Multiple Myeloma: How we think about and treat relapse

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Relapse

- Unfortunately it occurs in just about everyone.
- Relapses do more often occur much later now.
- I always tell patients that I may have very different ideas on what I might do when they relapse since the field is changing so quickly.
Patterns of Relapse

- Concept of “Multiple Myelomas”
- MM may not necessarily behave at relapse like it did at initial diagnosis
- “Darwinism” or “Clonal Evolution”
Patterns of Relapse Vary

Generally relapses occur in two ways (note: WAY simplified)
- Indolent or slow “laboratory relapse”
- Very fast, aggressive, often symptomatic relapse

We approach and treat the two very differently.
Indolent, Slow, First Relapse

Likely Single Agent Therapy with Bz or Len/Thal

- Initial Tx with Bz
- May consider single agent w/o Dex
- Underlying PN

- Initial Tx with IMiD
- Previous Bz therapy but good or long response
- Renal Dysfunction

- Transplant not part of initial therapy
- Long remission post transplant
Aggressive, Rapid, Multiple Relapse

Likely Combination Therapy
Do Not Wait for Symptomatic Relapse

Chemotherapy Based Salvage

- DCEP vs DT-PACE
- Oral vs IV chemo
- General health of Patient plays important role

Chemotherapy + Novel Agent

- Combinations of Len/Bz and other Chemo agents

Transplant Based Salvage

- Likely to be short lived
- Quick Disease control
- Can help restore blood counts if have been low
Solid Backbone of Therapy

### Proteasome Inhibitors
- Bortezomib IV/SQ
- Carfilzomib IV
- *Ixazomib PO
- *Oprozomib PO

*Not FDA approved

### IMiDs
- Thalidomide PO
- Lenalidomide PO
- Pomalidomide PO

Now some new guys:
- Panobinostat
- *Elotuzumab
- Other “antibodies”
- Remember Biaxin (antibiotic: clarithromycin)-can add to rev or pom
MM docs are artists

- We mix and match paints on the palette
- CRD/VRD/CyBOR-D
- V or C + panibinostat
- Pom or Rev plus anything, including biaxin
- I like PCP!

Important: at every relapse consider all options especially CLINICAL TRIALS
Carfilzomib, Lenalidomide, and Dexamethasone vs Lenalidomide and Dexamethasone in Patients with Relapsed Multiple Myeloma: Interim Results from ASPIRE, a Randomized, Open-Label, Multicenter Phase 3 Study

Randomization
N=792

Stratification:
• β₂-microglobulin
• Prior bortezomib
• Prior lenalidomide

28-day cycles

**KRd**
- Carfilzomib 27 mg/m² IV (10 min)
  - Days 1, 2, 8, 9, 15, 16 (20 mg/m² days 1, 2, cycle 1 only)
- Lenalidomide 25 mg Days 1–21
- Dexamethasone 40 mg Days 1, 8, 15, 22

After cycle 12, carfilzomib given on days 1, 2, 15, 16
After cycle 18, carfilzomib discontinued

**Rd**
- Lenalidomide 25 mg Days 1–21
- Dexamethasone 40 mg Days 1, 8, 15, 22
Primary Endpoint: Progression-Free Survival
ITT Population (N=792)

![Graph showing progression-free survival](image)

- **Proportion Surviving Without Progression**
- **KRd** vs. **Rd**
- **Median PFS, mo**
  - KRd: 26.3
  - Rd: 17.6
- **HR (KRd/Rd) (95% CI)**
  - 0.69 (0.57–0.83)
- **P value (one-sided)**
  - <0.0001

**No. at Risk:**

<table>
<thead>
<tr>
<th></th>
<th>KRd</th>
<th>Rd</th>
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<tr>
<td>396</td>
<td>332</td>
<td>287</td>
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<td>396</td>
<td>279</td>
<td>206</td>
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<tr>
<td>222</td>
<td>151</td>
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<td>112</td>
<td>72</td>
<td>18</td>
</tr>
<tr>
<td>24</td>
<td>18</td>
<td>1</td>
</tr>
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</table>

**Months Since Randomization**

0 6 12 18 24 30 36 42 48
Conclusions

- PFS was significantly improved by 8.7 months with KRd (HR, 0.69; P<0.0001)
  - An unprecedented median PFS of 26.3 months with KRd

- Interim OS analysis: trend in OS favoring the KRd group; Kaplan-Meier 24-month OS rates 73.3% (KRd) versus 65.0% (Rd)

- ORR was higher with KRd (87.1% vs 66.7%); significantly more patients achieved ≥CR (31.8% vs 9.3%)
Conclusions (continued)

- AEs led to fewer discontinuations in the KRd group, and patients remained on study treatment longer
  - Cardiac and renal events were reported at rates consistent with or lower than prior studies of single-agent carfilzomib
- KRd consistently improved health-related quality of life (Global Health Status) compared with Rd over 18 cycles of treatment
- KRd represents a new standard of care in relapsed MM
SAR650984: A Humanized IgG1 Monoclonal Antibody

1. Antibody-dependent cellular cytotoxicity (ADCC) and phagocytosis (ADCP)

2. Complement-dependent cytotoxicity (CDC)

3. Direct apoptosis induction without crosslinking

4. CD38 enzymatic activity inhibition

- Antibody
- Fc Receptor
- Complement
- NK cell, Macrophage
- CD38
- NAD
- cADPR ADPR
Preliminary Safety and Efficacy Data of Daratumumab in Combination with Lenalidomide and Dexamethasone in Relapsed or Refractory Multiple Myeloma

RESULTS

Table 1: Baseline Characteristics and Demography

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>2 mg/kg (N=3)</th>
<th>4 mg/kg (N=1)</th>
<th>8 mg/kg (N=4)</th>
<th>16 mg/kg (N=2)</th>
<th>Total (N=12)</th>
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<tbody>
<tr>
<td>Gender, n</td>
<td>2/1</td>
<td>0/1</td>
<td>1/2</td>
<td>1/1</td>
<td>1/2</td>
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<tr>
<td>Age, years</td>
<td>48-61</td>
<td>52-61</td>
<td>56-72</td>
<td>56-72</td>
<td>62-72</td>
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<tr>
<td>Prior lines of therapy</td>
<td>4 (3-4)</td>
<td>3 (2-4)</td>
<td>4 (3-4)</td>
<td>3 (1-4)</td>
<td>4 (1-4)</td>
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</tbody>
</table>

Table 2: Incidence of Most Frequent AEs Reported in >2 Patients

<table>
<thead>
<tr>
<th>% of patients</th>
<th>2 mg/kg (N=3)</th>
<th>4 mg/kg (N=1)</th>
<th>8 mg/kg (N=4)</th>
<th>16 mg/kg (N=2)</th>
<th>Total (N=12)</th>
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<td>Constipation</td>
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<td>Vomiting</td>
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<tr>
<td>Fatigue</td>
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<tr>
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<tr>
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<td>100</td>
<td>100</td>
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<td>80</td>
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</table>

Efficacy

Efficacy data for 11 patients have been collected. The best response in paraprotein indicates that all patients had a marked decrease in paraprotein (Figure 1).

Time to achieving PR was median 4.1 weeks (2.0-4.3) (Table 2). Eight of 11 patients have achieved PR or better and two patients have achieved MR (Table 3).

Table 3: Response Rate (number of patients achieving response rate)

<table>
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<tr>
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<th>8 mg/kg (N=4)</th>
<th>16 mg/kg (N=2)</th>
<th>Total (N=12)</th>
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<tr>
<td>MR</td>
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<td>1</td>
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<td>PD</td>
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</table>


CONCLUSION

- DARATUMUMAB is generally well tolerated, as expected based on Phase 1 data. There were no treatment-related AEs or deaths.
- The combination of DARATUMUMAB with LEN and DEX is an effective regimen for relapsed or refractory multiple myeloma.
- The combination has a manageable safety profile, and the most common adverse events were gastrointestinal and hematologic.
- Further studies are needed to evaluate the long-term safety and efficacy of this regimen.

REFERENCES

1. Jakubowiak et al. EHA 2013 abstract #1922
3. US Food and Drug Administration (FDA) labeling.
Background: Targeting KSP with ARRY-520 (Filanesib)

- **Filanesib** is a targeted Kinesin Spindle Protein (KSP) inhibitor
  - KSP is a microtubule motor protein critical to the function of proliferating cells

- KSP inhibition induces aberrant mitotic arrest and rapid cell death
  - Novel mechanism of action for MM
  - Preferentially acts on MCL-1 dependent cells including MM
  - Not expected to be cross-resistant with other drugs
MULTIPLE MYELOMA RESEARCH
IFM/DFCI 2009/CTN 1304/Alliance
Parallel Phase 3 Study
“The Determination Trial”

**Newly Diagnosed MM** (SCT candidates; overall n= 1360; USA 660; France 700)

**Randomize** → **Induction** → **Collection** → **Consolidation** → **Maintenance** → **Calibration**

- **Induction**:
  - RVDx3
  - CY (3g/m2)
  - MOBILIZATION
  - Goal: 5 x 10^6 cells/kg
  - Melphalan 200mg/m^2 + ASCT
  - RVD x 2
  - MRD @ CR

- **Consolidation**:
  - RVD x 3
  - CY (3g/m2)
  - MOBILIZATION
  - Goal: 5 x 10^6 cells/kg
  - RVD x 5
  - MRD @ CR

- **Maintenance**:
  - Revlimid until PD (US)
  - Revlimid for 1 yr (IFM)

- **Calibration**:
  - SCT at relapse

**MRD**

**IFM/DFCI 2009/CTN 1304/Alliance Parallel Phase 3 Study**

**Parallel Phase 3 Study**

**“The Determination Trial”**

**Newly Diagnosed MM** (SCT candidates; overall n= 1360; USA 660; France 700)
Other studies

- Oprozomib (upfront or relapse)
- Carfilzomib + ibrutinib
- Elo + rev + dex (smoldering & relapse)
- Glutaminase inhibitor CB 839
- Ganetespib + bortezomib
- Ixazomib following allo transplant
- LDE 225 + bortezomib
- Soon: dara/R/D vs RD up front
Questions?