Clinical trial results:
Phase II study of oral PHA-848125AC in patients with thymic carcinoma previously treated with chemotherapy

Summary

EudraCT number	2009-014338-79
Trial protocol	FR 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-006-SR.pdf)

Trial information

Trial identification

Sponsor protocol code	CDKO-125a-006

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01011439
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	TIZIANA LIFE SCIENCES PLC
Sponsor organisation address	3rd Floor, 11-12 St. James’s Square, LONDON, United Kingdom, SW1Y 4LB
Public contact	Vaseem Palejwala, TIZIANA LIFE SCIENCES PLC, +1 267 982 Ext. 9784, vpalejwala@tizianalifesciences.com
Scientific contact	Cristina Davite, CLinical Organization for Strategies & Solutions S.r.l. - CLIOSS S.r.l., +39 03311482, cristina.davite@clioss.com

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	24 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 as second-line treatment in patients with recurrent or metastatic, unresectable thymic carcinoma previously treated with chemotherapy. 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	22 February 2010
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	United States: 13
Country: Number of subjects enrolled	France: 23
Country: Number of subjects enrolled	Italy: 36
Worldwide total number of subjects	72
EEA total number of subjects	59

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)	57
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eighty two patients were recruited from 22 February 2010 to 05 April 2016.

Pre-assignment

Screening details:

Seventy-two patients were enrolled and treated with milciclib. Ten patients were screening failure due to inclusion /exclusion criteria not sactisfied (8 patients) or other reasons (2 patients).

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	Arm1

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 (PHA-848125AC) was administered orally at the dose of 150 mg/day (flat dose) once daily for 7 consecutive days of each treatment cycle. A treatment cycle comprised 7 days of milciclib maleate administration (Day 1 to 7) followed by 7 days of rest for a total of 14 days (2 weeks) period. After an overnight fasting, with free access to water, patients took the study drug with a large glass of plain water without ice. A light breakfast could be served 1.5-2 hours after study drug intake.
Each patient remained on treatment until disease progression, patient refusal, consent withdrawal, or the occurrence of unacceptable toxicity.

Number of subjects in period 1	Arm1
Started	72
Completed	56
Not completed	16
Adverse event, serious fatal	2
Sponsor's decision	4
Physician decision	2
Adverse event, non-fatal	6
Patient's refusal to continue the treatment	2

Baseline characteristics

Reporting groups	
Reporting group title	Arm1
Reporting group description:	
All patients treated with milciclib.	

Reporting group values	Arm1	Total	
Number of subjects	72	72	
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)	57	57	
From 65-84 years	15	15	
85 years and over	0	0	
Age continuous			
All treated patients			
Units: years			
median	55		
full range (min-max)	21 to 80	-	
Gender categorical			
Units: Subjects			
Female	37	37	
Male	35	35	
Race			
Units: Subjects			
Caucasian	50	50	
Black	2	2	
Asian	3	3	
Not listed	10	10	
Not allowed to ask per local regulations	6	6	
Missing	1	1	
Stage Disease			
All treated patients			
Units: Subjects			
Locally advanced	1	1	
Metastatic	71	71	
WHO Classification			
Units: Subjects			
Type A	0	0	
Type AB	0	0	

Type B1	0	0	
Type B2	0	0	
Type B3	20	20	
Type C	52	52	
Masaoka Clinical Stage at Study Entry Units: Subjects			
Stage I	0	0	
Stage IIa	0	0	
Stage IIb	0	0	
Stage III	1	1	
Stage IVa	13	13	
Stage IVb	51	51	
Not classified	7	7	
Number of Recurrences/Progressions Units: Subjects			
N° 1	69	69	
N° 2	3	3	
Prior Antitumor Therapies Units: Subjects			
Systemic only	10	10	
Surgery + Systemic	16	16	
Systemic + Radiotherapy	10	10	
Surgery + Systemic + Radiotherapy	36	36	

End points

End points reporting groups

Reporting group title	Arm1

Reporting group description:

All patients treated with milciclib.

Subject analysis set title	Evaluable patients
Subject analysis set type	Per protocol

Subject analysis set description:

• Patients Evaluable for Efficacy Analysis: This definition included the patient population for the primary efficacy analysis of PFS-3 rate and consisted of all treated patients who had fulfilled the following additional conditions:
- They had received histological confirmation of thymic carcinoma by an Independent Review Committee
- They had received at least 80% of drug in the first two cycles overall.
- They had undergone baseline and >/=1 on-treatment tumor/oncologic assessments or had died before tumor re-assessment.

Subject analysis set title	Patients with CR or PR
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Among the evaluable patients whose showing CR or PR.

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

End point title	Progression-free survival rate at 3 months (PFS-3 rate).[1]

End point description:

The PFS-3 rate was calculated as the proportion of evaluable patients known to be alive and progression-free at ≥ 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 33% was obtained, as expected. The p-value given by the exact binomial test (<.001) lead the rejection of the null hyphotesis (p=0.17) in favour of the althernative one (p=0.33).

End point values	Evaluable patients			
Subject group type	Subject analysis set			
Number of subjects analysed	54			
Units: Percent				
number (confidence interval 95%)				
Success	44.4 (30.9 to 58.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate

End point title	Objective Response Rate

End point description:

Confirmed Objective Response Rate (CR, completed response + PR, partial response) according to RECIST guideline (version 1.1). Point and 95% confidence interval estimates was to be calculated for the objective tumor response rate (confirmed CRs or PRs). The analysis was to be performed in the evaluable populations.

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	54			
Units: percent				
number (confidence interval 95%)				
CR + PR	3.7 (0.45 to 12.75)			

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	54			
Units: months				
median (confidence interval 95%)				
Progression Free Survival	6.83 (4.11 to 8.71)			

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 first met until the 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	Patients with CR or PR			
Subject group type	Subject analysis set			
Number of subjects analysed	2			
Units: months				
median (confidence interval 95%)	8.41 (6.9 to 9.92)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall Survival (OS) was defined as the time from the date of treatment start to the date of death from any cause

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	54			
Units: months				
median (confidence interval 95%)	24.18 (16.89 to 36.57)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signature of informed consent until to 28 days after the last milciclib intake. However, if the patient started a new anticancer therapy before 28 days after last milciclib intake , the AE reporting period ended when the new treatment started.

Adverse event reporting additional description:

AE follow up after the end of reporting period was done for: 1) All SAE with outcome "not recovered" or "unknown" at the end of reporting period and 2) non-serious related AEs with outcome "not recovered " at the end of reporting period. These events were followed until resolution or when they were considered "chronic or stable".

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Arm1

Reporting group description:

All patients treated wit milciclib maleate.

Serious adverse events	Arm1		
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 72 (30.56%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Vascular disorders			
Subclavian vein thrombosis			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Superior vena cava occlusion			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 72 (2.78%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Sudden death			
subjects affected / exposed	2 / 72 (2.78%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Asthenia			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	2 / 72 (2.78%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			

subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Syncope				
subjects affected / exposed	2 / 72 (2.78%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Cerebral ischaemia				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Muscle contractions involuntary				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
myas				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Neuralgia				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neurological symptom				

subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Myasthenia gravis			
subjects affected / exposed	2 / 72 (2.78%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Red cell aplasia			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 72 (2.78%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 72 (2.78%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Biliary dilatation			

subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Polymyositis			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infection			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	1 / 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	72 / 72 (100.00%)		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	48 / 72 (66.67%)		
occurrences (all)	249		
Chest pain			

subjects affected / exposed	14 / 72 (19.44%)		
occurrences (all)	30		
Fatigue			
subjects affected / exposed	14 / 72 (19.44%)		
occurrences (all)	34		
Pyrexia			
subjects affected / exposed	10 / 72 (13.89%)		
occurrences (all)	13		
Mucosal inflammation			
subjects affected / exposed	7 / 72 (9.72%)		
occurrences (all)	14		
Oedema peripheral			
subjects affected / exposed	5 / 72 (6.94%)		
occurrences (all)	10		
rigors			
subjects affected / exposed	5 / 72 (6.94%)		
occurrences (all)	5		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	24 / 72 (33.33%)		
occurrences (all)	35		
Dyspnoea			
subjects affected / exposed	20 / 72 (27.78%)		
occurrences (all)	28		
rhinitis			
subjects affected / exposed	9 / 72 (12.50%)		
occurrences (all)	13		
Bronchitis			
subjects affected / exposed	6 / 72 (8.33%)		
occurrences (all)	10		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	6 / 72 (8.33%)		
occurrences (all)	12		
Insomnia			

subjects affected / exposed	6 / 72 (8.33%)		
occurrences (all)	12		
Depression			
subjects affected / exposed	4 / 72 (5.56%)		
occurrences (all)	5		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	9 / 72 (12.50%)		
occurrences (all)	12		
Amylase increased			
subjects affected / exposed	8 / 72 (11.11%)		
occurrences (all)	32		
Lipase increased			
subjects affected / exposed	7 / 72 (9.72%)		
occurrences (all)	33		
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 72 (8.33%)		
occurrences (all)	7		
Weight decreased			
subjects affected / exposed	5 / 72 (6.94%)		
occurrences (all)	5		
Cardiac disorders			
Palpitations			
subjects affected / exposed	4 / 72 (5.56%)		
occurrences (all)	6		
Nervous system disorders			
Tremor			
subjects affected / exposed	25 / 72 (34.72%)		
occurrences (all)	159		
Headache			
subjects affected / exposed	15 / 72 (20.83%)		
occurrences (all)	34		
Dysgeusia			
subjects affected / exposed	13 / 72 (18.06%)		
occurrences (all)	37		
Dizziness			

subjects affected / exposed	12 / 72 (16.67%)		
occurrences (all)	28		
Paraesthesia			
subjects affected / exposed	8 / 72 (11.11%)		
occurrences (all)	10		
Dysphonia			
subjects affected / exposed	6 / 72 (8.33%)		
occurrences (all)	6		
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	12 / 72 (16.67%)		
occurrences (all)	32		
Neutropenia			
subjects affected / exposed	12 / 72 (16.67%)		
occurrences (all)	39		
Anaemia			
subjects affected / exposed	8 / 72 (11.11%)		
occurrences (all)	12		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	10 / 72 (13.89%)		
occurrences (all)	108		
Eye disorders			
Photopsia			
subjects affected / exposed	7 / 72 (9.72%)		
occurrences (all)	14		
Vision blurred			
subjects affected / exposed	6 / 72 (8.33%)		
occurrences (all)	6		
Conjunctivitis			
subjects affected / exposed	5 / 72 (6.94%)		
occurrences (all)	8		
Lacrimation increased			
subjects affected / exposed	4 / 72 (5.56%)		
occurrences (all)	5		
Visual disturbance			

subjects affected / exposed	4 / 72 (5.56%)		
occurrences (all)	5		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	65 / 72 (90.28%)		
occurrences (all)	448		
Diarrhoea			
subjects affected / exposed	56 / 72 (77.78%)		
occurrences (all)	457		
Vomiting			
subjects affected / exposed	47 / 72 (65.28%)		
occurrences (all)	192		
Abdominal pain			
subjects affected / exposed	11 / 72 (15.28%)		
occurrences (all)	28		
Abdominal pain upper			
subjects affected / exposed	8 / 72 (11.11%)		
occurrences (all)	10		
Constipation			
subjects affected / exposed	8 / 72 (11.11%)		
occurrences (all)	15		
Dysphagia			
subjects affected / exposed	4 / 72 (5.56%)		
occurrences (all)	4		
Stomatitis			
subjects affected / exposed	4 / 72 (5.56%)		
occurrences (all)	5		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	5 / 72 (6.94%)		
occurrences (all)	5		
Sweating increased			
subjects affected / exposed	4 / 72 (5.56%)		
occurrences (all)	7		
Musculoskeletal and connective tissue disorders			

Back pain subjects affected / exposed occurrences (all)	15 / 72 (20.83%) 19		
Arthralgia subjects affected / exposed occurrences (all)	12 / 72 (16.67%) 15		
Myalgia subjects affected / exposed occurrences (all)	5 / 72 (6.94%) 5		
Flank pain subjects affected / exposed occurrences (all)	4 / 72 (5.56%) 5		
Neck pain subjects affected / exposed occurrences (all)	4 / 72 (5.56%) 5		
Infections and infestations Influenza subjects affected / exposed occurrences (all)	4 / 72 (5.56%) 7		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	23 / 72 (31.94%) 45		
Hypophosphataemia subjects affected / exposed occurrences (all)	17 / 72 (23.61%) 72		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 January 2011	• To specifically state in inclusion criterion #2 (IC #2) that patients with histologically or cytologically proven diagnosis of unresectable B3 thymoma or thymic carcinoma, as per the World Health Organization (WHO) classification of tumours of the thymus, can be included in the study. • To specify the time window in days for performing the oncologic assessment at 3 months, i.e. between days 92 and 98 after first drug administration. • To add the possibility to investigate the baseline status of additional biomarkers related to the mechanism of action for the compound PHA-848125AC in tumor biopsies. • To delete the reference to an expert pathologist reviewing the tumor tissue slides used for biomarkers analyses. • To notify changes in Sponsor Study Management Personnel and Sponsor Additional Trial Personnel.
13 December 2011	• To change IC No. 10, by adding calculated creatinine clearance (CrCl) as a parameter to evaluate patients' renal function at study entry; • 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. • To add information related to a new IMP (Investigational Medicinal Product) packaging and labeling.
27 June 2014	• 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). • To reconsider study protocol indications on time points of oncological assessment at 3 months, as per protocol required between 92 to 98 days from first drug administration. In some instances, this requirement cannot be fulfilled by centers because of technical and logistical reasons thus causing oncologic assessment to be made beyond the 98th day. For the purpose of the analysis, the assessments performed before the next scheduled one, i.e. on day 135 (42 days after the 3rd month assessment) in the evaluation of the main endpoint was to be accounted with the outcome they had, regardless of the timing of measurement. • To better clarify the definition of "patients evaluable for efficacy analysis" since it was misleading in the study protocol. • 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.

09 March 2017	• To notify study discontinuation. Enrollment was completed on April 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 24 out of the 52 evaluable patients (46.2%) i.e., more than the 14 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. • End of study definition. End of study can only occur when the last patient had discontinued study therapy, and a follow up period would have no longer performed. • Administrative changes: Tiziana Life Sciences PLC entered as new Sponsor for CDKO-125a-006 trial. With this amendment the name of Nerviano Medical Sciences (NMS) has been replaced with Tiziana Life Sciences, PLC (Tiziana) throughout the whole documents.

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: