Sponsor

Novartis

Generic Drug Name

Patupilone (epothilone B, abbreviation EPO906)

Therapeutic Area of Trial

Colorectal cancer

Approved Indication

No (in development)

Study Number

CEPO906A2117

Title

EPO906 Phase I 6-arm trial to optimize administration exploring single dose bolus and continuous infusion over 1 or 5 days every 3 or 4 weeks in patients with pretreated advanced colon cancer with nutritional support treatment and intensive management of diarrhea

Phase of Development

Phase I

Study Start/End Dates

06 Nov 2003 to 06 Nov 2006

Study Design/Methodology

Open-label, non-randomized, multicenter, 6 arms, Phase I dose escalation study.

Centers

6 centers in 4 countries: Czech Republic (2), France (2), United Kingdom (1), Spain (1)

Publication

None

Objectives

Primary objective(s):

To determine the MTD of patupilone administered as:

- bolus infusion (bolus) once every 3 weeks (q3w) and every 4 weeks (q4w)*
- continuous infusion for 1 day (CIV 1-day) q3w and q4w*
- continuous infusion for 5 days (CIV 5-day) q3w and q4w*

Secondary objective(s):

- To assess the safety and tolerability
- To determine preliminary activity as defined by overall response rate (CR + PR) according to Response

Evaluation Criteria In Solid Tumor (RECIST)

- To determine early evidence of time to progression (TTP), duration of overall response and time to overall response
- To assess the incidence and the severity of diarrhea
- To evaluate the PK of patupilone in bolus and CIV arms

* q4w schedules were cancelled and never enrolled any patients

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

Patupilone was administered either as bolus (infusion over 20 minutes) or as a continuous infusion for 1 day (1 x 24 hours) or for 5 days (5x16 hours) q3w

Dose escalation was done in 0.5 mg/m^2 steps from 6.5 to 8.0 mg/m^2, and then in 1 mg/m^2 steps until MTD or until a maximum dose of 10 mg/m^2.

Reference Product(s), Dose(s), and Mode(s) of Administration

NA

Criteria for Evaluation

Primary variables:

Assessment of cycle 1 and 2 dose limiting toxicities (DLT).

Secondary variables:

Assessment of all measurable and non-measurable disease at screening and every 8 weeks prior to patupilone dose administration according to modified RECIST.

Safety and tolerability:

Frequency/severity of adverse events and serious adverse events, clinically notable laboratory abnormalities, vital signs, and ECG. Incidence, severity, duration and treatment of diarrhea.

Pharmacology:

Bolus arm: only MTD dose/cohort (pre-dose, end of infusion, 0.5, 1, 2, 4, 8, 24, 72, 168, 336, 504 h)

CIV 1 and 5 day: all dose levels (pre-dose, end of infusion, 0.5, 1, 2, 4, 8, 24, 72, 168, 336, 504 h)

Statistical Methods

A 3+3 design was used for dose escalation with six dose levels under consideration: 6.5, 7.0, 7.5, 8.0, 9.0 and 10.0 mg/m^2. Dose escalation was based DLTs from the first and second cycle for each cohort. Intrapatient dose escalation was not permitted. MTD was defined as the dose level immediately below that at which DLT was observed in at least two out of three to six patients. No dose higher than 10 mg/m^2 was to be tested even if MTD was not reached.

Tumor evaluations and the definition of best overall response were based on RECIST. The overall response rate was defined as the proportion of patients whose best overall response was complete response (CR) or partial response (PR). The best overall response was the best response recorded from the start of the treatment until disease progression/recurrence. To be assigned a status of PR or CR, changes in tumor measurements had to be confirmed by repeat assessments that were performed not less than 4 weeks after the criteria for response were first met.

CR = at least two determinations of CR at least 4 weeks apart before progression.

PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR).

SD = at least one SD assessment (or better) > 6 weeks after start of treatment (and not qualifying for CR or PR).

PD = progression or death due to underlying cancer ≤ 12 weeks after start of treatment (and not qualifying for CR, PR or SD). Patients with symptoms of rapidly progressing disease without radiologic evidence were classified as progression only when clear evidence of clinical deterioration was available and patient

discontinued due to 'Disease progression'.

UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

The overall best response for each patient was determined based on calculated overall lesion responses ('Calculated best overall response') as well as based on investigator assessments ('Investigator best overall response'). The best overall response rate based on calculated overall lesion responses was used as primary response rate.

Time to progression (TTP) was the time from date of start of treatment to the date of first documented progression or death due to underlying cancer. If a patient had not progressed or died due to underlying cancer, time to progression was censored at the time of last tumor assessment.

Duration of overall response (CR or PR) applied only to patients whose best overall response was CR or PR. The end date and censoring was defined as for time to progression, but the start date was the date of first documented response (CR or PR).

Time to overall response (CR or PR) was the time between date of start of treatment until first documented response (CR or PR). This analysis included all patients. Patients who did not achieve a confirmed PR or CR were censored at last tumor assessment date if they did not progress, or at maximum follow-up (i.e. FPFV to LPLV used for the analysis) when they had an event of progression or death.

Kaplan-Meier estimates of all time variables were calculated including the medians, confidence intervals and quartiles (25^{th} and 75^{th}).

Study Population: Inclusion/Exclusion Criteria and Demographics

Patients who met the following criteria were included:

- Patients with histologically or cytologically confirmed diagnosis of locally advanced progressive or metastatic colon cancer.
- Patients should have had at least one measurable lesion as defined by modified RECIST criteria.
- Patients who had up to 4 previous lines of chemotherapy for treatment of metastatic disease.
- Male or female patients of any ethnic group = 18 years old.
- Patients with Performance Status < 2 (WHO scale).
- Patients with life expectancy of at least 3 months.
- Patients with no impairment of hepatic, renal or hematological function as defined by the following parameters:
    - Hb ≥ 9.0 g/dL
    - platelet count ≥ 100 x 10^9/L (untransfused)
    - ANC ≥ 1.5 x 10^9/L
    - serum ALT (SGPT) or AST (SGOT) ≤ 2.5 x ULN (≤ 5 x ULN if liver metastases were present)
    - serum total bilirubin ≤ 1.5 x ULN
    - serum creatinine < 2.0 x ULN
- Female patients must have had a negative serum pregnancy test (not applicable to patients with bilateral oophorectomy and/or hysterectomy or those patients who were postmenopausal).
- All adults of reproductive potential must have agreed to use an effective method of birth control during the study and for at least 3 months following termination of treatment.
- All patients must have used a barrier method for contraception for sexual intercourse or avoid this for the first 5 days after patupilone infusion.
- Written informed consent must have been obtained.

Patients who met the following criteria were excluded:

- Patients who had not fully recovered from surgery for any cause.
- Patients who had received any chemotherapy, immunotherapy or any investigational agent within 28 days prior to study entry.

- Patients who had received previous pelvic or abdominal radiotherapy.
- Patients with ileo- or colostomy.
- Patients with a concurrent malignancy, unless they had remained free of the disease attributed to the malignancy for > 3 years. Patients with a history of non-melanomatous skin cancer and cervical carcinoma in situ were excluded only if there was evidence of active disease.
- Patients receiving hematopoietic growth factors except erythropoietin.
- Patients taking Coumadin® or other agents containing warfarin in doses higher than 1mg per day. Low dose of Coumadin® (1mg or less) administered prophylactically for maintenance of indwelling lines or ports was allowed.
- Patients with the presence of active or suspected acute or chronic uncontrolled infection, including abscess or fistulae.
- Presence of another nonmalignant disease which in the opinion of the investigator was incompatible with the protocol.
- Patients with clinical signs of symptomatic brain metastases or leptomeningeal disease.
- Patients with cardiac disease, with an abnormal ECG at baseline, classified under the New York Heart Association classification of III or IV.
- Patients with a known diagnosis of human immunodeficiency virus (HIV) infection.
- Patients with a history of noncompliance to medical regimens or patients who were considered potentially unreliable.
- Pregnant or lactating females.
- Patients with diarrhea > grade 1.
- Patients who were on prophylactic loperamide treatment.
- Patients with peripheral polyneuropathy > grade 1.
- Patients with known allergy to hen egg.
- Patients with hypersensitivity to Nutritional Supplement or any of its ingredients.
- Patients with known lactose intolerance.

Number of Subjects / Patient Disposition

	EPO906
Planned N	NA
Intent-to-treat population (ITT) n (%)	60 (100)
* Completed n (%)	20 (33.3)
Discontinued n (%)	60 (100)
- Due to adverse events n (%)	10 (16.7)
- Due to disease Progression n (%)	43 (71.7)
- Due to Death *-- Disease Progression* *-- Adverse event*	3 (5) *2 (3.3)* *1 (1.7)*
- Due to abnormal lab value n (%)	2 (3.3)
- Performance Status	1 (1.7)
- Withdrew consent (satisfactory response)	1 (1.7)
* Received 6 or more cycles	

Demographic and Background Characteristics

Arm **N (ITT)**	**CIV 1 day** **N = 26** **n (%)**	**CIV 5 day** **N = 3** **n (%)**	**Bolus** **N = 31** **n (%)**
Sex			
Male	14 (53.8)	2 (66.7)	20 (64.5)
Female	12 (46.2)	1 (33.3)	11 (35.5)
Race			
Caucasian	26 (100.0)	3 (100.0)	29 (93.5)
Black	0 (0.0)	0 (0.0)	2 (6.5)
Age (yr)			
N	26	3	31
Mean (SD)	60.1 (7.5)	67.0 (6.6)	58.7 (11.8)
Median	60	68	58
Min	44	60	28
Max	72	73	81
Weight (kg)			
N	26	3	31
Mean(SD)	79.4 (11.9)	79.7 (20.1)	75.7 (20.0)
Median	81	77	72
Min	49	61	47
Max	103	101	142
Performance Status			
0	12 (46.2)	2 (66.6)	25 (80.6)
1	14 (53.8)	1 (33.3)	6 (19.4)

Primary Objective Result(s)

Cycle 1 and 2 DLTs:

	CIV 1 q3w			**CIV 5 q3w**			**Bolus q3w**		
Dose (mg/m^2)	N	n	(%)	N	n	(%)	N	n	(%)
6.5	4	0		3	2	(66.7)	4	0	
7.0	4	0		-	-		3	0	
7.5	4	1	(25.0)	-	-		3	0	

8.0	7	1	(14.3)	-	-	-	3	0
9.0	7	1	(14.3)	-	-	-	6	0
10.0	-	-		-	-		12	0
Total	26	3	(11.5)	3	2	(66.7)	31	0

- MTD was met for the 5-day CIV arm at the first dose tested (6.5 mg/m^2)
- CIV 1-day stopped at 9 mg/m^2 due to increased toxicity arising after more than 2 cycles
- MTD not reached in Bolus Arm

Secondary Objective Result(s)

Efficacy Results (ITT population):

Best Overall Response (based on investigator's reading)	CIV 1 day N = 26 n (%)	CIV 5 day N = 3 n (%)	Bolus N = 31 n (%)
Complete Response (CR)	0	0	0
Partial Response (PR)	0	0	4 (12.9)
Stable Disease (SD)	10 (38.5)	3 (100.0)	14 (45.2)
Progressive Disease (PD)	14 (53.8)	0	11 (35.5)
Unknown	2 (7.7)	0	2 (6.5)
Overall response (CR or PR)	0	0	4 (12.9)
95% CI	NA	NA	3.6, 29.8
Median TTP (months, 95% CI)	2.0 (1.9, 3.4)	0	4.3 (2.2, 6.2)
Median duration of PR/SD (mo, 95% CI)	4.0 (3.4, 5.7)	0	6.2 (5.5, 8.0)

Safety Results

Adverse Events by System Organ Class

System Organ Class	CIV 1 day N = 26 n (%)	CIV 5 day N = 3 n (%)	Bolus N = 31 n (%)
Any System Organ Class	26 (100.0)	3 (100.0)	31 (100.0)
Gastrointestinal disorders	22 (84.6)	3 (100.0)	30 (96.8)
Musculoskeletal and connective tissue disorders	6 (23.1)	0 (0.0)	8 (25.8)
Nervous system disorders	5 (19.2)	0 (0.0)	15 (48.4)
General disorders and administration site conditions	15 (57.7)	2 (66.7)	16 (51.6)
Ear and labyrinth disorders	2 (7.7)	0 (0.0)	1 (3.2)
Eye disorders	1 (3.8)	0 (0.0)	2 (6.5)
Infections and infestations	4 (15.4)	0 (0.0)	8 (25.8)
Blood and lymphatic system disorders	1 (3.8)	0 (0.0)	2 (6.5)
Hepatobiliary disorders	4 (15.4)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	5 (19.2)	1 (33.3)	3 (9.7)
Investigations	8 (30.8)	2 (66.7)	14 (45.2)
Metabolism and nutrition disorders	6 (23.1)	2 (66.7)	15 (48.4)
Neoplasms benign, malignant and unspecified	1 (3.8)	0 (0.0)	1 (3.2)
Psychiatric disorders	4 (15.4)	0 (0.0)	4 (12.9)
Renal and urinary disorders	1 (3.8)	0 (0.0)	4 (12.9)
Reproductive system and breast disorders	1 (3.8)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	3 (11.5)	0 (0.0)	4 (12.9)
Skin and subcutaneous tissue disorders	1 (3.8)	0 (0.0)	2 (6.5)
Vascular disorders	1 (3.8)	1 (33.3)	1 (3.2)

Most Frequently Reported AEs Overall by Preferred Term

Adverse Event	CIV 1 day N = 26 n (%)	CIV 5 day N = 3 n (%)	Bolus N = 31 n (%)	Total N = 60 n (%)
TOTAL	26 (100.0)	3 (100.0)	31 (100.0)	60 (100.0)
Diarrhoea	19 (73.1)	3 (100.0)	26 (83.9)	48 (80.0)
Nausea	6 (23.1)	0 (0.0)	13 (41.9)	19 (31.7)
Vomiting	5 (19.2)	1 (33.3)	13 (41.9)	19 (31.7)

Weight decreased	5 (19.2)	2 (66.7)	11 (35.5)	18 (30.0)
Abdominal pain	6 (23.1)	0 (0.0)	10 (32.3)	16 (26.7)
Asthenia	8 (30.8)	1 (33.3)	7 (22.6)	16 (26.7)
Anorexia	3 (11.5)	2 (66.7)	8 (25.8)	13 (21.7)
Pyrexia	6 (23.1)	1 (33.3)	6 (19.4)	13 (21.7)
Flatulence	3 (11.5)	0 (0.0)	8 (25.8)	11 (18.3)
Dehydration	2 (7.7)	1 (33.3)	5 (16.1)	8 (13.3)
Blood creatinine increased	1 (3.8)	1 (33.3)	6 (19.3)	7 (11.7)
Paraesthesia	2 (7.7)	0 (0.0)	4 (12.9)	6 (10.0)
Pain in extremity	3 (11.5)	0 (0.0)	2 (6.5)	5 (8.3)
Procedural nausea	2 (7.7)	0 (0.0)	3 (9.7)	5 (8.3)
Arthralgia	1 (3.8)	0 (0.0)	3 (9.7)	4 (6.7)
Constipation	0 (0.0)	0 (0.0)	4 (12.9)	4 (6.7)
Fatigue	1 (3.8)	0 (0.0)	3 (9.7)	4 (6.7)
Hypokalaemia	2 (7.7)	0 (0.0)	2 (6.5)	4 (6.7)
Back pain	1 (3.8)	0 (0.0)	2 (6.5)	3 (5.0)
Cough	0 (0.0)	0 (0.0)	3 (9.7)	3 (5.0)
Dysaesthesia	0 (0.0)	0 (0.0)	3 (9.7)	3 (5.0)
Dyspnoea	2 (7.7)	0 (0.0)	1 (3.2)	3 (5.0)
Hypoaesthesia	0 (0.0)	0 (0.0)	3 (9.7)	3 (5.0)
Hyponatraemia	0 (0.0)	0 (0.0)	3 (9.7)	3 (5.0)
Insomnia	2 (7.7)	0 (0.0)	1 (3.2)	3 (5.0)
Neuropathy peripheral	1 (3.8)	0 (0.0)	2 (6.5)	3 (5.0)
Renal failure acute	0 (0.0)	0 (0.0)	3 (9.7)	3 (5.0)
Transaminases increased	2 (7.7)	0 (0.0)	1 (3.2)	3 (5.0)
Vertigo	2 (7.7)	0 (0.0)	1 (3.2)	3 (5.0)

Serious Adverse Events and Deaths

Event	CIV 1 day N = 26 n (%)	CIV 5 day N = 3 n (%)	Bolus N = 31 n (%)
Deaths *	2 (7.7)	0	1 (3.2)
SAEs	12 (46.2)	2 (66.7)	11 (35.5)
Grade 3/4 AEs	12 (46.2)	2 (66.7)	16 (51.6)
Discontinuation due to AE	5 (19.2)	2 (66.7)	9 (29.0)
Discontinuation due to grade 3/4 AE	5 (19.2)	1 (33.3)	4 (12.9)

* 2 deaths due to PD, 1 due to AE (renal failure/not related to study drug)

Other Relevant Findings

Date of Clinical Trial Report

02 July 2009

Date Inclusion on Novartis Clinical Trial Results Database

28 April 2010

Date of Latest Update