

INTRODUCTION

Although PD-1 and CTLA-4 blockade have led to broad improvements in prognosis for unresectable stage 3 and stage 4 melanomas most patients continue to suffer from disease progression and over half of patients will still die of their disease. PD-1 resistant melanomas remain challenging to treat and rational treatment strategies are still needed for patients with melanomas that progress despite PD-1 blockade.

Oncolytic viruses are immunomodulating agents with complementary mechanisms of antitumor efficacy to PD-1 blockade in their ability to promote tumor immune surveillance. Pre-clinically, ONCOS-102 (Ad5/3-D24-GM-CSF) and pembrolizumab have been shown to act synergistically in a melanoma model. Clinically, both induction of innate and adaptive immune responses have been seen in various solid tumors.

We show that combining ONCOS-102 with PD-1 blockade is safe and provide preliminary evidence of efficacy in patients whose melanomas progressed despite prior anti-PD-1 therapy.

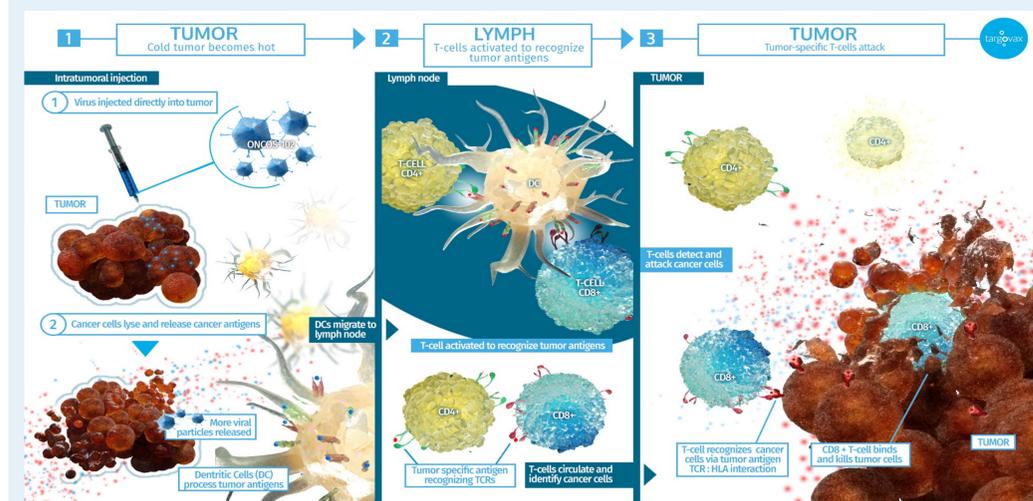
OBJECTIVE

The primary objective of the study is to assess the safety of ONCOS-102 in combination with pembrolizumab either given sequentially (Part 1) or combined (Part 2) for patients with aPD-1 resistant melanoma. Secondary objectives include overall response rate by RECIST 1.1 and the immune activation in tumor mass and peripheral blood, as well as correlation of immune markers and clinical outcome.

MECHANISM OF ACTION

ONCOS-102 is a serotype 5 adenovirus armed with a granulocyte-macrophage colony stimulating factor (GM-CSF) for enhanced immune stimulation with a unique ability to both prime and boost immune responses. ONCOS-102 represents a promising immunotherapy strategy for advanced cancer as it directly recruits antigen presenting cells (APC) to the tumor site leading to induction of adaptive tumor-specific CD8+ T cell response (Fig. 1).

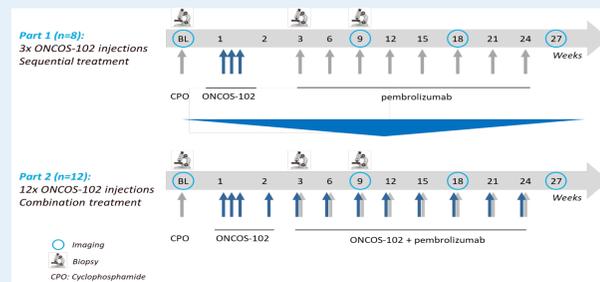
Fig 1: Mechanism of action of ONCOS-102.



METHOD

This is a phase 1 prospective, open-label, multi-center pilot safety study. Patients with advanced or unresectable melanoma who had experienced radiographic progression of disease despite prior PD-1 blockade were eligible as long as they have at least 1 lesion measurable by RECIST 1.1. The study consists of two parts: Part 1 with sequential ONCOS-102 injection (day 1, 4, 8) with cyclophosphamide (CPO) priming followed by Pembrolizumab (up to 8 doses every 3 weeks, n=9) and Part 2, with initial ONCOS-102 injections (day 1, 4, 8, 15) primed with CPO followed by a treatment phase where ONCOS-102 and Pembrolizumab is given in combination (up to 8 times every 3 weeks, n=12, Fig 2). Samples for immune analysis (Biopsy, PBMC, Serum, whole blood and shedding samples) were collected throughout the study. The median time from failed aPD1 and study start was 1.9 months. Part 2 patients had significantly more advanced disease with more lesions and relatively more stage IV to stage III patients.

Fig 2: Treatment schedule.



RESULTS – Clinical efficacy

Twenty patients were evaluable for efficacy. Across the study, 7 of 20 patients (35%) achieved a best objective response (BORR) during the treatment period using both RECIST 1.1 and irRECIST, including 1 patient with a complete response in recurrent in-transit lesion. In Part 1, 3 patients had CR or PR during the study according to RECIST 1.1 and irRECIST resulting in a BORR of 38%. In Part 2, 4 of 12 patients had CR or PR during the study according to RECIST 1.1 and irRECIST resulting in a BORR of 33% (Fig 3). A case example (image) is shown in Fig 4. Reduction in size of non-injected lesions was seen in 12/36 (33%) of targeted measured non-injected lesions with examples of complete disappearance of lesions in two patients. The combination treatment was well tolerated, mostly grade 1/2 with five grade 3/4 events in three patients attributed to pembrolizumab, ONCOS-102 or both.

Fig 3: Relative change (percent) in tumor burden measured by PET/CT from baseline to best response.

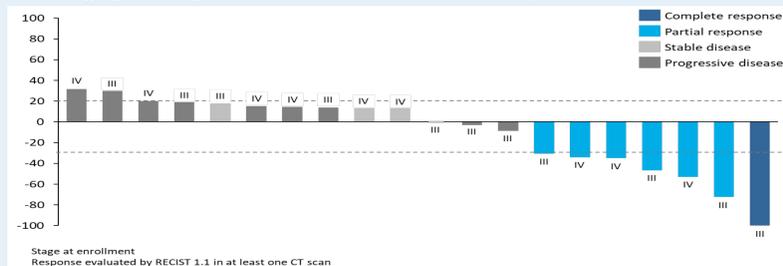


Fig 4: Case example of patient with partial response (week 9-27) refractory to both T-VEC and anti-PD-1.



RESULTS – Immune activation

Analysis of immune cell subsets in biopsies (multiplex immunohistochemistry (mIHC) / multicolour immunofluorescence (mIF) taken at baseline and on Day 22 and/or Day 64 of the same tumours indicated immuno-stimulatory effects of ONCOS-102 in combination with anti-PD1. Several biologically meaningful changes such as increased frequencies of CD8+ or CD4+ T-cells appeared to be more prominent in tumour samples from CR, PR and even SD patients as compared to patients with PD, in spite of the fact the observed differences between the groups of patients did not reach statistical significance (Fig 5). A case example showing mIHC from a patient with complete response (Fig 6).

Fig 5: Immune cell infiltrates: CD8+ and CD4+ T cells (average level by tumor).

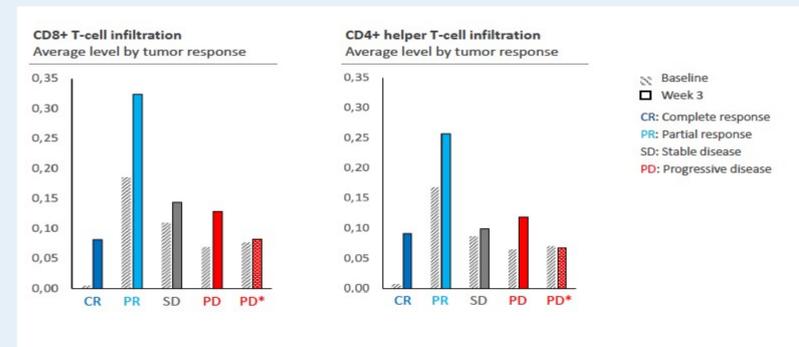
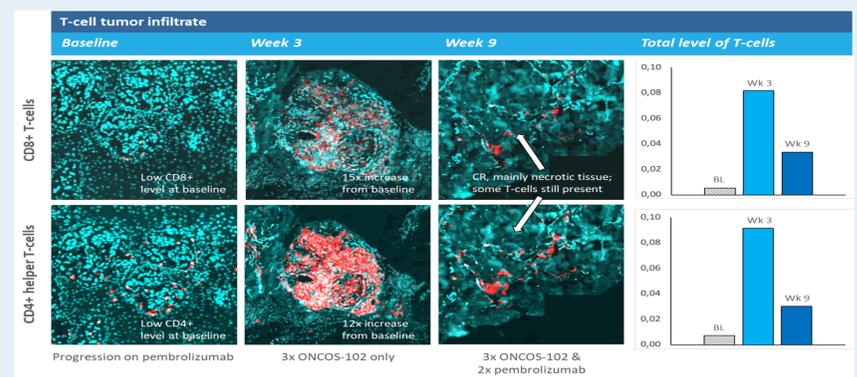


Fig 6: Case example of tumor infiltrating lymphocytes in patient with Complete response



CONCLUSION

We conclude that co-administration of ONCOS-102 and pembrolizumab is safe and feasible for patients with melanomas progressing on PD-1 blockade. Rapid clinical objective responses were seen in patients treated both sequentially and in combination, and immune markers demonstrating induction of beneficial TME changes support the role of ONCOS-102 as a complementary treatment with aPD1 and other IO modalities.

Disclosure

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