Clinical trial results:
Phase IV/II open label study for the early evaluation of the response to treatment with Cisplatin, Gemcitabine and Bevacizumab in patientes with advanced or metastatic non small cell lung cancer.

Summary

EudraCT number	2012-000459-15
Trial protocol	ES
Global end of trial date	13 September 2016

Results information

Result version number	v1 (current)
This version publication date	17 November 2021
First version publication date	17 November 2021

Trial information

Trial identification

Sponsor protocol code	IMPACT

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Fundació Clínic per la Recerca Biomèdica
Sponsor organisation address	Calle Villarroel, 170 , Barcelona, Spain, 08036
Public contact	Noemi Reguart, Noemi Reguart, 34 932275402na, nreguart@clinic.ub.es
Scientific contact	Noemi Reguart, Noemi Reguart, 34 932275402na, nreguart@clinic.ub.es

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	15 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 September 2016
Global end of trial reached?	Yes
Global end of trial date	13 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Co-primary variable 1: Evaluate the baseline results of the tumor to the treatment in terms of blood flow, blood volume, time at peak enhancement and permeability, and correlate it with the objective response (RC+ RP) (according to RECIST 1.1) to day +42.

Co-primary variable 2: Evaluate the results of the tumor's early response (day +7) to treatment in terms of blood flow, blood volume, time at peak enhancement and permeability, and correlate it with objective response (RC+ RP) (according to RECIST 1.1) per day + 42.

Protection of trial subjects:

All subjects received standard supportive care as determined by their treating physician.
There is no prohibit supportive treatment.
Any treatment for previous or concurrent diagnosed non malignant disease is allowed.

Background therapy:

All subjects received standard supportive care as determined by their treating physician.

Evidence for comparator:

NOT APPLICABLE

Actual start date of recruitment	11 April 2012
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	Spain: 17
Worldwide total number of subjects	17
EEA total number of subjects	17

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)	7
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

STUDY PERIOD: From: 24 July 2013 To: 13 September 2016
CENTERS: Hospital Clínic Barcelona.
PHASE OF DEVELOPMENT: Phase IV

Pre-assignment

Screening details:

locally advanced or metastatic (IIIB/IV) non-squamous non-small-cell lung cancer (NSCLC).
Patients with asymptomatic treated brain metastases are eligible for trial participation.
Patient with evidence of tumor compressing or invading a main blood vessel on imaging studies cannot be included.

Pre-assignment period milestones

Number of subjects started	17
Number of subjects completed	16

Pre-assignment subject non-completion reasons

Reason: Number of subjects	progression of disease: 1

Period 1

Period 1 title	Valid patients for assesment. (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	No RECIST responders at day +42

Arm description:

Patients with PD or ST at day +42

Arm type	NON RESPONDERS
Investigational medicinal product name	gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine 1250 mg/m2 days 1 and 8/3 weeks during 6 weeks

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Intracavernous use

Dosage and administration details:

bevacizumab 7.5 mg/Kg/3 weeks until progression or toxicity.

Investigational medicinal product name	CDDP
Investigational medicinal product code	
Other name	Cisplatinum

Pharmaceutical forms	Concentrate for concentrate for solution for infusion, Concentrate for solution for injection, Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatino 80 mg/ m2 IV el day 1/3 weeks during 6 weeks

Arm title	RECIST responders at day +42

Arm description:

Patients with RECIST response at day +42

Arm type	RECIST responders
Investigational medicinal product name	CDDP
Investigational medicinal product code	
Other name	Cisplatinum
Pharmaceutical forms	Concentrate for concentrate for solution for infusion, Concentrate for solution for injection, Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatino 80 mg/ m2 IV el day 1/3 weeks during 6 weeks

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

Dosage and administration details:

Gemcitabine 1250 mg/m2 days 1 and 8/3 weeks during 6 weeks

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Intracavernous use

Dosage and administration details:

bevacizumab 7.5 mg/Kg/3 weeks until progression or toxicity.

Number of subjects in period 1[1]	No RECIST responders at day +42	RECIST responders at day +42
Started	12	4
Completed	12	4

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 17 patients began a conventional treatment designed to analyze a possible relation between Ct Scan characteristics and RECIST responses at day +42.
A patient did not a radiologic evaluation at day +42, and he is invalid for the analysis.

Baseline characteristics

Reporting groups	
Reporting group title	Valid patients for assesment.

Reporting group description: -

Reporting group values	Valid patients for assesment.	Total	
Number of subjects	16	16	
Age categorical Units: Subjects			
Adults (18-64 years)	7	7	
From 65-84 years	9	9	
85 years and over	0	0	
Age continuous Units: years			
median	66.0		
standard deviation	± 10.804	-	
Gender categorical Units: Subjects			
Female	2	2	
Male	14	14	
Not recorded	0	0	

End points

End points reporting groups

Reporting group title	No RECIST responders at day +42
Reporting group description: Patients with PD or ST at day +42	

Reporting group title	RECIST responders at day +42
Reporting group description: Patients with RECIST response at day +42	

Primary: Evaluate the difference between day +7 and baseline blood flow, blood volume, permeability, and correlate it with the objective response at day +42.

End point title	Evaluate the difference between day +7 and baseline blood flow, blood volume, permeability, and correlate it with the objective response at day +42.

End point description:

Evaluate the results of the tumor's early response (day +7) to treatment in terms of blood flow, blood volume, time at peak enhancement and permeability, and correlate it with objective response (RC+ RP) (according to RECIST 1.1) at day + 42.

End point type	Primary
End point timeframe: base line, day +7 and day +42	

End point values	No RECIST responders at day +42	RECIST responders at day +42		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	4		
Units: Ml/min				
number (not applicable)				
Base line blood flow	12	4		
Base line blood volume	12	4		
baseline blood enhacement and permeability	12	4		
Blood flow at day +7	12	4		
blood volume alt day +7	12	4		
blood enhacement and permeability at day +7	12	4		

Statistical analyses

Statistical analysis title	Blood flow change between baseline and day +7
Comparison groups	No RECIST responders at day +42 v RECIST responders at day +42

Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	t-test, 2-sided

Statistical analysis title	Blood volume change between baseline and day +7
Comparison groups	No RECIST responders at day +42 v RECIST responders at day +42
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	t-test, 2-sided

Statistical analysis title	Permeability change between baseline and day +7
Comparison groups	No RECIST responders at day +42 v RECIST responders at day +42
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	t-test, 2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

11-04-2012 to 13-09-2016

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Arm 1

Reporting group description: -

Serious adverse events	Arm 1		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 17 (47.06%)		
number of deaths (all causes)	8		
number of deaths resulting from adverse events	1		
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Dysarthria			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	4 / 17 (23.53%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		

White blood cell count decreased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
esophagitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 17 (5.88%)		
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	Arm 1		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 17 (100.00%)		

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 17 (47.06%)		
occurrences (all)	21		
Phlebitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Deep vein thrombosis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Surgical and medical procedures			
Abscess drainage			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	16 / 17 (94.12%)		
occurrences (all)	64		
Chest pain			
subjects affected / exposed	5 / 17 (29.41%)		
occurrences (all)	7		
Pyrexia			
subjects affected / exposed	5 / 17 (29.41%)		
occurrences (all)	7		
general deteroriation of physical condition			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	4		
facial edema			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Infusion site phlebitis			

subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Adverse reactions to drugs			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Thoracic pain			
subjects affected / exposed	5 / 17 (29.41%)		
occurrences (all)	7		
Epistaxis			
subjects affected / exposed	4 / 17 (23.53%)		
occurrences (all)	6		
Dysphonia			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	3		
Hiccups			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	5		
Cough			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	4		
Hemoptysis			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	4		
Dyspnoea			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Pulmonary embolism			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Productive cough			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Psychiatric disorders			

Anxiety			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Abstinence syndrome			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	3		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 17 (35.29%)		
occurrences (all)	10		
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 17 (23.53%)		
occurrences (all)	7		
Weight decreased			
subjects affected / exposed	4 / 17 (23.53%)		
occurrences (all)	4		
Increased blood alkaline phosphatase			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Transaminases increased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Hypertriglyceridaemia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Injury, poisoning and procedural			

complications Lesion subjects affected / exposed occurrences (all)	 2 / 17 (11.76%) 2		
Congenital, familial and genetic disorders Cranial malformation subjects affected / exposed occurrences (all)	 1 / 17 (5.88%) 1		
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Neurotoxicity subjects affected / exposed occurrences (all) Neuropathy peripheral subjects affected / exposed occurrences (all) Syncope subjects affected / exposed occurrences (all)	 8 / 17 (47.06%) 12 5 / 17 (29.41%) 6 2 / 17 (11.76%) 2 2 / 17 (11.76%) 2 1 / 17 (5.88%) 1 1 / 17 (5.88%) 1		
Blood and lymphatic system disorders peripheral edema subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Anemia	 3 / 17 (17.65%) 3 12 / 17 (70.59%) 45		

subjects affected / exposed	10 / 17 (58.82%)		
occurrences (all)	17		
Thrombocytopenia			
subjects affected / exposed	8 / 17 (47.06%)		
occurrences (all)	34		
Leukopenia			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	4		
Thrombocytosis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	4		
Hypoacusis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Hearing disability			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Eye disorders			
Decreased visual acuity			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	10 / 17 (58.82%)		
occurrences (all)	21		
Constipation			
subjects affected / exposed	8 / 17 (47.06%)		
occurrences (all)	10		
Diarrhoea			
subjects affected / exposed	6 / 17 (35.29%)		
occurrences (all)	7		
Vomiting			

subjects affected / exposed	6 / 17 (35.29%)			
occurrences (all)	8			
Abdominal pain upper				
subjects affected / exposed	4 / 17 (23.53%)			
occurrences (all)	5			
Gastritis				
subjects affected / exposed	2 / 17 (11.76%)			
occurrences (all)	2			
Rectal haemorrhage				
subjects affected / exposed	2 / 17 (11.76%)			
occurrences (all)	2			
Dysphagia				
subjects affected / exposed	1 / 17 (5.88%)			
occurrences (all)	1			
Dyspepsia				
subjects affected / exposed	1 / 17 (5.88%)			
occurrences (all)	1			
Abdominal pain				
subjects affected / exposed	1 / 17 (5.88%)			
occurrences (all)	1			
dental pain				
subjects affected / exposed	1 / 17 (5.88%)			
occurrences (all)	1			
esophagitis				
subjects affected / exposed	1 / 17 (5.88%)			
occurrences (all)	1			
Gingival bleeding				
subjects affected / exposed	1 / 17 (5.88%)			
occurrences (all)	1			
Hemorrhoidal bleeding				
subjects affected / exposed	1 / 17 (5.88%)			
occurrences (all)	1			
mouth aphtha				
subjects affected / exposed	1 / 17 (5.88%)			
occurrences (all)	1			
Mucosal inflammation				

subjects affected / exposed	6 / 17 (35.29%)		
occurrences (all)	8		
Gingivitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Mouth ulceration			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	4 / 17 (23.53%)		
occurrences (all)	8		
Dermatitis acneiform			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
Erythema			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Skin lesion			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Madarosis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Petechiae			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	4 / 17 (23.53%)		
occurrences (all)	5		
Dysuria			

subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Acute kidney injury			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 17 (41.18%)		
occurrences (all)	7		
Back pain			
subjects affected / exposed	4 / 17 (23.53%)		
occurrences (all)	5		
Pain in extremity			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	3		
Neck pain			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Musculoskeletal pain			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Clubbed fingers			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Hypertrophyc osteoarthropathy			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Tendinitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Muscular weakness			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Infections and infestations			

Respiratory tract infection subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 3		
Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2		
Pneumonia subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 1		
Balanitis candida subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Oral candidiasis subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Folliculitis subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Furuncle subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Dental infection subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Fungal infection subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Tinea infection subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Metabolism and nutrition disorders Decreased appetite			

subjects affected / exposed	9 / 17 (52.94%)		
occurrences (all)	16		
Hypocalcaemia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	4		
Hypomagnesaemia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Cell death			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 July 2013	Non relevant amendment.
31 July 2013	Non relevant amendment.
24 November 2014	The reason for this relevant amendment is to modify the exclusion criteria to allow the inclusion of patients according to more realistic criteria consistent with clinical practice. In addition, another minor change is made, consisting of modifying Appendix 6, which replaces the Du Bois normogram with the Mosteller formula for body surface determination (SC), and thus adapting it to the usual clinical practice of the center.
10 November 2015	The reason for this relevant amendment is to shorten the follow-up period of patients and extend the study recruitment period in order to complete the inclusion of patients (n.20), and thus achieve the primary objective of the study. In this way, the follow-up period will be reduced for the last patients included in the study, however, a high average follow-up would be maintained taking into account the entire study population included since the start of recruitment (first patient included on July 26, 2013).

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.

Although the percentage change in blood volume has reached statistical significance, the number of patients is very small and should therefore be confirmed in a larger study.

Notes: