Multiple Myeloma: New Therapies and Evolving Aspects of Individualized Management

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The following relationships exist related to this presentation:

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- Advisory Board: Millennium-Takeda, and Gilead
- Scientific Founder: Oncopep, C4 Therapeutics

Off Label/Investigational Discussion
In accordance with Annenberg Health Sciences policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.
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

19 FDA approvals and median patient survival prolonged 3-4 fold
Bench to Bedside Translation of Novel Agents in Myeloma

Preclinical and Clinical Studies leading to FDA Approvals in MM

- 2006 Thalidomide
- 2003, 2005, 2008 Bortezomib (BTZ)
- 2006, 2014 Lenalidomide
- 2007 Doxil + BTZ
- 2012, 2015 Carfilzomib
- 2013, 2015 Pomalidomide
- 2015 Panobinostat
- 2015 Ixazomib
- 2015 Daratumumab
- 2015 Elotuzumab

Improvement in overall survival from median of 3 to 8-10 years

- 1960-65
- 1965-70
- 1970-75
- 1975-80
- 1980-85
- 1985-90
- 1990-95
- 1995-00
- 2000-05
- 2005-10

Immunomodulatory agent
Proteasome inhibitor
Monoclonal Antibody
HDAC inhibitor
Criteria for Diagnosis of Multiple Myeloma (MM)

**MGUS**
- ≤3 g M spike
- <10% PC

**Smoldering MM**
- ≥3 g M spike
- OR ≥10% PC

**Active MM**
- ≥10% PC
- M spike +

AND

No anemia, bone lesions, normal calcium and kidney function

AND

Anemia, bone lesions, high calcium or abnormal kidney function

Diagnosis of Active MM (IMWG)

Even without CRAB features, the following define active MM:

Bone marrow plasmacytosis > 60%

Abnormal FLC ratio > 100 (involved kappa) or <0.01 (involved lambda)

Focal bone marrow lesions on PET-CT and/or MRI

Protocols of novel agents/immune therapies to delay or prevent progression of smoldering to active MM.

### International Staging System (ISS) for Myeloma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>Median Survival (mo)</th>
</tr>
</thead>
</table>
| I     | $\beta_2 m < 3.5 \text{ mg/L}$  
albumin $> 3.5 \text{ g/dL}$ | 62 |
| II*   | Not stage I or III | 44 |
| III   | $\beta_2 m > 5.5 \text{ mg/L}$ | 29 |


**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.
The Effect of MRD Status on PFS (CR patients)

CR-achieving patients

- MRD-negative (n=389)
- MRD-positive (n=155)

\[ \chi^2 \text{ (adjusted)} = 35.85; \quad P < 0.0001 \]

<table>
<thead>
<tr>
<th>CR patients</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD-negative</td>
<td>56 months</td>
</tr>
<tr>
<td>MRD-positive</td>
<td>34 months</td>
</tr>
</tbody>
</table>

The Effect of MRD Status on OS (CR patients)

CR-achieving patients

$\chi^2$ (adjusted) = 15.06; $P < 0.0001$

<table>
<thead>
<tr>
<th>CR patients</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD-negative</td>
<td>112 months</td>
</tr>
<tr>
<td>MRD-positive</td>
<td>82 months</td>
</tr>
</tbody>
</table>

Munshi N et al., JAMA Oncol 2017; 3: 38-35
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
Triplets recommended in all patients except frail non transplant candidates

RVD versus Rd : PFS

Log-rank P value = 0.0018 (one sided)*

HR = 0.712 (0.560, 0.906)*

Durie et al, ASH 2015
Carfilzomib, Lenalidomide, and Dexamethasone (KRd) Followed By ASCT, KRd Consolidation, and Lenalidomide Maintenance

• Highly effective with 61% of sCR+CR at the completion of consolidation
• Compared to our standard intensive program with RVD regimen, time to response is fast with 78% pts in VGPR or better at time of transplant (vs 50%)
• At the completion of consolidation, 70% pts achieved MRD negativity by Flow that is similar to RVD regimen
• In our study, safety was an issue: 4 pts did not receive transplant because of toxicities, mechanisms of cardio-vascular events need to be evaluated

Roussel et al ASH 2016
### Ixazomib Len Dex Pre and Post ASCT with Ixa Maintenance

<table>
<thead>
<tr>
<th></th>
<th>Post-induction N = 42</th>
<th>Post-ASCT N = 37</th>
<th>Post-early Conso N = 37</th>
<th>Post-late Conso N = 34</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCR (%)</td>
<td>2.4</td>
<td>9.5</td>
<td>23.8</td>
<td>38.2</td>
</tr>
<tr>
<td>CR (%)</td>
<td>9.5</td>
<td>7.1</td>
<td>4.8</td>
<td>5.9</td>
</tr>
<tr>
<td>VGPR (%)</td>
<td>23.8</td>
<td>45.2</td>
<td>38.1</td>
<td>32.4</td>
</tr>
<tr>
<td>PR (%)</td>
<td>42.9</td>
<td>21.4</td>
<td>19</td>
<td>17.6</td>
</tr>
<tr>
<td>Stable (%)</td>
<td>14.3</td>
<td>4.8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PD (%)</td>
<td>4.8</td>
<td>0</td>
<td>2.4</td>
<td>5.9</td>
</tr>
<tr>
<td>NE (%)</td>
<td>2.4</td>
<td>11.9</td>
<td>11.9</td>
<td>0</td>
</tr>
<tr>
<td>&gt; PR (%)</td>
<td>81</td>
<td>83.3</td>
<td>85.7</td>
<td>94.1</td>
</tr>
<tr>
<td>&gt; VGPR (%)</td>
<td>38.1</td>
<td>61.9</td>
<td>66.7</td>
<td>76.5</td>
</tr>
<tr>
<td>&gt; CR (%)</td>
<td>11.9</td>
<td>16.7</td>
<td>28.6</td>
<td>44.1</td>
</tr>
</tbody>
</table>

Moreau et al, ASH 2016
Lenalidomide Maintenance After High-Dose Melphalan and Autologous Stem Cell Transplant in Multiple Myeloma: A Meta-Analysis of Overall Survival

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.

- CALGB (n = 460)
  - Favors LEN
  - HR (95% CI): 0.56 (0.42-0.76)

- IFM (n = 614)
  - Favors control
  - HR (95% CI): 0.91 (0.72-1.15)

- GIMEMA (n = 135)
  - Favors LEN
  - HR (95% CI): 0.66 (0.34-1.26)

- Pooled (N = 1209)
  - Favors control
  - HR (95% CI): 0.74 (0.62-0.89)

Attal et al ASCO 2016

*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.*
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.

Is Early Transplant Needed?
IFM/DFCI 2009 (N=1,360)

**Induction**
- **RVDx3**
- **Lenalidomide***
- **Melphalan 200mg/m²** + **ASCT**
- **CY (3g/m²)**
  - **MOBILIZATION**
    - Goal: 5 x 10⁶ cells/kg

**Calibration**
- **RVDx3**
- **CY (3g/m²)**
  - **MOBILIZATION**
    - Goal: 5 x 10⁶ cells/kg

**Collection**
- **MRD**
- **MRD**
- **MRD**
- **MRD**
- **MRD**

**Consolidation**
- **RVD x 2**
- **RVD x 3**

**Maintenance**
- **Lenalidomide***
- **MRD**

**Randomize**
- **SCT at relapse**

*Richardson et al, ASH 2014

*IFM vs. US: 1yr vs. Continuous
## 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>
</tr>
</thead>
<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 in press
Superior PFS with Early ASCT and Len Maintenance

P < 0.001

N at risk

<table>
<thead>
<tr>
<th></th>
<th>HDT</th>
<th>no HDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>months</td>
<td>350</td>
<td>350</td>
</tr>
<tr>
<td>12</td>
<td>309</td>
<td>296</td>
</tr>
<tr>
<td>24</td>
<td>261</td>
<td>228</td>
</tr>
<tr>
<td>36</td>
<td>153</td>
<td>128</td>
</tr>
<tr>
<td>48</td>
<td>27</td>
<td>24</td>
</tr>
</tbody>
</table>
Sequencing Distinguishes Outcome in FCM Negative Patients

P-value: p=0.0006

Patients without progression (%)

Avet-Loiseau et al, ASH 2015
BMT CTN 0702 Stem Cell Transplantation for Multiple Myeloma Incorporating Novel Agents: SCHEMA

Register and Randomize -> MEL 200mg/m²

MEL 200mg/m² -> VRD x 4*

VRD x 4* -> Lenalidomide Maintenance**

Lenalidomide Maintenance** -> MEL 200mg/m²

MEL 200mg/m² -> Lenalidomide Maintenance**

Lenalidomide Maintenance** -> Lenalidomide Maintenance**

N=750 pts (250 in each arm)

N=257

N=254

N=247

* 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
When to Consider Retreatment

- Patients with asymptomatic rise in M-protein (biochemical relapse) can be observed to determine the rate of rise and nature of the relapse.

- CRAB criteria are indications to treat in the relapsed setting:
  - C: Calcium elevation (> 11.5 mg/L or ULN)
  - R: Renal dysfunction (serum creatinine > 2 mg/dL)
  - A: Anemia (Hb < 10 g/dL or 2 g < normal)
  - B: Bone disease (lytic lesions or osteoporosis)

- In patients with asymptomatic progression, treatment can avoid CRAB.
Therapy for Relapsed MM Depends on Prior Treatment/Clinical Features

Relapse 1-3 prior therapies:

**Triplets preferred** Pomalidomide Bort/Dex, Kyprolis Len/Dex, Kyprolis Pom/Dex
Elotuzumab/Len/Dex, Ixazomib Len/Dex (all oral), activity in Len refractory MM unknown

**Doublets (frail patients):** Pomalidomide/Dex (oral) or Kyprolis/Dex : high risk, renal dysfunction, neuropathy
All oral Ixazomib Len Dex vs Len Dex in Relapsed/Refractory MM (1-3 lines prior Rx)

PFS benefit confirmed by time to progression (TTP) analysis: median 21.4 months versus 15.7 months with IRd versus Rd, HR 0.712; p=0.007

<table>
<thead>
<tr>
<th>Response rates, %</th>
<th>IRd (N=360)</th>
<th>Placebo-Rd (N=362)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR (≥PR)</td>
<td>78.3</td>
<td>71.5</td>
<td>p=0.035</td>
</tr>
<tr>
<td>CR+VGPR</td>
<td>48.1</td>
<td>39.0</td>
<td>p=0.014</td>
</tr>
<tr>
<td>Response categories</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>11.7</td>
<td>6.6</td>
<td>p=0.019</td>
</tr>
<tr>
<td>PR</td>
<td>66.7</td>
<td>64.9</td>
<td>–</td>
</tr>
<tr>
<td>VGPR</td>
<td>36.4</td>
<td>32.3</td>
<td>–</td>
</tr>
<tr>
<td>Median time to response, mos*</td>
<td>1.1</td>
<td>1.9</td>
<td>–</td>
</tr>
<tr>
<td>Median duration of response, mos</td>
<td>20.5</td>
<td>15.0</td>
<td>–</td>
</tr>
</tbody>
</table>

Moreau et al ASH 2015, NEJM 2016; 374: 1621-34.
# A phase I/II study of Carfilzomib, Pomalidomide and Dex in RRMM

<table>
<thead>
<tr>
<th></th>
<th>KPd once weekly (27 mg/m²)</th>
<th>Single agent Pom/Carf&lt;sup&gt;1,2&lt;/sup&gt;</th>
<th>KPd twice weekly (27x2 mg/m²)&lt;sup&gt;3,4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>&gt; nCR</strong></td>
<td>6%</td>
<td>1%/0%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>&gt; VGPR</strong></td>
<td>26%</td>
<td>5%/3.8%</td>
<td>28%</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>64%</td>
<td>31%/15%</td>
<td>64%</td>
</tr>
<tr>
<td><strong>CBR</strong></td>
<td>85%</td>
<td>39%/31%</td>
<td>80%</td>
</tr>
<tr>
<td><strong>Median PFS</strong></td>
<td>9.2</td>
<td>4.0/3.7</td>
<td>12.0</td>
</tr>
<tr>
<td><strong>At least 1 AE</strong></td>
<td>91%</td>
<td>-/98%</td>
<td>88%</td>
</tr>
<tr>
<td><strong>At least 1 grade 3 AE</strong></td>
<td>66%</td>
<td>61%/78%</td>
<td>62%</td>
</tr>
<tr>
<td><strong>At least 1 grade 4 AE</strong></td>
<td>20%</td>
<td>-/-</td>
<td>21%</td>
</tr>
<tr>
<td><strong>Dose reduction</strong></td>
<td>19%</td>
<td>27%/-</td>
<td>37%</td>
</tr>
<tr>
<td><strong>Discontinuation due AEs</strong></td>
<td>4%</td>
<td>14%/15%</td>
<td>19%</td>
</tr>
</tbody>
</table>

SLAMF7 (CS1) is highly and uniformly expressed at gene and protein level on patient MM and NK cells.

Elotuzumab (Elo) is a humanized monoclonal antibody targeting CS1, activates NK cells via CD16 and ADCC.

Clinical trial of elo in relapsed MM achieved SD.

ADCC activity of Elo against MM enhanced by lenalidomide (len) in preclinical models (Tai et al, Blood 2008).

Phase II trial: 92% response to len dex elo in relapsed MM, PFS 32.5 months.

Phase III trial: len dex elo prolongs PFS in relapsed MM by 5 months compared to len dex, leading to FDA approval (Lonial et al, NEJM 2016).
Therapy for Relapsed MM Depends on Prior Treatment/Clinical Features

Multiply relapsed therapy:

Daratumumab (high risk), Dara Bortezomib/Dex and Dara Len/Dex increase response and duration (both recently FDA approved in 1-3 prior therapies)

Panobinostat/Bort: Bort refractory, limited by AE

Immune and Targeted Therapy Protocols
Background

- **Daratumumab**
  - Human monoclonal antibody targeting CD38
  - Direct on-tumor and immunomodulatory MoA\(^1\)-\(^5\)

- **Approved**
  - As monotherapy for heavily pretreated RRMM by the FDA, EMA, Health Canada, Mexico, and Singapore
  - Combo with standard of care regimens for RRMM after ≥1 prior therapy (POLLUX and CASTOR) by the FDA

- **Early phase study of daratumumab in combination with bortezomib\(^6\)**
  - Deep and durable responses
  - Well tolerated with manageable adverse events
Efficacy of Daratumumab, Bortezomib, and Dexamethasone Versus Bortezomib and Dexamethasone in Relapsed or Refractory Multiple Myeloma: Updated Analysis of CASTOR

- Median (range) follow-up: 13.0 (0-21.3) months
- An additional 7% of patients receiving DVd achieved ≥CR with longer follow-up

Responses continue to deepen in the DVd group with longer follow-up

Palumbo et al NEJM 2016 Mateos et al ASH 2016
Daratumumab, Lenalidomide, and Dexamethasone Versus Lenalidomide and Dexamethasone for Relapsed or Refractory Multiple Myeloma (1 to 3 Prior Lines): Updated Analysis of POLLUX

Responses continue to deepen in the DRd group with longer follow-up

Dimopoulos et al NEJM 2016 Moreau et al ASH 2016
- Lower risk of progression in MRD-negative patients
- PFS benefit in MRD-positive patients who received daratumumab-containing regimens versus standard of care

Avet-Loiseau al ASH 2016
DARA can be combined safely with rHuPH20 (recombinant human hyaluronidase)

SC DARA was well tolerated with low IRR rates
  - SC injections were well tolerated

PK profile of the 1,800-mg dose was consistent with DARA 16 mg/kg IV

Efficacy was consistent with IV DARA in a similar patient population
  - 38% ORR, including deep responses (1 sCR)

Usmani et al ASH 2016
Immune Suppressive Microenvironment in MM

- IL-6, IL-10, TGFβ, PGE, ARG1, NO, ROS, COX2
- Depletion of cysteine
- Tumor promotion and induction of PD-L1 expression
- MM induced immune suppression
- Tumor promotion and induction of PD-L1 expression

Enhanced Activity of Combination Immune Therapies

Pembrolizumab, Lenalidomide/Dex in RR MM

- Heavily pretreated RRMM (median 4 prior therapies); Acceptable safety profile
- ORR 50% and disease control (CR, PR, or SD) was 98%
- Phase 3 trials now underway

Pembroluzumab Pomalidomide/Dex in RR MM

- Heavily pretreated RRMM (median of 3 prior therapies)
- ORR 56%; sCR 8%; VGPR 13%; PR 29%
- Median DOR: 8.8 months
- Double refractory ORR: 55%

NCT02036502
bb2121 has demonstrated substantial anti-tumor activity in heavily pretreated patients with multiple myeloma
- Patients with stringent complete responses and elimination of minimal residual disease
  - 100% ORR (6/6) with doses above $5 \times 10^7$ CAR+ T cells

bb2121 has been well tolerated, with mild-to-moderate cytokine release syndrome reported to date
- No dose-limiting toxicities yet identified and dose escalation continues

Dosing escalation and expansion will continue to identify recommended phase 2 dose
Complex and Evolving Mutational Landscape of Myeloma

Venetoclax (Targets Bcl-2) With Bortezomib (Targets Mcl-1) Relapsed/Refractory Multiple Myeloma

- Venetoclax with bortezomib and dexamethasone was well tolerated

- ORR for all patients was 67%; ORR 97% and ≥VGPR, 74% in bortezomib sensitive, 1-3 prior lines

- Responses durable among in MM sensitise to bortezomib (median TTP, 11.3 vs 1.8 months), and with 1–3 prior lines therapy (median TTP, 11.6 vs 4.3 months)

- Patients with t (11:14) and high BCL2 gene expression demonstrated higher clinical response

- Ongoing Phase 3 trial with this regimen in patients with relapsed/refractory MM for registration

Moreau et al ASH 2016
Summary and Conclusions

- Broader population of patients now eligible for therapy, even in the absence of CRAB features: 60% BM plasma cells; kappa:lambda >100; bone disease on MRI or PET/CT

- International Staging System now refined to include FISH profiling.

- In newly diagnosed patients, triplets prolong PFS and OS and are standard of care, with doublets only in frail patients.

- MRD portends for better patient outcome and is now a goal of therapy
Summary and Conclusions

- Triplets (carfilzomib pom dex) achieve increased extent and frequency of response in relapsed MM.

- Daratumumab combinations are very active, BCMA CAR T cells are promising, as are checkpoint inhibitors combined with immunomodulatory drugs.

- Genetic complexity and ongoing DNA damage is present at diagnosis and underlies relapse in MM.

- Venetoclax (targets Bcl-2) with bortezomib (targets Mcl-1) promising in t (11:14) MM with high Bcl-2 gene expression.