2. SYNOPSIS

Name of Sponsor/Company: Targovax OY
Name of Finished Product: Not applicable
Name of Active Ingredient: ONCOS-102
TITLE OF STUDY: A randomised Phase II open-label study with a Phase Ib safety lead-in cohort of ONCOS-102, an immune-priming GM-CSF coding oncolytic adenovirus, and pemetrexed/cisplatin in patients with unresectable malignant pleural mesothelioma (Protocol Number: ONCOS C719; EudraCT Number: 2015-005143-13)
PRINCIPAL/COORDINATING INVESTIGATOR NAME, NUMBER OF STUDY CENTRES AND COUNTRIES: Principal Investigator: Luis Paz-Ares MD, Spain. Two centres in France and 4 centres in Spain consented patients.
PUBLICATION (REFERENCES): None
STUDY PERIOD: Study Initiation Date (First Patient First Treatment): 30 June 2016 Study Completion Date (Last Patient 21 Month Follow-up): 28 January 2021 Further survival Follow-up data will be reported in the addendum to the clinical study report (CSR).
PHASE OF DEVELOPMENT: Phase II with a Phase Ib safety lead-in cohort
BACKGROUND AND RATIONALE FOR THE STUDY: ONCOS-102 is a serotype 5 adenovirus that has a genetically modified fibre with a serotype 3 knob for enhanced gene delivery to cancer cells. It is also armed with granulocyte macrophage colony stimulating factor (GM-CSF), a potent inducer of anti-tumour immunity. In the E1A region 23bp has been deleted in order to limit viral replication to cancer cells thus ensuring selectivity. Preclinical and clinical evidence indicate that ONCOS-102 has an acceptable safety profile. The anti-tumour efficacy of ONCOS-102 alone and in combination with pemetrexed plus cisplatin or carboplatin was examined in vitro and in a nude mouse model of mesothelioma; a synergistic effect was demonstrated with both chemotherapy regimens. In a Phase I exploratory study of ONCOS-102 with cyclophosphamide (CPO) in patients with various refractory injectable solid tumours indicated that the tumour-specific immune response elicited by treatment with ONCOS-102 was sufficiently robust to partially eradicate the tumour load. Importantly, increase in several immune markers such as CD8+ T-cells were statistically significantly correlated with increased survival. Two patients in this study had malignant pleural mesothelioma; data from these patients show how ONCOS-102 was able to immune activate their tumour lesions. There were no safety concerns or dose-limiting toxicities (DLTs) observed. The aim of this study was to explore the safety, efficacy, and immune activation of ONCOS-102 in combination with standard of care chemotherapy in patients with unresectable malignant pleural mesothelioma.
OBJECTIVES: Primary Objective: • To determine the safety and tolerability of ONCOS-102 in combination with pemetrexed/cisplatin. Secondary Objectives: • To determine and compare tumour-specific immunological activation in the peripheral blood in the Experimental Group (ONCOS-102 in combination with pemetrexed/cisplatin) and the Control Group (pemetrexed/cisplatin). • To determine and compare immunological activation in tumour mass in the Experimental Group and the Control Group.

- To determine and compare overall response rate (ORR) and progression-free survival (PFS) in the Experimental Group and the Control Group.
- To determine and compare overall survival (OS) in the Experimental Group and the Control Group.
- To analyse the correlation between immunological activation and clinical outcome.

METHODOLOGY: This was an open-label, parallel group, multicentre study that was conducted in 2 parts: a non-randomised Phase Ib safety part and a Phase II randomised part.

Phase Ib Safety Part: Eligible patients were pre-treated with an intravenous (i.v.) bolus injection of CPO between 1 and 3 days before the first administration of ONCOS-102. ONCOS-102 was administered in a priming cycle which comprised of injections on Days 1, 4, 8, and 36, followed by 2 treatment cycles at intervals of 6 weeks (Day 78 and Day 120) at a dose of 3×10^{11} virus particles (VP). Patients received a second pre-treatment with CPO between 1 and 3 days before administration of ONCOS-102 on Day 78. Patients were to be hospitalised for 1 day (including an overnight stay) for each dose of ONCOS-102. Patients also received standard of care pemetrexed in combination with cisplatin or carboplatin in 21-day cycles starting on Day 22. Patients were given vitamin supplementation with folic acid and vitamin B12, and dexamethasone according to the Summary of Product Characteristics (SPC) and/or local guidelines. If a patient had a Complete Response (CR, ie, lacked injectable tumour lesions), treatment with ONCOS-102 was to be stopped but treatment with pemetrexed/cisplatin could continue. Imaging was performed on Days 64 and 148.

When the first 3 patients had completed the Day 64 visit (ie, after 2 cycles of pemetrexed/cisplatin in combination with ONCOS-102), all available data were reviewed by the Data Safety Monitoring Board (DSMB). As deemed appropriate by the DSMB, a further 3 patients were recruited to the safety lead-in cohort. When these 3 patients had completed the Day 64 visit, safety data from all 6 patients were reviewed by the DSMB. At this second review, the DSMB recommended that the study should progress to the Phase II randomised part of the study at the same dose of ONCOS-102 as there had been no safety concerns or DLTs observed. The protocol allowed for an additional cohort of 6 patients to be recruited in this part of the study to receive a modified dose of ONCOS-102 if deemed necessary by the DSMB; this additional cohort was not recruited.

Phase II Randomised Part: It was planned to recruit a total of 24 patients in this part of the study; 14 patients were to be randomised to receive ONCOS-102 and pemetrexed in combination with cisplatin or carboplatin (the Experimental Group) and 10 patients were to receive standard of care i.e, pemetrexed in combination with cisplatin or carboplatin (the Control Group). The dose of ONCOS-102 was determined based on the outcome of the Phase Ib safety part of the study. Patients in the Phase II randomised part of the study were treated as follows:

- Experimental Group: Patients followed the same dosing schedule as patients in the Phase Ib safety part of the study
- Control Group: Patients received pemetrexed/cisplatin in 21-day cycles and continued treatment as applicable during the study period of 6 cycles of chemotherapy.

Patients were given vitamin supplementation with folic acid and vitamin B12, and dexamethasone according to the SPC and/or local guidelines. Patients were monitored for immunological assessment of lesional biopsies and peripheral blood mononuclear cells (PBMCs). PBMCs were also collected at Months 9 and 12 ie, after the End of Study visit.

NUMBER OF SUBJECTS (planned and analysed): It was planned to enrol between 30 and 36 patients: a total of 6 or 12 patients in the Phase Ib safety part and 24 patients in the Phase II randomised part.

A total of 31 patients were treated with 6 patients in the Phase Ib safety part and 25 patients in the Phase II randomised part (14 patients in the Experimental Group and 11 patients in the Control Group). As patients in both the Phase Ib safety part of the study and the Experimental Group of the Phase II randomised part of the study received the same dose of ONCOS-102 and followed the same dosing schedule, these patients (a total of 20) are presented together as the 'Experimental Group'.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION AND EXCLUSION: Male or female patients ≥18 years of age with histologically confirmed unresectable (advanced) malignant pleural mesothelioma who were not candidates for curative surgery and for whom therapy with pemetrexed in combination with cisplatin or carboplatin, was considered appropriate. Patients had to have measurable disease according to Response Evaluation Criteria In Solid Tumours (RECIST 1.1) by computed tomography (CT) scan and their tumour had to be accessible to intratumoural (i.t.) injections of ONCOS-102. Patients had to be eligible for use of the study specific chemotherapies, including CPO, according to the SPCs and local practice, have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1, and have acceptable liver, renal, and haematological function. Patients who, within 4 weeks of Day 1, had received oncolytic virus treatment or vaccination with a vaccine containing a live virus or had used significant immunosuppressive medication, including high dose corticosteroid (defined as the equivalent of >10 mg/day prednisolone), were excluded from the study.

TEST PRODUCT, DOSE, MODE OF ADMINISTRATION, BATCH NUMBERS: The planned total dose of ONCOS-102 on each dosing day was 3×10^{11} VP administered by i.t. injection. Per protocol, this could have been reduced to 1×10^{11} VP if deemed appropriate by the DSMB; however, based on review of available safety data, this dose modification was not deemed necessary. The amount of ONCOS-102 per deposit/lesion and the number of deposits could vary from patient to patient while the total dose of ONCOS-102 (VP) for each individual patient was to remain the same throughout the study. The total volume (2.5 mL) could either be injected in a single lesion with the entire amount of the virus or several lesions using the entire amount of the virus but with no less than 0.5 mL in any 1 lesion. The number of injected lesions was, therefore, limited to 5. ONCOS-102 was to be administered on Days 1, 4, 8, 36, 78, and 120.
Batch numbers: BX1002852, BX1008383-02, BX1008383-04, BX1008383-06, BX1010808-03 and BX1010808-06.

DURATION OF TREATMENT:
ONCOS-102: Patients could have continued to receive injections until emergence of unacceptable toxicity related to ONCOS-102, clinically relevant disease progression requiring alternative therapy as assessed by the patient's physician or the investigator, CR (ie, lacks injectable tumour lesions), or the last scheduled injection (Day 120).

Chemotherapy: Patients could have continued to receive pemetrexed/cisplatin/carboplatin for as long as clinically indicated. However, the study period included a maximum of 6 cycles of chemotherapy.

CONTROL PRODUCT, DOSE, MODE OF ADMINISTRATION, BATCH NUMBER(S):
Cyclophosphamide: Patients in the Phase Ib safety part and the Experimental Group of the Phase II randomised part of the study were to receive CPO between 1 and 3 days before the Day 1 and Day 78 doses of ONCOS-102. CPO was to be administered as an i.v. bolus of 300 mg/m^2 (dose could have been reduced if deemed necessary by the investigator). CPO was sourced from commercial stock; batch numbers not applicable.

Chemotherapy: All patients were to receive pemetrexed/cisplatin (or carboplatin if appropriate) chemotherapy in 21-day cycles. Pemetrexed 500 mg/m^2 was to be administered as an i.v. infusion over 10 minutes on Day 1 of each 21-day cycle. The recommended dose of cisplatin was 75 mg/m^2 infused i.v. over 2 hours beginning approximately 30 minutes after the end of pemetrexed infusion. For patients receiving carboplatin instead of cisplatin, the dose of carboplatin was to be calculated based on the glomerular filtration rate calculated as per standard practice at the study. Patients were to receive carboplatin AUC 5. Doses of pemetrexed, cisplatin or carboplatin could have been reduced if deemed necessary by the investigator. Patients in the Phase Ib safety part and the Experimental Group of the Phase II randomised part of the study

were to start chemotherapy on Day 22 of the study. Patients in the Control Group of the Phase II randomised part of the study were to start chemotherapy on Day 1. Chemotherapy drugs were sourced from commercial stock; batch numbers not applicable.

ENDPOINTS:

Primary Endpoint:

- Safety and tolerability profile of ONCOS-102 and pemetrexed/cisplatin.

Secondary Endpoints:

- Biological correlates by means of cellular and humoral immune responses in blood as well as biological changes in tumour biopsies.
- Response rate and PFS according to RECIST 1.1, modified immunologically relevant RECIST (irRECIST), and Positron Emission Tomography Response Criteria in Solid Tumours (PERCIST) 1.0.
- Overall survival.

STATISTICAL METHODS:

Safety endpoints were analysed using the ITT population (defined as all patients who received any amount of ONCOS-102 and/or pemetrexed/cisplatin/carboplatin; this population was identical to the Safety population). Adverse events (AEs), safety laboratory test values and vital signs values were summarised separately for the Experimental and Control Groups.

Efficacy variables were summarised using the ITT population and the Per Protocol (PP) population (defined as all patients in the ITT population who did not have a major protocol deviation). Day 1 was defined as the first administration of treatment (ONCOS-102 for the Experimental Group and pemetrexed/cisplatin/carboplatin for the Control Group).

PFS was determined as the time (weeks and months) from Day 1 until disease progression or death from any cause. For a patient who had not progressed at the date of data cut-off, the time until the last scan was used as the censored time of progression. PFS distribution in the Experimental Group versus the Control Group was compared using a log-rank test. The Kaplan-Meier method was applied in the estimation of PFS function. Per protocol, PFS was presented per RECIST 1.1, irRECIST, and PERCIST until the end of the treatment phase. However, in the follow-up phase of the study, data regarding disease progression were recorded but not the type of scan. Therefore, for patients who proceeded to the follow-up phase without progression recorded during the treatment phase, PFS was calculated based on the date of radiological confirmation of disease status, regardless of the scan modality. PFS was presented as the time (weeks and months) from Day 1 until disease progression per applicable scan modality or death from any cause during the treatment phase. Overall PFS was also presented as the time (weeks and months) from Day 1 until disease progression during the treatment phase per RECIST 1.1 or during the follow-up phase regardless of the scan modality or death from any cause. PFS was also summarised by previous use of chemotherapy (naïve/first-line and non-naïve).

OS was determined as the time (weeks and months) from Day 1 until death from any cause. OS distribution in the Experimental Group versus the Control Group was compared using a log-rank test. If a patient did not reach the endpoint, that patient was censored at the date last known to be alive. OS was also summarised by previous use of chemotherapy.

ORR, at any timepoint, was defined as: CR or Partial Response (PR) by RECIST 1.1; immune-related Complete Response (irCR) or immune-related Partial Response (irPR) by irRECIST; Complete Metabolic Response (CMR) or Partial Metabolic Response (PMR) by PERCIST. ORR was assessed separately by RECIST 1.1, irRECIST, and PERCIST; treatment differences were analysed using Fisher's exact test. ORR was also summarised by previous use of chemotherapy.

Disease control rate (DCR), at any timepoint, was defined as: CR, PR or Stable Disease (SD) by RECIST 1.1; irCR, irPR or immune-related Stable Disease (irSD) by irRECIST; CMR, PMR, or Stable Metabolic Response by PERCIST. DCR was assessed separately by RECIST 1.1, irRECIST, and PERCIST; treatment differences were analysed using Fisher's exact test.

ECOG Performance Status was summarised using frequency tables.

Per statistical analysis plans (SAP) Addendums 1.0 and 2.0, additional analyses of survival data were performed using data received after the last 9-month visit, 12-month visit, 18-month visit and at any later timepoint if needed. At the time of completion of this CSR, 9-month, 12-month, 18-month, and 21-month follow-up analyses had been performed. These analyses included available data from all patients at the point in time ie, minimum 9/12/18/21-month follow-up for the last patients enrolled in the study. The 21-month follow-up data are presented in this CSR.

Immunological Endpoints: The following endpoints were derived:

1. Mean per immunological marker per patient at baseline and on Day 36.
2. Fold change from baseline to Day 36 based on mean per immunological marker per patient.
3. Fold change from baseline to Day 36 based on mean for a subset of markers as a group (CD8+, CD8+ GranzB+, and CD8+ PD1+).
4. Change from baseline to Day 36 based on mean per immunological marker per patient.
5. Change from baseline to Day 36 based on mean for a subset of markers as a group (CD8+, CD8+ GranzB+, and CD8+ PD1+).

The above endpoints were derived using:

- normalised value (total cell count)
- normalised value (epithelial cell count)
- normalised value (stroma cell count)

The biopsy immunological markers are detailed in Appendix 6 of the SAP for immunological endpoints (provided in Appendix 16.1.9).

6. A positive PBMC result post-baseline at any timepoint during the study after baseline (de novo). If the baseline result was positive, the post-baseline result was positive if at any assessment at any post-baseline timepoint (count of number of stimulated cells – count of number of unstimulated cells) was higher than at baseline.

For the correlation analysis, data from the Experimental Group (injected lesions only) and Control Group were combined. Analyses were repeated for patients in the Experimental Group (injected lesions only). The aim was to assess whether the biological change in tumour environment post-baseline correlated with clinical endpoints.

SUMMARY OF RESULTS AND CONCLUSIONS:

Subject Disposition: A total of 6 patients were enrolled in the Phase Ib safety part of the study. In the Phase II randomised part of the study, a total of 25 patients were enrolled (14 patients in the Experimental Group and 11 patients in the Control Group). As patients in both the Phase Ib safety part of the study and the Experimental Group of the Phase II randomised part of the study received the same dose of ONCOS-102 and followed the same dosing schedule, these patients (a total of 20) are presented together as the 'Experimental Group'.

Of the 20 patients in the Experimental Group, 11 patients (55.0%) were chemotherapy naïve and 9 patients (45.0%) were chemotherapy non-naïve. In the Control Group, 6 patients (54.5%) were chemotherapy naïve and 5 patients (45.5%) were chemotherapy non-naïve.

A total of 20 patients (64.5%) completed the study; 14 patients (70.0%) in the Experimental Group and 6 patients (54.5%) in the Control Group. Of the 6 patients (30.0%) in the Experimental Group who withdrew from the study, 2 patients withdrew during the Phase Ib safety part of the study (both due to disease progression) and 4 patients withdrew in the Phase II randomised part of the study (3 due to disease progression and 1 due to a treatment-emergent AE [TEAE]). Of the 5 patients (45.5%) in the Control Group who withdrew from the study, 2 patients withdrew due to disease progression, 2 due to other reasons (could not/refused to attend End of Study visit), and 1 due to a TEAE.

One major protocol deviation was reported (did not meet inclusion criterion relating to creatinine clearance). This patient was excluded from the PP population.

Demography and Baseline Characteristics: A total of 31 patients (22 male and 9 female) aged between 36 and 80 years were enrolled in this study. Baseline demographic characteristics were comparable between the 2 treatment groups; the majority of patients in both treatment groups were male and white with an ECOG Performance Status of 1.

Baseline disease characteristics and mesothelioma history were not comparable between the 2 treatment groups with the Experimental Group having more advanced disease; the mean tumour burden by RECIST 1.1. was 87 mm compared to 46 mm in the Control Group, and 60% patients in the Experimental Group had Stage IV disease at enrolment compared to 46% in the Control Group. The majority of patients in both treatment groups had epithelioid mesothelioma (>70%) and were Stage III or IV at diagnosis and at enrolment (>70%).

Efficacy Results: The most mature data available for PFS and OS are reported as part of the 21-month follow-up analysis (when all patients had been in the study for at least 21 months) and these data are summarised below.

Of the 20 patients in the Experimental Group, 18 patients (90.0%) had a single tumour injected at baseline and 2 patients (10.0%) had 2 tumours injected at baseline. All patients received ONCOS-102 on Days 1, 4, and 8. One patient had discontinued prior to administration of ONCOS-102 on Day 36 resulting in 19 patients (95.0%) receiving ONCOS-102 on that day. On Days 78 and 120, 15 patients (75.0%) and 13 patients (65.0%), respectively, received treatment with ONCOS-102. The total number of ONCOS-102 injections per patient ranged from 3 to 10 (median of 6.0). Patients who received more than 6 injections of ONCOS-102 had 2 tumours injected at baseline.

Progression-free Survival: PFS at the time of the 21-month follow-up analysis (when all patients had been in the study for at least 21 months) is summarised for the ITT population (overall and by previous use of chemotherapy) in Table S1 and for the ITT, Randomised Part only population (overall and by previous use of chemotherapy) in Table S2.

Table S1: Progression-free Survival (ITT Population) – 21-month Follow-up Analysis

	Experimental Group	Control Group	Log-rank Experimental vs Control Rank test statistic (SE) p value	Hazard Ratio (95% CI) Experimental vs Control
ITT, Overall				
Events/Total number of patients (%)	18/20 (90.0)	10/11 (90.9)	0.0639 (2.4767) 0.8004	0.905 (0.416, 1.969)
Progression-free survival time (months)				
Minimum	1.3	1.5		
25th percentile (95% CI)	2.04 (1.35, 7.43)	6.21 (1.51, 8.31)		
Median (95% CI)	8.46 (1.97, 10.81)	8.31 (2.63, 10.48)		
75th percentile (95% CI)	12.12 (8.54, NA)	10.48 (6.83, NA)		
Maximum	36.7	21.0		
ITT, Chemotherapy Naïve				
Events/Total number of patients (%)	9/11 (81.8)	6/6 (100.0)	2.1039 (1.6158) 0.1469	0.457 (0.155, 1.349)
Progression-free survival time (months)				
Minimum	1.3	2.6		
25th percentile (95% CI)	8.38 (1.35, 8.87)	6.21 (2.63, 8.31)		
Median (95% CI)	8.87 (2.10, 15.80)	7.57 (2.63, 15.24)		
75th percentile (95% CI)	15.80 (8.71, NA)	8.84 (6.21, 15.24)		

Maximum	36.7	15.2		
ITT, Chemotherapy Non-naïve				
Events/Total number of patients (%)	9/9 (100.0)	4/5 (80.0)	1.1700 (1.7579) 0.2794	1.919 (0.578, 6.376)
Progression-free survival time (months)				
Minimum	1.8	1.5		
25th percentile (95% CI)	1.91 (1.84, 4.53)	6.47 (1.51, 10.48)		
Median (95% CI)	4.53 (1.84, 10.25)	8.54 (1.51, NA)		
75th percentile (95% CI)	7.43 (1.97, 17.68)	10.48 (1.51, NA)		
Maximum	17.7	21.0		

CI = confidence interval; NA = not applicable; SE = standard error.
Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley.

Table S2: Progression-free Survival (ITT, Randomised Part Only Population) – 21-month Follow-up Analysis

	Experimental Group	Control Group	Log-rank Experimental vs Control Rank test statistic (SE) p value	Hazard Ratio (95% CI) Experimental vs Control
ITT (Randomised Part Only), Overall				
Events/Total number of patients (%)	13/14 (92.9)	10/11 (90.9)	0.3572 (2.2989) 0.5501	0.778 (0.339, 1.783)
Progression-free survival time (months)				
Minimum	1.3	1.5		
25th percentile (95% CI)	7.39 (1.35, 8.71)	6.21 (1.51, 8.31)		
Median (95% CI)	8.79 (4.53, 13.44)	8.31 (2.63, 10.48)		
75th percentile (95% CI)	13.44 (8.71, NA)	10.48 (6.83, NA)		
Maximum	19.2	21.0		
ITT (Randomised Part Only), Chemotherapy Naïve				
Events/Total number of patients (%)	7/8 (87.5)	6/6 (100.0)	2.1992 (1.5655) 0.1381	0.426 (0.134, 1.357)
Progression-free survival time (months)				
Minimum	1.3	2.6		
25th percentile (95% CI)	8.62 (1.35, 10.81)	6.21 (2.63, 8.31)		
Median (95% CI)	9.84 (1.35, 15.80)	7.57 (2.63, 15.24)		
75th percentile (95% CI)	14.62 (8.71, NA)	8.84 (6.21, 15.24)		
Maximum	19.2	15.2		
ITT (Randomised Part Only), Chemotherapy Non-naïve				
Events/Total number of patients (%)	6/6 (100.0)	4/5 (80.0)	0.4048 (1.5627) 0.5246	1.511 (0.420, 5.437)
Progression-free survival time (months)				
Minimum	1.9	1.5		
25th percentile (95% CI)	4.53 (1.91, 7.43)	6.47 (1.51, 10.48)		
Median (95% CI)	7.41 (1.91, 17.68)	8.54 (1.51, NA)		

75th percentile (95% CI)	10.25 (4.53, 17.68)	10.48 (1.51, NA)
Maximum	17.7	21.0

CI = confidence interval; NA = not applicable; SE = standard error.
Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley.

Overall Survival: OS at the time of the 21-month follow-up analysis (when all patients had been in the study for at least 21 months) is summarised for the ITT population (overall and by previous use of chemotherapy) in Table S3 and for the ITT, Randomised Part only population (overall and by previous use of chemotherapy) in Table S4.

Table S3: Overall Survival (ITT Population) - 21-month Follow-up Analysis

	Experimental Group	Control Group	Log-rank (Experimental vs Control) Rank test statistic (SE) p value	Hazard Ratio (95% CI) Experimental vs Control
ITT, Overall				
Events/Total number of patients (%)	14/20 (70.0)	7/11 (63.6)	0.0327 (2.0758) 0.8566	0.918 (0.361, 2.332)
Overall survival time (months)				
Minimum	1.3	3.0		
25th percentile (95% CI)	5.68 (1.35, 10.91)	6.21 (3.02, 18.27)		
Median (95% CI)	16.59 (5.03, 31.47)	18.27 (3.12, NA)		
75th percentile (95% CI)	31.47 (18.37, NA)	NA (10.48, NA)		
Maximum	37.0	24.6		
Percent event-free probability estimates (survival rates) (95% CI)				
9 months	65.0 (40.3, 81.5)	63.6 (29.7, 84.5)		
12 months	55.0 (31.3, 73.5)	54.5 (22.9, 78.0)		
18 months	50.0 (27.1, 69.2)	54.5 (22.9, 78.0)		
21 months	40.0 (19.3, 60.0)	36.4 (11.2, 62.7)		
ITT, Chemotherapy Naïve				
Events/Total number of patients (%)	6/11 (54.5)	5/6 (83.3)	1.4471 (1.4933) 0.2290	0.486 (0.146, 1.614)
Overall survival time (months)				
Minimum	1.3	3.1		
25th percentile (95% CI)	8.87 (1.35, 20.27)	6.21 (3.12, 18.27)		
Median (95% CI)	20.27 (6.34, NA)	13.45 (3.12, NA)		
75th percentile (95% CI)	NA (14.82, NA)	19.75 (6.21, NA)		
Maximum	37.0	21.3		
Percent event-free probability estimates (survival rates) (95% CI)				
9 months	72.7 (37.1, 90.3)	50.0 (11.1, 80.4)		
12 months	63.6 (29.7, 84.5)	50.0 (11.1, 80.4)		
18 months	54.5 (22.9, 78.0)	50.0 (11.1, 80.4)		
21 months	45.5 (16.7, 70.7)	16.7 (0.8, 51.7)		

ITT, Chemotherapy Non-naïve				
Events/Total number of patients (%)	8/9 (88.9)	2/5 (40.0)	0.6857 (1.3704) 0.4076	1.951 (0.390, 9.759)
Overall survival time (months)				
Minimum	4.3	3.0		
25th percentile (95% CI)	4.57 (4.30, 10.35)	10.48 (3.02, NA)		
Median (95% CI)	10.35 (4.30, 30.42)	NA (3.02, NA)		
75th percentile (95% CI)	30.42 (5.03, 31.47)	NA (3.02, NA		
Maximum	31.5	24.6		
Percent event-free probability estimates (survival rates) (95% CI)				
9 months	55.6 (20.4, 80.5)	80.0 (20.4, 96.9)		
12 months	44.4 (13.6, 71.9)	60.0 (12.6, 88.2)		
18 months	44.4 (13.6, 71.9)	60.0 (12.6, 88.2)		
21 months	33.3 (7.8, 62.3)	60.0 (12.6, 88.2)		

CI = confidence interval; NA = not applicable; SE = standard error.
Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley.
% Event-free probability estimates are the estimated probabilities that a patient will remain event-free up to the specified time point. Survival rate (proportion of patients alive at a specific timepoint) is presented as % Event-free probability.
% Event-free probability estimates are obtained from the Kaplan-Meier survival estimates, Greenwood formula is used for CIs of Kaplan-Meier estimates.

Table S4: Overall Survival (ITT, Randomised Part Only Population) - 21-month Follow-up Analysis

	Experimental Group	Control Group	Log-rank (Experimental vs Control) Rank test statistic (SE) p value	Hazard Ratio (95% CI) Experimental vs Control
ITT (Randomised Part Only)				
Events/Total number of patients (%)	9/14 (64.3)	7/11 (63.6)	0.1450 (1.9080) 0.7034	0.821 (0.297, 2.268)
Overall survival time (months)				
Minimum	1.3	3.0		
25th percentile (95% CI)	8.87 (1.35, 18.37)	6.21 (3.02, 18.27)		
Median (95% CI)	19.32 (4.57, 30.42)	18.27 (3.12, NA)		
75th percentile (95% CI)	30.42 (18.37, 30.42)	NA (10.48, NA)		
Maximum	30.4	24.6		
Percent event-free probability estimates (survival rates) (95% CI)				
9 months	71.4 (40.6, 88.2)	63.6 (29.7, 84.5)		
12 months	64.3 (34.3, 83.3)	54.5 (22.9, 78.0)		
18 months	57.1 (28.4, 78.0)	54.5 (22.9, 78.0)		
21 months	42.9 (17.7, 66.0)	36.4 (11.2, 62.7)		

ITT (Randomised Part Only), Chemotherapy Naïve				
Events/Total number of patients (%)	4/8 (50.0)	5/6 (83.3)	1.7663 (1.4062) 0.1838	0.413 (0.108, 1.582)
Overall survival time (months)				
Minimum	1.3	3.1		
25th percentile (95% CI)	11.84 (1.35, NA)	6.21 (3.12, 18.27)		
Median (95% CI)	NA (1.35, NA)	13.45 (3.12, NA)		
75th percentile (95% CI)	NA (14.82, NA)	19.75 (6.21, NA)		
Maximum	26.3	21.3		
Percent event-free probability estimates (survival rates) (95% CI)				
9 months	75.0 (31.5, 93.1	50.0 (11.1, 80.4)		
12 months	75.0 (31.5, 93.1	50.0 (11.1, 80.4)		
18 months	62.5 (22.9, 86.1)	50.0 (11.1, 80.4)		
21 months	50.0 (15.2, 77.5)	16.7 (0.8, 51.7)		
ITT (Randomised Part Only), Chemotherapy Non-naïve				
Events/Total number of patients (%)	5/6 (83.3)	2/5 (40.0)	0.5120 (1.2164) 0.4743	1.847 (0.335, 10.175)
Overall survival time (months)				
Minimum	4.5	3.0		
25th percentile (95% CI)	4.57 (4.53, 18.37)	10.48 (3.02, NA)		
Median (95% CI)	14.36 (4.53, 30.42)	NA (3.02, NA)		
75th percentile (95% CI)	30.42 (4.57, 30.42)	NA (3.02, NA		
Maximum	30.4	24.6		
Percent event-free probability estimates (survival rates) (95% CI)				
9 months	66.7 (19.5, 90.4)	80.0 (20.4, 96.9)		
12 months	50.0 (11.1, 80.4)	60.0 (12.6, 88.2)		
18 months	50.0 (11.1, 80.4)	60.0 (12.6, 88.2)		
21 months	33.3 (4.6, 67.6)	60.0 (12.6, 88.2)		

CI = confidence interval; NA = not applicable; SE = standard error.
Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley.
% Event-free probability estimates are the estimated probabilities that a patient will remain event-free up to the specified time point. Survival rate (proportion of patients alive at a specific timepoint) is presented as % Event-free probability.
% Event-free probability estimates are obtained from the Kaplan-Meier survival estimates, Greenwood formula is used for CIs of Kaplan-Meier estimates.

Overall Response Rate:

Table S4: Overall Response Rate (ITT Population)

	Experimental Group N=20 n (%)	Control Group N=11 n (%)
RECIST 1.1		
Response	4 (21.1)	5 (45.5)
No response	15 (78.9)	6 (54.5)
p value	0.2252	
irRECIST		
Response	4 (21.1)	5 (45.5)
No response	15 (78.9)	6 (54.5)
p value	0.2252	
PERCIST		
Response	10 (55.6)	7 (63.6)
No response	8 (44.4)	4 (36.4)
p value	0.7167	

n = number of patients with best response defined as CR or PR at any time point; N = number of enrolled patients.
(%) = n/N*100 where N = number of patients with non-missing response.
p value was calculated using Fisher exact test.

Disease Control Rate: According to RECIST 1.1 (excluding missing data), 15 patients (78.9%) in the Experimental Group and 10 patients (90.9%) in the Control Group had a best response of CR, PR, or SD during the study. There was no statistically significant difference in DCR (defined as patients who had CR, PR or SD at any time point) between the Experimental Group and the Control Group.

Correlation Between Immunological Activation and Clinical Outcome: In general, there was no statistically significant evidence of a correlation between immunological activation in tumour mass and clinical outcome (OS, PFS, ORR, and DCR). However, there was a statistically significant correlation between clinical outcome (Kaplan-Meier median survival time, DCR and PFS) and increased frequencies of tumour specific T-cells (MAGE-A1) over baseline in the Experimental Group.

Immunological Activation: There were no statistically significant differences in changes of analysed immunological parameters in the peripheral blood or tumour mass between treatment groups. However, some biologically meaningful changes preferentially occurring in tumours from the Experimental Group were observed. These findings will be presented and discussed in detail in the addendum to this report. Also, cellular gene expression in baseline and on-treatment biopsies will be summarised and discussed, along with data generated using immunohistochemistry and immunofluorescence in the addendum.

Safety Results:

All patients in the study experienced at least 1 TEAE during the study. A total of 375 TEAEs were reported for the 20 patients in the Experimental Group compared with 137 TEAEs for the 11 patients in the Control Group. The most frequently reported PTs (reported by >50% patients in both treatment groups) were anaemia, neutropenia, and asthenia in both treatment groups. In addition, in the Experimental Group, pyrexia, and nausea were reported by >50% patients and in the Control Group, decreased appetite was reported by >50% patients.

The majority of TEAEs in both treatment groups were Grade 1 or 2 in severity (329 of 375 TEAEs [87.8%] in the Experimental Group and 120 of 137 TEAEs [87.6%] in the Control Group). Similar proportions of patients in each treatment group experienced Grade 1, 2, and 3 TEAEs. In the Experimental Group, 6 Grade 4 TEAEs (neutropenia, thrombocytopenia, and sepsis) were experienced by 4 patients (20.0%) and 1 patient died (cardiac failure). Five of the Grade 4 TEAEs were considered related to chemotherapy only and 1 (neutropenia) was considered probably related to ONCOS-102, CPO, and chemotherapy. The Grade 5 TEAE of cardiac failure was not considered related to ONCOS-102 or CPO (patient did not start

chemotherapy). In the Control Group, 1 patient (9.1%) had 2 Grade 4 TEAEs of neutropenia (considered related to chemotherapy only) and no patients died due to TEAEs.

In the Experimental Group, all patients had at least 1 TEAE considered related to ONCOS-102 (alone or in combination with CPO); with the exception of 1 Grade 3 event of pyrexia, all were Grade 1 or 2 in severity. The most frequently reported was pyrexia (reported for 75.0% patients). A total of 12 patients (60.0%) had at least 1 TEAE considered related to ONCOS-102 (alone or in combination with CPO) and 1 or more chemotherapies; with the exception of 1 Grade 4 event of neutropenia, all were Grade 1, 2 or 3 in severity. The most frequently reported (reported by >10% patients) were asthenia, neutropenia, and nausea.

Considering TEAEs considered related to chemotherapy only, 18 patients (90.0%) in the Experimental Group and all patients in the Control Group had at least 1 TEAE. The majority of these TEAEs were Grade 1 or 2 in severity. In total, 25 Grade 3 or 4 events were reported in the Experimental Group and 15 Grade 3 or 4 events were reported in the Control Group. The most frequently reported PTs considered related to chemotherapy only (reported by >20% patients in both treatment groups) were anaemia, neutropenia, nausea, and asthenia. In addition, vomiting was reported by >20% patients in the Experimental Group and thrombocytopenia and decreased appetite were reported by >20% patients in the Control Group.

A total of 16 serious adverse events were reported for 11 patients (55.0%) in the Experimental Group and 5 SAEs were reported for 4 patients (36.4%) in the Control Group. In the Experimental Group, 1 SAE was considered related to ONCOS-102 (either alone or in combination with CPO) by the investigator; a patient was hospitalised due to Grade 2 pyrexia considered related to ONCOS-102 only. Six SAEs in 4 patients (20.0%) in the Experimental Group were considered related to chemotherapy only (including 1 event each of anaemia, thrombocytopenia, vomiting, drug intolerance, sepsis, and acute kidney injury). In the Control Group, 3 SAEs in 2 patients (18.2%) were considered related to chemotherapy only (including 1 event each of anaemia, thrombocytopenia, and vomiting).

No patients discontinued treatment with ONCOS-102 or CPO due to TEAEs. One patient (5.0%) in the Experimental Group discontinued chemotherapy due to a TEAE of gastrointestinal disorder. In the Control Group, 1 patient (9.1%) discontinued chemotherapy due to a TEAE of general physical health deterioration and 1 patient (9.1%) discontinued treatment with cisplatin due to a TEAE of acute kidney injury and switched to treatment with carboplatin as permitted by the protocol. One patient in each treatment group were withdrawn from the study due to TEAEs (cardiac failure in the Experimental Group and general physical health deterioration in the Control Group). The patient in the Experimental Group subsequently died due to cardiac failure. No other patients died due to TEAEs.

Laboratory test results were generally as expected for patients receiving chemotherapy and their underlying malignant disease.

Conclusions:

- Administration of ONCOS-102 in combination with standard of care chemotherapy was generally well tolerated. The incidence and severity of TEAEs were comparable between the Experimental Group and the Control Group with the exception of pyrexia which was reported by more patients in the Experimental Group (75%) compared with the Control Group (18%); this AE is considered related to viral replication and has been observed in previous studies. TEAEs and laboratory test results were generally as expected for patients with underlying malignant disease receiving chemotherapy.
- For clinical efficacy, there was no significant difference in median PFS between the Experimental Group and Control Group (8.5 and 8.3 months, respectively). Of note, median PFS in chemotherapy naïve (first-line) patients, was 8.9 months in the Experimental Group compared to 7.6 months in the Control Group whereas in chemotherapy non-naïve (second-line) patients, median PFS was 4.5 months in the Experimental Group and 8.5 months in the Control Group. There was no significant difference in ORR between the Experimental Group and Control Group. However, numerically, the Control Group had a higher ORR according to RECIST 1.1 and irRECIST compared with the Experimental Group (45.5% and 21.1%, respectively).
- At the time of this report, survival data are still maturing. At the 21-month analysis, there was no significant difference in median OS between the Experimental Group and the Control Group (16.6 months and 18.3 months respectively). Considering patients in the randomised part of the

study only, median OS values were 19.3 months and 18.3 months in the Experimental Group and Control Group, respectively. However, OS data suggest that chemotherapy naïve (first-line) patients may benefit from treatment with ONCOS-102. At the time of the 21-month analysis, median OS for chemotherapy naïve patients in the randomised part of the study had not been met for the Experimental Group compared to 13.5 months for the Control Group. Median OS for chemotherapy non-naïve (second-line) patients was 14.4 months for the Experimental Group and had not been reached for the Control Group at the time of this analysis. In the same population (first-line patients in the randomised part of the study), 21-month survival rate was higher in the Experimental Group compared to the Control Group (50% and 17%, respectively), compatible with a trend towards improved efficacy and extended survival in first-line patients who receive ONCOS-102 in addition to standard of care chemotherapy.

- There was no statistically significant correlation between treatment groups in tumour-specific immunological activation in the peripheral blood or tumour mass.
- There was no statistically significant correlation between immunological activation in tumour mass and clinical outcome (OS, PFS, ORR, and DCR) for the majority of analysed immunological parameters. However, there was a significant correlation between Kaplan-Meier median survival time, DCR and PFS and increased frequencies of tumour specific T-cells (MAGE-A1) relative to baseline in the Experimental Group.
- In spite of lack of statistically significant correlations between changes in analysed immunological parameters in tumour mass and clinical outcomes (OS, PFS, ORR, and DCR), biologically meaningful changes supporting beneficial effects of the experimental therapy were observed predominantly in tumours from the Experimental group. These findings will be presented and discussed in detail in the addendum to this report.

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