



## Clinical trial results:

### Phase II study of oral PHA-848125AC in patients with malignant thymoma previously treated with multiple lines of chemotherapy

#### Summary

EudraCT number	2013-000344-25
Trial protocol	IT
Global end of trial date	17 December 2018

#### Results information

Result version number	v1 (current)
This version publication date	27 November 2019
First version publication date	27 November 2019
Summary attachment (see zip file)	Synopsis (Synopsis CDKO-125a-007-SR.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	CDKO-125a-007
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01301391
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	TIZIANA LIFE SCIENCES PLC
Sponsor organisation address	3rd floor, 11-12St. James's Square, LONDON, United Kingdom, SW1Y 4LB
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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	27 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 May 2017
Global end of trial reached?	Yes
Global end of trial date	17 December 2018
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

Assessment of the antitumor activity of PHA-848125AC in patients with recurrent or metastatic, unresectable B3 thymoma or thymic carcinoma who have received more than one line of prior systemic therapy for advanced / metastatic disease. Antitumor activity will be evaluated on the basis of the progression-free survival status at 3 months.

Protection of trial subjects:

Study protocol foresees that therapies considered necessary for the patient's well being might be given at the discretion of the Investigator, i.e., chronic treatments for concomitant medical conditions, as well as agents required for life-threatening medical problems.

Background therapy:

None.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	02 February 2011
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	Italy: 15
Country: Number of subjects enrolled	United States: 15
Worldwide total number of subjects	30
EEA total number of subjects	15

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	7
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Thirty-four patients were recruited from 02 February 2011 to 28 January 2016.

### Pre-assignment

Screening details:

Thirty patients were enrolled and treated with milciclib. Overall four patients were screening failure, due to inclusion /exclusion criteria not satisfied (one patient) or other reasons (3 patients).

### 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:

Not applicable.

### Arms

Arm title	Arm 1
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Arm description:

All patients treated with milciclib.

Arm type	Experimental
Investigational medicinal product name	Milciclib maleate
Investigational medicinal product code	PHA-848125AC
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Milciclib maleate was to be administered at the flat dose of 150 mg/day once daily for 7 consecutive days of each treatment cycle. Therefore, a treatment cycle included 7 days of milciclib administration (Days 1 to 7) followed by 7 days of rest (Days 8 to 14) for a total of a 14 days period (2-week cycle).

Number of subjects in period 1	Arm 1
Started	30
Completed	17
Not completed	13
Adverse event, serious fatal	1
Sponsor's decision	3
Physician decision	2
Adverse event, non-fatal	4
Lack of compliance with protocol requirements	1
Patient's refusal to continue the treatment	2



## Baseline characteristics

### Reporting groups

Reporting group title	Arm 1
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Reporting group description:

All patients treated with milciclib.

Reporting group values	Arm 1	Total	
Number of subjects	30	30	
Age categorical			
All treated patients.			
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	7	7	
85 years and over	0	0	
Age continuous			
Units: years			
median	54.5		
full range (min-max)	32 to 71	-	
Gender categorical			
Units: Subjects			
Female	15	15	
Male	15	15	
Race			
Units: Subjects			
White	23	23	
Black	2	2	
Asian	3	3	
Not listed	2	2	
Stage Disease			
Units: Subjects			
Locally advanced	0	0	
Metastatic	30	30	
WHO Classification			
Units: Subjects			
Type A	0	0	
Type AB	0	0	
Type B1	0	0	
Type B2	0	0	
Type B3	17	17	
Type C	13	13	

Masaoka Clinical Stage at Study Entry Units: Subjects			
Stage I	0	0	
Stage IIa	0	0	
Stage IIb	0	0	
Stage III	0	0	
Stage IVa	7	7	
Stage IVb	10	10	
Not Classified	6	6	
Missing	7	7	
Number of Recurrences/Progressions Units: Subjects			
N° 1	3	3	
N° 2	11	11	
N° >2	16	16	
Prior Antitumor Therapies Units: Subjects			
Systemic only	2	2	
Surgery + Systemic	4	4	
Systemic + Radiotherapy	3	3	
Surgery + Systemic + Radiotherapy	21	21	

## End points

### End points reporting groups

Reporting group title	Arm 1
Reporting group description: All patients treated with milciclib.	
Subject analysis set title	Evaluable patients
Subject analysis set type	Per protocol
Subject analysis set description: the patient population for the primary efficacy analysis of PFS-3 rate consisted of all treated patients who had fulfilled the following additional conditions: <ul style="list-style-type: none"><li>- They had received at least 80% of drug in the first two cycles overall.</li><li>- They had undergone baseline and <math>\geq 1</math> on-treatment tumor/oncologic assessments or had died before tumor re-assessment.</li></ul>	

### Primary: Progression-free survival rate at 3 months (PFS-3 rate)

End point title	Progression-free survival rate at 3 months (PFS-3 rate) <sup>[1]</sup>
End point description: The PFS-3 rate was calculated as the proportion of evaluable patients known to be alive and progression-free at $\geq 3$ months since study treatment start, out of the total number of evaluable patients.	
End point type	Primary
End point timeframe: From baseline to 3 months after the patient started the study 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: A PFS-3 rate of at least 25% was obtained, as expected. The p-value given by the exact binomial test ( $<.001$ ) lead the rejection of the null hypothesis ( $p=0.25$ ) in favour of the alternative one ( $p=0.50$ ).

End point values	Evaluable patients			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: percent				
number (confidence interval 95%)	54.2 (32.8 to 74.4)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Objective Response Rate (CR+PR)

End point title	Objective Response Rate (CR+PR)
End point description: Confirmed Objective Response Rate (CR + PR) according to RECIST guideline (version 1.1).	
End point type	Secondary
End point timeframe: During all study period	



End point values	Evaluable patients			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: percent				
number (confidence interval 95%)	4.2 (0.11 to 21.12)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression-free survival

End point title	Progression-free survival
End point description: The time from the date of treatment start to the date of first documentation of objective progression or of death due to any cause, whichever came first.	
End point type	Secondary
End point timeframe: During all study period	

End point values	Evaluable patients			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: Months				
median (confidence interval 95%)	9.76 (4.11 to 17.45)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of response

End point title	Duration of response
End point description: Duration of response was defined, for the subset of patients with CR or PR, as the time for when criteria for response were met until first date that recurrent or progressive disease had been objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).	
End point type	Secondary

End point timeframe:  
During all study period

End point values	Evaluable patients			
Subject group type	Subject analysis set			
Number of subjects analysed	1			
Units: Months				
median (full range (min-max))	2.76 (2.76 to 2.76)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival at 21 months

End point title	Overall Survival at 21 months
End point description: During all study period	
End point type	Secondary
End point timeframe: Overall survival was defined as the time from the date of treatment start to the date of death from any causes.	

End point values	Evaluable patients			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: percent				
number (confidence interval 95%)	53.3 (30.8 to 75.8)			

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

During all study period and followed until 28 days after the last dose administration of investigational product.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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### Reporting groups

Reporting group title	Arm1
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Reporting group description:

All patients treated with milciclib

Serious adverse events	Arm1		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 30 (46.67%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events	1		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Epididymitis			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cough			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea exertional			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood bilirubin increased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Extrapyramidal disorder			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal obstruction			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Erythema multiforme			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
sweating increased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Myalgia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Sepsis			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Arm1		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 30 (93.33%)		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	11 / 30 (36.67%)		
occurrences (all)	22		
Fatigue			
subjects affected / exposed	11 / 30 (36.67%)		
occurrences (all)	17		
Pyrexia			
subjects affected / exposed	7 / 30 (23.33%)		
occurrences (all)	9		
Oedema peripheral			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	5		
Chest pain			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Pain			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	4		
Pain exacerbated			

subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 30 (20.00%)		
occurrences (all)	8		
Dyspnoea			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Dyspnoea exertional			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Epistaxis			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Productive cough			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Investigations			
Lipase increased			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	11		
Alanine aminotransferase increased			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	5		
Amylase increased			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	6		
Weight decreased			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Aspartate aminotransferase increased			



subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 3		
Lymphocyte count decreased subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 5		
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Nervous system disorders Tremor subjects affected / exposed occurrences (all)	11 / 30 (36.67%) 30		
Dizziness subjects affected / exposed occurrences (all)	7 / 30 (23.33%) 12		
Paraesthesia subjects affected / exposed occurrences (all)	4 / 30 (13.33%) 5		
Dysgeusia subjects affected / exposed occurrences (all)	3 / 30 (10.00%) 3		
Headache subjects affected / exposed occurrences (all)	3 / 30 (10.00%) 3		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	8 / 30 (26.67%) 8		
Leukopenia subjects affected / exposed occurrences (all)	4 / 30 (13.33%) 5		
Neutropenia subjects affected / exposed occurrences (all)	4 / 30 (13.33%) 7		
Ear and labyrinth disorders			

Tinnitus subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 3		
Eye disorders			
Conjunctivitis subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 3		
Ocular discomfort subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Photopsia subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 3		
Gastrointestinal disorders			
Nausea subjects affected / exposed occurrences (all)	25 / 30 (83.33%) 92		
Diarrhoea subjects affected / exposed occurrences (all)	18 / 30 (60.00%) 70		
Vomiting subjects affected / exposed occurrences (all)	17 / 30 (56.67%) 66		
Constipation subjects affected / exposed occurrences (all)	4 / 30 (13.33%) 4		
Abdominal pain upper subjects affected / exposed occurrences (all)	3 / 30 (10.00%) 3		
Abdominal pain subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 4		
Dysphagia subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Gastrointestinal disorder			

subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 4		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Rash maculo-papular			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	5		
Dry skin			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Nail disorder			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	5		
Flank pain			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Muscle spasms			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	5		
Myalgia			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	3		
Infections and infestations			
Influenza			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	4		

Metabolism and nutrition disorders			
appetite decreased			
subjects affected / exposed	10 / 30 (33.33%)		
occurrences (all)	11		
Dehydration			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	4		
Hypokalaemia			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	5		
Hypomagnesaemia			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	3		
Hypophosphataemia			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	4		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 September 2011	<ul style="list-style-type: none"><li>- To change Inclusion Criterion # 10, by adding creatinine clearance (CrCl) as a parameter to evaluate patients' renal function at study entry,</li><li>- To better specify time window for oncologic assessment,</li><li>- To add the possibility to investigate the baseline status of additional biomarkers</li></ul>
13 December 2011	<ul style="list-style-type: none"><li>- To add the recommendation to monitor patients for events indicative of, or suggestive of, TMA/HUS (Thrombotic Microangiopathy/Hemolytic Uremic Syndrome) and in case of such events to temporarily hold study drug administration and to perform specific analyses to determine whether the events are compatible with TMA/HUS.</li><li>- To add information related to a new IMP (Investigational Medicinal Product) packaging and labeling.</li></ul>
30 July 2012	<ul style="list-style-type: none"><li>- To reduce the frequency of ocular examination. The amended ophthalmologic schedule was as follows: at baseline and at 1, 2, 3, 4.5, 7.5 months, and then after every three months until the end of last treatment cycle.</li><li>- To reduce the frequency of visits at the site for patients who had already received 6 treatment cycles and remain on treatment for a longer period of time (more than 6 cycles).</li><li>- To update the shelf life of the 50 mg and 100 mg capsules and to delete the 10 mg capsules since not used in the current study. In addition, the original formulation has been completely used and therefore it has been deleted.</li></ul>
24 January 2013	<ul style="list-style-type: none"><li>- To notify that the study, so far monocentric, changed into a multicenter phase II clinical study. Considering the rarity of the disease, it was decided to extend the number of the investigational sites to increase the accrual rate of patients.</li><li>- To notify that the histological diagnosis of thymic carcinoma, when made by another institution, had to be confirmed by pathologist of the investigational site to whom the patient is addressed.</li><li>- To delete the sentence related to the duration of accrual. In fact, due to the slow accrual rate, the NCI prevision to enroll 10-12 patients per year and to conclude the study within 2-3 years was not going to be satisfied.</li><li>- To allow for the evaluation of additional biomarkers to the ones already foreseen by the original protocol on tumor biopsies collected at baseline and to inform that the analysis will be performed in consenting patients in designated facilities in NMS and/or NIH/NCI. The baseline status of these additional markers under validation and related to the mechanism of action of milciclib will be investigated for any possible correlation with treatment efficacy. The additional analyses will not imply collection of additional tumor biopsies from patients.</li><li>- To report an administrative notification: from 01 November 2012, Nerviano Medical Sciences (NMS) had transferred its clinical development department to Clinical Organization for Strategies and Solutions (CLIOSS S. r. L). Therefore, all clinical and pharmacovigilance activities resulted delegated to CLIOSS S. r. L.</li></ul>

09 March 2017	<p>- To notify study discontinuation. Enrollment was completed on January 2016 and since sufficient data were already collected and the primary efficacy endpoint of the study was already achieved (i.e., the progression free survival status at 3 months was obtained in 13 out of the 24 evaluable patients (54.2%) i.e., more than the 12 successes required by protocol), a data cut-off on 31 May 2017 was planned, in order to proceed with clinical database closure and the preparation of the Clinical Study Report. The Sponsor continued to guarantee the supply of the investigational compound until the patients still on treatment would have benefit from the therapy. After the cut-off date, all the assessments data pertaining to the patients still on treatment were no longer collected in the Case Report Form, but only in the patient's medical notes. Safety was to be followed up for Serious Adverse Events only: SAEs were to be notified to CLIOSS Pharmacovigilance up to 28 days after the last patient had taken his/her milciclib maleate last dose. The intention with this data cut-off of 31 May 2017 was to bring the study schedule more closely aligned to standard clinical practice.</p> <p>- End of study definition. End of study can only occur when the last patient had discontinued study therapy and follow up period would have no longer been performed.</p> <p>- Administrative changes: Tiziana Life Sciences PLC entered as new Sponsor for CDKO-125a-007 trial. With this amendment the name of Nerviano Medical Sciences (NMS) has been replaced with Tiziana Life Sciences, PLC (Tiziana) throughout the whole documents.</p>
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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.

NA

Notes: