Evaluation of Panobinostat (LBH589) as Maintenance Therapy in Multiple Myeloma Following Autologous Hematopoietic Cell Transplantation

NCT02722941

Version 3

April 13, 2017

Panobinostat

Clinical Trial Protocol Number CLBH589DUS97T

"Evaluation of panobinostat (LBH589) as maintenance therapy in multiple myeloma following autologous hematopoietic cell transplantation"

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List of abbreviations

ADME	**absorption, distribution, metabolism and excretion**
AE	**adverse event**
ALT	**alanine aminotransferase/glutamic pyruvic transaminase/GPT**
AML	**acute myeloid leukemia**
ANC	**absolute neutrophil count**
APL	**acute promyelocytic leukemia**
AST	**aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT**
ATRA	**all trans-retinoic acid**
AUC	**area under the curve**
BCR-ABL	**a fusion gene of the BCR and ABL genes**
BMT CTN	**Blood and Marrow Transplant Clinical Trials Network**
bpm	**beat per minute**
BUN	**blood urea nitrogen**
CALGB	**Cancer and Leukemia Group B**
CBR	**clinical benefit rate**
CD	**cluster of differentiation**
CHF	**congestive heart failure**
CI	**confidence interval**
Cmax	**maximum concentration of drug**
CML	**chronic myelogenous leukemia**
CNS	**central nervous system**
CP	**clinical pharmacology**
CR	**complete response/remission**
CS&E	**clinical safety and epidemiology**
CTCAE	**NCI common terminology criteria for adverse events (version 4.03**
CTCL	**cutaneous T-cell lymphoma**
CV	**coefficient of variation**
CYP	**cytochrome P450**
DAC	**deacetylase**
DACi	**deacetylase inhibitor**
DLT	**dose-limiting toxicity**
DNA	**deoxyribose nucleic acid**
DSMP	**Data Safety and Monitoring Plan**
ECG	**12 lead electrocardiogram**
ECHO	**echocardiogram**
ECOG	**Eastern Cooperative Oncology Group**
EFS	**event-free survival**
eRT	**eResearchTechnology**
ETO	**eight-twenty-one**
FACT	**functional assessment of cancer therapy**
FDA	**Food and Drug Administration**
FLC	**free light chain**
G-CSF	**granulocyte colony-stimulating factor (e.g. filgrastim)**
GI	**gastrointestinal**

GM-CSF	**granulocyte-macrophage colony-stimulating factor (e.g. sargramostim)**
GMMG	**German Multicenter Myeloma Group**
H3, H4	**histones H3, H4**
HR	**hazard ratio**
HAT	**histone acetyltransferase**
HCT	**hematopoietic cell transplantation**
HDAC	**histone deacetylase**
HDACi	**histone deacetylase inhibitor**
hERG	**human ether-a-go-go related gene**
HIF	**Hypoxia inducible factor**
HIV	**human immunodeficiency virus**
HOVON	**Dutch-Belgian Hemato-Oncology Cooperative Group**
HR	**hazard ratio**
HR	**heart rate**
HSP	**heat shock protein**
i.v.	**intravenous(ly)**
ICH	**international conference on harmonization**
IEC	**independent ethics committee**
IFM	**Intergroupe Francophone du Myélome**
IHC	**immunohistochemistry**
IMWG	**International Myeloma Working Group**
IRB	**institutional review board**
KDR	**kinase insert domain receptor**
LCR	**light chain restricted**
LLN	**lower limit of normal**
LMWH	**low molecular weight heparin**
LVEF	**left ventricular ejection fraction**
MHC	**major histocompatibility complex**
mg/m2	**milligrams per square meter**
MTD	**maximum tolerated dose**
MR	**minimal response**
MRD	**minimal residual disease**
MRC	**Medical Research Council**
MUGA	**multiple uptake gated acquisition scan**
MWF	**Monday, Wednesday, Friday**
N/A	**not applicable**
NCI	**National Cancer Institute**
NCIC-CTG	**National Cancer Institute of Canada Clinical Trials Group**
nCR	**near complete response**
NHL	**non-Hodgkin's lymphoma**
NIH	**National Institutes of Health**
ORR	**overall response rate**
OS	**overall survival**

PANORAMA	**Pan-deacetylase Inhibitor Panobinostat in Combination with Bortezoimb and Dexamethasone in Relapsed and Bortezomib-refractory Multiple Myeloma**
PBMC	**peripheral blood mononuclear cell**
PCR	**polymerase chain reaction**
PD	**Pharmacodynamics**
PD	**progressive disease**
PETHEMA/GEM	**Programa para el Estudio y la Terapéutica de las Hemopatías Malignas/Grupo Español de Mieloma**
PFS	**progression-free survival**
P-gp	**p-glycoprotein**
PI	**princial investigator**
PK	**pharmacokinetic**
PLT	**platelet**
PLZF	**promyelocytic leukemia zinc finger**
PML	**promyelocytic leukemia**
PO	**by mouth**
PR	**partial response**
PRMC	**Protocol Review and Monitoring Commitee**
QOW	**every other week**
QW	**every week**
RAR	**retinoic acid receptor**
RCD	**Research Compliance Dvision**
REB	**research ethics board**
RNA	**ribonucleic acid**
SAE	**serious adverse event**
SAHA	**suberoylanilide hydroxamic acid**
sCR	**stringent complete response**
SD	**stable disease**
SD	**standard deviation**
SOP	**standard operating procedure**
SRC	**Scientific Review Committee**
T4	**Thyroxine**
TAA	**Tumor associated antigens**
Th	**helper T cell**
TIW	**three times per week**
TSH	**thyroid stimulating hormone**
TTP	**time to progression**
ULN	**upper limit of normal**
VEGF	**vascular endothelial growth factor**
VGPR	**very good partial response**
WBC	**white blood cell**
WNL	**within normal limits**
WOCBP	**women of childbearing potential**

1 Introduction

1.1 Overview of Maintenance Therapy in Multiple Myeloma

1.1.1 Myeloma maintenance therapy after transplant

Multiple myeloma is an incurable plasma cell malignancy despite recent advances in therapy with novel agents including lenalidomide and bortezomib.[1,2] High-dose melphalan followed by autologous hematopoietic cell transplantation (HCT) offers progression-free survival (PFS) and overall survival (OS) benefits when compared to conventional chemotherapy.[3-5] Recent phase 3 trials of lenalidomide maintenance post-autologous HCT demonstrated significant increase in PFS.[6,7] In the Cancer and Leukemia Group B (CALGB) 100104 study (Table 1-1), 462 multiple myeloma patients were randomized to lenalidomide 10 mg daily or placebo after single autologous HCT.[6] The median time to progression (TTP) was 46 months for the lenalidomide arm and 27 months for the placebo arm ($P < .001$). At a median follow-up of 34 months, the 3-year OS rates were 88% for the lenalidomide arm and 80% for the placebo arm ($P = .028$).[6] A total of 23 out of 231 patients (10%) on lenalidomide arm discontinued maintenance due to adverse events. Hematologic adverse events were more common in lenalidoimde group as well as grade 3 non-hematologic adverse events compared to the placebo group. In the Intergroupe Francophone du Myélome (IFM) 05-02 study (Table 1-1), 605 myeloma patients were randomized to lenalidomide 10 mg daily versus placebo until disease progression after single or tandem autologous HCT.[7] The median PFS was 41 months for the lenalidomide arm and 23 months for the placebo arm ($P < .001$). The OS was 74% for the lenalidomide arm and 76% for the placebo arm ($P = .7$) at a median follow-up of 45 months.[7] A total of 83 patients (27%) discontinued lenalidomide due to adverse events. Any Seventy-four percent of patients in the lenalidomide group experienced any grade 3-4 adverse events and hematologic was the most common adverse events. Approximately one third of patients experienced grade 3-4 non-hematologic adverse events.

Table 1-1. Lenalidomide maintenance therapy after autologous HCT

Study	N	Outcomes	
		Maintenance	**No Maintenance**
CALGB 100104 (McCarthy et al.)[6]	460	• Median TTP 46 months • 3-yr PFS 66% • Median EFS 43 months • 3-yr OS 88%	• Median TTP 27 months ($P < .001$) • 3-yr PFS 39% ($P < .001$) • Median EFS 27 months ($P < .001$) • 3-yr OS 80%
IFM 05-02 (Attal et al.)[7]	614	• Median PFS 41 months • 4-yr PFS 43% • Median EFS 40 months • 4-yr OS 73%	• Median PFS 23 months ($P < .001$) • 4-yr PFS 22% ($P < .001$) • Median EFS 23 months ($P < .001$) • 4-yr OS 75%

Abbreviations: EFS, event-free survival

There have been extensive studies evaluating other maintenance options including thalidomide and bortezomib (Tables 1-2 and 1-3).[8-18] Maintenance therapy can be associated with significant side effects such as constipation, fatigue, drug rash, cytopenias, peripheral neuropathy and thromboembolic events. Due to the complexity of potential side effects, these

choices may pose significant challenges to clinicians. As for lenalidomide, an increased incidence of second primary malignancies has been associated with its use.[6,7,19] Despite PFS and OS benefits shown in some studies, no single therapeutic agent has been established as the widely agreed-upon standard for maintenance therapy after autologous HCT in multiple myeloma. As was described by the International Myeloma Working Group (IMWG) consensus statement on maintenance therapy, maintenance treatment decisions for individual patients must balance potential benefits and risks carefully.[20]

Table 1-2. Thalidomide maintenance therapy after autologous HCT

Study	N	Outcomes	
		Maintenance	No Maintenance
IFM 99 (Attal et al.)[9]	597	• 3-yr EFS 52% • 4-yr OS 87%	• 3-yr EFS 37% ($P < .009$) • 4-yr OS 75% ($P < .04$)
Total Therapy 2 (Barlogie et al.)[10]	668	• 5-yr EFS 64% • 8-yr OS 57%	• 5-yr EFS 43% ($P < .001$) • 8-yr OS 44% ($P = .09$)
HOVON-50 (Lokhorst, et al.)[11]	556	• Median EFS 43 months • Median OS 73 months	• Median EFS 22 months ($P < .001$) • Median OS 60 months ($P = .77$)
Spencer et al.[13a]	243	• 3-yr PFS 42% • 3-yr OS 86%	• 3-yr PFS 23% ($P <.001$) • 3-yr OS 75% ($P = .004$)
MRC IX (Morgan et al.)[12b]	820	• Median PFS 30 months • 3-yr OS 75%	• Median PFS 23 months ($P = .003$) • 3-yr OS 80% ($P = .26$)
BMT CTN 0102 (Krishnan et al.)[14c]	436	• 3-yr PFS 49% • 3-yr OS 80%	• 3-yr PFS43% ($P = .08$) • 3-yr OS 81% ($P = .817$)
NCIC-CTG MY.10 (Stewart et al.)[16d]	332	• 4-yr PFS 32% • 4-yr OS 68%	• 4-yr PFS 14% ($P < .0001$) • 4-yr OS 60% ($P = .18$)

Abbreviations: BMT CTN, the Blood and Marrow Transplant Clinical Trials Network; HOVON, the Dutch-Belgian Hemato-Oncology Cooperative Group; MRC, the Medical Research Council; NCIC-CTG MY.10, the National Cancer Institute of Canada Clinical Trials Group, the Myeloma. 10

[a]In the Australian trial by Spencer et al., the study design was thalidomide plus prednisone vs. prednisone.

[b]The MRC IX study included 1970 patients who were treated with intensive therapy including autologous HCT vs. nonintensive therapy. The cohort for intensive therapy was randomized to thalidomide vs. observation.

[c]The BMT CTN 0102 study included 710 patients who were treated with autologous-allogeneic transplant vs. tandem autologous transplants. The cohort for tandem autologous transplants was randomized to thalidomide plus dexamethasone vs. observation.

[d]The NCIC-CTG MY.10 study randomized patients to thalidomide plus prednisone vs. prednisone.

Table 1-3. Bortezomib maintenance therapy after autologous HCT

Study	N	Outcomes	
		Maintenance	No Maintenance
HOVON-65/GMMG-HD4 (Sonneveld et al.)[17]	827	• Median PFS 35 months • 5-yr OS 61%	• Median PFS 28 months ($P = .002$) • 5-yr OS 55% ($P = .07$)
PETHEMA/GEM (Rosiñol)[18]	386	• 2-yr PFS 78% (bortezomib plus thalidomide)	• 2-yr PFS 63% (thalidomide) vs. 49% (IFN-α: $P = .01$)

Abbreviations: GMMG, the German Multicenter Myeloma Group; IFN, interferon; PETHEMA/GEM, Programa para el Estudio y la Terapéutica de las Hemopatías Malignas/Grupo Español de Mieloma

Although maintenance therapy is an attractive strategy to achieve longer disease control, relapse or progression of myeloma after autologous HCT remains inevitable. Myeloma progression after autologous HCT is likely secondary to the existence of minimal residual disease as high-dose melphalan fails to eliminate myeloma reservoirs including putative myeloma stem cells or B cell progenitors, and to reset the bone marrow stromal and immunologic niche which supports myeloma cell survival. There is an unmet need to improve treatment outcomes for myeloma patients and research strategy on maintenance therapy continues to evolve.

2 Overview of Panobinostat

2.1.1 Anticancer activity of DAC inhibitors

Alterations in chromosome structure play critical roles in the control of gene transcription. These epigenetic alterations include modification of histones and others proteins by acetylation and/or phosphorylation. Normally, these modifications are balanced finely and are highly reversible in normal tissues, but they may be imbalanced and heritable in tumor cells. Deacetylase (DAC) inhibitors increase histone acetylation, thereby modulating the expression of a subset of genes in a coordinated fashion. Several tumors suppressor genes associated with the malignant phenotype are repressed by epigenetic mechanisms in sporadic cancers. Thus therapy with DAC inhibitors may alter tumor phenotype and inhibit growth in such tumors.

Multiple hallmarks of cancer are regulated by acetylation/deacetylation:

- DAC inhibition targets both histone and nonhistone proteins. Targeting the acetylation status of nonhistone, tumor-associated proteins that mediate proliferation may be the underlying antitumor mechanism of DAC inhibitors.[21]
- Nonhistone proteins regulated by acetylation include α-tubulin, p53, HIF-1α, and HSP90. These proteins are substrates of DACs.[22]
- The ability of a single agent to target multiple molecular features of tumor cells may result in good efficacy against a range of different tumor types.
- HSP90 is involved in protein stability and degradation; the inhibition of HSP90 affects protein turnover in diseases such as multiple myeloma and B-cell malignancies.[23]
- Acetylated HIF-1α is degraded and can no longer act as a tumor growth factor. Class II DAC inhibitors target histone deacetylase (HDAC or DAC) 6, resulting in increased acetylation of HIF-1α and decreased vascular endothelial growth factor (VEGF), thereby inhibiting angiogenesis.[24]
- Both acetylation and ubiquitylation often occur on the same lysine residue, but these processes cannot occur simultaneously. Acetylation allows for increased stability, and ubiquitylation leads to protein degradation. Therefore, DACs decrease the half-life of a protein by exposing the lysine residue for ubiquitylation.[25]

2.1.2 Panobinostat (LBH589)

Panobinostat (LBH589) is a deacetylase inhibitor (DACi) belonging to a structurally novel cinnamic hydroxamic acid class of compounds. It is a potent class I/II pan-DAC inhibitor (pan-DACi) that has shown anti-tumor activity in pre-clinical models and cancer patients. Deacetylases (DAC) target lysine groups on chromatin and transcription factors and various non-histone proteins such as p53, tubulin, HSP90 and Rb. Panobinostat is formulated as an oral capsule and a solution for intravenous (i.v.) injection. Both the oral and i.v. formulations are currently being investigated in ongoing Phase I and Phase II studies in advanced solid tumors and hematological malignancies.

Inhibition of DAC provides a novel approach for cancer treatment. Histones are part of the core proteins of nucleosomes, and acetylation and deacetylation of these proteins play a role in the regulation of gene expression. Highly charged deacetylated histones bind tightly to the phosphate backbone of DNA, inhibiting transcription, presumably, by limiting access of transcription factors and RNA polymerases to DNA. Acetylation neutralizes the charge of histones and generates a more open DNA conformation. This conformation allows transcription factors and associated transcription apparatus access to the DNA, promoting expression of the corresponding genes. The opposing activities of two groups of enzymes, histone acetyltransferase (HAT) and DAC control the amount of acetylation. In normal cells a balance exists between HAT and DAC activity that leads to cell specific patterns of gene expression. Perturbation of the balance produces changes in gene expression.

Several lines of evidence suggest that aberrant recruitment of DAC and the resulting modification of chromatin structure may play a role in changing the gene expression seen in transformed cells. For example, silencing of tumor suppressor genes at the level of chromatin is common in human tumors,[26-33] and DAC complexes have been shown to be crucial to the activity of the AML-specific fusion proteins PLZF-RAR-α, PML-RAR-α, and AML1/ETO.[34-37] DAC inhibitors (DACi) have been shown to induce differentiation, cell cycle arrest or apoptosis in cultured tumor cells, and to inhibit the growth of tumors in animal models.[38-44] In addition, DACi have been shown to induce expression of p21, a key mediator of cell cycle arrest in G1 phase and cellular differentiation.[45-48]

Tumor growth inhibition and apoptosis in response to DACi treatment may also be mediated through changes in acetylation of non-histone proteins (e.g., HSP90, p53, HIF-1α, α-tubulin). For example, the chaperone protein HSP90 has been shown to be acetylated in cells treated with DACi.[49-51] Acetylation of HSP90 inhibits its ability to bind newly synthesized client proteins, thus preventing proper client protein folding and function. In the absence of HSP90 function, misfolded proteins are targeted for degradation in the proteasome. Many proteins that require HSP90 association are critical to cancer cell growth, including ErbB1, ErbB2, AKT, Raf, KDR, and BCR-ABL. Acetylation of HSP90 in cells treated with DACi inhibits the chaperone function of HSP90, leading to degradation of the client proteins and eventual cell death.

The potential clinical utility of the use of DACi in cancer therapy was first suggested by the activity of the DACi, sodium phenylbutyrate, against acute promyelocytic leukemia (APL). An adolescent female patient with relapsed APL, who no longer responded to all trans-

retinoic acid (ATRA) alone, achieved a complete clinical remission after treatment with a combination of ATRA and the DACi sodium phenylbutyrate.[52]

2.1.3 Overview of clinical experience

Currently, the clinical development of panobinostat focuses on the oral formulation. As of 31st December 2013, 36 clinical studies, including clinical pharmacology (CP), phase I and phase II trials, as well as 2 randomized phase III studies, have either been completed or are ongoing. A total of 2428 patients were enrolled (235 for i.v. and 2193 for oral), received at least one dose of panobinostat either as a single agent or in combination with other agents, and for whom safety data are available. These patients constitute the safety population.

The most common AEs, regardless of their study drug relationship, concern the gastrointestinal tract (nausea, diarrhea and vomiting mostly of grade 1/2). For the hematopoietic system, the most frequent findings continue to be thrombocytopenia, anemia and neutropenia, mostly of grade 3/4, while febrile neutropenia, as expected, has been noted much more frequently in patients being treated for hematologic malignancies involving the bone marrow. Additional common toxicities include fatigue Grade 3/4 reported with a frequency of 9.2% in an every week (QW) dosing schedule vs. 15.7% in an every other week (QOW) dosing schedule.

The most common ECG findings adjudicated by central review included post-baseline increase in frequency of sinus tachycardia, T-waves changes (flat, biphasic, inverted), as well as depressed ST segment findings.

The most frequently encountered laboratory abnormalities in both QW and QOW schedules and regardless of disease, refer to hematological parameters, including decreased WBC, platelet and neutrophil count and hemoglobin. Worsening of these hematologic parameters was more evident for the QW schedule and appears to be dose-dependent. Liver function tests alterations were mostly of grade 1/2 with either schedule, with grade 3 reported at the highest dose of 60 mg TIW QW. Decreasing electrolytes and elevated glucose was mostly grade 1/2 worsening from baseline, but again increased severity (up to grade 3) was seen at the highest dose of 60 mg with the QW schedule.

Thyroid function, as monitored by the measurement of TSH and free T4, did not reveal overt hyper- or hypo- thyroidism, with fluctuations in TSH values being within normal limits.

As the number of patients is quite different across doses, the following rules have been applied to report these events in the tables below: in doses where the number (n) of patients is ≥25 patients, AEs reported in ≥10% of patients are listed; in doses where n is <25 patients, AEs reported in ≥50% of patients are listed. If an AE frequency matches the criteria in one dose category, the frequency of that event is shown for all doses.

Table 2-1 All grade adverse events regardless of causality in patients receiving oral panobinostat three-times-a-week every-other-week (TIW QOW)

Primary System Organ Class Preferred term	**30 mg[a]** **N = 28** **n (%)**	**45 mg[a]** **N = 18** **n (%)**	**60 mg[a]** **N = 24** **n (%)**
Any primary system organ class	**28 (100.0)**	**18 (100.0)**	**24 (100.0)**
Blood and lymphatic system disorders	**16 (57.1)**	**14 (77.8)**	**21 (87.5)**
Anemia	5 (17.9)	6 (33.3)	11 (45.8)
Neutropenia	3 (10.7)	5 (27.8)	10 (41.7)
Thrombocytopenia	10 (35.7)	10 (55.6)	14 (58.3)
Gastrointestinal Disorders	**25 (89.3)**	**17 (94.4)**	**24 (100.0)**
Constipation	6 (21.4)	3 (16.7)	10 (41.7)
Diarrhea	15 (53.6)	11 (61.1)	16 (66.7)
Nausea	17 (60.7)	9 (50.0)	19 (79.2)
Vomiting	12 (42.9)	6 (33.3)	12 (50.0)
General Disorders and Site Conditions	**27 (96.4)**	**17 (94.4)**	**23 (95.8)**
Asthenia	5 (17.9)	5 (27.8)	4 (16.7)
Fatigue	18 (64.3)	12 (66.7)	15 (62.5)
Edema peripheral	6 (21.4)	5 (27.8)	4 (16.7)
Pyrexia	11 (39.3)	9 (50.0)	10 (41.7)
Investigations	**14 (50.0)**	**8 (44.4)**	**11 (45.8)**
Weight decreased	10 (35.7)	5 (27.8)	3 (12.5)
Metabolism and nutrition disorders	**22 (78.6)**	**9 (50.0)**	**18 (75.0)**
Anorexia	17 (60.7)	6 (33.3)	10 (41.7)
Hypokalemia	4 (14.3)	3 (16.7)	6 (25.0)
Musculoskeletal and connective tissue disorders	**16 (57.1)**	**7 (38.9)**	**13 (54.2)**
Arthralgia	3 (10.7)	0 (0.0)	6 (25.0)
Back Pain	3 (10.7)	4 (22.2)	3 (12.5)
Pain in extremity	3 (10.7)	2 (11.1)	3 (12.5)
Nervous system disorders	**17 (60.7)**	**6 (33.3)**	**14 (58.3)**
Headache	7 (25.0)	3 (16.7)	6 (25.0)

Primary System Organ Class Preferred term	30 mg[a] N = 28 n (%)	45 mg[a] N = 18 n (%)	60 mg[a] N = 24 n (%)
Respiratory, thoracic and mediastinal disorders	**15 (53.6)**	**8 (44.4)**	**17 (70.8)**
Cough	5 (17.9)	4 (22.2)	7 (29.2)
Dyspnea	9 (32.1)	6 (33.3)	6 (25.0)
Skin and subcutaneous tissue disorders	**12 (42.9)**	**5 (27.8)**	**9 (37.5)**
Pruritus	5 (17.9)	1 (5.6)	3 (12.5)
Rash	3 (10.7)	1 (5.6)	4 (16.7)

a. Includes patients from [B1101], [B2101], [B2102] (Group X and Y), [B2201], [B2202], [B2203], [B2211], [B2212], [E2214]; events occurring in ≥10% of patients
A patient with multiple occurrences of an AE in one SOC is counted only once in the AE category

As shown on the above Table 2-1, AEs have been reported for 70 patients (100% of the safety population) for the QOW schedule. The most commonly reported AEs across doses were fatigue and nausea in 45 patients each (64.3% each), diarrhea in 42 patients (60%), thrombocytopenia in 34 patients (48.6%) and anorexia in 33 patients (47.1%).

Of note, the safety profile appears to be qualitatively similar between the two schedules. At present, a quantitative comparison is limited by the significantly different number of patients available in both safety populations.

2.1.4 Human pharmacokinetics

After oral administration, panobinostat is rapidly absorbed with no observed lag phase. Maximum plasma concentrations were generally reached within 1 hour after oral dosing. The absolute bioavailability was 30% (data on file) and the mean (SD) half-life of panobinostat was comparable following i.v. and oral dosing ~15.0 (5) hours. Moderate drug accumulation was observed with oral three-times-a-week schedule but not with the weekly i.v. schedule (1.4-fold drug accumulation with oral three-times-a-week dosing), consistent with the terminal half-life of 15 hours and dosing interval.

Figure 2-1 Mean panobinostat plasma concentration versus time profiles following single oral or intravenous administration

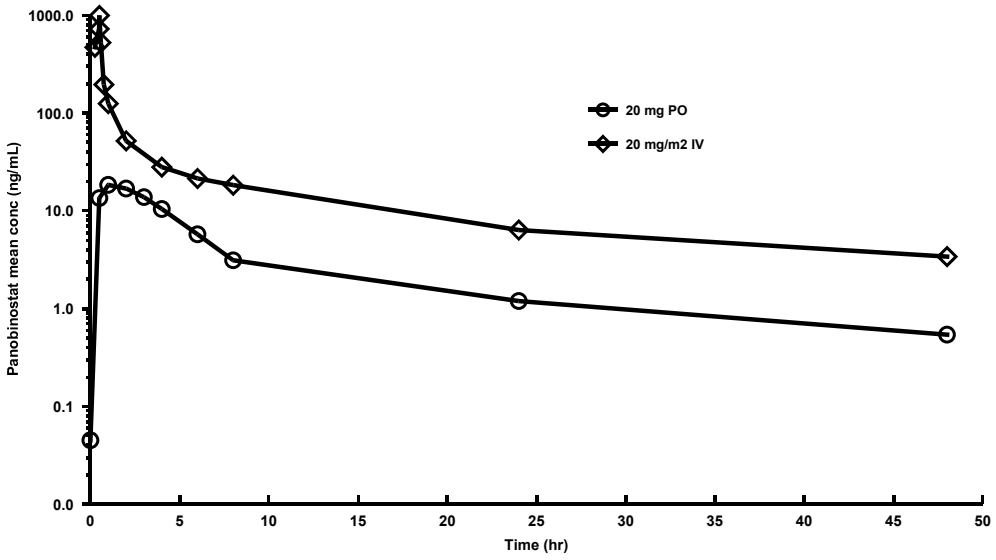


Table 2-2 Pharmacokinetic parameters of panobinostat in three ongoing Phase I studies [CLBH589A2101], [CLBH589B2101], and [CLBH589B2102]

Route of administration & Dose (No. of patients following single dose)	Mean (CV%) Single dose C_{max}(ng/mL)	Mean (CV%) Single dose $AUC_{0\text{-}inf}$ (ng*hr/mL)	Mean (CV%) Multiple dose $AUC_{0\text{-}48}$ (ng*hr/mL)
i.v. 20 mg/m^2 (n=31)	**784 (45)**	**1041 (38)**	**n/a**
p.o. 20 mg (n=45)	**22.8 (58)**	**194 (58)**	**258 (65)**
p.o. 30 mg (n=49)	**36.2 (62)**	**267 (54)**	**279 (54)**
p.o. 40 mg (n=24)	**58.0 (59)**	**329 (77)**	**270 (59)**
p.o. 60 mg (n=57)	**66.1 (68)**	**362 (62)**	**306 (50)**
p.o. 80 mg (n=18)	**63.5 (58)**	**397 (49)**	**369 (52)**
n/a: not applicable with weekly i.v. administration			

In vitro experiments suggested that the hepatic oxidative metabolism of panobinostat is mediated primarily by cytochrome P450 (CYP) 3A4, and to a lesser extent by CYP2D6 and CYP2C19. In addition to monooxygenation, hydrolysis of the hydroxamic sid chain (M43.5) were also found to be mediated (at least in-part) by the CYPs. These same metabolic pathways, were also observed in the recent human ADME and mass balance study [CLBH589B218].

Dose proportionality

A positive and linear dose-exposure relationship was found following single i.v. administration (1.2 to 20 mg/m^2, Rs = 0.83; p<0.0001). After oral dosing with 15 mg to 80

mg of panobinostat, dose-proportionality analysis indicated that systemic exposure increased nearly dose-proportionally at doses below 60 mg and there is less than proportional increase in AUC after 60 mg and 80 mg doses of panobinostat. It appears that absorption may become limiting at doses ≥ 60 mg of panobinostat.

Food Effect

Influence of food on panobinostat PK was evaluated in patients with advanced cancer who received 20 mg panobinostat twice a week and were randomized to receive panobinostat under fasting, high fat, and normal breakfast conditions [CLBH589B2111]. The overall exposure and inter-patient variability (CV 59%) in 34 patients remained unchanged with or without food, whereas C_{max} was transiently reduced by <45% and T_{max} prolonged by food (i.e., both normal and high fat breakfast). Since food did not alter the overall extent of absorption, food is unlikely to significantly impact panobinostat's systemic exposure in cancer patients. The findings from this formal food effect are consistent with the results from an earlier pilot food effect [CLBH589B2101] arm 1. Therefore, panobinostat can be administered without regard to food in future studies.

2.1.5 Cardiac Safety

As of 31 December 2013, cardiac safety data for 666 patients treated with oral panobinostat TIW QW are presented in Table 2-3. All patients underwent intensive pre- and post-dose ECG monitoring intended to measure the occurrence of QTcF (Fridericia Correction Formula) and to capture other ECG abnormalities as well. The most common finding continues to be a post-baseline QTcF increase of >30 and ≤60 msec with both dosing schedules (approximately 22%). No cases of torsades de pointes have been observed with either oral dosing schedule.

QTcF abnormalities are shown in Table 2-3, for the QW schedule.

Table 2-3 QTcF changes in patients receiving oral panobinostat three-times-a-week every-week (TIW QW)

QTcF variable	20 mg (N=309 Total n %)	30 mg (N=81) Total n %	40 mg (N=163) Total n %	60 mg (N=113) Total n %	TOTAL (N=666) Total n %
QTcF increase from baseline > 30 and <= 60 ms	309 47 (15.2)	81 12 (14.8)	163 46 (28.2)	113 38 (33.6)	666 143 (21.5)
QTcF increase from baseline > 60 ms	309 7 (2.3)	81 1 (1.2)	163 6 (3.7)	113 13 (11.5)	666 27 (4.1)
Absolute QTcF > 450 and <= 480 ms	305 38 (12.5)	81 10 (12.3)	162 13 (8.0)	110 27 (24.5)	658 88 (13.4)
Absolute QTcF > 480 ms and <= 500 ms	309 5 (1.6)	81 1 (1.2)	163 4 (2.5)	113 7 (6.2)	666 17 (2.6)
Absolute QTcF > 500 ms	309 1 (0.3)	81 0 (0.0)	163 0 (0.0)	113 5 (4.4)	666 6 (0.9)

N= Number of patients in the group.
n= Number of patients at risk for a designated change with both non-missing baseline and post-baseline values.
Patients are counted only for the worst grade observed post-baseline.

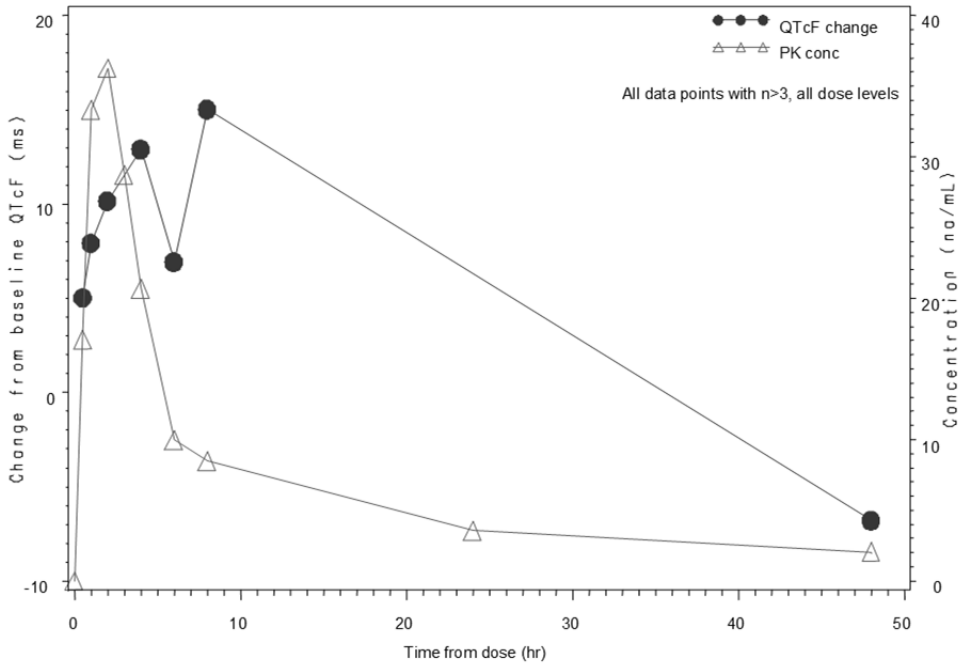
As shown in Table 2-3 above, post-baseline increase of >30 and ≤60 msec (Grade 1) was frequently reported (143 patients, 21.5%). A post-baseline increase of >60 msec was less frequent (27 patients, 4.1%). QTcF prolongation translating into an absolute value of 450 to 480 msec and of > 480 - 500 msec was measured in 88 patients (13.4%) and in 17 patients (2.6%), respectively. Absolute QTcF prolongation > 500 msec was uncommon (6 patients, 0.9%), mostly referred to 5 patients treated at 60 mg weekly dose level.

For the QOW schedule post-baseline increased values of >30 and ≤60 msec were observed in 16 (16.7%) patients. Post-baseline increase of >60 msec was less frequent (4 patients, 4.2%). Absolute QTcF prolongation values of 450 msec to 480 and of >480 to 500 msec were reported in 9 patients (9.6%) and in 1 patient (1.0%), respectively. Absolute QTcF prolongation above 500 msec was not observed.

2.1.5.1 Relationship between panobinostat plasma concentrations and QTcF

As presented in Figure 2-2 (po) below, the maximum change of QTcF from baseline does not coincide with the peak plasma concentration-time course of panobinostat suggesting a possible delayed effect.

Figure 2-2 QTcF change from baseline over time vs. panobinostat conc-time course following the first oral panobinostat doses of a MWF schedule



2.2 HDAC inhibition in Multiple Myeloma

2.2.1 Role of histone deacetylase inhibition in preclinical myeloma models

There are several HDAC inhibitors in development that induce protein acetylation and anti-myeloma activity. The first preclinical evidence of anti-myeloma activity of HDAC inhibitor comes from the study evaluating suberoylanilide hydraxamic acid (SAHA), the prototypic hydroxamic acid-based HDAC inhibitor, or vorinostat in cell lines and patient-derived samples.[53] Subsequent studies showed that molecular profile of myeloma cells exposed to SAHA contained an array of antiproliferative and/or proapoptotic molecular events.[54] SAHA also suppresses proteasomal activity and enhances myeloma cell sensitivity to proteasome inhibition. Combinations of a proteasome inhibitor and an HDAC inhibitor produced synergistic anti-myeloma activities.[55-57] HDAC inhibitors targeting HDAC6 prevent aggresome formation in myeloma cells that were treated with proteasome inhibitors.[58,59] Blockade of both the aggresomal and proteasomal protein degradation pathways produces misfolded protein accumulation and leads to apoptosis.[58,60,61] Agents that have been shown to enhance anti-myeloma activity in various preclinical models in combination with an HDAC inhibition include lenalidomide, pomalidomide, and melphalan.[54,55] HDAC inhibitors as single agents including panobinostat have also been shown to induce myeloma cell death in the U226 cell line primarily through the inhibition of class I HDACs (HDAC 1, 2, 3, and 8).[62] Bone marrow angiogenesis, mediated by VEGF ligand-receptor signaling, is also considered to be important in the pathogenesis of multiple myeloma.[63,64] HDAC inhibition has been shown to suppress the expression of VEGF and VEGF-induced angiogenesis via HIF1-α downregulation.[65-67] Other preclinical studies have suggested that HDAC inhibition may

target chaperone proteins such as heat shock proteins (including HSP27 and HSP90). Inhibition of HDACs and HSP90 downregulate proteins involved in cell proliferation and survival.[68,69] Combination of an HSP90 inhibitor and HDAC inhibitors can result in synergistic downregulation of HSP90 chaperone activity and is associated with myeloma cell death.[70] Single agent activity of both panobinostat and vorinostat has been demonstrated in the Vk*MYC transgenic mouse model of multiple myeloma.[71] Based on promising preclinical activity of HDAC inhibition, panobinostat has been evaluated for the treatment of multiple myeloma.

2.2.2 Role of histone deacetylase inhibition in multiple myeloma treatment

A phase 1a/2 , two-arm, open-label dose-escalation study of panobinostat administered in 2 oral dosing schedules in patients with hematologic malignancies including multiple myeloma has been conducted.[72] In patients with multiple myeloma, 40 mg was the recommended dose for phase 2 evaluation (formal MTD not determined) of weekly panobinostat, and 60 mg was the MTD for biweekly panobinostat. In early phase clinical trials, HDAC inhibitors were examined in heavily pretreated multiple myeloma patients. In the single-agent setting, panobinostat, vorinostat and romidepsin have all been demonstrated to have modest clinical activity.[73-76] In a phase 2 trial, 38 patients with relapsed/refractory multiple myeloma were treated with panobinostat (Table 2-4).[74] There was one patient with durable partial response (PR) and another patient had minimal response (MR). There were 9 other patients who achieved stable disease (SD) at best response. HDAC inhibitors such as panobinostat, romidepsin, vorinostat, and belinostat have also been evaluated in combination with multiple agents.[77-82] In a phase 1b study (Table 2-4), the combination of panobinostat and bortezomib was studied in relapse and refractory multiple myeloma.[78] The maximum tolerated dose (MTD) was established at panobinostat 20 mg plus bortezomib 1.3 mg/m^2. Grade 3/4 AEs included thrombocyotopenia (85.1%), neutropenia (63.8%), and asthenia (29.8%) in the dose escalation phase, and thrombocytopenia (66.7%), neutropenia (46.7%), and fatigue (20%) in the expansion phase. Among bortezomib-refractory patients, the overall response rate (ORR) was 26.3%, and 42.1% of patients had at least MR.[78] Panobinostat has also been examined in a phase 2 trial, PANORAMA 2 (Pan-deacetylase Inhibitor Panobinostat in Combination with Bortezomib and Dexamethasone in Relapsed and Bortezomib-refractory Multiple Myeloma) trial (Table 2-3).[79] In this heavily pretreated (median of 4 prior regimens), bortezomib-refractory (a median of 2 prior bortezomib-containing regimens) myeloma patient population (N = 55), an ORR of 34.5% and a CBR of 52.7% were observed. The safety profile was similar to the phase 1b dose-escalation study, with thrombocytopenia being the most commonly observed grade 3/4 AE (63.3%). Grade 3/4 diarrhea occurred in 20% of patients. In a phase 3 double-blinded study, PANORAMA 1, a total of 768 relapsed or refractory multiple myeloma patients were randomized to either panobinostat or placebo in combination with bortezomib and dexamethasone.[83] The primary endpoint was met with median PFS of 12 months versus 8.1 months ($P < .0001$; hazard ratio (HR) 0.63, 95% confidence interval (CI) 0.52 – 0.76) for the group treated with panobinostat versus placebo, respectively. OS data were not mature. AEs led to the discontinuation in 36% in the panobinostat group compared to 20% in the control group. The trial demonstrated significant PFS improvement with panobinostat in combination with bortezomib plus dexamethasone in patients with

relapsed/refractory multiple myeloma.[83] These promising results corroborate with preclinical studies underscoring the scientific rationale for the drug development. Other clinical trials evaluating the efficacy of panobinostat in multiple myeloma are in active development.

Table 2-4. Summary of selected clinical trials of panobinostat in multiple myeloma

Agent(s)/Study	Phase	N	Panobinostat Dose	Clinical Efficacy	Safety
Panobinostat single agent (Wolf et al.)[74]	2	38	20 mg PO TIW weekly every 21 days	PR n=1; MR n=1; SD n=9	Grade 3/4 neutropenia 31.6%; grade 3/4 thrombocytopenia 26.3%; grade 3/4 GI 10.5%
Panobinostat + bortezomib + dexamethasone (San-Miguel et al.)[78]	1b	62	20 mg PO TIW every weekly every 21 days	CBR* 61.3%; ORR 51.6%; PR 35.5%; VGPR 9.7%; MR 9.7%	Grade 3/4 thrombocytopenia 80.6%; grade 3/4 neutropenia 59.7%; grade 3/4 asthenia 25.8%; grade 3/4 anemia 17.7%
PANORAMA 2 (panobinostat + bortezomib + dexamethasone: Richardson et al.)[79]	2	55	20 mg PO TIW on a 2-weeks-on/1-week-off schedule, every 21 days	CBR 52.7%; ORR 34.5%; SD 36.4%; PR 32.7%; MR 18.2%	Grade 3/4 thrombocytopenia 63.6%; grade 3/4 diarrhea 20%; grade 3/4 neutropenia 14.6%
PANORAMA 1 (panobinostat + bortezomib + dexamethasone vs. placebo: Richardson et al.)[83]	3	768	20 mg PO TIW on a 2-weeks-on/1-week-off schedule, every 21 days	Median PFS 12 months vs. 8.1 months; ORR 61% vs. 55%; nCR/CR 28% vs. 16%	Grade 3/4 thrombocytopenia 67% vs. 31%; grade 3/4 neutropenia 35% vs. 11%; grade 3/4 diarrhea 26% vs. 8%
Panobinostat + melphalan (Berenson et al.)[77]	1/2	40	15 – 20 mg PO TIW 1 week or 2 weeks, every 4 weeks	At least PR n=3; SD n=23, PD n=14	Grade 3/4 neutropenia 30.8%; grade 3/4 thrombocytopenia 23.1%
Panobinostat + melphalan + thalidomide + prednisone (Offidani et al.)[80]	1/2	31	10 – 20 mg PO TIW on a 3-weeks-on/1-week off schedule, every 4 weeks	CR n=2; VGPR n=2; SD n=11	Grade 3/4 neutropenia 71%; grade 3/4 thrombocytopenia 35%

Abbreviations: CBR, clinical benefit rate; CR, complete response; GI, gastrointestinal; nCR, near complete response; PD, progressive disease; VGPR, very good partial response

*CBR is defined as the percentage of patients with a confirmed response of MR or better.

2.2.3 Targeting myeloma precursors with histone deacetylase inhibitor

Recent breakthroughs in the understanding of tumor biology shed light to the existence of cancer stem cells.[84-86] Previous work demonstrated that putative cancer stem cells in multiple myeloma may resemble the memory B cell fraction and express myeloma-type immunoglobulin genes without plasma cell characteristics. These so-called "clonotypic" B cells are characterized functionally and phenotypically as chemoresistant and are postulated to be partly responsible for disease recurrence.[87-89] There is an unmet need for targeted therapy to eliminate the resistant B cells progenitor clone. Boucher and colleagues at Moffitt Cancer Center evaluated clonotypic B cells ($CD19^{+}$) in primary human myeloma samples which

showed light chain restriction (termed light chain restricted, LCR) and showed panobinostat (an oral histone deacetylase inhibitor) induced apoptosis of LCR B cells with the same efficacy as malignant $CD138^+$ cells.[90] Therefore, we hypothesize that administration of panobinostat in a state of minimal residual disease after autologous HCT could potentially eradicate myeloma B cell progenitors implicated as a reservoir of minimal residual disease.

2.2.4 Potential immunologic anti-myeloma mechanisms of deacetylase inhibitor

Numerous immunotherapeutic strategies including immune modulation to reduce myeloma burden has been attempted.[91] Locke and colleagues at Moffitt Cancer Center have demonstrated persistence of T effectors against myeloma tumor associated antigens after autologous HCT. It has been shown that such cells have the ability to exert cytotoxic effects upon autologous myeloma cells, however, this response is blunted in vivo as they are unable to eradicate the tumor spontaneously.[92,93]

Several preclinical studies performed at Moffitt strongly suggest that panobinostat may increase immune responses against tumor. Both *in vitro* and *in vivo* studies by Woods and Villagra et al. showed that panobinostat increases the immunogenicity of tumors and promotes major histocompatibility complex (MHC) and costimulatory molecules upon tumors and increases antigen specific T cells.[94] Wang and colleagues showed elevated Th1 cytokines and increased immune activation when panobinostat was administered after in allogeneic HCT in a murine model.[95] Skewing of T cells toward the Th1 cytokine profile may enhance cytotoxic T-cell mediated anti-tumor activity.

Vaccination with heptavalent pneumococcal conjugate vaccine (PCV13, Prevnar^{TM}: pneumococcal protein + adjuvant CRM protein), is performed as standard of care typical around day +90 after autologous HCT for myeloma. We have demonstrated that this vaccine leads to measurable humoral immunity against pneumococcal serotypes, and T-cell mediate immunity against the CRM protein. Administration of panobinostat after autologous HCT may augment the T-cell immune responses against known myeloma tumor associated antigens; produce skewing of the cytokine profile to Th1 subtype; and augment responses against a standard of care pneumococcal vaccine.[96,97]

2.2.5 High-throughput sequencing technology to assess myeloma clones

Depth of myeloma response has been considered one of the prognostic indicators following HCT and it may be critical to achieve deeper responses for long-term disease control.[98] Multi-parameter flow cytometry is a viable method for minimal residual disease monitoring in majority of myeloma patients by differentiating normal and neoplastic plasma cells based on the surface marker expression.[99] However, a sensitivity of flow cytometry is limited to 0.01%,[100,101] and there is an increasing need for more sensitive minimal residual disease monitoring techniques with more broader applicability.

Emerging technology such as high-throughput sequencing of lymphoid receptors (including B cells and T cells) can provide comprehensive disease monitoring after high-dose melphalan followed by autologous HCT. The Illumina HiSeq platform for multiplex PCR is useful for

sequencing clonal either B-cell or T-cell receptor complementarity-determining region 3 (CDR3).[102] The high-throughput sequencing was more sensitive than flow cytometry in patients with acute T-lymphoblastic leukemia.[102] Similar technology was used on determination of germline IgH repertoires.[103] The high-throughput sequencing to track IgH and IgL sequences in malignant plasma cells would be an ideal method for minimal residual disease monitoring following high-dose therapy and autologous HCT and could potentially be correlated with better long-term disease control.

Previous study evaluated the high-throughput sequencing of PCA-amplified IgH (VDJ and DJ) and kappa/lambda (VJ) rearrangements from bone marrow aspirates of patients with multiple myeloma (n=9) and other plasma cell disorders (n=3). In many of the sample (9/12), an aliquot was enriched for CD138+ cells by immunomagnetic separation. In 11/12 samples, a clearly dominant IgH and/or kappa/lambda rearrangement (> 2.7% of sequences, range 2.7 – 99.9%) was identified with clear separation from background frequency (at least 2.7-fold higher frequency than next most common clone). In 9/9 cases with paired CD138-enriched samples, the dominant sequences in the enriched and un-enriched samples were identical, indicating successful identification of the malignant clonal Ig rearrangements in the un-enriched sample.

In our preliminary study (unpublished) with limited sample size, we compared two different bone marrow samples (CD138 selected DNA extract vs. formalin-fixed paraffin embedded (FFPE) bone marrow clot section) from same patients (from Moffitt Cancer Center) and demonstrated that high-throughput sequencing technology by Adaptive Biotechnologies can identify the index myeloma clones (data not shown). We hypothesize that high-throughput sequencing technology using PCR on CDR3 sequences will identify minimal residual disease in myeloma patients after autologous HCT followed by panobinostat maintenance and bone marrow samples will be obtained prospectively to analyze this technology.

3 Study rationale/purpose

Optimal maintenance therapy after autologous HCT in multiple myeloma has not been defined. Based on preclinical and clinical data demonstrating anti-myeloma activity of panobinostat, we propose an open-label, trial to determine the safety and tolerability of 2 dosing schedules of panobinostat maintenance therapy in patients with multiple myeloma who underwent autologous HCT. As noted in prior maintenance therapy in myeloma, the dose of maintenance single agent is usually started at a lower dose (such as 10 mg starting dose for lenalidomide maintenance compared to 25 mg full dose in relapsed/refractory disease treatment) due primarily to (1) lower disease burden after autologous HCT and (2) limited tolerability and susceptibility to cytopenias immediately after autologous HCT. Panobinostat maintenance therapy will be initiated between 90 days and 180 days after autologous HCT at a starting dose of (a) 20 mg PO three times a week, every other week, every 4 weeks (Cohort A), or (b) 10 mg po daily x 7 days, every other week, every 4 weeks (Cohort B). Maintenance therapy will be prescribed for a maximum for 12 cycles (4 weeks x 12 cycles = 48 weeks) for both cohorts. The dose delivered to each cohort would be 60 mg per week for Cohort A and 70 mg per week for Cohort B. Long-term tolerability of each dose schedule of panobinostat

maintenance therapy after autologous HCT is unknown and the study intends to evaluate the safety and tolerability in multiple myeloma patients.

4 Study objectives

4.1 Primary

To determine tolerability and safety profile of 2 different dosing schedule of single agent panobinostat maintenance therapy for a maximum of 12 intended cycles after autologous HCT in patients with multiple myeloma. We will calculate relative dose intensity (RDI) for each cohort.

4.2 Secondary

- To evaluate the complete response rate to panobinostat maintenance therapy after autologous HCT.
- To determine the 2-year PFS and OS of autologous HCT followed by panobinostat maintenance therapy in patients with multiple myeloma.
- **Exploratory secondary objectives:**
    - To evaluate histone acetylation (H3 and/or H4) of peripheral blood mononuclear cells
    - To isolate and identify clonotypic B cell progenitors in multiple myeloma patients from the bone marrow, peripheral blood and stem cell grafts.
    - To evaluate T-cell immune response against known myeloma tumor associated antigens while on panobinostat maintenance.
    - To evaluate humoral immunity against pneumococcal serotypes included in the standard of care heptavalent pneumococcal conjugate vaccine, and to assess cellular immune responses against CRM adjuvant found in the heptavalent pneumococcal conjugate vaccine.
    - To evaluate minimal residual disease (MRD) after autologous HCT followed by panobinostat maintenance therapy using flow cytometry
    - To evaluate MRD after autologous HCT followed by panobinostat maintenance therapy using multiplex PCR for CDR3 seqeunces

5 Overall study design

This is an open-label trial to determine the safety and tolerability of 2 different dosing schedules of single agent panobinostat maintenance therapy in patients with multiple myeloma who underwent high-dose melphalan followed by autologous HCT in patients with multiple myeloma. It is unknown whether the toxicity profile of panobinostat will be accentuated in patients after autologous HCT in the setting of maintenance therapy, hence the dose chosen for maintenance therapy is lower than MTD dosing or other phase 2 studies. There are 2 dosing schedules evaluated in this protocol in order to assess optimal tolerable schedule for panobinostat maintenance therapy after autologous HCT. As secondary

objectives, we will evaluate response after completion of treatment, and 2-year PFS and OS. As correlative studies, we plan to evaluate MRD, and to assess clonotypic B cells following an autologous HCT. We also plan to evaluate T effector immune response after autologous HCT while on panobinostat maintenance therapy.

The trial includes the option for patients to provide peripheral blood, stem cell graft and bone marrow samples prior to receiving high-dose melphalan and autologous HCT for additional research on multiple myeloma. The screening consent for research samples will be offered to potential subjects while they undergo pre-transplant workup prior to autologous HCT and prior to enrollment on this maintenance study.

6 Study population

6.1.1 Patient population

Adult patients with multiple myeloma who received high-dose melphalan (from 140 mg/m^2 to 200 mg/m^2) followed by autologous HCT are eligible. A total of 30 patients (15 for each maintenance cohort) will be enrolled to the study.

Potentially eligible patients will be approached prior to autologous HCT for an optional research sample collection (where peripheral blood, bone marrow including archived formalin-fixed paraffin embedded bone marrow clot, and stem cell graft will be obtained) using a screening consent. Enrollment to the panobinostat maintenance therapy will occur after autologous HCT.

6.1.2 Inclusion/exclusion criteria (research sample collection: screening consent)

Patients will be contacted while undergoing pre-HCT workup for research sample collection. Patients will be approached for the research sample collection of peripheral blood, bone marrow, and stem cell graft. Peripheral blood sample and bone marrow sample will be obtained after they agree to participate in the research sample collection study while undergoing pre-HCT vital organ testing. Stem cell graft (apheresis) sample will be obtained after autologous stem cell collection. Please refer to the correlative study section for the details of sample analysis.

Inclusion criteria (for research sample collection)

1. Adult patients age ≥ 18 years old with histologically confirmed diagnosis of multiple myeloma
2. Considered for high-dose melphalan followed by autologous hematopoietic cell transplantation and undergoing pre-HCT workup.

Exclusion criterion (for research sample collection)

1. Myeloma patients who are not candidates for high-dose melphalan followed by autologous HCT based on institutional standards.

6.1.3 Inclusion and exclusion criteria (for panobinostat maintenance)

Patients will be enrolled to the panobinostat maintenance therapy study after receiving autologous HCT. Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. Results of all baseline evaluations confirming eligibility must be reviewed by the Principal Investigator (or co-investigator) prior to enrollment of that patient. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

Inclusion criteria (for panobinostat maintenance)

1. Adult patients, age ≥ 18 years old
2. Ability to provide written informed consent obtained prior to participation in the study and any related procedures being performed
3. Histologically confirmed diagnosis of multiple myeloma
4. Meeting the criteria for symptomatic multiple myeloma ("CRAB" criteria – See **Appendix B**) before the initiation of systemic chemotherapy
5. Received high-dose melphalan (≥ 140 mg/m^2) followed by autologous HCT based on the institutional guidelines and within +45 and +180 after autologous HCT at the time of panobinostat maintenance initiation.
6. Patients must have achieved at least PR prior to autologous HCT and must not have progressive disease (PD) prior to the initiation of maintenance therapy (See **Appendix C** for response criteria)
7. Patients must meet the following laboratory criteria (prior to the initiation of panobinostat maintenance):
   - ANC ≥ 1 x 10^9/L
   - Hemoglobin ≥ 8 g/dl
   - Platelets ≥ 50 x 10^9/L (without transfusion support)
   - Creatinine clearance ≥ 40 ml/min or serum creatinine ≤ 2.5 x ULN
   - AST and ALT ≤ 2.5 x ULN
   - Serum bilirubin ≤ 1.5 x ULN
   - Albumin > 3.0 g/dl
   - Clinically euthyroid. Note: Patients are permitted to receive thyroid hormone supplements to treat underlying hypothyroidism.

8. Baseline (pre-HCT) MUGA or ECHO must demonstrate LVEF ≥ the LLN of the institutional normal.
9. ECOG Performance Status of ≤ 2 or Karnofsky performance status ≥ 70% (See **Appendix D** and **Appendix E**)
10. Prior HDAC, DAC, HSP90 inhibitors or valproic acid for the treatment of cancer is allowed.

Exclusion criteria (panobinostat maintenance)

1. Patients who have purely non-secretory multiple myeloma (i.e., the absence of a measurable protein in serum by electrophoresis and immunofixation and the absence of Bence-Jones protein in the urine defined by use of electrophoresis and immunofixation)
2. Prior allogeneic HCT
3. Prior solid organ transplant requiring immunosuppressive therapy
4. Patients who will need valproic acid for any medical condition during the study or within 5 days prior to first panobinostat treatment
5. Impaired cardiac function or clinically significant cardiac diseases, including any one of the following:
   - History or presence of sustained ventricular tachyarrhythmia. (Patients with a history of atrial arrhythmia are eligible but should be discussed with Novartis prior to enrollment)
   - Any history of ventricular fibrillation or torsade de pointes
   - Bradycardia defined as HR< 50 bpm. Patients with pacemakers are eligible if HR ≥ 50 bpm.
   - Screening ECG with a QTc > 470 msec
   - Right bundle branch block + left anterior hemiblock (bifascicular block)
   - Patients with myocardial infarction or unstable angina ≤ 12 months prior to starting study drug
   - Other clinically significant heart disease (e.g., CHF NY Heart Association class III or IV, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen)
4. Patients with diarrhea > CTCAE grade 2
5. Other concurrent severe and/or uncontrolled medical conditions (e.g., uncontrolled diabetes or active or uncontrolled infection) including abnormal laboratory values, that could cause unacceptable safety risks or compromise compliance with the protocol
6. Patients using medications that have a relative risk of prolonging the QT interval or inducing torsade de pointes (see Table 17-1) if treatment cannot be discontinued or switched to a different medication prior to starting study drug
7. Patients who have received targeted agents within 2 weeks or within 5 half-lives of the agent and active metabolites (whichever is longer) and who have not recovered from side effects of those therapies.

8. Patients who have received either immunotherapy within ≤ 8 weeks; chemotherapy within ≤ 4 weeks; or radiation therapy to > 30% of marrow-bearing bone within ≤ 2 weeks prior to starting study treatment; or who have not yet recovered from side effects of such therapies.
9. Patients who have undergone major surgery ≤ 4 weeks prior to starting study drug or who have not recovered from side effects of such therapy
10. Women who are pregnant or breast feeding or women of childbearing potential (WOCBP) not using an effective method of birth control. WOCBP are defined as sexually mature women who have not undergone a hysterectomy or who have not been naturally postmenopausal for at least 12 consecutive months (i.e., who has had menses any time in the preceding 12 consecutive months). Women of childbearing potential must have a negative serum pregnancy test within 24hrs of receiving the first dose of study medication.
11. Male patients whose sexual partners are WOCBP not using effective birth control
12. Patients with a prior malignancy with in the last 5 years (except for basal or squamous cell carcinoma, or *in situ* cancer of the cervix)
13. Patients with known positivity for human immunodeficiency virus (HIV) or hepatitis C; baseline testing for HIV and hepatitis C is not required
14. Patients with any significant history of non-compliance to medical regimens or unwilling or unable to comply with the instructions given to him/her by the study staff.

7 Treatments

7.1 Investigational therapy

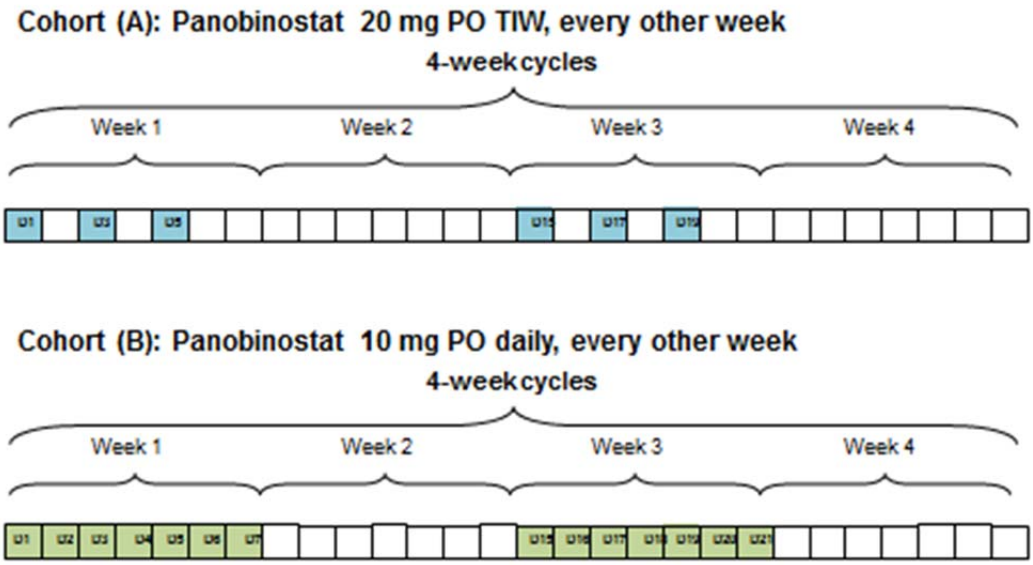
Screening consents will be signed prior to autologous HCT to access pre-HCT stem cell graft, bone marrow and peripheral blood samples for the correlative studies. Patients will be enrolled after autologous HCT. Patients will be initiated on panobinostat maintenance therapy between day +90 and +180 after autologous HCT. Patients who develop disease progression before day +90 after autologous HCT will be ineligible for the study.

Panobinostat (also known as LBH589) will be provided by Novartis. Oral panobinostat will be supplied as 5-mg, 10-mg, 15-mg or 20-mg pink/opaque-colored, hard gelatin capsules.

Medication labels will comply with US legal requirements and be printed in English. They will supply no information about the patient. The storage conditions for study drug will be described on the medication label.

During the study, panobinostat will be administered orally as either (1) once daily dose of 20 mg (1 x 20-mg capsule) three times per week, every other week, of a 28-day schedule (Cohort A), or (2) once daily dose of 10 mg (1 x 10-mg capsule) daily x 7 days, every other week, of a 28-day schedule (Cohort B). Both cohorts will receive a maximum of 12 cycles of maintenance therapy (Figure 7-1).

Figure 7-1. Panobinostat maintenance schedule



Patients should be instructed to take their once-a-day oral dose of panobinostat at the same time each morning. Each dose of panobinostat should be taken with an 8 oz / 240 ml glass of water. Patients should be instructed to swallow the capsules whole and not chew them. Patients must avoid grapefruit or grapefruit juice and seville (sour) oranges during the entire study.

If a subject experiences toxicity, the dose of panobinostat will be reduced to one level lower (Table 7-1) and maintained at this level for all subsequent cycles unless further toxicities occur. Panobinostat dose modifications will be made according to the toxicity grading. Once a subject's dose of panobinostat is reduced, then that dose will be the maximal dose administered.

On the days of ECG monitoring, drug administration should be supervised by study center personnel and administration time should be recorded.

If the patient forgets to take his/her dose during the morning on scheduled treatment day (i.e., day 1 of each cycle), then he/she should take panobinostat (LBH589) on that same day within 12 hours after the missed dose if possible. After more than 12 hours, that day's dose should be withheld, and the patient should wait to take panobinostat (LBH589) until the next scheduled treatment day (i.e., patients should be instructed not to try to make-up the missed dose after 12 hours). The patient should then continue treatment with the original dosing schedule

The investigator should instruct the patient to take the study drug exactly as prescribed (promote compliance). All dosages prescribed and dispensed to the patient and all dose changes during the study should be recorded.

7.1.1 Cardiac precautions

All patients must have an assessment of serum potassium, magnesium, and calcium (total corrected for albumin, or ionized calcium) ≤ 72 hours prior to the administration of oral panobinostat on day 1 of cycle 1 and the results must all be ≥ LLN before the first dose of panobinostat is administered. Throughout the study serum biochemistry values including serum potassium, calcium, phosphorous and magnesium will be monitored closely. On any day and time in which serum potassium, calcium, phosphorous and magnesium are assessed, if the value is < LLN, then the patient's potassium, calcium, phosphorous or magnesium should be immediately supplemented following the availability of that laboratory result, in order to minimize the time patients have low values. Patients must then undergo a repeat chemistry tests for repleted electrolytes (potassium, calciu, phosphorous or magnesium) to demonstrate values ≥ LLN. These values must be ≥ LLN before the patient is re-dosed with oral panobinostat.

Patients must be instructed to not take panobinostat if their most recent biochemistry values demonstrates potassium, calcium, phosphorous or magnesium < LLN. At a minimum, potassium, magnesium, phosphorous and calcium will be checked according to the protocol. More frequent testing should be done if clinically indicated, e.g. patient has had prior low values, patient is taking medications (e.g., diuretics) that can result in lowering of their potassium, magnesium, phosphorous or calcium levels.

7.2 Treatment assignment

This is an open label, oral panobinostat maintenance therapy trial evaluating 2 different dosing schedules (cohorts A and B). Patients will be sequentially enrolled to alternating cohorts. There will be no randomization procedure involved in this study.

7.3 Treatment cycle and duration

One treatment cycle consists of oral panobinostat either (1) 20 mg PO three times per week, every other week, of a 28-day schedule, or (2) 10 mg PO daily x 7 days, every other week, of a 28-day schedule. Patients may continue treatment with oral panobinostat until they experience unacceptable toxicity that precludes further treatment, disease progression, and/or at the discretion of the investigator. The planned treatment is for a total of 12 cycles (48 weeks).

7.4 Interruption or discontinuation of treatment

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the patient on study drug. If administration of panobinostat must be interrupted because of unacceptable toxicity, drug dosing will be interrupted or modified according to rules described in Tables 7-1, 7-2, and 7-2. Toxicity will be assessed using the NIH-NCI Common Terminology Criteria for Adverse Events, version 4.0 (CTCAEv4.03,(http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf). All interruption or changes to study drug administration must be recoded.

7.4.1 Dose reduction for panobinostat

This is an open-label trial to determine the safety and tolerability of single agent panobinostat (2 dosing schedules) as maintenance therapy after autologous HCT in patients with multiple myeloma. Patients will receive either 20 mg PO TIW, every other week, every 28-days (Cohort A) or 10 mg po daily x 7 days, every other week, every 4 weeks (Cohort B). If no grade 3 or 4 toxicities occur after completing a 28-day cycle of panobinostat maintenance therapy, and all non-hematologic toxicities improved to grade 1 or better, then the next cycle of panobinostat will be initiated as long as the minimal hematologic parameters are met (ANC $\geq$ 1 x 10^9/L; hemoglobin $\geq$ 8 g/dl; platelets 50 x 10^9/L) prior to each cycle. If a subject experiences toxicity, the dose of panobinostat will be reduced to one level lower (Table 7-1) and maintained at this level for all subsequent cycles unless further toxicities occur. Panobinostat dose modifications will be made according to the toxicity grading. Once a subject's dose of panobinostat is reduced, then that dose will be the maximal dose administered. The provisional dose levels of panobinostat (LBH589) to be investigated in this study are described in Table 7-1.

Table 7-1 Provisional dose reduction for panobinostat (LBH589)

	Panobinostat oral dose	
Dose level#	**Cohort A (TIW, every other week, every 4 weeks)**	**Cohort B (Daily x 7 days, every other week, every 4 weeks)**
1 (starting dose level)	20 mg	10 mg
-1	15 mg	10 mg on days 1, 3, 5, and 7

7.4.2 Dose modifications for study drug-related toxicity (see section 7.4.3 for dose modifications for prolonged QTc):

The criteria for dose modifications for study drug-related toxicity are detailed in Table 7-2.

Table 7-2 Criteria for dosing delays, dose-reductions, and re-initiation of treatment due to study drug-related toxicity (excluding QT prolongation)

Worst Toxicity CTCAE Grade* unless otherwise specified (Value)		**Dose Modification Guidelines At any time during a cycle of therapy (including intended day of dosing)**
HEMATOLOGICAL TOXICITIES		
Thrombocytopenia	Grade 3 (<50 and ≥ 25 x 10^9/L) with bleeding and Grade 4 (< 25 x 10^9/L)	Temporarily discontinue panobinostat dosing until resolved to ≤ grade 2, or baseline, then, restart panobinostat at reduced level as per Table 7-1

Worst Toxicity **CTCAE Grade* unless otherwise specified (Value)**		**Dose Modification Guidelines** **At any time during a cycle of therapy (including intended day of dosing)**
Neutropenia (ANC)	Grade 4 (ANC < 0.5 x 10^9/L)	Temporarily discontinue panobinostat dosing until resolved to ≤ grade 3, or baseline, then: • If resolved within 7 days after suspending panobinostat, then restart panobinostat at an unchanged dose level • If resolved in more than 7 days after suspending panobinostat, then restart panobinostat reduced by one dose level
	Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)	Temporarily discontinue panobinostat dosing until fever resolved and ANC ≤ grade 2, then restart panobinostat reduced by one dose level
NON-HEMATOLOGICAL TOXICITIES		
CARDIAC		
Cardiac - Prolonged QT interval**		**Please refer to Section 7.4.3.**
GASTROINTESTINAL		
Diarrhea	Grade 2 (4-6 stools/day over baseline, etc) despite the use of optimal antidiarrheal medications	Temporarily discontinue panobinostat dosing until resolved to ≤ grade 1, or baseline, then restart at unchanged dose level
	Grade 3 (≥ 7 stools/day over baseline, etc) despite the use of optimal antidiarrheal medications	Temporarily discontinue panobinostat dosing until resolved to ≤ grade 1, or baseline, then restart panobinostat reduced by one dose level
	Grade 4 (life-threatening consequences, hemodynamic collapse, etc) despite the use of optimal antidiarrheal medications	Discontinue panobinostat dosing
Vomiting/Nausea***	Grade 1 & 2 not requiring treatment or controlled using standard anti-emetics	Maintain dose level
	Grade 3 or 4 vomiting or Grade 3 nausea that cannot be controlled despite the use of standard anti-emetics	Temporarily discontinue panobinostat dosing until resolved to ≤ grade 1, or baseline, then restart panobinostat reduced by one dose level

Fatigue		
Fatigue	Grade 3	Temporarily discontinue panobinostat dosing until resolved to ≤ grade 2, or baseline, then: • If resolved within 7 days after suspending panobinostat, then restart panobinostat at an unchanged dose level • If resolved in more than 7 days after suspending panobinostat, then restart panobinostat reduced by one dose level
	Grade 4	Temporarily discontinue panobinostat dosing until resolved to ≤ grade 2, or baseline, then: • restart panobinostat reduced by one dose level
HEPATIC		
Total Bilirubin	Grade 3 or 4	Temporarily discontinue panobinostat dosing until resolved to ≤ grade 2, or baseline, then restart panobinostat reduced by one dose level
Note: If Grade 3 or Grade 4 hyperbilirubinemia is due to the indirect component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then reduction of one dose level and continuation of treatment is at the discretion of the Investigator.		
AST/SGOT, ALT/SGPT	> 5-10 x ULN	Temporarily discontinue panobinostat dosing until resolved to ≤ grade 1 (or ≤ grade 2 if liver infiltration with tumor is present), or baseline, then: • If resolved within 7 days, then: • restart panobinostat at unchanged dose level • If resolved in more than 7 days, then reduce panobinostat by one dose level
	> 10 x ULN	Temporarily discontinue panobinostat dosing until resolved to ≤ grade 1, or baseline, then: • restart panobinostat reduced by one dose level
All dose modifications should be based on the worst preceding toxicity.		
* Common Terminology Criteria for Adverse Events (CTCAE Version 4.03)		
** It is critical that electrolyte abnormalities be followed closely and corrected prior to dosing		
*** See also concomitant medication Section 7.5		

7.4.3 Dose modifications for prolonged QTc

All cardiac events should be treated as per the local standard of care and referred to a cardiologist if clinically indicated. The localized readings of ECGs will use the Fridericia correction for QTc interval assessment: QTcF. Any final decisions concerning dose modifications or permanently discontinuing the patient from study drug due to QTcF prolongation will be based on the Investigator's clinical assessment. Any plan to deviate from these guidelines must be previously discussed and agreed upon with Novartis.

Patients must have QTcF < 470 msec to be eligible for the trial. If QTcF is ≥ 470 msec or above 60 msec from baseline on a screening or pre-dose ECG, correct any electrolyte abnormalities (hypokalemia, hypomagnesemia, hypocalcemia), and conduct triplicate ECGs (5 minutes apart) and calculate average QTcF. If the average QTcF from the triplicate ECGs remains ≥ 470 ms, patient must not be dosed. Pre-dose ECG monitoring is mandatory on days 1 and 5 of cycle 1, and day 1 of cycles 2 through 4. Post dose ECG (3 hours (± 15 minutes) post dosing) is mandatory only on days 1and 5 of cycle 1.
If a screening, pre-dose, or post-dose ECG shows a QTcF ≥ 500 ms, patient is not eligible for further treatment. If any of these mandatory ECGs show QTcF ≥ 470 msec or 60 msec above baseline, dosing should be held and the above specified measures including follow-up triplicate ECGs and correction of electrolyte abnormalities should be performed. If QTcF abnormality resolves, patients should resume treatment and have QTcF checked pre-dose on day 1 of each cycle for at least the next 3 subsequent cycles. Additional QTcF monitoring should be performed if clinically indicated. If a patient cannot be dosed due to prolonged QTcF for more than 7 days since last dose, patient must be discontinued from study treatment.

Table 7-3 Dose Reductions for QTc Prolongation

Time Point	Average QTcF*	Action
Screening and pre-dose cycle 1 day 1	≥ 470 msec	Delay treatment Correct any electrolyte abnormal values ** and repeat ECG, if the average QTcF ≥ 470 msec, do not dose
	Above 500 msec	Patient is not eligible
Pre-dose cycle 1 day 5 Pre-dose day 1 of subsequent cycles	≥ 470 msec or above 60 msec from baseline for any pre-dose ECG after the patient has commenced treatment***	Omit dose If unresolved within 7 days, discontinue treatment If resolved within 7 days, resume treatment at prior dose for initial occurrence or at reduced dose if recurrent
	Above 500 msec	Permanently discontinue treatment
*QTcF: Heart rate corrected QT interval using the Fredericia formula: QTc=QT/RR0.33 **: serum potassium, magnesium, calcium, ***If a single pre-dose QTcF is ≥ 470 msec or 60 msec from baseline, subsequent ECGs should be performed in triplicate		

7.4.4 Study drug discontinuation

It will be documented whether or not each patient completed the clinical study. If for any patient either study treatment or observations were discontinued, the reason will be recorded.

Reasons that a patient may discontinue treatment are considered to constitute one of the following:

1. Disease progression
2. Adverse event(s) related to the study drug
3. Abnormal laboratory value(s) related to the study drug
4. Abnormal test procedure result(s) related to the study drug
5. Protocol violation
6. Subject withdrew consent
7. Lost to follow-up
8. Administrative problems
9. New cancer therapy
10. Death

7.4.5 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value must be followed until resolution or stabilization of the event, whichever comes first.

If a patient requires a dose delay of > 28 days from the intended day of the next scheduled dose, then the patient must be discontinued from the study. If however the patient was clearly benefiting from panobinostat therapy, the patient may be able to continue treatment with a dose reduction at the Investigator discretion, after resolution of the adverse event. All patients will be followed for adverse events and serious adverse events for at least 4 weeks following the last dose of oral panobinostat.

7.5 Other concomitant medications

Patients must be instructed not to take any additional medications (including over-the-counter products) during the trial without prior consultation with the investigator. All medications taken within 30 days of enrollment should be recorded. If concomitant therapy must be added or changed within 30 days of enrollment, the reason and name of the drug/therapy should be recorded. Other concomitant medications are collected once at enrollment (within 30 days of screening).

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient are allowed, including drugs given prophylactically (e.g. antiemetics) with the following exceptions:

- Any medications listed in Appendix 17.1.1 which may cause QTc prolongation or inducing torsades de pointes should not be used.

- Any medications that have the potential to alter serum electrolytes (e.g., diuretics) should be monitored very closely for electrolyte abnormalities as these can contribute to the risk of QT prolongation and ventricular arrhythmias.
- No other investigational therapy should be given to patients
- No anticancer agents other than the study medications administered as part of this study protocol should be given to patients. If such agents are required for a patient then the patient must first be withdrawn from the study.
- Leukocyte growth factors (e.g.G-CSF and GM-CSF) are not to be administered systematically but may be prescribed by the investigator for severe neutropenia if this is thought to be appropriate.
- Medications known to be substrates of the isoenzyme CYP2D6 should be used with caution with panobinostat as panobinostat can inhibit isoenzyme CYP2D6 at low micromolar ranges. Please refer to Appendices 17.1.2 and 17.1.3 for the lists of CYP2D6 substrates. .
- Concomitant use of CYP3A4 inhibitors with panobinostat should be used with caution due to a potential increase in panobinostat exposure during concomitant treatment with these drugs.
- Oral contraceptives are generally metabolized by CYP3A4. Since the induction potential of panobinostat to induce CYP3A4 is unknown, patients who are using oral contraceptives as a method of contraception, and are sexually active, should use another effective contraceptive method.

7.5.1 Anti-coagulant therapy

Panobinostat therapy is commonly associated with mild to moderate degree of thrombocytopenia. This may lead to an increase in the risk of bleeding with concomitant sodium warfarin (Coumadin®). It is recommended that patients who require anticoagulation therapy while on panobinostat therapy use low molecular weight heparin (LMWH). However, if the use of LMWH is not feasible, patients on sodium warfarin may continue such therapy while on panobinostat but for such patients, a close and frequent monitoring of the coagulation parameters, including PT/INR should be followed and they should be maintained within a therapeutic range. The dose of sodium warfarin may be adjusted as needed while on panobinostat. For patients requiring anti-platelet therapy while on panobinostat, aspirin $\leq$ 325 mg or clopidogrel $\leq$ 75mg daily are allowed while on study. It is recommended that anti-platelet therapy be held if platelet counts fall below 50 x 10^9/L.

7.5.2 CYP2D6 Substrates

In *in vitro* assays, panobinostat was shown to inhibit the cytochrome P450 isoenzyme CYP2D6 at low micromolar ranges, thereby suggesting a potential risk of drug-drug interactions with concomitant medications that are also metabolized by CYP2D6. A clinical drug-drug interaction study with dextromethorphan (a CYP2D6 probe drug) and panobinostat is currently ongoing in cancer patients. In the meantime, medications that are known to be CYP2D6 substrates should be used with caution when given concomitantly with panobinostat. Patients must be carefully monitored for signs of toxicity as a result of concomitant

medication which may require dose titration or reduction of the CYP2D6 substrate as medically necessary. Please see Appendices 17.1.2 and 17.1.3, and refer to the following website: http://medicine.iupui.edu/flockhart/table.htm for a list of substrates of CYP2D6.

7.5.3 Drugs that can inhibit/induce CYP3A4/5

7.5.3.1 Drugs that can inhibit CYP3A4/5

Panobinostat is metabolized in vitro by CYP3A4/5. A clinical drug-drug interaction study with ketoconazole and panobinostat has recently been completed. The less than 2-fold increase in panobinostat AUC upon co-administration with ketoconazole suggests that CYP3A contribution to the total clearance of panobinostat is low. The observed interaction is not considered clinically relevant, as panobinostat doses at least 2-fold greater than 20 mg (40 and 60 mg) have been safely administered in patients. CYP3A4 inhibitors should have no major impact on the exposure of panobinostat and may be co-administered when medically necessary.

7.5.3.2 Drugs that are potent CYP3A4/5 inducers

As it is with other medications that are metabolized by CYP3A4, clinical judgment is to be exercised when potent CYP3A4 inducers are concomitantly taken with panobinostat.

7.5.4 Pneumococcal-13 conjugate vaccine administration (standard of care)

As a standard of care, pneumococcal-13 conjugate vaccine (Prevnar-13^{TM}) will be administered to many of autologous HCT recipients at around day +90 (prior to the initiation of maintenance therapy).

7.6 Treatment compliance

Records of study medication used, dosages administered, and intervals between visits will be recorded during the study. Drug accountability will be noted and patients will be asked to return all unused study medication.

8 Visit schedule and assessments

8.1 Visit schedule

Table 8-1 Evaluation and visit schedule

	Pre-HCT (Screening, not required)	**Prior to maintenance (Enrollment: +45 to +180)[$]**	**Cycle #1 (start between +90 and +180)**	**Cycle #2******	**Cycle #3******	**Cycle #4******	**Cycle #5******	**Cycle #6******	**Cycle #7******	**Cycle #8******	**Cycle #9******	**Cycle #10******	**Cycle #11******	**Cycle #12******	**End of study visit (4 weeks (± 14 days) follow up after the first dose of cycle #12)**
Consent	X[+]	X													
Enrollment		X													
H&P (SOC)		X	X[$$$]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X													
Toxicity (adverse event (AE)) assessment[$$]			X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (SOC)		X[++]	X	X	X	X	X	X	X	X	X	X	X	X	X
EKG		X	X*	X**	X**	X**									
CBC and CMP (SOC)		X	X***	X***	X	X	X	X	X	X	X	X	X	X	X
PT/INR/PTT		X			X			X							X
LDH, cholesterol panel, GGT, uric acid		X													
Urinalysis		X													X
TSH, free T4		X													X
Serum pregnancy test[+++]		X	X	X	X	X	X	X	X	X	X	X	X	X	
SPEP, UPEP and serum free		X			X			X			X			X	

light chains (SOC)															
Pneumococcal-13 conjugate vaccine (at around day +90 – SOC)		X[#]													
Peripheral blood research samples	X	X	X[++++]	X	X			X			X				X
Bone marrow research samples	X[@]	X													X
Stem cell graft research samples	X														

*Single 12 lead EKG will be performed for pre-dose and 3 hours (± 15 minutes) post-dose on days 1 and 5 of cycle 1. A total of 4 EKGs during cycle 1 will be performed.
**Single 12 leak EKG will be performed for pre-dose on day 1 of cycle 2 and beyond at each cycle (at least through cycle 4). If no significant QTcF prolongation is noted during the first cycle, then QTc monitoring is no longer required beyond cycle 4 (and may be performed at the investigator's discretion). One EKG per cycle from cycle 2 to 4 (minimum).
***CBC to be performed weekly during cycle #1 and #2. CBC/CMP will also be performed on day 5 of cycle 1.
****Window to start cycles #2 to #12 would be ±7 days from the planned first day of each cycle.
[+]Screening consent for research samples (bone marrow, peripheral blood and stem cell graft)
[++]Height will be measured at screening visit prior to starting panobinostat maintenance therapy
[+++]Only for women of child bearing potential
[++++]Peripheral blood research samples will be also collected on day 5 of cycle 1.
[#]It is advised that the standard of care heptavalent pneumococcal conjugate vaccine be administered at around day +90 prior to the initiation of maintenance therapy.
[@]Archived (formalin-fixed paraffin embedded) bone marrow clot will be accessed to identify myeloma index clones for high-throughput sequencing.
[$]Patients can be enrolled after autologous HCT without having the pre-HCT screening visit (which is not require).
[$$]Only grade $\geq$ 3 adverse event (AE) will be collected.
[$$$]Patients will be evaluated (history and physical) on day 5 of cycle 1.
Abbreviations: SOC, standard of care

8.2 Efficacy assessments

All subjects will be evaluated every 3 months with multiple myeloma restaging (standard of care) including serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP) and serum free light chains. Response assessment will be performed approximately at cycle 3, 6, 9, and 12 of maintenance panobinostat therapy. Responses will be classified by according to the IMWG response criteria (Appendix C).

8.3 Safety assessments

Safety assessments will consist of monitoring and recording unexpected grades ≥ 3 adverse events and serious adverse events, the regular monitoring of hematology, blood chemistry and urine values, vital signs, ECOG performance status, and the regular physical examinations and ECG assessments. All patients will be seen on day 1 of each cycle throughout the maintenance therapy until disease progression or unacceptable toxicities occur (Table 8-1). Additional evaluations may be performed if clinically indicated.

Adverse events will be assessed according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03. CTCAE v4.0 can be accessed on the NIH/NCI website at (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf)

8.3.1 Adverse events

Information about unexpected grades ≥ 3 adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. the severity grade (moderate, severe) or (grade 3-4) – only grades adverse events will be reported its relationship to the study drug(s) (suspected/not suspected)
2. its duration (start and end dates or if continuing at final exam)
3. action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
4. whether it constitutes a serious adverse event (SAE)

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or

any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the [Investigators' Brochure] or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.3.2 Vital signs

Vital sign assessment consists of height (first visit), pulse, blood pressure, respiration rate, temperature and weight. Blood pressure, pulse and respiration rate should be measured on patients after at least 3 minutes in the sitting position

8.3.3 Physical examination

Physical examination will be performed which comprises examination of skin, lungs, heart, abdomen, lymph nodes, and extremities at minimum.

Significant findings made after the start of study drug which meet the definition of an grades ≥ 3 Adverse Event must be recorded.

8.3.4 Laboratory evaluations

Laboratory evaluation should be done at baseline (within ≤ 72 hours prior to dosing prior to the first administration of oral LBH589), during the course of the study and at the time of the study treatment completion visit. Results must be reviewed prior to administering LBH589. More frequent examinations may be performed if medically indicated; results should be recorded.

Hematology

Hematology must include hemoglobin, hematocrit, platelets, total white blood cell count (WBC) and differential. The coagulation profile includes a prothrombin time or International Normalized Ratio (INR), activated partial thromboplastin time and fibrinogen.

Blood chemistry

Biochemistry includes the following parameters: BUN, creatinine, sodium, potassium, chloride, CO_2 (HCO_3), glucose, calcium, albumin, total protein, total bilirubin, alkaline phosphatase, LDH, AST/SGOT, ALT/SGPT, phosphorous, magnesium. If total bilirubin is greater than the upper limit of normal, direct and indirect bilirubin may be performed. Biochemistry tests should be obtained after patient has fasted, if possible.

Urinalysis

Standard urinalysis dipstick assessment (pH, protein, glucose, blood, ketones, and leukocytes) should be performed. This must be supplemented with laboratory quantification of any potentially relevant abnormalities.

Thyroid function test

Thyroid Stimulating Hormone (TSH) and free T4 (thyroxine) will be measured at baseline and at study treatment completion.

8.3.5 Serum pregnancy test

All females of childbearing potential should complete a serum pregnancy test within 7 days prior to the administration of LBH589 on day 1 of cycle 1. The pregnancy test should be repeated in week 1 of every cycle (except for cycle 1). Postmenopausal women must have been amenorrheic for ≥ 12 months in order to be considered "of non-childbearing potential".

8.3.6 ECG

A screening 12-lead ECG will be performed to assess study eligibility. Additional 12-lead ECGs will be performed at a minimum at scheduled time points as indicated in Table 8-2. Pre-dose ECG monitoring is required for the first four cycles of treatment. Post-dose ECGs will be required during cycle one, on days 1 and 5. Additional ECG monitoring should be done at the discretion of the Investigator, as clinically indicated. All ECGs will be read locally.

Table 8-2 Cardiac assessment monitoring schedule

Cycle	Day of cycle	ECG monitoring [a]
	Screening [b]	Single ECG to assess eligibility
Cycle 1	1, 5	Pre-dose: Single 12 lead ECG
	1, 5	3 hours (± 15 minutes) post dose: Single 12 lead ECG
Cycle 2 and beyond	1	Pre-dose: Single 12 lead ECG

[a] Refer to Table 7-3 for the recommended dose modifications due to QTc interval prolongation
[b] The screening ECGs will be analyzed locally to assess eligibility of the patient. (Note: the mean QTc interval at baseline must be ≤ 470 msec for the patient to be eligible for participation in the trial)
Note: If no significant QTcF prolongation is noted during the first 4 cycles, the QTc monitoring is no longer required and may be performed at the Investigator's discretion, if medically indicated.

All cardiac events should be treated as per the local standard of care and referred to a specialist if clinically indicated. The localized readings of ECGs will use the Fridericia correction with MUSE system: QTcF. Any final decisions concerning dose modifications or permanently discontinuing the patient from study drug due to QTcF prolongation will be based on the assessment performed by the Investigators using QTcF correction derived from MUSE system. Any plan to deviate from these guidelines should be previously discussed and

agreed upon with Novartis. If a patient cannot be dosed due to prolonged QTcF for more than 7 days since last dose, patient should be discontinued from study.

8.3.6.1 Performance status

Performance status will be assessed using Karnofsky performance score at baseline, at day 1 of each cycle and at the end of stud visit.

8.4 Drug levels and pharmacokinetic assessments

- Drug levels and pharmacokinetic assessments will not be performed as part of this study.

9 Correlative studies

9.1 Assessment of minimal residual disease and B cell precursors

Aliquots of 50uL bone marrow aspirate in sodium heparin will be incubated in the dark for 15 minutes at room temperature with combination of fluorescent-labeled antiobodies, followed by red blood cell lysis with FACS lysing solution (BD biosciences). Cytoplasmic staining will be performed by permeabilizing cells with Fix & Perm reactives (Caltag), followed by incubation in the dark with fluorescent-labeled antibodies for 5 minutes at 4ºC. Standarized 10-color antibody combinations will be used (Pac Blue/Krome Orange/FITC/PE/ECD/PerCP-Cy5.5/CD7-PE-Cy7/APC/APC-Alexa-Fluor-700/APC-Alexa-Fluor 750), including an isotype control tube plus 4 tubes:

- cytoplasmic-κ/cytoplasmic-λ/CD56/CD138/isotype/CD20/CD19/CD117/CD38/CD45
- CD49d/CD52/CD13/Cd138/CD33/CD40/isotype/CD44/CD38/CD45
- CD28/CD81/CD27/CD138/isotype/CD200/isotype/CD117/CD38/CD45
- isotype/CD319/CD56/CD138/isotype/CD269/CD19/CD117/CD38/CD45

Stained cells will be resuspended in phosphate buffered saline containing 2% paraformaldehyde. At least 500,000 events were acquired on a Gallios 10-color flow cytometer (Beckman Coulter). Flow cytometry data will be analyzed on ad-hoc templates created on Kaluza version 1.2 (Beckman Coulter) using standardized gating strategies to identify and characterize neoplastic clonal plasma cells, residual benign plasma cell populations, maturing B-cell precursors and mature B-cells. In particular, B-cells will be analyzed to identify putative clonal stem cell populations.

Peripheral blood and peripheral blood stem cell graft samples will also be collected, and multi-parameter flow cytometry will be performed for phenotype characterization of B cell precursors as described above.

Pharmacodynamic effects on various cell subtypes and evaluation of protein acetylation with panobinostat maintenance therapy

In order to determine whether 2 different panobinostat maintenance dosing schedules have any correlation with HDACs enzymatic activity, we will evaluate HDAC enzymatic activity in peripheral blood from patients. Peripheral blood samples will be obtained at baseline (before starting panobinostat), on day 5 of cycle 1, at cycle #6 and after the completion of maintenance. To this end we will use a HDAC fluorimetric cellular activity assay (Biomol, Catalog # AK503). A fluorogenic-cell permeable substrate, Fluor de Lys, is added to peripheral blood mononuclear cells (PBMC) grown in patient's serum and enter the cells where if there is remaining HDAC activity, the fluor de lys gets deacetylated producing a fluorescent signal. A detergent is used to allow contact between the non-cell permeable developer and both intra and extracellular deacetylated substrate. In addition, the HDACi trichostatin A is added along with the detergent to insure that no deacetylation occurs after cell lysis. To run this test approximately 1 x 10^5 PBMC are required/sample.

In order to determine the level of protein acetylation and more specifically of hyper-acetylated histones (H3 and/or H4), we will use a multiparameter flow cytometry assay for peripheral blood mononuclear cells. If acetyl-group removal from HDAC substrates is blocked we speculate that will lead to an overall increase in the number of acetylated proteins being the vast majority of these proteins the histones in cells population in peripheral blood. The blood leukocyte count will be obtained using a Coulter A^c-T Hematology analyzer. Multiparameter staining protocol will be adjusted from Chun and/or Ronzoni et al. In summary, whole blood will be collected at baseline, on day 5 of cycle 1, at cycle #6 and after the completion of panobinostat maintenance therapy. PBMCs (5-10x10^6) will be obtained by gradient separation on Ficoll-Paque. Aliquots of PBMs will be briefly incubated with Zombie Yellow (Biolegend) to stain and gate-out non-viable cells. Cells will then be washed and incubated with antibodies conjugated to methanol-resistant fluorophore (BD Horizon V450/Brilliant Violet-711-/FITC/Alexa Fluor 647) on a 2-tube/4-color panel for surface antigens: CD3/CD4/CD8/CD19 and CD3/CD7/CD45/CD14. Stained cells will be fixed in 2% formaldehyde for 30 min at 4ºC and then permeabilized in 100% ice-cold methanol for 10 minutes at 4ºC. After fixation and permeabilization, cells will be stained with anti-acetyl histone H3 and anti-acetyl tubulin, conjugated to PE and PerCP-Cy5.5, respectively. Events will be acquired on a FACSDiva flow-cytometer (BD) and analyzed on Kaluza v1.2 (Beckman Coutler) with appropriate controls. Gating strategies will be devised using surface markers to assess the level of acetyl histone H3 and acetyl tubulin on CD4 T-cells, CD8 T-cells, NK cells, B-cells, monocytes and neutrophils.

9.2 Assessment of immune response

Bone marrow research samples obtained (only for those who consent for screening research sample consents) will be analyzed to determine the presence of common multiple myeloma tumor associated antigens (TAAs) including survivin, WT-1, NY-ESO, and MAGE using immunohistochemistry (IHC) or polymerase chain reaction (PCR). Prior biopsy specimens may be requested if available, in order to perform IHC for the described TAAs. Research blood samples will be obtained prior to transplant, at baseline (prior to the initiation of maintenance), after 3 cycles of maintenance therapy, and after panobinostat maintenance

(after completing of therapy) to evaluate for the presence of T-cell precursors against individual patient's identified TAA using peptide pools.

As a standard of care, all autologous HCT recipients will receive heptavalent pneumococcal conjugate vaccine (PCV13, Prevnar^{TM}) at around 3 months from the time of transplant. We hypothesize that patients immunized with heptavalent pneumococcal conjugate vaccine, who then receive panobinostat maintenance therapy, may have augmented immune responses. (stan Each vaccine specific serotype IgG level will serve as a marker for immune response. We propose to measure following anti-pneumococcal IgG antibody serotype panel at baseline, at cycle #6 and after completion of maintenance (completion of 12 cycles) to assess immune reconstitution with panobinostat maintenance therapy. The antibody panel contains serotypes 1, 4, 5, 7F, 8, 9V, 9N, 12F and 18C. A positive response of IgG antibody is considered to be greater than or equal to 1 microgram/mL. Patients may also receive standard of care pneumococcal conjugate vaccine (usually at 6 months and 12 months after autologous HCT).

T cell response in the setting of panobinostat maintenance therapy will be evaluated at baseline, after cycle #3 and cycle #6, and after completion of maintenance therapy (completion of 12 cycles). Specifically we will measure the % of T1 cells and cytotoxic T cells specific for intracellular IFN-gamma production after co-culture of patients with T cells with the inactivated diphtheria conjugate (CRM197) which is a component of the pneumococcal conjugate vaccine.

In addition, we will evaluate the phenotype of T cells at baseline, after cycle #3 and #6, and after completion of maintenance therapy (completion of 12 cycles). We will employ flow cytometry panels. In brief, whole PBMCs will be stained with flow cytometry antibodies for CD3, CD4, CD8, CD62L, CD45RO, and CD95 in order to evaluate for naïve, effector memory, or central memory phenotype. We will also test for CD4, CD8, PD-1, PD-L1, CLTA-4, CD25, CD127, and FOXP3 to evaluate for costimulatory molecules and regulatory T cells.

9.3 High-throughput sequencing of CDR3 from IgH, IgK and IgL somatic rearrangements

Adaptive Biotechnologies have developed assays that use multiplex PCR to amplify rearranged CDR3 sequences from the adaptive immune receptor loci (T-cell receptors in T-cells, Immunoglobulins in B-cells) that exploit the capacity of high-throughput sequencing technology to sequence thousands to millions of CDR3 chains simultaneously in a sample. At all IG loci, forward primers were selected for each V segment, upstream of the recombination signal sequence (RSS), and reverse primers were selected for each J segment, downstream of the RSS. In the IGH assay forward primers are also selected upstream of the D segments, allowing for amplification of immature DJ rearrangements (Fig 1C). In the IGK assay a forward primer is also selected for iRSS, and a reverse primer for KDE, allowing for amplification of iRSS/KDE and V/KDE junctions (Fig 1H), as well as VJ CDR3 segments. The forward and reverse primers for each locus are separated by many thousands of base pairs in the germline, but each somatic rearrangement event brings one pair within 300 bp. The multiplex PCR reaction amplifies only these rearranged sequences, and incorporates external adaptor sequences allowing the amplified library to be directly sequenced.

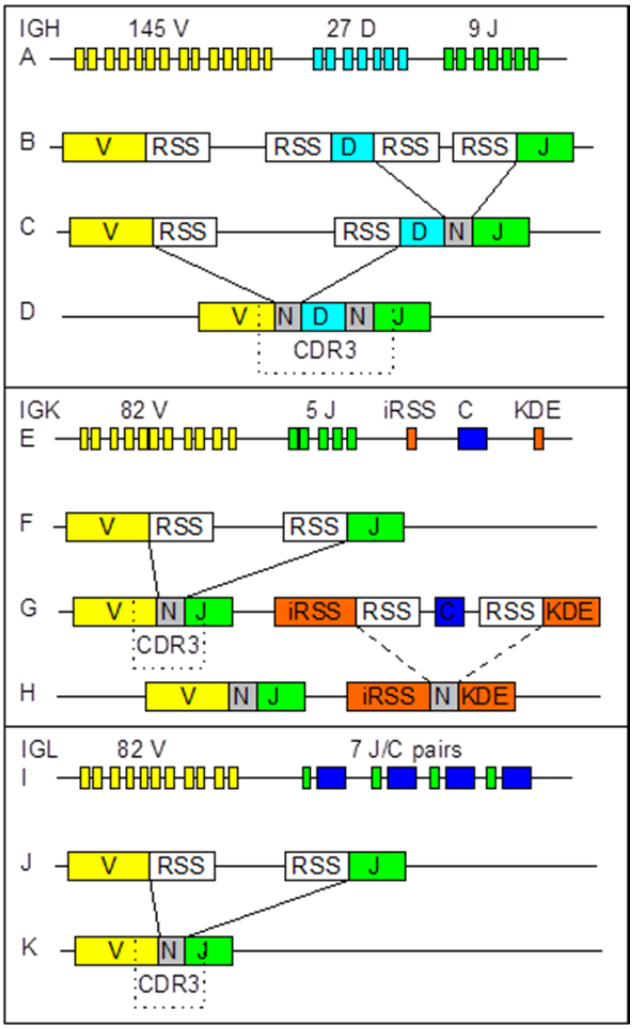


Figure 1: Somatic rearrangement of the IG loci.

Any multiplex PCR system is susceptible to amplification bias for specific templates, so they designed a panel of synthetic templates representing all possible V/J pairings at each locus.[104] Amplification and sequencing from an equimolar mixture of these synthetic templates allows them to directly measure amplification bias. In both assays, primer amplification effects are independent for forward and reverse primers, so primer concentrations are titered to minimize amplification differentials within the assay, yielding a final primer mix that amplifies all synthetic templates with between 0.5X and 2X cumulative yield after 35 cycles of PCR, relative to the median yield. The residual differential in amplification efficiency is highly

reproducible within each assay, so the frequency of each sequence after amplification can be computationally adjusted for the specific forward and reverse primer that amplified that clone, yielding a direct estimate of the frequency of each clonal CDR3 rearrangement in the starting template material. If the high-throughput sequencing is performed on a sample containing one million nucleated cells, then its sensitivity in that circumstance is estimated to be 1 in a million.

Sequencing CDR3 regions:

IGH CDR3 regions can be amplified and sequenced from DNA samples. Amplification and sequencing of *IGH* CDR3 regions will be carried out on the *ClonoSEQ*™ platform (Adaptive Biotechnologies, Seattle, WA). The sequences for *IGH* CDR3 regions are delineated according to the definition established by the International ImMunoGeneTics collaboration.[105,106] A standard algorithm is used to identify which V, D, and J segments contributed to each *IGH* CDR3 sequence and which V and J segments contributed to each CDR3 sequence.[105,106] Rearranged CDR3 sequences are classified as non-productive if insertions or deletions were identified that resulted in frame-shifts or premature stop-codons.

Bone marrow samples (with CD138 selected DNA) will be obtained prior to autologous HCT, prior to the initiation of HCT, at cycle #6 of maintenance and after completion of planned panobinostat maintenance therapy to evaluate myeloma clones. To identify index myeloma clones, archived FFPE bone marrow clot sections (prior to start of systemic chemotherapy) will be obtained at Moffitt Cancer Center.

Table 9-1 Research Sample Acquisition Schedule

	Pre-HCT	Pre-maintenance	Cycle #1 (days 1, 5)	Cycle #2	Cycle #3	Cycle #6	Cycle #9	End of study
Peripheral blood	1 tiger top/6 green top	1 tiger top/6 green top	1 tiger top/6 green top (day 1); 2 green top (day 5)	1 tiger top/6 green top	1 tiger top/6 green top	1 tiger top/6 green top	1 tiger top/6 green top	1 tiger top/6 green top
Bone marrow	1 tiger top/4 green top	1 tiger top/4 green top	-	-	-	-	-	1 tiger top/4 green top
Stem cell graft (Apheresis)	3mL in a 50mL falcon tube	-	-	-	-	-	-	-

10 Safety monitoring

10.1.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening

- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

10.1.2 Reporting

All SAEs will be reportedas assessed by the investigator. SAEs will be followed until resolution or until clinically relevant improvement or stabilization.

To ensure patient safety, every SAE with suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form as outlined per contractual agreement; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department.

The telephone and telefax number of the contact persons in the local department of Drug Safety and Epidemiology (DS&E) are included in the contractual agreement. The original

copy of the SAE Report Form and the fax confirmation sheet should be kept with the case report form documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

10.2 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the panobinostat any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

10.3 Data Safety and Monitoring Plan

The Data Safety & Monitoring Plan (DSMP) will ensure that this trial is well designed, responsibly managed, appropriately reported, and that it protects the rights and welfare of patients. The following internal and external review and monitoring processes provide oversight and active monitoring of this trial:

- The Principal Investigators (PI)

- The Scientific Review Committee (SRC)
- The Protocol Review and Monitoring Committee (PRMC);
- The Research Compliance Division (RCD) of the Cancer Center's Compliance Office;
- Institutional Review Board (IRB).

The protocol includes a section that specifies the following with respect to Adverse Event reporting: what constitutes an adverse event (versus what is a serious adverse event), the entities to which adverse events should be reported, the timing of this reporting, and the person or persons responsible for reporting. This includes prompt (within one day of knowledge of the event) reporting to the IRB for unanticipated risks to subjects and reporting in writing within five working days to the IRB and the supporting company (Novartis).

10.4 Initial and Ongoing Monitoring and Review

10.4.1 Principal Investigator (PI)

The PI of the study has primary responsibility for ensuring that the protocol is conducted as approved by the SRC and the IRB. The PI will ensure that the monitoring plan is followed, that all data required for oversight of monitoring are accurately reported to the Scientific Review Committee (SRC), Protocol Review and Monitoring Committee (PRMC) and IRB as required, and that all adverse events are appropriately reported.

10.4.2 The Scientific Review Committee (SRC)

The Cancer Center's internal Scientific Review Committee (SRC) provides for a formal internal peer review of all protocols and general scientific oversight of interventional clinical research. The Committee has a defined membership representing all of the major research divisions of the Cancer Center, including biostatisticians. All new protocol submissions must contain the required elements of the protocol, and must include a DSMP prior to approval by the Committee. The plan has to be appropriate for the phase and risk of the proposed study.

10.4.3 The Protocol Review and Monitoring Committee (PRMC)

The Protocol Review and Monitoring Committee (PRMC) will monitor this trial for safety, progress, protocol compliance, accrual, adverse event reporting, and data integrity. The membership of the PRMC includes physician representation from each program area and a biostatistician. In addition to the existing stopping rules, the PRMC is authorized to suspend a trial for non-compliance with a DSMP or as a result of audit findings deemed unacceptable.

The PRMC will report significant findings to the IRB, the supporting company (Novartis), and the applicable regulatory body. Interim meetings are scheduled to address specific issues that require immediate attention to ensure safety of research participants.

10.4.4 The Research Compliance Division of the Cancer Center's Compliance Office (RCD)

The Research Compliance Division (RCD) Office conducts internal audits of all clinical trials conducted at the Cancer Center and its affiliates. The purpose of the internal audit program is to:

1. Assure patient safety by monitoring compliance
2. Assure regulatory compliance by reviewing consent and adverse event reporting
3. Assure scientific value by monitoring accuracy and completeness of data collection
4. Monitor and coordinate research compliance activities associated with institutional and individual conflict of interest
5. Make recommendations for modification of research practices as necessary and provide education on issues that are critical to good research practices

Audits are conducted by the RCD in accordance with applicable regulatory standards. Investigator initiated trials, such as the one proposed here, receive the highest priority for audit. The RCD will conduct and report the findings of audits to the PMC in accordance with a protocol's annual review. The PRMC will determine the findings to be acceptable with minor deviations, acceptable with corrective action, or unacceptable with suspension or closure. The PRMC Chairperson will notify the IRB of the audit findings. The RCD will follow-up to ascertain whether corrective actions, which have been agreed to, are achieving the desired results. The PRMC will be informed of all significant open follow-up items. For those observations where no action has been taken, the Research Compliance Office will inform the PRMC and may conduct a focused audit.

11 Protocol amendments, or changes in study conduct

Any change or addition to this protocol requires a written protocol amendment that must be reviewed by Novartis and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the IRB. A copy of the written approval of the IRB must be provided to Novartis.

12 Data Review and Management

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by Novartis in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons Novartis must be notified and the IRB must be informed immediately. Data review and management

Internal Monitoring Plan Data will be captured in Oncore, Moffitt's Clinical Trials Database. Regulatory documents and case report forms will be reviewed routinely by the MCC Clinical Research Monitoring Core for accuracy, completeness and source verification of data entry, validation of appropriate informed consent process, adherence to study procedures, and reporting of SAEs and protocol deviations according to MCC Monitoring Policies.

12.1 Data collection and monitoring

Investigators must enter the information required by the protocol onto Case Report Forms (CRFs) for unexpected grades ≥ 3 adverse events and serious adverse events. Additional data to be captured may be identified at the time of study activation or review by ongoing monitoring committees.

13 Statistical methods

13.1 Statistical methods and data analysis

This is an open label study of 2 different panobinostat maintenance dosing schedules after autologous HCT in patients with multiple myeloma. There are 2 cohorts and patients will be enrolled sequentially to cohort A, then to cohort B. The sample size is 30 patients for this trial (15 for each cohort). We expect that at least 2/3 of each cohort will complete 12 cycles of maintenance panobinostat (regardless of dose modification) and will be evaluable for the primary endpoint. The widths of 95% confidence interval (CI) are 0.356, 0.438, 0.487, 0.514, and 0.522 when the proportions of patients tolerating 12 cycles of maintenance are 0.9, 0.8, 0.7, 0.6, and 0.5, respectively.

A patient who withdraws from the study due to reasons other than death, disease progression or toxicity will be replaced and is considered as non-evaluable for primary endpoint. The proportion of patients tolerating the therapy will be reported with 95% CI. All 30 patients are eligible for secondary endpoints. We will compute the overall response rates before the transplant, after autologous HCT, and after the completion of maintenance therapy, and at best response. The OS and PFS will be estimated using the Kaplan-Meier method. We will also report the incidences of all grades and grade ≥ 3 toxicities. The two-sided 95% CIs for

proportion, and OS and PFS will be computed using the Clopper-Pearson method and the Greenwood formula, respectively. In addition, the frequency of B cell precursor as well as other cell subsets, and their 95% CI will be evaluated using t-distribution. If data do not meet normality assumption, the power transformation (e.g., log-transformation) will be conducted. Those patients who are not in CR before the transplant would be most suitable for T-effector activity analysis. This will be examined by the paired t-test or the Wilcoxon signed-rank test, depending on the data distribution.

Relative dose intensity (RDI) represents the ratio of the amount of a drug actually delivered [actual dose intensity (DI)] to the amount planned (planned DI). The purpose of calculating RDI is to evaluate whether the planned DI of a chemotherapy treatment was actually achieved which may suggest the feasibility of planned treatment regimen. There are multitude of reports demonstrating a correlation between RDI and survival in cancer treatment.

RDI = (total dose received by the patient = mg)/(planned full dose of drug = mg)

Optimal RDI for maintenance therapy in multiple myeloma has not been fully defined though it would be a surrogate measure for treatment feasibility. We intend to calculate RDI on two cohorts both together and separately. Missed doses, dose reduction and dose delay will be reportedly per cohort. The investigator will review the tolerability as a whole for 2 different cohorts and report feasibility of each cohort.

13.1.1 Populations for analysis

This is an open-label, panobinostat maintenance therapy trial evaluating 2 different dosing schedules after autologous HCT in patients with multiple myeloma. Eligible patients have histologically confirmed multiple myeloma and have chemosensitive disease prior to starting the maintenance therapy. Fifteen patients per cohort will be enrolled and a total of 30 patients will be on this study.

13.1.2 Patient demographics/other baseline characteristics

Standard patient demographics and baseline disease characteristics will be collected: age, gender, immunophenotype, Durie-Salmon staging system, International Staging System, albumin, beta-2 microglobulin, myeloma risk stratification (high versus standard), prior systemic therapy, number of prior therapy, chemotherapy conditioning regimen and dose, and stem cell dose. Results will be tabulated.

13.1.3 Primary objective and hypothesis

The primary objective of this study is to determine the tolerability and safety profile of 2 different dosing schedules of single agent panobinostat maintenance therapy for a maximum of 12 cycles after autologous HCT in patients with chemosensitive multiple myeloma. We hypothesize that at least two-thirds of patients will be able to complete 12 cycles of intended maintenance therapy. The completion rate of 12 cycles of maintenance therapy in 15

evaluable patients will be reported along with 95% confidence intervals using the exact binomial distribution. We plan to calculate RDI for each cohort.

13.1.4 Secondary objective and hypothesis

The secondary objectives of the study are to evaluate following parameters in patients who receive panobinostat maintenance therapy after autologous HCT: overall response rate, best response rate, 2-year PFS and 2-year OS. The exploratory secondary objectives include evaluation of minimal residual disease, frequency of B cell precursors and immune subsets, protein acetylation, and immune response against pneumococcal vaccines and CRM. The association of minimal residual disease, B cell precursors, and immune response with response, PFS and OS will be evaluated using the Cox proportional hazards regression model.

13.1.5 Early stopping rule

No early stopping rule is considered in this study but the safety and efficacy data will be continuously monitored by PI and the supporting company (Novartis). Patient accrual will be temporarily suspended if the completion rate of maintenance therapy at the end of 12 cycles is equal to or less than 60% or if the non-hematologic grade 3 or 4 toxicity rate is 40% or higher. The PI and the supporting company (Novartis) will review safety data, and the study may be early terminated based on the review results.

14 Procedures and instructions

14.1 Publication of results

Any formal presentation or publication of data from this trial may be published after review and comment by Novartis and prior to any outside submission. Novartis must receive copies of any intended communication in advance of publication (at least fifteen working days for presentational materials and abstracts and thirty working days for manuscripts). These requirements acknowledge Novartis' responsibility to provide peer input regarding the scientific content and conclusions of such publications or presentations. Principal Investigation/Institution shall have the final authority to determine the scope and content of its publications, provided such authority shall be exercised with reasonable regard for the interests of Novartis and, in accord with the trial contract and shall not permit disclosure of Novartis confidential or proprietary information.

14.2 Disclosure and confidentiality

The investigator agrees to keep all information provided by Novartis in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by Novartis (investigators' brochures and other material) will be stored appropriately to ensure their confidentiality. The information provided by Novartis to the investigator may not be disclosed to others without direct written authorization from Novartis, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

14.3 Discontinuation of study

Novartis reserves the right to discontinue any study under the conditions specified in the clinical trial agreement.

15 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and the principles of Good Clinical Practice, as described in Novartis standard operating procedures and:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects).

The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

15.1 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. Any amendments to the protocol, other than administrative ones, must be reviewed by Novartis approved by this committee.

15.2 Informed consent

The investigators and/or designee (including clinical trial coordinators or advanced practice professionals) must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally

appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB/IEC/REB approval.

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Appendices

16.1 Appendix A: Medications requiring caution for potential drug-drug interactions

16.1.1 Medications which have a risk of causing Torsades de pointes ventricular arrhythmia should be avoided

Patients who are currently receiving treatment of the medications in Table 17-1 and cannot either discontinue from this treatment or switch to an alternative medication prior to enrollment in a panobinostat clinical study, will be excluded from the study. Patients may not begin panobinostat treatment with any of the medications listed in Table 17-1 unless this is discussed with the supporting company (Novartis) and an approval is granted by the supporting company (Novartis). The supporting company (Novartis) may agree to temporarily discontinue panobinostat treatment (e.g., for 72 hours) during administration with these drugs or withheld medications in Table17-1 for at least 72 hours when panobinostat is to be administered.

NOTE: It is of great importance to avoid combining drugs listed below in Table 17-1 and Table 17-2 (CYP3A inhibitors) especially in the presence of electrolyte abnormalities, notably decreased potassium or magnesium levels commonly associated with diuretic usage.

In general, medications listed in Table 17-1 should be avoided while medications listed in Tables 17-2 and 17-3 are to be used with caution when co-administered with panobinostat. Please select the most stringent recommendation for concomitant medications (i.e., to be avoided) which are common among the tables (e.g., erythromycin, clarithromycin)

Table 17-1 Medications which have a risk of causing Torsades de pointes to be avoided

All **Class IA antiarrhythmics** • **quinidine** • **procainamide** • **disopyramide** • **any other class IA antiarrhythmic drug**
All **Class III antiarrhythmics** **amiodarone** **sotalol** **bretylium** **disopryramide** **dofetilide** **ibutilide** **any other class III antiarrhythmic drug**

Antibiotics **Macrolide antibiotics*** • **erythromycin** • **clarithromycin** • **telithromycin** **Quinolone antibiotics*** **sparfloxacin**
Antipsychotics **thioridazine** **mesoridazine** **chlorpromazine** **pimozide**
Antimalarials • **halofantrine** • **chloroquine**
Miscellaneous drugs • **arsenic trioxide** • **astemizole** • **bepridil** • **domperidone** • **levomethadyl** • **methadone** • **pentamidine** • **droperidol**
***Note: azithromycin, ciprofloxacin, levofloxacin, pefloxacin, ofloxacin, tosufloxacin, difloxacin, temafloxacin, fleroxacin, acrosoxacin, nalidixic acid and enoxacin are allowed.**

This is not a comprehensive list of medications which may prolong the QT interval or have a risk of causing Torsades de pointes. This list of medications was developed in collaboration with an external cardiology consultant, and represents those medications which are deemed to have an unacceptable risk of co-administration with panobinostat.

The following website may be referenced as a supplemental guide for drugs which have been associated with Torsades de pointes or prolonging the QT interval but at this point lack substantial evidence for causing Torsades de pointes:

http://www.qtdrugs.org/medical-pros/drug-lists/drug-lists.htm#.

Medications listed on the website which do not appear in Table 17-1 above may be used with caution at the discretion of the investigators.

The serotonin ($5HT_3$) antagonists, often used as antiemetics, such as ondansetron, dolasetron, (also are known CYP2D6 substrates, see Table 17-3), or granisetron have been associated with Torsades de points and QT prolongation but have not been shown to cause Torsades de pointes. Therefore, $5HT_3$ antagonists are not per se prohibited but close monitoring for signs and symptoms of QT prolongation is recommended. Caution is to be exercised when using these or other agents that may prolong QT intervals in combination with panobinostat.

16.1.2 Medications which are known strong CYP3A4/5 inhibitors to be used with caution

Panobinostat is a substrate of CYP3A4 with minor involvement of CYP2D6, and CYP2C19 in *in vitro* evaluation of its metabolism. Thus, a clinical drug-drug interaction study was conducted using ketoconazole, a strong CYP3A inhibitor, in combination with panobinostat in study CLBH589B2110.

Multiple ketoconazole doses at 400 mg increased C_{max} and AUC of panobinostat by 1.6- and 1.8-fold, respectively, but with no change in T_{max} or half-lives in 14 cancer patients. The less than 2-fold increase in panobinostat AUC upon co-administration of a strong CYP3A inhibitor is considered a weak drug inhibition and not clinically relevant, as panobinostat doses at least 2-fold greater than the evaluated 20 mg dose (i.e., 40 mg and 60 mg) have been safely administered in patients. Thus, co-administration of panobinostat with a moderate or weak CYP3A inhibitor is allowed. However, clinical monitoring of signs and symptoms of panobinostat treatment related adverse events is recommended when long-term (≥ 1 week) concomitant administration of any strong CYP3A inhibitors and panobinostat is medically indicated or investigated in a clinical study.

Patients with impaired liver function (as defined by NCI CTEP criteria)[1] are recommended not to receive panobinostat concomitantly with strong CYP3A inhibitors because potential interaction has not been established in this population.

Table 17-2 Medications which are known strong CYP3A4/5 inhibitors to be used with caution

Macrolide antibiotics* • **clarithromycin** • **telithromycin** • **troleandomycin** • **erythromycin**
Antifungals (azoles)* • **ketoconazole**

• **itraconazole** • **fluconazole**
Antidepressants • **nefazodone**
Calcium channel blockers* • **diltiazem** • **verapamil**
HIV protease inhibitors: • **indinavir** • **nelfinavir** • **ritonavir** • **saquinavir**
Miscellaneous drugs or products • **aprepitant** • **grapefruit product or juice**
*** azithromycin, voriconazole, regular orange juice and dihydropyridine calcium channel blockers (e.g. amlodipine, felodipine, nicardipine, nifedipine) are allowed.**

This is not a comprehensive list of medications which may inhibit CYP3A4/5. Additional updated versions with moderate and weak CYP3A inhibitors, which are meant to be used as a guide, may be found at the following website: http://medicine.iupui.edu/clinpharm/DDIs

16.1.3 Medications which are known CYP2D6 substrates to be used with caution

Panobinostat was also shown to be a CYP2D6 inhibitor (K_i 0.17 μM) *in vitro*. Thus, clinical drug-drug interaction study with panobinostat as CYP2D6 inhibitor and dextromethorpan as CYP2D6 substrate was recently conducted in study CLBH589B2109.

Multiple panobinostat doses increased C_{max} and AUC of dextromethorphan by a mean of 1.8- and 1.6-fold respectively, but with no change in T_{max} in 17 cancer patients. An approximately 2-fold increase in dextromethorphan AUC upon co-administration with panobinostat indicated that *in vivo* CYP2D6 inhibition of panobinostat is weak.

As the study was conducted using a sensitive CYP2D6 substrate which resulted in a weak inhibition, drugs with a large therapeutic index such as anti-emetics, anti-hypertensives, and anti-depressants are generally safe to be co-administered with panobinostat.

Patients should be carefully monitored for potential signs and symptoms of toxicity and may require dose titration or dose reduction of a sensitive CYP2D6 substrate which also have a

narrow therapeutic window (e.g., the ratio of toxicity exposure is ≤ 2-fold higher than the efficacious or therapeutic exposure).

Table 17-3 Medications which are known CYP2D6 substrates to be used with caution

Beta blockers (listed below):	**Antipsychotics** (listed below):
carvedilol	aripiprazole
metoprolol	haloperidol
propafenone	perphenazine
timolol	risperidone
Antidepressants (listed below):	thioridazine
amitriptyline	zuclopenthixol
chlormipramine	amphetamine
desipramine	alprenolol
imipramine	bufuralol
fluoxetine	chloropheniramine
paroxetine	**Antiarrhythmics** (listed below):
venlafaxine	quinidine
bupropion	lidocaine
duloxetine	mexiletine
Antiemetics (listed below):	propafenone
dolasetron	**Others**:
ondansetron	oxycodone
metoclopramide	codeine
	hydrocodone
	terbinafine
	promethazine
	tamoxifen
	tramadol

This is not a comprehensive list of CYP2D6 substrates. Additional updated versions of this list, which are meant to be used as a guide, may be found at the following website: http://medicine.iupui.edu/clinpharm/DDIs

Reference:

1. Synold TW, Takimoto CH, Doroshow JH, Gandara D, Mani S, Remick SC, Mulkerin DL, Hamilton A, Sharma S, Ramanathan RK, Lenz HJ, Graham M, Longmate J, Kaufman

BM, Ivy SP. Dose-Escalating and Pharmacological Study of Oxaliplatin in Adult Cancer Patients with Impaired Hepatic Function: A National Cancer Institute Organ Dysfunction Working Group Study, Clin Cancer Res. 2007 *13;* 3660

16.2 Appendix B: Criteria for Symptomatic Multiple Myeloma

All three required:

1. Monoclonal plasma cells in the bone marrow ≥ 10% and/or presence of a biopsy-proven plasmacytoma
2. Monoclonal protein present in the serum and/or urine[a]
3. Myeloma-related organ dysfunction (1 or more)[b]
   - (C) Calcium elevation in the blood (serum calcium > 10.5 mg/L or upper limit of normal)
   - (R) Renal insufficiency (serum creatinine > 2 mg/dL)
   - (A) Anemia (hemoglobin < 10 g/dL)
   - (B) Lytic bone lesions or osteoporosis[c]

*Note: These criteria identify Stage IB and Stages II and III A/B myeloma by Durie-Salmon stage. Stage IA becomes smoldering or indolent myeloma.

[a]If no monoclonal protein is detected (nonsecretory disease), then ≥30% monoclonal bone marrow plasma cells and/or a biopsy-proven plasmacytoma required.
[b]A variety of other types of end organ dysfunctions can occasionally occur and lead to a need for therapy. Such dysfunction is sufficient to support classification as myeloma if proven to be myeloma-related.
[c]If a solitary (biopsy-proven) plasmacytoma or osteoporosis alone (without fractures) are the sole defining criteria, then ≥30% plasma cells are required in the bone marrow.

Reference:

*Myeloma management guidelines: a consensus report from the Scientific Advisors of the International Myeloma Foundation. *The Hematology Journal* 2003;4:379-398

16.3 Appendix C: Uniform Response Reporting Criteria for Multiple Myeloma by the International Myeloma Working Group (IMWG)

Response subcategory	*Response Criteria*
sCR[1]	• CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or 2- to 4-color flow cytometry
CR[2]	• Negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas, and < 5% plasma cells in bone marrow
VGPR[2]	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-component plus urine M-component < 100 mg per 24 hours
PR	• ≥ 50% reduction of serum M-protein and reduction in 24 hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours • If the serum and urine M-protein are not measurable, a decrease ≥ 50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. • If serum and urine M-protein and serum FLC are not measurable, and serum free light assay is also not measurable, ≥ 50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% • In addition to the above listed criteria, if present at baseline, ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
SD	• Not meeting criteria for CR, VGPR, PR, or PD
PD[1]	• Increase of 25% from lowest response value in any of the following: - Serum M-component (absolute increase must be ≥ 0.5 g/dL) - Urine M-component (absolute increase must be ≥ 200 mg/24 h) - Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL) - Only in patients without measurable serum and urine M protein levels and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute percentage must be ≥ 10%) - Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas - Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder

Footnotes:

1: Clarifications to IMWG criteria for coding PD: Bone marrow criteria for PD are to be used only in patients without measurable disease by M protein and by FLC levels; “25% increase” refers to M protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia and the “lowest response value” does not need to be a confirmed value.

2: Clarifications to IMGW criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such patients requires a > 90% decrease in the difference between involved and uninvolved FLC levels.

Reference:

Rajkumar SV et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood* 2011; 117:4691-4694

16.4 Appendix D: ECOG Performance Status Score

SCORE	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

16.5 Appendix E: Karfnosky Performance Score

Percentage	
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most of his/her needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled, hospitalization indicated. Death not imminent
20	Very sick, hospitalization necessary, active supportive treatment necessary
10	Moribund, fatal processes, progressing rapidly
0	Dead

Reference:

Karnofsky DA: Meaningful clinical classification of therapeutic responses to anti-cancer drugs. Editorial: *Clin Pharmacol Ther* 2:709-712, 1961.