Clinical trial results:
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

Summary

EudraCT number	2015-005143-13
Trial protocol	ES FR
Global end of trial date	08 October 2019

Results information

Result version number	v1
This version publication date	07 August 2021
First version publication date	07 August 2021
Summary attachment (see zip file)	CSR Synopsis (Clinical_Study_Report_Synopsis_ONCOS C719_version_1.0_dated_25 May 2021.pdf)

Trial information

Trial identification

Sponsor protocol code	ONCOS-C719

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02879669
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Targovax Oy
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 May 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the safety and tolerability of ONCOS-102 in combination with the standard of care treatment: pemetrexed plus either cisplatin or carboplatin.
Safety was assessed per standard procedures i.e., evaluation of Adverse Events, laboratory test results, and vital signs. In addition, viral shedding was assessed in this study.

Protection of trial subjects:

Visits schedule designed to monitor patients safety and treatment efficacy.

Patient Confidentiality
The Investigator(s) will respect and protect the confidentiality of the patient in all possible ways. Patient identification, other than the patient's study number, and date of birth, will not appear in any eCRF pages or other documents given to the Sponsor. Only the Investigator and the persons authorised to verify the quality and integrity of the study data will have an access to patient records where the patient can be identified.

Insurance
The Sponsor was responsible for insuring all study subjects against any harm caused by study procedures or investigational product.

Background therapy:

Patients were given vitamin supplementation with folic acid and vitamin B12, and dexamethasone according to the Summary of Product Characteristics and/or local guidelines.

Evidence for comparator:

The following comparators were used in this study: pemetrexed plus either cisplatin or carboplatin.
If cisplatin was considered to be too toxic after 1 or more cycles, patients could change to carboplatin during the study. In addition, if the investigator considered treatment with cisplatin to be too toxic for a patient due to age, presence of neurological toxicities or other relevant medical conditions, carboplatin could have been administered from the start of the study.
Pemetrexed 500 mg/m2 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/m2 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.

Actual start date of recruitment	17 June 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	21 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 26
Country: Number of subjects enrolled	France: 5
Worldwide total number of subjects	31
EEA total number of subjects	31

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	10
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient enrolled: 17 June 2016
Last patient 21 month follow-up: 28 January 2021
Study participants recruited at six centres; two centres in France and four centres in Spain.
One of these centres in Spain consented patients but did not treat any patients. Another centre in Spain was initiated but did not consent any patients.

Pre-assignment

Screening details:

Patients had to be ≥18 years 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 their tumour be accessible to i.t. injections of ONCOS-10.

Period 1

Period 1 title	Phase 2 with a Phase 1b lead-in cohort (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Experimental Group

Arm description:

Eligible patients were pre-treated with an intravenous (i.v.) bolus injection of cyclophosphamide (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 x 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 also received standard of care pemetrexed in combination with either 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 (SmPC) and/or local guidelines.

Arm type	Experimental
Investigational medicinal product name	ONCOS-102
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intratumoral use

Dosage and administration details:

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 x 10^11 virus particles (VP).

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	CPO
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

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. Patients received a second pre-treatment with CPO between 1 and 3 days before administration of ONCOS-102 on Day 78. CPO was to be administered as

an i.v. bolus of 300 mg/m2 (dose could have been reduced if deemed necessary by the investigator).

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

All patients were to receive chemotherapy in 21-day cycles. The recommended dose of cisplatin was 75 mg/m2 infused i.v. over 2 hours beginning approximately 30 minutes after the end of pemetrexed infusion. Doses of cisplatin could have been reduced if deemed necessary by the investigator.

Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	PEMETREXED DISODIUM
Other name	
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pemetrexed was administered in combination with cisplatin or carboplatin as standard of care in 21-day cycles starting on Day 22. Pemetrexed 500 mg/m2 was to be administered as an intravenous infusion over
10 minutes on Day 1 of each 21-day cycle. Doses of pemetrexed could have been reduced if deemed necessary by the investigator.

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received standard of care pemetrexed in combination with carboplatin (or cisplatin if appropriate) in 21-day cycles starting on Day 22. 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 carboplatin could have been reduced if deemed necessary by the investigator.

Arm title	Control Group

Arm description:

Patients received pemetrexed in combination with either cisplatin or carboplatin in 21-day cycles and continued treatment as applicable during the study period of 6 cycles of chemotherapy.
Pemetrexed 500 mg/m2 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/m2 infused i.v. over 2 hours beginning approximately 30 minutes after the end of pemetrexed infusion. The dose of carboplatin was to be calculated based on the glomerular filtration rate calculated as per site's standard practice. Patients were to receive carboplatin AUC 5.
Patients were given vitamin supplementation with folic acid and vitamin B12, and dexamethasone according to the SmPC and/or local guidelines.

Patients in the Control Group did not receive ONCOS-102.

Arm type	Active comparator
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

All patients were to receive chemotherapy in 21-day cycles. The recommended dose of cisplatin was 75 mg/m2 infused i.v. over 2 hours beginning approximately 30 minutes after the end of pemetrexed infusion. Doses of cisplatin could have been reduced if deemed necessary by the investigator.

Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	PEMETREXED DISODIUM
Other name	

Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pemetrexed was administered in combination with cisplatin or carboplatin as standard of care in 21-day cycles starting on Day 22. Pemetrexed 500 mg/m2 was to be administered as an intravenous infusion over
10 minutes on Day 1 of each 21-day cycle. Doses of pemetrexed could have been reduced if deemed necessary by the investigator.

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received standard of care pemetrexed in combination with carboplatin (or cisplatin if appropriate) in 21-day cycles starting on Day 22. 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 carboplatin could have been reduced if deemed necessary by the investigator.

Number of subjects in period 1	Experimental Group	Control Group
Started	20	11
Completed	14	6
Not completed	6	5
Adverse event, non-fatal	1	1
could not/refused to attend End of Study visit	-	2
Lack of efficacy	5	2

Baseline characteristics

Reporting groups

Reporting group title	Phase 2 with a Phase 1b lead-in cohort

Reporting group description:

This study was conducted in 2 parts: a non-randomised Phase 1b safety part and a Phase 2 randomised part.
A total of 31 patients were treated with 6 patients in the Phase 1b safety part and 25 patients in the Phase 2 randomised part (14 patients in the Experimental Group and 11 patients in the Control Group). The DSMB reviewed data when the first 3 patients had completed all safety assessments and again when all 6 patients had completed all safety assessments during Phase 1b. At the second review, the DSMB recommended that the study should progress to the Phase 2 randomised part of the study at the same dose of ONCOS-102 as there were no safety concerns or Dose-Limiting Toxicities observed.

As patients in both the Phase 1b safety part of the study and the Experimental Group of the Phase 2 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'.

Reporting group values	Phase 2 with a Phase 1b lead-in cohort	Total	
Number of subjects	31	31	
Age categorical			
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;			
Units: Subjects			

Age continuous			
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;			
Units: years			
median	68.0		
full range (min-max)	36 to 80	-	
Gender categorical			
Units: Subjects			
Female	9	9	
Male	22	22	
Race			
Units: Subjects			
White	26	26	
Other	5	5	
ECOG Performance Status			
Units: Subjects			
equals 0	8	8	
equals 1	23	23	

Subject analysis sets

Subject analysis set title	Experimental Group
Subject analysis set type	Intention-to-treat

Subject analysis set description:

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 x 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 also received standard of care pemetrexed in combination with either 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 (SmPC) and/or local guidelines.

Subject analysis set title	Control Group
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients received pemetrexed in combination with either cisplatin or carboplatin in 21-day cycles and continued treatment as applicable during the study period of 6 cycles of chemotherapy. Patients in the Control Group did not receive ONCOS-102. Patients were given vitamin supplementation with folic acid and vitamin B12, and dexamethasone according to the SmPC and/or local guidelines.

Reporting group values	Experimental Group	Control Group	
Number of subjects	20	11	
Age categorical			
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;			
Units: Subjects			
Age continuous			
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;			
Units: years			
median	66.0	68.0	
full range (min-max)	36 to 80	61 to 75	
Gender categorical			
Units: Subjects			
Female	6	3	
Male	14	8	
Race			
Units: Subjects			
White	17	9	
Other	3	2	
ECOG Performance Status			
Units: Subjects			
equals 0	6	2	
equals 1	14	9	

End points

End points reporting groups

Reporting group title	Experimental Group

Reporting group description:

Eligible patients were pre-treated with an intravenous (i.v.) bolus injection of cyclophosphamide (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 x 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 also received standard of care pemetrexed in combination with either 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 (SmPC) and/or local guidelines.

Reporting group title	Control Group

Reporting group description:

Patients received pemetrexed in combination with either cisplatin or carboplatin in 21-day cycles and continued treatment as applicable during the study period of 6 cycles of chemotherapy.
Pemetrexed 500 mg/m2 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/m2 infused i.v. over 2 hours beginning approximately 30 minutes after the end of pemetrexed infusion. The dose of carboplatin was to be calculated based on the glomerular filtration rate calculated as per site's standard practice. Patients were to receive carboplatin AUC 5.
Patients were given vitamin supplementation with folic acid and vitamin B12, and dexamethasone according to the SmPC and/or local guidelines.

Patients in the Control Group did not receive ONCOS-102.

Subject analysis set title	Experimental Group
Subject analysis set type	Intention-to-treat

Subject analysis set description:

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 x 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 also received standard of care pemetrexed in combination with either 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 (SmPC) and/or local guidelines.

Subject analysis set title	Control Group
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients received pemetrexed in combination with either cisplatin or carboplatin in 21-day cycles and continued treatment as applicable during the study period of 6 cycles of chemotherapy. Patients in the Control Group did not receive ONCOS-102. Patients were given vitamin supplementation with folic acid and vitamin B12, and dexamethasone according to the SmPC and/or local guidelines.

Primary: Safety and tolerability profile of ONCOS-102 and pemetrexed/cisplatin - any TEAE

End point title	Safety and tolerability profile of ONCOS-102 and pemetrexed/cisplatin - any TEAE

End point description:

All AEs are categorised as baseline findings or treatment emergent AEs (TEAEs). Baseline findings are pre-existing and ongoing medical events recorded prior to the start of treatment. Safety data are presented for the safety population by treatment group. Safety was assessed per standard procedures ie, evaluation of AEs, laboratory test results, and vital signs. In addition, viral shedding was assessed in this study.
Laboratory/vital sign abnormalities were not to be reported as AEs unless they were considered clinically significant, the abnormality caused study drug dose adjustment or led to the patient’s discontinuation from the study, or if the investigator insisted the abnormality was to be reported as an AE.
This study was conducted in 2 parts: a non-randomised Phase 1b safety part and a Phase 2 randomised part.

End point type	Primary

End point timeframe:

All AEs/SAEs that occurred during the course of the study (from the date of informed consent through to the End of Study visit) or 30 days after the last dose of ONCOS-102 or chemotherapy (whichever was administered last) were to be reported.

End point values	Experimental Group	Control Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	11		
Units: number of all TEAE				
Any TEAE	375	137		
TEAE related to CPO	1	0		
TEAE related to ONCOS-102	82	0		
TEAE related to ONCOS-102 and chemotherapy	33	0		
TEAE related to chemotherapy only	110	78		
Unrelated TEAEs	144	59		

Statistical analyses

Statistical analysis title	Patient and event counts of AEs by SOC and PT

Statistical analysis description:

All AEs were coded for body system and preferred term using MedDRA.

Comparison groups	Experimental Group v Control Group
Number of subjects included in analysis	31
Analysis specification	Post-hoc
Analysis type	other[1]
P-value	≤ 0.05 [2]
Method	Fisher exact

Notes:

[1] - All AEs are summarized using descriptive statistics.

[2] - All statistical analyses are exploratory. 95% confidence intervals will be calculated for the difference between the groups in order to evaluate the size and the uncertainty of the potential treatment effect.

Primary: Safety and tolerability profile of ONCOS-102 and pemetrexed/cisplatin - serious TEAE

End point title	Safety and tolerability profile of ONCOS-102 and pemetrexed/cisplatin - serious TEAE

End point description:

An SAE was defined as any untoward medical occurrence that at any dose:
• Resulted in death.
• Was immediately life-threatening.
• Required inpatient hospitalisation or prolongation of existing hospitalisation.
• Resulted in persistent or significant disability/incapacity.
• Was a congenital abnormality/birth defect.
• Was considered an important medical event ie, may not have been immediately life-threatening or result in death/hospitalisation but may have jeopardised the patient or may have required intervention to prevent one of the other outcomes listed above.
In relation to any deaths during the study, as for all other SAEs, these were to be reported if they occurred within the study period or within 30 days of the last dose of ONCOS-102 or

pemetrexed/cisplatin/carboplatin (whichever was administered last). All deaths considered unequivocally due to disease progression were not to reported.

End point type	Primary

End point timeframe:

All SAEs that occurred during the course of the study (from the date of informed consent through to the End of Study visit) or 30 days after the last dose of ONCOS-102 or chemotherapy (whichever was administered last) were to be reported.

End point values	Experimental Group	Control Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	11		
Units: number of serious TEAEs				
Serious TEAEs	16	5		
Serious TEAE related to CPO	0	0		
Serious TEAE related to ONCOS-102	1	0		
Serious TEAE related to ONCOS-102 & chemotherapy	0	0		
Serious TEAE related to chemotherapy only	6	3		
Unrelated serious TEAEs	9	2		

Statistical analyses

Statistical analysis title	Patient and event counts of SAEs by SOC and PT

Statistical analysis description:

All SAEs were coded for body system and preferred term using MedDRA.

Comparison groups	Experimental Group v Control Group
Number of subjects included in analysis	31
Analysis specification	Post-hoc
Analysis type	other[3]
P-value	≤ 0.05 [4]
Method	Fisher exact

Notes:

[3] - All SAE were summarized using descriptive statistics.

[4] - All statistical analyses are exploratory. 95% confidence intervals will be calculated for the difference between the groups in order to evaluate the size and the uncertainty of the potential treatment effect.

Secondary: Efficacy - Overall Response Rate according to RECIST 1.1 in ITT population

End point title	Efficacy - Overall Response Rate according to RECIST 1.1 in ITT population

End point description:

ORR is summarised by RECIST 1.1 for the ITT population.

End point type	Secondary

End point timeframe:

Overall Response Rate is presented per RECIST 1.1 during the treatment phase.
Overall response is defined as Complete Response (CR) or Partial Response (PR) at any time point.

End point values	Experimental Group	Control Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	11		
Units: number				
Response	4	5		
No response	15	6		
Missing	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy - Overall PFS - 21-month Follow-up Analysis

End point title	Efficacy - Overall PFS - 21-month Follow-up Analysis

End point description:

PFS is presented per RECIST 1.1, irRECIST, and PERCIST until the end of the treatment phase. Changes in tumour metabolism and size were evaluated using diagnostic CT imaging and fluorodeoxy-D-glucose PET. The investigator was to make an evaluation of disease status after each PET-CT and CT scan. In the follow-up phase of the study, data regarding disease progression were recorded but not the type of scan. The latest available data for PFS are reported as part of the 21-month follow-up analysis (when all patients had been in the study for at least 21 months).
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.

End point type	Secondary

End point timeframe:

Overall PFS was defined as the time from start of treatment (Day 1) until disease progression or during the follow-up phase regardless of the scan modality or death from any cause.

End point values	Experimental Group	Control Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	10		
Units: month				
number (not applicable)				
PFS Minimum	1.3	1.5		
PFS Maximum	36.7	21		

Attachments (see zip file)	Overall PFS/ONCOS C719-study-report-body - Overall_PFS.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy - Overall survival (OS) - 21-month Follow-up Analysis

End point title	Efficacy - Overall survival (OS) - 21-month Follow-up Analysis

End point description:

A log-rank test was applied for OS. If a patient did not reach the endpoint, that patient was censored at the date last known to be alive.

End point type	Secondary

End point timeframe:

OS was determined as the time (weeks and months) from Day 1 until death from any cause.

End point values	Experimental Group	Control Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	7		
Units: month				
number (not applicable)				
OS Time Minimum	1.3	3.0		
OS Time Maximum	37.0	24.6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs/SAEs were recorded from date of signing of informed consent until up to 30 days after the study treatment.
After 30 days, only AEs/SAEs considered related to the study treatment or significant were reported.

Adverse event reporting additional description:

Any AEs which were considered unequivocally due to worsening of a patient's condition, attributable to the disease under study or that occurred after informed consent but before the patient was registered, did not have to be reported as AEs/SAEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Experimental Group

Reporting group description:

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 x 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 also received standard of care pemetrexed in combination with either cisplatin or carboplatin in 21-day cycles starting on Day 22. Pemetrexed 500mg/m2 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 75mg/m2 infused i.v. over 2h beginning approximately 30 min after the end of pemetrexed infusion. The dose of carboplatin was to be calculated based on the glomerular filtration rate calculated as per site's standard practice.

Reporting group title	Control Group

Reporting group description:

Patients received pemetrexed in combination with either cisplatin or carboplatin in 21-day cycles and continued treatment as applicable during the study period of 6 cycles of chemotherapy. Pemetrexed 500 mg/m2 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/m2 infused i.v. over 2 hours beginning approximately 30 minutes after the end of pemetrexed infusion. The dose of carboplatin was to be calculated based on the glomerular filtration rate calculated as per site's standard practice. Patients were to receive carboplatin AUC 5. Patients were given vitamin supplementation with folic acid and vitamin B12, and dexamethasone according to the SmPC and/or local guidelines.

Serious adverse events	Experimental Group	Control Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 20 (55.00%)	4 / 11 (36.36%)	
number of deaths (all causes)	8	4	
number of deaths resulting from adverse events	1	0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Nervous system disorders			
Myasthenia gravis crisis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug intolerance			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 20 (5.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Breast pain			

subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 20 (10.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Experimental Group	Control Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 20 (100.00%)	11 / 11 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 20 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Thrombophlebitis			
subjects affected / exposed	2 / 20 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	17 / 20 (85.00%)	7 / 11 (63.64%)	
occurrences (all)	25	9	
Chest pain			
subjects affected / exposed	6 / 20 (30.00%)	3 / 11 (27.27%)	
occurrences (all)	6	3	
Influenza like illness			
subjects affected / exposed	2 / 20 (10.00%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
General physical health deterioration			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Infusion site pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Injection site oedema			

subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Injection site pain			
subjects affected / exposed	4 / 20 (20.00%)	0 / 11 (0.00%)	
occurrences (all)	6	0	
Injection site papule			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Mucosal inflammation			
subjects affected / exposed	1 / 20 (5.00%)	1 / 11 (9.09%)	
occurrences (all)	1	2	
Non-cardiac chest pain			
subjects affected / exposed	0 / 20 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	2	
Oedema			
subjects affected / exposed	2 / 20 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	3	0	
Oedema peripheral			
subjects affected / exposed	2 / 20 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Pain			
subjects affected / exposed	4 / 20 (20.00%)	0 / 11 (0.00%)	
occurrences (all)	5	0	
Puncture site erythema			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Puncture site pain			
subjects affected / exposed	2 / 20 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Pyrexia			
subjects affected / exposed	14 / 20 (70.00%)	2 / 11 (18.18%)	
occurrences (all)	39	3	
Temperature regulation disorder			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			

Hypersensitivity			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 20 (30.00%)	1 / 11 (9.09%)	
occurrences (all)	11	1	
Dyspnoea			
subjects affected / exposed	3 / 20 (15.00%)	2 / 11 (18.18%)	
occurrences (all)	7	2	
Hiccups			
subjects affected / exposed	1 / 20 (5.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Hypoxia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Orthopnoea			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Pleural effusion			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Pleuritic pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Pneumothorax			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Productive cough			
subjects affected / exposed	1 / 20 (5.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Rhinorrhoea			

subjects affected / exposed	1 / 20 (5.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Sputum discoloured			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	2	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Depressed mood			
subjects affected / exposed	1 / 20 (5.00%)	2 / 11 (18.18%)	
occurrences (all)	1	2	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 20 (5.00%)	2 / 11 (18.18%)	
occurrences (all)	1	3	
Amylase increased			
subjects affected / exposed	2 / 20 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	4	0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 20 (5.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Blood cholesterol			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Blood cholesterol increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
C-reactive protein			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
C-reactive protein increased			

subjects affected / exposed	7 / 20 (35.00%)	4 / 11 (36.36%)	
occurrences (all)	9	4	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Weight decreased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Headache			
subjects affected / exposed	2 / 20 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	5	0	
Myasthenia gravis crisis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Neuropathy peripheral			
subjects affected / exposed	1 / 20 (5.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Neurotoxicity			
subjects affected / exposed	2 / 20 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Seizure			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Syncope			

subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	14 / 20 (70.00%)	9 / 11 (81.82%)	
occurrences (all)	17	11	
Eosinophilia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Leukocytosis			
subjects affected / exposed	2 / 20 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Leukostasis syndrome			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Lymphopenia			
subjects affected / exposed	4 / 20 (20.00%)	1 / 11 (9.09%)	
occurrences (all)	5	1	
Neutropenia			
subjects affected / exposed	14 / 20 (70.00%)	8 / 11 (72.73%)	
occurrences (all)	34	17	
Neutrophilia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Thrombocytopenia			
subjects affected / exposed	5 / 20 (25.00%)	4 / 11 (36.36%)	
occurrences (all)	15	5	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 20 (5.00%)	2 / 11 (18.18%)	
occurrences (all)	1	3	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	3 / 20 (15.00%)	0 / 11 (0.00%)	
occurrences (all)	3	0	
Abdominal pain upper			
subjects affected / exposed	1 / 20 (5.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Constipation			
subjects affected / exposed	5 / 20 (25.00%)	4 / 11 (36.36%)	
occurrences (all)	6	5	
Diarrhoea			
subjects affected / exposed	5 / 20 (25.00%)	3 / 11 (27.27%)	
occurrences (all)	8	3	
Gastrointestinal disorder			
subjects affected / exposed	2 / 20 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Haemorrhoids			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	15 / 20 (75.00%)	5 / 11 (45.45%)	
occurrences (all)	28	10	
Odynophagia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Proctalgia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	9 / 20 (45.00%)	1 / 11 (9.09%)	
occurrences (all)	17	3	
Skin and subcutaneous tissue disorders			
Blister			

subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Dry skin			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Hyperhidrosis			
subjects affected / exposed	2 / 20 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	4	0	
Night sweats			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Petechiae			
subjects affected / exposed	2 / 20 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Prurigo			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	1 / 20 (5.00%)	2 / 11 (18.18%)	
occurrences (all)	1	2	
Skin lesion			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 20 (10.00%)	1 / 11 (9.09%)	
occurrences (all)	3	1	
Micturition disorder			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Renal failure			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Urethral pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	

Urinary retention			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 20 (5.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Musculoskeletal chest pain			
subjects affected / exposed	5 / 20 (25.00%)	0 / 11 (0.00%)	
occurrences (all)	6	0	
Pain in extremity			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 20 (5.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Candida infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	2	
Cellulitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Conjunctivitis			
subjects affected / exposed	1 / 20 (5.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Herpes virus infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Oral herpes			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			

subjects affected / exposed	3 / 20 (15.00%)	0 / 11 (0.00%)	
occurrences (all)	3	0	
Tracheobronchitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	1 / 20 (5.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	7 / 20 (35.00%)	6 / 11 (54.55%)	
occurrences (all)	8	9	
Diabetes mellitus			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Dyslipidaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Fluid overload			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Hypercholesterolaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Hyperglycaemia			
subjects affected / exposed	2 / 20 (10.00%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
Hyperkalaemia			
subjects affected / exposed	2 / 20 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Hyperuricaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	

Hypoalbuminaemia			
subjects affected / exposed	2 / 20 (10.00%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
Hypocalcaemia			
subjects affected / exposed	2 / 20 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Hypokalaemia			
subjects affected / exposed	2 / 20 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Hypomagnesaemia			
subjects affected / exposed	2 / 20 (10.00%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
Hyponatraemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Hypophosphataemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Hypoproteinaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 December 2018	This amendment to the protocol introduced: A) Biological sampling (serum, PBMCs and biopsies) for immunological assessments to be performed at dedicated study sites only. B) Progression Free Survival added to assessments in the Follow-up phase. C) Immune data will be monitored on an ongoing basis, to assess and ensure adequate immune activation in the combination cohort, allowing any necessary adjustments in the frequency or timing of the dosing. D) Patients randomized that did not start treatment will be replaced. In addition, updated were timelines to be in line with the current status of the study and the revised project plan.
21 February 2019	Added information that the trial will be also conducted in US sites. Added information that carboplatin can substitute cisplatin and be accepted in combination with pemetrexed from start of study in certain patients. In patients where treatment with cisplatin is deemed to be too toxic by the investigator due to age, presence of neurological toxicities or other relevant medical conditions, carboplatin can be administered from start of study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes: