Clinical Trials in Multiple Myeloma in Arizona: Past, Present and Future

AZMN Roundtable
March 2013

Scottsdale, Arizona
Rochester, Minnesota
Jacksonville, Florida

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Staff Hematologist, Mayo Clinic Arizona
Managing myeloma: the components

- Transplant Eligible Patients
  - Initial Therapy
  - Consolidation
  - Maintenance
  - Treatment of Relapsed disease

- Transplant Ineligible Patients
  - Consolidation/ Maintenance/ Continued therapy

Supportive Care
Objectives

1. Review the progress in clinical trials in myeloma worldwide

2. Outline the size and scope of the Myeloma Program at Mayo Clinic in Arizona

3. Discuss the major trials that have been conducted at Mayo Clinic in Arizona

4. Look into the future of myeloma in Arizona...
Myeloma at Mayo

- 5 Clinical Physicians
  - Rafael Fonseca
  - Keith Stewart
  - Leif Bergsagel
  - Joseph Mikhael
  - Craig Reeder

- 3 Labs
  - Fonseca – 7
  - Bergsagel - 6
  - Stewart - 5
Myeloma at Mayo

- Tissue Bank – Dr. Esteban Braggio and Greg Ahmann
- Clinical Trial coordinators (6)
- Phase 1 program
- 3 Nurse Coordinators (Jacy, Joyce, Jennifer)
- Other allied health – secretaries, social workers, technicians…
Treatment sequence

NEW

Thal/Dex
VD
Rev/Dex
CyBorD
VTD
VRD

SCT
VD/VRD

Nothing
Thalidomide?
Bortezomib?
Lenalidomide?

Bortezomib
Lenalidomide
Carfilzomib
Pomalidomide
Elotuzumab
HDAC
Bendamustine

OLD

VAD
DEX
SCT

Nothing
Prednisone
Thalidomide

Few options
Clinical Trials in the Treatment of Myeloma

Phase I
Tests safety

Phase II
Tests how well treatment works

Phase III
Compares new treatment to standard treatment
Combinations for Induction in Myeloma

Percent Response

Induction Regimen

- VAD
- TD
- RD
- PAD
- VTD
- RVD
- CVRD
- CyBorD
- CarRD*
Trials at Mayo Clinic Arizona 2007-2013

• Summary
  • 33 Myeloma Trials
    • 15 initiated by Mayo
  • Across spectrum
    • Phase 1, 2, 3
    • Pre/transplant/post
    • Young and old
  • Over 300 patients enrolled
Highlights of Major Trials

• Pomalidomide
  • 112 patients (!!!)
  • 27 patients in first 3 weeks of enrolment
  • Overall Mayo has treated more patients (450) than the rest of North America combined
  • Major contribution to its approval by FDA in February 2013
Highlights of Major Trials

- **Carfilzomib**
  - Several trials (newly diagnosed and relapsed)
  - Keith Stewart PI of Phase 3 Carfilzomib-Lenalidomide-Dex vs Lenalidomide-Dex (ASPIRE)
  - 003 and 004 studies that led to approval in July 2012
  - CYCLONE and NCCN recommendations last week
Clinical Trials

- Information available at: [www.clinicaltrials.gov](http://www.clinicaltrials.gov)
- Currently 1619 listed under myeloma!
  - 529 still accruing
- 16 open clinical trials at Mayo Clinic Arizona
Novel Agents

- “newer” versions of current drugs
  - Pomalidomide
  - Carlfizomib
  - Newer proteasome inhibitors (oprozomib, MLN 9708, marizonib)

- Novel agents
  - Bendamustine
  - Perifosine
  - Vorinostat
  - LBH589
  - RAD001
  - SGN 40
  - Obatoclax
  - HGF inhibitors
  - BHQ
  - AUY922
  - Monoclonal antibodies (esp CD38)
  - Dasatinib
  - Vaccines
  - cdk Inhibitor SCH 727965
  - MLN8237 (Aurora A Kinase Inhibitor)
  - TAK-901
Single-Agent Activity of 39 Drugs Tested in Multiple Myeloma

≥PR (%)
Implications

1. In high risk disease multiple genomic clones
   (combination chemotherapy a necessity)

2. In high risk disease genome is unstable
   (avoid DNA damaging agents ?)

3. Re-Emergence of drug sensitive clones
   (Once resistant not always resistant)
Results From the Phase II Dose Expansion of Cyclophosphamide, Carfilzomib, Thalidomide and Dexamethasone (CYCLONE) in Patients with Newly Diagnosed Multiple Myeloma


Scottsdale, Arizona  Rochester, Minnesota  Jacksonville, Florida
Newly Diagnosed: CYCLONE Phase II

- Carfilzomib
- Cyclophosphamide
- Thalidomide
- Dexamethasone

Newly Diagnosed MM

Response
PFS
Toxicity
Stem cell harvest
Results Levels 0 and 1 – Response n=27

- Overall Response 96%

CR: 7
VGPR: 13
PR: 6
MR: 1

≥ VGPR 74%

CR: 26%
VGPR: 48%
PR: 22%
MR: 4%
### Response by Cycle

<table>
<thead>
<tr>
<th>Cycle</th>
<th>CR</th>
<th>VGPR</th>
<th>PR</th>
<th>MR</th>
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<td>Cycle 1</td>
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<td>16</td>
<td>11</td>
<td>6</td>
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<tr>
<td>Cycle 2</td>
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<td>Cycle 3</td>
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<td>8</td>
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<td>Cycle 4 &amp; Beyond</td>
<td>13</td>
<td>13</td>
<td>6</td>
<td>1</td>
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</table>

**ORR**
- 81%
- 93%
- 96%
- 96%
Molecular Structure of Thalidomide, Lenalidomide and Pomalidomide

**Thalidomide**
- 100-200 mg/d
- Neuropathy
- Constipation
- Sedation
- DVT

**Lenalidomide**
- 15-25 mg/d
- Myelosuppression
- Skin rash
- DVT

**Pomalidomide**
- 1-4 mg/d

Structurally similar, but functionally different both qualitatively and quantitatively.
<table>
<thead>
<tr>
<th>Patient population</th>
<th>N</th>
<th>Regimen/dose</th>
<th>ORR</th>
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<tbody>
<tr>
<td><strong>Phase 1 Pomalidomide trials</strong></td>
<td></td>
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<tr>
<td>Schey</td>
<td>24</td>
<td>Pom dose escalation MTD 2mg 28/28</td>
<td>54%</td>
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<tr>
<td>Streetly</td>
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<td>Pom +/- dex MTD 5 mg QOD 28/28</td>
<td>50%</td>
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<td>Richardson</td>
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<td>Pom +/- dex MTD 4 mg 21/28</td>
<td>25%</td>
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<tr>
<td><strong>Phase 2 Pomalidomide trials</strong></td>
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<td>Richardson</td>
<td>120</td>
<td>Pom +/- dex, 4 mg, 21/28</td>
<td>25%</td>
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<tr>
<td>Lacy</td>
<td>60</td>
<td>Pom/dex 2 mg, 28/28</td>
<td>63%</td>
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<tr>
<td>Lacy</td>
<td>34</td>
<td>Pom/dex 2 mg, 28/28</td>
<td>47%</td>
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<tr>
<td>Lacleu</td>
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<td>Pom/dex 4 mg, 21/28</td>
<td>30%</td>
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<td>Pom/dex 4 mg, 28/28</td>
<td>47%</td>
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<tr>
<td>Lacy</td>
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<td>Pom/dex 2 mg, 28/28</td>
<td>49%</td>
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<td>43%</td>
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<td>Mark</td>
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<td>Cla/ Pom +/- dex, 4 mg, 21/28</td>
<td>60%</td>
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Lacy Blood 2012, 120(21): abstr 201
Open Trials for Newly Diagnosed

- MC0982 A Phase I/II Trial of Cyclophosphamide, Carfilzomib, Thalidomide and Dexamethasone (CYCLONE) in Patients with Newly Diagnosed Active Multiple Myeloma
Open Relapsed Trials at Mayo

1. PrE1003 A Phase I/II Study of the Tolerability of Lenalidomide and Low Dose Dexamethasone in Previously Treated Multiple Myeloma Patients with Impaired Renal Function

2. MFG4809g An Open-Label, Multicenter, Phase I Trial of the Safety and Pharmacokinetics of Escalating Doses of MFGR1877S in Patients with Relapsed or Refractory t(4;14)-Positive Multiple Myeloma

3. MC1181 Phase 2 Trial of MLN9708 in Patients with Relapsed Multiple Myeloma Not Refractory to Bortezomib

4. MC1082 A Phase I/II Trial of Pomalidomide, Bortezomib and Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma
5. PKB115125 A Phase Ib Study of Oral AKT Inhibitor GSK 2110183 Administered with Bortezomib and Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma

6. TED10893 A Phase I Dose Escalation Safety and Pharmacokinetic Study of Multiple Intravenous Administrations of a Humanized Monoclonal Antibody (SAR650984) Against CD38 in Patients with Selected CD38+ Hematological Malignancies

7. MC088A Phase I/II Study of Combination of Aurora Kinase Inhibitor MLN8237 and Bortezomib in Relapsed or Refractory Multiple Myeloma

8. MC1182 Phase II Trial of nab-paclitaxel (Abraxane) in Patients With Relapsed or Refractory Multiple Myeloma

Others coming soon – Oprozomib, CRM1 Inhibitor, ABT101 and many others…
**Molecular Prognostic Model**

Survival probability vs. months

- **t(11;14)**
- **Δ13**
- **All others including**
  - **t(4;14)**
  - **t(14;16)**
  - **-17p13**

- **Poor**
  - Survival probability: **24.7 mos**
- **Intermediate**
  - Survival probability: **42.3 mos**
- **Good**
  - Survival probability: **51.0 mos**

*Fonseca et al. Blood 101:4569, 2003*
mSMART

*Mayo Stratification for Myeloma And Risk-adapted Therapy*

Newly Diagnosed Myeloma

*Website: www.msmart.org*
mSMART 2.0: Classification of Active MM

High-Risk
- FISH
  - Del 17p
  - t(14;16)
  - t(14;20)
- GEP
  - High risk signature

Intermediate-Risk*
- FISH
  - t(4;14)‡
- Cytogenetic
  - Deletion 13 or hypodiploidy
- PCLI \( \geq 3\% \)

Standard-Risk*†
- All others including:
  - Hyperdiploid
  - t(11;14)**
  - t(6;14)

*† Mikhael et al Mayo Clinic Proceedings April 2013
mSMART 2.0: Classification of Active MM

High-Risk 20%
- FISH
  - Del 17p
  - t(14;16)
  - t(14;20)
- GEP
  - High risk signature

Intermediate-Risk 20%
- FISH
  - t(4;14)*
- Cytogenetic Deletion 13 or hypodiploidy
- PCLI ≥3%

Standard-Risk 60%
- All others including:
  - Hyperdiploid
  - t(11;14)
  - t(6;14)

3 years                      4-5 years                         8-10 years
mSMART – Off-Study

**Transplant Eligible**

**High Risk**
- VRD x 4
- ASCT, especially if not in CR
- VRD maintenance for minimum of 1 year

**Intermediate Risk**
- Induction with CyBorD
- Autologous stem cell transplant (ASCT)
- Bortezomib based consolidation for minimum of 1 year

**Standard Risk**
- 4 cycles of Rd\(^a\) or CyBorD
- Collect Stem Cells\(^b\)
- Autologous stem cell transplant (ASCT)
- Continue Rd\(^f\)
- Consider Lenalidomide maintenance\(^*\)

* Mikhael et al Mayo Clinic Proceedings April 2013
mSMART – Off-Study
*Transplant Ineligible

**High Risk**
- VRd*

**Intermediate Risk**
- MP + weekly Bortezomib**
  or weekly CyBorD
- Bortezomib maintenance

**Standard Risk**
- Rd\[^{b,c}\]
- Observation

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Mikael et al Mayo Clinic Proceedings April 2013
Thank You!

• Email me anytime:
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