Advances in the treatment of Multiple Myeloma: to infinity and beyond!

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Outline

1. Some good news:
   – What do things look like for me, is this bad?

2. Risk in Multiple Myeloma:
   – What is my stage?

3. Improvements in newly diagnosed multiple myeloma

4. General principles of treating relapsed disease

5. New therapies of note for relapsed disease

http://www.ffrmg.org/us/myeloma-and-mgus/
• **1844** – First documented case of myeloma
• 39-year-old Sarah Newbury
• Fatigue and multiple bone fractures.
• Passed away 4 years after onset of symptoms

**Treatments:**
• Rhubarb pills
• Orange peel infusions
• Dover powder
• Leeches: the first “maintenance therapy”
SEER registry study from US: 1993-2012

- Improvement in 5 year survival: seen in all ages and ethnic groups:
  - < 65 years of age:
    - 38.2% → 61.8
  - 65-74 years of age:
    - 29.0% → 48.4%
  - >75 years of age:
    - 21.1%-34.0%
Risk and Myeloma

“Doctor, what stage is my cancer?”
Risk in Myeloma: at diagnosis

- Blood tests and bone marrow biopsy
- High Risk features:
  - High risk FISH changes on the bone marrow biopsy
  - Elevated levels of LDH in the blood
- 5-year OS by stage
  - I: 82%
  - II: 62%
  - III: 40%

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Criteria</th>
</tr>
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<tbody>
<tr>
<td>ISS stage</td>
<td>Serum β₂-microglobulin &lt; 3.5 mg/L, serum albumin ≥ 3.5 g/dL</td>
</tr>
<tr>
<td></td>
<td>Not ISS stage I or III</td>
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<tr>
<td></td>
<td>Serum β₂-microglobulin ≥ 5.5 mg/L</td>
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<tr>
<td>CA by iFISH</td>
<td>Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)</td>
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<tr>
<td></td>
<td>No high-risk CA</td>
</tr>
<tr>
<td>LDH</td>
<td>Serum LDH &lt; the upper limit of normal</td>
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<tr>
<td></td>
<td>Serum LDH &gt; the upper limit of normal</td>
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</table>

A new model for risk stratification for MM

| R-ISS stage | ISS stage I and standard-risk CA by iFISH and normal LDH |
|            | Not R-ISS stage I or III |
| III        | ISS stage III and either high-risk CA by iFISH or high LDH |

Abbreviations: CA, chromosomal abnormalities; iFISH, interphase fluorescent in situ hybridization; ISS, International Staging System; LDH, lactate dehydrogenase; MM, multiple myeloma; R-ISS, revised International Staging System.

Palumbo et al, JCO 2015; 33(26): 2863-2869
Newly Diagnosed treated with Autologous Transplant

Newly Diagnosed treated without Autologous Transplant

Palumbo et al, JCO 2015; 33(26): 2863-2869
Relapsed and Refractory Multiple Myeloma

Risk readjusted: talk to your doctor so you understand expectations of therapy

– Are there any new high risk FISH/Cytogenetics in the bone marrow
– How long did the I go from initiation of first line therapy (or transplant) until relapse?
– How will my medical problems and “fitness” affect my ability to tolerate therapies

.......
A quick note on MM drugs: not chemotherapy!

- **Immunomodulators:**
  - Drugs: Lenalidomide (R—revlimid) and Pomalidomide (P—pomalyst)
  - How does it work:
    - Modify the immune system to fight for you!
    - Inhibits blood flow to the cancer cells
    - Directly kills the myeloma cells to some degree

- **Proteosome inhibitors:**
  - Drugs: Bortezomib (V—velcade), Carfilzomib (K—kyprolis), Ixazomib
  - How does it work:
    - Directly kill myeloma cells by “stressing” their metabolic function and causes cell death

- **Monoclonal antibodies:**
  - Drugs: Daratumumab (D—darzalex), Isatuximab, Elotuzumab
  - Brings your immune cells (NK and T-cells) to the cancer cells to kill them
  - Immunomodulatory effects like the IMIDs above
  - Directly kills the myeloma cells to some degree
Improvements in Newly Diagnosed MM: Transplant Eligible

FORTE trial:

• KRD induction

• Randomization:
  – KRD v ASCT consolidation

• Outcomes: follow up 4 years
  – PFS:
    • Not-reached !!! v 57m
  – 3- year OS:
    • ~ 90 % in both arms !!!
Improvements in Newly Diagnosed MM: not transplant Eligible

**MAIA study:**

- **Randomized phase 3:**
  - Dara-Len-Dex
  - Len-Dex
- **Outcomes: ~ 5 years follow up**
  - Progression free survival:
    - Not reached vs 34.4 months
  - Overall survival:
    - Not reached in either group but favors Daratumumab
- **Toxicity?**
  - 5 patients (1%) patients discontinued only daratumumab due to toxicity

Facon Lan Onc 2021
Relapsed and Refractory Multiple Myeloma

• Encourage all patients to participate in clinical trials
• Many of the same principles apply as in newly diagnosed MM:
  – 3 drugs are better than 2
  – Treat until progressive disease
  – Ongoing importance of supportive care
• Lack of head to head clinical trials to compare different myeloma regimens
• There is no one best treatment regimen/approach for any given patient
• Treatment tailored to tolerance and comorbidities
• There is no curative therapy (yet 😊)
## Cellular Therapy in Multiple Myeloma

<table>
<thead>
<tr>
<th>Mechanisms of Action</th>
<th>CAR-T: Chimeric Antigen Receptor Modified T (CAR T) cells</th>
<th>BiTE: “bispecific T cell engager”</th>
<th>Immunoconjugate: Belantamab</th>
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<tbody>
<tr>
<td>Collect patients T-cells then engineer them to “attack” the myeloma cancer cell</td>
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</table>

### Clinical Trial Data

<p>| | | | |</p>
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CAR-T

- Donor lymphocytes (or T-cells) are removed from patients then “engineered” to fight cancer
  - Various chimeric antigen receptors (CARs) are transduced into the T-cells to then target cancer antigens

- Targets
  - BCMA: B-Cell Maturation Antigen

Srivastava et al, The Journal of Immunology 2018
Shah et al, Leukemia 2020; 34: 985-1005
CAR-T Therapy in MM

• Advantages:
  – A “memory phenotype” can be created
  – More robust data for deep response in heavily pre-treated patients

• Disadvantages
  – Cytokine Release Syndrome
  – Need for apheresis and lymphodepletion
  – Production time – off the shelf?
Idecabtagene Vicleucel (Idecel; bb2121) Relapsed Refractory Multiple Myeloma

- KarMMa study
- Phase 2
- Enrolled 140 patients
- 35% were high risk
- Median 6 lines of previous therapy (range 3-16)
  - 26% penta-refractory
- Overall progression free time of 8.8 months

Munshi et al NEJM 2021; 384(8): 705-716
<table>
<thead>
<tr>
<th>Study/NCT#</th>
<th>Institutions</th>
<th>Study phase and planned enrollment</th>
<th>Inclusion Criteria</th>
<th>CAR-T Construct</th>
<th>Treatment Arms</th>
</tr>
</thead>
</table>
| CARTITUDE-4 NCT04181827 | Multicenter  | Phase III                          | • 1-3 lines previous therapy  
• PI and IMID exposed                                                                    | JNJ-4528        | CAR-T v PVD or DPD              |
| KarMMa-2 NCT03601078 | Multicenter worldwide | Phase 2; N=181                   | • 4-cohorts  
• ≥3 prior lines                                                                   | bb2121          | Single arm                      |
| KarMMa-3 NCT03651128 | Multicenter worldwide | Phase 3; N=381                 | • 2-4 prior lines;  
• PI/IMiD/CD38mAb exposed  
• refractory to last line                                                           | bb2121          | 2:1 Randomization Arm-A: CAR T Arm-B: SOC |
| KarMMa-4 NCT04196491 | Multicenter US           | Phase 1 N=60                  | • High Risk                                                                         | bb2121          | Induction → CART→ Len maintenance |
| CARTIFAN-1 NCT03758417 | Multicenter China         | Phase 2; N=60                  | • ≥3 prior lines;  
• PI/IMiD exposed  
• PD on last treatment or within 12m from its end                           | LCAR-B38M (JNJ-4528) | Single arm                      |
| BMT-CTN 1901 and 1902 | Multicenter US           | “Parallel” Phase 2              | • High Risk Post-ASCT  
• Suboptimal response post -ASCT                                                    | Bb2121          | Single arm                      |
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<td>Helps the body’s immune system target cancer cells: brings the T-cells to the cancer</td>
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- **CAR-T:** Chimeric Antigen Receptor Modified T (CAR T) cells
- **BiTE:** “bispecific T cell engager”
- **Immunoconjugate:** Belantamab
What is a “BiTE”

• BiTEs are antibodies with two arms.
  – One arm of the drug attaches to a specific protein on the tumor cell.
  – The other arm of the BiTE activates immune cells in the patient to kill the cancer cells.
Clinical trials of BiTEs targeting MM

<table>
<thead>
<tr>
<th>Targets</th>
<th>Drug name</th>
<th>Design</th>
<th>Trial type</th>
<th>Estimated enrollment</th>
<th>Estimated completion</th>
<th>References</th>
</tr>
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<tr>
<td>BCMA × CD3</td>
<td>PF-06863135</td>
<td>IgG2a Fc region</td>
<td>Phase 1</td>
<td>80</td>
<td>Early 2022</td>
<td>NCT03269136</td>
</tr>
<tr>
<td>BCMA × CD3</td>
<td>TNB-383B</td>
<td>IgG4 Fc region</td>
<td>Phase 1</td>
<td>72</td>
<td>Late 2021</td>
<td>NCT03933735</td>
</tr>
<tr>
<td>BCMA × CD3</td>
<td>REGN5458</td>
<td>Fc region, Fab arms</td>
<td>Phase 1/2</td>
<td>56</td>
<td>Late 2022</td>
<td>NCT03761108</td>
</tr>
<tr>
<td>BCMA × CD3</td>
<td>REGN5459</td>
<td>Fc region, Fab arms</td>
<td>Phase 1/2</td>
<td>56</td>
<td>Late 2023</td>
<td>NCT04083534</td>
</tr>
<tr>
<td>BCMA × CD3</td>
<td>CC-93269</td>
<td>Trivalent, Fc region</td>
<td>Phase 1</td>
<td>19</td>
<td>Mid 2022</td>
<td>NCT03486067</td>
</tr>
<tr>
<td>BCMA × CD3</td>
<td>JNJ-64007957</td>
<td>IgG1 Fc region</td>
<td>Phase 1</td>
<td>120</td>
<td>Mid 2020</td>
<td>NCT03145181</td>
</tr>
<tr>
<td>BCMA × CD3</td>
<td>AMG420</td>
<td>BiTE</td>
<td>Phase 1</td>
<td>120</td>
<td>Early 2025</td>
<td>NCT02514239</td>
</tr>
<tr>
<td>BCMA × CD3</td>
<td>AMG701</td>
<td>Half-life extended BiTE (scFvs plus Fc region)</td>
<td>Phase 1</td>
<td>135</td>
<td>Mid 2025</td>
<td>NCT03287908</td>
</tr>
<tr>
<td>CD38 × CD3</td>
<td>AMG424</td>
<td>Fc region, scFv x Fab arms</td>
<td>Phase 1</td>
<td>20</td>
<td>Late 2022</td>
<td>NCT03445663</td>
</tr>
<tr>
<td>CD38 × CD3</td>
<td>GBR1342</td>
<td>Fc region, scFv x Fab arms</td>
<td>Phase 1</td>
<td>125</td>
<td>Early 2021</td>
<td>NCT03309111</td>
</tr>
<tr>
<td>CD19 × CD3</td>
<td>Blinatumomab</td>
<td>BiTE</td>
<td>Phase 1</td>
<td>20</td>
<td>Mid 2020</td>
<td>NCT03173430</td>
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<tr>
<td>FcRL5 × CD3</td>
<td>BFCR4350A</td>
<td>IgG1 Fc region</td>
<td>Phase 1</td>
<td>80</td>
<td>Mid 2021</td>
<td>NCT03275103</td>
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<tr>
<td>GPRC5D × CD3</td>
<td>JNJ-64407564</td>
<td>IgG1 Fc region</td>
<td>Phase 1</td>
<td>185</td>
<td>Mid 2021</td>
<td>NCT03399799</td>
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</table>
**REGN 5485**

- Phase 1
- Enrolled 45 patients
- 22% were R-ISS III
- Median 5 (range 2-17) lines previous therapy
  - 55% were pentarefractory
- 60% Overall Response Rate in highest dose level
- Manageable adverse events

Madduri et al BLOOD 2020; 136(sup 1): 41-42

**PF-06863135**

- Phase 1
- Reported on 23 patients
- 26% were R-ISS III
- Median 10 lines previous therapy
  - 55% were pentarefractory
- 80% Overall response rate
- Manageable adverse events

Raje et al BLOOD 2019; 134(sup 1): 1869
Pros/cons

• Potential advantages
  – Off the shelf – no multi-week manufacturing required
  – Not as impacted by the “fitness” of your immune system
  – No “additional” therapy needed such as lymphodepletion
  – They act quicker

• Potential disadvantages
  – Still see CRS but less than with traditional CAR therapy
  – Efficacy is likely determined solely by the persistence/exposure of the drug
  – May be insufficient T-cells to engage in the bone marrow or in plasmacytomas
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- Delivers a “toxic” directly to the myeloma cell killing it

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- Delivers a “toxic” directly to the myeloma cell killing it
Belantamab Mafodotin: BCMA-Targeted ADC

- Payload: monomethyl auristatin F (MMAF)
- Given IV every 3 weeks

Anti-BCMA, humanized IgG1 mAb that binds to BCMA-expressing MM cells

MMAF, microtubule-disrupting cytotoxic agent that leads to apoptosis of BCMA-expressing MM cells

Protease-resistant, maleimidocaproyl linker that joins the MMAF to the mAb

Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study

<table>
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<th>Efficacy Endpoints</th>
<th>All Patients (n = 97)</th>
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<tbody>
<tr>
<td>ORR, % (97.5% CI)</td>
<td>31 (21.7-43.6)</td>
</tr>
<tr>
<td>Median DoR, mos (95% CI)</td>
<td>11.0 (4.2-NR)</td>
</tr>
</tbody>
</table>

- Unique toxicity: keratopathy
  - Reversible if monitored closely
  - ~ 2/3 will have some keratopathy but usually mild
  - Need to see an ophthalmologist prior to each dose
  - Given ~ 3 weeks as a subcutaneous injection
Important Supportive Care

- Ca/Vit-D supplementation for bone health
- Bisphosphonate or RANK-ligand therapy to reduce “skeletal events”
- Aspirin or low dose blood thinners to help prevent blood clots
- Antiviral therapy to help prevent viral reactivation (particularly shingles)
- **Immunizations** --
  - COVID, Influenza, Shingles, Pneumonia
- Psychiatric and psychological support – heavy disease burden
Thank you for your attention!

- Patrick A Hagen, MD, MPH
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