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Original Research

Real-life results from the overall population and key subgroups within the Italian cohort of nivolumab expanded access program in non-squamous non–small cell lung cancer

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Abstract ***Background:*** Nivolumab was the first immune checkpoint inhibitor approved for previously treated advanced non–small cell lung cancer (NSCLC). Before its introduction in the market, nivolumab was made available to NSCLC patients through an expanded access program (EAP). Here we present the Italian cohort of patients with non-squamous NSCLC enrolled in a worldwide nivolumab EAP, with subgroup analyses involving elderly patients, patients with central nervous system (CNS) metastases and patients receiving nivolumab beyond progression.
Methods: Pretreated patients with advanced non-squamous NSCLC received nivolumab at 3 mg/kg every 2 weeks up to 24 months. Efficacy data (investigator-assessed tumour response, progression date and survival) and safety data were collected.
Findings: 1588 patients were treated across 153 Italian centres. Overall response rate and disease control rate were 18% and 44%, respectively; median overall survival (OS) was 11.3 months (95% CI: 10.2–12.4). Elderly patients (≥70 n = 522; ≥75 n = 232) achieved outcomes similar to the global study population; patients with CNS metastases (n = 409) had an OS of 8.6 months (95% CI: 6.4–10.8), and a 1-year OS rate of 43%. Nivolumab was administered beyond progression to 276 patients (26%), 57 of whom achieved subsequent disease control; the median OS of patients receiving nivolumab beyond progression was 16.2 months (95% CI: 14.0–18.4), while 1-year OS rate was 62%.
Interpretation: To date, this is the largest clinical experience with nivolumab in a real-world setting. Our data support its use in clinical practice for pretreated non-squamous NSCLC, including patients with older age or CNS metastases.

1. Introduction

Advanced non–small cell lung cancer (NSCLC) is the main cause of cancer-related death, and its most frequent form is represented by non-squamous histology, which accounts for approximately 70–80% of NSCLC [1]. Targeted therapies directed towards specific gene aberrations have dramatically improved the outcomes of selected patients affected by advanced non-squamous NSCLC harbouring actionable molecular targets; however, these individuals represent a minority among non-squamous NSCLC patients [2]. Recently, the management of advanced NSCLC has been revolutionised by the availability of immune checkpoint inhibitors targeting programmed death 1 (PD-1) and its ligand (PD-L1) [3]. Nivolumab, a fully human antibody directed against PD-1, was the first of such agents approved for the management of previously treated advanced NSCLC after achieving a significant improvement in overall survival (OS) over docetaxel in two randomised trials, one designed to enrol patients affected by squamous NSCLC (CheckMate 017) [4], and one designed to enrol patients with non-squamous NSCLC (CheckMate 057) [5]. This benefit was subsequently confirmed after 3 years of follow-up [6]. Although these results proved pivotal for the current clinical practice in NSCLC, some questions remained unanswered, with particular reference to the benefit of nivolumab over chemotherapy in poorly represented subgroups, including patients with advanced age or with central nervous system (CNS) metastases. In addition, another open question is represented by the efficacy of continuing nivolumab beyond progression in presence of clinical benefit.

In the time span between the approval of nivolumab and its introduction in the market, this drug was made available to patients affected by previously treated advanced NSCLC within a worldwide expanded access program (EAP). Compared to controlled clinical trials, EAPs generally have broader inclusion criteria and are close to the daily clinical practice; hence, these experiences might provide useful data involving the actual performance of newly introduced compounds in real-life settings. Both patients with squamous and non-squamous histology were included in the nivolumab NSCLC EAP. Here, we present comprehensive data from the entire Italian cohort of patients with non-squamous NSCLC enrolled in this program.

2. Methods

2.1. Eligible patients

To enter the nivolumab EAP, the following criteria were required: age ≥18 years, cytologically or histologically confirmed stage IIIB or IV NSCLC, Eastern Cooperative Oncology Group performance status (ECOG-PS) ≤ 2, adequate organ function, and life expectancy of at least 6 weeks. Progression after at least one line of systemic treatment for advanced or metastatic disease was required; patients developing recurrent disease during or within 6 months of completion of platinum-based adjuvant or neoadjuvant chemotherapy or definitive chemoradiation for locally advanced disease were also considered eligible. Patients with treated CNS metastases were considered eligible provided that such metastases had been stable for at least two weeks before enrolment and no more than 10 mg/day of prednisone (or equivalent steroid dose) was required. Any patient with 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, was considered ineligible. In addition, other exclusion criteria included prior therapy with any drug specifically targeting T cell co-stimulation or immune checkpoints, or the presence of carcinomatous meningitis, symptomatic interstitial lung disease. Notably, PD-L1 assessment was not mandatory for inclusion in the study. All the enrolled patients provided written informed consent to their participation in the EAP.

2.2. Study design and treatment

The Ethical Committee of each participating centre approved the EAP guidelines, and nivolumab was made available upon physician request for each individual patient after verification of the eligibility criteria. Nivolumab was administered intravenously at 3 mg/kg every 2 weeks for up to 24 months or until disease progression, unacceptable toxicity, or withdrawal of consent. No dose reduction was planned, while dose delay was allowed in case of toxicity. The patients could continue to receive nivolumab beyond progression with the following requirements: presence of investigator-assessed clinical benefit, absence of rapid disease progression, stable or improved performance status, and good tolerance of nivolumab.

2.3. Assessments

The enrolled patients were monitored for safety throughout the whole treatment with nivolumab by periodic assessments of ECOG-PS, physical examination, blood collection for hematology and clinical chemistry tests, as well as thyroid function tests; the timing for assessments was based on local regulations and standard of care; more specifically, CT-scan evaluations were normally performed every 6–8 weeks of treatment. Any reported adverse event (AE) was defined according to the common terminology criteria for adverse events (CTCAE) v. 4.0, and the investigators in each participating centre were asked to determine the causal association between each AE and nivolumab.

No formally specified efficacy end-point was defined for the nivolumab EAP. However, investigators in each participating centre were encouraged to assess objective tumour response and disease progression to collect progression-free survival (PFS) data; in addition, OS data were collected. With specific regards to tumour response assessment, no subsequent radiologic confirmation of progressive disease (PD) was formally required.

2.4. Statistical analysis

Both efficacy and safety analyses included all the enrolled patients who received at least one dose of nivolumab. The efficacy analyses included PFS and OS; in addition, the following activity parameters were assessed: objective response rate (ORR), disease control rate (DCR; defined as the combined rates of complete response, partial response and stable disease). Both ORR and DCR analyses were calculated on the entire population, without any exclusion, and those cases in which the patient did not undergo evaluation of response (e.g. due to early discontinuation) were considered as failures in terms of response analysis. No central review of the response evaluation was performed.

PFS and OS were estimated using the Kaplan–Meier method and 95% CIs were derived using the asymptotic variance Greenwood method; PFS was calculated from the start of nivolumab treatment until evidence of progressive disease or death, whichever occurred first, whereas OS was calculated from the start of nivolumab until death. A logistic regression model using OS > 3 months as end-point was implemented; odds ratios (ORs) and their 95% confidence interval were calculated for each factor. All factors were considered for multivariate analysis according to a stepwise forward selection method based on Wald statistics. Enter and remove P values were set to 0.05 and 0.10, respectively.

3. Results

3.1. Overall study population

1588 patients with non-squamous NSCLC received at least one dose of nivolumab across 153 centres from June 2015 to April 2016. Most patients were male (65%), current or former smokers (71%) and had ECOG-PS = 1 (51%); notably, only 7% of the overall study

population had ECOG-PS = 2. With regards to prior systemic treatments, most patients (75%) had received two or more lines. The patients' characteristics are reported in detail in Table 1. With regards to subgroups based on age and the presence of CNS metastases, the following differences with the overall population were observed: elderly subgroups (≥70 and ≥ 75 years) had a higher proportion of male patients ($p < 0.0001$ for both), a lower proportion of current smokers compared to former smokers ($p = 0.002$ for ≥ 70 and $p < 0.0001$ for ≥ 75), a lower proportion of CNS metastases ($p < 0.0001$ for both) and liver metastases ($p = 0.02$ for ≥ 70 and $p = 0.04$ for ≥ 75); patients aged ≥ 75 had more frequently received only one previous line of treatment as compared with younger patients ($p = 0.02$). The subgroup of patients with brain metastases had a higher proportion of liver metastases ($p < 0.00001$) and had more frequently received two or more lines of previous antineoplastic treatment ($p = 0.01$). No other baseline differences were observed among subgroups, including in particular ECOG-PS.

3.2. Activity and efficacy within the overall population

The enrolled patients received a median of 7 doses (range: 1–55) of nivolumab, with a median follow-up of 8.1 months (range: 1.0–27.4). Within the overall population, ORR was 18%, while DCR was 44%. With regards to survival, median OS was 11.3 months (95% CI: 10.2–12.4), and the OS rate at 1 year was 48%, while median PFS was 3.0 months (95% CI: 2.9–3.1), and the PFS rate at 1 year was 22%. The efficacy data for the overall population are fully reported in Table 2, while the Kaplan–Meier estimates for OS and PFS are reported in Fig. 1.

Notably, at the time of the analysis, 1053 patients (66%) had developed PD, and 276 (26%) received nivolumab beyond progression; the baseline characteristics of such patients were similar to the overall population and are reported in Table 1; the only features which were less common in patients treated beyond progression were ECOG-PS = 2 ($p < 0.001$) and the presence of liver metastases ($p = 0.01$). Patients treated beyond PD received a median of 11 doses (range: 4–50), with a median follow-up of 11.6 months (range: 1.5–27.2). Most patients receiving nivolumab beyond progression experienced further PD at the first subsequent evaluation (67%), although they were still allowed to receive nivolumab in case of maintained clinical benefit irrespective of CT-scans; by contrast, 57 patients (21%) achieved a subsequent tumour burden reduction or stabilisation after the progression, based on local comparison of CT scan. Median OS of patients receiving nivolumab beyond PD was 16.2 months (95% CI: 14.0–18.4), while the OS rate at 1 year was 62%. Notably, among the 198 patients who had developed PD as best response (and hence were considered as not responding to nivolumab), 36 (18%) subsequently achieved disease control on continuation of nivolumab. No difference in terms of postprogression DCR was observed between patients experiencing PD as best initial response and patients experiencing disease stabilisation or response before progression (chi squared $p = 0.106$). Detailed responses of the patients treated

Table 1
Baseline characteristics of the patients with non-squamous non–small cell lung cancer enrolled in the Italian nivolumab expanded access program.

		Overall N = 1588	Treated beyond PD N = 276	≥70 years, N = 522	≥75 years, N = 232	CNS metastases N = 409
Age	*Years (median; range)*	66 (27–89)	63 (27–86)	74 (70–89)	77 (75–89)	63 (29–84)
Gender	*Male*	1029 (65%)	166 (60%)	388 (74%)	181 (78%)	264 (65%)
	Female	559 (35%)	110 (40%)	134 (26%)	51 (22%)	145 (35%)
Smoking status	*Current smokers*	360 (23%)	58 (21%)	79 (15%)	30 (13%)	98 (24%)
	Former smokers	765 (48%)	148 (54%)	289 (55%)	127 (55%)	193 (47%)
	Never-smokers	305 (19%)	56 (20%)	102 (20%)	54 (23%)	72 (18%)
	Unknown	158 (10%)	14 (5%)	52 (10%)	21 (9%)	46 (11%)
ECOG-PS	*ECOG-PS 0*	648 (41%)	137 (50%)	203 (39%)	84 (36%)	152 (37%)
	ECOG-PS 1	815 (51%)	126 (46%)	277 (53%)	132 (57%)	225 (55%)
	ECOG-PS 2	108 (7%)	9 (3%)	39 (7%)	15 (6%)	30 (7%)
	Unknown[a]	17 (1%)	4 (1%)	3 (1%)	1 (<1%)	2 (1%)
Specific metastatic sites	*CNS*	409 (26%)	79 (29%)	91 (17%)	31 (13%)	409 (100%)
	Liver	327 (21%)	41 (15%)	90 (17%)	36 (15%)	191 (47%)
Number of prior systemic regimens	*1*	378 (24%)	61 (22%)	141 (27%)	72 (31%)	74 (18%)
	2	562 (35%)	96 (35%)	176 (34%)	81 (35%)	147 (36%)
	3	332 (21%)	57 (21%)	104 (20%)	40 (17%)	99 (24%)
	≥4	307 (19%)	62 (22%)	97 (19%)	36 (16%)	88 (22%)
	Unknown[a]	9 (1%)	0 (0%)	4 (1%)	3 (1%)	1 (<1%)

CNS = central nervous system; ECOG-PS = Eastern Cooperative Oncology Group performance status; PD = progressive disease.
[a] Some data involving ECOG-PS at baseline and number of prior systemic regimens were missing, although included among eligibility criteria, as the data collection for statistical analyses was performed retrospectively.

Table 2
Efficacy data of the overall population and subpopulations comprising non-squamous non–small cell lung cancer patients within the nivolumab Italian expanded access program.

	Overall population, N = 1588	≥70 years, N = 522	≥75 years, N = 232	CNS metastases, N = 409
ORR	290 (18%)	108 (21%)	58 (25%)	68 (17%)
DCR	704 (44%)	253 (48%)	122 (53%)	164 (40%)
BOR				
CR	10 (1%)	2 (<1%)	0 (0%)	4 (1%)
PR	280 (18%)	106 (20%)	58 (25%)	64 (16%)
SD	414 (26%)	145 (28%)	64 (28%)	96 (23%)
PD	688 (43%)	203 (39%)	90 (39%)	192 (47%)
Death before assessment	130 (8%)	41 (8%)	11 (5%)	35 (9%)
Not determined	66 (4%)	5 (5%)	9 (4%)	18 (4%)
Median OS	11.3 months (95% CI: 10.2–12.4)	11.5 months (95% CI: 10.0–13.0)	12.0 months (95% CI: 9.2–14.8)	8.6 months (95% CI: 6.4–10.8)
Median PFS	3.0 months (95% CI: 2.9–3.1)	4.0 months (95% CI: 3.6–4.4)	4.2 months (95% CI: 3.0–5.4)	3.0 months (95% CI: 2.7–3.3)

BOR = best overall response; CR = complete response; DCR = disease control rate; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease.

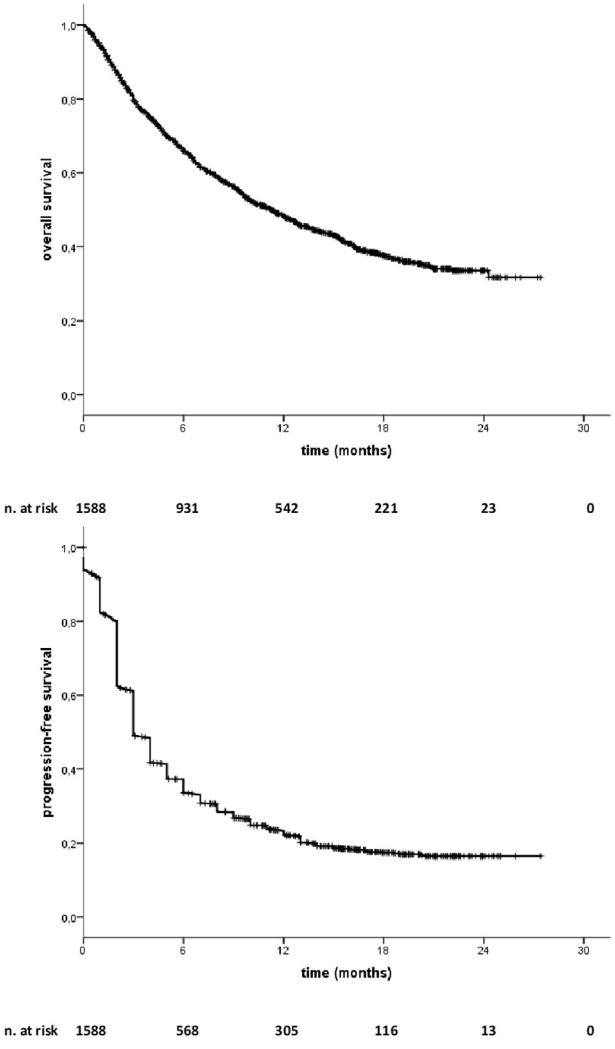

Fig. 1. Kaplan–Meier estimates for overall survival (OS) and progression-free survival (PFS) in the overall population of patients with non-squamous non–small cell lung cancer.

beyond PD are reported in Supplementary Table 1, while the Kaplan–Meier estimate for OS is reported in Fig. 2.

Notably, the follow-up data of those patients within the general population who completed 24 months of treatment are currently ongoing, and this analysis will be the subject of further research.

3.3. Efficacy in specific patients' subgroups

In addition to the efficacy data involving the overall population, we analysed the outcomes of specific

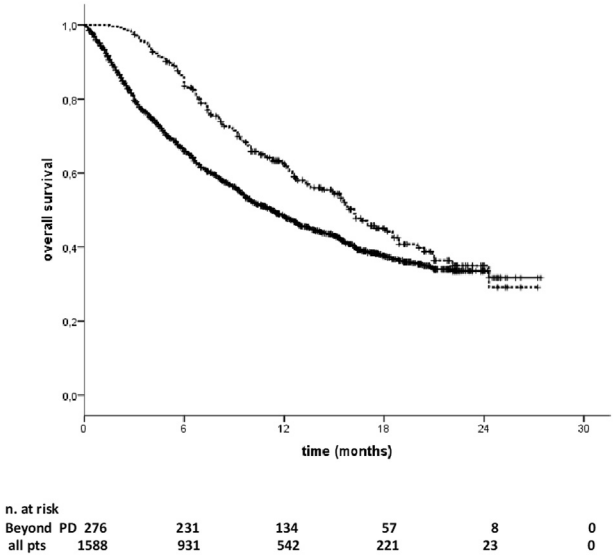

Fig. 2. Kaplan–Meier estimate for overall survival (OS) in the populations of patients treated beyond progression (dotted line). The estimate for OS in all the patients (continuous line) is reported for comparison.

subgroups; notably, the outcomes of never-smokers and of patients harbouring actionable oncogenic drivers (such as activating mutations of the epidermal growth factor receptor gene) of the Italian nivolumab EAP population have been reported separately [7]. With regards of age, we explored the outcomes of patients aged ≥70 and ≥ 75 years; their baseline characteristics are reported in Table 1. Among the 522 patients aged ≥70 years, 456 were evaluable for response, with a median follow-up of 7.6 months (range: 0.1–20.8) and a median of 9 doses of nivolumab (range: 1–44); in this subgroup, ORR and DCR were 21% and 48%, respectively, while median OS was 11.5 months (95% CI: 10.0–13.0), and OS rate at 1 year was 48%. Among the 232 patients aged ≥ 75 years, 212 were evaluable for response, with a median follow-up of 8.3 months (range: 0.1–20) and a median of 11 doses of nivolumab (range: 1–39); in this subgroup, ORR and DCR were 25% and 53%, respectively, while median OS was 12.0 months (95% CI: 9.2–14.8), and OS rate at 1 year was 50%. Response data are reported in Table 2, while the Kaplan–Meier estimates for OS are reported in Fig. 3.

Among the evaluable patients, 409 had controlled CNS metastases; their characteristics are reported in Table 1. Of these, 117 patients (29%) were receiving corticosteroids at baseline, while 74 patients (18%) had undergone brain radiation. These patients received a median of 7 doses of nivolumab (range: 1–54), and their median follow-up was 6.4 months (range: 0.1–27.2). The median OS of patients with CNS metastases was 8.6 months (95% CI: 6.4–10.8), and the OS rate at 1 year was 43%. Response data are reported in Table 2, while the Kaplan–Meier estimates for OS are reported in Fig. 4. More comprehensive data involving patients with CNS metastases within the Italian nivolumab EAP can be found in a separate publication focused on this subgroup [8].

3.4. Safety

Thirty-two percent of patients reported a treatment-related AE of any grade; however, grade 3–4 events were reported only in 6% of the patients. The discontinuation rate due to treatment-related AEs was 5%. With regards to those patients who received nivolumab beyond PD, AEs of any grade were reported in 18% of cases, while grade 3–4 AEs were observed in 6% of the patients; the discontinuation rate due to treatment-related AEs in this group of patients was 5%. No treatment-related deaths were reported. The most common AEs were fatigue (11%), pain (5%), dyspnoea (55), diarrhoea (4%), and nausea/vomiting (4%); the most common grade 3–4 toxicity was fatigue (2%), while other grade 3–4 AEs were reported with a frequency < 1%. The AEs in patients receiving nivolumab beyond PD and in subpopulations defined by age and CNS metastases seemed generally consistent with the general population, as reported in Table 3.

3.5. Early survival analysis

Because a post hoc analysis of CheckMate 057 reported an increased number of early deaths (within 3 months) among patients with unfavourable prognostic factors and no PD-L1 expression in the nivolumab arm [9], we performed a post hoc early survival analysis based on the aforementioned 3-month cutoff. Of 1559 patients with available survival data, 365 (23.4%) died within the first 3 months; notably, no treatment-related death occurred in patients with OS ≤ 3 months. The clinical characteristics of patients on the basis of OS cutoff ≤ 3 months are reported in Supplementary Table 2. The post hoc OS analysis showed that the following characteristics were more frequent among the patients with

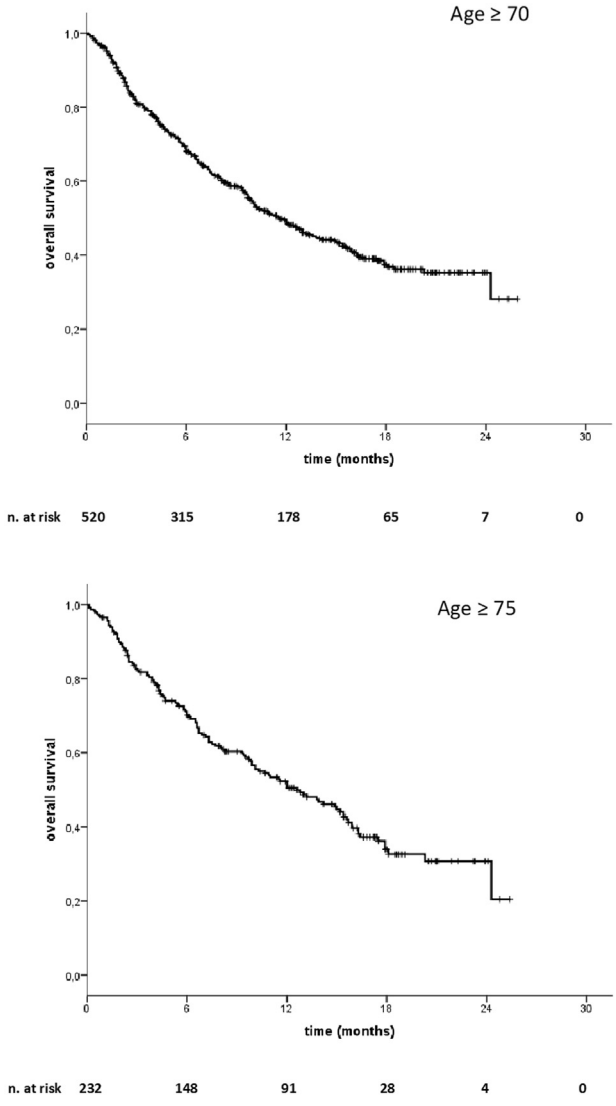

Fig. 3. Kaplan–Meier estimates for overall survival (OS) in patients aged ≥ 70 and ≥ 75 years.

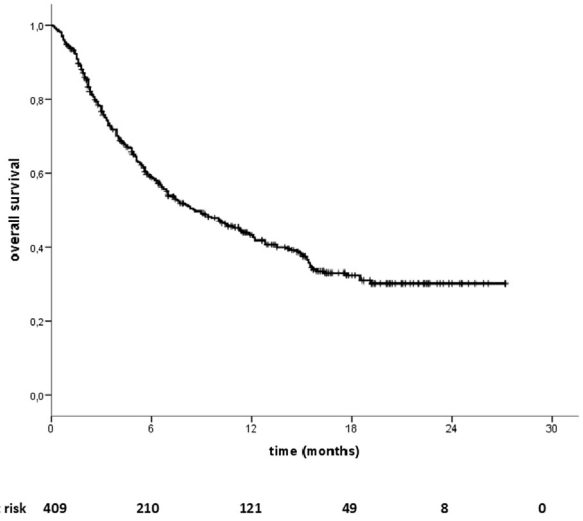

Fig. 4. Kaplan–Meier estimates for overall survival (OS) in patients with central nervous system (CNS) metastases.

OS ≤ 3 months: male gender, ECOG-PS = 2, no prior maintenance with chemotherapy, and presence of liver metastases (odds ratio and p values are reported in Table 4). However, most patients with these characteristics were still alive at 3 months and experienced substantial subsequent benefit. The median OS of the subgroup of patients surviving over 3 months was 16.2 months (14.6–17.8).

4. Discussion

In our study, the efficacy of nivolumab in the real-world setting of the EAP was largely similar to what had previously been observed within CheckMate 057; more specifically, ORR was 18% in the EAP and 19% in CheckMate 057, while median OS was 11.3 months in the EAP and 12.2 months in CheckMate 057 [5]. In addition, we reported specific baseline characteristics that were associated with increased risk of early death (OS ≤ 3 months). Such "unfavorable" features included ECOG-PS = 2, liver metastases, no prior maintenance; however, consistently with CheckMate 057, most patients with "unfavorable" clinical features were still alive at 3 months [9]; of note, patients with baseline ECOG-PS = 2 have generally been excluded from randomised phase III trials, including CheckMate 057 [10]. In our study, there was a short interval between the minimal life expectancy inclusion criteria (6 weeks) and the chosen cutoff of 3 months; the former was based on standard inclusion criteria for similar clinical studies, while the latter was based on the post hoc cutoff analysis performed in CheckMate 057.

To our knowledge, this is the largest reported clinical experience involving a PD-1 blocking agent in advanced non-squamous NSCLC to date, with data collected from 1588 patients. Furthermore, this EAP adds some relevant insight on specific subgroups of interest, generally underrepresented in pivotal trials involving PD-1/PD-L1-disrupting agents in NSCLC, with particular regard to patients with CNS involvement and elderly patients. CheckMate 057 included only few patients aged ≥75 years (N = 43), and the study did not demonstrate a clear advantage of nivolumab (n = 23) over docetaxel (n = 20) in terms of OS (HR = 0.90) in this subgroup, although the 95% CI was wide (0.43–1.87) [5]. The limited evidence available so far

Table 3
Treatment-related adverse events (AEs) in the overall population and in subgroups defined by treatment beyond progressive disease (PD), age, and central nervous system (CNS) metastases.

AE; n (%)	Overall, N = 1588		Treated beyond PD, N = 276		≥70 years, N = 522		≥75 years, N = 232		CNS metastases N = 409	
GRADE	Any	3–4	Any	3–4	Any	3–4	Any	3–4	Any	3–4
Any treatment-related AEs	*523 (33%)*	*102 (6%)*	*100 (36%)*	*15 (5%)*	*172 (33%)*	*34 (7%)*	*79 (34%)*	*16 (7%)*	*144 (35%)*	*27 (7%)*
Fatigue/asthenia	175 (11%)	26 (2%)	34 (12%)	5 (2%)	59 (11%)	11 (2%)	29 (12%)	6 (3%)	47 (11%)	6 (1%)
Dyspnoea	79 (5%)	19 (1%)	13 (5%)	1 (<1%)	30 (6%)	6 (1%)	19 (8%)	4 (2%)	22 (5%)	5 (1%)
Pain	83 (5%)	8 (<1%)	18 (7%)	1 (<1%)	20 (4%)	1 (<1%)	12 (5%)	2 (1%)	23 (6%)	0 (0%)
Diarrhoea	73 (4%)	6 (<1%)	17 (6%)	1 (<1%)	24 (5%)	1 (<1%)	8 (3%)	0 (0%)	20 (5%)	1 (<1%)
Pyrexia	58 (4%)	2 (<1%)	9 (3%)	0 (0%)	16 (3%)	0 (0%)	7 (3%)	0 (0%)	12 (3%)	0 (0%)
Nausea/vomiting	69 (4%)	2 (<1%)	25 (6%)	1 (<1%)	10 (2%)	0 (0%)	1 (<1%)	0 (0%)	25 (6%)	1 (<1%)
Lack of appetite/ anorexia	57 (4%)	2 (<1%)	12 (4%)	1 (<1%)	15 (3%)	0 (0%)	6 (3%)	0 (0%)	17 (4%)	1 (<1%)
Rash	52 (3%)	6 (<1%)	9 (3%)	3 (1%)	11 (2%)	0 (0%)	7 (3%)	0 (0%)	7 (2%)	2 (<1%)
Hypothyroidism	37 (2%)	2 (<1%)	10 (4%)	0 (0%)	10 (2%)	1 (<1%)	4 (2%)	0 (0%)	7 (2%)	1 (<1%)
Hyperthyroidism	37 (2%)	2 (<1%)	7 (2%)	0 (0%)	13 (2%)	0 (0%)	9 (4%)	0 (0%)	6 (1%)	0 (0%)
Pneumonitis	39 (2%)	9 (<1%)	7 (2%)	2 (1%)	8 (2%)	1 (<1%)	5 (2%)	1 (<1%)	10 (2%)	4 (1%)
Increased transaminase	21 (1%)	9 (<1%)	1 (<1%)	0 (0%)	9 (2%)	4 (1%)	4 (2%)	2 (1%)	5 (1%)	1 (<1%)
Increased lipase/amylase	17 (1%)	6 (<1%)	7 (2%)	3 (1%)	8 (2%)	4 (1%)	3 (1%)	1 (1%)	5 (1%)	2 (<1%)
Anaemia	22 (1%)	6 (<1%)	7 (2%)	3 (1%)	10 (2%)	2 (<1%)	5 (2%)	1 (<1%)	2 (<1%)	1 (<1%)

Table 4
Univariate and multivariate early survival analysis (cutoff: 3 months).

Characteristics	Univariate, OR (95% CI)	Multivariate, OR (95% CI)
Gender (male vs. female)	0.79 (0.62–1.02) P = 0.07	–
CNS metastases (yes vs. no)	0.80 (0.61–1.03) P = 0.09	–
Liver metastases (yes vs. no)	0.46 (0.36–0.61) P < 0.0001	0.47 (0.35–0.61) P < 0.0001
Lymph node metastases (yes vs. no)	0.80 (0.61–1.06) P = 0.12	–
ECOG-PS (2 vs. 0/1)	0.27 (0.18–0.41) P < 0.0001	0.29 (0.19–0.44) P < 0.0001
Prior maintenance (yes vs. no)	1.45 (1.08–1.94) P = 0.01	1.49 (1.10–2.01) P = 0.009

CNS = central nervous system; ECOG-PS = Eastern Cooperative Oncology Group Performance Status.
Since the end-point is OS > 3 months, odds ratio (OR) < 1 indicates a lower probability of reaching the 3-month OS cutoff for subgroups with the characteristic considered, while OR > 1 indicates a higher probability of surviving over the 3-month OS cutoff. Only statistically significant variables have been reported in the multivariate OR column.

suggested a similar tolerance compared to young patients, but different efficacy according to the specific type of treated malignancy [11]. The EAP included 232 patients aged ≥75 years, all treated with nivolumab, and the outcomes of such patients were substantially consistent with data from the global EAP population, thus confirming the efficacy and the tolerability of PD-L1 inhibition in this population. These results are generally consistent with already published data from the Italian nivolumab EAP involving patients affected by squamous NSCLC [12]; however, as compared with the squamous NSCLC population, our analysis included a larger number of elderly patients treated with nivolumab for advanced NSCLC. Our results are supported by recent data involving patients aged ≥70 years (n = 556) within the CheckMate 153 trial; in this study, elderly patients achieved benefits similar to the global trial population (10.3 vs. 9.1 months), and similar incidence of treatment-related AEs [13].

With regards to patients with CNS metastases, only 68 patients were included in CheckMate 057, and no significant advantage of nivolumab over docetaxel was observed (HR = 1.04; 95% CI: 0.62–1.76) [5]. Furthermore, other available publications involving PD-1/PD-L1-disrupting agents in presence of CNS metastases, albeit encouraging, usually include small populations [14–16]. By contrast, the Italian EAP included 409 patients with CNS involvement, with a 1-year OS rate equal to 43% and the early survival univariate analysis showing a non-significant difference between patients with and without CNS metastases, hence supporting the use of nivolumab in this specific subpopulation [8].

An additional issue of relevance in the management of immunotherapy in NSCLC involves the opportunity to continue the administration of nivolumab beyond radiological disease progression in the presence of clinical benefit. While this approach was allowed in CheckMate 057, only few patients (N = 71) underwent nivolumab continuation [5]. In the EAP, 276 patients received nivolumab beyond PD, on the basis of perceived clinical benefit; among these, 57 patients (21%) achieved a subsequent disease control (objective response or stabilisation), as well as a median OS of 16.2 months and 1-year OS rate of 62%. Such results are consistent with data from patients receiving the anti-PD-L1 agent atezolizumab beyond PD in the phase III OAK trial [17], supporting the use of immune checkpoint inhibitors beyond radiologic progression, as long as clinical benefit is perceived. Furthermore, in a recent publication involving NSCLC patients treated with nivolumab within clinical practice, 60 of 176 patients experiencing progression during immunotherapy with nivolumab continued to receive the same agent beyond progression (the choice was made on the basis of investigator-assessed clinical benefit). In this study, patients treated beyond progression achieved longer OS compared to those patients who discontinued nivolumab at progression (10.7 vs. 3.4 months in a landmark analysis of evaluable patients beginning 6 weeks from first progression); these data are consistent with our findings in supporting the role of immune checkpoint blockade beyond progression when clinical benefit is perceived [18].

Finally, with regards to safety, nivolumab-related toxicities observed in our population were similar to data observed in controlled trials involving PD-1/PD-L1 blocking agents [19], thus confirming the generally manageable safety profile of this drug class; this profile was generally consistent among different subpopulations within the EAP, including elderly patients, for whom toxicity of antineoplastic agents is especially relevant.

In conclusion, while we acknowledge the limitations of this study, based on its non-randomised nature and the lack of prespecified efficacy end-points, as well as lack of systematic evaluation of disease response, our results further confirm data from trials and support the thesis that nivolumab is a safe and effective therapy for previously treated patients with advanced non-squamous NSCLC in routine clinical practice, including patient subgroups generally underrepresented in randomised clinical trials.

Conflict of interest statement

The authors declare the following honoraria. F. Grossi: Amgen, Astra Zeneca, Boehringer Ingelheim,

BMS, MSD, Roche. C. Genova: Astra Zeneca, Boehringer Ingelheim, BMS, MSD, Roche. D. Signorelli: Astra Zeneca, BMS, MSD, Roche. A. Passaro: Astra Zeneca, BMS, Dako/Agilent, Genentech, MSD, Roche. M. Tiseo: BMS. G. Tonini: Italfarmaco, Molteni, Novartis, Pfizer, Roche. L. Toschi: BMS. The other authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.09.011.

References

[1] Howlader N, Noone A, Krapcho M, Miller D, Bishop K, Kosary CL, et al. SEER cancer statistics review. Bethesda, MD: National Cancer Institute; 2017. p. 1975–2014. based on November 2016 SEER data submission, posted to the SEER web site, April 2017, https://seer.cancer.gov/csr/1975_2014/.

[2] Yoda S, Dagogo-Jack I, Hata AN. Targeting oncogenic drivers in lung cancer: recent progress, current challenges and future opportunities. Pharmacol Ther 2019;193:20–30.

[3] Meyers DE, Bryan PM, Banerji S, Morris DG. Targeting the PD-1/PD-L1 axis for the treatment of non-small-cell lung cancer. Curr Oncol 2018;25(4):e324–34.

[4] Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 2015;373(2):123–35.

[5] Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced non-squamous non-small-cell lung cancer. N Engl J Med 2015;373(17):1627–39.

[6] Vokes EE, Ready N, Felip E, Horn L, Burgio MA, Antonia SJ, et al. Nivolumab versus docetaxel in previously treated advanced non-small-cell lung cancer (CheckMate 017 and CheckMate 057): 3-year update and outcomes in patients with liver metastases. Ann Oncol 2018;29(4):959–65.

[7] Garassino MC, Gelibter AJ, Grossi F, Chiari R, Soto Parra H, Cascinu S, et al. Italian nivolumab expanded access program in nonsquamous non-small cell lung cancer patients: results in never-smokers and EGFR-mutant patients. J Thorac Oncol 2018;13(8):1146–55.

[8] Crinò L, Bronte G, Bidoli P, Cravero P, Minenza E, Cortesi E, et al. Nivolumab and brain metastases in patients with advanced non-squamous non-small cell lung cancer. Lung Cancer 2019;129:35–40.

[9] Peters S, Cappuzzo F, Horn L, Paz-Ares L, Borghaei H, Barlesi F, et al. OA03.05 analysis of early survival in patients with advanced non-squamous NSCLC treated with nivolumab vs docetaxel in CheckMate 057. J Thorac Oncol 2017;12(1):S253.

[10] Passaro A, Spitaleri G, Gyawali B, de Marinis F. Immunotherapy in non-small-cell lung cancer patients with performance status 2: clinical decision making with scant evidence. J Clin Oncol 2019:JCO1802118.

[11] Daste A, Domblides C, Gross-Goupil M, Chakiba C, Quivy A, Cochin V, et al. Immune checkpoint inhibitors and elderly people: a review. Eur J Cancer 2017;82:155–66.

[12] Grossi F, Crino L, Logroscino A, Canova S, Delmonte A, Melotti B, et al. Use of nivolumab in elderly patients with advanced squamous non-small-cell lung cancer: results from the Italian cohort of an expanded access programme. Eur J Cancer 2018;100:126–34.

[13] Spigel DR, McCleod M, Jotte RM, Einhorn L, Horn L, Waterhouse DM, et al. Safety, efficacy, and patient-reported health-related quality of life and symptom burden with nivolumab in patients with advanced non-small cell lung cancer, including patients aged 70 Years or older with poor performance status (CheckMate 153). J Thorac Oncol 2019.

[14] Gauvain C, Vauleon E, Chouaid C, Le Rhun E, Jabot L, Scherpereel A, et al. Intracerebral efficacy and tolerance of nivolumab in non-small-cell lung cancer patients with brain metastases. Lung Cancer 2018;116:62–6.

[15] Goldberg SB, Gettinger SN, Mahajan A, Chiang AC, Herbst RS, Sznol M, et al. Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. Lancet Oncol 2016;17(7):976–83.

[16] Gadgeel SM, Lukas RV, Goldschmidt J, Conkling P, Park K, Cortinovis D, et al. Atezolizumab in patients with advanced non-small cell lung cancer and history of asymptomatic, treated brain metastases: exploratory analyses of the phase III OAK study. Lung Cancer 2019;128:105–12.

[17] Gandara DR, von Pawel J, Mazieres J, Sullivan R, Helland A, Han JY, et al. Atezolizumab treatment beyond progression in advanced NSCLC: results from the randomized, phase III OAK study. J Thorac Oncol 2018;13(12):1906–18.

[18] Ricciuti B, Genova C, Bassanelli M, De Giglio A, Brambilla M, Metro G, et al. Safety and efficacy of nivolumab in patients with advanced non-small-cell lung cancer treated beyond progression. Clin Lung Cancer 2019;20(3):178–185 e2.

[19] Genova C, Rossi G, Rijavec E, Biello F, Barletta G, Tagliamento M, et al. Releasing the brake: safety profile of immune check-point inhibitors in non-small cell lung cancer. Expert Opin Drug Saf 2017;16(5):573–85.