The real-world experience with nivolumab in previously treated patients with advanced non-small cell lung cancer from a cancer center in India

Waseem Abbas, Rudra Prasad Acharya, Archit Pandit, Saurabh Gupta, Ranga Raju Rao

Abstract

Background: PDL-1 inhibitors have emerged as the new standard of care for second line treatment of NSCLC. **Methods:** Eligible patients included, histologically proven NSCLC, ECOG (Eastern Cooperative Oncology Group) performance status of 0, 1 or 2, age 18 years and above, availability of pre-treatment tumor specimen, adequate end organ function, at least one prior platinum-based therapy. Patients who received a minimum of 6 doses of nivolumab were eligible. **Results:** Eleven previously treated patients with chemotherapy, started on nivolumab from April of 2016 to December of 2018, were retrospectively studied and analysed. The median age of patients was 58 years. Eight (72.73%) of the eleven patients were male. Seven (63.64%) of the patients were current or former smokers. Majority of patients had non-squamous histology; seven (63.64%) adenocarcinoma and four (36.36%) squamous cell carcinoma. 5 (45.46%) of the patients received one prior therapy, three (27.27%) received two prior therapies, and three (27.27%) received three prior therapies. Four (36.36%) of the patients had brain metastasis. Two (18.18%) of the patients were more than 70 years of age. Median number of cycles of nivolumab administered were 10 (range, 6 to 21). At the time of analysis, the median PFS was 8 months (95% CI, 1.52-14.47) and median OS was 15 months (95% CI, 6.9-23.09). Treatment was well tolerated and generally side effects were grade 1 and grade 2, except two patients who develop grade 3/4 pneumonitis. **Conclusions:** This is a real-world study of eleven previously treated patients with chemotherapy, started on Nivolumab from April of 2016 to December of 2018. Although, our sample size was small, our data supports the use of nivolumab as a new treatment option for patients of stage 4 NSCLC.

Key words: Immunotherapy in lung cancer, nivolumab in carcinoma lung, real-world data of nivolumab

Introduction

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer and accounts for more than 80% of all lung cancer cases. About 60% of NSCLC cases present with metastatic disease and 5-year survival remains poor.[1] Standard of care for stage four, driver mutation-negative NSCLC till now remained platinum doublet therapy with 1-year median survival.[2] After disease progression, few treatment options were available, i.e., docetaxel and pemetrexed (pemetrexed for the treatment of only adenocarcinoma). There was an unmet need for second-line treatment options that will improve overall survival (OS) with a better side-effect profile.

In a multicohort Phase 1 study involving previously untreated patients with NSCLC (CheckMate 012), 12 durable responses were seen in patients who received nivolumab. Median progression-free survival (PFS) was 10.6 months, and response rates were 50%. Clinical activity was not only seen in patients with increasing Programmed Death Ligand-1 (PDL-1) levels but also with a low-PDL-1 expression level or with no PDL-1 expression.

In two pivotal CheckMate trials,[3,4] comparing nivolumab to docetaxel in the second-line setting, nivolumab resulted in longer OS in both squamous and nonsquamous advanced NSCLC. Nivolumab was the first checkpoint inhibitor that was compared to docetaxel and approved as second-line option for both squamous and adenocarcinoma [Table 1].

After the two pivotal CheckMate trials,[3,4] nivolumab became standard of care in second-line setting for both histological subtypes (adenocarcinoma and squamous cell carcinoma) irrespective of PDL-1 status and showed a survival benefit in previously treated patients.

In clinical trials conducted so far, <30% of patients benefited from nivolumab. Therefore, the identification of biomarker for predicting nivolumab efficacy is crucial.[5-8]

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Materials and Methods

This is a retrospective study of 11 NSCLC patients, who progressed on chemotherapy, treated with nivolumab in our center from April 2016 to December 2018.

Informed consent was obtained from all 11 patients involved in the study.

Eligible patients included, histologically proven NSCLC, Eastern Cooperative Oncology Group (ECOG) performance status of zero, one, or two, age 18 years and above, availability of pretreatment tumor specimen, adequate end organ function, at least one prior platinum-based therapy. Patients who received a minimum of six doses of nivolumab were eligible.

Criteria for exclusion were autoimmune disease, symptomatic interstitial lung disease, systemic immunosuppression, or prior therapy with T-cell co-stimulation or checkpoint-targeted agents.

The PFS was calculated from the 1st day of the administration of nivolumab until any progression based on imaging available (local or distant).

The OS was calculated from the 1st day of nivolumab administration until death.

Tumor response was assessed using the the data was analyzed using IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.

Results

Eleven previously treated patients with chemotherapy, started on nivolumab from April 2016 to December 2018, were retrospectively studied and analyzed. The median age of patients was 58 years. Eight (72.73%) of the eleven patients were male. Seven (63.64%) of the patients were current or former smokers. Majority of patients had nonsquamous

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Table 1: Nivolumab clinical trials in second-line treatment for Stage 4 lung cancer

Study	Line of Treatment	Agent	Trial Phase	RR	Median OS	Median PFS
Checkmate 017. (3)	Second Line	Nivolumab vs Docetaxel	III	20 vs 9	9.2 vs 6	3.5 vs 2.8
Checkmate 057. (4)	Second Line	Nivolumab vs Docetaxel	III	19 vs 12	12.2 vs 9.4	2.3 vs 4.2

RR=Response rate, OS=Overall survival, PFS=Progression-free survival

Table 2: Patient characteristics

Patients	Age	Sex	History of smoking	Histology	Metastasis to brain	Number of prior lines of therapy	Radiotherapy prior to immunotherapy	Time interval between last therapy and start of immunotherapy (days)	ORR
Patient-1	74	M	YES	ADENO	NO	2	NO	60	CR
Patient-2	73	M	YES	SCC	YES	2	YES	30	PD
Patient-3	58	M	YES	SCC	YES	1	NO	30	PD
Patient-4	62	F	NO	ADENO	NO	1	NO	60	PD
Patient-5	65	M	YES	ADENO	NO	1	YES	5	PD
Patient-6	56	M	YES	ADENO	NO	3	NO	15	PD
Patient-7	52	M	NO	ADENO	YES	3	YES	135	PR
Patient-8	40	F	NO	SCC	YES	1	YES	110	SD
Patient-9	50	F	NO	ADENO	NO	1	NO	30	PR
Patient-10	67	M	YES	SCC	NO	2	YES	285	SD
Patient-11	42	M	YES	ADENO	NO	3	YES	20	SD

ADENO=Adenocarcinoma, SCC=Squamous cell carcinoma, ORR=Overall response rates, M=Male, F=Female, CR=Complete response, PD=Progressive disease, PR=Partial response, SD=Stable disease

Table 3: Overall response rates

Items	Data (number of patients)	Percentage
Objective response	6	54.54
Complete response	1	9.09
Partial response	2	18.18
Stable disease	3	27.27
Progressive disease	5	45.45

Table 4: Adverse events

Adverse Events	Grade 1-2, *n* (%)	Grade 3-4, *n* (%)
Pneumonitis		2 (18.18)
Pruritis/rash	8 (72.73)	
Hypothyroidism	6 (54.55)	
Renal toxicity	1 (9.09)	
Nausea	1 (9.09)	
Diarrhea	1 (9.09)	
Fatigue	6 (54.55)	
Vomiting	1 (9.09)	

histology; 7 (63.64%) adenocarcinoma and 4 (36.36%) squamous cell carcinoma.

All of the patients included in the study received platinum-based therapy before immunotherapy. Five (45.46%) patients received one prior therapy, 3 (27.27%) received two prior therapies, and 3 (27.27%) received three prior therapies.

Four (36.36%) of the patients had brain metastasis.

Two (18.18%) of the patients were more than 70 years of age [Table 2].

All patients included in the analysis received at least six cycles of nivolumab at the standard dose of 3 mg/kg of body weight every 2 weeks. The median number of cycles of nivolumab administered was ten (range, 6–21).

At the time of analysis, the median PFS was 8 months (95% confidence interval [CI], 1.52–14.47) and median OS was 15 months (95% CI, 6.9–23.09) [Figure 1a and b].

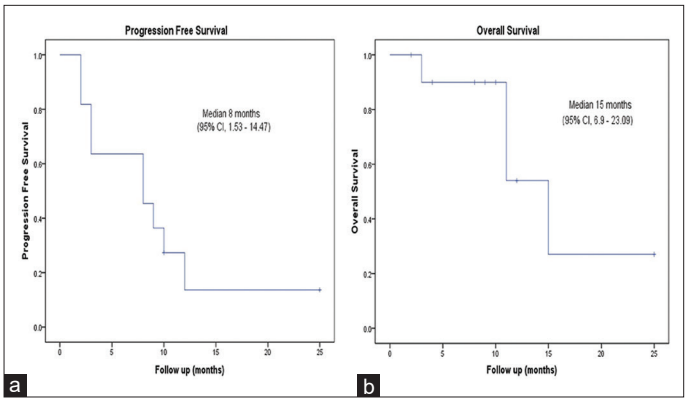

Figure 1: Kaplan–Meier curves. (a) Progression-free survival; (b) overall survival (CI=Confidence Interval)

Response rates

Among 11 patients studied, 1 (9.09%) had complete response (CR), 2 (18.18%) partial response, 3 (27.27%) stable disease, and 5 (45.45%) progressive disease [Table 3].

Adverse events

Pruritus was the most common side effect, seen in 8 (72.73%) of 11 patients. Fatigue and hypothyroidism were seen in 6 of 11 patients (54.55%). Two of 11 patients (18.18%) developed Grade 3–4 pneumonitis. Both these patients, despite the prolonged hospital stay and high-dose corticosteroids, did not recover from Grade 3–4 pneumonitis [Table 4].

Discussion

Limited progress, related to second-line therapy in NSCLC, has been made since the approval of docetaxel as second-line chemotherapy for metastatic lung cancer. Despite the increased number of treatment options for NSCLC, survival remains poor. PDL-1 inhibitors have emerged as the new standard of care for the second-line treatment of NSCLC. In addition, pembrolizumab has been approved for patients with metastatic NSCLC, having PDL-1 expression of more than or equal to 50%.

It is important to evaluate the benefit shown in clinical trials to the lung cancer population in real-world settings.

Both squamous and nonsquamous histological subtypes of NSCLC were analyzed in two separate clinical trials. In CheckMate 017, median PFS was 3.5 months with nivolumab and 2.8 months with docetaxel, and median OS was 9.2 months with nivolumab versus 6.2 months with docetaxel. There were higher response rates (20 vs. 9%) and longer duration of response (25.2 vs. 8.4 months) favoring nivolumab versus docetaxel. In CheckMate 057, higher response rates were seen with nivolumab (19 vs. 12%). The median OS was higher with nivolumab (12.2 vs. 9.5), but median PFS was higher with docetaxel as compared to nivolumab (4.2 vs. 2.3 months).

In our study, the response was observed in 6 (54.54%) patients, 1 (9.09%) patient had CR, 2 (18.18%) had a partial response, and 3 (27.27%) had stable disease. Progressive disease was seen in 5 (45.45%) patients.

Treatment with nivolumab was well tolerated, and generally, side effects were Grade 1 and Grade 2, except two patients who developed Grade 3/4 pneumonitis.

The median PFS was 8 months (95% CI, 1.52–14.47) and median OS was 15 months (95% CI, 6.9–23.09) in our study, which was more than the CheckMate studies, probably because all patients in our study had good performance status (ECOG 1), sample size was small, unselected nonclinical trial population and was a retrospective study.

Conclusion

Nivolumab proved its meaningful survival benefit in clinical practice since the effectiveness appears to be higher in this unselected nonclinical trial population as compared to the results of the clinical trials. Although our sample size was small, our data support the use of nivolumab as a new treatment option for patients of stage four NSCLC.

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Conflicts of interest

There are no conflicts of interest.

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