

**Clinical trial results:**

A multicenter, international, non-controlled, phase II trial to identify the molecular mechanisms of resistance and sensitivity to palbociclib re-challenge upon progression to a palbociclib combination in ER-positive metastatic breast cancer patients (BioPER). Code: MedOPP089.

Summary

EudraCT number	2015-003892-31
Trial protocol	ES IT
Global end of trial date	27 October 2020

Results information

Result version number	v1 (current)
This version publication date	28 May 2022
First version publication date	28 May 2022

Trial information**Trial identification**

Sponsor protocol code	MedOPP089
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03184090
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medica Scientia Innovation Research (MEDSIR)
Sponsor organisation address	Av Diagonal 211, Torre Glories - 27th floor, Barcelona, Spain, 08018
Public contact	Sr Global Project Manager, Medica Scientia Innovation Research (MedSIR), +34 93221 41 35, alicia.garcia@medsir.org
Scientific contact	Sr Global Project Manager, Medica Scientia Innovation Research (MedSIR), +34 93221 41 35, alicia.garcia@medsir.org

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	03 November 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 October 2020
Global end of trial reached?	Yes
Global end of trial date	27 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- Biological objective: To characterize the molecular patterns of resistance [with a special focus on retinoblastoma (Rb) status] upon progression to palbociclib plus endocrine therapy in patients who previously achieved clinical benefit with the combination. The biological markers analysed must cover the entire CDK4/6-Cyclin D-Rb axis, including Cyclin D and E, as the latter appears to play an important role in the mechanism of resistance to palbociclib.
- Clinical objective: To define the clinical activity of the combination of palbociclib and endocrine therapy after prior progression to palbociclib in endocrine-sensitive patients.

Protection of trial subjects:

Standard of Care

Background therapy:

Palbociclib is an oral and selective inhibitor of CDK4/6. CDK4 and CDK6 promote cell-cycle entry by phosphorylating retinoblastoma (Rb) protein and other proteins in order to initiate cell transition from the G1 phase to the S phase in the cell cycle.

Evidence for comparator:

not applicable, single-arm

Actual start date of recruitment	17 May 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	Spain: 27
Country: Number of subjects enrolled	Italy: 6
Worldwide total number of subjects	33
EEA total number of subjects	33

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)	23
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between May 2017 and Apr 2019, a total of 33 patients with HR+ and HER2- MBC were enrolled at 21 sites. Due there's only one arm, all the patients will receive palbociclib in combination with endocrine therapy until disease progression, death or discontinuation from the study.

Pre-assignment

Screening details:

Females \geq 18 years.

ECOG score \leq 1.

Histologically confirmed HR+ and HER2- MBC.

Life expectancy \geq 12w.

Treated with a stable dose of palbociclib during the last 4w in the previous palbociclib line.

Must have measurable disease (RECIST v1.1).

No more than 2 prior lines of endocrine therapy and 1 of chemotherapy for metastatic disease.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Open-label

Arms

Arm title	Experimental arm
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Arm description:

Palbociclib capsules orally for 21 days every four weeks in combination with endocrine therapy until disease progression (with the exception of patients who develop isolated progression in the brain), unacceptable toxicity, death, or discontinuation from the study treatment for any other reason.

Patients discontinuing the study treatment period will enter a post- treatment follow-up period during which survival and new anti-cancer therapy information will be collected every six months (\pm 14 days) from the last dose of investigational product. The treatment follow-up period will conclude at six months after the last patient has received first treatment dose in the study.

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

Dosage and administration details:

Palbociclib capsules will be taken orally once daily beginning on Day 1 of hormonotherapy and continuing through Day 21 of every 28-day. Patients must start palbociclib treatment on cycle 1 at the same dose level received when completing the previous palbociclib-based treatment (either 125 mg/day, 100 mg/day or 75 mg/day). Patients who completed the previous palbociclib-based treatment at dose level of 75 mg/day must have been treated at least during the last eight weeks with the same dose and should not have experienced any grade 3-4 adverse event related to palbociclib.

Patients discontinuing the study treatment period will enter a post-treatment follow-up period during which survival and new anti-cancer therapy information will be collected every six months (\pm 14 days) from the last dose of investigational product. The treatment follow-up period will conclude at six months after the last patient is included in the study.

Number of subjects in period 1	Experimental arm
Started	33
Completed	33

Baseline characteristics

Reporting groups

Reporting group title	Experimental arm
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Reporting group description:

Palbociclib capsules orally for 21 days every four weeks in combination with endocrine therapy until disease progression (with the exception of patients who develop isolated progression in the brain), unacceptable toxicity, death, or discontinuation from the study treatment for any other reason. Patients discontinuing the study treatment period will enter a post- treatment follow-up period during which survival and new anti-cancer therapy information will be collected every six months (\pm 14 days) from the last dose of investigational product. The treatment follow-up period will conclude at six months after the last patient has received first treatment dose in the study.

Reporting group values	Experimental arm	Total	
Number of subjects	33	33	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	23	23	
From 65-84 years	10	10	
85 years and over	0	0	
Age continuous			
Units: years			
median	59.5		
full range (min-max)	42 to 80	-	
Gender categorical			
Units: Subjects			
Female	33	33	
Male	0	0	

Subject analysis sets

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Considering all patients included regardless of whether they received the required study drug exposure and protocol processing

Subject analysis set title	Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

Considering all patients that receive at least one drug exposure.

Reporting group values	ITT	Safety	
Number of subjects	32	33	
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)	22	23	
From 65-84 years	10	10	
85 years and over	0		
Age continuous			
Units: years			
median	59.5	59.5	
full range (min-max)	42 to 80	42 to 80	
Gender categorical			
Units: Subjects			
Female	32	33	
Male	0	0	

End points

End points reporting groups

Reporting group title	Experimental arm
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Reporting group description:

Palbociclib capsules orally for 21 days every four weeks in combination with endocrine therapy until disease progression (with the exception of patients who develop isolated progression in the brain), unacceptable toxicity, death, or discontinuation from the study treatment for any other reason. Patients discontinuing the study treatment period will enter a post- treatment follow-up period during which survival and new anti-cancer therapy information will be collected every six months (\pm 14 days) from the last dose of investigational product. The treatment follow-up period will conclude at six months after the last patient has received first treatment dose in the study.

Subject analysis set title	ITT
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

Considering all patients included regardless of whether they received the required study drug exposure and protocol processing

Subject analysis set title	Safety
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Considering all patients that receive at least one drug exposure.

Primary: Primary Biological Endpoint

End point title	Primary Biological Endpoint
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End point description:

Percentage of patients with Rb loss [as defined by loss of expression, copy number variation (CNV), somatic mutation, or methylation dependent silencing]. The evaluation criteria will be the characterization of the molecular patterns of resistance with greater than 20% prevalence.

End point type	Primary
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End point timeframe:

From baseline until end of treatment

End point values	Experimental arm	ITT	Safety	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	32	33	
Units: Rb loss				
number (not applicable)	33	32	33	

Statistical analyses

Statistical analysis title	Retinoblastoma loss
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Comparison groups	Experimental arm v ITT
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Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)

Primary: Primary Clinical Endpoint

End point title	Primary Clinical Endpoint
End point description:	Percentage of patients that achieve clinical benefit (CBR) defined as complete response, partial response, or stable disease for at least 24 weeks per RECIST criteria v.1.1.
End point type	Primary
End point timeframe:	Baseline to end of treatment

End point values	Experimental arm	ITT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	32	32		
Units: CBR				
number (not applicable)	11	11		

Attachments (see zip file)	BioPER_primary clinical efficacy endpoint/EudraCT number
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Statistical analyses

Statistical analysis title	Clinical Benefit Rate
Comparison groups	Experimental arm v ITT
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.025
Method	t-test, 1-sided
Parameter estimate	Number of patients
Point estimate	34.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.6
upper limit	53.2

Secondary: Secondary Efficacy

End point title Secondary Efficacy

End point description:

The ORR defined as the proportion of patients with best overall response of confirmed complete response or partial response based on local investigator's assessment according to Response Evaluation Criteria In Solid Tumours (RECIST) criteria v. 1.1 (22).

End point type Secondary

End point timeframe:

Baseline until end of Treatment

End point values	Experimental arm	ITT	Safety	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	32	33	
Units: ORR	33	32	33	

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Molecular objectives

End point title Secondary Molecular objectives

End point description:

Mesure Hscore levels of the following targets: Cyclin D, cyclin E, p16 (Ink4a), p18 (Ink4c), p21, and p27.

Other pRb pathway's targets (E2F, DNMT, HIF1alpha, and SKP2).

Markers of proliferation and apoptosis (Ki67 and active caspase 3).

Collect data about the differences in expression profiles, assessed by RNA microarrays.

End point type Secondary

End point timeframe:

From treatment start until progression or end of study date, whichever occurs first.

End point values	Experimental arm	ITT	Safety	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	32	33	
Units: Histoscore	33	32	33	

Statistical analyses

No statistical analyses for this end point

Secondary: Safety

End point title	Safety
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End point description:

Patient safety and AEs will be assessed using the National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) v.4.0.3. Grade 3 and 4 AEs and SAEs will be assessed to determine the safety and tolerability of the different drug combinations.

End point type	Secondary
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End point timeframe:

From treatment start until progression or end of study date, whichever occurs first.

End point values	Experimental arm	ITT	Safety	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	32	33	
Units: SAE	33	32	33	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline after 30 days of last dose exposure

Adverse event reporting additional description:

All study patients will be carefully monitored for the occurrence of AEs (including SAEs and AESIs) during the above specified adverse event reporting period.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22
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Reporting groups

Reporting group title	Experimental arm
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Reporting group description:

Single-arm trial: palbociclib + endocrine therapy

Serious adverse events	Experimental arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 33 (9.09%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Psychiatric disorders			
Alcohol abuse			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mental disorder			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Coronavirus infection			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Non-serious adverse events	Experimental arm		
Total subjects affected by non-serious adverse events subjects affected / exposed	33 / 33 (100.00%)		
Vascular disorders			
Hot flush subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	4		
Thromboembolic event subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Surgical and medical procedures			
Dental root extraction subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia subjects affected / exposed	5 / 33 (15.15%)		
occurrences (all)	6		
Edema in upper left limb subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Fatigue subjects affected / exposed	10 / 33 (30.30%)		
occurrences (all)	18		
Fever subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Flue-like symptoms subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Injection site reaction subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	2		
Local skin reaction subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		

Pain subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Pain on the right side subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 3		
Respiratory, thoracic and mediastinal disorders Bronchospasm subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Cough subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Dysphonia subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		
Score throat subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Irritability subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		
Alkaline phosphatase increased subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 5		

Blood creatinine increased subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Headache subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Paraesthesia subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Blood and lymphatic system disorders			
Neutropenia subjects affected / exposed occurrences (all)	14 / 33 (42.42%) 37		
Leukopenia subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 12		
Anemia subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 5		
Haemoglobin decreased subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		
Lymphocyte count decreased subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Lymphocytopenia subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Neutrophil count abnormal			

subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Neutrophil count decreased subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 14		
Platelet count decreased subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 3		
White blood cell count decreased subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 3		
Gastrointestinal disorders			
Constipation subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Diarrhoea subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 11		
Dispepsia subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Epigastric discomfort subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Nausea subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3		
Oral cavity mucositis subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Vomiting subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		

<p>Skin and subcutaneous tissue disorders</p> <p>Alopecia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 33 (3.03%)</p> <p>1</p>		
<p>Intertrigo</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 33 (3.03%)</p> <p>1</p>		
<p>Nail loss</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 33 (3.03%)</p> <p>1</p>		
<p>Rash (zoster)</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 33 (3.03%)</p> <p>1</p>		
<p>Renal and urinary disorders</p> <p>Dysuria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 33 (3.03%)</p> <p>1</p>		
<p>Musculoskeletal and connective tissue disorders</p> <p>Altromialgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 33 (3.03%)</p> <p>1</p>		
<p>Arthralgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 33 (3.03%)</p> <p>1</p>		
<p>Bone pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 33 (3.03%)</p> <p>1</p>		
<p>Cramps</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 33 (3.03%)</p> <p>1</p>		
<p>Fracture pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 33 (3.03%)</p> <p>1</p>		
<p>Joint discomfort</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 33 (3.03%)</p> <p>1</p>		

Lower back pain subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 2		
Musculoskeletal pain subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		
Right Hip Pain subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Scapula pain subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Infections and infestations			
Cold subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Dental Abscess subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 2		
Foliculitis subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Herpes zoster subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Tooth infection subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Tooth phlegmon subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Urinary tract infection			

subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 3		
Vaginal infection subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 July 2017	<p>Revision of inclusion criteria 2 to clarify minimum pre-treatment conditions with LHRH analogues.</p> <p>Revision of inclusion criteria 15 to clarify adequate value of ANC and ALP to grade 1 as determined by the National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) v.4.0.3</p> <p>Revision of exclusion criteria 17 to clarify that patients coming from studies in which they were treated with Palbociclib do not need to wait 30 days before entering the study.</p> <p>Revision of dose modifications guidelines for palbociclib</p> <ul style="list-style-type: none">• Main changes affect to the management of neutropenia during the first two cycles of treatment: Neutropenia grade 3 does not require immediate palbociclib treatment interruption but only if persists for more than 1 week• In addition, dose modifications for QTc interval prolongations are aligned with the other non-hematologic toxicities based on later data showing that palbociclib does not prolong QTc interval. <p>Revision of bilirubin assessment to specify that direct bilirubin should be measured only when the total value is out of range.</p>
31 January 2018	<p>Revision of inclusion criteria 8 to allow patients treated at the lowest level of palbociclib (75 mg/day) treated for at least eight weeks with no adverse event related to palbociclib to participate in the study.</p>
04 November 2019	<p>Revision of End of Study (EoS) definition to extend the follow-up period up to 18 months from last patient first visit (LPFV) or until progression of the last patient in treatment.</p> <p>Inclusion of Interstitial Lung Disease (ILD) / pneumonitis as an adverse drug reaction to palbociclib.</p> <ul style="list-style-type: none">• An interim analysis has been planned to analyse the first co-primary endpoint (clinical benefit rate) after last patient included in the study has achieved a 6 months follow-up. We will also evaluate safety and secondary efficacy outcomes (first data base closure and interim analysis). However, the follow-up period of patients will be extended until 18 months after the first patient started the study treatment.• After the extended follow-up period, we will analyse all molecular endpoints and extended efficacy and safety outcomes (final analysis and database closure).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported