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**Title:**

Clinical activity and safety of Pembrolizumab in Ipilimumab pre-treated patients with uveal melanoma.

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**List of abbreviations and acronyms:**

AE Adverse Event

ALT Alanine aminotransferase

AST Aspartate aminotransferase

CM Cutaneous Melanoma

CTCAE Common Terminology Criteria for Adverse Events

EAP Expanded Access Programme

ECOG Eastern Cooperative Oncology Group

irAE immune-related AE

irRC immune-related Response Criteria

LDH Lactate Dehydrogenase

OS Overall Survival

PD Progressive disease

PFS Progression Free Survival

PS Performance Status

RFA Radiofrequency ablation

SIRT Selective internal radiation therapy

TACE Transcatheter arterial chemoembolization

TIL Tumour infiltrating lymphocytes

ULN Upper Limit of Normal

UM Uveal Melanoma

**Abstract**

**Background:**

Untreated metastatic uveal melanoma (“UM”) carries a grave prognosis. Unlike cutaneous melanoma (“CM”) there are no established treatments known to significantly improve outcomes for a meaningful proportion of patients. Inhibition of the PD1-PDL1 axis has shown promise in the management of cutaneous melanoma and we here report a two centre experience of UM patients receiving pembrolizumab.

**Methods:**

To assess the efficacy and safety of pembrolizumab we retrospectively analysed outcome data of 25 consecutive UM patients participating in the MK3475 expanded access programme who received pembrolizumab at 2mg/kg 3 weekly. Tumour assessment was evaluated using RECIST 1.1 and immune-related Response Criteria (“irRC”) by CT scanning. Toxicity was recorded utilising Common Terminology Criteria for Adverse Events (“CTCAE”) v4.03.

**Results:**

25 patients were identified receiving a median of 6 cycles of treatment. Two patients achieved a partial response and 6 patients stable disease. After a median follow-up of 225 days median progression free survival was 91 days and overall survival was not reached. There was a significant trend for improved outcomes in patients with extrahepatic disease progression as opposed to liver only progression at the outset. 5 patients experienced grade 3 or 4 adverse events; there were no treatment related deaths.

**Conclusions:**

Pembrolizumab 2mg/kg q3w is a safe option in UM patients. Disease control rates, particularly in the subgroup of patients without progressive liver disease at the outset are promising; these results merit further investigation in clinical trials possibly incorporating liver targeted treatment modalities.

**Introduction**

Uveal Melanoma(“UM”) is the most common malignancy of the eye; it is significantly rarer and carries a genetic profile that is markedly discordant from cutaneous melanoma(“CM”). 1 UMs typically demonstrate a relatively lower degree of aneuploidy and genomic instability compared with other cancer types 2–4 and a mutational load significantly lower than CM. 5,6

Even in the pre-immunotherapy and targeted therapy era, outcomes of metastatic UM were worse than metastatic CM with median survival in unselected series as low as 4 months. 7 This possibly relates to the predilection of UM for hepatic metastases - seen in >85% of cases with liver the sole site of metastatic disease in around 50% 7, compared to 25% in CM. 8

Cytotoxic chemotherapy offers little benefit in UM and is no more effective than in CM when site and extent of disease is considered. 9 The absence of activating BRAF mutations in the majority of UM patients limits the use of BRAF inhibitors. Alternative targeted approaches are sought, e.g. the MEK inhibitor selumetinib 10, however at the time of writing none have demonstrated significant activity in large Phase III trials.

Immunotherapy has revolutionised the treatment of metastatic CM; immune checkpoint inhibition with ipilimumab 11 – an anti-CTLA4 antibody - and anti-PD1 agents alone 12 or in combination 13,14 results in durable disease control in a significant proportion of patients. UM patients were excluded from taking part in Phase III trials, so evidence of efficacy in this setting is limited.

Small studies and retrospective analyses 15–17 have shown that partial and even complete responses to ipilimumab in UM are possible, but rare. Median overall survival (“OS”) of 5.2-9.6 months , 1 year OS rates of 22-34%, and 1 year progression free survival (“PFS”) rates of <11% were comparable to standard chemotherapy 10 but lower than in unselected CM cohorts.

One explanation why immunotherapeutics might be less effective in UM compared to CM could be different driving mutations. 1,5,18 Furthermore, the overall mutational load is significantly lower 5 compared to CM 3 and expression of cancer-testis antigens is significantly rarer. 19 Consequently the number and quality of (neo-)antigens presented to the immune system is likely to be different. Additionally UM may rely on different immune escape mechanisms most clearly evidenced by the observation that higher numbers of infiltrating T-cells in the primary are linked to a worse outcome. 20

Very little information exists in the public domain regarding the efficacy of anti-PD1 agents in UM; the largest case series reported consists of data from 7 patients who received pembrolizumab. 21 We herein report a two centre experience of 25 patients who have received pembrolizumab in in the UK Expanded Access Programme (“EAP”).

**Patients and treatments**

**Patient Eligibility**

Patients treated in the pembrolizumab EAP in our institutions with a diagnosis of metastatic UM were included in this retrospective study. All subjects had received previous ipilimumab and a BRAF inhibitor if eligible. Resolution of adverse events (“AEs”) due to previous cancer therapy to grade 0 or 1 was required. Additional previous immunotherapies were allowed as long as no severe or life threatening immune-related AEs (“irAEs”) were experienced and there was no ongoing requirement for systemic steroids for the management of irAEs.

Eastern Cooperative Oncology Group performance status (“PS”) 0/1 was mandated as well as a minimum age of 12. Inclusion criteria included AST and ALT ≤2.5 X upper limit of normal (“ULN”) or ≤5 X ULN with liver metastases, serum total bilirubin ≤1.5 X ULN or direct bilirubin ≤ULN for patients with total bilirubin level >1.5 ULN. Patients with a history of clinically severe autoimmune diseases, pneumonitis, organ transplant, HIV or active Hepatitis B or C infections and active central nervous system metastases were also excluded. Concomitant systemic antineoplastic therapies were not allowed.

**Treatment**

Pembrolizumab was administered at 2 mg/kg in 3-weekly intervals until progression by immune-related Response Criteria 22 (“irRC”), complete response, unacceptable toxicity or for up to 2 years. Frequency of radiological tumour assessment was as per standard of care, typically with body CT scans every 2-3 months and liver MRIs to optimally monitor liver disease. Blood samples were taken before each infusion to allow assessment of renal, liver, thyroid and bone marrow function for safety and toxicity monitoring. Adverse events were scored using Common Terminology Criteria for Adverse Events version 4.03.

**Response Evaluation**

Tumour response was evaluated using the following radiological scoring systems: RECIST 1.1 23 and irRC. 22 Best overall response was determined based on irRC criteria where possible to capture delayed anti-tumour responses.

**Data capture and analysis**

Patients receiving pembrolizumab were identified from the oncology pharmacy database. Data was collected retrospectively from patients’ notes and electronic records and stored into a Microsoft Access database; statistical analysis and graphing was done using GraphPad Prism Version 6.01. Survival curves were calculated using the Kaplan–Meier method. The log-rank test was used to compare curves and determine the P value.

**Results**

**Patient characteristics**

Twenty-five patients with metastatic uveal melanoma were enrolled into the pembrolizumab EAP between the 1/06/2014 and 1/8/2015 at our centres. All patients had systemic disease spread at baseline and had received a median of 1previous lines of systemic treatment; 11 patients (44%) had also received a median of 2 liver directed therapies. All patients had previously completed a course of ipilimumab, none had experienced an objective response though nine patients (36%) had a period of stable disease; baseline patient characteristics are presented in Table 1. All 7 patients with available cytogenetic results had chromosome 3 losses and chromosome 8 gains in the primary tumours.

**Response Analysis**

All patients received at least 1 cycle of pembrolizumab. At data collection cut-off time a median of 6 cycles of pembrolizumab had been administered per patient and 2 patients were continuing on treatment. Radiological assessments took place as clinically indicated, typically every 3-4 cycles (9-12 weeks). Figure 1 shows a flow diagram outlining treatment course and outcomes.

Four subjects deteriorated rapidly due to disease progression and were withdrawn before the first radiological assessment after receiving only one cycle. Eight patients were withdrawn after having only a single radiological assessment demonstrating disease progression due to rapid clinical deterioration. One patient continuing after an initial scan revealing PD exhibited subsequent disease stabilisation and remains on treatment. There were 2 partial responses, one early that was not maintained and one late that remains on treatment. Table 2 summarises response types and duration.

**Survival analysis**

After a median follow-up of 225 days at the time of data cut-off median OS was not reached but will be >225 days with a 1 year survival rate of >28%; median PFS was 91 days (Table 2). Eight evaluable patients (32%) achieved disease control (partial response or stable disease) for more than 3 months and median PFS for this subgroup is projected to be > 9.8 months with a median OS > 13.5 months. A Kaplan-Meier plot of OS and PFS of all patients is presented in Figure 2A, including censored data for patients who are still responding to treatment.

Patients with liver only disease progression at baseline imaging had significantly worse PFS (Figure 2C) and on immature data there was a trend for worse OS (Figure 2D). This group had also shorter lead in times from diagnosis of stage IV disease (Figure 3A), as did patients who had no previous liver directed treatments (Figure 3B) but in the latter case there was no significant difference in PFS (Figure 2E).

In contrast, PFS and OS was significantly worse in patients who had more than 1 previous systemic treatment as compared to only 1 despite similar lead in times (Figures 2F and 3C). Previous disease stabilisation in response to ipilimumab did not appear to predict response to pembrolizumab (Figure 2B).

In addition both serum lactate dehydrogenase (“LDH”) and PS at baseline were associated with a worse PFS and OS (Figures 2G-H); notably all patients with normal LDH at baseline are still alive as opposed to only one with raised LDH.

**Safety Analysis**

Pembrolizumab was tolerated well overall with a frequency and type of adverse events (“AEs”) commensurate with those reported in larger studies12. Five patients (20%) experienced at least one grade 3/4 treatment related AE (Table 3): one patient experienced grade 4 transaminitis after the first dose and one grade 3 skin rash and pruritus after the second dose; both had to discontinue treatment; 2 patients experienced grade 3 hypophysitis requiring long term steroid replacement, one of these also had an episode of grade 3 diarrhoea that settled spontaneously. Finally one patient experienced grade 3 fatigue and elected to discontinue treatment.

**Discussion**

Anti-PD-1 agents are now approved for use in US and European markets for the treatment of metastatic CM pre and post ipilimumab. As entry criteria of the registration trials excluded UM, data on efficacy of anti-PD-1 based immunotherapy in UM is limited.

In our patients objective response rates were lower than in CM studies 12, however PFS rates were comparable and a significant number (>32%) of patients experienced prolonged (>3 months) periods of disease stabilisation with 28% maintaining disease control for >6 months.

High LDH and poorer PS at baseline - known markers of disease burden and/or aggressiveness - predicted a shorter duration of benefit. While not surprising this provides additional prognostic information. AEs seen were in line with safety analyses from larger studies 12 and confirm that pembrolizumab is well tolerated in this patient population.

The most dramatic observation relates to the role of uncontrolled intrahepatic metastases. Patients with liver deposits as the only site of progression had significantly shorter PFS as compared to subjects with extrahepatic sites (median of 63 vs 153 days, Figure 2C); additionally, the former uniformly went on to develop disease progression in the liver alone.

The reasons behind this behaviour are unclear and likely multifactorial. The liver microenvironment is known to facilitate immune escape 24 and the specific mechanisms involved may account both for the predilection of UM for liver metastases and the reduced efficacy of immunotherapeutic agents in patients with liver disease. A related and not mutually exclusive possibility is that extrahepatic sites of disease allow better priming of an anticancer immune response which can then control intrahepatic disease. Finally, the pattern of metastatic spread may reflect underlying biological differences – e.g. mutational load, underlying immune escape mechanisms - that influence the ability of checkpoint inhibitors such as pembrolizumab to drive an effective immune response.

While this is a small study, it has significant implications for the management of UM if the findings are confirmed. Firstly, while pembrolizumab may not reproduce the impressive response rates seen in CM, it nevertheless appears to achieve disease control of clinically meaningful duration for a significant proportion of patients, justifying its use in the single agent setting, particularly in the absence of alternative effective systemic treatment options.

Secondly, active liver metastases in the absence of extrahepatic disease appear to have major prognostic significance as in those circumstances pembrolizumab appears to be ineffective. This finding – if confirmed - advocates against pembrolizumab single agent use in this setting.

Finally, a multimodality approach could target intrahepatic immune escape , utilising liver directed treatments both prior to commencing pembrolizumab and/or during treatment in response to liver only progression. There is a growing body of evidence 25 suggesting that liver directed treatments such as metastasectomy, hepatic arterial embolization, and percutaneous hepatic chemoperfusion can result in clinically meaningful periods of disease control; some approaches may additionally stimulate or boost adaptive immune responses through immunogenic cell death and dysregulation of local immune escape mechanisms. 26,27

**Conclusion**

Pembrolizumab as a single agent can be used in the management of metastatic UM with an acceptable toxicity profile and provides clinically meaningful benefit in a significant proportion of patients. Prospective clinical trials are needed to characterise the magnitude of benefit and whether specific groups would be best served by alternative or combination treatments and determine the optimal modalities and sequencing. Further research on underlying immune escape mechanisms is needed to drive the rational design of future studies for this rare malignancy.

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**Disclosure**

CO has had consulting/advisory roles and has received funding for travel and speaker's honoraria with Merck Sharp & Dohme. All remaining authors have declared no conflicts of interest.

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**Figure Legends:**

**Figure 1:** Disease status of UM patients participating in the Pembrolizumab EAP. Treatment was administered at 3 weekly intervals with tumour assessments performed at baseline and every 3 cycles of treatment or as clinically indicated.

**Figure 2:** Kaplan-Meier plots of overall and progression free survival of UM patients treated with pembrolizumab at 2mg/kg as part of the expanded access programme. (A) Curves for entire group, median OS not reached. (B-H) Curves stratified by best previous response to ipilimumab (B), site of disease progression at baseline (C-D), number of liver directed treatments received prior to enrolling to the EAP (E), number of previous systemic treatments (F), serum LDH (G) and ECOG PS (H).

**Figure 3:** Plots demonstrating lead- in times from diagnosis of UM recurrence to commencing pembrolizumab stratified by (A) location of disease progression at time of commencing pembrolizumab, (B) number of liver directed treatments received prior to enrolling to the EAP and (C) number of previous systemic treatments.

**Tables**

**Table 1.** Baseline patient characteristics

|  |  |  |
| --- | --- | --- |
| a. Demographic Characteristics |  |  |
| Number of patients | N= | (%) |
| Patient gender | **Male** | 13 | 52% |
| **Female** | 12 | 48% |
| Eastern Co-operative Oncology Group performance status | **0** | 12 | 48% |
| **1** | 12 | 48% |
| **2** | 1 | 4% |
|  | Median | Range |
| Age at 1st pembrolizumab cycle (years) | 58  | 32-83  |
| Time from primary diagnosis (months) | 47  | 9-186  |
| Time from original systemic recurrence (months) | 11.3  | 3.7-65.1  |

|  |  |  |
| --- | --- | --- |
| b. Disease Characteristics |  |  |
|  | No of patients | (%) |
| Site of metastatic disease at baseline | Liver only | 5 | 20% |
| Extrahepatic only | 6 | 24% |
| Liver & Extrahepatic | 17 | 68% |
| Site of radiological disease progression at baseline | Liver only | 11 | 44% |
| Extrahepatic only | 5 | 20% |
| Liver & Extrahepatic | 7 | 28% |
| None | 2 | 8% |
| LDH at baseline | <=ULN | 7 | 28% |
| 1-2\*ULN | 11 | 44% |
| >2\*ULN | 4 | 16% |
| Liver function test (ALT/AST and/or bilirubin) abnormalities at baseline | <=ULN | 16 | 64% |
| Grade 1 | 5 | 20% |
| Grade 2 | 3 | 12% |

|  |  |
| --- | --- |
| c. Previous treatments |  |
|  | No of patients treated (%) |
| Liver directed therapy |  |
|  | **Any** | 11 (44%) |
| **Surgery** | 3 (12%) |
| **Melphalan chemoperfusion** | 8 (32%) |
| **SIRT** | 2 (8%) |
| **TACE** | 3 (12%) |
| **RFA** | 1 (4%) |
| Systemic treatment other than ipilimumab | 7 (28%) |
|  | **Interferon α2b** | 4 (16%) |
| **Autologous TILs** | 1 (4%) |
| **Temozolamide** | 3 (12%) |
| **Lomustine** | 2 (8%) |
| **Carboplatin based** | 2 (8%) |
| Previous ipilimumab | 25(100%) |
| Best response to ipilimumab | **Progressive disease** | 16(64%) |
| **Stable disease** | 9(36%) |

**Table 2:** Best radiological disease response to pembrolizumab; 9 patients were alive, 1 with an ongoing partial response and 2 with stable disease at the time of writing hence median overall and progression free survival was not reached (“NR”) for several subgroups

|  |  |  |
| --- | --- | --- |
| Table 2: Disease Response |  |  |
| Response | No of patients  | % | Median PFS(days) | Range(Days) | Median OS (days) | Range(days) |
|  | **PR** | 2 | 8% | NR(>325) | 153-498+ | NR(>427) | 498-357 |
|  | **SD** | 6 | 24% | NR(>293.5) | >112-321+ | NR(>405) | 286-483 |
|  |  | **on initial assessment** | 3 | 12% | 252 | >112-321+ | NR(>384) | 286-483 |
|  |  | **after initial PD** | 3 | 12% | 303 | >129-293+ | NR(>427) | 303-431 |
|  | **PD** | 17 | 68% | 63 | 7-146 | NR(>=163) | 7-423 |
| Overall | 25 | 100% | 91 | 9-321+ | NR(>=225) | 7-498 |

**Table 3**: Treatment related adverse events

|  |  |  |  |
| --- | --- | --- | --- |
| Table 3: Treatment related adverse events |  |  |  |
| AE | **Any Grade** | **Grade 3-4** |
|  | No of patients  | **%** | No of patients  | **%** |
| Fatigue | **8** | 32% | 1 | 4% |
| Rash | **6** | 24% | 1 | 4% |
| Pruritus | **5** | 20% | 1 | 4% |
| Diarrhoea | **4** | 16% | 1 | 4% |
| Hypophysitis | **2** | 12% | 2 | 8% |
| Transaminitis | **1** | 4% | 1 | 4% |
| Pancreatic insufficiency | **1** | 4% | 0 |  |
| Muscle weakness | **1** | 4% | 0 |  |
| Oral mucositis | **1** | 4% | 0 |  |
| Low Testosterone | **1** | 4% | 0 |  |
| Sjogren’s | **1** | 6% | 0 |  |