Ongoing Trials

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This just in from the channel tunnel...

#WhatHaveWeDone
### MRD studies in Clinical Trials.Gov

**June 20 2016 Search terms – Myeloma MRD = 41 studies**

**Review – 28 studies**

<table>
<thead>
<tr>
<th></th>
<th>NDMM</th>
<th>RRMM</th>
<th>IST</th>
<th>company</th>
<th>Primary EP</th>
<th>Secondary EP</th>
<th>TE</th>
<th>NTE</th>
<th>NGS</th>
<th>Flow 3</th>
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<th>UKN 3</th>
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<td>10</td>
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<td><strong>NGS</strong></td>
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<td>Flow 3</td>
<td>Both 4</td>
<td>Both 4</td>
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</table>

little detail about the timing of MRD, or whether studies are powered for the end points
Recent Data

• MRD response rate with novel treatments
  – FCM
  – NGS

• MRD and outcome
  – FCM
  – NGS

• NDMM and RMM
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

Primary Endpoint
• PFS

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

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

• Cycles 1-8: repeat every 21 days
• Cycles 9+: repeat every 28 days

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.

Palumbo et al
Progression-free Survival

Median : not reached

Median : 7.2 months

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

1-year PFS*

DVd

60.7%

Vd

26.9%

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

*KM estimate; HR, hazard ratio.
70% reduction in the risk of disease progression for DVd vs Vd

Palumbo et al
Overall Response Rate

- ORR: 83, 63%
- ≥VGPR: 59, 29%
- ≥CR: 19, 9%

- MRD-neg (10^-4): 14, 3%

- Response-evaluable population.

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Palumbo et al

ASCO ANNUAL MEETING '16

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POLLUX: Study Design

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

Primary endpoint
- PFS

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

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

Pre-medication for the DRd treatment group consisted of dexamethasone 20 mg, paracetamol, and an antihistamine

Dimopoulos MA, et al. EHA 2016
63% reduction in the risk of disease progression or death for DRd vs Rd

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

Dimopoulos MA, et al. EHA 2016
POLLUX: Overall Response Rate

- Median duration of response: Not reached for DRd vs 17.4 months for Rd
- Median time to response: 1.0 month for DRd vs 1.3 months for Rd

Dimopoulos MA, et al. EHA 2016
POLLUX: MRD-negative Rate

Significantly higher MRD-negative rates for DRd vs Rd

Dimopoulos MA, et al. EHA 2016
MRD by NGS

Pollux (MMY3003)
Rd vs. DRd

- MRD testing using ClonoSIGHT™
- MRD thresholds of $10^{-5}$ and $10^{-6}$ were also evaluated
- Evaluated in those suspected of CR (ie VGPR and CR)

Dimopoulos et al.; EHA 2016
Palumbo et al.; ASCO 2016 and EHA 2016

Castor (MMY3004)
Vd vs. DVd

- $P < 0.0001$

$30\%$ DRd
$8\%$ Rd
$14\%$ DVd
$3\%$ Vd
Does the threshold matter?

Minimal residual disease in myeloma by flow cytometry: independent prediction of survival benefit per log reduction

Figure 1. Sequential improvements in PFS and OS for each log depletion in MRD level, as assessed by multiparameter flow cytometry. This effect is demonstrable in all patients (A) PFS; (B) OS as well as those achieving conventional CR (C) PFS; (D) OS.

Rawstron et al  Blood 2015
Phase III IFM 2009: RVD ± ASCT in Newly Diagnosed Younger MM Pts

Stratified by ISS stage and cytogenetics

Pts 65 yrs old of age or younger with symptomatic NDMM; ECOG PS < 2 with organ damage and measurable disease*; treated with 1 cycle RVD† (N = 700)

RVD† Cycles 2, 3
PBSC collection
Cyclophosphamide 3 g/m² + G-CSF
RVD† Cycles 4-8
(n = 350)

RVD† Cycles 2, 3
PBSC collection
Cyclophosphamide 3 g/m² + G-CSF
ASCT with MEL200
RVD† Cycles 4, 5
(n = 350)

Lenalidomide Maintenance
10-15 mg/day for 12 mos

Primary objective: PFS
Secondary objectives
- Response rate
- MRD
- Time to progression
- OS
- Toxicity

*Serum M-protein > 10 g/L and/or urine M-protein > 200 mg/24 hrs and/or serum FLC > 100 mg/L if serum FLC ratio is abnormal.
†Lenalidomide 25 mg/day on Days 1-14; bortezomib 1.3 mg/m² on Days 1, 4, 8, 11; dexamethasone 20 mg/day on Days 1, 2, 4, 5, 8, 9, 11, 12.

Median follow up 41 months
31% reduced risk of progression or death (P < .001)


PFS (9/2015)

IFM 2009: PFS (9/2015)

Median PFS at 4 years improved with HDT by 8.8 months

P < .001

N=350 in each arm

34 vs 43 months

N at risk

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<thead>
<tr>
<th></th>
<th>HDT</th>
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<tbody>
<tr>
<td>N</td>
<td>350</td>
<td>350</td>
</tr>
<tr>
<td>0 months</td>
<td>350</td>
<td>350</td>
</tr>
<tr>
<td>12 months</td>
<td>309</td>
<td>296</td>
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<tr>
<td>24 months</td>
<td>261</td>
<td>228</td>
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<tr>
<td>36 months</td>
<td>153</td>
<td>128</td>
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<tr>
<td>48 months</td>
<td>27</td>
<td>24</td>
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</table>

Patients (%)

Months of follow-up
IFM 2009: Responses

- important that MRD performed at a number of different time points

<table>
<thead>
<tr>
<th>Response, %</th>
<th>RVD (n = 350)</th>
<th>Transplantation (n = 350)</th>
<th>P Value</th>
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<tr>
<td>CR</td>
<td>49</td>
<td>59</td>
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<td>VGPR</td>
<td>29</td>
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<tr>
<td>PR</td>
<td>20</td>
<td>11</td>
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<tr>
<td>&lt; PR</td>
<td>2</td>
<td>1</td>
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<tr>
<td>≥ VGPR</td>
<td>78</td>
<td>88</td>
<td>.001</td>
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<tr>
<td>Negative MRD by FCM</td>
<td>65</td>
<td>80</td>
<td>.001</td>
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## IFM 2009: PFS Prognostic Factors

<table>
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<tr>
<th>PFS Prognostic Factor</th>
<th>Multivariate Analysis: Adjusted HR</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>Treatment arm: no transplant vs transplant</td>
<td>0.80</td>
<td>.02</td>
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<tr>
<td>ISS stage</td>
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<tr>
<td>• II vs I</td>
<td>1.33</td>
<td>.02</td>
</tr>
<tr>
<td>• III vs I</td>
<td>1.45</td>
<td>.01</td>
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<tr>
<td>FISH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• High risk vs standard risk</td>
<td>2.22</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>CR</td>
<td>0.58</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Negative MRD by flow cytometry</td>
<td>0.39</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

- Median PFS with negative MRD significantly longer in each arm ($P < .001$)
- TTP significantly different between arms ($P < .001$)

IFM/DFCI 2009: PFS According to MRD Post Maintenance

NGS

RVD Arm

Transplant Arm

MRD at post-maintenance for arm A

MRD at post-maintenance for arm B

P-value : p=0.0007

P-value : p<0.0001

IFM/DFCI 2009: In Flow-Based MRD-Negative Patients
Molecular MRD Status Predicts Survival Post Maintenance

MRD at post-maintenance for MRD neg (FCM)

$P = .0006$

N at risk (events)

MRD neg ($<10^{-6}$)

<table>
<thead>
<tr>
<th>Months since randomization</th>
<th>MRD neg ($&lt;10^{-6}$)</th>
<th>MRD positive</th>
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<tr>
<td>0</td>
<td>69</td>
<td>42</td>
</tr>
<tr>
<td>6</td>
<td>69 (0)</td>
<td>42 (0)</td>
</tr>
<tr>
<td>12</td>
<td>69 (0)</td>
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<td>69 (0)</td>
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<td>36</td>
<td>63 (2)</td>
<td>31 (4)</td>
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<td>42</td>
<td>50 (4)</td>
<td>21 (5)</td>
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<tr>
<td>48</td>
<td>29 (0)</td>
<td>5 (1)</td>
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</table>

TOURMALINE-MM1: Study Design

- Randomized, double-blind, placebo-controlled phase III trial¹

Stratified by prior therapy (1 vs 2-3), ISS stage (I-II vs III), and prior PI exposure (yes vs no)

RRMM patients with measurable disease;
- 1-3 prior treatments
- CrCl ≥ 30 mL/min
- Not refractory to PIs or lenalidomide (N = 722)

Ixazomib 4 mg PO D1, 8, 15 +
Lenalidomide 25 mg* D1-21 +
Dexamethasone 40 mg D1, 8, 15, 22
(n = 360)

Placebo D1,8,15 +
Lenalidomide 25 mg* D1-21 +
Dexamethasone 40 mg D1,8,15,22
(n = 362)

*10 mg for pts with CrCl ≤60 or ≤50 mL/min.

28-day cycles until PD or unacceptable toxicity

- Primary endpoint: PFS by IRC per IMWG criteria²
- Secondary endpoints (data not yet mature): OS, OS in del(17p) patients

TOURMALINE-MM1: PFS

- Addition of ixazomib to Rd resulted in 35% improvement in PFS vs Rd alone


• PFS benefit with ixazomib seen in all prespecified subgroups, including cytogenetic high risk, PI and IMiD exposed
TOURMALINE-MM1:
Outcomes by Cytogenetic Risk Group

<table>
<thead>
<tr>
<th></th>
<th>ORR, %</th>
<th>≥VGPR, %</th>
<th>≥CR, %</th>
<th>Median PFS, months</th>
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<tbody>
<tr>
<td></td>
<td>IRd</td>
<td>Placebo-Rd</td>
<td>IRd</td>
<td>Placebo-Rd</td>
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<tr>
<td>All patients</td>
<td>78.3*</td>
<td>71.5</td>
<td>48.1*</td>
<td>39</td>
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<tr>
<td>Standard-risk patients</td>
<td>80</td>
<td>73</td>
<td>51</td>
<td>44</td>
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<tr>
<td>All high-risk patients</td>
<td>79*</td>
<td>60</td>
<td>45*</td>
<td>21</td>
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<tr>
<td>Patients with del(17p)†</td>
<td>72</td>
<td>48</td>
<td>39</td>
<td>15</td>
</tr>
<tr>
<td>Patients with t(4;14) alone</td>
<td>89</td>
<td>76</td>
<td>53</td>
<td>28</td>
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</table>

*P < .05 for comparison between regimens. †Alone or in combination with t(4;14) or t(14;16)
Data not included on patients with t(14;16) alone due to small numbers (n = 7)

- Median OS was not reached in either arm
- In the IRd arm, median PFS in high-risk patients was similar to that in the overall patient population and in patients with standard-risk cytogenetics

MRD measurements in Tourmaline MM trials

- **Tourmaline MM2**
  - NDMM (Ixazomib/Rd vs Placebo/Rd) [enrollment complete]
  - MRD measurement done in Bone Marrow using flow. Samples taken from patient achieving CR and at cycle 18

- **Tourmaline MM3**
  - NDMM post-SCT - maintenance trial (Ixazomib vs Placebo) [enrollment complete]
  - MRD measurements done in Bone Marrow using flow and NGS, and in blood using NGS. Samples taken from all CR and VGPR patients at screening and after 1 and 2 years of therapy. Patients entering the trial with a PR, and upgrading their response to CR, will be also assessed for MRD
  - Genomic characterization of MRD positive samples, if available

- **Tourmaline MM4**
  - NDMM no-SCT - maintenance trial (Ixazomib vs Placebo) [currently enrolling]
  - MRD measurements done in Bone Marrow using flow and NGS. Samples taken from all CR patients at screening and after 1 and 2 years of therapy. Patients entering the trial with a PR, and upgrading their response to CR, will be also assessed for MRD
  - Genomic characterization of MRD positive samples, if available
Venetoclax (ABT-199) + Vd in R/R MM: Background

- Venetoclax: potent, selective inhibitor of BCL2 that promotes apoptosis\(^1\)
  - Resistance likely mediated via MCL-1

- Bortezomib: MCL-1 inhibitor, active by promoting expression of NOXA, which neutralizes MCL-1 and induces degradation

- Addition of venetoclax to bortezomib enhanced tumor growth inhibition and DoR in MM xenograft models\(^2\)

- Current study evaluated safety, activity of adding venetoclax to Vd in R/R MM pts\(^3\)

Venetoclax + Vd in R/R MM: Study Design

- Multicenter, open-label phase Ib study of venetoclax in combination with Vd; dose escalation and expansion cohorts planned
  - Venetoclax 50-1200 mg PO for cycles 1-12+
  - Bortezomib 1.3 mg/m³ SC on Days 1, 4, 8, 11 for cycles 1-8 and Days 1, 8, 15, and 22 for cycles 9-11
  - Dexamethasone 20 mg PO on Days 1, 2, 4, 5, 8, 9, 11, 12 for cycles 1-8 and Days 1, 2, 8, 9, 15, 16, 22, 23 for cycles 9-11
  - Dosing cycle: 21 days for cycles 1-8, 35 days subsequently

- Primary objectives: safety and tolerability, MTD, RP2D, PK
- Secondary/exploratory objectives: ORR, TTP, DoR, biomarkers

Venetoclax + Vd in R/R MM: Phase 3

- Encouraging safety and response rates observed in phase 1b
  - 58% ORR in overall cohort
  - Higher ORRs in pts not refractory to bortezomib (84%) and those who had received only 1-3 prior lines of therapy (84%)
  - Higher BCL2 expression associated with improved response
- planned phase III trial of this regimen in R/R MM pts
- V-Vel Dex vx placebo Vel Dex
- MRD secondary endpoint in patients who potentially achieve CR by NGS

Conclusions

• Numerous Commercial and Investigator led studies with MRD as secondary end point
  – Multi-centre
  – Can be measured
  – FCM and NGS
  – QA/QC
Outstanding Questions

Is MRD the same in a high risk patient
   eg IFM 700 patient study – if looking at FCM negative patients and splitting by NGS result = 100 pts ……is there enough power to look at HRMM?

Who should we be measuring it in………
All patients or just those that achieve a CR
Needs to be clearly stated

Timing
Potentially easier in TE patients (defined disease phases)
When is appropriate in NTE
One time point or multiple