# 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<br>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<br>Units: years | | | |
| median | 66 | | |
| full range (min-max) | 40 to 81 | - | |
| Gender categorical<br>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<br>subjects affected / exposed<br>occurrences (all) | 2 / 29 (6.90%)<br>2 | | |
| Blood and lymphatic system disorders<br>Anemia<br>subjects affected / exposed<br>occurrences (all) | 17 / 29 (58.62%)<br>22 | | |
| Eye disorders<br>Eye disorders - Other, specify<br>subjects affected / exposed<br>occurrences (all) | 2 / 29 (6.90%)<br>2 | | |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all) | 5 / 29 (17.24%)<br>5 | | |
| Constipation<br>subjects affected / exposed<br>occurrences (all) | 7 / 29 (24.14%)<br>7 | | |
| Diarrhea<br>subjects affected / exposed<br>occurrences (all) | 3 / 29 (10.34%)<br>3 | | |
| Dysphagia<br>subjects affected / exposed<br>occurrences (all) | 2 / 29 (6.90%)<br>2 | | |
| Gastrointestinal pain<br>subjects affected / exposed<br>occurrences (all) | 2 / 29 (6.90%)<br>2 | | |
| Mucositis oral<br>subjects affected / exposed<br>occurrences (all) | 5 / 29 (17.24%)<br>6 | | |
| Nausea<br>subjects affected / exposed<br>occurrences (all) | 6 / 29 (20.69%)<br>7 | | |
| Stomach pain<br>subjects affected / exposed<br>occurrences (all) | 3 / 29 (10.34%)<br>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<br>subjects affected / exposed<br>occurrences (all) | 2 / 29 (6.90%)<br>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