Increasing Number of New Drugs

**In Trials**
- IXAZOMIB
- Anti-CD38
- ELOTUZ
- HDAC
- POM
- CAR
- LEN
- BTZ

**Approved**
- STEROIDS
- RAD
- ME
- SCT
- HD
- VAD
- STEROIDS
- RAD
- ME
- 1st SCT
- BISPH
- THAL
- SCT
- HD
- VAD
- STEROIDS
- RAD
- ME
- 2nd SCT
- BISPH
- THAL

- Oral proteasome inhibitor
- Anti-CD38 Antibodies
- ELOTUZ = Elotuzumab
- HDAC = HDAC inhibitors
- POM = Pomalidomide
- CAR = Carfilzomib
- LEN [REVLIMID] = Lenalidomide
- BTZ [VELCADE] = Bortezomib
- BISPH = Bisphosphonates
- THAL = Thalidomide
- SCT = Stem cell transplantation
- HDC = High-dose chemotherapy
- VAD = Vincristine, doxorubicin, dexamethasone

Improving Overall Survival in Myeloma: Impact of Transplant and Novel Therapies


Overall survival 1971–2006

Diagnosis period | Median OS
--- | ---
Last decade | 45 months
Before last decade | 30 months

p < 0.001

50% improvement

...further increases expected

The Starting Point for New Drugs

Decisions about new therapy

Assessment of relapse

International Myeloma Foundation
### Treatment Sequence

**NEW**
- Thal/Dex
- Rev/Dex
- Cyclo/vel/dex
- VD
- RevVel
- VTD

- Front line treatment
- Induction

- Consolidation

- Post consolidation

**OLD**
- VAD
- DEX
- SCT

- Maintenance

- Nothing

- Prednisone

- Thalidomide

- Few options

**Relapsed**

- Bortezomib
- Lenalidomide
- Thalidomide
- Carfilzomib
- Pomalidamide
- Anti-CD38 Antibodies
- Elotuzumab
- HDAC
- Bendamustine

- Rescue

### Approach to Relapse

- Monitor low risk biochemical relapse
- Assess prior response(s)
- Try combos before new agents
- Consider salvage transplant
- Switch to “continuous” therapy

CHECK IF NEW AGENT TRIAL IS APPROPRIATE
Putting Together New Combos

- Thalidomide
- Bortezomib
- Steroids
- Lenalidomide
- Stem Cell Transplant
- Chemotherapy

Important Factors:
- Age
- High Risk cytogenetics
  - Renal disease
  - Convenience/location
  - Blood counts
  - Steroid “status”
- Previous therapy and Patient Preference

Individualizing Care
Newer Therapies 2015

TOP 10

- Anti-CD 38 monoclonal antibodies (MAb) daratumumab and SAR 650984
- Elotuzumab
- Anti-CD 138 monoclonal antibody (BT062)
- Check point inhibitors (anti PD-1/PD-L1)
- MLN 9708 (ixazomib citrate)
- ARRY 520
- ACY-1215
- Selinexor (also known as KPT-330)
- CAR T-cell therapy
- Measles virotherapy

DARA – Response*

IMWG Criteria

<table>
<thead>
<tr>
<th>Treatment</th>
<th>RR (%)</th>
<th>N</th>
<th>PR</th>
<th>VGPR</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 mg/kg</td>
<td>35%</td>
<td>30</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>16 mg/kg</td>
<td>10%</td>
<td>20</td>
<td>2</td>
<td>1</td>
<td>2</td>
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</tbody>
</table>

* Presented at ASCO 2014
**DARA Monotherapy: Best Paraprotein Paraprotein (%)**

IMWG Criteria (for measurable disease at baseline)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Monotherapy</th>
<th>Best Paraprotein Paraprotein (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>8mg/kg</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>8mg/kg</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>8mg/kg</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>16mg/kg</td>
<td></td>
</tr>
</tbody>
</table>

S- Serum, U- Urine, F- FLC

*Presented at ASCO 2014

**Daratumumab in Double Refractory MM: Sirius Trial**

Patients were heavily pretreated and most patients were refractory to multiple lines of PI and IMiD treatment

- 97% refractory to their last line of therapy
- 95% double refractory
- 66% refractory to 3 or 4 therapies (bortezomib, lenalidomide, carfilzomib, and pomalidomide)
- 63% refractory to pomalidomide
- 48% refractory to carfilzomib

Lonial et al: ASCO 2015
Daratumumab Single-Agent: Efficacy

- ORR: 29%
  - 9% VGPR
  - 3% sCR

PFS: 3.7 months median
OS: 65% @ 1 year

SAR650984: Maximal Change in Paraprotein*
Myeloma Patients Treated at Doses of 1 mg/kg Q2W or Higher

One patient at 3.0 mg/kg and 20 mg/kg with 0% change; one patient at 20 mg/kg not evaluable

*Martin T, Mikhael J et al, ASH 2013
Which New Drugs Will Have an Impact and Why?

Bottom line: ARS survey at IMWG Summit in Milano

- Most excited about anti-CD38 Rx: 85% ranked as #1 new agent
- Need PFS improvement ≥ 4 months to show value
- Prefer single agent activity versus synergy

ELOQUENT-2 Trial: ASCO/NEJM 2015

Phase III; 1-3 Relapses

321 patients  Elo/Len/Dex
325 patients  Len/Dex

PFS

- 19.4 months  $p = 0.0004$
- 14.9 months

At 2 years: PFS

- 41%
- 27%
**PD-1 and PD-L1 Inhibitors**

“Check Point Inhibitors”

- RG7446 (Roche)
- MEDI-4736 (AstraZeneca)
- Avelumab (Merck KGaA)
- BMS – 936559 (Bristol Myers Squibb)
- STI – A1010 (Sorrento)
- Opdivo (Bristol Myers Squibb)
- Keytruda (Merck & Co.)
- Pidilizumab (Cure Tech)
- AMP – 224 (Glace SmithKline)
- STI – A1110 (Sorrento)

**Panobinostat/HDAC Inhibitor**

**Results Asco 2014**

- Velcade/dex ± Panobinostat
- Randomized phase III trial
- Efficacy:
  - PFS: 12 months versus 8.1 months
  - ORR: 60.7% versus 54.6%
  - ≥ VGPR: 27.6% versus 15.7%
- Tolerability
  - Grade 3/4 toxicities
    - Thrombocytopenia 67% v 31%
    - Diarrhea 26% v 8%
    - Fatigue 17% v 9%

*Abstract #8510 Richardson et al*
Panobinostat/Velcade/Dex: PFS

- Primary endpoint was met ($P < .0001$), with clinically relevant increase in median PFS of 3.9 months for PAN-BTZ-Dex arm

### Median PFS (95% CI) in months

<table>
<thead>
<tr>
<th>Events</th>
<th>Median PFS</th>
<th>HR (95% CI)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAN-BTZ-Dex</td>
<td>207/387</td>
<td>12.0 (10.3, 12.9)</td>
<td>0.63 (0.52-0.76)</td>
</tr>
<tr>
<td>Pbo-BTZ-Dex</td>
<td>260/381</td>
<td>8.1 (7.6, 9.2)</td>
<td></td>
</tr>
</tbody>
</table>

*PANORAMA 1 trial; Novartis Data; presented at ASCO

Carfilzomib/Pomalidomide/Dexamethasone in Double Refractory Myeloma

**Example of New Therapy Trial**

**Progression-Free Survival**

- Median PFS = 11.1 months

**Overall Survival**

- Median OS = 24.6 months

*Update Jan 2015*
Anti-CD19 CAR-T Cells*

*June at el. Immunotherapy Symposium
San Francisco, CA; March 2015

Measles Virotherapy

> Treatment results for 2 measles sero negative myeloma patients with IV infusion of $10^{11} \text{TCID}_{50}$ infectious units of MV-NIS: engineered measles virus

International Myeloma Foundation
Measles Virotherapy

Mayo Clinic trial: Massive blast of measles vaccine wipes out cancer

Article by DAN BROWNING, Star Tribune | Updated: May 14, 2014 - 8:03 AM

Mayo Clinic's blitzkrieg approach to overwhelm tumors virally will get more study.

How Measles Virotherapy Works

KEY
- CD46 receptor
- measles virus
- measles attachment protein
- engineered virus destroyed by defenses in normal cell

Possible destruction by antibodies

Many CD46

Massive injection of engineered measles virus

MYELOMA CELLS

NORMAL CELLS

Few CD46
MV-NIS Measles Virotherapy Results

PHASE I TRIAL

• Cohorts of 3 patients/dose level
• Dose levels $10^6$ TCID$_{50}$ up to $10^{11}$ TCID$_{50}$
• 6 patients treated at $10^{11}$ dose level
• Results reported for 2 sero negative patients

TWO REPORTED PATIENTS

Patient 1
• CR at 7 months
• Recurrent plasmacytoma at 9 months
• Transient response of EMD (muscle)
• Definite MV-NIS uptake documented

Patient 2

What next?

• MV-NIS single agent phase II trial
  • measles antibody negative patients
  • opens September

• Also in the works:
  • MV-NIS in cell carriers
  • MV-NIS plus cyclophosphamide
  • MV-NIS plus iodine-131
  • VSV-IFNβ-NIS
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- Selinexor (also known as KPT-330)
- CAR T-cell therapy
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Plus more:
Several inhibitors:
- Akt
- Bcl
- IAP
- CDK
- PIM
- BET

What does the future hold?

- More options
- Better combos
- Longer remissions
- CURE!
WHAT NEW THERAPIES ARE MOST IMPORTANT IN 2013/2014?