MRD in the Transition of Smoldering MM to Symptomatic MM

Advances in Minimal Residual Disease Testing in Myeloma
New York Hilton Midtown

Christoph Heuck, MD | Director, Clinical Research | June 24th, 2016
Current Options for MRD Assessment in MM
MRD by NGS

ClonoSIGHT

Step 1. Presentation

- Collect sample before treatment
- Run clonality test for all receptors
  - IGH-VDJ
  - IGH-DJ
  - IGK
  - TRB
  - TRD
  - TRG

Step 2. Follow-Up

- Collect serial follow-up samples
- Run clonality test for positive receptors
  - IGH-VDJ
  - TRD

Monitor MRD over time in serial follow-up samples
MRD by NGS

Pollux (MMY3003)
Vd vs. DVd

- MRD testing using ClonoSIGHT™
- MRD thresholds of $10^{-5}$ and $10^{-6}$ were also evaluated

Addition of Dara results in a significantly higher MRD negativity rate

Dimopoulos et al., EHA 2016; Palumbo et al., ASCO 2016 and EHA 2016
MRD by Flow Cytometry

31 subjects MFC neg. but not in CR

Focal Snapshot of MRD
Focal Snapshot of MRD

Choice of sampling site has influence on results

Weinhold et al.; EHA 2016
MRD by PET/CT

IFM/DFCI 2009
n=700

Randomize

ARM A
- RVDx3
- HSC Mobilization
- RVD x 5
- Revlimid 1 year
- ASCT at relapse

ARM B
- RVDx3
- HSC Mobilization
- Mel200 ASCT
- RVD x 2
- Revlimid 1 year
MRD by PET/CT

IFM/DFCI 2009
n=700

Randomize

ARM A
RVDx3
HSC Mobilization
RVD x 5
Revlimid 1 year

ARM B
RVDx3
HSC Mobilization
Mel200 ASCT
RVD x 2
Revlimid 1 year

ASCT at relapse

IMAJEM
n=134

PET-CT / MRI

n=700

PET-CT / MRI
MRD by PET/CT

- 86 subjects with paired PET-CT and MRD(flow) data

<table>
<thead>
<tr>
<th>MRD</th>
<th>PET-CT pos</th>
<th>PET-CT neg</th>
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<tbody>
<tr>
<td>pos</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>neg</td>
<td>14</td>
<td>41</td>
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Fisher exact test: $p = 0.33$
McNemmar test: $p = 0.39$

Improved outcome for double negative subjects

Moreau et al. ASH 2015
Circulating Multiple Myeloma Cells
• Several published studies evaluating CMMCs using flow cytometry
• Presence of >400 CMMC at presentation in newly diagnosed MM negatively impacts survival
• Presence of >100 CMMC at relapse is associated with worse survival
• High level of circulating PCs is associated with progression of MGUS and SMM to symptomatic MM

Gonsalves et al., Br J Hematol. 2014; Gonsalves et al., Leukemia 2014; Bianchi et al., Leukemia 2013; Kumar et al., JCO 2005
Capturing Circulating MM Cells

- Peripheral blood
- CellSearch platform
- Newly diagnosed MM from CoMMpass study
- High risk SMM from SiltuximabSMM2001 study
- Healthy Donors commercially sourced

CMMC isolation and detection

CMMCs can be enumerated and captured for further genomic analysis

Foulk et al. AACR 2016
Evaluation of Circulating MM cells

CMMC counts by disease state

CMMC counts by ISS stage

Foulk et al. AACR 2016
Evaluation of Circulating MM cells

Bone marrow plasma cells vs. peripheral blood CMMC

Peripheral blood plasma cells CMMC method vs flow

CellSearch technology can capture CMMCs in ‘flow negative’ samples

Foulk et al. AACR 2016
Impact of CMMC on outcome

Patients with <100 CMMCs at remission have better outcome

Foulk et al. AACR 2016
Incorporation of MRD into clinical trials
Selecting the right MRD modality

Cassiopeia (MMY3006; IFM/HOVON)

**Screening**

**Randomization #1**

- VTD x4
- HDT + ASCT
- VTD x2

**Randomization #2**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment</th>
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<tr>
<td>&lt; PR</td>
<td>Observation until PD 2 year max</td>
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<tr>
<td>≥ PR</td>
<td>VTD + D x4</td>
</tr>
<tr>
<td></td>
<td>HDT + ASCT</td>
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<tr>
<td></td>
<td>VTD + D x2</td>
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</table>

**Follow-up**

- New diagnosis MM
- n=1080
- 1° Endpoint: sCR rate after Consolidation
- Co-1° Endpoint: PFS after maintenance with Dara

**Endpoints**

- Consolidation: sCR rate
- Maintenance: PFS until PD

**Follow-up**

- Observation until PD 2 year max
- Dara q 8w until PD 2 year max
Selecting the right MRD modality

Cassiopeia (MMY3006; IFM/HOVON)

Screening

Randomization #1

VTD x4

HDT +
ASCT

VTD x2

Randomization #2

≤ PR

≥ PR

VTD + D x4

HDT +
ASCT

VTD + D x2

Observation
until PD
2 year max

Dara q 8w
until PD
2 year max

Follow-up

CassioPET

- MRD by Flow cytometry
- MRD by NGS
- PET /CT

- MRD by Flow cytometry
- MRD by NGS
- PET/CT
MRD in SMM
Role of MRD testing in SMM

- No conclusive data for MRD in SMM yet
- One small study of KRd in high-risk SMM
  - 11/12 subjects MRD(flow) negative; 9/12 subjects MRD(NGS) negative
- Health authorities in the US (FDA) and Europe (EMA) recognize MRD negativity as an important secondary endpoint
Role of MRD testing in SMM

Centaurus (SMM2001)

- **Screening**
  - Randomize

- **Arm A**
  - Dara 16 mg/kg iv
  - Cycle 1: 8 weekly doses
  - Cycle 2-3: q2 weeks
  - Cycle 4-7: q4 weeks
  - Cycle 8-20: q8 weeks

- **Arm B**
  - Dara 16 mg/kg iv
  - Cycle 1: 8 weekly doses
  - Cycle 2-20: q8 weeks

- **Arm C**
  - Dara 16 mg/kg iv
  - Cycle 1: 8 weekly doses

- **Observation**

- **Follow Up until End of Study**
  - (4 years after LFD)

- **High risk SMM**

- **1° Endpoint:** CR rate

- **2° Endpoints:** ORR, PFS

At Presentation and CR:
- MRD (NGS) – bone marrow
- CMMCs – peripheral blood
- Immunphenotyping – peripheral blood
Thank you

cheuck@its.jnj.com