Management of Multiple Myeloma: The Changing Paradigm

Clinical Trials

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Professor of Medicine
Director, Myeloma Program, University of Chicago
Goal of Clinical Trials: Making Progress Against Myeloma

• Develop treatments and strategies to potentially lengthen the lives
  – Improve the way we use currently available drugs and regimens
  – Develop new medications

• Increase the understanding of the disease
  – Identify rationale selection of existing drugs
  – Identify new potential targets for new generation of drugs
Goal of Clinical Trials: Making Progress Against Myeloma

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Cure the disease!
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: Thalidomide, Revlimid, Pomalyst
  – Proteasome inhibitors: Velcade, Kyprolis, Ninlaro
  – Histone deacetylase inhibitor: Farydak
  – Monoclonal antibodies: Darzalex, Empliciti
  – Chemotherapy: Doxil/Velcade
• Many new drugs being studied in clinical trials
• Understanding of the biology of myeloma improving, with the eventual goal of personalized medicine

IMiD, immunomodulatory drug
Some of the Current Research Questions

• Should patients with smoldering multiple myeloma be treated?
• What is the best treatment for newly diagnosed (untreated) multiple myeloma?
• What are the best drugs and combinations of drugs for relapsed/refractory multiple myeloma?
• What are the important biologic targets and genomic subtypes?
• How can treatments be matched to patients’ subtypes/genomics (personalized medicine)?
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• What are the important biologic targets and genomic subtypes?

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

Clinical trials can help to answer these questions
Participation in Clinical Trial
Participation in Clinical Trial

Why would I take a risk?
Participation in Clinical Trial

Why would I take a risk?

The risk is reasonable and you can end-up better off than with an alternative standard option.
Participation in Clinical Trial

Why would I take a risk?

The risk is reasonable and you can end-up better off than with an alternative standard option.

And for your stage of disease we truly do not know what is the best option.
Misconceptions About Cancer Clinical Trials

<table>
<thead>
<tr>
<th>Misconceptions</th>
<th>Facts</th>
</tr>
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Misconceptions About Cancer Clinical Trials

**Misconceptions**

Participation provides no direct benefit to me and I may get a sugar pill (placebo) instead of real therapy.

**Facts**

You’ll have access to promising new drugs and procedures. No placebos alone are given—every patient receives treatment. Quality of care is never sacrificed and all patients undergo close monitoring.

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The Cleveland Clinic. 10 Biggest Cancer Clinical Trial Myths Busted.
Most patients receive care that exceeds expectations and will not even feel as though they are in a study.

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- You’ll have access to promising new drugs and procedures. No placebos alone are given—every patient receives treatment. Quality of care is never sacrificed and all patients undergo close monitoring.
- Most patients receive care that exceeds expectations and will not even feel as though they are in a study.
- Sometimes they are, but many involve an adjustment to a standard of care that may improve outcome or quality of life.

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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

- Phases 1, 2, and 3
- Patients receive either the experimental treatment or the current standard treatment
New Drug Development

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Step 2: Confirm the anticancer activity in laboratory and animal studies

Step 3: Clinical trials (human studies) to determine safety, dosing and effectiveness
  - Phases 1, 2, and 3
  - Patients receive either the experimental treatment or the current standard treatment

Rigorous Studies before Moving to Clinic
# Types of Clinical Trials

<table>
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<tr>
<th></th>
<th>Phase 1</th>
<th>Phase 2*</th>
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<tr>
<td><strong>Objectives</strong></td>
<td>• Optimal dose</td>
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<td>• Two arms: patients randomly assigned to an arm</td>
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*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
# Types of Clinical Trials

We exhausted standard options

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| **Treatment**    | • Single arm (all patients receive experimental therapy)                  | • Single arm  
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| **Study Size**   | Small (<50)                                                               | Varies                                       | >200                                         |

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## Types of Clinical Trials

We exhausted standard options  
Treatment is new but looks very promising

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## Types of Clinical Trials

### We exhausted standard options

- **Objectives**
  - Optimal dose
  - Side effects
  - Metabolism

- **Treatment**
  - Single arm (all patients receive experimental therapy)

- **Study Size**
  - Small (<50)

### Treatment is new but looks very promising

- **Objectives**
  - Preliminary efficacy
  - Additional safety

- **Treatment**
  - Single arm
  - Two arms of different treatments or doses: patients randomly assigned to an arm

- **Study Size**
  - Varies

### We do not know which treatment is better

- **Objectives**
  - Definitive efficacy and safety

- **Treatment**
  - Two arms: patients randomly assigned to receive experimental therapy or standard therapy

- **Study Size**
  - >200

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Example of Phase I Clinical Trial

Carfilzomib (Kyprolis) is an approved drug for advanced myeloma
What to do if it stops working and all other options have been tried?
Example of Phase I Clinical Trial

Carfilzomib (Kyprolis) is an approved drug for advanced myeloma. What to do if it stops working and all other options have been tried? New drug Selinexor may help to overcome resistance to Kyprolis.
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New drug Selinexor may help to overcome resistance to Kyprolis.

*Turner et al, AACR 2014*
Example of Phase I Clinical Trial

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New drug Selinexor may help to overcome resistance to

---

**Figure 1:**

8226 CFZ Resistant vs Parental

- Untreated control
- CFZ 30nM
- KPT330 0.5μM
- KPT/CFZ
- KOS-2464 10nM
- KOS/CFZ

**Turner et al, AACR 2014**

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**Figure 2:**

NOD-SCID mice implanted s.c. with NCI H929 cells

- Vehicle
- Carfilzomib (3 mg/kg)
- Selinexor (10 mg/kg)
- Selinexor (10 mg/kg)
- Carfilzomib (3 mg/kg)

Example of Phase I Clinical Trial

Carfilzomib (Kyprolis) is an approved drug for advanced myeloma. What to do if it stops working and all other options have been tried?

New drug Selinexor may help to overcome resistance to Carfilzomib.

Phase I clinical trial of SEL-Kd completed enrollment.
Example of Phase I Clinical Trial

Carfilzomib (Kyprolis) is an approved drug for advanced myeloma. What to do if it stops working and all other options have been tried?

New drug Selinexor may help to overcome resistance to

Phase I clinical trial of SEL-Kd completed enrollment

71% of pts progressing on carfilzomib combination in last line of treatment responded!

Rosebeck et al, Mol Cancer Ther. 2016;15(:60-71

Jakubowiak et al, ASH 2015
Example of Phase I/II Clinical Trial

Finding Best Drug and Combination for Relapsed/Refractory Myeloma

This is my 2nd relapse. Do you have something good for me? We have so many new drugs.
Example of Phase I/II Clinical Trial

Finding Best Drug and Combination for Relapsed/Refractory Myeloma

How about his trial using KPd regimen? We already know effective and safe dose.

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Finding Best Drug and Combination for Relapsed/Refractory Myeloma

How about his trial using KPd regimen? We already know effective and safe dose.

This is my 2nd relapse. Do you have something good for me? We have so many new drugs.

Example of Phase III Clinical Trial

**Finding which Drug Combination is Better**

**POLLUX: Study Design**

- **Randomize 1:1**
- **Key eligibility criteria**
  - RRMM
  - ≤1 prior line of therapy
  - Prior lenalidomide exposure, but not refractory
  - Patients with creatinine clearance ≥30 mL/min

**DRd (n = 286)**
- Daratumumab 16 mg/kg IV
- Q4W in Cycles 1-2, q6W in Cycles 3-6, then q4W until PD
- R 25 mg PO
d 40 mg PO
- 40 mg weekly until PD

**Rd (n = 283)**
- R 25 mg PO
- D 40 mg PO
- Days 1-21 of each cycle until PD
- 40 mg weekly until PD

**Primary endpoint**
- PFS

**Secondary endpoints**
- TTP
- OS
- ORR, VGPR, CR
- MRD
- Time to response
- Duration of response

**Statistical analyses**
- 295 PFS events: 85% power for 7.7 month PFS improvement
- Interim analysis: ~177 PFS events

**Cycles:** 28 days
Example of Phase III Clinical Trial

Finding which Drug Combination is Better

POLLUX: Study Design

Multicenter, randomized (1:1), open label, active-controlled phase 3 study

DRd (n = 286)
- Key eligibility criteria:
  - RRMM
  - ≥1 prior line of therapy
  - Prior lenalidomide exposure, but not refractory
  - Patients with creatinine clearance ≥30 mL/min

- DRd regimen:
  - Daratumumab 16 mg/kg IV
  - Q2w in Cycles 1-2, Q4w in Cycles 3-6, then Q4w until PD
  - Rx: 25 mg PO
  - Days 1-21 of each cycle until PD
  - d = 40 mg PO
  - 40 mg weekly until PD

- Primary endpoint:
  - PFS

Rd (n = 283)
- Rd regimen:
  - R 25 mg PO
  - Days 1-21 of each cycle until PD
  - d = 40 mg PO
  - 40 mg weekly until PD

- Stratification factors:
  - No prior lines of therapy
  - ISS stage at study entry
  - Prior lenalidomide

- Cycles: 28 days

Overall Response Rate

<table>
<thead>
<tr>
<th>ORR</th>
<th>P &lt; 0.0001</th>
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<tr>
<td>DRd</td>
<td>93%</td>
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<td>Rd</td>
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- 295 PFS events: 85% power for 7.7-month PFS improvement
- Interim analysis: ~177 PFS events

Progression-Free Survival

- 12-month PFS: 83%
- 18-month PFS: 78%

- Median PFS: 10.4 months

- HR: 0.27 (95% CI, 0.27-0.52; P < 0.0001)
Example of Phase III Clinical Trial

Finding which Drug Combination is Better

**POLLUX: Study Design**
- Multi-center, randomized (1:1), open-label, active-controlled phase 3 study

**DRd (n = 286)**
- Daratumumab 16 mg/kg IV q2w in Cycles 1-2, q4w in Cycles 3-6, then q4w until PD
- Rev/Dex
- Days 1-21 of each cycle until PD
- 40 mg PO daily
- 40 mg weekly until PD

**Rd (n = 283)**
- Rev/Dex
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**Overall Response Rate**

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<tr>
<th>ORR (%)</th>
<th>P Value</th>
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<tr>
<td>DRd (n=281)</td>
<td>93%</td>
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<tr>
<td>Rd (n=276)</td>
<td>76%</td>
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**Progression-Free Survival**

- 12-month PFS: 83%
- 18-month PFS: 78%

**Addition of daratumumab to Rev/Dex shows remarkable benefit in relapsed and refractory myeloma**

*Dimopoulos et al, EHA 2016, presidential symp*
Other Types of Clinical Trials

**Longitudinal Studies**
- Long-term studies with a large number of patients
- The MMRF CoMMpass™ Study
  - Collecting information from approximately 1,000 multiple myeloma patients for at least 10 years. Focus is on the genomics of myeloma throughout the disease course

**Registry Studies**
- Patients are treated using available therapies
- Efficacy and safety are analyzed following treatment
- Typically involve a large number of patients
- Collect information on wider use of drugs than that gained in Phase 1–3 trials

**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 for a clinical trial and which trial would be best for you
- Meet with the research nurse for the study to learn more
- Carefully review the informed consent paperwork to better understand the study and any potential safety concerns related to the experimental medication
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
• Ask before starting any new medications, vitamins, or dietary supplements
• Keep a diary of any side effects you experience
• Take study medications as directed; keep days and times the same
• Inform the study center of any treatments or tests done outside of the medical facility: bring all records
• Keep your appointments
• Inform study personnel if you wish to stop study therapy
• Ask the study team any questions you may have
## 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 RR MM • Pomalyst + dex ± pembrolizumab</td>
<td>• Myelosuppression • Pneumonia • Infection</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>Xgeva* (denosumab, AMG 162)</td>
<td>IV</td>
<td>Bone-targeted antibody</td>
<td>Newly diagnosed MM • Xgeva vs Zometa</td>
<td>• Hypocalcemia • Nausea, anemia, dyspnea, fatigue, constipation</td>
</tr>
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*FDA-approved for non-MM indication
Investigational Therapies Targeting Myeloma Cells in the Bone Marrow Microenvironment

Cell surface targets

T cells
M cells
NK cells

Cytokines, growth factors
IL-6, VEGF, IGF-1, SDF-1α, BAFF, APRIL, BSF-3

MM cell

Targeting MM cell
- Monoclonal antibodies: isatuximab, pembrolizumab, nivolumab
- HSP90 inhibitor: ganetespib
- BTK inhibitor: imbruvica
- BCL-2 inhibitor: ABT-199
- KSP inhibitor: filanesib
- SINE: selinexor
- IGF inhibitor: OSI-906
- p97 inhibitor: CB-5083

Targeting MM cell and BM microenvironment
- Proteasome inhibitors: oprozomib, marizomib

Targeting BM microenvironment
- CXCR4 inhibitor: plerixafor

Bone marrow stromal cell

Adhesion

Cell cycle
Survival
Anti-apoptosis

Migration
GSK-3β
FKHR
Caspase-9
NF-κB
mTOR
Bad

PI3-K
Akt

Bcl-xL
Mcl-1

JAK/STAT3
Raf
MEK/ERK

Cyclin-D
IAP

NF-κB

NF-κB

Smad, ERK

CD138
BAFF-R
IGF1R
CD38
VEGFR

NK

VLA-4
MUC-1
LFA-1
ICAM-1

VCAM-1, fibronectin

Adhesion molecules

### Drugs in Development: Phase 2 Trials

<table>
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<tr>
<th>Type</th>
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</tr>
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<tbody>
<tr>
<td>Anti-CXCL12/SDF-1</td>
<td>NOX-A12</td>
</tr>
<tr>
<td>BTK inhibitor</td>
<td><strong>Imbruvica (ibrutinib, PCI-32765)</strong></td>
</tr>
<tr>
<td>CDK inhibitor</td>
<td>• Palbociclib (PD0332991)</td>
</tr>
<tr>
<td></td>
<td>• Dinaciclib (SCH727965)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Treanda (bendamustine)</td>
</tr>
<tr>
<td>CXCR4 inhibitor</td>
<td>Mozobil (plerixafor)</td>
</tr>
<tr>
<td>HDAC inhibitor</td>
<td>Zolinza (vorinostat)</td>
</tr>
<tr>
<td>Hedgehog pathway inhibitor</td>
<td>Erismodegib</td>
</tr>
<tr>
<td>KSP inhibitor</td>
<td>Filanesib (ARRY-520)</td>
</tr>
<tr>
<td>MEK inhibitor</td>
<td>Selumetinib (AZD6244)</td>
</tr>
<tr>
<td>MET inhibitor</td>
<td>Tivantinib (ARQ 197)</td>
</tr>
<tr>
<td>Monoclonal antibody</td>
<td>Tabalumab (LY2127399)</td>
</tr>
<tr>
<td>Protease inhibitor</td>
<td>Nelfinavir</td>
</tr>
<tr>
<td>Selective inhibitor of nuclear export (SINE)</td>
<td><strong>Selinexor (KPT-330)</strong></td>
</tr>
<tr>
<td>SMAC mimetic</td>
<td>LCL161</td>
</tr>
<tr>
<td>Telomerase inhibitor</td>
<td>Imetelstat (GRN163L)</td>
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*Bold = treatments studied in MMRC trials*
## Drugs in Development: Phase 1/2 Trials

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<tr>
<td>CDK inhibitor</td>
<td>AT7519M</td>
</tr>
<tr>
<td>HDAC inhibitor</td>
<td>• Ricolinostat (ACY-1215)</td>
</tr>
<tr>
<td></td>
<td>• Romidepsin</td>
</tr>
<tr>
<td>Heat shock protein inhibitor (Hsp 90)</td>
<td>KW-2478</td>
</tr>
<tr>
<td>Hypoxia-activated prodrug</td>
<td>TH-302</td>
</tr>
<tr>
<td>IGF inhibitor</td>
<td>OSI-906 (linsitinib, ASP 7487)</td>
</tr>
<tr>
<td>IL-15RaSu/Fc fusion protein</td>
<td>ALT-803</td>
</tr>
<tr>
<td>Inhibitor of the nuclear export receptor XPO1</td>
<td>KPT-8602</td>
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<tr>
<td>Melphalan</td>
<td>Melflufen</td>
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<tr>
<td>Monoclonal antibody</td>
<td>• Indatuximab (BT062)</td>
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<tr>
<td></td>
<td>• Milatuzumab (hLL1-DOX)</td>
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<td></td>
<td>• MOR03087 (MOR202)</td>
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<tr>
<td>P53-MDM2 inhibitor</td>
<td>Idasanutlin (RG-7388)</td>
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<tr>
<td>Pan-Pim kinase inhibitor</td>
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<td>Proteasome inhibitor</td>
<td>• Oprozomib (ONX0912)</td>
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<td>• Marizomib (NPI-0052)</td>
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<td></td>
<td>• VLX1570</td>
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<tr>
<td>PARP inhibitor</td>
<td>Veliparib</td>
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<tr>
<td>Targets IL-3R</td>
<td>SL-401</td>
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<tr>
<td>Tyrosine kinase inhibitor</td>
<td>Cometriq (cabozantinib)</td>
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<td>R-(-)-Gossypol acetic acid</td>
<td>AT101</td>
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# Drugs in Development: Phase 1

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<td>AKT Inhibitor</td>
<td>Afuresertib (GSK2110183)</td>
</tr>
<tr>
<td>BCL-2 inhibitor</td>
<td>Venetoclax (ABT-199)</td>
</tr>
<tr>
<td>HDAC inhibitor</td>
<td>Quisinostat</td>
</tr>
<tr>
<td>Hedgehog pathway inhibitor</td>
<td>• BMS 833923 (XL139)</td>
</tr>
<tr>
<td></td>
<td>• Erivedge (vismodegib)</td>
</tr>
<tr>
<td>Heparin-like polymer</td>
<td>Roneparstat (SST0001)</td>
</tr>
<tr>
<td>Hsp90 (heat shock protein) inhibitor</td>
<td>Ganetespib (STA-9090)</td>
</tr>
<tr>
<td>Monoclonal antibody</td>
<td>• Atezolizumab</td>
</tr>
<tr>
<td></td>
<td>• Ulocuplumab (BMS 936564)</td>
</tr>
<tr>
<td></td>
<td>• DFRF4539A</td>
</tr>
<tr>
<td></td>
<td>• <em>Isatuximab (SAR650984)</em></td>
</tr>
<tr>
<td></td>
<td>• Durvalumab (MEDI4736)</td>
</tr>
<tr>
<td>Monoclonal antibody-drug conjugate</td>
<td>• Lorvotuzumab mertansine (IMGN901, BB-10901)</td>
</tr>
<tr>
<td></td>
<td>• 90Y-BC8-DOTA</td>
</tr>
<tr>
<td></td>
<td>• ABBV-838</td>
</tr>
<tr>
<td>p97 inhibitor</td>
<td>CB-5083</td>
</tr>
<tr>
<td>Tyrosine kinase inhibitor</td>
<td>TG02</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

![Diagram showing direct effects of monoclonal antibodies on myeloma cells.](image)

**Active**

- Chimeric antigen receptor (CAR) T cells

![Diagram showing steps of CAR T cell therapy.](image)

- Vaccines (therapeutic, not preventive)

![Diagram showing steps of vaccine therapy.](image)

**Steps for CAR T cell therapy**

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

**Steps for vaccine therapy**

- Vaccines (therapeutic, not preventive)
- Infuse MM-targeted cells back to patient
## 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</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
Race for Cure

Race for Cure

More New Agents
More Smart Studies
Increased Patients Participating

Race for Cure

More New Agents
More Smart Studies
Increased Patients Participating
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Race for Cure

More New Agents
More Smart Studies
Increased Patients Participating

Focus on newly diagnosed and smoldering myeloma

Path to a Cure of Myeloma
Path to a Cure of Myeloma

Extended treatment with KRd with and w/o transplant

<table>
<thead>
<tr>
<th>KRd w/o ASCT</th>
<th>KRd + ASCT†</th>
</tr>
</thead>
<tbody>
<tr>
<td>At CR</td>
<td>At landmark time points</td>
</tr>
<tr>
<td>MRD negative, %</td>
<td></td>
</tr>
<tr>
<td>n=26</td>
<td>n=33</td>
</tr>
<tr>
<td>n=16</td>
<td>n=29</td>
</tr>
<tr>
<td>51∗</td>
<td>82</td>
</tr>
<tr>
<td>39†</td>
<td>66</td>
</tr>
</tbody>
</table>

∗Estimated rate based on 23 of 26 evaluated pts assessed for MRD by flow cytometry at CR/ suspected CR
†Estimated rate based on percentage of 13 pts in CR/sCR negative by NGS
†Actual MRD rates in subgroup of pts evaluated for MRD at the end of 8 and 18 cycles as per new IMWG MRD criteria (pts were considered MRD – negative only if in CR/sCR)
Path to a Cure of Myeloma

Extended treatment with KRd with and w/o transplant

- Improved MRD-negative rates

KRd w/o ASCT
At CR

<table>
<thead>
<tr>
<th>MRD negative, %</th>
<th>n=26</th>
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KRd + ASCT†
At landmark time points

<table>
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<tbody>
<tr>
<td>82</td>
<td>66</td>
<td>89</td>
<td>71</td>
<td></td>
</tr>
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Jakubowiak et al, EHA 2016
...which are associated with longer remissions

**KRd w/o ASCT**

- Negative (NGS)
- Negative (MFC)
- Positive (MFC)/unknown

**KRd + ASCT**

- Negative (MFC) / Negative (NGS)
- Positive (MFC)/unknown

<table>
<thead>
<tr>
<th>PFS Rate</th>
<th>1-yr</th>
<th>2-yr</th>
<th>3-yr</th>
<th>4-yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRd w/o ASCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=23</td>
<td>100%</td>
<td>91%</td>
<td>87%</td>
<td>78%</td>
</tr>
<tr>
<td>n=23</td>
<td>100%</td>
<td>91%</td>
<td>71%</td>
<td>60%</td>
</tr>
</tbody>
</table>

*Excludes 7 pts who discontinued to pursue ASCT

**Zimmerman et al, ASCO 2015, Jakubowiak et al EHA 2016**
Path to a Cure

This looks really promising
What next?
Path to a Cure

Incorporation of immunotherapy
Trials of combinations with antibodies in new MM
Adaptive designs based on biology and MRD status
Evaluating cure strategies in smoldering MM

This looks really promising
What next?
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 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