Management of Multiple Myeloma: The Changing Paradigm

Clinical Trials
Goal of Clinical Trials: Making Progress Against Myeloma

• Increase understanding of the disease
  – Improve the way we use currently available drugs
  – Identify new potential treatments

• Develop new medications that improve, and potentially lengthen, the lives of those with cancer

• No placebos!
Impact of Clinical Trials in Myeloma: Dramatic Improvements in Survival in <10 Years

- Survival rates have nearly doubled; further improvements expected in near future
- Ten new drugs approved since 2003
  - IMiDs: Thalomid, Revlimid, Pomalyst
  - Proteasome inhibitors: Velcade, Pomalyst, Ninlaro
  - Histone deacetylase inhibitor: Farydak
  - Monoclonal antibodies: Darzalex, Empliciti
  - Chemotherapy: Doxil
- Many new drugs being studied in clinical trials
- Understanding of the biology of myeloma improving, with the eventual goal of personalized medicine
Current Research Questions

• How can treatments be matched to patients’ subtypes/genomics (personalized medicine)?

• What are the best drugs and combinations of drugs for multiple myeloma at all stages of disease?
### Misconceptions About Cancer Clinical Trials

<table>
<thead>
<tr>
<th>Misconceptions</th>
<th>Facts</th>
</tr>
</thead>
<tbody>
<tr>
<td>I may get a sugar pill (placebo) instead of real therapy.</td>
<td>No placebos are given—every patient receives treatment.</td>
</tr>
<tr>
<td>I’ll be treated like a guinea pig.</td>
<td>Most patients receive care that exceeds expectations.</td>
</tr>
<tr>
<td>Clinical studies are for people with no other options.</td>
<td>Many involve an adjustment to a standard of care that may improve outcome or quality of life</td>
</tr>
</tbody>
</table>

*The more people who participate, helps to speed drug development.*

New Drug Development

**STEP 1**
Identify a target for therapy in the laboratory

**STEP 2**
Confirm the anticancer activity in laboratory and animal studies

**STEP 3**
Clinical trials (human studies) to determine safety, dosing and effectiveness
# Clinical Trial Types

<table>
<thead>
<tr>
<th></th>
<th>Phase 1</th>
<th>Phase 2*</th>
<th>Phase 3†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objectives</strong></td>
<td>• Optimal dose</td>
<td>• Preliminary efficacy</td>
<td>• Definitive efficacy and safety</td>
</tr>
<tr>
<td></td>
<td>• Side effects</td>
<td>• Additional safety</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Metabolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>• Single arm (all patients receive experimental therapy)</td>
<td>• Single arm</td>
<td>• Two arms: patients randomly assigned to an arm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Two arms of different treatments or doses: patients randomly assigned to an arm</td>
<td></td>
</tr>
<tr>
<td><strong>Study Size</strong></td>
<td>Small (&lt;50)</td>
<td>Varies</td>
<td>&gt;200</td>
</tr>
</tbody>
</table>

*When no standard treatment is available, FDA may approve drugs based on trial results
†Conducted to receive FDA approval of new drugs, in most cases
### Other Types of Clinical Trials

#### Longitudinal Studies
- Long-term studies with a large number of patients
- The MMRF CoMMpass<sup>SM</sup> Study

#### Registry Studies
- Patients are treated using available therapies
- Efficacy and safety are analyzed following treatment
- Typically involve a large number of patients

#### Expanded Access Programs
- Allow early access to experimental therapies when no alternatives are available
Considering Entering Clinical Trials

- Talk to your doctor about your eligibility
- Meet with the research nurse to learn more
- Carefully review the informed consent paperwork
Commonly Asked Questions

- How does the study work? How often will I need to see my doctor or visit the cancer center?
- Will I need to undergo additional tests?
- What is currently known about the new drug or combination?
- What benefits can I expect?
- What side effects should I expect? Who should I notify if I have side effects?
- Can I take my vitamins or other medications?
- Can I get the treatment with my local doctor?
- Will my insurance pay for my participation in the clinical trial?
Participating in the Study

• Tell study personnel about what medications, vitamins, or dietary supplements you are taking, including the dose
• Keep a diary of any side effects you experience
• Take study medications as directed; keep days and times the same
• Keep your appointments
• Ask questions
## Drugs in Development: Phase 3 Trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Administration</th>
<th>Type</th>
<th>Trials</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>IV</td>
<td>Monoclonal antibody</td>
<td>Newly diagnosed MM • Revlimid + dex ± pembrolizumab</td>
<td>• Myelosuppression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RR MM • Pomalyst + dex ± pembrolizumab</td>
<td>• Pneumonia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Infection</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>IV</td>
<td>Monoclonal antibody</td>
<td>RR MM • Nivolumab, Empliciti, Pomalyst, and dex</td>
<td>• TBD</td>
</tr>
<tr>
<td>Xgeva* (denosumab, AMG 162)</td>
<td>IV</td>
<td>Bone-targeted antibody</td>
<td>Newly diagnosed MM • Xgeva vs Zometa</td>
<td>• Hypocalcemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Nausea, anemia, dyspnea, fatigue, constipation</td>
</tr>
</tbody>
</table>
Drugs in Development: Phase 2 Trials

**Small Molecule Inhibitors**
- Ibrutinib
- Palbociclib
- Dinaciclib
- Erismodegib
- Filanesib
- Selumetinib
- Tivantinib
- Nelfinavir
- Selinexor

**Monoclonal Antibodies**
- Tabalumab

**Bold** = treatments studied in MMRC trials
## Drugs in Development: Phase 1/2 Trials

### Small Molecule Inhibitors
- AT7519M
- Ricolinostat
- Romidepsin
- KW-2478
- TH-302
- Linsitinib
- KPT-8602
- Idasanutlin
- Oprozomib
- Marizomib
- VLX1570
- Veliparib

### Monoclonal Antibodies
- Indatuximab
- Milatuzumab
- MOR03087

**Bold** = treatments studied in MMRC trials
**Drugs in Development: Phase 1**

<table>
<thead>
<tr>
<th>Small Molecule Inhibitors</th>
<th>Monoclonal Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afuresertib</td>
<td>Atezolizumab</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>Ulocuplumab</td>
</tr>
<tr>
<td>Quisinostat</td>
<td>DFRF4539A</td>
</tr>
<tr>
<td>BMS 833923</td>
<td>Isatuximab</td>
</tr>
<tr>
<td>Ganetespib</td>
<td>Durvalumab</td>
</tr>
<tr>
<td>CB-5083</td>
<td>Lorvotuzumab mertansine</td>
</tr>
</tbody>
</table>

*Bold = treatments studied in MMRC trials*
Harnessing the Immune System to Fight Myeloma

Types of Immunotherapy, Immuno-Oncology

Passive

Monoclonal antibodies

- Direct effects
- Myeloma cell
- Antigen
- CDC
- C1q
- MAC

Active

Chimeric antigen receptor (CAR) T cells

1. Extract WBCs from patient
2. Modify and expand cells in lab
3. Infuse MM-targeted cells back to patient

Active

Vaccines (therapeutic, not preventive)

- Infuse MM-targeted cells back to patient
- Modify and expand cells in lab
- Extract WBCs from patient

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## Immune Cell Therapy in Development

<table>
<thead>
<tr>
<th>Type</th>
<th>Trial</th>
<th>Patient Types</th>
<th>Study Phase</th>
<th>Site(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CAR T</strong></td>
<td>CART-19 for multiple myeloma</td>
<td>Relapsed/ refractory</td>
<td>1</td>
<td>University of Pennsylvania</td>
</tr>
<tr>
<td></td>
<td>Safety study of CAR-modified T cells targeting NKG2D-ligands</td>
<td>Relapsed/ refractory</td>
<td>1</td>
<td>Dana-Farber Cancer Institute</td>
</tr>
<tr>
<td></td>
<td>Study of T cells targeting B-cell maturation antigen (BCMA) for previously treated multiple myeloma</td>
<td>Relapsed/ refractory</td>
<td>1</td>
<td>National Cancer Institute University of Pennsylvania</td>
</tr>
<tr>
<td><strong>MILs</strong></td>
<td>Tadalafil and lenalidomide maintenance with or without activated marrow infiltrating lymphocytes (MILs) in high-risk myeloma</td>
<td>Newly diagnosed; relapsed (without prior ASCT)</td>
<td>2</td>
<td>Sidney Kimmel Comprehensive Cancer Center</td>
</tr>
<tr>
<td></td>
<td>Adoptive immunotherapy with activated marrow-infiltrating lymphocytes and cyclophosphamide graft-versus-host disease prophylaxis in patients with relapse of hematologic malignancies after allogeneic hematopoietic cell transplantation</td>
<td>Relapsed/ refractory</td>
<td>1</td>
<td>Sidney Kimmel Comprehensive Cancer Center</td>
</tr>
<tr>
<td><strong>Affinity-enhanced T cells</strong></td>
<td>Engineered autologous T cells expressing an affinity-enhanced TCR specific for NY-ESO-1 and LAGE-1</td>
<td>Relapsed/ refractory</td>
<td>1/2</td>
<td>City of Hope University of Maryland</td>
</tr>
<tr>
<td><strong>DLI</strong></td>
<td>CD3/CD28 activated Id-KLH primed autologous lymphocytes</td>
<td>Post-transplant</td>
<td>2</td>
<td>University of Pennsylvania</td>
</tr>
</tbody>
</table>
# Therapeutic Vaccines in Development

<table>
<thead>
<tr>
<th>MM Vaccine</th>
<th>Patient Types</th>
<th>Study Phase</th>
<th>Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dendritic cell fusion vaccine + CT-011 (monoclonal antibody)</td>
<td>Post-transplant*</td>
<td>2</td>
<td>Beth Israel Deaconess Medical Center/Dana-Farber, Baylor Institute for Immunology Research (Dallas).</td>
</tr>
<tr>
<td>Hiltonol (MAGE-A3 vaccine Poly-ICLC)</td>
<td>Post-transplant*</td>
<td>2</td>
<td>University of Pennsylvania</td>
</tr>
<tr>
<td>Oncolytic measles virus (MV-NIS)</td>
<td>RR</td>
<td>1</td>
<td>Mayo Clinic (Rochester, MN)</td>
</tr>
<tr>
<td>Oncolytic measles virus (MV-NIS)</td>
<td>RR</td>
<td>2</td>
<td>University of Arkansas</td>
</tr>
<tr>
<td>PVX-410</td>
<td>SMM</td>
<td>1/2</td>
<td>Emory/Illinois Cancer Specialists/Beth Israel Deaconess Medical Center/Massachusetts General Hospital/MD Anderson Cancer Center</td>
</tr>
<tr>
<td>PVX-410</td>
<td>Post-transplant</td>
<td>2</td>
<td>Emory University</td>
</tr>
</tbody>
</table>

*Goal of eliminating any remaining cancer cells
Smoldering Multiple Myeloma: Drugs in Development

- Monoclonal antibodies are in Phase 2 trials:
  - Empliciti
  - Darzalex
  - BI-505
  - Siltuximab (CNTO328)
- Other drugs currently used for active/symptomatic myeloma are also being studied:
  - Revlimid, Phase 3
  - Kyprolis, Phase 2
Summary: Clinical Trials in Multiple Myeloma

• Clinical trials advance multiple myeloma care and speed new drug development
• No one receives a placebo
• EVERYONE who is eligible should consider participating in clinical trials
  – The more participants, the faster new treatments and new uses for existing treatments are developed

To find a clinical trial, contact the MMRF
Call 1-866-603-(MMCT) 6628
or visit www.myelomatrials.org