Clinical trial results:
NEO -ADJUVANT CHEMO/IMMUNOTHERAPY FOR THE TREATMENT OF RESECTABLE STAGE IIIA NON SMALL CELL LUNG CANCER (NSCLC): A PHASE II MULTICENTER EXPLORATORY STUD

Summary

EudraCT number	2016-003732-20
Trial protocol	ES
Global end of trial date	18 October 2023

Results information

Result version number	v1 (current)
This version publication date	30 October 2024
First version publication date	30 October 2024
Summary attachment (see zip file)	Lancet Oncol article_NADIM (NADIM I_Provencio _ The Lancet Onco 2020.pdf)

Trial information

Trial identification

Sponsor protocol code	GECP16/03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03081689
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fundación GECP
Sponsor organisation address	Avda. Meridiana 358, Barcelona, Spain, 08027
Public contact	Eva Pereira, Fundación GECP, +34 934302006, epereira@gecp.org
Scientific contact	Eva Pereira, Fundación GECP, +34 934302006, epereira@gecp.org

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	19 March 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 October 2023
Global end of trial reached?	Yes
Global end of trial date	18 October 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Estimate progression-free survival (PFS) at 24 months from diagnosis

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 February 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 46
Worldwide total number of subjects	46
EEA total number of subjects	46

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	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between April 26, 2017, and Aug 25, 2018, we screened 51 patients for eligibility, of whom 46 patients were enrolled from 25 different sites and received neoadjuvant treatment.

Pre-assignment

Screening details:

Screening details: Patients eligible for the trial are those with a histological diagnosis or cytologically proven operable and resectable non-small-cell lung cancer, stage IIIA.

Period 1

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

Arms

Arm title	Experimental

Arm description:

Patients received the following drugs intravenously, as neoadjuvant treatment: nivolumab (360 mg), paclitaxel (200 mg/m²), and carboplatin (area under the curve 6; 6 mg/mL per min), on day 1 of each 21-day cycle, for three cycles before surgical resection. After completion of neoadjuvant chemoimmunotherapy, surgery was planned 42–49 days after the first day of the third treatment cycle. Resection of the primary tumour and lymph nodes was done according to standard institutional procedures. Once the patients were deemed fully recovered from surgery, adjuvant treatment with nivolumab was scheduled to commence 3–8 weeks after surgery. Patients received intravenous nivolumab as adjuvant treatment at a fixed dose of 240 mg every 2 weeks for 4 months, followed by a fixed dose of 480 mg every 4 weeks, until month 12.

Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	BMS-936558 or MDX1106
Other name	Opdivo
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

- Neoadjuvant treatment: Nivolumab 360 mg IV Q3W + Paclitaxel 200mg/m2 + Carboplatin AUC 6 IV Q3W, 3 cycles
- Surgery
- Adjuvant treatment: Nivolumab 240 mg Q2W for 4 months and Nivolumab 480 mg Q4W for 8 months (1 year) after surgical resection

Dose reductions were not permitted for nivolumab; however, nivolumab treatment could be interrupted, delayed, or discontinued depending on tolerability

Number of subjects in period 1	Experimental
Started	46
Completed	46

Baseline characteristics

Reporting groups	
Reporting group title	Overall study (overall period)

Reporting group description: -

Reporting group values	Overall study (overall period)	Total	
Number of subjects	46	46	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	63.1		
standard deviation	± 8.9	-	
Gender categorical Units: Subjects			
Female	34	34	
Male	12	12	
ECOG performance status Units: Subjects			
ECOG 0	25	25	
ECOG 1	21	21	
Smoking status Units: Subjects			
Former smoker (≥ 1 year)	25	25	
Current smoker	21	21	
Never smoker	0	0	
Histology Units: Subjects			
Adenocarcinoma	26	26	
Squamous cell carcinoma	16	16	
Not specified or undifferentiated	4	4	
Tumor node, metastasis staging classification			

8th ed. TNM for Lung Cancer
Primary tumor (T)
T1-T4 describe the size & location of the tumor, on a scale of 1 to 4. A larger tumor or a tumor that has grown deeper into nearby tissue will get a higher number.
Distant metastasis (M)
M1: Cancer has spread to other parts of the body or not (M0)

Regional lymph nodes (N) N0: No regional lymph node metastases N1: Metastasis in ipsilateral peribronchial or ipsilateral hilar lymph nodes & intrapulmonary N2: Metastasis in ipsilateral mediastinal or subcarinal lymph node N3:Metastasis in contralateral hilar, scalene or supraclavicular lymph node			
Units: Subjects			
T1N2M0	15	15	
T2N1M0	1	1	
T2N2M0	6	6	
T3N1M0	1	1	
T3N2M0	13	13	
T4N0M0	9	9	
T4N1M0	1	1	
Tumour lesion size			
Units: millilitre(s)/millilitre			
median	35		
full range (min-max)	23 to 60	-	

End points

End points reporting groups

Reporting group title	Experimental

Reporting group description:

Patients received the following drugs intravenously, as neoadjuvant treatment: nivolumab (360 mg), paclitaxel (200 mg/m²), and carboplatin (area under the curve 6; 6 mg/mL per min), on day 1 of each 21-day cycle, for three cycles before surgical resection. After completion of neoadjuvant chemoimmunotherapy, surgery was planned 42–49 days after the first day of the third treatment cycle. Resection of the primary tumour and lymph nodes was done according to standard institutional procedures. Once the patients were deemed fully recovered from surgery, adjuvant treatment with nivolumab was scheduled to commence 3–8 weeks after surgery. Patients received intravenous nivolumab as adjuvant treatment at a fixed dose of 240 mg every 2 weeks for 4 months, followed by a fixed dose of 480 mg every 4 weeks, until month 12.

Primary: Progression Free Survival at 24 months

End point title	Progression Free Survival at 24 months[1]

End point description:

Rate of PFS at 24 months from diagnosis defined as the rate of patients free of disease progression or death from any cause whichever occurs first as determined by the investigator according to RECIST v1.1. criteria for systemic disease.

End point type	Primary

End point timeframe:

At 24 months from diagnosis

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Progression-free survival, compared with that reported for these patients in previous studies (ranging from 40% in patients receiving standard therapy, considered here as the null hypothesis, to 55% in patients receiving the analysed treatment),15–17 with a one-sided type I error of 5%. We used the Kaplan-Meier method to estimate progression-free survival and overall survival and corresponding 95% CIs.

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: Subject				
number (confidence interval 95%)	77.1 (59.9 to 87.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Percentage of patients are still alive

End point type	Secondary

End point timeframe:

At 3 years from the first dose of neoadjuvant treatment

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: Subjects				
number (confidence interval 95%)	89.9 (74.5 to 96.2)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any adverse event or breakdown occurring during the course of the study.
The investigator will have to collect all adverse events once they have signed informed consent, during treatment and 30 days after the last dose study treatment administration.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	As-treated population

Reporting group description: -

Serious adverse events	As-treated population		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 46 (6.52%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Increased lipase			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	As-treated population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 46 (93.48%)		
Nervous system disorders			
Neurotoxicity			

subjects affected / exposed	13 / 46 (28.26%)		
occurrences (all)	13		
Paraesthesia			
subjects affected / exposed	8 / 46 (17.39%)		
occurrences (all)	8		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 46 (15.22%)		
occurrences (all)	7		
Increased aminotransferases			
subjects affected / exposed	5 / 46 (10.87%)		
occurrences (all)	5		
Increased creatinine level			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	3		
Increased lipase			
subjects affected / exposed	4 / 46 (8.70%)		
occurrences (all)	4		
General disorders and administration site conditions			
Asthenia or fatigue			
subjects affected / exposed	23 / 46 (50.00%)		
occurrences (all)	23		
Constipation			
subjects affected / exposed	8 / 46 (17.39%)		
occurrences (all)	8		
Decreased appetite or anorexia			
subjects affected / exposed	9 / 46 (19.57%)		
occurrences (all)	9		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	11 / 46 (23.91%)		
occurrences (all)	11		
Nausea			
subjects affected / exposed	11 / 46 (23.91%)		
occurrences (all)	11		
Vomiting			

subjects affected / exposed	8 / 46 (17.39%)		
occurrences (all)	8		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	8 / 46 (17.39%)		
occurrences (all)	8		
Pruritus			
subjects affected / exposed	13 / 46 (28.26%)		
occurrences (all)	13		
Skin disorders (rash)			
subjects affected / exposed	19 / 46 (41.30%)		
occurrences (all)	19		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	12 / 46 (26.09%)		
occurrences (all)	12		
Myalgia			
subjects affected / exposed	9 / 46 (19.57%)		
occurrences (all)	9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 June 2017	New protocol version: Modify the version of TNM required for staging patients from TNM 7th edition to TNM 8th editing and clarify schedule of study procedures
09 May 2018	New version of protocol: Add the option to replace invalid patients to complete the patient sample initially calculated in order to meet the initially set statistical objectives and clarify an inclusion criterion in relation to the version of the TNM accepted by protocol
15 January 2019	Change of Sponsor of study
20 June 2019	Changes in the protocol: The information contained in the protocol is reviewed regarding the pharmacogenetic analyzes to be performed on the samples extracted from the patients included in the study. A more detailed description of said analyzes and the objectives that are intended to be met with said analyzes is made.
16 November 2020	Changes in the protocol: The information contained in the protocol is reviewed regarding the analyzes to be performed on the computed tomography (CT) scans of the patients included in the study. A new analysis is added that can contribute to better understanding the clinical evolution of patients with lung cancer by obtaining predictions of the results of possible treatments.
22 September 2022	Changes in the protocol: The follow-up period of the NADIM study was planned to last 3 years and will be extended to 5 years. The analysis of these 2 additional years may contribute to better understanding the clinical evolution of patients with lung cancer.

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/35576508

http://www.ncbi.nlm.nih.gov/pubmed/32979984