Phase II: Carfilzomib, Lenalidomide, and Dexamethasone in Newly Diagnosed Multiple Myeloma

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Measures of tumor burden

Yesterday: CR
Today: MRD
Tomorrow: ???

Tools:
- SPEP
- IFE
- Flow Cytometry
- CD19 PE
- Functional Imaging
- Molecular Profiling Assays
Study Design and Dosing

Phase II study open for newly diagnosed 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
<table>
<thead>
<tr>
<th><strong>CRd in Newly Diagnosed MM</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase I/II, n=53</strong></td>
</tr>
<tr>
<td><strong>Phase II, n=45</strong></td>
</tr>
<tr>
<td><strong>Combination Therapy</strong></td>
</tr>
<tr>
<td>• CRd (Phase II Cfz 20/36 mg/m²) 8 cycles</td>
</tr>
<tr>
<td><strong>Extended dosing</strong></td>
</tr>
</tbody>
</table>
| • CRd (CFZ every other week) 16 cycles  
• Off protocol Rev 25 mg D1-21 after 16 cycles | • Rev 10 mg D1-21 12 cycles |  
| **Transplant** |  
| • > PR stem cell collection  
• HDM optional | • Stem cell collection |  
| **Correlatives** |  
| • Flow cytometry – MRD | • Flow cytometry – MRD (3-4 x 10⁶)  
• PET-CT  
• Proteasome assays  
• GEP  
• Whole genome sequencing |  

* Jakubowiak A. et al., Blood, 2012; 120(9): 1801-8
Objectives of Study

Primary Objective
≥ Grade 3 neuropathy

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

Designed to enroll 45 patients
• Phase II study, two stage-design:
  • Stage I: Patients 1-20 - If 4 or more develop ≥ grade 3 neuropathy, then study stops
  • Stage II: Patients 21-45
**Blood and urine collected baseline, C1 D8, C1 C15, and day 1 of every cycle**
Bone Marrow Studies

- Flow Cytometry
- DNA/RNA profiling
- Proteasomes
- PCR assays DNA/RNA
- Microenvironment studies
- Biomarkers, e.g. miRNA

Bone marrow aspirate
- CD138+
- CD138-
- Supernatant
# Patient Characteristics and Time on Therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients enrolled (Dec -12)</td>
<td>28</td>
</tr>
<tr>
<td>Patients completed two cycles (evaluable)</td>
<td>20</td>
</tr>
<tr>
<td>Median age, yrs (range)</td>
<td>60 (42-83)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>11 (55)</td>
</tr>
<tr>
<td>Isotype, n (%)</td>
<td></td>
</tr>
<tr>
<td>* IgG</td>
<td>11 (55)</td>
</tr>
<tr>
<td>* IgA</td>
<td>5 (25)</td>
</tr>
<tr>
<td>* Kappa</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Cytogenetics, n/N (%)*</td>
<td></td>
</tr>
<tr>
<td>Hyperdiploid</td>
<td>4/18 (22)</td>
</tr>
<tr>
<td>Del 13</td>
<td>1/18 (6)</td>
</tr>
<tr>
<td>Normal</td>
<td>13/18 (72)</td>
</tr>
<tr>
<td>FISH, n/N (%)**</td>
<td></td>
</tr>
<tr>
<td>- RB1 deletion (13q14)</td>
<td>10/16 (63)</td>
</tr>
<tr>
<td>- 7q31/7cen</td>
<td>7/16 (44)</td>
</tr>
<tr>
<td>- IGH (14q32)</td>
<td>4/16 (25)</td>
</tr>
<tr>
<td>- P53 (17p13.1)</td>
<td>5/12 (42)</td>
</tr>
<tr>
<td>Median (range) cycles of CRd-R received</td>
<td>7 cycles (2-15)</td>
</tr>
<tr>
<td>Patients completed 8 cycles of CRd</td>
<td>8</td>
</tr>
</tbody>
</table>

* Cytogenetics not available for 2 patients
** FISH not available for 4 patients (-RB1 deletion, -7q31/7cen, -IGH rearrangement) and 6 patients (-p53 deletion)
Primary Objective

- In the first 20 patients, no patients have developed $\geq$ grade 3 neuropathy

- Second stage accrual has begun
Response Rates and Mean M-protein Concentration (g/dL)

≥VGPR (n/N): 10/20 16/18 13/14 7/8

<table>
<thead>
<tr>
<th>Cycles of CRd delivered</th>
<th>Baseline</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>n(%)</td>
<td>sCR</td>
<td>nCR</td>
<td>VGPR</td>
<td>PR</td>
<td>SD</td>
</tr>
<tr>
<td>1(5)</td>
<td>9(45)</td>
<td>6(33.3)</td>
<td>5(35.7)</td>
<td>4(50)</td>
<td></td>
</tr>
<tr>
<td>4(20)</td>
<td>5(25)</td>
<td>6(33.3)</td>
<td>5(35.7)</td>
<td>4(50)</td>
<td></td>
</tr>
<tr>
<td>1(5)</td>
<td>1(5)</td>
<td>1(5.5)</td>
<td>1(7.1)</td>
<td>1(12.5)</td>
<td></td>
</tr>
<tr>
<td>1(5.5)</td>
<td>1(5.5)</td>
<td>2(14.3)</td>
<td>2(12.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1(12.5)</td>
<td>1(12.5)</td>
<td>1(12.5)</td>
<td>1(12.5)</td>
<td></td>
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</tr>
</tbody>
</table>
## Response Rates

<table>
<thead>
<tr>
<th>Response</th>
<th>2 cycles n/N(%)</th>
<th>8 cycles n/N(%)</th>
<th>*Best response n/N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (≥PR)</td>
<td>19/20(95)</td>
<td>7/8(87.5)</td>
<td>19/20(95)</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>10/20(50)</td>
<td>7/8(87.5)</td>
<td>17/20(85)</td>
</tr>
<tr>
<td>nCR/sCR</td>
<td>5/20(25)</td>
<td>6/8(75)</td>
<td>15/20(75)</td>
</tr>
<tr>
<td>VGPR</td>
<td>5/20(25)</td>
<td>1/8(12.5)</td>
<td>2/20(20)</td>
</tr>
<tr>
<td>PR</td>
<td>9/20(45)</td>
<td>0</td>
<td>2/20(10)</td>
</tr>
<tr>
<td>SD</td>
<td>1/20(5)</td>
<td>1/8(12.5)</td>
<td>1/20(5)</td>
</tr>
</tbody>
</table>

* Median 7 cycles of CRd-R

- Response rates based on FISH/cytogenetics are non-differential
Individual Response Rates

- Median time to sCR: 4.5 cycles (range: 2-7)
- 7 patients currently on rev extended dosing
- 1 patient (patient 8) came off study after 8 combination cycles of CRd due to personal reasons – maintains sCR 6 months after stopping therapy
- 1 patient (patient 2) had PD by biochemical progression
### Toxicity

<table>
<thead>
<tr>
<th>Nonhematologic</th>
<th>Grade 3/4, n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LFT elevation</td>
<td>4(20)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3(15)</td>
</tr>
<tr>
<td>Rash/Pruritus</td>
<td>3(15)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2(10)</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>2(10)</td>
</tr>
<tr>
<td>Constitutional (chills, fever, anorexia, hot flashes)</td>
<td>1(5)</td>
</tr>
<tr>
<td>Mood alterations (anxiety, cognition, confusion, insomnia)</td>
<td>1(5)</td>
</tr>
<tr>
<td>Electrolyte disturbances</td>
<td>1(5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hematologic</th>
<th>Grade 3/4, n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphopenia</td>
<td>12(60)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1(5)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
</tr>
</tbody>
</table>

**Dose Reductions on 7 patients**
4 decreased Dex for fatigue/anxiety/dyspnea, 2 decreased Len for fatigue, 3 decreased Len for rash, 2 decreased carfilzomib for dyspnea/heart failure
Individual Patient Responses
Histopathology Patients 7 and 8

Pt #7: 83 y/o Caucasian female: 70-80% PCs on bone marrow, M-spike 3.1 g/dL

Pt #8: 42 y/o African male: 70-80% PCs on bone marrow and K/L ratio of 322.35

Baseline CD 138+ IHC

Post CRd CD 138+ IHC

nCR after 8 cycles

sCR after 6 cycles

Provided by Irina Maric and Katherine Calvo
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
MRD Status after CRd therapy

Flow cytometry

Among 10 nCR/sCR patients assessed by flow, all 10 are MRD negative

Patient #7
Pre CRd: Abnormal PC’s CD19-, CD45 dim, CD56dim+

Post CRd: Normal PC’s CD19+, normal CD45, CD56-
FDG PET-CT in nCR/sCR patients

Mean SUV Decline in FDG avid lytic lesions after CRd therapy: 49.3% decrease

L Acetabular Lesion
SUV 10
At MM diagnosis
sCR obtained

Mean SUV

At MM diagnosis
At nCR/sCR
Proteasome subunits

- Carfilzomib
  - 1° targets $\beta_5$ and LMP7
  - 2° targets LMP2 and MECL1

Proteasome activity assay (Pro-CISE)

- 20S CT-L Proteasome activity decreases by 80% 24 hrs after carfilzomib exposure
- Patient obtains sCR after 6 cycles

<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 MM diagnosis</td>
<td>0.62 ± 0.14 (7%)</td>
<td>8.74 ± 0.98 (93%)</td>
<td>9.36 ± 0.6</td>
</tr>
<tr>
<td>After 1 dose CFZ</td>
<td>0.00</td>
<td>1.84 ± 0.15</td>
<td>1.84 ± 0.15</td>
</tr>
</tbody>
</table>

Provided by Adriana Zingone
Proteasome Gene Expression
Pre and post carfilzomib exposure

- Post carfilzomib exposure shows increase in proteasome gene expression

Provided by Peter Wu
Summary and Conclusions

- Among first 20 patients, none developed \( \geq \) grade 3 neuropathy; limited severe toxicities

- Rapid and deep responses; median time to sCR: 4.5 cycles (range: 2-7)

- Best response rate (median 7 cycles)
  - nCR/sCR = 75%
  - ORR (PR or better) = 95%
Summary and Conclusions

- Among 10 nCR/sCR patients assessed by flow cytometry, all were MRD negative

- Abnormal mean SUV uptake (6 pts) by PET/CT, decreased by 49.3% after CRd therapy

- Pre/post (24 hours) exposure to carfilzomib shows 80% inhibition of proteasome (20s CT-L) activity in MM cells; proteasome GEP increased
Labs and collaborators

NCI/NIH
Multiple myeloma Section
Metabolism Branch
  • Dr. Landgren
  • Dr. Roschewski
  • Dr. Manasanch
  • Dr. Flanders
  • Dr. Kwok
  • Dr. Zingone
  • Mr. Costello
  • RN Mulquin
  • RN Zuchlinski
  • Peter Wu

NIH Labs
  • Dr. Staudt - Molecular pathogenesis and targeted therapy
  • Dr. Choyke, Lindenberg, Kurtziel - Molecular imaging program
  • Seth Steinberg - Statistics
  • Drs. Maric, Calvo, Braylan – Hematopathology
  • Dr. Arthur – Cytogenetics and FISH
  • Drs. Stetler-Stevenson, Yuan, Tembhare - Flow cytometry
  • Dr. Raffeld – Molecular pathology
  • Dr. Trepel - Pharmacodynamic assay development
  • Dr. Annunziata - Molecular therapy
  • 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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Future Directions

• With more effective therapies, we need better markers to assess residual tumor burden beyond “traditional” CR rates