Extended Survival Analysis of Ipilimumab for the treatment of advanced malignant melanoma in pre-treated patients. Five-year long-term follow-up of the South African Expanded Access Program.

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Background

Melanoma

- In South Africa, melanoma is the eighth most common documented cancer in men, with a lifetime risk of one in every 213 men; in women, melanoma is the ninth most common cancer, with a lifetime risk of one in every 341 women.
- According to the South African National Cancer Registry (2011), whites are at higher risk; melanoma is the fourth most common cancer among white men and remains the sixth most common cancer in white women.[1]
- Survival for stage IV disease, in particular, remains poor, with median survival times across studies ranging from 6 to approximately 12 months.[2,3]
- Prior to the availability of checkpoint inhibitors, the treatment of metastatic melanoma represented a considerable unmet medical need.
- Ipilimumab is a human monoclonal IgG1 antibody against CTLA-4 that has been shown to prolong the overall survival of patients with advanced pre-treated melanoma.[4]
- Due to the limited data reported on the use of ipilimumab in metastatic malignant melanoma in developing countries, the current retrospective study was undertaken to evaluate the long-term outcomes of ipilimumab, administered within the SA-EAP in pre-treated advanced melanoma patients.

Methods

- In 2015, a retrospective, multi-center, non-interventional analysis was performed on data collected from the ipilimumab expanded access programme in South Africa (SA-EAP), with last follow-up date (or death) in December 2014.
- The current study extends this analysis by follow-up on the long-term survival of pre-treated metastatic patients up to September 2016.
- 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:

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

Exclusion Criteria:

- Known 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.

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 with immune-therapy.
- Disease related factors included melanoma subtype and stage, presence of brain or liver metastases, lactate dehydrogenase values, BRAF mutational status and ECOG performance status.
- Treatment related information included history of concomitant drug use, ipilimumab data (date of first dose, number of infusions, reason for discontinuation or omission), date of first measured disease progression (PD) and survival dates.
- A follow-up questionnaire was sent to participating investigators who had to confirm whether patients were still alive, the date of death or last contact, clinical response at last contact, and whether the patient was still responding to ipilimumab.

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. Overall survival (OS) was estimated using the Kaplan-Meier method, with 95% CIs reported. A Cox proportional hazards model was used to identify covariates independently associated with survival. OS was analyzed using time from ipilimumab initiation date and date of most recent visit or death, whichever occurred first. follow-up questionnaire was sent to participating investigators who had to confirm whether patients were still alive, the date of death or last contact, clinical response at last contact, and whether the patient was still responding to ipilimumab.

Results

- There were 108 patients, 84 (78%) had cutaneous melanoma and 24 patients (22%) had non-cutaneous melanoma, including uveal, mucosal, and melanoma of unknown primary. Twenty patients previously received two or more lines of treatment for metastatic melanoma. The median age was 59 years (range 27 – 86) and there were 73 (68%) males and 35 (32%) females. Baseline ECOG PS was 0 in 33%, PS 1 in 58% and PS 2 in 6% of patients. The longest follow-up time available was 5.4 years.
- The median OS was 9.36 months (95% CI 7.48 – 11.84). One-year survival was 39% (95% CI 29% - 48%), 2-year survival was 22% (95% CI 15% - 30%), 3-year survival was 19% (95% CI 12% - 27%), 4- and 5-year survival was 15% (95% CI 8% - 21%).

		Lower bound	Upper bound
1 Year	39%	29%	48%
2 Years	22%	15%	30%
3 Years	19%	12%	27%
4 Years	15%	8%	21%
5 Years	15%	8%	21%

Table 1. Overall Survival at year 1, 2, 3, 4 and 5 with corresponding 95% confidence intervals.

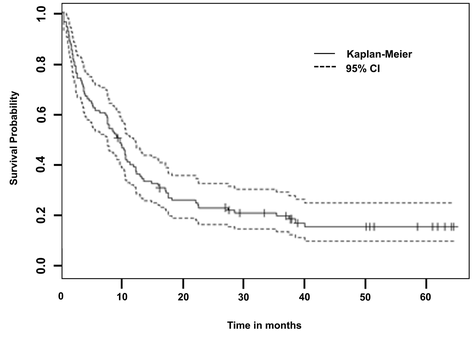

Figure 1. Kaplan Meier of Extended Overall Survival over 60 months.

- In the group of cutaneous melanoma patients, the 4- and 5-year survival was 17% (95% CI 9% - 25%) while in the non-cutaneous group the 4- and 5-year survival was 6% (95% CI 0% - 16%).
- Clinical response at last contact is shown in Table 2.

		Lower bound	Upper bound
Complete Response	16%	8%	25%
Partial Response	7%	1%	14%
Stable Disease	12%	4%	20%
Progressive Disease	64%	53%	76%

Table 2. Percentage responders with 95% CI.

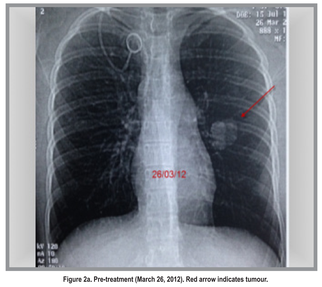

Figure 2a. Pre-treatment (March 26, 2012). Red arrow indicates tumour.

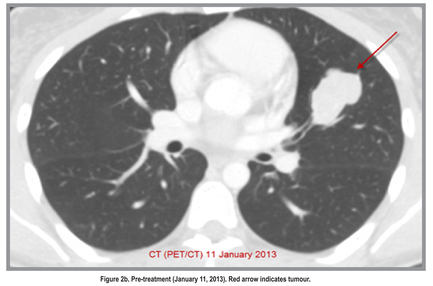

Figure 2b. Pre-treatment (January 11, 2013). Red arrow indicates tumour.

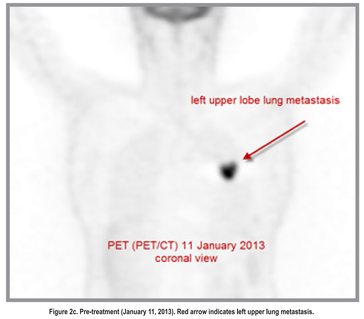

Figure 2c. Pre-treatment (January 11, 2013). Red arrow indicates left upper lung metastasis.

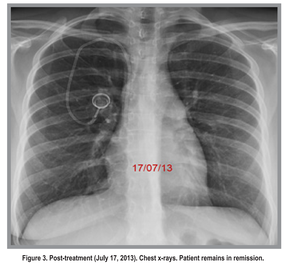

Figure 3. Post-treatment (July 17, 2013). Chest x-rays. Patient remains in remission.

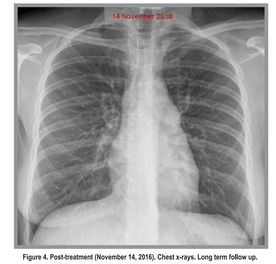

Figure 4. Post-treatment (November 14, 2016). Chest x-rays. Long term follow up.

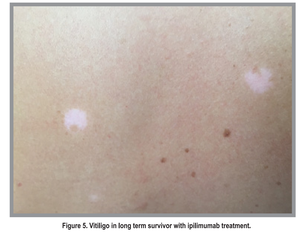

Figure 5. Vitiligo in long term survivor with ipilimumab treatment.

Conclusions

This long-term follow-up analysis demonstrates that ipilimumab is associated with durable remissions and long-term survival.

Our study of ipilimumab in the South African setting found that the efficacy and tolerability of ipilimumab at 3 mg/kg for the treatment of unresectable metastatic melanoma in pre-treated patients align with data reported in several studies published worldwide with similar treatment doses and patient populations.

References

1. The South African National Cancer Registry: Summary statistics of cancer diagnosed histologically in 2005 http://www.nioh.ac.za/assets/files/Cancer%20Tables%202005.pdf.
2. Niezgoda A, Niezgoda P, Czajkowski R: Novel approaches to treatment of advanced melanoma: A review on targeted therapy and immunotherapy. BioMed Res Int 2015:851387, 2015.
3. Serrone L, Zeuli M, Sega FM, et al.: Dacarbazine-based chemotherapy for metastatic melanoma: Thirty-year experience overview. J Exp Clin Cancer Res 19:21-34, 2000
4. Weber J. Review: anti-CTLA-4 antibody ipilimumab: case studies of clinical response and immune-related adverse events. Oncologist. 12(7):864-72, 2007.

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