Sponsor

Novartis

Generic Drug Name

Panobinostat

Therapeutic Area of Trial

Acute myelogenous leukemia (AML)

Approved Indication

- None

Protocol Number

CLBH589B2213

Title

A phase II study of oral single agent panobinostat in patients with refractory de novo or secondary acute myelogenous leukemia (AML)

Phase of Development

Phase II

Study Start/End Dates

27-Aug-2009 to 03-Feb-2012 (first patient first visit to last patient last visit)

Study enrollment was stopped at the conclusion of Stage 1 for both strata (de novo or secondary AML) due to lack of evidence of activity (N=59).

Study Design/Methodology

This phase II multi-center, open-label trial was undertaken for patients with the challenging diagnosis of either refractory de novo or secondary AML (associated with myelodysplastic syndrome/antecedent hematopoietic disorder [MDS/AHD]) for whom no effective salvage or treatment regimen was available. Single agent panobinostat was administered orally at a dose of 60 mg three times a week (TIW), every other day, on a weekly administration schedule.

A 2-stage design was applied with the same assumptions in the two patient groups (refractory de novo AML (Stratum A) and refractory AML secondary to AHD/MDS (Stratum B). For Stage 1, recruitment was continued until 26 patients had been enrolled. The study design allowed early termination of the study enrollment if at least 4 patients had not responded after the first 26 patients in each stratum had been entered and independently assessed for the primary endpoint of efficacy (complete remission rate [CRR] including complete remission [CR] and complete remission with residual neutropenia or thrombocytopenia [CRi] assessed up to 6 cycles of treatment).

Centers

31 participating centers in 11 countries: Australia (4), Belgium (3), France (3), Germany (3), Italy (3), Korea (1), Peru (1), Spain (2), Switzerland (2), United Kingdom (4), United States (5).

Outcome measures

Primary outcome measures

- Determination of response to treatment as complete remission rate (CRR), defined as complete remission (CR) + CR with incomplete blood count recovery (residual neutropenia or thrombocytopenia) (CRi) in Stratum A and Stratum B

Secondary outcome measures

- Assessment of partial response
- Assessment of time to remission and duration of remission
- Assessment of overall and event-free survival
- Safety and tolerability profile

Test Product, Dose, and Mode of Administration

Single agent panobinostat, 60 mg administered orally every other day three-times in a week (TIW), every week in a 28-day cycle.

Statistical Methods

The Full Analysis Set (FAS) is the same as the Safety set and includes all patients who received at least one dose of study drug. The FAS was used for final efficacy analysis. Final analysis of the primary endpoint was performed when all patients had been discontinued from the study, including follow-up for 28 days after end of treatment for safety.

Prior to the final analyses, based on the study design, a preliminary review of responses (Stage 1 review) was conducted after Stage 1 enrollment completed (26 patients in each stratum) which led to early stopping of enrollment in each stratum due to lack of evidence of activity (less than 4 patients experienced CR or CRi among the first 26 patients enrolled in each stratum).

The data were analyzed by Novartis and Experis using SAS® Version 9.2.

Study Population: Inclusion/Exclusion Criteria and Demographics

Adult male or female patients (≥ 18 years old) who met the inclusion criteria were enrolled into:

Stratum A: Refractory AML with confirmed initial diagnosis of de novo AML but excluding acute promyelocytic leukemia (APL).

Stratum B:

- Refractory AML with confirmed initial diagnosis of AML (excluding APL) secondary to precedent AHD or MDS with either condition being diagnosed at least 3 months before confirmed diagnosis of AML
- Patients may have received either no prior treatment or treatment with conventional care regimens (including best supportive care, low dose cytarabine, intensive chemotherapy, hypomethylating agents (azacitidine, decitabine), or other therapies, e.g. lenalidomide) for precedent MDS

Inclusion Criteria

Patients were included who met the following criteria:

- Written informed consent obtained prior to study-specific screening procedures
- Patients with refractory AML whose disease:
- is primary refractory (no complete remission following initial induction therapy), OR
- has relapsed within 12 months after first complete remission (CR1) and for whom salvage (re-induction) chemotherapy is not indicated for documented clinical reasons OR documented patient refusal OR
- has relapsed within 12 months after CR1 and patient has failed one salvage re-induction, i.e. failure at or relapse after second complete remission (CR2).
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.
- Electrolyte panel within normal limits (WNL) for the institution (potassium and magnesium values < lower limit of normal (LLN) must be corrected to WNL prior to dosing).
- Total calcium (corrected for albumin) or ionized calcium WNL for the institution
- Aspartate aminotransferase/glutamic oxaloacetic transaminase (AST/SGOT) and alanine aminotransferase/glutamic pyruvic transaminase (ALT/SGPT) ≤ 2.5 × upper limit of normal (ULN) (common terminology criteria for adverse events [CTCAE] Grade 1)
- Serum creatinine ≤ 1.5 × ULN (CTCAE Grade 1)
- Serum bilirubin ≤ 1.5 × ULN unless attributed to underlying disease (CTCAE Grade 1)
- International normalized ratio (INR) ≤ 1.5 and partial thromboplastin time (PTT) WNL. Patients receiving anticoagulation therapy (e.g. coumadin, heparin) are eligible provided anticoagulation therapy can be discontinued or changed to parenteral medications while the platelet count is < 50,000/mm^3.
- Negative serum pregnancy test (within 7 days of first dose)
- Negative urine pregnancy test immediately prior to first dose
- Clinically euthyroid (hypothyroidism corrected with supplementation is permitted).

- Patient has received a minimum of one and a maximum of three administrations of conventional remission induction therapy (this may include consolidation and/or hematopoietic stem cell transplantation) for newly diagnosed AML.
- Previous therapy for AML has stopped at least 2 weeks or at least 5 half-lives whichever is longer, before the first dose of study drug.
- Patient has recovered from toxicity of previous AML treatment, including Grade ≤ 1 non-hematologic toxicity prior to the first dose of study drug.

Exclusion Criteria

Patients were excluded who met the following criteria:

- Patients with initial diagnosis of AML secondary to ionizing radiation/cytotoxic therapy (e.g. alkylating agents) for previous malignancy
- Patients requiring valproic acid for any medical condition during the study or within 5 days prior to the first dose of study drug
- Clinical symptoms suggesting central nervous system (CNS) leukemia; patients with neurologic symptoms must undergo lumbar puncture and a computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain to exclude CNS involvement
- Patients receiving supportive therapy related to complications of allogeneic transplantation, including infections or graft versus host disease-directed therapy
- Patients who have received either hydroxyurea or glucocorticosteroids for prevention of leukostasis less than 24 hours before the first dose of study drug
- Patients with another malignancy (with the exception of prior MDS in patients with initial diagnosis of AML secondary to MDS/AHD) unless disease free for at least 3 years following the completion of curative intent therapy. Patients with treated non-melanoma skin cancer, in situ carcinoma, or cervical intraepithelial neoplasm regardless of the disease-free duration, are eligible if definitive treatment for the condition has been completed.
- Complete left bundle branch block or use of a permanent cardiac pacemaker, congenital long QT syndrome, history or presence of ventricular tachyarrhythmias, clinically significant resting bradycardia (< 50 bpm), QTcF ≥ 450 ms on screening electrocardiogram (ECG), or right bundle branch block + left anterior hemiblock (bifascicular block)
- Left ventricular ejection fraction (LVEF) < lower limit of institutional normal, as assessed by echocardiogram (ECHO) or multiple uptake gated acquisition scan (MUGA)
- Presence of unstable atrial fibrillation (ventricular response rate >100 bpm). Patients with stable atrial fibrillation are eligible provided they do not meet the other cardiac exclusion criteria
- Angina pectoris or acute myocardial infarction within 6 months
- Other clinically significant heart disease (e.g. uncontrolled hypertension or history of poor compliance with an antihypertensive regimen)
- Other concurrent severe and/or uncontrolled medical conditions (e.g. uncontrolled diabetes mellitus, chronic obstructive or chronic restrictive pulmonary disease including dyspnea at rest from any cause) or history of serious organ dysfunction or disease involving the heart, kidney, or liver and/or known seropositivity for human immunodeficiency virus (HIV) (HIV screening testing is not required).

- Patient has an impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of oral panobinostat (e.g. ulcerative disease, uncontrolled vomiting, Grade > 1 diarrhea, malabsorption syndrome, obstruction, or stomach and/or small bowel resection)
- Psychiatric disorder that interferes with ability to understand the study and give informed consent, and/or would impact study participation or follow-up.

Participant Flow

Patient disposition by stratum

	Panobinostat 60 mg		
	Stratum A N=32 n (%)	**Stratum B N=27 n (%)**	**Total N=59 n (%)**
Enrolled (treated patients)	32 (100)	27 (100)	59 (100)
Discontinued treatment [1]	32 (100)	27 (100)	59 (100)
Primary reason for end of treatment			
Adverse Event(s)	10 (31.3)	9 (33.3)	19 (32.2)
Subject withdrew consent	3 (9.4)	4 (14.8)	7 (11.9)
Lost to follow-up	0	1 (3.7)	1 (1.7)
Death [2]	4 (12.5)	2 (7.4)	6 (10.2)
New cancer therapy	1 (3.1)	0	1 (1.7)
Disease progression	13 (40.6)	11 (40.7)	24 (40.7)
Protocol deviation	1 (3.1)	0	1 (1.7)
Discontinued study [3]	26 (81.3)	20 (74.1)	46 (78.0)
Entered post-treatment evaluation			
Patients continuing to be followed [4]	10 (31.3)	5 (18.5)	15 (25.4)
Primary reason for end of study			
Subject withdrew consent	1 (3.1)	3 (11.1)	4 (6.8)
Death [5]	16 (50.0)	13 (48.1)	29 (49.2)
New cancer therapy	6 (18.8)	0	6 (10.2)
Disease progression	3 (9.4)	4 (14.8)	7 (11.9)

AHD = antecedent hematopoietic disorder; AML = acute myelogenous leukemia; CRF = case report form; MDS = myelodysplastic syndrome

Stratum A: refractory de novo AML, Stratum B: refractory AML secondary to MDS/AHD

[1] Patient completed End of Treatment CRF page

[2] Includes only those patients for whom death was reported as the primary reason for end of treatment

[3] Only patients with end of study CRF page completed.

[4] Patients still being followed after end of treatment.

[5] Includes only those patients for whom death was reported as the primary reason for end of study

Baseline Characteristics

Demographic and baseline characteristics (FAS)

	Panobinostat 60 mg		
Demographic variable	**Stratum A N = 32**	**Stratum B N = 27**	**Total N = 59**
Sex - n (%)			
Male	12 (37.5)	19 (70.4)	31 (52.5)
Female	20 (62.5)	8 (29.6)	28 (47.5)
Age [years]			
n	32	27	59
Mean	63.0	68.5	65.5
SD	12.13	7.75	10.65
Median	63.0	68.0	66.0
Min	27	49	27
Max	83	84	84
Age - n (%)			
< 65 years	18 (56.3)	8 (29.6)	26 (44.1)
≥ 65 years	14 (43.8)	19 (70.4)	33 (55.9)
Race - n (%)			
Caucasian	29 (90.6)	26 (96.3)	55 (93.2)
Asian	1 (3.1)	0	1 (1.7)
Other	2 (6.3)	1 (3.7)	3 (5.1)
Weight [kg]			
n	32	26	58
Mean	72.2	71.9	72.1
SD	13.88	14.74	14.14
Median	69.0	71.8	70.0
Min	48	40	40
Max	105	95	105
Height [cm]			
n	31	26	57
Mean	167.4	169.4	168.3
SD	9.04	8.56	8.80
Median	169.0	171.0	170.0
Min	147	153	147
Max	182	185	185
ECOG status - n (%)			
0	11 (34.4)	5 (18.5)	16 (27.1)
1	14 (43.8)	17 (63.0)	31 (52.5)
2	7 (21.9)	5 (18.5)	12 (20.3)
>2	0	0	0

AHD = antecedent hematopoietic disorder; AML = acute myelogenous leukemia; ECOG = Eastern Cooperative Oncology Group; MDS = myelodysplastic syndrome
Stratum A: refractory de novo AML; Stratum B: refractory AML secondary to MDS/AHD

Outcome measures

Primary Outcome Results

Best response as per Investigator assessment by stratum (FAS)

	Panobinostat 60 mg	
	Stratum A N = 32	Stratum B N = 27
Best response		
Complete remission rate (CR/CRi) (n, %)	1 (3.1)	2 (7.4)
Complete remission (CR) (n, %)	0	1 (3.7)
Complete remission with incomplete blood count recovery (CRi) (n, %)	1 (3.1)	1 (3.7)
Partial remission (PR) (n, %)	0	0
Treatment failure (n, %)	13 (40.6)	11 (40.7)
Unknown (n, %)	18 (56.3)	14 (51.9)
Relapse (n,%)[1]	0	2 (100)

AHD = antecedent hematopoietic disorder; AML = acute myelogenous leukemia; CCR = complete remission rate; CR = complete remission; CRi = complete remission with incomplete blood count recovery; FAS = full analysis set; MDS = myelodysplastic syndrome; PR = partial remission
Stratum A: refractory de novo AML; Stratum B: refractory AML secondary to MDS/AHD
[1] Relapse is based on patients with CRR.

Secondary Outcome Results

No secondary analyses were performed since the study enrollment was stopped early at Stage 1 for lack of evidence of activity (N=59).

Safety Results

Adverse events, regardless of study drug relationship, by primary system organ class and by treatment - Safety set

	Panobinostat 60 mg					
	Stratum A N = 32		Stratum B N = 27		Total N = 59	
Primary system organ class	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Total	32 (100)	31 (96.9)	27 (100)	25 (92.6)	59 (100)	56 (94.9)
Gastrointestinal disorders and administration site conditions	29 (90.6)	10 (31.3)	25 (92.6)	8 (29.6)	54 (91.5)	18 (30.5)
General disorders and administration site conditions	28 (87.5)	11 (34.4)	21 (77.8)	8 (29.6)	49 (83.1)	19 (32.2)
Infections and infestations	24 (75.0)	19 (59.4)	15 (55.6)	9 (33.3)	39 (66.1)	28 (47.5)

Blood and lymphatic system disorders	22 (68.8)	22 (68.8)	16 (59.3)	16 (59.3)	38 (64.4)	38 (64.4)
Metabolism and nutrition disorders	18 (56.3)	7 (21.9)	17 (63.0)	11 (40.7)	35 (59.3)	18 (30.5)
Investigations	11 (34.4)	7 (21.9)	10 (37.0)	8 (29.6)	21 (35.6)	15 (25.4)
Respiratory, thoracic and mediastinal disorders	13 (40.6)	1 (3.1)	8 (29.6)	2 (7.4)	21 (35.6)	3 (5.1)
Psychiatric disorders	12 (37.5)	4 (12.5)	5 (18.5)	1 (3.7)	17 (28.8)	5 (8.5)
Nervous system disorders	9 (28.1)	2 (6.3)	7 (25.9)	3 (11.1)	16 (27.1)	5 (8.5)
Vascular disorders	6 (18.8)	3 (9.4)	8 (29.6)	2 (7.4)	14 (23.7)	5 (8.5)
Cardiac disorders	2 (6.3)	1 (3.1)	6 (22.2)	2 (7.4)	8 (13.6)	3 (5.1)

AHD = antecedent hematopoietic disorder; AML = acute myelogenous leukemia;
MDS = myelodysplastic syndrome
Stratum A: refractory de novo AML; Stratum B: refractory AML secondary to MDS/AHD

Frequent adverse events (≥ 10% in any treatment group), regardless of study drug relationship, by preferred term and treatment – Safety set

	Panobinostat 60 mg		
Preferred Term	**Stratum A N = 32 n (%)**	**Stratum B N = 27 n (%)**	**Total N = 59 n (%)**
Total	32 (100)	27 (100)	59 (100)
Diarrhoea	27 (84.4)	16 (59.3)	43 (72.9)
Nausea	19 (59.4)	14 (51.9)	33 (55.9)
Pyrexia	19 (59.4)	8 (29.6)	27 (45.8)
Thrombocytopenia	15 (46.9)	12 (44.4)	27 (45.8)
Vomiting	14 (43.8)	9 (33.3)	23 (39.0)
Fatigue	13 (40.6)	9 (33.3)	22 (37.3)
Decreased appetite	10 (31.3)	9 (33.3)	19 (32.2)
Febrile neutropenia	11 (34.4)	5 (18.5)	16 (27.1)
Anaemia	9 (28.1)	2 (7.4)	11 (18.6)
Hypokalaemia	9 (28.1)	2 (7.4)	11 (18.6)
Constipation	7 (21.9)	4 (14.8)	11 (18.6)
Asthenia	5 (15.6)	5 (18.5)	10 (16.9)
Dehydration	4 (12.5)	5 (18.5)	9 (15.3)
Neutropenia	4 (12.5)	4 (14.8)	8 (13.6)
Platelet count decreased	5 (15.6)	2 (7.4)	7 (11.9)
Oedema peripheral	4 (12.5)	3 (11.1)	7 (11.9)
Insomnia	5 (15.6)	2 (7.4)	7 (11.9)
Dyspnoea	6 (18.8)	1 (3.7)	7 (11.9)
Pain	5 (15.6)	2 (7.4)	7 (11.9)
Hypotension	3 (9.4)	4 (14.8)	7 (11.9)
Sepsis	3 (9.4)	3 (11.1)	6 (10.2)
Epistaxis	4 (12.5)	2 (7.4)	6 (10.2)

Abdominal pain	3 (9.4)	3 (11.1)	6 (10.2)
Urinary tract infection	5 (15.6)	0	5 (8.5)
Weight decreased	4 (12.5)	1 (3.7)	5 (8.5)
Hyperglycaemia	1 (3.1)	4 (14.8)	5 (8.5)
Gingival bleeding	4 (12.5)	0	4 (6.8)
Hypocalcaemia	4 (12.5)	0	4 (6.8)
Hypocalcaemia	4 (12.5)	0	4 (6.8)
Electrocardiogram QT prolonged	1 (3.1)	3 (11.1)	4 (6.8)
Atrial fibrillation	1 (3.1)	3 (11.1)	4 (6.8)
Hyperuricaemia	0	3 (11.1)	3 (5.1)

AHD = antecedent hematopoietic disorder; AML = acute myelogenous leukemia; MDS = myelodysplastic syndrome
Stratum A: refractory de novo AML; Stratum B: refractory AML secondary to MDS/AHD

Number of patients who died, had a serious adverse event, discontinued because of an adverse event, had a grade 3/4 adverse event or had a clinically notable adverse event, by treatment - Safety set

	Panobinostat 60 mg		
	Stratum A N = 32 n (%)	**Stratum B N = 27 n (%)**	**Total N = 59 n (%)**
Patients with AEs [1]	32 (100)	27 (100)	59 (100)
All Deaths [2]	23 (71.9)	19 (70.4)	42 (71.2)
On treatment deaths [3]	14 (43.8)	9 (33.3)	23 (39.0)
All SAEs	29 (90.6)	23 (85.2)	52 (88.1)
Study-drug-related SAEs	10 (31.3)	13 (48.1)	23 (39.0)
AEs leading to discontinuations [4]	9 (28.1)	9 (33.3)	18 (30.5)
Grade 3/4 AEs	31 (96.9)	25 (92.6)	56 (94.9)
Clinically notable AEs	29 (90.6)	26 (96.3)	55 (93.2)

AE = adverse event; AHD = antecedent hematopoietic disorder; AML = acute myelogenous leukemia; CRF = case report form; MDS = myelodysplastic syndrome; SAE = serious adverse event
Stratum A: refractory de novo AML, Stratum B: refractory AML secondary to MDS/AHD
[1] AEs that occurred on treatment and up to 28 days after last dose of study drug
[2] includes deaths as reported in end of treatment and study evaluation completion CRF pages
[3] includes deaths up to 28 days after last dose of study drug
[4] as reported in AE CRF page

Other Relevant Findings

Overall, 6 (10.2%) patients had an increase in QTcF of > 60 ms from baseline and 18 (30.5%) patients between > 30 ms and 60 ms. A maximum post-baseline QTcF value > 500 ms was observed in 2 (7.4%) patients in Stratum B only and QTcF between > 480 ms and 500 ms occurred in 4 patients overall. No cardiac AEs which occurred in this study were directly related to QT prolongation.

Other common ECG abnormalities included T-wave morphologic changes and depressed ST-segment. There were no reported cases of Torsade de Pointes.

Date Inclusion on Novartis Clinical Trial Results Database

29-Apr-2013

Date Inclusion on Novartis Clinical Trial Results Database

30-Apr-2013

Date of Latest Update