A Phase 1/2 Study of Carfilzomib as a Replacement for Bortezomib for Multiple Myeloma (MM) Patients (pts) Refractory to a Bortezomib-Containing Combination Regimen

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Background

- **Carfilzomib** is a novel proteasome inhibitor: a tetrapeptide epoxyketone-based inhibitor specific for the chymotrypsin-like active site of the 20S proteasome
  - This drug results in sustained inhibition of the proteasome with reduced off-target effects compared to the proteasome inhibitor bortezomib
- Single-agent carfilzomib has proven effective for the treatment of relapsed/refractory (R/R) multiple myeloma (MM)[1-4]
- Carfilzomib has also shown promise as an agent in combination regimens to treat R/R MM patients[5] as well as newly diagnosed patients[6]
- Recent data has suggested that single-agent carfilzomib can produce a response for MM patients refractory to previous regimens containing bortezomib[7]
  - Patients were treated with carfilzomib via 30-minute IV infusion
  - Pre-treated patients who received 36-70 mg/m² of carfilzomib were shown to respond, even if prior regimens contained bortezomib
  - The treatment was well tolerated at 56 mg/m² with no episodes of worsening peripheral neuropathy or hepatoxicity

Purpose

- For MM patients who have relapsed within 12 weeks of receiving or were refractory to their most recent bortezomib-containing regimen, we investigated the safety and efficacy of using the same combination regimen with carfilzomib replacing bortezomib. The regimen was identical to their prior bortezomib-containing regimen except that carfilzomib replaced bortezomib.

Design

- Phase 1/2 multi-center, open-label, nonrandomized study
- Planned enrollment: 45 patients
  - Group A: treatment contains immunomodulatory drugs (N = 15)
  - Group B: treatment does not contain immunomodulatory drugs (N = 30)

Eligible patients

- Currently have MM with measurable disease
- Age ≥ 18 years, life-expectancy ≥ 3 months, ECOG performance status 0-2
- Progressed while receiving their most recent bortezomib-containing regimen or relapsed within 12 weeks of the last dose of the most recent bortezomib-containing regimen
  - Received at least four doses of bortezomib at ≥ 1.0 mg/m²
  - ≤ 4 weeks per cycle
  - Bortezomib-containing regimen must have contained bortezomib and any combination of the following:
    - alkylating agent (melphalan, cyclophosphamide or bendamustine)
    - anthracycline (doxorubicin or pegylated liposomal doxorubicin [PLD])
    - Immunomodulatory drugs (thalidomide and/or lenalidomide)
    - steroids (prednisone, dexamethasone or methylprednisolone)

Assessments

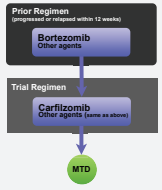
- Responses were determined according to a modified version of the European Blood and Marrow Transplantation (EMBT) criteria for evaluating disease response and progression among patients with MM,[8] utilizing some components of the updated International Myeloma Working Group (IMWG) criteria[9]
  - Disease assessment occurred between D22-25 of each cycle
- Safety assessments graded by Common Terminology Criteria for Adverse Events (CTCAE) v4.0

MTD

- Maximum-tolerated dose (MTD) was determined as the highest dose achieved with no more than 1 dose-limiting toxicity (DLT) among 6 patients per unique combination regimen (only 3 patients required if no DLT).
  - DLT defined as: G3 or G4 hematological toxicity, thrombocytopenia with G3 or G4 hemorrhage; G3 or G4 nausea or vomiting refractory to anti-emetic therapy; G3 or G4 diarrhea or constipation refractory to anti-diarrheal or constipation therapy; any study treatment-related G2, G3, or G4 non-hematological toxicity; any drug-related death

Drug Administration

- Carfilzomib on a 28-day cycle replaced bortezomib in the qualifying bortezomib-containing regimen
  - Otherwise, the regimen was identical (drug[s], dose and schedule) to the patient's previous bortezomib-containing regimen
- Carfilzomib administered IV on days 1, 2, 8, 9, 15, and 16 on a 28-day cycle
  - 20 mg/m² (cycle 1)
  - Escalated from 27 to 36 to 45 mg/m² during cycles 2, 3 and 4, respectively (assuming no DLT)
  - MTD determined separately for each unique regimen
  - Once MTD has been determined per regimen, additional patients enrolled in Phase 2 portion



Results

*Data Cutoff: 10/9/12

Demographics

- 33 patients actively enrolled with 29 evaluable for efficacy
- Patients received a median of 5 prior regimens, with a median of 2 prior bortezomib-containing regimens
- Patients were largely unresponsive to the bortezomib-containing regimen (≥ MR: 24%)

Table 1. Patient demographics

Patient Demographics	
No. enrolled	33
No. currently evaluable for safety	33
No. currently evaluable for efficacy	29
Median age in years (range)	67 (47-79)
Sex (M,F)	22, 11
Prior Regimens	
Median no. of prior regimens (range)	5 (1-18)
Median no. of prior bortezomib-containing regimens (range)	2 (1-13)

Table 2. Combination regimen and trial details

Trial Regimen Details	
Regimen in addition to carfilzomib (grouped by active agents)	**n/33 (%)**
Dexamethasone	10 (30.3%)
Melphalan	1 (3%)
Cyclophosphamide+ascorbic acid	5 (15.2%)
Cyclophosphamide+ascorbic acid +dexamethasone	1 (3%)
Bendamustine	3 (9.1%)
Bendamustine+methylprednisolone	1 (3%)
PLD	1 (3%)
PLD+dexamethasone	5 (15.2%)
Thalidomide+dexamethasone	1 (3%)
Lenalidomide	2 (6.1%)
Lenalidomide+dexamethasone	1 (3%)
Lenalidomide+dexamethasone+PLD	1 (3%)
Thalidomide+lenalidomide+bendamustine +methylprednisolone+clarithromycin	1 (3%)
Regimen details	
Previous cycle length: 21-day, 28-day	9, 24
Median no. of treatment cycles completed (range)	3 (0-16)
Median no. of total cycles completed w/ maintenance (range)	3 (0-24)
Median follow-up time in months (range)	7.75 (1.2-16.7)
No. of unique combinations of agents used in trial	13

Dexamethasone
Alkylating agent
PLD
Immunomodulatory drug

- Treatment regimens consisted of 13 unique combinations of agents
  - Dosage and schedule variations among the 33 patients included 27 unique combination regimens
  - We have enrolled 27 of 30 planned non-immunomodulatory and 6 of 15 planned immunomodulatory patients so far
- Patients have completed a median of 3 cycles so far
- To date, one MTD has been observed at the maximum dose of carfilzomib (45 mg/m²) for patients treated with ascorbic acid + cyclophosphamide (2.2 mg/kg)

Efficacy

- Nearly two-thirds of patients (65.5%) achieved ≥ MR
- Nearly one-fourth of patients (24.1%) have already achieved ≥ VGPR even with only a median of 3 cycles completed
- 8 patients progressed on study, 6 of whom progressed after initial response

Table 3. Response rates

Best Response	Patients (n=29)	%
CR	2	6.9%
VGPR	5	17.2%
PR	6	20.7%
MR	6	20.7%
SD	8	27.6%
PD	2	6.9%
Overall Response Rate (≥PR)	13	44.8%
Clinical Benefit Rate (≥MR)	19	65.5%

PD: progressive disease; SD: stable disease; MR: minimal response; PR: partial response; VGPR: very good partial response; CR: complete response

Table 4. Response per regimen

Regimen in addition to carfilzomib (grouped by active agents)	Best Response
Dexamethasone	5 SD; 1 MR; 2 PR; 1 VGPR
Melphalan	1 CR
Cyclophosphamide+ascorbic acid	1 SD; 2 MR; 2 PR
Cyclophosphamide+ascorbic acid +dexamethasone	1 CR
bendamustine	1 PD; 1 SD; 1 VGPR
Bendamustine+methylprednisolone	1 SD
PLD	1 VGPR
PLD+dexamethasone	3 MR; 1 VGPR
Thalidomide+dexamethasone	1 PD
Lenalidomide	(N/A)
Lenalidomide+dexamethasone	1 VGPR
Lenalidomide+dexamethasone+PLD	1 PR
Thalidomide+lenalidomide +bendamustine+methylprednisolone +clarithromycin	1 PR

- Response (≥ MR) has been achieved with 77% of the unique combinations of agents used in the trial
- Response seen for all drug classes: alkylating agents, anthracyclines, immunomodulatory drugs, and glucocorticoids and corticosteroids
- Response (≥ MR) with carfilzomib and
  - dexamethasone: 44% (4/9)
  - all other combinations: 75% (15/20)

Table 5. Time-to-event data

Time-to-event	Time (mo)
Time to progression (TTP)	
Median (Kaplan-Meier)	9.9
95% confidence interval	7.2-12.6
Progression-free survival (PFS)	
Median (Kaplan-Meier)	8.3
95% confidence interval	3.0-13.7
Duration of response (DOR)	
Median (Kaplan-Meier)	8.5
95% confidence interval	7.3-9.7
Overall survival (OS)	
Median (Kaplan-Meier)	14.0
95% confidence interval	10.6-17.4

- Time-to-event data looks promising so far
- Assessment of response, time-to-event, and survival data will benefit from increased follow-up

Figure 1: Progression-free Survival (Kaplan-Meier)

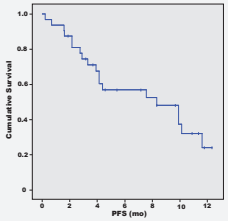
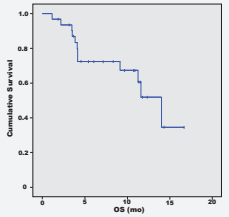


Figure 2: Overall Survival (Kaplan-Meier)



Safety

(Safety population = 33 of 33 enrolled patients)

Hematological

- The most common hematological adverse events (all grades) were thrombocytopenia (60.6%), anemia (48.6%), neutropenia (42.4%), lymphopenia (42.4%), and hyperglycemia (42.4%)
- ≥ G3 hematological adverse events included thrombocytopenia (27.3% ≥ G3), lymphopenia (24.3% ≥ G3), neutropenia (15.2% ≥ G3), leukopenia (15.2% ≥ G3), anemia (9.1% ≥ G3), decreased RBC (3% ≥ G3), hyperglycemia (3% ≥ G3), increased creatinine (3% ≥ G3), and hypokalemia (3% ≥ G3)
- There were four (12.2%) G4 hematological adverse events: two instances of lymphopenia and two instances of thrombocytopenia (one of each occurring in the same patient).
- There were two (6%) hematologic serious adverse events (SAE): neutropenia and thrombocytopenia

Non-hematological

- The most common non-hematological adverse events were insomnia (39.4%), nausea (33.3%), headache (30.3%), and fever (30.3%)
- ≥ G3 non-hematological adverse events included fever (6.1% ≥ G3), pneumonia (9.0% ≥ G3), sepsis (3% ≥ G3), chills (3% ≥ G3), urinary tract infection (3% ≥ G3), tumor lysis syndrome (3% ≥ G3), tachyarrhythmia (3% ≥ G3), renal dysfunction/failure (3% ≥ G3), migraine (3% ≥ G3), generalized weakness (6.1% ≥ G3), hypoechoic liver lesions (3% ≥ G3), hyponatremia (3% ≥ G3), dehydration (3% ≥ G3), and cellulitus (3% ≥ G3)
- There were three (9.1%) G4 non-hematological adverse events: pneumonia, sepsis, and tachyarrhythmia
- There was one (3%) AE that contributed to death (G5): pneumonia
- There were 12 (36.4%) non-hematologic serious adverse events: cellulitis, dehydration, fever w/chills, 2 instances of generalized weakness, pneumonia, rectal bleeding, renal dysfunction/failure, sepsis, tachyarrhythmia, tumor lysis syndrome, and urinary tract infection

DLT

- There have been 10 DLTs so far across 8 of the 13 unique regimen combinations:
  - One instance of G2 abdominal pain; four instances of G4 thrombocytopenia; two instances of G3 neutropenia; G3 sepsis; G3 congestive heart failure; G3 tumor lysis syndrome
- Note that DLTs resulted in study discontinuation for 4 patients with ≤ 1 cycle completed

Table 6. Number of DLTs

DLT Information	Patients (n=33)
DLTs (total events)	10
Pts off study for DLT	8
off during 1st cycle	2
off after 1 cycle complete	2
off after 2 cycles	2
off after 3 or more	2

Table 7. Number of patients experiencing selected adverse events (highest grade; any cause). Listed are all adverse events occurring in ≥ 13% of evaluable patients, as well as all ≥ G3 or serious adverse events.

Adverse Event	Patients per grade [n (%)]: 33 total						
	G1	G2	G3	G4	G5	Total	SAE
Hematologic							
Anemia	2 6.1%	11 33.3%	3 9.1%	0 0%	0 0%	16 48.5%	0 0%
ALT (increased)	6 18.2%	0 0%	0 0%	0 0%	0 0%	6 18.2%	0 0%
AST (decreased)	5 15.2%	0 0%	0 0%	0 0%	0 0%	5 15.2%	0 0%
AST (increased)	6 18.2%	1 3.0%	0 0%	0 0%	0 0%	7 21.2%	0 0%
Decreased ALP	6 18.2%	1 3.0%	0 0%	0 0%	0 0%	7 21.2%	0 0%
Decreased total protein	9 27.3%	0 0%	0 0%	0 0%	0 0%	9 27.3%	0 0%
Decreased RBC	2 6.1%	0 0%	1 3.0%	0 0%	0 0%	3 9.1%	0 0%
Hematocrit (decreased)	5 15.2%	1 3.0%	0 0%	0 0%	0 0%	6 18.2%	0 0%
Hyperglycemia	12 36.4%	1 3.0%	1 3.0%	0 0%	0 0%	14 42.4%	0 0%
Hypoalbumenia	4 12.1%	2 6.1%	0 0%	0 0%	0 0%	6 18.2%	0 0%
Hypocalcemia	6 18.2%	3 9.1%	0 0%	0 0%	0 0%	9 27.3%	0 0%
Hypokalemia	7 21.2%	0 0%	1 3.0%	0 0%	0 0%	8 24.2%	0 0%
Increased BUN	10 30.3%	1 3.0%	0 0%	0 0%	0 0%	11 33.3%	0 0%
Increased creatinine	7 21.2%	2 6.1%	1 3.0%	0 0%	0 0%	10 30.3%	0 0%
Leukopenia	4 12.1%	2 6.1%	5 15.2%	0 0%	0 0%	11 33.3%	0 0%
Lymphopenia	0 0%	6 18.2%	6 18.2%	2 6.1%	0 0%	14 42.4%	0 0%
Neutropenia (G3 was febrile)	2 6.1%	7 21.2%	5 15.2%	0 0%	0 0%	14 42.4%	1 3.0%
Thrombocytopenia	8 24.2%	3 9.1%	7 21.2%	2 6.1%	0 0%	20 60.6%	1 3.0%
Non-hematologic							
Cellulitus (due to cat bite)	0 0%	0 0%	1 3.0%	0 0%	0 0%	1 3.0%	1 3.0%
Chills	4 12.1%	0 0%	1 3.0%	0 0%	0 0%	5 15.2%	0 0%
Constipation	5 15.2%	1 3.0%	0 0%	0 0%	0 0%	6 18.2%	0 0%
Cough	6 18.2%	0 0%	0 0%	0 0%	0 0%	6 18.2%	0 0%
Decreased appetite	4 12.1%	0 0%	0 0%	0 0%	0 0%	4 12.1%	0 0%
Dehydration	1 3.0%	0 0%	1 3.0%	0 0%	0 0%	2 6.1%	1 3.0%
Diarrhea	5 15.2%	1 3.0%	0 0%	0 0%	0 0%	6 18.2%	0 0%
Fever	8 24.2%	0 0%	2 6.1%	0 0%	0 0%	10 30.3%	1 3.0%
Headache	8 24.2%	2 6.1%	0 0%	0 0%	0 0%	10 30.3%	0 0%
Hypoechoic liver lesions	0 0%	0 0%	1 3.0%	0 0%	0 0%	1 3.0%	0 0%
Hyponatremia	7 21.2%	0 0%	1 3.0%	0 0%	0 0%	8 24.2%	0 0%
Fatigue	6 18.2%	3 9.1%	0 0%	0 0%	0 0%	9 27.3%	0 0%
Generalized weakness	0 0%	0 0%	2 6.1%	0 0%	0 0%	2 6.1%	2 6.1%
Insomnia	13 39.4%	0 0%	0 0%	0 0%	0 0%	13 39.4%	0 0%
Migraine	1 3.0%	1 3.0%	1 3.0%	0 0%	0 0%	3 9.1%	0 0%
Nausea	11 33.3%	0 0%	0 0%	0 0%	0 0%	11 33.3%	0 0%
Peripheral neuropathy	2 6.1%	3 9.1%	0 0%	0 0%	0 0%	5 15.2%	0 0%
Pneumonia	0 0%	1 3.0%	1 3.0%	1 3.0%	1 3.0%	4 12.1%	1 3.0%
Rectal bleeding	0 0%	1 3.0%	0 0%	0 0%	0 0%	1 3.0%	1 3.0%
Renal dysfunction/failure	0 0%	1 3.0%	1 3.0%	0 0%	0 0%	2 6.1%	1 3.0%
Sepsis	0 0%	0 0%	0 0%	1 3.0%	0 0%	1 3.0%	1 3.0%
Tachyarrhythmia	0 0%	0 0%	0 0%	1 3.0%	0 0%	1 3.0%	1 3.0%
Tumor lysis syndrome	0 0%	0 0%	1 3.0%	0 0%	0 0%	1 3.0%	1 3.0%
Urinary tract infection	2 6.1%	0 0%	1 3.0%	0 0%	0 0%	3 9.1%	1 3.0%
Vomiting	4 12.1%	3 9.1%	0 0%	0 0%	0 0%	7 21.2%	0 0%

Conclusions

- Carfilzomib is able to achieve responses (≥ MR) in nearly two-thirds (65.5%) of patients who progressed while receiving bortezomib in the same treatment combination
  - Carfilzomib + dexamethasone = 44% (≥ MR); carfilzomib + all other agents = 75% (≥ MR)
- These responses were robust with a wide variety of combinations and drug classes, including alkylating agents, anthracyclines, glucocorticoids, corticosteroids, and immunomodulatory drugs
  - Six patients have been enrolled with combination treatments with immunomodulatory drugs so far; future enrollment will focus on regimens containing immunomodulatory drugs
  - Responses were achieved rapidly and appear to be durable
- Treatment has been well tolerated at doses up to 45 mg/m² with these different combinations with a low incidence of AEs
  - Ongoing treatment will establish MTDs for additional regimens

This intrapatient phase 1/2 trial suggests that replacing bortezomib with carfilzomib is a very effective and well-tolerated treatment strategy for MM patients who progressed while receiving their most recent bortezomib-containing combination regimen

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Conflict of Interest disclosures

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