An Evolving Era in Multiple Myeloma: Immunotherapies and Targeted Agents

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Disclosures

• Consultant and study participant – The Dedham Group, Oncology and Specialty Therapeutics Consulting

• Off-label discussion will be included in this presentation
Objectives

- Identify the developing role of and management strategies for antibody-based therapy in multiple myeloma treatment approaches
- Review the efficacy of and clinical considerations for the novel small molecule inhibitors
- Develop treatment, monitoring, and supportive strategies for small molecule targeted and immunotherapies in multiple myeloma
- Interpret available data on the use of immune mediated therapies in myeloma, inclusive of checkpoint inhibitors, T-cell engaging monoclonal antibodies, and novel immunomodulatory agents
Multiple Myeloma (MM)

- Accounts for 17% of US hematologic malignancies, 1.8% overall cancers

- Rates of new diagnosis rising each year over past decade at the same rate as annual deaths over the same period
  —32,110 new cases, 12,960 associated deaths in US in 2019

- Survival improved notably in recent years

- 5 year survival rate in 2003 estimated as 34% → 2016 estimated 49%

Treatment Paradigm

Not curable, goal is to achieve a deep response, complete remission (CR), and optimize progression-free survival (PFS)

Induction: RVd
CyBorD

Consolidation: Autologous Hematopoietic Stem Cell Transplant (if eligible) OR Doublet/Triplet regimens

Maintenance: IMiD PI

Relapsed/Refractory: Plethora


RVD: lenalidomide, bortezomib, dexamethasone
CyBorD: cyclophosphamide, bortezomib, dexamethasone
IMiD: immunomodulating agents
PI: proteasome inhibitor
Evolving Treatment Options for Myeloma

Cyclophosphamide
- Melphalan
- Carmustine
- Doxorubicin
- Bendamustine

Thalidomide
- Lenalidomide
- Pomalidomide
- Iberdomide

Darahumumab
- Elotuzumab

CAR-T (multiple)
- TriTAC

Dexamethasone
- Prednisone

Bortezomib
- Carfilzomib
- Ixazomib

Panobinostat

Selinexor

Venetoclax

Pembrolizumab
- Nivolumab

BiTE (multiple)
- Belantamab
- Mafodotin
Monoclonal Antibodies in Multiple Myeloma
Monoclonal Antibodies in Multiple Myeloma

- Identified targets:
  - Elotuzumab: SLAMF7/CS1
  - Daratumumab: CD38

- Mechanisms of oncolytic activity:
  - Antibody-dependent cell cytotoxicity
  - Complement-mediated cell cytotoxicity
  - Antibody-dependent cell phagocytosis
  - Apoptosis
  - Inhibition of enzymatic activity

Zonder JA et al. Blood 2012; 120: 552-559
Elotuzumab

• Monoclonal antibody targets SLAMF7

• Approved in combination with lenalidomide or pomalidomide and dexamethasone after 1-3 prior therapies

• Pearls:
  — Infusion reactions primary concern
  • Premedication regimen (30-90 minutes prior): diphenhydramine (25-50mg), ranitidine (50mg), acetaminophen (650-1000mg)
  • Split PO and IV dexamethasone dosing, IV given 45-90 minutes before infusion
  — Lymphopenia, leukopenia, thrombocytopenia
  — Electrolyte changes (hyperkalemia, low bicarbonate)
ELOQUENT-2

- Lenalidomide-dexamethasone triplet
  — RD ± elotuzumab for relapsed and relapsed/refractory MM patients having received 1-3 prior lines of therapy
  — ERD, 28-day cycle:
    • elotuzumab 10mg/kg weekly cycles 1 & 2 then days 1 & 15
    • lenalidomide 25mg daily days 1-21
    • dexamethasone 40mg on weeks without elotuzumab and 8mg + 28mg on elotuzumab days

- PFS and ORR significantly improved in ERD
  — Similar safety profiles, ERD with increased risk of herpes zoster and risk of infusion reactions
  — Patient reported quality of life similar in both groups

ELOQUENT-3

• Pomalidomide-dexamethasone (PD) triplet
  — PD ± elotuzumab (EPD) for relapsed and relapsed/refractory MM patients having received 1-3 prior lines of therapy
  — EPD, 28-day cycle:
    • elotuzumab 10mg/kg weekly cycles 1 & 2, then 20mg/kg day 1 each cycle after
    • pomalidomide 4mg daily days 1-21
    • dexamethasone 40mg on weeks without elotuzumab and 8mg + 28mg on elotuzumab days

• PFS significantly improved in the EPD group (10.3 vs 4.7 months)
  — Early and sustained separation in risk of progression or death identified between groups
  — ORR higher and improved rates of VGPR or better responses in EPD group
  — Rate of adverse events similar between groups, mostly hematologic and infection


VGPR: very good partial response
## Elotuzumab in Refractory Myeloma

<table>
<thead>
<tr>
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<th>ELOQUENT-2</th>
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<th>ELOQUENT-3</th>
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<td></td>
<td>RD</td>
<td>ERD</td>
<td>PD</td>
<td>EPD</td>
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<tr>
<td>T, med (range)</td>
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<td>3 (2-8)</td>
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<td>IMiD-refractory</td>
<td>6%</td>
<td>5%</td>
<td>84%</td>
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<tr>
<td>PI-refractory</td>
<td>71%</td>
<td>68%</td>
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<td>100%</td>
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<tr>
<td>High risk</td>
<td>32%</td>
<td>32%</td>
<td>25%</td>
<td>22%</td>
</tr>
<tr>
<td>ORR</td>
<td>66%</td>
<td>79%</td>
<td>25%</td>
<td>58%</td>
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<tr>
<td>≥VGPR</td>
<td>28%</td>
<td>33%</td>
<td>9%</td>
<td>20%</td>
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<tr>
<td>Median PFS, mos</td>
<td>14.9</td>
<td>19.4</td>
<td>4.7</td>
<td>10.3</td>
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<tr>
<td>Median OS, mos</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

ERD category 1 recommended consideration for previously treated myeloma, EPD alternative after multiple lines

Daratumumab

• Variety of approved indications and combinations
  — New diagnosed HCT eligible and ineligible patients, relapsed/refractory after 1-3+ therapies
  — Monotherapy, combinations with dexamethasone, prednisone, lenalidomide, pomalidomide, thalidomide, bortezomib, melphalan

• Pearls:
  — Disrupts Coombs test, interferes with antibody screening/ cross matching – important to screen
  — High rate of infusion reactions (specifically 1st dose)
    • Infusion duration, volume, premedications (post-steroid?)
    • (Not on package insert) premedicate with montelukast, especially immediately prior to initial doses
  — Neutropenia
  — Diarrhea

POLLUX

• Lenalidomide-dexamethasone triplet
  —Phase III RD ± daratumumab (DRd) for relapsed and relapsed/refractory MM patients having received ≥1 prior line of therapy

• Median PFS was not reached in DRd group, significantly improved
  —ORR improved in DRd, OS comparison ongoing
  —Daratumumab with a notable side effect profile but manageable with less DRd discontinuation


DRd: daratumumab + lenalidomide + dexamethasone
CASTOR

- Bortezomib-dexamethasone triplet
  - Phase III study of bortezomib-dex ± daratumumab for relapsed and relapsed/refractory MM patients having received ≥1 prior line of therapy

- Median PFS was not reached in DVd group, significantly improved
  - ORR improved in DVd, OS comparison ongoing

EQUULEUS

• Pomalidomide triplet combination
  — Phase 1b study, open-label study of daratumumab combined with multiple therapies, results of daratumumab + pomalidomide-dexamethasone (DPd) reported in 103 cases of relapsed/refractory MM ≥1 line of therapy

• Median PFS 8.8 months, 12-month PFS 42%
  — ORR 60% (42% VGPR, CR, sCR)

Chari A et al. Blood 2017; 130(8): 974-981
Daratumumab plus Carfilzomib/Dexamethasone

• Carfilzomib triplet therapy
  —Phase 1b, open-label nonrandomized multicenter study in a variety of backbone regimens for newly diagnosed and relapsed/refractory multiple myeloma, 85 patients received daratumumab + carfilzomib/dexamethasone (DKd)
  —DKd, 28-day cycle
  • Ten patients received a single first daratumumab dose (16 mg/kg) on day 1 cycle 1. The remaining patients received the first dose of daratumumab split over 2 days (8 mg/kg on days 1 and 2 of cycle 1) to collect safety and pharmacokinetic data for split dosing

• ORR 84% in all treated patients, 71% ≥VGPR (33% ≥CR)
  —Median PFS not reached, 12- and 18-month PFS 74% and 66% (less but >50% in bortezomib-refractory)
  —Hematologic events and infections most common (all-grade cardiac events 28%)
  —Rates of IRR similar between single first-dose infusion and split-dose daratumumab

CANDOR

- Carfilzomib-dexamethasone triplet
  - Carfilzomib-dexamethasone ± daratumumab (DKd) phase 3 trial for relapsed/refractory multiple myeloma patients after 1-3 prior lines of therapy

- Deeper responses with daratumumab, MRD negativity, ORR, CR
  - Higher rates of grade ≥3 adverse events in triplet arm, similar rates of discontinuation
  - Rate of grade ≥3 cardiac failure lower in DKd arm (3.9% vs 8.5%)
  - 5 deaths, all in DKd (pneumonia, sepsis, septic shock, Acinetobacter infection, cardiorespiratory arrest)

## Daratumumab Relapsed/Refractory Comparisons

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<thead>
<tr>
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<th>POLLUX</th>
<th>EQUULEUS</th>
<th>CANDOR</th>
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<td></td>
<td>Vd</td>
<td>DVd</td>
<td>Rd</td>
<td>DRd</td>
</tr>
<tr>
<td>T</td>
<td>2 (1-10)</td>
<td>2 (1-9)</td>
<td>1 (1-3)</td>
<td>&gt;3 (52%)</td>
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<tr>
<td>Previous IMiD</td>
<td>75.7%</td>
<td>85.6%</td>
<td>99%</td>
<td>42.3%</td>
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<tr>
<td>Previous PI</td>
<td>65.5%</td>
<td>55.2%</td>
<td>100%</td>
<td>90.3%</td>
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<tr>
<td>High risk</td>
<td>21.3%</td>
<td>22.7%</td>
<td>16.6%</td>
<td>15.4%</td>
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<tr>
<td>ORR</td>
<td>63.2%</td>
<td>82.9%</td>
<td>76.4%</td>
<td>92.9%</td>
</tr>
<tr>
<td>≥CR</td>
<td>9.0%</td>
<td>19.2%</td>
<td>19.2%</td>
<td>43.1%</td>
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<tr>
<td>Median PFS, mos</td>
<td>7.2</td>
<td>NR</td>
<td>8.8</td>
<td>15.8</td>
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<tr>
<td>Median OS, mos</td>
<td>NR</td>
<td>NR</td>
<td>2-yr 86.6%</td>
<td>17.5</td>
</tr>
</tbody>
</table>

DVd & DRd category 1 recommended consideration previously treated myeloma, DPD & DKd alternative after multiple lines

Chari A et al. Blood 2017; 130(8): 974-981

T = previous lines of therapy
mos = months
HCT Ineligible Patients

ACYCLONE

- Bortezomib/melphalan triplet therapy with daratumumab
  - Bortezomib, melphalan, prednisone ± daratumumab (DVMP) phase 3 trial
- Addition of daratumumab significantly improved PFS and OS
  - Reduced risk of disease progression and first study demonstrating survival advantage
  - Median time to subsequent therapy not reached with daratumumab, 25.9 months in VMP

MAIA

- Lenalidomide doublet regimen with daratumumab
  - Lenalidomide and dexamethasone ± daratumumab (DRd) phase 3 trial
- Improved PFS, ORR (CR, VGPR) with daratumumab, across all subgroups
  - More lenalidomide dose modifications in daratumumab group due to adverse events

Mateos M et al. ASH 2019 Abstract 859.

HCT: Hematopoietic cell transplantation
DVMP: daratumumab, bortezomib, melphalan, prednisone
DRd: daratumumab, lenalidomide, dexamethason
## Front-line Daratumumab HCT Ineligible Comparison

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<th>ACYCLONE</th>
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<tbody>
<tr>
<td></td>
<td>MPV</td>
<td>DMPV</td>
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<tr>
<td>High-risk</td>
<td>15%</td>
<td>17%</td>
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<tr>
<td>ORR</td>
<td>74%</td>
<td>91%</td>
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<tr>
<td>≥CR</td>
<td>24.4%</td>
<td>42.6%</td>
</tr>
<tr>
<td>MRD negativity</td>
<td>7%</td>
<td>28%</td>
</tr>
<tr>
<td>Median PFS, mos</td>
<td>19.3</td>
<td>36.4</td>
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<tr>
<td>Median OS, mos</td>
<td>NR</td>
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<tr>
<td>42-mos OS</td>
<td>75%</td>
<td>62%</td>
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<tr>
<td>Adverse Events</td>
<td></td>
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<tr>
<td>Neutropenia</td>
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<td>Thrombocytopenia</td>
<td>38.7%</td>
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<tr>
<td></td>
<td>37.6%</td>
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<tr>
<td>Infections</td>
<td>14.7%</td>
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<tr>
<td>Pneumonia</td>
<td>4.0%</td>
<td>11.3%</td>
</tr>
<tr>
<td>MRD negativity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS, mos</td>
<td>19.3</td>
<td>36.4</td>
</tr>
<tr>
<td>Median OS, mos</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>42-mos OS</td>
<td>75%</td>
<td>62%</td>
</tr>
</tbody>
</table>

DRd category 1 preferred consideration in HCT ineligible, DMPV category 1 other recommended regimen

Mateos M et al. ASH 2019 Abstract 859

HCT: hematopoietic cell transplantation
MRD: minimal residual disease
HCT Eligible Patients

**CASSIOPEIA**
- Bortezomib/thalidomide triplet with daratumumab
  - Bortezomib, thalidomide, dexamethasone (VTd) ± daratumumab (DVTd) phase 3 trial
  - 4 cycles induction, following by chemo-mobilization to aHCT, then those at ≥PR randomized to daratumumab maintenance at D+100
- Improved PFS, responses, MRD-negativity with daratumumab
  - OS better with daratumumab but median not reached in either group

**GRIFFIN**
- Daratumumab, bortezomib, lenalidomide, dexamethasone (DRVd) induction
  - Phase 2 study patients received 4 induction cycles, high-dose therapy, aHCT, 2 consolidation cycles, and 24 months of maintenance with RVd with or without daratumumab
- Addition of daratumumab improved sCR by the end of consolidation with durable PFS and OS
  - Stem cell mobilization and autologous HCT feasible, without notable effect on reconstitution


PR: partial response
AEs: adverse events
aHCT: autologous hematopoietic cell transplantation
# Front-line Daratumumab HCT Eligible Comparison

<table>
<thead>
<tr>
<th></th>
<th>CASSIOPEIA</th>
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<tr>
<td></td>
<td>VTd</td>
<td>DVTd</td>
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<tr>
<td>High-risk</td>
<td>16%</td>
<td>15%</td>
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<tr>
<td>ORR</td>
<td>89.9%</td>
<td>92.6%</td>
</tr>
<tr>
<td>sCR</td>
<td>20%</td>
<td>29%</td>
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<tr>
<td>≥CR</td>
<td>26%</td>
<td>39%</td>
</tr>
<tr>
<td>MRD negativity</td>
<td>44%</td>
<td>64%</td>
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<tr>
<td>Median PFS, mos</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Median OS, mos</td>
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<td>NR</td>
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<tr>
<td>Adverse Events, %</td>
<td>Any grade (Grade 3/4)</td>
<td>Any grade (Grade 3/4)</td>
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<td></td>
<td>17 (15)</td>
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<td>12 (10)</td>
<td>18 (17)</td>
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<tr>
<td></td>
<td>63 (9)</td>
<td>59 (9)</td>
</tr>
<tr>
<td></td>
<td>57 (20)</td>
<td>65 (22)</td>
</tr>
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</table>

DVTd considered useful front-line in HCT eligible patients in certain circumstances

Daratumumab Administration Innovation

Rapid Administration

- Rapid daratumumab protocol:
  - Received initial 2 doses (Cycle 1 days 1 and 8) at standard administration rates
  - Starting with 3rd dose 20% of dose given over 30 minutes (200mL/hour), then remaining 80% over 60 minutes (450mL/hour)
  - Standard premedication strategy extended to initial rapid dose, then off

- No additional IRR risk identified
  - Data developing inclusive of amyloidosis

- Cost modeling suggests cost benefit

Split Dose

- Initial dose(s) can infuse for up to 8 hours, consideration may be given to splitting doses over 2 days

- Three reports (452 patients total) suggest similar IRR rates as initial single dose, infusion durations 4.5-5 hours, no obvious compromised efficacy

- With shorter infusions this may be an option for community oncology clinics with limited hours to consider

Arnall JR et al. Leuk Lymphoma 2019; 60(9): 2295-2298
Subcutaneous Daratumumab (PAVO)

• Daratumumab formulated with recombinant human hyaluronidase PH20
  —Phase 1b study, 2-part study on safety and pharmacokinetics (part 1 reported)
    • Doses evaluated at flat doses of 1200 mg (60 mL over 20 minutes) or 1800 mg (90 mL over 30 minutes), preinfusion and postinfusion medications

• PK concentrations SC 1800 mg consistent with previous reports with 16 mg/kg IV
  —IRRs in 1 (12.5%) patients in 1200 mg and 11 (24.4%) in 1800 mg, mostly grades 1/2
  —12 patients experienced 32 IRRs mostly developed during or within 6 hours after the start of the SC infusion, 46.9% IRRs 3-6 hours, all well-controlled

Isatuximab (SAR650984)

- Chimeric IgG1 anti-CD38 monoclonal antibody
  - Targeting different amino acid sequence epitope of CD38 than daratumumab
  - Direct toxic effect on myeloma cells

- Not FDA approved at this time
  - Single agents studies suggest ORR 24-29% in RRMM
  - Phase 1 studies in RRMM in combination with IMiDs

- Pearls:
  - Most common non-infusion adverse effects (single agent): nausea, fatigue, dyspnea, cough
    - Infections (respiratory), neutropenia, lymphopenia, thrombocytopenia
  - Infusion reactions in 49% patients, 94% during first infusion (none after 4th infusion)
    - Premedications include steroid, diphenhydramine, ranitidine, acetaminophen
    - Early studies have not incorporated montelukast

Isatuximab combinations

**Isatuximab-Rd**
- Phase 1b dose-escalation study
  - Reactions most common at rate of 250 mg/h compared to 175 mg/h
  - Durations of infusion 3.1-4.9 hours initially, 2.3-4.6 hours subsequently

**Isatuximab-Pd**
- Phase 1b dose-escalation study
  - Initial infusion rates 175 mg/h in 10 and 20 mg/kg cohorts, the infusion rate was increased by 50 mg/h (first infusion) or 100 mg/h (subsequent infusions) every 30 minutes to a maximum of 400 mg/h

### Comparison of CD38 Monoclonal Antibodies in RRMM

<table>
<thead>
<tr>
<th></th>
<th>Daratumumab</th>
<th>Isatuximab</th>
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<tr>
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<td>POLLUX</td>
<td>EQUULEUS</td>
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<tr>
<td>Rd</td>
<td>DRd</td>
<td>DPd</td>
</tr>
<tr>
<td>T</td>
<td>1 (1-3)</td>
<td>&gt;3 (52%)</td>
</tr>
<tr>
<td>Previous IMiD</td>
<td>85.6%</td>
<td>99%</td>
</tr>
<tr>
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</tr>
<tr>
<td>Median PFS, mos</td>
<td>18.4</td>
<td>NR</td>
</tr>
<tr>
<td>Median OS, mos</td>
<td>NR</td>
<td>NR</td>
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</table>

Chari A et al. Blood 2017; 130(8): 974-981  

T: previous lines of therapy  
ref: specifically refractory to previous line of therapy (IMiD or PI)  
mos: months
MOR202

• Human combinatorial antibody derived human IgG1 CD38 monoclonal antibody
  —Induces antibody-dependent cell-mediated cytotoxicity and antibody-dependent cellular phagocytosis
  —Does not act by complement dependent cytotoxicity, suspected to be a major cause of infusion-related reactions seen with other anti-CD38 antibodies

• Preliminary results revealed excellent tolerability with infusion-related reactions in only 10% of patients, all ≤grade 2
  —Comparing favorably with infusion reactions with daratumumab and isatuximab

Ongoing and Future Monoclonal Antibody Considerations

- Induction, consolidation, maintenance
- Combination regimens (including novel agents)

Across treatment phases

- B-cell maturation antigen (BCMA)
- A proliferation-inducing ligand (APRIL)
- CD138

Additional targets

- Access/administration
- Utility/benefit of subcutaneous routes
- More rapid infusions
- Holistic cost and QOL analyses

Financial toxicity

- Preventing infusion related reactions
- Infections

Supportive care

QOL: quality of life
A 62 YOM with a PMH inclusive of HTN, asthma, T2DM, and multiple myeloma on lenalidomide maintenance, is now experiencing an initial biochemical progression of his multiple myeloma and is planned to start therapy with daratumumab, bortezomib, and dexamethasone (DVd). He receives therapy at a community infusion center closer to home and the pharmacist calls you stating that the site hours are unable to accommodate the daratumumab day 1 infusion. You recommend to:

a) Send the patient to your infusion center which has longer hours to accommodate the regimen
b) Admit the patient for the first cycle, he’s high risk for a serious infusion related reaction anyway

c) Ensure package label-identified premedications, add montelukast prior to the dose, and utilize a split-dose schedule for initial infusions

d) Use the daratumumab rapid infusion rate for the initial dose
Novel Immunomodulatory Drugs and Small Molecule/Targeted Inhibitors in Multiple Myeloma
Selinexor

- Selective nuclear exportin 1 inhibitor
  - Blocks exportin 1 (XPO1) and forces nuclear accumulation and activation of tumor suppressor proteins, inhibits nuclear factor κB, and reduces oncoprotein messenger RNA translation

- Indicated after ≥4 prior therapies, refractory to 2 proteasome inhibitors, 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody

Selinexor

• Pearls:
  — Consider dose modifications early for adverse effect management, dosage form (20 mg) and packaging
  — Thrombocytopenia most common hematologic adverse effect (73%) with few clinically significant bleeds
    • Thrombocytopenia most frequent in those with thrombocytopenia at baseline
  — Hyponatremia concern (7-26%), occurrence higher in MM than solid tumors, discussion on limited free-water hydration, altered mental status, and scheduled lab check at therapy initiation important
    • Mostly asymptomatic, transient, and effectively managed with dose reductions or salt tablets/electrolyte fluids
  — Gastrointestinal disturbances common, ondansetron dosed prior to and as needed, olanzapine and neurokinin-1 receptor antagonists allowed (olanzapine encouraged in practice)

STORM

• Selinexor and dexamethasone (Sd) doublet in RRMM
  —Phase 2b, patients having received prior bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab, glucocorticoids and an alkylating agents
  —28-day cycles: 80 mg oral selinexor with dexamethasone 20 mg given days 1 and 3 weekly
  —Dose adjustments: 100 mg weekly → 80 mg weekly → 60 mg weekly

• Minimal response or better in 39% patients, responses had 15.6 month OS
  —Adverse events leading to dose modification or interruption occurred in 80% patients, majority occurring in cycles 1 or 2
Selinexor with Proteasome Inhibitors

Selinexor with bortezomib (SVd)

- Phase 1b/2 study
  - 35-day cycle: selinexor 80-100 once weekly, dexamethasone 40 mg weekly, bortezomib 1.3 mg/m² SC weekly
  - 21-day cycle: selinexor 80 mg weekly, dexamethasone 40 mg weekly, bortezomib 1.3 mg/m² SC 1, 4, 8, 11
  - 35-day cycle: selinexor 60-80 mg twice weekly to day 24, dexamethasone 20 mg twice weekly, bortezomib 1.3 mg/m² SC weekly to day 22

Selinexor with carfilzomib (SKd)

- Phase 1 dose escalation study
  - 28-day cycle: selinexor 20, 40, 60 mg day 1 and 3 weekly, carfilzomib 20/27, 36, 45, 56 mg/m² days 1 & 2 weekly, dexamethasone 10-20 mg
- Comparable ORR with proteasome inhibitors
  - STOMP trial - also included triplet combinations with lenalidomide and daratumumab


ORR: overall response rate
## Selinexor Results

<table>
<thead>
<tr>
<th></th>
<th>Sd (STORM)</th>
<th>SVd</th>
<th>SKd</th>
</tr>
</thead>
<tbody>
<tr>
<td>T (range)</td>
<td>7 (3-18)</td>
<td>3 (1-11)</td>
<td>4 (2-10)</td>
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<tr>
<td>High risk</td>
<td>53%</td>
<td>9%</td>
<td>57%</td>
</tr>
<tr>
<td>ORR (PI-refractory)</td>
<td>39%</td>
<td>63% (43%)</td>
<td>48% (62%)</td>
</tr>
<tr>
<td>CR</td>
<td>2%</td>
<td>8%</td>
<td>0</td>
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<tr>
<td>Median PFS, mos (PI-refractory)</td>
<td>3.7</td>
<td>9.0 (6.1)</td>
<td>3.7 (3.7)</td>
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<tr>
<td>Median OS, mos</td>
<td>8.6</td>
<td>NA</td>
<td>22.4</td>
</tr>
<tr>
<td>Adverse Events</td>
<td></td>
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<tr>
<td>• Thrombocytopenia</td>
<td>% Grade 3/4</td>
<td>% Grade 3/4</td>
<td>% Grade 3/4</td>
</tr>
<tr>
<td></td>
<td>25/33</td>
<td>17/29</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>43/1</td>
<td>12/0</td>
<td>33</td>
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<tr>
<td></td>
<td>18/3</td>
<td>21/2</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>25/0</td>
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<td>14</td>
</tr>
<tr>
<td></td>
<td>10/0</td>
<td>5/0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>21/1</td>
<td>5/0</td>
<td>5</td>
</tr>
<tr>
<td>• Anemia</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>• Neutropenia</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>• Fatigue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Nausea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Hyponatremia</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


T: previous lines of therapy
mos: months
Venetoclax

• BH3 mimetic, B-cell lymphoma 2 (BCL-2) inhibitor
  Subset of myeloma cells identified with high Bcl-2 expression characterized by the presence of the translocation (11;14), accounting for 20% MM patients

• FDA approved for adult patients with CLL/SLL and in patients with AML in combination with hypomethylating agents
  - Not FDA approved in multiple myeloma

• Pearls:
  — Screen for t(11;14), should be considered standard in myeloma FISH panel
  — Laboratory tumor lysis syndrome (TLS) rare in myeloma, no allopurinol formally recommended
    • Quick dose escalation 200-400 mg over a week to 800 mg
    • Intensive TLS considerations in renal dysfunction (CrCl <80 mL/min)
  — Studied in doses up to 1200 mg/day with acceptable safety/efficacy profile, 800 mg dose recommended and generally utilized
  — Most common toxicities hematologic, gastrointestinal

CrCl: creatinine clearance
Venetoclax in Multiple Myeloma

- Majority of respondents (>80%) between studies with t(11;14)
  — ORR as high as 94% in highly expressing BCL-2 subgroups

- Additional case reports suggest activity in heavily pretreated multiple myeloma with t(11;14)
  — Most frequent translocation in plasma cell leukemia is t(11;14) suggesting utility (supported via case reports)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>Med ORR (%)</th>
<th>Med PFS (mos)</th>
<th>Med OS (mos)</th>
</tr>
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<tbody>
<tr>
<td>Venetoclax-Vd</td>
<td>66</td>
<td>67</td>
<td>NR</td>
<td>NR</td>
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<td>Venetoclax</td>
<td>66</td>
<td>21</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Venetoclax-Kd</td>
<td>23</td>
<td>47</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Venetoclax-d</td>
<td>21</td>
<td>65</td>
<td>NR</td>
<td>NR</td>
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<td>Venetoclax-Dd</td>
<td>24</td>
<td>92</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Venetoclax-DVd</td>
<td>24</td>
<td>88</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Venetoclax in Myeloma Controversy

• In March 2019, phase 3 BELLINI trial (Vd +/- venetoclax) put on hold by the US FDA for increased risk of patient death with venetoclax
  —Risk of death with venetoclax, with 41 out of 194 (21.1%) patients and 11 out of 97 (11.3%) patients dying in the venetoclax and placebo arms, respectively
  —Patients with t(11;14) showed clear benefit (ORR 90% vs 47%, p=0.004)

• In June 2019 FDA lifted partial clinical hold on phase III CANOVA trial (venetoclax and pomalidomide/dexamethasone) in RRMM with t(11;14)
Iberdomide

- Immunomodulatory drug (IMiD), cereblon E3 ligase modulator
- Not FDA approved
- Pearls:
  — Expected associated REMS program
  — Synergistic activity with bortezomib and daratumumab
  — Grade 3/4 adverse events included neutropenia (26%), anemia (15.2%), thrombocytopenia (11%), infection (10.6%), and neuropathy (2%), none appearing dose-related

Iberdomide in RRMM

- Phase Ib/IIa dose-escalation study of iberdomide alone or in combination with chemotherapy in RRMM
  - 28-day cycles: iberdomide oral daily days 1-21 (doses 0.3-1.3 mg), dexamethasone 40 mg weekly
  - Combination cohorts with daratumumab, bortezomib, carfilzomib

- Clinical activity observed early and across all dose levels

<table>
<thead>
<tr>
<th></th>
<th>Iberdomide + dex</th>
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<tbody>
<tr>
<td>All evaluable (n=59)</td>
<td></td>
</tr>
<tr>
<td>• ORR (%)</td>
<td>32.2</td>
</tr>
<tr>
<td>• ≥MR (%)</td>
<td>49.2</td>
</tr>
<tr>
<td>IMiD refractory (n=51)</td>
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</tr>
<tr>
<td>• ORR (%)</td>
<td>35.3</td>
</tr>
<tr>
<td>• ≥MR (%)</td>
<td>52.9</td>
</tr>
<tr>
<td>Dara/Pom refractory (n=27)</td>
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</tr>
<tr>
<td>• ORR (%)</td>
<td>29.6</td>
</tr>
<tr>
<td>• ≥MR (%)</td>
<td>44.4</td>
</tr>
<tr>
<td>Adverse effects</td>
<td></td>
</tr>
<tr>
<td>• Anemia</td>
<td>Grade 3/4 (%)</td>
</tr>
<tr>
<td>• Neutropenia</td>
<td>22.7/1.5</td>
</tr>
<tr>
<td>• Thrombocytopenia</td>
<td>15.2/13.6</td>
</tr>
<tr>
<td>• Infection</td>
<td>4.5/7.6</td>
</tr>
<tr>
<td></td>
<td>22.7/3.0</td>
</tr>
</tbody>
</table>
Additional Novel Targeted Therapies

• MCL1 inhibitors
  — MIK665 (NCT02992483)
  — AMG176 (NCT02675452)

• Histone deacetylase inhibitors
  — Ricolinostat (HDAC6 inhibitor)

• EZH2 inhibitors
  — Tazemetostat

• Mitogen-activated protein kinase pathway inhibitors
  — Trametinib (MEK inhibitor)
  — Afuresertib (AKT inhibitor)

• Immunomodulatory drugs
  — CC-92480

A 76 YOM with high risk RRMM status post 8 lines of therapy inclusive of lenalidomide, pomalidomide, thalidomide, bortezomib, carfilzomib, daratumumab, panobinostat, and melphalan is experiencing a biochemical progression. His hematologist believes that selinexor/dexamethasone is his next best option, or at least may be a bridge to clinical trial with a BCMA T-cell engager therapy, however is wary of this therapy due to the patient’s age and comorbidities. Your response is:

a) He is right to be wary, no way we should use this toxic medication in this patient, consider a venetoclax-based regimen instead

b) No worries, incorporate an aggressive supportive care approach with empiric ondansetron, olanzapine, and loperamide, weekly labs, and move forward

c) Consider a dose-adjusted initial approach with 80 mg twice weekly for 3 weeks on and 1 week off per 28 day cycle

d) Consider a dose-adjusted initial approach with 100 mg weekly with aggressive supportive care, +/- carfilzomib
Immunotherapy in Multiple Myeloma
Checkpoint Inhibitors in MM

- Programmed death receptor-1 (PD-1)-blocking antibody
- Not FDA approved in multiple myeloma
- Pearls:
  — Expression of PD-1 on CD4+ and CD8+ T cells in MM and surge in expression in RRMM, higher expression has suggested better response rates
  — Most frequent grade ≥3 AEs (when combined with IMiDs) hematologic, infections, hyperglycemia; frequent irAEs included pneumonitis, hypothyroidism


irAEs: immune mediated adverse events
# Pembrolizumab in MM

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>Setting</th>
<th>Med T</th>
<th>ORR, n (%)</th>
<th>CR, n (%)</th>
<th>SD, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>100</td>
<td>RRMM</td>
<td>4</td>
<td>0/30 (0)</td>
<td>0/30 (0)</td>
<td>17/30 (57)</td>
</tr>
<tr>
<td>Pembrolizumab- Rd</td>
<td>115</td>
<td>RRMM</td>
<td>4</td>
<td>20/40 (50)</td>
<td>1/40 (3)</td>
<td>19/40 (48)</td>
</tr>
<tr>
<td>Pembrolizumab- Pd</td>
<td>48</td>
<td>RRMM</td>
<td>3</td>
<td>29/48 (60)</td>
<td>4/48 (8)</td>
<td>14/48 (30)</td>
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<tr>
<td>Pembrolizumab- Rd (post-aHCT high risk MM)</td>
<td>43</td>
<td>NDMM RRMM</td>
<td>N/A</td>
<td>12/12 (100)</td>
<td>1/12 (8)</td>
<td>N/A</td>
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<tr>
<td>Pembrolizumab- R (post-aHCT)</td>
<td>50</td>
<td>NDMM</td>
<td>0</td>
<td>29/29 (100)</td>
<td>7/23 (31)</td>
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<tr>
<td>Pembrolizumab</td>
<td>20</td>
<td>NDMM RRMM</td>
<td>0</td>
<td>3/14 (21)</td>
<td>2/14 (14) sCR 1/14 (7) CR</td>
<td>5/11 (42)</td>
</tr>
<tr>
<td>a)Rd</td>
<td>640</td>
<td>NDMM</td>
<td>0</td>
<td>93/150 (62)</td>
<td>97/150 (64)</td>
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<tr>
<td>b)Pembrolizumab-Rd</td>
<td></td>
<td></td>
<td>1</td>
<td>50/124 (40)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>a)Pd</td>
<td>300</td>
<td>RRMM</td>
<td>N/A</td>
<td>43/125 (34)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>b)Pembrolizumab-Pd</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Med T: median prior lines of therapy
Post-aHCT: post-autologous stem cell transplantation

## Nivolumab in MM

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>Setting</th>
<th>Med T</th>
<th>ORR, n (%)</th>
<th>CR, n (%)</th>
<th>SD, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>375</td>
<td>RRMM</td>
<td>3</td>
<td>0/27 (0)</td>
<td>0/7 (0)</td>
<td>17/27 (63)</td>
</tr>
<tr>
<td>Nivolumab/ ipilimumab</td>
<td></td>
<td></td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab/ ipilimumab (consolidation post-aHCT)</td>
<td>42</td>
<td>NDMM RRMM</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4/4 (100)</td>
<td>4/4 (100)</td>
<td></td>
</tr>
</tbody>
</table>

Med T: median prior lines of therapy
Post-aHCT: post-autologous stem cell transplantation

Checkpoint Inhibitors in Myeloma Controversy

• All studies stopped prematurely with an increased mortality identified in patients receiving pembrolizumab or nivolumab
  — HR death 1.61 KEYNOTE-183, 2.06 KEYNOTE-185, 1.19 CheckMate 602
  — No increased ORR at that time
  — No specific cause of death observed

• Results have raised doubts regarding the utility in MM, at least in combination with immunomodulatory agents
  — Immune dysfunction is different in MM as compared to solid tumors
  — Alternative combinations with checkpoint inhibitors
  — Utility around HCT and CAR-T

**AMG 420**

- Bispecific T-cell engager (BiTE) that targets BCMA on multiple myeloma cells and CD3 on T cells
  — 6-week cycles: 400 – 600 mcg/day given as a continuous IV infusion followed by a 2 week treatment-free interval

- Phase 1/2 results demonstrate responses in RRMM

- Pearls:
  — Cytokine release syndrome (CRS) and peripheral polyneuropathy dose-limiting toxicities, generally mild and manageable; lower rates of CRS than BCMA CAR-T cells
  — No neurotoxicity seen in studies reported so far
  — Noted high rates of infection

## Bispecific T-Cell Engaging Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Source</th>
<th>Trial ID</th>
</tr>
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<tbody>
<tr>
<td>AMG 420</td>
<td>BCMA</td>
<td>Amgen</td>
<td>NCT02514239</td>
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<td>AMG 701</td>
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<td>NCT03287908</td>
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<td>CC-93269</td>
<td>BCMA</td>
<td>Celgene</td>
<td>NCT03486067</td>
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<tr>
<td>JNJ-64007957</td>
<td>BCMA</td>
<td>J&amp;J</td>
<td>NCT03145181</td>
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<tr>
<td>PF-06863135</td>
<td>BCMA</td>
<td>Pfizer</td>
<td>NCT03269136</td>
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<td>REGN5458</td>
<td>BCMA</td>
<td>Regeneron</td>
<td>NCT03761108</td>
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<td>JNJ-64407564</td>
<td>GPRC5D</td>
<td>J&amp;J</td>
<td>NCT03399799</td>
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<tr>
<td>GBR1342</td>
<td>CD38</td>
<td>Glenmark</td>
<td>NCT03309111</td>
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</tbody>
</table>

HPN 217

• Tri-Specific T-cell Activating Construct (TriTAC), engineered to have long circulating half-life that re-directs T cells to kill BCMA-positive cancer cells
  – Engineering of an HSA binding domain into HPN217 represents a unique strategy in extending serum half-life, giving the TriTAC molecule a small molecular size and flexibility

• Phase 1/2 dose escalation and dose expansion study of safety, tolerability, and pharmacokinetics of HPN217 (monotherapy) in patients with RRMM recruiting

Belantamab mafodotin

- Anti-BCMA monoclonal antibody conjugated by to monomethyl auristatin F (MMAF)
  - Induces apoptosis, enhances ADCC and ADCP, induces immunogenic cell death
  - 21-day cycles: infused over 30 minutes on Day 1 each cycle
  - ORR 60% in phase 1 DREAMM-1

- Considerations and Pearls
  - Keratopathy most common cause of dose delays and reduction, reversible
    - Steroid eye drops ineffective preventing
  - Infusion-related reactions grade 1-2, occurred with the first infusion
    - <10% with multiple infusion reactions

<table>
<thead>
<tr>
<th></th>
<th>DREAM-2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bm 2.5mg/kg</td>
</tr>
<tr>
<td>T (median, range)</td>
<td>7 (3-11)</td>
</tr>
<tr>
<td>High risk</td>
<td>42%</td>
</tr>
<tr>
<td>ORR</td>
<td>31%</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>19%</td>
</tr>
<tr>
<td>Median PFS, mos</td>
<td>2.9</td>
</tr>
</tbody>
</table>

- Adverse Events
  - Keratopathy 27% 21%
  - Thrombocytopenia 20% 33%
  - Anemia 20% 25%
  - Pneumonia 4% 11%

Lonial S et al. Lancet Oncol 2019; [Epub ahead of print]

BCMA: B-cell maturation antigen
ADCC: antibody-dependent cellular cytotoxicity
ADCP: antibody-dependent cellular phagocytosis
URI: Upper respiratory tract infection
## Belantamab mafodotin trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Primary Endpoint(s)</th>
<th>Treatment</th>
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<tr>
<td>DREAMM-4 (NCT03848845)</td>
<td>II</td>
<td>ORR</td>
<td>Belantamab mafodotin + pembrolizumab</td>
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<td>DREAMM-5 (NCT04126200)</td>
<td>I/II</td>
<td>DLTs, safety, ORR</td>
<td>Belantamab mafodotin ± GSK3174998 or GSK3359609</td>
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<td>DREAMM-6 (NCT03544281)</td>
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<td>DLTs, safety, ORR</td>
<td>Belantamab mafodotin + Rd or Vd</td>
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<td>NCT03489525</td>
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<td>Safety</td>
<td>MEDI2228</td>
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<tr>
<td>NCT04036461</td>
<td>I</td>
<td>Safety</td>
<td>CC-99712</td>
</tr>
</tbody>
</table>

Trudell et al. Lancet Oncol 2018; 19; 1641.
Question #3

Your oncologist has a 58 YOM with RRMM having received prior treatment with dexamethasone, lenalidomide, bortezomib, carfilzomib, and panobinostat. After speaking with the patient, they are leaning towards a daratumumab-based regimen, however the patient saw commercials for pembrolizumab on TV recently, and knows several cancer patients getting this medication and wanted to know if they could get it as well in their regimen. The oncologist wondered your thoughts on this?

a) No obvious issues with this combination, plus everyone should get to try a checkpoint inhibitor
b) Pembrolizumab is not needed in this patient, an apparent regimen likely to elicit an adequate response is daratumumab-pomalidomide (DPd)
c) Checkpoint inhibitors should be considered in the context of a clinical trial until more can be ascertained about their utility and toxicity
d) A and B
e) B and C
Approaching a New Era in Multiple Myeloma

<table>
<thead>
<tr>
<th>Induction</th>
<th>Consolidation</th>
<th>Maintenance</th>
<th>Relapsed/refractory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytotoxic chemotherapy</td>
<td>Thalidomide, Lenalidomide</td>
<td>Pomalidomide, Iberdomide</td>
<td>Bortezomib, Carfilzomib, Ixazomib</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Daratumumab, Elotuzumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Isatuximab</td>
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<tr>
<td></td>
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<td>Venetoclax with t(11;14)</td>
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<td>Selinuxor</td>
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<td>Panobinostat</td>
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<td>Pembrolizumab, Nivolumab, others</td>
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<td>CAR-T (multiple), CAR-T (multiple), BiTE (multiple), ADC</td>
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<td></td>
<td></td>
<td></td>
<td>TriTAC</td>
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</tbody>
</table>

CURE vs CHRONIC CONDITION
Question #4

A 62 YOF with a PMH of HTN, asthma, T2DM presents to clinic with newly diagnosed multiple myeloma having been diagnosed with osteolytic bone lesions and hypercalcemia managed during a recent admission. Her disease is standard risk cytogenetics inclusive of t(11:14), ISS stage II. The hours of your infusion center are a hard 8am-4pm. What initial regimen would you recommend for her multiple myeloma?

a) RVd  
b) Venetoclax-RVd  
c) DVTd  
d) DRVd
Take Away Points

• Since the arrival of new agents and novel mechanisms in the landscape of multiple myeloma therapy, researchers seek optimal combinations and sequencing to achieve the earliest and deepest responses
  — Daratumumab combinations are showing particularly notable promise, therefore strategies for optimizing access and use should be considered

• Small molecule inhibitors/targeted therapies may play a limited role now but their use is evolving with promise, and may require specialized supportive considerations

• More insight is needed into the role of checkpoint inhibitors in multiple myeloma, but immunotherapy broadly (BiTE, CAR-T) shows promise in RRMM with several agents (and targets inclusive of BCMA) in the pipeline to consider
Recommended references


An Evolving Era in Multiple Myeloma: Immunotherapies and Targeted Agents

Justin Arnall, PharmD, BCOP
CHS Specialty Pharmacy Services, Atrium Health, Charlotte, NC