# SYNOPSIS

| | |
|---|---|
| **Name of Company:** Tiziana Life Sciences, PLC<br>**Name of Finished Product:** Not applicable<br>**Name of Active Ingredient:** Milciclib Maleate (PHA-848125AC) | *(For National Authority Use only)* |
| **Title of Study:** Phase II study of oral PHA-848125AC in patients with malignant thymoma previously treated with multiple lines of chemotherapy | |
| **Protocol Number:** CDKO-125a-007 | |
| **Investigators:** 1) Maria Chiara Garassino; 2) Rajan Arun; 3) Giuseppe Giaccone. | |
| **Study Centers:**<br>1) Coordinating Site: Fondazione IRCCS Istituto Nazionale dei Tumori Milano (MI) Italy;<br>2) National Cancer Institute Center for Cancer Research, Bethesda, USA;<br>3) Georgetown Lombardi Comprehensive Cancer Center, Washington D.C., USA. | |
| **Publication Reference:** | |
| **Studied Period (Years):** 02 February 2011<br>31 May 2017 | **Phase of Development:**<br>Phase II |

**Objectives:**

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

**Secondary:** Assessment of additional measures of tumor control to further characterize the efficacy profile of milciclib in recurrent or metastatic, unresectable B3 thymoma or thymic carcinoma patients who had received more than one line of prior systemic therapy for advanced / metastatic disease.

Evaluation of the safety profile of repeated administrations of milciclib in patients with recurrent or metastatic, unresectable B3 thymoma or thymic carcinoma who had received more than one line of prior systemic therapy for advanced / metastatic disease.

**Exploratory objective:** Characterization of p53, p21, p27, cyclin D1, p75, and TRKA basal expression by IHC and TRKA copy number by FISH in tumor tissue involved in the PHA-848125AC mechanism of action to be performed in tumor tissue of consenting patients. Additional biomarkers under validation may also be evaluated. Assessments were done on paraffin embedded material, obtained from patients before study entry.

**Methodology:** In consideration of the exploratory nature of the study, a single-arm, open-label, multicenter phase II clinical trial design was adopted, including an early stopping rule in case of identification of a clearly unacceptable progression free proportion by 3 months of treatment.
Histological diagnosis of thymic carcinoma, when made by another institution, had to be confirmed by pathologists of the investigational site to whom the patient is addressed.

**Number of Subjects (Planned and Analyzed):**
Unless an early stopping rule is invoked, 30 patients who had received more than one line of prior systemic therapy for advanced / metastatic disease were to be enrolled. Accounting for a 10%-15% proportion of non-evaluable patients, an accrual ceiling up to 35 patients was to be set for completing the trial.

Thirty patients were enrolled and 24 were evaluable for the primary efficacy analysis.

| | |
|---|---|
| **Name of Company:** Tiziana Life Sciences, PLC<br>**Name of Finished Product:** Not applicable<br>**Name of Active Ingredient:** Milciclib Maleate (PHA-848125AC) | *(For National Authority Use only)* |

**Diagnosis and Main Criteria for Inclusion:**

**Subject Inclusion Criteria**

1. Signed and dated IRB/IEC-approved Informed Consent
2. Histologically or cytologically proven diagnosis of unresectable B3 thymoma or thymic carcinoma recurrent or progressing after more than one prior systemic therapy for advanced / metastatic disease. **Note:** Any adjuvant or neoadjuvant systemic therapy followed by the recurrence of the disease within 12 months after the start of the adjuvant treatment was considered as one therapy for advanced / metastatic disease
3. Presence of measurable disease defined as at least one lesion that could be accurately measured by CT scan in at least one dimension, as > 10 mm for non-nodal lesions (longest diameter to be recorded) and ≥ 15 mm for lymph nodal lesions (short axis to be recorded). (CT scan was the desirable method for lesion measurement. Other measurement techniques [*eg* MRI] were acceptable [but not for lung lesions] provided that the size of the measurable lesion is twice the slice thickness of the MRI).
   Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, were usually not considered measurable unless progression in the lesion had been demonstrated.
4. Age ≥ 18 years
5. ECOG (WHO) performance status 0-1
6. Estimated life expectancy of at least 3 months
7. Negative pregnancy test (if female in reproductive years)
8. Agreement upon the use of effective contraceptive methods (hormonal or barrier method of birth control, or abstinence) prior to study entry and for the duration of study participation, if men and women of child producing potential
9. Adequate liver function:
   - Total Serum Bilirubin ≤ 1.5 x upper limit of normal (ULN)
   - Transaminase AST (SGOT), ALT (SGPT) ≤2.5 ULN (if liver metastases were present, then ≤ 5 ULN was allowed)
   - Alkaline phosphatase ≤ 2.5 ULN (if liver and/or bone metastases were present, then ≤ 5 ULN was allowed)
10. Adequate renal function:
    - Serum creatinine ≤ ULN
    or
    - Creatinine Clearance calculated by Cockcroft and Gault's formula > 60 mL/min
11. Adequate hematologic status:
    - ANC ≥ 1,500 cells/$mm^3$
    - Platelet count ≥ 100,000 cells/$mm^3$
    - Hemoglobin ≥ 9.0 g/dL
12. At the time of treatment start, at least 2 weeks or 5 medication half-lives (whichever is longer) must had elapsed since completion of prior systemic therapy and at least 2 weeks since completion of minor surgery and radiotherapy (provided that no more than 25% of bone marrow reserve had been irradiated)
13. Except for alopecia, resolution of all acute toxic effects of any prior chemotherapy, surgery, radiotherapy to NCI CTC (Version 3.0) grade ≤ 1 and to the baseline laboratory values as defined in Inclusion Criteria Number 9, 10, 11

| | |
|---|---|
| **Name of Company:** Tiziana Life Sciences, PLC<br>**Name of Finished Product:** Not applicable<br>**Name of Active Ingredient:** Milciclib Maleate (PHA-848125AC) | *(For National Authority Use only)* |

14. Able and willing to comply with scheduled visits, therapy plans, and laboratory tests required in this protocol
15. Capability to swallow capsules intact (without chewing, crushing, or opening).

**Subject Exclusion Criteria**

1. Any of the followings in the past 6 months: myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, pulmonary embolism, deep vein thrombosis
2. Grade >1 retinopathy as determinated by an ophtalmologist
3. Known brain metastases
4. Major surgery, other than diagnostic surgery, within 4 weeks prior to treatment
5. Active, uncontrolled bacterial, viral, or fungal infections
6. Known infection with HIV, active hepatitis B or hepatitis C
7. Pregnant or breast-feeding women
8. Previous (within the last 5 years) or current malignancies at other sites, except for adequately treated basal cell or squamous cell skin cancer or in situ carcinoma of the cervix uteri
9. Current enrollment in or participation in another therapeutic clinical trial within 4 weeks preceding treatment start
10. Diabetes mellitus uncontrolled
11. Gastrointestinal disease (e.g. Crohn's disease, ulcerative colitis, or short gut syndrome) that would have impacted on drug absorption
12. Patients under treatment with anticoagulants or with coagulation disorders or with signs of hemorrhage at baseline
13. Patients with previous history or current presence of neurological disorders disorders (with the exception of myasthenia gravis), including epilepsy (although controlled by anticonvulsant therapy), Parkinson's disease and extra-pyramidal syndromes
14. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that might have increased the risk associated with study participation or might have interfered with the interpretation of study results and, in the judgment of the Investigator, would have made the patient inappropriate for entry into this study or could have compromised protocol objectives in the opinion of the Investigator and/or the Sponsor.

| | |
|---|---|
| **Name of Company:** Tiziana Life Sciences, PLC<br>**Name of Finished Product:** Not applicable<br>**Name of Active Ingredient:** Milciclib Maleate (PHA-848125AC) | *(For National Authority Use only)* |

**Test Product, Dose and Mode of Administration, Batch Number:**

**Milciclib maleate (PHA-848125AC)** is formulated as oral 10 mg, 50 mg and 100 mg capsules to be swallowed intact (without chewing, crushing or opening). The compound was administered once daily at the flat dose of 150mg/day for 7 days on / 7 days off in a 2-week cycle.
**The batch numbers used** for this study were:
N1001842, N1100005, N1100161, N1200177, N1200494, N1200775, N1300441, N1300749, N1301035, N1400772, N1401103, N1501700, N1501832, N1600811, N1601074, N1700192, N1700244, N1700318, N1700459, N1700590 **(50 mg caps),**
N1001844, N1100006, N1100162, N1200178, N1200495, N1300442, N1300750, N1301036, N1400773, N1401104, N1500767, N1500969, N1501701, N1501833 **(100 mg caps).**
No batches of 10 mg strength were used.

**Reference Therapy, Dose and Mode of Administration, Batch Number:** Not applicable.

**Duration of Treatment**: Patients could continue study treatment until disease progression, refusal or withdrawal of patient consent, or the occurrence of unacceptable toxicity and were to be followed up for survival up to the end of the study and in any case for no more than 2 years from the end of treatment. However, according to Amendment 5 the duration of study was censored at the cut-off date of 31 May 2017, since sufficient data had been already collected for the efficacy primary endpoint

**Endpoints and Criteria for Evaluation:**
Primary endpoint:

- Progression-free survival rate at 3 months (PFS-3 rate). The PFS-3 rate was to be 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.

Secondary endpoints:

- Objective tumor response according to RECIST [Therasse P. et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst. 2000; 92 (3):205-216];
- Disease Control Rate (Objective Response Rate + ≥ 6 weeks SD rate);
- Progression-free survival, calculated as 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;
- Duration of Response measured from the time measurement criteria were first met for CR/PR (whichever was first recorded) until the first date that recurrent or progressive disease was objectively documented (taking as reference for progressive disease the smallest measurements recorded on study);
- Overall Survival (OS), i.e. the time from the date of treatment start to the date of death from any cause;
- Overall safety profile, evaluated on the basis of laboratory and clinical safety parameters (i.e. hematology and blood chemistry, urinalysis, vital signs, ophthalmologic examinations and adverse events emerging during the trial). The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 3.0 was used for the severity grading of adverse events and hematological and blood chemistry abnormalities.

Exploratory endpoint**:**

Characterization of p53, p21, p27, cyclin D1, p75, and TRKA basal expression by IHC and TRKA copy number by FISH in tumor tissue involved in the PHA-848125AC mechanism of action to be performed in

| | |
|---|---|
| **Name of Company:** Tiziana Life Sciences, PLC<br>**Name of Finished Product:** Not applicable<br>**Name of Active Ingredient:** Milciclib Maleate (PHA-848125AC) | *(For National Authority Use only)* |

tumor tissue of consenting patients. Amendment 4 allowed modification in the list of the explored biomarkers, according to preliminary results observed in CDKO-125a-006 study.

**Statistical Methods:**

In consideration of the exploratory nature of the study, a single-arm, open-label, multicenter phase II clinical trial design is adopted, including an early stopping rule in case of identification of a clearly unacceptable progression free proportion by 3 months of treatment.

The primary endpoint of the study was the progression-free survival status at 3 months and the primary efficacy analysis was to be performed on the proportion of successes (i.e. patients alive and in a progression-free status at 3 months since treatment start) out of the total number of evaluable patients (PFS-3 rate).

Under the assumption of an uninteresting PFS-3 rate of 25% (corresponding to a median PFS of 1.5 months) against an interesting one of 50% (corresponding to a median PFS of 3 months), $\alpha$=0.05 and $\beta$=0.10, 30 evaluable patients were required for a single stage trial.
If at the end of the trial 12 or more out of 30 evaluable patients would have been alive and progression-free at 3 months since the treatment start date, the null hypothesis is rejected. The probability of this occurring was 5.1% if the true probability of avoiding progression by 3 months would be 25% while the probability of this occurring was 90.0% if the true probability of avoiding progression by 3 months would be 50%.

To ensure that the study would not continue in the event that the agent was not providing adequate prevention of progression, a Fleming multiple-testing procedure was to be utilized for the computation of acceptance and rejection critical boundaries at the interim look. If 3 or fewer patients out of the first 15 were progression-free at 3 months, accrual would have stopped for futility as soon as this can be determined. If 4 or more patients out of 15 were progression free, the trial would have continued until 30 evaluable patients were available.

A two-tailed 90% CI on 12 out of 30 (40.0%) evaluable patients alive and in progression-free status at 3 months would have ranged from 25.0% to 56.6%, whereas the two-tailed 90% CI of 4 out of 15 (26.7%) would have ranged between 9.7% to 51% thus showing substantial consistency with the set of hypotheses.

Supportive analyses of the primary endpoint would have included the estimation of the PFS-3 rate together with its exact, two-tail, 95% confidence interval and the estimation of the PFS curve by the Kaplan-Meier method in both the evaluable and the treated patient population. The other efficacy endpoints including the confirmed objective response rate, the disease control rate, the duration of response, and the overall survival were descriptively analyzed in both the evaluable and the treated patient populations. Kaplan-Meier estimates were generated and plotted for the overall survival endpoint.

Patients' baseline characteristics, treatment exposure and safety data were to be analyzed in the treated patient population and, if clinically interesting, in other subsets such as the evaluable patient population.
Descriptive statistical analyses and individual data listings were to be used to report all collected data including patient disposition, protocol deviations, baseline characteristics, treatment exposure, efficacy, and safety data

Patient Populations:

- *Screened Patients*: This population included all patients who were screened for potential eligibility for the trial, regardless of whether they were enrolled in the study. This population was to be evaluated in the analysis of patients' disposition.
- *Enrolled Patients*: This population included all the enrolled patients, regardless of whether or not they received the study drug. This population was to be evaluated in the analysis of patients' disposition.

| | |
|---|---|
| **Name of Company:** Tiziana Life Sciences, PLC<br>**Name of Finished Product:** Not applicable<br>**Name of Active Ingredient:** Milciclib Maleate (PHA-848125AC) | *(For National Authority Use only)* |

- *Treated Patients:* The treated patient population consisted of all enrolled patients who had received at least one study drug administration. This population was to be evaluated in the analysis of patient disposition, baseline characteristics, treatment efficacy and safety and treatment exposure.
- *Patients Evaluable for Efficacy Analysis*: This definition included the patient population for the primary efficacy analysis of 12-week PD-free rate and consisted of all treated patients who had fulfilled the following additional conditions:
  a) They had received at least 80% of drug in the first two cycles overall;
  b). They had undergone baseline and ≥1 on-treatment tumor/oncologic assessments or had died before tumor re-assessment.

**SUMMARY OF RESULTS:**

**Disposition of Subjects and Baseline Characteristics:**

In the present trial 30 patients (15 males and 15 females, with mean age of 54.2 years) with malignant thymomas were enrolled and treated with a flat dose of 150 mg/day of milciclib once daily for 7 consecutive days (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). All patients had received at least one prior systemic therapy, and, in addition, 4 patients underwent surgery, 3 patients had radiotherapy and 21 patients had both surgery and radiotherapy.

All patients had metastatic disease at study entry and the most frequent sites of metastases were lung (60%), lymph nodes (40%), liver (33%) and bones (33%). ECOG PS was reported in 28 patients and scored 0 and 1 in 14 patients, respectively. The main reasons for treatment discontinuation (off –treatment reason) were progression of disease in 17 patients (57%), adverse events in 5 patients (17%), while the off-study reasons were death (13 patients, 43%), sponsor's decision (8 patients, 27%), FU completed as per protocol (4 patients, 13%). When more than the 12 successes required by protocol had already been obtained, collected data were considered sufficient for the primary efficacy endpoint; therefore the Sponsor decided to stop collecting data in CRF and to just guarantee drug supply and safety monitoring, in order to close the database, prepare the present CSR and plan for further investigations. Amendment 5 was released and at the cut-off date of 31 May 2017, patients' data were no longer collected in the CRFs but only in the patients' medical notes. Three patients were still on treatment at that time and all the related information was censored at the cut-off date and patients considered off-study as reported in all tables and listings.

**Treatment exposure**: Milciclib maleate was administered for 7 days on/7 days off in a 2-week cycle at the flat dose of 150 mg/day with a median dose intensity of 388.5 mg/week (min-max: 255.6– 525.0 mg/week). A total of 342 cycles were administered, and the median number of cycles per patient was 5.5 (min-max: 1-48). *Treatment modifications* (delay/reduction) were implemented at cycle start or intra-cycle and occurred due to *hematological toxicity* (mainly neutropenia and anemia) in 4 patients (13%), *non-hematological toxicity* (mainly nausea, diarrhoea and vomiting) in 18 patients (60%) and modifications due to *other reasons* (i.e: logistic reasons) also in 18 patients (60%). *Treatment compliance*: over a total number of 342 cycles, the percentage of the administered *vs* scheduled dose by cycle was full dose in 142 cycles (41%), between 80% and full dose in 7 cycles (2%), between 50% and 80% in 186 cycles (54%) and less than 50% in 7 cycles (2%).

**Efficacy Results:**

The primary endpoint of the study, i.e., the progression free survival status at 3 months, has been achieved in 13 out of the 24 evaluable patients (54%), with median *PFS* of 9.76 months with lower and upper 95% confidence limits of 4.11 and 17.45 months, respectively. The median OS was not reached in the evaluable patient population.

One PR and 19 SD were observed among the evaluable patients. The disease control rate (CR + PR + ≥6 weeks of SD) for the 24 evaluable patients was 83.3%

| | |
|---|---|
| **Name of Company:** Tiziana Life Sciences, PLC<br>**Name of Finished Product:** Not applicable<br>**Name of Active Ingredient:** Milciclib Maleate (PHA-848125AC) | *(For National Authority Use only)* |

*Biomarkers*,
According to Amendment 4 and on the basis of preliminary statistical analysis of biomarker data obtained from study CDKO-125a-006, in the present study analysis was performed for p53, p27, cyclin D1, pYES and Ki67 expression; TRKA and p21 were not evaluated because no significant correlation with response to milciclib treatment was observed in patients enrolled in the CDKO-125a-006 trial. Whereas p75 protein evaluation was not performed because the IHC specific antibody, after evaluation on CDKO-125a-006 tumor samples, was considered not reliable.
Tumor samples from 14 patients were evaluable from an immunohystological point of view. Nine were classified as B3 thymoma and five as C thymic carcinoma. The results of IHC analysis distinguished responsive patients (identified as the patients free from progression of the disease at 3 months) from unresponsive patients. An exploratory analysis of each biomarker was not performed due to the low number of evaluable patients.

**Safety Results:**
All the 30 treated patients experienced at least 1 AE in the first or subsequent cycles and 29 patients presented drug related events. The safety data confirm the already known toxicological profile of milciclib maleate, as emerged from the clinical studies performed so far. The safety pattern of the compound is mainly represented by mild/moderate gastrointestinal toxicity (i.e: nausea, diarrhea, vomiting) only sporadically severe, asthenia and fatigue, neurological effects (tremor,, anorexia and anaemia; all were reversible upon drug discontinuation or dose reduction. ALT, AST and serum lipase increase were also reported, as already identified in previous clinical studies with milciclib. No significant ocular effects were reported in this study.

Three deaths occurred on study (i.e. occurred within 28 days from the last administered dose) and were reported to the Sponsor as unrelated to milciclib.

**Pharmacokinetic Results:**
No Pharmacokinetics analysis was performed in this study

**CONCLUSIONS:**
Data obtained from the present study demonstrated that treatment with milciclib administered at the adopted dose-schedule (i.e.: 150 mg/day for 7-day on/ 7-day off q2wks) have met the progression free survival at 3 months primary endpoint. The median overall survival was not reached in this patient population. This confirms earlier observations regarding the overall safety profile of milciclib suggesting that long term administration of milciclib at the adopted dose-schedule of 150 mg/day for 7-day on/ 7-day off q2wks is well tolerated with no new emerging safety issues, and therefore could be further evaluated in other tumor types.

**Date of the Report:**
04 March 2019