Advances in the Management of Myeloma

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Induction/Transplant/Maintenance- what does it get us?

UPDATED OS DATA from CALGB 100104 & IFM 2005-02

Median Overall Survival for Maintenance Studies 1 and 2

- **Study 1 (US)**
  - n=231
  - REVLIMID: 9.3 years (95% CI 8.5, NE)
  - Placebo: 7.0 years (95% CI 5.9, 8.6)

- **Study 2 (EU)**
  - n=307
  - REVLIMID: 8.8 years (95% CI 7.4, NE)
  - Placebo: 7.3 years (95% CI 6.7, 9.0)

REF: https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm542791.htm
THE THREE AGES OF MAN

Younger than your doctor

The same age as your doctor

Older than your doctor
# Quest for a Better Initial Therapy for MM

## KRD-Dara vs KRD

<table>
<thead>
<tr>
<th>Outcome (%)</th>
<th>After 4 Cycles</th>
<th>After 8 Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KRD-DARA N = 21</td>
<td>KRD Non-SCT N = 49</td>
</tr>
<tr>
<td>CR/sCR</td>
<td>5%</td>
<td>18%</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>71%</td>
<td>69%</td>
</tr>
</tbody>
</table>

Judging with limited data is fraught with error

<table>
<thead>
<tr>
<th>Evolution</th>
<th>Kumar</th>
<th>CyBorD</th>
<th>41% &gt; VGPR</th>
<th>53% &gt; VGPR</th>
<th>1 year PFS -100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVD</td>
<td>32%</td>
<td>51%</td>
<td>&gt;VGPR</td>
<td>&gt;VGPR</td>
<td>1 year PFS - 83%</td>
</tr>
<tr>
<td>CVRD</td>
<td>33%</td>
<td>58%</td>
<td>&gt;VGPR</td>
<td>&gt;VGPR</td>
<td>1 year PFS - 86%</td>
</tr>
</tbody>
</table>


# MM Risk Categories

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Standard Risk (80%) (Expected OS: 6-7 Yrs)</th>
<th>High Risk (20%) (Expected OS: 2-3 Yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FISH</td>
<td>t(11;14), t(6;14)</td>
<td>del(17p), t(4;14)* t(14;16), +1q21</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>Hyperdiploidy</td>
<td>Hypodiploidy del(13q)</td>
</tr>
<tr>
<td>(\beta_2)-microglobulin*</td>
<td>Low (&lt; 3.5 mg/L)</td>
<td>High ((\geq 5.5) mg/L)</td>
</tr>
<tr>
<td>PCLI</td>
<td>(&lt; 3%)</td>
<td>High ((\geq 3%)</td>
</tr>
<tr>
<td>Gene expression profile</td>
<td>Good risk</td>
<td>High risk</td>
</tr>
</tbody>
</table>

- **Other high risk features:**
  - Extramedullary disease
  - Plasma cell leukemia
  - Plasmablastic morphology

*Patients with t(4;14), \(\beta_2\)-microglobulin < 4 mg/L, and Hb \(\geq 10\) g/dL may have intermediate-risk disease.*

Phase III Stamina Trial—BMT CTN0702

Any induction therapy

Randomize

MEL 200mg/m² ASCT

Lenalidomide Maintenance**

VRD x 4*

Lenalidomide Maintenance**

MEL 200mg/m² ASCT

Lenalidomide Maintenance**

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

**Lenalidomide 15 mg daily x 3years

• Estimated study completion date: 2020
• Estimated primary initial completion date: 5/2016

ClinicalTrials.gov Identifier: NCT01109004
## BMT CTN0702 STaMINA Trial

### Results

<table>
<thead>
<tr>
<th>Post induction + ASCT-1 followed by:</th>
<th>R Maint only n=257</th>
<th>RVD→R n=254</th>
<th>Double ASCT→R n=247</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mos</td>
<td>52.2</td>
<td>56.7</td>
<td>56.5</td>
</tr>
<tr>
<td>Median OS, mos</td>
<td>83.4</td>
<td>85.7</td>
<td>82.0</td>
</tr>
<tr>
<td>High-risk patients, n</td>
<td>59</td>
<td>65</td>
<td>57</td>
</tr>
<tr>
<td>Median PFS, mos</td>
<td>40.2</td>
<td>48.3</td>
<td>42.2</td>
</tr>
<tr>
<td>Median OS, mos</td>
<td>79.5</td>
<td>77.5</td>
<td>79.3</td>
</tr>
</tbody>
</table>

No significant difference between the study arms
VRd Maintenance After ASCT in High Risk Disease

- 45 patients received VRd maintenance after ASCT for 2 years
  - Bortezomib $1.3mg/m^2$ weekly
  - Lenalidomide $10mg$ d1-21
  - Dexamethasone $40mg$ weekly.

High-risk Features

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del 17p</td>
<td>19 (42)</td>
</tr>
<tr>
<td>Del 1p</td>
<td>9 (20)</td>
</tr>
<tr>
<td>T (4;14)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>T (14;16)</td>
<td>5 (11)</td>
</tr>
<tr>
<td>PCL</td>
<td>11 (24)</td>
</tr>
<tr>
<td>Others (aggressive presentation)</td>
<td>7 (16)</td>
</tr>
<tr>
<td>&gt; 1 Cytogenetic abnormalities</td>
<td>34 (75)</td>
</tr>
</tbody>
</table>

PFS: 32 months
3-year OS: 93%

<table>
<thead>
<tr>
<th>Study</th>
<th>Sponsor/Study Director</th>
<th>Intervention</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eloquent-1 NCT01335399</td>
<td>Bristol-Myers Squibb/AbbVie</td>
<td>Len/dex +/- Elotuzumab</td>
<td>Ongoing, but not recruiting</td>
</tr>
<tr>
<td>MAIA Trial NCT02252172</td>
<td>Janssen Research &amp; Development, LLC</td>
<td>Len/dex +/- Daratumumab</td>
<td>Currently recruiting</td>
</tr>
<tr>
<td>KEYNOTE-185 NCT02579863</td>
<td>Merck Sharp &amp; Dohme Corp.</td>
<td>Len/dex +/- Pembrolizumab</td>
<td>Currently recruiting</td>
</tr>
</tbody>
</table>
## Emerging Proteasome-inhibitor–based Regimens For Transplant Ineligible Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>≥ VGPR</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ixazomib, Lenalidomide, dex x12 → Ixazomib maintenance(^{[1]})</td>
<td>65</td>
<td>58%</td>
<td>95%</td>
</tr>
<tr>
<td>Ixazomib, Cyclophosphamide 300/400, dex x13 → Ixazomib maintenance(^{[2]})</td>
<td>70</td>
<td>27/23%</td>
<td>80/73%</td>
</tr>
<tr>
<td>Carfilzomib*, Cyclophosphamide, dex x9 → Carfilzomib maintenance(^{[3]})</td>
<td>58</td>
<td>71%</td>
<td>95%</td>
</tr>
<tr>
<td>Weekly Carfilzomib**, Cyclophosphamide, dex x9 → Carfilzomib maintenance(^{[4]})</td>
<td>47</td>
<td>87%</td>
<td>87%</td>
</tr>
</tbody>
</table>

*twice a week dosing 20mg/m\(^2\) on day 1, 2 and 36mg/m\(^2\) on day 8 and afterwards

**weekly dosing 70 mg/m\(^2\) on days 1, 8, 15

“I ran all of your symptoms through the computer and now the computer is sick too.”
MODERN TRIPLETS FOR RELAPSE

<table>
<thead>
<tr>
<th>Carfilzomib – Len – Dex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ixazomib – Len – Dex</td>
</tr>
<tr>
<td>Elotuzumab – Len – Dex</td>
</tr>
<tr>
<td>Daratumumab – Len – Dex</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bortezomib – Panabinostat – Dex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib – Daratumumab – Dex</td>
</tr>
</tbody>
</table>
ASPIRE—Len/Dex ± Carfilzomib in R/R MM: PFS

Proportion Surviving w/o Progression

Months Since Randomization

Control Group (Rd): 17.6 months
Carfilzomib (KRd): 26.3 months

Median PFS:

<table>
<thead>
<tr>
<th>Risk Group by FISH</th>
<th>KRd (n = 396)</th>
<th>Rd (n = 396)</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Median PFS, Mos</td>
<td>n</td>
<td>Median PFS, Mos</td>
</tr>
<tr>
<td>High</td>
<td>48</td>
<td>23.1 Mos</td>
<td>52</td>
<td>13.9 Mos</td>
</tr>
<tr>
<td>Standard</td>
<td>147</td>
<td>29.6 Mos</td>
<td>170</td>
<td>19.5 Mos</td>
</tr>
</tbody>
</table>

HR 0.69 (95%CI, 0.57 - 0.83) P < .0001

ELOQUENT-2—Len/Dex ± Elotuzumab in R/R MM: PFS

Progression-free Survival

1-Yr progression-free survival
2-Yr progression-free survival

Hazard ratio, 0.70 (95% CI, 0.57–0.85)
P<0.001

No. at Risk
Elotuzumab group 321 303 279 259 232 215 195 178 157 143 128 117 85 59 42 32 12 7 1 0
Control group 325 295 249 216 192 173 158 141 123 106 89 72 48 36 21 13 7 2 0 0

Figure from Lonial, S. et al. *N Engl J Med*. 2015; 373:621-663.
TOURMALINE-MM1—Len/Dex ± Ixazomib: PFS

**Median PFS:**
- IRd: 20.6 months
- Placebo-Rd: 14.7 months

Log-rank test $P=0.012$
Hazard ratio (95% CI): 0.742 (0.587, 0.939)
Number of events: IRd 129; placebo-Rd 157

- Median number of cycles IRD 13 (1-26) vs 12 Rd (1-25)
- 55% (IRd) and 52% (IR) of patients remain on treatment

Moreau, P. et al. ASH 2015 Abstract 727
Summary of PFS

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>PFS Invest. arm</th>
<th>PFS Rd arm</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASPIRE</td>
<td>Rd vs KRd</td>
<td>26.3mo</td>
<td>17.6mo</td>
<td>0.69</td>
</tr>
<tr>
<td>TOURMALINE</td>
<td>Rd vs IRd</td>
<td>19.4mo</td>
<td>14.9mo</td>
<td>0.70</td>
</tr>
<tr>
<td>ELOQUENTENT-2</td>
<td>Rd vs EloRd</td>
<td>20.6mo</td>
<td>14.7mo</td>
<td>0.74</td>
</tr>
</tbody>
</table>

MAb-Based Targeting of Myeloma

Antibody-dependent cellular cytotoxicity (ADCC)

Effector cells:

- Elotuzumab (SLAMF7)
- Daratumumab (CD38)
- SAR650984 (CD38)

Complement-dependent cytotoxicity (CDC)

- Daratumumab (CD38)
- SAR650984 (CD38)

Apoptosis/growth arrest via targeting signaling pathways

CD38 Antibodies – Immune Effects

**Daratumumab** binds to CD38

**Direct ON-TUMOR Actions**
- CDC: Complement-dependent cytotoxicity
- ADCC: Antibody-dependent cell-mediated cytotoxicity
- ADCP: Antibody-dependent cellular phagocytosis
- Apoptosis: via crosslinking

**IMMUNOMODULATORY Actions**
- Modulation of Tumor Microenvironment via reduction of immunosuppressive CD38 enzymatic activity
- Depletion of CD38+ Immunosuppressive Cells
- Increase in CD8+ Cytotoxic T Cells & CD4+ Helper T Cells

**Myeloma cell death**
CASTOR: Study Design
Multicenter, randomized, open-label, active-controlled phase 3 study

**Key eligibility criteria**
- RRMM
- ≥1 prior line of therapy
- Prior bortezomib exposure, but not refractory

**DVd (n = 251)**
Daratumumab (16 mg/kg IV)
- Every week - cycle 1-3
- Every 3 weeks - cycle 4-8
- Every 4 weeks - cycles 9+
Vel: 1.3 mg/m² SC, days 1,4,8,11 - cycle 1-8
dex: 20 mg PO-IV, days 1,2,4,5,8,9,11,12 - cycle 1-8

**Vd (n = 247)**
Vel: 1.3 mg/m² SC, days 1,4,8,11 - cycle 1-8
dex: 20 mg PO-IV, days 1,2,4,5,8,9,11,12 - cycle 1-8

**Primary Endpoint**
- PFS

**Secondary Endpoints**
- TTP
- OS
- ORR, VGPR, CR
- MRD
- Time to response
- Duration of response

**Daratumumab IV administered in 1000 mL to 500 mL; gradual escalation from 50 mL to 200 mL/min permitted**

RRMM, relapsed or refractory multiple myeloma; DVd, daratumumab/bortezomib/dexamethasone; IV, intravenous; Vel, bortezomib; SC, subcutaneous; dex, dexamethasone; PO, oral; Vd, bortezomib/dexamethasone; PFS, progression-free survival; TTP, time to progression; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease.
Progression-free Survival

No. at risk
Vd 247 182 106 25 5 0
DVd 251 215 146 56 11 0

Proportion surviving without progression

1-year PFS*
Median: not reached
DVd
60.7%

Median: 7.2 months
Vd
26.9%

HR: 0.39 (95% CI, 0.28-0.53); P<0.0001

61% reduction in the risk of disease progression or death for DVd vs Vd

*KM estimate; HR, hazard ratio.
**POLLUX – LENALIDOMIDE + DARA**

**POLLUX: Study Design**

Multicenter, randomized (1:1), open-label, active-controlled phase 3 study

- **DRd (n = 286)**
  - Daratumumab 16 mg/kg IV
    - Qw in Cycles 1-2, q2w in Cycles 3-6, then q4w until PD
  - R 25 mg PO
    - Days 1-21 of each cycle until PD
d 40 mg PO
    - 40 mg weekly until PD

- **Rd (n = 283)**
  - R 25 mg PO
    - Days 1-21 of each cycle until PD
d 40 mg PO
    - 40 mg weekly until PD

**Key eligibility criteria**
- RRMM
- ≥1 prior line of therapy
- Prior lenalidomide exposure, but not refractory
- Patients with creatinine clearance ≥30 mL/min

**Stratification factors**
- No. prior lines of therapy
- ISS stage at study entry
- Prior lenalidomide

**Primary endpoint**
- PFS

**Secondary endpoints**
- TTP
- OS
- ORR, VGPR, CR
- MRD
- Time to response
- Duration of response

**Statistical analyses**
- 295 PFS events: 85% power for 7.7 month PFS improvement
- Interim analysis: ~177 PFS events

**Cycles: 28 days**
POLLUX STUDY

Progression-free Survival

HR: 0.37 (95% CI, 0.27-0.52; P < 0.0001)

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>Rd</th>
<th>DRd</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>283</td>
<td>286</td>
</tr>
<tr>
<td>3</td>
<td>249</td>
<td>266</td>
</tr>
<tr>
<td>6</td>
<td>206</td>
<td>248</td>
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<tr>
<td>9</td>
<td>179</td>
<td>232</td>
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<tr>
<td>12</td>
<td>139</td>
<td>189</td>
</tr>
<tr>
<td>15</td>
<td>36</td>
<td>55</td>
</tr>
<tr>
<td>18</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>21</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Median PFS: 18.4 months

12-month PFS*: 83%
18-month PFS*: 78%

DRd

Rd
### 4 Major Triplets for Relapsed MM

<table>
<thead>
<tr>
<th></th>
<th>POLLUX DRd vs Rd</th>
<th>ASPIRE KRd vs Rd¹</th>
<th>ELOQUENT-2 ERd vs Rd²³</th>
<th>TOURMALINE-MM1 NRd vs Rd⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS HR (95% CI)</strong></td>
<td>0.37 (0.27-0.52)</td>
<td>0.69 (0.57-0.83)</td>
<td>0.73 (0.60-0.89)</td>
<td>0.74 (0.59-0.94)</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>93%</td>
<td>87%</td>
<td>79%</td>
<td>78%</td>
</tr>
<tr>
<td><strong>≥VGPR</strong></td>
<td>76%</td>
<td>70%</td>
<td>33%</td>
<td>48%</td>
</tr>
<tr>
<td><strong>≥CR</strong></td>
<td>43%</td>
<td>32%</td>
<td>4%</td>
<td>14%</td>
</tr>
<tr>
<td><strong>Duration of response, mo</strong></td>
<td>NE</td>
<td>28.6</td>
<td>20.7</td>
<td>20.5</td>
</tr>
<tr>
<td><strong>OS HR (95% CI)</strong></td>
<td>0.64 (0.40-1.01)</td>
<td>0.79 (0.63-0.99)</td>
<td>0.77 (0.61-0.97)</td>
<td>NE</td>
</tr>
</tbody>
</table>
Do we know which triplet is better?

<table>
<thead>
<tr>
<th>Triplet</th>
<th>Med PFS</th>
<th>1 year PPS</th>
<th>≥ PR</th>
<th>MRD Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRD</td>
<td>NR</td>
<td>61%</td>
<td>83%</td>
<td>14%</td>
</tr>
<tr>
<td>IRD</td>
<td>7.2 months</td>
<td>27%</td>
<td>63%</td>
<td>3%</td>
</tr>
<tr>
<td>ERD</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.001*</td>
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<tr>
<td>DRD</td>
<td>DARA Vd</td>
<td>Vd Alone</td>
<td>P-value</td>
<td></td>
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<tr>
<td>DVD</td>
<td>DARA Vd</td>
<td>Vd Alone</td>
<td>P-value</td>
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</tr>
<tr>
<td>DPD</td>
<td>DARA Vd</td>
<td>Vd Alone</td>
<td>P-value</td>
<td></td>
</tr>
</tbody>
</table>

*HR 0.39 (v 0.53 KRD; 0.72 EloRd)

Robert Z. Orlowski @Myeloma_Doc - 19 May 2013
Cancer patients (including myeloma) with depressive symptoms are at increased risk of death (1.usa.gov/14k72Bj). Hazard ratio 2.07.

Anita D'Souza and 40 others follow

Jack Aiello @JackMAiello - Apr 20
That's an impressive Hazard Ratio myeloma

Saad Usmani @szusmani
Wow, Dara-Vel-Dex trumps Vel-Dex with HR of 0.39!
ROLE OF RETRANSPANTATION

Second Transplant at Relapse

“It’s nothing a few stem cells and another 75 years of research can’t fix.”
Myeloma X: Salvage Transplant at Relapse

Randomized 1:1

R/R MM; >18 mos after prior ASCT (N = 293)

PAD induction 2-4 cycles

Melphalan 200mg/m² IV + ASCT (n = 89)

Cyclophosphamide 400mg/m² PO/wk x12 cycles (n = 85)

Clinical Trials

Stages of Clinical Trials

- **Preclinical**: several years
- **Phase 1**: months
- **Phase 2**: months to years
- **Phase 3**: years to decades
- **Phase 4**: ongoing
Immune Suppressive Microenvironment in MM

- MM
- Tumor promotion and induction of PD-L1 expression
- Depletion of cysteine
- IL-6, IL-10, TGFβ, PGE, ARG1, NO, ROS, COX2
- Induction of T reg
- Tumor promotion

Treg
CD8
NK
B
CD4
MM
MDSC
NKT
pDC
TAM

CAR-T cells

Generating super-soldiers
the production of CAR-T cells

Apheresis → T cell activation

Virus: Retrovirus/ Lentivirus
Electroporation: RNA/DNA

CAR Transduction

T cell infusion

Expansion
Myeloma CAR therapy

- Multiple promising targets:
  - CD19, CD138, CD38, CD56, kappa, Lewis Y, CD44v6, CS1, BCMA
- Functional CAR T cells can be generated from MM patients
- CAR T and NK cells have in vitro and in vivo activity against MM
- Clinical trials underway
  - Anecdotal prolonged responses but no robust efficacy data available yet
- Many questions remain about CAR design:
  - optimal co-stimulatory domains
  - optimal vector
  - optimal dose and schedule
  - need for chemotherapy
  - Perhaps ‘cocktails’ of multiple CARs or CARs + chemotherapy will be required for best outcomes

Stadtmauer et al, 2015
MM Patient #1: Response to CD19 CAR Therapy

Additional regimens including...
- carfilzomib
- pomalidomide
- vorinostat
- elotuzomab

CTL019 first undetectable MRD-negative

sCR, MRD neg
Now d +307
TTP after ASCT #1 d190
Remission inversion

Garfall et al, NEJM 2015; 373: 1040-7
CAR-BCMA T cells specifically recognized BCMA
Exhibited antamyeloma activity in humans.

Reliable Elimination of MM plasma cells
Even works in chemotherapy refractory
Need higher doses than CART19?
Deep Remissions induced
Toxicity incl. CRS
Relapses noted despite CR
Soluble BCMA – Not a factor
BCMA CART – early data

11 pts screened, and 6 treated in cohort 1.
Grade 4 PRES
Grade 3 CRS
Allogeneic Transplantation can cure some patients with MM

Gösta Gahrton, M.D., Sante Tura, M.D., Per Ljungman, M.D., Coralie Belanger, M.D., Lena Brandt, B.Sc., Michele Cavo, M.D., Thierry Facon, M.D., Alberto Granena, M.D., Martin Josy

Abstract
Ectologous bone marrow allograft might cause long-term tumor regressions. The phase of treatment with bone marrow allograft was performed in 1989.

Results
months after and 43 were bone marrow transplantations and 9 were bone marrow transplantations. The stage

The stage

"Tail of survival"

Figure 1. Kaplan–Meier Curve for Actuarial Survival after Bone Marrow Transplantation in All Patients.

Can upfront Allotransplant “cure” high risk?

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>HIGH RISK DEFINITION</th>
<th>High risk Allo vs. Auto</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBMT NMAM</td>
<td>92</td>
<td>Deletion 13 q</td>
<td>PFS - 8 years 21% vs. 5% OS - 8 years 47% vs. 31%</td>
</tr>
<tr>
<td>Knop</td>
<td>199</td>
<td>DEL 13q + DEL 17p</td>
<td>Median PFS NR vs. 6 mo Median OS NR vs. 23 mo</td>
</tr>
</tbody>
</table>

Knop S et al; ASH abstract 2014 Dec #43
Research – Costs / Benefits

An Uphill Battle Imagine leading an expedition where every step is more difficult than the last...

The long journey begins in the lab, where scientists spend years testing thousands of ideas. Next, crossing the so-called "Funding Valley of Death" requires the resources and time needed to complete clinical trials, testing safety and effectiveness among what could end up being thousands of volunteers. At the end of this steep financial and scientific climb: Food and Drug Administration approval for a new treatment. Ultimately, it may have taken up to 15 years and more than $1 billion to bring this treatment to the market.

<table>
<thead>
<tr>
<th>3 to 6 years</th>
<th>6 to 7 years</th>
<th>0.5 to 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic Research/Drug Discovery</td>
<td>Pre-Clinical/Translational</td>
<td>Clinical Trials</td>
</tr>
<tr>
<td>5,000-10,000 Potential Treatments</td>
<td>250 Potential Treatments</td>
<td>5 Potential Treatments</td>
</tr>
<tr>
<td>Phase 1</td>
<td>Phase 2</td>
<td>Phase 3</td>
</tr>
<tr>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

"Funding Valley of Death"

By the end of the expedition, you may have spent up to 15 years and more than $1 billion to bring one product to the market.

For more information, visit: brightfocus.org/clinicaltrials

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1. Although we are using the word "treatment," clinical trials also involve medical research studies in which people participate as volunteers to test new methods of prevention, screening, and diagnosis of disease.

2. After approval, the product is manufactured for sale on the market, and the process enters Phase 4 (Post-Marketing Monitoring/Clinical Trials). At this point, the FDA monitors for public safety and adverse events, and the sponsor company may begin Phase 4 Clinical Trials to obtain information about long-term effects or to test the product in special patient populations.

3. The "Funding Valley of Death" is the financial challenge many promising treatments face in having the opportunity to be scientifically tested in a clinical trial. In many cases, further financial support or partnerships are necessary to proceed.

* The cost of bringing a drug to market depends on a number of variables, but could be more than $1 billion, including approximately $50-840 million for Basic Research/Drug Development and Pre-Clinical/Translational research, and approximately $50-920 million to complete all three Phases of the Clinical Trials.
## Additional Agents Currently in Early Phase Development

<table>
<thead>
<tr>
<th>Agent</th>
<th>MOA</th>
<th>Clinical Trial Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib</td>
<td>Tyrosine kinase inhibitor (BTK, ERK1/2, others)</td>
<td>I and II</td>
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<tr>
<td>Filanesib</td>
<td>Kinesin spindle protein inhibitor</td>
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<td>Indatuximab ravidansine</td>
<td>CD138 antibody-drug conjugate</td>
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</tr>
<tr>
<td>Ricolinostat</td>
<td>HDAC inhibitor</td>
<td>I and I/II</td>
</tr>
<tr>
<td>Selinexor (KPT-330)</td>
<td>XPO₁ nuclear transport inhibitor</td>
<td>I and II</td>
</tr>
<tr>
<td>MOR202 (MOR03087)</td>
<td>anti-CD38 antibody</td>
<td>I/II</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>Selective BCL-2 inhibitor</td>
<td>I</td>
</tr>
</tbody>
</table>

Clinicaltrials.gov
Clinical Trials – involve a lot of work
Emerging Agents in MM

Novel agents targeting 3 different pathways:

- Apoptotic Pathway: Venetoclax
- Nuclear Transport Pathway: Selinexor
- T Cell Activation: Pembrolizumab

- BCL-2 inhibitor: Induces cell death
- Targets XPO1: Inhibits nuclear export
- Antibody to PD-1 (checkpoint inhibitor): Induces T cell activation
Lenalidomide Enhances Checkpoint Blockade Induced Cytotoxicity Against MM cells

# Phase 1 Trial of Pembrolizumab + Lenalidomide and Low Dose Dexamethasone in RRMM

<table>
<thead>
<tr>
<th>N (%)</th>
<th>Total N = 17</th>
<th>Len Refractory* N = 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate</td>
<td>13 (76)</td>
<td>5 (56)</td>
</tr>
<tr>
<td>Very Good Partial Response</td>
<td>4 (24)</td>
<td>2 (22)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>9 (53)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Disease Control Rate†</td>
<td>15 (88)</td>
<td>7 (78)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>3 (18)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>1 (6)</td>
<td>1 (11)</td>
</tr>
</tbody>
</table>

*3 patients double refractory and 1 triple refractory (Len/Bor +Pom)

†Disease Control Rate = CR +VGPR + PR + SD >12 weeks.

Data cutoff date: September 22, 2015

San Miguel et al ASH 2015
Correlative Studies

- Effects of anti-PD-1 on T- and NK-cell function
- Correlation of immune cell phenotypes in the autologous graft and outcomes

Study Schema

- Melphalan
- Pembrolizumab 200 mg IV
- Lenalidomide

* Graft Sample
* Blood Samples

- CR conversion rate at day 180
Yes, we carry placebos, but you’ll need a fake prescription.
Venetoclax Monotherapy
*R/R MM Dose Escalation*

**Patients**
- N=66
- Median age 63
- Median of 5 prior lines of therapy
- Study was enriched with patients with t(11;14) MM

**Efficacy**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>ORR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>68</td>
<td>21%</td>
</tr>
<tr>
<td>t(11;14)</td>
<td>30</td>
<td>40%</td>
</tr>
<tr>
<td>No t(11;14)</td>
<td>36</td>
<td>6%</td>
</tr>
</tbody>
</table>

**Toxicity**
- At 600mg, 2 patients DLT of abdominal pain, nausea
- Serious AE (>5%) include pneumonia (8%), sepsis (5%)
- No tumor lysis syndrome

Venetoclax, Bortezomib, and Dex

R/R MM, Phase 1b

- N=66
- Median age 64
- Median of 3 prior lines of therapy

<table>
<thead>
<tr>
<th>Patients</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>ORR, %</td>
</tr>
</tbody>
</table>

| All patients         | 66  | 67% |
| Not refractory       | 39  | 90% |
| Bortezomib refractory| 26  | 31% |
| 1 to 3 prior therapies| 37  | 89% |
| 4 to 6 prior therapies| 29  | 38% |
| BCL2 high            | 18  | 94% |
| BCL2 low             | 27  | 59% |

- Venetoclax/bor/dex is well tolerated with MTD not reached
- Clinical benefit was higher in patients with fewer lines of therapy; not bortezomib refractory; and those with high BCL2 expression

XPO inhibitor for 17p deleted disease
STORM Study

Selinexor Plus Dexamethasone in R/R MM

- N=79
- Highly refractory patient population
  - Quad: refractory to Bor, Car, Len, Pom, n=48
  - Penta: Refractory to Bor, Car, Len, Pom, and anti-CD38 antibodies, n=31
- Median of 7 prior therapies

Patients:

<table>
<thead>
<tr>
<th>CBR, %</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>21%</td>
</tr>
<tr>
<td>Quad refractory</td>
<td>21%</td>
</tr>
<tr>
<td>Penta refractory</td>
<td>20%</td>
</tr>
</tbody>
</table>

Efficacy

Toxicity

- Primary toxicities were thrombocytopenia, nausea, anorexia, fatigue, and anemia

### Selinexor/PI Combinations

#### R/R MM

<table>
<thead>
<tr>
<th>Selinexor/Carfilzomib/Dex</th>
<th>Selinexor/Bortezomib/Dex</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase 1, N=19</strong></td>
<td><strong>Phase 1b/2, N=22</strong></td>
</tr>
<tr>
<td><strong>Grade 3 or 4 toxicities (&gt;10%)</strong></td>
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</tr>
<tr>
<td>- Thrombocytopenia, anemia, neutropenia, lymphopenia, GI disorders, fatigue</td>
<td>- Thrombocytopenia, anemia, neutropenia, GI disorders, fatigue</td>
</tr>
<tr>
<td>- 2 serious AE: 1 infection; 1 GI bleed</td>
<td></td>
</tr>
<tr>
<td><strong>Efficacy: ≥PR</strong></td>
<td><strong>Efficacy: ORR</strong></td>
</tr>
<tr>
<td>- 63% overall population (n=19)</td>
<td>- 77% overall population</td>
</tr>
<tr>
<td>- 67% carfilzomib refractory population (n=12)</td>
<td>- 67% in PI refractory population (n=15)</td>
</tr>
<tr>
<td></td>
<td>- 100% in PI non-refractory population (n=7)</td>
</tr>
</tbody>
</table>

Selinexor XPO inhibitor

Selinexor

Outcomes

- Median OS = 9.3 months
  - Responders = N/R (> 11 months)
  - Non responders = 5.7 months

- DOR 5 months

- High risk FISH = 33% ORR
  - Responses observed despite:
    - Del17p, t(14;16), t (4;14)

Abstract 491
## Agents Currently in Early Phase Development

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<tr>
<td>BiTEs</td>
<td>BCMA-CD3 engagers</td>
<td>I</td>
</tr>
</tbody>
</table>

Clinicaltrials.gov
Myeloma Survival

- Two major issues to address now:
  - HIGH RISK DISEASE
  - AFTER MULTIPLE RELAPSE
- Hope that immune therapy will have an impact!
FUTURE TRIALS – PERSONALIZED and RESPONSE ADAPTED
More Personalization

Venetoclax

- ORR 40%
- sCR 4%
- CR 10%
- VGPR 13%
- PR 13%
- ORR 6%

- t(11;14) n=30
- non-t(11;14) n=36

Time to Progression

% Not progressed

Abstract 488
BMT CTN 1401 Vaccine Trial

[Diagram showing immune cell interactions with cancer cells, including CD83, CD54, CD86, CD80, CD40L, MUC1, Idiotyp, CD38, CD136, and HLA Class I and II.]

Courtesy Avigan D
Hovon/IFM: Daratumumab Trial in Transplant-eligible NDMM

**Endpoints:**
- sCR
- PFS, OS

**Induction**
- 4 cycles
  - VTD + Dara

**Consolidation**
- 2 cycles
  - VTD + Dara

**Maintenance**
- Until progression
  - Dara
  - Observation

**CAN WE STOP MAINTENANCE?**

**Stratify by:** dara treatment, response, MRD status

---

R, randomize; V, bortezomib; T, thalidomide; D, dexamethasone; Dara, daratumumab; ASCT, autologous stem-cell transplant; sCR, stringent complete response; PFS, progression-free survival; OS, overall survival

Slide Courtesy of P Sonneveld
Repurposing an old drug

Nelfinavir – SAKK 39/13 trial

A phase II study of Bort/Dex + Nelfinavir in Bort-refractory myeloma

<table>
<thead>
<tr>
<th>Patient population (n=34)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, med</td>
<td>67 (42-82)</td>
</tr>
<tr>
<td>Prior therapy, med</td>
<td>5 (2-10)</td>
</tr>
<tr>
<td>Prior SCT (%)</td>
<td>76</td>
</tr>
<tr>
<td>Poor risk cyto (%)</td>
<td>38</td>
</tr>
<tr>
<td>Bort refractory (%)</td>
<td>100</td>
</tr>
<tr>
<td>Len refractory (%)</td>
<td>79</td>
</tr>
<tr>
<td>Pom refractory (%)</td>
<td>44</td>
</tr>
</tbody>
</table>

Response rates:

<table>
<thead>
<tr>
<th></th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall RR (≥ PR)</td>
<td>65</td>
</tr>
<tr>
<td>- high risk FISH</td>
<td>77</td>
</tr>
<tr>
<td>- bort + len refractory</td>
<td>70</td>
</tr>
<tr>
<td>- bort + len + pom ref</td>
<td>60</td>
</tr>
</tbody>
</table>

Abstract 487
IN A CLASS BY ITSELF—
The RECTO ROTOR

THE LATEST AND MOST EFFICIENT INVENTION FOR THE QUICK RELIEF OF
PILES, CONSTIPATION
AND PROSTATE TROUBLE

ACTUAL SIZE

Lubricating Vent Holes

Actual Size
Large Enough to be Efficient Small Enough for Anyone Over 15 Years Old.

The RECTO ROTOR is the only device that reaches the Vital Spot effectively. This picture tells its own story. Note especially those little vent holes in the nozzle through which the unguent inserted in the chamber below (a) may be forced out by turning the knurled cap (b). No other appliance in the world is so constructed: none other able to reach the Vital Spot to such good purpose.

The RECTO ROTOR obtains its amazingly quick results without the use of medicine, electricity, operations, or massage by an attendant. It gets results because of its scientific construction. It is made for the purpose of relieving congestion in the prostate gland, lubricating the colon and massaging the muscles of the rectal region. It is used by the patient himself in the privacy of his own home.

The RECTO ROTOR Lubricating Dilator is the only improvement ever made on the common “dilator” which hitherto was the most successful appliance for the relief of Piles and Constipation.