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ORIGINAL ARTICLE

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

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Background: Long-term data with immune checkpoint inhibitors in non-small-cell lung cancer (NSCLC) are limited. Two phase III trials demonstrated improved overall survival (OS) and a favorable safety profile with the anti-programmed death-1 antibody nivolumab versus docetaxel in patients with previously treated advanced squamous (CheckMate 017) and nonsquamous (CheckMate 057) NSCLC. We report results from ≥3 years' follow-up, including subgroup analyses of patients with liver metastases, who historically have poorer prognosis among patients with NSCLC.

Patients and methods: Patients were randomized 1 : 1 to nivolumab (3 mg/kg every 2 weeks) or docetaxel (75 mg/m^2 every 3 weeks) until progression or discontinuation. The primary end point of each study was OS. Patients with baseline liver metastases were pooled across studies by treatment for subgroup analyses.

Results: After 40.3 months' minimum follow-up in CheckMate 017 and 057, nivolumab continued to show an OS benefit versus docetaxel: estimated 3-year OS rates were 17% [95% confidence interval (CI), 14% to 21%] versus 8% (95% CI, 6% to 11%) in the pooled population with squamous or nonsquamous NSCLC. Nivolumab was generally well tolerated, with no new safety concerns identified. Of 854 randomized patients across both studies, 193 had baseline liver metastases. Nivolumab resulted in improved OS compared with docetaxel in patients with liver metastases (hazard ratio, 0.68; 95% CI, 0.50–0.91), consistent with findings from the overall pooled study population (hazard ratio, 0.70; 95% CI, 0.61–0.81). Rates of treatment-related hepatic adverse events (primarily grade 1–2 liver enzyme elevations) were slightly higher in nivolumab-treated patients with liver metastases (10%) than in the overall pooled population (6%).

Conclusions: After 3 years' minimum follow-up, nivolumab continued to demonstrate an OS benefit versus docetaxel in patients with advanced NSCLC. Similarly, nivolumab demonstrated an OS benefit versus docetaxel in patients with liver metastases, and remained well tolerated.

Clinical trial registration: CheckMate 017: NCT01642004; CheckMate 057: NCT01673867.

Key words: nivolumab, NSCLC, liver metastases

Introduction

Lung cancer is the leading cause of cancer-related deaths [1], and patients with non-small-cell lung cancer (NSCLC) account for 85% to 90% of lung cancers [2]. The programmed death (PD)-1 receptor suppresses antitumor immunity in a number of malignancies, including NSCLC. Nivolumab is a fully human PD-1 immune checkpoint inhibitor antibody approved in the United States, the European Union, and other countries for the treatment of patients with metastatic NSCLC and disease progression on or after platinum-based chemotherapy [3, 4]. In the CheckMate 017 and CheckMate 057 studies, nivolumab demonstrated improved overall survival (OS) and a favorable safety profile compared with docetaxel in patients with previously treated advanced squamous and nonsquamous NSCLC, respectively [5–7].

Despite recent advances in NSCLC, patients with metastatic disease generally continue to have a poor prognosis. The liver is a common metastatic site in patients with NSCLC, and treatment of symptomatic metastases consists mainly of systemic and palliative therapy [8, 9]. Patients with NSCLC and liver metastases have an unfavorable prognosis. A recent study involving over 20, 000 patients with lung cancer reported OS of 3 months in patients with liver metastases [10]. Outcomes with chemotherapy remain poor [9], with response rates of 27% according to abdominal ultrasound in one analysis [11]. In another analysis, median survival time was 4 months in patients with liver metastases versus 10 months in patients with other metastatic sites [12]. Data on PD-1 inhibitors in patients with poor prognosis, including those with central nervous system (CNS) [13, 14] and liver metastases [9], are limited. Reports from several single institution/country experiences from early access programs that evaluated nivolumab monotherapy suggest that patients with poor prognostic factors, including bone and liver metastases, appeared to have poor outcomes [15]; however, these reports did not compare nivolumab benefit with standard-of-care chemotherapy. Subgroup analysis from CheckMate 017 and 057 demonstrated that nivolumab improved OS versus docetaxel and was well tolerated in patients with advanced NSCLC and previously treated, asymptomatic CNS metastases [16]. Here we report efficacy and safety of nivolumab in patients with NSCLC, and subgroup analyses of the pooled study populations from CheckMate 017 and 057 with liver metastases, with a minimum follow-up of 3 years.

Methods

Patients

Eligibility criteria for CheckMate 017 and CheckMate 057 have been previously described [5, 6]. Patients with stage IIIB/IV NSCLC squamous (CheckMate 017) or nonsquamous (CheckMate 057) histology and disease recurrence or progression during or after prior platinum-based chemotherapy were eligible. Patients were ≥18 years of age, had an Eastern Cooperative Oncology Group performance status of 0 or 1, and had measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [17]. In CheckMate 057, an additional line of prior targeted tyrosine kinase inhibitor therapy was permitted in patients with *EGFR* mutations or *ALK* translocations. Patients who had received more than 1 systemic therapy for metastatic disease were excluded from CheckMate 017.

Study design

CheckMate 017 and CheckMate 057 were international, randomized, open-label phase III studies [5, 6]. In each trial, patients were randomized 1 : 1 to receive nivolumab (3 mg/kg every 2 weeks) or docetaxel (75 mg/m^2 every 3 weeks) (supplementary Figure S1, available at *Annals of Oncology* online). Randomization was stratified by prior paclitaxel use and geographic region in CheckMate 017 and prior maintenance treatment and line of therapy in CheckMate 057.

Patients continued study treatment until disease progression, unacceptable toxicity, or other protocol-specified reasons. Per investigator, patients in the nivolumab groups were permitted to continue study treatment after disease progression, and patients in the docetaxel groups who were no longer deriving benefit were eligible to receive nivolumab in the crossover/extension phases.

The studies were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation guidelines on good clinical practice, and are registered on ClinicalTrials.gov (CheckMate 017: NCT01642004; CheckMate 057: NCT01673867). The study protocols were approved by an institutional review board or independent ethics committee at each site. All patients provided written informed consent.

Assessments

Tumors were assessed by investigators per RECIST v1.1 at baseline, week 9, and every 6 weeks thereafter for the first year on treatment, then every 12 weeks. Patients were followed continuously for survival while receiving study treatment and every 3 months after discontinuation.

Adverse events (AEs) and laboratory assessments were monitored throughout the treatment period and at two follow-up visits within 100 days from last dose, or before the start of crossover treatment. Severity of AEs was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Select AEs, those with a potential immunologic cause that may require management through immune-modulating medications, were grouped according to prespecified categories.

Subgroup analyses of patients with liver metastases included all patients who had target or nontarget liver lesions at baseline, identified and measured based on RECIST v1.1 guidelines. Nontarget lesions were recorded as present, absent, or unequivocal progression. Multiple nontarget lesions involving the same organ could be recorded as a single item.

Statistical analysis

Efficacy was assessed in all randomized patients, and safety was assessed in all patients who received at least 1 dose of study drug. The primary end point of each study (OS) and secondary end points [objective response rate, progression-free survival (PFS), and efficacy according to tumor programmed death ligand 1 (PD-L1) expression] have been reported [5, 6]. For this update (database lock: 22 June 2017), a safety analysis was conducted using pooled data from CheckMate 017 and CheckMate 057.

Survival curves and rates were estimated using the Kaplan–Meier method. Hazard ratios (HRs) and confidence intervals (CIs) were estimated using a stratified Cox proportional hazards model in the separate trials; an unstratified model was used in pooled population and in subgroup analyses of patients with liver metastases.

Results

Patients and treatment

As previously reported [5–7], baseline characteristics were generally well balanced between patients randomized to receive nivolumab (CheckMate 017: $n = 135$; CheckMate 057: $n = 292$) and docetaxel (CheckMate 017: $n = 137$; CheckMate 057: $n = 290$). Patient disposition in each study (minimum follow-up of 40.3 months among patients alive and on study) is summarized in supplementary Figure S2, available at *Annals of Oncology* online.

At 3 years, 7 of 131 (5%) nivolumab-treated patients with squamous NSCLC and 19 of 287 (7%) nivolumab-treated patients with nonsquamous NSCLC remained on treatment; no docetaxel-treated patients remained on treatment. In the nivolumab group, 57 (42%) patients with squamous NSCLC and 141 (48%) patients with nonsquamous NSCLC received other systemic therapy subsequent to study treatment (supplementary Table S1, available at *Annals of Oncology* online); 48 (35%) patients and 156 (54%) patients treated with docetaxel, respectively, received other systemic therapy subsequent to study treatment. In the docetaxel groups, 11 (8%) patients with squamous NSCLC and 32 (11%) with nonsquamous NSCLC received immunotherapy, either during crossover or as subsequent therapy post-study.

After 3 years' minimum follow-up, the mean (standard deviation) treatment duration in the pooled CheckMate 017/057 studies for patients treated with nivolumab and docetaxel was 8.3 (12.4) months and 3.1 (3.0) months, respectively; median treatment duration was 2.8 (range, 0–51.8+) months and 2.1 (range, 0–20.0) months, respectively.

Efficacy

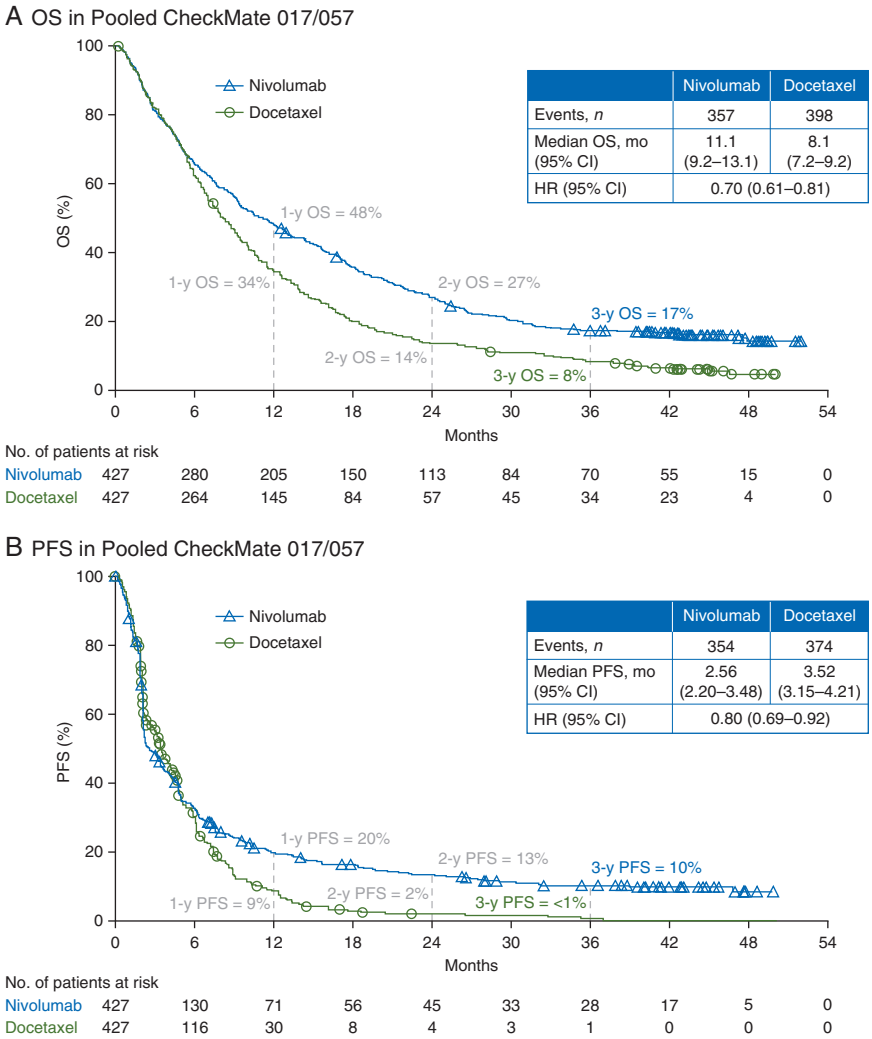
OS was longer with nivolumab versus docetaxel in the pooled population with squamous and nonsquamous NSCLC (HR, 0.70; 95% CI, 0.61–0.81); estimated 3-year OS rates were 17% (95% CI, 14% to 21%) with nivolumab versus 8% (95% CI, 6% to 11%) with docetaxel (Figure 1A). As reported in the primary analyses and 2-year follow-up [5–7], OS was longer with nivolumab versus docetaxel regardless of histology (supplementary Figure S3, available at *Annals of Oncology* online). In both studies, the majority of deaths between 2 and 3 years were due to disease (35 of 40 deaths in the nivolumab arm and 16 of 22 in the docetaxel arm). Of 3-year survivors treated with docetaxel, the majority [74% (25 of 34 patients)] received subsequent immunotherapy. PFS rates consistently favored nivolumab over docetaxel at 1, 2, and 3 years (Figure 1B). Estimated 3-year PFS rates in the pooled population were 10% (95% CI, 7% to 14%) with nivolumab versus <1% (95% CI, <1% to 2%) with docetaxel.

Objective response rates were consistent with those previously reported [5–7] and were higher with nivolumab than with docetaxel (supplementary Table S2, available at *Annals of Oncology* online). Of confirmed responders in the nivolumab group, 20 of 83 (24%) patients with squamous or nonsquamous NSCLC had ongoing responses after 3 years' minimum follow-up; no patients treated with docetaxel had ongoing responses. Median duration of response was longer with nivolumab than with docetaxel [23.8 (95% CI, 11.4–36.1) months versus 5.6 (95% CI, 4.4–7.0) months]. Of the patients treated with nivolumab who were alive at 3 years ($n = 70$), 4 (6%) patients had a complete response, 42 (60%) had partial response, and 18 (26%) had stable disease. Of 3-year survivors treated with docetaxel ($n = 34$), 13 (38%) patients had partial response and 12 (35%) had stable disease.

Pooled analysis of patients with liver metastases. Of 854 randomized patients from CheckMate 017 and 057, 193 (23%) had liver metastases at baseline. Among patients with liver metastases, baseline characteristics were generally similar between treatment groups except for a slight imbalance in histology, and patients with liver metastases had more sites of disease compared with the overall pooled population (supplementary Table S3, available at *Annals of Oncology* online). Nivolumab resulted in a greater OS benefit compared with docetaxel in patients with liver metastases (HR, 0.68; 95% CI, 0.50–0.91), consistent with results for the overall pooled study population (HR, 0.70; 95% CI, 0.61–0.81) (Figure 2). Estimated 3-year OS rates in the pooled CheckMate 017/057 population were 8% (95% CI, 4% to 14%) with nivolumab versus 2% (95% CI, 0.4% to 7%) with docetaxel in patients with liver metastases. Both (2 of 2, 100%) 3-year survivors with liver metastases on the docetaxel arm received subsequent immunotherapy. After 3 years' minimum follow-up, the mean (standard deviation) treatment duration in patients with liver metastases treated with nivolumab and docetaxel, respectively, was 4.8 (8.8) months and 2.2 (2.1) months; median (range) treatment duration was 1.8 (<1–43.8+) months and 1.5 (<1–12.2) months.

Safety

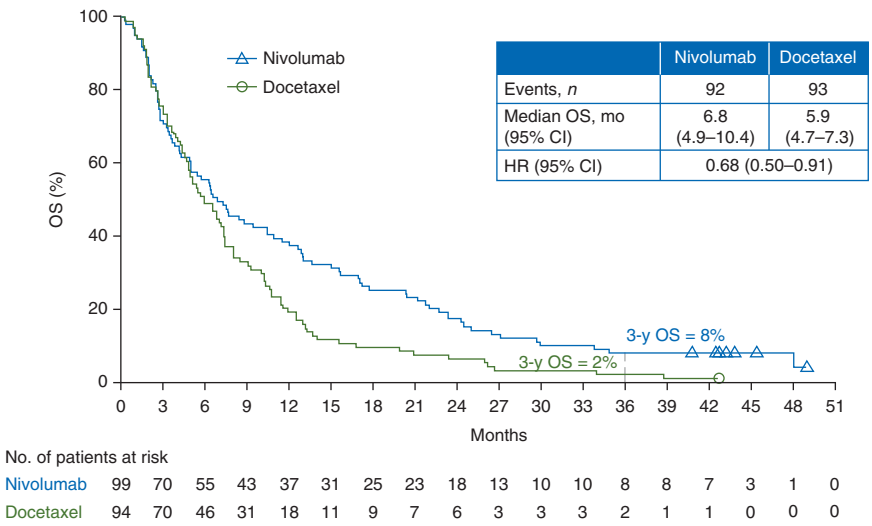
No patient remained on docetaxel treatment for more than 2 years; therefore, updated safety data are presented in nivolumab-treated patients only. Treatment-related AEs after 3 years' minimum follow-in nivolumab-treated pooled patients are reported in Table 1. Between 2 and 3 years' minimum follow-up, 3 new grade 3–4 treatment-related AEs (arthralgia, joint effusion, interstitial lung disease) were reported, consistent with previous reports showing the majority of treatment-related select AEs occur within the first 3 months of nivolumab treatment (supplementary Figure S4, available at *Annals of Oncology* online) [5–7]. Of the most frequent treatment-related AEs, 1 new case each of grade 1–2 fatigue, pruritus, and decreased appetite occurred. No



	Nivolumab	Docetaxel
Events, *n*	357	398
Median OS, mo (95% CI)	11.1 (9.2–13.1)	8.1 (7.2–9.2)
HR (95% CI)	0.70 (0.61–0.81)	

	Nivolumab	Docetaxel
Events, *n*	354	374
Median PFS, mo (95% CI)	2.56 (2.20–3.48)	3.52 (3.15–4.21)
HR (95% CI)	0.80 (0.69–0.92)	

Figure 1. Kaplan–Meier curves of (A) overall survival (OS) and (B) progression-free survival (PFS)[a] in all randomized pooled patients with squamous or nonsquamous non-small-cell lung cancer (NSCLC) with 3 years' minimum follow-up. [a]Investigator-assessed. CI, confidence interval; HR, hazard ratio.



	Nivolumab	Docetaxel
Events, *n*	92	93
Median OS, mo (95% CI)	6.8 (4.9–10.4)	5.9 (4.7–7.3)
HR (95% CI)	0.68 (0.50–0.91)	

Figure 2. Estimated overall survival (OS) with 3 years' minimum follow-up in patients with liver metastases from pooled CheckMate 017 and CheckMate 057. CI, confidence interval; HR, hazard ratio.

Table 1. Pooled analysis of the frequency of treatment-related AEs in nivolumab-treated patients (all pooled patients with squamous and nonsquamous NSCLC and pooled patients with liver metastases)

Events, *n* (%)	All pooled patients (*n*=418)		Patients with liver metastases (*n* = 96)	
	Any grade	Grade 3–4[a]	Any grade	Grade 3–4[a]
Treatment-related AEs	283 (68)	44 (10)	58 (60)	8 (8)
Treatment-related AEs leading to discontinuation	25 (6)	17 (4)	3 (3)	1 (1)
Treatment-related AEs in ≥5% of patients				
Fatigue	71 (17)	4 (1)	13 (14)	1 (1)
Decreased appetite	46 (11)	1 (<1)	9 (9)	1 (1)
Nausea	46 (11)	2 (<1)	8 (8)	1 (1)
Asthenia	44 (10)	1 (<1)	8 (8)	0
Diarrhea	37 (9)	4 (1)	9 (9)	0
Rash	34 (8)	2 (<1)	4 (4)	0
Pruritus	29 (7)	1 (<1)	6 (6)	0
Hypothyroidism	25 (6)	0	3 (3)	0
Arthralgia	24 (6)	1 (<1)	6 (6)	0
Vomiting	21 (5)	0	2 (2)	0
Alanine aminotransferase increased	14 (3)	1 (<1)	5 (5)	0
Aspartate aminotransferase increased	13 (3)	2 (<1)	6 (6)	0

[a]There were no grade 5 treatment-related AEs in nivolumab-treated patients. AE, adverse event; NSCLC, non-small-cell lung cancer.

new treatment-related deaths were reported since the primary analyses [5, 6].

Treatment-related select AEs and median times to onset of treatment-related select AEs were consistent with previous analyses [5–7]; the majority of treatment-related select AEs occurred within the first 3 months of nivolumab treatment (supplementary Figure S4, available at *Annals of Oncology* online). Median times to onset of treatment-related select AEs by category were <3 months after initiating nivolumab treatment, with the exception of pulmonary events (7.0 months). The most common treatment-related select AEs observed were skin-related (Table 2). Of the 49 patients on treatment between 2 and 3 years' minimum follow-up, 3 (6%) patients had hepatic AEs and 1 (2%) patient had a pulmonary AE (grade 3–4 interstitial lung disease); of the 31 patients on treatment after 3 years' minimum follow-up, 2 (6%) patients had gastrointestinal AEs and 1 (3%) patient had a skin AE.

Safety analysis of patients with liver metastases. Treatment-related AEs in nivolumab-treated patients with liver metastases were similar to those seen in the overall nivolumab-treated patients (Table 1). Rates of treatment-related select AEs in nivolumab-treated patients with liver metastases were generally similar to the overall nivolumab-treated patients, except for a slight increase in hepatic and renal events (Table 2). Most hepatic events in patients with liver metastases (88%) were grade 1–2 liver enzyme elevations (supplementary Table S4, available at *Annals of Oncology* online), and none required treatment discontinuation. Of the 90 docetaxel-treated patients with liver metastases at 2 years minimum follow-up, there were three grade 1–2 hepatic events (increased aspartate aminotransferase, increased alanine aminotransferase, and hyperbilirubinaemia) and one grade 3–4 increased blood alkaline phosphatase; none led to discontinuation. As in the overall population, the most common treatment-related select AEs were skin-related.

Discussion

PD-(L)1 agents have become the standard of care for patients with previously treated advanced NSCLC [4], and nivolumab—with 3 years' minimum follow-up in the CheckMate 017 and 057 studies—continued to demonstrate long-term survival and PFS benefit in patients with advanced squamous and nonsquamous NSCLC [5–7]. Nivolumab demonstrated a durable clinical benefit compared with docetaxel, with approximately one-quarter of patients who responded to nivolumab experiencing ongoing tumor responses compared with no docetaxel-treated patients. No new safety signals were identified for nivolumab, and rates of treatment-related AEs were similar to those reported previously [7].

As with CNS metastases, the presence of liver metastases has been identified as an unfavorable prognostic factor in patients with lung cancer, across various histologic types [9, 10, 18–20]. A recent study demonstrated that the presence of liver metastases in patients with NSCLC was associated with shorter PFS and decreased likelihood of response to PD-1 inhibition compared with patients without liver metastases; however, the relative clinical benefit versus chemotherapy is unknown [21]. While patients with liver metastases had worse prognosis than the overall study population in both treatment arms, OS benefit derived from nivolumab versus docetaxel in this study was similar in patients with liver metastases (HR, 0.68; 95% CI, 0.50–0.91) and the overall study population (HR, 0.70; 95% CI, 0.61–0.81). Due to the

Table 2. Pooled analysis of the frequency of treatment-related select AEs[a] in nivolumab-treated patients (all pooled patients with squamous and nonsquamous NSCLC and pooled patients with liver metastases)

Category	Select AE, *n* (%)			
	All pooled patients (*n* = 418)		Patients with liver metastases (*n* = 96)	
	Any grade	Grade 3–4[b]	Any grade	Grade 3–4[b]
Skin	68 (16)	4 (1)	11 (12)	0
Gastrointestinal	38 (9)	5 (1)	9 (9)	0
Endocrine	36 (9)	0	5 (5)	0
Hepatic	24 (6)	4 (1)	10 (10)	2 (2)
Pulmonary	19 (4)	6 (1)	5 (5)	2 (2)
Renal	11 (3)	1 (<1)	5 (5)	1 (1)
Hypersensitivity/infusion reaction	10 (2)	0	2 (2)	0

[a]Select AEs are those with a potential immunologic cause.
[b]There were no grade 5 treatment-related select AEs in nivolumab-treated patients. AE, adverse event; NSCLC, non-small-cell lung cancer.

exploratory nature of the subgroup analysis, slight imbalances between treatment arms in the patients with liver metastases may exist and limit interpretation. Similarly, a previous analysis in patients with pretreated CNS metastasis demonstrated longer OS with nivolumab versus docetaxel [median OS (95% CI), 8.4 (5.0–11.6) months versus 6.2 (4.4–9.2) months] [16]. Notably, all 3-year survivors with liver metastases received nivolumab treatment, including the two patients who received docetaxel initially and subsequently crossed over to nivolumab. While rates of treatment-related hepatic AEs were slightly higher in nivolumab-treated patients with liver metastases than in the overall study population, they were primarily grade 1–2 liver enzyme elevations, and nivolumab was generally well tolerated, with no new safety concerns [5–7]. Patients with NSCLC and metastatic disease continue to have a poor prognosis despite recent advances in treatments; however, these data suggest that these patients may benefit from treatment with an anti–PD-1 inhibitor. These updated analyses from CheckMate 017 and CheckMate 057 demonstrate long-term clinical benefit with nivolumab in previously treated patients with advanced squamous and nonsquamous NSCLC, including those with liver metastases.

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