

## Background

- ▶ 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 Non-small cell lung cancer (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) (1).
- ▶ Nivolumab was approved 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) (2).
- ▶ There is almost no prospective data on these toxicities and guidelines or recommendations are mostly based on symptomatic management from the ongoing clinical trials.
- ▶ This retrospective, single centre, non-interventional analysis was performed on data collected from the nivolumab expanded access programme in South Africa (SA-EAP). It describes the clinical experience of pneumonitis and other pulmonary infiltrates associated with nivolumab treatment in NSCLC patients.

## Patient Population

### Inclusion Criteria:

- ▶ The patient has histologically- or cytologically- documented locally advanced squamous or non-squamous NSCLC
- ▶ Patient has 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

### Other Inclusion Criteria:

- ▶ Aged  $\geq$  18 years of age
- ▶ ECOG performance status of  $\leq$  2
- ▶ All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue have resolved to Grade 1 or baseline
- ▶ The patient must have signed consent

### Exclusion Criteria:

- ▶ Known, active or suspected autoimmune disease, HIV, Hepatitis B or C
- ▶ Symptomatic brain metastases
- ▶ Other active, concurrent, malignant disease, with the exception of adequately treated basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix
- ▶ Receiving other concurrent systemic anti-cancer treatments for NSCLC
- ▶ Life expectancy of less than 6 weeks
- ▶ The patient has previously participated in, or is eligible for an accessible, nivolumab clinical study
- ▶ The patient has received prior therapy with an anti-PD-1, anti-PD-L1 or anti-PD-L2, anti CT137 or any other antibody and other T-cell co-stimulation or checkpoint pathways
- ▶ The patient has 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 has any known active chronic liver disease
- ▶ The patient has a known medical condition (e.g. a condition associated with diarrhea or acute diverticulitis)
- ▶ The patient has not recovered from major surgery
- ▶ The patient has a history of severe hypersensitivity reactions to other monoclonal antibodies

## Study Design

- ▶ Single centre, retrospective study to evaluate the pulmonary infiltrations associated with nivolumab in patients with NSCLC.
- ▶ Each patient signed informed consent and institutional ethics approval was obtained from the Human Sciences Research Council (HSRC) of South Africa.

## Data Collection

- ▶ Data from different points in time throughout a patient's medical history were reviewed.
- ▶ The data included four aspects of treatment history: demographic features, disease characteristics, initial treatment at the time of enrollment in the SA-EAP, and courses of treatment.
- ▶ Treatment-related information included history of concomitant drug use, details of nivolumab treatment (date of first nivolumab doses, number of infusions, and reason for discontinuation or omission).
- ▶ Adverse events reported by patients were routinely documented and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

## Statistical Analysis

- ▶ The analyses of data collected in this study will be mainly descriptive. All collected data and endpoint variables were summarised using descriptive statistics.

## Results

- ▶ A total of 18 patients (10 males, 8 females) were analyzed.
- ▶ The median age was 66 years (range 46-85).
- ▶ Adenocarcinoma was documented in 15 patients and squamous cell carcinoma in 3 patients.
- ▶ All patients failed frontline treatment as per requirement of EAP: 14 patients failed platinum based chemotherapy and 4 patients failed TKI therapy (3 on erlotinib and 1 on crizotinib).
- ▶ Patients received a median of 4 cycles of nivolumab (range 1-16 cycles).
- ▶ The median PS was 1 (range 0-2).

- ▶ The median number of metastatic sites was 3 (range 1-5).
- ▶ Documented toxicities included pneumonitis in 2 patients (responded to corticosteroids) bacterial chest infection in 3 patients and opportunistic infection in 1 patient (documented pulmonary TB).
- ▶ Other pulmonary infiltrates were mainly due to disease progression, lymphangitis carcinomatosa and pleural effusions.

## Conclusions

- ▶ Pneumonitis and other pulmonary infiltrates are complications associated with nivolumab treatment.
- ▶ A variety of infectious and non-infectious aetiologies can lead to pulmonary infiltrates in these patients.
- ▶ A differential diagnosis includes: Pneumonitis as an IrAE, disease progression including lymphangitis, carcinomatosa, metastatic disease and pleural effusions. Normal infections and opportunistic infections such as viral, parasitic, pneumocystis, fungal and tuberculosis. Pseudo-progression is also a consideration.
- ▶ Diagnostic evaluation of pulmonary infiltrates may require additional non-invasive investigations such as high resolution CT and serological studies. In other patients, where diagnosis is not clear, definitive investigations such as bronchoscopy and bronchoalveolar lavage or even surgical lung biopsy may be required.

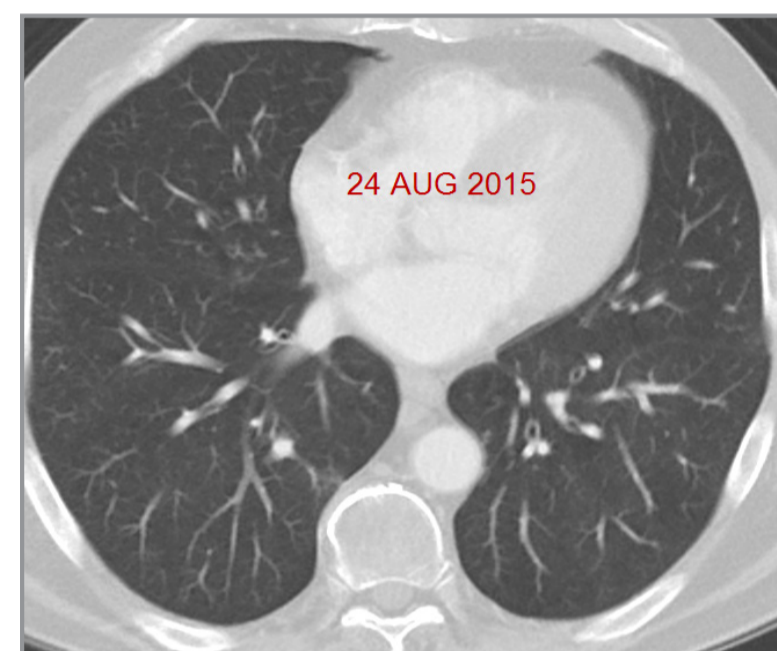


Figure 1. Pneumonitis in a patient treated with Nivolumab.

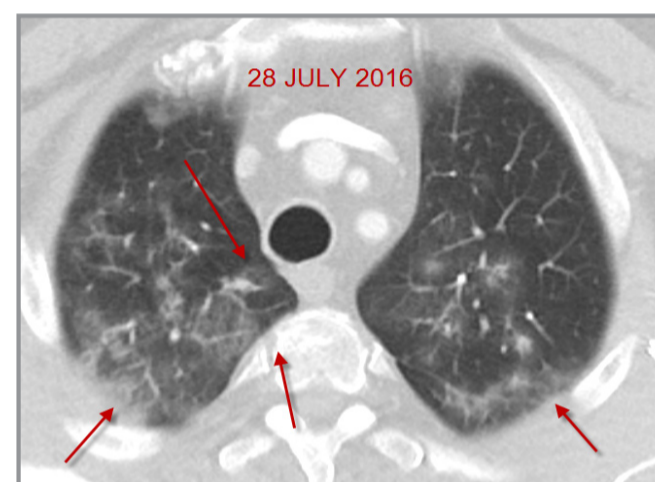


Figure 2. Pneumonitis in a patient treated with Nivolumab.



Figure 3. Pneumonitis in a patient treated with Nivolumab.

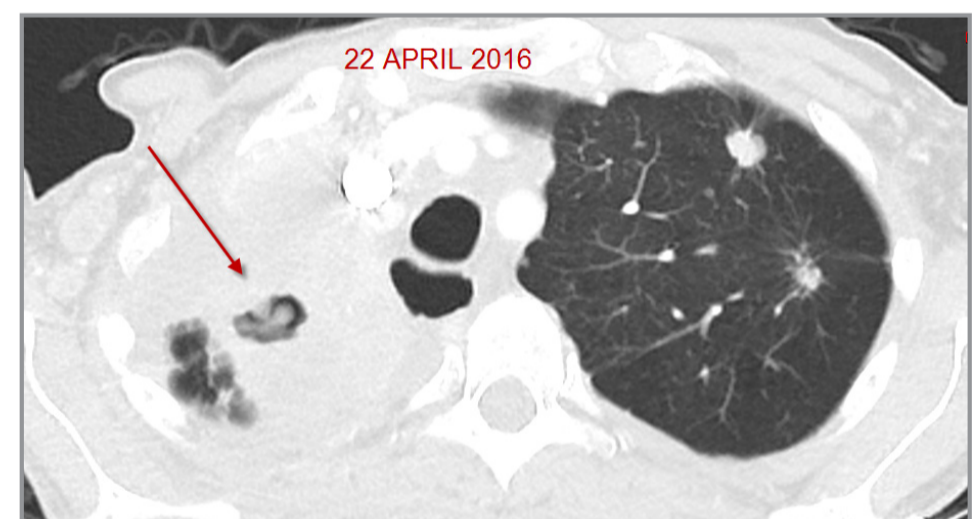


Figure 4. TB During Nivolumab Therapy.

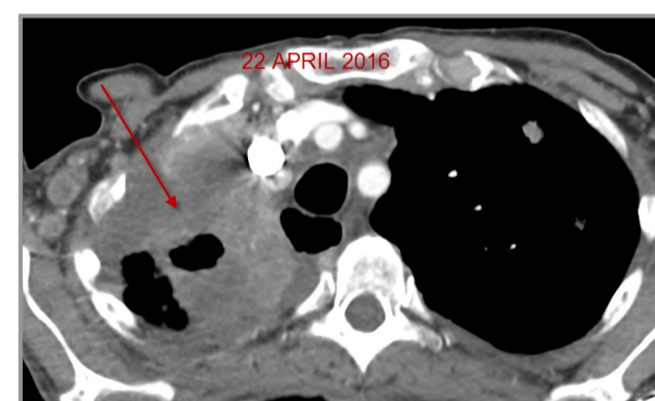


Figure 5. TB During Nivolumab Therapy.



Figure 6. TB During Nivolumab Therapy.

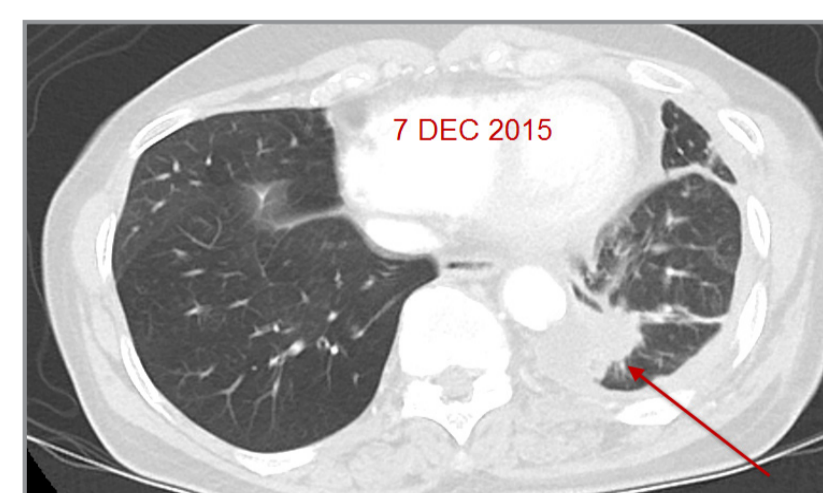


Figure 7. Disease Progression During Nivolumab Therapy.

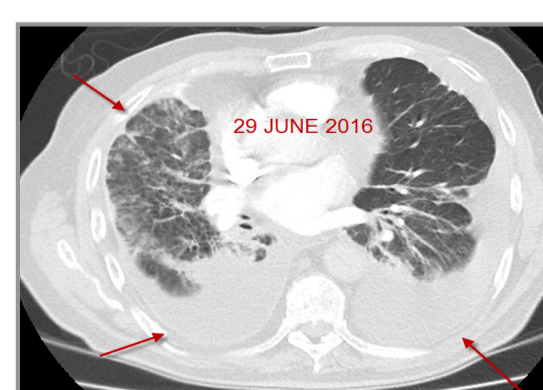


Figure 8. Disease Progression During Nivolumab Therapy.

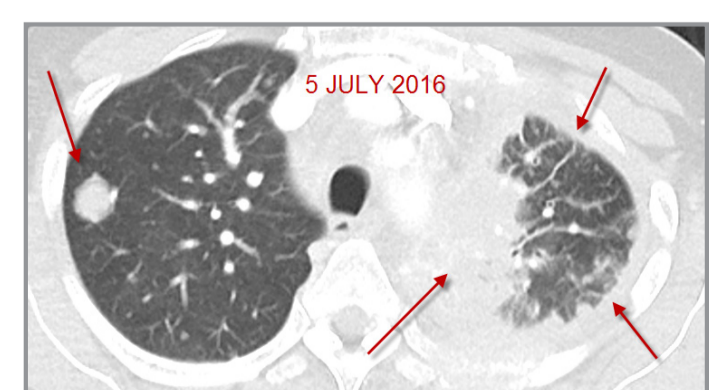


Figure 9. Disease Progression During Nivolumab Therapy.