## Sponsor

Novartis

## Generic Drug Name

Patupilone

## Therapeutic Area of Trial

Non-small cell lung cancer (NSCLC)

## Approved Indication

Investigational

## Protocol Number

CEPO906A2227

## Title

An open-label, multi-center, Phase II study to evaluate the activity of patupilone (EPO906), in the treatment of recurrent or progressive brain metastases in patients with non-small cell lung cancer.

## Phase of Development

Phase II

## Study Start/End Dates

16-Nov-2005 to 27-Jul-2010

## Study Design/Methodology

This was an open-label, single arm, multi-center Phase II study in NSCLC patients with brain metastases who had progressed after chemotherapy, surgery and/or radiation. Patients were administered patupilone 10 mg/m$^2$ as a 20-minute infusion repeated once every three weeks (21 days-one treatment cycle). This study used a multinomial two-stage design for enrollment, with 25 patients expected to be enrolled during the first stage with an additional 25 patients during the second stage. A decision was to be made at the end of the first stage to either stop the trial due to inactivity or effectiveness, or continue on to Stage 2.

## Centers

19 centers in United States

## Publication

None

## Outcome measures

### Primary Outcome measure

**Efficacy:** The primary efficacy endpoints included a combination of early progression and response rate.

Early progression rate was defined as the proportion of patients who progress or die within the time interval [Cycle 1 Day 1 to Cycle 1 Day 21].

Response rate was defined as the proportion of patients who are alive without progression up to [Cycle 4 Day 1 and beyond].

The secondary endpoints were best overall response rate, duration of best overall response, Time to progression (TTP), duration of stable disease and overall response. The analysis of secondary end points was not conducted based on decision that further development with EPO906 will not be pursued.

### Secondary Outcome measures

**Safety:** Safety analysis was presented in summary tables by dose levels. The assessment of safety was based primarily on the frequency of AEs and laboratory abnormalities. Other safety data (e.g., vital signs, ECG) were considered as appropriate. All safety evaluations were performed based on the Safety Set.

**Pharmacokinetics:** Blood PK of patupilone was evaluated in patients after patupilone administration. Blood samples were to be collected on Day 1 immediately prior to and immediately at the end of the infusion and at 1 hour, 2 hours, 4 hours, 8 hours, 24 hours, 72 hours, 168 hours, 336 hours, 504 hours (immediately prior to next patupilone dose) during Cycle 1 and Cycle 3.

The PK parameters of patupilone ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}tau}$, $C_{max}$, $C_{min}$, CL, $t_{½}$, R and $V_{ss}$) were determined using non-compartmental methods.

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

Patupilone 10 $mg/m^2$ as a 20-minute infusion repeated once every three weeks (21 days-one treatment cycle).

## Statistical Methods

The primary analysis was based on the full analysis set (FAS). The analysis was repeated on the Per-Protocol Set (PPS), but the intent of this analysis was only supportive.

Point estimates and exact binomial confidence intervals (CIs) (implemented using SAS procedure FREQ with EXACT statement for one-way tables) were calculated for the proportion of patients with early progression and response. Since the statistical boundary for efficacy was crossed at the end of the first stage, the cumulative information at the end of the second stage was for purely descriptive analysis and no formal testing criteria were used. Thus, no special adjustments were required in the construction of the confidence intervals to account for the sequential nature of the design.

## Study Population: Inclusion/Exclusion Criteria and Demographics

**Inclusion criteria**

- Age ≥ 18 years.
- WHO performance status (PS) of 0, 1 or 2 (corresponding to Karnofsky PS of 50 or better).
- Patients with radiologically proven (by gadolinium-enhanced magnetic resonance imaging [Gd-MRI]) parenchymal brain metastases from histologically confirmed NSCLC (the primary disease may be quiescent). Gd-MRI was performed within 2 weeks of study entry.
- Patients with at least one recurrent bi-dimensionally measurable intracranial lesion of minimum 1 cm (1cm being the product of the largest perpendicular diameters) as defined by Gd-MRI. If the patient had previous radiation to the marker lesion(s), there must be evidence of residual disease ≥ 1 cm.
- Patients who progressed on radiotherapy, and had a 25% increase in the size of the previously radiated intracranial lesion based on the Neuro-Oncology Criteria of Tumor Response (NOCTR) for CNS tumors with a tumor size of ≥ 1 cm (1 cm being the product of the largest perpendicular diameters) or appearance of any new lesions (in brain scan with 5 mm slices, the target lesion threshold could be defined at 1.0 cm for contiguous slices).
- Patients controlled on medication and neurologically stable: stable on steroids and anticonvulsants for at least 1 week prior to obtaining the baseline Gd-MRI of the brain, and/or at least 1 week prior to beginning study treatment.
- Patients with adequate hematologic parameters: All tests were performed within 72 hours of first dose of study medication.
  - Absolute neutrophil count (ANC) ≥ 1.5 x $10^9$/L
  - Hemoglobin (Hb) ≥ 10.0 g/dL
  - Platelet count ≥ 100 x $10^9$/L
- Patients with the following blood chemistry laboratory values:
  - Total bilirubin ≤ 1.5 x upper limit normal (ULN)
  - Aspartate aminotransferase (AST)/Alanine aminotransferase (ALT) ≤ 2.5 X ULN
  - Alkaline phosphatase ≤ 3 x ULN
  - Serum creatinine < 1.5 x ULN
- Female patients with a negative serum pregnancy test at screening. (Not applicable to patients with bilateral oophorectomy and/or hysterectomy or to those patients who were postmenopausal).
- Patients of reproductive potential using an effective method of contraception during the study and three months following termination of treatment.
- Written informed consent was obtained.

**Exclusion criteria**

- Clinical evidence of leptomeningeal disease.
- Patients with extracranial disease in more than 3 organ sites including the primary tumor.

- Patients who received any investigational compound within the past 28 days or who were planning to receive other investigational drugs while participating in the study.
- Prior administration of epothilone(s).
- Patients with peripheral neuropathy > grade 1.
- Patients with unresolved diarrhea within the last 7 days prior to start of treatment. Grade 0 was mandatory at entry.
- Patients who were receiving known diarrheogenic agents had to stop treatment with these agents prior to enrollment in the study.
- Radiotherapy < 3 weeks prior to study entry.
- Patients with prior intracranial surgery< 3 weeks prior to study entry (had to recover from surgery prior to study entry).
- Chemotherapy < 3 weeks prior to study entry; < 6 weeks from prior nitrosoureas.
- Severe cardiac insufficiency (NYHA III or IV), with uncontrolled and/or unstable cardiac or coronary artery disease.
- Radiotherapy was not permitted while on study (Palliative radiotherapy of metastasis in extremities was allowed, but such lesions were not used as target or non-target lesions).
- Patients with the presence of active or suspected acute or chronic uncontrolled infection.
- Patients known to be HIV positive.
- Serious inter current medical illness/liver dysfunction/active Hepatitis B or C.
- History of another malignancy within 3 years prior to study entry, except curatively treated non-melanotic skin cancer or cervical cancer in situ.
- Pregnant or lactating females.
- Patients receiving hematopoietic growth factors except erythropoietin.
- Patients taking Coumadin® or other agents containing warfarin, with the exception of low dose Coumadin® (1 mg or less daily) administered prophylactically for maintenance of indwelling lines or ports.
- A history of noncompliance to medical regimens or inability or unwillingness to return for all scheduled visits.
- Any of the following exclusion criteria to MRI imaging:
  - Cardiac pacemaker
  - Ferromagnetic metal implants other than those approved as safe for use in MRI scanners (Example: some types of aneurysm clips, shrapnel)
  - Claustrophobia
  - Obesity (exceeding the equipment limits)

## Participant Flow

Patient disposition - n (%) of patients (FAS)

| Disposition/Reason | Patupilone 10 mg/m$^2$ N = 50 n (%) |
|---|---|
| Treated | 50 (100.0) |
| Discontinued | 50 (100.0) |
| Adverse event(s) | 13 (26.0) |
| Abnormal laboratory value(s) | 0 |
| Abnormal test procedure result(s) | 1 (2.0) |
| Patient's condition no longer requires study drug | 0 |
| Protocol violation | 0 |
| Patient withdrew consent | 4 (8.0) |
| Lost to follow-up | 0 |
| Administrative problems | 1 (2.0) |
| Death | 0 |
| Death from study indication | 0 |
| Death from other causes | 0 |
| New cancer therapy | 0 |
| Disease progression | 31 (62.0) |
| Missing | 0 |
| In treatment | 0 |

## Baseline Characteristics

Demographic summary (FAS)

| Variable | Patupilone 10 mg/m$^2$ N = 50 n (%) |
|---|---|
| **Age (years)** | |
| n | 50 |
| Mean | 57.3 |
| SD | 9.80 |
| Median | 59.5 |
| Minimum | 33.0 |
| Maximum | 74.0 |
| **Age group (years) – n (%)** | |
| < 45 | 7 (14.0) |
| 45 - 65 | 33 (66.0) |
| > 65 | 10 (20.0) |
| **Gender – n (%)** | |

| | |
|---|---|
| Female | 21 (42.0) |
| Male | 29 (58.0) |
| **Race – n (%)** | |
| Caucasian | 47 (94.0) |
| Black | 1 (2.0) |
| Oriental | 1 (2.0) |
| Other | 1 (2.0) |
| **Weight (kg)** | |
| n | 50 |
| Mean | 74.1 |
| SD | 15.97 |
| Median | 72.5 |
| Minimum | 44.2 |
| Maximum | 119.2 |
| **Height (cm)** | |
| n | 48 |
| Mean | 169.6 |
| SD | 9.22 |
| Median | 170.0 |
| Minimum | 147.0 |
| Maximum | 188.0 |

Note: Baseline weight is the last available weight collected on or before the first dose.

## Outcome measures

## Primary Outcome Result(s)

Early progression & response (FAS)

| | **Patupilone 10 mg/m$^2$ N = 50 n (%)** |
|---|---|
| Number of early progressors (EP) | 13 (26.0) |
| Number of responders (R) | 18 (36.0) |
| Neither early progression nor response | 19 (38.0) |
| 95% CI for early progression rate[1] | (0.1, 0.4) |
| 95% CI for response rate[1] | (0.2, 0.5) |

[1]95% exact binomial CI's is computed using SAS procedure FREQ
EP are those who progress or die within the time interval [Cycle 1 Day 1 to Cycle 1 Day 21]
R are those who are alive without progression up to Cycle 4 Day 1 and beyond (i.e., with at least one tumor assessment and at least one neurological assessment on or after Cycle 4 Day 1, both indicating no progression, and all available assessment before that did not have evidence of progression).

## Safety Results

## Adverse Events by System Organ Class

Adverse events, regardless of study drug relationship by primary system organ class, preferred terms, maximum severity grade - (greater than 10% of all grades) (Safety set)

| **Primary system organ class**<br>**Preferred Term** | **Patupilone 10 mg/m$^2$ N = 50** | |
|---|---|---|
| | **Grade 3/4 n (%)** | **All Grade n (%)** |
| **Any Primary system organ class** | 30 (60.0) | 50 (100.0) |
| **Gastrointestinal disorders** | 13 (26.0) | 42 (84.0) |
| Diarrhea | 12 (24.0) | 38 (76.0) |
| Nausea | 0 | 14 (28.0) |
| Constipation | 0 | 9 (18.0) |
| Vomiting | 0 | 7 (14.0) |
| **Nervous system disorders** | 7 (14.0) | 32 (64.0) |
| Headache | 1 (2.0) | 11 (22.0) |
| Neuropathy peripheral | 2 (4.0) | 8 (16.0) |
| Convulsion | 2 (4.0) | 6 (12.0) |
| Peripheral sensory neuropathy | 0 | 6 (12.0) |
| **General disorders and administration site conditions** | 5 (10.0) | 31 (62.0) |
| Fatigue | 1 (2.0) | 25 (50.0) |
| Edema peripheral | 1 (2.0) | 6 (12.0) |
| **Musculoskeletal and connective tissue disorders** | 2 (4.0) | 21 (42.0) |
| Muscular weakness | 0 | 8 (16.0) |
| **Infections and infestations** | 5 (10.0) | 18 (36.0) |
| **Metabolism and nutrition disorders** | 8 (16.0) | 18 (36.0) |
| Dehydration | 3 (6.0) | 7 (14.0) |
| **Skin and subcutaneous tissue disorders** | 0 | 16 (32.0) |
| Rash | 0 | 6 (12.0) |
| **Respiratory, thoracic and mediastinal disorders** | 4 (8.0) | 15 (30.0) |
| Dyspnea | 0 | 6 (12.0) |
| **Psychiatric disorders** | 2 (4.0) | 13 (26.0) |
| Insomnia | 0 | 7 (14.0) |
| **Investigations** | 5 (10.0) | 11 (22.0) |
| **Injury, poisoning and procedural complications** | 1 (2.0) | 10 (20.0) |
| **Eye disorders** | 1 (2.0) | 9 (18.0) |
| **Vascular disorders** | 2 (4.0) | 7 (14.0) |

Ten Most Frequently Reported AEs Overall (regardless of study drug relationship) by Preferred Term n (%)

| **Preferred Term** | **Patupilone 10 mg/m$^2$ N = 50 All Grade n (%)** |
|---|---|
| Diarrhea | 38 (76.0) |
| Fatigue | 25 (50.0) |
| Nausea | 14 (28.0) |
| Headache | 11 (22.0) |
| Constipation | 9 (18.0) |
| Muscular weakness | 8 (16.0) |
| Neuropathy peripheral | 8 (16.0) |
| Dehydration | 7 (14.0) |
| Vomiting | 7 (14.0) |
| Insomnia | 7 (14.0) |

## Serious Adverse Events and Deaths

Deaths, other serious or grade 3/4 adverse events or related discontinuations (Safety set)

| | **Patupilone 10 mg/m$^2$ N = 50 n (%)** |
|---|---|
| Patients with AE(s) | 50 (100.0) |
| Death | 3 (6.0) |
| SAE(s) | 25 (50.0) |
| Grade 3/4 AE(s) | 30 (60.0) |
| Discontinued due to SAE(s) | 8 (16.0) |
| Discontinued due to grade 3/4 AE(s) | 8 (16.0) |
| Note: Only deaths leading to discontinuation or occurring within 28 days after last dose are reported. | |

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|---|
| **Other Relevant Findings**<br>None |
| **Date of Clinical Trial Report**<br>02-Mar-2012 |
| **Date Inclusion on Novartis Clinical Trial Results Database**<br>29-Mar-2012 |
| **Date of Latest Update** |