Multiple Myeloma: Current and Emerging Therapies

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Conflict of Interest

Principal Investigator Role: none
Employee: none
Consultant: Takeda, Bristol Myers Squibb
Major Stockholder: none
Speakers Bureau: none
Scientific Advisory Board: C4 Therapeutics, Oncopep
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

Target MM in the BM microenvironment, alone and in combination, to overcome conventional drug resistance *in vitro* and *in vivo*

Effective in relapsed/refractory, relapsed, induction, consolidation, and maintenance therapy

20 FDA approvals and median patient survival prolonged 3-4 fold, from 3 to 8-10 years.
Active MM (IMWG)

Hypercalcemia Renal Dysfunction Anemia Bone Disease (CRAB)

Even without CRAB features, the following events define active MM:

- Bone marrow plasmacytosis $\geq 60\%$
- Abnormal FLC ratio $\geq 100$ (involved kappa) or $<0.01$ (involved lambda)
- Focal bone marrow lesions on PET-CT and/or MRI

Standard of care for smoldering MM is followup every three months. Protocols are evaluating novel agents and immune therapies to delay or prevent progression of smoldering to active MM.

## Risk of Progression of Smoldering to Active MM

<table>
<thead>
<tr>
<th>Criteria</th>
<th>1/3 Criteria (Low risk)</th>
<th>2/3 Criteria (Intermediate risk)</th>
<th>3/3 Criteria (High risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mayo Clinic</strong>³</td>
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<tr>
<td>3 Criteria:</td>
<td></td>
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</tr>
<tr>
<td>1. M-protein ≥3 g/dL</td>
<td></td>
<td>25%</td>
<td>76%</td>
</tr>
<tr>
<td>2. ≥10% clonal bone marrow plasma cells</td>
<td></td>
<td>51%</td>
<td></td>
</tr>
<tr>
<td>3. Free light-chain &lt;0.125 or &gt;8</td>
<td></td>
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<td></td>
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<tr>
<td><strong>PETHEM A</strong>⁴</td>
<td></td>
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</tr>
<tr>
<td>2 Criteria:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. ≥95% abnormal plasma cells</td>
<td></td>
<td>4%</td>
<td>72%</td>
</tr>
<tr>
<td>2. Low uninvolved serum immunoglobulins</td>
<td></td>
<td>46%</td>
<td></td>
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</tbody>
</table>

SMM, smoldering multiple myeloma; MM, multiple myeloma.
Vaccines Targeting Specific Peptides to Delay Progression 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
(5 of 12 pts progressed to active MM with vaccine; only 1 of 9 pts progressed to active MM with vaccine + len)

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

Bae et al, Leukemia 2015
Bae et al Leukemia 2017
Daratumumab Monotherapy For Patients With Intermediate or High-risk Smoldering Multiple Myeloma (SMM): CENTAURUS, a Randomized, Open-label, Multicenter Phase 2 Study

Screening

1:1:1 RANDOMIZATION

Arm A (16 mg/kg IV; 8-week cycles); Long

n = 41

Cycle 1: QW

Cycles 2 & 3: Q2W

Cycles 4-7: Q4W

Cycles 8-20: Q8W

Arm B (16 mg/kg IV; 8-week cycles); Intermediate

n = 41

Cycle 1: QW

Cycles 2-20: Q8W

Arm C (16 mg/kg IV; one 8-week cycle); Short

n = 41

Cycle 1: QW

Following until PD or end of study (4 years from LPFD)

Primary endpoints:
• CR
• % patients with PD\textsuperscript{a} or death per patient-year

As defined by 2014 IMWG criteria for SMM.

Hofmeister et al, ASH 2017

IV, intravenous; QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; PD, progressive disease; LPFD, last patient, first dose; CR, complete response.

CENTAURUS: PFS (Biochemical or Diagnostic)

- Biochemical/diagnostic PFS is defined as the earlier of time to biochemical or diagnostic progression or death
  - Biochemical progression: measurable disease increase from nadir by ≥25% in 2 subsequent assessments per IMWG\(^1\)
  - Diagnostic progression: SLiM-CRAB criteria
- Post-hoc analysis comparing Arm A + Arm B versus Arm C: \(P\) value = 0.0002

Hofmeister et al ASH 2017

Carfilzomib, lenalidomide dexamethasone (KRd), HDT-ASCT, KRd consolidation, Rd maintenance

Induction
6 x 28-day cycles

Consolidation
2 x 28-day cycles

Maintenance
24 x 28-day cycles

High-risk* Smouldering MM patients N=90

Carfilzomib i.v. 20/36 mg/m²
Days 1, 2, 8, 9, 15, 16
Lenalidomide
25 mg
Days 1–21
Dexamethasone
40 mg
Days 1, 8, 15 & 22

High-dose Melphalan [200 mg/m²] Followed by ASCT

Carfilzomib i.v. 20/36 mg/m²
Days 1, 2, 8, 9, 15, 16
Lenalidomide
25 mg
Days 1–21
Dexamethasone
40 mg
Days 1, 8, 15 & 22

Lenalidomide 10 mg
Days 1–21
Dexamethasone
20 mg
Days 1, 8, 15 & 22

*High-risk SMM was defined according to the Mayo and/or Spanish models

Mateos et al ASH 2017
**GEM-CESAR:** Improved quality of response with treatment (n=35)

<table>
<thead>
<tr>
<th></th>
<th>Induction (KRdx6) N = 35</th>
<th>HDT/ASCT N = 35</th>
<th>Consolidation (KRdx2) N = 35</th>
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<tbody>
<tr>
<td>≥CR</td>
<td>49%</td>
<td>62%</td>
<td>74%</td>
</tr>
<tr>
<td>VGPR</td>
<td>37%</td>
<td>23%</td>
<td>20%</td>
</tr>
<tr>
<td>PR</td>
<td>14%</td>
<td>14%</td>
<td>6%</td>
</tr>
<tr>
<td>MRD-negative</td>
<td>26%</td>
<td>47%</td>
<td>62%</td>
</tr>
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</table>

Mateos et al ASH 2017
# International Staging System (ISS) for Myeloma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>Median Survival (mo)</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>$\beta_2m &lt; 3.5$ mg/L and albumin $&gt;3.5$ g/dL</td>
<td>62</td>
</tr>
<tr>
<td>II*</td>
<td>Not stage I or III</td>
<td>44</td>
</tr>
<tr>
<td>III</td>
<td>$\beta_2m &gt; 5.5$ mg/L</td>
<td>29</td>
</tr>
</tbody>
</table>

*$\beta_2m < 3.5$ mg/L and albumin $< 3.5$ g/dL or $\beta_2m$ $3.5 - < 5.5$ mg/dL, any albumin


Revised ISS (R-ISS) incorporates LDH and high risk FISH abnormalities

Chromosomes and Prognosis in Multiple Myeloma

For conventional low and high dose therapy:

Nonhyperdiploid worse prognosis than hyperdiploid
\( t(11;14), \) hyperdiploidy -standard risk
\( t(4;14), t(14;16), t(14;20), \) del(17p), del(13q14) - high risk

For novel treatments
Bortezomib, but not lenalidomide, can at least partially overcome \( t(4;14), \) del(13q14) -
del(17p) p53 remains high risk
International Myeloma Working Group (IMWG) Criteria for MRD

- **MRD Negative:** Absence of aberrant clonal plasma in bone marrow aspirate, ruled out by an assay with minimum sensitivity of $1:10^5$ nucleated cells or higher (*i.e.*, $10^{-5}$ sensitivity)* Current methods are flow cytometry or NGS.

- **Sustained MRD- negative:** MRD negativity in the marrow (Flow or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart.

- **Imaging plus MRD-negative:** MRD negativity as defined by Flow or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue

- Kumar et al., Lancet Oncol 2016; 17: 328-46.
Initial Therapy for Newly Diagnosed MM

Transplant candidates (several cycles)

Triplets preferred: Lenalidomide/ Dex/Bortezomib (RVD) or Cyclophosphamide/Bortezomib/Dex (CyBorD)
Kyrpolis RD (KRD) if neuropathy.

Doublets rarely used, ie Bort/Dex to improve renal dysfunction, then add Len

Maintenance Len in standard risk, Bort or Len Bort in high risk

Transplant ineligible (until progression)

Triplets preferred RVD, CyBorD, KRD but at reduced doses. Ixazomib Len Dex all oral regimen.

Doublets only in frail patients RD, VD at reduced doses
Combinations in the Upfront Treatment of MM

Stewart AK, Richardson PG, San Miguel JF Blood 2009
Daratumumab (DARA) With Carfilzomib, Lenalidomide, and Dexamethasone (KRd) in Newly Diagnosed Multiple Myeloma: Updated Results of Phase 1b Study

Treated for up to 13 cycles (28 days/cycle) or until elective discontinuation for ASCT

- Daratumumab 16 mg/kg (intravenous) was administered weekly (Days 1, 8, 15, and 22) during Cycles 1 and 2, every 2 weeks (Days 1 and 15) during Cycles 3 to 6, and every 4 weeks thereafter
  • All patients received the first dose of daratumumab as a split dose over 2 days: 8 mg/kg on Days 1 and 2 of Cycle 1

- Carfilzomib was administered weekly on Days 1, 8, and 15 of each 28-day cycle as a 30-minute infusion
  • Patients received an initial dose of 20 mg/m² on Cycle 1 Day 1 and escalated to 70 mg/m² at Cycle 1 Day 8+ if deemed tolerable

- Lenalidomide was given at a dose of 25 mg on Days 1 through 21 of each cycle

- Dexamethasone was administered at a dose of 40 mg per week in patients aged ≤75 years and at a dose of 20 mg per week in patients >75 years of age

Chari et al, ASH 2017
Conclusions

- Daratumumab plus KRd is highly effective, with a 100% ORR, including 91% of patients with ≥VGPR and 57% of patients with ≥CR
  - Depth of response deepens with longer follow-up
  - MRD-negative rate at $10^{-5}$ was 14%
- Daratumumab with KRd was well tolerated
  - Safety profile is consistent with daratumumab and KRd
- There was no adverse impact on stem cell collection (median CD34+ $10.6 \times 10^6$ cells/kg)
  - Daratumumab is feasible as part of induction therapy
  - Deep responses (3 sCRs; 3 VGPRs) were achieved prior to stem cell harvest
  - As responses were not assessed following stem cell transplantation, further deepening of responses induced by daratumumab plus KRd could not be captured in patients electing ASCT

Chari et al, ASH 2017
Daratumumab plus bortezomib melphalan prednisone (D-VMP) versus VMP in newly diagnosed transplant ineligible MM

Efficacy: PFS

- Median (range) follow-up: 16.5 (0.1-28.1) months

![Graph showing PFS](image)

- 12-month PFS: 87%
- 18-month PFS: 72%

*HR, 0.50 (95% CI, 0.38-0.65; P <0.0001)*

50% reduction in the risk of progression or death in patients receiving D-VMP

Mateos et al ASH 2017
DARA + VMP vs. VMP ~ Efficacy: ORR and MRD (NGS; 10^{-5} Threshold)

Significantly higher ORR, ≥VGPR, and ≥CR with D-VMP
>3-fold higher MRD-negativity rate with D-VMP

Mateos et al ASH 2017
# IFM: RVD and Early vs Late ASCT

<table>
<thead>
<tr>
<th></th>
<th>RVD arm N=350</th>
<th>Transplant arm N=350</th>
<th>p-value</th>
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<tbody>
<tr>
<td>CR</td>
<td>49%</td>
<td>59%</td>
<td></td>
</tr>
<tr>
<td>VGPR</td>
<td>29%</td>
<td>29%</td>
<td>0.02</td>
</tr>
<tr>
<td>PR</td>
<td>20%</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>&lt;PR</td>
<td>2%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>At least VGPR</td>
<td>78%</td>
<td>88%</td>
<td>0.001</td>
</tr>
<tr>
<td>Neg MRD by FCM , n (%)</td>
<td>228 (65%)</td>
<td>280 (80%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Attal et al NEJM 2017; 376: 1311-20
MRD in Multiple Myeloma: Final Analysis IFM2009 Trial

Sensitivity \(10^{-6}\) (next generation sequencing) predicts better outcome: PFS and OS in both RVD and RVD ASCT arms, including both standard and high risk patients.

Requirement to include MRD in all the upcoming trials.

MRD could become the primary endpoint of future trials.

MRD will be central in the definition of cure.

MRD will be essential to stratify patients:
- consolidation randomization?
- maintenance randomization?
- maintenance duration?
- earlier définition of molecular relapses?

Avet-loiseau et al, ASH 2017
GEM2012MENOS65: Study Design

Induction VRDx6

- R
  - Mel-200
  - Bu-Mel

Consolidation

- VRD x 2

MRD

Pavia et al ASH 2017

Rosiñol L, et al. ASH 2017; abstract 2017
Conclusions

• NGF (next generation flow cytometry) is feasible in large multicenter clinical trials (n=1,134), allows the identification of hemodiluted BM samples inadequate for MRD assessment, and is highly-sensitive

• MRD levels as low as $10^{-5}$ and $10^{-6}$ conferred significantly inferior PFS

• Risk of relapse among MRD-negative patients was remarkably reduced (3%), and was particularly associated with bone-related plasmacytomas

• Overall, MRD-negativity is the most relevant clinical endpoint for both standard- and high-risk transplant-eligible MM patients

Pavia et al ASH 2017
BMT CTN 0702 Stem Cell Transplantation for Multiple Myeloma Incorporating Novel Agents: SCHEMA

N=750 pts (250 in each arm)

Register and Randomize → MEL 200mg/m² → Lenalidomide Maintenance

VRD x 4* → Lenalidomide Maintenance

MEL 200mg/m² → Lenalidomide Maintenance

* Bortezomib 1.3mg/m² days 1, 4, 8, 11
Lenalidomide 15mg days 1-15
Dexamethasone 40mg days 1, 8, 15
Every 21 days

** Lenalidomide x 3 years:
10mg/d for 3 cycles, then 15 mg/d
Amendment in 2014 changed Lenalidomide maintenance until disease progression after report of CALGB 100104.

Stadtmauer et al ASH 2016
Largest randomized comparison of post transplant approaches in myeloma in the United States

Demographics well balanced among auto/auto, auto/RVD, auto/maintenance

At 38 months follow-up no difference in OS:
Auto/auto 82%, auto/RVD 85.7%, auto/maint 83.4%

At 38 months follow-up no difference in PFS:
Auto/auto 56.5%, auto/RVD 56.7%, auto/maint 52.2% (high-risk worse than standard risk, but no difference by treatment arm)

Cumulative incidence of first secondary malignancy in the first 38 months similar for all 3 arms
5.9% (95% CI: 3.3%, 9.6%) in the Auto/Auto arm
6.0% (95% CI: 3.4%, 9.6%) in the Auto/RVD arm
4.0% (1.9%, 7.2%) in the Auto/Maintenance arm
EMN02/HO95 MM Trial Design

- Stratification according to center and ISS disease stage (I vs. II vs. III)
- Randomization to VMP or HDM was 1:1 in centers with a fixed single ASCT policy
- Randomization to VMP or HDM-1 or HDM-2 was 1:1:1 in centers with a double ASCT policy

**VMP x 4 cycles**
- Bortezomib 1.3 mg/m² d 1,4,8,11,22,25,29,32/42
- Melphalan 9 mg/m² d 1-4/42
- Prednisone 60 mg/m² d 1-4/42
  - (497 pts)

**Melphalan (HDM) 200 mg/m² x 1-2 courses* + single or double ASCT**
  - (695 pts)

**VCD induction x 3-4 cycles + PBSC collection**

**VRD consolidation x 2 cycles**

**Maintenance lenalidomide**

Cavo et al ASH 2017
Conclusions

• Upfront ASCT was associated with a significant improvement in PFS and ≥VGPR as compared to VMP across subgroups of patients at low and high risk

• No OS difference between the two treatment groups was seen in the overall patient population, but OS was prolonged in patients at high risk

• Upfront double ASCT was associated with a significant improvement in PFS and OS as compared to single ASCT in the overall patient population

• Double ASCT overcame the adverse prognosis imparted by high risk cytogenetic abnormalities

Cavo et al ASH 2017
Lenalidomide Maintenance After High-Dose Melphalan and Autologous Stem Cell Transplant in Multiple Myeloma: A Meta-Analysis of Overall Survival Leading to FDA Approval

- The size of the box is related to the size of the individual study. The confidence interval is a function of the overall sample size. HR, hazard ratio.

HR (95% CI)

- CALGB (n = 460) 0.56 (0.42-0.76)
- IFM (n = 614) 0.91 (0.72-1.15)
- GIMEMA (n = 135) 0.66 (0.34-1.26)
- Pooled (N = 1209) 0.74 (0.62-0.89)

Attal et al ASCO 2016
Maintenance Therapy Post-Transplant with Lenalidomide, Bortezomib and Dexamethasone (RVD) in High Risk Patients

1. Stringent CR 51%, 96% VGPR
2. Median PFS 32 months
3. Three year OS 93%

Incorporate both lenalidomide and bortezomib in maintenance therapy of high risk MM.

MRC IX Transplant Eligible: Lenalidomide Improved OS Irrespective of Cytogenetic Risk

Standard risk: HR 0.35
High risk: HR 0.58
Ultra-high risk: HR 0.38

- High risk - presence of any one of t(4;14), t(14;16), t(14;20), del(17p), or gain(1q).
- Ultra-high risk - presence of more than one lesion.
- Standard risk - absence of any of the above lesions.

Jackson et al ASH 2017
**Ixazomib Maintenance Therapy in Non Transplant Patients**: integrated Analysis of Four Phase ½ Studies

**ORR 93%**
- 7 sCR
- 15 CR
- 35 VGPR
- 36 PR
- 7 SD

**ORR 94%**
- 17 sCR
- 18 CR
- 28 VGPR
- 31 PR
- 5 SD

▶ **28 (23%) patients improved their response during ixazomib maintenance:**
- 4 CR to sCR, 7 VGPR to sCR, 8 VGPR to CR, 1 PR to CR, 6 PR to VGPR, and 2 *de novo* responses (SD to PR)

Dimopoulos et al ASH 2017
Phase II Study of Ixazomib with Lenalidomide Maintenance Following ASCT in Multiple Myeloma

- Ixa/Len (10mg daily with Ixa 3mg d1,8,15) as maintenance therapy post upfront ASCT
- ORR: ≥ 90% VGPR of and 81% estimated 2-year PFS
- 29 pts (45%) improved best overall response from post transplant baseline
- 8 of 14 patients with high risk disease progressed.
- Peripheral neuropathy was limited to grade 1/2 and 6 grade 3 events
- Hematological adverse events were manageable with dose reductions

Patel et al ASH 2017
Phase II Study of Lenalidomide-Elotuzumab maintenance post- ASCT in Multiple Myeloma

- Lenalidomide-elotuzumab is a well tolerated maintenance therapy

- 36% of patients achieved improvement in quality of response while on therapy
  - 20% have converted to sCR/CR
  - Combined effect of AuSCT + lenalidomide-elotuzumab

- The number of patients achieving CR may be underestimated due to elotuzumab interference with electrophoretic measurements
  - 19 of 33 patients not achieving CR had GK paraproteins

- Additional follow up is required to determine if the improved quality of responses translates into improvements in PFS and OS

Thomas et al ASH 2017
Treatment of Myeloma Complications

1. Bone disease and hypercalcemia—intravenous bisphosphonates: Zoledronic acid; Targetting RankL:Denosumab especially with renal dysfunction.

2. Hyperviscosity—IgM, IgG3; plasmapheresis as adjunct.

3. Recurrent infections—IV Ig only for recurrent life threatening infections.


5. Cardiac failure: amyloid, hyperviscosity, anemia.

6. Anemia: BM tumors, renal dysfunction, myelosuppression, low endogenous erythropoietin.


8. Thrombosis: disease and/or therapy related.
Therapy for Relapsed MM Depends on Prior Treatment/Clinical Features

Relapse 1-3 prior therapies: Triplets preferred

Active In Len and Bort refractory MM
- Kyprolis Pom Dex (no neuropathy)
- Dara Pom Dex (deep responses)

Activity in Len refractory MM unknown:
- Elotuzumab/Len/Dex (indolent relapse), Ixazomib
- Len/Dex (all oral), Kyprolis Len/Dex (no neuropathy),
- Dara Len dex (MRD- responses)

Activity in Bort refractory MM unknown:
- Pom Bort/Dex, Dara Bort Dex (MRD- responses)
Therapy for Relapsed MM Depends on Prior Treatment/Clinical Features

Doublets (frail patients): Pomalidomide/Dex (oral) or Kyrpolis/Dex (high risk, renal dysfunction, no neuropathy)

Multiply relapsed therapy: Daratumumab alone or in combination (high risk), Panobinostat/Bort: Bort refractory

Targeted and Immune Therapy Protocols
Pomalidomide Cytoxan Dex (PCD) for relapse MM after Lenalidomide Bortezomib Dex (RVD)

- The all oral combination of pomalidomide 4mg d1-21, cyclophosphamide 300mg d1,8,15,22, and dexamethasone 40mg d1-4 and 15-18 treatment at first relapse following lenalidomide, bortezomib and dexamethasone, with or without ASCT, achieves 85% ≥ PR after 4 cycles

- Toxicity is mostly hematological and manageable

- 94% (45/48, arm A) of transplant naive patients could proceed to a first ASCT after 4 courses of PCD following first relapse post RVD

Gardaret et al ASH 2017
Final Analysis of Phase 3 Kyprolis 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

ELd

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>14</th>
<th>16</th>
<th>18</th>
<th>20</th>
<th>22</th>
<th>24</th>
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Ld

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>14</th>
<th>16</th>
<th>18</th>
<th>20</th>
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<tr>
<td>Patients</td>
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</tr>
</tbody>
</table>

HR = 0.78 (95% CI: 0.63–0.96)

Median OS

ELd: 483 mo (403–644)

Ld: 396 mo (333–454)

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

Dimopououlos et al ASH 2017
**Subcutaneous Daratumumab in Relapsed or Refractory Multiple Myeloma (RRMM): PAVO, an Open-label, Multicenter, Dose Escalation Phase 1b Study**

- DARA co-formulated with recombinant human hyaluronidase (DARA SC) enables dosing in 3 to 5 minutes
- DARA SC 1,800 mg achieves greater maximum $C_{\text{trough}}$ compared with standard IV dose at C3D1
- DARA SC was well tolerated
  - Rate of IRRs with DARA SC was 12%; IRRs for DARA IV range between 45%-56% in RRMM$^{1-6}$
- Clinical responses with DARA SC were observed, with rates similar to DARA-IV
- Ongoing phase 3 studies evaluating DARA SC 1800 mg

Chari et al ASH 2017
Isatuximab Triggers ADCC, ADPC, CDC, and Lysosomal MM Cell-Death

Direct Cytotoxicity

Isatuximab triggers ADCC, ADPC, CDC, and lysosomal MM cell-death through the following mechanisms:

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

Indirect Cytotoxicity

Isatuximab interacts with NK cells and effector cells, leading to the release of cytotoxic factors that induce cell death in p53mut MM cells.

Bone Marrow Stromal Cell

Tai et al. Leukemia 2016;30:399
Isatuximab + Pom/Dex in RRMM TCD14079 Phase 1b

- Acceptable and manageable safety profile.
- Isatuximab PK parameters not affected by Pom.
- ORR 60%; ORR with isatuximab 10 mg/kg 61.3%. ORR in IMiD-refractory patients 54.1%.
- MTD for combination not reached.
- A Global Phase III study of isatuximab plus Pom/dex in RRMM patients ongoing (NCT02990338).

Richardson PG., et al. Abs #1887, ASH 2017
A BCMA Auristatin Immunotoxin Induces Strong Anti-MM Effects

Aptoptotic MM cells

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

Inhibition of NFκB signaling

APRIL, BAFF

NFκB

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 Myeloma

- Median follow-up 6.6 months; study is ongoing
- ORR of 60% in heavily pre-treated MM
  - 51% of patients in Part 2 had VGPR or better
- 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

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 Immunotherapies

CD3
BCMA
Cytotoxic granule

T cell proliferation

T cell
BCMA-BiTE

MM cell lysis

bb2121: An Anti-BCMA Chimeric Antigen Receptor T Cell Product Candidate  Berdaja et al ASH 2017

- bb2121 is autologous T cells transduced with a lentiviral vector encoding a novel CAR incorporating an anti-BCMA scFv, a 4-1BB costimulatory motif to promote proliferation and persistence, and a CD3ζ T cell activation domain

- Construct demonstrated potent preclinical *in vivo* activity with low tonic signaling

**bb2121 demonstrates low antigen-independent signaling**

**bb2121 improves survival and drives tumor clearance in MM mice**

*IFN-*

![bb2121 construct](image)

![anti-BCMA CARs](image)

![Tumor volume](image)

![Survival](image)

*Morgan et al, ESGCT 2016*
Clinical Trial of bb2121: An Anti-BCMA Chimeric Antigen Receptor T Cell Product

3 + 3 Dose Escalation of CAR+ T Cells

Leukapheresis
Screening

50 x 10^6
150 x 10^6
450 x 10^6
800 x 10^6
1200 x 10^6*

*1200 x 10^6 dose cohort no longer planned

bb2121 manufacturing (10 days) + release

bb2121 infusion

1st Response Assessment (Wk 4)

Sample collections for T cell expansion & cytokines

Day 0

Flu 30 mg/m^2
Cy 300 mg/m^2
Days -5,-4,-3

BM BX (Wk 2)
BM BX (Wk 4)

Study Status (Escalation Phase)

Cells Collected
N=24

Dosed
N=21

Evaluable for Response
N=21

Manufacturing success rate of 100%

Clinical deterioration n=3

Berdeja et al ASH 2017
Conclusion: b2121 Demonstrates Deep and Durable Responses with Manageable Safety Profile

**bb2121 at active doses (150 – 800 × 10^6 CAR+ T cells)**

94% ORR, 89% VGPR or better, 56% CR or better
- Median PFS not reached with follow up of 40 weeks
- MRD negative results in 90% of MRD evaluable patient samples
- Disease progression in 4 patients; 3 of 3 evaluable patients remain BCMA positive at progression

**bb2121 manageable through doses as high as 800 × 10^6 CAR+ T cells**
- The 2 reported events of grade 3 CRS resolved within 24 hours
- 1 case of delayed onset, reversible grade 4 neurotoxicity associated with tumor lysis syndrome and CRS
  - Patient with highest tumor burden on the trial
  - Rapid myeloma response (VGPR) in tumor with low BCMA expression (1% of plasma cells)

**Global Pivotal Trial (KarMMa) is open for enrollment**
- bb2121 dose range: 150-300 × 10^6 CAR+ T cells

Berjada et al ASH 2017
BCMA CAR T After Cyclophosphamide Conditioning in Relapsed Refractory MM

Study design

Lenti Transduction, Expansion & Cryopreservation

Screening & Eligibility

Apheresis

Wk-4

+/- Cytoxan

D-7

D-3

D0 D1 D2

CART-BCMA

Clinical/Lab Assessments:
Screening, pre-tx***, D0,+1,2,4,7,10,14,21,28**

MM Assessments:
Screening, pre-tx***, D14, D28**

Pre-Tx
BM asp/Bx

D28

BM asp/Bx

D90

* Patients may receive therapy during manufacturing to maintain disease control
** After first 28 days, follow-up is q4 wks up to 6 mos., then q3 mos. up to 2 years
*** Pre-tx = pre-treatment, 3 to 7 days before CAR T cell infusion

Cohen et al ASH 2017
Clinical activity

Cohort 1
1-5 x 10^8 CART-BCMA

Cohort 2
Cytox + 1-5 x 10^7 CART-BCMA

Cohort 3
Cytox + 1-5 x 10^8 CART-BCMA

**Measurable by PET/CT: FDG-neg at d28, d90

ORR (≥PR) = 11/24 (46%)
• ≥MR = 16/24 (67%)
ORR (≥PR) @ 10^8 = 10/19 (53%)

Median DOR = 4 months
Conclusions

- CART-BCMA has activity in heavily pre-treated MM
- Lymphodepletion is not required for robust expansion and response
- Cyclophosphamide may increase frequency of patients with strong expansion
- CART-BCMA detectable by qPCR up to 21 months
  - typically 4-6+ months
- Toxicities remain CRS and neurotoxicity
  - No increased toxicity with cyclophosphamide
- Responses: $\geq$PR in 11/24 (47%)
  - 4 ongoing at 3+, 3+, 6+ and 24+ months
  - 1-5 x10^8 dose more active
  - Not clearly associated with baseline BCMA expression or sBCMA concentration
- Decreased BCMA expression may be escape mechanism
Mutational Landscape or Cloud of Myeloma

Therapies Targeting Ras Raf MAPK Pathway Achieve Transient Responses

Responses to Venetoclax (Target BCL-2) by \textit{BCL2:BCL2L1} Ratio Among t(11;14)-Positive Patients with RRMM

Gene expression ratio among t(11;14) patients

\text{ORR} 88\%

\text{High} \quad \text{(n=9)}

\text{High} \quad \text{BCL2:BCL2L1 (BCL-X\textsubscript{L})}

\text{ORR} 20\%

\text{Low} \quad \text{(n=15)}

\text{Low} \quad \text{BCL2:BCL2L1}

Kumar et al, ASH 2016
Integrative Oncogenomic Analysis: Combining Whole Genome, Transcriptome, and Epigenome Identifies Altered Chromatin Accessibility Landscape and New Targets in Multiple Myeloma

Szalat et al ASH 2017
Conclusions

1. We have analyzed the open chromatin landscape in MM and identified myeloma signatures

2. The integration of epigenomic and genomic data reveals:
   - High number of mutations in regulatory regions
   - Epigenomic profile is impacted by mutations in promoter/enhancer regions
   - Expression changes are influenced by epigenomic dysregulation and chromosomai structural variants

We are validating new potential therapeutic targets

Szalat et al ASH 2017
Model of KDM3A-KLF2-IRF4 Axis in MM cells

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

Ohguchi et al Nat Comm 2016; 7:10258
cfDNA Allows Discovery-Oriented Sequencing in MM Patients

• Discovery-oriented low-pass WGS and WES is possible from cfDNA in MM
  – Requires sufficient tumor fraction
  – Cost-effective markers predict efficiency of cfDNA sequencing

• cfDNA is an excellent proxy for clonal events in BM of MM patients

• cfDNA and BM may reveal distinct subclonal information

• cfDNA is useful as a marker for disease progression and clonal evolution
  – Potentially useful for non-secreting MM

Lohr et al ASH 2017
Summary and Conclusions

- Clinical trials of novel targeted and immune agents to delay or prevent progression of SMM.

- In newly diagnosed patients, triplets are standard of care, with doublets only in frail patients, and four drug regimens now being evaluated.

- Maintenance with lenalidomide is standard, proteasome inhibitors and combinations in high risk MM

- ASCT remains standard of care; double transplant in high risk MM
Summary and Conclusions

- Triplets achieve increased extent and frequency of response, PFS, and OS in relapsed MM.

- Daratumumab and isatuximab combinations, BCMA immunotoxins, and BCMA CAR T cells achieve deep responses.

- Venetoclax in MM with t (11:14) and high Bcl-2 gene expression is an example of personalized medicine in MM.

- Future studies will integrate genomic and epigenomic signatures, and probe PB, ie cell free DNA (cfDNA) versus BM.
Future Directions

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

Collaborative effort of academia, biotech/pharma, NIH/NCI, FDA, and advocacy- International Myeloma Society-will facilitate continued advances.

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.
Case 1
A 50 year old man who is asymptomatic is found at the time of a routine physical exam to have elevated total protein and IgG lambda of 2.5 gm/dL. Hct 47%, Creat 1.0mg/dL, and Ca 9.0mg/dL. BM 20% plasma cells FISH t(11;14), and serum kappa:lambda 2.3. Bone survey normal and MRI reveal no bone disease.

What is the diagnosis and what would you do now?
1. Smoldering MM at low risk of progression, follow expectantly off all therapy
2. Smoldering MM at intermediate risk of progression, consider clinical trial
3. Smoldering MM at high risk of progression, treat with lenalidomide, bortezomib, and dexamethasone
4. Active MM, treat with lenalidomide/bortezomib/dexamethasone, stem cell harvest, and lenalidomide maintenance until progression
5. Active MM, treat with lenalidomide/bortezomib/dexamethasone, stem cell harvest, high dose therapy/stem cell transplant, and lenalidomide maintenance until progression
CASE 1

The correct answer is choice 1.
There is no hypercalcemia, renal dysfunction, anemia, or bone disease, nor is there a defining event (<60% bone marrow plasma cells, kappa:lambda >100 fold abnormal or bone disease on PET/CT or MRI) to make this active multiple myeloma (MM). It is not monoclonal gammopathy of undetermined significance (MGUS, <3gm M protein, <10% BM plasma cells) due to 20% BM plasma cells. It is smoldering MM (SMM, > 3gm monoclonal protein or > 10% BM plasma cells without MM defining event). Within SMM, risk factors for progression to active MM include monoclonal protein > 3g/dL , > BM10% plasma cells, and kappa:lambda <0.125 or >8. Risk of progression is low, intermediate, and high with 1 of 3, 2 of 3, and 3 of 3 of these criteria, respectively. This patient has a low risk of progression, and therefore should be followed expectantly off all therapy, with monitoring every 3 months of the myeloma profile (serum protein electrophoresis, kappa:lambda). Patients with intermediate and high risk of progression to active MM are eligible for clinical protocols of novel targeted and/or immune agents to delay time to progression to active MM.

A 37 year old man presented with back pain and fatigue. Hct 30%, Creat 2.3mg/dL, Ca 8.0mg/dL, and compression fracture at L3-4. Serum IgG lambda 8.5gm/dL, BM 80% plasma cells with FISH del 17p. He is treated with lenalidomide bortezomib dexamethasone, high dose melphalan and ASCT, followed by lenalidomide/bortezomib maintenance. Relapse occurs 6 months later with rising IgA M protein and new bone disease.

Optimal therapy at this time would be:
1. Carfilzomib lenalidomide dexamethasone
3. Ixazomib lenalidomide dexamethasone
3. Elotuzumab lenalidomide dexamethasone
4. Carfilzomib pomalidomide dexamethasone
5. Daratumumab lenalidomide dexamethasone
CASE 2

The correct answer is choice 4. This gentleman presented with high risk multiple myeloma (MM) by virtue of his deletion 17p and was treated due to anemia, bone disease, and renal dysfunction with lenalidomide bortezomib dexamethasone induction, high dose melphalan and stem cell transplantation, and then lenalidomide and bortezomib combination maintenance post transplant. Although lenalidomide is FDA approved as maintenance until progression posttransplant due to prolongation of PFS and OS, the benefit is predominantly in standard risk MM. Nooka et al have shown that bortezomib and lenalidomide can decrease the rate of early relapse that is characteristic of high risk myeloma, and clinical trials of lenalidomide, ixazomib, lenalidomide and ixazomib, lenalidomide and elotuzumab maintenance therapy are ongoing to assess their impact, especially in high risk MM.

CASE 2

This relapse of disease occurred while patient was receiving lenalidomide and bortezomib therapy, and MM is therefore resistant to these agents. Second generation immunomodulatory agent pomalidomide combined with second generation proteasome inhibitor carfilzomib is therefore the most reasonable option. The other choices include either carfilzomib, ixazomib, elotuzumab, or daratumumab, in each case combined with lenalidomide dexamethasone; they were all FDA approved based upon randomized trials in relapsed MM when compared to lenalidomide dexamethasone, and were done in the setting of relapsed, but lenalidomide sensitive, MM. The activities of these regimens in lenalidomide and bortezomib refractory MM, as in this patient, is unknown.

Stewart et al NEJM 2015;372:142.
Moreau et al NEJM 2016;374:1621.
Lonial et al MEJM 2015;373:621.
Lokhorst et al NEJM 2015;373:1207.
Palumbo et al NEJM 2016;375:754.
Dimopouos et al NEJM 2016;375:1319.
Chim et al Leukemia 2018;32:252.