MM Therapy Paradigm Shift (?)

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Multiple Myeloma

GOAL

CURE

Maryland half marathon
Pre malignant states
MGUS  SMM  Myeloma defining event

Sub clones; median no.=7

BM environment...Immune effects

MM Therapy

1958 Melphalan
1962 Corticosteroids
1968 Auto SCT
1983 Lenalidomide
1999 Thalidomide
2002 Bortezomib
2003 Pomalidomide
2003 Panabinostat
2010 Carfilzomib
2012 Ixuzumib
2015 Daratumumab
2015 Elotuzumab
2015 Panabinostat
2015 PD-1 Inh
2015 XPO-1 Inh
2015 Bcl-2 Inh
2015 Bite

Improved OS in MM

Targeted Therapy
MM Therapy---2018

3-Drug regimen

1-Auto-SCT

Maintenance

RVD +/- SCT
CR 59% vs. 48%

Maintenance-lenalidomide
Meta-analysis

RVD +/- SCT

Post induction + ASCT-1
followed by:

RVD→R
n=254

RVD alone
N=350

PFS 50 m vs. 36 m

Median PFS, mos
52.2
56.7
56.5

Median OS, mos
83.4
85.7
82.0

McCarthy P; et al. JCO 2017, 35, 3279-3289.
BMT CTN0702 STaMINA Trial
Daratumumab Plus KRD In Newly Dx MM

After 4 cycles
(n = 21)

After 8 cyclesa
(n = 15)

Best Response
(n = 21)

a5 patients who proceeded to ASCT before Cycle 8 and 1 patient who discontinued due to progressive disease at Cycle 7 were excluded.
RVD VERSUS RD IN ELDERLY MM NOT ELIGIBLE FOR SCT

N=525

- **Initial therapy:** RVd for eight 21-day cycles vs Rd for six 28-day cycles in patients not intending to proceed to transplant, followed by Rd in both arms

MM Therapy---2018

VMP +/- Daratumumab in NDMM not eligible for SCT

Key eligibility criteria:
- Transplant-ineligible NDMM
- ECOG 0-2
- Creatinine clearance ≥40 mL/min
- No peripheral neuropathy grade ≥2

Stratification factors:
- ISS (I vs II vs III)
- Region (EU vs other)
- Age (<75 vs ≥75 years)

1:1 Randomization (N = 706)

D-VMP × 9 cycles (n = 350)
- Bortezomib: 1.3 mg/m² SC
  - Cycle 1: twice weekly
  - Cycles 2-9: once weekly
- Melphalan: 9 mg/m² PO on Days 1-4
- Prednisone: 60 mg/m² PO on Days 1-4

D cycles 10+
- 16 mg/kg IV
  - Every 4 weeks: until PD

Same VMP schedule

Follow-up for PD and survival

Primary endpoint:
- PFS

Secondary endpoints:
- ORR
- ≥VGPR rate
- ≥CR rate
- MRD (NGS; 10⁻⁵ Threshold)
- OS
- Safety

50% reduction in risk of progression

ORR = 74%

ORR = 91%

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>VMP (n = 356)</th>
<th>D-VMP (n = 350)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>≥CR</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>24</td>
<td>29</td>
</tr>
<tr>
<td>≥sCR</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

ORR = 91%

MRD –ve 22% versus 6%

Mateos MV, et al, NEJM 2018
Lenalidomide Maintenance Meta-analysis

There is a 26% reduction in risk of death, representing an estimated 2.5-year increase in median survival.

Log-rank test and Cox model stratified by study to assess impact of Len maintenance on OS. Median for len treatment arm was extrapolated to be 115 mo based on median of control arm and HR (median, 86 mo; HR = 0.74).

Role of SCT
Trends of Auto SCT in The USA
OS after auto-SCT for MM

![Graph showing survival probability over years with different time periods and sample sizes.](graph.png)

- 2001-2004 (n=10,625)
- 2005-2008 (n=12,083)
- 2009-2012 (n=18,978)
- 2013-2015 (n=16,944)

*p < .0001*
Salvage SCT In MM

![Graph showing survival rates for Salvage auto (n=3,629) and Salvage allo (n=1,102)]

- Probability, %
- Years
- p < .0001

Salvage auto (n=3,629)

Salvage allo (n=1,102)
Auto-SCT for Newly Dx MM in the Era of Novel Agents: Meta-analysis

Table 1. Baseline Demographics of Relevant Randomized Clinical Trials

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients, No.</th>
<th>ISS III, %</th>
<th>High-Risk Cytogenetics, %</th>
<th>Follow-up, mo.</th>
<th>Induction</th>
<th>Conditioning</th>
<th>SDT Regimen</th>
<th>Maintenance (HDT + SDT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palumbo et al, 8 2014</td>
<td>273</td>
<td>23.6</td>
<td>28.8</td>
<td>51.2</td>
<td>RD</td>
<td>MEL 200 x 2</td>
<td>MPR</td>
<td>LEN until progression vs none</td>
</tr>
<tr>
<td>Gay et al, 7 2015</td>
<td>256</td>
<td>29.0</td>
<td>21.8</td>
<td>52</td>
<td>RD</td>
<td>MEL 200 x 2</td>
<td>CRD</td>
<td>LEN + P vs LEN until progression</td>
</tr>
<tr>
<td>Attal et al, 5 2015</td>
<td>700</td>
<td>18.0</td>
<td>12.8</td>
<td>44</td>
<td>RVD</td>
<td>MEL 200</td>
<td>RVD for 8 cycles</td>
<td>LEN for 1 y</td>
</tr>
<tr>
<td>Cavo et al, 6 2016</td>
<td>1192</td>
<td>21.0</td>
<td>25</td>
<td>26</td>
<td>CyborD</td>
<td>MEL 200 x 1 or 2</td>
<td>VMP for 4 cycles</td>
<td>LEN until progression</td>
</tr>
</tbody>
</table>
A  Complete response

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio (95% CI)</th>
<th>Favors SDT</th>
<th>Favors HDT</th>
</tr>
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<tbody>
<tr>
<td>Palumbo et al, 2014</td>
<td>1.37 (0.76-2.45)</td>
<td></td>
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<tr>
<td>Gay et al, 2015</td>
<td>1.17 (0.56-2.47)</td>
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<tr>
<td>Attal et al, 2015</td>
<td>1.51 (1.12-2.04)</td>
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<tr>
<td>Cavo et al, 2016</td>
<td>1.00 (0.76-1.32)</td>
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<tr>
<td>Univariate summary, P = .11</td>
<td>1.24 (0.95-1.61)</td>
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<tr>
<td>Heterogeneity (Q = 4.16, P = .24; I² = 38.1%)</td>
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<tr>
<td>Multivariate summary, P = .07</td>
<td>1.27 (0.98-1.65)</td>
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B  Progression-free survival

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<th>Favors HDT</th>
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<tr>
<td>Palumbo et al, 2014</td>
<td>0.44 (0.32-0.61)</td>
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<td>Gay et al, 2015</td>
<td>0.40 (0.25-0.63)</td>
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<tr>
<td>Attal et al, 2015</td>
<td>0.65 (0.53-0.80)</td>
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<tr>
<td>Cavo et al, 2016</td>
<td>0.73 (0.61-0.88)</td>
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<tr>
<td>Univariate summary, P &lt; .001</td>
<td>0.56 (0.43-0.74)</td>
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<tr>
<td>Heterogeneity (Q = 11.28, P = .01; I² = 77.2%)</td>
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<tr>
<td>Multivariate summary, P &lt; .001</td>
<td>0.55 (0.41-0.74)</td>
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C  Overall survival

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<tr>
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<td>0.55 (0.32-0.94)</td>
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<td>Gay et al, 2015</td>
<td>0.42 (0.23-0.76)</td>
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<tr>
<td>Attal et al, 2015</td>
<td>1.16 (0.80-1.68)</td>
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<tr>
<td>Cavo et al, 2016</td>
<td>0.67 (0.36-1.24)</td>
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<td></td>
</tr>
<tr>
<td>Univariate summary, P = .20</td>
<td>0.67 (0.36-1.24)</td>
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<tr>
<td>Heterogeneity (Q = 10.24, P = .01; I² = 78.7%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Multivariate summary, P = .36</td>
<td>0.76 (0.42-1.37)</td>
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Is Transplant Necessary?
“Upfront” SCT is the standard of care pts < 65 yrs

• **My Opinion…**
  • SCT
    • Increase CR rate …impact PFS & OS (?)
    • Increase depth of response to molecular level more (?)
    • 1 SCT is adequate with maintenance (2rd one may be beneficial?)
  • Relapse after SCT is salvageable with novel agents…
  • Patients are more fit
  • Salvage SCT
    • Less benefit (?)
    • Not done in 40%

• **If MRD negativity is achieved do we need more therapy??**
BONE DISEASE
BONE DISEASE

Bisphosphonates
- Zoledronic acid
- Pamidronate

Rank Ligand Inhibitors
- Denosumab

Denosumab vs. Zometa in solid trs & MM (n=1776) OS analysis, MM subset (n=180)

Denosumab vs. zometa in newly Dx MM (n=1718) Phase 3

Time to SRE

OS & PFS
Zometa is the standard of care for patients with MM lytic bone disease.

Denosumab is a new standard of care for patients with renal insufficiency & bone disease.

It may replace “Bisphosphonates” if Survival benefit can be confirmed in other studies.
Thank you