



Clinical trial results:

Multicenter phase II trial of Nintedanib plus docetaxel in second line of treatment in patients with no squamous non small cell lung cancer refractory to first line chemotherapy (REFRACT study)

Summary

EudraCT number	2015-000475-27
Trial protocol	FR
Global end of trial date	16 September 2020

Results information

Result version number	v1 (current)
This version publication date	14 May 2021
First version publication date	14 May 2021
Summary attachment (see zip file)	Refract_manuscript (REFRACT_Article.docx)

Trial information

Trial identification

Sponsor protocol code	I14041
-----------------------	--------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02531737
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CHU de Limoges
Sponsor organisation address	25 Avenue Martin Luther King, Limoges, France, 87042
Public contact	Dr Jean-Bernard AULIAC, Centre Hospitalier de Créteil, 33 0157022092, Jean-Bernard.auliac@chicreteil.fr
Scientific contact	Dr Jean-Bernard AULIAC, Centre Hospitalier de Créteil, 33 0157022092, Jean-Bernard.auliac@chicreteil.fr

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	16 September 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	16 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Efficacy of the the nintedanib- docetaxel combination in second-line treatment in patients with no squamous non small cell lung cancer refractory to first line chemotherapy

Protection of trial subjects:

The informed consent of a patient is obtained prior to any study related procedures as per Good Clinical Practices (GCP) as set forth in the ICH guidelines.

Documentation that informed consent occurred prior to the patient's entry into the study and of the informed consent process is recorded in the patient's source documents. In addition, if a protocol is amended and it impacts on the content of the informed consent, patients participating in the study are informed and re-consente is required.

Finally, a DSMB was set up to monitor the progress of the trial and the adverse effects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 May 2015
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	France: 53
Worldwide total number of subjects	53
EEA total number of subjects	53

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)	14

From 65 to 84 years	39
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 59 patients in 23 French centers were enrolled and followed from December 7, 2015 to December 24, 2019

Pre-assignment

Screening details:

The key inclusion criteria : histologically confirmed non-squamous stage IV NSCLC; no activating EGFR mutation; no ALK translocation or unknown status; at least one measurable lesion (RECIST 1.1); refractory disease, PS0 or 1; no history of other malignancy within the last 5 years ; normal hepatic, renal function and hematological function.

Period 1

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

Arms

Arm title	Nintedanib+Docetaxel
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	nintedanib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

200 mg X 2 /day from Day 2 to Day 21 until progression or unacceptable toxicity
possible reduction of nintedanib to 300 mg/day or 200 mg/day

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

75 mg/m² by intravenous infusion on Day 1
Possible reduction in the dose of docetaxel to 60 mg/m²

Number of subjects in period 1	Nintedanib+Docetaxel
Started	53
Completed	53

Baseline characteristics

Reporting groups

Reporting group title	overall trial
-----------------------	---------------

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	53	53	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	14	14	
From 65-84 years	39	39	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	58.5		
standard deviation	± 8.5	-	
Gender categorical			
Units: Subjects			
Female	14	14	
Male	39	39	

End points

End points reporting groups

Reporting group title	Nintedanib+Docetaxel
Reporting group description: -	

Primary: Rate of PFS at 12 weeks after inclusion

End point title	Rate of PFS at 12 weeks after inclusion ^[1]
End point description:	

End point type	Primary
End point timeframe:	
12 weeks after inclusion	

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: The primary analysis associated with main objectif was a description of the percentage of patients who did not progress up to 12 week.

The 95% confidence interval of this percentage was also estimated using the exact method

End point values	Nintedanib+Docetaxel			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: percent				
number (confidence interval 95%)	39.6 (26.5 to 54)			

Attachments (see zip file)	Efficacy results ("As treated" population)/Table 2. Efficacy
-----------------------------------	--

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)
End point description:	

End point type	Secondary
End point timeframe:	
At one year	

End point values	Nintedanib+Docetaxel			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: Month				
number (confidence interval 95%)	11.8 (4.8 to 22.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Median PFS

End point title	Median PFS
End point description:	
End point type	Secondary
End point timeframe:	
At one year	

End point values	Nintedanib+Docetaxel			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: Month				
number (confidence interval 95%)	2.7 (1.4 to 4.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival
End point description:	
End point type	Secondary
End point timeframe:	
At one year	

End point values	Nintedanib+Docetaxel			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: Percent				
number (confidence interval 95%)	32.1 (19.8 to 45.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival
End point description:	
End point type	Secondary
End point timeframe:	
At 18 months	

End point values	Nintedanib+Docetaxel			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: percent				
number (confidence interval 95%)	27.6 (16.1 to 40.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Best Response

End point title	Best Response
End point description:	
Best response to treatment observed according to the RECIST 1.1 criteria over the patient's period of participation, ie one year.	
End point type	Secondary
End point timeframe:	
At 12 months	

End point values	Nintedanib+Docetaxel			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: Number of patients	10			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Are concerned patients who received at least one dose of experimental treatment (docetaxel or nintedanib). The adverse events are those occurring between the date of the first administration and the end of the patient's participation + 30 days.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	22.1
--------------------	------

Reporting groups

Reporting group title	Overall trial
-----------------------	---------------

Reporting group description: -

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 53 (54.72%)		
number of deaths (all causes)	11		
number of deaths resulting from adverse events	9		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to meninges			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Disease progression			

subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General physical health deterioration			
subjects affected / exposed	6 / 53 (11.32%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 3		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 1		
Pulmonary embolism			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Investigations			
Weight decreased			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Pericardial effusion			

subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Monoplegia			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neuralgia			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Partial seizures			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile bone marrow aplasia			
subjects affected / exposed	5 / 53 (9.43%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Vomiting			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	11 / 53 (20.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile colitis			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			

subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malnutrition			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 53 (98.11%)		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 53 (7.55%)		
occurrences (all)	10		

Alanine aminotransferase increased subjects affected / exposed occurrences (all)	3 / 53 (5.66%) 10		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all)	14 / 53 (26.42%) 18 8 / 53 (15.09%) 12		
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all) Anaemia subjects affected / exposed occurrences (all)	20 / 53 (37.74%) 51 12 / 53 (22.64%) 12		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	24 / 53 (45.28%) 33 18 / 53 (33.96%) 21 9 / 53 (16.98%) 10		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	8 / 53 (15.09%) 8		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	11 / 53 (20.75%) 13		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported