Four-year survival with nivolumab in patients with previously treated advanced non-small-cell lung cancer: a pooled analysis

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Summary

Background Phase 3 clinical data has shown higher proportions of patients with objective response, longer response duration, and longer overall survival with nivolumab versus docetaxel in patients with previously treated advanced non-small-cell lung cancer (NSCLC). We aimed to evaluate the long-term benefit of nivolumab and the effect of response and disease control on subsequent survival.

Methods We pooled data from four clinical studies of nivolumab in patients with previously treated NSCLC (CheckMate 017, 057, 063, and 003) to evaluate survival outcomes. Trials of nivolumab in the second-line or later setting with at least 4 years follow-up were included. Comparisons of nivolumab versus docetaxel included all randomised patients from the phase 3 CheckMate 017 and 057 studies. We did landmark analyses by response status at 6 months to determine post-landmark survival outcomes. We excluded patients who did not have a radiographic tumour assessment at 6 months. Safety analyses included all patients who received at least one dose of nivolumab.

Findings Across all four studies, 4-year overall survival with nivolumab was 14% (95% CI 11–17) for all patients (n=664), 19% (15–24) for those with at least 1% PD-L1 expression, and 11% (7–16) for those with less than 1% PD-L1 expression. In CheckMate 017 and 057, 4-year overall survival was 14% (95% CI 11–18) in patients treated with nivolumab, compared with 5% (3–7) in patients treated with docetaxel. Survival subsequent to response at 6 months on nivolumab or docetaxel was longer than after progressive disease at 6 months, with hazard ratios for overall survival of 0·18 (95% 0·12–0·27) for nivolumab and 0·43 (0·29–0·65) for docetaxel; for stable disease versus progressive disease, hazard ratios were 0·52 (0·37–0·71) for nivolumab and 0·80 (0·61–1·04) for docetaxel. Long-term data did not show any new safety signals.

Interpretation Patients with advanced NSCLC treated with nivolumab achieved a greater duration of response compared with patients treated with docetaxel, which was associated with a long-term survival advantage.

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Introduction

Lung cancer, which is the most common type of cancer worldwide,[1] has historically been associated with poor outcomes. In the USA, the proportion of patients with metastatic lung cancer alive at 5 years after diagnosis between 2008–15 was estimated to be about 5%.[2] The advent of immunotherapy as a second-line treatment for patients with advanced non-small-cell lung cancer (NSCLC) in 2014 was an important milestone in the improvement of outcomes for these patients. Based on data from multiple randomised controlled trials,[3–6] single-agent immunotherapy with antibodies directed against PD-1 or PD-L1 has become the standard of care for patients with metastatic NSCLC who progressed during or after treatment with platinum chemotherapy and had not previously received immunotherapy.[7] CheckMate 003,[8] a dose-escalation study of the anti-PD-1 antibody nivolumab in patients with solid tumours, has the longest reported follow-up for survival in patients with NSCLC who were treated with immunotherapy after disease progression on other therapies. The estimated proportion of patients alive at 5 years after the start of nivolumab treatment was 16% in this patient population.[8] Results of the phase 3 CheckMate 017 and 057 studies[3,4] showed that nivolumab significantly prolonged overall survival versus docetaxel in patients with previously treated advanced squamous and non-squamous NSCLC, respectively, with an unprecedented 17% of patients treated with nivolumab alive at 3 years versus 8% for docetaxel.[9,10]

In CheckMate 017 and 057,[3,4] the proportion of patients with an objective response was improved with nivolumab versus docetaxel, and median duration of response increased by almost three times.[9] Furthermore, subgroup analyses suggested that the overall survival benefit associated with nivolumab versus docetaxel was

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Research in context

Evidence before this study

We searched the scientific literature for long-term survival outcomes with approved PD-1 and PD-L1 inhibitors in the treatment of previously treated advanced NSCLC. We used the search terms "atezolizumab" AND "nivolumab" AND "pembrolizumab" AND "non-small cell lung cancer" AND "overall survival" AND "previously treated" to search for publications in PubMed from Jan 24, 2014 to Jan 22, 2019, and for congress abstracts presented in 2018 at annual congresses of the American Association of Cancer Research, the American Society of Clinical Oncology, the European Society for Medical Oncology, and the World Conference on Lung Cancer. Our search results showed that monotherapy with PD-1 or PD-L1 inhibitor antibodies in randomised controlled trials improves survival compared with docetaxel in patients with advanced NSCLC previously treated with chemotherapy. Key benefits of these immunotherapies are the durability of responses and the improved long-term survival compared with docetaxel. In addition, greater maximum reduction in tumour target lesions (depth of response) has been associated with longer progression-free survival and overall survival. However, the effect of response status on long-term survival has not been evaluated in detail or in a large patient population to provide more robust analyses.

Added value of this study

Our analyses of 4-year survival outcomes in pooled populations from four studies, including two randomised studies comparing nivolumab and docetaxel, represent, to our knowledge, the longest follow-up to date for immunotherapy in a large population of patients with previously treated advanced NSCLC. The results show a continued long-term survival advantage with nivolumab versus docetaxel up to and beyond 4 years. Six-month landmark analyses of overall survival by response category show that patients with a response (at 6 months) had the greatest post-landmark survival benefit. Additionally, stable disease at the landmark provided a survival benefit versus progressive disease. A survival benefit of response was maintained even after loss of response. In nivolumab-treated patients with disease progression, those who had a previous complete or partial response had the longest overall survival post-progression. A smaller post-progression survival benefit was noted in patients with disease progression after initial achievement of stable disease.

Implications of all the available evidence

Although it has been known for some time that nivolumab is associated with much longer duration of response than docetaxel in patients with previously treated advanced NSCLC, to our knowledge, the current analyses show for the first time that an objective response to nivolumab is associated with an exceptionally durable survival benefit, with the median not reached at 4 years from the time of response. Part of this sustained benefit is attributable to extended survival even after disease progression. Corresponding survival benefits with docetaxel were substantially smaller. Overall, the results show that responses to nivolumab compared with docetaxel are more durable and have a more sustained effect on survival, even after loss of response.

greatest among patients who achieved an objective response.[9]

The long-term and durable overall survival provided by immunotherapy was first shown with ipilimumab in a large population of patients with melanoma using a pooled analysis from 12 studies with up to 10 years of follow-up.[11] Herein, to determine if nivolumab provides similar durable benefit for patients with lung cancer, we assessed duration of response, overall survival, and progression-free survival in a large population of patients with previously treated advanced NSCLC with a minimum follow-up of 4 years. We pooled patients treated with nivolumab from four studies: CheckMate 017,[3] 057,[4] 063,[12] and 003.[8,13]

Methods

Study design and data collection

We analysed long-term outcomes in patients with previously treated advanced NSCLC from pooled populations of four nivolumab studies with a minimum follow-up of 4 years: CheckMate 017,[3] 057,[4] 063,[12] and 003.[8,13] Study designs, eligibility criteria, and primary outcomes for these studies have been reported previously,[3,4,12,13] and additional details are provided in the appendix (p 4). To analyse survival and safety outcomes with nivolumab only, we pooled data from all nivolumab-treated patients with previously treated NSCLC in the four studies. For comparative analyses of survival outcomes with nivolumab and docetaxel, we pooled data from the intention-to-treat populations of CheckMate 017 and 057. The pooled analyses did not account for study-level clustering.

CheckMate 017 and 057 were randomised, controlled phase 3 studies of nivolumab 3 mg/kg every 2 weeks versus docetaxel 75 mg/m² every 3 weeks in patients with previously treated squamous (CheckMate 017) and non-squamous NSCLC (CheckMate 057).[3,4] After the readout of the primary endpoint of CheckMate 017 and 057, patients treated with nivolumab could transition to nivolumab 480 mg every 4 weeks. Eligible patients in the docetaxel groups without treatment benefit could move to nivolumab treatment, either 3 mg/kg every 2 weeks or 480 mg every 4 weeks. CheckMate 063 included 117 patients who were treated with nivolumab 3 mg/kg every 2 weeks for advanced, refractory, squamous NSCLC.[12] The NSCLC cohort from CheckMate 003, a phase 1 dose-escalation, cohort-expansion study in patients with select solid tumours, included 129 patients with squamous or non-squamous tumour histology who were treated with nivolumab 1 mg/kg, 3 mg/kg, or 10 mg/kg every 2 weeks.[8,13]

See Online for appendix

Patients were treated with nivolumab until disease progression or unacceptable toxicity, except in CheckMate 003 where treatment was restricted to 96 weeks, with the possibility of drug rechallenge if patients progressed while on the study.[8] Data on response to subsequent treatment after disease progression were not collected in any of the studies included in this analysis.

Procedures

Survival outcomes reported include overall survival and progression-free survival from the time of randomisation in the combined CheckMate 017 and 057 population or treatment initiation in the pooled four studies. To determine the effect of response on survival, we did exploratory analyses of overall survival from a 6-month landmark for patients categorised by their response status (complete response or partial response, stable disease, or progressive disease) at the 6-month timepoint. Landmark analyses avoid introducing bias from the estimation of overall survival from randomisation on subsequently observed response categories during the study—an approach that can overstate the effect of response on survival (immortal time bias).[14] We excluded patients who did not have a radiographic tumour assessment at 6 months (owing to death or loss to follow-up). In the landmark analysis, response categories were determined on the basis of information at 6 months only and are different from those used to determine the best overall response, which was based on all data from study follow-up. We chose the 6-month timepoint to avoid misclassifying patients who responded as non-responders, while allowing sufficient follow-up to assess the effect of landmark response status on long-term survival. In most patients with a complete or partial response, responses were observed within the first 6 months of treatment and were ongoing at 6 months; few responses occurred after this timepoint. A previous sensitivity analysis[15] of data from CheckMate 057 showed that landmark survival assessed at 4 and 8 months yielded results that were qualitatively similar to those at 6 months, providing the rationale for using the 6-month timepoint in the current analyses.

In a separate exploratory analysis, we assessed overall survival from time of response (overall survival post response) in all patients with a best overall response (at any timepoint before the database lock) of complete response or partial response. We calculated the percent change from baseline in target tumour burden for patients who survived for at least 4 years after treatment was started in the nivolumab and docetaxel groups as a preliminary assessment of the association of depth and duration of response and long-term survival. To determine the effect of progression on overall survival, we did an exploratory analysis of overall survival from time of disease progression in all patients who had progressive disease as best overall response or had documented radiographic disease progression after a best overall response of complete or partial response or stable disease. We excluded patients who died without radiographic evidence of previous disease progression. Safety analyses included all patients who received at least one dose of nivolumab.

Outcomes

All endpoints in this post-hoc pooled analysis were exploratory. Survival outcomes reported include overall survival and progression-free survival from the time of randomisation in the combined CheckMate 017 and 057 population or from treatment initiation in the pooled four studies, 6-month landmark analysis, post-response overall survival in all patients and by best overall response of complete or partial response, and post-progression overall survival. Treatment-related adverse events included all events reported from the time of the first dose to 30 days after the last dose. We calculated exposure-adjusted incidence for categories of treatment-related adverse events with potential immunologic aetiology.

Statistical analysis

We estimated survival curves and rates from time-to-event endpoints (overall survival, progression-free survival, and duration of response) using the Kaplan-Meier method. We calculated unstratified hazard ratios (HRs) and 95% CIs to compare treatment groups or subgroups within treatment groups by using a Cox proportional hazards regression model with treatment group and subgroup, respectively, as the covariate. We used SAS version 9.2 (TS2M3) for all statistical analyses.

Role of the funding source

The sponsor designed the analyses in collaboration with the lead and senior authors. Data were collected by the sponsor and analysed and interpreted in collaboration with all authors. The sponsor paid for writing and editorial support. All authors had full access to all of the data in the analyses, and the corresponding author had final responsibility for the decision to submit for publication.

Results

Across all four studies, 664 patients were treated with nivolumab, including 129 in CheckMate 003, 117 in CheckMate 063, 131 in CheckMate 017, and 287 in CheckMate 057. Analysis populations are summarised in the appendix (pp 5–6). Baseline characteristics for the pooled study populations are shown in table 1. Most patients treated with nivolumab (572 [86%] of 664) received 3 mg/kg every 2 weeks; 33 (5%) patients received 1 mg/kg every 2 weeks and 59 (9%) patients received 10 mg/kg every 2 weeks in CheckMate 003. Seven patients in CheckMate 017 and 15 patients in CheckMate 057 transitioned to nivolumab 480 mg every 4 weeks, including one patient in each study who crossed over from docetaxel. The median duration of nivolumab treatment was 2·7 months (IQR 1·4–7·2) in CheckMate 003,

	CheckMate 017 and 057*		CheckMate 003, 063, 017, and 057†
	Nivolumab (n=427)	Docetaxel (n=427)	Nivolumab (n=664)
Median age, years (IQR)	61 (56–67)	64 (57–70)	63 (56–68)
Age ≥65 years	164 (38%)	199 (47%)	285 (43%)
Sex			
Male	262 (61%)	265 (62%)	419 (63%)
Female	165 (39%)	162 (38%)	245 (37%)
Current or former smoker	352 (82%)	356 (83%)	562 (85%)
Previous lines of systemic therapy			
1	340 (80%)	351 (82%)	359 (54%)
2	84 (20%)	70 (16%)	158 (24%)
3	3 (<1%)	6 (1%)	84 (13%)
≥4	0	0	63 (9%)
ECOG performance status			
0	111 (26%)	132 (31%)	163 (25%)
1	314 (74%)	293 (69%)	499 (75%)
≥2	0	1 (<1%)	2 (<1%)
Not reported	2 (<1%)	1 (<1%)	0
Histology			
Squamous	132 (31%)	137 (32%)	299 (45%)
Non-squamous	295 (69%)	290 (68%)	364 (55%)
CNS metastases	45 (11%)	42 (10%)	49 (7%)
Liver metastases	99 (23%)	94 (22%)	154 (23%)
Tumour PD-L1 expression			
<1%	163 (38%)	153 (36%)	222 (33%)
≥1%	185 (43%)	179 (42%)	262 (39%)
≥10%	121 (28%)	112 (26%)	167 (25%)
Not quantifiable	79 (19%)	95 (22%)	180 (27%)

Data are n (%) unless otherwise specified. ECOG=Eastern Cooperative Oncology Group. NSCLC=non-small-cell lung cancer. *All patients randomly allocated to treatment. †All patients treated with nivolumab for advanced NSCLC.

Table 1: **Baseline characteristics by analysis populations**

2·3 months (1·0–6·21) in CheckMate 063, 3·2 months (1·4–9·5) in CheckMate 017, and 2·6 months (1·4–8·1) in CheckMate 057. The corresponding mean duration of nivolumab treatment was 9·0 (SD 14·2), 8·8 (14·3), 6·0 (10·2), and 5·6 (6·7) months, respectively. The median duration of docetaxel treatment was 1·4 months (IQR 0·7–3·2) in CheckMate 017 and 2·3 months (1·4–4·4) in CheckMate 057. The mean duration of docetaxel treatment was 2·5 (SD 3·0) and 3·3 (3·0) months, respectively. In the pooled CheckMate 017 and 057 studies, subsequent immunotherapy was received by 17 (4%) of 427 patients in the nivolumab group and 43 (10%) of 427 patients in the docetaxel group, which included 23 patients who crossed over from docetaxel to nivolumab. Five (26%) of 19 patients randomised to docetaxel and still alive at database lock received subsequent immunotherapy. 185 (43%) of 427 patients in the nivolumab group and 154 (36%) of 427 patients in the docetaxel group received subsequent chemotherapy.

For the overall pooled CheckMate population, the minimum follow-up (time from date of last patient enrolment to the data cut-off date for these analyses) was 51·6 months; this value was 51·6 months for CheckMate 017 and 057, 75·2 months for CheckMate 003, and 56·3 months for CheckMate 063. The median follow-up for overall survival was 9·2 (IQR 4·6–23·8) for CheckMate 017, 12·2 (4·1–25·7) for CheckMate 057, 9·2 (4·3–19·1) for CheckMate 003, and 8·0 (3·68–20·8) months for CheckMate 063. The median overall survival in all patients treated with nivolumab was 10·3 months (95% CI 9·2–11·9), and the estimated 4-year overall survival was 14% (95% CI 11–17; figure 1) The estimated 4-year overall survival was higher in patients with at least 1% PD-L1 expression (19% [95% CI 15–24]) than in those with less than 1% PD-L1 expression (11% [7–16]; appendix p 16), but was similar between patients with squamous and non-squamous tumour histology (appendix p 17). Baseline characteristics of nivolumab-treated patients who survived for at least 4 years are shown in the appendix (p 7). They were generally similar to those of the overall analysis populations (table 1), except that more 4-year survivors had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, PD-L1 expression of at least 1%, and PD-L1 expression of at least 10%, and fewer patients had liver metastases.

The estimated 4-year progression-free survival overall was 8% (95% CI 6–11; appendix p 18), and was higher in patients with at least 1% PD-L1 than in those with less than 1% PD-L1 expression; however, tumour histology had no effect on long-term progression-free survival (appendix pp 19–20). Overall survival and progression-free survival outcomes in each of the four individual studies are shown in the appendix (pp 21–22). Notably, the CheckMate 003 study has the longest follow-up of PD-1 agents in NSCLC and 6-year overall survival was 15% (95% CI 9–22; appendix p 21).

To assess the effect of objective response and disease control on long-term survival, we did a landmark analysis of overall survival (n=430). Of 664 patients treated with nivolumab, 122 had a complete or partial response, such that the proportion of patients with an objective response was 18%; of those, 103 (84%) had a response at 6 months. Of patients with a complete or partial response (n=103) at 6 months, overall survival at 4 years post-landmark was 56% (95% CI 45–65). However, of those with stable disease at 6 months (n=100), overall survival was 19% (12–27) at 4 years post-landmark, compared with 4% (2–7) for those with progressive disease (n=227) at 6 months (figure 2). Of the 234 patients treated with nivolumab who were not included in this analysis, 228 had died before 6 months, five withdrew consent, and one patient discontinued study participation owing to an adverse event (infusion-related reaction).

For the 122 patients with a complete or partial response to nivolumab, median duration of response was 19·1 months (95% CI 14·7–29·9) and median overall survival from time of response was 63·2 months

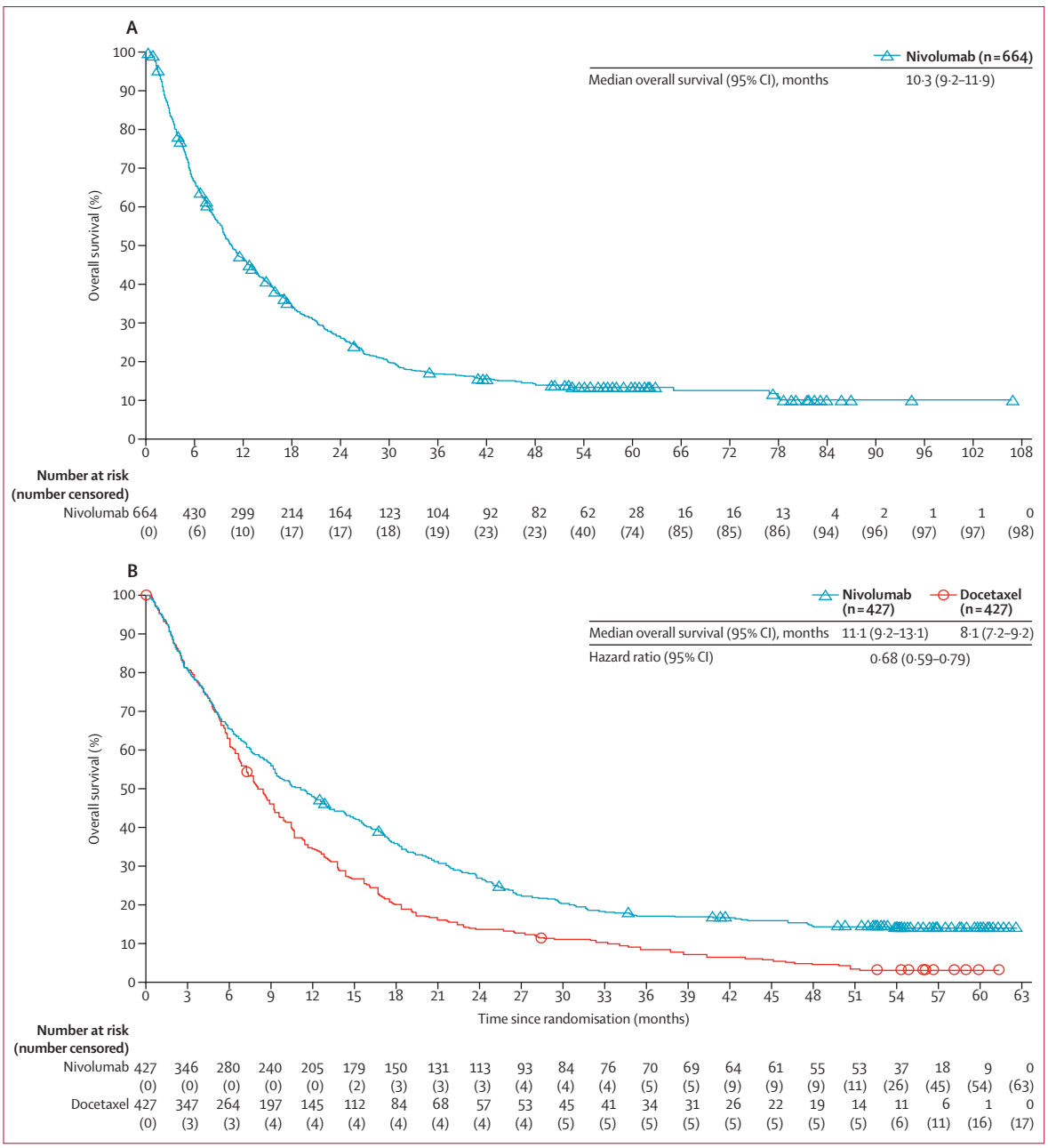

Figure 1: **Overall survival in all patients treated with nivolumab (A) and in the combined CheckMate 017 and 057 population (B)**
(A) Data are for all patients treated with nivolumab in CheckMate 017, 057, 063, and 003; 566 (85%) of 664 patients had an event. (B) Data are for all patients in the intention-to-treat populations of CheckMate 017 and 057; 364 (85%) of 427 in the nivolumab group and 410 (96%) of 427 patients in the docetaxel group had an event.

(29·8–not reached). The estimated 4-year overall survival was 53% (44–61; appendix p 23).

Across all four studies, seven patients achieved a complete response to nivolumab. Of those, six patients were alive at database lock, including five who remained progression-free; four of the six survivors were continuing nivolumab treatment. The one patient who achieved a complete response with docetaxel died about 27 months after treatment started.

The estimated median overall survival post-progression for all patients who progressed was 6·6 months (95% CI 5·7–7·7) and 3-year overall survival from time to progression was 8% (6–11; appendix p 24). However, 3-year overall survival post-progression was higher for patients who progressed after a best overall response of complete or partial response (29% [95% CI 18–41]) or stable disease (12% [7–18]) than for patients with a best overall response of progressive disease (3% [1–5]).

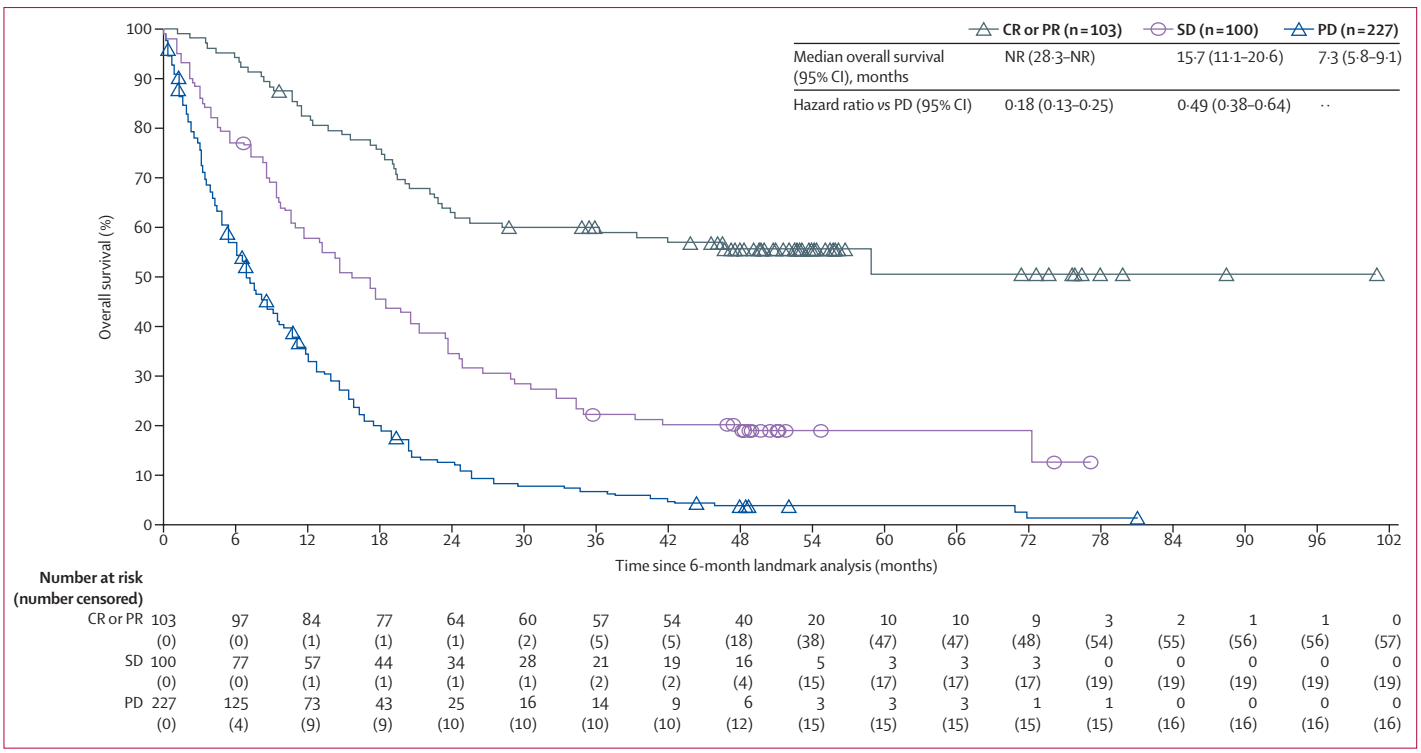

***Figure 2*: Overall survival landmark analysis by response category at 6 months in the pooled CheckMate population of patients treated with nivolumab**
Overall survival is shown from the time of the landmark response assessment at 6 months. Patients with no response assessment at 6 months owing to death or loss to follow-up were excluded. 46 (45%) of 103 patients with CR or PR, 81 (81%) of 100 patients with SD, and 211 (93%) of 227 patients with PD at 6 months had an event. CR=complete response. NR=not reached. PD=progressive disease. PR=partial response. SD=stable disease.

Compared with progressive disease as best overall response, a best overall response of complete or partial response had an HR for post-progression death of 0·34 (95% CI 0·25–0·48), and best overall response of stable disease with an HR of 0·57 (0·46–0·71; appendix p 25).

Overall survival outcomes with nivolumab in the pooled CheckMate 017 and 057 population (figure 1) were similar to those in the pooled analysis of the four studies (figure 1), and median overall survival was substantially longer with nivolumab than with docetaxel. The 4-year overall survival was higher with nivolumab (14% [95% CI 11–18]) than with docetaxel (5% [3–7]; figure 1). The 4-year overall survival was higher with nivolumab (9% [95% CI 5–14]) than that with docetaxel (4% [2–8]) in patients with less than 1% PD-L1 expression and higher with nivolumab (20% [14–26]) than with docetaxel (5% [2–8]) in patients with at least 1% PD-L1 expression (appendix p 26).

In the combined CheckMate 017 and 057 population, 83 (19%) of 427 patients had an objective response to nivolumab, compared with 48 (11%) of 427 patients with docetaxel. The median time to response was 2·1 months (IQR 2·0–3·5) for nivolumab and 2·2 months (2·0–3·6) for docetaxel. The proportion of patients with an objective response to nivolumab versus docetaxel was 73 (88%) of 83 patients versus 41 (85%) of 48 patients at 4 months, 78 (94%) versus 43 (90%) at 6 months, and 79 (95%) versus 46 (96%) at 8 months, respectively. Of the patients who achieved an objective response (complete response or partial response) with nivolumab or docetaxel, more patients who received nivolumab versus docetaxel had ongoing responses at 6 months (70 [84%] of 83 patients for nivolumab, 34 [71%] of 48 patients for docetaxel). Similar to the analyses of the four pooled studies, we estimated post-landmark overall survival by response category to determine the effect of response on long-term survival. We also did a corresponding post-landmark progression-free survival analysis. Of all randomised patients, 280 (66%) of 427 patients in the nivolumab and 264 (62%) of 427 in the docetaxel group were alive and had a response assessment at 6 months. The median post-landmark progression-free survival among patients with a complete or partial response was higher with nivolumab than with docetaxel. The corresponding estimated progression-free survival at 4 years post-landmark were 38% (95% CI 25–50) for nivolumab (appendix p 27) and 0% (95% CI not reached) for docetaxel. Among patients assigned to nivolumab who had stable disease at 6 months, progression-free survival was 14% (95% 6–25) at 4 years post-landmark. Among patients treated with nivolumab, complete response or partial response versus stable disease at landmark was associated with an HR for progression of 0·42 (95% 0·27–0·65; appendix p 27). The median post-landmark

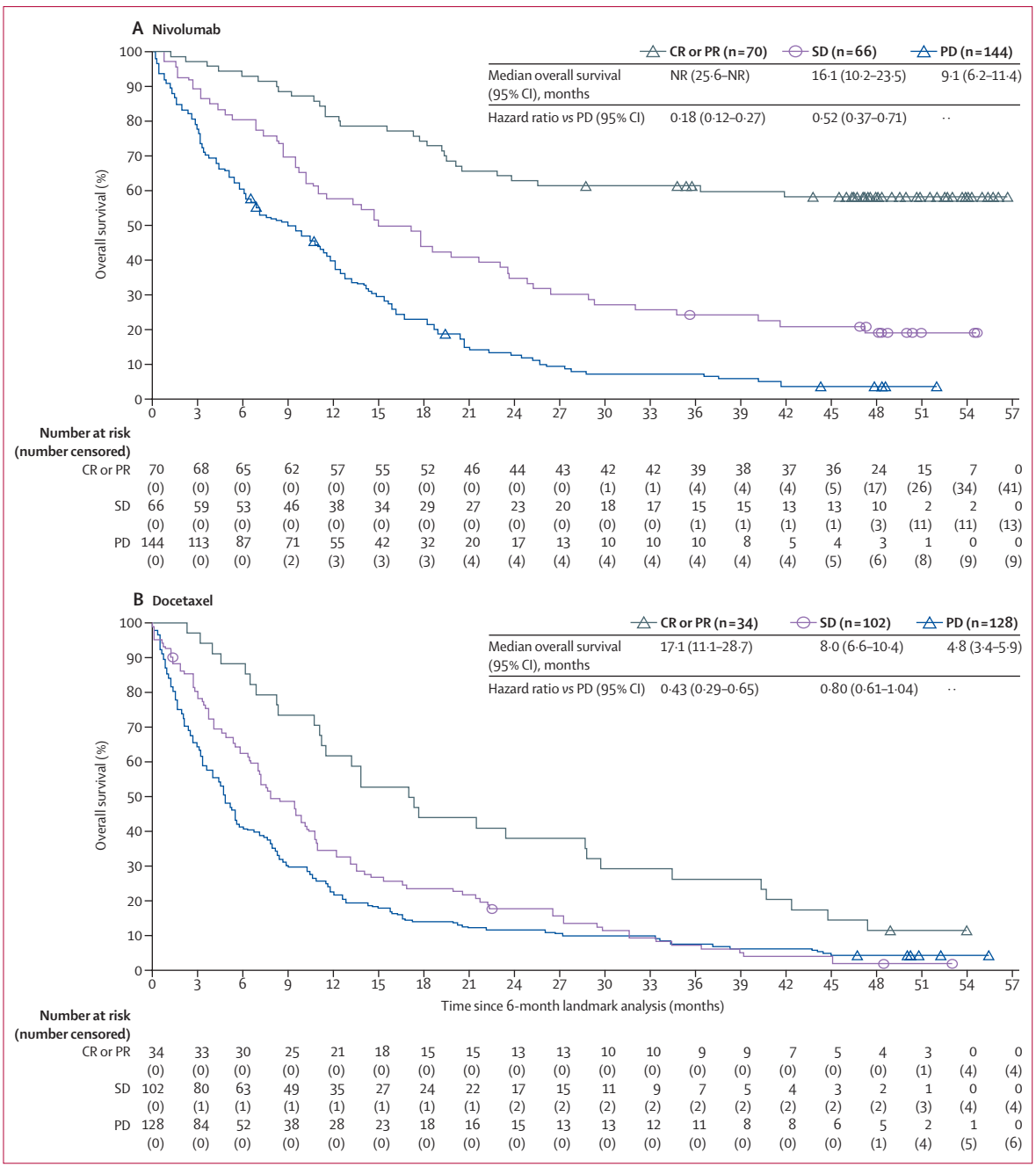

Figure 3: **Overall survival landmark analysis by response category at 6 months in the combined CheckMate 017 and 057 population**
Overall survival is shown from the time of the landmark response assessment at 6 months. Patients with no response assessment at 6 months owing to death or loss to follow-up were excluded. In the nivolumab group, 29 (41%) of 70 patients with CR or PR, 53 (80%) of 66 patients with SD, and 135 (94%) of 144 patients with PD at 6 months had an event. In the docetaxel group, 30 (88%) of 34 patients with CR or PR, 98 (96%) of 102 patients with SD, and 122 (95%) of 128 patients with SD at 6 months had an event. CR=complete response. NR=not reached. PD=progressive disease. PR=partial response. SD=stable disease.

overall survival among patients with a complete or partial response was not reached (95% CI 25·6–not reached) with nivolumab and 17·1 months (11·1–28·7) with docetaxel; the corresponding overall survival at 4 years post-landmark was 58% (95% CI 46–69) for nivolumab and 12% (4–25) for docetaxel (figure 3). Of patients with stable disease at 6 months, overall survival at 4 years post-landmark was 19% (95% CI 11–30) with nivolumab and 2% (0–7) with docetaxel. Patients with progressive disease at 6 months had transient benefit with nivolumab, with overall survival at 1 year post-landmark of 40% (32–48) for nivolumab versus 22% (15–29) for docetaxel; however, overall survival post-landmark was similar at 2 years and beyond. Survival subsequent to

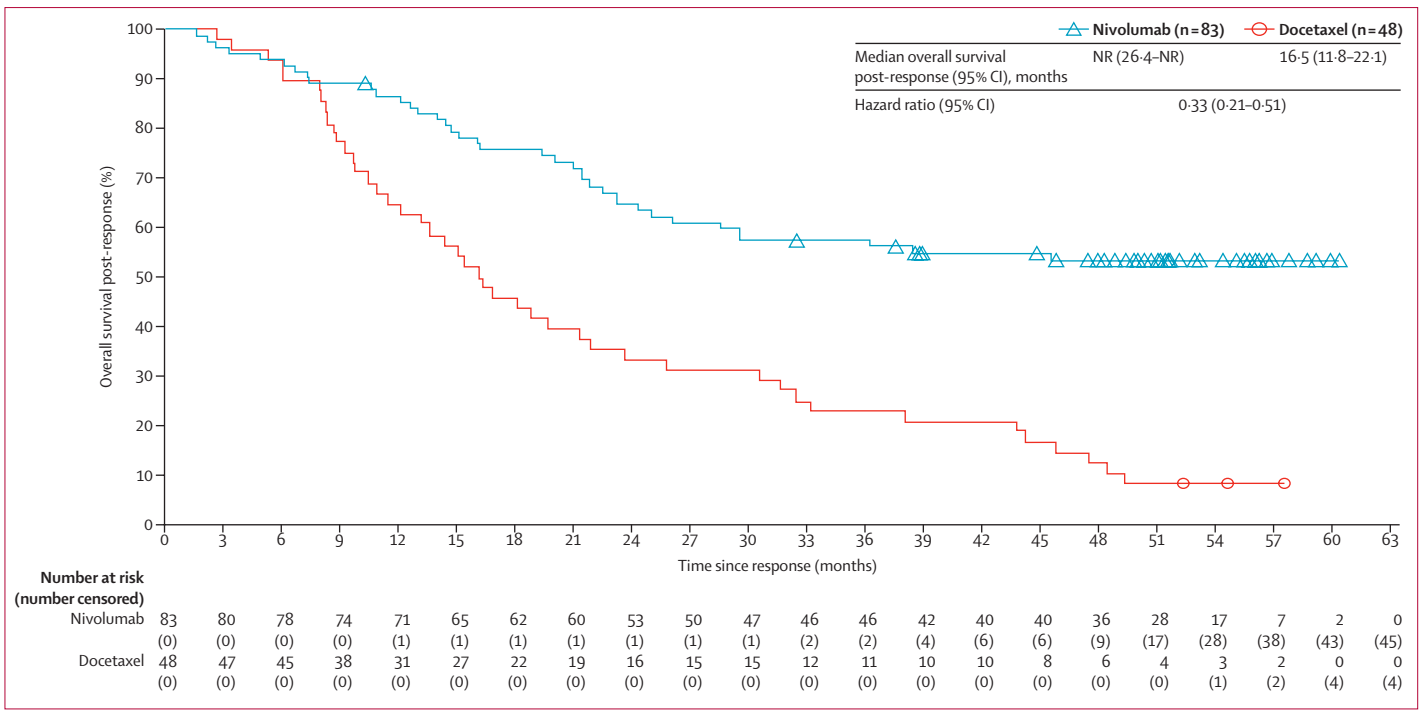

Figure 4: **Overall survival post-response in the combined CheckMate 017 and 057 population of patients who achieved a CR or PR**
Overall survival was calculated from the time of response of each patient. In the nivolumab group, 38 (46%) of 83 patients had an event; in the docetaxel group, 44 (92%) of 48 patients had an event. CR=complete response. NR=not reached. PR=partial response.

complete or partial response versus progressive disease at 6 months was longer; HRs for overall survival were 0·18 (95% 0·12–0·27) for nivolumab and 0·43 (0·29–0·65) for docetaxel. The corresponding HR values for stable disease versus progressive disease at 6 months were 0·52 (0·37–0·71) for nivolumab and 0·80 (0·61–1·04) for docetaxel (figure 3). 147 patients died before the landmark analysis at 6 months and, thus, were not included in the landmark analysis.

The estimated median duration of response among all responders in the combined CheckMate 017 and 057 population was 23·8 months (95% CI 11·4–36·1) for nivolumab and 5·6 months (4·4–7·0) for docetaxel. Responders to nivolumab had longer subsequent survival than did responders to docetaxel, with 4-year overall survival from time of response of 54% (95% CI 42–64) for nivolumab and 13% (5–23) for docetaxel (figure 4). A preliminary assessment of depth and duration of response in patients surviving for at least 4 years showed that most 4-year survivors in the nivolumab group had deeper and more durable responses than did 4-year survivors in the docetaxel group (appendix pp 28–29).

The median overall survival post-progression in all patients with disease progression was 6·8 months (95% CI 5·4–8·2) with nivolumab and 5·4 months (4·2–6·1) with docetaxel (appendix p 30); corresponding 3-year overall survival was 8% (95% CI 5–12) for nivolumab and 7% (5–10) for docetaxel. In both treatment groups, overall survival post-progression was longer among patients with a complete response or partial response or stable disease as best overall response than among patients with progressive disease as best overall response (figure 5). An overall survival benefit post-progression with nivolumab versus docetaxel was seen for patients with stable disease as best overall response; median overall survival post-progression was 10·0 months (95% CI 7·8–13·8) with nivolumab versus 5·9 months (4·4–7·2) with docetaxel for a HR of death between treatment groups of 0·63 (95% CI 0·47–0·85). Corresponding 3-year overall survival was 13% (95% CI 6–21) for nivolumab and 6% (3–11) for docetaxel (figure 5). After a best overall response of complete response or partial response, median overall survival post-progression was 13·9 months (8·4–26·1) with nivolumab versus 11·1 months (8·2–14·2) with docetaxel. Corresponding 3-year overall survival was 26% (95% CI 12–43) versus 13% (5–26; figure 5).

Long-term safety data for nivolumab pooled from all four studies did not reveal any new safety signals (table 2). Overall, grade 3–4 treatment-related adverse events occurred in 86 (13%) of 664 patients, serious treatment-related adverse events (any grade) occurred in 64 (10%) patients, including two patients who died (grade 5), and treatment-related adverse events (any grade) leading to discontinuation occurred in 58 (9%) patients, including one patient who died (grade 5). The most common treatment-related adverse event was fatigue, affecting 144 (22%) of 664 patients. Pneumonitis

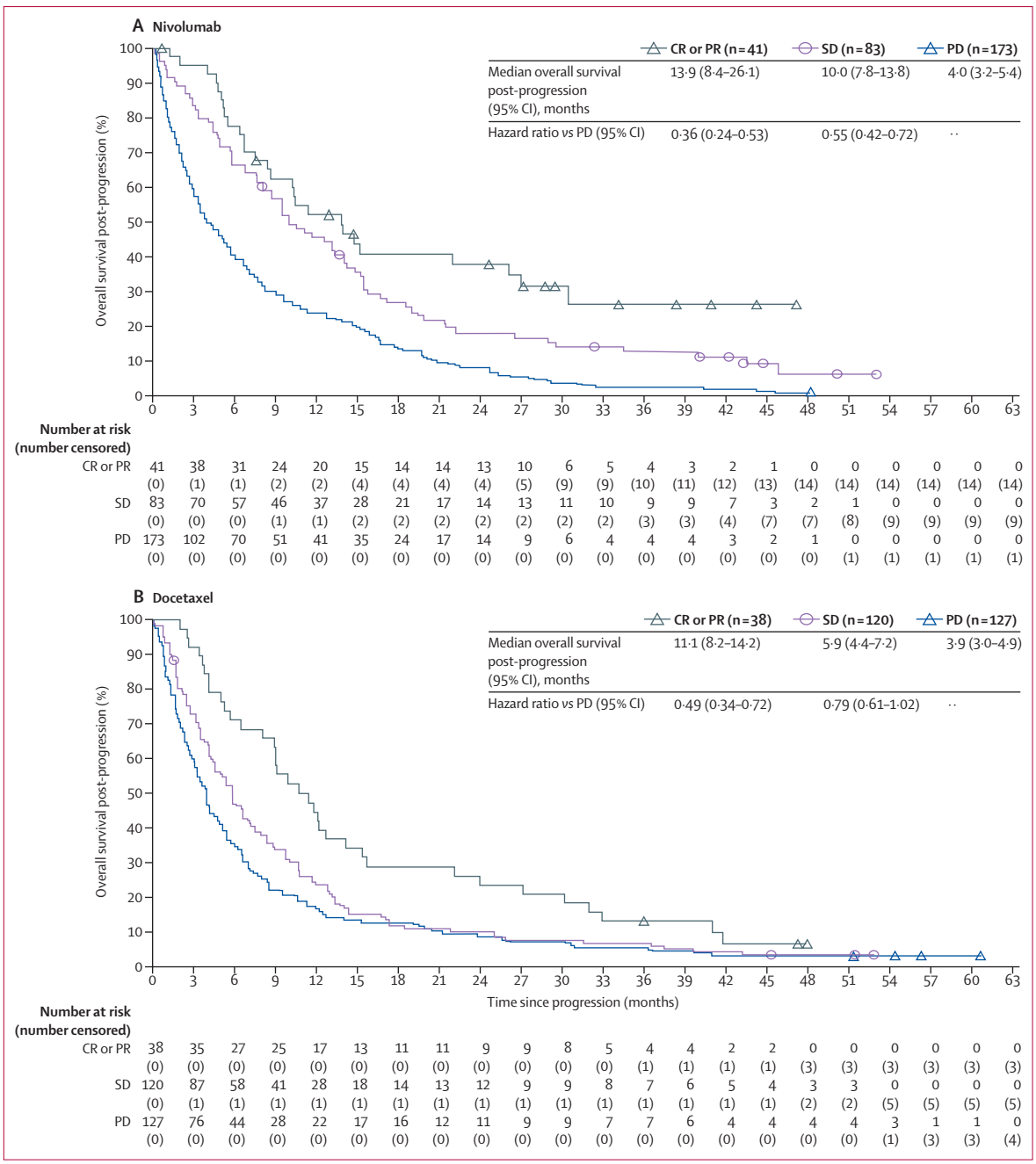

Figure 5: **Overall survival post-progression in the combined CheckMate 017 and 057 population by best overall response**
Data are for all patients who had a best overall response of PD or disease progression after a best overall response of CR or PR or SD. In the nivolumab group, 273 (92%) of 297 patients had an event, including 27 (66%) of 41 with CR or PR, 74 (89%) of 83 patients with SD, and 172 (99%) of 173 patients with PD as best overall response. In the docetaxel group, 273 (96%) of 285 patients had an event, including 35 (92%) of 38 patients with CR or PR, 115 (96%) of 120 patients with SD, and 123 (97%) of 127 patients with PD as best overall response. Patients who died without previous radiographic evidence of disease progression (56 treated with nivolumab and 86 treated with docetaxel) were excluded. CR=complete response. PD=progressive disease. PR=partial response. SD=stable disease.

was the most frequent serious treatment-related adverse event, occurring in 18 (3%) of 664 patients (appendix p 8). The most common treatment-related adverse events of potentially immune-related aetiology were skin reactions, with an exposure-adjusted incidence rate of 38·6 per 100 person-years. Incidence was highest during the first year of follow-up (table 3). Overall, six patients died of causes considered to be related to treatment, including three patients in CheckMate 003 (one of sepsis and two of pneumonitis),[8,16] two in CheckMate 063 (one of ischemic stroke and one of hypoxic pneumonia after rapid tumour progression and bronchial

	Grade 1–2	Grade 3	Grade 4
Any TRAE	375 (56%)	72 (11%)	14 (2%)
Serious TRAE	26 (4%)	29 (4%)	7 (1%)
TRAE leading to discontinuation	21 (3%)	28 (4%)	8 (1%)
Most frequent grade 1–2 TRAEs (occurring in ≥10% of patients)			
Fatigue	131 (20%)	13 (2%)	0
Decreased appetite	82 (12%)	2 (<1%)	0
Nausea	74 (11%)	3 (<1%)	0
Any frequency TRAEs of grade 3–4 (with grade 1–2 occurring in <10% of patients)			
Asthenia	59 (9%)	1 (<1%)	0
Diarrhoea	56 (8%)	8 (1%)	0
Rash	55 (8%)	3 (<1%)	0
Pruritus	45 (7%)	2 (<1%)	0
Arthralgia	35 (5%)	1 (<1%)	0
Dyspnoea	23 (3%)	3 (<1%)	0
Pneumonitis	21 (3%)	10 (2%)	2 (<1%)
Cough	21 (3%)	1 (<1%)	0
Myalgia	18 (3%)	3 (<1%)	0
Anaemia	16 (2%)	2 (<1%)	0
Alanine aminotransferase increased	16 (2%)	0	1 (<1%)
Weight decreased	15 (2%)	1 (<1%)	0
Aspartate aminotransferase increased	14 (2%)	1 (<1%)	1 (<1%)
Hypophosphataemia	10 (2%)	2 (<1%)	0
Abdominal pain	9 (1%)	1 (<1%)	0
Back pain	9 (1%)	1 (<1%)	0
Hypersensitivity	6 (1%)	1 (<1%)	1 (<1%)
Lymphopenia	5 (1%)	3 (<1%)	1 (<1%)
Abdominal pain upper	5 (1%)	1 (<1%)	0
Hyponatraemia	5 (1%)	2 (<1%)	0
Hypocalcaemia	4 (1%)	1 (<1%)	0
Hypoxia	4 (1%)	2 (<1%)	0
Colitis	3 (<1%)	3 (<1%)	0
Interstitial lung disease	3 (<1%)	2 (<1%)	0
Blood uric acid increased	3 (<1%)	1 (<1%)	1 (<1%)
Lymphocyte count decreased	2 (<1%)	2 (<1%)	0
Transaminases increased	2 (<1%)	1 (<1%)	1 (<1%)
Pericardial effusion	2 (<1%)	0	2 (<1%)
Peripheral sensory neuropathy	2 (<1%)	1 (<1%)	0
Upper respiratory tract infection	2 (<1%)	1 (<1%)	0
Neutrophil count decreased	2 (<1%)	0	1 (<1%)
CD4 lymphocytes decreased	1 (<1%)	3 (<1%)	0
Dermatitis bullous	1 (<1%)	1 (<1%)	0
Flank pain	1 (<1%)	1 (<1%)	0
Hyperkalaemia	1 (<1%)	1 (<1%)	0
Polymyalgia rheumatica	1 (<1%)	1 (<1%)	0
Pulmonary embolism	1 (<1%)	1 (<1%)	0
Syncope	1 (<1%)	1 (<1%)	0
Herpes zoster	1 (<1%)	1 (<1%)	0
Tubulointerstitial nephritis	1 (<1%)	1 (<1%)	0
Pneumonia	0	2 (<1%)	0
Gamma-glutamyltransferase increased	0	1 (<1%)	1 (<1%)
Lipase increased	0	1 (<1%)	1 (<1%)
Lymphocyte count abnormal	0	1 (<1%)	0
Joint effusion	0	1 (<1%)	0
Osteonecrosis	0	1 (<1%)	0
Myasthenic syndrome	0	1 (<1%)	0
Adrenal insufficiency	0	1 (<1%)	0
Leukopenia	0	1 (<1%)	0
Dermatitis	0	1 (<1%)	0
Diverticulitis	0	1 (<1%)	0
Encephalitis	0	1 (<1%)	0
Anaphylactic reaction	0	1 (<1%)	0
Basal cell carcinoma	0	1 (<1%)	0
Bowen's disease	0	1 (<1%)	0
Hypertransaminasaemia	0	1 (<1%)	0
Amylase increased	0	0	1 (<1%)
Myositis	0	0	1 (<1%)
Cerebrovascular accident	0	0	1 (<1%)
Polyneuropathy	0	0	1 (<1%)
Vasculitis	0	0	1 (<1%)
Cardiac tamponade	0	0	1 (<1%)
Sepsis	0	0	0

Data are n (%). Includes events reported between the first dose and 30 days after the last dose. According to practices of the study sponsor, only events that lead to death within 24 hours are documented as grade 5. Events leading to death >24 h after onset are reported with the worst grade before death. Deaths in all patients treated with nivolumab, including the reason for death, are summarised in the appendix (p 10). TRAE=treatment-related adverse event.

Table 2: **Safety summary for all patients treated with nivolumab (n=664)**

obstruction with possible associated opportunistic infection),[12] and one in CheckMate 057 (encephalitis).[4] All deaths in the pooled analysis of patients treated with nivolumab are summarised in the appendix (p 10). Incidence for treatment-related adverse events of potentially immune-related aetiology in the combined CheckMate 017 and 057 population (appendix p 11) were similar to those in the pooled population of all four studies. Long-term safety data with nivolumab versus docetaxel in the pooled CheckMate 017 and 057 population were consistent with the expected differences in safety profiles of the two treatments (appendix pp 12–15).

Discussion

Our survival analyses are based on a minimum follow-up of 4 years, which is—to our knowledge—the longest follow-up to date for an anti-PD-1 or anti-PD-L1 therapy in a large population of patients with previously treated advanced NSCLC. Across all four studies, nivolumab showed long-term survival benefit, with estimated 4-year overall survival of 14% overall, 11% in patients with less

than 1% PD-L1 expression, and 19% in patients with at least 1% PD-L1 expression. The proportions of patients alive with nivolumab mostly stabilised at 3 years, as was previously seen for ipilimumab in the large pooled analysis of long-term overall survival in melanoma.[11] The corresponding proportions of patients alive with nivolumab in the combined CheckMate 017 and 057 population were similar to those of the pooled analysis of all four studies. This finding indicates that the nivolumab group of CheckMate 017 and 057 was representative of patients treated with nivolumab across all four studies, while having the advantage of allowing for comparisons with docetaxel in the setting of a randomised study population. Although patients in CheckMate 003 were more heavily pretreated than were those in the other three studies and included patients treated with potentially non-optimal doses of nivolumab (ie, 1 mg/kg and 10 mg/kg), the median overall survival (9·9 months)[8] was similar to that across all four studies (10·3 months); thus, including patients who received 1 mg/kg and 10 mg/kg would be unlikely to affect the current findings. Additionally, the 4-year overall survival was high, remained unchanged at 5 years (16%),[8] and here we have reported the overall survival at 6 years, which was only slightly lower (15%). By contrast to our findings of nivolumab, 4-year overall survival was only 5% for patients treated with docetaxel in CheckMate 017 and 057, irrespective of PD-L1 expression. Notably, the most recent estimate of the proportion of patients alive at 5 years since diagnosis for metastatic lung cancer in the USA is 5% for 2008–15,[2] which largely preceded the availability of immunotherapy for lung cancer. Our results suggest that subsequent updates of overall survival statistics might show substantial improvements in the long-term survival of patients with this disease.

Achievement of a complete or partial response was associated with greatly improved overall survival post-response in patients treated with nivolumab or docetaxel. However, consistent with the increased response duration with nivolumab versus docetaxel, the long-term overall survival benefit was much larger for responders to nivolumab than to docetaxel. This finding suggests that PD-1 inhibitors provide greater durability of response benefit than cytotoxic chemotherapy. Furthermore, even among 4-year survivors, nivolumab was associated with longer and deeper responses than was docetaxel, which probably reflects the different mechanisms of action of PD-1 inhibition and cytotoxicity. Depth of response to PD-1 inhibitor therapy has previously been associated with progression-free survival and overall survival in metastatic NSCLC.[17] By contrast, some studies[18,19] found—at best—weak associations of objective responses or depth of response with progression-free survival and overall survival in NSCLC treated with targeted therapy or chemotherapy.

The results of our landmark analysis of CheckMate 017 and 057 suggest that response at 6 months was associated with increased long-term survival post-landmark in both treatment groups. However, patients with a complete response, partial response, or stable disease at 6 months had longer subsequent overall survival with nivolumab than with docetaxel. Furthermore, the HRs for subsequent death in patients with a complete or partial response or stable disease versus progressive disease were more favourable with nivolumab than with docetaxel. Post-landmark progression-free survival was also longer in patients treated with nivolumab who had a complete or partial response than in those who had stable disease, which is consistent with the long-term survival benefit of response to nivolumab.

Nivolumab was well tolerated, with few treatment-related deaths and no new or unexpected safety signals. This finding is consistent with previous results from the individual studies included in the present analyses, including CheckMate 017 and 057, which have shown the superior safety and tolerability profile of nivolumab versus docetaxel.[3,4] However, although most potentially immune-related, treatment-related adverse events with nivolumab occurred in the first 2–3 years of treatment, our findings suggest that vigilance should continue even at 4 years, particularly for skin reactions and gastrointestinal adverse events.

Randomised controlled trials have shown long-term overall survival benefit with PD-1 or PD-L1 inhibitor therapy versus docetaxel in patients with previously treated advanced NSCLC.[9,10,20,21] However, identifying who in this patient population is most likely to achieve long-term survival with immunotherapy is a key challenge. Associations of baseline characteristics (eg, smoking status, tumour histology, CNS metastases, and ECOG performance status) and biomarker status (PD-L1 expression and tumour mutational burden) with overall survival in previously treated patients who received PD-1 or PD-L1 inhibitor therapy for advanced NSCLC have been explored previously.[6,8–10,21–25] In the present post-hoc analyses, owing to restricted tissue availability (tissue

	Total number of events	Overall (N=664*)	0 to <1 year (n=664*)	1 to <2 years (n=122*)	2 to <3 years (n=59*)	3 to <4 years (n=34*)	≥4 years (n=26*)
Skin	184	38·6	51·3	22·8	22·0	10·2	0
Gastrointestinal	99	20·7	26·4	16·3	6·6	13·6	0
Hepatic	65	13·6	16·4	13·0	11·0	0	0
Endocrine	59	12·4	18·8	4·3	0	0	0
Pulmonary	45	9·4	11·0	9·8	8·8	0	0
Hypersensitivity or infusion reaction	28	5·9	8·2	4·3	0	0	0
Renal	22	4·6	6·8	2·2	0	0	0

Data are incidence per 100 person-years of exposure, which is calculated as (number of events × 100)/person-years of exposure. Includes events reported between the first dose and 30 days after the last dose. TRAE=treatment-related adverse event. *Number of patients on treatment at the start of the time interval.

Table 3: **Exposure-adjusted rates of potentially immune-related TRAEs for all patients treated with nivolumab**

samples were not mandatory in nivolumab studies in previously treated patients with NSCLC), only survival outcomes according to tumour histology and PD-L1 expression were assessed. Evaluation of potential baseline characteristics correlating with long-term responders to nivolumab are planned in a future analysis of CheckMate 017 and 057. In addition, we expect that patients who maintain their clinical response for 6 months or longer have a disease that is biologically different and more sensitive to treatment than patients who experience shorter durations of response. To better understand these biological differences, additional analyses, such as serial biopsies at progression, are needed; however, serial biopsies are difficult to do in patients with lung cancer. Herein, we focused on the effect of response on long-term survival. This relationship in patients with advanced NSCLC has been evaluated in large-scale, multi-trial analyses of patient populations receiving chemotherapy or targeted therapy (or both), and correlations between response and progression-free survival and between response and overall survival were seen at the patient level.[17,25,26] However, similar analyses have not been done with immunotherapy trials in patients with NSCLC.

Given the long duration of responses to PD-1 or PD-L1 inhibitors in patients with previously advanced NSCLC, the association between response and overall survival could be expected to be particularly strong in this setting. However, few studies have explored this question, and the corresponding analyses used were restricted, given that they were based on shorter follow-up durations and smaller study populations than our present analyses. 2-year data from the phase 3 OAK study[21] in patients with previously treated NSCLC showed that response to atezolizumab or docetaxel was associated with increased overall survival, and the benefit of response to atezolizumab was more pronounced; however, no landmark analyses were done and overall survival post-response and post-progression were not evaluated.[21] Landmark analyses were previously used in two of the four studies included in our analyses (CheckMate 063 and 057) to examine the relationship between response and overall survival. A preliminary exploratory landmark analysis[27] from CheckMate 063 based on less than 18 months of follow-up showed that response to nivolumab at 3·5 months (the median time to response) was associated with increased overall survival versus stable disease or progressive disease. In CheckMate 057, multivariable Cox regression analyses of overall survival adjusted for age, sex, ECOG performance status, and time from diagnosis to randomisation showed a stronger association of response at 6 months to subsequent overall survival with nivolumab (HR for death between responders and non-responders 0·24 [95% CI 0·15–0·39]) versus docetaxel (0·55 [0·34–0·88]) confirming comparable estimates obtained from unadjusted univariable analysis. Additionally, sensitivity analyses of 4-month and 8-month landmarks yielded qualitatively similar results.[15] An alternative approach to landmark analysis, which also avoids immortal time bias, is an extended multivariate Cox regression analysis with response status as a time-varying covariate.[14,28] Using this approach, Santi and colleagues[15] showed that response with nivolumab was associated with a 57% reduction in the risk of death versus response to docetaxel ($p<0·01$).[15] These initial analyses, which were based on 2 years of follow-up, showed the appropriateness of landmark analyses for the evaluation of response-survival relationship.[15]

To minimise heterogeneity, the pooled individual patient data analysis of the four studies only included patients treated for advanced NSCLC with nivolumab who had previously received at least one line of systemic chemotherapy. The most likely sources of heterogeneity potentially affecting outcomes in individual patients are tumour histology, which differed between studies, and PD-L1 expression. To document possible effects of these heterogeneities, overall survival and progression-free survival outcomes for PD-L1 and histology subgroups are provided, as well as outcomes in the individual trials. However, treatment comparisons between nivolumab and docetaxel were not at risk of heterogeneity, because both studies included in this analysis were identically designed randomised trials, except that CheckMate 017 was done in patients with squamous NSCLC and CheckMate 057 in patients with non-squamous NSCLC. Furthermore, the baseline characteristics show that the treatment groups were well matched for PD-L1 distribution in the pooled population. Furthermore, overall survival outcomes with nivolumab were virtually identical in the two randomised studies and across all four studies. Taken together, these data suggest both analyses are representative of a previously treated population with advanced NSCLC, with some expected variability in outcomes among subgroups.

Our analyses have advantages and limitations. Landmark analyses have the advantage that comparisons across response status for a particular treatment are based on information collected before a fixed timepoint and thus avoid immortal time bias in the estimation of subsequent overall survival.[14] It is not a primary goal of a landmark analysis to determine a treatment difference from randomisation; for comparisons in randomised studies, landmark categories might not provide a consistent view of overall survival between treatment groups if overall survival at the landmark is different across groups. Nonetheless, overall survival estimates for all randomised patients in CheckMate 017 and 057 during the first 6 months were virtually identical in the two treatment groups. Although overall survival analyses can be potentially confounded by subsequent therapy, the use of subsequent immunotherapy in the nivolumab group of the CheckMate 017 and 057 population was low (4% of patients). A limitation of the overall survival

post-progression analysis by best overall response is the exclusion of patients who remained in response or maintained stable disease at the time of database lock. Because the percentage of patients who fall into this category was higher for nivolumab than for docetaxel, these analyses probably underestimate the overall survival benefit post-progression for nivolumab versus docetaxel. Moreover, more patients died without documented progression in the docetaxel than in the nivolumab group. The exclusion of these patients from the post-progression survival analysis might further contribute to an underestimation of the survival advantage associated with nivolumab.

In summary, our analyses provide evidence that response and disease control with nivolumab strongly benefit long-term survival, even after progression. A smaller overall survival benefit was associated with stable disease versus progressive disease at 6 months in the landmark analysis. Although response to docetaxel also favoured longer-term survival, the association between response and survival was less pronounced than with nivolumab. Additional analyses assessing the effect of various factors on long-term survival with immunotherapy versus chemotherapy are planned.

Contributors

All authors had full access to all of the data in these analyses, analysed and interpreted the data, and drafted or critically revised the manuscript for important intellectual content. AL did the statistical analyses. All authors approved the final version of the manuscript to submit for publication.

Declaration of interests

SJA is on the advisory board or scientific advisory board of Bristol-Myers Squibb, Novartis, Merck, CBMG, Boehringer Ingelheim, AstraZeneca/MedImmune, Memgen, FLX Bio, Nektar, and Veen; has done contracted research for Novartis; was previously employed by H Lee Moffitt Cancer Center & Research Institute (Tampa, FL, USA); and is currently employed by Duke Cancer Institute (Durham, NC, USA). HB reports grants from Bristol-Myers Squibb, Celgene, Lilly, Merck, and Millennium; personal fees for consultancy or advisory board services (or both) from Bristol-Myers Squibb, Celgene, Genentech, Lilly, EMD-Serono, Merck, Millennium, Pfizer, Boehringer Ingelheim, AstraZeneca, Genmab, Novartis, Regeneron, BioNTech, Cantargia AB, Amgen, and Axiom; has provided educational services for AbbVie and Axiom; and has served on a Data and Safety Monitoring Board for Takeda. SSR reports grants from AstraZeneca, Merck and Tesaro, and personal fees for consultant or advisory board services from Amgen, AbbVie, Bristol-Myers Squibb, Lilly, Genentech, Takeda, and Luxo. LH reports grants from Boehringer Ingelheim and Xcovery; non-financial support from Xcovery; and personal fees from AbbVie, AstraZeneca, Bristol-Myers Squibb, Merck, Genentech, Incyte, EMD Serono, and Tesaro. JDCC reports personal fees from Bristol-Myers Squibb, AstraZeneca, MSD, and Roche. AP reports personal fees from Bristol-Myers Squibb, AstraZeneca, Boehringer Ingelheim, MSD, Pfizer, and Roche, and non-financial support from Bristol-Myers Squibb, Boehringer Ingelheim, and Roche. MG reports personal fees from Bristol-Myers Squibb, AstraZeneca, Boehringer Ingelheim, Eli Lilly, MSD, Novartis, Otsuka Pharma, Celgene, Roche, Pfizer, Incyte, Inivata, and Takeda, and has served as principal investigator or conducted patient enrolment in clinical trials (or both) for Bristol-Myers Squibb, AstraZeneca, Eli Lilly, MSD, Novartis, Otsuka Pharma, Celgene, Roche, Pfizer, Tiziana Sciences, Clovis, Merck Serono, and Bayer. LQMC reports grants from Bristol-Myers Squibb, AstraZeneca/MedImmune, Genentech, Novartis, Merck, Lilly/ImClone, Incyte, Pfizer, VentiRx, Seattle Genetics and Dynavax; and personal fees from Bristol-Myers Squibb, Amgen, AstraZeneca/MedImmune, Genentech, Novartis, Merck, Pfizer, Sanofi-Genzyme, Seattle Genetics, Synthorx, Takeda, and Dynavax. SG served as a consultant or advisor (or both) to Bristol-Myers Squibb and NEKTAR; reports research funding from Bristol-Myers Squibb; and reports financial support to his institution from Iovance, Takeda/ARIAD and Genentech for clinical trials. DP reports honoraria from Bristol-Myers Squibb, AstraZeneca, Boehringer, Celgene, Novartis, Pfizer, MSD, Roche, prIME Oncology, and peer CME for services as a consultant, advisor, or lecturer; travel expenses from AstraZeneca, Roche, Novartis, prIME Oncology, and Pfizer, and financial support to his institution from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck, Novartis, Pfizer, Roche, Medimmune, Sanofi-Aventis, Taiho Pharma, Novocure, and Daiichi Sankyo for clinical trials. CB reports honoraria from Bristol-Myers Squibb, AstraZeneca, Boehringer Ingelheim, Merck, and Pfizer. AD reports honoraria from Medscape, Onclive, PeerVoice, Physicians Education Resources, Tyra Biosciences, Targeted Oncology, MORE Health, Research to Practice, Foundation Medicine, Peerview, AstraZeneca, Genentech and Bayer, and has served as a consultant or advisor to Ignyta, Loxo, TP Therapeutics, AstraZeneca, Pfizer, BluePrint Medicines, Genentech, Takeda, Helsinn Therapeutics, BeiGene, Hengrui Therapeutics, Exelixis, and Bayer. GAO reports grants from Bristol-Myers Squibb, AstraZeneca, Merck, Genentech, and Pfizer, and consultant fees for his institution from Merck, Novartis, Pfizer and Takeda. SA and JRP are employed by and own stocks in Bristol-Myers Squibb. AL is employed by Bristol-Myers Squibb. JB reports grants and travel expenses from Bristol-Myers Squibb and personal fees from AstraZeneca, Genentech, and Merck. MAB, LC, and JW-T declare no competing interests.

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References

1 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68:** 394–424.

2 Noone AM, Howlader N, Krapcho M, et al. SEER Cancer Statistics Review, 1975–2015, National Cancer Institute. https://seer.cancer.gov/csr/1975_2015/ (accessed Feb 15, 2019).

3 Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med* 2015; **373:** 123–35.

4 Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* 2015; **373:** 1627–39.

5 Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016; **387:** 1540–50.

6 Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet* 2017; **389:** 255–65.

7 Ettinger DS, Wood DE, Aisner DL, et al. National Comprehensive Cancer Network. Non-small cell lung cancer. Version 2.2019. 2018. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (accessed March 14, 2019).

8 Gettinger S, Horn L, Jackman D, et al. Five-year follow-up of nivolumab in previously treated advanced non-small-cell lung cancer: Results from the CA209-003 Study. *J Clin Oncol* 2018; **36:** 1675–84.

9 Horn L, Spigel DR, Vokes EE, et al. Nivolumab versus docetaxel in previously treated patients with advanced non-small-cell lung cancer: Two-year outcomes from two randomized, open-label, phase III Trials (CheckMate 017 and CheckMate 057). *J Clin Oncol* 2017; **35:** 3924–33.

10 Vokes EE, Ready N, Felip E, et al. Nivolumab versus docetaxel in previously treated advanced non-small-cell lung cancer (CheckMate 017 and CheckMate 057): 3-year update and outcomes in patients with liver metastases. *Ann Oncol* 2018; **29:** 959–65.

11 Schadendorf D, Hodi FS, Robert C, et al. Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in unresectable or metastatic melanoma. *J Clin Oncol* 2015; **33:** 1889–94.

12 Rizvi NA, Mazières J, Planchard D, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. *Lancet Oncol* 2015; **16:** 257–65.

13 Gettinger SN, Horn L, Gandhi L, et al. Overall survival and long-term safety of nivolumab (anti-programmed death 1 antibody, BMS-936558, ONO-4538) in patients with previously treated advanced non-small-cell lung cancer. *J Clin Oncol* 2015; **33:** 2004–12.

14 Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response. *J Clin Oncol* 1983; **1:** 710–19.

15 Santi I, Johal S, Yuan Y, Penrod JR. The impact of response at a landmark on overall survival: implication for the economic evaluation of the value of immuno-oncology treatment in non-small cell lung cancer. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 23rd Annual International Meeting; May 19–23, 2018; Baltimore, MD, USA.

16 Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti PD-1 antibody in cancer. *N Engl J Med* 2012; **366:** 2443–54.

17 McCoach CE, Blumenthal GM, Zhang L, et al. Exploratory analysis of the association of depth of response and survival in patients with metastatic non-small-cell lung cancer treated with a targeted therapy or immunotherapy. *Ann Oncol* 2017; **28:** 2707–14.

18 Blumenthal GM, Karuri SW, Zhang H, et al. Overall response rate, progression-free survival, and overall survival with targeted and standard therapies in advanced non-small-cell lung cancer: US Food and Drug Administration trial-level and patient-level analyses. *J Clin Oncol* 2015; **33:** 1008–14.

19 Lee CK, Lord S, Marschner I, et al. The value of early depth of response in predicting long-term outcome in EGFR-mutant lung cancer. *J Thorac Oncol* 2018; **13:** 792–800.

20 Herbst RS, Garon EB, Kim D, et al. Long-term survival in patients (pts) with advanced NSCLC in the KEYNOTE-010 study overall and in pts who completed 2 years of pembrolizumab (pembro). European Society for Medical Oncology Congress; Oct 19–23, 2018; Munich, Germany.

21 von Pawel J, Bordoni R, Satouchi M, et al. Long-term survival in patients with advanced non-small-cell lung cancer treated with atezolizumab versus docetaxel: Results from the randomised phase III OAK study. *Eur J Cancer* 2019; **107:** 124–32.

22 Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med* 2015; **372:** 2018–28.

23 Fehrenbacher L, von Pawel J, Park K, et al. Updated efficacy analysis including secondary population results for OAK: a randomized phase III study of atezolizumab versus docetaxel in patients with previously treated advanced non-small cell lung cancer. *J Thorac Oncol* 2018; **13:** 1156–70.

24 Gandara DR, Paul SM, Kowanetz M, et al. Blood-based tumor mutational burden as a predictor of clinical benefit in non-small-cell lung cancer patients treated with atezolizumab. *Nat Med* 2018; **24:** 1441–48.

25 Clarke JM, Wang X, Ready NE. Surrogate clinical endpoints to predict overall survival in non-small cell lung cancer trials-are we in a new era? *Transl Lung Cancer Res* 2015; **4:** 804–08.

26 Goring S, Briggs A, Penrod JR, et al. The validity of objective response rate as a surrogate for progression-free and overall survival in the evaluation of first-line chemotherapy for advanced non-small cell lung cancer. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 20th Annual European Congress; Nov 4–8, 2017; Glasgow, Scotland.

27 Kazandjian D, Blumenthal GM, Zhang L, et al. An exploratory responder analyses of best RECIST response and survival in patients with metastatic squamous NSCLC treated with nivolumab. 16th World Conference on Lung Cancer; Sept 6–9, 2015; Denver, Colorado, USA.

28 Mantel N, Byar DP. Evaluation of response-time data involving transient states: an illustration using heart-transplant data. *J Am Stat Assoc* 1974; **69:** 81–86.