Clinical trial results:
Pharmacogenetic study in castration-resistant prostate cancer patients treated with abiraterone acetate

Summary

EudraCT number	2012-005036-28
Trial protocol	FR
Global end of trial date	06 March 2020

Results information

Result version number	v1 (current)
This version publication date	24 December 2021
First version publication date	24 December 2021

Trial information

Trial identification

Sponsor protocol code	2012/41

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01858441
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Centre Antoine Lacassagne
Sponsor organisation address	33 av de Valombrose, Nice, France,
Public contact	LOVERA Christine, CENTRE ANTOINE LACASSAGNE, +33 492031618, christine.lovera@nice.unicancer.fr
Scientific contact	LOVERA Christine, CENTRE ANTOINE LACASSAGNE, +33 492031618, christine.lovera@nice.unicancer.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	30 August 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 March 2020
Global end of trial reached?	Yes
Global end of trial date	06 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective will be to investigate the relationships between candidate-gene polymorphisms specifically related to AA pharmacology: CYP17A1, SLCO2B1 and SLCO2B3 (13 single nucleotide polymorphisms) and the clinical efficacy of AA in terms of progression-free survival. Such relationships will take into account relevant histo-prognostic factors of metastatic CRPC cancers (clinical staging, pre-treatment PSA, Gleason score) and treatment compliance.

Protection of trial subjects:

In order to ensure the protection of the rights, safety and well-being of trials subjects, this clinical trial was performed in accordance with the Protocol, the Public Health Code Article 1121-1 and following of the law n ° 2004-806 of the Public Health Code, its decrees and orders in force, Good Clinical Practice, 24 November 2006, the European Directive 2005/28/EC of 8 April 2005 and 2011/20/CE, the decision published in the OJ of 30/11/2006 laying down rules of good clinical practice for biomedical research relating to medicinal products for human and guide of good clinical practice (including guideline CT-1).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 April 2015
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: 148
Worldwide total number of subjects	148
EEA total number of subjects	148

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)	20
From 65 to 84 years	120
85 years and over	8

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients who have had disease progression after failure of androgen deprivation therapy. Over 330 expected patients, 148 patients have been screened and included, including 2 patients wrongly included.

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	Patient with mCRPC

Arm description:

- Abiraterone acetate 1000 mg (500 mg x 2 tablets) daily
- Prednisone or prednisolone 10 mg daily, or any other corticotherapy based on the investigator's choice and the standard of care of each center

Arm type	Experimental
Investigational medicinal product name	Abiraterone acetate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Abiraterone acetate 1000 mg (500 mg x 2 tablets) daily

Number of subjects in period 1	Patient with mCRPC
Started	148
Completed	119
Not completed	29
Adverse event, serious fatal	2
Consent withdrawn by subject	7
Physician decision	5
second cancer	1
Adverse event, non-fatal	6
Protocol deviation	7
Irradiation on the only lesion	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	148	148	
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			
arithmetic mean	73.45		
inter-quartile range (Q1-Q3)	53.4 to 93	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	148	148	

End points

End points reporting groups

Reporting group title	Patient with mCRPC

Reporting group description:

- Abiraterone acetate 1000 mg (500 mg x 2 tablets) daily
- Prednisone or prednisolone 10 mg daily, or any other corticotherapy based on the investigator's choice and the standard of care of each center

Subject analysis set title	study patient cohort
Subject analysis set type	Per protocol

Subject analysis set description:

Included patients with mCRPC

Primary: Radiologic survival-free progression

End point title	Radiologic survival-free progression

End point description:

End point type	Primary

End point timeframe:

Radiologic survival-free progression up to 36 months

End point values	Patient with mCRPC	study patient cohort		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	102	102		
Units: month				
median (confidence interval 95%)	13 (8 to 22)	13 (8 to 22)		

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

Relationships between candidate-gene polymorphisms specifically related to AA pharmacology: CYP17A1, SLCO2B1 and SLCO2B3 (13 single nucleotide polymorphisms) and the clinical efficacy of AA in terms of radiographic progression-free survival. Such relationships will take into account relevant histo-prognostic factors of metastatic CRPC cancers (clinical staging, pre-treatment PSA, Gleason score).

Comparison groups	Patient with mCRPC v study patient cohort
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 5
Method	Logrank

Notes:

[1] - Relationships between polymorphisms and radiologic SFP

Secondary: biological survival-free progression

End point title	biological survival-free progression

End point description:

End point type	Secondary

End point timeframe:
biological survival-free progression up to 36 months

End point values	Patient with mCRPC			
Subject group type	Reporting group			
Number of subjects analysed	102			
Units: month				
median (confidence interval 95%)	9 (5 to 17)			

Statistical analyses

No statistical analyses for this end point

Secondary: global survival

End point title	global survival

End point description:

End point type	Secondary

End point timeframe:
global survival up to 36 months

End point values	Patient with mCRPC			
Subject group type	Reporting group			
Number of subjects analysed	102			
Units: month				
median (confidence interval 95%)	44 (35 to 55)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Overall period of the study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23

Reporting groups	
Reporting group title	Experimental arm

Reporting group description: -

Serious adverse events	Experimental arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 145 (24.14%)		
number of deaths (all causes)	102		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	2 / 145 (1.38%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cancer pain			
subjects affected / exposed	2 / 145 (1.38%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 145 (1.38%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	3 / 145 (2.07%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	3 / 145 (2.07%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	3 / 145 (2.07%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Lung disorder			
subjects affected / exposed	2 / 145 (1.38%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	2 / 145 (1.38%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Drug-induced liver injury			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 145 (2.07%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Dysuria			
subjects affected / exposed	2 / 145 (1.38%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Haematuria			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Spinal pain			
subjects affected / exposed	2 / 145 (1.38%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis			
subjects affected / exposed	2 / 145 (1.38%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	2 / 145 (1.38%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 145 (1.38%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Experimental arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	138 / 145 (95.17%)		
Investigations			

Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	11 / 145 (7.59%) 18		
Vascular disorders Hypertension subjects affected / exposed occurrences (all) Hot flush subjects affected / exposed occurrences (all)	 23 / 145 (15.86%) 28 25 / 145 (17.24%) 26		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all)	 41 / 145 (28.28%) 68 32 / 145 (22.07%) 52		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 16 / 145 (11.03%) 25		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	 20 / 145 (13.79%) 20 17 / 145 (11.72%) 19 14 / 145 (9.66%) 17		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	 14 / 145 (9.66%) 17		
Musculoskeletal and connective tissue disorders			

Back pain subjects affected / exposed occurrences (all)	27 / 145 (18.62%) 30		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 August 2013	- Addition of precautions for use in handling Zytiga - Establishment of a serum library over the duration of the study in the context of hormonal assays
03 March 2014	- Modification of the protocol in view of recent developments and recommendations with regard to the therapeutic management of patients with metastatic hormone-resistant prostate cancer. - Abiraterone Acetate (AA) has received Marketing Authorization for first-line metastatic administration. - The Scientific Committee of the study therefore deemed it appropriate to no longer consider patients who received a first line of metastatic chemotherapy with Docetaxel, but patients indicated to receive AA in the first metastatic line.
18 June 2014	- Modification of the inclusion criteria - Change of principal investigator at center 03 (Institut BERGONIE in BORDEAUX) following the departure of Dr Nadine HOUEDE - Removal of center 06 (AP-HP - Saint Louis Hospital) - Addition of 6 new research centers
28 October 2015	• Addition of a paragraph presenting the optional ancillary studies which have been added to the protocol: o Study of mutations in the gene encoding the androgen receptor (AR) offered only to patients included outside CAL for reasons of the quantity of tubes collected. o Feasibility study on AR-V7, a predictor of response to AA treatment. This study will only be carried out on consenting patients included in CAL (center 1) for reasons of logistical simplicity. • In view of the rhythm of inclusions, the inclusion period and the total duration of the study were reviewed. • Beyond 6 months of treatment, clinical examinations were spaced every 3 months.
06 January 2016	Declaration of new co-investigators
21 November 2018	Change of principal investigator in centers
05 June 2019	This modification is made following the request of the pharmaceutical sponsor who produces the study treatment (ZYTIGA®): From June 1, 2019, only the 500 mg tablet form will be available in pharmacies. The protocol as well as the study documents have been modified accordingly. In addition, the protocol has been brought into regulatory compliance with the addition of the GDPR to the regulatory framework. An information letter was sent to the centers to inform the patients included in the study in November 2018.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported