Pilot study: Carfilzomib, Lenalidomide, and Dexamethasone in High-Risk Smoldering Multiple Myeloma

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Multiple Myeloma Section, National Cancer Institute, NIH
International Myeloma Workshop, Kyoto, Japan, 2013
Disclosures

• No disclosures
• Off-label use of carfilzomib
## Risk of Developing Multiple Myeloma Varies Greatly in SMM

### Mayo Clinic \(n=273\)

<table>
<thead>
<tr>
<th>No. of risk factors</th>
<th>No. of patients, (n) (%)</th>
<th>Progression at 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>76 (28)</td>
<td>25%</td>
</tr>
<tr>
<td>2</td>
<td>115 (42)</td>
<td>51%</td>
</tr>
<tr>
<td>3</td>
<td>82 (30)</td>
<td>76%</td>
</tr>
</tbody>
</table>

**Risk factors:**
- BMPCs >10%
- M-protein >3 g/dL
- FLC-ratio <0.125 or >8

### PETHEMA Study Group \(n=89\)

<table>
<thead>
<tr>
<th>No. of risk factors</th>
<th>No. of patients, (n) (%)</th>
<th>Progression at 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>28 (31)</td>
<td>4%</td>
</tr>
<tr>
<td>1</td>
<td>22 (25)</td>
<td>46%</td>
</tr>
<tr>
<td>2</td>
<td>39 (44)</td>
<td>72%</td>
</tr>
</tbody>
</table>

**Risk factors:**
- ≥95% abnormal plasma cells*
- Immunoparesis

*Incl decreased CD38 expression, expression of CD56, and absence of CD19 and/or CD45

Dispenzieri et al. *Blood* 2008  
Pérez-Persona et al. *Blood* 2007
Current IMWG Clinical Recommendations for SMM\(^1\)

- Repeat lab tests after 2-3 months. If stable, repeat every 4-6 months for a year, and if stable every 6-12 months.

- Treatment not indicated unless part of a clinical trial. Consider clinical trials designed to delay and/or prevent MM.

- In high-risk SMM, Rev/Dex has a 12% CR rate. Compared to observation, Rev/Dex has better PFS (HR=5.6) and OS (HR=3.5)\(^2\)

\(^1\)Kyle et al. *Leukemia* 2010;  \(^2\)San-Miguel et al. *ASH* 2012
Study Design and Dosing

Study open for high-risk smoldering multiple myeloma pts ≥18 years old

8 cycles CRd Combination Therapy

- Carfilzomib 20/36 mg/m², day 1, 2, 8, 9, 15, 16
- Lenalidomide 25 mg/day, day 1-21
- Dexamethasone 20/10 mg, day 1, 2, 8, 9, 15, 16, 22, 23

12 cycles Rev Extended Dosing

- Lenalidomide 10 mg/day, day 1-21

- Each cycle is 28 days
- Stem cell harvest after ≥4 cycles of CRd for patients <70-75 yrs
- C1D1/2 – Carfilzomib dose is 20 mg/m²
- C1- 4 – Dex dose is 20 mg, C5- 8 – Dex dose is 10 mg
Objectives of Study

Primary Objective
Response rate

Secondary Objectives
- Correlatives: GEP, biomarkers, proteasomes, flow cytometry, PCR, FDG PET-CT
- Clinical: DOR, PFS, OS, toxicity

Designed to enroll 12 evaluable patients
- Single arm, Phase II (pilot) study designed to evaluated efficacy of CRd in high-risk SMM patients
- Targeting 5 or more patients with a VGPR provides strong evidence that the true probability of a VGPR is consistent with >50%
**Approach to Correlatives**

**Baseline**
- CFZ single drug

**Day 2**
- CRd x 8

**CR/Post cycle 8**
- Rev x 12

**Post 1 yr Rev Extended Dosing**

**Blood and urine collected baseline, C1 D8, C1 C15, and day 1 of every cycle**
Bone Marrow Studies

Bone marrow aspirate

- CD138+
  - DNA/RNA profiling
  - Flow Cytometry
  - Proteasomes
  - PCR assays DNA/RNA

- CD138-
  - Micro-environment studies

- Supernatant
  - Biomarkers, e.g. miRNA
## Results: Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients enrolled (Mar -13)</td>
<td>10</td>
</tr>
<tr>
<td>Patients completed two cycles (evaluable)</td>
<td>8</td>
</tr>
<tr>
<td>Median age, yrs (range)</td>
<td>55 (48-61)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>3 (37.5)</td>
</tr>
<tr>
<td>Isotype, n (%)</td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td>7 (87.5)</td>
</tr>
<tr>
<td>Kappa light-chain</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td>Cytogenetics n/N(%)*</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>8/8 (100)</td>
</tr>
<tr>
<td>FISH n/N(%)**</td>
<td></td>
</tr>
<tr>
<td>-RB1 deletion (13q14)</td>
<td>4/4 (100)</td>
</tr>
<tr>
<td>-7q31/7cen</td>
<td>1/4 (25)</td>
</tr>
<tr>
<td>-IGH (14q32)</td>
<td>1/4 (25)</td>
</tr>
<tr>
<td>-P53 (17p13.1)</td>
<td>1/4 (25)</td>
</tr>
<tr>
<td>Median cycles of CRd-R received</td>
<td>5.5 cycles (2-9)</td>
</tr>
<tr>
<td>Patients completed 4 cycles of CRd</td>
<td>5</td>
</tr>
</tbody>
</table>

*Cytogenetics not available for 1 patient; **FISH not available for 4 patients
Response Rate (≥VGPR)

• Primary Objective:
  • In the first 8 patients, 7 have obtained a ≥VGPR
# Response Rates and Mean M-protein Concentration (g/dL)

<table>
<thead>
<tr>
<th>≥VGPR (n/N):</th>
<th>4/8</th>
<th>5/5</th>
<th>4/4</th>
<th>2/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>M-protein concentration (g/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 0.4</td>
<td>1 (12.5)</td>
<td>2 (25)</td>
<td>4 (50)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>0.4-0.8</td>
<td>1 (12.5)</td>
<td></td>
<td>2 (40)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>0.8-1.2</td>
<td></td>
<td></td>
<td>2 (60)</td>
<td>1 (50)</td>
</tr>
<tr>
<td>1.2-1.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.6-2.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Response Rates
- **CR/sCR**: 1 (50)
- **nCR**: 1 (50)
- **VGPR**: 2 (40), 5 (50), 4 (50), 2 (50)
- **PR**: 3 (60), 2 (60), 2 (60), 1 (50)
# Response Rates

*Median 5.5 cycles of CRd-R*

<table>
<thead>
<tr>
<th>Response</th>
<th>2 cycles n/N(%)</th>
<th>4 cycles n/N(%)</th>
<th>*Best response n/N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (≥PR)</td>
<td>8/8(100)</td>
<td>5/5(100)</td>
<td>8/8(100)</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>4/8(50)</td>
<td>0</td>
<td>7/8(87.5)</td>
</tr>
<tr>
<td>nCR/CR/sCR</td>
<td>2/8(25)</td>
<td>5/5(100)</td>
<td>6/8(75)</td>
</tr>
<tr>
<td>VGPR</td>
<td>2/8(25)</td>
<td>0</td>
<td>1/8(12.5)</td>
</tr>
<tr>
<td>PR</td>
<td>4/8(50)</td>
<td>0</td>
<td>1/8(12.5)</td>
</tr>
<tr>
<td>SD</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Based on small numbers, response rates are non-differential by FISH/cytogenetics*
Among 4/8 patients reaching CR/sCR, the median time was 107 days.
- 1 patient currently on rev extended dosing
- 1 patient (patient # 4) came off study after 6 combination cycles of CRd due to CHF and decrease in EF% – maintains sCR 3 months after stopping therapy
## Toxicity

<table>
<thead>
<tr>
<th>Nonhematologic</th>
<th>Grade 3/4, n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LFT elevation</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
</tr>
<tr>
<td>Rash/Pruritus</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td>Constitutional (chills, fever, anorexia, hot flashes)</td>
<td>0</td>
</tr>
<tr>
<td>Mood alterations (anxiety, cognition, confusion, insomnia)</td>
<td>0</td>
</tr>
<tr>
<td>Electrolyte disturbances</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hematologic</th>
<th>Grade 3/4, n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphopenia</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1 (12.5)</td>
</tr>
</tbody>
</table>

Dose Reductions on 2 patients (1 patient had two dose reductions): decreased Dex for mood alterations (n=1), decreased lenalidomide for rash (n=2)
Individual Patient Response
Histopathology

Baseline

H&E

CD138

Post CRd

H&E

CD138

Provided by Irina Maric
Assessing MRD by Flow Cytometry

- Analyze 3-4 x 10^6 bone marrow cells

- 8-color flow panel*
  - CD38
  - CD138
  - CD19
  - CD20
  - CD56
  - CD45
  - CD27
  - CD28

- MRD negative: <20 abnormal plasma cells detected

*European Myeloma Network Gating Criteria

Gating strategy to analyze plasma cells (CD138+CD38+)
MRD Status after CRd therapy
Flow cytometry of bone marrow aspirate

Among patients achieving sCR/CR/nCR, 4/5 (80%) are MRD negative

Abnormal PC’s CD19-, CD45 -, CD56 +, CD 27-

Before therapy

Post therapy
MRD Status after CRd therapy
Flow cytometry of peripheral blood

Before therapy

Post therapy

- Analyze 3-4 x 10^6 peripheral blood cells
- 8-color flow panel
- Circulating abnormal peripheral plasma cells (PB-aPC +) positive:
  <20 abnormal cells = MRD neg
4/7 patients demonstrate circulating PB-aPC+ at baseline
Among the 5 patients assessed after CRd therapy thus far, 3 became PB-aPC- after CRd and 2 remain PB-aPC–

Patient #3 baseline sample not performed
• During screening for the trial, many SMM patients had bone lesions detectable by CT or PET-CT; these patients were ineligible for the trial (due to multiple myeloma)

• Among SMM without bone lesions, ~30% had increased PET uptake in the bone marrow
Proteasome subunits

- Carfilzomib
  - 1º targets β5 and LMP7
  - 2º targets LMP2 and MECL1

Proteasome activity
Pre and post carfilzomib exposure

• Proteasome activity assay (*Pro-CISE*)

• 20S CT-L Proteasome activity decreases by 80% 24 hrs after carfilzomib exposure

• Patient obtained PR after 1 cycle

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<table>
<thead>
<tr>
<th>Proteasome Level</th>
<th>β5 (ng/ug of protein) (% total 20S)</th>
<th>LMP7 (ng/ug of protein) (% total 20S)</th>
<th>Total 20S CT-L (ng/ug of protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At SMM diagnosis</td>
<td>0.19 ± 0.01 (11%)</td>
<td>1.54 ± 0.08 (89%)</td>
<td>1.73 ± 0.09</td>
</tr>
<tr>
<td>After 1 dose CFZ</td>
<td>0.00</td>
<td>0.40 ± 0.01</td>
<td>0.40 ± 0.15</td>
</tr>
</tbody>
</table>

Provided by Adriana Zingone
Among first 8 patients, 7 obtained \( \geq \) VGPR; limited severe toxicities

Rapid and deep responses; median time to CR/sCR (4 pts) was 107 days

Best response rate (median 5.5 cycles)
- nCR/sCR = 75% (6/8)
- ORR (PR or better) = 100% (8/8)
• Among 5 patients in nCR/sCR, 4 were MRD negative by flow cytometry

• Abnormal PET/CT uptake in the bone marrow in 1/3 of SMM pts prior therapy

• Pre/post (24 hours) exposure to carfilzomib shows 80% inhibition of proteasome (20s CT-L) activity in MM cells
Future Directions

• With more effective therapies used in “early myeloma” (high-risk SMM), we need better markers to assess residual tumor burden beyond “traditional” CR rates
Detection of minimal residual disease (MRD) using VDJ sequencing

Tumor cells
Extract DNA
Multiplex PCR to amplify VDJ
Common PCR to prepare for sequencing
Sequence ~1M 100bp reads

Sensitivity limited by total assessed cell number (>10^6)

Landgren, Willis et al, *unpublished data*
Labs and collaborators

NCI/NIH
Multiple myeloma Section
Metabolism Branch
• Dr. Korde
• Dr. Roschewski
• Dr. Manasanch
• Dr. Tageja
• Dr. Bhutani
• Dr. Mailankody
• Dr. Kwok
• Dr. Kanzandjan
• Dr. Flanders
• Dr. Zingone
• Mr. Costello
• RN Mulquin
• RN Zuchlinsiki
• Peter Wu

NIH Labs
• Dr. Staudt - Molecular pathogenesis and targeted therapy
• Dr. Choyke, Kurdzieł - Molecular Imaging program
• Seth Steinberg - Statistics
• Drs. Maric, Calvo, Braylan – Hematopathology
• Dr. Arthur – Cytogenetics and FISH
• Drs. Stetler-Stevenon, Yuan - Flow cytometry
• Dr. Raffeld – Molecular pathology
• Dr. Trepel - Pharmacodynamic assay development
• Dr. Mock - Molecular therapy
• Dr. Robey - Bone marrow microenvironment
• Dr. Kuehl - Molecular pathogenesis

Navy/Walter Reed Medical Center
Mayo Clinic
Dana-Farber Cancer Institute
Karolinska Institute
Signal Genetics
Thank you to our patients!

www.multiplemyeloma.cancer.gov

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