Management of Multiple Myeloma: The Changing Paradigm

Promising Clinical Trials in Multiple Myeloma

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Impact of Clinical Trials in Myeloma: Dramatic Improvements in Survival in <10 Years

Goal of Clinical Trials: Making Progress Against Myeloma

- Increase understanding of the disease
  - Improve the way we use currently available drugs
  - Identify new treatments
- Develop new medications that improve, and potentially lengthen, the lives of patients with cancer
- Reduce toxicities/side effects
- No placebos!
Pertinent Research Questions

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

Venetoclax Monotherapy for Relapsed/ Refractory Multiple Myeloma: Safety and Efficacy Results From a Phase 1 Study

BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins.3-5

Venetoclax binds selectively to BCL-2, freeing pro-apoptotic proteins that initiate programmed cell death (apoptosis).6-8
Objective Response Rates in All Patients and by t(11;14) Status


Pertinent Research Questions

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

• What are the best drugs and drug combinations for multiple myeloma at all stages of disease?
Efficacy of Daratumumab, Bortezomib, and Dexamethasone Versus Bortezomib and Dexamethasone in Relapsed or Refractory Multiple Myeloma Based on Prior Lines of Therapy: Updated Analysis of CASTOR

MV Mateos, J Estell, W Barreto, P Corradini, C-K Min, E Medvedova, M Qi, J Schecter, H Amin, X Qin, W Deraedt, T Casneuf, C Chiu, AK Sasser, and A Nooka

Updated Efficacy

- Median (range) follow up: 13.0 (0–21.3) months
- An additional 7% of patients receiving DVd achieved ≥CR with longer follow up

Responses continue to deepen in the DVd group with longer follow-up
**PFS: Prior Lines of Treatment**

**1 prior line**

- 12-month PFS: 77% (DVd)
- 12-month PFS: 25% (Vd)
- Median: 7.9 months
- HR: 0.22 (95% CI, 0.14–0.34; \( P < 0.0001 \))

**2 to 3 prior lines**

- 12-month PFS: 44% (DVd)
- 12-month PFS: 22% (Vd)
- Median: 6.3 months
- HR: 0.51 (95% CI, 0.36–0.73; \( P < 0.0002 \))

**DVd is superior to Vd regardless of prior lines of therapy, with greatest benefit observed in 1 prior line**

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**Question 1**

Which of the following statements is **not** correct?

A. Enrollment in clinical trials using investigational agents is voluntary.
B. Once you sign the consent form, you are bound to continue the study even if you change your mind.
C. The goal of clinical trials is to develop new therapeutic choices.
## 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 greater the number of people who participate, the faster drug development can proceed.

The Cleveland Clinic. 10 Biggest Cancer Clinical Trial Myths Busted. Available at [http://health.clevelandclinic.org/2014/04/10-biggest-cancer-clinical-trial-myths-busted/](http://health.clevelandclinic.org/2014/04/10-biggest-cancer-clinical-trial-myths-busted/)

### New Drug Development

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

**STEP 2**
Confirm the anti-cancer 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>Phase 1</th>
<th>Phase 2*</th>
<th>Phase 3†</th>
</tr>
</thead>
</table>
| Objectives | • Optimal dose  
• Side effects  
• Metabolism | • Preliminary efficacy  
• Additional safety | • Definitive efficacy and safety |
| Treatment | • Single arm (all patients receive experimental therapy) | • Single arm  
• Two arms of different treatments or doses: patients randomly assigned to an arm | • Two arms: patients randomly assigned to receive experimental therapy or standard therapy |
| Study Size | Small (<50) | Varies | >200 |

*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

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## Other Types of Clinical Trials

### Longitudinal Studies
- Long-term studies with a large number of patients
- The MMRF CoMMpass℠ 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
Question 2

Which of the following statements is true? Please select the best answer from the following statements.
A. All adverse events are closely monitored in a clinical trial.
B. The efficacy of the investigational agents is closely monitored and confirmed in a clinical trial.
C. Both A and B are true.
D. Both A and B are false.

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 • Pomalyst + dex ± pembrolizumab</td>
<td>Myelosuppression • Pneumonia • Infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RR MM • Pomalyst + dex ± pembrolizumab</td>
<td></td>
</tr>
<tr>
<td>Nivolumab</td>
<td>IV</td>
<td>Monoclonal antibody</td>
<td>RR MM • Nivolumab, Empliciti, Pomalyst, and dex</td>
<td>Fatigue • Skin rash • Muscle pain</td>
</tr>
<tr>
<td>Daratumumab</td>
<td>IV</td>
<td>Monoclonal antibody</td>
<td>Newly diagnosed MM • VTD vs VTD+dara</td>
<td>Myelosuppression • IRRs • Infection</td>
</tr>
<tr>
<td>Xgeva* (denosumab, AMG 162)</td>
<td>IV</td>
<td>Bone-targeted antibody</td>
<td>Newly diagnosed MM • Xgeva vs Zome ta</td>
<td>Hypocalcemia • Nausea, anemia, dyspnea, fatigue, constipation</td>
</tr>
</tbody>
</table>

RRMM, relapsed/refractory multiple myeloma; IRR, infusion-related reaction
*FDA-approved for non-MM indication
Drugs in Development: Phase 2 Trials

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

**Monoclonal Antibodies**
- Tabalumab

**Selinexor and Low Dose Dexamethasone (Sd) in Patients with Lenalidomide, Pomalidomide, Bortezomib, Carfilzomib & anti-CD38 mAb Refractory MM: STORM Study**

Selinexor Mechanism of Action


Treatment-Related Adverse Events ≥10%

<table>
<thead>
<tr>
<th>AE Team</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Total (N=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>8%</td>
<td></td>
<td>73%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>3%</td>
<td>49%</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>4%</td>
<td>44%</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5%</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td>Dehydration</td>
<td>3%</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>Dehydration</td>
<td></td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td><strong>Constitutional</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>15%</td>
<td></td>
<td>63%</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>1%</td>
<td></td>
<td>33%</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>25%</td>
<td>34%</td>
<td>73%</td>
</tr>
<tr>
<td>Anemia</td>
<td>27%</td>
<td>1%</td>
<td>49%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>13%</td>
<td>1%</td>
<td>32%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>11%</td>
<td>6%</td>
<td>24%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>9%</td>
<td>1%</td>
<td>14%</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>22%</td>
<td></td>
<td>42%</td>
</tr>
<tr>
<td>CPK Increase</td>
<td>3%</td>
<td></td>
<td>10%</td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Fever</td>
<td>1%</td>
<td></td>
<td>10%</td>
</tr>
</tbody>
</table>

Refractory Status
• Median time to response: 1 month
• Median duration of response: 5 months

A Phase II Study of Pembrolizumab, Pomalidomide and Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma

A Badros, M Kocoglu, N Ma, A Rapoport, E Lederer, S Philip, P Lesho, C Dell, N Hardy, J Yared, O Goloubeva, and Z Singh
University of Maryland
Baltimore, MD

Investigator initiated study supported partially by Merck
ClinicalTrials.gov # NCT02289222
Efficacy and Safety (n=48)

- The median age of participating patients was 64 years
- Patients had a median of three lines of prior therapy (range, 2–5)
- Toxicities
  - Hematologic toxicities (≥grade 3): neutropenia, anemia, lymphopenia, and thrombocytopenia.
  - Nonhematologic: hyperglycemia, upper respiratory tract infections, fatigue, and rash; pneumonitis occurred in 6 patients
- Response rates
  - ≥ partial response: 29 (60%); stringent complete response: 3 (6%) very good partial response (VGPR): 10 (21%); and partial response: 16 (33%), 3 (6%) patients had minimal response, 11 (23%) had stable disease, 2 progressed, and 3 were not evaluable for response
- DOR and PFS
  - Median DOR for responding patients was 16.3 months; progression-free survival was 17.4 months


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 MMRF trials
Drugs in Development: Phase 1

**Small Molecule Inhibitors**
- Afuresertib
- Venetoclax
- Quisinostat
- BMS 833923
- Ganetesplb
- CB-5083

**Monoclonal Antibodies**
- Atezolizumab
- Ulocuplumab
- DFRF4539A
- Isatuximab
- Durvalumab
- Lorvotuzumab mertansine
- 90Y-BC8-DOTA
- ABBV-838

**Question 3**
Which of the following statements is true of a phase 3 trial?
A. Safety is established in a phase 3 trial.
B. Preliminary efficacy is established in a phase 3 trial.
C. Both safety and preliminary efficacy are established in early phase trials. Phase 3 trial compares the investigational agent or its combination to the current standard of care.
Immune Cell Therapy

What is it?

- It is an infusion of autologous MM-directed T cells

In two main ways:

1. Patient’s T cells are harvested and then engineered in a lab to be able to identify specific surface markers on MM cells
2. These engineering T cells are then stimulated in a lab to make them more active and to proliferate and grow

How are the T cells directed to MM cells?

- Infused, MM-directed T cells directly kill MM cells and stimulate T-cell immunity

How does it work against myeloma?

- It is an infusion of autologous MM-directed T cells

Types of Immune Cell Therapy

- Chimeric antigen receptor (CAR) T cells
- T-Cell Receptor (TCR) engineered T cells
- Marrow-infiltrating lymphocytes (MILs)
Engineered T Cell Therapy

Peripheral blood T cells
TCR transgene
OR
Chimeric antigen receptor (CAR) transgene
Tumor-specific CAR (for example, anti-CD19)
Myeloma-specific TCR (eg MAGE-A3 TCR)

In vitro T cell expansion
Adoptive T cell therapy

T cells kill myeloma cells

CAR T Cell Therapy in Multiple Myeloma

- CART T cell therapy: CTL019
- MM precursor cell surface target: CD19
- Preliminary results of phase 1 study
  - 10 patients treated
  - 6 patients with ongoing responses
  - 1 patient (so far) attained minimal residual disease (MRD)-negative sCR for > 1 year

Myeloma patients with disease progression within 1 yr of prior ASCT
Second ASCT
CTL019 infusion
Patient outcome evaluated


sCR, stringent complete response
### 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>CAR T</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)</td>
<td>Relapsed/refractory</td>
<td>1</td>
<td>National Cancer Institute</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>University of Pennsylvania</td>
</tr>
<tr>
<td>MILs</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></td>
<td>Affinity-enhanced T cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></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>DLI</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</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>Oncoytic measles virus (MV-NIS)</td>
<td>RR</td>
<td>1</td>
<td>Mayo Clinic (Rochester, MN)</td>
</tr>
<tr>
<td>Oncoytic 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
  - Nivolumab
  - Siltuximab (CNTO328)

- Other drugs currently used for active/symptomatic myeloma are also being studied:
  - Revlimid, phase 3
  - Kyprolis, phase 2

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**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 participate in clinical trials
  - The greater the number of 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