Clinical trial results:
A PHASE II PROSPECTIVE IMMUNE NEOADJUVANT THERAPY STUDY OF DURVALUMAB (MEDI4736) IN EARLY STAGE NON-SMALL CELL LUNG CANCER

Summary

EudraCT number	2016-001849-15
Trial protocol	FR
Global end of trial date	28 August 2019

Results information

Result version number	v1 (current)
This version publication date	11 August 2022
First version publication date	11 August 2022

Trial information

Trial identification

Sponsor protocol code	IFCT-1601 IONESCO

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03030131
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	IFCT
Sponsor organisation address	10 rue de la Grange-Batelière, Paris, France, 75009
Public contact	Contact, IFCT, 33 156811045, contact@ifct.fr
Scientific contact	Contact, IFCT, 33 156811045, contact@ifct.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	06 May 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 August 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the impact of neo-adjuvant therapy with durvalumab given by intravenous infusion for one month on the complete resection (R0).

Protection of trial subjects:

Algorithms for management of adverse events were provided in the protocol.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 April 2017
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	France: 50
Worldwide total number of subjects	50
EEA total number of subjects	50

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)	35
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 50 patients were recruited from April 2017 to August 2019 in 20 sites, of whom 46 met the eligibility criteria and received durvalumab.

Pre-assignment

Screening details:

Histologically confirmed NSCLC, classified as stage IB (only ≥4 cm), IIA, IIB, or IIIA non N2. Brain imaging, FDG-PET and a thoraco abdominopelvic CT scan were performed within one month prior to inclusion. Patients ≥18 years old with an ECOG performance status score of 0 1 were eligible. Pre therapeutic tissue was required.

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	Durvalumab

Arm description:

Monotherapy arm

Arm type	Experimental
Investigational medicinal product name	Durvalumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

750 mg at D1, D15 and D29 over 60 minutes

Number of subjects in period 1	Durvalumab
Started	50
Completed	43
Not completed	7
Lack of efficacy	3
Protocol deviation	4

Baseline characteristics

Reporting groups

Reporting group title	Overall trial (overall period)

Reporting group description: -

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	50	50	
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	61.0		
full range (min-max)	46.0 to 80.4	-	
Gender categorical Units: Subjects			
Female	15	15	
Male	35	35	
Smocking status Units: Subjects			
Smockers	47	47	
Never smockers	3	3	
ECOG performance status Units: Subjects			
PS 0	40	40	
PS 1	10	10	
Histology Units: Subjects			
Adenocarcinoma	25	25	
Squamous cell carcinoma	21	21	
Other	4	4	
Stage Units: Subjects			
IB	5	5	
IIA	14	14	
IIB	29	29	
IIIA	1	1	
Other stages	1	1	

Histological evidence Units: Subjects			
Yes	49	49	
No	1	1	
Cytological evidence Units: Subjects			
Yes	12	12	
No	38	38	
Diagnosis Units: Subjects			
Echoendoscopy	6	6	
Fibroscopy	24	24	
Fibroscopy + Echoendoscopy	1	1	
Transthoracic puncture	19	19	
Smocking details Units: Pack Year			
median	40.0		
full range (min-max)	2 to 100	-	
Weight Units: kilogram(s)			
median	74		
full range (min-max)	44 to 101	-	

End points

End points reporting groups

Reporting group title	Durvalumab
Reporting group description: Monotherapy arm	
Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description: All included patients	
Subject analysis set title	Safety population - Durvalumab
Subject analysis set type	Safety analysis
Subject analysis set description: All patients who had received at least one dose of durvalumab	
Subject analysis set title	Efficacy population - Durvalumab
Subject analysis set type	Per protocol
Subject analysis set description: Eligible patients without any major deviations from the inclusion/exclusion criteria	
Subject analysis set title	Efficacy population - Durvalumab and surgery
Subject analysis set type	Per protocol
Subject analysis set description: all eligible patients who had received at least one dose of durvalumab and who undergone surgery	

Primary: Surgical Resection R0

End point title	Surgical Resection R0[1]
End point description: Patient percentage of surgical resection R0 after a maximum of 3 cycles of immune therapy	
End point type	Primary
End point timeframe: 2 months	

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: Not applicable as the study was single arm

End point values	Durvalumab			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: % of participants				
number (confidence interval 95%)				
Complete resection (R0)	89.1 (80.1 to 98.1)			
Microscopically incomplete resection (R1)	4.3 (0.0 to 10.2)			
Not evaluable/Not done	6.5 (0.0 to 13.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Delay Between Surgery and Start of Treatment

End point title	Delay Between Surgery and Start of Treatment

End point description:

End point type	Secondary

End point timeframe:

After 28 days (3 cycles of immune therapy maximum)

End point values	Durvalumab			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: Days				
median (full range (min-max))	37.0 (29 to 46)			

Statistical analyses

No statistical analyses for this end point

Secondary: Response Rate (RECIST 1.1)

End point title	Response Rate (RECIST 1.1)

End point description:

Response Rate include patient with complete response (disappearance of all target lesions) or partial response (at least a 30% decrease in the sum of diameters of target lesions since inclusion) as evaluated with Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1).

End point type	Secondary

End point timeframe:

After 28 days (3 cycles of immune therapy maximum)

End point values	Durvalumab			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: % of participants				
Partial response	4			
Stable disease	36			
Progressive disease	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Major Pathological Response

End point title	Major Pathological Response

End point description:

Major Pathological Response is defined as ≤10% remaining viable tumour cells (RVT).

End point type	Secondary

End point timeframe:

2 months

End point values	Durvalumab			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: % of participants				
RVT ≤10%	8			
RVT >10%	35			
Unknown	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-Free Survival (DFS)

End point title	Disease-Free Survival (DFS)

End point description:

Time from the date of inclusion to the date of first documented disease relapse or the occurrence of a new invasive primary malignancy or death from any cause

End point type	Secondary

End point timeframe:

18 months

End point values	Durvalumab			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: % of participants				
number (confidence interval 95%)				
12-month DFS	78.3 (63.4 to 87.7)			
12-month DFS - RVT ≤10%	100 (100 to 100)			

12-month DFS - RVT >10%	77.1 (59.5 to 87.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Time from the inclusion to the date of death of any cause, or censored at their last known alive date

End point type	Secondary

End point timeframe:

18 months

End point values	Durvalumab			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: % of participants				
number (confidence interval 95%)				
12-month OS	89.1 (75.8 to 95.3)			
12-month OS - RVT ≤ 10 %	100 (100 to 100)			
12-month OS - RVT > 10 %	88.6 (72.4 to 95.6)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected for a patient from the date of signature of inform consent form, during treatment period and until 100 days after the last dose of study treatment.
Deaths were collected until data analysis.

Adverse event reporting additional description:

The maximal grade of adverse events was collected by cycle of treatment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	Safety population

Reporting group description: -

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 48 (39.58%)		
number of deaths (all causes)	8		
number of deaths resulting from adverse events			
Blood and lymphatic system disorders			
Haemolytic anaemia			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Chest pain			

subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Respiratory distress				
subjects affected / exposed	4 / 48 (8.33%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			
Tracheal stenosis				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung disorder				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	2 / 48 (4.17%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Haemothorax				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tracheal fistula				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Bronchial fistula				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chylothorax				

subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Skin and subcutaneous tissue disorders			
Subcutaneous emphysema			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Pain in extremity			

subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia bacterial			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Sepsis			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 48 (97.92%)		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	17 / 48 (35.42%)		
occurrences (all)	25		
Chest pain			
subjects affected / exposed	12 / 48 (25.00%)		
occurrences (all)	18		
Pain			
subjects affected / exposed	4 / 48 (8.33%)		
occurrences (all)	4		
Ear and labyrinth disorders			

Vertigo subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 4		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all)	 6 / 48 (12.50%) 7 6 / 48 (12.50%) 7 3 / 48 (6.25%) 3		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Haemoptysis subjects affected / exposed occurrences (all) Respiratory distress subjects affected / exposed occurrences (all) Pneumothorax subjects affected / exposed occurrences (all) Lung disorder subjects affected / exposed occurrences (all)	 14 / 48 (29.17%) 23 12 / 48 (25.00%) 26 6 / 48 (12.50%) 9 5 / 48 (10.42%) 6 4 / 48 (8.33%) 4 3 / 48 (6.25%) 3		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	 3 / 48 (6.25%) 5		

Rash subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 3		
Renal and urinary disorders Urinary retention subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 3		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Musculoskeletal chest pain subjects affected / exposed occurrences (all)	4 / 48 (8.33%) 4 3 / 48 (6.25%) 4 3 / 48 (6.25%) 4		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	5 / 48 (10.42%) 9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 June 2017	A first substantial modification was done in order: • to adapt the protocol to the 8th edition of the UICC TNM classification • to delete "Drug-induced liver injury" from serious adverse events lists • to add a section for the management of myocarditis and similar toxicities
16 May 2018	A second substantial modification was done in order: • to extent inclusion criteria to stage IIIA non-N2 NSCLC • to make frozen tissue collection optional
08 January 2019	A third substantial modification was done in order to: • to clarify and update inclusion criteria specifying the size of the tumor • to delete the exclusion criteria about ECG that is no longer required. • to add a central review of all patients before inclusion. • to add a suspension of inclusions after the 57th patients in order to perform a statistical analysis of tolerance data (90-days postoperative). In addition, a definitive discontinuation of the study was planned in case of occurrence of a new death (any cause combined) occurring within 90 days of surgery. • to add collection of feces before starting study treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
28 August 2019	Enrolment was stopped on August 28, 2019 at the request of the independent committee due to excessive 90-day postoperative mortality, with 4 unexpected deaths (8.7% of the 46 eligible patients).	-

Notes:

Limitations and caveats

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

The main study limitation was the small sample size, due to the premature ending of the trial. Another limitations were the prevalence of risk factors in the study population and finally, the heterogenity due to the involvement of 20 active centers.

Notes: