Carfilzomib and other New Proteasome Inhibitors: *Clinical Data*

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Disclosures

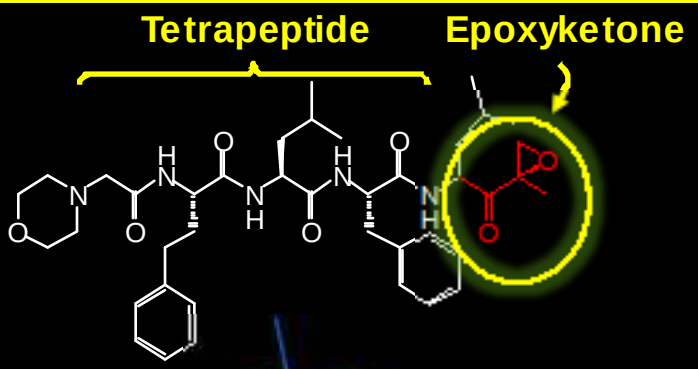
- Consultant without honoraria for Millennium, Onyx, and Bristol-Myers-Squibb

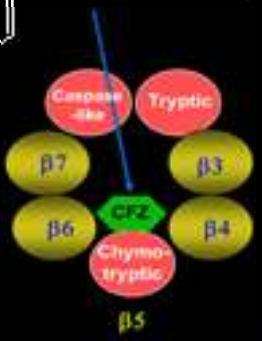
Background

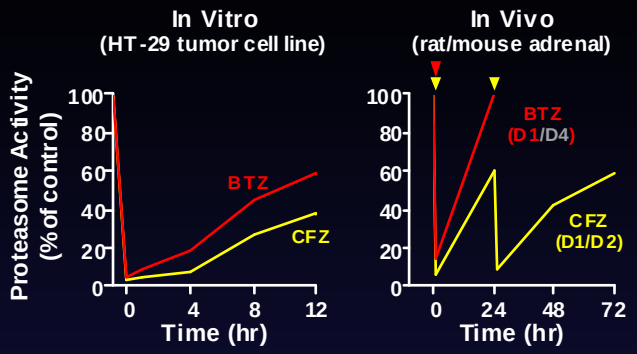
- Since the introduction of bortezomib, proteasome inhibition has been validated as a highly effective strategy in the treatment of multiple myeloma.
- The development of peripheral neuropathy and other toxicities can limit extended use of bortezomib at full dose and thus curtail its potential effectiveness.
- Moreover, resistance to bortezomib-based therapy can emerge over time.
- A second generation of proteasome inhibitors, have entered clinical trials with the intent of
  - Reducing side effects
  - Overcoming resistance
  - Improving efficacy
  - More convenient drug delivery

Carfilzomib (PR-171): Unique Features

- New chemical class
- Selective inhibitor of chemotryptic site
- Irreversible - more sustained target inhibition







Overcomes bortezomib resistance in preclinical models

Adapted from Kuhn DJ, et al. *Blood*. 2007; Demo SD *Cancer Res*. 2007; Kirk, CJ *ASH* 2008; Arastu-Kapur *ASH* 2008

Carfilzomib Phase II 003 Study: Study Design and Efficacy

Study Population

Progressive disease required at study entry

Relapsed from ≥2 prior lines of therapy

- Must include BTZ
- Must include THAL or LEN

Refractory to last regimen

Study expanded to pivotal trial

003-A1 *(N=266)*

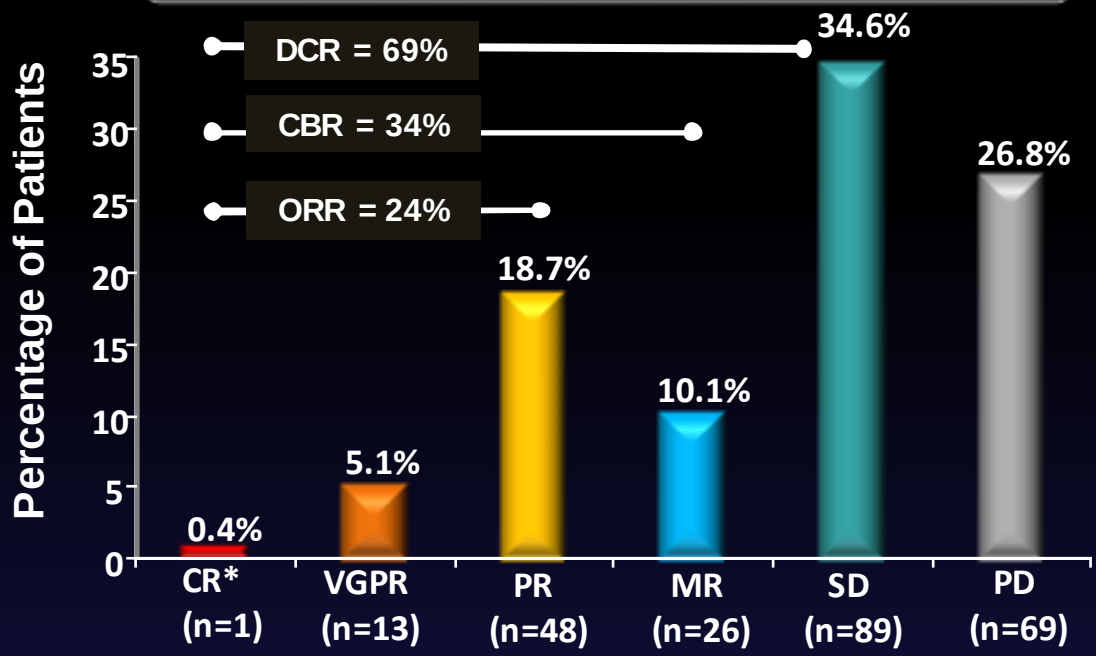
Carfilzomib
Dose escalation to 27 mg/m² after 1st cycle
(maximum 12 cycles)

003-A0 *(N=46)*

Carfilzomib
20 mg/m² IV
QD x 2 for 3 weeks
(28-day cycle)

Median years since dx	5.4
Median lines of therapy	5
PD at study entry, %	100
Prior bortezomib, %	99.6
Refractory to Btz, %	73
Intolerant to Btz, %	15

DOR (≥ PR) and (≥ MR) = 8.3 mo



* CR IRC determined; 11 patients did not have a response that could be confirmed

Siegel DS, et al. Blood (ASH Annual Meeting Abstracts). 2010;116:Abstract 985 (oral presentation).

Carfilzomib 003-A1: Additional Study Highlights

- Bortezomib-refractory patients
  - Response rates comparable to overall population
- Well-tolerated
  - Low rate of neutropenia
  - Very limited peripheral neuropathy
  - No emergence of cumulative toxicity after extended treatment

Martin T, *et al. IMW 2011:* Abstract O-13

Carfilzomib 003-A1 Study: Impact of Cytogenetics

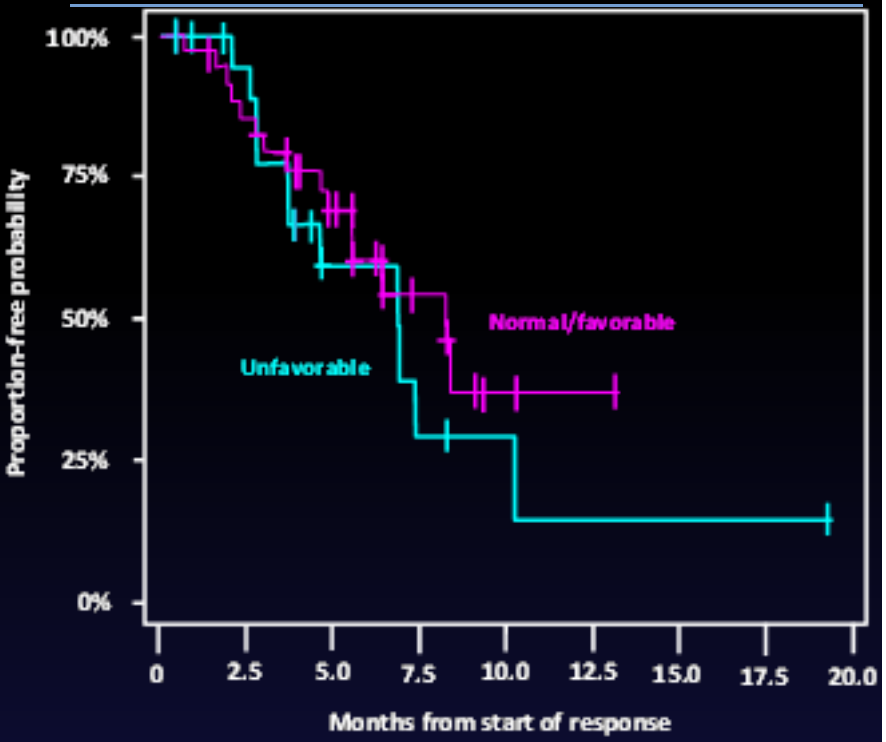
Efficacy

	Normal/favorable (N=158)	Unfavorable* (N=71)
Overall response rate (≥PR) % (95% CI)	24.1 (17.6-31.5)	28.2 (18.1-40.1)
Clinical benefit rate (≥MR) % (95% CI)	37.3 (29.8-45.4)	32.4 (21.8-44.5)

*Hypodiploidy or chromosome 13 deletion by metaphase, and/or del 17p13, t(4:14), or t(14;16) by FISH

DOR

	Normal/favorable (N=158)	Unfavorable (N=71)
Median mo (95% CI)	8 (6–10)	7 (4–10)



‡Estimate using the Kaplan-Meier method

Jakubowiak AJ, *et al*. *Blood (ASH Annual Meeting Abstracts)*. 2010;116:Abstract 1942.

Carfilzomib Phase II - 004 Study

Study Design

Study Population

Relapsed or refractory after 1–3 prior lines of therapy

- At least MR to first line
- Included Btz – naïve pts

Cohort #1 *(N=59)*

Carfilzomib
20 mg/m² IV
QD x 2 for 3 weeks
(28-day cycle)

Cohort #2 *(N=66)*

Carfilzomib
Dose escalation
to 27 mg/m²
after 1st cycle
(maximum 12 cycles)

- Median lines of prior therapy: 2 (range 1–4)
- Refractory to most recent regimen 44 (35%)

Clinical Data

	Cohort 1 20 mg/m² (N=59)	Cohort 2 20/27 mg/m² (N=64)
Best response, n (%)		
ORR (CR + VGPR + PR)	25 (42)	34 (53)
CBR (ORR + MR)	35 (59)	40 (63)
TTP, mo (95% CI)	8.3 (6.0–12.3)	NR (10.2–NR)

- Response rate in bortezomib naïve patients was 54%
- Comparable toxicity profile to 003 study
  - Only very limited peripheral neuropathy

Vij R, *et al*. *Blood (ASH Annual Meeting Abstracts)*. 2010;116:Abstract 1938.

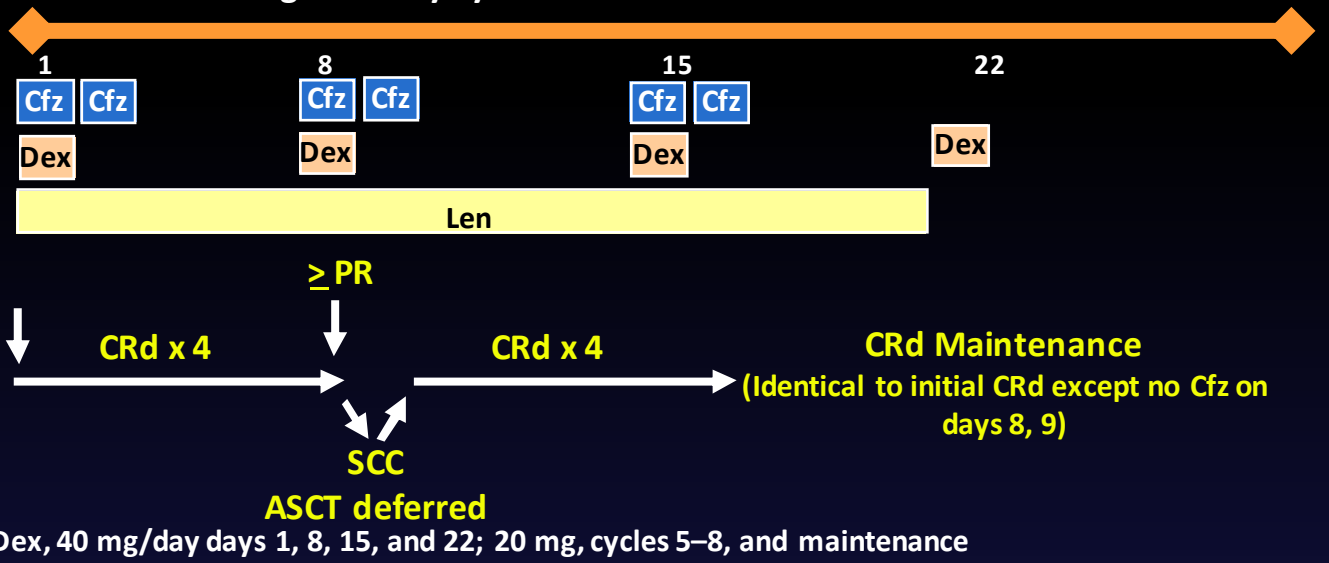
Carfilzomib in Newly Diagnosed Myeloma: CRd Frontline Study

Rationale

- Combining Cfz with other anti-myeloma drugs and moving to newly diagnosed myeloma was a next logical step
- The combination of Cfz + Len + Dex (CRd) has shown synergy in preclinical studies and promising activity and tolerability in relapsed/refractory MM[1,2]

Frontline CRd Study Schema

Eligibility: Newly diagnosed MM requiring first line therapy *(transplant eligible and ineligible)*
Initial Treatment: Eight 28-day cycles



1. Niesvizky R, *et al. Blood (ASH Meeting Abstracts).* 2009;114:Abstract 304.; 2. Martin T, *et al,* Presented at the 2010 Lymphoma and Myeloma Conference. New York.

CRd Frontline Study: Updated Phase I Results

- MTD not reached
- MPD of Cfz 36 mg/m^2, Len 25 mg, Dex 40 mg established as ph II dose

Response, %	Best Response (n=33*)	2 cycles (n=33)	4 cycles (n=29)	8 cycles (n=18)
sCR/CR/nCR	60	27	41	61
sCR	27			
CR/nCR	33			
≥VGPR	82	42	62	83
≥PR	97	97	97	100

*As of data cutoff: 28 February 2011

Jakubowiak AJ, *et al. IMW 2011:* Abstract P-251

CRd Frontline Study: Phase I experience

- **Well-tolerated**
  - Low rate of neutropenia (8% all grades, 2% G3/4)
    - no neutropenic fevers
  - No significant decline of ANC or platelets in consecutive cycles
  - Very low rate of PN (11%, only grade 1 or 2)
- **Extended tolerability**
  - Patients continue CRd maintenance for extended periods , most with no dose modification
- **Time to Event**
  - At a median follow-up of 9 months
    - 100% of patients are free of progression, 100% alive

Dose Modifications	n (%)
Cfz	3 (8)
Len	7 (20)
Dex	3 (9)

Phase II is expected to complete enrollment in the 1-2 months

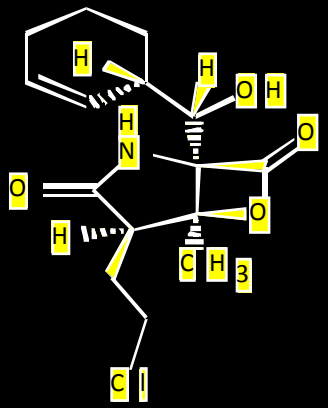
Evaluation of other Cfz combinations is ongoing

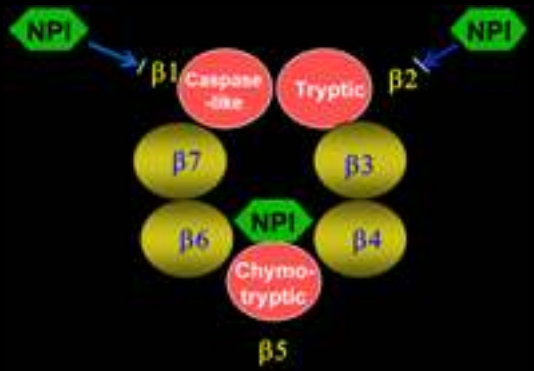
Jakubowiak AJ, *et al. IMW 2011:* Abstract P-251

Salinosporamide (NPI-0052)

Unique features

- **New chemical class** (non-peptide based, natural product)
- Prolonged inhibition **of all 3** proteolytic activities
- **Overcomes Btz resistance** in preclinical models





Preliminary Clinical Data

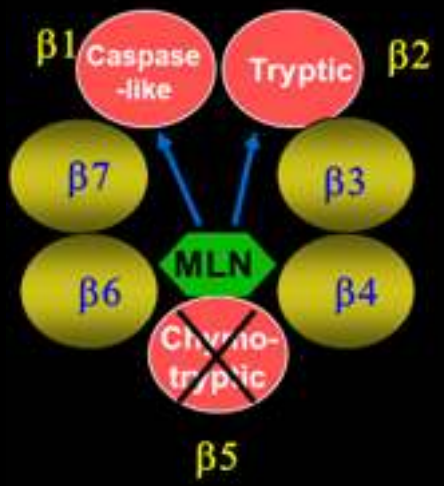
- Decreases in M-protein observed, including in pts refractory to Btz
- Prolonged SD seen, even at low doses
- Inhibition of proteasome activity at levels seen for effective doses of Btz
- Appears to have less neuropathy than Btz
- Enrollment continues to assess an alternate formulation and schedule.

Hofmeister CC, *et al*, *J Clin Oncol*. 2009;27:Abstract 8505.

MLN9708: Oral Proteasome Inhibitor

Similarities to bortezomib

- Boronic acid-based; reversibly inhibits the chymotryptic site



Unique features

- Orally bioavailable, hydrolyzes to active drug MLN2238
- More rapidly dissociates from the proteasome
- Greater tissue penetration

Preliminary Clinical Data

- MTD at 2.0 mg/m^2 given orally on Days 1,4, 8 and 11 of a 21-day cycle
- A partial response in 2 patients, and stable disease in 17 (71%)
- Antitumor activity is reflected by duration of treatment
  - 10 patients completed at least 5 cycles, 6 $\geq$ 10 cycles.
- Toxicities are manageable
  - The frequency and severity of peripheral neuropathy appeared low
- Combination studies with Len and Dex in the upfront setting are now underway.

Richardson *et al*, Presented at the 2011 International Myeloma Workshop. Paris

Other Novel PIs in Clinical Studies

- **CEP-18770**
  - Another **boronic acid-based** inhibitor
  - Encouraging initial results reported

- **ONX 0912**
  - A potent, irreversible, **orally bioavailable**, peptide epoxyketone PI and a **structural analog of Cfz**
  - Currently undergoing clinical evaluation in a phase I trial in patients with advanced solid tumors with plans for studies in MM.

Novel Proteasome Inhibitors: Key Conclusions from Clinical Studies to Date

- Encouraging early results showing unique clinical features of individual PIs
- Single agent (superior ?) activity
  - Carfilzomib shows high activity in relapsed and bortezomib-naïve pts
  - MLN9708 shows objective early evidence of response in heavily pretreated patients
- Emergence of ability to overcome bortezomib resistance
- Improved tolerance
  - Carfilzomib shows very low rate of neuropathy, low rates of neutropenia
  - Emergence evidence of lower neuropathy for other agents including MLN9708 and NPI-0052
- Very encouraging early experience with combinations
  - Cfz + Len + Dex (CRd) very active in relapsed
  - CRd is highly active in newly diagnosed MM
    - Compares favorably to other frontline regimens