Prospective Evaluation of MRI and PET-CT at Diagnosis and before Maintenance Therapy in Symptomatic Patients with Multiple Myeloma Included in the IFM/DFCI 2009 Trial

**Rationale**

MRI and PET-CT are important imaging techniques to detect bone lesions in multiple myeloma at diagnosis.

Both MRI and PET-CT have been described to have prognostic value for PFS and/or OS (at diagnosis, during follow-up).
AT DIAGNOSIS

EFS by MRI-FL

<table>
<thead>
<tr>
<th>Event / N</th>
<th>30-Month Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI-FL ≤ 7 at Baseline</td>
<td>39 / 171</td>
</tr>
<tr>
<td>MRI-FL &gt; 7 at Baseline</td>
<td>25 / 68</td>
</tr>
</tbody>
</table>

Logrank P-value = .03

Months from enrollment

AT DIAGNOSIS

FOLLOW-UP / DYNAMIC

OS by suppression of PET-FL at first transplant

Logrank P-value = .0002

FOLLOW-UP / DYNAMIC

Zamagni et al, Blood 2011;118:5989-5995
Few trials have compared prospectively MRI and PET-CT in the setting of recent frontline intensive therapy programs.
IFM/DFCI 2009 Study
Newly Diagnosed MM Pts (SCT candidates)

ARM A

Randomize

ARM B

RVDx3

CY (3g/m2) MOBILIZATION
Goal: 5 x 10^6 cells/kg

RVD x 5

Revlimid 1 year

Frontine ASCT

ASCT at relapse

RVDx3

CY (3g/m2) MOBILIZATION
Goal: 5 x 10^6 cells/kg

Melphalan 200mg/m^2* + ASCT

RVD x 2

Revlimid 1 year
IFM 2009: PFS, 700 patients

Attal et al. ASH 2015

Stratified Log-rank test: p=0.00019
Critical p-value: p=0.0152

N at risk (events)
Conventional: 350 (15) 332 (35) 296 (26) 260 (28) 228 (34) 185 (24) 108 (18) 41 (5) 18
High Dose: 350 (17) 332 (21) 309 (22) 285 (17) 259 (28) 212 (23) 128 (18) 59 (2) 13

Patients without progression (%)

Months since randomization

0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

0 6 12 18 24 30 36 42 48

Arm A - Conventional
Arm B - High dose

Stratified Log-rank test: p=0.00019
Critical p-value: p=0.0152
**IMAJEM (NCT01309334), 134 patients**

**ARM A**
- RVDx3
- CY (3g/m2) MOBILIZATION
  - Goal: 5 x10⁶ cells/kg
- RVD x 5
- Revlimid 1 year

**ARM B**
- RVDx3
- CY (3g/m2) MOBILIZATION
  - Goal: 5 x10⁶ cells/kg
- Melphalan 200mg/m² + ASCT
- RVD x 2
- Revlimid 1 year

**Randomize**

**ASCT at relapse**
**IMAJEM (NCT01309334), 134 patients**

**ARM A**
- **RVDx3**
  - **CY (3g/m2) MOBILIZATION**
    - Goal: $5 \times 10^6$ cells/kg
  - **RVD x 5**
  - Revlimid 1 year
- ASCT at relapse

**ARM B**
- **RVDx3**
  - **CY (3g/m2) MOBILIZATION**
    - Goal: $5 \times 10^6$ cells/kg
  - Melphalan 200mg/m$^2$* + ASCT
  - **RVD x 2**
  - Revlimid 1 year

**Randomize**
- PET-CT / MRI at diagnosis
**IMAJEM (NCT01309334), 134 patients**

**Randomize**

**ARM A**
- RVDx3
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- RVD x 2
- Revlimid 1 year

**PET-CT / MRI at diagnosis**
- PET-CT / MRI after 3 cycles

**ASCT at relapse**
**IMAJEM (NCT01309334), 134 patients**

**ARM A**
- RVDx3
- CY (3g/m2) MOBILIZATION
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**Randomize**
- PET-CT / MRI at diagnosis
- PET-CT / MRI after 3 cycles

**ARM B**
- RVDx3
- CY (3g/m2) MOBILIZATION
  - Goal: 5 x 10^6 cells/kg
  - Melphalan 200mg/m^2 * + ASCT
  - RVD x 2
- Revlimid 1 year
Primary end-point: DIAGNOSIS / STAGING

Compare MRI (spine and pelvis) vs PET-CT regarding the number of bone lesions at diagnosis
Secondary end-points: PROGNOSTIC IMPACT

- Evaluate prognostic impact of PET-CT vs MRI after 3 cycles of induction therapy with RVD (PFS / OS → PET negativity / MRI negativity)

- Evaluate prognostic impact of PET-CT vs MRI before maintenance (PFS / OS → PET negativity / MRI negativity)
Secondary end-points : PROGNOSTIC IMPACT

- Evaluate prognostic impact of PET-CT vs MRI after 3 cycles of induction therapy with RVD (PFS / OS → PET negativity / MRI negativity)

- Evaluate prognostic impact of PET-CT vs MRI before maintenance (PFS / OS → PET negativity / MRI negativity)

All 134 x 3 MRI and 134 x 3 PET-CT were centrally reviewed by 2 x 2 experts, blinded to treatment arm (2 radiologists / 2 nuclear medicine physicians)
### Patients characteristics

<table>
<thead>
<tr>
<th></th>
<th>n = 134</th>
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</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>59 (37-65)</td>
</tr>
<tr>
<td>Male / female</td>
<td>83 / 51 (62% / 38%)</td>
</tr>
<tr>
<td>ISS1</td>
<td>41 (31%)</td>
</tr>
<tr>
<td>ISS2</td>
<td>74 (55%)</td>
</tr>
<tr>
<td>ISS3</td>
<td>19 (14%)</td>
</tr>
<tr>
<td>Median Calcium mM/L (range)</td>
<td>2.28 (2.04-2.95)</td>
</tr>
<tr>
<td>Median LDH UI (range)</td>
<td>211 (71-843)</td>
</tr>
<tr>
<td>Median Hb g/dL (range)</td>
<td>10.9 (8-14.6)</td>
</tr>
<tr>
<td>Median creatinine µM/L (range)</td>
<td>78 (39-162)</td>
</tr>
<tr>
<td>t(4;14) yes/no</td>
<td>6 / 129</td>
</tr>
<tr>
<td>del17p</td>
<td>5 / 129</td>
</tr>
<tr>
<td>Arm A, n (%)</td>
<td>71 (53%)</td>
</tr>
<tr>
<td>Arm B, n (%)</td>
<td>63 (47%)</td>
</tr>
</tbody>
</table>
Primary end-point: DIAGNOSIS / STAGING

Compare MRI (spine and pelvis) vs PET-CT regarding the number of bone lesions at diagnosis
• At diagnosis, MRI was positive in 127/134 (94.7%), and PET-CT in 122/134 (91%) patients, (McNemar test = 0.94, p-value = 0.33).

• MRI of the spine and pelvis and whole-body PET-CT are **equally** effective to detect bone involvement in symptomatic patients at diagnosis.
• MRI patterns of marrow involvement were the following:

- normal in 7 cases (5%)
- focal lesions (FL) in 46 cases (34%); 
- homogeneous diffuse infiltration in 41 cases (31%)
- combined diffuse infiltration and FL in 35 cases (26%)
- variegated or "salt-and-pepper" pattern with inhomogeneous bone marrow in 5 cases (4%)
• **PET-CT patterns were the following:**
  - normal in 12 cases (9%);
  - FL in 44 cases (33%);
  - diffuse infiltration in 12 cases (9%);
  - combined diffuse infiltration and FL in 66 cases (49%)
  - extramedullary disease in 10 cases (7.5%).

• The median number of FL assessed by PET-CT was 3 (0 to >10), with a median SUVmax of 4.1 (range 1.5-28.4).
Secondary end-point: PROGNOSTIC IMPACT

PET-CT vs MRI

after 3 cycles of induction therapy with RVD
MRI normalisation following 3 cycles of RVD
Impact on PFS (3% normalised)

$p = 0.29$

61.6%
MRI normalisation following 3 cycles of RVD
Impact on OS (3% normalised)

\[ p = 0.61 \]

86.1\%
PET-CT normalisation following 3 cycles of RVD
Impact on PFS (32% normalised)

\[ p = 0.04 \]

78.7%
54.8%
PET-CT normalisation following 3 cycles of RVD
Impact on OS (32% normalised)

$p = 0.12$

92.8%
81.8%
Secondary end-point: PROGNOSTIC IMPACT

PET-CT vs MRI

before maintenance
MRI normalisation before maintenance
Impact on PFS (11% normalised)

p = 0.30
MRI normalisation before maintenance
Impact on OS (11% normalised)

\[ p = 0.30 \]

85.1%
PET-CT normalisation before maintenance
Impact on PFS (62% normalised)

$p < 0.001$
PET-CT normalisation before maintenance
Impact on OS (62% normalised)
Univariate analysis for PFS / 134 patients

Variables tested:
Gender, age, Ca, creatinine, ISS, response after 3 cycles of induction, response pre-maintenance, cytogenetics, MRI after 3 cycles, PET-CT after 3 cycles, MRI pre-maintenance, PET-CT pre-maintenance

- PET-CT after 3 cycles, $p = 0.04$
- PET-CT pre-maintenance, $p < 0.001$
- Response after 3 cycles ($\geq$ VGPR), $p = 0.04$
Univariate analysis for OS / 134 patients

Variables tested:
Gender, age, Ca, creatinine, ISS, response after 3 cycles of induction, response pre-maintenance, cytogenetics, MRI after 3 cycles, PET-CT after 3 cycles, MRI pre-maintenance, PET-CT pre-maintenance

- PET-CT pre-maintenance, \( p = 0.003 \)
PET-CT pre-maintenance is a prognostic factor for PFS in Arm A: RVD x 8 cycles

Adjusted on other prognostic factors $p = 0.009$
Univariate log-rank, $p = 0.027$
PET-CT pre-maintenance is a prognostic factor for PFS in Arm B: frontline ASCT

Adjusted on other prognostic factors p = 0.01
Univariate log-rank, p = 0.01
PET-CT pre-maintenance is a prognostic factor for OS in Arm B: frontline ASCT

Adjusted on other prognostic factors $p = 0.008$
Univariate log-rank, $p < 0.001$
86 / 134 patients had also MRD evaluation pre-maintenance by CMF*

<table>
<thead>
<tr>
<th></th>
<th>PET-CT pos</th>
<th>PET-CT neg</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD pos</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>MRD neg</td>
<td>14</td>
<td>41</td>
</tr>
</tbody>
</table>

Fisher exact test: $p = 0.33$
McNemmar test: $p = 0.39$

* Avet-Loiseau et al. ASH 2015
PFS for patients with negative PET-CT and negative MRD by flow (47.7% of patients) pre-maintenance vs others
Conclusions

- PET-CT and MRI are equally effective to detect bone involvement in symptomatic patients at diagnosis.

- MRI is not a good imaging method during follow-up.

- PET-CT after 3 cycles of RVD and pre-maintenance is a powerful prognostic marker for PFS.

- PET-CT pre-maintenance is a powerful prognostic marker for OS.

- PET-CT and CMF are complementary tools to evaluate minimal residual disease.
SCREEN

Induction
- VTD + DARA x 4 cycles
- VTD x 4 cycles

Stem cell mobilization/Conditioning and ASCT

Consolidation
- VTD + DARA x 2 cycles
- VTD x 2 cycles

≥ PR

Randomize

Maintenance
- DARA Q8W for 2 years
- Observation

Part 1

Part 2

≥ PR

≥ PR

www.clinicaltrials.gov; NCT02541383
CASSIOPEIA trial
CASSIOPEIA trial

**Induction**
- VTD + DARA x 4 cycles
- VTD x 4 cycles

**Consolidation**
- Stem cell mobilization/Conditioning and ASCT
  - VTD + DARA x 2 cycles
  - VTD x 2 cycles

**Maintenance**
- DARA Q8W for 2 years
- Observation

**Screen**
- RANDOMIZE

**Follow-up**

PET / FLOW / NGS

- ≥PR

Part 1

Part 2

www.clinicaltrials.gov; NCT02541383

CASSIOPEIA trial

PET / FLOW / NGS
Intergroupe Francophone du Myélome