Initial report of intratumoral tavokinogene telseplasmid with pembrolizumab in advanced melanoma: an approach designed to convert PD-1 antibody progressors into responders (NCT03132675)

Victoria Atkinson1, Andrew Haydon2, Philip Parento1, Tom van Hagen2, Gregory A. Danielis2, Pablo Fernandez-Penar2, Mark Motter1, Igor Puzanov2, Sajeve Thomas1, Robert H. Andtbacka3, Clements Kreple2, Rachel Roberts-Thomson2, Alain Algazi1, Sajeve Thomas2, Igor Puzanov2

1Petersen Alexander Hospital, Wollongong, Australia; 2The Alfred Hospital, Melbourne, Australia; 3Eastern Health Monash University, Melbourne, Australia; 4St John of God Hospital, Subiaco, Australia; 5University of California San Diego, San Diego, CA, USA; 6Perkins Hospital, Sydney, Australia; 7University of Miami, Miami, USA; 8Swedish Park Comprehensive Cancer Center, Buffalo, NY, USA; 9Aberdeen Cancer Center in Ontario, Toronto, ON, Canada; 10University of Utah, Salt Lake City, USA; 11Cancer North Adelaide Hospital, North Adelaide, Australia; 12UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; 13Memorial Medical Center, San Diego, CA, USA

INTRODUCTION

- The combination of local intratumoral administration of tavokinogene telseplasmid (interleukin-12 plasmid) followed by electroporation (KEYTRUDA®) with the anti-programmed cell death protein 1 (anti-PD-1) antibody pembrolizumab (KEYTRUDA®) has been granted fast-track designation for evaluation for accelerated approval for patients with PD-1 antibody progression from advanced melanoma.1

OBJECTIVES

- To evaluate peripheral and intratumoral treatment-related immunologic changes in patients with locally advanced or metastatic melanoma
- To determine the ability of KEYTRUDA® to reverse anti-PD-1 resistance in stage IV/MR melanoma whose tumors have unexpectedly progressed after a full course of PD-1 antibody therapy
- To evaluate peripheral and intratumoral treatment-related immunologic changes in responding and non-responding patients

STUDY DESIGN AND INTERVENTIONS

- KEYTRUDA® is an ongoing, global, registration-directed multifactorial Phase 2, open-label study (NCT03132675) of KEYTRUDA® combined with pembrolizumab (PD-1) plasmid electroporation in patients with unresectable, advanced melanoma
- Eligible patients have refractory, locally advanced or metastatic disease defined as unresectable stage III or stage IV melanoma, which had definitively progressed on full course of anti-PD-1 treatment with pembrolizumab or nivolumab. Key eligibility criteria include the definitive nature of anti-PD-1 failure, as included in Figure 1, and patients are treated with 0.5 mg/m2 KEYTRUDA® to the accessible lesions on days 1, 8, and 15 every 28 days, with 300 mg IV pembrolizumab on day 1 of each 28-day cycle for 27 weeks (Figure 1). KEYTRUDA® is injected at a dose volume of ~1/4 of the calculated lesion volume, with a minimum least 1 dimension

RESULTS

- Of the 23 patients enrolled in the study, 12 patients (52%) had PD-L1 expression ≥50% in the tumor microenvironment, and 9 patients (39%) had ≥50% of tumor-infiltrating lymphocytes expressing PD-L1. Following 1 cycle of combined therapy, a significant treatment-related increase in TIL density was observed in responder vs non-responder patients (Table 2, Figure 5).

RESPONSE

- When feasible, at least 1 distal, non-target lesion remains untreated with KEYTRUDA® (Figure 7).

SAFETY

- 10% of patients reported treatment-related serious adverse events, and 54% of patients reported grade 3 or 4 treatment-related adverse events (Table 3). No patients experienced treatment-related grade 5 adverse events (Table 3).

CONCLUSIONS

- KEYTRUDA® and pembrolizumab are well tolerated, with nearly all grade 1-2 adverse events, and 1 grade 3 event
- The registration-directed study demonstrated that patients who definitively progressed on multiple courses of anti-PD-1 treatment with pembrolizumab or nivolumab experienced substantial reductions in both treated and untreated tumors, with a 22.2% BORR (95%) and a 35.3% disease control rate (DCR) of 95%
- The intratumoral treatment-related increase in TIL density, accompanied upregulated immune-based transcripts in the tumor, as well as reduced frequencies of PD-1 expression on the peripheral intratumoral T cells, collectively are evidence of strong systemic immune response following KEYTRUDA®/pembrolizumab combination in patients who definitively failed prior treatment with either pembrolizumab or nivolumab
- Early clinical and immunologic evidence of reversing anti-PD-1 resistance demonstrates the potential of KEYTRUDA® to convert definitive pembrolizumab or nivolumab progressors into responders.

REFERENCES:


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