Emerging Treatment Options for Relapsed / Refractory Multiple Myeloma

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Outline

• Targeting apoptosis
  • Venetoclax

• Targeting BCMA
  • CAR T cells
  • Bispecific monoclonal antibodies
  • Antibody drug conjugates

• Individualized Medicine

• Conclusions
Bcl-2 Inhibition in Multiple Myeloma

- The Bcl-2 specific inhibitor venetoclax has preclinical activity in a subset of human myeloma cell lines (HMCLs)
- Predictors of activity:
  - $t(11;14)^+$
  - High Bcl2 / Mcl1 mRNA ratio

Touzeau C et al. Leukemia 2014;28:210-212
Venetoclax Monotherapy for Relapsed / Refractory Multiple Myeloma

- Phase I study
- 66 patients
- Median age: 63 (31 – 79)
- t(11;14)+: 30 patients
  - 5 with del(17p)
- t(11;14)-: 36 patients
- Median no. of prior therapies: 5 (1 – 15)
  - Lenalidomide + bortezomib refractory: 61%
  - Carfilzomib refractory: 38%
  - Pomalidomide refractory: 59%
  - Refractory to the last prior therapy: 79%

Patients treated with 50 – 400 mg of venetoclax daily with doses titrated up to 300 – 1200 mg by week 3.

* 2 responses: 1 in a pt with an IgH translocation with unknown partner, 1 in a pt with unknown CGs
Venetoclax Monotherapy for Relapsed / Refractory Multiple Myeloma

- Median TTP: 2.6 months (95% CI 1.9 – 4.7)
- Median DOR: 9.7 months (95% CI 7.0 – NR)

Shaji Kumar et al. Blood 2017;130:2401-2409
Bortezomib treatment of human myeloma cell lines leads to upregulation of proapoptotic Noxa and down-regulation of apoptotic Mcl-1

Punnoose E et al. Mol Cancer Ther 2016;15:1132-1144
Venetoclax, Bortezomib and Dexamethasone for Relapsed / Refractory Multiple Myeloma

- Phase I study
- 66 patients
- Median age: 64 (38 – 79)
- t(11;14)+: 9 patients
- Del(17p): 15 patients
- Median no. of prior therapies: 3 (1 – 13)
  - Bortezomib refractory: 39%
  - Lenalidomide refractory: 53%
  - Refractory to the last prior therapy: 61%

Patients treated with 100 – 1200 mg of venetoclax daily.

Philine Moreau et al. Blood 2017;130:2392-2400
Venetoclax, Bortezomib and Dexamethasone for Relapsed / Refractory Multiple Myeloma

BCL2 level predictive of response and TTP

ORR 94% for BCL2 high (n = 18)
33% sCR/CR
33% VGPR
28% PR

ORR 59% for BCL2 low (n = 27)
7% sCR/CR
15% VGPR
37% PR

Median TTP 11.6 months for BCL2 high
Median TTP 5.7 months for BCL2 low

Philippe Moreau et al. Blood 2017;130:2392-2400
Venetoclax, Bortezomib and Dexamethasone for Relapsed / Refractory Multiple Myeloma

- Median TTP: 9.5 months (95% CI 5.7 – 10.4)
- Median DOR: 9.7 months (95% CI 7.4 – 15.8)
- Median TTP best in less heavily pretreated patients and those with bortezomib sensitive disease

Philippe Moreau et al. Blood 2017;130:2392-2400
Venetoclax, Carfilzomib and Dexamethasone in Relapsed / Refractory Multiple Myeloma

Phase II Study, 1 – 3 prior lines therapy, carfilzomib naive

Costa L et al. ASCO 2018

- 42 pts enrolled
- 30 evaluable (≥3 cycles or PD)
- 28-day cycle
  - Vtx 400 or 800 mg daily
  - CFZ 27 or 56 mg/m² IV on days 1, 2, 8, 9, 15 and 16 or 70 mg/m² on days 1, 8 and 15
- Median age: 67 (37 – 79)
- Median prior line of therapy: 2 (1 – 3)
- PI Refractory: 50%
- IMID refractory: 62%
- Double refractory: 33%
BCMA in Multiple Myeloma

- B cell maturation antigen
- Expressed on late memory B cells committed to PC differentiation and PCs
- BCMA is critical for survival of long-lived PCs

**BCMA expression in PC**

*In normal physical functions*
- Support survival of long-lived PCs
- Production of antibodies
- Class switch of immunoglobulin

*In MM*
- Promote proliferation and survival of MM cells.
- Associated with immunosuppressive BM microenvironment.
- Increased sBCMA level is associated with disease progression and poorer outcome.

Cho SF et al. Front Immunol 2018;10:1821
BCMA CAR T Cell Therapy in Relapsed / Refractory Multiple Myeloma: bb2121

≥50% BCMA expression (n=12)

<50% BCMA expression (n=10)

Dose range: 150–450 × 10⁶ CAR+ cells

Raje N et al. ASCO 2018
<table>
<thead>
<tr>
<th>Prior therapies, n (%)</th>
<th>Escalation (N=21)</th>
<th>Expansion (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exposed</td>
<td>Refractory</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>21 (100)</td>
<td>14 (67)</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>19 (91)</td>
<td>12 (57)</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>21 (100)</td>
<td>19 (91)</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>19 (91)</td>
<td>15 (71)</td>
</tr>
<tr>
<td>Daratumumab</td>
<td>15 (71)</td>
<td>10 (48)</td>
</tr>
<tr>
<td>Exposed/Refractory, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bort/Len</td>
<td>21 (100)</td>
<td>14 (67)</td>
</tr>
<tr>
<td>Bort/Len/Car/Pom/Dara</td>
<td>15 (71)</td>
<td>6 (29)</td>
</tr>
</tbody>
</table>

Raje N et al. ASCO 2018
BCMA CAR T Cell Therapy in Relapsed / Refractory Multiple Myeloma: bb2121

Raje N et al. ASCO 2018

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**Tumor Response By Dose**

- **ORR=33.3%**
  - mDOR=1.9 mo

- **ORR=57.1%**
  - mDOR=NE

- **ORR=95.5%**
  - mDOR=10.8 mo

**Tumor Response By BCMA Expression**

- **ORR=100%**
  - Low BCMA (n=8)
  - Median follow-up (min, max), d: 168 (121, 184)

- **ORR=91%**
  - High BCMA (n=11)
  - Median follow-up (min, max), d: 311 (46, 556)
BCMA CAR T Cell Therapy in Relapsed / Refractory Multiple Myeloma: bb2121

PFS at Inactive (50 × 10⁶) and Active (150–800 × 10⁶) Dose Levels

- **50 × 10⁶** (n=3)
  - mPFS (95% CI), mo: 2.7 (1.0–2.9)
- **150–800 × 10⁶** (n=18)
  - mPFS (95% CI), mo: 11.8 (8.8–NE)

**Events**
- 3
- 10

mPFS = 11.8 mo

mPFS = 2.7 mo

PFS in MRD-Negative Patients

- **150–800 × 10⁶** (n=16)
  - mPFS (95% CI), mo: 17.7 (5.8–NE)

Raje N et al. ASCO 2018
BCMA CAR T Cell Therapy in Relapsed / Refractory Multiple Myeloma: bb2121

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dosed Patients (N=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with a CRS event, n (%)</td>
<td>27 (63)</td>
</tr>
<tr>
<td>Maximum CRS gradea</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>16 (37)</td>
</tr>
<tr>
<td>1</td>
<td>16 (37)</td>
</tr>
<tr>
<td>2</td>
<td>9 (21)</td>
</tr>
<tr>
<td>3</td>
<td>2 (5)</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Median (min, max) time to onset, d</td>
<td>2 (1, 25)</td>
</tr>
<tr>
<td>Median (min, max) duration, d</td>
<td>6 (1, 32)</td>
</tr>
<tr>
<td>Tocilizumab use, n (%)</td>
<td>9 (21)</td>
</tr>
<tr>
<td>Corticosteroid use, n (%)</td>
<td>4 (9)</td>
</tr>
</tbody>
</table>

Cytokine Release Syndrome Parameters

Raje N et al. ASCO 2018
Bispecific T-Cell Engagers (BiTEs):

Patrick A. Baeuerle, and Carsten Reinhardt Cancer Res 2009;69:4941-4944
BCMA-Targeted BiTEs: AMG 420

- First-in-human, phase I dose escalation study
- 35 patients
- 6-week cycle
  - 4-week continuous infusion followed by a 2-week break
  - Up to 10 cycles of therapy
- Doses from 0.2 – 800 mcg / day
- CRS seen in 3 patients (2 grade 1, 1 grade 3)
- 6 CRs (1 each at 6.5, 100, and 200 mcg / day, 3 at 400 mcg / day)
  - 3/3 CRs at 400 mcg / day are MRD negative
- 1 PR (50 mcg / day), 1 VGPR (800 mcg / day)
- Confirmation cohort (400 mcg / day): 2 of 3 with PRs

Topp M et al. ASH 2018
GSK285916: a BCMA-Targeted Antibody Drug Conjugate

- GSK2857916 is a humanized, afucosylated IgG1 anti-BCMA antibody conjugated to a microtubule disrupting agent MMAF via a stable, protease resistant maleimidocaproyl linker
  - Preclinical studies demonstrate its selective and potent activity\(^1\)

ADC, antibody-drug conjugate; ADCC, antibody-dependent cell-mediated cytotoxicity; BCMA, B-cell maturation antigen; Fc, Fragment crystallizable; IgG, immunoglobulin G; MMAF, monomethyl auristatin-F

DREAMM-1: Efficacy

Response

ORR = 60% (21/35; 95% CI: 42.1%, 76.1%)
• 1 sCR, 2 CR, 15 VGPR, 3 PR

Progression-Free Survival

Median PFS 7.9 months

Trudel S et al. ASH 2017
## DREAMM-1: Safety

### Any event

<table>
<thead>
<tr>
<th>Event</th>
<th>Any grade</th>
<th>≥Grade 3*</th>
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</thead>
<tbody>
<tr>
<td>Any event</td>
<td>35 (100)</td>
<td>28 (80)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>20 (57)</td>
<td>12 (34)</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>16 (46)</td>
<td>0</td>
</tr>
<tr>
<td>Dry eye</td>
<td>12 (34)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Anemia</td>
<td>10 (29)</td>
<td>5 (14)</td>
</tr>
<tr>
<td>AST increased</td>
<td>10 (29)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Cough</td>
<td>9 (26)</td>
<td>0</td>
</tr>
<tr>
<td>IRR</td>
<td>8 (23)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (23)</td>
<td>0</td>
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<tr>
<td>Photophobia</td>
<td>8 (23)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>8 (23)</td>
<td>0</td>
</tr>
<tr>
<td>Chills</td>
<td>8 (23)</td>
<td>0</td>
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<tr>
<td>Fatigue</td>
<td>7 (20)</td>
<td>0</td>
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</table>

### Maximum Grade, n (%)

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vision blurred</td>
<td>2 (6)</td>
<td>14 (40)</td>
<td>0</td>
<td>16 (46)</td>
</tr>
<tr>
<td>Dry eye</td>
<td>6 (17)</td>
<td>5 (14)</td>
<td>1 (3)</td>
<td>12 (34)</td>
</tr>
<tr>
<td>Photophobia</td>
<td>5 (14)</td>
<td>3 (9)</td>
<td>0</td>
<td>8 (23)</td>
</tr>
<tr>
<td>Lacrimation increased</td>
<td>2 (6)</td>
<td>2 (6)</td>
<td>0</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Keratitis</td>
<td>0</td>
<td>1 (3)</td>
<td>2 (6)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Eye pain</td>
<td>1 (3)</td>
<td>0</td>
<td>1 (3)</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Keratopathy</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>0</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Eye pruritus</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Night blindness</td>
<td>0</td>
<td>1 (3)</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Any event</td>
<td>4 (11)</td>
<td>15 (43)</td>
<td>3 (9)</td>
<td>22 (63)</td>
</tr>
</tbody>
</table>

Trudel S et al. ASH 2017
Genomic Heterogeneity in Multiple Myeloma

Interpatient Heterogeneity

- Syn. (23%)
- Non syn. (77%)

Intra-patient Heterogeneity

- KRAS
- NRAS
- TP53
- DIS3
- FAM46C
- BRAF
- TRAF3
- PRDM1
- CYLD
- RB1
- ACTG1

Focal lesion at 4th lumbar vertebra:
- GEP70 high risk
- Non-Hyperdiploid
- Del(1p12)
- Del(1p32)
- Del(13q)
- Biallelic TP53 del


Rasche L et al. Nat Commun 2017;8:268
Myeloma-Developing Regimens Using Genomics (MyDRUG)

Functional High Risk Patients

Profiling for alterations (NCT02884102)

- No detectable “actionable” alterations
  - Other
  - MEKi + Dex
  - IDHi + IPD
  - CDKi + IPD
  - FGFR3i + IPD
  - Otheri
  - BCLi + IPD

- RAF/RAS mutations
  - Anti-CD38 + IPD
  - Other + IPD

- IDH activating mutations
  - Other + IPD

- CDK pathway activating alterations
  - Other + IPD

- FGFR3 activating alterations

- Other activating alterations
  - t(11;14)

- 2 cycles
Conclusions

• **Bcl-2 inhibition promising**
  • t(11;14) a predictor of response to monotherapy
  • Combination therapy may not require t(11;14) but may be more active in disease with high Bcl-2 expression
  • Mcl-1 inhibitors in development

• **BCMA-targeted therapy represents the most promising class of therapeutics currently in development**
  • CAR T cell therapy exciting but the bi-specifics and ADCs are also performing well

• **Individualized medicine in evolution**
  • Inter- and intrapatient (spatial) genomic heterogeneity argue to add mutation-guided therapy to standard plasma cell combinations
How research contributes to Treatment options

• ALL of the new drugs we have today are the result of clinical trials with patient participation
  • Thalidomide, lenalidomide, pomalidomide
  • Carfilzomib, bortezomib, ixazomib, daratumumab, elotuzumab, panobinostat
  • Pamidronate, zoledronate, denosumab

• Newer drugs such as Car T cells, BiTE molecules, antibody drug conjugates will ONLY be available in the future from clinical trials;

• at present patients who participate in ongoing trials can gain early access to new drugs