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ORIGINAL ARTICLE

# Second-line nivolumab in relapsed small-cell lung cancer: CheckMate 331☆

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**Background:** Patients with relapsed small-cell lung cancer (SCLC) have few treatment options and dismal survival. Phase I/II data show activity of nivolumab in previously treated SCLC.

**Patients and methods:** CheckMate 331 is a randomized, open-label, phase III trial of nivolumab versus standard chemotherapy in relapsed SCLC. Patients with relapse after first-line, platinum-based chemotherapy were randomized 1 : 1 to nivolumab 240 mg every 2 weeks or chemotherapy (topotecan or amrubicin) until progression or unacceptable toxicity. Primary endpoint was overall survival (OS).

**Results:** Overall, 284 patients were randomized to nivolumab and 285 to chemotherapy. Minimum follow-up was 15.8 months. No significant improvement in OS was seen with nivolumab versus chemotherapy [median OS, 7.5 versus 8.4 months; hazard ratio (HR), 0.86; 95% confidence interval (CI), 0.72-1.04; $P = 0.11$]. A survival benefit with nivolumab was suggested in patients with baseline lactate dehydrogenase $\leq$ upper limit of normal and in those without baseline liver metastases. OS (nivolumab versus chemotherapy) was similar in patients with programmed death-ligand 1 combined positive score $\geq$1% versus <1%. Median progression-free survival was 1.4 versus 3.8 months (HR, 1.41; 95% CI, 1.18-1.69). Objective response rate was 13.7% versus 16.5% (odds ratio, 0.80; 95% CI, 0.50-1.27); median duration of response was 8.3 versus 4.5 months. Rates of grade 3 or 4 treatment-related adverse events were 13.8% versus 73.2%.

**Conclusion:** Nivolumab did not improve survival versus chemotherapy in relapsed SCLC. No new safety signals were seen. In exploratory analyses, select baseline characteristics were associated with improved OS for nivolumab.

**Key words:** small-cell lung cancer, immunotherapy, PD-1, biomarkers

## INTRODUCTION

Initial response rates to first-line treatment of small-cell lung cancer (SCLC) are high[1,‡]; however, nearly all patients relapse.[2,3] The only approved second-line agents are topotecan in many countries worldwide (for platinum-based chemotherapy-sensitive disease) and amrubicin in Japan. However, responses to these agents are modest and lack

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‡ 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.

durability.[4-6] In a large, multinational, randomized, phase III trial comparing amrubicin and topotecan in patients with relapsed/refractory and sensitive SCLC, overall response rates (ORRs) were 31% and 17%, and response durations were 4.8 and 4.2 months, respectively.[5]

Immuno-oncology agents have recently proven to provide clinical benefits in patients with SCLC. The programmed death-ligand 1 (PD-L1) inhibitors atezolizumab and durvalumab are approved in the United States, EU, and Japan as first-line therapies for SCLC with etoposide and platinum-based chemotherapy.[7-10] The programmed death-1 (PD-1) inhibitor pembrolizumab is approved in the United States, EU, and Japan as a third- or later-line treatment option for extensive-stage SCLC.[11] Nivolumab is a fully human anti-PD-1 antibody that has demonstrated a durable overall survival (OS) benefit in multiple tumor types and is approved globally for the treatment of several types of cancer.[12-14] It is approved in the United States for metastatic SCLC in patients with progression after platinum-based chemotherapy and at least one other line of therapy based on durable responses and tolerability demonstrated by the phase I/II CheckMate 032 trial (NCT01928394).[12,15,16]

To address the need for improved survival in patients with SCLC in the second-line setting, CheckMate 331 (NCT02481830) compared nivolumab monotherapy with topotecan or amrubicin chemotherapy in patients with relapsed SCLC after first-line platinum-based chemotherapy. Exploratory analyses to assess associations of PD-L1 combined positive score (CPS) and tumor mutational burden (TMB) with survival were also carried out. Here we report efficacy and safety results from this trial.

## PATIENTS AND METHODS

### *Patients*

Adult patients were eligible if they had histologically or cytologically confirmed limited- or extensive-stage SCLC with recurrence or progression after first-line platinum-based chemotherapy or chemoradiation therapy, an Eastern Cooperative Oncology Group performance status of 0 or 1, and measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[17] Patients were required to have had at least four cycles of first-line platinum-based chemotherapy; if fewer than four cycles were received, patients must have had a partial or complete response as their best overall response upon completion of chemotherapy. All patients (excluding those in China) were required to have tumor tissue (either archival or from a recent biopsy) collected by a central laboratory before randomization. Additional eligibility criteria are described in the Supplementary Materials, available at https://doi.org/10.1016/j.annonc.2021.01.071.

### *Trial design and treatment*

CheckMate 331 was an international, open-label, randomized, phase III trial (ClinicalTrials.gov number, NCT02481830). The trial was conducted at 142 sites across 24 countries[18] (the complete list of CheckMate 331 investigators is shown in the Supplementary Materials, available at https://doi.org/10.1016/j.annonc.2021.01.071). Patients were randomly assigned (1 : 1) to receive nivolumab or chemotherapy with either topotecan or amrubicin (upon investigator's choice, where locally approved). Randomization was carried out via a central interactive voice response system using a permuted block method stratified by duration of disease control after first-line platinum-based treatment [progression-free interval after completion of platinum therapy $\geq$90 days (sensitive) versus $<$90 days (resistant)] and brain metastases at baseline (yes versus no). Nivolumab (240 mg) was administered as a 30-min intravenous infusion every 2 weeks. Topotecan was given as a 30-min intravenous infusion (1.5 mg/m$^2$) or as an oral capsule (2.3 mg/m$^2$) once daily on days 1 to 5 of a 3-week cycle. Amrubicin 40 mg/m$^2$ (Japan only) was administered as a 5-min intravenous infusion once daily on days 1 to 3 of a 3-week cycle. Treatment continued until disease progression or unacceptable toxicity, withdrawal of consent, or study completion. Patients receiving nivolumab could receive treatment beyond initial progression if they met specific criteria (Supplementary Materials, available at https://doi.org/10.1016/j.annonc.2021.01.071).

The trial was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice, the ethical principles underlying the European Directive 2001/20/EC, and the United States Code of Federal Regulations, Title 21, Part 50. An institutional review board or independent ethics committee for each site approved the protocol, consent form, and any other written information provided to patients. All patients gave written informed consent. A blinded data monitoring committee provided oversight and independently reviewed safety data.

### *Endpoints and assessments*

The primary endpoint was OS. Key secondary endpoints included investigator-assessed progression-free survival (PFS), ORR, and duration of objective response. PFS was defined as the time from randomization to first documented tumor progression according to RECIST v1.1,[17] or death due to any cause. Investigator-assessed response was determined according to RECIST v1.1[17] and confirmed at least 4 weeks after the response criteria were met. Efficacy by CPS score and TMB status, as well as safety, were exploratory.

Computed tomography scanning or magnetic resonance imaging was carried out at baseline and at prespecified timepoints throughout treatment until disease progression. All known or suspected sites of disease were assessed at screening and at subsequent assessments, with imaging of the pelvis and brain required at screening. Adverse events (AEs) were monitored during study treatment and up to 100 days following the last dose of nivolumab and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0. Events with an outcome of death were reported with the grade occurring at initial presentation. PD-L1 expression level on

tumor cells and immune cells was determined using the Dako PD-L1 IHC 28-8 PharmDx assay.[19] CPS was defined as the total number of PD-L1-positive cells (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells, multiplied by 100.[20] All efficacy outcomes were assessed by CPS score (≥1% versus <1%). TMB was assessed using the FoundationOne CDx™ assay and reported as the number of mutations per megabase. Efficacy endpoints were explored for patients with high/low TMB using multiple cutoff values (10, 11, 13, 14, 15 mut/mb).

### Statistical analysis

The final analysis was planned at 34 months after randomization of the first patient, with no interim analysis. A sample of 560 patients with approximately 480 deaths at the time of analysis was estimated to provide 90% power to detect a hazard ratio (HR) of ∼0.745 for OS between the treatment arms, using a log-rank test with a two-sided type I error of 0.05 (Supplementary Materials, available at https://doi.org/10.1016/j.annonc.2021.01.071).

A hierarchical testing procedure was used for the key secondary endpoints of PFS and ORR to preserve the type I error of 0.05. Formal statistical testing for PFS would be carried out if the OS comparison was statistically significant; testing for ORR would be carried out if OS and PFS comparisons were both statistically significant. OS and PFS curves were estimated using the Kaplan–Meier product-limit method; censoring criteria are described in the Supplementary Materials, available at https://doi.org/10.1016/j.annonc.2021.01.071. Median OS and PFS and associated two-sided 95% confidence intervals (CIs) were constructed based on Brookmeyer and Crowley methodology using log-log transformation for constructing the CIs.[21] Time to event distributions were compared using a two-sided log-rank test stratified by platinum sensitivity and presence of brain metastases at baseline. The HR and corresponding two-sided 95% CIs were estimated using a stratified Cox proportional-hazards model, with randomized arm as a single covariate. An exploratory piecewise analysis of OS was conducted using 3-month intervals, selected based on the shapes of the observed OS curves (i.e. timing of early benefit of chemotherapy). Exploratory analyses of OS by baseline characteristics were conducted by estimating the unstratified HR and 95% CI for select patient subgroups. To examine the potential predictive effect of baseline characteristics on OS, *post hoc* subgroup analyses using an unstratified Cox proportional-hazards model with interaction term included were conducted for each candidate baseline variable. Cox models were adjusted for select prognostic factors. A significant interaction ($P$ value <0.20) between treatment and candidate variable demonstrated treatment effect heterogeneity (Supplementary Materials, available at https://doi.org/10.1016/j.annonc.2021.01.071). ORRs were compared using a two-sided stratified Cochran–Mantel–Haenszel test, with exact 95% CIs calculated using the Clopper–Pearson method.

## RESULTS

### Patients

A total of 781 patients were enrolled, of whom 569 were randomly assigned to nivolumab ($n$ = 284) or chemotherapy ($n$ = 285) between 28 August 2015 and 24 April 2017 (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2021.01.071). Among all randomized patients, 282 and 265 received at least one dose of nivolumab or chemotherapy, respectively. Baseline characteristics were balanced between the two groups (Table 1).

The minimum follow-up for OS (from randomization of the last patient to the last patient's last visit date) was 15.8 months. The last patient was randomized on 24 April 2017, and the last patient's last visit was on 17 August 2018. In the nivolumab and chemotherapy groups, the median follow-up (from randomization to the last known vital status date) was 7.0 months and 7.6 months, respectively. At database lock (28 September 2018), the median (range) duration of therapy was 1.4 months (0.0-32.7+, where the plus sign indicates an ongoing status) with nivolumab and 2.2 months (0.1-30.3+) with chemotherapy, with some patients continuing treatment in each group. In the nivolumab group, 89 patients received treatment beyond progression.

### Efficacy

**Intent-to-treat population.** At the time of database lock, 225 patients (79.2%) in the nivolumab group and 245 patients (86.0%) in the chemotherapy group had died; 59 patients (20.8%) and 40 patients (14.0%) were censored for OS, respectively. There was no statistically significant difference in OS between treatment groups (Figure 1A). Median OS was 7.5 months (95% CI, 5.6-9.2) with nivolumab versus 8.4 months (95% CI, 7.0-10.0) with chemotherapy (HR, 0.86; 95% CI, 0.72-1.04; $P$ = 0.11). OS rates with nivolumab and chemotherapy were 54.5% and 59.9% at 6 months and 36.6% and 34.1% at 12 months, respectively, with the curves crossing at approximately 11 months.

An exploratory analysis of OS by 3-month intervals demonstrated that the HR (nivolumab versus chemotherapy) decreased over time, with an estimated HR value >1 for the first 6 months and <1 thereafter (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2021.01.071). Exploratory analyses by baseline characteristics showed that OS was similar across most patient subgroups; however, a trend toward a benefit with nivolumab was observed in select predefined groups of patients including those with lactate dehydrogenase (LDH) no greater than the upper limit of normal (ULN) (HR, 0.70; 95% CI, 0.53-0.90), those with resistance to first-line platinum-based therapy (a stratification criterion) (HR, 0.71; 95% CI, 0.54-0.94), and those without liver metastases (HR, 0.77; 95% CI, 0.61-0.97) (Figure 2). Kaplan–Meier curves for OS in these patient subgroups are shown in Supplementary Figures S2-S4, available at https://doi.org/10.1016/j.annonc.2021.01.071. In exploratory multivariate analyses adjusting for prognostic

**Table 1. Patient demographics and baseline characteristics**

| | Nivolumab ($n$ = 284) | Chemotherapy ($n$ = 285) |
|---|---|---|
| Age, median (range), years | 62 (37-85) | 61 (34-82) |
| Age | | |
| <65 years | 184 (64.8) | 177 (62.1) |
| ≥65 years | 100 (35.2) | 108 (37.9) |
| Sex, male | 174 (61.3) | 177 (62.1) |
| Region | | |
| United States/Canada | 24 (8.5) | 27 (9.5) |
| Europe | 174 (61.3) | 168 (58.9) |
| Asia | 70 (24.6) | 71 (24.9) |
| Rest of world | 16 (5.6) | 19 (6.7) |
| Race | | |
| White | 211 (74.3) | 211 (74.0) |
| Asian | 70 (24.6) | 71 (24.9) |
| Other | 3 (1.1) | 3 (1.1) |
| ECOG performance status[a] | | |
| 0 | 75 (26.4) | 81 (28.4) |
| 1 | 209 (73.6) | 203 (71.2) |
| 2 | 0 | 1 (0.4) |
| Smoking status | | |
| Current/former smoker | 256 (90.1) | 260 (91.2) |
| Never smoked | 26 (9.2) | 24 (8.4) |
| Unknown | 2 (0.7) | 1 (0.4) |
| Disease classification at initial diagnosis | | |
| Extensive disease | 210 (73.9) | 191 (67.0) |
| Limited disease | 74 (26.1) | 94 (33.0) |
| Tumor histologic findings | | |
| Small-cell carcinoma | 284 (100.0) | 284 (99.6) |
| Other | 0 | 1 (0.4) |
| Response to first-line therapy[b] | | |
| Platinum sensitive | 163 (57.4) | 160 (56.1) |
| Platinum resistant | 121 (42.6) | 125 (43.9) |
| Central nervous system metastases | | |
| Yes | 50 (17.6) | 46 (16.1) |
| No | 234 (82.4) | 239 (83.9) |
| Baseline lactate dehydrogenase[c] | | |
| ≤ upper limit of normal | 137 (48.2) | 156 (54.7) |
| > upper limit of normal | 138 (48.6) | 108 (37.9) |
| ≤2 × upper limit of normal | 239 (84.2) | 235 (82.5) |
| >2 × upper limit of normal | 36 (12.7) | 29 (10.2) |
| Not reported | 9 (3.2) | 21 (7.4) |
| Liver metastases | | |
| Yes | 97 (34.2) | 108 (37.9) |
| No | 187 (65.8) | 176 (61.8) |
| Not reported | 0 | 1 (0.4) |
| PD-L1 CPS[d] | | |
| ≥1 | 78 (45.6) | 68 (45.3) |
| <1 | 93 (54.4) | 82 (54.7) |

Data presented as $n$ (%) unless otherwise indicated.
CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1.
[a] ECOG performance status scores range from 0 to 5, with higher scores indicating greater disability.
[b] Platinum sensitive was defined as a progression-free interval ≥90 days after completion of platinum therapy, per case report form; platinum resistant was defined as a progression-free interval <90 days after completion of platinum therapy, per case report form.
[c] Lactate dehydrogenase defined per laboratory standards.
[d] Percentages are based on patients evaluable for PD-L1 CPS (nivolumab, $n$ = 171; chemotherapy, $n$ = 150).

factors, LDH ≤ ULN and absence of liver metastases at baseline remained associated with improved OS with nivolumab versus chemotherapy [HR, 0.76 (95% CI, 0.59-0.98), and 0.74 (95% CI, 0.59-0.94), respectively; Table 2].

A total of 258 patients (90.8%) in the nivolumab group and 235 patients (82.5%) in the chemotherapy group experienced disease progression or died; 26 patients (9.2%) and 50 patients (17.5%) were censored for PFS, respectively. Median PFS was 1.4 months (95% CI, 1.4-1.5) with nivolumab versus 3.8 months (95% CI, 3.0-4.2) with chemotherapy (HR, 1.41; 95% CI, 1.18-1.69; Figure 1B). PFS rates with nivolumab and chemotherapy were 19.7% and 26.5% at 6 months and 10.9% and 10.0% at 12 months, respectively.

Investigator-assessed tumor responses are summarized in Table 3. The ORR was 13.7% with nivolumab versus 16.5% with chemotherapy (odds ratio, 0.80; 95% CI, 0.50-1.27). The median duration of response was 8.3 months (95% CI, 7.0-12.6) with nivolumab versus 4.5 months (95% CI, 4.1-5.8) with chemotherapy (Table 3; Figure 1C).

Subsequent cancer therapy was received by 51.4% of patients in the nivolumab group and 47.7% of those in the chemotherapy group (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2021.01.071). In the chemotherapy group, 4.9% of patients received subsequent immunotherapy (nivolumab, 4.6%; ipilimumab, 0.7%; durvalumab, 0.4%; nivolumab in combination with ipilimumab, 0.4%).

### *Biomarker analysis*

After excluding patients from China (nivolumab, $n$ = 39; chemotherapy, $n$ = 43), for whom biomarker assessments were not carried out, 171 patients (69.8%) and 150 patients (62.0%) in the nivolumab and chemotherapy groups, respectively, were evaluable for CPS. Baseline characteristics were generally comparable between the CPS-evaluable and intent-to-treat populations (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2021.01.071). Among CPS-evaluable patients, a CPS ≥1% was reported for 78/171 (45.6%) in the nivolumab group and 68/150 (45.3%) in the chemotherapy group (Table 1). Median OS for nivolumab versus chemotherapy in the CPS-evaluable population was 7.0 months (95% CI, 5.1-9.2) versus 8.6 months (95% CI, 7.2-11.1), with an HR of 0.93 (95% CI, 0.73-1.18); these results are consistent with the HR estimate using all randomized patients, excluding the China cohort (HR, 0.91; 95% CI, 0.75-1.11).

Baseline characteristics in the CPS ≥1% and CPS <1% populations are shown in Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2021.01.071. HRs for OS with nivolumab versus chemotherapy were similar between patients with a CPS ≥1% and those with a CPS <1% (HR, 0.96 and 0.91, respectively; Figure 3A). PFS HRs for nivolumab versus chemotherapy were also comparable between the CPS ≥1% and CPS <1% populations (HR, 1.52 and 1.68, respectively; Figure 3B). CPS cutoffs of up to 5% were also investigated, although these analyses are limited by small patient numbers and are not reported.

Only 55% of patients in the all-randomized population were TMB evaluable, including 155 patients in the nivolumab arm (54.6% of all randomized) and 157 patients in the chemotherapy arm (55.1% of all randomized). Biomarker analyses were not carried out on samples from Chinese patients ($n$ = 82); therefore, TMB was evaluated in 487 out

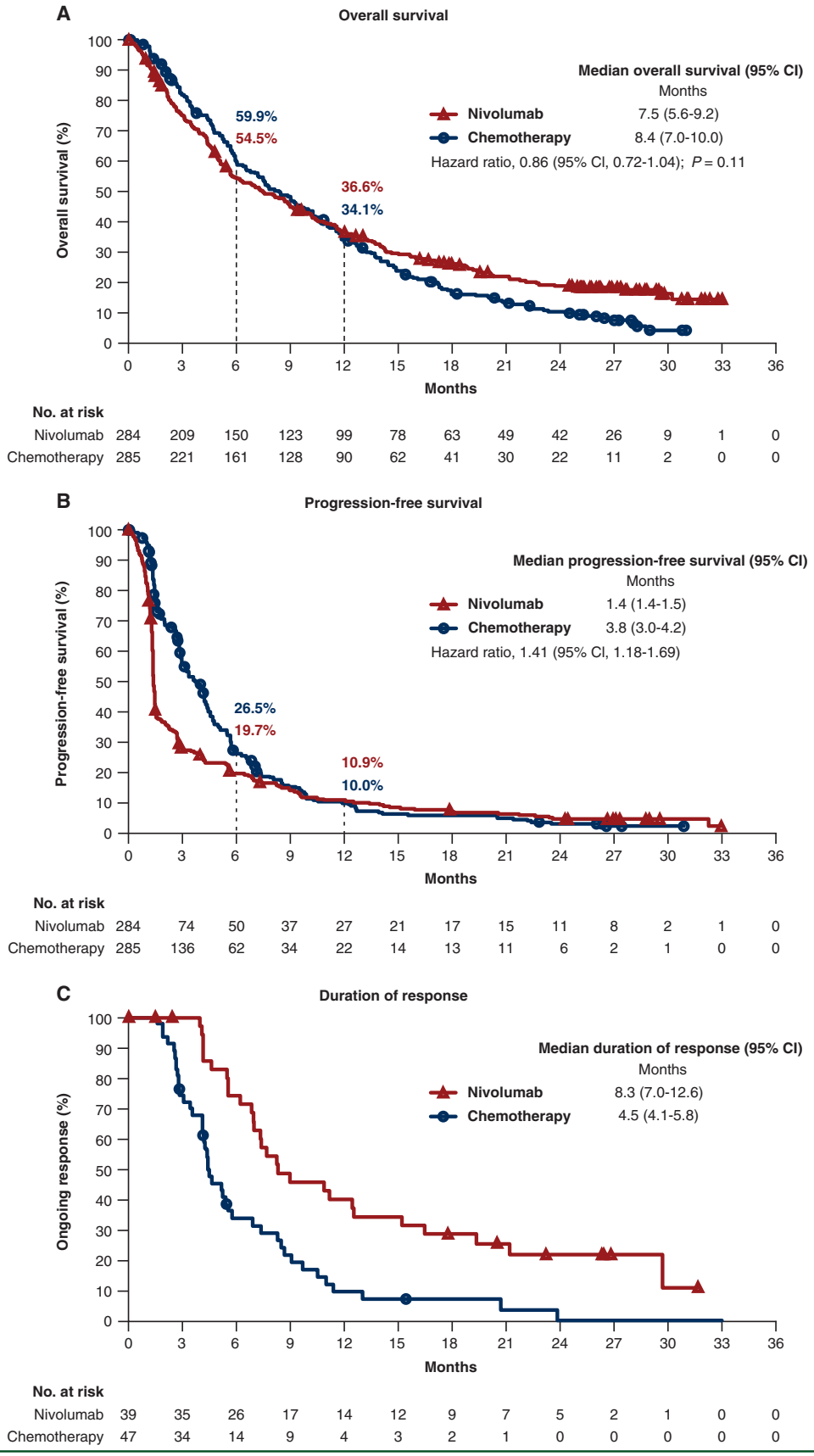


**Figure 1. Efficacy of nivolumab versus chemotherapy.**
(A) Kaplan–Meier estimates of overall survival. (B) Kaplan–Meier estimates of progression-free survival. (C) Kaplan–Meier estimates of duration of response. Hazard ratios are based on a stratified Cox proportional-hazards model. For overall survival, 59 patients (20.8%) in the nivolumab arm and 40 patients (14.0%) in the chemotherapy arm were censored; for progression-free survival, 26 patients (9.2%) in the nivolumab arm and 50 patients (17.5%) were censored.
CI, confidence interval.


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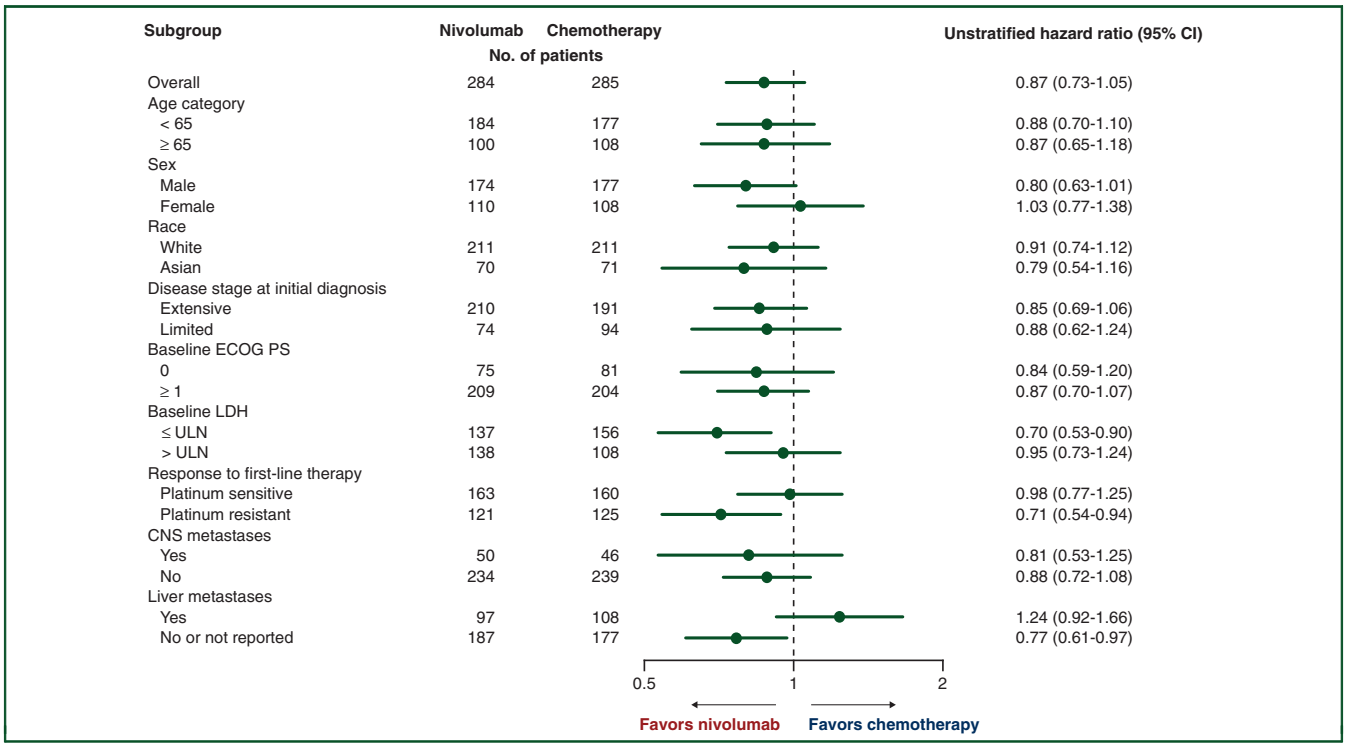


**Figure 2. Exploratory subgroup analysis of overall survival.**
LDH was defined per laboratory standards.
CI, confidence interval; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ULN, upper limit of normal.

of the 569 randomized patients, and of these, only 312 had a valid TMB result. Baseline characteristics were comparable between TMB-evaluable and non-evaluable populations, and between treatment arms (Supplementary Table S5 available at https://doi.org/10.1016/j.annonc.2021.01.071). Median OS for nivolumab versus chemotherapy in the TMB-evaluable population was 5.7 months (95% CI, 4.9-8.3) versus 7.9 months (95% CI, 6.6-10.0) (HR, 1.04; 95% CI, 0.82-1.32), substantially different from that of the TMB non-evaluable population, which had median OS of 9.4 months

**Table 2. Multivariate analysis for overall survival[a]**

| Baseline characteristic | Unstratified HR (95% CI) Nivolumab versus chemotherapy | Interaction *P* value |
|---|---|---|
| Baseline LDH | | 0.1485[b] |
| > upper limit of normal | 0.99 (0.76-1.30) | |
| ≤ upper limit of normal[c] | 0.76 (0.59-0.98) | |
| Response to first-line therapy[d] | | 0.7896 |
| Platinum resistant | 0.83 (0.63-1.11) | |
| Platinum sensitive | 0.88 (0.69-1.12) | |
| Baseline liver metastases | | 0.0477[b] |
| Yes | 1.08 (0.81-1.45) | |
| No[e] | 0.74 (0.59-0.94) | |

CI, confidence interval; HR, hazard ratio; LDH, lactate dehydrogenase.
[a] Unstratified Cox proportional-hazards models including treatment, subgroup, and treatment by subgroup interaction, adjusted for baseline Eastern Cooperative Oncology Group performance status, baseline LDH, baseline liver metastases, and time from initial diagnosis to randomization.
[b] Below cutoff of 0.20 for statistical significance.
[c] Included 9 and 21 patients with no reported data in the nivolumab and chemotherapy groups, respectively.
[d] Platinum sensitive was defined as a progression-free interval ≥90 days after completion of platinum therapy, per case report form; platinum resistant was defined as a progression-free interval <90 days after completion of platinum therapy, per case report form.
[e] Included one patient with no reported data in the chemotherapy group.

**Table 3. Summary of tumor response**

| | Nivolumab (*n* = 284) | Chemotherapy (*n* = 285) |
|---|---|---|
| Objective response[a] | | |
| Patients with response, *n* | 39 | 47 |
| % of patients (95% CI) | 13.7 (10.0-18.3) | 16.5 (12.4-21.3) |
| Estimated odds ratio (95% CI) | 0.80 (0.50-1.27) | |
| Duration of objective response, months[b] | | |
| Median (95% CI) | 8.3 (7.0-12.6) | 4.5 (4.1-5.8) |
| Range | 0.0+ to 31.7+ | 1.6-23.9 |
| Best overall response, *n* (%) | | |
| Complete response | 1 (0.4) | 1 (0.4) |
| Partial response | 38 (13.4) | 46 (16.1) |
| Stable disease | 58 (20.4) | 116 (40.7) |
| Progressive disease | 150 (52.8) | 67 (23.5) |
| Could not be determined | 37 (13.0) | 55 (19.3) |

+ sign indicates censored values; CI, confidence interval.
[a] Objective response was defined as the number of patients with a best overall response of complete or partial response, as determined by the investigator according to RECIST v1.1,[17] divided by the number of randomized patients. The odds ratio was estimated using a two-sided stratified Cochran—Mantel—Haenszel test and the 95% CI was calculated using the Clopper—Pearson method.
[b] Duration of objective response was defined as the time from first confirmed partial or complete response to the date of first documented tumor progression as determined by the investigator according to RECIST v1.1,[17] or death due to any cause. Patients who started any subsequent anticancer therapy without a prior reported progression were censored at the last evaluable tumor assessment before or on the date of initiation of the subsequent anticancer therapy.

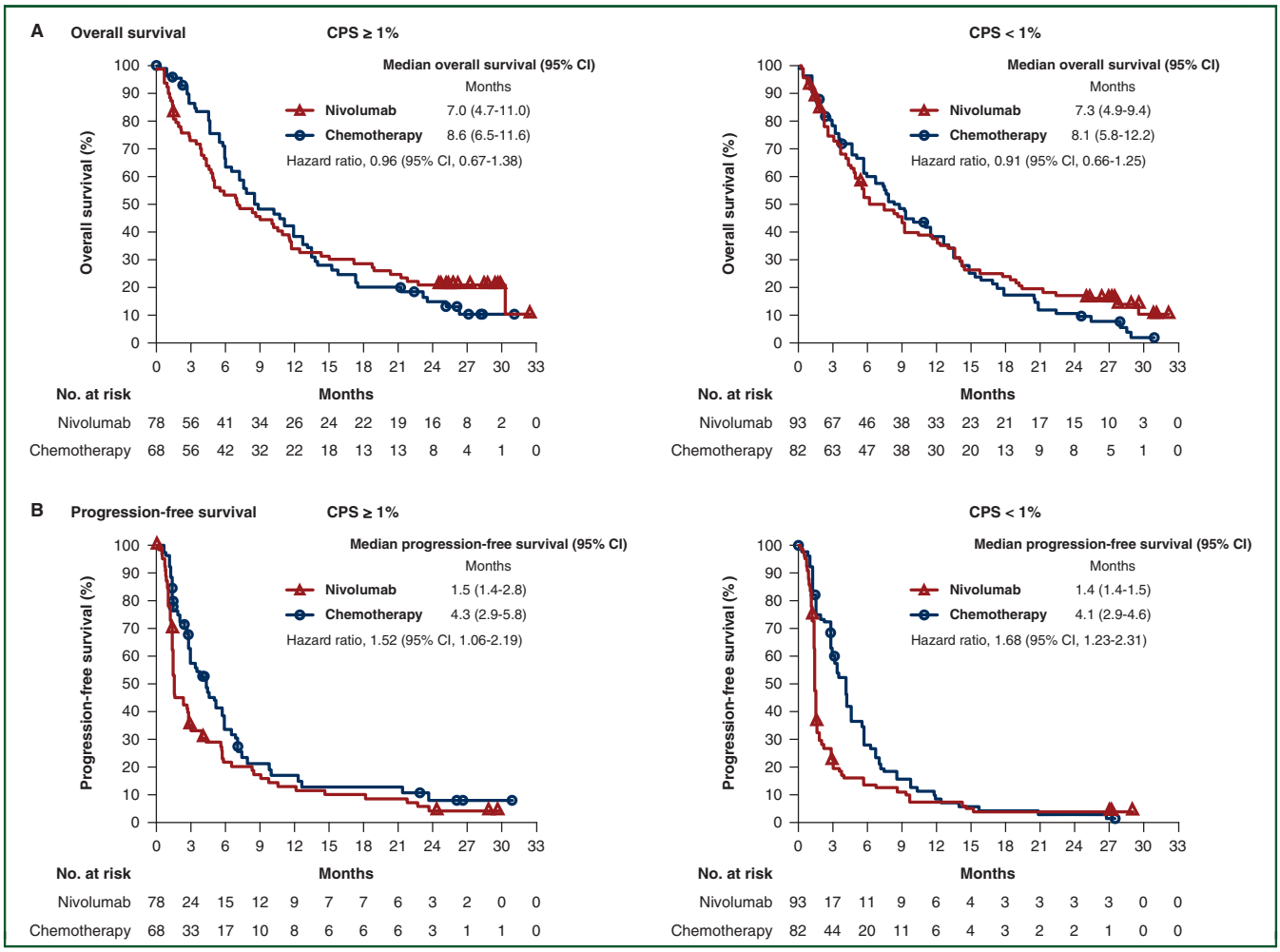


**Figure 3. Efficacy by PD-L1 CPS.**
(A) Kaplan–Meier estimates of overall survival. (B) Kaplan–Meier estimates of progression-free survival.
Hazard ratios are based on an unstratified Cox proportional-hazards model.
CI, confidence interval; CPS, combined positive score; PD-L1, programed death-ligand 1.

(95% CI, 4.7-12.4) versus 9.2 months (95% CI, 6.0-11.6) (HR, 0.73; 95% CI, 0.52-1.02) for nivolumab versus chemotherapy (Supplementary Figure S5 available at https://doi.org/10.1016/j.annonc.2021.01.071). In exploratory analyses to assess the association of TMB with survival, TMB did not appear to predict clinical outcome (*P* value for interaction of TMB by treatment >0.20 for all cutoffs, suggesting no evidence of a higher treatment effect in TMB high versus low with any TMB cutoff). Moreover, OS outcomes were also dissimilar between TMB-evaluable and intention-to-treat (ITT) populations.

### *Safety*

A safety summary for nivolumab and chemotherapy is presented in Table 4. Rates of any treatment-related adverse events (TRAEs) were lower in patients treated with nivolumab than in patients treated with chemotherapy (55.3% versus 90.2%), including grade 3 or 4 events (13.8% versus 73.2%). Compared with chemotherapy, nivolumab was also associated with a lower incidence of serious TRAEs (13.1% versus 32.8%) and TRAEs leading to discontinuation (6.0% versus 14.3%). The most common select TRAEs (those immunologic in nature) with nivolumab were endocrine (11.7%), skin (11.3%), and gastrointestinal (7.1%) events.

Deaths that were attributed to study treatment occurred in two patients with nivolumab (one each from neurologic neoplastic syndrome and atrial fibrillation with acute heart failure) and three patients with chemotherapy (two from febrile neutropenia with sepsis and one from pancytopenia).

## DISCUSSION

The CheckMate 331 trial did not meet its primary endpoint of improved OS with nivolumab versus chemotherapy as second-line treatment in patients with SCLC whose disease relapsed after first-line platinum-based chemotherapy. Although nivolumab demonstrated activity in third- or later-line settings in the phase I/II CheckMate 032 trial,[15] no survival advantage compared with chemotherapy was seen in the current second-line study. Data suggest an initial survival advantage with chemotherapy, with later crossing of the survival curves indicating higher long-term survival

**Table 4. Treatment-related adverse events**[a]

| | Nivolumab ($n$ = 282) | | Chemotherapy ($n$ = 265) | |
|---|---|---|---|---|
| | Any grade | Grade 3 or 4 | Any grade | Grade 3 or 4 |
| Any | 156 (55.3) | 39 (13.8) | 239 (90.2) | 194 (73.2) |
| Serious | 37 (13.1) | 22 (7.8) | 87 (32.8) | 81 (30.6) |
| Led to discontinuation | 17 (6.0) | 12 (4.3) | 38 (14.3) | 25 (9.4) |
| Occurred in ≥15% of patients in either group (by preferred term) | | | | |
| Asthenia | 25 (8.9) | 2 (0.7) | 42 (15.8) | 17 (6.4) |
| Fatigue | 25 (8.9) | 0 | 54 (20.4) | 13 (4.9) |
| Decreased appetite | 21 (7.4) | 1 (0.4) | 40 (15.1) | 5 (1.9) |
| Anemia | 13 (4.6) | 0 | 147 (55.5) | 68 (25.7) |
| Nausea | 14 (5.0) | 0 | 47 (17.7) | 2 (0.8) |
| Platelet count decreased | 5 (1.8) | 1 (0.4) | 63 (23.8) | 34 (12.8) |
| Thrombocytopenia | 5 (1.8) | 0 | 80 (30.2) | 56 (21.1) |
| White blood cell count decreased | 4 (1.4) | 1 (0.4) | 45 (17.0) | 30 (11.3) |
| Leukopenia | 4 (1.4) | 0 | 43 (16.2) | 31 (11.7) |
| Neutropenia | 4 (1.4) | 1 (0.4) | 91 (34.3) | 73 (27.5) |
| Neutrophil count decreased | 0 | 0 | 58 (21.9) | 45 (17.0) |
| Select (by system organ class)[b] | | | | |
| Endocrine | 33 (11.7) | 2 (0.7) | 0 | 0 |
| Skin | 32 (11.3) | 1 (0.4) | 3 (1.1) | 1 (0.4) |
| Gastrointestinal | 20 (7.1) | 3 (1.1) | 24 (9.1) | 4 (1.5) |
| Hepatic | 13 (4.6) | 7 (2.5) | 15 (5.7) | 1 (0.4) |
| Pulmonary | 13 (4.6) | 4 (1.4) | 1 (0.4) | 0 |
| Hypersensitivity | 12 (4.3) | 0 | 16 (6.0) | 2 (0.8) |
| Renal | 6 (2.1) | 1 (0.4) | 5 (1.9) | 0 |
| Treatment-related death[c] | 2 (0.7) | | 3 (1.1) | |

Data presented as $n$ of patients with an event (%).
[a] Includes events reported between the first dose and 30 days after the last dose of study drug.
[b] Select treatment-related adverse events are those with potential immunologic etiology that require frequent monitoring/intervention.
[c] Treatment-related deaths in the nivolumab arm were from neurologic neoplastic syndrome and atrial fibrillation with acute heart failure (in one patient each); deaths in the chemotherapy arm were from febrile neutropenia with sepsis (in two patients) and pancytopenia (in one patient).

with nivolumab in a subset of patients. Exploratory piecewise analysis of OS also showed that HRs at later timepoints (from 6 months) favored nivolumab. An initial benefit of chemotherapy was seen in PFS, although after approximately 8 months, the nivolumab and chemotherapy curves were highly similar. The ORR was numerically higher with chemotherapy versus nivolumab; however, the duration of response was greater with nivolumab, suggesting a prolonged benefit of nivolumab in patients with a response, as previously reported in several cancer types.[12] These data are consistent with other second-line studies of immunotherapy in SCLC; the IFCT-1603 trial,[22] a phase II, randomized, non-comparative trial evaluating atezolizumab monotherapy as a second-line treatment option for SCLC, also failed to show significant efficacy (response rate, 2.3%; median PFS, 1.4 months; median OS, 9.5 months). Data on the tolerability of nivolumab monotherapy in CheckMate 331 were also consistent with those reported in other studies in SCLC[15,23,24] and other tumor types,[12] with no new safety signals observed. TRAEs and serious TRAEs were less common with nivolumab versus chemotherapy.

Exploratory *post hoc* multivariate analyses of OS by baseline characteristics suggested that baseline LDH ≤ ULN and absence of liver metastases at baseline were associated with increased clinical activity of nivolumab versus chemotherapy, after adjusting for baseline prognostic factors. Although the biologic reasons that nivolumab versus chemotherapy may exhibit greater activity in certain subgroups are unclear, these findings are consistent with previous studies in other cancer types.[25-29] LDH may be an indicator of tumor burden and it has been suggested that elevated LDH levels may impair immune checkpoint efficacy via mechanisms including altered metabolism, nutrient availability, and an acidic microenvironment.[30] Additionally, the relatively immune-tolerant microenvironment of the liver has been suggested to limit immune checkpoint efficacy in patients with liver metastases.[28,30] Furthermore, elevated LDH and liver metastases are both prognostic of poor survival in SCLC,[31-33] and therefore may limit patients' chances of surviving long enough to receive clinical benefit from nivolumab.

Findings from a phase II (KEYNOTE-158; $N = 107$) study of pembrolizumab, an anti-PD-1 monoclonal antibody, suggested that PD-L1 CPS may be a predictive marker of outcomes in patients with advanced SCLC.[34] However, a pooled analysis of KEYNOTE-158 and KEYNOTE-028 including patients with recurrent or metastatic SCLC who had received two or more lines of therapy ($N = 83$) suggested antitumor activity regardless of PD-L1 expression.[35] Similarly, in CheckMate 331, CPS status at a cutoff of 1% did not affect OS or PFS outcomes with nivolumab versus chemotherapy. TMB status as determined by whole-exome sequencing has also been suggested to be predictive of improved outcomes with nivolumab; in CheckMate 032 ($N = 401$), a phase I/II trial of nivolumab with or without ipilimumab, patients in the highest tertile for TMB level, experienced improved immunotherapy efficacy compared with those in the low- or medium-TMB tertiles.[36] In the current study, differences in

OS outcomes suggested that patients with non-evaluable TMB were different from those with evaluable TMB and that data on outcomes by TMB category would not be representative of the ITT population, precluding any meaningful analysis of efficacy by TMB status (an exploratory endpoint). Moreover, due to the low TMB data availability and lack of overall treatment effect in the TMB-evaluable population, indicative that the sample was not representative of the ITT population, conditions were not optimal to assess TMB as a predictor of response to immunotherapy.

A key limitation of this study is the limited availability of data on biomarkers predictive of clinical benefit in SCLC, precluding the selection of a patient population most likely to benefit from nivolumab. Furthermore, the Kaplan—Meier curves for OS crossed at approximately 11 months. Primary analysis of OS was based on the stratified log-rank test, which failed to show significance, partly due to loss of power with a crossing hazards situation. The estimated HR from the Cox model represents a time-averaged HR and thus does not adequately describe the difference between nivolumab and chemotherapy groups when the proportional-hazards assumption does not hold. We further described the treatment effect by providing piecewise HRs by 3-month intervals, which showed that HRs at later timepoints (from 6 months) favored nivolumab.

In conclusion, nivolumab monotherapy did not significantly improve OS compared with chemotherapy in patients with relapsed SCLC after first-line platinum-based chemotherapy, although the median duration of response was greater with nivolumab. Nivolumab had a more favorable safety profile than chemotherapy. Further studies may be useful in determining whether specific cutoffs of TMB or other biomarkers can be used to identify certain groups of patients with SCLC who are most likely to benefit from nivolumab.

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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.

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