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Italian Cohort of the Nivolumab EAP in Squamous NSCLC: Efficacy and Safety in Patients With CNS Metastases

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Abstract. *Background/Aim: Brain metastases are an additional challenge in patients with non-small-cell lung cancer (NSCLC) because most chemotherapy agents cannot cross the blood–brain barrier. Nivolumab has demonstrated efficacy in patients with advanced squamous NSCLC, but because patients with central nervous system (CNS) metastases are typically excluded from registration trials, 'field-practice' data are needed. Patients and Methods: Patients in the Italian cohort of the Expanded Access Program (EAP) who had CNS metastases at baseline were analyzed. Results: Thirty-seven patients with CNS metastases received a median of six doses of nivolumab. Three patients (8%) had grade 3-4 adverse events and one patient discontinued due to an adverse event. The objective response rate was 19%. Median overall survival was 5.8 (95% confidence interval=1.9-9.8) months and median progression-free survival was 4.9 (95% confidence interval=2.7-7.1) months. Conclusion: The safety and efficacy of nivolumab in patients with CNS metastases appear to be similar to those seen in the overall EAP cohort in Italy.*

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Key Words: Brain metastases, immunotherapy, PD1 inhibitor, real-world evidence.

Squamous non-small-cell lung cancer (NSCLC) is a distinct clinical and pathological subtype of NSCLC, characterized by a high mutation rate and substantial genomic complexity, which may contribute to its poor prognosis (1). Recently, the treatment paradigm for NSCLC has changed with the introduction of immune checkpoint inhibitors (nivolumab, pembrolizumab, and atezolizumab and durvalumab) that block the programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) pathway and restore the antitumor immune response (2-7).

Nivolumab, a fully human PD1 antibody, has been approved in the USA and the European Union for the treatment of patients with locally advanced or metastatic NSCLC whose disease progresses during or after platinum-based chemotherapy (8, 9). Median overall survival (OS) was significantly longer with nivolumab compared to docetaxel in patients who were previously treated for advanced squamous NSCLC in CheckMate 017 [9.2 *vs.* 6.0 months; hazard ratio for death=0.59; 95% confidence interval (CI)=0.44-0.79; $p<0.001$] (3), with 2-year OS rates

of 23% with nivolumab and 8% with docetaxel (10, 11). Comparable results were obtained in CheckMate 057 (4).

The expanded access program (EAP) for nivolumab in advanced NSCLC allowed patients from several countries who were unable to participate in local nivolumab clinical trials to obtain treatment with nivolumab before it became commercially available. Patients with central nervous system (CNS) metastases are commonly excluded from trials. CNS metastases are an adverse prognostic factor, in part because most cytotoxic chemotherapy agents do not readily cross the blood–brain barrier (12). An analysis of preliminary data from the entire Italian cohort of patients with squamous NSCLC enrolled in the nivolumab NSCLC EAP was recently reported (13). Here, we present preliminary data for a subset of these patients who had CNS metastases.

Patients and Methods

Patients. Eligibility criteria for the EAP were: age ≥ 18 years; histologically or cytologically confirmed stage IIIB or IV squamous NSCLC; disease progression or disease recurrence during or after ≥1 prior systemic treatments for advanced or metastatic disease; recurrent disease within 6 months after completion of platinum-based chemoradiation for locally advanced disease; Eastern Cooperative Oncology Group (ECOG) performance status ≤2; prior chemotherapy, tyrosine kinase inhibitor treatment, immunotherapy or palliative radiotherapy completed ≥2 weeks before initiation of nivolumab; resolution or stabilization of all adverse events (AEs) prior to baseline; adequate organ function; life expectancy ≥6 weeks; treated metastatic CNS lesions without neurological symptoms related to those lesions for ≥2 weeks before enrolment and no need of corticosteroids or on a stable or a decreasing dose ≤10 mg of prednisone daily (or equivalent).

Exclusion criteria were: autoimmune disease (except type 1 diabetes mellitus, residual hypothyroidism due to an autoimmune condition requiring hormone replacement therapy or psoriasis not requiring systemic treatment); HIV infection; carcinomatous meningitis; symptomatic interstitial lung disease; prior therapy with any drug specifically targeting T-cell co-stimulation or checkpoint pathways, or eligibility for another clinical study with nivolumab. All patients provided written, informed consent.

Study design and treatment. Physicians requested nivolumab through the EAP and complied with good clinical practice and ethical standards. The EAP guidelines were approved by the Institutional Review Board at each participating center. Patients received i.v. nivolumab 3 mg/kg/2 weeks for up to 24 months or until disease progression, unacceptable toxicity, or consent withdrawal. Dose reduction was not allowed, but delayed treatment was permitted in the event of toxicity.

Assessments. There were no pre-specified study endpoints. Safety evaluation: AEs record, physical examination, ECOG performance status, haematology and clinical chemistry tests, and thyroid function tests according to local regulations and standards of care. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (14), and their causal relationship to treatment was determined by the investigators. Efficacy: investigator-assessed objective tumor response, date of disease progression (time from the first drug administration to disease progression or death from any cause), and survival.

Table I. *Patient demographic and baseline characteristics*.

Characteristic	CNS metastases (n=37)	All patients (n=371)
Gender, n (%)		
Male	24 (65)	298 (80)
Female	13 (35)	73 (20)
Age, years		
Median	64	68
Range	31-77	31-91
≥75, n (%)	1 (3)	70 (19)
Smoking status, n (%)		
Smoker	11 (30)	83 (22)
Former smoker	18 (49)	225 (61)
Never smoker	5 (13)	31 (8)
Unknown	3 (8)	32 (9)
ECOG PS, n (%)		
0	14 (38)	134 (36)
1	22 (59)	215 (58)
2	1 (3)	22 (6)
Site of metastasis, n (%)		
CNS	37 (100)	37 (10)
Liver	7 (19)	63 (17)
Bone	16 (43)	120 (32)
Other	29 (78)	331 (89)
Number of prior systemic therapies, n (%)		
1	11 (30)	162 (44)
2	18 (48)	120 (32)
3	7 (19)	68 (18)
≥4	1 (3)	21 (6)

CNS: Central nervous system; ECOG: Eastern Cooperative Oncology Group performance status.

Statistical analysis. Patients included in the safety and efficacy analyses received at least one dose of nivolumab. Objective response rate (ORR), disease control rate [DCR; the combined rates of complete response (CR), partial response, and stable disease], progression-free survival (PFS), and OS were evaluated. Median PFS and OS were estimated using the Kaplan–Meier method, with 95%CIs derived using the asymptotic variance Greenwood method. PFS was calculated as the time between the first nivolumab cycle and evidence of progressive disease (PD) or death.

Results

Patients and treatment. A total of 371 patients (Table I) were enrolled in the EAP between April and September 2015 at 96 centers in Italy and received at least 1 (median=6, range=1-22) dose of nivolumab. Median follow-up was 7.1 months (range=0.1-16.4 months).

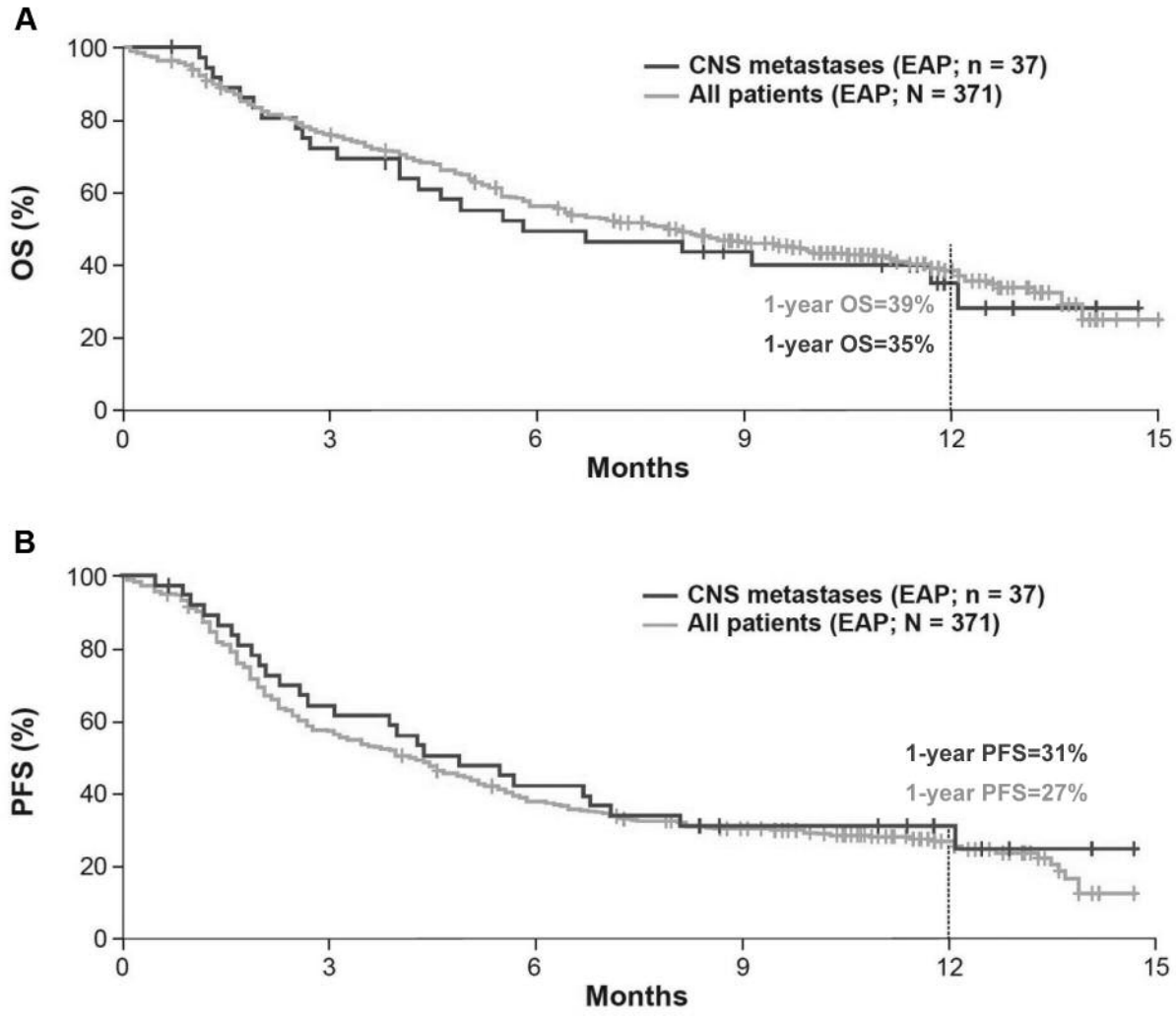

Figure 1. *Kaplan–Meier estimates of overall survival (OS; A) and progression-free survival (PFS; B). CNS: Central nervous system; EAP: expanded access program.*

CNS metastases were diagnosed in 37/371 (10%) (Table I). In this subgroup, 22% had received corticosteroids and 57% had received prior radiotherapy. Median number of nivolumab doses was 6 (range=1-18), median follow-up 5.5 months (range=0.7-15 months). Six (16%) and two (5%) patients received concomitant corticosteroids and radiotherapy, respectively, during the EAP for the control of symptoms related to CNS metastases.

At the time of the analysis, nivolumab had been discontinued in 281 patients (76%) in the overall population, primarily because of PD [n=167 (59%)] or death [n=68 (24%)]. Among patients with CNS metastases, 33 (89%) had discontinued nivolumab, mainly for PD [n=18 (55%)] or death [n=9 (27%)]. Four patients (11%) with CNS metastases continued treatment.

Safety. Safety data are reported in Table II. Treatment-related AEs (grade 2 skin reaction and mucositis) led to discontinuation in one/33 (3%) patients with CNS metastases who discontinued treatment. CNS events (seizure, loss of balance, postural instability, disorientation, and stupor) were reported in five patients (14%) with CNS metastases; none of these events were grade 3-4 in severity or considered to be treatment-related.

No treatment-related deaths were reported in the overall study population. Treatment-related AEs with a potential immunologicaI aetiology were addressed using protocol-defined toxicity management algorithms. Treatment-related AEs led to discontinuation in 14/281 (5%) patients in the overall population who discontinued treatment.

Efficacy. Efficacy results are reported in Table III.

Table II. *Frequency [n (%)] of treatment-related adverse events occurring in ≥1% of all patients.*

Category/adverse event	CNS metastases (n=37)		All patients (N=371)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any adverse event	12 (32)	3 (8)	109 (29)	21 (6)
General	7 (19)	1 (3)	34 (9)	2 (1)
Fatigue/asthenia	6 (16)	1 (3)	24 (6)	2 (1)
Pyrexia	0	0	10 (3)	0
Lack of appetite/anorexia	2 (5)	0	9 (2)	0
Skin and mucosal	5 (14)	2 (5)	42 (11)	5 (1)
Rash	3 (8)	1 (3)	31 (8)	3 (1)
Gastrointestinal	1 (3)	0	27 (7)	4 (1)
Diarrhoea	0	0	18 (5)	4 (1)
Pain	0	0	19 (5)	3 (1)
Endocrine	0	0	16 (4)	1 (<1)
Hypothyroidism	0	0	10 (3)	0
Hyperthyroidism	0	0	5 (1)	1 (<1)
Respiratory/pulmonary	0	0	12 (3)	4 (1)
Pneumonitis	0	0	3 (1)	1 (<1)
Haematological	0	0	10 (3)	1 (<1)
Anaemia	0	0	9 (2)	1 (<1)
Hepatic/pancreatic	0	0	8 (2)	4 (1)
Transaminase increase	0	0	6 (2)	4 (1)
Lipase/amylase increase	0	0	2 (1)	0

CNS: Central nervous system.

Table III. *Response to treatment.*

Tumour response	CNS metastases (n=37)		All patients (n=371)	
	First assessment, n (%)	Best response, n (%)	First assessment, n (%)	Best response, n (%)
Objective response rate	7 (19)	7 (19)	51 (14)	67 (18)
Disease control rate[a]	18 (49)	18 (49)	151 (41)	175 (47)
Best response				
Complete response	0	1 (3)	1 (<1)	4 (1)
Partial response	7 (19)	6 (16)	50 (13)	63 (17)
Stable disease	11 (30)	11 (30)	100 (27)	108 (29)
Progressive disease	19 (51)	19 (51)	212 (57)	189 (51)
Could not be determined	0	0	8 (2)	7 (2)

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

The OS rate at 1 year was 35% for patients with CNS metastases and 39% for the overall population (Figure 1A). Median OS was 5.8 (95%CI=1.8-9.8) months for patients with CNS metastases and 7.9 (95%CI=6.2-9.6) months for the overall population.

The PFS rate at 1 year was 31% for patients with CNS metastases and 27% for the overall population (Figure 1B). The median PFS was 4.9 (95%CI=2.7-7.1) months for patients with CNS metastases and 4.2 (95%CI=3.4-5.0) months for the overall population.

Discussion

Nivolumab was well tolerated in patients with squamous NSCLC and CNS metastases from the Italian EAP cohort, and the safety profile appeared to be similar to that of the overall EAP population. The frequency of grade 3-4 treatment-related AEs was comparable in patients with CNS metastases (8%) and in the overall EAP population (6%). The percentage of patients who discontinued nivolumab treatment because of a treatment-related AE was 3% in the

subgroup with CNS metastases and 5% in the overall EAP population.

Efficacy with nivolumab in the subset of EAP patients with CNS metastases appeared to be similar to that observed in the overall EAP population: the 1-year OS rates were 35% and 39%, respectively, and the 1-year PFS rates were 31% and 27%, respectively.

Some limitations of this study should be considered: possible patient selection bias and inconsistencies in assessment timing, absence of formal and specific radiological assessment, the small patient number and exclusion of patients with symptomatic CNS metastases, PD-L1 expression was not detected.

Our data were consistent with results reported for the nivolumab arm of CheckMate 017 (3), where the 12-month OS rate was 42% and 1-year PFS rate was 21%. Grade 3-4 treatment-related AEs occurred in 7% of patients in the nivolumab arm, and 3% of patients discontinued the drug because of a treatment-related AE.

Response in CNS lesions have been reported in clinical trials and in case reviews, in patients treated with nivolumab alone or in combination with other therapies (2, 15). Based on encouraging results, the Radiation Therapy Oncology Group has begun a randomized phase III study, RTOG 3505, to evaluate post-chemoradiation nivolumab compared to placebo in patients with unresectable stage 3 NSCLC (16).

Cases of pseudo-progression (an apparent tumor size increase, possibly due to lymphocyte infiltration) with nivolumab in lung cancer have been reported (17), and physicians must make decisions about continuing or discontinuing nivolumab for disease progression based on their assessment of the risks and potential benefits.

Conflicts of Interest

LC received fees for speakers' bureau participation from AstraZeneca, Bristol-Myers Squibb, and Novartis. DG received fees for speakers' bureau participation from Boehringer Ingelheim and Lilly, and travel, accommodation, and expenses from Bristol-Myers Squibb. AA received honoraria from Boehringer Ingelheim, Bristol-Myers Squibb, and Lilly, and served in a consulting/advisory role for Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Lilly, and MSD Oncology. DC received honoraria from Roche, MSD, Boehringer Ingrlheim and served in a consulting/advisory for MSD, BMS, Boehirnger Ingelheim, AZ. FG received honoraria from Bristol-Myers Squibb, MSD, AstraZeneca, Roche and served in a consulting/advisory role for Boehringer Ingelheim, Bristol-Myers Squibb, MSD, Roche, Pierre Fabre, Astra Zeneca. MRM received Honoraria /advisory role from Boehringer Ingelheim, Bristol-Myers Squibb, AstraZeneca, Pfizer.

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Nivolumab Expanded Access Program in Squamous NSCLC: Investigators in Italy

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