Clinical trial results:
A Phase I/II Study to Evaluate Safety and Efficacy of DCVAC/LuCa Added to Standard First Line Chemotherapy with Carboplatin and Paclitaxel +/- Immune Enhancers (Interferon-alpha and Hydroxychloroquine) vs Chemotherapy alone in Patients with Stage IV Non-Small Cell Lung Cancer

Summary

EudraCT number	2014-003084-37
Trial protocol	CZ SK
Global end of trial date	22 November 2021

Results information

Result version number	v1 (current)
This version publication date	28 August 2022
First version publication date	28 August 2022

Trial information

Trial identification

Sponsor protocol code	SLU01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02470468
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	SCTbio a.s. (formerly SOTIO a.s.)
Sponsor organisation address	Jankovcova 1518/2, Prague, Czechia, 170 00
Public contact	Clinical trials, SCTbio a.s. (formerly SOTIO a.s.), +420 224 175 111, clinicaltrial@sotio.com
Scientific contact	Clinical trials, SCTbio a.s. (formerly SOTIO a.s.), +420 224 175 111, clinicaltrial@sotio.com

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	22 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 November 2021
Global end of trial reached?	Yes
Global end of trial date	22 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective in protocol versions 1.0, 1.1, 2.0, and 3.0 was to compare the efficacy of DCVAC/LuCa together with chemotherapy with/without immune enhancers vs. chemotherapy alone in patients with stage IV non-small cell lung cancer (NSCLC), as measured by progression-free survival (PFS). The primary objective in protocol versions 4.0, 5.0, and 6.0 was to compare the efficacy of DCVAC/LuCa together with chemotherapy without immune enhancers vs. chemotherapy alone in patients with stage IV NSCLC, as measured by overall survival (OS).

Protection of trial subjects:

Not applicable

Background therapy:

Paclitaxel 175 mg/m2 intravenously over 3 hours followed by carboplatin area under the curve (AUC) 6 mg/mL per minute intravenously over 15-30 minutes

Evidence for comparator: -

Actual start date of recruitment	30 December 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Slovakia: 5
Country: Number of subjects enrolled	Czech Republic: 107
Worldwide total number of subjects	112
EEA total number of subjects	112

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)	44

From 65 to 84 years	68
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Fifteen sites in the Czech Republic and 2 sites in Slovakia screened at least 1 patient.
Patients:
Screened: 129
Randomized: 112
Analyzed for efficacy: 107
Analyzed for safety: 101

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A

Arm description:

Patients in this arm received DCVAC/LuCa subcutaneously every 3 weeks for the first 5 doses and then every 6 weeks in up to a total of 15 doses. DCVAC/LuCa was administered concurrently with chemotherapy (carboplatin and paclitaxel) for 3 to 5 cycles on day 15 (±3 days), starting from the second chemotherapy cycle. A total of 4 cycles of chemotherapy were to be administered to all patients. Patients with stable disease, partial response, or complete response could continue chemotherapy for up to a total of 6 cycles at the discretion of the investigator.

Arm type	Experimental
Investigational medicinal product name	DCVAC/LuCa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersion for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injection of approximately 1×10e7 autologous dendritic cells

Arm title	Group B

Arm description:

Patients in this arm received DCVAC/LuCa subcutaneously every 3 weeks for the first 5 doses and then every 6 weeks in up to a total of 15 doses. DCVAC/LuCa was administered concurrently with chemotherapy (carboplatin and paclitaxel) for 3 to 5 cycles on day 15 (±3 days), starting from the second chemotherapy cycle. A total of 4 cycles of chemotherapy were to be administered to all patients. Patients with stable disease, partial response, or complete response could continue chemotherapy for up to a total of 6 cycles at the discretion of the investigator. Patients also received pegylated IFN-α2b and hydroxychloroquine.

Arm type	Experimental
Investigational medicinal product name	DCVAC/LuCa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersion for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injection of approximately 1×10e7 autologous dendritic cells

Investigational medicinal product name	Pegylated IFN-α2b
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Pegylated IFN-α2b, 1 µg/kg, was divided into 2 doses and administered subcutaneously within a 10 cm radius from the DCVAC/LuCa injection site after each administration of DCVAC/LuCa.

Investigational medicinal product name	Hydroxychloroquine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Hydroxychloroquine was administered as 2 doses of 400 mg orally daily on a continuous basis for 7 consecutive days starting 1 day after each administration of DCVAC/LuCa.

Arm title	Group C

Arm description:

Patients in this arm received chemotherapy (carboplatin and paclitaxel) alone. A total of 4 cycles of chemotherapy were to be administered to all patients. Patients with stable disease, partial response, or complete response could continue chemotherapy for up to a total of 6 cycles at the discretion of the investigator.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Group A	Group B	Group C
Started	45	29	38
Completed	40	28	36
Not completed	5	1	2
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	-	1	1
Leukapheresis failure	2	-	-
Start of new anticancer treatment	-	-	1
DCVAC/LuCa production failure	2	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Group A
Reporting group description:	
Patients in this arm received DCVAC/LuCa subcutaneously every 3 weeks for the first 5 doses and then every 6 weeks in up to a total of 15 doses. DCVAC/LuCa was administered concurrently with chemotherapy (carboplatin and paclitaxel) for 3 to 5 cycles on day 15 (±3 days), starting from the second chemotherapy cycle. A total of 4 cycles of chemotherapy were to be administered to all patients. Patients with stable disease, partial response, or complete response could continue chemotherapy for up to a total of 6 cycles at the discretion of the investigator.	
Reporting group title	Group B
Reporting group description:	
Patients in this arm received DCVAC/LuCa subcutaneously every 3 weeks for the first 5 doses and then every 6 weeks in up to a total of 15 doses. DCVAC/LuCa was administered concurrently with chemotherapy (carboplatin and paclitaxel) for 3 to 5 cycles on day 15 (±3 days), starting from the second chemotherapy cycle. A total of 4 cycles of chemotherapy were to be administered to all patients. Patients with stable disease, partial response, or complete response could continue chemotherapy for up to a total of 6 cycles at the discretion of the investigator. Patients also received pegylated IFN-α2b and hydroxychloroquine.	
Reporting group title	Group C
Reporting group description:	
Patients in this arm received chemotherapy (carboplatin and paclitaxel) alone. A total of 4 cycles of chemotherapy were to be administered to all patients. Patients with stable disease, partial response, or complete response could continue chemotherapy for up to a total of 6 cycles at the discretion of the investigator.	

Reporting group values	Group A	Group B	Group C
Number of subjects	45	29	38
Age categorical Units: Subjects			
Adults (18-64 years)	13	11	20
From 65-84 years	32	18	18
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	14	8	10
Male	31	21	28

Reporting group values	Total		
Number of subjects	112		
Age categorical Units: Subjects			
Adults (18-64 years)	44		
From 65-84 years	68		
85 years and over	0		
Gender categorical Units: Subjects			
Female	32		
Male	80		

End points

End points reporting groups

Reporting group title	Group A

Reporting group description:

Patients in this arm received DCVAC/LuCa subcutaneously every 3 weeks for the first 5 doses and then every 6 weeks in up to a total of 15 doses. DCVAC/LuCa was administered concurrently with chemotherapy (carboplatin and paclitaxel) for 3 to 5 cycles on day 15 (±3 days), starting from the second chemotherapy cycle. A total of 4 cycles of chemotherapy were to be administered to all patients. Patients with stable disease, partial response, or complete response could continue chemotherapy for up to a total of 6 cycles at the discretion of the investigator.

Reporting group title	Group B

Reporting group description:

Patients in this arm received DCVAC/LuCa subcutaneously every 3 weeks for the first 5 doses and then every 6 weeks in up to a total of 15 doses. DCVAC/LuCa was administered concurrently with chemotherapy (carboplatin and paclitaxel) for 3 to 5 cycles on day 15 (±3 days), starting from the second chemotherapy cycle. A total of 4 cycles of chemotherapy were to be administered to all patients. Patients with stable disease, partial response, or complete response could continue chemotherapy for up to a total of 6 cycles at the discretion of the investigator. Patients also received pegylated IFN-α2b and hydroxychloroquine.

Reporting group title	Group C

Reporting group description:

Patients in this arm received chemotherapy (carboplatin and paclitaxel) alone. A total of 4 cycles of chemotherapy were to be administered to all patients. Patients with stable disease, partial response, or complete response could continue chemotherapy for up to a total of 6 cycles at the discretion of the investigator.

Primary: Overall survival, modified intention-to-treat population

End point title	Overall survival, modified intention-to-treat population

End point description:

All randomized patients regardless of whether they received treatment or not, except patients who did not start DCVAC/LuCa treatment due to leukapheresis or DCVAC/LuCa production failure

End point type	Primary

End point timeframe:

From the date of randomization to the date of death due to any cause or to the end of the study on 22-Nov-2021

End point values	Group A	Group B	Group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	29	38	
Units: Days				
median (inter-quartile range (Q1-Q3))	471.0 (253.0 to 721.0)	443.0 (166.0 to 604.0)	359.0 (151.0 to 476.0)	

Statistical analyses

Statistical analysis title	Primary
Comparison groups	Group A v Group C
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0065
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	0.83

Primary: Overall survival, per protocol population

End point title	Overall survival, per protocol population

End point description:

All randomized patients who received at least one cycle of chemotherapy and, for Group A and Group B, one dose of DCVAC/LuCa and, for Group B, one dose of one of immune enhancers, and did not have any major protocol deviation (protocol violation)

End point type	Primary

End point timeframe:

From the date of randomization to the date of death due to any cause or to the end of the study on 22-Nov-2021

End point values	Group A	Group B	Group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	26	28	
Units: Days				
median (inter-quartile range (Q1-Q3))	499.0 (278.0 to 721.0)	458.0 (173.0 to 604.0)	367.0 (243.5 to 476.5)	

Statistical analyses

Statistical analysis title	Supportive
Comparison groups	Group A v Group C
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0116
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.51

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	0.87

Secondary: Progression-free survival, modified intention-to-treat population

End point title	Progression-free survival, modified intention-to-treat population

End point description:

All randomized patients regardless of whether they received treatment or not, except patients who did not start DCVAC/LuCa treatment due to leukapheresis or DCVAC/LuCa production failure

End point type	Secondary

End point timeframe:

From the date of randomization to the date of an event defined as the first progression or death due to any cause or to the cut-off date of 21-Nov-2018

End point values	Group A	Group B	Group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	29	38	
Units: Days				
median (inter-quartile range (Q1-Q3))	205.0 (164.0 to 282.0)	182.0 (135.0 to 232.0)	171.0 (90.0 to 230.0)	

Statistical analyses

Statistical analysis title	Secondary
Comparison groups	Group A v Group C
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0334
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	0.97

Secondary: Progression-free survival, per protocol population

End point title	Progression-free survival, per protocol population

End point description:

All randomized patients who received at least one cycle of chemotherapy and, for Group A and Group B, one dose of DCVAC/LuCa and, for Group B, one dose of one of the immune enhancers, and did not have any major protocol deviation (protocol violation)

End point type	Secondary

End point timeframe:

From the date of randomization to the date of an event defined as the first progression or death due to any cause or to the cut-off date of 21-Nov-2018

End point values	Group A	Group B	Group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	26	28	
Units: Days				
median (inter-quartile range (Q1-Q3))	225.0 (176.0 to 282.0)	184.5 (136.0 to 232.0)	180.0 (92.0 to 268.0)	

Statistical analyses

Statistical analysis title	Secondary
Comparison groups	Group A v Group C
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0587
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	1.03

Secondary: Objective response rate, modified intention-to-treat

End point title	Objective response rate, modified intention-to-treat

End point description:

All randomized patients regardless of whether they received treatment or not, except patients who did not start DCVAC/LuCa treatment due to leukapheresis or DCVAC/LuCa production failure

End point type	Secondary

End point timeframe:

From the date of randomization to the cut-off date of 21-Nov-2018

End point values	Group A	Group B	Group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	29	38	
Units: Percentage				
number (confidence interval 95%)	45 (29.3 to 61.5)	42.3 (23.4 to 63.1)	34.3 (19.1 to 52.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate, per protocol population

End point title	Objective response rate, per protocol population

End point description:

All randomized patients who received at least one cycle of chemotherapy and, for Group A and Group B, one dose of DCVAC/LuCa and, for Group B, one dose of one of the immune enhancers, and did not have any major protocol deviation (protocol violation)

End point type	Secondary

End point timeframe:

From the date of randomization to the cut-off date of 21-Nov-2018

End point values	Group A	Group B	Group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	26	28	
Units: Percentage				
number (confidence interval 95%)	54.5 (36.4 to 71.9)	47.8 (26.8 to 69.4)	46.2 (26.6 to 66.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response, modified intention-to-treat population

End point title	Duration of response, modified intention-to-treat population

End point description:

All randomized patients regardless of whether they received treatment or not, except patients who did not start DCVAC/LuCa treatment due to leukapheresis or DCVAC/LuCa production failure

End point type	Secondary

End point timeframe:

From the date of complete/partial response to disease progression or death or the cut-off date of 21-Nov-2018

End point values	Group A	Group B	Group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	29	38	
Units: Days				
median (inter-quartile range (Q1-Q3))	102.0 (78.0 to 276.0)	108.0 (44.0 to 181.0)	89.5 (48.0 to 239.5)	

Statistical analyses

Statistical analysis title	Secondary
Comparison groups	Group A v Group C
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2539
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	1.39

Secondary: Duration of response, per protocol population

End point title	Duration of response, per protocol population

End point description:

All randomized patients who received at least one cycle of chemotherapy and, for Group A and Group B, one dose of DCVAC/LuCa and, for Group B, one dose of one of the immune enhancers, and did not have any major protocol deviation (protocol violation)

End point type	Secondary

End point timeframe:

From the date of complete/partial response to disease progression or death or the cut-off date of 21-Nov-2018

End point values	Group A	Group B	Group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	26	28	
Units: Days				
median (inter-quartile range (Q1-Q3))	102.0 (78.0 to 276.0)	108.0 (44.0 to 181.0)	89.5 (48.0 to 239.5)	

Statistical analyses

Statistical analysis title	Secondary
Comparison groups	Group A v Group C
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2539
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	1.39

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs): started/worsened at/after start of study treatment and before 30 days after study treatment end; related serious AEs, AEs of special interest: collected beyond 30 days after study treatment end; deaths: consent signature to study end

Adverse event reporting additional description:

Only treatment-emergent AEs (TEAEs) were analyzed (see the definition above); the tables include information on TEAEs, serious TEAEs, and all deaths; causality was assessed by investigators; disease progression or AEs related to disease progression were reported as AEs but not as SAEs (regardless of outcome or seriousness criteria)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Group A

Reporting group description:

Patients in this arm received DCVAC/LuCa subcutaneously every 3 weeks for the first 5 doses and then every 6 weeks in up to a total of 15 doses. DCVAC/LuCa was to be administered concurrently with chemotherapy (carboplatin and paclitaxel) for 3 to 5 cycles on day 15 (±3 days) during each cycle and was to start during the second cycle of chemotherapy.

Reporting group title	Group B

Reporting group description:

Patients in this arm received DCVAC/LuCa subcutaneously every 3 weeks for the first 5 doses and then every 6 weeks in up to a total of 15 doses. DCVAC/LuCa was to be administered concurrently with chemotherapy (carboplatin and paclitaxel) for 3 to 5 cycles on day 15 (±3 days) during each cycle and was to start during the second cycle of chemotherapy. Pegylated IFN-α2b, 1 µg/kg, was to be divided into 2 doses and administered to patients in Group B subcutaneously within a 10 cm radius from the injection site of DCVAC/LuCa after each DCVAC/LuCa administration. Hydroxychloroquine was to be administered to patients in Group B in 2 doses of 400 mg orally daily on a continuous basis for 7 consecutive days starting 1 day after each dosing of DCVAC/LuCa.

Reporting group title	Group C

Reporting group description:

Chemotherapy (carboplatin and paclitaxel) alone

Serious adverse events	Group A	Group B	Group C
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 40 (32.50%)	13 / 27 (48.15%)	9 / 34 (26.47%)
number of deaths (all causes)	9	9	2
number of deaths resulting from adverse events	9	9	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pericardial effusion malignant			
subjects affected / exposed	0 / 40 (0.00%)	1 / 27 (3.70%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Injury, poisoning and procedural complications			
Procedural pneumothorax			
subjects affected / exposed	0 / 40 (0.00%)	1 / 27 (3.70%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	1 / 40 (2.50%)	0 / 27 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Venous thrombosis			
subjects affected / exposed	1 / 40 (2.50%)	0 / 27 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 40 (2.50%)	0 / 27 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 40 (0.00%)	0 / 27 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac tamponade			
subjects affected / exposed	0 / 40 (0.00%)	1 / 27 (3.70%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 40 (0.00%)	0 / 27 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Supraventricular tachycardia			

subjects affected / exposed	1 / 40 (2.50%)	0 / 27 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Demyelinating polyneuropathy			
subjects affected / exposed	0 / 40 (0.00%)	0 / 27 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 40 (7.50%)	1 / 27 (3.70%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	1 / 40 (2.50%)	1 / 27 (3.70%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 27 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 40 (2.50%)	2 / 27 (7.41%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 40 (0.00%)	1 / 27 (3.70%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 40 (0.00%)	1 / 27 (3.70%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 40 (0.00%)	1 / 27 (3.70%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	1 / 40 (2.50%)	1 / 27 (3.70%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 27 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 40 (0.00%)	0 / 27 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal infarction			
subjects affected / exposed	1 / 40 (2.50%)	0 / 27 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 40 (0.00%)	1 / 27 (3.70%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal ulcer haemorrhage			
subjects affected / exposed	1 / 40 (2.50%)	0 / 27 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 40 (0.00%)	0 / 27 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 40 (2.50%)	1 / 27 (3.70%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 40 (2.50%)	0 / 27 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 40 (0.00%)	1 / 27 (3.70%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea at rest			
subjects affected / exposed	0 / 40 (0.00%)	0 / 27 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 27 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiccups			
subjects affected / exposed	0 / 40 (0.00%)	0 / 27 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 40 (2.50%)	0 / 27 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 40 (0.00%)	1 / 27 (3.70%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 40 (2.50%)	2 / 27 (7.41%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 40 (2.50%)	0 / 27 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 40 (0.00%)	1 / 27 (3.70%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 40 (0.00%)	1 / 27 (3.70%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 40 (2.50%)	0 / 27 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 40 (0.00%)	1 / 27 (3.70%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 40 (0.00%)	1 / 27 (3.70%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	0 / 40 (0.00%)	1 / 27 (3.70%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hypokalaemia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 27 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Group A	Group B	Group C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 40 (97.50%)	27 / 27 (100.00%)	33 / 34 (97.06%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 40 (2.50%)	2 / 27 (7.41%)	1 / 34 (2.94%)
occurrences (all)	1	2	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 40 (2.50%)	4 / 27 (14.81%)	1 / 34 (2.94%)
occurrences (all)	1	4	1
Chills			
subjects affected / exposed	1 / 40 (2.50%)	4 / 27 (14.81%)	0 / 34 (0.00%)
occurrences (all)	1	4	0
Fatigue			
subjects affected / exposed	16 / 40 (40.00%)	5 / 27 (18.52%)	7 / 34 (20.59%)
occurrences (all)	16	5	7
General physical health deterioration			
subjects affected / exposed	7 / 40 (17.50%)	3 / 27 (11.11%)	0 / 34 (0.00%)
occurrences (all)	7	3	0
Influenza like illness			
subjects affected / exposed	0 / 40 (0.00%)	2 / 27 (7.41%)	0 / 34 (0.00%)
occurrences (all)	0	2	0
Oedema peripheral			
subjects affected / exposed	2 / 40 (5.00%)	2 / 27 (7.41%)	0 / 34 (0.00%)
occurrences (all)	2	2	0
Immune system disorders			

Pyrexia			
subjects affected / exposed	2 / 40 (5.00%)	6 / 27 (22.22%)	2 / 34 (5.88%)
occurrences (all)	2	6	2
Hypersensitivity			
subjects affected / exposed	3 / 40 (7.50%)	0 / 27 (0.00%)	1 / 34 (2.94%)
occurrences (all)	3	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 40 (10.00%)	4 / 27 (14.81%)	1 / 34 (2.94%)
occurrences (all)	4	4	1
Dysphonia			
subjects affected / exposed	1 / 40 (2.50%)	2 / 27 (7.41%)	0 / 34 (0.00%)
occurrences (all)	1	2	0
Dyspnoea			
subjects affected / exposed	5 / 40 (12.50%)	4 / 27 (14.81%)	1 / 34 (2.94%)
occurrences (all)	5	4	1
Pleural effusion			
subjects affected / exposed	4 / 40 (10.00%)	3 / 27 (11.11%)	0 / 34 (0.00%)
occurrences (all)	4	3	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 40 (0.00%)	2 / 27 (7.41%)	1 / 34 (2.94%)
occurrences (all)	0	2	1
Depression			
subjects affected / exposed	0 / 40 (0.00%)	2 / 27 (7.41%)	1 / 34 (2.94%)
occurrences (all)	0	2	1
Insomnia			
subjects affected / exposed	6 / 40 (15.00%)	1 / 27 (3.70%)	1 / 34 (2.94%)
occurrences (all)	6	1	1
Investigations			
Weight decreased			
subjects affected / exposed	4 / 40 (10.00%)	2 / 27 (7.41%)	2 / 34 (5.88%)
occurrences (all)	4	2	2
Cardiac disorders			
Tachycardia			

subjects affected / exposed	0 / 40 (0.00%)	2 / 27 (7.41%)	1 / 34 (2.94%)
occurrences (all)	0	2	1
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 40 (5.00%)	2 / 27 (7.41%)	0 / 34 (0.00%)
occurrences (all)	2	2	0
Neuropathy peripheral			
subjects affected / exposed	4 / 40 (10.00%)	2 / 27 (7.41%)	2 / 34 (5.88%)
occurrences (all)	4	2	2
Paraesthesia			
subjects affected / exposed	11 / 40 (27.50%)	7 / 27 (25.93%)	6 / 34 (17.65%)
occurrences (all)	11	7	6
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 40 (2.50%)	2 / 27 (7.41%)	2 / 34 (5.88%)
occurrences (all)	1	2	2
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	20 / 40 (50.00%)	8 / 27 (29.63%)	7 / 34 (20.59%)
occurrences (all)	20	8	7
Anaemia			
subjects affected / exposed	12 / 40 (30.00%)	11 / 27 (40.74%)	11 / 34 (32.35%)
occurrences (all)	12	11	11
Leukopenia			
subjects affected / exposed	6 / 40 (15.00%)	3 / 27 (11.11%)	4 / 34 (11.76%)
occurrences (all)	6	3	4
Thrombocytopenia			
subjects affected / exposed	10 / 40 (25.00%)	12 / 27 (44.44%)	10 / 34 (29.41%)
occurrences (all)	10	12	10
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 40 (0.00%)	4 / 27 (14.81%)	1 / 34 (2.94%)
occurrences (all)	0	4	1
Constipation			
subjects affected / exposed	8 / 40 (20.00%)	1 / 27 (3.70%)	2 / 34 (5.88%)
occurrences (all)	8	1	2
Diarrhoea			

subjects affected / exposed	7 / 40 (17.50%)	5 / 27 (18.52%)	3 / 34 (8.82%)
occurrences (all)	7	5	3
Nausea			
subjects affected / exposed	9 / 40 (22.50%)	12 / 27 (44.44%)	6 / 34 (17.65%)
occurrences (all)	9	12	6
Vomiting			
subjects affected / exposed	8 / 40 (20.00%)	5 / 27 (18.52%)	8 / 34 (23.53%)
occurrences (all)	8	5	8
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	10 / 40 (25.00%)	8 / 27 (29.63%)	14 / 34 (41.18%)
occurrences (all)	10	8	14
Alopecia totalis			
subjects affected / exposed	5 / 40 (12.50%)	5 / 27 (18.52%)	1 / 34 (2.94%)
occurrences (all)	5	5	1
Pruritus			
subjects affected / exposed	0 / 40 (0.00%)	4 / 27 (14.81%)	0 / 34 (0.00%)
occurrences (all)	0	4	0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 40 (0.00%)	2 / 27 (7.41%)	1 / 34 (2.94%)
occurrences (all)	0	2	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 40 (20.00%)	4 / 27 (14.81%)	7 / 34 (20.59%)
occurrences (all)	8	4	7
Back pain			
subjects affected / exposed	4 / 40 (10.00%)	0 / 27 (0.00%)	5 / 34 (14.71%)
occurrences (all)	4	0	5
Bone pain			
subjects affected / exposed	0 / 40 (0.00%)	2 / 27 (7.41%)	0 / 34 (0.00%)
occurrences (all)	0	2	0
Myalgia			
subjects affected / exposed	4 / 40 (10.00%)	1 / 27 (3.70%)	3 / 34 (8.82%)
occurrences (all)	4	1	3
Pain in extremity			

subjects affected / exposed	4 / 40 (10.00%)	3 / 27 (11.11%)	4 / 34 (11.76%)
occurrences (all)	4	3	4
Spinal pain			
subjects affected / exposed	1 / 40 (2.50%)	2 / 27 (7.41%)	0 / 34 (0.00%)
occurrences (all)	1	2	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	5 / 40 (12.50%)	1 / 27 (3.70%)	0 / 34 (0.00%)
occurrences (all)	5	1	0
Candida infection			
subjects affected / exposed	1 / 40 (2.50%)	2 / 27 (7.41%)	0 / 34 (0.00%)
occurrences (all)	1	2	0
Urinary tract infection			
subjects affected / exposed	3 / 40 (7.50%)	2 / 27 (7.41%)	1 / 34 (2.94%)
occurrences (all)	3	2	1
Viral infection			
subjects affected / exposed	3 / 40 (7.50%)	0 / 27 (0.00%)	0 / 34 (0.00%)
occurrences (all)	3	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	9 / 40 (22.50%)	9 / 27 (33.33%)	6 / 34 (17.65%)
occurrences (all)	9	9	6
Dehydration			
subjects affected / exposed	2 / 40 (5.00%)	3 / 27 (11.11%)	1 / 34 (2.94%)
occurrences (all)	2	3	1
Hypokalaemia			
subjects affected / exposed	2 / 40 (5.00%)	3 / 27 (11.11%)	2 / 34 (5.88%)
occurrences (all)	2	3	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 December 2014	Non-substantial changes: - The reason for the update was to delete country specification of the trial, as it was decided to extend the trial to other countries - Linguistic corrections or rewording
26 May 2016	Substantial changes: - Addition of population with large cell carcinoma - Update of timing of the primary efficacy analysis due to prolonged recruitment - Update of estimated study duration from 36 to 48 months resulting from prolonged patient recruitment - Update of wording of inclusion criteria to clarify requirement for recovery from toxicity - Addition of sections and wording to allow patient replacement and addition of patients in case of leukapheresis failures, to reach a total of 105 evaluable patients - Update of wording on prohibited medications to better reflect current practices - Addition of acceptable time window for the EoT visit - Clarification on timing of research samples collection in patients with disease progression - Clarification that CT scan is not needed at the EoT visit in case of prior documented progression - Clarification wording on censoring patients in case of protocol violations Non-substantial change: - Clarifications and correction of typos
28 July 2016	Substantial change: - Omission of Group B
14 August 2017	Substantial changes: - Omission of Group B in the analysis (except for safety tables and listings) - Changing the primary endpoint from PFS to OS - Due to harmonization with other studies, time from randomization is used in the analyses (and not time from the initiation of chemotherapy as in the previous protocol versions)
09 October 2018	Substantial change: - Addition of exploratory research on predictive and prognostic biomarkers, which requires the collection of archived tissue samples after obtaining appropriate informed consent from all randomized patients regardless of the protocol version according to which they were randomized
19 November 2018	Substantial change: - Study extension by 3 years to collect additional survival data for ongoing patients Non-substantial change: - Clarification of the timing of statistical analyses

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34284344