Clinical experience with Nivolumab in pre-treated patients with NSCLC. Single center experience.

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Background

Non Small Cell Lung Cancer

- Lung cancer is the leading cause of cancer death with only 17.4% 5 year survival[1]. In 2015, an estimated number of 221,200 new cases were diagnosed and 158,040 deaths occurred[2].
- Approximately 85% of lung cancers can be classified as non-small cell lung cancer (NSCLC), divided into two major groups by histology: squamous and non-squamous.
- Half of patients have already distant metastatic disease at diagnosis with a 5-year survival rate of less than 5%.
- The use of chemotherapy has produced objective responses and small improvement in survival for patients with metastatic disease[3].
- For patients who have relapsed after platinum-based chemotherapy, second-line therapy can be considered.
- A meta-analysis of five trials assessing the efficacy and safety of chemotherapy reported a survival of approximately 26 weeks. Additionally, chemotherapy was associated with severe toxicity[4-5].
- Prior to the availability of checkpoint inhibitors the treatment of progressive metastatic NSCLC represented a considerable unmet medical need.
- Nivolumab is a fully human IgG4 monoclonal antibody that binds to and blocks the activation of PD-1 by its ligand.
- Nivolumab was initially approved in March 2015 for advanced squamous NSCLC based on improvement of overall survival (OS) in an open-label, multicenter, randomized phase III trial (CheckMate 017) (overall survival nivolumab 9.2 vs docetaxel 6 months)[6].
- Approval of nivolumab for advanced non-squamous NSCLC was issued in October 2015, based on demonstration of improvement in OS in an international, multicenter, open-label phase III clinical trial (CheckMate 057) (nivolumab 12.2 months vs docetaxel 9.4 months groups)[7].

Methods

- A retrospective, single center, non-interventional analysis was performed on data collected from the nivolumab expanded access programme in South Africa (SA-EAP).
- The study investigated clinical outcomes and toxicity associated with nivolumab in patients with relapsed metastatic NSCLC.
- Each patient signed informed consent and institutional ethics approval was obtained from the Human Sciences Research Council (HSRC) of South Africa.

Patient Population

Inclusion Criteria:

- The patient had histologically- or cytologically-documented locally advanced squamous or non-squamous NSCLC.
- Patients progressed on or after treatment with a minimum of 1 prior systemic treatment for stage IIIB or stage IV disease or with recurrent or progressive disease following multimodal therapy.
- Aged ≥ 18 years of age.
- ECOG performance status of ≤ 2.
- All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue had resolved to Grade 1 (NCI CTCAE v4.0) or baseline.
- Patients had to sign informed consent.

Exclusion Criteria:

- Active, known or suspected autoimmune disease, HIV, Hepatitis B or C.
- Symptomatic brain metastases.
- Received other concurrent systemic anti-cancer treatments for NSCLC.
- Life expectancy of less than 6 weeks.
- The patient had previously participated in, or is eligible for an accessible, nivolumab clinical study.
- The patient had received prior therapy with an anti-PD-1, anti-PD-L1 or anti-PD-L2, anti CT137 or any other antibody including ipilimumab and other T-cell costimulation or checkpoint pathways.
- The patient had a condition requiring systemic treatment with either corticosteroids (> 10 mg/day prednisone equivalent) or other immunosuppressive medications within 14 days of administration of nivolumab.
- The patient had any known active chronic liver disease.
- The patient had previous malignancies unless a complete remission was achieved at least 3 years prior to administration of nivolumab.
- The patient had a known medical condition (e.g. a condition associated with diarrhea or acute diverticulitis).
- The patient had another active malignancy requiring concurrent intervention.
- The patient had not recovered from major surgery.
- The patient had a history of severe hypersensitivity reactions to other monoclonal antibodies.

Data Collection

- Data from different points in time throughout the patients' medical history were reviewed.
- The data included four aspects of treatment history: Demographic features, disease characteristics, treatment history and number of cycles received.
- Disease related factors included history of smoking, NSCLC histology and mutations (EGFR, ALK and ROS 1), metastatic sites and ECOG performance status.
- Treatment related information included history of concomitant drug use, nivolumab data (date of first dose, number of infusions, reason for discontinuation or omission), date of first measured disease progression (PD) and survival dates.

Statistical Analysis

- The collected data were statistically analyzed using descriptive statistics, with medians and ranges of continuous variables and frequencies and percentages for categorical variables. OS was estimated using the Kaplan-Meier method, with 95% CIs reported. OS was analyzed using time from nivolumab initiation date and date of most recent visit or death, whichever occurred first.

Results

- A total of 18 patients (10 males and 8 females) were included in the analysis. Two patients were non evaluable.
- The median age was 66 years (range 46 - 85).
- Adenocarcinoma was documented in 15 patients and squamous cell carcinoma in 3 patients. A ROS 1 positive mutation was documented in 1 patient, 3 EGFR positive mutations were recorded and no patients tested positive for ALK.
- All patients failed frontline treatment: 14 patients failed platinum based chemotherapy and 4 patients failed TKI-inhibitors (3 on erlotinib and 1 on crizotinib).
- Patients received a median of 4 cycles of nivolumab (range 1 - 16). The performance status ranged from 0 to 2 (median 1).
- The median number of metastatic sites was 3 (range 1 - 5).
- Four partial responses were documented (3.43%, 23.5%) with CI 95%, with response durations of 232, 113, 63 and 30 days.
- Disease stabilization was documented in 8 patients.
- There were no complete responses so far, and 6 patients showed progressive disease.
- One patient was non-evaluable (died due to progresive diease before treatment initiation). One patient's death was most likely related to a pulmonary embolism.
- No responses were seen amongst the patients who received prior TKI treatment.

Progression Free Survival

- The median progression free survival was 106 days (13 - 289) (See Figure 1).

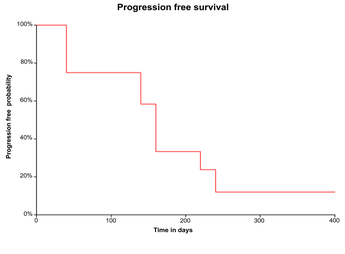

Figure 1. Progression Free Survival.

Overall Survival

- The median overall survival was 124 days (13 - 289) (See Figure 2).
- Documented toxicities included pneumonitis in 2 patients, chest infections in 4 patients (one patient with documented tuberculosis), fatigue in 4 patients and skin rash, diarrhoea and headaches in 1 patient, respectively. One patient developed autoimmune thrombocytopenia and nephritis.

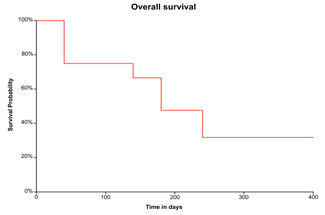

Figure 2. Survival Plot.

- Clinical response at last contact is shown in Table 1

		Lower bound	Upper bound
Complete Response	0%	0%	0%
Partial Response	4 (22.2%)	6.40%	47.60%
Stable Disease	8 (44.4%)	21.50%	69.2%
Progressive Disease	6 (33.3%)	13.3%	59.0%

Table 1.Clinical response at last contact.

CONCLUSIONS

- In this retrospective study nivolumab was an active and well tolerated treatment in patients with pre-treated NSCLC.

Responses

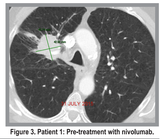

Figure 3. Patient 1: Pre-treatment with nivolumab.

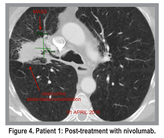

Figure 4. Patient 1: Post-treatment with nivolumab.

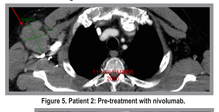

Figure 5. Patient 2: Pre-treatment with nivolumab.

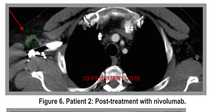

Figure 6. Patient 2: Post-treatment with nivolumab.

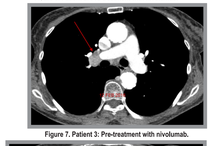

Figure 7. Patient 3: Pre-treatment with nivolumab.

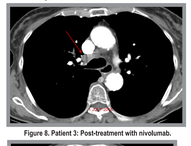

Figure 8. Patient 3: Post-treatment with nivolumab.

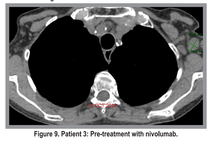

Figure 9. Patient 3: Pre-treatment with nivolumab.

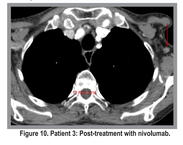

Figure 10. Patient 3: Post-treatment with nivolumab.

Immune-related Adverse Events

PNEUMONITIS

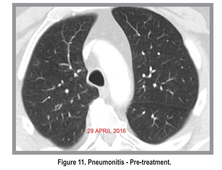

Figure 11. Pneumonitis - Pre-treatment.

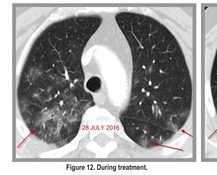

Figure 12. During treatment.

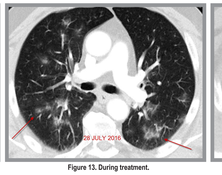

Figure 13. During treatment.

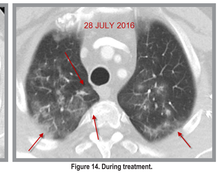

Figure 14. During treatment.

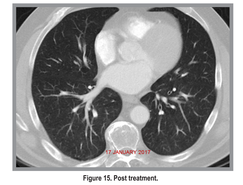

Figure 15. Post treatment.

TUBERCULOSIS

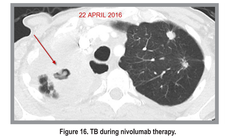

Figure 16. TB during nivolumab therapy.

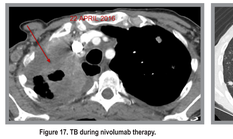

Figure 17. TB during nivolumab therapy.

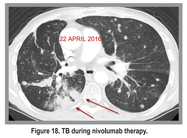

Figure 18. TB during nivolumab therapy.

References

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