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Lung Cancer

Italian Cohort of Nivolumab Expanded Access Program in Squamous Non-Small Cell Lung Cancer: Results from a Real-World Population

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Squamous non-small cell lung cancer • Immunotherapy • Nivolumab • Expanded access program • Real-world • Treatment beyond disease progression

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Abstract

Background. Nivolumab has shown a survival benefit compared with docetaxel as second-line treatment for patients with previously treated advanced squamous non-small cell lung cancer (NSCLC) in a randomized phase III trial. The experiences of patients and physicians in routine clinical practice are often different from those in a controlled clinical trial setting. We present data from the entire Italian cohort of patients with squamous NSCLC enrolled in a worldwide nivolumab NSCLC expanded access program.

Patients and Methods. Patients with pretreated advanced squamous NSCLC received nivolumab 3 mg/kg every 2 weeks for up to 24 months. Safety was monitored throughout; efficacy data collected included objective tumor response, date of progression, and survival information.

Results. The Italian cohort comprised 371 patients who received at least one dose of nivolumab. In the overall population, the objective response rate (ORR) was 18%, the disease control rate (DCR) was 47%, and median overall survival (OS) was 7.9 months (95% confidence interval 6.2–9.6). In subgroup analyses, ORR, DCR, and median OS were, respectively, 17%, 48%, and 9.1 months in patients previously treated with two or more lines of therapy (n = 209) and 8%, 40%, and 10.0 months in patients treated beyond disease progression (n = 65). In the overall population, the rate of any-grade and grade 3–4 adverse events was 29% and 6%, respectively. Treatment-related adverse events led to treatment discontinuation in 14 patients (5%). There were no treatment-related deaths.

Conclusion. To date, this report represents the most extensive clinical experience with nivolumab in advanced squamous NSCLC in current practice outside the controlled clinical trial setting. These data suggest that the efficacy and safety profiles of nivolumab in a broad, real-world setting are consistent with those obtained in clinical trials. ***The Oncologist*** 2019;24:e1165–e1171

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Implications for Practice: Nivolumab is approved in the U.S. and Europe for the treatment of advanced non-small cell lung cancer (NSCLC) after failure of prior platinum-based chemotherapy. In this cohort of Italian patients with previously treated, advanced squamous NSCLC treated in a real-world setting as part of the nivolumab expanded access program, the efficacy and safety of nivolumab was consistent with that previously reported in nivolumab clinical trials.

Introduction

Squamous non-small cell lung cancer (NSCLC) comprises almost 30% of all NSCLC cases [1]. Relatively few treatment options are available for advanced stages of this disease once progression occurs after first-line systemic therapy. Docetaxel has been the standard of care for many years, despite providing limited clinical benefit [2]. Discrete genetic alterations are rarely observed in squamous NSCLC, and molecularly targeted agents are not indicated in squamous NSCLC [3].

Nivolumab is a fully human programmed death 1 (PD-1) immune checkpoint inhibitor antibody that was shown to provide a long-term survival benefit in patients with previously treated advanced squamous NSCLC in the randomized phase III trial CheckMate 017, which compared nivolumab with docetaxel in patients after failure of first-line platinum-based chemotherapy [4]. Median overall survival (OS) was 9.2 months in the nivolumab group compared with 6.0 months in the docetaxel group, and a 41% reduction in the risk of death was observed with nivolumab treatment (hazard ratio [HR] 0.59, 95% confidence interval [CI] 0.44–0.79; $p < .001$). This OS benefit was sustained with longer follow-up: 2-year OS rates were 23% with nivolumab and 8% with docetaxel [5]. Nivolumab has also been shown to provide similar benefit in patients with previously treated advanced nonsquamous NSCLC in the randomized phase III trial CheckMate 057 [6]. On the basis of these results, nivolumab was approved in the U.S. and the European Union for locally advanced/metastatic NSCLC with disease progression after prior platinum-based chemotherapy.

A nivolumab expanded access program (EAP) in advanced squamous NSCLC was conducted worldwide to allow patients who were unable to take part in local nivolumab clinical trials to gain access to treatment before it became commercially available. The experience of patients and physicians in routine clinical practice is often different from that in a controlled clinical trial setting. EAPs, with their comparatively broad entry criteria, more closely mimic the real-world setting and provide opportunities to evaluate common treatment scenarios. Here, we present comprehensive data from the entire Italian cohort of patients with squamous NSCLC enrolled in the nivolumab NSCLC EAP.

Materials and Methods

Patients

Eligible patients were aged 18 years or older with histologically or cytologically confirmed stage IIIB or IV squamous NSCLC. All patients had disease progression or recurrence during or after one or more prior systemic treatments for advanced or metastatic disease; patients who developed recurrent disease within 6 months of completing platinum-based adjuvant, neoadjuvant, or definitive chemoradiation therapy for locally advanced disease were also eligible. Patients with treated central nervous system (CNS) metastases that had been stable for ≥2 weeks were eligible, provided that they did not require corticosteroids or were on a stable or decreasing dose of no more than 10 mg prednisone daily (or equivalent). Other key inclusion criteria were an Eastern Cooperative Oncology Group (ECOG) performance status ≤2; completion of prior chemotherapy, tyrosine kinase inhibitors, tumor vaccine, cytokines, or palliative radiotherapy ≥2 weeks before starting nivolumab, with resolution of all adverse events to baseline or stabilization; adequate organ function; and life expectancy ≥6 weeks. Patients were excluded if they had active, known, or suspected autoimmune disease, with the exception of type 1 diabetes mellitus, residual hypothyroidism due to an autoimmune condition requiring hormone replacement therapy, or psoriasis not requiring systemic treatment. Other exclusion criteria included carcinomatous meningitis, prior therapy with any drug specifically targeting T-cell costimulation or checkpoint pathways, symptomatic interstitial lung disease, and eligibility for another clinical study with nivolumab. All patients provided written, informed consent to their participation in the study.

Study Design and Treatment

Nivolumab was made available upon physician request through the EAP. The EAP guidelines were approved at each participating center, and participating physicians had to comply with generally accepted good clinical practice and ethical standards.

All patients received nivolumab 3 mg/kg administered intravenously every 2 weeks for up to 24 months or until disease progression, unacceptable toxicity, or withdrawal of consent. No reduction in nivolumab dose was allowed, but treatment was delayed in the event of toxicity. Patients could continue nivolumab treatment beyond progression if they were deriving investigator-assessed clinical benefit in the absence of rapid disease progression, provided that they were also tolerating the study drug, they had stable performance status, and that such treatment would not delay any intervention to prevent serious complications of disease progression.

Assessments

Safety was monitored throughout the program by continuous assessment of adverse events, physical examination, ECOG performance status, hematology and clinical chemistry tests, and thyroid function tests, according to local regulations and standard of care. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0, and their causal relationship to treatment was determined by the investigators.

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Although there were no prespecified endpoints for this EAP, investigators were encouraged to make every effort to document objective disease progression always according to RECIST criteria. In situations of doubtful responses, the cases were discussed with the principal investigator of the trial who revised retrospectively all the instrumental records according to RECIST criteria. Efficacy data collected included investigator-assessed objective tumor response, date of progression, and survival information. In addition to the overall population, efficacy and safety data were collected for the following subgroups: patients who had received two or more prior lines of therapy and patients treated with nivolumab beyond initial disease progression.

Statistical Analysis

The population for both efficacy and safety analyses included all patients who received at least one dose of nivolumab. Objective response rate (ORR), disease control rate (DCR, defined as the combined rates of complete response, partial response, and stable disease), progression-free survival (PFS), and OS were evaluated. Progression-free survival and OS were estimated using the Kaplan-Meier method, and 95% CIs were derived using the asymptotic variance Greenwood method. Progression-free survival was calculated as the time from the start of nivolumab treatment until evidence of progressive disease or death, whichever occurred first. A Cox regression model was used to explore the association between patient characteristics and OS; HRs and their 95% CIs were reported.

Results

Patients and Treatment

Between April 2015 and September 2015, 371 patients were enrolled in the EAP at 96 centers in Italy and received at least one dose of nivolumab. Most patients were male (80%), and the majority were former smokers (61%; Table 1). Twenty-two patients (6%) had an ECOG performance status of 2, 70 (19%) were 75 years of age or older, and 37 (10%) had CNS metastases. More than half of the population was heavily pretreated: 209 patients (56%) had received at least two lines of prior systemic therapy.

Patients received a median of six doses of nivolumab (range, 1–22) and had a median follow-up of 7.1 months (range, 0.1–16.4). Patients in the subgroup that had received two or more prior lines of therapy were treated with a median of eight doses of nivolumab (range, 1–24) and had a median follow-up of 7.1 months (range, 0.1–24.5.4). Sixty-five patients (18%) were treated beyond disease progression and received a median of ten doses of nivolumab (range, 4–29), with a median follow-up of 9.1 months (range, 2.1–16.4). At the time of analysis, 281 patients (76%) had discontinued treatment in the overall population, mostly because of progressive disease (*n* = 167; 59%) or death (*n* = 68; 24%; Table 2); 90 patients (24%) remained on treatment.

Efficacy

In the overall population, the ORR was 18%, including four complete responses (1%) and 63 partial responses (17%); an additional 108 patients had stable disease, giving a DCR of 47% (Table 3). The 1-year OS rate was 39% and median OS was 7.9 months (95% CI 6.2–9.6; Fig. 1A), whereas the 1-year PFS rate was 27% and median PFS was 4.2 months (95% CI 3.4–5.0; Fig. 1B). Multivariate analysis showed that OS was adversely affected by the presence of liver and bone metastases and by ECOG performance status above zero (Table 4). However, the presence of stable, asymptomatic CNS metastases had no measurable impact on OS.

In patients who had received two or more prior lines of therapy, the ORR was 17%, which included all four complete responses seen in the overall population, and the DCR was 48% (Table 3). The 1-year OS rate in this subgroup was 42%, and median OS was 9.1 months (95% CI 6.1–12.1; Fig. 1A); 1-year and median PFS were, respectively, 28% and 4.2 months (95% CI 2.8–5.6; Fig. 1B). In particular, patients who received nivolumab in the second line had a median OS of 7.2 months (95% CI 5.6–8.7) with a 1-year OS rate of 34.8% and a 18-month OS rate of 21.8%.

Twenty-six of the 65 patients treated beyond progression derived unconventional benefit from the extended treatment, with subsequent tumor reduction or lesion stabilization. Twenty-three (88.5%) of these patients were male, 25 (96.1%) had an ECOG performance status of 0–1;

Table 1. Baseline patient characteristics

Characteristic	All patients (*n* = 371)	≥2 prior therapies (*n* = 209)	Treated beyond PD (*n* = 65)
Median age (range), years	68 (31–91)	67 (31–84)	70 (44–81)
≥75 years, *n* (%)	70 (19)	30 (14)	16 (25)
Sex, *n* (%)			
Male	298 (80)	165 (79)	54 (83)
Female	73 (20)	44 (21)	11 (17)
Smoking status, *n* (%)			
Smoker	83 (22)	46 (22)	11 (17)
Former smoker	225 (61)	126 (60)	42 (65)
Never smoker	31 (8)	21 (10)	7 (11)
Unknown	32 (9)	16 (8)	5 (8)
ECOG PS, *n* (%)			
0	134 (36)	74 (35)	25 (38)
1	215 (58)	121 (58)	36 (55)
2	22 (6)	14 (7)	4 (6)
Site of metastasis, *n* (%)			
CNS	37 (10)	26 (12)	4 (6)
Liver	63 (17)	36 (17)	13 (20)
Bone	120 (32)	66 (32)	24 (37)
Number of prior systemic therapies, *n* (%)			
1	162 (44)	0	26 (40)
2	120 (32)	120 (57)	18 (28)
3	68 (18)	68 (33)	17 (26)
≥4	21 (6)	21 (10)	4 (6)

Percentages within some categories may not total 100% exactly because of rounding.
Abbreviations: CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; PD, progressive disease.

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Table 2. Summary of treatment discontinuations

Discontinuation	All patients (*n* = 371), *n* (%)	≥2 prior therapies (*n* = 209), *n* (%)	Treated beyond PD (*n* = 65), *n* (%)
Discontinued treatment	281 (76)	152 (73)	49 (75)
Reason for discontinuation			
PD	167 (59)	94 (62)	39 (80)
Death	68 (24)	40 (26)	6 (12)
Other	20 (7)	7 (5)	2 (4)
Adverse events or serious adverse events	26 (9)	11 (7)	2 (4)

Percentages may not total 100% exactly because of rounding.
Abbreviation: PD, progressive disease.

Table 3. Response to treatment

Response type	All patients (*n* = 371), *n* (%)	≥2 prior therapies (*n* = 209), *n* (%)	Treated beyond PD (*n* = 65), *n* (%)
Objective response rate	67 (18)	36 (17)	5 (8)
Disease control rate[a]	175 (47)	100 (48)	26 (40)
Best response			
Complete response	4 (1)	4 (2)	0
Partial response	63 (17)	32 (15)	5 (8)
Stable disease	108 (29)	64 (31)	21 (32)
Progressive disease	189 (51)	104 (50)	33 (51)
Could not be determined	7 (2)	5 (2)	6 (9)

[a]Defined as the combined rate of complete response, partial response, and stable disease.
Abbreviation: PD, progressive disease.

20 (76.9%) were current or previous smokers. Two of them (7.7%) had brain metastasis, nine (34.6%) had bone metastasis, and four (15.4%) had liver metastasis. Overall, this subgroup had an ORR of 8% (all partial responses) and DCR of 40% (Table 3). Median OS was 10.0 months (95% CI 7.6–12.4), and 1-year OS was 42% (Fig. 1A).

Safety

Of the 371 patients in the overall population, 109 (29%) had adverse events considered to be treatment related, which were grade 3–4 in 21 patients (6%; Table 5). The most common treatment-related adverse events of any grade were rash (8%), fatigue/asthenia (6%), diarrhea (5%), and pain (5%). Grade 3–4 treatment-related adverse events occurring in more than one patient comprised diarrhea and increased transaminases (*n* = 4 each; 1%); pain and rash (*n* = 3 each; 1%); and fatigue/asthenia (*n* = 2; 1%). Three patients had treatment-related pneumonitis, including one case of grade 3–4 pneumonitis, which resolved. Overall, 281 patients (76%) discontinued nivolumab treatment (Table 2). In 26 patients (9%), discontinuation was due to adverse events: these were treatment-related in 14 patients (5%) and included pneumonitis (*n* = 3); diarrhea, hepatotoxicity, and skin toxicity (*n* = 2 each); and bilateral exophthalmos, dyspnea, headache, paralytic ileus, and psoriasis (*n* = 1 each).

In the subgroup that had received two or more prior lines of therapy, treatment-related grade 3–4 adverse events were reported in 12 patients (6%) and included most commonly transaminase increase (*n* = 3; 1%), diarrhea (*n* = 2; 1%), fatigue/asthenia (*n* = 2; 1%), and pulmonary toxicity (*n* = 4; 1%). In total, 152 patients from of this subgroup (73%) discontinued treatment, 11 (7%) because of adverse events. Five patients (3%) experienced treatment-related adverse events leading to discontinuation, comprising headache, pneumonitis, hepatic toxicity, bilateral exophthalmos, and dyspnea.

Two patients (3%) treated beyond progression had treatment-related grade 3–4 adverse events (both diarrhea). Forty-nine patients (75%) in this subgroup discontinued treatment; two patients (4%) did so because of adverse events, but in neither case were these considered treatment-related.

Treatment-related adverse events of immune etiology (select adverse events) were managed using protocol-defined toxicity management algorithms. There were no treatment-related deaths.

Discussion

This report details the most extensive clinical experience with nivolumab in advanced squamous NSCLC in current practice outside a controlled clinical trial setting to date. Our population (*n* = 371) included 56% of patients treated with two or more previous systemic regimens, 6% of patients with ECOG performance status 2, 19% of patients aged 75 years or older, and 10% of patients with CNS metastases. Despite the poor prognosis of this population, we observed a median OS of 7.9 months, an ORR of 18%, and a DCR of 47% with the caveat that a few cases were discussed retrospectively for response and PFS with the principal investigator in presence of doubtful data. As expected, we found that poorer prognostic factors, such as the presence of liver and bone metastases and ECOG performance status above zero, adversely affected OS in multivariate analysis, confirming the validity of the data in this study. Our finding that CNS metastases had no measurable impact on OS may have been influenced by the small number of affected patients (*n* = 37) and by the exclusion of patients with symptomatic CNS metastases per the program's eligibility criteria. Nivolumab was well tolerated in this Italian cohort, with only 5% of patients discontinuing therapy because of treatment-related adverse events. Most adverse events were mild to moderate, and the proportion of patients who had grade 3–4 treatment-related adverse events was low (6%).

The efficacy of nivolumab in this real-world setting largely mirrored that observed in the nivolumab arm of the phase III CheckMate 017 trial in patients with advanced squamous NSCLC (median OS, 9.2 months; ORR, 20%; DCR, 49%) [4]. The safety profile of nivolumab in the Italian cohort was also consistent with that in CheckMate 017 (7% of patients with grade 3–4 events and 3% with treatment-related events leading to discontinuation). In addition, the results achieved with nivolumab were similar to those seen in randomized trials with other anti-PD-1 or anti-programmed death ligand 1 therapies [7, 8].

In this EAP, efficacy and safety results obtained both in patients who received nivolumab after two or more prior lines

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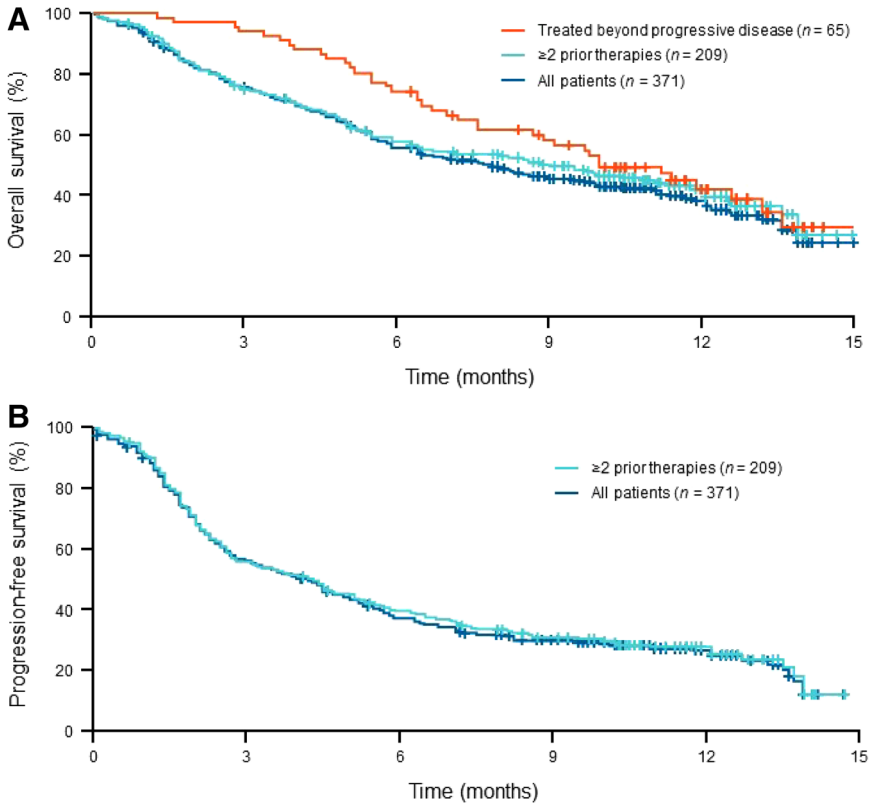

Figure 1. Overall survival and progression-free survival in study population. Kaplan-Meier estimates of overall survival **(A)** and progression-free survival **(B)**.

Table 4. Association between patient characteristics and overall survival

	Univariate analysis		Multivariate analysis	
Characteristic	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Age, years: ≥75 vs. <75	1.23 (0.89–1.70)	.21		
Sex: Male vs. female	1.10 (0.79–1.53)	.58		
Smoking status				
Former vs. current	0.91 (0.66–1.26)	.57		
Never vs. current	0.74 (0.42–1.30)	.30		
Unknown vs. current	0.73 (0.42–1.26)	.26		
ECOG PS				
1 vs. 0	1.65 (1.23–2.22)	.001	1.57 (1.17–2.11)	.003
2 vs. 0	2.75 (1.64–4.60)	<.0001	2.76 (1.65–4.62)	<.0001
Metastatic site, yes vs. no				
CNS	1.12 (0.72–1.72)	.62		
Liver	1.61 (1.17–2.21)	.003	1.44 (1.04–1.98)	.03
Bone	2.02 (1.55–2.64)	<.0001	1.93 (1.47–2.53)	<.0001
Number of prior therapies: >1 vs. 1	0.86 (0.66–1.11)	.25		

Abbreviations: CI, confidence interval; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio.

of therapy and in those treated beyond progression (noting the small number of patients in this subgroup) appeared similar to the results of the overall population of the study. Measurement of disease progression by RECIST version 1.1 may not fully capture patient benefit from immunotherapies, and some immunotherapy studies including this EAP have therefore explored continuation of therapy beyond progression if patients demonstrate ongoing clinical benefit [9]. In this Italian cohort, some patients treated beyond progression achieved sustained reductions or stabilization of tumor burden with

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Table 5. Treatment-related adverse events occurring in ≥1% of patients

	All patients (n = 371), n (%)		≥2 prior therapies (n = 209), n (%)		Treated beyond PD (n = 65), n (%)	
Adverse event	**Any grade**	**Grade 3–4**	**Any grade**	**Grade 3–4**	**Any grade**	**Grade 3–4**
Any adverse event	109 (29)	21 (6)	59 (28)	12 (6)	25 (38)	2 (3)
Skin and mucosal	42 (11)	5 (1)	20 (10)	2 (1)	11 (17)	0
Rash	31 (8)	3 (1)	18 (9)	1 (<1)	10 (15)	0
General	34 (9)	2 (1)	19 (9)	2 (1)	10 (15)	0
Fatigue/asthenia	24 (6)	2 (1)	13 (6)	2 (1)	6 (9)	0
Pyrexia	10 (3)	0	5 (2)	0	1 (2)	0
Lack of appetite/anorexia	9 (2)	0	5 (2)	0	3 (5)	0
Gastrointestinal	27 (7)	4 (1)	11 (5)	2 (1)	6 (9)	2 (3)
Diarrhea	18 (5)	4 (1)	6 (3)	2 (1)	3 (5)	2 (3)
Pain	19 (5)	3 (1)	7 (3)	0	1 (2)	0
Endocrine	16 (4)	1 (<1)	5 (2)	0	2 (3)	0
Hypothyroidism	10 (3)	0	3 (1)	0	1 (2)	0
Hyperthyroidism	5 (1)	1 (<1)	2 (1)	0	1 (2)	0
Respiratory/pulmonary	12 (3)	4 (1)	4 (2)	3 (1)	2 (3)	0
Pneumonitis	3 (1)	1 (<1)	1 (<1)	1 (<1)	1 (2)	0
Hematologic	10 (3)	1 (<1)	5 (2)	0	1 (2)	0
Anemia	9 (2)	1 (<1)	4 (2)	0	1 (2)	0
Hepatic/pancreatic	8 (2)	4 (1)	5 (2)	3 (1)	1 (2)	0
Transaminase increase	6 (2)	4 (1)	5 (2)	3 (1)	1 (2)	0
Lipase/amylase increase	2 (1)	0	0	0	0	0

Abbreviation: PD, progressive disease.

manageable toxicity. Clinical benefit from continuing nivolumab at disease progression has been reported previously in patients with NSCLC [4], as well as other tumor types [9, 10].

Evaluation of PD-L1 expression was not planned in this trial given that there is no evidence that it is an effective predictive biomarker in squamous cell carcinoma in second-line setting and beyond, as demonstrated in the CheckMate 017 trial [5].

Conclusion

Acknowledging the inherent limitations of a study of this type, data from this cohort of Italian patients with previously treated advanced squamous NSCLC suggest that the efficacy and safety profiles of nivolumab in a broad, real-world setting are consistent with those obtained in clinical trials [4]. Nivolumab provided clinical activity coupled with a manageable safety profile in patients treated with at least two lines of prior therapy and in those treated beyond progression, and further investigation may be warranted in these populations. Taken together, these results suggest that nivolumab can provide a much needed addition to the currently limited treatment options for patients with advanced squamous NSCLC.

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Disclosures

Paolo Bidoli: Eli Lilly & Co., Boehringer (C/A); **Francesco Grossi:** Bristol-Myers Squibb, Merck Sharp & Dohme, AstraZeneca, Pierre Fabre (SAB); **Andrea Ardizzoni:** Bristol-Myers Squibb, Celgene (RF), Bristol-Myers Squibb, Merck Sharp & Dohme, Boehringer, Pfizer (H); Bristol-Myers Squibb, Celgene, Merck Sharp & Dohme, Boehringer (SAB); **Federico Cappuzzo:** Bristol-Myers Squibb, Roche, Pfizer, AstraZeneca (C/A). The other authors indicated no financial relationships.

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