# Experience of Immune-Related Adverse Events Associated with Ipilimumab and Nivolumab in a Single Center

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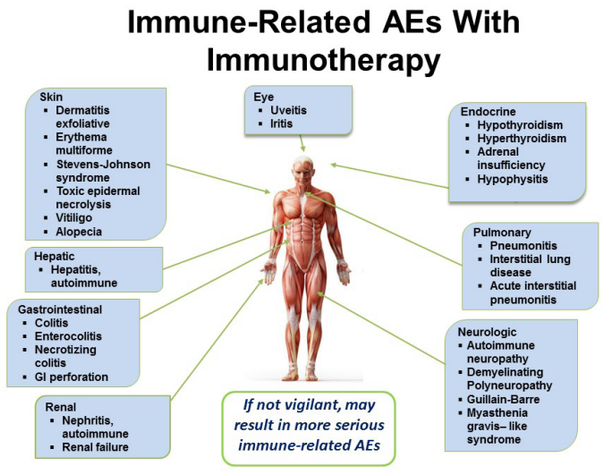
# Background

## Immune-related adverse events

- Immune checkpoint inhibitors have been approved for use in a many different cancers including metastatic melanoma, advanced non-small cell lung cancer, metastatic renal cell carcinoma, refractory Hodgkin's lymphoma, metastatic bladder cancer, advanced head and neck cancer and the list keeps growing each day.
- Screening for latent TB infection (LTBI) and treatment of patients with active disease has reduced reactivation rates. However, the risk of TB infection still remain high. The use of biologic therapy in patients with a lower risk of TB is a high priority.
- There is almost no prospective data on these toxicities and guidelines or recommendations are mostly based on symptomatic management from ongoing clinical trials.
- This study describes the clinical experience associated with ipilimumab, nivolumab and pembrolisumab in a single center in Johannesburg, South Africa.
- A retrospective, single center, non-interventional analysis was performed on data collected from the ipilimumab, nivolumab and pembrolisumab expanded access programme in South Africa (SA-EAP) , as well as post-registration treatment for these drugs.
- The restropective study investigated toxicity and Immune-related adverse events (IrAE) associated with ipilimumab, nivolumab and pembrolisumab in patients with relapsed metastatic NSCLC, relapsed melanoma, relapsed Hodgkin's disease (HD) and relapsed renal cell carcinoma (RCC).

Figure 1. Immune-related AEs with immunotherapy.




# Methods

## Inclusion Criteria

### NIVOLUMAB

### NSCLC

- 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.

### MALIGNANT MELANOMA

- The patient has previously treated unresectable stage III or stage IV melanoma and has progressed on or after treatment with an anti-CTLA-4 containing therapy.
- The patient has stable CNS metastases.
- In addition, patients must either be weaned off corticosteroids or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent).

### RCC

- The patient has histologically confirmed advanced or metastatic RCC with a clear cell component.
- The patient has progressed on treatment or after treatment with a minimum of 1 prior line of therapy, including but not limited to sunitinib, pazopanib, axitinib, tivozanib, bevacizumab, mTOR inhibitors, in the advanced or metastatic setting.
- Prior cytokine therapy (e.g. IL-2, IFN-α), vaccine therapy or treatment of cytotoxics is allowed.

### HD

- The patient is ineligible for or has received prior high-dose conditioning chemotherapy followed by ASCT, and must have received brentuximab vedotin* as a part of salvage therapy for cHL.
- The patient meets one of the following criteria according to the 2007 IWG criteria:
  - Documented absence of CR after 90 days from stem cell infusion for the most recent ASCT
  - Documented failure to achieve at least PR

### IPILIMUMAB

- Histologically confirmed stage III (unresectable) or stage IV (metastatic) cutaneous, ocular or mucosal melanoma and patients with brain metastases should be asymptomatic.
- Failure or intolerance to at least 1 prior systemic treatment; aged ≥ 18 years of age.
- ECOG performance status of ≤ 2.

## Other Inclusion Criteria

- 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.
- The patient had to sign informed consent.

## Exclusion Criteria

- Known, active or suspected autoimmune disease, HIV, Hepatitis B or C.
- Symptomatic brain metastases.
- Received other concurrent systemic anti-cancer treatments for melanoma.
- 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.
- Received other concurrent systemic anti-cancer treatments for NSCLC.
- Life expectancy of less than 6 weeks.
- The patient had previously participated in a nivolumab clinical study.
- The patient had received prior therapy with an anti-PD-1 or an anti-PD-L1 antibody.
- 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 not recovered from major surgery.
- The patient had a history of severe hypersensitivity reactions to other monoclonal antibodies.
- 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 not recovered from major surgery.
- The patient had a history of severe hypersensitivity reactions to other monoclonal antibodies.

### POST-REGISTRATION TREATMENT

- Patients on post-registration treatment were included in this analysis.
- Patient with a good performance status, and adequate haematology, liver and renal function were included.
- Ipilimumab – 4 patients, pembrolisumab – 4 patients, nivolumab – no post registration treatment.

# 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 start of treatment and during courses of treatment.
- Treatment-related information included history of concomitant drug use, details of ipilimumab, nivolumab and pembrolisumab treatment (date of first treatment 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 are mainly descriptive. All collected data and endpoint variables were summarised using descriptive statistics in addition to statistical modelling.

# Results

- A total of 53 patients (36 male and 17 female) were analyzed.
- The median age was 60 (30-86 years)
- The median PS was 1.

## Nivolumab Group

- Metastatic melanoma 4 patients
- NSCLC: 19 patients
- RCC: 2 patients
- HD: 2 patients
- Nivolumab 266 cycles (median = 4, range 1-52)

## Ipilimumab Group

- Metastatic melanoma 22 patients
- Ipilimumab 88 cycles (median = 4 cycles, range 1 - 4)

## Pembrolizumab Group

- NSCLC: 1 patient
- Metastatic Melanoma: 4 patients
- Pembrolisumab 33 cycles (median 9, range 2-10)

Table 1. Immune-related Adverse Events.

| IrAE's | | |
|---|---|---|
| **NIVOLUMAB** | **IPILIMUMAB** | **PEMBROLIZUMAB** |
| **Thirty-six IrAEs were documented out of 27 patients.** | **Eight IrAEs were documented out of 22 patients.** | **No IrAE reported at the time of this analysis.** |
| Pneumonitis 2 patients. | Endocrinopathy 3 patients (hypophysitis in 1 patient and hypothyroidism in 2 patients). | |
| Skin rash 6 patients. | Colitis Grade 3 or 4 reported in 3 patients (1 required infliximab). | |
| Diarrhea 4 patients. | Hepatitis 2 patients. | |
| Uveitis 1 patient. | | |
| Autoimmune thrombocytopenia, nephritis 1 patient. | | |
| Chest infection 3 patients (including pulmonary tuberculosis in a NSCLC patient). | | |
| PRES (posterior reversible encephalopathy syndrome) 1 patient | | |
| Pleuritis 1 patient | | |
| Increased TSH 1 patient | | |
| Muscle pain 1 patient | | |
| Vitiligo 1 patient | | |
| Pruritis 1 patient | | |
| Eczema 1 patient | | |
| Dry eyes 1 patient | | |
| Fatigue 7 patients | | |
| Headaches 1 patient | | |
| Encephalopathy - 1 patient | | |
| Athralgia - 1 patient | | |

**No IrAE related deaths were documented.**

Figure 2. CT SCAN Pre-treatment.

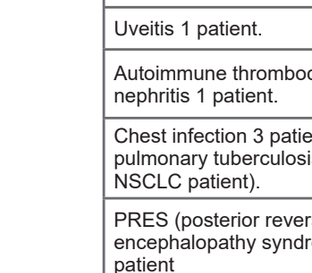



Figure 3. CT shown pneumonitis during nivolumab treatment.

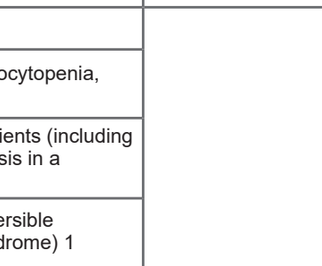



Figure 4. CT shown pneumonitis during nivolumab treatment.




Figure 5. Post-treatment with corticosteroids and pneumonitis resolution.




Figure 6. Complication of treatment: TB during nivolumab therapy.

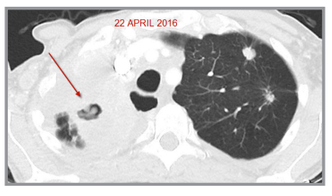



Figure 7. Skin rash.

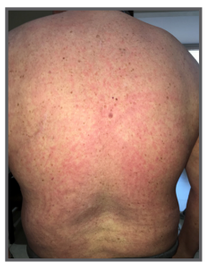


Figure 8. Skin rash.

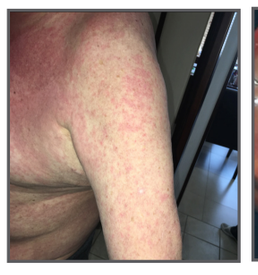


Figure 9. Severe Colitis.

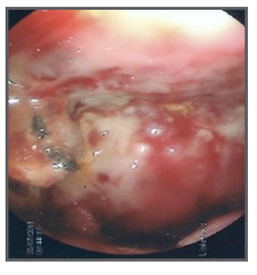
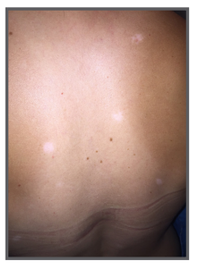


Figure 10. Vitiligo.



# Conclusions

- An association between the response and IrAE was documented among the Ipilimumab patients, while no clear association was documented among the pembrolisumab and nivolumab patients in terms of toxicity and response to treatment.