Clinical trial results:
Efficacy and Safety of PD-0332991 in Patients with Advanced Gastrointestinal Stromal Tumors Refractory to Imatinib and Sunitinib: A Phase 2 study

Summary

EudraCT number	2013-000283-28
Trial protocol	FR
Global end of trial date	01 February 2019

Results information

Result version number	v1 (current)
This version publication date	20 January 2022
First version publication date	20 January 2022
Summary attachment (see zip file)	Study protocol (CYCLIGIST.pdf)

Trial information

Trial identification

Sponsor protocol code	IB_2013–01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01907607
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Institut Bergonié
Sponsor organisation address	229 cours de l'Argonne, Bordeaux, France, 33076
Public contact	Regulatory Affairs Management Desk, Institut Bergonié, drci@bordeaux.unicancer.fr
Scientific contact	Regulatory Affairs Management Desk, Institut Bergonié, drci@bordeaux.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	01 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 December 2016
Global end of trial reached?	Yes
Global end of trial date	01 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the antitumor activity of PD-0332991 in terms of non-progression at 16 weeks (after centralized review) in patients with documented disease progression while on therapy with imatinib and sunitinib for unresectable and/or metastatic GIST.

Protection of trial subjects:

A supervisory committee is constitued to evaluate the benefit/risk ratio along the study period.

Background therapy:

The treatment of advanced GIST patients is based on imatinib followed with sunitinib in case of resistance/intolerance. However, the median progression-free survival (PFS) on sunitinib is frequently short, and after failure with both imatinib and sunitinib, treatment remains controversial.

Previous studies on GISTs have linked 9p21 alterations to tumor progression (El-Rifai et al. 2000; Kim et al., 2000; Schneider-Stock et al., 2003; Schneider-Stock et al., 2005; Romeo et al. 2009; Haller et al., 2008) but the driver gene was not positively identified (CDKN2A, CDKN2B, or MTAP) (Astolfi et al., 2010; Belinsky et al., 2009; Perrone et al., 2005; Assamaki et al. 2007; Huang et al., 2009). A recent study has shown that homozygous 9p21 deletions target CDKN2A and more specifically p16INK4a 4. Most of the CINSARC genes are known to be under the transcriptional control of E2F. RB1 sequesters E2F, which is released from the complex upon RB1 phosphorylation by CDK4. CDK4 is, in turn, inhibited by p16INK4a. Hence, we hypothesize that alteration of the restriction point via deletion of p16INK4a (and more rarely of RB1: 20% of cases) gene in GISTs is likely to be a causative event that leads to the overexpression of CINSARC genes, which in turn induce chromosome instability and ultimately metastasis. Low p16INK4a expression was associated with response to PD-0332991 in several in vitro tumor model(Konecny et al. 2011; Katsumi et al. 2011; Finn et al. 2009). Considering our molecular data, we believed that PD-0332991 warrants clinical investigation in advanced gastrointestinal stromal tumors with alteration of p16INK4a. This alteration is detectable by comparative genomic hybridization which is a technique highly manageable in the context of routine clinical care and clinical trial.

Evidence for comparator:

Not applicable / no comparator

Actual start date of recruitment	01 August 2013
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: 29
Worldwide total number of subjects	29
EEA total number of subjects	29

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	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between February 2014 and July 2016, 71 patients were screened across 8 French Sarcoma Group centers–29 (41%) met the molecular eligibility criteria and started treatment, of whom 23 were assessable for the primary efficacy endpoint.

Pre-assignment

Screening details:

Adults with metastatic or unresectable locally advanced, histologically confirmed malignant GIST, previously treated with at least imatinib and sunitinib, measurable and documented progression as per RECIST 1.1, and CDKN2A gene deletion centrally assessed by array-comparative genomic hybridization (CGH) were eligible.

Period 1

Period 1 title	Baseline Period (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable / SIngle-arm trial / no blinding

Arms

Arm title	PD-0332991

Arm description: -

Arm type	Experimental
Investigational medicinal product name	PD-0332991
Investigational medicinal product code	
Other name	Palbociclib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

PD-0332991 is formulated as gelatin capsules of 100 mg and 25 mg respectively.

PD-0332991 will be administrated orally, formulated as gelatin capsules of 100 mg and 25 mg respectively.: PD-0332991 dosed on a flat scale of 125 mg (1 capsule x 100 mg/day, 1 capsule x25 mg/day) will be administrated orally o.d on a 21 days on / 7 days off dosing schedule. One cycle is considered to consist of 4 weeks of PD-0332991 administration.

Number of subjects in period 1	PD-0332991
Started	29
Completed	29

Baseline characteristics

Reporting groups	
Reporting group title	PD-0332991

Reporting group description: -

Reporting group values	PD-0332991	Total	
Number of subjects	29	29	
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	66		
full range (min-max)	40 to 81	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	22	22	

End points

End points reporting groups

Reporting group title	PD-0332991
Reporting group description: -	
Subject analysis set title	Population evaluable for efficacy
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All patients eligible and for whom the following conditions are satisfied: (i) Received at least one complete or two incomplete treatment cycles, (ii) At least one disease measurement recorded not less than four weeks after treatment onset.

Primary: Number of Participants With Non Progression at 4 Months

End point title	Number of Participants With Non Progression at 4 Months[1]

End point description:

End point type	Primary

End point timeframe:

16 weeks after first administration of treatment

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: Single -arm trial - No statistical test was performed.

End point values	Population evaluable for efficacy			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Subjects	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival Time

End point title	Progression-free Survival Time

End point description:

Progression-free survival time is defined as the time from the first administration of treatment to progression (as per RECIST v1.1) or death of any cause, whichever occurs first.

Progression is defined using Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.0), as a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions.

End point type	Secondary

End point timeframe:

up to 18 months following first administration of treatment

End point values	Population evaluable for efficacy			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: years				
median (confidence interval 95%)	1.74 (0.92 to 3.45)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

up to 24 months following first administration of treatment

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10

Reporting groups

Reporting group title	All included subjects

Reporting group description: -

Serious adverse events	All included subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 29 (41.38%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	0		
Investigations			
Neutropenia			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Disease progression			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Vascular disorders			
Left ilio femoral phebilits			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Phlebitis			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	4 / 29 (13.79%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Flu-like syndrom			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sudden death at home			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal disorders			
Hemoperitoneum			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric hemorrhage			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric pain			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnea			

subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal insuficiency			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Deterioration of renal function			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bladder globe			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal insufficiency			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urinary infection			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypercalcemia			

subjects affected / exposed	1 / 29 (3.45%)		
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	All included subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 29 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumor pain			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Phlebitis			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Thromboembolic event			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	3		
General disorders and administration site conditions			
Edema limbs			
subjects affected / exposed	4 / 29 (13.79%)		
occurrences (all)	4		
Fatigue			
subjects affected / exposed	10 / 29 (34.48%)		
occurrences (all)	11		
Fever			

subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	3		
Flu like symptoms			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Pain			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	3		
General disorders and administration site conditions			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	3		
Voice alteration			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Investigations			
Creatinine increased			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	3		
Neutrophil count decreased			
subjects affected / exposed	12 / 29 (41.38%)		
occurrences (all)	17		
Platelet count increased			
subjects affected / exposed	4 / 29 (13.79%)		
occurrences (all)	4		
White blood cell decreased			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Cardiac disorders			

Sinus tachycardia subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2		
Blood and lymphatic system disorders Anemia subjects affected / exposed occurrences (all)	17 / 29 (58.62%) 22		
Eye disorders Eye disorders - Other, specify subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	5 / 29 (17.24%) 5		
Constipation subjects affected / exposed occurrences (all)	7 / 29 (24.14%) 7		
Diarrhea subjects affected / exposed occurrences (all)	3 / 29 (10.34%) 3		
Dysphagia subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2		
Gastrointestinal pain subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2		
Mucositis oral subjects affected / exposed occurrences (all)	5 / 29 (17.24%) 6		
Nausea subjects affected / exposed occurrences (all)	6 / 29 (20.69%) 7		
Stomach pain subjects affected / exposed occurrences (all)	3 / 29 (10.34%) 3		
Vomiting			

subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	3		
Gastrointestinal disorders - Other			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
other			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Renal and urinary disorders - Other			
subjects affected / exposed	4 / 29 (13.79%)		
occurrences (all)	4		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	4		
Myalgia			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorder - Other			
subjects affected / exposed	4 / 29 (13.79%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	4 / 29 (13.79%)		
occurrences (all)	4		
Hyperglycemia			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		

Hypertriglyceridemia subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2		

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