## Sponsor

Novartis

## Generic Drug Name

Ribociclib

## Trial Indication(s)

Advanced solid tumors

## Protocol Number

CLEE011X1101

## Protocol Title

A phase I study of LEE011 in Asian patients with advanced solid tumors

## Clinical Trial Phase

Phase I

## Phase of Drug Development

Phase III

## Study Start/End Dates

20 Jun 2013 to 28 Jan 2015

## Reason for Termination (If applicable)

Dose expansion part, which was to be conducted in esophageal squamous cell carcinoma (ESCC) patients, was cancelled before initiation of enrollment in the expansion because no signs of anti-tumor activity of LEE011 were observed in 9 of the ESCC patients enrolled in the dose escalation part. The study was terminated upon discontinuation of all patients in the dose escalation part.

## Study Design/Methodology

This was a phase I, multi-center, open-label dose-escalation study in patients with solid tumors that had progressed despite standard therapy or for which no further effective standard therapy was available. In the dose escalation part, LEE011 was administered orally once daily for 21 days followed by a 7-day rest period (28-day cycle) with a starting dose of 400 mg and enrollment to successive cohorts continued until the maximum tolerated dose (MTD)/ recommended dose for expansion (RDE) was determined. In the dose expansion part, LEE011

was to be administered using the most appropriate dosing schedule at the MTD/RDE in ESCC patients.

## Centers

2 centers in Japan

## Publication

None

## Objectives:

The primary objective was to estimate the MTD and/or RDE and to assess the dosing schedule as a single agent of LEE011 when administered orally to Japanese patients with advanced solid tumors.

The secondary objectives were:

- To characterize the safety and tolerability of LEE011;
- To characterize the PK profiles of LEE011 and any other clinically significant metabolites that may be identified; and
- To assess any preliminary anti-tumor activity that may be associated with LEE011 treatment.

## Test Product (s), Dose(s), and Mode(s) of Administration

LEE011 capsules were taken orally at a dose of 400 mg or 600 mg for 21 days followed by 7-day rest.

## Statistical Methods

Estimation of the MTD(s)/RDE was based upon the probability of DLT during Cycle 1 for patients in the dose-determining set (DDS). The dose escalation was guided by the Bayesian Logistic Regression Model (BLRM) along with escalation with overdose control (EWOC) principle. The MTD/RDE was the one with the highest posterior probability of DLT rate falling in the target toxicity interval [0.16, 0.33) among the tested doses fulfilling the EWOC, such that there was less than 25% chance that the true DLT rate at the dose would fall in the excessive toxicity interval [0.33, 1].

Unless otherwise noted, the other safety and efficacy analyses were conducted by dose cohort. For continuous variables, descriptive statistics (n, Mean, standard deviation [SD], Median, Min, Max) were used. For discrete variables, the number and percentage of patients or events were presented. All data were listed appropriately.

## Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Male or female patients ≥18 years
- Patient with a histologically confirmed diagnosis of a solid tumor
- ECOG PS <2
- Good organ function at screening visit
- A sufficient interval must have elapsed between the last dose of prior anti-cancer therapy

Exclusion Criteria:

- Impairment of GI function
- Patients with concurrent severe and/or uncontrolled concurrent medical conditions
- Known diagnosis of HIV or active viral hepatitis
- Pregnant or nursing (lactating) women

## Participant Flow Table

### Patient disposition by treatment (FAS)

| | LEE011 400 mg N=4 n (%) | LEE011 600 mg N=13 n (%) | All patients N=17 n (%) |
|---|---|---|---|
| **Patients treated** | | | |
| Treatment discontinued | 4 (100) | 13 (100) | 17 (100) |
| Treatment ongoing* | 0 | 0 | 0 |
| **Primary reason for discontinuation** | | | |
| Physician Decision | 1 (25.0) | 1 (7.7) | 2 (11.8) |
| Progressive Disease | 3 (75.0) | 12 (92.3) | 15 (88.2) |
| **Study evaluation after completion of treatment** | | | |
| Patients no longer being followed for study evaluation completion | 4 (100) | 13 (100) | 17 (100) |
| Patients continuing to be followed* for study evaluation completion | 0 | 0 | 0 |
| **Primary reason for study evaluation completion** | | | |
| Completed | 4 (100) | 11 (84.6) | 15 (88.2) |
| New Therapy For Study Indication | 0 | 2 (15.4) | 2 (11.8) |

* Patients ongoing at the time of the cut-off.

## Baseline Characteristics

## Demographics by treatment (FAS)

| | LEE011 400 mg N=4 | LEE011 600 mg N=13 | All patients N=17 |
|---|---|---|---|
| **Age (Years, at screening)** | | | |
| N | 4 | 13 | 17 |
| Mean | 57.8 | 56.6 | 56.9 |
| SD | 12.28 | 11.30 | 11.15 |
| Median | 58.5 | 57.0 | 57.0 |
| Minimum | 44 | 33 | 33 |
| Maximum | 70 | 73 | 73 |
| **Age category (Years, at screening) – n (%)** | | | |
| <65 | 2 (50.0) | 10 (76.9) | 12 (70.6) |
| >=65 | 2 (50.0) | 3 (23.1) | 5 (29.4) |
| **Sex -n (%)** | | | |
| Female | 2 (50.0) | 7 (53.8) | 9 (52.9) |
| Male | 2 (50.0) | 6 (46.2) | 8 (47.1) |
| **Weight (kg, at baseline)** | | | |
| N | 4 | 13 | 17 |
| Mean | 51.30 | 57.41 | 55.97 |
| SD | 12.196 | 11.961 | 11.930 |
| Median | 49.00 | 56.30 | 55.50 |
| Minimum | 39.4 | 40.1 | 39.4 |
| Maximum | 67.8 | 84.3 | 84.3 |
| **Body mass index (kg/m$^2$)** | | | |
| N | 4 | 13 | 17 |
| Mean | 19.42 | 21.88 | 21.30 |
| SD | 3.461 | 3.771 | 3.751 |
| Median | 18.70 | 22.24 | 21.67 |
| Minimum | 16.0 | 16.7 | 16.0 |
| Maximum | 24.3 | 28.2 | 28.2 |
| **BMI category (kg/m$^2$) -n (%)** | | | |
| <25 | 4 (100) | 9 (69.2) | 13 (76.5) |
| >=25 | 0 | 4 (30.8) | 4 (23.5) |
| **ECOG PS -n (%)** | | | |
| 0 | 3 (75.0) | 8 (61.5) | 11 (64.7) |
| 1 | 1 (25.0) | 5 (38.5) | 6 (35.3) |

## Disease history by treatment (FAS)

| | LEE011 400 mg N=4 | LEE011 600 mg N=13 | All patients N=17 |
|---|---|---|---|
| **Primary site of cancer - n (%)** | | | |
| Breast | 1 (25.0) | 3 (23.1) | 4 (23.5) |
| Oesophagus | 2 (50.0) | 7 (53.8) | 9 (52.9) |
| Peritoneum | 1 (25.0) | 2 (15.4) | 3 (17.6) |
| Soft tissue | 0 | 1 (7.7) | 1 (5.9) |
| Missing | 0 | 0 | 0 |
| **Histological grade - n (%)** | | | |
| Well differentiated | 1 (25.0) | 3 (23.1) | 4 (23.5) |
| Moderately differentiated | 2 (50.0) | 1 (7.7) | 3 (17.6) |
| Poorly differentiated | 1 (25.0) | 0 | 1 (5.9) |
| Undifferentiated | 0 | 1 (7.7) | 1 (5.9) |
| Unknown | 0 | 8 (61.5) | 8 (47.1) |
| Missing | 0 | 0 | 0 |
| **Types of lesions at baseline - n (%)** | | | |
| Non-target only | 1 (25.0) | 0 | 1 (5.9) |
| Both target and non-target | 3 (75.0) | 13 (100) | 16 (94.1) |
| Missing | 0 | 0 | 0 |

## Summary of Efficacy

## Primary Outcome Result(s)

Refer to Safety Result section for primary outcome result.

## Secondary Outcome Result(s)

## Summary of Safety

## Safety Results

## Determination of MTD/RDE

| | |
|---|---|
| RDE | 600 mg QD on the 21-days on/7-days off schedule in Japanese patients with solid tumors |
| MTD | Not determined |

## Dose-limiting toxicities occurring during the first cycle by primary system organ class, preferred term, maximum grade and treatment (DDS)

| Primary system organ class<br>Preferred term<br>Maximum Grade | LEE011 400 mg N=4 n (%) | LEE011 600 mg N=13 n (%) | All patients N=17 n (%) |
|---|---|---|---|
| Any primary system organ class | | | |
| Grade 3 | 1 (25.0) | 1 (7.7) | 2 (11.8) |
| Grade 4 | 0 | 2 (15.4) | 2 (11.8) |
| Blood And Lymphatic System Disorders | | | |
| -Total | | | |
| Grade 3 | 1 (25.0) | 1 (7.7) | 2 (11.8) |
| Grade 4 | 0 | 2 (15.4) | 2 (11.8) |
| Febrile Neutropenia | | | |
| Grade 3 | 1 (25.0) | 1 (7.7) | 2 (11.8) |
| Neutropenia | | | |
| Grade 4 | 0 | 1 (7.7) | 1 (5.9) |
| Thrombocytopenia | | | |
| Grade 4 | 0 | 1 (7.7) | 1 (5.9) |
| Investigations | | | |
| -Total | | | |
| Grade 3 | 0 | 2 (15.4) | 2 (11.8) |
| Electrocardiogram QT Prolonged | | | |
| Grade 3 | 0 | 2 (15.4) | 2 (11.8) |

## Adverse events observed in at least 2 of all patients, regardless of study drug relationship, by primary system organ class, preferred term and treatment (Safety set)

| | LEE011 400 mg N=4 | | LEE011 600 mg N=13 | | All patients N=17 | |
|---|---|---|---|---|---|---|
| Primary system organ class<br>Preferred term | All Grades n (%) | Grade 3/4 n (%) | All Grades n (%) | Grade 3/4 n (%) | All Grades n (%) | Grade 3/4 n (%) |
| -Any primary system organ class | | | | | | |
| -Total | 4 (100) | 3 (75.0) | 13 (100) | 13 (100) | 17 (100) | 16 (94.1) |
| Blood and lymphatic system disorders | | | | | | |
| -Total | 4 (100) | 3 (75.0) | 13 (100) | 13 (100) | 17 (100) | 16 (94.1) |
| Leukopenia | 4 (100) | 3 (75.0) | 13 (100) | 11 (84.6) | 17 (100) | 14 (82.4) |
| Neutropenia | 3 (75.0) | 3 (75.0) | 13 (100) | 10 (76.9) | 16 (94.1) | 13 (76.5) |
| Lymphopenia | 2 (50.0) | 0 | 12 (92.3) | 10 (76.9) | 14 (82.4) | 10 (58.8) |
| Thrombocytopenia | 3 (75.0) | 0 | 9 (69.2) | 4 (30.8) | 12 (70.6) | 4 (23.5) |

| Primary system organ class<br>Preferred term | LEE011 400 mg N=4<br>All Grades n (%) | <br>Grade 3/4 n (%) | LEE011 600 mg N=13<br>All Grades n (%) | <br>Grade 3/4 n (%) | All patients N=17<br>All Grades n (%) | <br>Grade 3/4 n (%) |
|---|---|---|---|---|---|---|
| Anaemia | 1 (25.0) | 0 | 9 (69.2) | 3 (23.1) | 10 (58.8) | 3 (17.6) |
| Febrile neutropenia | 1 (25.0) | 1 (25.0) | 1 (7.7) | 1 (7.7) | 2 (11.8) | 2 (11.8) |
| Gastrointestinal disorders | | | | | | |
| -Total | 4 (100) | 0 | 12 (92.3) | 2 (15.4) | 16 (94.1) | 2 (11.8) |
| Nausea | 2 (50.0) | 0 | 8 (61.5) | 0 | 10 (58.8) | 0 |
| Vomiting | 1 (25.0) | 0 | 7 (53.8) | 0 | 8 (47.1) | 0 |
| Constipation | 3 (75.0) | 0 | 3 (23.1) | 0 | 6 (35.3) | 0 |
| Diarrhoea | 2 (50.0) | 0 | 2 (15.4) | 0 | 4 (23.5) | 0 |
| General disorders and administration site conditions | | | | | | |
| -Total | 2 (50.0) | 0 | 6 (46.2) | 0 | 8 (47.1) | 0 |
| Fatigue | 2 (50.0) | 0 | 2 (15.4) | 0 | 4 (23.5) | 0 |
| Pyrexia | 0 | 0 | 4 (30.8) | 0 | 4 (23.5) | 0 |
| Influenza like illness | 0 | 0 | 2 (15.4) | 0 | 2 (11.8) | 0 |
| Malaise | 0 | 0 | 2 (15.4) | 0 | 2 (11.8) | 0 |
| Investigations | | | | | | |
| -Total | 2 (50.0) | 0 | 11 (84.6) | 3 (23.1) | 13 (76.5) | 3 (17.6) |
| Blood creatinine increased | 2 (50.0) | 0 | 7 (53.8) | 1 (7.7) | 9 (52.9) | 1 (5.9) |
| Electrocardiogram QT prolonged | 1 (25.0) | 0 | 6 (46.2) | 2 (15.4) | 7 (41.2) | 2 (11.8) |
| Alanine aminotransferase increased | 0 | 0 | 2 (15.4) | 0 | 2 (11.8) | 0 |
| Aspartate aminotransferase increased | 0 | 0 | 2 (15.4) | 0 | 2 (11.8) | 0 |
| Blood bilirubin increased | 0 | 0 | 2 (15.4) | 1 (7.7) | 2 (11.8) | 1 (5.9) |
| Metabolism and nutrition disorders | | | | | | |
| -Total | 3 (75.0) | 1 (25.0) | 7 (53.8) | 0 | 10 (58.8) | 1 (5.9) |
| Decreased appetite | 1 (25.0) | 0 | 4 (30.8) | 0 | 5 (29.4) | 0 |
| Hyperkalaemia | 0 | 0 | 2 (15.4) | 0 | 2 (11.8) | 0 |
| Hypophosphataemia | 2 (50.0) | 1 (25.0) | 0 | 0 | 2 (11.8) | 1 (5.9) |
| Musculoskeletal and connective tissue disorders | | | | | | |
| -Total | 0 | 0 | 5 (38.5) | 0 | 5 (29.4) | 0 |
| Back pain | 0 | 0 | 2 (15.4) | 0 | 2 (11.8) | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | | | | |

| Primary system organ class<br>Preferred term | LEE011 400 mg N=4<br>All Grades n (%) | <br>Grade 3/4 n (%) | LEE011 600 mg N=13<br>All Grades n (%) | <br>Grade 3/4 n (%) | All patients N=17<br>All Grades n (%) | <br>Grade 3/4 n (%) |
|---|---|---|---|---|---|---|
| -Total | 2 (50.0) | 0 | 2 (15.4) | 0 | 4 (23.5) | 0 |
| Tumour pain | 2 (50.0) | 0 | 2 (15.4) | 0 | 4 (23.5) | 0 |
| Nervous system disorders | | | | | | |
| -Total | 2 (50.0) | 0 | 3 (23.1) | 0 | 5 (29.4) | 0 |
| Headache | 1 (25.0) | 0 | 1 (7.7) | 0 | 2 (11.8) | 0 |
| Psychiatric disorders | | | | | | |
| -Total | 0 | 0 | 3 (23.1) | 0 | 3 (17.6) | 0 |
| Insomnia | 0 | 0 | 3 (23.1) | 0 | 3 (17.6) | 0 |
| Respiratory, thoracic and mediastinal disorders | | | | | | |
| -Total | 1 (25.0) | 0 | 4 (30.8) | 0 | 5 (29.4) | 0 |
| Cough | 1 (25.0) | 0 | 3 (23.1) | 0 | 4 (23.5) | 0 |
| Skin and subcutaneous tissue disorders | | | | | | |
| -Total | 2 (50.0) | 0 | 4 (30.8) | 0 | 6 (35.3) | 0 |
| Dermatitis acneiform | 0 | 0 | 2 (15.4) | 0 | 2 (11.8) | 0 |
| Palmar-plantar erythrodysaesthesia syndrome | 1 (25.0) | 0 | 1 (7.7) | 0 | 2 (11.8) | 0 |

## Deaths, serious adverse events and discontinuation due to AEs (Safety set)

| | LEE011 400 mg N=4 n (%) | LEE011 600 mg N=13 n (%) | All patients N=17 n (%) |
|---|---|---|---|
| Death | 0 | 0 | 0 |
| SAE(s) | 0 | 3 (23.1) | 3 (17.6) |
| Discontinued due to AE(s) | 0 | 0 | 0 |

## Other Relevant Findings

## Conclusion:

- RDE of LEE011 was determined to be 600 mg on a dosing schedule of once daily for 21 days followed by a 7-day rest period (28-day cycle) in Japanese patients with solid tumors.
- Up to 600 mg of LEE011 administered once daily for 21 days followed by a 7-day rest period showed an acceptable safety and tolerability profile in Japanese patients with solid tumors. Toxicities were manageable by dose adjustment or interruption.

## Date of Clinical Trial Report

29 July 2015

## Date of Initial Inclusion on Novartis Clinical Trial Results website

9-Sep-2015

## Date of Latest Update

Not applicable

## Reason for Update

Not applicable