Phase 1b dose escalation study of oral quisinostat, a histone deacetylase inhibitor, in combination with bortezomib and dexamethasone for patients with relapsed multiple myeloma

Abstract 8530

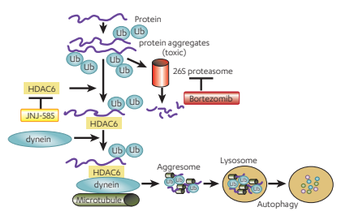
X. Leleu,[1] C. Touzeau,[2] L. Benboubker,[3] T. Facon,[1] M. Delain,[3] N. Fourneau,[4] C. Phelps,[5] A. Forslund,[4] P. Hellemans,[4] H. Smit,[4] J. Badamo-Dotzis,[6] P. Moreau[2]

[1]Hôpital Claude Huriez, CHRU de Lille, Service des Maladies du Sang, Lille, France; [2]Hôpital Hôtel Dieu, CHU Nantes, Service d'Hématologie, Nantes, France; [3]CHRU Bretonneau, Centre H. Kaplan, Service Hématologie CHU Tours-Hôpital Bretonneau, Tours, France; [4]Janssen Research & Development, LLC, Beerse, Belgium; [5]Janssen Research & Development, LLC, Raritan, NJ, USA; [6]Quintiles Transnational, Moulineaux, France

BACKGROUND

- Clinical outcomes for patients with multiple myeloma (MM) have improved in recent years due to the use of immunomodulatory drugs and proteasome inhibitors. Nevertheless, most patients will relapse or become refractory to these agents[1]
- Proteasome inhibitors (eg, bortezomib) cause accumulation of misfolded ubiquitinylated proteins, resulting in apoptosis (**Figure 1**).[2] One mechanism of resistance to bortezomib is the upregulation of aggresome formation, an alternative store for misfolded proteins. Histone deacetylase (HDAC) 6 is required for the transport of misfolded proteins to the aggresome[3]

Figure 1. Synergistic mode of action of bortezomib and quisinostat[2]



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- Bortezomib has been shown to downregulate HDAC1–3 in MM cell lines[4]
- Quisinostat is a novel hydroxamate, second-generation, potent, orally available pan HDAC inhibitor that has demonstrated sub-nM potency against HDAC 1, 2, 4, and low nM potency against HDAC 3, 5, and 6–9.[5] Quisinostat has excellent tissue distribution properties,[6] and a broad spectrum of preclinical antitumor activity[6,7]
- Quisinostat has demonstrated antitumor activity in vitro in MM cell lines and in primary MM patient samples.[8] Quisinostat has demonstrated potent antitumor activity in murine models of MM as single agent and in combination with bortezomib[9,10]
- The recommended phase 2 dose for quisinostat as a single agent was determined as 12 mg on days 1, 3, and 5 of each treatment week[11]

OBJECTIVES

Primary

- To determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of quisinostat in combination with bortezomib and dexamethasone

Secondary

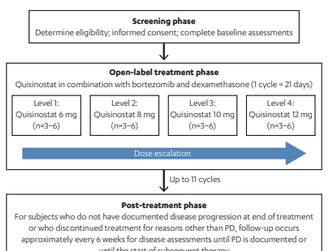
- To determine overall response rate (ORR)
- To determine the duration of response (DOR)
- To assess the pharmacokinetics (PK) of quisinostat in the presence of bortezomib
- To assess pharmacodynamic markers of quisinostat and bortezomib activity

METHODS

Study design

- Open-label, multicenter, phase 1b study in accordance with a "3 + 3" escalation design (**Figure 2**)

Figure 2. Study flow chart



Treatment schedule

- Patients received quisinostat, administered orally, at escalated doses (6, 8, 10, and 12 mg) on days 1, 3, and 5 of each treatment week
- Bortezomib was administered by subcutaneous injection at a dose of 1.3 mg/m^2 on days 1, 4, 8, and 11 of each 21-day cycle (cycles 1–8) and on days 1, 8, 15, and 22 of each 35-day cycle (cycles 9–11)
- Dexamethasone was administered orally at a dose of 20 mg on the day of and the day after bortezomib

Eligibility criteria

- Inclusion: adults aged ≥18 years; measurable or secretory MM, which has relapsed or progressed following prior systemic antineoplastic therapy; Eastern Cooperative Oncology Group (ECOG) performance status score ≤2; left ventricular ejection fraction (LVEF) within normal limits; adequate renal, hepatic, and bone marrow function
- Exclusion: prior HDAC inhibitor therapy; ≥3 previous lines of therapy; peripheral neuropathy or neuralgia grade (G) ≥2; presence of cardiac risk factors (angina/myocardial infarction within 12 months, congestive heart failure New York Heart Association class II–IV; significant rhythm or conduction abnormality); QTcF >450 ms in males/ >470 ms in females

Safety monitoring, DLT, and MTD

- Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.0
- Standard dose modification guidelines for bortezomib and dexamethasone and study-specific dose modification guidelines for quisinostat were used
- DLTs were defined as:
  - Complete treatment interruption of >7 days for G ≥2 toxicity
  - ≥G3 nonhematological nonhematological toxicity (excluding G3 nausea and vomiting responsive to anti-emetics; G3 diarrhea responsive to treatment; G3 fatigue/asthenia unless persisting for 7 days after stopping quisinostat)
  - G4 hematological toxicity defined as G4 neutropenia >7 days, febrile neutropenia; G4 thrombocytopenia >7days except when responding to transfusion support
- MTD was defined as the highest dose at which <33% of patients experienced DLT

Efficacy

- Disease response was assessed according to International Myeloma Working Group (IMWG) 2009 criteria[12]

PK and biomarkers

- PK was assessed during cycle 1 on days 1 (quisinostat alone), 2 (bortezomib alone), and 8 (combination of quisinostat and bortezomib)
- Peripheral blood mononuclear cells (PBMCs) and circulating MM cells (CMMCs) were collected pre- and postdose during cycles 1 (day 1 and day 8 [only PBMCs]) and 2 (day 1)
  - CMMCs may be used for monitoring response
  - Acetylated histone 3 (AcH3) was measured in PBMCs. An increase in AcH3 indicates target inhibition of Class I HDAC enzymes

RESULTS

- A total of 18 patients were enrolled and received combination therapy. Three patients each received quisinostat 6 and 8 mg, respectively, and 6 patients each received quisinostat 10 and 12 mg, respectively
- Baseline patient characteristics are summarized in **Table 1**

Table 1. Demographics and baseline characteristics

Characteristic	Total (n=18)
Age, y Median (range)	69 (50–82)
Gender, n (%) Female Male	8 (44) 10 (56)
ECOG performance status, n (%) 0 1 2	8 (44) 9 (50) 1 (6)
Multiple myeloma stage at entry, n (%) IA IIIA	2 (11) 16 (89)
No. of lines of prior therapy, n (%) 1 2 3	7 (39) 9 (50) 2 (11)
Prior bortezomib therapy Yes No	9 (50) 9 (50)

DLT

- At the 12 mg quisinostat dose level, 2 patients had DLT
  - An 82-year-old female patient with G3 QTcF prolongation and TdP in cycle 1 qualifying as DLT. A few days after stopping all study drugs she experienced an acute episode of hypotension G3 and dyspnea G3. Subsequently she developed septic shock and died
  - A 77-year-old male patient developed asymptomatic atrial fibrillation G3 during cycle 1, which persisted after discontinuation of quisinostat
- The MTD for quisinostat in combination with bortezomib and dexamethasone was established as 10 mg given on days 1, 3, and 5 of each treatment week

Safety

- Drug-related AEs (all-grade) are shown in **Table 2**; most common AEs were asthenia (56%) and thrombocytopenia (50%)
- Drug-related AEs with worst toxicity ≥G3 are shown in **Table 3**; most common ≥G3 AEs were thrombocytopenia (39%), asthenia (11%), and insomnia (11%)
- Cardiac toxicity was observed in 3 subjects in the 12- and 10-mg dose cohorts
  - Two events qualified as DLT (detailed above)
  - A 56-year-old female patient experienced cardiac arrest in cycle 6 due to ventricular fibrillation. After resuscitation and admission to ICU she recovered without sequelae
- Hematological toxicity (≥G3) is shown in **Table 4**. Dose reduction or interruption of bortezomib was required for thrombocytopenia (≥G3) in 4 patients at dose levels of ≥10 mg
- Of 18 patients, 5 (27.8%) completed 11 cycles of treatment; 12 patients prematurely discontinued study treatment (3 due to AEs, 6 due to lack of efficacy, and 3 refused further therapy); 1 patient is currently on ongoing therapy (cycle 6)
- Dose reduction of quisinostat was required in 4 patients due to asthenia

Activity

- Best overall response is shown in **Table 5**
- Overall, the duration of response ranged from 1.9 to 16.7 months

Preliminary PK data

- Concentration of quisinostat in plasma (ng/mL) when given alone or in combination with bortezomib is shown in **Figure 3**
- AUC from zero time until the last measurable concentration (AUC_{last}) of bortezomib alone and in combination with quisinostat is shown in **Figure 4**

Table 2. Drug-related* AEs in >20% of subjects

	G1/2, n	G3/4, n	Total, N	Total, %
Asthenia	8	2	10	56
Thrombocytopenia	2	7	9	50
Diarrhea	8	0	8	44
Peripheral edema	7	0	7	39
Peripheral sensory neuropathy	7	0	7	39
Constipation	6	0	6	33
Insomnia	3	2	5	28
Neuralgia	5	0	5	28
Vomiting	4	1	5	28
Nausea	3	1	4	22

Abbreviation: G, grade.
*Drug-related = Related to quisinostat, bortezomib, or dexamethasone

Table 3. Drug-related* AEs ≥G3

	Thrombocytopenia	Asthenia	Insomnia	Atrial fibrillation	Cardiac arrest	Abdominal pain	Nausea	Vomiting	Dyspnea	Pneumopathy	Herpes zoster	QT prolongation	Hypotension
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
6 mg (n=3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
8 mg (n=3)	2 (67)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
10 mg (n=6)	2 (33)	2 (33)	1 (17)	0 (0)	1 (17)	1 (17)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
12 mg (n=6)	3 (50)	0 (0)	1 (17)	1 (17)	0 (0)	0 (0)	1 (17)	1 (17)	1 (17)	1 (17)	1 (17)	1 (17)	1 (17)
Total (n=18)	7 (39)	2 (11)	2 (11)	1 (6)	1 (6)	1 (6)	1 (6)	1 (6)	1 (6)	1 (6)	1 (6)	1 (6)	1 (6)

Abbreviation: G, grade.
*Drug-related = Related to quisinostat, bortezomib, or dexamethasone

Preliminary biomarker data

- Most patients (9/12) showed a decrease in the number of CMMCs after 1 cycle (**Figure 5**)
- An increase in AcH3 was observed in 5 of 6 patients in at least 1 timepoint (**Figure 6**).

Table 4. Hematological toxicity ≥G3

Quisinostat dose	Hb	WBC	ANC	Platelets
	n (%)	n (%)	n (%)	n (%)
6 mg (n=3)	0 (0)	0 (0)	0 (0)	1 (33)
8 mg (n=3)	0 (0)	0 (0)	0 (0)	2 (67)
10 mg (n=6)	0 (0)	1 (17)	2 (33)	3 (50)
12 mg (n=6)	0 (0)	0 (0)	1 (17)	3 (50)
Total (n=18)	0 (0)	1 (6)	3 (17)	9 (50)

Abbreviation: G, grade; Hb, hemoglobin; WBC, white blood cells; ANC, absolute neutrophil count.

Figure 3. Mean plasma concentration of quisinostat when given alone (day 1) and in combination with bortezomib (day 8)

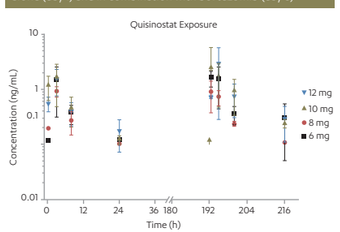
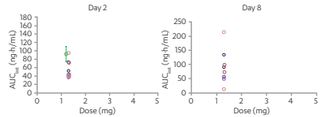


Figure 4. AUC from zero time until the last measurable concentration (AUC_{last}) of bortezomib alone (day 2) and bortezomib in combination with quisinostat (day 8)



Cohort 1 Cohort 2 Cohort 3 Cohort 4
Green circle represents data from CAN10004 study (bortezomib at same dose and administration route) to provide a known population mean value).

Figure 5. Number of CMMCs per 4mL blood on cycle 1, day 1, and cycle 2, day 1 (n=12)

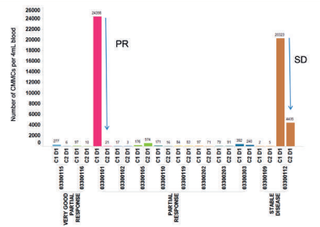


Figure 6. Percentage change from baseline in acetylated histone 3 in peripheral blood mononuclear cells during the first cycle for patients according to best response (n=6)

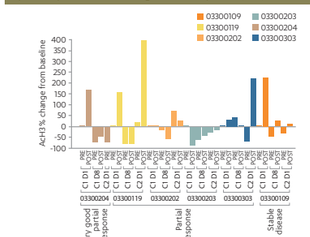


Table 5. Best overall response

Patients with response, n (%)	6 mg n=3 n(%)	8 mg n=3 n(%)	10 mg n=6 n(%)	12 mg n=5* n(%)	Total n = 17 n(%)
Complete response (CR) Stringent complete response	0 0	1 (33) 0	0 0	0 0	1 (6) 0
Partial response (PR) Very good partial response (VGPR)	3 (100) 0	2 (67) 0	4 (67) 1 (17)	5 (100) 2 (40)	14 (82) 3 (18)
Stable disease	0	0	2 (33)	0	2 (12)
Progressive disease	0	0	0	0	0
Not evaluable	0	0	0	0	0
Objective response (CR + PR)	3 (100)	3 (100)	4 (67)	5 (100)	15 (88)

*1 patient in the 12-mg dose cohort died on day 14 of cycle 1 and is therefore not included;
**including VGPR

CONCLUSIONS

- The MTD of quisinostat in combination with bortezomib and dexamethasone is 10 mg
- The most common G3/4 drug-related AE was thrombocytopenia (39%)
  - In a phase III study of bortezomib, grade 3/4 thrombocytopenia was observed in 13–19% of patients[13]
- Quisinostat doses of ≥10 mg in combination with bortezomib and dexamethasone were associated with cardiac toxicity
- The combination of quisinostat, bortezomib, and dexamethasone is active in the treatment of relapsed MM. 1 complete response and 14 partial responses were observed resulting in an ORR of 88%
  - This compares favorably with the ORR of subcutaneous bortezomib in relapsed MM in a phase III study (42%)[13]
- Quisinostat systemic exposures in the presence of bortezomib were comparable to those observed in quisinostat monotherapy; bortezomib exposure appeared similar to previously observed exposures
- Based on the limited systemic exposure data no apparent drug-drug interaction could be observed
- In general, the number of CMMCs decreased after 1 cycle of treatment. An increase in AcH3 was observed indicating a Class I HDAC target effect

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REGISTRATION

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