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Effectiveness and safety of nivolumab in advanced non-small cell lung cancer: The real-life data

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ABSTRACT

Objectives: Nivolumab has recently received regulatory approval as a 2nd-line treatment of non-small cell lung cancer (NSCLC). The data regarding its effectiveness and safety in real life setting is lacking.
Materials and methods: 260 consecutive patients with advanced NSCLC treated with nivolumab at five Israeli cancer centers between January 2015 and March 2016 were evaluated for overall survival (OS) and toxicity. OS was analyzed by the Cox proportional-hazards regression model. Overall response rate (ORR) and progression-free survival (PFS) were assessed in 49 patients using RECIST, v.1.1.
Results: Median age was 67y (41–99); males 68%; smokers 76%; ECOG PS ≥2 46%; non-squamous/squamous/other/NR 70%/23%/6%/1%; brain metastases 21%; liver metastases 21%; treatment line: 1st/2nd/3rd + -line/NR 6%/64%/26%/4%. With median survival follow-up of 18.5 months (range, 12.0–26.9), 155 (60%) patients died; median OS comprised 5.9 months (95% CI 4.7–7.4). In univariate and multivariate analysis, the only variable which significantly correlated with OS was ECOG PS. Median OS of patients with ECOG PS 0/1 and ECOG PS ≥2 comprised 9.5 months (95% CI, 6.7-NR) and 3.5 months (95% CI, 2.6–4.5), respectively. For 49 patients evaluable for response (median follow-up of 8.4 months (range, 2–16.8), ORR was 35%, median PFS was 2.8 months (95% CI, 1.8–7.7), incidence of pseudo-progression was 9%. The nivolumab safety profile was in accordance with the literature data, except for febrile neutropenia and pericarditis (observed in 1 case each).
Conclusion: In real life setting, the effectiveness of nivolumab is reasonable yet less prominent than it has been demonstrated in clinical trials. ECOG PS ≥2 is associated with poor prognosis.

Abbreviations: ALK, anaplastic lymphoma kinase; anti-PD-1, anti-programmed cell death protein; BRAF, v-Raf murine sarcoma viral oncogene homolog B; CI, confidence interval; CTC, v.4.03, Common Toxicity Criteria, version 4.03; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; FDA, US Food and Drug Administration agency; HR, hazard ratio; KRAS, Kirsten rat sarcoma viral oncogene homolog; mets, metastases; mo, months; non-sq, non-squamous-cell carcinoma; NR, not reported/not reached; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; pts, patients; RECIST, v.1.1–Revised Response Evaluation Criteria in Solid Tumors, version 1.1; RET, rearranged during transfection; Sq, squamous-cell carcinoma

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1. Introduction

Most recently, significant advances have been made in the field of immune check-point blockade. Several anti-programmed cell death protein-1 (anti-PD-1) agents (e.g., nivolumab, pembrolizumab, atezolizumab) have demonstrated promising systemic activity in patients with non-small cell lung cancer (NSCLC). Nivolumab, a fully human IgG4 anti-PD-1 immune check-point inhibitor, received US Food and Drug Administration agency (FDA) and European Medicines Agency (EMA) approval for the second line treatment of NSCLC based on the results of CheckMate 017 and CheckMate 057 trials demonstrating superior outcomes compared to docetaxel [1,2]. Specifically, nivolumab demonstrated a statistically significant improvement in overall survival (OS) among patients with both squamous-cell and non-squamous-cell histological subtypes (median OS of 9.2 months versus 6.0 months [1], and 12.2 months versus 9.4 months [2], respectively).

It is well known that poor-prognosis patients, such as elderly, patients with Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2, multiple co-morbidities and brain metastases are underrepresented in the randomized clinical trials [3,4]. On the other hand, these individuals comprise 30–50% of the patient population typically seen in a thoracic oncology clinic [5–8]. Importantly, the magnitude of benefit from systemic therapies in this category of patients tends to be smaller, and they are especially prone to toxic treatment effects [7,9–13]. All that makes the extrapolation of data obtained in the randomized clinical trials less reliable and adds further complexity into the decision making process. Thus, observational and registry-based data becomes the only reliable source to guide treatment decisions when treating this patient subset.

In Israel, nivolumab has been available for treatment of advanced NSCLC since June 2015. At first, the drug was provided by the Bristol-Myers Squibb within the expanded access program. Later on, in January 2016, nivolumab became commercially available for the FDA/EMA-approved indication while some patients continued to receive nivolumab provided by the manufacturer. In this study, we reviewed the Israeli experience with nivolumab given either within an expanded access program or as a standard of care treatment for advanced NSCLC. In view of debate regarding the criteria for assessment of response to immunotherapy [14,15], we primarily focused on examining the overall survival (OS). Our secondary goal was defining clinical predictors of treatment effectiveness and assessing the safety profile. Overall, our series illustrates treatment outcomes with nivolumab in a real life setting.

2. Materials and methods

We collected data of consecutive patients with advanced lung cancer (stage IVa/b or recurrent disease necessitating a systemic approach) who have been treated with nivolumab at five Israeli cancer centers between January 2015 and March 2016.

Patients' charts and hospital electronic medical records were retrospectively reviewed. Thirteen medical oncologists whose main focus of expertise is lung cancer provided the relevant clinical data for the series. All the patients were followed from first nivolumab dosing to end-of-data collection (May 2016). Additionally, survival data was updated in March 2017.

Survival was calculated as the time from initiation of nivolumab until death from any cause or last follow-up. OS was analyzed by a Cox proportional-hazards regression model for baseline clinical and pathologic characteristics. The safety profile was assessed and graded by using Common Toxicity Criteria, version 4.03 (CTC, v.4.03) [16]. In addition, computed tomography/positron emission computed tomography/magnetic resonance images available from the Davidoff Cancer registry were reviewed by the board-certified radiology specialist, and response and progression-free survival (PFS) were assessed using Revised Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST, v.1.1) [17]. PFS was calculated as the time from initiation of nivolumab until objective tumor progression determined by RECIST, v.1.1 [17], death from any cause or last follow-up whichever occurred first. The frequency of pseudo-progression was assessed, and defined by a ≥30% decrease from baseline in the sum of the longest diameters of target lesions following documentation of progressive disease by RECIST, v.1.1 [18]. Progressive disease was defined by one of the following: a ≥20% increase in the sum of the longest diameters of target lesions, or unequivocal progression of non-target lesions, or appearance of a new lesion [18].

Statistical analysis was fully descriptive in nature. The sample size was determined by the available patients meeting the inclusion criteria. The statistical analysis was generated using SAS Software, version 9.4. Categorical variables were presented by numbers and percentiles, medians and ranges were reported for continuous variables. OS for categorical variables and PFS were assessed by Kaplan-Meier method, with the log-rank test. OS for continuous variables was assessed by the Cox proportional-hazards regression model. The Cox proportional-hazards regression model was also used for multivariate survival analysis. T-test was used to compare the age distribution between ECOG PS groups. Two-sided p values less than 0.05 were considered statistically significant.

The study was conducted in accordance with the principles of good clinical practice, and institutional review board approval was obtained before reviewing the patients' charts and electronic medical records.

3. Results

3.1. Patients

Overall, among 342 patients with advanced lung cancer considered for nivolumab therapy, a total of 260 patients were selected. Thirty two patients, who applied for the nivolumab compassionate use program and did not receive the drug because of rapid deterioration/death, were excluded from the analysis. Forty five patients, who initiated nivolumab after March 31, 2016, were excluded from the analysis because of inadequate follow-up. Four patients receiving a combined treatment with nivolumab and ipilimumab (1 patient), crizotinib (2 patients), or neratinib (1 patient) were excluded; 1 additional patient with concurrent lung and pancreatic cancer was excluded as well.

Baseline demographics and clinical characteristics for the 260 included patients are displayed in Table 1. Importantly, 23% of patients were ≥75 years old, 46% of patients were reported to have ECOG PS ≥ 2 at the time of treatment initiation (e.g., at the time of first treatment cycle administration), and at least 21% and 21% of patients had brain and liver metastases, respectively. The majority of patients in the cohort were smoking males. Patients with non-squamous cell histology predominated, 4 patients with large-cell neuroendocrine tumor and 3 patients with mixed tumors were included, 2 patients had small-cell lung cancer. Molecular tumor testing was limited and mostly included testing of tumors with non-squamous histology for common mutations in the *EGFR* gene and *ALK*-rearrangements. Next-generation sequencing was only performed in the minority of cases. The majority of tumors included in the analysis did not harbor any molecular abnormality; *KRAS* and *EGFR* mutations were reported in 19 cases (7%) and 13 cases (5%), respectively. Other targetable molecular aberrations seen were: *BRAF K601V* mutation (1 patient), *RET-KIF5 B* rearrangement (2 patients), and *MET* exon 14 skipping mutation (1 patient). No routine tumor staining for programmed death-ligand 1 (PD-L1) has been done.

3.2. Treatment

Nivolumab was given at a standard dose of 3 mg/kg every 2 weeks. According to the treating physician's decision, the treatment schedule was modified to 3 mg/kg every 3 weeks in five patients after a partial/

Table 1
Baseline patient and disease characteristics. Abbreviations: ALK − anaplastic lymphoma kinase, ECOG PS − Eastern Cooperative Oncology Group performance status, EGFR − epidermal growth factor receptor, KRAS − Kirsten rat sarcoma viral oncogene homolog, NR- not reported, pts − patients, Tx − treatment.

Baseline patient/disease characteristics	n-260
Age, median (range), years	67 (41–99)
Gender, n (% of pts)	
Males	176 (68)
Females	84 (32)
Smoking history, n (% of pts)	
Smokers	197 (76)
Never-smokers	40 (15)
NR	23 (9)
ECOG PS score at the time of nivolumab initiation, n (% of pts)	
0/1	121 (46)
≥2	119 (46)
NR	20 (8)
Histological subtype, n (% of pts)	
Non-squamous cell ca	183 (70)
Squamous cell ca	59 (23)
Other	16 (6)
NR	2 (1)
Tumor molecular aberration, n (% of pts)	
None	157 (60)
KRAS mutation	19 (7)
EGFR mutation	13 (5)
ALK rearrangement	0 (0)
Other	10 (4)
NR	61 (24)
Brain metastases, n (% of pts)	55 (21)
Liver metastases, n (% of pts)	55 (21)
Number of prior systemic Tx regimens, n (% of pts)	
0	15 (6)
1	167 (64)
≥2	68 (26)
NR	10 (4)

complete response was achieved. In two additional responding patients the treatment schedule was modified to 3 mg/kg every 4 weeks and 3 mg/kg every 8 weeks. With median follow-up of 8.4 months (range, 2–16.8), median treatment duration was 2.7 months (range, 0.1–15.5). A median of 6 doses (range, 1–26) of nivolumab was administered. 27% of patients were still receiving nivolumab at the time of last follow-up.

3.3. Effectiveness

The median follow-up duration for OS was 18.5 months (range, 12.0–26.9). At the time of last follow-up 155 patients (60%) had died. The median OS was 5.9 months (95% CI, 4.7–7.4) (Fig. 1A).

In the univariate analysis, ECOG PS score at the time of nivolumab initiation was the only factor which significantly correlated with overall survival (Fig. 1B). Median OS of patients with ECOG PS 0/1 and ECOG PS ≥2 comprised 9.5 months (95% CI, 6.7-NR) and 3.5 months (95% CI, 2.6–4.5), respectively ($p < 0.0001$). No significant correlation was observed between the survival and any of the other parameters examined: age ($p = 0.3$, Fig. 1C), sex ($p = 0.9$), smoking status ($p = 0.8$), tumor histological subtype ($p = 0.9$), presence of liver metastases ($p = 0.2$) or brain metastases ($p = 0.5$) and number of previous lines of systemic treatment ($p = 0.5$) (Fig. 2A–F, Supplementary material). In the multivariate analysis, ECOG PS score remained the only factor significantly related to survival ($p < 0.0006$) (Table 2).

For 49 patients with measurable disease at the time of nivolumab initiation for whom images were available for radiological review, response and PFS were assessed using RECIST, v.1.1. With median follow-up of 8.4 months (range, 2–16.8), overall response rate was 35%; median time to response was 2.3 months (range, 1.5–6.2). Thirty-four patients have progressed; median PFS was 2.8 months (95% CI, 1.8–7.7) (Fig. 3A). Twenty-one patient continued nivolumab beyond progression by RECIST v.1.1. The median duration of treatment beyond progression was 2.4 months (range, 0.3–9.9). The frequency of pseudo-progression was 4% (2/49) in patients evaluable for response and 9% (2/21) in patients who continued nivolumab beyond progression (Fig. 3B).

3.4. Safety

Median follow-up for safety data collection was 8.4 months (range, 2–16.8). Treatment-related adverse events observed in ≥3% of patients are listed in Table 3. The most common toxicities seen were fatigue, anorexia, nausea, rash, pruritus, musculoskeletal pain, diarrhea, and elevation of creatinine and liver transaminases, the majority of which were transient and low-grade. Infusion-related reactions were rarely seen (observed in 2 patients, low-grade in both cases), and did not recur with subsequent dosing after appropriate premedication. One patient developed grade 2 adrenal insufficiency which was successfully managed with steroids. Ten cases of pneumonitis were seen, including 3 cases of pneumonitis grade 3; noteworthy, in 1 out of 3 cases the relation to treatment was equivocal; in 2 out of 10 patients nivolumab was successfully re-initiated without symptoms worsening. Four patients developed Grade 3 diarrhea. High-grade transaminase elevation/bilirubin elevation was observed in 7 patients (4 patients − grade 3, 2 patients − grade 4, 1 patient − grade 5). The latter patient had died because of hemorrhagic shock following performance of a liver biopsy. Two cases of nivolumab-related encephalopathy were seen (1 patient − grade 2, 1 patient − grade 4). Two cases of grade 2 peripheral neuropathy and 1 case of grade 3 myelitis were observed. Grade 2 pancreatitis and grade 3 new-onset diabetes were seen in 3 and 1 cases, respectively. 1 patients developed parotitis, 1 patient developed grade 4 pericarditis. One patient with Crohn's disease receiving concurrent treatment with mesalazine died of febrile neutropenia.

At least one toxicity-related dose delay occurred in 23 patients. In 9 cases nivolumab was permanently discontinued because of treatment-related toxicity. Forty six patients required steroid administration for management of adverse events.

4. Discussion

In the real life, the effectiveness of nivolumab in advanced NSCLC is less prominent than it has been demonstrated in randomized controlled clinical trials. Specifically, in our poor prognosis cohort, the median overall survival of patients with squamous and non-squamous cell histological subtype comprised only 6.1 months (95% CI, 4.0–8.6) and 5.8 months (95% CI, 4.5–8.6), respectively. This compares unfavorably with the median overall survival of 9.2 months (95% CI, 7.3–13.3) months and 12.2 months (95% CI, 9.7–15.0) months for patients with squamous and non-squamous cell NSCLC in CheckMate 017 [1] and CheckMate 057 [2] trials, respectively.

Notably, in our series, ECOG PS seems to be the most important survival-related variable which demonstrated a negative correlation in both univariate and multivariate analysis. Importantly, OS of patients with ECOG PS 0/1 in our series of 9.5(95% CI, 6.7-NR) comes in line with the literature data, confirming the results of CheckMate 017 [1] and CheckMate 057 [2] trials. On the other hand, overall survival of patients with ECOG PS ≥ 2 was much worse (3.5 months (95% CI, 2.6–4.5).

Little data exists with regards to safety and efficacy of anti-PD1/anti-PDL1 agents in patients with poor ECOG PS. The only data available comes from the CheckMate 153 study (NCT02066636) [19] evaluating safety of nivolumab in pretreated patients with advanced NSCLC. Sixty five patients were enrolled into one of the study cohorts evaluating nivolumab in ECOG PS 2 patients while 3 other cohorts enrolled 742 patients with ECOG PS 0/1. According to the presented data, the frequency of treatment-related adverse events was similar between patients with ECOG PS 0/1 and those with ECOG PS 2, confirming good treatment tolerability in poor ECOG PS patients and

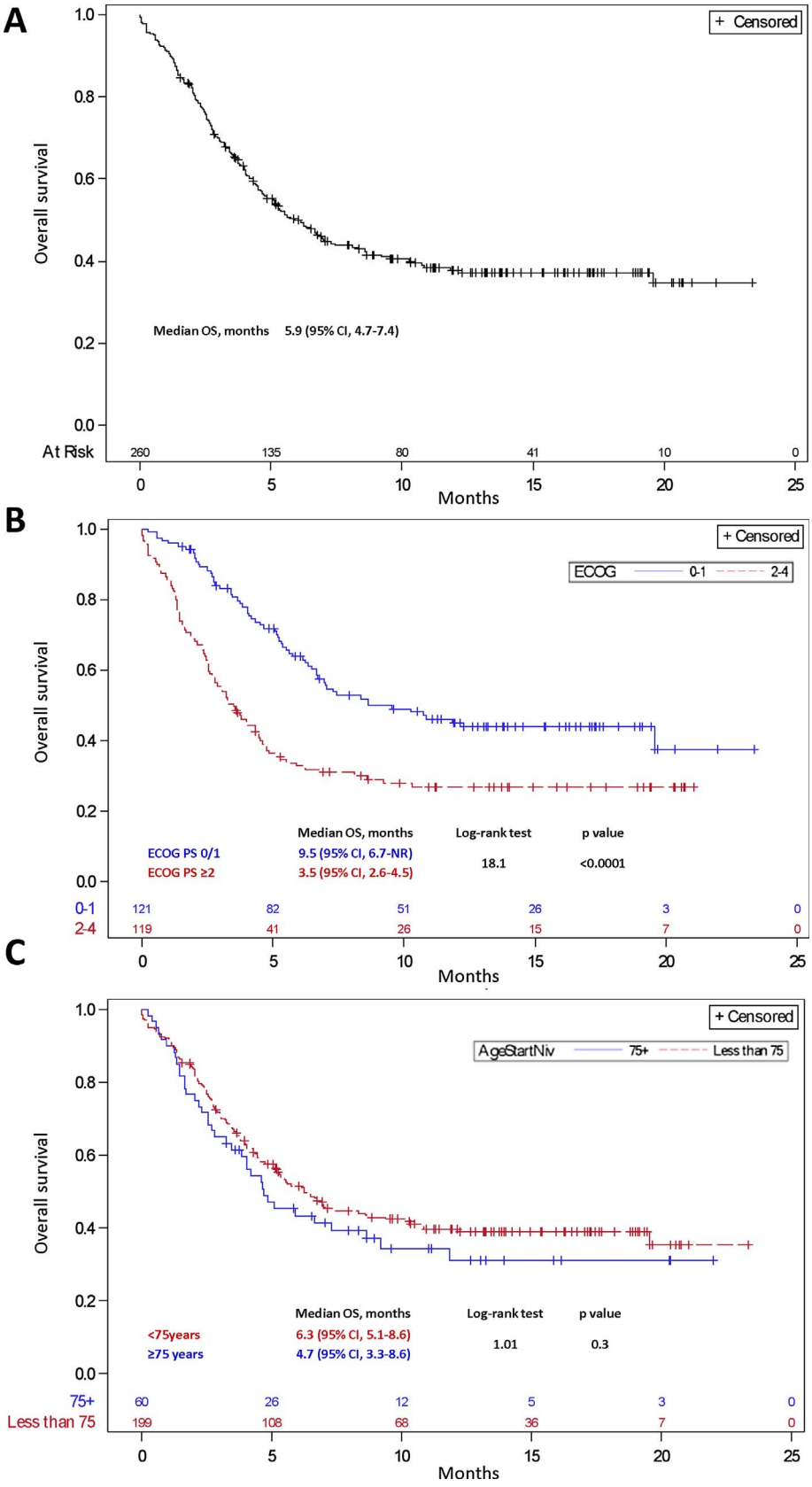

Fig. 1. Panel A demonstrates Kaplan–Meier curve for overall survival (n-260). Panel B demonstrates Kaplan-Meier curves for overall survival stratified according to ECOG PS (ECOG PS 0/1 and ECOG PS ≥2, n-240). Panel C demonstrates Kaplan-Meier curves for overall survival stratified according to patient age (< 75years and ≥75 years old, n-260). Median follow-up – 18.5 months (range, 12.0–26.9). Abbreviations: CI – confidence interval, ECOG PS – Eastern Cooperative Oncology Group performance status, NR – not reached, OS – overall survival.

supporting our findings. 7/35 patients with ECOG PS 2 responded to treatment; ORR comprised 20% and 11% for ECOG PS 2 and ECOG PS 0/1 patients, respectively. No long-term outcomes were published yet. Thus, our series is the first one to provide effectiveness data with nivolumab in poor ECOG PS patients based on long-term outcomes. Our results, as opposed to the CheckMate 153 data, clearly point to inferior survival in ECOG PS ≥ 2 patients as compared to patients with ECOG PS 0/1.

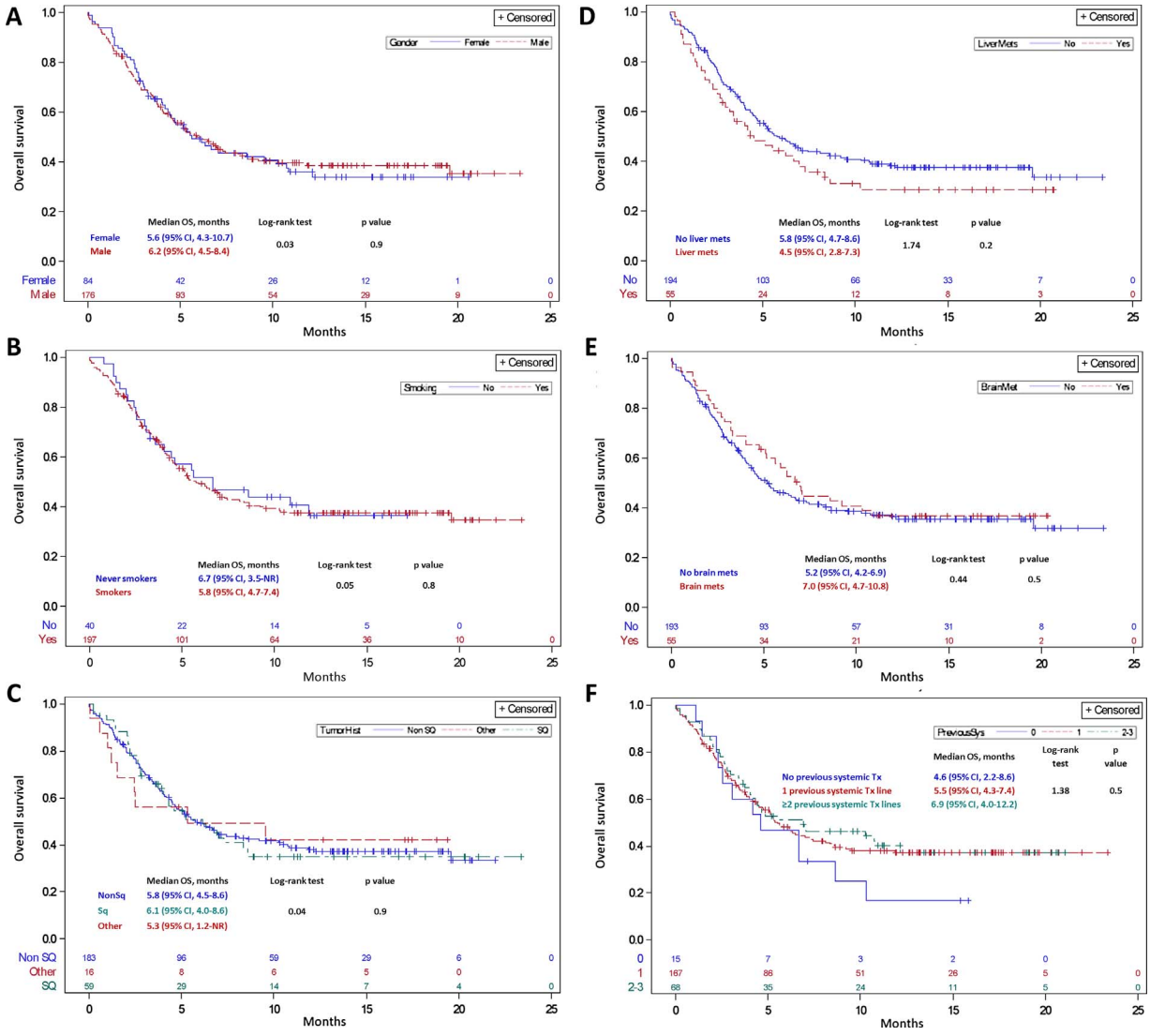

Fig. 2. Panel A demonstrates Kaplan-Meier curve for progression-free survival (n-49). Panel B demonstrates percent change in the sum of the diameters of the target lesions from baseline over time; only includes patients who continued nivolumab beyond progression by RECIST v.1.1 (n-21). Median follow-up − 8.4 months (range, 2–16.8). Horizontal lines denote 20% increase, 30% decrease, and no change. Patients demonstrating pseudo-progression are depicted in green. Abbreviations;: CI − confidence interval, PFS − progression-free survival, Tx-treatment.

Table 2
The results of multivariate analysis of overall survival by the Cox proportional-hazards regression model. Abbreviations: CI − confidence interval, ECOG PS − Eastern Cooperative Oncology Group performance status, HR − hazard ratio, Non-sq − non-squamous-cell carcinoma, mets − metastases, OS − overall survival, Sq − squamous-cell carcinoma; Tx − treatment.

Parameter	OS			
	HR	95% HR CI		p value
Age	1.02	0.99	1.04	0.06
Gender	1.16	0.79	1.69	0.43
Smoking	1.27	0.76	2.10	0.36
Histology (Sq *vs* Non-sq)	1.12	0.73	1.70	0.61
Histology (other *vs* Non-sq)	0.83	0.37	1.83	0.64
Liver mets	0.78	0.53	1.17	0.24
Brain mets	0.90	0.59	1.36	0.62
ECOG PS (≥2 *vs* 0/1)	1.86	1.31	2.65	0.0006
Previous Tx lines (1 *vs* ≥2)	1.14	0.75	1.72	0.54
Previous Tx lines (0 *vs* 1)	1.16	0.60	2.21	0.66
Previous Tx lines (0 *vs* ≥2)	1.32	0.66	2.61	0.43

Table 3
Treatment-related adverse events (AE, CTCAE v4.0) reported in ≥3% of patients. *1 patient − grade 5. Median follow-up − 8.4 months (range, 2–16.8).

AE	Frequency of AE, % (n)	
	Grade 1/2	Grade 3/4
AE reported in ≥5% of patients		
Fatigue	38 (100)	6 (15)
Rash	10 (27)	1 (3)
Pruritus	10 (27)	
Musculoskeletal pain	10 (27)	
Anorexia	19 (50)	2 (5)
Nausea	9 (24)	1 (3)
Diarrhea	7 (19)	1 (4)
Abdominal pain	5 (12)	
Hypothyroidism	6 (15)	1 (1)
Hyperthyroidism	5 (12)	
Creatinine↑	11 (29)	
ALT/AST↑	8 (20)	2 (6)*
AE reported in < 5% of patients		
Bilirubin↑	2 (5)	1 (2)*
Pneumonitis	3 (7)	1 (3)
Infection	2 (6)	1 (4)

Systemic treatment of ECOG PS ≥ 2 patients with advanced NSCLC whose tumors do not harbor a targetable molecular aberration and who failed 1st-line platinum-based chemotherapy remains a highly unmet medical need. Specifically, individuals with ECOG PS 3/4 do not benefit from any systemic treatment while ECOG PS 2 patients derive only a minor benefit from epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) [20]. According to results of randomized clinical trials in which patients with ECOG PS 2 comprised at least 10% of the study population, ORR with EGFR TKIs was 8%-18%, mPFS and mOS comprised 1.6-3.75 months, and 5.3-8.2 months, respectively [21–27]. ECOG PS 2 patients, however, perform worse [22,25]. Whether anti-PD-1/anti-PD-L1 agents have a superior efficacy to EGFR TKIs and may provide a clinically relevant benefit to this category of patients for whom therapeutic options are limited remains an important question which warrants further evaluation in a prospective randomized controlled trial.

Importantly, in our series, no negative correlation between the patients' age and OS was demonstrated implying that elderly with good ECOG PS derive the same benefit from nivolumab as their younger counterparts. These findings are in accordance with the results of CheckMate 057 [2], KEYNOTE-010 [28], and OAK studies [29], demonstrating similar benefit across all age subgroups.

In our series, as opposed to CheckMate 057 [2], the presence of brain metastases did not predict inferior survival with nivolumab. The intracranial activity of nivolumab, although modest [30,31], may explain the lack of correlation. According to our findings, the presence of liver metastases was not associated with inferior survival either. Surprisingly, we have not observed any correlation between smoking status and treatment outcomes, whereas such a correlation was previously reported by several investigators [2,32,33]. It might be the duration of smoking exposure and not the smoking status that predicts the outcomes with nivolumab [32]. In accordance with the literature data, the survival rates were similar in patients with squamous and non-squamous histologies [32].

Our series provides important information with regards to nivolumab tolerability in the real life. Although the treatment was well-tolerated overall, several new safety signals were received. In particular, it is the second report in the literature on febrile neutropenia in association with nivolumab as a treatment of solid tumors [34,35]. While there are several reports on cardiotoxicity in association with immune check-point inhibitors, mostly in the form of myocardial damage [33,36,37], our series is the first to report on nivolumab-related pericarditis.

ORR and PFS in our series were in line with the data reported in the randomized clinical trials [1,2]; however, it was only assessed in a small cohort that was not necessarily representative of the whole study population. Interestingly enough, we have clear documentation of a significant tumor shrinkage in 9% of patients who continued nivolumab beyond progression by RECIST, v.1.1, which supports the data regarding the frequency of pseudo-progression during the anti-PD-1/anti-PD-L1 therapy presented by Kazandjian and colleagues [18]. These cases should not be missed since those patients may represent long-term survivors [15].

Unfortunately, in our cohort a routine tumor PD-L1 staining has not been done, whereas PD-L1-expression emerges as an important predictive biomarker of response with anti-PD1/anti-PD-L1 agents [2,33,38,39] and its performance in the real world warrants further investigation. Additional and important shortcomings of our series are its retrospective nature, limited follow-up, and absence of a central radiological assessment for all the patients included in the cohort.

5. Conclusions

In summary, our results should urge clinicians to look beyond randomized controlled clinical trials to observational data in order to inform decision making. Efficacy of anti-PD-1/anti-PD-L1 agents in ECOG PS 2/3 patients with advanced NSCLC should be explored further.

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Conflict of interest

Peled Nir and Bar Jair have received honoraria from BMS, other authors declared no conflict of interests.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.lungcan.2017.11.015.

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