Multiple Myeloma: Induction, Consolidation and Maintenance Therapy

James R. Berenson, MD
Medical & Scientific Director
Institute for Myeloma & Bone Cancer Research
Los Angeles, CA
Establish the Goals of Therapy for the Individual Myeloma Patient

► Patient wants the longest life (OVERALL SURVIVAL and not simply a delay in disease returning) possible w/ therapy and a disease that has the least impact on their life!

► That does not necessarily mean they want the regimen w/ the highest % of CRs

  ➢ Remember that CRs in myeloma are
    ❖ based on paraprotein
    ❖ NOT really molecular CRs even when MRD is negative

  ➢ Very little difference in tumor burden between pts w/ stable disease and so-called CR
Individualize your choice for the myeloma patient based on:

- Co-morbid conditions
- Disease
- Work/Lifestyle
- Co-morbid conditions

- Renal, Bone, Marrow, Subjective, Rate of Progression Genetics?
- How active is the patient? Mobility?
- Is potential neuropathy an issue? (e.g.- surgeon, pianist)
- Diabetes mellitus (steroids)
- Cardiac (Adriamycin, Doxil)
- Neuropathy (Thalidomide)
Advances in Induction Therapy 2018

- Triplets show superior outcome to doublets
  - R(Len)V(Bort)Dex vs RD SWOG study\(^1\)
  - Many different triplets w/ Dex
    - Proteasome inhibitor-based
      - Bortezomib w/ R, PLD, CY, or MEL
      - Carfilzomib w/ R, CY
    - Lenalidomide (R)-based - above
- Quadruplets show superior outcome to triplets - Daratumumab+VMP vs VMP study\(^2\)

\(^1\)Durie et al. Lancet 2017; \(^2\)Mateos et al. N Engl J Med 2018
Advances in Induction Therapy 2018

- Triplets show superior outcome to doublets
  - R(Len)V(Bort)Dex vs RD SWOG study\textsuperscript{1}
  - Many different triplets w/ Dex
    - Proteasome inhibitor-based
      - Bortezomib w/ R, PLD, CY, or MEL
      - Carfilzomib w/ R, CY
    - Lenalidomide (R)-based- above

- Quadruplets show superior outcome to triplets- Daratumumab+VMP vs VMP study\textsuperscript{2}

\textsuperscript{1}Durie et al. Lancet 2017; \textsuperscript{2}Mateos et al. N Engl J Med 2018
Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): A randomised, open-label, phase 3 trial
Advances in Induction Therapy 2018

- Triplets show superior outcome to doublets
  - R(Len)V(Bort)Dex vs RD SWOG study\textsuperscript{1}
  - Many different triplets w/ Dex
    - Proteasome inhibitor-based
      - Bortezomib w/ R, PLD, CY, or MEL
      - Carfilzomib w/ R, CY
    - Lenalidomide (R)-based- above

- Quadruplet show superior outcome to triplets- Daratumumab+VMP vs VMP study\textsuperscript{2}

\textsuperscript{1}Durie et al. Lancet 2017; \textsuperscript{2}Mateos et al. N Engl J Med 2018
Advances in Induction Therapy 2018

Triplet therapy shows superior outcome to doublet therapy:

- **R(Len)V(Bort)Dex vs RD SWOG study**¹
- Many different triplets with Dex
  - Proteasome inhibitor-based
    - Bortezomib with R, PLD, CY, or MEL
    - Carfilzomib with R, CY
  - Lenalidomide (R)-based - above

Quadruplets show superior outcome to triplets - Daratumumab+VMP vs VMP study²

**ALCYONE: A Randomized, Open-Label, Active-Controlled, Multicenter, Phase 3 Trial of Daratumumab + VMP vs VMP**

**Patient Population** (N=706)¹
- Newly diagnosed patients with multiple myeloma ineligible for autologous stem cell transplant

**Randomize** 1:1
- **Daratumumab + VMP** (n=350)¹
- **VMP** (n=356)¹

**Primary Endpoint**²
- PFS†

**Key Secondary Endpoints**²
- Overall response rate
- Very good partial response or better
- Complete response or better
- Minimal residual disease
- Overall survival

**Additional endpoints**²
- Safety
- Side-effect profile
- Time to response
- Duration of response

**Daratumumab treatment continued until disease progression or unacceptable toxicity¹**

**VMP up to 9 cycles**⁴

**VMP** up to 9 cycles*¹

**Daratumumab 16 mg/kg IV once weekly for 6 weeks (cycle 1), followed by 16 mg/kg every 3 weeks (cycles 2-9) and every 4 weeks from week 55 onwards + VMP up to 9 cycles**¹²

*Participants received bortezomib 1.3 mg/m² as subcutaneous injection, twice weekly at weeks 1, 2, 4, and 5 (cycle 1) followed by once weekly at weeks 1, 2, 4, and 5 (cycles 2 to 9); melphalan 9 mg/m²; and prednisone 60 mg/m² were orally administered on days 1 to 4 of the nine 6-week cycles (cycles 1-9). Per protocol, control arm discontinued VMP treatment after 9 cycles. Follow up for long-term survival is ongoing. ¹Futility was evaluated by FFS based on International Myeloma Working Group criteria.

²Treatment with VMP has previously been established as an effective therapy for patients with newly diagnosed multiple myeloma who are ineligible for stem cell transplant in several trials³⁻⁵


Mateos et al. *N Engl J Med* 2018
Median follow-up was 16.5 months\(^2\)

Median PFS had not yet been reached with Daratumumab + VMP vs 18.1 months with VMP alone\(^1\)

Daratumumab + VMP Significantly Improved PFS vs VMP Alone*

Progression-Free Survival\(^1\)

HR = hazard ratio

*Efficacy was evaluated by PFS based on International Myeloma Working Group criteria.

Significant Improvement in ORRs with Daratumumab + VMP

91% ORR with Daratumumab + VMP vs 74% ORR with VMP alone (P<0.0001)

Speed of Response
• In the Daratumumab + VMP arm, the median time to response was 0.79 months (range: 0.4 to 15.5 months) vs 0.82 months (range: 0.7 to 12.6 months) in the VMP group

Depth of Response
• 42.6% of patients achieved CR or better with Daratumumab + VMP vs 24.4% with VMP alone

Duration of Response
• Median duration of response had not yet been reached with Daratumumab + VMP vs 21.3 months with VMP alone (range: 0.5+ to 23.7+), at a median follow-up of 16.5 months

CR = complete response; ORR = overall response rate; PR = partial response; sCR = stringent complete response; VGPR = very good partial response.


Mateos et al. N Engl J Med 2018
ALCYONE Trial

- Addition of daratumumab to VMP improves ORR, CR and most importantly PFS
- No additional safety issues were identified including cytopenias

- However, VMP is not a widely used upfront regimen in the United States
  - Whether a similar advantage of adding daratumumab to other triplets such as RVD is unknown
  - Whether this adds to ASCT is unknown

Mateos et al. N Engl J Med 2018
None really of significance

However, let’s consider autologous transplant as consolidation therapy and discuss its role in 2018
Arguments for Transplant in Myeloma

- Highest CR rates
  - Higher CR associated with:
    - delay in time to progression (TTP)
    - prolonged progression free survival (PFS)

- Older randomized trials show PFS/TTP and in some cases an overall survival advantage

- No additional therapy required following the transplant
Arguments for Transplant in Myeloma

- Highest CR rates and
  - Higher CR are associated with:
    - delay in TTP
    - prolonged PFS

- Older randomized trials show PFS/TTP and in some cases an overall survival advantage

- No additional therapy required following the transplant
Now the Highest CR Rates are w/o HDT: Frontline Carfilzomib, Lenalidomide and Dexamethasone

<table>
<thead>
<tr>
<th></th>
<th>Overall n=53</th>
<th>4+ Cycles n=49</th>
<th>8+ Cycles n=36</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥nCR Response</td>
<td>62%</td>
<td>67%</td>
<td>78%</td>
</tr>
<tr>
<td>sCR Response</td>
<td>42%</td>
<td>45%</td>
<td>61%</td>
</tr>
<tr>
<td>Median Cycles</td>
<td>12 cycles (range 1–25)</td>
<td>13 cycles (range 4–25)</td>
<td>16 cycles (range 8–25)</td>
</tr>
</tbody>
</table>

Why does CR compared to < CR delay TTP/PFS w/o improvement in OS?

- These are not true CRs
  - based on M-protein becoming undetectable
- PCR-based molecular and FC CRs are only as sensitive as the assay

Why do higher CR rates consistently delay TTP?

M-protein detectable

0 True CR

Tumor Burden

Time

Easy to detect this relapse

CR (M-protein is absent)
Arguments for Transplant in Myeloma

- Highest CR rates and
  - Higher CR rates are associated with:
    - delay in TTP (cannot measure progression)
    - prolonged PFS (cannot measure progression)

- Older randomized trials show PFS/TTP and in some cases an overall survival advantage

- No additional therapy required following the transplant
Transplants: Results from Randomized Trials and Meta-analyses

- No consistent advantage in overall survival (OS) from randomized Phase III trials EVEN PRIOR to the availability of new drugs (IMiDs, PIs)
  - Older French & MRC trials- Yes!
  - PETHEMA trial- No!

- Only PFS BUT no OS advantage in recent trials
  - Palumbo et al.- even w/ tandem transplants vs MP
  - IFM French trial- vs RVD
  - Meta-analyses show PFS BUT no OS advantage

- Early vs Late (at time of progressive disease)
  - No difference in overall survival from French and US Intergroup trials

Arguments for Transplant in Myeloma

► Highest CR rates
  ➢ Higher CR associated w/
    ❖ delay in time to progression (TTP)
    ❖ prolonged progression free survival (PFS)

► Older randomized trials show PFS/TTP and in some cases an overall survival advantage

► No additional therapy required following the transplant
Maintenance Studies 1 (US) and 2 (EU) evaluated lenalidomide 10 mg daily until progression or unacceptable toxicity in >1000 patients post auto-HSCT\textsuperscript{1,2}

**Trial Design**

- Randomized, double-blind, placebo-controlled studies conducted in newly diagnosed patients post auto-HSCT following induction therapy

**Select Inclusion Criteria**

- Patients aged 18-70 years in Study 1; <65 years in Study 2 at the time of diagnosis
- In both studies, patients needed at least a stable disease response following hematologic recovery and CrCl \( \geq 30 \text{ mL/min} \)

CrCl, creatinine clearance.

*PFS was defined from randomization to the date of progression or death, whichever occurred first.*

Overall Survival Data for Lenalidomide (LEN) Maintenance Therapy From the Two Pivotal Post-Autotransplant Studies

Median Overall Survival for Maintenance Studies 1 and 2

<table>
<thead>
<tr>
<th>Study</th>
<th>LEN</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance Study 1</td>
<td>9.3 years (95% CI 8.5, NE)</td>
<td>7.0 years (95% CI 5.9, 8.6)</td>
<td>0.59 (0.44, 0.78)</td>
<td>231</td>
</tr>
<tr>
<td>Maintenance Study 2</td>
<td>8.8 years (95% CI 7.4, NE)</td>
<td>7.3 years (95% CI 6.7, 9.0)</td>
<td>0.90 (0.72, 1.13)</td>
<td>307</td>
</tr>
</tbody>
</table>

Thus, maintenance LEN therapy is standard of care posttransplant.
Transplants in 2017 for Myeloma

- No overall survival (OS) advantage of early autotransplant from any recent randomized trials
- Highest CR rates are w/o transplant (i.e. CLD)
- All patients now receive posttransplant maintenance lenalidomide so there is no treatment-free interval
- Treatment options are rapidly increasing
  - Thus, compromising a patient’s ability to receive these options because of toxicity from high dose therapy is important to consider
  - Also be careful interpreting results (especially OS) from trials where treatment options are limited
- As MM patients are living longer, optimizing QOL becomes of increasing importance
MM-020: A Phase 3 trial in MM that evaluated > 1600 newly diagnosed MM patients\(^1,\!^2\)

MM-020 was a randomized, multicenter, open-label, 3-arm study that evaluated lenalidomide (LEN) + dex (Rd) until progression in newly diagnosed patients who did not receive an auto-HSCT

- Patients were ≥65 years OR <65 years and refused or did not have access to an auto-HSCT

**MM-020 Study Design (N=1623)**

- **Rd Continuous arm (n=535)**
  - LEN + low-dose dex until progression or unacceptable toxicity

- **Rd18 arm (n=541)**
  - LEN + low-dose dex up to 18 cycles (72 weeks)

- **MPT arm (n=547)**
  - Melphalan + prednisone + thalidomide up to 12 cycles (72 weeks)

- Primary endpoint was PFS
- The primary comparison for efficacy was between the Rd Continuous and MPT arms
- Secondary endpoints included OS and response rates
- All patients received prophylactic anticoagulation, with the most commonly used being aspirin

- The dose of LEN in the clinical trial was 25 mg orally once daily on Days 1 to 21 of repeated 28-day cycles with low-dose oral dex on Days 1, 8, 15, and 22 for 18 cycles
  - The dose for dex is 40 mg orally for patients ≤75 years or 20 mg orally for patients >75 years
- In RD Continuous arm, LEN and dex were continued

Rd Continuous extended PFS vs Rd 18

Median PFS in MM-020

Rd Continuous also reduced the risk of progression or death by 28% compared with fixed-cycle MPT treatment
TOURMALINE-MM3 is a randomized, placebo-controlled, double-blind Phase 3 study of 656 patients, designed to determine the effect of ixazomib maintenance therapy on progression-free survival (PFS), compared to placebo, in participants with multiple myeloma who have had a response (complete response [CR], very good partial response [VGPR], or partial response [PR]) to induction therapy followed by high-dose therapy (HDT) and autologous stem cell transplant (ASCT). The primary endpoint is progression-free survival (PFS). A key secondary endpoint includes overall survival (OS). For additional information:


_Abstract to be Submitted for Presentation at the 2018 ASH Annual Meeting_
A Role for JAK inhibitors for MM Patients

Phase 1 Trial of Ruxolitinib (RUX), Lenalidomide and Methylprednisolone for Relapsed/Refractory Multiple Myeloma Patients

Background

- RUX is an oral, selective inhibitor of JAK1 and JAK2
- FDA-approved for the treatment of myelofibrosis and polycythemia vera
- Enhances the inhibition of growth of multiple myeloma (MM) by lenalidomide and dexamethasone in
  - MM cell lines and primary MM cells
  - human MM xenografts in immunodeficient mice
    - LAG\(_\kappa\)-1A (bortezomib/melphalan-sensitive)
    - LAG\(_\kappa\)-2 (bortezomib/melphalan-resistant)

Berenson et al. ASCO 2018
## Study Design

### Dose escalation/de-escalation schema

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Ruxolitinib Days 1-28</th>
<th>Lenalidomide Days 1-21</th>
<th>Methylprednisolone Days 1-28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose Level -2</td>
<td>5 mg QD</td>
<td>2.5 mg QD</td>
<td>40 mg QOD</td>
</tr>
<tr>
<td>Dose Level -1</td>
<td>5 mg BID</td>
<td>2.5 mg QD</td>
<td>40 mg QOD</td>
</tr>
<tr>
<td>Dose Level 0</td>
<td>5 mg BID</td>
<td>5 mg QD</td>
<td>40 mg QOD</td>
</tr>
<tr>
<td>Dose Level 1</td>
<td>10 mg BID</td>
<td>5 mg QD</td>
<td>40 mg QOD</td>
</tr>
<tr>
<td>Dose Level 2</td>
<td>15 mg BID</td>
<td>5 mg QD</td>
<td>40 mg QOD</td>
</tr>
<tr>
<td>Dose Level 3</td>
<td>15 mg BID</td>
<td>10 mg QD</td>
<td>40 mg QOD</td>
</tr>
</tbody>
</table>

NO DLTs OBSERVED

28-days/cycle
Response Summary/Efficacy Endpoints

- Response rates for all 26 evaluable patients

<table>
<thead>
<tr>
<th>Response Status</th>
<th># of Pts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (CR)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Very Good Partial Response (VGPR)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>8 (31)</td>
</tr>
<tr>
<td>Minimal Response (MR)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>10 (39)</td>
</tr>
<tr>
<td>Progressive Disease (PD)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>ORR (CR+VGPR+PR)</td>
<td>10 (39)</td>
</tr>
<tr>
<td>CBR (CR+VGPR+PR+MR)</td>
<td>13* (50)</td>
</tr>
</tbody>
</table>

*All 13 responding pts were refractory to lenalidomide (progressed while on or w/i 8 wks of last dose)
Best Response: Waterfall Plot of % Change in Myeloma Markers

Change relative to baseline (%)

Reduced levels
Increased levels

26 pts (2pts were analyzed for response using both M-protein and 24h urine M-protein)
Conclusions

- This is the first clinical trial demonstrating activity of JAK inhibitors for treating MM patients

- The combination of the JAK1/2 inhibitor ruxolitinib, lenalidomide and methylprednisolone overcomes resistance to lenalidomide for half of heavily pre-treated RRMM patients
  - All responding patients were lenalidomide refractory

- This all oral combination was well tolerated with few ≥ Grade 3 AEs, including cytopenias

- These promising results have led to expansion of the current trial, and provide the basis for exploration of this and other JAK inhibitor-containing combinations for treating patients with MM and other malignant diseases
Serum B-cell Maturation Antigen (sBCMA) Levels in MM Patients

- Are elevated
- Correlate with clinical status (response vs progressive disease)
- Can be used to track response to treatment
- Predicts PFS and OS

Ghermezi et al. Haematologica 2017; Udd et al. IMW 2017
sBCMA Levels* Are Increased in Patients w/ Monoclonal Gammopathies

Median Serum BCMA Levels (ng/mL):
Healthy Donors: 37.9 (range, 14.1-958.1)
MGUS: 53.6 (range, 11.7-693.3)
Smoldering MM: 85.1 (range, 31.6-2956.0)
Active, Untreated MM: 521.6 (range, 17.8-9027.0)

p-values:
Healthy Donors vs MGUS: p=0.0109
Healthy Donors vs Smoldering MM: p<0.0001
Healthy Donors vs Active, Untreated MM: p<0.0001
MGUS vs Smoldering MM: p=0.0006
MGUS vs Active, Untreated MM: p<0.0001
Smoldering MM vs Active, Untreated MM: p<0.0001

*serum diluted 1:500

Ghermezi et al. Haematologica 2017
sBCMA Levels Above Median Predict Shorter Progression-free\(^1\) And Overall Survival\(^2\) of MM Patients

**Median PFS:**
- Below median: 9.0 months
- Above median: 3.6 months

**Median OS:**
- Below median: 155 Months
- Above median: 98 months

\(^1\)obtained at start of new treatment

\(^2\)from first sample

---

**Range (ng/mL):**
- Below median: 14.39 – 320.31
- Above median: 332.56 – 23051.74

**Median BCMA:**
- Median = 332.56 ng/mL

**Quartile 4 BCMA cutoff:**
- >988.42 ng/mL

**PFS (months):**
- Below median (n = 93): 
- Above median (n = 94):

\[ p = 0.0004^{***} \]
Compare Changes in sBCMA to Both Serum M-Protein and SFLC among MM Patients Receiving New Therapy³

Rationale

• sBCMA has a much more rapid turnover in blood (half-life in blood is 24-36 hours¹) than M-protein

• sBCMA levels are independent of renal function unlike SFLC²

Thus, sBCMA may provide a more rapid and accurate assessment of response status for MM patients

Patient 2832
Comparison of sBCMA to M-Protein During First Cycle of DVD*

Baseline sBCMA: 684.9 ng/mL
Baseline serum M-Protein: 3.6 g/dL
Baseline SFLC: 270.9 mg/L kappa; 6.4 mg/L lambda
Baseline serum creatinine: 0.7 mg/dL
Baseline QIGS: IgG: 4200 mg/dL; IgA: 15 mg/dL; IgM: 16 mg/dL

Patient achieved PR on C4 D22 (Day 134)

*DVD = dexamethasone, bortezomib and pegylated liposomal doxorubicin

IgG kappa MM
Response (by IMWG) as of C1 D22: SD
**Patient 2763**

**Comparison of sBCMA to M-Protein During First Cycle of IAC-D**

- Baseline sBCMA: 444.3 ng/mL
- Baseline serum M-Protein: 3.3 g/dL
- Baseline SFLC: 49.6 mg/L kappa; 1.6 mg/L lambda
- Baseline serum creatinine: 1.7 mg/dL
- Baseline QIGS: IgG: 2620 mg/dL; IgA: 15 mg/dL; IgM: 15 mg/dL

*Patient Progressed on C1 D22 (Hypercalcemia, 24 hr urine M-Protein increased from 0 to 491 mg/24h)*

*IAC-D = ixazomib, vitamin C, cyclophosphamide, dexamethasone*

IgG kappa MM
Response (by IMWG) as of C1 D22: PD
Time on treatment based on percentage change (≥25% or < 25%) in sBCMA levels on C1D8

-  ≥25% Increase: 1.61 months
-  <25% Increase: 3.82 months

P = .0012
Serum B-cell Maturation Antigen (sBCMA) Levels in MM Patients

- Are elevated
- Correlate with clinical status (response vs progressive disease)
- Can be used to track response to treatment
  - rapid turnover allows quicker assessment of response
  - independent of renal function
  - more reliable than SFLC
  - those with nonsecretory disease
- Predicts PFS and OS

Ghermezi et al. Haematologica 2017; Udd et al. IMW 2017