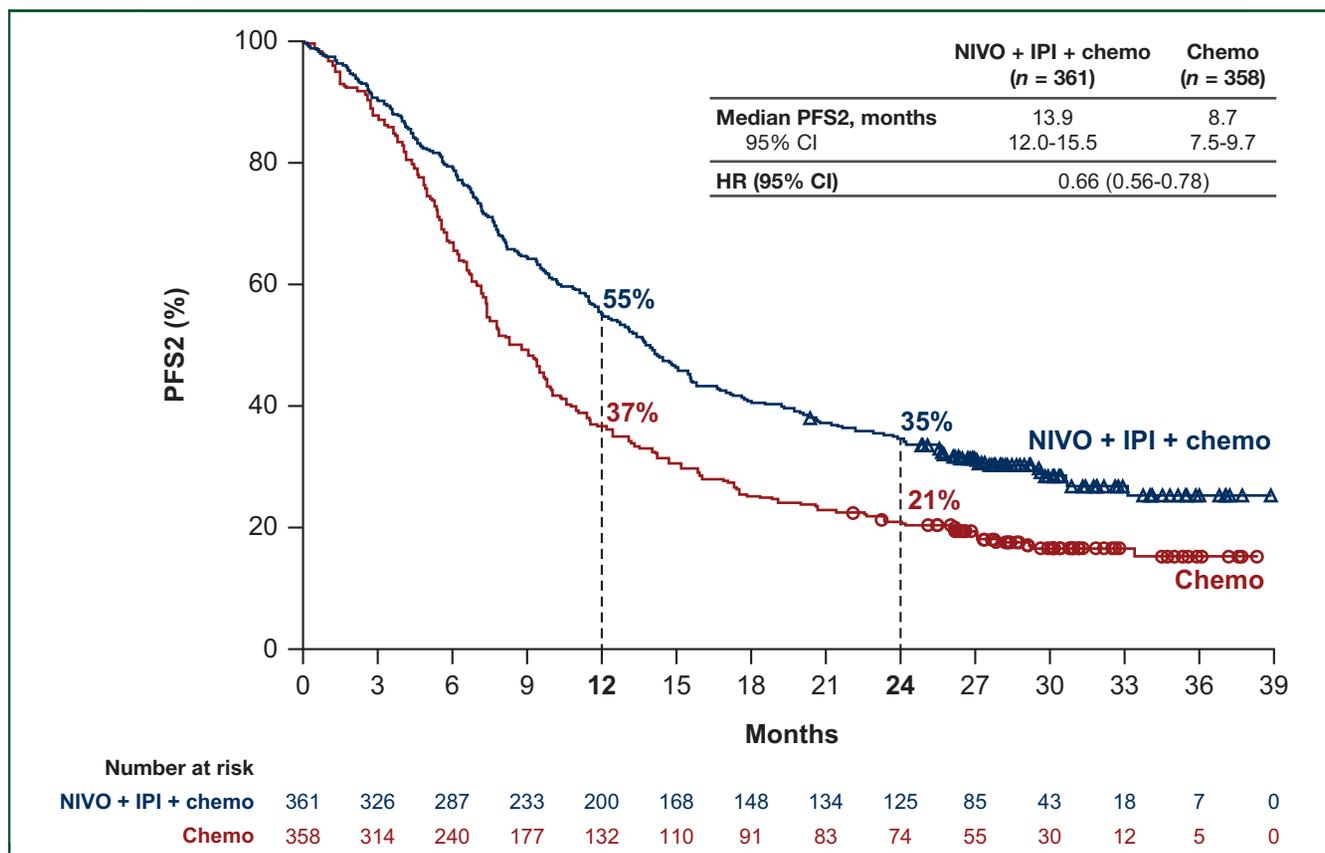


Figure 3. PFS2 in all randomized patients.

Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; PFS2, progression-free survival after next line of treatment. 23.3 Months minimum follow-up.

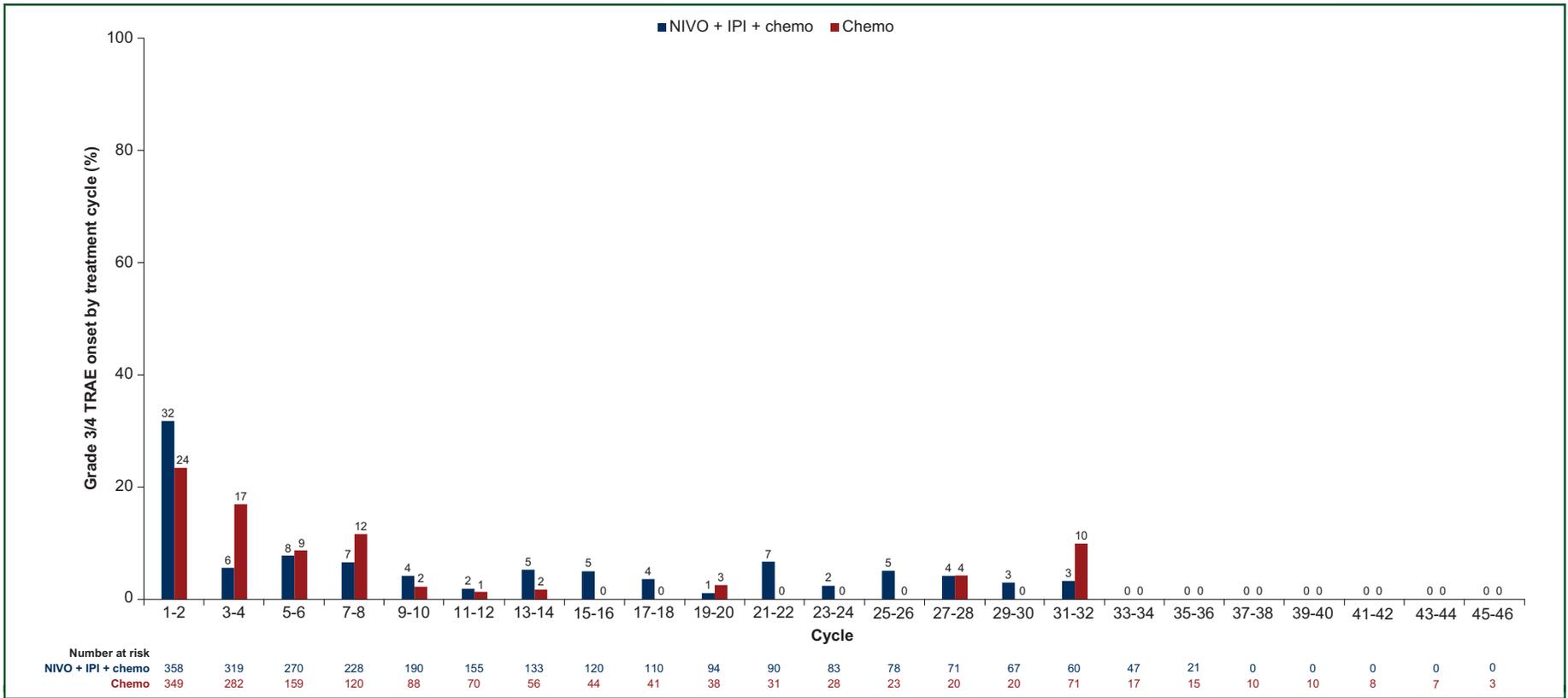
subsequent systemic therapy was chemotherapy [21% of all patients who discontinued (15% received platinum-doublet chemotherapy)] (Supplementary Table S11, available at <https://doi.org/10.1016/j.esmoop.2021.100273>). Treatment characteristics of individual patients who discontinued nivolumab plus ipilimumab due to TRAEs are shown in Supplementary Figure S13, available at <https://doi.org/10.1016/j.esmoop.2021.100273>.

## DISCUSSION

In CheckMate 9LA, with a follow-up of at least 2 years, first-line nivolumab plus ipilimumab with two cycles of chemotherapy demonstrated durable survival and clinical benefits versus four cycles of chemotherapy alone, regardless of PD-L1 expression level or histology. Overall, almost 40% of patients in the experimental arm were alive at 2 years, PFS benefit was sustained, and responses were durable. Consistent with the previous report,<sup>8</sup> clinical benefit in the experimental arm was observed across most predefined patient subgroups, including CNS metastases at baseline, however, patients who never smoked and those aged  $\geq 75$  years did not appear to derive benefit. Of note, these subgroups were not the basis for stratification factors and had small patient numbers, which may limit interpretation of results due to potential imbalances in prognostic factors between the two treatment arms. PFS2 was substantially

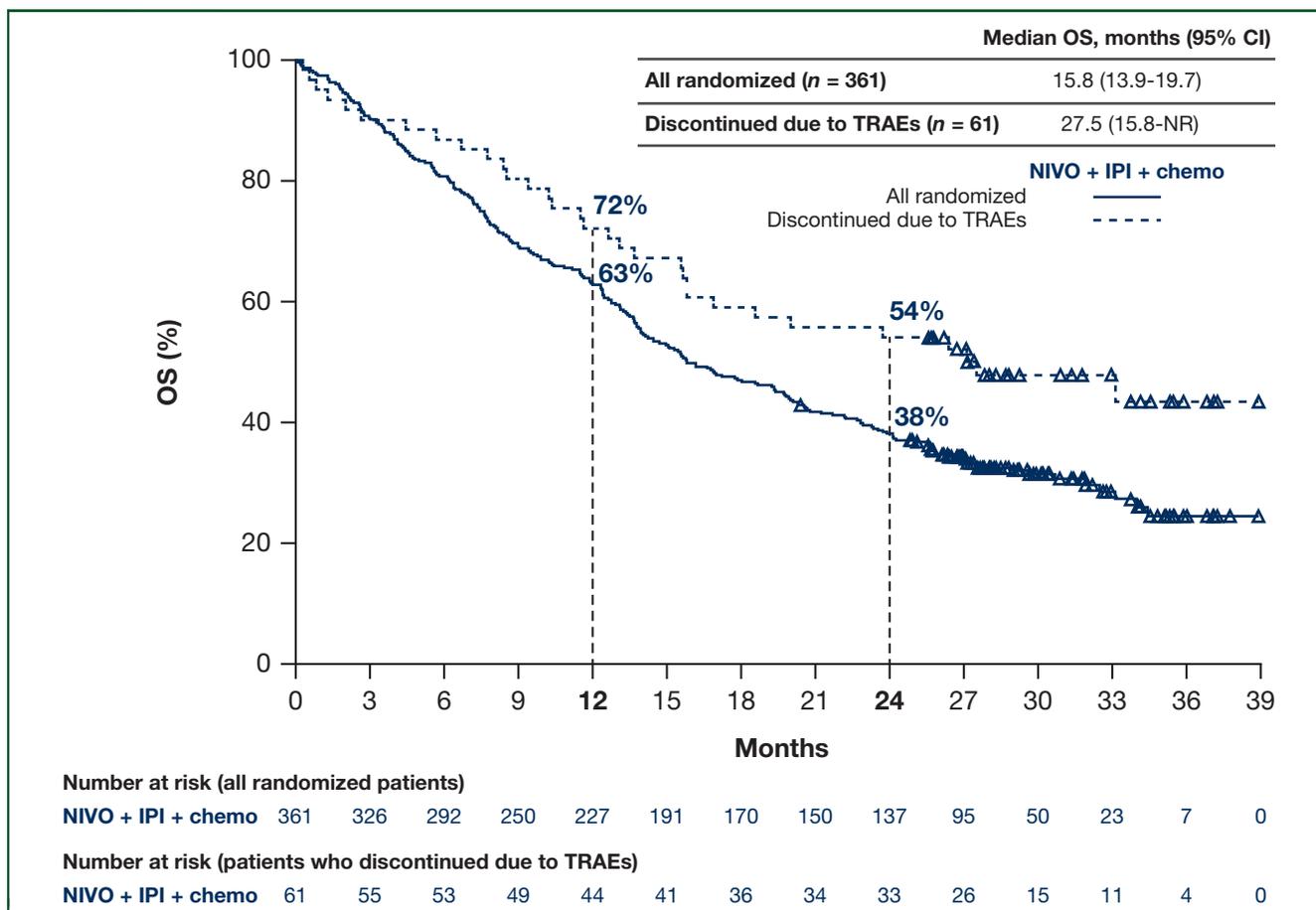
improved in the experimental versus control arm regardless of PD-L1 expression or histology. In addition, no new safety signals were reported with additional follow-up. The onset of grade 3/4 TRAEs in the experimental arm occurred mostly during the limited (two cycles) course of chemotherapy in this regimen.

In this 2-year update, nivolumab plus ipilimumab with chemotherapy continued to show consistent OS improvements compared with chemotherapy alone in both tumor PD-L1 non-expressors and expressors, including those with expression levels  $\geq 50\%$  (HRs, 0.67-0.70). Responses in the experimental arm were also durable versus the control arm across all PD-L1 subgroups, with at least threefold higher rates of ongoing responses at 2 years. These benefits were observed in both non-squamous and squamous histology subgroups among patients with PD-L1  $<1\%$  or PD-L1  $\geq 1\%$ . Interestingly, in exploratory analyses, patients with non-squamous histology appeared to derive similar OS benefit in the experimental versus control arm in both PD-L1  $<1\%$  (HR 0.75) and  $\geq 1\%$  (HR 0.71) populations. Patients with squamous histology and PD-L1  $<1\%$  (a population with a high unmet need) seemed to derive greater benefit (HR 0.48) compared with those with PD-L1  $\geq 1\%$  (HR 0.70).<sup>24</sup> Patients with CNS metastases at baseline, a known poor prognosis factor,<sup>25</sup> derived encouraging benefit with nivolumab plus ipilimumab with chemotherapy compared with



**Figure 4. Grade 3/4 TRAE onset by treatment cycle.**

Chemo, chemotherapy; IPI, ipilimumab; NIVO, nivolumab; TRAE, treatment-related adverse event. Includes events reported between first dose and 30 days after last dose of study therapy. Overlapping TRAEs with same preferred term per patient were clustered and reported as unique TRAE. Patient is considered at risk in a pooled two-cycle reporting interval if exposed to any study drug in that interval. Patient is counted once in each TRAE grade category for each pooled two-cycle reporting interval with TRAE incidence.



**Figure 5. OS in patients treated with nivolumab plus ipilimumab plus two cycles of chemotherapy who discontinued treatment due to TRAEs.** Chemo, chemotherapy; CI, confidence interval; IPI, ipilimumab; NIVO, nivolumab; NR, not reached; OS, overall survival; TRAE, treatment-related adverse event. *Post hoc* analysis includes patients with TRAEs (reported between first dose and 30 days after last dose of study treatment) that were considered leading to discontinuation of all components of study treatment.

chemotherapy alone, as previously seen with the nivolumab plus ipilimumab regimen in patients with advanced NSCLC and melanoma.<sup>26,27</sup>

These updated efficacy results further support the clinical rationale of adding a limited course of chemotherapy to dual immunotherapy (nivolumab plus ipilimumab), with early separation of OS and PFS curves and continued reduced rates of primary disease progression compared with chemotherapy in this study, and relative to nivolumab plus ipilimumab alone.<sup>1</sup> Interestingly, most of the subsequent treatment in patients who progressed in the experimental arm was platinum-doublet chemotherapy, which highlights a unique aspect of the limited course of chemotherapy in this regimen. Most importantly, these results confirm that nivolumab plus ipilimumab with chemotherapy versus chemotherapy alone provides durable benefit across all efficacy outcomes, with four patients improving from partial response to complete response since the prior DBL and one-third of responders still in response at 2 years. The durable benefit is potentially linked to the ability of ipilimumab to induce *de novo* antitumor T-cell responses and memory T cells.<sup>11-13</sup>

Continued improvements in outcomes with nivolumab plus ipilimumab with chemotherapy were observed despite 37% of patients with PFS events in the chemotherapy arm

receiving subsequent immunotherapy. Indeed, the 2-year OS rate of 26% in the control arm compares favorably with historical data,<sup>28-31</sup> potentially reflecting that patients in this arm received additional benefit with immunotherapy in the second-line setting and beyond. In addition, presented here for the first time is the impact on PFS2 of nivolumab plus ipilimumab with chemotherapy. Median PFS2 was almost 1.6-fold greater (HR 0.66) in patients treated with first-line nivolumab plus ipilimumab with chemotherapy compared with chemotherapy alone, regardless of PD-L1 expression or histology. This suggests that the treatment effect in the experimental arm could be maintained into the next line of therapy.

With a 2-year minimum follow-up and a median duration of treatment 2.4-fold greater in the experimental versus chemotherapy arm, the safety profile of nivolumab plus ipilimumab combined with two cycles of chemotherapy was as expected from combining drugs with distinct mechanisms of action and remained consistent with the prior report; no new safety signals were identified.<sup>1,8,32</sup> The incidence of exposure-adjusted TRAEs remained similar between the experimental and control arms (714.8 and 880.0 per 100 patient-years, respectively). In addition, rates of TRAEs typically associated with chemotherapy (e.g. nausea, anemia, neutropenia)

continued to be lower in the experimental versus the control arm, which supports limiting chemotherapy to two cycles. Notably, a *post hoc* analysis showed that the onset of most new grade 3/4 TRAEs occurred within the first 2 cycles in the experimental arm, corresponding to the limited course of chemotherapy, as opposed to the onset of most new grade 3/4 TRAEs being seen up to cycles 7-8 in the control arm.

As the benefit-risk profile is key in treatment selection, safety and discontinuation of treatment due to TRAEs is particularly important to clinicians. In CheckMate 9LA, 17% of patients in the experimental arm discontinued all components of nivolumab plus ipilimumab with chemotherapy treatment due to any-grade TRAEs; a *post hoc* analysis showed that clinical outcomes were not negatively impacted in this patient population compared with all randomized patients (2-year OS rates, 54% and 38%). Moreover, responders who discontinued this regimen due to TRAEs could maintain durable responses after treatment discontinuation. These findings are consistent with observations previously reported from similar analyses in phase III trials of nivolumab plus ipilimumab as first-line treatment in advanced renal cell carcinoma and advanced melanoma, and might be reflective of the biologic effect of ipilimumab on the immune system.<sup>11-14,33</sup>

Treatment decisions in clinical practice are currently based on PD-L1 expression or histology. The current standard of care for untreated patients with either squamous or non-squamous advanced NSCLC and with PD-L1  $\geq 50\%$  is anti-PD-(L)1 monotherapy,<sup>2,3,7,19-21</sup> while patients with higher disease burden or lower levels of PD-L1 expression tend to receive immunotherapy plus chemotherapy.<sup>4-6,9,19-21,34</sup> This treatment algorithm is based on the outcomes of several studies which showed that the clinical activity of PD-(L)1 inhibitors as monotherapy in patients with NSCLC is driven mostly by high tumor PD-L1 expression.<sup>2,3,7</sup> Although the combination of these agents with chemotherapy showed clinical activity, it is also driven by PD-L1 expression with limited clinical activity in patients with low tumor PD-L1 expression.<sup>4,9</sup> The updated data on nivolumab plus ipilimumab with a limited course of chemotherapy in this report compare favorably to current standard-of-care options in these patient populations with consistent and continued clinical benefit across PD-L1 expression levels and histologies, with potentially more interesting activity in patients with no tumor PD-L1 expression or squamous histology. It is crucial to continue to assess longer term outcomes for patients in CheckMate 9LA and other immunotherapy combination studies, to fully characterize response benefits and the potential plateau of the survival curve. Patient selection remains key for the choice of treatment regimens, and it is imperative for future translational research and analyses to understand how these different first-line immunotherapy combination treatment options can meet individual patient needs, especially in the long term.

A key limitation of this 2-year update analysis from the CheckMate 9LA study is the relatively short duration of follow-

up at the time of DBL, evidenced by the high censoring rates on the OS and DOR curves at approximately 2 years and beyond. This limited the ability to assess long-term clinical benefits of nivolumab plus ipilimumab combined with two cycles of chemotherapy as first-line treatment of patients with advanced NSCLC. Continued follow-up is critical to address this important question. As noted in the primary analysis of the study, another limitation is the use of chemotherapy as the control arm, which is no longer a standard of care as a result of treatment advances in first-line advanced NSCLC during the conduct of CheckMate 9LA.<sup>8</sup>

In conclusion, first-line nivolumab plus ipilimumab with two cycles of chemotherapy continued to demonstrate durable efficacy benefits versus four cycles of chemotherapy alone in patients with advanced NSCLC, regardless of tumor PD-L1 expression or histology. These updated results continue to support nivolumab plus ipilimumab combined with two cycles of chemotherapy as an efficacious first-line treatment option for patients with advanced NSCLC.

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The study was designed by the steering committee and the funder. The funder contributed to data collection with the investigators, to data analysis and interpretation in collaboration with the authors, and to the writing of the report by funding professional medical writing assistance. All authors had full access to all the data in the study.

## DISCLOSURE

MR reports advisory/consulting fees from AbbVie, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Mirati Therapeutics, MSD Oncology, Novartis, Pfizer, Roche/Genentech, and Samsung Bioepis; speaker fees from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Merck Serono, Mirati

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## DATA SHARING

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>.

## REFERENCES

- 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.
- 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(19):1823-1833.
- 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(10183):1819-1830.
- 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(21):2040-2051.
- 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(7):924-937.
- 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(8):1351-1360.
- 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. Paper presented at the European Society for Medical Oncology 2019 Congress. 2019; Barcelona, Spain.
- 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(2):198-211.
- 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.
- 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(22):2093-2104.
- Sharma P, Allison JP. Dissecting the mechanisms of immune checkpoint therapy. *Nat Rev Immunol*. 2020;20(2):75-76.
- Wei SC, Duffy CR, Allison JP. Fundamental mechanisms of immune checkpoint blockade therapy. *Cancer Discov*. 2018;8(9):1069-1086.
- Das R, Verma R, Szoln M, et al. Combination therapy with anti-CTLA-4 and anti-PD-1 leads to distinct immunologic changes in vivo. *J Immunol*. 2015;194(3):950-959.
- 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(16):1535-1546.
- 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(10272):375-386.
- Paz-Ares LG, Ciuleanu T-E, Lee J-S, et al. Nivolumab (NIVO) plus ipilimumab (IPI) versus chemotherapy (chemo) as first-line (1L) treatment for advanced non-small cell lung cancer (NSCLC): 4-year update from CheckMate 227. *J Clin Oncol*. 2021;39(suppl 15):9016.
- Paz-Ares LG, Ciuleanu T-E, Lee J-S, et al. Nivolumab (NIVO) plus ipilimumab (IPI) versus chemotherapy (chemo) as first-line (1L) treatment for advanced non-small cell lung cancer (NSCLC): 4-year update from CheckMate 227. Paper presented at the ASCO Annual Meeting. 2021; Virtual.
- Albiges L, Tannir NM, Buratto M, et al. Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial. *ESMO Open*. 2020;5(6):e001079.
- 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.
- Planchard DPS, Popat S, Kerr S, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2020. Available at <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>. Accessed April 23, 2021.
- 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(suppl 4):iv192-iv237.
- Bristol Myers Squibb. Opdivo® (nivolumab) prescribing information. 2021. Available at [https://packageinserts.bms.com/pi/pi\\_opdivo.pdf](https://packageinserts.bms.com/pi/pi_opdivo.pdf). Accessed June 17, 2021.
- ecancer. EU approves first-line treatment option for advanced non-small cell lung cancer. November 9, 2020. Available at <https://ecancer.org/en/news/19041-eu-approves-first-line-treatment-option-for-advanced-non-small-cell-lung-cancer>. Accessed June 17, 2021.
- Socinski MA, Obasaju C, Gandara D, et al. Current and emergent therapy options for advanced squamous cell lung cancer. *J Thorac Oncol*. 2018;13(2):165-183.
- Sperduto PW, Yang TJ, Beal K, et al. Estimating survival in patients with lung cancer and brain metastases: an update of the Graded Prognostic Assessment for Lung Cancer Using Molecular Markers (Lung-molGPA). *JAMA Oncol*. 2017;3(6):827-831.
- Borghaei H, Pluzanski A, Bernabe Caro R, et al. Nivolumab plus ipilimumab as first-line treatment for patients with advanced non-small cell lung cancer with brain metastases: results from CheckMate 227 Part 1. Paper presented at the American Association for Cancer Research (AACR) Annual Meeting. 2020; Virtual.
- Tawbi HA, Forsyth PA, Algazi A, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the Brain. *N Engl J Med*. 2018;379(8):722-730.
- Danson S, Middleton MR, O'Byrne KJ, et al. Phase III trial of gemcitabine and carboplatin versus mitomycin, ifosfamide, and cisplatin or mitomycin, vinblastine, and cisplatin in patients with advanced non-small cell lung carcinoma. *Cancer*. 2003;98(3):542-553.
- Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med*. 2002;346(2):92-98.
- Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol*. 2008;26(21):3543-3551.
- Georgoulis V, Ardavanis A, Tsiafaki X, et al. Vinorelbine plus cisplatin versus docetaxel plus gemcitabine in advanced non-small-cell lung cancer: a phase III randomized trial. *J Clin Oncol*. 2005;23(13):2937-2945.
- 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(1):31-41.
- Tannir NM, Motzer RJ, Plimack ER, et al. Outcomes in patients (pts) with advanced renal cell carcinoma (aRCC) who discontinued (DC) first-line nivolumab + ipilimumab (N+I) or sunitinib (S) due to treatment-related adverse events (TRAEs) in CheckMate 214. *J Clin Oncol*. 2019;37(suppl 7):581.
- Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med*. 2018;378(24):2288-22301.