Myeloma: Opportunities & Challenges in Moving Toward a Cure
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Opportunities & Challenges
in Moving Toward a Cure

Moderator
Mike Rice, MS, MBA, Senior Consultant, Defined Health

Panelists
• Rafael Amado, MD, Chief Medical Officer, Adaptimmune
• Kenneth C. Anderson, MD, Kraft Family Professor of Medicine, Harvard Medical School; Director, Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute
• Louis J. DeGennaro, PhD, President & CEO, The Leukemia & Lymphoma Society
• Stanley R. Frankel, MD, FACP, Corporate VP, Head, Immuno-Oncology Clinical R&D, Celgene
• Anne Quinn Young, MPH, VP, Development & Strategic Partnerships, Multiple Myeloma Research Foundation
Multiple Myeloma is a Relatively Low Incidence Oncology Indication

- 26,850 MM patients diagnosed each year in the US (~100k Prevalence)
- ~230k new diagnoses each year WW
Yet, Myeloma is Projected to Become One of the Largest Oncology Markets

- $8B market in 2015, significant growth through 2020 reaching $14B (11% CAGR)
- IMiDs serve as the treatment backbone in most MM Settings, account for roughly half of sales in MM

WW Myeloma Market Through 2020

Adis R&D Insight, EvaluatePharma
Cancer Progress by Defined Health
New York, NY | March 8 - 9, 2016
MM Will Yield 3 of the Top 15 Oncology Blockbusters — Including Celgene’s Top Selling Revlimid

<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>Class</th>
<th>2020 Revenue</th>
<th>Patent Expiry</th>
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<tbody>
<tr>
<td>Revlimid</td>
<td>Celgene</td>
<td>IMiD</td>
<td>$10,183</td>
<td>Mar 2022</td>
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<tr>
<td>Opdivo</td>
<td>BMS</td>
<td>PD-1 MAb</td>
<td>$9,276</td>
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<td>Avastin</td>
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<td>VEGF MAb</td>
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<td>Imbruvica</td>
<td>Janssen, AbbVie</td>
<td>BTK Inhibitor</td>
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<td>Herceptin</td>
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<td>Her2 MAb</td>
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<td>Xtandi</td>
<td>Astellas Pharma</td>
<td>Other cytostatics</td>
<td>$5,198</td>
<td>Aug 2027</td>
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<tr>
<td>Rituxan</td>
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<tr>
<td>Keytruda</td>
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<td>Perjeta</td>
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<td>Atezolizumab</td>
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<td>Tasigna</td>
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<td>Pomalyst</td>
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<tr>
<td>Jakafi</td>
<td>Incyte</td>
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<td>$1,868</td>
<td>Dec 2027</td>
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</table>
MM Treatment is Rapidly Evolving With Three New Drug Classes, And Expanding Indications

- **Patient with MGUS**
  - <70, HIGH PS
    - Low Risk
      - Front-line Induction/Conditioning: CyBorD, VRd, RD, VD (preferred for CKD)
      - Auto BMT
    - Intermediate Risk
      - Maintenance/Consolidation: Lenalidomide or bortezomib maintenance, Observation
      - Auto BMT
  - High Risk
    - Front-line Induction/Conditioning: Triplet: VRd
    - Auto BMT
    - Maintenance/Consolidation: Triplet: VRd or Rd, Lenalidomide maintenance
    - Observation

- **Patient with Smoldering MM**
  - Low Risk
    - Front-line Induction/Conditioning: Doublet or Triplet: CyBorD, VRd, RD, VD
    - Auto BMT
    - Maintenance/Consolidation: Lenalidomide or bortezomib maintenance, Observation
    - Auto BMT
  - Intermediate Risk
    - Front-line Induction/Conditioning: Triplet: VRd
    - Auto BMT
    - Maintenance/Consolidation: Lenalidomide or bortezomib maintenance
    - Observation
  - High Risk
    - Front-line Induction/Conditioning: Triplet: VRd
    - Auto BMT
    - Maintenance/Consolidation: Lenalidomide or bortezomib maintenance
    - Observation

- **Patient with Active MM**
  - <70, HIGH PS
    - Front-line Induction/Conditioning: CyBorD, VRd, RD, VD (preferred for CKD)
    - Auto BMT
    - Maintenance/Consolidation: Lenalidomide or bortezomib maintenance, Observation
    - Auto BMT
  - >70, LOW PS (High, Int., or Low risk)
    - Elderly/Non Transplant Front-Line Induction: VRd, RD, VD, CyBorD, MP/T
    - Maintenance/Consolidation: Lenalidomide or bortezomib maintenance, Observation
    - Observation

- **2nd-Line**
  - Auto BMT
  - Rechallenge or sequence doublet/triplet regimen: CyBorD, VRd, RD, VD, elo-Rd, Ixa-Rd
  - Auto BMT
  - Allo BMT
  - Clinical Trails
  - Novel Agents: carfil, pom, pano, dara

- **3rd Plus –Line / Salvage**
  - Auto BMT
  - Allo BMT
  - Clinical Trails
  - Novel Agents: carfil, pom, pano, dara
  - Clinical trails, novel agents, chemotherapy, palliation

NCCN; DH primary research and analysis

*Cancer Progress by Defined Health*

New York, NY | March 8 - 9, 2016
However, MM remains a relatively poor-prognosis among the blood cancers

- 75-85% of patients are symptomatic, warranting medical treatment
- Relative to other hematological malignancies, the mortality risk is high in MM, and >11,000 deaths occur from MM each year in the US

**Comparison of Diseases by Survival Rate, Age of Onset & Incidence**

- AML
- MM
- NHLs
- CLL
- MDS
- CML
- MPDs
- HL
- ALL

SEER; DH Analysis

Cancer Progress by Defined Health
New York, NY | March 8 - 9, 2016
Unmet Needs of Myeloma Patients Serve as Opportunities for Continued Impact in MM

**Myeloma remains incurable**
- Approved agents do not effectively target molecular drivers of disease progression
- RVd (lenalidomide, bortezomib and dexamethasone) induce remissions, but is rarely curative.
- The prognosis for others such as high-risk and relapse/refractory patients remains grim.

**Curative therapies far off**
- Immunotherapy (CARTs, anti-PD1 mAbs) promises more durable responses, but still in early days.
- Advances are being made in the use of transplantation (e.g. allogeneic SCT, T-cell depletion with DLI add-back), but complex, center-specific protocols are generally not exportable to the broader community.
- Selective targeting of malignant stem cell populations remains an important but as yet unachievable goal.

**Empirical treatment decisions**
- Few (if any) tools to select which patients are most likely to respond to certain drug classes. One cannot even predict which patients will respond to newly-approved mAbs since their targets are somewhat broadly expressed.
- Absence of minimal residual disease (MRD) following transplant is emerging as a possible surrogate for response durability but has yet to be adopted by the broader clinical or regulatory community.
- Cytogenetics and gene expression profiling are not routinely incorporated in patient stratification and therapy decisions.

**Rising cost of therapy**
- 3- and 4-drug regimens composed of multiple branded drugs are becoming increasingly expensive, particularly in the US where payers have historically not been equipped to effectively negotiate (e.g. unlike single-payer systems).
- Biomarker-guided treatment strategies and generic competition can only address this so much, at least in the near term.
MM has the Most Competitive Pipeline Among the Heme Malignancies

Pipeline Volume vs. Market Size

Cancer Progress by Defined Health
New York, NY | March 8 - 9, 2016
While Advances in IO Trails Other Cancers, Recent Progress in MM Fuels Investment

Adis Insight; Thomas Reuters Cortellis
### Non-profits are Addressing Gaps in MM Research, Patient Education, and Providing Access to Therapy

<table>
<thead>
<tr>
<th>Headquarters</th>
<th>White Plains, NY</th>
<th>Norwalk, CT</th>
<th>North Hollywood, CA</th>
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<tbody>
<tr>
<td>Yr. Founded</td>
<td>1949</td>
<td>1998</td>
<td>1990</td>
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</tbody>
</table>
| Leadership         | Chairman: James Davis  
CEO: Louis DeGennaro | Chairman: Kathy Giusti  
CEO: Paul Giusti | Chairman: Brian Durie  
President: Susie Novis |
| Total Revenue      | $299.7M          | $26.6M      | $11.0M              |
| Mission Statement  | To cure leukemia, lymphoma, Hodgkin’s disease, and myeloma and improve the quality of life of patients and their families | Helps accelerate the development of next generation multiple myeloma treatments to extend patient’s lives, and lead to a cure | Improving the quality of life of myeloma patients while working toward prevention and a cure |

LLS, MMRF, IMF websites & annual reports

**Cancer Progress by Defined Health**  
New York, NY | March 8 - 9, 2016
Patient Advocacy Funding Basic, Translational, and Risk Sharing Clinical Research

Biotech Accelerator TAP Pipeline

Legend
- Novel Agents/Mechanisms
- Antibodies and Immune
- PIs and HIVs

<table>
<thead>
<tr>
<th>TARGET THERAPY</th>
<th>INDICATION(S)</th>
<th>PRECLINICAL</th>
<th>PHASE I</th>
<th>PHASE II</th>
<th>PHASE III</th>
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<tr>
<td>Apoptosis</td>
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<td>CD19</td>
<td>DLBCL, PMBCL &amp; TFL</td>
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<td>Cell Therapy</td>
<td>Haplo-identical transplant (AML &amp; ALL)</td>
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<td>Waldenstrom's Macroglobulinemia</td>
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<td>BET</td>
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<td>Lymphoma</td>
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Patient Advocacy Seeking Understanding of MM Genetics and Personalized Treatment

- The Multiple Myeloma Genomics Initiative has mapped the full genomes of over 200 MM patients and the results were made widely available to hundreds of researchers worldwide via a public portal.
- The MMRF is also leading the charge toward personalized medicine with the CoMMpass study, which aims to recruit 1000 patients and learn how their unique genetic profiles impact the progression of their illness and their response to treatments.
Patient Advocacy Addressing Increasing Economic Burden of MM
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