Five-Year Outcomes From the Randomized, Phase III Trials CheckMate 017 and 057: Nivolumab Versus Docetaxel in Previously Treated Non–Small-Cell Lung Cancer

Hossein Borghaei, DO, MS1; Scott Gettinger, MD2; Everett E. Vokes, MD3; Laura Q. M. Chow, MD, FRCPC4; Marco Angelo Burgio, MD5; Javier de Castro Carpeno, MD, PhD6; Adam Pluzanski, MD, PhD7; Oscar Arieta, MD, MSc8; Osvaldo Áñez Frontera, MD9; Rita Chiarri, MD, PhD10; Charles Butts, MD, FRCP(C)11; Joanna Wójcik-Tomaszewska, MD12; Bruno Coudert, MD13; Marina Chiara Garassino, MD14; Neal Ready, MD, PhD15; Enriqueta Felip, MD, PhD16; Miriam Alonso García, MD17; David Waterhouse, MD, MPH18; Manuel Domíne, MD, PhD19; Fabrice Barlesi, MD, PhD20; Scott Antonia, MD, PhD21; Markus Wohlleber, MD22; David R. Spigel, MD23; Lucio Crino, MD24; Wilfried Enst Erich Eberhardt, MD25; Ang Li, MS26; Sathiya Marimuthu, MD27; and Julie Brahmer, MD, MSc28

abstract

PURPOSE Immunotherapy has revolutionized the treatment of advanced non–small-cell lung cancer (NSCLC). In two phase III trials (CheckMate 017 and CheckMate 057), nivolumab showed an improvement in overall survival (OS) and favorable safety versus docetaxel in patients with previously treated, advanced squamous and nonsquamous NSCLC, respectively. We report 5-year pooled efficacy and safety from these trials.

METHODS Patients (N = 854; CheckMate 017/057 pooled) with advanced NSCLC, ECOG PS ≤ 1, and progression during or after first-line platinum-based chemotherapy were randomly assigned 1:1 to nivolumab (3 mg/kg once every 2 weeks) or docetaxel (75 mg/m² once every 3 weeks) until progression or unacceptable toxicity. The primary end point for both trials was OS; secondary end points included progression-free survival (PFS) and safety. Exploratory landmark analyses were investigated.

RESULTS After the minimum follow-up of 64.2 and 64.5 months for CheckMate 017 and 057, respectively, 50 nivolumab-treated patients and nine docetaxel-treated patients were alive. Five-year pooled OS rates were 13.4% versus 2.6%, respectively; 5-year PFS rates were 8.0% versus 0%, respectively. Nivolumab-treated patients without disease progression at 2 and 3 years had an 82.0% and 93.0% chance of survival, respectively, and a 59.6% and 78.3% chance of remaining progression-free at 5 years, respectively. Treatment-related adverse events (TRAEs) were reported in 8 of 31 (25.8%) nivolumab-treated patients between 3–5 years of follow-up, seven of whom experienced new events; one (3.2%) TRAE was grade 3, and there were no grade 4 TRAEs.

CONCLUSION At 5 years, nivolumab continued to demonstrate a survival benefit versus docetaxel, exhibiting a five-fold increase in OS rate, with no new safety signals. These data represent the first report of 5-year outcomes from randomized phase III trials of a programmed death-1 inhibitor in previously treated, advanced NSCLC.

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ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Historically, 5-year survival rates of patients with advanced non–small-cell lung cancer (NSCLC) who received chemotherapy were < 5%. Effective treatment options for patients without targetable molecular alterations, particularly for those who progressed after first-line chemotherapy, were limited until recently. With clinically meaningful survival benefits, durable responses, and favorable safety profiles versus chemotherapy, immune checkpoint inhibitors have become the standard of care for patients who progressed on or after platinum-based chemotherapy. Immune checkpoint inhibitors are also effective as first-line treatment and are recommended, with or without chemotherapy, as the standard of care for treatment-naive patients with advanced NSCLC.

Nivolumab, a fully human, monoclonal, anti–programmed death-1 (PD-1) antibody, was the first PD-1 inhibitor to demonstrate clinically meaningful activity in NSCLC. Nivolumab is approved in the United States, the European Union, and other countries for second-line treatment of advanced NSCLC, based on improved
overall survival (OS) and a favorable safety profile versus docetaxel in two randomized, open-label, phase III trials in advanced squamous (CheckMate 017; NCT01642004) and nonsquamous (CheckMate 057; NCT01673867) NSCLC with disease progression following platinum-based chemotherapy.\(^4,5,16,17\)

At 2-, 3-, and 4-year follow-ups, OS rate and progression-free survival (PFS) rate from these trials continued to favor nivolumab over docetaxel, with no new safety signals identified for nivolumab.\(^18-20\) Here, we present the pooled 5-year survival and safety data from CheckMate 017 and 057, representing the longest follow-up to date for randomized phase III trials of an immune checkpoint inhibitor in previously treated, advanced NSCLC.

**METHODS**

**Patients**

Eligibility criteria for both trials have been previously described.\(^4,5\)

**Study Design**

CheckMate 017 (previously treated squamous NSCLC) and CheckMate 057 (previously treated nonsquamous NSCLC) were international, randomized, open-label, phase III trials. Patients were randomly assigned 1:1 to receive nivolumab (3 mg/kg once every 2 weeks) or docetaxel (75 mg/m\(^2\) once every 3 weeks) in both trials (Appendix Fig A1, online only). Random assignment was stratified by prior paclitaxel use and geographical location in CheckMate 017 and by prior maintenance treatment and line of therapy (second vs third) in CheckMate 057.

Treatment continued until disease progression, unacceptable toxicity, or other protocol-specifed reasons. Further details on treatment beyond progression in the nivolumab group and crossover in the docetaxel group are given in the Appendix (online only).

Both trials were conducted in accordance with the International Conference on Harmonisation Good Clinical Practice Guidelines and the Declaration of Helsinki. An institutional review board or independent ethics committee at each site approved the trial Protocols (online only). All patients provided written informed consent.

**Assessments**

Tumor assessments were performed by investigators according to RECIST v1.1 at baseline, at 9 weeks, every 6 weeks thereafter during the first year of treatment, and then every 12 weeks until disease progression or discontinuation of therapy in patients receiving nivolumab beyond progression. Patients were followed continuously for survival while receiving treatment and every 3 months after discontinuation.

Safety was assessed throughout the treatment period and at two follow-up visits, which occurred within 100 days of last dose or before the start of crossover treatment. Beyond 100 days from the last dose of treatment, patients with ongoing treatment-related adverse events (TRAEs) were followed until the TRAE resolved, returned to baseline, or was deemed irreversible. The severity of adverse events (AEs) was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Select AEs were defined as having a potential immunologic cause that may require management through immune-modulating medication.

Archival or recent pretreatment tumor biopsy specimens were assessed for expression of PD-1 ligand 1 (PD-L1) protein at a central laboratory using a validated automated immunohistochemical assay (PD-L1 IHC 28-8 pharmDx; Dako, Carpinteria, CA) as previously described.\(^4,5\)
Statistical Analyses
Efficacy and safety were assessed in all randomly assigned patients and in all patients who received at least one dose of the trial drug, respectively, using pooled data from CheckMate 017 and 057 studies. The primary end point was OS for both studies; secondary end points included objective response rate (ORR), PFS, and efficacy by tumor PD-L1 expression. Data for these end points have been previously reported. To investigate the impact of progression-free status on long-term survival, an exploratory landmark analysis of OS at 5 years based on progression-free status at 2, 3, and 4 years was performed. The probability of patients remaining progression-free at later timepoints based on their progression-free status at 2, 3, and 4 years was also assessed.
Survival curves and rates, landmark analyses, and duration of response (DOR) were estimated using the Kaplan-Meier method. Hazard ratios (HRs) and CIs were estimated using a Cox proportional hazard model.

RESULTS
At the database locks (May 8, 2019, for CheckMate 017 and May 16, 2019, for CheckMate 057) for this analysis, the minimum follow-up was 64.2 months and 64.5 months, respectively; the corresponding median follow-up was 69.5 months and 69.4 months.

Baseline characteristics of patients randomly assigned

Patients and Treatment
Baseline characteristics of patients randomly assigned to nivolumab (CheckMate 017: n = 135; CheckMate 057: n = 292) and docetaxel (CheckMate 017: n = 137; CheckMate 057: n = 290) were generally well balanced (Appendix Table A1, online only). Patient disposition is summarized in the Appendix Figure A2, online only. Following a protocol amendment, 23 nivolumab-treated patients transitioned to nivolumab 480 mg once every 4 weeks. Of 427 docetaxel-treated patients, 23 nivolumab-treated patients transitioned to nivolumab 480 mg once every 4 weeks per protocol amendments. At 5 years, 50 of 427 patients randomly assigned to nivolumab and 9 of 427 patients randomly assigned to docetaxel were still alive; 18 of 418 (4.3%) nivolumab-treated patients remained on treatment for ≥5 years; no patients remained on docetaxel. The median (range) number of nivolumab (3 mg/kg) and docetaxel doses in CheckMate 017 was 8.0 (1-151) and 3.0 (1-29), respectively, and in CheckMate 057, the median (range) was 6.0 (1-139) and 4.0 (1-23), respectively.

OS
In the pooled CheckMate 017/057 population, OS remained longer with nivolumab versus docetaxel (HR: 0.68; 95% CI, 0.59 to 0.78). Pooled 5-year OS rates were 13.4% (95% CI, 10.4 to 16.9) with nivolumab versus 2.6% (95% CI, 1.4 to 4.5) with docetaxel (Fig 1A). Consistent with previous reports, most deaths between 3 and 5 years with nivolumab (12 of 14 deaths) and docetaxel (20 of 23 deaths) were due to disease.

Pooled OS rates at 5 years were similar with squamous and nonsquamous histology: 12.3% (95% CI, 7.4 to 18.5) and 14.0% (95% CI, 10.2 to 18.3) with nivolumab and 3.6% (95% CI, 1.4 to 7.8) and 2.1% (95% CI, 0.9 to 4.4) with docetaxel, respectively (Figs 1B and 1C). OS benefit continued to be observed with nivolumab versus docetaxel regardless of tumor PD-L1 expression (Figs 1D and 1E); 5-year OS rates were 18.3% (95% CI, 13.0 to 24.2) versus 3.4% (95% CI, 1.4 to 6.8) in patients with PD-L1 expression ≥1% and 8.0% (95% CI, 4.4 to 13.0) versus 2.0% (95% CI, 0.5 to 5.3) in those with PD-L1 expression <1%.

OS benefit was observed with nivolumab across several subgroups, including patients with baseline liver metastases (HR, 0.67 [95% CI, 0.50 to 0.89]); adrenal metastases (HR, 0.41 [95% CI, 0.27 to 0.60]), neutrophil-to-lymphocyte ratio < median (HR, 0.63 [95% CI, 0.51 to 0.77]), lactate dehydrogenase ≥ upper limit of normal (HR, 0.74 [95% CI, 0.59 to 0.93]), and those with no baseline proton pump inhibitor use (HR, 0.61 [95% CI, 0.51 to 0.72]; Appendix Fig A3, online only).

PFS
PFS rates consistently favored nivolumab versus docetaxel over time (Fig 2A). Pooled 5-year PFS rates were 8.0% (95% CI, 5.4 to 11.2) versus 1.4% and 4.5% with nivolumab and 0% with docetaxel. PFS rates by histology and for patients with PD-L1 expression ≥1% and <1% are shown in the Appendix Figure A4, online only.

Landmark Survival Analyses
Landmark analysis of PFS and OS by progression-free status at 2, 3, and 4 years showed that a high proportion of nivolumab-treated patients remained progression-free at 5 years; no patients were progression-free at 5 years and a 0% chance of being progression-free at 5 years and a 0% chance of PFS with PD-L1 expression ≥1% and <1% are shown in the Appendix Figure A4, online only.

Tumor Response
Consistent with previous reports, the pooled ORR was higher with nivolumab (19.7% [95% CI, 16.0 to 23.8]) than docetaxel (11.2% [95% CI, 8.4 to 14.6]; Appendix Table A2, online only). Since the primary analysis of CheckMate 057, one patient treated with nivolumab improved from
FIG 1. OS of all treated patients: (A) overall, (B) by SQ tumor histology, (C) by NSQ tumor histology, (D) by ≥ 1% PD-L1 expression, and (E) by < 1% PD-L1 expression. Minimum follow-up: CheckMate 017: 64.2 months; CheckMate 057: 64.5 months. HR, hazard ratio; mo, months; No., number; NSQ, nonsquamous; OS, overall survival; PD-L1, programmed death ligand 1; SQ, squamous.
stable disease to partial response (PR) and another, also treated with nivolumab, improved from PR to complete response (CR). No patients from CheckMate 017 experienced a change in the response since the primary analysis.

Median DOR was longer with nivolumab (19.9 months [95% CI, 11.4 to 30.8]) versus docetaxel (5.6 months [95% CI, 4.4 to 7.0]) in the pooled population. Longer DOR with nivolumab was observed regardless of histology or tumor PD-L1 expression (Appendix Fig A5, online only). The pooled

![Graph A](image)

**FIG 2.** (A) PFS\(^a\) and (B) DOR\(^a\) among all treated patients. \(^a\)Per local investigator; minimum follow-up: CheckMate 017: 64.2 months; CheckMate 057: 64.5 months. Since the primary analysis of the CheckMate 057 trial, one patient’s response changed from SD to PR and one from PR to CR. DOR for these two patients was determined according to their latest response category. DOR, duration of response; HR, hazard ratio; mo, months; No., number; PFS, progression-free survival.

FIG 3. PFS and OS landmark analyses by PFS at 2, 3, and 4 years. \(^*\)Based on Kaplan-Meier estimates; \(^b\)Number of patients at risk. OS, overall survival; PFS, progression-free survival.
5-year DOR rate with nivolumab was 32.2% (95% CI, 21.9 to 43.0); no patients in the docetaxel arm had ongoing responses at 5 years (Fig 2B).

5-Year Survivors

Baseline characteristics of patients who survived ≥ 5 years in the nivolumab arm (n = 50) and docetaxel arm (n = 9) were generally similar to the overall population and those who survived < 1 year (n = 222 and n = 282, respectively), despite numerical differences in ECOG PS 0 (in both arms), PD-L1 expression ≥ 1% (nivolumab arm), and stage IIIB NSCLC (docetaxel arm; Appendix Fig A3).

Among the 50 patients who survived ≥ 5 years in the nivolumab arm (including 18 who had switched to nivolumab 480 mg once every 4 weeks), 21 (42.0%) had not progressed by 5 years and 21 (42.0%) had progressed (Fig 5A; Appendix Fig A6, online only), and eight (16.0%) had been censored for PFS. The median (range) duration of treatment for nivolumab and docetaxel in 5-year survivors was 36.9 months (1.8-76.2± months) and 3.5 months (0.7-20.0 months), respectively; 35 patients received nivolumab treatment for ≥ 2 years and 18 remained on nivolumab at 5 years. Of the 32 patients who had discontinued nivolumab, the median duration of treatment was 27.7 months. Aside from disease progression, reasons for discontinuation included TRAEs, AEs unrelated to the study drug, or maximum clinical benefit.

Of the patients who survived ≥ 5 years in the nivolumab arm (n = 50), 5 patients had CRs and 34 patients had PRs. A total of eight and three patients had stable and progressive disease, respectively. In the docetaxel arm, four of the 5-year survivors (n = 9) had a PR, two patients had stable disease, and three patients had progressive disease. No docetaxel-treated survivors had a CR.

A total of 24 nivolumab-treated patients were known to receive subsequent therapy, of whom 10 had subsequent immunotherapy (Appendix Tables A4 and A5, online only). At 5 years, 5 of 50 nivolumab-treated patients were progression-free and did not require subsequent therapy (Appendix Fig A6); reasons for discontinuing nivolumab (after 8.8-43.5 months of treatment) were TRAEs (n = 3), maximum clinical benefit (n = 1), and AE unrelated to study drug (n = 1). Among the 9 patients who survived ≥ 5 years in the docetaxel arm (including two patients who crossed over to receive nivolumab 3 mg/kg once every 2 weeks and one who received 3 mg/kg and 480 mg once every 4 weeks), eight had progressed and one was censored for PFS. All nine patients received subsequent therapy; four had subsequent immunotherapy (excluding patients who crossed over to nivolumab; Appendix Table A4; Fig 5B).

Safety

No patients received treatment with docetaxel for more than 2 years; therefore, updated safety data as of the 5-year follow-up are presented only for patients who received nivolumab. At 5 years, 284 of 418 patients (67.9%) treated with nivolumab experienced TRAEs; 45 patients (10.8%) had grade 3-4 events. No new safety signals were observed. Between 3- and 5-year minimum follow-ups, eight of 31 patients (25.8%) still receiving nivolumab had TRAEs (Table 1), of whom one patient (3.2%) had a grade 3 event (increased lipase); there were no grade 4 events. A total of
Overall, 27 (6.5%) nivolumab-treated patients experienced TRAEs of any grade leading to discontinuation; the most common (in ≥ 2 patients) were pneumonitis (n = 6; 1.4%) and interstitial lung disease (n = 3; 0.7%), and colitis,
increased alanine aminotransferase, increased AST, and rash (n = 2; 0.5%). Since the 3-year follow-up, one patient in the nivolumab arm experienced a TRAE, leading to discontinuation (grade 2 nummular eczema).\textsuperscript{19} At the time of database lock, no new treatment-related deaths had occurred since the primary analyses (n = 1 in the nivolumab arm and n = 4 in the docetaxel arm).\textsuperscript{4,5} Consistent with previous reports, few treatment-related select AEs occurred after the 3-year minimum follow-up (Fig 4).\textsuperscript{18,19} Of the 31 patients who remained on treatment within nivolumab between 3 and 5 years of follow-up, five patients (16.1%) experienced treatment-related select AEs: four patients (12.9%) with skin or subcutaneous tissue disorders (one each of grade 1-2 erythema, pruritus, rash, and skin exfoliation) and two patients (6.5%) with a GI disorder (grade 1-2 diarrhea). A total of eight different events were reported in these five patients between 3 and 5 years of treatment, of which two events were recurrent (pruritus and rash occurring in one patient each).

### DISCUSSION

This is the longest follow-up to date for randomized phase III trials of a PD-1 inhibitor in previously treated, advanced NSCLC. After a 5-year minimum follow-up in the CheckMate 017 and 057 studies, nivolumab continued...
to demonstrate clinically meaningful OS, PFS, and DOR benefits versus docetaxel and maintained a favorable safety profile. The pooled 5-year OS rate was 13.4% with nivolumab, representing a five-fold increase over docetaxel (2.6%). These findings are consistent with previously reported 5-year and 6-year OS rates with nivolumab among patients with previously treated, advanced NSCLC in CheckMate 003 trial (15.6% and 14.7%, respectively).20 Notably, the majority of patients without docetaxel (8.0% and 0%, respectively) was consistent with previously reported findings.21 The OS rates detailed here are also similar to the five-year OS rates observed in the single-arm, phase I trial of pembrolizumab in patients with previously treated NSCLC (15.5%).22 OS benefit with nivolumab versus docetaxel was observed regardless of tumor histology. Notably, OS benefit (HR < 1) was observed with nivolumab versus docetaxel in patients with tumor PD-L1 expression ≥ 1% (5-year OS rates, 18.3% v 3.4%) or < 1% (8.0% v 2.0%) and across a variety of patient subgroups, demonstrating the potential for nivolumab to improve outcomes in a diverse patient population. In this analysis, no baseline clinical or tumor characteristics were identified to clearly distinguish long-term or short-term survivors in either treatment arm and, because of the disparity in sample sizes across treatment arms, multivariate analysis was not considered appropriate; only nine patients were alive in the docetaxel group at 5 years, making subgroup analysis unfeasible.

The pooled 5-year PFS rate with nivolumab versus docetaxel (8.0% and 0%, respectively) was consistent with previous analyses.20 Notably, the majority of patients without disease progression at 2, 3, and 4 years after treatment with nivolumab remained progression-free at 5 years and survived ≥ 5 years. Although exploratory, these findings provide new information about the probability of remaining progression-free at subsequent timepoints and alive at 5 years, by progression-free status at 2, 3, and 4 years. This analysis provides insight into long-term efficacy outcomes and management of previously treated, advanced NSCLC following treatment with nivolumab. Consistent with the 2- and 3-year follow-ups, responses achieved with nivolumab were durable;18,19 nearly one-third of patients who achieved an objective response had ongoing responses at 5 years versus none with docetaxel. The 5-year timepoint is considered a clinical landmark to evaluate long-term survival, and data beyond 5 years are scarce; a longer follow-up may be required to assess the outcomes of these patients.23

In both this analysis and a pooled analysis across four nivolumab trials in previously treated NSCLC, the proportion of nivolumab-treated patients who remained alive appeared to stabilize at approximately 3 years and plateau thereafter.20 A similar observation was noted in a pooled analysis of ipilimumab in patients with unresectable or advanced melanoma, where the survival curve extended beyond 5 years.24 This suggests that long-term survival beyond 5 years may also be possible in NSCLC; however, this remains to be addressed in future analyses. Indeed, patients with previously treated NSCLC who received nivolumab in CheckMate 003, which has the longest survival follow-up to date among trials of PD-1 inhibitors in previously treated, advanced NSCLC, exhibited similar OS rates at 4, 5, and 6 years (15.6%, 15.6%, and 14.7%, respectively).20 Importantly, no new safety signals were observed with a 5-year follow-up; nivolumab maintained a favorable safety profile versus docetaxel, without long-term toxicity. No evidence of late-onset grade 3-4 treatment-related select AEs was observed.

Among ≥ 5-year survivors in the nivolumab arm (n = 50), the median duration of therapy was 36.9 months and 18 of 50 remained on nivolumab at 5 years, suggesting that some patients may achieve long-term survival with continuous nivolumab treatment. In contrast, median duration off-treatment among the 5-year survivors who had discontinued nivolumab was 41.9 months, and 10.0% (n = 5) of 5-year survivors in the nivolumab arm were off treatment, without subsequent therapy, and had not progressed, suggesting benefit even for patients who stopped nivolumab treatment. Meanwhile, exploratory data from CheckMate 153 suggested a survival benefit with continuous nivolumab treatment beyond 1 year versus stopping treatment at 1 year.25 The optimal treatment duration of nivolumab and PD-1 inhibitors in general for patients with advanced NSCLC remains to be fully elucidated.

In conclusion, 5-year outcomes from the randomized phase III CheckMate 017 and 057 trials demonstrate that nivolumab can provide long-term survival benefit with durable responses and a tolerable safety profile in patients with previously treated, advanced NSCLC. Furthermore, some patients appear to maintain prolonged disease control even after stopping systemic therapy. These findings represent an important advancement in the treatment of lung cancer.

**AFFILIATIONS**

1Fox Chase Cancer Center, Philadelphia, PA
2Yale Comprehensive Cancer Center, New Haven, CT
3University of Chicago Medicine and Biologic Sciences Division, Chicago, IL
4University of Washington, Seattle Cancer Care Alliance, Seattle, WA
5Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy
6Hospital De Madrid, Norte Sanchinarro, Madrid, Spain
7Maria Sklodowska-Curie Inst of Oncology, Warsaw, Poland
8Instituto Nacional De Cancerologia, Mexico City, Mexico
9Centro de Investigación Clínica Bradford Hill and Centro Internacional de Estudios Clínicos, Santiago, Chile
10Ospedale S. Maria Della Misericordia, Perugia, Italy
11Cross Cancer Institute, Edmonton, AB, Canada
12Provincial Center of Oncology in Gdańsk, Gdańsk, Poland
13Centre Georges-François Leclerc, Dijon, France
14Istituto Nazionale per Lo Studio e La Cura, Milano, Italy
Author Contributions

Conception and design: Scott Gettinger, Javier de Castro Carpeno, Neal Ready, Enriqueta Felip, David R. Spigel, Wilfried Enst Erich Eberhardt, Ang Li, Julie Brahmer

Financial support: Enriqueta Felip

Administrative support: Enriqueta Felip

Provision of study materials or patients: Everett E. Vokes, Laura Q. M. Chow, Marco Angelo Burgio, Javier de Castro Carpeno, Oscar Arrieta, Osvaldo Arén Frontera, Charles Butts, Bruno Coudert, Neal Ready, Enriqueta Felip, David Waterhouse, Fabrice Barlesi, Markus Wohlieber, David E. Gerber, David R. Spigel, Lucio Crino, Wilfried Enst Erich Eberhardt, Julie Brahmer

Collection and assembly of data: Hossein Borghaei, Scott Gettinger, Laura Q. M. Chow, Marco Angelo Burgio, Javier de Castro Carpeno, Adam Puzanski, Oscar Arrieta, Osvaldo Arén Frontera, Joanna Wójcik-Tomaszewksa, Bruno Coudert, Neal Ready, Enriqueta Felip, Miriam Alonso Garcia, David Waterhouse, Manuel Domine, Fabrice Barlesi, Scott Antonio, Markus Wohlieber, David E. Gerber, Grzegorz Czyzewicz, Lucio Crino, Wilfried Enst Erich Eberhardt, Ang Li, Sathiya Marimuthu, Julie Brahmer

Data analysis and interpretation: Hossein Borghaei, Scott Gettinger, Everett E. Vokes, Laura Q. M. Chow, Javier de Castro Carpeno, Adam Puzanski, Rita Chiari, Charles Butts, Bruno Coudert, Marina Chiara Garassino, Neal Ready, Enriqueta Felip, David Waterhouse, Manuel Domine, Fabrice Barlesi, Scott Antonio, Markus Wohlieber, David R. Spigel, Lucio Crino, Wilfried Enst Erich Eberhardt, Ang Li, Sathiya Marimuthu, Julie Brahmer

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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Corresponding Author

Hossein Borghaei, DO, MS, Fox Chase Cancer Center, 333 Cottman Avenue, Philadelphia, PA 19111; e-mail: hossein.borghaei@fccc.edu

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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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**Hossein Borghaei**  
**Honoraria:** Bristol Myers Squibb, Celgene, Axiom Biotechnologies, Pfizer  
**Consulting or Advisory Role:** Bristol Myers Squibb, Lilly, Celgene, Genentech, Pfizer, Boehringer Ingelheim, EMD Serono, Trovagene, Novartis, Merck, AstraZeneca, Genmab, Regeneron, Cantargia AB, BioNTech AG, Abbvie, PharmaMar, Takeda, Amgen, HUYA Bioscience International, SonettBio, Rgenix  
**Research Funding:** Millennium, Merck, Celgene, Bristol Myers Squibb, Lilly  
**Travel, Accommodations, Expenses:** Bristol Myers Squibb, Lilly, Clovis Oncology, Celgene, Genentech, Novartis, Merck, Amgen  
**Other Relationship:** University of Pennsylvania, Takeda, Incyte  

**Scott Gettinger**  
**Consulting or Advisory Role:** Bristol Myers Squibb, Nektar  
**Research Funding:** Bristol Myers Squibb, Genentech, ARIAD/TAKEDA, Iovance Biotherapeutics  

**Everett E. Vokes**  
**Stock and Other Ownership Interests:** Coordination Pharmaceuticals  
**Honoraria:** Abbvie, Amgen, AstraZeneca, Bristol Myers Squibb, Celgene, Lilly, EMD Serono, Genentech, GlaxoSmithKline, Merck, Novartis, Regeneron, Takeda, Radius Health, Ascendis Pharma  
**Consulting or Advisory Role:** Abbvie, Amgen, AstraZeneca, Bristol Myers Squibb, Celgene, Lilly, Merck, Regeneron, Novartis, EMD Serono, Genentech, GlaxoSmithKline, Takeda, Radius Health, Ascendis Pharma  
**Research Funding:** Abbvie, Bristol Myers Squibb, Celgene, Novartis, Lilly  
**Travel, Accommodations, Expenses:** Abbvie, Amgen, Bristol Myers Squibb, Celgene, Lilly, EMD Serono, Genentech, GlaxoSmithKline, Merck, Novartis, Regeneron  

**(OPTIONAL) Open Payments Link:** https://openpaymentsdata.cms.gov/physician/930740

**Laura Q. M. Chow**  
**Consulting or Advisory Role:** Merck, Dynavax, Alkermes, Novartis, Pfizer, Cullinan Management Inc, Elicio, Daichi Sankyo  
**Research Funding:** Pfizer, Genentech, Novartis, LillyImmClone, Merck, AstraZeneca/MedImmune, Bristol Myers Squibb, Incyte, Seattle Genetics, Dynavax, ALX Oncology, Alkermes  

**Javier de Castro Carpeno**  
**Consulting or Advisory Role:** AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Merck Sharp & Dohme, Roche, Pfizer, Pierre Fabre, Takeda, Tesaro, Teva  
**Research Funding:** Roche  
**Travel, Accommodations, Expenses:** AstraZeneca Spain, Merck Sharp & Dohme, Roche  

**Adam Puzanski**  
**Honoraria:** Roche, Bristol Myers Squibb, AstraZeneca, MSD, Pfizer, Takeda  
**Consulting or Advisory Role:** Boehringer Ingelheim  
**Travel, Accommodations, Expenses:** Pfizer, Bristol Myers Squibb, AstraZeneca  

**Oscar Arrieta**  
**Honoraria:** Pfizer, AstraZeneca, Boehringer Ingelheim, Roche  
**Consulting or Advisory Role:** AstraZeneca, Roche, Lilly, Merck, Bristol Myers Squibb  
**Research Funding:** Roche, Bristol Myers Squibb, Merck, AstraZeneca  
**Travel, Accommodations, Expenses:** Lilly  

**Oswaldo Aréñ Frontera**  
**Employment:** Pfizer  
**Stock and Other Ownership Interests:** Pfizer  
**Honoraria:** Pfizer  
**Consulting or Advisory Role:** Bristol Myers Squibb, BMS COLOMBIA  

**Rita Chiari**  
**Speakers’ Bureau:** Takeda  

**Charles Butts**  
**Research Funding:** Bristol Myers Squibb, AstraZeneca, Merck (per-patient funding for clinical trials; paid to institution, not investigator)  

**Joanna Wojcik-Tomaszewska**  
**Research Funding:** Bristol Myers Squibb, MSD Oncology, Roche, Lilly, AVED, ICON Clinical Research  

**Bruno Coudert**  
**Honoraria:** Roche Laboratories France, AstraZeneca, Bristol Myers Squibb  
**Consulting or Advisory Role:** Roche Laboratories France  

**Marina Chiara Garassino**  
**Honoraria:** MSD Oncology, AstraZeneca/MedImmune, GlaxoSmithKline, Takeda, Roche, Bristol Myers Squibb  
**Consulting or Advisory Role:** Bristol Myers Squibb, MSD, AstraZeneca, Novartis, Takeda, Roche, Tiziana Life Sciences, Sanofi, Celgene, Daiichi Sankyo, Inivata, Incyte, Pfizer, Seattle Genetics, Lilly, GlaxoSmithKline, Bayer, Blueprint Medicines, Janssen  
**Speakers’ Bureau:** Janssen, Takeda, MSD Oncology, Celgene, Incyte, Roche, Bristol Myers Squibb, Otsuka, Lilly  
**Research Funding:** Bristol Myers Squibb, MSD, Roche/Genentech, AstraZeneca/MedImmune, AstraZeneca, Pfizer, GlaxoSmithKline, Novartis, Merck, Incyte, Takeda, Spectrum Pharmaceuticals, Blueprint Medicines, Lilly, AstraZeneca, Ipsen, Turning Point Therapeutics, Janssen, Exelixis, MedImmune, Array BioPharma, Sanofi  
**Travel, Accommodations, Expenses:** Pfizer, Roche, AstraZeneca  

**Neal Ready**  
**Consulting or Advisory Role:** Bristol Myers Squibb, Novartis, Merck, Abbvie, Celgene, Merck Serono, AstraZeneca, G1 Therapeutics, Jazz Pharmaceuticals  
**Speakers’ Bureau:** Bristol Myers Squibb  
**Research Funding:** Bristol Myers Squibb, Merck  

**Enriqueta Felip**  
**Consulting or Advisory Role:** Consulting or Advisory Role: Roche, Boehringer Ingelheim, AstraZeneca, Bristol Myers Squibb, Guardant Health, Novartis, Takeda, Abbvie, Blueprint Medicines, Lilly, Merck KGaA, Merck Sharp & Dohme, Springer, GlaxoSmithKline, JANSSEN, MEDISCAPE, Merck KGaA, Bayer, Amgen, Pfizer, Puma Biotechnology, Genzyme  
**Speakers’ Bureau:** AstraZeneca, Bristol Myers Squibb, Novartis, Boehringer Ingelheim, Merck Sharp & Dohme, Roche, Pfizer, Lilly, Takeda, mediscape, Prime Oncology, Touchine, PEER VOICE, Springer  
**Research Funding:** FUNDACIÓN MERCK SALUD, EMD Serono  
**Other Relationship:** GRIFOLS  

**David Waterhouse**  
**Consulting or Advisory Role:** Bristol Myers Squibb, AZTherapies, Abbvie, Amgen, Celgene, MCgVenny Global, CTI, Janssen Oncology, Seattle Genetics, Jazz Pharmaceuticals, Exelixis  
**Speakers’ Bureau:** Bristol Myers Squibb, Janssen Oncology  
**Travel, Accommodations, Expenses:** Bristol Myers Squibb  

**Manuel Domíne**  
**Consulting or Advisory Role:** AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, MSD Oncology, Pfizer, Roche  
**Travel, Accommodations, Expenses:** AstraZeneca, Boehringer Ingelheim, Lilly, Pfizer, Roche  

**Fabrice Barlesi**  
**Honoraria:** Genentech/Roche, Pfizer, Pierre Fabre, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Lilly, Novartis, Pierre Fabre, Merck Serono, MSD Oncology, Takeda, Bayer  
**Consulting or Advisory Role:** Roche/Genentech, Pfizer, Novartis, Pierre Fabre, Bristol Myers Squibb, AstraZeneca/MedImmune, Boehringer Ingelheim, Lilly, Merck Serono, MSD Oncology, Takeda, Bayer  
**Research Funding:** Roche/Genentech, AstraZeneca/MedImmune, Bristol Myers Squibb, Pierre Fabre, Pierre Fabre, Amgen, Bayer, Boehringer Ingelheim, Eisai, Lilly, Ipsen, Innate Pharma, Novartis, Merck Serono, MSD Oncology, Pfizer, Sanofi/Aventis, Takeda  
**Travel, Accommodations, Expenses:** Roche/Genentech, Bristol Myers Squibb, AstraZeneca/MedImmune, MSD Oncology  

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Scott Antonia
Stock and Other Ownership Interests: Cellular Biomedicine Group
Honoraria: AstraZeneca, Bristol Myers Squibb, Merck, Boehringer Ingelheim, Novartis, CBMG, Memgen
Consulting or Advisory Role: Bristol Myers Squibb, AstraZeneca, Merck, Boehringer Ingelheim, Novartis, Memgen, FLX Bio
Travel, Accommodations, Expenses: Bristol Myers Squibb, AstraZeneca, Merck, Boehringer Ingelheim, FLX Bio, Novartis

Markus Wohlieber
Consulting or Advisory Role: Bristol Myers Squibb
Travel, Accommodations, Expenses: Bristol Myers Squibb, AstraZeneca

David E. Gerber
Stock and Other Ownership Interests: Gilead Sciences
Consulting or Advisory Role: Samsung Bioepis, Catalyst Pharmaceuticals
Research Funding: BerGenBio, Karyopharm Therapeutics, AstraZeneca
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Uncompensated Relationships: Bristol Myers Squibb

Wilfried Enst Erich Eberhardt
Honoraria: AstraZeneca, Roche Pharma AG, Bristol Myers Squibb, MSD Oncology, Boehringer Ingelheim, Lilly, Takeda, Pfizer, Amgen, Novartis, Abbvie
Consulting or Advisory Role: AstraZeneca, Roche, Bristol Myers Squibb, MSD Oncology, Bayer Health, Lilly, Boehringer Ingelheim, Takeda, Pfizer
Research Funding: AstraZeneca, Lilly, Bristol Myers Squibb

Sathiya Marimuthu
Employment: Bristol Myers Squibb
Stock and Other Ownership Interests: Bristol Myers Squibb
Travel, Accommodations, Expenses: Bristol Myers Squibb

Julie Brahmer
Honoraria: Roche/Genentech
Consulting or Advisory Role: Bristol Myers Squibb, Lilly, Celgene, Syndax, Janssen Oncology, Merck, Amgen, Genentech
Research Funding: Bristol Myers Squibb, AstraZeneca, Incyte, Spectrum Pharmaceuticals, Revolution
Travel, Accommodations, Expenses: Bristol Myers Squibb, Roche/Genentech
Other Relationship: Bristol Myers Squibb, Merck, Janssen Oncology

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APPENDIX 1. SUPPLEMENTARY METHODS

Patients

Patients were ≥ 18 years of age and had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, measurable disease according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), and disease recurrence or progression during or after one prior platinum-based chemotherapy regimen. In CheckMate 057, an additional line of prior therapy with a tyrosine kinase inhibitor was permitted in patients with known epidermal growth factor receptor mutations or anaplastic lymphoma kinase rearrangements.

Study design

Patients in the nivolumab arm were permitted to continue treatment after initial disease progression if they met protocol-defined criteria, including if the trial drug was tolerated and patients were obtaining clinical benefit as determined by the investigator. Those in the docetaxel group who no longer derived benefit were eligible to receive nivolumab in the crossover and/or extension phases of the trials following a 3-week washout period. After the readout of the primary end point, the protocol was amended such that nivolumab-treated patients were allowed to transition to nivolumab 480 mg every 4 weeks; docetaxel-treated patients who ended treatment at any time during the trials could cross over to nivolumab, either 3 mg/kg every 2 weeks or 480 mg every 4 weeks.

FIG A1. Study design.a,b aNCT01642004; database lock: May 8, 2019; minimum follow-up for OS, 64.2 months; bNCT01673867; database lock: May 16, 2019; minimum follow-up for OS, 64.5 months; cOptional switch to nivolumab 480 mg every 4 weeks allowed as per the protocol amendment in September 2016; dAfter completion of the primary analyses, patients in the docetaxel arms who ended treatment at any time during the trials were allowed to cross over to nivolumab; eDefined by RECIST 1.1; patients receiving nivolumab may be treated beyond progression under protocol-defined circumstances; fAs assessed by investigator. ALK, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; IV, intravenous; NSCLC, non–small-cell lung cancer; NSQ, nonsquamous; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; PROs, patient-reported outcomes; Q2W, every 2 weeks; Q3W, every 3 weeks; R, randomized; SQ, squamous; TKI, tyrosine kinase inhibitor. Reprinted from Annals of Oncology, 29(4), Waterhouse M, Domine M, Garassino LQM, et al, “Nivolumab Versus Docetaxel in Previously Treated Advanced Nonsmall-Cell Lung Cancer (CheckMate 017 and CheckMate 057): 3-Year Update and Outcomes in Patients With Liver Metastases,” 959-965, 2018, with permission from Elsevier.
A

n = 352 assessed for eligibility

n = 80 ineligible
• n = 67 no longer met study criteria
• n = 6 AEs
• n = 3 withdrew consent
• n = 3 deaths
• n = 1 other

n = 272 enrolled

n = 135 randomly assigned to nivolumab
• n = 4 did not receive study treatment

n = 135 included in efficacy analyses
n = 131 included in safety analyses

n = 131 received nivolumab

n = 5 ongoing

n = 129 received docetaxel

n = 0 ongoing

n = 129 included in efficacy analyses
n = 129 included in safety analyses

n = 126 discontinued treatment
• n = 95 disease progression
• n = 10 study drug toxicity
• n = 8 AE unrelated to study drug
• n = 5 patient request
• n = 5 consent withdrawal
• n = 1 maximum clinical benefit
• n = 1 poor/non-compliance
• n = 1 no longer met study criteria

n = 129 discontinued treatment
• n = 79 disease progression
• n = 13 study drug toxicity
• n = 13 AE unrelated to study drug
• n = 5 consent withdrawal
• n = 4 patient request
• n = 2 no longer met study criteria
• n = 1 death
• n = 3 not reported

FIG A2. CONSORT diagram of patient disposition for (A) CheckMate 017 and (B) CheckMate 057. AE, adverse event.
B

N = 792 assessed for eligibility

n = 210 ineligible
• n = 163 no longer met study criteria
• n = 24 withdrew consent
• n = 5 deaths
• n = 4 AEs
• n = 1 lost to follow-up
• n = 1 administrative reason by sponsor
• n = 12 other

n = 582 enrolled

n = 292 randomly assigned to nivolumab
• n = 5 did not receive study treatment

n = 287 received nivolumab

n = 275 discontinued treatment
• n = 209 disease progression
• n = 23 study drug toxicity
• n = 23 AE unrelated to study drug
• n = 7 patient request
• n = 5 consent withdrawal
• n = 2 no longer met study criteria
• n = 1 maximum clinical benefit
• n = 1 death
• n = 4 other

n = 12 ongoing

n = 292 included in efficacy analyses
n = 287 included in safety analyses

n = 290 randomly assigned to docetaxel
• n = 22 did not receive study treatment

n = 268 received docetaxel

n = 268 discontinued treatment
• n = 179 disease progression
• n = 43 study drug toxicity
• n = 11 AE unrelated to study drug
• n = 17 patient request
• n = 10 maximum clinical benefit
• n = 5 consent withdrawal
• n = 1 death
• n = 2 other

n = 0 ongoing

n = 290 included in efficacy analyses
n = 268 included in safety analyses

FIG A2. (Continued).
FIG A3. Forest plot of OS in predefined subgroups. Hazard ratios were not reported for subgroups with fewer than 10 patients per treatment group. *Not reported in two and one patients with nivolumab and docetaxel, respectively. †Unknown in seven and four patients with nivolumab and docetaxel, respectively. Median NLR was 4.80. NLR was not reported in two patients each in nivolumab and docetaxel arms. ‡Not reported in three and two patients with nivolumab and docetaxel, respectively. ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PD-L1, programmed death ligand 1; PPI, proton pump inhibitor; ULN, upper limit of normal.

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FIG A4. PFS in patients with (A) SQ tumor histology, (B) NSQ tumor histology, (C) $\geq 1\%$ PD-L1 expression, and (D) $< 1\%$ PD-L1 expression. *Per local investigator; minimum follow-up: CheckMate 017: 64.2 months and CheckMate 057: 64.5 months. HR, hazard ratio; NC, not calculable; No., number; NSQ, nonsquamous; PD-L1, programmed death ligand 1; PFS, progression-free survival; SQ, squamous.
FIG A5. DOR* in all treated patients with (A) SQ tumor histology, (B) NSQ tumor histology, (C) ≥ 1% PD-L1 expression, and (D) < 1% PD-L1 expression. *Per local investigator. DOR, duration of response; NC, not calculable. No., number; NSQ, nonsquamous; PD-L1, programmed death ligand 1; SQ, squamous.
FIG A6. Treatment status of survivors at 5 years. *Median (range) nivolumab treatment duration: 36.9 (1.8-76.2 months). †The other 3 patients progressed (1.8, 4.5, and 44.2 months, respectively) after discontinuing nivolumab treatment. ‡After nivolumab treatment. §Information on subsequent therapy was not available as of database lock. **Nivolumab treatment durations for individual patients: 8.8, 21.7, 36.6, 43.3, and 43.5 months. ††Median (range) nivolumab treatment duration: 68.4 (62.9-76.2 months). ‡‡Includes two patients treated with nivolumab as first subsequent therapy. §§Because of the receipt of subsequent therapy. AE, adverse event; TRAEs, treatment-related adverse events.
| Characteristic, n (%) | Pooled CheckMate 017 and 057 | CheckMate 017 | CheckMate 057 |
|----------------------|-------------------------------|---------------|---------------|
| | Nivolumab (n = 427) | Docetaxel (n = 427) | Nivolumab (n = 135) | Docetaxel (n = 137) | Nivolumab (n = 292) | Docetaxel (n = 290) |
| Median age, years (range) | 61.0 (37-85) | 64.0 (21-85) | 62.0 (39-85) | 64.0 (42-84) | 61.0 (37-84) | 64.0 (21-85) |
| < 65 | 263 (61.6) | 228 (53.4) | 79 (58.5) | 73 (53.3) | 184 (63.0) | 155 (53.4) |
| ≥ 65 | 164 (38.4) | 199 (46.6) | 56 (41.5) | 64 (46.7) | 108 (37.0) | 135 (46.6) |
| Male | 262 (61.4) | 265 (62.1) | 111 (82.2) | 97 (70.8) | 151 (51.7) | 168 (57.9) |
| ECOG PS | | | | | | |
| 0 | 111 (26.0) | 132 (30.9) | 27 (20) | 37 (27.0) | 84 (28.8) | 95 (32.8) |
| 1 | 314 (73.5) | 293 (68.6) | 106 (78.5) | 100 (73.0) | 208 (71.2) | 193 (66.6) |
| Smoking status | | | | | | |
| Current or former | 352 (82.4) | 356 (83.4) | 121 (89.6) | 129 (94.2) | 231 (79.1) | 227 (78.3) |
| Never | 68 (15.9) | 67 (15.7) | 10 (7.4) | 7 (5.1) | 58 (19.9) | 60 (20.7) |
| Stage IIIb | 49 (11.5) | 48 (11.2) | 29 (21.5) | 24 (17.5) | 20 (6.8) | 24 (8.3) |
| Stage IV | 377 (88.3) | 378 (88.5) | 105 (77.8) | 112 (81.8) | 272 (93.2) | 266 (91.7) |
| Histology | | | | | | |
| SQ | 132 (30.9) | 137 (32.1) | 132 (97.8) | 137 (100.0) | 0 | 0 |
| NSQ | 295 (69.1) | 290 (67.9) | 3 (2.2) | 0 | 292 (100.0) | 290 (100.0) |
| CNS metastases | 45 (10.5) | 42 (9.8) | 9 (6.7) | 8 (5.8) | 36 (12.3) | 34 (11.7) |
| Liver metastases | 99 (23.2) | 94 (22.0) | 27 (20.0) | 34 (24.8) | 72 (24.7) | 60 (20.7) |
| PD-L1 status | | | | | | |
| Evaluable | 348 (81.5) | 332 (77.8) | 117 (86.7) | 108 (78.8) | 231 (79.1) | 224 (77.2) |
| < 1% | 163 (46.8) | 153 (46.1) | 54 (46.2) | 52 (48.1) | 109 (47.2) | 101 (45.1) |
| ≥ 1% | 185 (53.2) | 179 (53.9) | 63 (53.8) | 56 (51.9) | 122 (52.8) | 123 (54.9) |

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; NSQ, nonsquamous; PD-L1, programmed death ligand 1; SQ, squamous.

*In the docetaxel arm of CheckMate 057, ECOG PS was not reported for one patient and one patient had an ECOG PS of 3. In the nivolumab arm of CheckMate 017, ECOG PS was not reported for two patients.

*In CheckMate 017, smoking status was not reported for four patients in the nivolumab arm and one patient in the docetaxel arm; in CheckMate 057, smoking status was not reported for three patients in both treatment arms.

*Disease stage was not reported for one patient in each treatment arm of CheckMate 017.

*Calculated as a percentage of PD-L1-evaluable patients.
### TABLE A2. Tumor Response in All Randomly Assigned Patients and by Trial

|                  | Pooled Population | CheckMate 017 | CheckMate 057 |
|------------------|-------------------|---------------|---------------|
|                  | Nivolumab<sup>a</sup> (n = 427) | Docetaxel (n = 427) | Nivolumab (n = 135) | Docetaxel (n = 137) | Nivolumab<sup>a</sup> (n = 292) | Docetaxel (n = 290) |
| **ORR**          |                   |               |               |                   |                   |
| n/N              | 84/427            | 48/427        | 27/135        | 12/137            | 57/292            | 36/290          |
| %                | 19.7              | 11.2          | 20.0          | 8.8               | 19.5              | 12.4            |
| **BOR, n (%)**   |                   |               |               |                   |                   |
| CR               | 6 (1.4)           | 1 (0.2)       | 1 (0.7)       | 0                 | 5 (1.7)           | 1 (0.3)         |
| PR               | 78 (18.3)         | 47 (11.0)     | 26 (19.3)     | 12 (8.8)          | 52 (17.8)         | 35 (12.1)       |
| SD               | 112 (26.2)        | 168 (39.3)    | 39 (28.9)     | 47 (34.3)         | 73 (25.0)         | 121 (41.7)      |
| PD               | 185 (43.3)        | 133 (31.1)    | 56 (41.5)     | 48 (35.0)         | 129 (44.2)        | 85 (29.3)       |
| NE               | 46 (10.8)         | 78 (18.3)     | 13 (9.6)      | 30 (21.9)         | 33 (11.3)         | 48 (16.6)       |
| **DOR**          |                   |               |               |                   |                   |
| Median (95% CI), months | 19.9 (11.4 to 30.8) | 5.6 (4.4 to 7.0) | 25.2 (9.8 to NR) | 7.5 (2.8 to 14.0) | 17.2 (10.8 to 30.8) | 5.6 (4.4 to 6.9) |
| HR (95% CI)      | 0.26 (0.16 to 0.40) | 0.30 (0.12 to 0.75) |                   |                   | 0.26 (0.15 to 0.43) |               |

Abbreviations: BOR, best overall response; CR, complete response; DOR, duration of response; HR, hazard ratio; NE, not evaluable; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

<sup>a</sup>Since the primary analysis of the CheckMate 057 trial, one patient’s response changed from SD to PR, and one from PR to CR. ORR, BOR, and DOR were reported according to the latest response category for these two patients.
### Table A3. Baseline Characteristics of < 1-Year and ≥ 5-Year Survivors on Nivolumab and Docetaxel in the Pooled CheckMate 017 and 057 Population

| Characteristic, n (%) | < 1-Year Survivors (n = 222) | 5-Year Survivors (n = 50) | < 1-Year Survivors (n = 282) | 5-Year Survivors (n = 9) |
|-----------------------|-----------------------------|--------------------------|-----------------------------|--------------------------|
| **Median age, years (range)** | 62.0 (37-85) | 60.0 (41-74) | 64.0 (21-85) | 67.0 (49-75) |
| < 65                  | 136 (61.3) | 33 (66.0) | 150 (53.2) | 3 (33.3) |
| ≥ 65                  | 86 (38.7) | 17 (34.0) | 132 (46.8) | 6 (66.7) |
| Male                  | 140 (63.1) | 31 (62.0) | 181 (64.2) | 5 (55.6) |
| **ECOG PS**           |               |                      |                      |                      |
| 0                     | 37 (16.7) | 20 (40.0) | 61 (21.6) | 5 (55.6) |
| 1                      | 183 (82.4) | 30 (60.0) | 219 (77.7) | 4 (44.4) |
| **Smoking status**    |               |                      |                      |                      |
| Current or former     | 185 (83.3) | 42 (84.0) | 239 (84.8) | 7 (77.8) |
| Never                 | 33 (14.9) | 6 (12.0) | 41 (14.5) | 2 (22.2) |
| **Stage IIIb**        | 25 (11.3) | 9 (18.0) | 29 (10.3) | 3 (33.3) |
| Stage IV              | 197 (88.7) | 41 (82.0) | 253 (89.7) | 6 (66.7) |
| **Histology**         |               |                      |                      |                      |
| SQ                    | 77 (34.7) | 14 (28.0) | 104 (36.9) | 4 (44.4) |
| NSQ                   | 145 (65.3) | 36 (72.0) | 178 (63.1) | 5 (55.6) |
| **Liver metastases**  | 31 (14.0) | 4 (8.0) | 31 (11.0) | 0 |
| **CNS metastases**    | 62 (27.9) | 6 (12.0) | 76 (27.0) | 0 |
| **EGFR mutation status** |           |                      |                      |                      |
| Positive              | 26 (11.7) | 2 (4.0) | 20 (7.1) | 3 (33.3) |
| Not detected          | 78 (35.1) | 23 (46.0) | 109 (38.7) | 1 (11.1) |
| Not reported          | 118 (53.2) | 25 (50.0) | 153 (54.3) | 5 (55.6) |
| **ALK mutation status** |           |                      |                      |                      |
| Positive              | 3 (1.4) | 1 (2.0) | 3 (1.1) | 0 |
| Not detected          | 59 (26.6) | 14 (28.0) | 84 (29.8) | 2 (22.2) |
| Not reported          | 160 (72.1) | 35 (70.0) | 195 (69.1) | 7 (77.8) |
| **PD-L1 status**      |               |                      |                      |                      |
| Evaluable             | 176 (79.3) | 40 (80.0) | 221 (78.4) | 7 (77.8) |
| < 1%                  | 90 (51.1) | 10 (25.0) | 103 (46.6) | 3 (42.9) |
| ≥ 1%                  | 86 (48.9) | 30 (75.0) | 118 (53.4) | 4 (57.1) |
| ≥ 10%                 | 47 (26.7) | 26 (65.0) | 81 (36.7) | 2 (28.6) |
| ≥ 50%                 | 27 (15.3) | 22 (55.0) | 43 (19.5) | 2 (28.6) |

Abbreviations: ALK, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; NSQ, nonsquamous; PD-L1, programmed death ligand 1; SQ, squamous.

*Not reported in two patients (< 1-year survivors) in the nivolumab arm and one patient (< 1-year survivor) in the docetaxel arm; one patient (< 1-year survivor) in the docetaxel arm had an ECOG PS of 3.

*Unknown for four patients (< 1-year survivors) and two patients (≥ 5-year survivors) in the nivolumab arm, and two patients (< 1-year survivors) in the docetaxel arm.

*Calculated as a percentage of PD-L1–evaluable patients.

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## TABLE A4. Subsequent Therapies Received by 5-Year Survivors

| Subsequent Therapy, n (%)<sup>a</sup> | Nivolumab (n = 50)<sup>b</sup> | Docetaxel (n = 9)<sup>c</sup> |
|--------------------------------------|------------------------------|-----------------------------|
| Any<sup>d</sup>                      | 24 (48.0)                    | 9 (100.0)                   |
| Radiotherapy                        | 16 (66.7)                    | 5 (55.6)                    |
| Surgery                             | 7 (29.2)                     | 2 (22.2)                    |
| Local therapy only                  | 6 (25.0)                     | 1 (11.1)                    |
| Systemic therapy                    | 18 (75.0)                    | 8 (88.9)                    |
| Immunotherapy                       | 10 (41.6)                    | 4 (44.4)<sup>d</sup>       |
| Nivolumab                           | 10 (41.6)                    | 2 (22.2)                    |
| Other anti–PD-(L)1                  | 0                            | 2 (22.2)                    |
| Anti–CTLA-4                          | 1 (4.2)                      | 1 (11.1)                    |
| Investigational or unspecified      | 2 (8.3)                      | 1 (11.1)                    |
| Chemotherapy                        | 7 (29.2)                     | 4 (44.4)                    |
| ALK/EGFR inhibitor                  | 3 (12.5)                     | 3 (33.3)                    |
| VEGF/VEGFR inhibitor                | 1 (4.2)                      | 1 (11.1)                    |
| Investigational agent or other      | 1 (4.2)                      | 1 (11.1)                    |

Abbreviations: ALK, anaplastic lymphoma kinase; CTLA-4, cytotoxic T lymphocyte antigen-4; EGFR, epidermal growth factor receptor; PD-1, programmed death-1; PD-L1, programmed death ligand 1, VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

<sup>a</sup>Percentages are based on patients who received subsequent treatment excluding the category any therapy for which the percentages are based on the number of 5-year survivors.

<sup>b</sup>A total of eight patients in the nivolumab arm and one patient in the docetaxel arm were censored.

<sup>c</sup>Includes patients still continuing trial treatment; patients may have received > 1 subsequent therapy.

<sup>d</sup>A total of three of nine patients crossed over to receive on study nivolumab treatment (3 mg/kg every 2 weeks).
| Country            | Investigators                                                                 |
|--------------------|-------------------------------------------------------------------------------|
| Argentina          | E. Korbenfeld (Buenos Aires), C. M. Martin (Buenos Aires), N. Pilnik (Cordoba), G. Recondo (Buenos Aires), J. J. Zarba (Tucuman) |
| Australia          | J. Adams (Elizabeth Vale), M. Brown (Adelaide), B. Markman (East Bentleigh), F. X. Parnis (Kurralla Park) |
| Austria            | J. Eckmayr (Wels), A. Kavina (Vienna), M. Studnicka (Salzburg) |
| Canada             | S. Banerji (Winnipeg), K. Marquis (Rimouski) |
| Chile              | O. Aren Frontera (Recoleta), L. Matamala (Antofagasta) |
| Czech Republic     | L. Havel (Praha) |
| France             | F. Barlesi (Marseille), A. Bizieux (La Roche sur Yon), J. Fayette (Lyon), W. Hilgers (Avignon), H. Lena (Rennes), B. Mennecier (Strasbourg), C. Raspaud (Toulouse), G. Zalcman (Caen) |
| Germany            | W. Eberhardt (Essen), W. Engel-Riedel (Koeln), M. Kohlhaeufi (Geringen), M. Reck (Grosshansdorf), M. Steins (Heidelberg) |
| Hungary            | E. Juhasz (Budapest), K. Udud (Budapest) |
| Ireland            | O. Breathnach (Dublin) |
| Italy              | D. Amadori (Ravenna), R. Chiari (Perugia), M. Garassino (Milano), G. Pasello (Padova) |
| Mexico             | O. Arrieta-Rodriguez (Tlalpan), M. Aviles (Hermosillo), M. D. L. Garcia (Col. Doctores), J. L. Gonzalez Trujillo (Leon) |
| Netherlands        | J. G. J. V. Aerts (Rotterdam), P. Baas (Amsterdam) |
| Norway             | A. Helland (Oslo) |
| Peru               | L. Mas (Lima), E. A. Vargas (Arequipa) |
| Poland             | G. Czyzewicz (Kraków), J. Jassem (Gdańsk), A. Pluzanski (Warszawa), P. Rozanowski (Olsztyn), P. Serwatowski (Szczecin) |
| Romania            | C. Cainap (Cluj-Napoca), S. Curescu (Timisoara), C. H. Ianul (Bucharest), D. Lungulescu (Craiova), C. Volovat (Iași) |
| Russian Federation | V. A. Gorbunova (Moscow), N. A. Karaseva (St. Petersburg), D. Komov (Moscow), L. Manzyuk (Moscow) |
| Spain              | M. Alonso (Seville), M. Domine (Madrid), E. Felip (Barcelona), F. Javier de Castro Carpeno (Madrid), G. Lopez-Vivanco (Barakaldo) |
| United Kingdom     | M. Lind (Cottingham), C. Ottensmeier (Southampton), Y. J. Summers (Withington), P. J. Woll (Sheffield) |
| United States      | M. Almubarak (Morgantown, WV), S. J. Antonia (Tampa, FL), G. R. Blumenschein (Houston, TX), H. Borghaei (Philadelphia, PA), J. Brahmer (Baltimore, MD), D. B. Daniel (Chattanooga, TN), D. E. Gerber (Dallas, TX), S. Gettinger (New Haven, CT), R. C. Hermann (Marietta, GA), L. Horn (Nashville, TN), F. J. Kudrik (Columbia, SC), B. W. Lash (Sayre, PA), N. Ready (Durham, NC), K. Reckamp (Duarte, CA), R. E. Reilly (Langhorne, PA), H. J. Ross (Scottsdale, AZ), C. Rudin (New York, NY), J. G. Schneider (Mineola, NY), A. Shaw (Boston, MA), D. R. Spigel (Nashville, TN), E. E. Vokes (Chicago, IL), D. M. Waterhouse (Cincinnati, OH), H. J. West (Seattle, WA) |
| Country          | Investigators                                                                 |
|------------------|-------------------------------------------------------------------------------|
| Argentina        | D. Kaen (La Rioja), E. Korbenfeld (Buenos Aires), L. Lupinacci (Buenos Aires), C. Martin (Buenos Aires), G. Recondo (Buenos Aires) |
| Australia        | E. Abdi (Tweed Heads), M. Brown (Adelaide), V. Ganju (Frankston), E. McCaffrey (Woolloongabba), M. Moore (Melbourne), F. Parnis (Adelaide) |
| Austria          | J. Bollitschek (Linz), J. Eckmayr (Wels), A. Kavina (Wien), M. Studnicka (Salzburg) |
| Brazil           | C. H. Barrios (Porto Alegre), J. Dias (Barretos), I. Lima (Fortaleza), C. Mathias (Salvador), R. Pereira (Porto Alegre), V. Santos (Rio De Janeiro) |
| Canada           | C. A. Butts (Edmonton), K. Marquis (Quebec)                                    |
| Chile            | O. Aren Frontera (Santiago), P. Gonzalez Mella (Viña del Mar), P. Salman (Santiago) |
| Czech Republic   | J Krejci (Prague)                                                             |
| France           | F. Barlesi (Marseille), C. Chouaid (Creteil), B. Coudert (Dijon), J. Fayette (Lyon), C. Lamour (Poitiers), H. Lena (Rennes), M. Marcq (La Roche-sur-Yon), C. Raspaud (Toulouse) |
| Germany          | L. Bullinger (Ulm), T.-O. Emde (Recklinghausen), W. Engel-Riedel (Cologne), C. Kortsik (Mainz), M. Reck (Grosshansdorf), C. -P. Schneider (Bad Berka), M. Steins (Heidelberg), M. Wohleber (Gerlingen) |
| Hong Kong        | J. C. M. Ho (Pok Fu Lam), J. Li (Kowloon)                                      |
| Hungary          | K. Udud (Budapest)                                                            |
| Italy            | D. Amadori (Ravenna), A. Bettini (Bergamo), R. Chiari (Perugia), M. Garassino (Milan), M. Maio (Siena), B. Melotti (Bologna), G. Pasello (Padova), M. Tiseo (Parma) |
| Mexico           | O. Arrieta-Rodriguez (Tlalpan), Y. Bautista (Mexico City), F. Medina-Soto (Monterrey) |
| Norway           | O. T. Brustugun (Oslo)                                                        |
| Peru             | C. Lozada ( Lima), L. Mas ( Lima), E. A. Vargas (Arequipa)                    |
| Poland           | G. Czyzewicz (Kraków), A. Pluzanski (Warsaw), M. Suszko-Kazanowicz (Olsztyn), J. Wojcik-Tomaszewska (Gdańsk) |
| Romania          | C. Cainap (Cluj-Napoca), S. Curescu (Tîrgu-Mureș), C. H. Ianuli (București), D. Lungulescu (Craiova), C. Volovat (Iași) |
| Russian Federation | V. Gorbunova (Moscow), E. Podrubkaya (Moscow)                              |
| Singapore        | A. Y. Chang (Singapore City), D. Lim (Singapore City)                          |
| Spain            | A. Alonso (Sevilla), M. Domine (Madrid), E. Felip (Barcelona), F. Javier de Castro Carpeno (Madrid), G. Lopez-Vivanco (Bilbao) |
| Switzerland      | R. Cathomas (Chur), A. Zippelius (Basel)                                      |
| United States    | M. Almubarak (Morgantown, WV), S. Antonia (Tampa, FL), M. Awad (Boston, MA), G. R. Blumenschein (Houston, TX), D. Bodkin (San Diego, CA), H. Borghaei (Philadelphia, PA), J. Brahmer (Baltimore, MD), L. Q. M. Chow (Seattle, WA), D. B. Daniel (Chattanooga, TN), K. Dragnev (Lebanon, NH), E. Gamboa (Kennesaw, WA), L. Gandhi (Boston, MA), D. E. Gerber (Dallas, TX), S. Gettinger (New Haven, CT), R.C. Herrmann (Marietta, GA), A. Kramer (San Francisco, CA), F. Kudrit (Columbia, SC), B. Lash (San Diego, CA), B. Salvo (Norfolk, VA), N. Ready (Durham, NC), K. Reckamp (Duarte, CA), R. E. Reilly (Langhome, PA), H.J. Ross (Scottsdale, AZ), C. Rudin (New York, NY), J.G. Schneider (Mineola, NY), D. R. Spigel (Nashville, TN), E.E. Vokes (Chicago, IL), D.M. Waterhouse (Cincinnati, OH), H.J. West (Seattle, WA) |