New Horizons in the Treatment of Relapsed and Refractory Myeloma

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Disclosures

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- Advisory Board: Millennium-Takeda, Celgene, Gilead, Bristol Myers Squibb
- Scientific Founder: Oncopep, C4 Therapeutics
Integration of Novel Therapy Into Myeloma Management

Proteasome inhibitors: Bortezomib, carfilzomib, ixazomib; immunomodulatory drugs: thalidomide, lenalidomide, pomalidomide; HDAC inhibitor: panobinostat; monoclonal antibodies: elotuzumab and daratumumab

Triplet therapies in newly diagnosed and relapsed MM achieve deep and durable responses. Quadruplet studies are the future (ie Dara or Elo RVD under evaluation, Dara VMP approved) Combination maintenance therapies (RVD) can overcome early relapses in high risk disease.

Long term disease free survival and potential cure of MM will require combination targeted and immune therapy to achieving minimal residual disease negativity and restore host immunity
## Factors to Be Considered for Relapsed MM Therapy

<table>
<thead>
<tr>
<th>Patient-Related Factors</th>
<th>Disease/Treatment Related Factors</th>
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<tbody>
<tr>
<td>Age</td>
<td>Prior treatment received and response duration Retreat if sensitive, relapse off Rx</td>
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<tr>
<td>Comorbidities, eg, cardiac dysfunction Avoid carfilzomib</td>
<td>Refractory status (progression on prior therapy) Second generation vs switch class</td>
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<tr>
<td>Renal impairment Proteasome inhibitor</td>
<td>Toxicities from prior therapies</td>
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<tr>
<td>Neuropathy Avoid Thal/Bort</td>
<td>Tumor burden: Biochemical vs aggressive relapse; presence of EMD or PCL DCEP</td>
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<tr>
<td>VTE risk Proteasome inhibitor</td>
<td>Poor-risk cytogenetics; advanced R-ISS stage MoAbs, immune therapies</td>
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<tr>
<td>Performance status</td>
<td></td>
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<td>Geography (drug availability in country/region; access to clinic)</td>
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<td>Lifestyle/quality of life</td>
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<td>Prior history of malignancy</td>
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Therapy for Relapsed MM Depends on Prior Treatment/Clinical Features: Triplets Preferred With Second Generation IMiDs, Pis, MoAbs

Active In Len and Bort refractory MM
- Carfilzomib Pom Dex (no neuropathy)
- Dara Pom Dex (deep responses)
- Elo Pom Dex (well tolerated)

Active in Bort refractory MM
- Elotuzumab/Len/Dex (indolent relapse), Ixazomib Len/Dex (all oral), Carfilzomib Len/Dex (no neuropathy), Dara Len dex (MRD- responses)

Active in Len refractory MM
- Pom Bort/Dex, Dara Bort Dex (MRD- responses)

Pom, Car, Ixa, Dara, Elo all achieve responses in del17p MM
Final Analysis of Phase 3 Carfilzomib Lenalidomide Dex (KRD) vs RD ASPIRE Trial: Overall Survival

• KRd demonstrated a statistically significant and clinically meaningful reduction in the risk of death vs Rd, improving median OS by 7.9 months (48.3 vs 40.4 months; HR, 0.79, \( P=0.0045 \))

• The KRd efficacy advantage is most pronounced at first relapse, with an 11-month improvement in median OS (47.3 vs 35.9 months; HR, 0.81)

• Treatment with KRd did not compromise OS after relapse

Stewart et al, ASH 2017
Overall Survival: Elotuzumab Lenalidomide Dex (Rd) vs Rd in Relapsed MM

Patients at risk

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients at Risk</th>
<th>Median OS (95% CI)</th>
<th>1-year OS</th>
<th>2-year OS</th>
<th>3-year OS</th>
<th>4-year OS</th>
</tr>
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<tbody>
<tr>
<td>ELd</td>
<td>321</td>
<td>483 mo (403-544)</td>
<td>90%</td>
<td>75%</td>
<td>60%</td>
<td>50%</td>
</tr>
<tr>
<td>Ld</td>
<td>325</td>
<td>396 mo (333-454)</td>
<td>84%</td>
<td>69%</td>
<td>55%</td>
<td>43%</td>
</tr>
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</table>

HR = 0.78 (95% CI: 0.63-0.96)

Dimopoulos et al, EHA 2017
• Deeper responses were more common on DRd and were associated with longer PFS
• MRD negativity was associated with longer PFS
Novel Strategies in MM
Targeting ubiquitin proteasome receptors RA190

IMiD based therapies
Degronimids, CSNs, TP53 related protein kinase

Novel immune therapies: April MoAb, BCMA immunotoxin, Bites, CAR T cells

SynNotchT memory cells, universal normal donor CAR T cells, peptide stimulated T cells

Genomic Targets: MEK/ERK, Venetoclax, MyDrug

Epigenomic Targets: KDM3A/6B, PRMT5
Targeting Ubiquitin Receptor Rpn13

Song et al, Leukemia 2016; 30:1877-86.
Blockade of Ubiquitin Receptor Rpn13 with RA190 Inhibits Myeloma Cell Growth and Induces Polyubiquitination

Target UbR alone or with PI to enhance PI or overcome PI resistance

Song et al., Leukemia, 2016: 30:1877-86.
Mechanism of Action of Immunomodulatory Drugs

Degronimids: Link to ubiquitin 3 ligase complexes

Kronke et al, Science, 2014

Lu et al, Science, 2014
Degronimids Trigger Degradation of Selective Substrates (ie MEK/ERK and IZF1/3 in MM)

Bradner et al, Science, 2015

Ubiquitin 3 ligases: cereblon, VHL, MDM2

Substrates: EGFR, BTK, BRD4, USP7, rpn13, STK4, PRPK
CRISPR Signalosome (CSN) Gene Knockout Confers IMiD Resistance by Downregulating Cereblon

Loss of signalosome (CSN) subunits activates SCF^{Fbxo7} E3 ligase-Mediated Cereblon (CRBN) degradation, abrogates IKZF3 degradation, and Confers IMiD resistance.

These studies provide rationale for novel agent IMiD combination therapies To restore CSN, CRBN, and IMiDs sensitivity.

Liu et al., Leukemia, in press
IMiDs Bind and Inhibit TP53RK: a Cereblon-Independent Mechanism of MM Growth Inhibition

Isatuximab Anti-CD38 MoAb Triggers ADCC, ADPC, CDC, and Lysosomal MM Cell-Death

Direct Cytotoxicity

Indirect Cytotoxicity

1. Homotypic aggregation
2. LMP increase
3. ROS production
4. Apoptosis

Tai et al Leukemia 2016;30:399
Phase I Clinical Trial of Isatuximab + Pom/Dex in Relapsed/Refractory Multiple Myeloma

• The combination of isatuximab with Pom or with Len augments T and NK cell mediated lysis of MM cells and decreases Tregs

• The combination of isatuximab with Pom/dex has an acceptable and manageable safety profile in patients with RRMM.

• Isatuximab PK not affected by Pom co-administration.

• ORR 60%, including 61.3% ORR treated at isatuximab 10 mg/kg and 54.1% in IMiD-refractory patients

• Global Phase III study of isatuximab +/- Pom/dex in RRMM patients (NCT02990338) fully accrued

Tai et al Clin Cancer Res 2017;23:4290
Richardson PG., et al, ASH 2017
BCMA Growth, Survival, Drug Resistance Signaling in MM

Ligands
by neutrophil, myeloid cell, DC, osteoclasts, tumor cell

Affinity to BCMA:
APRIL (nM) >> BAFF (µM)
Elevated in sera of MM patients

Receptors
on B cells

BCMA >> TACI
by ~2-100-fold in MM
(loss of BAFF-R in MM)

Tai & Anderson
Targeting APRIL in MM for Direct Cytotoxicity and to Confer Immune Sensitivity

A BCMA Auristatin Immunotoxin Induces Strong Anti-MM Effects

MMAF released at lysosome to induce G₂/M arrest followed by apoptosis

Inhibition of NFκB signaling

Bone Marrow Stromal Cell

Tai et al Blood 2014; Tai & Anderson 2015
GSK2857916 Aurostatin Immunotoxin Targeting BCMA in Relapsed/Refractory Multiple Multiple Myeloma

- BCMA Selectively expressed on MM/plasma cells
- BCMA MoAb linked to aurostatin immunotoxin
- Median follow-up 6.6 months
- ORR of 60% in heavily pre-treated MM
- Median PFS 7.9 months
- Well tolerated and side effects manageable
  - Thrombocytopenia and corneal events most frequent AEs
  - IRRs occurred in only 23% of patients without pre-medication; no IRRs occurred on subsequent infusions
- Additional monotherapy and combination studies are planned-preclinical studies show enhanced activity with IMiDs

Trudel et al ASH 2017

DOR, duration of response; IRR, infusion-related reaction; MM, multiple myeloma; ORR, overall response rate; PFS, progression-free survival; VGPR, very good partial response
BCMA-BiTE-Based Immunotherapy

Preclinical studies suggest IMiDs enhance MM cytotoxicity

CRB-401 BCMA CAR T: Phase 1 Study in RRMM

Dose Escalation (N=21) Prior IMiD + PI

≥50% BCMA expression

- 50 x 10^6
- 150 x 10^6
- 450 x 10^6
- 800 x 10^6

Dose Expansion (N=22) Prior IMiD + PI + Dara

<50% BCMA expression (n=10)
≥50% BCMA expression (n=12)
Dose range: 150–450 x 10^6 CAR+ cells

CRB 401 BCMA CAR T cells

bb2121 at active doses (≥150 × 10^6 CAR+ T cells) induces deep and durable responses in a heavily pretreated population with R/R MM

- Median PFS of 11.8 months for patients in the dose escalation cohort
- MRD-negative results in 100% of 16 evaluable responding patients; median PFS of 17.7 months
- Mostly grade 1/2 CRS observed with infrequent tocilizumab and corticosteroid use
- Ongoing trial for FDA approval.

Future Combination BCMA Cellular Therapies

- Novel constructs, vectors for combination targets
- Combination expansion to enhance T memory cells (PI3K inhibitor)
- Combination of fixed ratio T4 and T8 cells
- “Universal” CAR T cells combination strategy to prevent GVHD/rejection
- Combination of peptide stimulated T-cells with vaccine
- Combinations ie, IMiDs, checkpoint inhibitors to prevent exhaustion
“On” Switch (SynNotch) CAR T cells

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<tr>
<th><strong>BCMA CAR T Cell Program</strong></th>
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<tbody>
<tr>
<td><strong>bb2121</strong></td>
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<tr>
<td><strong>bb21217</strong></td>
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<tr>
<td><strong>JCARH125</strong></td>
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<thead>
<tr>
<th><strong>Binder</strong></th>
<th>Murine</th>
<th>Murine</th>
<th>Human</th>
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<tr>
<td><strong>Costimulatory Domain</strong></td>
<td>4-1BB</td>
<td>4-1BB</td>
<td>4-1BB</td>
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<tr>
<td><strong>Vector</strong></td>
<td>Lentivirus</td>
<td>Lentivirus</td>
<td>Lentivirus</td>
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<tr>
<td><strong>Manufacturing Process</strong></td>
<td>Unselected T cells at culture initiation</td>
<td>Unselected T cells at culture initiation + PI3K inhibitor during T cell culture</td>
<td>1:1 ratio of CD4/CD8 T cells at culture initiation</td>
</tr>
<tr>
<td><strong>T Cell Phenotype</strong></td>
<td>Non-enriched T cell population</td>
<td>Enriched for T\textsubscript{n} and T\textsubscript{cm} cells</td>
<td>Enriched for T\textsubscript{cm} cells</td>
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<tr>
<td><strong>Preclinical</strong></td>
<td>Low tonic signaling No inhibition by sBCMA</td>
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<tr>
<td><strong>Stage of Development</strong></td>
<td>KarMMA™ pivotal trial initiated Q4 2017</td>
<td>Phase I trial initiated Q3 2017</td>
<td>Phase I trial initiated Q1 2018</td>
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Universal SLAMF7-Specific CAR T (abs 502)

- “Off-the-shelf”
- Normal healthy PB donors
- Inactivation of the $TCR\alpha$ constant ($TRAC$) gene using gene-editing technology to prevent GVHD and expression of T cell SLAMF7.

- Campath MoAb targeting CD 52 can be used if needed to prevent host rejection of normal donor CAR T cells

Combination CAR T and CAMPATH MoAb Treatment
Vaccines Targeting MM Specific Peptides in Smoldering Multiple Myeloma

Goal is to prevent evolution of smoldering to active myeloma

• Cocktails of immunogenic HLA-A2-specific XBP1, CD138, CS1 peptides to induce MM-specific and HLA-restricted CTL responses

Clinical trials (LLS TAP Program):

Immune responses to vaccine in all patients including tetramer positive cells and type I cytokines

Lenalidomide with vaccine augments these immune response

Lenalidomide, PDL-1, LAG3, HDAC 6i 241 with vaccine to induce memory Immune response against myeloma

Bae et al, Leukemia 2015, 2017
Nooka et al, JAMA Oncol 2018
Generation of CD8⁺ Memory CTL by Stimulation with Heteroclitic BCMA peptide

Bae et al, 2018
Patients are vaccinated with heteroclitic BCMA peptide to generate autologous memory cytolytic T cell anti-MM response.

T cells are harvested by pheresis and expanded ex vivo in the presence of heteroclytic BCMA peptide to increase memory cytolytic T cells.

T cells are reinfused as adoptive immunotherapy, without adverse side effects.

BCMA peptide vaccinations can be given subsequently to maintain memory anti-MM specific responses.
Personalized Medicine: Responses to Venetoclax (Target BCL-2) and Bortezomib (Target Bcl-1) by BCL2:BCL2L1 Ratio Among t(11;14)-Positive Patients with RRMM

Kumar et al., Moreau et al. ASH 2016
Targeting Mutations in Multiple Myeloma

Therapies Targeting Ras Raf MAPK Pathway Achieve Only Transient Responses, Combination Clinical Trials Ongoing

MY DRUG (MMRF TRIAL)

Functional High Risk Patients

Profiling for alterations (NCT02884102)

- No detectable “actionable” alterations
  - RAF/RAS mutations
    - IDH activating mutations
    - CDK pathway activating alterations
    - FGFR3 activating alterations
    - Other activating alterations
      - t(11;14)

- Other activating alterations
  - MAPKi + Dex
  - IDHi + Dex
  - CDKi + Dex
  - FGFRi + Dex
  - Otheri

2 cycles

- Anti-CD38 + IPD
- Other + IPD
- MAPK + IPD
- IDHi + IPD
- CDKi + IPD
- FGFRi + IPD
- Otheri + IPD
- Anti-BCLi + IPD
Epigenetic Therapy Targeting KDM3A-KLF2-IRF4 Axis in MM cells

KDM3A catalyses removal of H3K9 mono- and di-methylation in MM

Ohguchi et al Nat Comm 2016; 7:10258
Epigenetic Therapy: Pharmacological Inhibition of Protein Arginine Methyltransferase 5 (PRMT5) by EPZ015666

- Potent inhibition of PRMT5:MEP50 complex
  - SAM uncompetitive, peptide competitive inhibition
- Highly selective vs. other PMTs
- Orally bioavailable
- Potent methyl mark inhibition with excellent correlation to killing of cells in vitro
- Potent in vivo efficacy in animal models of MCL following inhibition of target methyl mark

Summary and Conclusions

- PRMT5 is highly expressed in MM patients and cell lines and associated with poor clinical outcome

- PRMT5 expression correlates with Arginine methylation status in MM cell lines

- PRMT5 silencing or pharmacological inhibition impacts MM cell growth

- Ongoing studies suggest inhibition of NF-κB signaling and autophagy in MM

- Oral EPZ015666 treatment inhibits tumor growth of MM xenografts in NOD SCID mice.

- Preclinical rationale for clinical trials of EPZ015666, alone and in combination, to improve patient outcome in MM.

Gullà et al, *Leukemia* 2018; 32:996-1002
Future Directions

Combination therapies defined in preclinical studies will be used to treat subsets of patients, defined by profiling and informed by biomarkers.

Universal normal donor CAR T cells, peptide stimulated T cells will allow anti-MM memory T cell responses.

Long term disease free survival and potential cure of MM will require both 1. achieving minimal residual disease negativity, and 2. combined immune therapies to restore host immunity.
## United Nations Against Myeloma: Bench to Bedside Research Team

<table>
<thead>
<tr>
<th>Country</th>
<th>Members</th>
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<tbody>
<tr>
<td>USA</td>
<td>Kenneth Anderson, Nikhil Munshi, Paul Richardson, Robert Schlossman, Irene Ghobrial, Steven Treon, Jacob Laubach, Deborah Doss, Kathleen Colson, Mary McKenney, Kim Noonan, Tina Flaherty, Kathleen Finn, Muriel Gannon, Stacey Chuma, Janet Kunsman, Diane Warren, Carolyn Revta, Andrea Freeman, Alexis Fields, Andrea Kolligian, John Feather, Farzana Masood, Nora Loughney, Heather Goddard, Tiffany Poon, Nicole Stavitzski, Ranjit Banwait, Shawna Corman, Heather Goddard, Meghan Marie Leahy, Caitlin O’Gallagher, Christina Tripsas, Karin Anderson, Shannon Viera, Katherine Redman, Amber Walsh, Samir Amin, Wanling Xie, Parantu Shah, Holly Bartel, Lisa Popitz, Jeffrey Sorrell</td>
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