A randomised open-label phase I/II study adding ONCOS-102 to pemetrexed/cisplatin in patients with unresectable malignant pleural mesothelioma – 24-months analysis of clinical outcomes

Luis Paz-Ares[1], Susana Cedres[2], Xavier Serres[3], Charles Ricordel[4], Nicolas Isambert[5], Santiago Ponce Aix[1], Victor Levitsky[6], Lukasz Kuryk[6], Anne-Sophie Moller[6], Sylvia Vetrhus[6], Erik Wiklund[6], Vivi Refsnes[6], Magnus Jaderberg[6]

[1]Medical Oncology, Hospital 12 Octubre, Madrid, Spain [2]Medical Oncology, University Hospital Vall d'Hebron, Barcelona, Spain [3]Radiology, University Hospital Vall d'Hebron, Barcelona, Spain [4]Pulmonology, Centre Hospitalier Universitaire de Rennes, France [5]Medical Oncology, Centre Hospitalier Universitaire de Poitiers, France [6]Research & Development, Targovax ASA, Norway.

INTRODUCTION

Malignant pleural mesothelioma (MPM) is a rare, aggressive malignancy without curative treatment. Majority of patients receive pemetrexed/cisplatin as standard of care (SoC). Expected median overall survival in first line patients with standard of care chemotherapy is between 12-14 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. Here we report the 24-month overall survival and immunological findings.

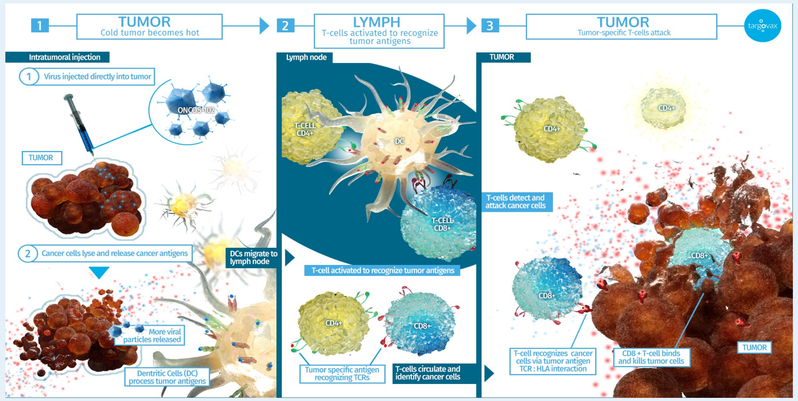
OBJECTIVE

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 is a serotype 5 adenovirus armed with a granulocyte-macrophage colony stimulating factor (GM-CSF) transgene payload for enhanced immune stimulation with a unique ability to both prime and boost immune responses. ONCOS-102 drives TLR9 alarm signalling, oncolysis and multi-faceted pro-inflammatory reprogramming of the TME. 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**).

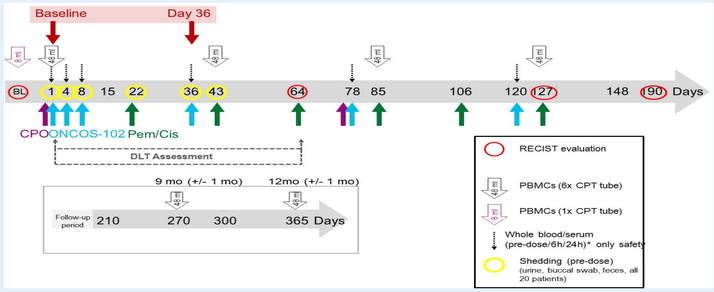
Fig 1: Mechanism of action of ONCOS-102.



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.

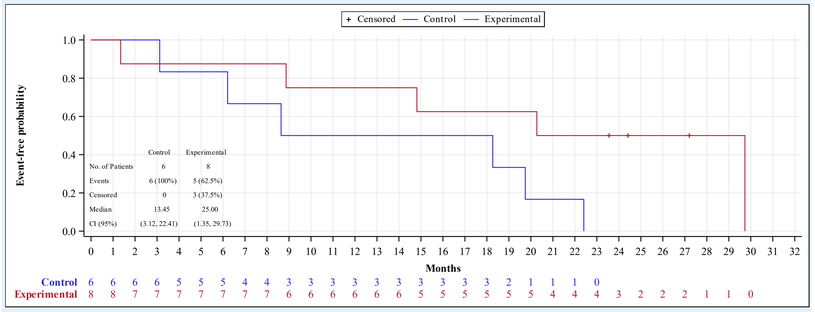
Fig 2: Treatment schedule and sample collection for the experimental group.



RESULTS – Clinical efficacy (25 randomized patients)

Median Progression Free Survival (mPFS) for first line patients was 9.8 months in the experimental group (n=8) vs 7.6 months (N.S.) in the control group (n=6) 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 1st line patients, 24-month survival was 50% vs 0%. Median Overall Survival across both 1st and 2nd line patients was 19.3 vs 14.8 months (N.S.) while in 1st line patients at least 21.9 months (patients still censored/mOS not yet reached) vs 13.5 months (mOS reached), experimental versus control groups respectively (N.S.). The patients continue to be followed and final mOS in 1st line patients will be published as they become available. Survival rates are encouraging compared to the standard of care checkpoint inhibitor combination nivolumab/ipilimumab [2] **(Fig. 3).**

Fig 3: 24-months mOS in 1st line patients by previous use of chemotherapy – Kaplan-Meier plot (Randomized phase)



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 (**Fig. 4 and Fig. 5**). Tumor biopsies at Day 36 compared to baseline showed increased CD4+ and CD8+ T-cell tumour infiltration in clinical responders (CR, PR and SD) and associated with improved survival in patients who received ONCOS-102. This 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.

Fig 4: Multiplex immunohistochemistry (mIHC) – patient case example (SD). A) CD8+ Expression at baseline and day 36. **B)** Fold change of selected immune cell markers from baseline to day 36.

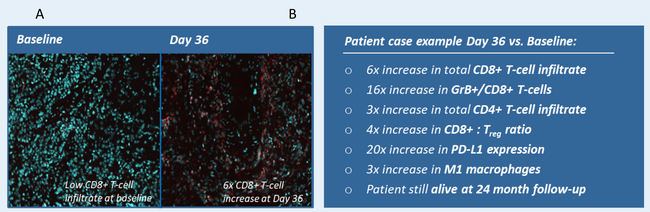
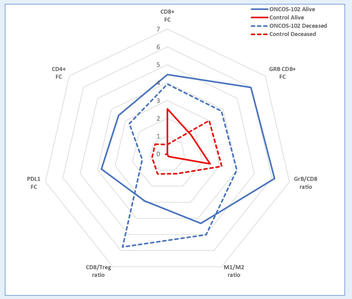


Fig 5: Multiplex immunohistochemistry (mIHC) Fold change (FC) of selected immune cell markers, PDL1 expression, M1/M2 ratio from baseline to day 36



CONCLUSION

- Encouraging PFS and survival data in ONCOS-102 plus pemetrexed/cisplatin treated first line patients, comparable to nivolumab/ipilimumab
- Mechanistic evidence of profound immune activation in ONCOS-102-treated patients
- ONCOS-102 induced immune activation was associated with improved survival
- 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
2. Baas 2020

www.Targovax.com
E-mail: magnus.jaderberg@targovax.com