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Original Research

CheckMate 171: A phase 2 trial of nivolumab in patients with previously treated advanced squamous non-small cell lung cancer, including ECOG PS 2 and elderly populations

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Abstract ***Background:*** CheckMate 171 (NCT02409368) is an open-label, multicentre, phase 2 trial of nivolumab in previously treated advanced squamous non-small cell lung cancer (NSCLC), conducted as part of a post-approval commitment to the European Medicines Agency (EMA). We report outcomes from this trial.
Methods: Patients with Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2 and disease progression during/after ≥1 systemic treatment (≥1 being platinum-based chemotherapy) for advanced or metastatic disease were treated with nivolumab 3 mg/kg every 2 weeks until progression or unacceptable toxicity. The primary end-point was incidence of grade 3–4 treatment-related select adverse events (AEs). Other end-points included overall survival (OS) and safety.
Results: Of 811 patients treated, 103 had ECOG PS 2; 278 were aged ≥70 years and 125 were ≥75 years of age. Minimum follow-up was ~18 months. Safety was similar across populations; the most frequent grade 3–4 treatment-related select AEs in all treated patients were diarrhoea (1%), increased alanine aminotransferase (ALT, 1%), pneumonitis (0.7%), colitis (0.6%) and increased aspartate aminotransferase (AST, 0.5%). Median OS was similar in all treated patients and those aged ≥70 and ≥75: 10.0 months, 10.0 months and 11.2 months, respectively. Median OS was 5.2 months in patients with ECOG PS 2.
Conclusion: These results suggest that nivolumab is well tolerated and active in patients with advanced, relapsed squamous NSCLC, including the elderly, with OS outcomes consistent with phase 3 data. In patients with ECOG PS 2, nivolumab had similar tolerability, but outcomes were worse, as expected in this difficult-to-treat, poor prognosis population.
Clinical trial registration: NCT02409368.
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1. Introduction

Non-small cell lung cancer (NSCLC) accounts for >80% of all diagnosed lung cancers [1,2], of which 25–30% are classified as squamous cell carcinoma [3,4]. Prior to the advent of immuno-oncology therapies, patients with relapsed squamous NSCLC had relatively limited treatment options and median overall survival (OS) of only 4.8–6.4 months [5,6]. A number of factors contribute to this poor prognosis; patients are commonly diagnosed at an advanced stage and at an older age, and often carry comorbidities associated with tobacco exposure [1,7–11]. Such patients are typically under-represented in clinical trials [12–14].

Nivolumab is a fully human programmed death-1 (PD-1) immune checkpoint inhibitor antibody [15]. In the phase 3 CheckMate 017 trial (NCT01642004), second-line nivolumab was associated with significantly longer overall survival [OS] (~3 months improvement), regardless of programmed death ligand 1 expression, and a more favourable safety profile compared with docetaxel [16]. Based on these results, nivolumab gained approval for previously treated advanced squamous NSCLC in multiple regions, including European Union (EU) countries in 2015 [17,18]. Approval was further supported by results from the phase 2 single-arm CheckMate 063 trial (NCT01721759), which showed that nivolumab had clinically meaningful activity and manageable safety in the second-line setting and beyond [19]. Furthermore, with 4 years of follow-up, pooled data from these and other studies of patients with squamous and non-squamous NSCLC showed long-term OS benefits with nivolumab [20]. However, these pivotal trials provided limited data on patients with squamous NSCLC and poor prognostic factors. More recently, real-world studies have shown that nivolumab is effective and well tolerated in elderly patients and those with poor performance status [7,21,22].

CheckMate 171 (NCT02409368) is a phase 2 clinical trial with broader eligibility criteria than standard trials,

conducted as part of a post-approval commitment to the European Medicines Agency. Herein, we present the final analysis of safety and efficacy outcomes from this trial, including patients with Eastern Cooperative Oncology Group performance status (ECOG PS) 2 and elderly patients (≥70 and ≥ 75 years of age).

2. Methods

2.1. Patients

Eligible patients were ≥18 years of age with histologically or cytologically confirmed squamous NSCLC, stage IIIB or IV disease or recurrent/progressive disease following definitive therapy for localised or locally advanced disease, disease progression during or after ≥1 systemic treatment (≥1 being platinum doublet-based chemotherapy) for advanced or metastatic disease and ECOG PS 0–2. Patients with previously treated or neurologically asymptomatic untreated central nervous system (CNS) metastases were also eligible provided they were not administered corticosteroids or received a stable or decreasing dose of <10 mg daily prednisone (or equivalent). Patients were required to have evaluable disease by computed tomography (CT) or magnetic resonance imaging (MRI) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [23] and have completed prior lines of antineoplastic therapy 28 days before the first nivolumab dose. Key exclusion criteria were untreated symptomatic central nervous system (CNS) metastases, carcinomatous meningitis, existing or suspected autoimmune disease, prior immunotherapy, systemic treatment with corticosteroids or other immunosuppressive medication taken within 14 days of the first nivolumab dose.

2.2. Study design and treatment

CheckMate 171 is an open-label, multicentre, phase 2 trial in which patients received nivolumab 3 mg/kg in a 60-min intravenous infusion every 2 weeks until disease progression, unacceptable toxicity or withdrawal of consent. Treatment beyond initial investigator-assessed RECIST 1.1–defined progression was permitted if the patient provided written consent and continued to show clinical benefit (as assessed by the investigator), tolerance of the study drug and stable ECOG PS; continued treatment was not permitted if it delayed any imminent intervention to prevent serious complications of progression.

2.3. End–points and assessments

The primary end-point was the incidence of grade 3–4 treatment-related select adverse events (AEs; select AEs are those with a potential immunological cause) as per the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 of the US National Cancer Institute. Secondary end-points were incidence and time to onset and resolution of all-cause grade 3–4 select AEs, OS and investigator-assessed tumour response rate. Exploratory end-points included safety and tolerability as assessed by the incidence of AEs, serious AEs and deaths.

AEs were monitored continuously throughout the study, with scheduled assessments at screening, the beginning of each 2-week cycle and approximately 6 and 16 weeks after the last dose of study drug. AEs included events reported between the first dose and 30 days after the last dose of study treatment. All ongoing AEs and serious AEs were monitored for ≥100 days after the last dose of study drug until resolution or stabilisation. Treatment-related AEs (TRAEs) and serious TRAEs were followed until resolved, symptoms returned to

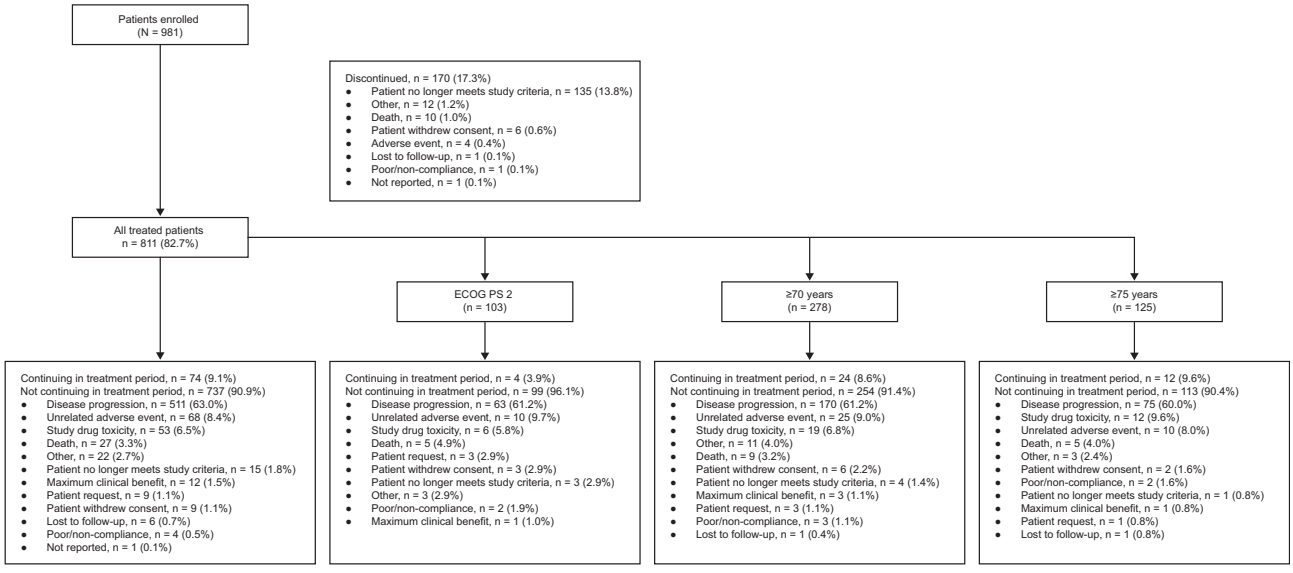

Fig. 1. Diagram of patient disposition. ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 1
Patient baseline characteristics.[a]

Characteristic	All treated (N = 811)	ECOG PS 2 (n = 103)	≥70 years (n = 278)[b]	≥75 years (n = 125)
Age, median (range)	66 (31–86)	68 (42–86)	74 (70–86)	77 (75–86)
Male, n (%)	640 (78.9)	81 (78.6)	228 (82.0)	106 (84.8)
ECOG PS, n (%)				
0	173 (21.3)	0	41 (14.7)	13 (10.4)
1	534 (65.8)	0	192 (69.1)	92 (73.6)
2	103 (12.7)	103 (100.0)	44 (15.8)	20 (16.0)
3	1 (0.1)	0	1 (0.4)	0
Smoking status, n (%)				
Current/former	760 (93.7)	99 (96.1)	263 (94.6)	117 (93.6)
Never	43 (5.3)	3 (2.9)	11 (4.0)	7 (5.6)
Unknown	7 (0.9)	1 (1.0)	3 (1.1)	1 (0.8)
Not reported	1 (0.1)	0	1 (0.4)	0
Disease stage, n (%)				
Stage III	127 (15.7)	19 (18.4)	39 (14.0)	21 (16.8)
Stage IV	682 (84.1)	84 (81.6)	238 (85.6)	104 (83.2)
Unknown/not reported	2 (0.2)	0	1 (0.4)	0
CNS metastases, n (%)	32 (3.9)	3 (2.9)	7 (2.5)	4 (3.2)
Number of prior lines of therapy, n (%)				
1	336 (41.4)	37 (35.9)	137 (49.3)	65 (52.0)
2	329 (40.6)	47 (45.6)	100 (36.0)	49 (39.2)
Other	146 (18.0)	19 (18.4)	41 (14.7)	11 (8.8)
Prior systemic therapy, n (%)[c]				
EGFR TKI	81 (10.0)	12 (11.7)	26 (9.4)	12 (9.6)
Platinum-based chemotherapy	811 (100.0)	103 (100.0)	278 (100.0)	125 (100.0)
Other chemotherapy	808 (99.6)	103 (100.0)	277 (99.6)	125 (100.0)
Investigational therapy	51 (6.3)	6 (5.8)	23 (8.3)	12 (9.6)
Unassigned	2 (0.2)	0	1 (0.4)	1 (0.8)
Prior surgery related to cancer, n (%)	212 (26.1)	16 (15.5)	71 (25.5)	38 (30.4)
Prior radiotherapy, n (%)	466 (57.5)	70 (68.0)	145 (52.2)	61 (48.8)
Best response to most recent prior systemic therapy, n (%)				
CR or PR	198 (24.4)	17 (16.5)	75 (27.0)	36 (28.8)
SD	265 (32.7)	35 (34.0)	86 (30.9)	39 (31.2)
PD	259 (31.9)	37 (35.9)	84 (30.2)	37 (29.6)
Unknown/not reported	89 (11.0)	14 (13.6)	33 (11.9)	13 (10.4)

CNS, central nervous system; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor; PD, progressive disease; PR, partial response; SD, stable disease.

[a] A small number of patients with non-squamous histology were included in this study: 16 patients with adenocarcinoma, 1 patient with broncho-alveolar carcinoma, and 8 patients with other cell type histology were included in the all-treated population; 2 patients with adenocarcinoma and 1 patient with other cell type histology were included in the ECOG PS 2 group; 5 patients with adenocarcinoma and 4 patients with other cell type histology were included in the ≥70 years group; 1 patient with adenocarcinoma and 1 patient with other cell type histology were included in the ≥75 years group.

[b] Includes patients in the ≥75 years subgroup.

[c] Some patients may have been treated with more than one type of therapy.

baseline, the TRAE was considered irreversible, disease progression, the patient was lost to follow up/death or withdrawal of consent.

Survival was assessed every 2 weeks; patients were followed beyond disease progression until death, withdrawal of consent, if patient was lost to follow-up or study end. Mandatory image-based tumour assessments were carried out at weeks 8/9 and 52 (±5 days) using RECIST v1.1. Additional imaging assessments were performed according to local standards of care or at the investigator's discretion and were recommended every 8–12 weeks, but were not centrally collected.

Measurement of tumour PD-L1 or other biomarker status was not mandated and local tumour biomarker data were not collected.

2.4. Statistical analysis

Safety and efficacy outcomes except tumour response were reported for all treated patients (those who received ≥1 dose of nivolumab) and by ECOG PS 2, ≥70 years and ≥75 years of age. Tumour response, based on the first tumour assessment at week 8/9, was reported for patients with baseline and week 8/9 (±5 days) on-study tumour assessment. Tumour response rate (complete response [CR] + partial response [PR]) was based on the total number of patients with CR, PR, stable disease (SD), progressive disease (PD) and patients who were not evaluable.

Time to onset and resolution of all-cause and treatment-related select AEs and OS were estimated using the Kaplan–Meier (K-M) method. Medians

Table 2
Treatment exposure.

	All treated (N = 811)	ECOG PS 2 (n = 103)	≥70 years (n = 278)	≥75 years (n = 125)
Number of nivolumab doses received				
Median, n (range)	10.0 (1–70)	4.0 (1–62)	9.0 (1–70)	10.0 (1–70)
Mean (SD)	15.0 (15.4)	10.6 (13.9)	15.2 (15.7)	15.9 (16.3)
1, n (%)	66 (8.1)	15 (14.6)	25 (9.0)	14 (11.2)
2, n (%)	56 (6.9)	16 (15.5)	21 (7.6)	10 (8.0)
3, n (%)	61 (7.5)	15 (14.6)	26 (9.4)	7 (5.6)
4, n (%)	61 (7.5)	9 (8.7)	22 (7.9)	12 (9.6)
>4, n (%)	567 (69.9)	48 (46.6)	184 (66.2)	82 (65.6)
Duration of therapy				
Median, months (95% CI)	4.2 (3.7–4.6)	1.4 (1.2–2.5)	4.2 (3.2–4.9)	4.6 (2.3–5.7)
Mean, months (SD)	6.9 (7.5)	4.8 (6.8)	7.0 (7.7)	7.3 (8.0)
Relative dose intensity, n (%)				
≥110%	3 (0.4)	0	1 (0.4)	0
90% to <110%	652 (80.4)	84 (81.6)	223 (80.2)	104 (83.2)
70% to <90%	143 (17.6)	15 (14.6)	52 (18.7)	21 (16.8)
50% to <70%	12 (1.5)	4 (3.9)	2 (0.7)	0
Missing	1 (0.1)	0	0	0

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation.

for time-to-event end-points and associated two-sided 95% confidence intervals (CIs) were based on the Brookmeyer and Crowley method. OS rates at predefined timepoints were calculated from K-M estimates; associated 2-sided 95% CIs were calculated using the Greenwood formula. Tumour response assessments at week 8/9 were summarised using binomial response rates and associated two-sided 95% exact CIs using the Clopper–Pearson method. Analyses were based on the 14th March 2018 database lock and performed using SAS software (version 9.3 or higher).

Table 3
Treatment-related select AEs in ≥1% of all treated patients.

Treatment-related select AEs[a] in ≥1% of all treated patients, n (%)	All treated (N = 811)		ECOG PS 2 (n = 103)		≥70 years (n = 278)		≥75 years (n = 125)	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Skin	143 (17.6)	8 (1.0)	15 (14.6)	0	52 (18.7)	2 (0.7)	27 (21.6)	1 (0.8)
Rash	46 (5.7)	1 (0.1)	6 (5.8)	0	17 (6.1)	0	7 (5.6)	0
Pruritus	43 (5.3)	1 (0.1)	8 (7.8)	0	15 (5.4)	0	11 (8.8)	0
Maculopapular rash	25 (3.1)	0	1 (1.0)	0	13 (4.7)	0	6 (4.8)	0
Pruritic rash	21 (2.6)	2 (0.2)	2 (1.9)	0	9 (3.2)	1 (0.4)	3 (2.4)	0
Generalised pruritus	16 (2.0)	0	1 (1.0)	0	6 (2.2)	0	2 (1.6)	0
Macular rash	8 (1.0)	0	1 (1.0)	0	2 (0.7)	0	0	0
Endocrine	89 (11.0)	7 (0.9)	5 (4.9)	0	27 (9.7)	2 (0.7)	10 (8.0)	1 (0.8)
Hypothyroidism	54 (6.7)	1 (0.1)	3 (2.9)	0	17 (6.1)	0	9 (7.2)	0
Hyperthyroidism	24 (3.0)	1 (0.1)	1 (1.0)	0	7 (2.5)	1 (0.4)	1 (0.8)	1 (0.8)
Increased blood TSH	8 (1.0)	0	1 (1.0)	0	3 (1.1)	0	0	0
Gastrointestinal[b]	85 (10.5)	11 (1.4)	12 (11.7)	0	40 (14.4)	5 (1.8)	23 (18.4)	2 (1.6)
Diarrhoea	84 (10.4)	8 (1.0)	12 (11.7)	0	40 (14.4)	3 (1.1)	23 (18.4)	1 (0.8)
Hepatic	55 (6.8)	16 (2.0)	9 (8.7)	2 (1.9)	20 (7.2)	4 (1.4)	6 (4.8)	2 (1.6)
Increased aspartate aminotransferase	30 (3.7)	4 (0.5)	4 (3.9)	0	10 (3.6)	1 (0.4)	1 (0.8)	0
Increased alanine aminotransferase	27 (3.3)	8 (1.0)	3 (2.9)	1 (1.0)	8 (2.9)	2 (0.7)	1 (0.8)	0
Increased blood alkaline phosphatase	13 (1.6)	2 (0.2)	3 (2.9)	0	4 (1.4)	1 (0.4)	0	0
Pulmonary	39 (4.8)	7 (0.9)	2 (1.9)	0	14 (5.0)	3 (1.1)	9 (7.2)	1 (0.8)
Pneumonitis	38 (4.7)	6 (0.7)	2 (1.9)	0	13 (4.7)	2 (0.7)	9 (7.2)	1 (0.8)
Renal	28 (3.5)	4 (0.5)	2 (1.9)	1 (1.0)	14 (5.0)	3 (1.1)	5 (4.0)	1 (0.8)
Increased blood creatinine	17 (2.1)	0	1 (1.0)	0	8 (2.9)	0	3 (2.4)	0
Hypersensitivity/infusion-related reaction	13 (1.6)	0	3 (2.9)	0	3 (1.1)	0	1 (0.8)	0
Infusion-related reaction	11 (1.4)	0	3 (2.9)	0	3 (1.1)	0	1 (0.8)	0

AE, adverse event; ECOG PS, Eastern Cooperative Oncology Group performance status; TSH, thyroid stimulating hormone.

[a] Includes events reported between the first dose and 30 days after last dose of study therapy.

[b] Any-grade and grade 3–4 colitis was reported in 7 (0.9%) and 5 (0.6%) all treated patients, 1 (1.0%) and 0 patients with ECOG PS 2, 3 (1.1%) and 2 (0.7%) of patients aged ≥70 years and 2 (1.6%) and 1 (0.8%) of patients aged ≥75 years, respectively.

Table 4
Treatment-related select AEs leading to discontinuation.

Treatment-related select AEs[a] leading to discontinuation	All treated (N = 811)		ECOG PS 2 (n = 103)		≥70 years (n = 278)		≥75 years (n = 125)	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Pulmonary	13 (1.6)	6 (0.7)	1 (1.0)	0	6 (2.2)	3 (1.1)	3 (2.4)	1 (0.8)
Pneumonitis	12 (1.5)	5 (0.6)	1 (1.0)	0	5 (1.8)	2 (0.7)	3 (2.4)	1 (0.8)
Interstitial lung disease	1 (0.1)	1 (0.1)	0	0	1 (0.4)	1 (0.4)	0	0
Hepatic	10 (1.2)	7 (0.9)	2 (1.9)	2 (1.9)	3 (1.1)	2 (0.7)	1 (0.8)	1 (0.8)
Increased alanine aminotransferase	4 (0.5)	4 (0.5)	1 (1.0)	1 (1.0)	1 (0.4)	1 (0.4)	0	0
Autoimmune hepatitis	4 (0.5)	2 (0.2)	2 (1.9)	2 (1.9)	0	0	0	0
Increased aspartate aminotransferase	3 (0.4)	2 (0.2)	1 (1.0)	0	1 (0.4)	1 (0.4)	0	0
Increased blood alkaline phosphatase	1 (0.1)	1 (0.1)	0	0	1 (0.4)	1 (0.4)	0	0
Increased blood bilirubin	1 (0.1)	1 (0.1)	0	0	1 (0.4)	1 (0.4)	0	0
Drug-induced liver injury	1 (0.1)	0	0	0	1 (0.4)	0	0	0
Hepatotoxicity	1 (0.1)	1 (0.1)	0	0	0	0	0	0
Increased liver function test	1 (0.1)	1 (0.1)	0	0	1 (0.4)	1 (0.4)	1 (0.8)	1 (0.8)
Gastrointestinal	6 (0.7)	4 (0.5)	1 (1.0)	0	2 (0.7)	2 (0.7)	1 (0.8)	1 (0.8)
Diarrhoea	4 (0.5)	2 (0.2)	1 (1.0)	0	2 (0.7)	2 (0.7)	1 (0.8)	1 (0.8)
Colitis	2 (0.2)	2 (0.2)	0	0	0	0	0	0
Renal	4 (0.5)	1 (0.1)	1 (1.0)	1 (1.0)	3 (1.1)	1 (0.4)	0	0
Increased blood creatinine	2 (0.2)	0	0	0	1 (0.4)	0	0	0
Acute kidney injury	1 (0.1)	1 (0.1)	1 (1.0)	1 (1.0)	1 (0.4)	1 (0.4)	0	0
Nephritis	1 (0.1)	0	0	0	1 (0.4)	0	0	0
Endocrine	3 (0.4)	1 (0.1)	0	0	1 (0.4)	0	0	0
Thyroid disorder	1 (0.1)	0	0	0	1 (0.4)	0	0	0
Hyperthyroidism	1 (0.1)	0	0	0	1 (0.4)	0	0	0
Thyroiditis	1 (0.1)	0	0	0	1 (0.4)	0	0	0
Adrenal disorder	1 (0.1)	0	0	0	0	0	0	0
Adrenal insufficiency	1 (0.1)	0	0	0	0	0	0	0
Pituitary disorder	1 (0.1)	1 (0.1)	0	0	0	0	0	0
Hypophysitis	1 (0.1)	1 (0.1)	0	0	0	0	0	0
Skin	3 (0.4)	1 (0.1)	0	0	1 (0.4)	1 (0.4)	1 (0.8)	1 (0.8)
Rash	2 (0.2)	0	0	0	0	0	0	0
Generalised rash	1 (0.1)	1 (0.1)	0	0	1 (0.4)	1 (0.4)	1 (0.8)	1 (0.8)

AE, adverse event; ECOG PS, Eastern Cooperative Oncology Group performance status.
[a] Includes events reported between the first dose and 30 days after last dose of study therapy.

2.5. Trial oversight

This study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki. The study protocol was approved by an institutional review board or independent ethics committee at each site, prior to study initiation. All patients gave written informed consent. 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.

3. Results

3.1. Patients

Patients were enrolled from April 2015 until July 2016 at 65 sites across 13 European countries. Of 981 enrolled patients, 811 were treated with nivolumab (Fig. 1). Of patients treated, 103 (12.7%) had ECOG PS 2, 278 (34.3%) were aged ≥70 years and 125 (15.4%) were aged ≥75 years (Table 1). Within the all-treated population, 475 (58.6%) patients received ≥2 prior lines of therapy. Baseline characteristics were generally well balanced between populations (Table 1), with the exception of response to prior therapy, which was numerically lower in patients with ECOG PS 2.

At database lock, minimum follow-up was ~18 months for all treated patients, and 74/811 of all treated patients (9.1%) continued to receive study treatment, including 4/103 patients (3.9%) with ECOG PS 2, 24/278 patients (8.6%) aged ≥70 years and 12/125 patients (9.6%) aged ≥75 years. The main reason for discontinuation across all populations was disease progression (Fig. 1). Treatment exposure was similar between all treated patients and those aged ≥70 and ≥ 75 years, but reduced in patients with ECOG PS 2. The majority of patients (>80%) across populations received ≥90% of the planned dose intensity (Table 2).

3.2. Safety

The most frequently reported grade 3–4 treatment-related select AEs (primary end-point) in all treated patients were diarrhoea (1%), increased alanine

Table 5
Incidence, time to onset and resolution of treatment-related select AEs.

	Incidence, n (%)		Median time to onset, weeks (range)		Resolved, n (%)[a]		Median time to resolution, weeks (range)	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Skin								
Total	143 (17.6)	8 (1.0)	8.0 (0.1–92.1)	10.1 (2.1–44.3)	83 (58.0)	5 (62.5)	14.6 (0.1–123.1+)	17.5 (0.1–73.3+)
ECOG PS 2	15 (14.6)	0	10.0 (2.1–56.0)	NA	10 (66.7)	NA	5.7 (1.1–58.7+)	NA
≥70 years	52 (18.7)	2 (0.7)	8.0 (0.1–64.7)	20.9 (16.4–25.3)	30 (57.7)	0	12.3 (0.4–107.1+)	NR (26.7+–31.3+)
≥75 years	27 (21.6)	1 (0.8)	9.6 (0.4–64.7)	16.4 (16.4–16.4)	15 (55.6)	0	34.6 (0.6–75.1+)	NR (31.3+–31.3+)
Endocrine								
Total	89 (11.0)	7 (0.9)	12.1 (1.9–112.0)	19.9 (7.0–40.6)	32 (36.0)	4 (57.1)	NR (1.0–108.3+)	3.6 (1.4–84.0+)
ECOG PS 2	5 (4.9)	0	13.3 (6.1–55.4)	NA	2 (40.0)	NA	NR (6.1–88.0+)	NA
≥70 years	27 (9.7)	2 (0.7)	10.1 (1.9–70.1)	9.3 (7.0–11.6)	7 (25.9)	0	NR (1.0–108.1+)	NR (41.7+–84.0+)
≥75 years	10 (8.0)	1 (0.8)	16.1 (3.9–70.1)	7.0 (7.0–7.0)	0	0	NR (7.6+–108.1+)	NR (41.7+–41.7+)
GI								
Total	85 (10.5)	11 (1.4)	11.7 (0.1–131.0)	26.1 (5.9–69.9)	73 (85.9)	11 (100.0)	3.0 (0.1–89.1+)	2.1 (0.1–10.0)
ECOG PS 2	12 (11.7)	0	15.0 (0.3–64.3)	NA	11 (91.7)	NA	1.3 (0.1–29.9+)	NA
≥70 years	40 (14.4)	5 (1.8)	12.4 (0.1–131.0)	22.7 (5.9–37.4)	34 (85.0)	5 (100.0)	3.2 (0.1–37.9+)	2.0 (0.1–5.0)
≥75 years	23 (18.4)	2 (1.6)	7.1 (0.1–131.0)	16.0 (5.9–26.1)	18 (78.3)	2 (100.0)	3.9 (0.1–37.9+)	3.5 (2.0–5.0)
Hepatic								
Total	55 (6.8)	16 (2.0)	14.1 (2.0–97.0)	19.5 (2.1–82.3)	44 (81.5)	14 (87.5)	4.4 (0.3+–92.6)	4.0 (1.0–32.4+)
ECOG PS 2	9 (8.7)	2 (1.9)	8.0 (2.0–82.1)	44.3 (6.3–82.3)	6 (66.7)	2 (100.0)	3.6 (0.6+–32.1+)	3.2 (2.4–4.0)
≥70 years	20 (7.2)	4 (1.4)	15.4 (2.0–97.0)	29.6 (2.1–38.1)	17 (89.5)	4 (100.0)	4.1 (1.0–84.4+)	1.1 (1.00–8.9)
≥75 years	6 (4.8)	2 (1.6)	14.3 (2.1–45.3)	15.1 (2.1–28.1)	5 (83.3)	2 (100.0)	2.1 (1.1–84.4+)	1.1 (1.1–1.1)
Pulmonary								
Total	39 (4.8)	7 (0.9)	17.7 (0.9–68.0)	7.4 (0.9–50.1)	31 (79.5)	6 (85.7)	3.7 (0.1+–105.0+)	2.7 (0.1+–25.6)
ECOG PS 2	2 (1.9)	0	16.8 (7.3–26.3)	NA	1 (50.0)	NA	NR (2.3–50.7+)	NA
≥70 years	14 (5.0)	3 (1.1)	12.8 (3.7–50.9)	5.6 (4.1–24.3)	12 (85.7)	2 (66.7)	3.0 (0.1+–15.3+)	3.4 (0.1+–4.9)
≥75 years	9 (7.2)	1 (0.8)	11.7 (3.7–34.3)	4.1 (4.1–4.1)	8 (88.9)	0	3.4 (0.1+–13.1)	NR (0.1+–0.1+)
Renal								
Total	28 (3.5)	4 (0.5)	27.6 (1.4–107.1)	25.4 (1.4–31.1)	20 (71.4)	2 (50.0)	6.1 (0.1+–107.1+)	1.3 (0.7+–107.1+)
ECOG PS 2	2 (1.9)	1 (1.0)	6.6 (1.4–11.9)	1.4 (1.4–1.4)	1 (50.0)	0	59.1 (0.7+–59.1)	NR (0.7+–0.7+)
≥70 years	14 (5.0)	3 (1.1)	15.9 (1.4–107.1)	22.7 (1.4–28.1)	9 (64.3)	2 (66.7)	6.1 (0.1+–27.1+)	1.2 (0.7+–1.3)
≥75 years	5 (4.0)	1 (0.8)	12.9 (2.1–28.1)	28.1 (28.1–28.1)	4 (80.0)	1 (100.0)	2.3 (0.6–6.1+)	1.1 (1.1–1.1)
Hypersensitivity/IR								
Total	13 (1.6)	0	2.1 (2.0–73.4)	NA	13 (100.0)	NA	0.1 (0.1–1.7)	NA
ECOG PS 2	3 (2.9)	0	2.1 (2.1–2.1)	NA	3 (100.0)	NA	0.1 (0.1–0.1)	NA
≥70 years	3 (1.1)	0	2.1 (2.1–2.1)	NA	3 (100.0)	NA	0.1 (0.1–0.1)	NA
≥75 years	1 (0.8)	0	2.1 (2.1–2.1)	NA	1 (100.0)	NA	0.1 (0.1–0.1)	NA

Symbol + indicates a censored value.
Total patients in each group: Total, N = 811; ECOG PS 2, n = 103; ≥70 years, n = 278; ≥75 years, n = 125.
AE, adverse event; ECOG PS, Eastern Cooperative Oncology Group performance status; GI, gastrointestinal; IR, infusion reaction; NA, not applicable; NR, not resolved.
[a] Percentage calculated using total number of any grade or grade 3–4 as the denominator.

aminotransferase (ALT, 1%), pneumonitis (0.7%), colitis (0.6%) and increased aspartate aminotransferase (AST, 0.5%). The majority of treatment-related select AEs were grade 1–2; the most frequently reported events in all treated patients were diarrhoea (10.4%), hypothyroidism (6.7%), rash (5.7%), pruritus (5.3%) and pneumonitis (4.7%). In general, similar event types and rates were reported in all subgroups, with the exception of low-grade diarrhoea, which was more common in patients aged ≥70 years and ≥75 years (Table 3). The most common treatment-related select AE leading to discontinuation was pneumonitis (1.5% in the all-treated population); the majority of treatment-related select AEs leading to discontinuation occurred in ≤1% of patients across all populations (Table 4). Median times to onset and resolution of treatment-related select AEs were generally similar between populations (Table 5). Reports of all-cause select AEs were consistent with treatment-related select AEs (Table 6).

Any-grade TRAEs were reported in 57.3% of all treated patients, 47.6% with ECOG PS 2, 62.9% aged ≥70 years and 68.8% aged ≥75 years (Table 7). Grade 3–4 TRAEs were reported in 13.9% of all treated patients, 6.8% with ECOG PS 2, 15.8% aged ≥70 years and 18.4% aged ≥75 years. The most frequent TRAEs in all treated patients were fatigue (12.2%), asthenia (10.6%) and diarrhoea (10.4%); this was generally similar across subgroups. TRAEs leading to discontinuation occurred in 8.3% of all treated patients, 7.8% of patients with ECOG PS 2, 9.4% in patients ≥70 years and 12.0% in patients ≥75 years; the majority of these were grade 3–4.

Table 6
Incidence, time to onset and resolution of all-cause select AEs.

	Incidence, n (%)		Median time to onset, weeks (range)		Resolved, n (%)[a]		Median time to resolution, weeks (range)	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Skin								
Total	174 (21.5)	8 (1.0)	8.4 (0.1–92.1)	10.1 (2.1–44.3)	95 (54.6)	5 (62.5)	17.0 (0.1–123.1+)	17.5 (0.1–73.3+)
ECOG PS 2	18 (17.5)	0	12.6 (2.1–81.7)	NA	10 (55.6)	NA	6.9 (1.1–70.0+)	NA
≥70 years	67 (24.1)	2 (0.7)	8.3 (0.1–64.7)	20.9 (16.4–25.3)	36 (53.7)	0	34.6 (0.3–107.1+)	NR (26.7+–31.3+)
≥75 years	35 (28.0)	1 (0.8)	10.0 (0.3–64.7)	16.4 (16.4–16.4)	15 (42.9)	0	63.0 (0.6–106.6+)	NR (31.3+–31.3+)
Endocrine								
Total	104 (12.8)	9 (1.1)	11.6 (1.9–112.0)	13.7 (2.0–40.6)	34 (32.7)	4 (44.4)	NR (1.0–108.3+)	NR (1.4–84.0+)
ECOG PS 2	7 (6.8)	0	13.9 (6.1–55.4)	NA	2 (28.6)	NA	NR (6.1–88.0+)	NA
≥70 years	33 (11.9)	3 (1.1)	10.0 (1.9–70.1)	7.0 (2.0–11.6)	9 (27.3)	0	NR (1.0–108.1+)	NR (6.0+–84.0+)
≥75 years	12 (9.6)	1 (0.8)	10.1 (2.3–70.1)	7.0 (7.0–7.0)	0	0	NR (7.6+–108.1+)	NR (41.7+–41.7+)
GI								
Total	140 (17.3)	12 (1.5)	8.4 (0.1–88.1)	27.3 (5.9–69.9)	121 (86.4)	11 (91.7)	2.0 (0.1–109.9+)	2.5 (0.1–19.0+)
ECOG PS 2	17 (16.5)	0	6.0 (0.3–64.3)	NA	14 (82.4)	NA	2.0 (0.1–78.1+)	NA
≥70 years	61 (21.9)	6 (2.2)	8.4 (0.1–88.1)	24.4 (5.9–37.4)	51 (83.6)	5 (83.3)	2.0 (0.1–78.1+)	2.9 (0.1–19.0+)
≥75 years	33 (26.5)	3 (2.4)	4.3 (0.1–81.3)	26.4 (5.9–31.0)	26 (78.8)	2 (66.7)	2.1 (0.1–78.1+)	5.0 (2.0–19.0+)
Hepatic								
Total	81 (10.0)	25 (3.1)	10.9 (1.4–85.9)	20.4 (2.0–85.9)	52 (65.0)	18 (72.0)	5.0 (0.1+–92.7+)	4.0 (0.7–35.0+)
ECOG PS 2	10 (9.7)	3 (2.9)	7.2 (2.0–82.1)	49.3 (6.3–82.3)	7 (70.0)	3 (100.0)	3.1 (0.6+–32.1+)	2.6 (2.4–4.0)
≥70 years	26 (9.4)	6 (2.2)	11.1 (2.0–85.9)	29.6 (2.0–85.9)	18 (72)	5 (83.3)	6.3 (1.0–84.4+)	2.3 (1.0–25.1+)
≥75 years	7 (5.6)	2 (1.6)	22.1 (2.1–45.3)	15.1 (2.1–28.1)	6 (85.7)	2 (100.0)	4.1 (1.1–84.4+)	1.1 (1.1–1.1)
Pulmonary								
Total	49 (6.0)	12 (1.5)	13.9 (0.1–94.0)	5.6 (0.1–94.0)	40 (81.6)	11 (84.6)	3.6 (0.1+–105.0+)	2.1 (0.1+–25.6)
ECOG PS 2[b]	4 (3.9)	1 (1.0)	3.9 (0.1–26.3)	0.4 (0.1–0.6)	2 (50.0)	1 (50.0)	2.3 (0.1+–50.7+)	1.0 (0.1+–1.0)
≥70 years	18 (6.5)	7 (2.5)	11.1 (0.1–94.0)	4.1 (0.1–94.0)	16 (88.9)	6 (85.7)	2.1 (0.1+–15.3+)	2.0 (0.1+–6.7)
≥75 years	12 (9.6)	3 (2.4)	10.3 (0.1–94.0)	2.4 (0.1–94.0)	11 (91.7)	3 (75.0)	3.0 (0.1+–13.1)	1.0 (0.1+–6.7)
Renal								
Total	64 (7.9)	8 (1.0)	14.0 (0.7–107.1)	29.6 (1.4–103.7)	35 (54.7)	4 (50.0)	8.1 (0.1–108.9+)	4.3 (0.4–107.1+)
ECOG PS 2	7 (6.8)	1 (1.0)	10.3 (1.4–52.9)	1.4 (1.4–1.4)	2 (28.6)	0	59.1 (0.6–59.1)	NR (0.7+–0.7+)
≥70 years	27 (9.7)	4 (1.4)	12.9 (1.1–107.1)	25.4 (1.4–103.7)	12 (44.4)	2 (50.0)	25.1 (0.1+–64.1+)	2.0 (0.7+–14.9+)
≥75 years	13 (10.4)	2 (1.6)	13.1 (1.1–52.9)	65.9 (28.1–103.7)	7 (53.8)	1 (50.0)	3.4 (0.1+–64.1+)	NR (1.1–14.9+)
Hypersensitivity/IR								
Total	19 (2.3)	1 (0.1)	2.1 (0.3–73.4)	28.6 (28.6–28.6)	17 (89.5)	1 (100.0)	0.1 (0.1–82.3+)	0.7 (0.7–0.7)
ECOG PS 2	4 (3.9)	1 (1.0)	2.1 (2.1–28.6)	28.6 (28.6–28.6)	4 (100.0)	1 (100.0)	0.1 (0.1–0.7)	0.7 (0.7–0.7)
≥70 years	5 (1.8)	0	2.1 (1.7–4.1)	NA	4 (80.0)	NA	0.1 (0.1–82.3+)	NA
≥75 years	2 (1.6)	0	3.1 (2.1–4.1)	NA	1 (50.0)	NA	NR (0.1–82.3+)	NA

Symbol + indicates a censored value.
Total patients in each group: Total, N = 811; ECOG PS 2, n = 103; ≥70 years, n = 278; ≥75 years, n = 125.
AE, adverse event; ECOG PS, Eastern Cooperative Oncology Group performance status; GI, gastrointestinal; IR, infusion reaction; NA, not applicable; NR, not resolved.
[a] Percentage calculated using total number of any grade or grade 3–4 as the denominator.
[b] One patient with ECOG PS 2 had grade 5 acute respiratory failure.

One treatment-related death due to inflammation of the tumour, potentially as a result of immune response to the study drug, causing occlusion of the airway was locally reported; the patient was aged <70 years with ECOG PS 1.

3.3. Efficacy

Median OS was 10.0 months (95% CI 9.2–11.2) for all treated patients; 5.2 months (95% CI 3.0–7.6) for patients with ECOG PS 2; 10.0 months (95% CI 8.3–11.4) for patients aged ≥70 years and 11.2 months (95% CI 7.9–14.2) for patients ≥75 years (Fig. 2). OS rates at 12 months were 42.7% in all treated patients, 26.7% in patients with ECOG PS 2, 41.4% and 46.8% in patients aged ≥70 and ≥ 75 years, respectively. OS rates at 18 months were 29.1%, 14.5%, 31.0% and 33.4%, respectively.

At week 8/9, tumour response assessments were available for 472/811 of all treated patients; 39/103, 151/278 and 66/125 patients were evaluable in the ECOG PS 2, ≥70 years, and ≥75 years patient subgroups, respectively. Response rate based on first tumour assessment at week 8/9 was 11.0% among all treated patients; this was similar in patients aged ≥70 years (12.6%) and ≥75 years (13.6%) but lower in patients with ECOG PS 2 (2.6%; Table 8).

Third-line or greater subsequent cancer therapy was received by 136/811 (16.8%) all treated patients, 9/103 (8.7%) patients with ECOG PS 2, 37/278 (13.3%) and 15/125 (12.0%) patients aged ≥70 years and ≥75 years, respectively.

Table 7
TRAE summary.

AE,[a] n (%)	All treated (N = 811)		ECOG PS 2 (n = 103)		≥70 years (n = 278)		≥75 years (n = 125)	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Any TRAE	465 (57.3)	113 (13.9)	49 (47.6)	7 (6.8)	175 (62.9)	44 (15.8)	86 (69)	23 (18)
Serious TRAEs	63 (7.8)	40 (4.9)	6 (5.8)	3 (2.9)	18 (6.5)	12 (4.3)	8 (6)	6 (5)
TRAEs leading to discontinuation	67 (8.3)	37 (4.6)	8 (7.8)	5 (4.9)	26 (9.4)	14 (5.0)	15 (12)	10 (8)
Most frequent TRAEs (≥5%)								
Fatigue	99 (12.2)	13 (1.6)	9 (8.7)	3 (2.9)	36 (12.9)	4 (1.4)	15 (12.0)	2 (1.6)
Asthenia	86 (10.6)	13 (1.6)	9 (8.7)	1 (1.0)	35 (12.6)	7 (2.5)	19 (15.2)	6 (4.8)
Diarrhoea	84 (10.4)	8 (1.0)	12 (11.7)	0	40 (14.4)	3 (1.1)	23 (18.4)	1 (0.8)
Decreased appetite	56 (6.9)	4 (0.5)	6 (5.8)	0	27 (9.7)	4 (1.4)	13 (10.4)	3 (2.4)
Hypothyroidism	54 (6.7)	1 (0.1)	3 (2.9)	0	17 (6.1)	0	9 (7.2)	0
Rash	46 (5.7)	1 (0.1)	6 (5.8)	0	17 (6.1)	0	7 (5.6)	0
Nausea	44 (5.4)	0	5 (4.9)	0	15 (5.4)	0	4 (3.2)	0
Increased aspartate aminotransferase	30 (3.7)	4 (0.5)	4 (3.9)	0	10 (3.6)	1 (0.4)	1 (0.8)	0
Dyspnoea	42 (5.2)	5 (0.6)	1 (1.0)	0	19 (6.8)	2 (0.7)	11 (8.8)	1 (0.8)
Pruritus	43 (5.3)	1 (0.1)	8 (7.8)	0	15 (5.4)	0	11 (8.8)	0
Dry skin	29 (3.6)	1 (0.1)	4 (3.9)	0	9 (3.2)	0	2 (1.6)	0
Maculopapular rash	25 (3.1)	0	1 (1.0)	0	13 (4.7)	0	6 (4.8)	0
Treatment-related deaths	1 (0.1)[b]		0		0		0	

AE, adverse event; ECOG PS, Eastern Cooperative Oncology Group performance status; TRAE, treatment-related AE.
[a] Includes events reported between the first dose and 30 days after last dose of study therapy.
[b] Due to tumour swelling as a result of immune response to the study drug, causing occlusion of the airway.

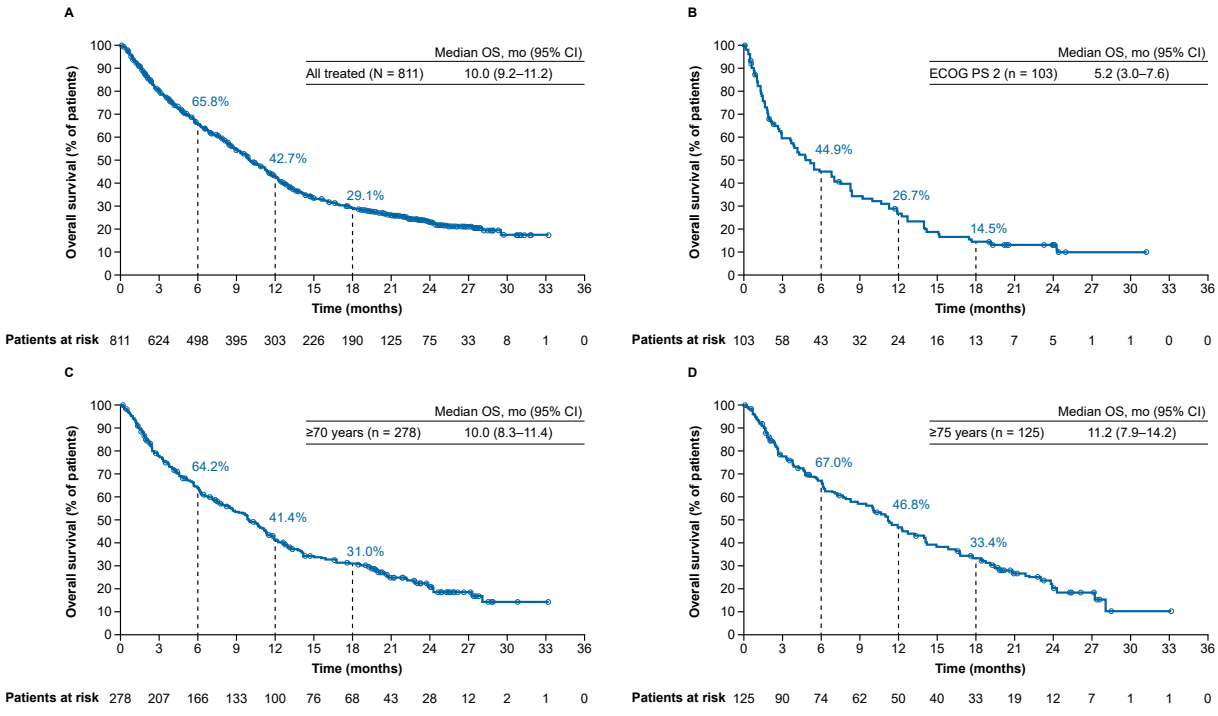

Fig. 2. Overall survival in all-treated patients (A), patients with ECOG PS 2 (B), patients ≥70 years (C) and patients ≥75 years (D). CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; mo, months; OS, overall survival.

4. Discussion

To our knowledge, this is the largest trial of nivolumab in previously treated patients with advanced squamous NSCLC, with the longest follow-up in a broad patient population including those with poor prognostic factors. Nivolumab was well tolerated as second- and later-line treatment in this setting. Furthermore, this study provides robust new insights into the clinical profile of nivolumab in populations that are often excluded from clinical trials: patients with poor performance status and the elderly, who represent the majority of patients in routine clinical practice and for whom there is an unmet need for tolerable treatments. The toxicity profile in these patients was similar to the all-treated population; no new safety signals were reported.

Table 8
Tumour response.

	All evaluable	ECOG PS 2	≥70 years	≥75 years
Tumour response at week 8/9				
Patients evaluable	472	39	151	66
Response rate				
n/N	52/472	1/39	19/151	9/66
%, (95% CI)	11.0 (8.3–14.2)	2.6 (0.1–13.5)	12.6 (7.7–19.0)	13.6 (6.4–24.3)
Response at week 8/9, (%)				
CR	1 (0.1)	0	1 (0.4)	0
PR	51 (7.6)	1 (1.6)	18 (8.0)	9 (8.7)
SD	278 (41.4)	27 (42.2)	90 (40.0)	43 (41.7)
PD	136 (20.3)	10 (15.6)	40 (17.8)	13 (12.6)
NE	6 (0.9)	1 (1.6)	2 (0.9)	1 (1.0)

CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

The results from this trial are comparable with previous studies of nivolumab [16,19,24]. Moreover, the patient population in the present study was heavily pretreated; almost 60% of patients had received ≥2 lines of prior treatment, confirming nivolumab activity in very advanced disease, as observed in previous studies [19,22]. Subsequent systemic cancer therapy was received in 17% of the all-treated population in the present study, which is lower than that reported in CheckMate 017 (36%) and CheckMate 063 (24%) [16,19]. This could reflect the high proportion of patients in the present study who received multiple lines of prior therapy and therefore had fewer alternative therapies available. In addition, since this study included elderly patients and those with poor performance status, there may have been concerns over further treatment due to potential reduced tolerance to treatment, increased risk of comorbidities and drug interactions [25–27].

Nivolumab was well tolerated in patients with ECOG PS 2, consistent with the all-treated population of the present study and CheckMate 153, a large North American safety study, which included patients with squamous NSCLC and poor performance status [24]. As expected, patients with ECOG PS 2 in the present study had shorter survival compared with the all-treated population. Of note, treatment exposure in patients with ECOG PS 2 was lower compared with the all-treated population (Table 2). Historically, patients with ECOG PS > 1 treated with chemotherapy had poor outcomes, with median OS of 1.8–3.6 months [28–30], one-year survival rates of <20% [31], tumour response rates of 16–22% [32], and a high incidence of grade 3–5 TRAEs (44%) [33]. The results presented herein and the findings from previous studies of nivolumab and other anti–PD-1 agents [7,24,34,35] suggest that patients with ECOG PS 2 may derive benefit from immunotherapy, with median survival of 4.0–6.8 months [7,24], one-year survival rates of 27% (current study), objective response rates of 11–30% [34–36], and lower incidences of grade 3–4 TRAEs (7% in the current study and 8–12% in previous studies) [24,35]. However, there are concerns over immunotherapy due to the lack of clinical data supporting a favourable benefit–risk profile in this heterogenous population with multiple factors that may contribute to poor performance [37]; randomised studies are warranted to assess clinical benefit in these patients.

Safety and efficacy of nivolumab in elderly patients were generally consistent with that of the all-treated population and were similar between the ≥70-year and ≥75-year subgroups. Studies of other immunotherapies in elderly patients with NSCLC have shown similar results [38,39], although efficacy appeared to be reduced in elderly versus younger patients in one study [38]. Rates of TRAEs were numerically higher in elderly patients compared with the all-treated population; however, most events were low grade, and no new safety signals were identified. Median OS of 10.0 months in patients ≥70 years of age and 11.2 months in patients ≥75 years of age was like that in the all-treated population of this trial and CheckMate 153 [24]. In comparison, the HR did not favour nivolumab over docetaxel in patients ≥75 years of age in CheckMate 017, although these results should be interpreted with caution due to the small number of elderly patients included [16]. In addition, median OS was lower (5.8 months) in patients ≥75 years of age compared with the overall population in the Italian expanded access program, potentially due to the high proportion of elderly patients with comorbidities in this study [21]. Response rates in elderly patients were similar to the overall population of this trial and to earlier reports of nivolumab in previously treated patients with squamous NSCLC [19].

Study limitations included the frequency of tumour assessments and the method of reporting tumour response to nivolumab treatment. Tumour assessments were collected at week 8/9 and week 52, and the response rate reported was based solely on the week 8/9 time point. However, several patients had tumour scans outside the predefined week 8/9 window and therefore were not included in tumour response assessments. In contrast, previous studies of nivolumab in patients with

NSCLC reported best overall response based on multiple tumour assessments conducted throughout the study period, rather than at one specific timepoint [16,19]. Furthermore, the time to response in these studies was ~2–3 months [16,19], so at least half of the patients in the current study may not have responded at the time of assessment. These marked differences, and the exclusion of tumour scan data due to protocol deviations, should be taken into account when interpreting tumour response data from this study. The single-arm study design makes it difficult to fully assess the survival benefit with nivolumab observed in this study, with prognostic factors potentially impacting OS. Finally, tumour PD-L1 status was not assessed, so particular subgroups of patients with ECOG PS 2 or the elderly that may have derived greater benefit were not determined.

5. Conclusions

These results suggest that nivolumab is well tolerated and active in patients with advanced, relapsed squamous NSCLC, including the elderly, similar to findings from the phase 3 CheckMate 017 study. In patients with ECOG PS 2, nivolumab was well tolerated, consistent with findings in the overall population; however, outcomes were worse, as expected in this difficult-to-treat population with poor prognosis.

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Conflict of interest statement

E.F. reports receiving personal fees from AbbVie, AstraZeneca, Blueprint medicines, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Guardant Health, Janssen, Medscape, Merck KGaA, Merck Sharp & Dohme, Novartis, Pfizer, priME Oncology, Roche, Samsung, Springer, Takeda, and Touchtime, outside the submitted work. A.A. reports receiving personal fees from Boehringer Ingelheim, Eli Lilly, MSD, and Pfizer, grants from Celgene, and grants and personal fees from Bristol-Myers Squibb and Roche, outside the submitted work. T.C. reports receiving personal fees from Amgen, Astellas, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Ipsen, Janssen, MSD, Novartis/GSK, Pfizer, Roche, Sanofi, and Servier, outside the submitted work. M.C., K.L., M.S., E.C., M.A.G., D.I., and J.M. have nothing to disclose. R.C. reports receiving grants from Bristol-Myers Squibb during the conduct of the study, and personal fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Lilly Oncology, MSD, Novartis, Pfizer, Roche, and Takeda, outside the submitted work. R.G. reports receiving personal fees from Bristol-Myers Squibb, outside the submitted work. L. P-A. reports receiving personal fees from Amgen, Bayer, Blueprint, Eli Lilly, Incyte, Merck, MSD, Novartis, Roche, and Takeda, and grants and personal fees from AstraZeneca and Bristol-Myers Squibb, outside the submitted work. R.D. reports receiving travel grants from Amgen and Roche, receiving travel grants and holding advisory position for Pfizer, and acting in an advisory role for Ely Lilly and Novartis, outside the submitted work. J.J. reports receiving personal fees from AstraZeneca, Bristol-Myers Squibb, MSD, Pfizer, Roche, and Takeda, and receiving travel support from Roche, outside the submitted work. W.A. reports receiving non-financial support from Boehringer Ingelheim and Bristol-Myers Squibb, personal fees from AstraZeneca and Pfizer, personal fees and non-financial support from Amgen and Roche, outside the submitted work. J.P.V.M. reports receiving travel support from Bristol-Myers Squibb and institutional grants from Pfizer, outside the submitted work. J.W. reports receiving personal fees from AbbVie, AstraZeneca, Blueprint, Boehringer Ingelheim, Chugai, Eli Lilly, Ignyta, Loxo, Roche, and Takeda, and grants and personal fees from Bristol-Myers Squibb, Janssen, MSD, Novartis, and Pfizer, outside the submitted work. A.L. and A.A. were employees of Bristol-Myers Squibb during the conduct of the study and A.A. has received company stock from Bristol-Myers Squibb. S.P. reports receiving personal fees from Bristol-Myers Squibb during the conduct of the study; personal fees from AbbVie, AstraZeneca, Boehringer Ingelheim, Elsevier, EMD Serono, Guardant Health, Medscape, MSD, Novartis, OncLive, Pfizer, Roche, Takeda, and Tesaro, outside the submitted work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.11.019.

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