Sponsor

Novartis

Generic Drug Name

Panobinostat

Therapeutic Area of Trial

Refractory cutaneous T-Cell lymphoma

Approved Indication

Investigational drug

Protocol Number

CLBH589B2201

Title

A Phase II study of oral LBH589 in adult patients with refractory cutaneous T-Cell lymphoma

Study Phase

Phase II

Study Start/End Dates

02-Jan-2007 to 24-Jun-2013

Study Design/Methodology

This was a multi-center, multinational, open-label, non-randomized, single-agent study with a 2-stage Simon design. Patients with mycosis fungoides (MF) or Sézary syndrome (SS) refractory to standard therapy were enrolled into 2 groups based on whether they had previously received bexarotene treatment or not. Patients received oral panobinostat 20 mg/day, 3 days per week. The primary analysis of efficacy was performed when all patients had received at least 6 months of follow-up or had discontinued and an interim report was written.

At the time of the database lock for the interim CSR there were 18 ongoing patients who continued in this study until alternative drug access (panobinostat) was available and the study was closed. A final report was written containing cumulative safety data for the patients treated in this study.

Centers

41 centers in 12 countries: Argentina (2), Australia (2), Belgium (2), Canada (2), Finland (1), France (3), Germany (3), Hungary (1), Italy (5), Spain (3), Switzerland (1), United States (16)

Test Product, Dose, and Mode of Administration

Panobinostat was supplied as hard gelatin capsules at dose strengths of 5 mg or 20 mg and administered orally at a dose of 20 mg/day on 3 days per week.

Statistical Methods

For the evaluation of the primary objective, a sample size of 59 patients was calculated to have 90% power under H_a (π=0.18) using the 2-stage design. One-sided type I error of 0.025 was used.

No formal interim analysis was performed for this study. A separate two-stage analysis was performed using a Simon optimal design for Group 1 and Group 2. The null and alternative hypotheses were H_0: π=0.05 and H_a: π=0.18. Duration of response and time to response were summarized. A Kaplan-Meier analysis of time to progression was performed, including estimation and 95% confidence interval of the median time to progression and progression-free survival.

An analysis of the objective response rate was performed when all Stage 1 patients had been followed for 6 months or come off study and was continued to Stage 2. Duration of response and time to response were summarized. A Kaplan-Meier analysis of time to progression was performed, including estimation and 95% confidence interval of the median time to progression and progression-free survival.

Two sensitivity analyses were defined for analyzing the overall response rate: 1. disease flare was not considered to be progression (in this analysis disease progression had to be confirmed by a second assessment), and 2. progressive disease was defined as a 50% increase in mSWAT from nadir, instead of the protocol-specified 25%.

For this study, the primary analysis of efficacy and safety has been performed and the results have been reported in an interim CSR. Eighteen patients continued the study at the time of the data base lock for the interim CSR. When study ended, a final report containing cumulative safety data for the patients treated in this study was written.

Unless otherwise specified, all data collected until the date of cut-off was used in all safety analyses, irrespective of how long a patient was in the trial.

The following populations were defined for analysis:

- Full analyses set (FAS) population was defined according to the intention-to-treat principle. This population included all patients enrolled into the study.
- Evaluable population consisted of a subset of the FAS consisting of those patients who have a baseline skin assessment and at least one post-baseline skin assessment. This population was used to describe results in the interim CSR and was not used in the current analysis for the final CSR.
- Safety analysis population (SAP) consisted of all patients who received at least one dose of study drug and had at least one valid post-baseline assessment.

Per-protocol population consisted of a subset of the patients in the FAS who did not have any major protocol deviations. This population was used to describe results in the interim CSR and was not used in the analysis for the final CSR.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

1. Written informed consent obtained prior to any screening procedures.
2. Age greater than or equal to 18 years old.
3. Patients with biopsy-confirmed stages IB-IVA mycosis fungoides or Sézary syndrome (SS). Patients with SS who had bone marrow involvement were also eligible. Patients with transformed CTCL were eligible.
4. Patients must have been treated with an HDAC inhibitor given for the treatment of CTCL. Patients must have had disease progression on or following treatment with an HDAC inhibitor. Patients are also eligible if they had an inadequate response to an HDAC inhibitor defined as stable disease as the best response after at least 3 months of therapy. Patients previously treated with an HDAC inhibitor are also eligible if they experienced intolerance due to adverse events.

Exclusion criteria

1. Patients with a history of visceral disease including CNS involvement (i.e. stage IVB CTCL). Patients who had SS with bone marrow involvement were eligible.
2. Impaired cardiac function.
3. Concomitant use of drugs with a risk of causing torsades de pointes.
4. Patients who have received chemotherapy or any investigational drug or undergone major surgery $\leq$ 3 weeks prior to starting study drug or who have not recovered from side effects of such therapy.
5. Less than 3 months since prior electron beam therapy
6. Women who were pregnant or breast feeding, or women of childbearing potential not willing to use a double method of contraception during the study and 3 months after the end of treatment.

Participant Flow

Patient disposition (Full Analysis Set)

n (%)	Bexarotene Exposed N=79	Bexarotene Naive N=60	All N=139
Enrolled[1]	79 (100)	60 (100)	139 (100.0)
Treatment ongoing[2]	0	0	0
Discontinued treatment	79 (100)	60 (100)	139 (100.0)
Discontinued study	76 (96.2)	60 (100)	136 (97.8)
Primary reason for end of treatment			
Adverse Event(s)	25 (31.6)	15 (25.0)	40 (28.8)
Patient withdrew consent	11 (13.9)	8 (13.3)	19 (13.7)
Lost to follow-up	0	1 (1.7)	1 (0.7)
Administrative problems	3 (3.8)	0	3 (2.2)
Death[3]	1 (1.3)	2 (3.3)	3 (2.2)
New cancer therapy	2 (2.5)	1 (1.7)	3 (2.2)
Disease progression	36 (45.6)	33 (55.0)	69 (49.6)
Protocol deviation	1 (1.3)	0	1 (0.7)
Primary reason for end of study			
Patient withdrew consent	20 (25.3)	12 (20.0)	32 (23.0)
Lost to follow-up	2 (2.5)	2 (3.3)	4 (2.9)
Administrative problems	1 (1.3)	0	1 (0.7)
Death	3 (3.8)	4 (6.7)	7 (5.0)
New cancer therapy	7 (8.9)	7 (11.7)	14 (10.1)
Disease progression	43 (54.4)	35 (58.3)	78 (56.1)

[1] Treated patients.

[2] Patients were still on treatment at the time of cut-off (12-Jul-2013).

[3] Includes only those patients for whom death was reported as the primary reason for discontinuation of therapy.

Baseline Characteristics

Demographics and baseline characteristics (Full Analysis Set - iCSR)

Demographic variable	Bexarotene exposed N=79	Bexarotene naive N=60	All N=139
Sex, n (%)			
Male	47 (59.5)	41 (68.3)	88 (63.3)
Female	32 (40.5)	19 (31.7)	51 (36.7)
Baseline Age (Years)			
Total	79	60	139
Mean (SD)	57.9 (14.70)	62.1 (11.51)	59.7 (13.53)
Median	58.0	63.0	61.0
Min, Max	25.0, 88.0	33.0, 82.0	25.0, 88.0
Baseline Age category (Years), n (%)			
<65	56 (70.9)	33 (55.0)	89 (64.0)
≥ 65	23 (29.1)	27 (45.0)	50 (36.0)
Race, n (%)			
Caucasian	68 (86.1)	54 (90.0)	122 (87.8)
Black	3 (3.8)	3 (5.0)	6 (4.3)
Asian	3 (3.8)	1 (1.7)	4 (2.9)
Other	5 (6.3)	2 (3.3)	7 (5.0)
Baseline Weight (kg)			
Total	79	60	139
Mean (SD)	78.2 (17.12)	83.7 (19.07)	80.6 (18.13)
Median	75.0	80.0	78.0
Min, Max	41.5, 122.0	53.2, 147.7	41.5, 147.7
Baseline Height (cm)			
Total	76	55	131
Mean (SD)	168.8 (10.14)	170.4 (9.98)	169.5 (10.07)
Median	169.0	170.2	170.0
Min, Max	145.0, 191.0	150.0, 192.0	145.0, 192.0

Disease characteristics (Full Analysis Set - iCSR)

Disease history	**Bexarotene exposed** N=79	**Bexarotene naive** N=60	**All** N=139
Type of disease, n (%)			
CTCL - Mycosis fungoides	57 (72.2)	47 (78.3)	104 (74.8)
CTCL - Sézary syndrome	21 (26.6)	12 (20.0)	33 (23.7)
CTCL - Other	1 (1.3)	1 (1.7)	2 (1.4)
Time since first diagnosis of CTCL to start of treatment (Months), n (%)			
<6 months	3 (3.8)	3 (5.0)	6 (4.3)
≥ 6 months to <1 year	3 (3.8)	9 (15.0)	12 (8.6)
≥ 1 year to <2 years	19 (24.1)	15 (25.0)	34 (24.5)
≥ 2 years to <5 years	22 (27.8)	17 (28.3)	39 (28.1)
≥ 5 years	32 (40.5)	16 (26.7)	48 (34.5)
Time since first diagnosis of CTCL to start of treatment, (months), median(range)	44.1(1.3-370.4)	26.8(2.1-505.0)	35.4(1.3-505.0)
Time since most recent recurrence/relapse to start of treatment, n (%)			
≤ 3 months	47 (59.5)	37 (61.7)	84 (60.4)
>3 months to ≤ 6 months	7 (8.9)	10 (16.7)	17 (12.2)
>6 months to ≤ 12 months	7 (8.9)	2 (3.3)	9 (6.5)
>12 months to ≤ 24 months	3 (3.8)	1 (1.7)	4 (2.9)
>24 months	2 (2.5)	1 (1.7)	3 (2.2)
Missing	13 (16.5)	9 (15.0)	22 (15.8)
Time since most recent recurrence/relapse to start of treatment (months), median(range)	1.7 (0.2-60.3)	1.8 (0.5-152.8)	1.8 (0.2-152.8)
Number of prior therapies, n (%)			
0 to 1	2 (2.5)	2 (3.3)	4 (2.9)
2	8 (10.1)	19 (31.7)	27 (19.4)
3	8 (10.1)	18 (30.0)	26 (18.7)
>3	61 (77.2)	21 (35.0)	82 (59.0)
Number of prior therapies, median (range)	5.0 (1-15)	3.0 (1-9)	4.0 (1-15)
Best responses to prior therapies, n (%)			
Complete response	1 (1.3)	2 (3.3)	3 (2.2)
Partial response	20 (25.3)	8 (13.3)	28 (20.1)
Stable disease	20 (25.3)	20 (33.3)	40 (28.8)
Progressive disease	26 (32.9)	18 (30.0)	44 (31.7)
Unknown	7 (8.9)	10 (16.7)	17 (12.2)
Not applicable	5 (6.3)	2 (3.3)	7 (5.0)
Number of prior systemic therapies, n (%)			

Disease history	Bexarotene exposed N=79	Bexarotene naive N=60	All N=139
0 to 1	2 (2.5)	6 (10.0)	8 (5.8)
2	15 (19.0)	27 (45.0)	42 (30.2)
3	13 (16.5)	11 (18.3)	24 (17.3)
>3	49 (62.0)	15 (25.0)	64 (46.0)
Missing	0	1 (1.7)	1 (0.7)
Number of prior systemic therapies, median (range)	5.0(1-15)	2.0(1-7)	3.0(1-15)
Oral Bexarotene best response, n (%)			
Complete response	1 (1.3)	0	1 (0.7)
Partial response	30 (38.0)	0	30 (21.6)
Stable disease	21 (26.6)	0	21 (15.1)
Progressive disease	14 (17.7)	0	14 (10.1)
Unknown	9 (11.4)	0	9 (6.5)
Not applicable	4 (5.1)	60 (100)	64 (46.0)
Reason for discontinuation of oral Bexarotene			
Adverse Event(s)	19 (24.1)	0	19 (13.7)
Disease progression	46 (58.2)	0	46 (33.1)
Other	13 (16.5)	0	13 (9.4)
Not applicable	0	60 (100)	60 (43.2)
Missing	1 (1.3)	0	1 (0.7)
Stage of disease, n (%)			
IA	1 (1.3)	0	1 (0.7)
IB	16 (20.3)	11 (18.3)	27 (19.4)
IIA	4 (5.1)	4 (6.7)	8 (5.8)
IIB	22 (27.8)	18 (30.0)	40 (28.8)
IIIA	9 (11.4)	7 (11.7)	16 (11.5)
IIIB	8 (10.1)	6 (10.0)	14 (10.1)
IVA	16 (20.3)	12 (20.0)	28 (20.1)
IVB	3 (3.8)	2 (3.3)	5 (3.6)
Performance status (ECOG), n (%)			
0	47 (59.5)	41 (68.3)	88 (63.3)
1	28 (35.4)	17 (28.3)	45 (32.4)
2	3 (3.8)	2 (3.3)	5 (3.6)
Missing	1 (1.3)	0	1 (0.7)

CTCL: cutaneous T-cell lymphoma; ECOG: the Eastern Cooperative Oncology Group.

Outcome measures

Primary Outcome Results

Overall response rates (Full Analysis Set - iCSR)

	Bexarotene exposed	Bexarotene naive	All
	N=79	N=60	N=139
Overall response (CR/PR[1]) (mSWAT + CT) f.i.p.			
Number of responders	12	12	24
Estimated response rate (%)[2] (p-value[3])	16.7 (<0.001)	20.3 (<0.001)	18.5 (<0.001)
95% CI[4] of response rate (%)	(8.1, 25.0)	(10.8, 32.3)	(11.4, 24.6)
Overall response (CR/PR[1]) (mSWAT + CT) f.n.p.			
Number of responders	14	13	27
Estimated response rate (%)[2] (p-value[3])	18.5 (<0.001)	21.8 (<0.001)	20.2 (<0.001)
95% CI[4] of response rate (%)	(10.0, 27.9)	(12.1, 34.2)	(13.2, 27.0)
Overall response (CR/PR[1]) (mSWAT + CT) f.n.p., alternative PD			
Number of responders	14	13	27
Estimated response rate (%)[2] (p-value[3])	18.5 (<0.001)	21.8 (<0.001)	20.2 (<0.001)
95% CI[4] of response rate (%)	(10.0, 27.9)	(12.1, 34.2)	(13.2, 27.0)

[1] Best response.
[2] Uniformly minimum variance unbiased estimate.
[3] Exact p-value.
[4] Exact confidence interval.

CI: confidence interval; CR: complete response, CT: computed tomography; f.i.p: flare considered as disease progression; f.n.p.: flare was not considered disease progression; mSWAT : modified severity-weighted assessment tool; PD : progressive disease; PR: partial response.

Secondary Outcome Results

Skin response rates (Full Analysis Set - iCSR)

	Bexarotene exposed	Bexarotene naive	All
	N=79	N=60	N=139
mSWAT skin response[1] (CR/PR) f.i.p.			
Number of responders	12	14	26
Estimated response rate (%)[2]	15.2	23.3	18.7
95% CI[3] of response rate (%)	(8.1, 25.0)	(13.4, 36.0)	(12.6, 26.2)
mSWAT skin response[1], f.n.p.			
Number of responders	14	16	30
Estimated response rate (%)[2]	17.7	26.7	21.6
95% CI[3] of response rate (%)	(10.0, 27.9)	(16.1, 39.7)	(15.1, 29.4)
mSWAT skin response[1], f.n.p., alternative PD			
Number of responders	14	18	32
Estimated response rate (%)[2]	17.7	30.0	23.0
95% CI[3] of response rate (%)	(10.0, 27.9)	(18.8, 43.2)	(16.3, 30.9)
Physician's Global Assessment – n (%)			
CR	3 (3.8)	0	3 (2.2)
PR	12 (15.2)	18 (30.0)	30 (21.6)
SD	54 (68.4)	35 (58.3)	89 (64.0)
PD	6 (7.6)	4 (6.7)	10 (7.2)
Missing	4 (5.1)	3 (5.0)	7 (5.0)
Responder (CR/PR)	15 (19.0)	18 (30.0)	33 (23.7)
Non responder	60 (76.0)	39 (65.0)	99 (71.2)
95% CI[3] for responder	(0.116, 0.308)	(0.199, 0.5)	(0.179, 0.333)

[1] Best response.
[2] Number of responders / N.
[3] Confidence interval ignores two-stage nature of the study design.

CI: confidence interval; CR: complete response, CT: computed tomography; f.i.p: flare considered as disease progression; f.n.p.: flare was not considered disease progression; mSWAT: modified severity-weighted assessment tool; PD: progressive disease; PR: partial response; SD: stable disease.

Time to response for responders (Full Analysis Set - iCSR)

	Bexarotene exposed N=79	Bexarotene naive N=60	All N=139
Time to response (CR/PR[1]) f.i.p.			
Number of responders – n (%)	12 (15.2)	12 (20.0)	24 (17.3)
Number censored – n (%)	0	0	0
25th, 75th percentiles[2]	(43.0, 127.0)	(29.5, 114.0)	(29.5, 114.0)
Median (days) (95% CI)[2]	69.5 (29.0, 141.0)	85.5 (29.0, 115.0)	82.0 (30.0, 113.0)
Range (days)	(29, 197)	(29, 197)	(29, 197)
Time to response (CR/PR[1]) f.n.p.			
Number of responders – n (%)	14 (17.7)	13 (21.7)	27 (19.4)
Number censored – n (%)	0	0	0
25th, 75th percentiles[2]	(57.0, 141.0)	(30.0, 115.0)	(30.0, 141.0)
Median (days) (95% CI)[2]	82.0 (29.0, 141.0)	86.0 (29.0, 115.0)	85.0 (57.0, 115.0)
Range (days)	(29, 253)	(29, 283)	(29, 283)
Time to response (CR/PR[1]) f.n.p., alternative PD			
Number of responders – n (%)	14 (17.7)	13 (21.7)	27 (19.4)
Number censored – n (%)	0	0	0
25th, 75th percentiles[2]	(57.0, 141.0)	(30.0, 115.0)	(30.0, 141.0)
Median (days) (95% CI)[2]	82.0 (29.0, 141.0)	86.0 (29.0, 115.0)	85.0 (57.0, 115.0)
Range (days)	(29, 253)	(29, 283)	(29, 283)

[1] Response is based on modified severity-weighted assessment tool and computed tomography.

[2] Using the Kaplan-Meier method.

CI: confidence interval; CR: complete response; f.i.p: flare considered as disease progression; f.n.p.: flare was not considered disease progression; PR: partial response.

Duration of response (Full Analysis Set - iCSR)

	Bexarotene exposed N=79	Bexarotene naive N=60	All N=139
Duration of response (CR/PR[1]) f.i.p.			
Number of responders – n (%)	12 (15.2)	12 (20.0)	24 (17.3)
Number censored – n (%)	2 (2.5)	8 (13.3)	11 (7.9)
25th, 75th percentiles[2]	(99.0, 294.0)	(167.0, -)	(113.5, 311.0)
Median (days) (95% CI)[2]	170.0 (86.0, 294.0)	- (84.0, -)	280.0 (115.0, 311.0)
Range (days)	(84, 819)	(56, 728)	(56, 819)
Duration of response (CR/PR[1]) f.n.p.			
Number of responders – n (%)	14 (17.7)	13 (21.7)	27 (19.4)
Number censored – n (%)	4 (5.1)	10 (16.7)	14 (10.1)
25th, 75th percentiles[2]	(115.0, 336.0)	(224.0, -)	(168.0, -)
Median (days) (95% CI)[2]	280.0 (112.0, 336.0)	- (224.0, -)	280.0 (170.0, -)
Range (days)	(84, 819)	(56, 728)	(56, 819)
Duration of response (CR/PR[1]) f.n.p., alternative PD			
Number of responders – n (%)	14 (17.7)	13 (21.7)	27 (19.4)
Number censored – n (%)	9 (11.4)	11 (18.3)	20 (14.4)
25th, 75th percentiles[2]	(280.0, -)	(224.0, -)	(280.0, -)
Median (days) (95% CI)[2]	336.0 (143.0, -)	- (224.0, -)	- (280.0, -)
Range (days)	(84, 819)	(56, 728)	(56, 819)

[1] Response is based on modified severity-weighted assessment tool and computed tomography.

[2] Using the Kaplan-Meier method.

CI: confidence interval; CR: complete response; f.i.p: flare considered as disease progression, f.n.p.: flare was not considered disease progression; PD : progressive disease; PR: partial response.

Progression-free survival (Full Analysis Set - iCSR)

	Bexarotene exposed N=79	Bexarotene naive N=60	All N=139
Progression-free survival[1] f.i.p.			
25th, 75th percentiles[2]	(78.0, 232.0)	(71.0, 199.0)	(78.0, 232.0)
Median (95% CI)[2]	127.0 (87.0, 197.0)	113.0 (85.0, 142.0)	114.0 (87.0, 143.0)
Number censored – n (%)	29 (36.7)	19 (31.7)	48 (34.5)
Range	(0, 876)	(0, 813)	(0, 876)
Progression-free survival[1] f.n.p.			
25th, 75th percentiles[2]	(85.0, 283.0)	(80.0, 365.0)	(85.0, 283.0)
Median (95% CI)[2]	141.0 (113.0, 225.0)	114.0 (87.0, 186.0)	127.0 (113.0, 197.0)
Number censored – n (%)	32 (40.5)	23 (38.6)	55 (39.6)
Range	(0, 876)	(0, 813)	(0, 876)
Progression-free survival[1] f.n.p., alternative PD			
25th, 75th percentiles[2]	(99.0, -)	(85.0, -)	(87.0, -)
Median (95% CI)[2]	225.0 (141.0, 393.0)	199.0 (114.0, 365.0)	206.0 (169.0, 302.0)
Number censored – n (%)	47 (59.5)	33 (55.0)	80 (57.6)
Range	(0, 876)	(0, 813)	(0, 876)

[1] Progression defined as PD in modified severity-weighted assessment tool or computed tomography progression.

[2] Using the Kaplan-Meier method.

CI: confidence interval; f.i.p: flare considered as disease progression; f.n.p.: flare was not considered disease progression; PD: progressive disease.

Skindex-29 measurements by oral bexarotene exposure up to Cycle 12 (Full Analysis Set)

Timepoint	Emotions						Functioning						Symptoms					
	Bexarotene Exposed (N=79)			Bexarotene Naive (N=60)			Bexarotene Exposed (N=79)			Bexarotene Naive (N=60)			Bexarotene Exposed (N=79)			Bexarotene Naive (N=60)		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Baseline	79	52.2	22.66	57	50.6	22.26	79	46.7	24.44	57	44.7	25.33	78	60.1	19.03	57	55.3	20.35
Cycle 2[#]	71	48.6	23.79	53	46.6	24.18	71	43.5	26.27	53	43.3	24.53	70	51.4	23.10	53	47.7	20.28
Cycle 3[*,#]	57	45.9	21.53	40	44.1	24.37	57	42.6	25.58	40	39.2	26.38	56	51.1	21.92	40	42.9	21.72
Cycle 4[#]	40	40.8	23.87	29	34.7	21.59	40	38.8	25.91	29	30.7	22.91	40	47.3	22.16	29	35.2	16.66
Cycle 5[#]	30	35.8	22.19	26	34.4	20.53	30	32.8	23.35	26	31.4	21.38	31	43.2	23.96	26	35.6	18.81
Cycle 6[#]	25	34.5	22.72	24	35.4	20.74	25	33.0	27.79	24	29.5	21.25	26	43.5	24.72	24	36.2	19.02
Cycle 7[#]	22	39.3	24.98	20	36.8	22.61	22	33.1	26.04	20	28.3	22.98	23	45.5	23.67	20	37.7	18.66
Cycle 8[#]	17	39.4	20.03	17	35.8	22.39	17	34.4	22.73	17	30.5	25.16	18	42.7	21.45	17	36.5	19.29
Cycle 9[#]	20	44.6	23.09	17	32.8	18.36	19	37.2	25.28	17	28.7	19.54	20	47.1	23.42	17	35.9	15.79
Cycle 10[†,#]	18	43.6	20.48	13	43.5	24.10	17	35.2	25.21	13	41.5	27.22	18	46.8	23.11	13	47.0	21.17
Cycle 11[#]	14	48.3	20.92	10	43.5	22.86	14	40.0	24.47	10	38.1	25.46	14	46.7	22.04	10	48.3	19.44
Cycle 12[#]	11	42.0	16.80	8	43.1	21.29	10	26.3	12.79	8	36.2	20.95	11	37.7	15.52	8	45.1	21.93

Data (N >8) was truncated at Cycle 12 out of 57.

[*] Median time to treatment response=82 days (approximately Cycle 3), as per the efficacy analysis for the interim CSR.

[†] Median duration of treatment response=280 days (approximately Cycle 10), as per the efficacy analysis for the interim CSR.

[#] Post-baseline.

Summary statistics of panobinostat pharmacokinetics parameters on Days 1 and 8 (iCSR)

	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng*hr/ml)	AUC_{0-48} (ng*hr/ml)	AUC_{0-inf} (ng*hr/ml)	C_{last} (ng/mL)	T_{last} (hr)
Day 1							
n	109	109	109	107	93	109	109
Mean (SD)	11.379 (6.6608)		110.138 (58.0235)	132.019 (69.3453)	134.828 (64.9389	0.632 (0.9737)	
CV% mean	58.5		52.7	52.5	48.2	154	
Median	10.7	1.5	102	119	121	0.4	47.9
Min-Max	0.50 ; 36.70	0.00-4.00	8.00-286.00	11.00-376.00	44.00-334.00	0.10-9.70	23.40-49.50
Day 8							
n	60	60	60	52	52	60	60
Mean (SD)	13.490 (6.4529)		134.033 (61.5203)	159.750 (64.2278)	162.673 (65.0664)	1.524 (0.9076)	
CV% mean	47.8		45.9	40.2	40	59.5	
Median	12.7	1.5	129	150	152	1.323	
Min-Max	1.10-30.60	0.25-3.50	17.00-339.00	51.00-374.00	52.00-377.00	0.30-5.10	16.80-47.00

Summary statistics of BJB432 (reductive metabolite of panobinostat) pharmacokinetics parameters on Days 1 and 8 (iCSR)

	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng*hr/ml)	AUC_{0-48} (ng*hr/ml)	C_{last} (ng/mL)	T_{last} (hr)
Day 1						
n	105	105	103	65	105	105
Mean (SD)	1.304 (0.7219)		22.951 (13.6715)	45.692 (30.5404)	0.754 (0.6051)	
CV% mean	55.4		59.6	66.8	80.2	
Median	1.1	24	19	37	0.6	48
Min-Max	0.30-4.60	0.00-47.97	4.00-99.00	8.00-203.00	0.10-4.20	23.40-49.50
Day 8						
n	61	61	51	0	61	61
Mean (SD)	2.650 (1.7456)		50.804 (33.5613)		2.277 (1.7654)	
CV% mean	65.9		66.1		77.5	
Median	2.3	21.5	45		1.9	24.9
Min-Max	0.50-8.50	1.25-27.58	11.00-177.00		0.40-8.50	16.80-47.00

Safety Results

Adverse events, regardless of study drug relationship, by preferred term (occurring in at least 10% of the overall population) and oral bexarotene exposure (Safety Set)

Patients with AE(s), n(%)	Bexarotene Exposed N=79		Bexarotene Naive N=60		All N=139	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Any AE	78 (98.7)	48 (60.8)	60 (100.0)	40 (66.7)	138 (99.3)	88 (63.3)
Diarrhoea	46 (58.2)	5 (6.3)	38 (63.3)	2 (3.3)	84 (60.4)	7 (5.0)
Thrombocytopenia	44 (55.7)	15 (19.0)	25 (41.7)	10 (16.7)	69 (49.6)	25 (18.0)
Fatigue	26 (32.9)	3 (3.8)	29 (48.3)	4 (6.7)	55 (39.6)	7 (5.0)
Nausea	32 (40.5)	0	22 (36.7)	1 (1.7)	54 (38.8)	1 (0.7)
Pruritus	32 (40.5)	6 (7.6)	16 (26.7)	3 (5.0)	48 (34.5)	9 (6.5)
Decreased appetite	20 (25.3)	1 (1.3)	17 (28.3)	1 (1.7)	37 (26.6)	2 (1.4)
Asthenia	22 (27.8)	3 (3.8)	12 (20.0)	0	34 (24.5)	3 (2.2)
Anaemia	22 (27.8)	2 (2.5)	9 (15.0)	1 (1.7)	31 (22.3)	3 (2.2)
Headache	16 (20.3)	0	12 (20.0)	1 (1.7)	28 (20.1)	1 (0.7)
Dysgeusia	13 (16.5)	0	12 (20.0)	1 (1.7)	25 (18.0)	1 (0.7)
Neutropenia	14 (17.7)	10 (12.7)	10 (16.7)	6 (10.0)	24 (17.3)	16 (11.5)
Blood creatinine increased	15 (19.0)	0	8 (13.3)	0	23 (16.5)	0
Oedema peripheral	10 (12.7)	1 (1.3)	12 (20.0)	1 (1.7)	22 (15.8)	2 (1.4)
Pyrexia	12 (15.2)	2 (2.5)	10 (16.7)	1 (1.7)	22 (15.8)	3 (2.2)
Hypophosphataemia	15 (19.0)	4 (5.1)	6 (10.0)	1 (1.7)	21 (15.1)	5 (3.6)
Hyperglycaemia	11 (13.9)	1 (1.3)	9 (15.0)	3 (5.0)	20 (14.4)	4 (2.9)
Hypertriglyceridaemia	10 (12.7)	0	10 (16.7)	1 (1.7)	20 (14.4)	1 (0.7)
Constipation	8 (10.1)	0	11 (18.3)	0	19 (13.7)	0
Hypoalbuminaemia	12 (15.2)	0	6 (10.0)	0	18 (12.9)	0
Vomiting	11 (13.9)	1 (1.3)	7 (11.7)	0	18 (12.9)	1 (0.7)
Abdominal pain	12 (15.2)	2 (2.5)	5 (8.3)	1 (1.7)	17 (12.2)	3 (2.2)
Dizziness	11 (13.9)	1 (1.3)	6 (10.0)	2 (3.3)	17 (12.2)	3 (2.2)
Dyspnoea	14 (17.7)	1 (1.3)	3 (5.0)	0	17 (12.2)	1 (0.7)
Weight decreased	10 (12.7)	0	6 (10.0)	1 (1.7)	16 (11.5)	1 (0.7)
Arthralgia	11 (13.9)	0	4 (6.7)	0	15 (10.8)	0
Cough	9 (11.4)	0	6 (10.0)	0	15 (10.8)	0
Hypertension	11 (13.9)	0	4 (6.7)	0	15 (10.8)	0
Hypocalcaemia	11 (13.9)	1 (1.3)	4 (6.7)	1 (1.7)	15 (10.8)	2 (1.4)
Hypothyroidism	9 (11.4)	0	5 (8.3)	0	14 (10.1)	0
Insomnia	9 (11.4)	0	5 (8.3)	0	14 (10.1)	0
Nasopharyngitis	8 (10.1)	0	6 (10.0)	0	14 (10.1)	0

Preferred terms are sorted by frequency in descending order, as report in “All” column.

Deaths, other serious or clinically significant adverse events or related discontinuations by oral bexarotene exposure (Safety Set)

Serious or significant AEs, n (%)	Bexarotene Exposed N=79	Bexarotene Naive N=60	All N=139
All Deaths	3 (3.8)	4 (6.7)	7 (5.0%)
On treatment deaths[1]	3 (3.8)	3 (5.0)	6 (4.3)
All SAEs	33 (41.8)	23 (38.3)	56 (40.3)
Study-drug related SAEs	14 (17.7)	9 (15.0)	23 (16.5)
AEs leading to discontinuation	26 (32.9)	18 (30.0)	44 (31.7)
Clinically notable AEs	70 (88.6)	52 (86.7)	122 (87.8)

[1] Includes deaths occurring up to 28 days after the last dose of study drug.
AE: adverse event; SAE: serious adverse event.

Serious adverse events with at least 2% incidence, regardless of study drug, by preferred terms and oral bexarotene exposure (Safety Population)

Preferred term, n (%)	Bexarotene Exposed N=79	Bexarotene Naive N=60	All N=139
At least one AE	33 (41.8)	23 (38.3)	56 (40.3)
Pyrexia	3 (3.8)	3 (5.0)	6 (4.3)
Thrombocytopenia	4 (5.1)	2 (3.3)	6 (4.3)
Abdominal pain	3 (3.8)	0 (0.0)	3 (2.2)
Angina pectoris	2 (2.5)	1 (1.7)	3 (2.2)
Asthenia	1 (1.3)	2 (3.3)	3 (2.2)
Chest pain	3 (3.8)	0 (0.0)	3 (2.2)
General physical health deterioration	3 (3.8)	0 (0.0)	3 (2.2)
Pneumonia	0 (0.0)	3 (5.0)	3 (2.2)
Squamous cell carcinoma	3 (3.8)	0 (0.0)	3 (2.2)

Preferred terms are sorted by frequency in descending order, as report in All column.

Other Relevant Findings

No other relevant findings were reported.

Date of Clinical Trial Report

16 December 2013

Date Inclusion on Novartis Clinical Trial Results Database

24 February 2014

Date of Latest Update