Welcome and Introductions

Anne Quinn Young, MPH
Senior Vice President, Marketing & Communications
Multiple Myeloma Research Foundation
Faculty

Sagar Lonial, MD, FACP
Winship Cancer Institute of Emory University
Atlanta, GA

David Siegel, MD, PhD
John Theurer Cancer Center of Hackensack University Medical Center
Hackensack, NJ

CoMMpassSM, Smoldering Myeloma, Induction, and Stem Cell Transplants

Sagar Lonial, MD, FACP
Winship Cancer Institute of Emory University
Atlanta, GA
Overall Trends in 2016

- MMRF CoMMpass℠ Study to accelerate precision medicine
- Possible benefits of early treatment for high-risk smoldering MM (83% PR+)
- Role of induction, consolidation, and maintenance therapies before and after autologous stem cell transplant (ASCT) in newly diagnosed MM (NDMM)
- Darzalex™ (daratumumab) for early relapsed/refractory multiple myeloma (RRMM)
- Novel therapies for highly pretreated RRMM
  - Keytruda® (pembrolizumab)
  - Selinexor
  - Chimeric antigen receptor T cells (CAR T cells), especially those directed against B-cell maturation antigen (BCMA)

PR+, partial response or better

MMRF CoMMpass℠ Study

- Longitudinal observational study with 1,000 patients+ worldwide
- Largest genomics data set of any cancer
- Database is publicly available for all researchers to access
- Next-generation RNA sequencing technologies can help identify high-risk MM patients
- MMRF’s CoMMpass-based research provides insight into cancer genomes with unprecedented detail
A total of 19 studies were presented using data from the MMRF CoMMpassSM Study, covering such topics as:

- Best methods of genetic sequencing
- Specific chromosomal mutations found in MM
- Role of patient race in treatment patterns
- Outcomes in patients ineligible for clinical trials
- Individual genetic differences affecting a patient’s response to certain medications


Smoldering Multiple Myeloma

- How do we identify smoldering MM (SMM)?
  - Calcium, renal, anemia, bone lesions (CRAB) criteria
  - Plasma cell infiltration
  - Free light chain assay
  - PET/CT imaging

- Who is at high risk for progression to symptomatic MM?

CT, computed tomography; MM, multiple myeloma; PET, positron-emission tomography.
**Empliciti™ for High-Risk SMM**

- **Empliciti™** (elotuzumab) – an anti-SLAMF7 monoclonal antibody
- **Study goal:**
  - In high-risk SMM, can we delay or prevent progression to overt MM using early treatment with Empliciti (EM), Revlimid® (lenalidomide; REV), and dexamethasone (DEX) (combination called ERd), compared with REV and DEX (Rd)?

- **Rationale:**
  - Demonstrated benefits of Rd vs. no treatment in the SMM population
  - Demonstrated benefits of EM and REV in RRMM population


**Empliciti for High-Risk SMM (cont.)**

- Study is ongoing, but early results of ERd are encouraging
  - 82.6% had a partial response or better
  - Safe and well tolerated in patients with high-risk SMM

- Long-term follow up is needed to determine whether ERd is better than observation or Rd alone in this population

**Conclusion:** There may be a shift towards redefining high-risk SMM as MM

ERd, Empliciti (elotuzumab); MM, multiple myeloma; Revlimid (lenalidomide), and dexamethasone; Rd, Revlimid (lenalidomide) and dexamethasone; SMM, smoldering multiple myeloma.

Research Questions About NDMM

- Upfront ASCT is the standard of care in NDMM, but many patients relapse, even with complete response to ASCT
- Can ASCT outcomes be improved with:
  - Double or “tandem” ASCT?
  - Triplet therapy using an immunomodulatory drug (IMiD) and a proteasome inhibitor (PI) for induction (before transplant)?
  - IMiD- and PI-based triplet therapy for consolidation (after transplant)?
  - Triplet therapy for BOTH induction and consolidation?

ASCT, autologous stem cell transplant; NDMM, newly diagnosed multiple myeloma.

Triplet Induction Therapy Before ASCT

- Phase 2 study update: induction therapy with KRd followed by ASCT and 2 years of REV maintenance (KRd-R)
- Excellent results:
  - Overall response rate (ORR) was 98%
  - Progression-free survival (PFS) at 48 months was 82%
  - Overall survival (OS) at 58 months was 86%

Conclusion: KRd-R induction/maintenance produced deep complete responses (CR) regardless of age or genetic risks

ASCT, autologous stem cell transplant; KRd, Kyprolis (carfilzomib), Revlimid (lenalidomide), and dexamethasone; KRd-R, Kyprolis (carfilzomib), Revlimid (lenalidomide), and dexamethasone followed by Revlimid maintenance; REV, Revlimid (lenalidomide).

**Single ASCT vs. Double ASCT vs. Single Plus Consolidation in NDMM**

- **StaMINA Phase 3 Trial – 3 study groups:**
  - Single ASCT with REV maintenance
  - Double ASCT with REV maintenance
  - Single ASCT followed by consolidation with bortezomib (Velcade®, VEL), REV, and DEX (VRd) and then REV maintenance
- **Results:** PFS and OS were very similar in all 3 groups

**Conclusion:** Addition of VRd consolidation or a second ASCT was *not* superior to a single ASCT followed by REV maintenance

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**Triplet Therapy Before and After Transplantation (IFM Studies)**

<table>
<thead>
<tr>
<th></th>
<th>Moreau¹</th>
<th>Roussel²</th>
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</thead>
<tbody>
<tr>
<td>Triplet therapy for both induction and consolidation</td>
<td>IRd</td>
<td>KRd</td>
</tr>
<tr>
<td>Maintenance</td>
<td>I</td>
<td>R</td>
</tr>
<tr>
<td>Response rates (after consolidation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VGPR or better</td>
<td>80%</td>
<td>92.5%</td>
</tr>
<tr>
<td>CR/sCR</td>
<td>44%</td>
<td>69%</td>
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</table>

*CR/sCR, complete response/stringent complete response; IRd, Ninlaro (ixazomib), Revlimid (lenalidomide), and dexamethasone; I, Ninlaro (ixazomib); KRd, Kyprolis (carfizomib), Revlimid (lenalidomide), and dexamethasone; R, Revlimid (lenalidomide); VGPR, very good partial response.*

**Conclusion:** IRd and KRd triplet therapy before and after transplant produced very good responses, but safety and efficacy remain open questions

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Summary

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Relapsed/Refractory Multiple Myeloma

David Siegel, MD, PhD
John Theurer Cancer Center of Hackensack University Medical Center
Hackensack, NJ
CASTOR and POLLUX trials: Darzalex™ (Daratumumab) for RRMM

- 2016 approval based on CASTOR¹ and POLLUX² trials
  - twin multicenter, phase 3, randomized, open-label controlled trials of Darzalex™ (daratumumab; DARA) for patients with RRMM and a median of 2 prior lines of therapy
- Initial results were presented at ASCO and EHA meetings in June 2016
  - DARA resulted in >60% reduction in risk of disease progression or death in both studies
- New information: presentations at ASH 2016 examined different endpoints and broke down results within certain subgroups

ASCO, American Society of Clinical Oncology; EHA, European Hematology Association; RRMM, relapsed/refractory multiple myeloma.


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Study Design of CASTOR and POLLUX

CASTOR
- RRMM
- ≥1 prior therapy
- Not refractory to VEL

DARA + VEL + DEX (DVd)

VEL + DEX (Vd)

POLLUX
- RRMM
- ≥1 prior therapy
- Not refractory to LEN

DARA + REV + DEX (DRd)

REV + DEX (Rd)

Endpoints:
- PFS
- OS, ORR, CR, VGPR
- MRD
- Time to progression
- Time to response
- Duration of response

CR, complete response; DARA, Darzalex (daratumumab); DEX, dexamethasone; REV, Revlimid (lenalidomide); MRD, minimal residual disease; PFS, progression-free survival; ORR, overall response rate; OS, overall survival; RRMM, relapsed/refractory multiple myeloma; VEL, Velcade (bortezomib); VGPR, very good partial response.

Minimal Residual Disease and DARA

- **Minimal residual disease** (MRD) – more sensitive than traditional definitions of clinical response\(^1,2\)
- MRD-negativity is associated with longer PFS and OS in NDMM patients\(^1,2\)
  - MRD may become a primary endpoint for clinical studies
- Results: DARA induced MRD negativity in over 3 times as many patients as standard of care regimens

DARA, Darzalex (daratumumab); NDMM, newly diagnosed multiple myeloma; OS, overall survival; PFS, progression-free survival.


DARA Outcomes by Subgroups

- Two additional studies\(^1,2\) grouped the CASTOR and POLLUX results into subgroups of patients based on several factors, including:
  - Number of prior lines of therapy (1 vs. 2–3)
  - High-risk cytogenetics
  - Refractoriness to prior lines
  - Treatment-free interval (time since last therapy)

**Conclusion: DARA was superior to the standard of care in all subgroups analyzed**

DARA, Darzalex (daratumumab).

Venclexta® (Venetoclax) + Velcade (Bortezomib)

- **Venclexta®** (Venetoclax; VEN) – formerly known as ABT-199
  - A BCL-2 inhibitor that is FDA approved for use in chronic lymphocytic leukemia
- **Rationale**: BCL-2 and MCL-1 both promote MM cell survival
  - VEL inhibits MCL-1, while VEN inhibits BCL-2
  - When used together, VEN enhances the efficacy of VEL
- **Goal**: MMRC phase 1b dose-escalation study of VEN + VEL + DEX in patients with RRMM to determine safety, efficacy, and optimal dose

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Venclexta Results

- ORR was 68%, and 40% achieved VGPR or better
- Response rates were higher in those with no prior VEL treatment, those not refractory to VEL, and those with fewer prior lines of therapy
- Responses were better in patients with a t(11;14) gene translocation than in those without the mutation
  - Can be used as targeted therapy for the t(11;14) high-risk subgroup

**Conclusion**: VEN + VEL + DEX has an acceptable safety profile and promising efficacy for RRMM, particularly in patients with a t(11;14) gene mutation

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Patients (N = 9) had heavily pretreated RRMM
- Median of 8 prior lines of therapy, including proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and ASCT
- Previously exposed to Pomalyst (pomalidomide; POM)

Acceptable safety profile, with adverse events similar to those seen in other studies of Keytruda (pembrolizumab) and POM

ORR was 33%; clinical benefit rate (3 PR, 2 MR, 3 SD) was 89%

Conclusion: Results are promising; phase 3 studies of Keytruda (pembrolizumab) are now underway

Selinexor and Proteasome Inhibitors

In an MMRC phase 1 study, selinexor (SEL) was combined with Kyprolis™ (carfilzomib; CFZ) and DEX in patients with RRMM and at least 2 prior treatment regimens

Even in patients who were CFZ-refractory, response rates were strong:
- MR or better in 73%
- PR or better in 64%
- VGPR or better in 18%

Similar results were seen in the phase 1b/2 STOMP² trial, which used VEL as the PI instead of CFZ

Conclusion: Early clinical evidence suggests that SEL can overcome PI resistance in RRMM
**Selinexor for Highly Refractory MM**

- The STORM trial used SEL for patients highly refractory to previous combinations
  - All patients were at least “quad-refractory” to 2 IMiDs (both REV and POM) and 2 PIs (both VEL and CFZ)
  - Some patients were “penta-refractory” to both IMiDs, both PIs, plus 1 anti-CD38 antibody (DARA or isatuximab)
- ORR was 21% for quad patients and 20% for penta patients
- Clinical benefit rates (MR+) were 32% for all, 29% for quad, and 37% for penta

**Conclusion:** SEL shows promising anti-tumor activity in the quad- and penta-refractory MM populations, and expansion of this trial is planned

CFZ, Kyprolis (carfilzomib); DARA, Darzalex (daratumumab); IMiD, immunomodulatory drug; MR+, minimal response or better; ORR, overall response rate; PI, proteasome inhibitor; POM, Pomalyst (pomalidomide); REV, Revlimid (lenalidomide); SEL, selinexor; VEL, Velcade (bortezomib).


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**Anti-BCMA Therapy: Preliminary Results**

- **B-cell maturation antigen** (BCMA) – highly expressed on the surface of myeloma cells
- Ongoing phase 1 study of GSK2857916, a novel anti-BCMA antibody, conducted in 24 patients with RRMM
- Clinical benefit seen at higher doses (1 VGPR, 3 PR, 2 MR)
- Well tolerated with manageable adverse events; eye-related problems were most frequent reason for dose changes

MR, minimal response; PR, partial response; RRMM, relapsed/refractory multiple myeloma; VGPR, very good partial response.

Anti-BCMA CAR T Cells

- **Chimeric antigen receptor T cells (CAR T cells)** – patient’s own T cells are genetically modified to express chimeric antigen receptors (CARs) directed at MM antigens
  - After being genetically altered, cells are infused back into the patient
- BCMA is a promising target for CAR T-cell activity
- Current study evaluated anti-BCMA CAR T-cell infusion for treatment of advanced MM in heavily pretreated patients

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Anti-BCMA CAR T Cells in MM: Design and Results

- Ongoing phase 1 trial studying anti-BCMA CAR T cells alone or with cyclophosphamide
  - Patients had advanced RRMM, were IMiD and PI refractory, and had a median of 9 prior lines of therapy
- BCMA levels declined and correlated with depth of response
- Some severe toxicities were seen
- One patient showed anti-BCMA CAR T-cell persistence, with ongoing stringent complete response at 7 months and MRD-negative bone marrow

**Conclusion: Anti-BCMA CAR T cells show promising expansion and clinical activity**

BCMA, B-cell maturation antigen; MM, multiple myeloma; MRD, minimal residual disease; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma.

Other Promising Studies on BCMA and CAR T Cells

- A study in the preclinical evaluation stage is working on creating a treatment based on allogeneic (donor) anti-BCMA CAR T cells\(^1\)
  - CAR T cells that do not need to be custom made from each patient’s own cells could lead to an “off-the-shelf” immunotherapy for MM

- Other researchers showed that REV strengthens the anti-tumor activity of anti-CS1 CAR T cells in mice\(^2\)
  - Human trial planned using REV to enhance CAR T-cell activity

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Novel Therapies to Watch For

<table>
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<tr>
<th>Antibody (Target)</th>
<th>Proteasome inhibitors</th>
<th>HDAC inhibitors</th>
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<tbody>
<tr>
<td>B-B4, DL101 (CD138)</td>
<td>Marizomib*</td>
<td>ACY-241(^1)</td>
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<tr>
<td>Indatuximab (CD38)</td>
<td>Oprozomib</td>
<td>Ricolinostat</td>
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<tr>
<td>Lucatumumab (CD40)</td>
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<tr>
<td>IPH-2101 (KIR)</td>
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<tr>
<td>Atezolizumab (PD-L1)*</td>
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<td>Durvalumab (PD-L1)</td>
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<tr>
<td>Nivolumab (PD-1)</td>
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HDAC, histone deacetylase.
* Drugs studied in the

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BCMA, B-cell maturation antigen, CAR T cells, chimeric antigen receptor T cells; MM, multiple myeloma; REV, Revlimid (lenalidomide); RRMM, relapsed/refractory multiple myeloma.

# Novel Therapies to Watch For (cont)

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Agents</th>
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<tr>
<td>SINE XPO1 antagonists</td>
<td>KPT-8602&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>AKT inhibitor</td>
<td>GSK2141795&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>MEK1/2 inhibitor</td>
<td>Trametinib&lt;sup&gt;2,3&lt;/sup&gt;</td>
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<tr>
<td>KSP inhibitors</td>
<td>Filanesib (ARRY-520)&lt;sup&gt;4&lt;/sup&gt;</td>
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<tr>
<td>BTK inhibitors</td>
<td>Ibrutinib*, AVL-292</td>
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<tr>
<td>CDK inhibitors</td>
<td>PD0332991*, SCH727965, AT7519*</td>
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<tr>
<td>HSP90 inhibitors</td>
<td>Ganetespib (STA-9090)*</td>
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<tr>
<td>FGFR3 inhibitor/antibodies</td>
<td>TKI258*, MFR1877S</td>
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<tr>
<td>Mutant B-Raf inhibitor</td>
<td>Vemurafenib</td>
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* Drugs studied in the


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# Summary

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Question & Answer

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David Siegel, MD, PhD
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 Closing Remarks

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To learn more about the MMRF, please visit: www.multiplemyeloma.org
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