Multiple Myeloma: Relapsed and Refractory

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Myeloma treatment paradigm

- **Induction**
- **Consolidation**
- **Maintenance**

- **SCT eligible**
- **SCT ineligible**

Induction followed by continuous therapy

Tumor Burden
Case 1

- A 65-yr-old male with ISS stage 1, standard risk MM received Velcade, Revlimid, dexamethasone induction therapy for 4 cycles followed by transplant. He declined lenalidomide maintenance treatment and was in CR for 2 yrs
- He now presents with M protein of 0.6 g/dL and no anemia or other abnormalities on skeletal survey
- Hb is 14 g/dL, UPEP is negative, serum free light chain ratio is 2:1, and creatinine and calcium levels are normal
- 3 mos later, repeat testing shows M protein of 0.8 g/dL
- 6 mos later, M protein is 0.9 g/dL with no changes in the other laboratory values
What would you do now?

A. Re-treat the patient
B. Observe the patient
C. I don’t know
When to Consider Retreatment

• Differences between biochemical relapse and symptomatic relapse need to be considered.

• Patients with asymptomatic rise in M protein can be observed to determine the rate of rise and nature of the relapse.

  Caveat: patients with known aggressive or high-risk disease should be considered for salvage even in the setting of biochemical relapse.

• CRAB criteria are still listed as the indication to treat in the relapse setting.

  C: Calcium elevation (> 11.5 mg/L or ULN)
  R: Renal dysfunction (serum creatinine > 2 mg/dL)
  A: Anemia (Hb < 10 g/dL or 2 g < normal)
  B: Bone disease (lytic lesions or osteoporosis)
Case 2

- A 65-yr-old female presents with ISS stage 2 MM. She is treated with RVD (Revlimid, Velcade, Dex) followed by autologous transplant. Posttransplantation, she achieves a VGPR and is started on Revlimid maintenance therapy.
- After 2 yrs, she progresses on Revlimid maintenance therapy. She has no neuropathy.
- M protein is 1.2 g/dL, Hb is 9.3 g/dL, calcium is normal, serum free light chain ratio is 6:1, and IgG is 2900 mg/dL.
- Skeletal survey shows new lytic disease. UPEP is negative, bone marrow shows 10% to 20% plasma cells with normal cytogenetics.
What would you do now?

A. Re-treat the patient
B. Observe the patient
C. I don’t know
What treatment would you choose?

A. Revlimid-based
B. Velcade-based
C. Velcade/Revlimid/dexamethasone (VRD)
D. Darzalex-based
E. Kyprolis-based
F. Empliciti-based
Post-HCT: Patterns of Relapse\textsuperscript{1}

What is relapsed/refractory disease?

- **Relapsed:** recurrence after a response to therapy
- **Refractory:** progression despite ongoing therapy
Restarting Therapy and Prognostic Factors in Relapsed Myeloma

- No prospective studies; patients can have an indolent course

**Indications to start therapy**
- CRAB features
- Rapid rise in M protein
- High levels of free light chain with renal presentation
- High-risk cytogenetics with biochemical progression

**Prognostic factors**
- Duration of initial response
- Acquisition of new abnormalities (1qamp, del17p)
- ISS/RISS
- Performance status
- Presence of EMD
- Circulating plasma cells

Choosing Therapy for Relapsed/Refractory Myeloma

• **What do we know about the patient’s myeloma?**
  – What prior therapy has been used?
  – How well did it work?
  – Did the myeloma progress on active therapy?
  – High-risk cytogenetics/FISH/GEP?

• **What do we know about the patient?**
  – Age
  – Other medical problems
    • Diabetes
    • Blood clots
  – Lasting side effects from past therapies
    • Peripheral neuropathy
  – Personal preferences and values
Evolution of Multiple Myeloma Treatment: 11 New Drugs Approved in ≤15 Years

Conventional Therapy
- High-dose chemotherapy with autologous bone marrow transplant
  - VAD
- High-dose melphalan
- High-dose dexamethasone
- Bisphosphonates

Novel Therapy
- Revlimid
- Thalomid
- Velcade
- Doxil
- Kyprolis
- Ninlaro
- Pomalyst
- Farydak
- Empliciti
- Darzalex
- Xgeva

Chemotherapy, IMiD, HDAC inhibitor, Monoclonal antibody, Bone support.
Factors to Consider in Treatment Selection

**DISEASE-RELATED**
- DOR to initial therapy
- FISH/cytogenetics/genomics profile

**PRIOR TREATMENT–RELATED**
- Prior drug exposure
- Toxicity of regimen
- Mode of administration
- Previous SCT

**PATIENT-RELATED**
- Pre-existing toxicity
- Presence of other conditions
- Age
- General health
- Personal lifestyle and preferences

DOR, duration of response; FISH, fluorescence in situ hybridization; SCT, stem cell transplant.

Continuing Evolution of Multiple Myeloma Treatment: New Classes and Targets

Novel Therapies and Immunotherapy

PLD, pegylated liposomal doxorubicin; IMiD, immunomodulatory drug; HDAC, histone deacetylase; KSP, kinesin spindle protein, SINE, selective inhibitor of nuclear export

*Not yet FDA-approved; only available in clinical trials
†Treatments studied in MMRC trials
‡FDA-approved for a non-MM indication

IMiD
Proteasome inhibitor
HDAC inhibitor
Chemotherapy
Monoclonal antibody
Adoptive T cell therapy
Vaccines
Checkpoint inhibitors
CDK inhibitor
Bone support
Bcl-2 inhibitor
Anti-BCMA antibodies

Doxil
Kyprolis
Velcade
Thalomid
Revlimid
Pomalyst
Farydak
Empliciti
Ninlaro
Pembrolizumab
Nivolumab
Atezolizumab
Isatuximab
Dinaciclib
CAR-T
Oprozomib
Vaccines
Dinaciclib
Venetoclax
Selinexor
Xgeva
Bcl-2 inhibitor
GSK2857916, AMG 224

Options for Relapsed/Refractory Disease Continue to Increase

When did you relapse from your initial therapy?

- ≤6 months
  - Different therapy
  - Stem cell transplant

- >6 months
  - Repeat initial therapy
  - Different therapy
  - Stem cell transplant
  - Clinical trial
How to Choose From Treatment Options for Relapsed and Refractory Myeloma

Factors to consider
- Treatment related factors
- Disease related factors
- Patient related factors

Symptomatic relapse
Consider clinical trial

Prior SCT

Relapse within first 12 months
- Newer combination strategies CRD, CPD, RVD, or clinical trial
- Allogeneic transplant clinical protocol

Relapse beyond the first 12 months
*Bortezomib ± dexamethasone
*Lenalidomide + dexamethasone
*Bortezomib ± PLD
RVD, VTD, CFZ, CRD, VCD, RCD, DCEP±V, DT-PACE±V, Cytoxan, Pd, T

Transplant eligible; has good PS
- Primary refractory- SCT
- Relapsed/refractory- SCT

Transplant ineligible
- If patient has previously responded to the therapy, tolerated and relapsed at least 6 months after prior drug exposure
  - Repeat prior therapy
- Otherwise, consider
  - *Bortezomib ± dexamethasone
  - *Bortezomib + PLD
  - *Lenalidomide + dexamethasone
  - RVD, VTD, CFZ, CRD, VCD, RCD, DCEP, DT-PACE±V, Cytoxan, Pd, T

No

Yes

Relapse within 12 months
- Newer combination strategies CRD, CPD, RVD, or clinical trial
- Allogeneic transplant clinical protocol

Relapse after transplantation
- If patient has previously responded to the therapy, tolerated and relapsed at least 6 months after prior drug exposure
  - Repeat prior therapy
- Otherwise, consider
  - *Bortezomib ± dexamethasone
  - *Bortezomib + PLD
  - *Lenalidomide + dexamethasone
  - RVD, VTD, CFZ, CRD, VCD, RCD, DCEP, DT-PACE±V, Cytoxan, Pd, T

Subsequent relapse

Relapse with maintenance therapy after SCT

Relapse without maintenance therapy after SCT

SCT2

NCCN category 1 recommendations
### Available Anti-Myeloma Agents: So Many Choices!

<table>
<thead>
<tr>
<th>IMiDs</th>
<th>Proteasome Inhibitors</th>
<th>Chemotherapy Anthracyclines</th>
<th>Chemotherapy Alkylators</th>
<th>Steroids</th>
<th>HDAC Inhibitors</th>
<th>mAbs</th>
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<tbody>
<tr>
<td>Thalomid (thalidomide)</td>
<td>Velcade (bortezomib)</td>
<td>Adriamycin</td>
<td>Cytoxan (cyclophosphamide)</td>
<td>Dexamethasone</td>
<td>Farydak (panobinostat)</td>
<td>Empliciti (elotuzumab)</td>
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<td>Revlimid (lenalidomide)</td>
<td>Kyprolis (carfilzomib)</td>
<td>Doxil (liposomal doxorubicin)</td>
<td>Bendamustine</td>
<td>Prednisone</td>
<td>Zolinza (vorinostat)</td>
<td>Darzalex (daratumumab)</td>
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<td>Pomalyst (pomalidomide)</td>
<td>Ninlaro (ixazomib)</td>
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<td>Melphalan</td>
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New formulations, new dosing, and new combinations, too!

IMiD, immunomodulatory drug; HDAC, histone deacetylase; mAb, monoclonal antibody.
Possible Anti-Myeloma Regimens: So Many Choices!

<table>
<thead>
<tr>
<th>Pomalyst (pomalidomide)</th>
<th>Kyprolis (carfilzomib)</th>
<th>Darzalex (daratumumab)</th>
<th>Empliciti (elotuzumab)</th>
<th>Ninlaro (ixazomib)</th>
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<td>KD</td>
<td>Dara</td>
<td>Elo RD</td>
<td>Ixa</td>
<td>Pano VD</td>
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<td>Car Pom D</td>
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<td>Car Pano Dex</td>
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<td>Len Pano</td>
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<td>Dara Carfil</td>
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<tr>
<td>Pom Cy Dex</td>
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Dara, Darzalex (daratumumab); Pom, Pomalyst (pomalidomide); Car/K/Carfil, Kyprolis (carfilzomib); Ixa/I, Ninlaro (ixazomib); Bort/V, Velcade (bortezomib); Elo, Empliciti (elotuzumab); Dex/D, dexamethasone; R/Len, Revlimide (lenalidomide); Cy, cyclophosphamide; Pano, Farydak (panobinostat).
Therapy for relapsed disease

MYELOMA THERAPY\textsuperscript{14,12}

Therapy for Previously Treated Multiple Myeloma (assess for response after each cycle)

**Preferred Regimens**
- Repeat primary induction therapy (if relapse at >6 mo)
- Bortezomib/lenalidomide/dexamethasone
- Carfilzomib (twice weekly)\textsuperscript{9}/dexamethasone (category 1)\textsuperscript{9}
- Carfilzomib\textsuperscript{9}/lenalidomide/dexamethasone (category 1)\textsuperscript{13}

**Other Recommended Regimens**
- Bendamustine/bortezomib/dexamethasone
- Bendamustine/lenalidomide/dexamethasone
- Bortezomib/posomol doxorubicin/dexamethasone (category 1)
- Bortezomib/cyclophosphamide/dexamethasone
- Carfilzomib\textsuperscript{5}/cyclophosphamide/dexamethasone
- Carfilzomib (weekly)\textsuperscript{5}/dexamethasone\textsuperscript{9}
- Cyclophosphamide/lenalidomide/dexamethasone
- Bortezomib/dexamethasone (category 1)\textsuperscript{9}
- Daratumumab\textsuperscript{14,16}
- Daratumumab\textsuperscript{14}/pomalidomide\textsuperscript{30}/dexamethasone
- Elotuzumab/bortezomib/dexamethasone
- Ixazomib\textsuperscript{17}/lenalidomide/dexamethasone (category 1)\textsuperscript{13}

**Useful in Certain Circumstances**
- Bendamustine
- Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)\textsuperscript{21}
- Ixazomib\textsuperscript{17}/dexamethasone
- Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE)\textsuperscript{21} ± bortezomib (VTD-PACE)\textsuperscript{21}
- High-dose cyclophosphamide

*Selected, but not inclusive of all regimens.

\textsuperscript{9}Seperates zoster prophylaxis for patients treated with proteasome inhibitors or daratumumab.

\textsuperscript{12}Substantial use of bortezomib is the preferred method of administration.

\textsuperscript{13}Full-dose aspirin recommended with immunomodulatory-based therapy. Therapeutic anticoagulation recommended for those at high risk for thrombosis.

\textsuperscript{15}Can potentially cause cardiac and pulmonary toxicity, especially in elderly patients.

\textsuperscript{16}Triple regimens should be used as the standard therapy for patients with multiple myeloma; however, elderly or frail patients may be treated with doublet regimens.

\textsuperscript{17}Consideration for appropriate regimen is based on the context of clinical relapse.

\textsuperscript{18}Clinical trials with these regimens primarily included patients who were lenalidomide-naive or with lenalidomide-sensitive multiple myeloma.

\textsuperscript{19}May interfere with serological testing and cause false-positive indirect Coombs test (See MYEL-E).

\textsuperscript{20}Indicated in combination with lenalidomide and dexamethasone for the treatment of patients who have received one to three prior therapies.

\textsuperscript{21}Indicated for the treatment of patients who have received at least three prior therapies, including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double refractory to PI and immunomodulatory agent.

\textsuperscript{22}Indicated for the treatment of patients who have received at least one prior therapy.

\textsuperscript{23}Consider single-agent lenalidomide or pomalidomide for steroid-intolerant individuals.

\textsuperscript{24}Indicated for the treatment of patients who have received at least two prior regimens, including bortezomib and an immunomodulatory agent.

\textsuperscript{25}Indicated for the treatment of patients who have received at least two prior therapies including an immunomodulatory agent and a proteasome inhibitor and who have demonstrated disease progression on or within 60 days of completion of the last therapy.

\textsuperscript{26}Generally reserved for the treatment of aggressive multiple myeloma.

Second or later Relapse \* Off-Study

Not Plasma Cell Leukemia (PCL) or Similar extramedullary disease (EMD)

- Dual-Refractory (Bortezomib and Lenalidomide)**
- Triple-Refractory (Bortezomib, Lenalidomide and Carfilzomib)**
- TRIPLE-Refractory (Bortezomib, Len, and Pomalidomide)**

- KRD or Pom+Ix to maximum response or 18 months, then Rd
- PCD, PVD or Car-Pom-Dex to maximum response or 18 months, then Pom+Ix
- KRD or Car-Pom-Dex to maximum response or 18 months, then Rd or Pom+Ix

* If single refractory, refer to First Relapse algorithm; **Auto transplant is an option, if transplant candidate and feasible; Doubles such as Cyto-Pred, Rd or Kd could be considered in patients with indolent disease.
Clinical Trials
How do clinical trials work?

Phase I investigates for safety and side effects, dosage and best way to give treatment—includes 20 or more people.

Phase II determines effectiveness and safety—typically includes fewer than 100 (may include up to 300) people.

Phase III looks at effectiveness, side effects and safety in comparison with other treatments—includes 100s to 1000s of people.

Phase IV gathers more information after FDA approval & drug is on market.
Placebos are rarely used in cancer clinical trials and only in the context of another active drug.
Clinical trials

• Are an important option for everyone
• Can be for people newly diagnosed, with limited disease or advanced disease
• Are appropriate for people of different age, gender, and race, depending on the purpose and phase of the study
• Take into account all the above factors as well as stage of disease, other treatments used and presence of any other illness

Remember...communication with your healthcare team is important in making treatment decisions about standard treatment or clinical trial treatment
Why Do So Few Cancer Patients Participate in Clinical Trials?

Patients may:

• Be unaware of clinical trials
• Lack access to trials
• Fear, distrust, or be suspicious of research
• Have practical or personal obstacles
• Face insurance or cost problems
• Be unwilling to go against their physicians’ wishes
Benefits of Clinical Trials

• You will have normal standard of care in terms of office visits, lab work, etc
• You may even have additional care and investigation as a part of the clinical trial
• You will generally see your health care providers and will also have a research coordinator involved in your care
• You will likely even have a higher standard of care than normal!
Questions That Can be Addressed by Conducting Clinical Trials

- 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?
- How can treatments be matched to patients’ subtypes/genomics (personalized medicine)?
Impact of Clinical Trials in Myeloma:
Dramatic Improvements in Survival in <10 Years

- Survival rates have nearly doubled; further improvements expected in near future.
- 11 new drugs approved since 2003.
- Many new drugs being studied in clinical trials.
- Understanding of the biology of myeloma improving, with the eventual goal of personalized medicine.
How do I find a clinical trial?

1. Ask your treating hematologist/oncologist about any available trials
2. Check with any academic medical centers close to your home
3. The National Cancer Institute (www.cancer.gov)
4. The IMF/MMRF/LLS
# New Agents in Myeloma Therapy

<table>
<thead>
<tr>
<th>New IMiDs</th>
<th>Oral proteasomes</th>
<th>Kinase inhibitors</th>
<th>Novel MOA</th>
<th>HDAC inhibitors</th>
<th>Immuno-therapies</th>
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<tbody>
<tr>
<td>Lenalidomide</td>
<td>Bortezomib</td>
<td>Vemurafenib</td>
<td>Venetoclax</td>
<td>Panobinostat</td>
<td>Monoclonal antibodies</td>
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<td>Pomalidomide</td>
<td>Carfilzomib</td>
<td>Afuresertib</td>
<td>Selinexor</td>
<td>Ricolinostat</td>
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<td>Dinaciclib</td>
<td>Filanesib</td>
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<td>– Elotuzumab</td>
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<td>Idasanutlin</td>
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<td>Antibody-drug conjugates</td>
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<td>Dabrafenib</td>
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<td>Sotatercept</td>
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<td>CB-5083</td>
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IMiD, immunomodulatory drug; HDAC, histone deacetylase inhibitor, MOA, mechanism of action, BiTE, bispecific T-cell engager; CAR-T, chimeric antigen receptor (CAR) T cells
New Drug in a New Class: Selinexor

- Exportin 1 (XPO1) is the nuclear exporter for the majority of tumor suppressor proteins (and also steroid receptor) that put the brakes on MM growth.

- Selinexor* is a first-in-class XPO1 inhibitor.

*Investigational agent; not yet approved by the FDA.
Efficacy of Selinexor in Relapsed/Refractory Myeloma: Selinexor + Dexamethasone

- 48 pts refractory to REV, POM, V, K (Quad)
- 31 pts refractory to above + anti-CD38 mAbs (Penta)

<table>
<thead>
<tr>
<th>Safety, n (%)</th>
<th>All patients</th>
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<tr>
<td>Gr 3/4 (≥10%)</td>
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<tr>
<td>Thrombocytopenia</td>
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<tr>
<td>Neutropenia</td>
<td>21</td>
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<tr>
<td>Anemia</td>
<td>25</td>
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<tr>
<td>Fatigue</td>
<td>14</td>
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<td>Hyponatremia</td>
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Efficacy

<table>
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<th></th>
<th>All</th>
<th>Quad</th>
<th>Penta</th>
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<tbody>
<tr>
<td>ORR</td>
<td>21%</td>
<td>21%</td>
<td>20%</td>
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</table>

STORM Trial

The combination of selinexor and dexamethasone has an overall response rate of 21% in patients with heavily pretreated, refractory myeloma with limited therapeutic options.
New Drug in a New Class: Venetoclax

- Bcl-2 inhibitor; targets myeloma growth and proliferation
- Approximately 15% of myeloma patients have t(11;14) which is the primary target of the Bcl-2 inhibitor

*Approved for a non-MM indication*
Efficacy of Venetoclax in Relapsed/Refractory Myeloma: Venetoclax Monotherapy

<table>
<thead>
<tr>
<th>Status</th>
<th>ORR 21% (n=66)</th>
<th>t(11;14) (n=30)</th>
<th>Non-t(11;14) (n=36)</th>
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<tbody>
<tr>
<td>sCRs</td>
<td>3%</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>CR</td>
<td>4%</td>
<td>10%</td>
<td>3%</td>
</tr>
<tr>
<td>VGPR</td>
<td>8%</td>
<td>13%</td>
<td>3%</td>
</tr>
<tr>
<td>PR</td>
<td>6%</td>
<td>13%</td>
<td>3%</td>
</tr>
</tbody>
</table>

**Median TTP:**
- t(11;14): 6.6 mos vs 1.9 mos without t(11;14)

Efficacy of Venetoclax in Relapsed/Refractory Myeloma: Venetoclax + Velcade + Dexamethasone

Objective Responses Rates for Patients with R/R MM

Efficacy of Venetoclax in Relapsed/Refractory Myeloma: Carfilzomib + Venetoclax

1 PR was unconfirmed as of 18 Apr 2018.
Drugs in Development: Phase 1–2 Trials

<table>
<thead>
<tr>
<th>Small-Molecule Inhibitors</th>
<th>Monoclonal Antibodies</th>
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<tbody>
<tr>
<td>AT7519M</td>
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<tr>
<td>BMS 833923</td>
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<td>• Mepitelum</td>
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<td>• Tabalumab</td>
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<td>• Ulocuplumab</td>
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</tbody>
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**Bold** = treatments studied in MMRC trials
Main Targets for Immunotherapy

- Directly targeting myeloma cell markers
- Overcoming immune suppression
- Boosting myeloma-fighting T cells
- Activating myeloma-specific immunity

Monoclonal antibodies
CAR T cells
IMiDs, checkpoint inhibitors
Vaccines

Monoclonal Antibody: Darzalex (daratumumab)

**Current Indications**
- For newly diagnosed myeloma patients who are ineligible for autologous stem cell transplant (ASCT), in combination with Velcade, melphalan, and prednisone
- For relapsed/refractory myeloma alone or in combination with Revlimid and dexamethasone, or Velcade and dexamethasone, or Pomalyst and dexamethasone

**How is Darzalex administered?**
- Intravenously
- Once a week for the first 8 weeks then every 2 weeks for 4 months then monthly
- Pre- and post-medication for infusion reactions
- Future SC administration may decrease infusion reactions and infusion time

**What are the possible side effects?**
- Infusion reactions 40%
- Fatigue
- Upper respiratory tract infection
POLLUX and CASTOR Study Designs\textsuperscript{1,2}

Open-label, multicenter, randomized (1:1), active-controlled, phase 3 studies in RRMM patients with \geq 1 prior line of therapy

**POLLUX**

- DRd (n = 286)
  - D 16 mg/kg IV
    - Every week: Cycles 1-2
    - Every 2 weeks: Cycles 3-6
    - Every 4 weeks until PD
  - R 25 mg PO (similar to Rd alone)
  - d 40 mg (similar to Rd alone)

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

**CASTOR**

- DVd (n = 251)
  - D 16 mg/kg IV
    - Every week: Cycles 1-3
    - Every 3 weeks: Cycles 4-8
    - V 1.3 mg/m\textsuperscript{2} SC (similar to Vd alone)
  - d 20 mg (similar to Vd alone)

- Vd (n = 247)
  - V 1.3 mg/m\textsuperscript{2} SC on Days 1, 4, 8, 11 for 8 cycles
  - d 20 mg on Days 1, 2, 4, 5, 8, 9, 11, 12 for 8 cycles

**Patient characteristics**
- Median (range) prior lines: 1 (1-11)
- Prior V: 84%
- Prior R: 18%

**Patient characteristics**
- Median (range) prior lines: 2 (1-10)
- Prior V: 66%
- Prior R: 42%

---


Presented By Katja Weisel at 2017 ASCO Annual Meeting
POLLUX: 1-Year Update

- Median follow-up of 25.4 months

**ITT**

- 24-month PFS: 68% DRd (n = 286) Median not reached
- HR, 0.41 (95% CI, 0.31-0.53; P < 0.0001)

**1 Prior Line**

- 24-month PFS: 70% DRd (n = 149) Median not reached
- HR, 0.39 (95% CI, 0.26-0.58; P < 0.0001)

Rd (n = 283) Median 17.5 mo

Rd (n = 146) Median 19.6 mo

---

**Notes:**

- ITT, intent-to-treat; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval
- Kaplan-Meier estimates; exploratory analyses based on 1-year update clinical cut-off date of March 7, 2017.

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Presented By Katja Weisel at 2017 ASCO Annual Meeting
CASTOR: 1-Year Update

- Median follow-up of 19.4 months

**ITT\(^1\)**
- 18-month PFS\(^a\)
- 48%存活
- HR: 0.31 (95% CI, 0.24-0.39; \(P < 0.0001\))
- Median 16.7 mo

**1 Prior Line\(^1\)**
- 18-month PFS\(^a\)
- 68%存活
- HR, 0.19 (95% CI, 0.12-0.29; \(P < 0.0001\))
- Median not reached

Adding daratumumab to SOC regimens significantly prolongs PFS

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**SOC, standard of care**

**Kaplan-Meier estimates; exploratory analyses based on 1-year update clinical cut-off date of January 11, 2017.**

**Lentiwit S, et al. Poster presentation at ASCO 2017. Abstract 6036.**

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**Presented by: Katja Weisel**
Monoclonal Antibody: Empliciti (elotuzumab)

Current Indications
• For relapsed/refractory myeloma in combination with Revlimid or Pomalyst and dexamethasone

How is Empliciti administered?
• Intravenously
• Once a week for the first 8 weeks then every 2 or 4 weeks
• Premedication in anticipation of infusion reactions

What are the possible side effects?
• Fatigue
• Diarrhea
• Fever
• Constipation
• Cough
• Peripheral neuropathy
• Infusion reactions
• Nasopharyngitis
• Upper respiratory tract infection
• Decreased appetite
• Pneumonia
• Small chance of second new cancer
Efficacy of Empliciti in Relapsed/Refractory Myeloma: Empliciti + Revlimid + Dexamethasone

- Compared to Revlimid and dexamethasone alone, the addition of elotuzumab significantly increased:
  - Progression-free survival
  - Overall response rates
- The triple combination resulted in a 30% reduction in the risk of disease progression or death
- Another phase 3 trial comparing the same combinations is under way in patients with newly diagnosed disease

ELOQUENT-2 Trial
Efficacy of Empliciti in Relapsed/Refractory Myeloma: Empliciti + Revlimid + Dexamethasone
Extended Four-Year Follow-Up Data

HR, hazard ratio
ELOQUENT-2 Trial
Efficacy of Empliciti in Relapsed/Refractory Myeloma: Empliciti + Pomalyst + Dexamethasone

• 46% reduction in the risk of progression or death with EPd
• Median PFS was more than twice as long with EPd vs Pd

ITT, intent-to-treat; NE, not estimable
ELOQUENT-3
Types of Monoclonal Antibodies

- Naked
  - Nothing is attached

- Drug conjugates
  - A toxin or radioactive isotope is attached

- Bispecific
  - Examples: BiTE, PD-1, CD3, CD16, PD-1, CD3
  - Targets: BiTE (CD33, CD19, etc), PD-1, CD3, CD16, PD-1
  - In MM: BCMA, SLAMF7, CD38
Bispecific Antibodies

- Clinical trials
- Several ongoing trials
- Too early for data results
- Some of the molecules and targets
  - GBR1342-101 (CD38 × CD3)\(^1\)
  - PF-06863135 (BCMA × CD3)\(^2\)
  - JNJ-64407564 (GPRC5D × CD3)\(^3\)
  - GO39775 (FcRH5 × CD3)\(^4\)
  - JNJ-644007957 (BCMA × CD3)\(^5\)
  - CC-93269 (BCMA × CD3)\(^6\)

BiTE, bispecific T-cell engager

### BiTEs to Watch

<table>
<thead>
<tr>
<th><strong>AMG 420</strong>[^1]</th>
<th><strong>AMG 701</strong>[^2]</th>
<th><strong>Others</strong></th>
</tr>
</thead>
</table>
| - Binds to the CD3 molecule on T cells and the BCMA molecule on myeloma cells  
- Phase 1 clinical trial results  
  - 42 relapsed myeloma patients  
  - 70% of patients responded  
  - Therapy was associated with infections  
- This drug will continue its clinical development in 2019 | - Similar to AMG 420 but has an extended half-life (longer time in the bloodstream)  
- Preclinical analysis  
  - Kills MM cells (and is enhanced by Revlimid)  
  - Promotes the activation of T cells | **BCMA targets**  
- BLI836909[^†]  
- PF-06863135[^‡]  
- CC-93269[^¶]  
**Other targets**  
- Blinatumomab (CD19)*  
- GBR1342-101 (CD38)[^§]  
- JNJ-64407564 (GPRC5D)[^**]  
- BFCR4350A (FcRH5)[^††] |

*Amgen; †Boehringer Ingelheim; ‡Pfizer; ¶Celgene; §Glenmark Pharmaceuticals; **Janssen; ††Genentech
New Monoclonal Antibody: Antibody-Drug Conjugate (ADC)

- 35 patients with relapsed/refractory MM (many who had previously received more than 5 different regimens) were treated with GSK2857916 via an intravenous (IV) infusion.
- Results from the trial revealed that 60% of patients had a response.
- The most commonly occurring side effects were corneal events (such as blurred vision, dry eye) and low platelet counts.

Anti-BCMA ADC GSK2857916*

*Investigational agent; not yet approved by the FDA
**Immune Cell Therapy**

**What is it?**

- It is an infusion of autologous *myeloma-directed* T cells

**How are the T cells directed to myeloma cells?**

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

**How does it work against myeloma?**

- Infused, myeloma-directed T cells directly kill myeloma cells and stimulate T-cell immunity
Normal T Cells vs CAR T Cells

Natural T cell with T cell receptor (TCR)

- Needs a jump start to target and kill myeloma cells

Engineered T cell with chimeric antigen receptor (CAR)

- Homing beacon built in to target and kill myeloma cells

Engineered MM cell seeker
The CAR-T therapy Process

1. A patient's leukocytes are collected by apheresis

2. Patient receives lymphocyte-depleting chemotherapy prior to T-cell infusion

Ex-vivo cell processing

T-cell activation

CAR transduction

Virus: retrovirus, lentivirus
Electroporation: RNA/DNA

T-cell proliferation

3. Patient receives CAR T-cell infusion

Lekha Mikkilineni, and James N. Kochenderfer Blood 2017;130:2594-2602
Boosting Our Own Cancer-Killing Cells

White blood cells known as T-cells protect the body from disease and infection. CAR T-cell therapy gives T-cells the power to fight cancer.

1. Collection
   T-cells are collected from patient's blood and sent to the lab. This is the same basic process as when a person donates blood.

2. Conversion
   In the lab, T-cells are changed genetically so that they grow chimeric antigen receptors (CARs) on their surfaces, turning them into CAR T-cells that can find and kill cancer cells.

3. Replication
   CAR T-cells are expanded in the lab.

4. Infusion
   Patient receives infusion of CAR T-cells.

5. Expansion
   The number of CAR T-cells continues to expand in the patient as they seek out and contact their target cancer cells.

6. Cancer cells destroyed
   CAR T-cells in the patient destroy the cancer cells, and remain on alert for many months for any cancer cells that may have initially escaped.
# BCMA-Directed CAR T Cells in Multiple Myeloma

<table>
<thead>
<tr>
<th></th>
<th>NCI(^1)</th>
<th>PENN(^2)</th>
<th>BB2121 BLUEBIRD(^3)</th>
<th>LCAR-B38M LEGEND(^4)</th>
<th>MCARH171 MSK/JUNO(^5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>26 (16*)</td>
<td>24 (19*)</td>
<td>21 (18*)</td>
<td>35 (30*)</td>
<td>6</td>
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<tr>
<td># Prior Tx</td>
<td>10</td>
<td>7</td>
<td>7</td>
<td>3–4</td>
<td>7.5</td>
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<td>Efficacy</td>
<td></td>
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<tr>
<td>ORR</td>
<td>81%*</td>
<td>53%*</td>
<td>94%*</td>
<td>100%</td>
<td>NR</td>
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<tr>
<td>CR</td>
<td>18%</td>
<td></td>
<td>56%</td>
<td>63% (sCR)</td>
<td>NR</td>
</tr>
<tr>
<td>Toxicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRS</td>
<td>81%</td>
<td>83%</td>
<td>71%</td>
<td>83%</td>
<td>50%</td>
</tr>
<tr>
<td>CRS (Gr 3/4)</td>
<td>37%</td>
<td>33%</td>
<td>10%</td>
<td>5.7%</td>
<td>None</td>
</tr>
</tbody>
</table>
| Neurotoxicity (all grades) | 19% | 25% | 24% | None | None | *Responses at therapeutic CAR T dose levels

CAR T-Cell Therapy Future Directions

Race to FDA approval
- Global pivotal phase 2 trial (KarMMa) is open for enrollment
  - bb2121 dose range: 150–450 \times 10^6 \text{ CAR+ T cells}
  - 9 sites in US and 10 in Europe
- Legend/Janssen soon to start pivotal trial of LCAR-B38M
- Others not far behind

Improving efficacy
- Understand why CAR T cells fail or stop working
- Next-generation or “armored” CAR T cells

Improving safety
- Identify correlates to predict and reduce rates of cytokine release syndrome and neurotoxicity
- Safety switches to induce suicide or eliminate CAR T cells

Improving access
- Allogeneic off-the-shelf CAR T cells
- CAR T-cell therapy for other stages of disease, new disease targets
Key Points

Everyone is excited about CAR T, but this is a strategy that is still very toxic and of very limited availability.

We still don’t know the long-term outcome for CAR T.

What are the best targets? How do we identify them?

Antibody drug conjugates are very exciting; a number are already in clinical trials.