A randomised open-label phase I/II study adding ONCOS-102 to pemetrexed/cisplatin in patients with unresectable malignant pleural mesothelioma – 12-month analysis of biomarkers and clinical outcomes

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INTRODUCTION

Malignant pleural mesothelioma (MPM) is a rare, aggressive malignancy without curative treatment. Majority of patients receive pemetrexed/cisplatin as standard of care (SoC). Median overall survival in unresectable disease is 12 months.

The study is an open-label, exploratory phase I/II study adding ONCOS-102 to standard of care (SoC) chemotherapy (pemetrexed/cisplatin) in first and second (and later) line MPM to assess safety, immune activation and clinical efficacy vs SoC (NCT02879669). In total, 31 patients have been treated in the study, with 20 patients in the experimental group receiving the ONCOS-102 and SoC combination, and 11 patients in the control group receiving SoC only. The 31 patients have now completed the 12-month follow-up.

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.

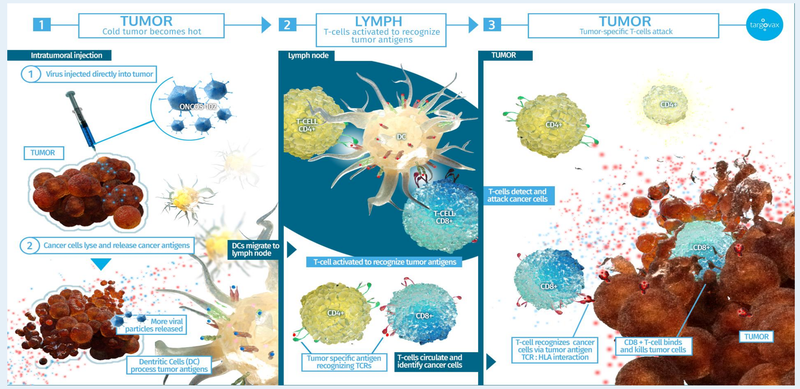
OBJECTIVE

The primary objective of the study is to assess the safety and tolerability of ONCOS-102 in combination with SOC. Secondary objectives include immune activation in tumor mass and peripheral blood, PFS and OS as well as correlation of immune markers and clinical outcome.

MECHANISM OF ACTION

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**).

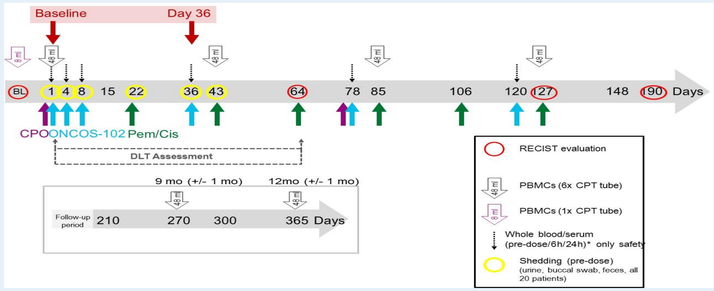
Fig 1: Mechanism of action of ONCOS-102.



METHOD

This is an open-label, parallel group, multicentre study conducted in 2 phases: a non-randomised safety phase and a randomised phase. Eligible patients (experimental group, n=20) received ONCOS-102 given intratumorally under CT or US guidance at a dose of 3 x 10^{11} VP on Day 1, 4, 8, 36, 78 and 120 plus six cycles of SoC starting on Day 22 (**Fig. 2**). The control group (n=11) received six cycles of SoC only, starting at Day 1.

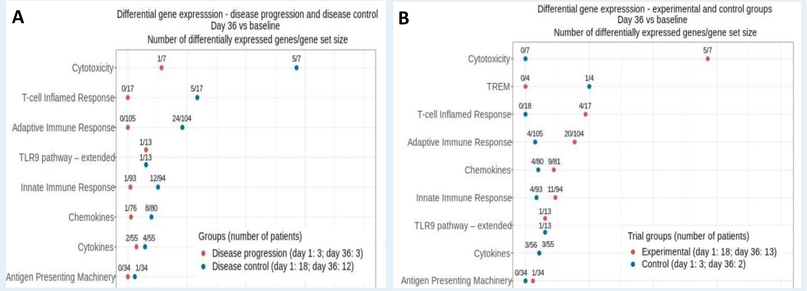
Fig 2: Treatment schedule and sample collection for the experimental group.



RESULTS – Immune activation

The treatment with ONCOS-102 induced strong upregulation of multiple genes associated with immune activation in tumor lesions. Fraction of genes upregulated in experimental vs control group and disease progression vs disease control are shown in **Fig. 3**.

Fig 3: Gene expression data: A Differential gene expression analyses: Disease progression vs disease control. **B** Differential gene expression analyses: Experimental vs control.

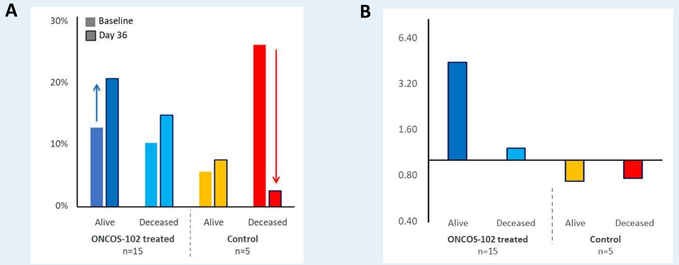


Tumor biopsy immunohistochemistry and gene expression analyses confirm the predicted mode of action of ONCOS-102. Importantly, profound innate and adaptive immune activation was observed in the ONCOS-102 treated patients compared to the control group, and this immune activation was associated with better clinical outcome.

RESULTS – Immune activation

Immune activation was hallmarked by an increase in intra-tumoral cytotoxic T-cells and upregulation of adaptive immunity and cytotoxicity related gene expression along with polarization from M2 to M1 macrophage phenotype and upregulation of PD-L1 expression, indicating that ONCOS-102 is driving a favorable remodeling of the tumor microenvironment. This powerfully demonstrates the immune activation potential of ONCOS-102 far beyond what is achieved by chemotherapy alone and suggests that patients may be effectively sensitized to treatment with an anti-PD1/L1 antagonist, thereby providing strong scientific rationale for the combination of ONCOS-102 and checkpoint inhibition in mesothelioma (**Fig. 4**).

Fig 4: Multiplex immunohistochemistry (mIHC). A % CD8+ Expression. **B** Fold change of PD-L1 from baseline to day 36. Alive /deceased was assessed at 12 month follow up.



RESULTS – Clinical efficacy

Median Progression Free Survival (mPFS) for first line patients was 8.9 months in the experimental group vs 7.6 months in the control group. While there are still some censored patients, these data can be regarded as close to final and compare favourably to historical control of SOC chemotherapy which have shown mPFS of 5.7-7.3 months [1]. In the same group of first line patients, 12-month survival rate was 64% in the experimental group compared to 50% in the control group (median Overall Survival not yet reached). The patients continue to be followed and updated survival figures including mOS will be published as they become available. The 12-month survival rate is encouraging compared to the control group and similar to recent data on the PD-L1 check point inhibitor durvalumab in combination with SoC chemotherapy showing 70% 12-month survival rate (Ref. P. Forde, ASCO 2020).

CONCLUSION

- Encouraging PFS and survival data in ONCOS-102-treated first line patients as 31 patients have now completed 12 month follow-up
- Mechanistic evidence of profound immune activation in ONCOS-102-treated patients
- ONCOS-102 induced immune activation was associated with better clinical outcomes
- Immune data provide scientific rationale for anti-PD1/L1 checkpoint inhibitor combination therapies

References:
1. Vogelzang 2003, Ceresoli 2006, Zalcman 2015, Tsao 2019, Scagliotti 2019