Myeloma MRD: UK data

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What do we need?

- Applicability
- Independent prediction of outcome in multivariate models
- Quantitative effect
- Independent of biological risk
- Independent of treatment received
- Impact demonstrable at presentation and relapse
Which trials?

• **Upfront**
  - Myeloma IX
  - Myeloma XI/XI+
  - PADIMAC
  - CARDAMON (ongoing)
  - MUK nine (ongoing)

• **Relapse**
  - Myeloma X
  - MUK five
  - ACCORD / Myeloma XII (ongoing)

• **Planned** – Myeloma XIV and XV
Flow cytometric disease monitoring in multiple myeloma: the relationship between normal and neoplastic plasma cells predicts outcome after transplantation


blood
Minimal Residual Disease Assessed by Multiparameter Flow Cytometry in Multiple Myeloma: Impact on Outcome in the Medical Research Council Myeloma IX Study


![Graphs showing progression-free survival and overall survival over time since MRD assessment.](image)

- **Progression-Free Survival**
  - Blue line: MRD− (n = 247)
  - Yellow line: MRD+ (n = 150)
  - $\chi^2 = 24.00$  
  - $P < .001$

- **Overall Survival**
  - Blue line: MRD− (n = 247)
  - Yellow line: MRD+ (n = 150)
  - $\chi^2 = 5.566$  
  - $P = .0183$
LYMPHOID NEOPLASIA

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

Andy C. Rawstron,1 Walter M. Gregory,2 Ruth M. de Tute,1 Faith E. Davies,3 Sue E. Bell,2 Mark T. Drayson,4 Gordon Cook,1 Graham H. Jackson,5 Gareth J. Morgan,3 J. Anthony Child,2 and Roger G. Owen1
Multivariate analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>PFS</th>
<th>OS</th>
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<tbody>
<tr>
<td></td>
<td>Univariate</td>
<td>Multivariate</td>
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<tr>
<td></td>
<td>χ²</td>
<td>p-value</td>
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<tr>
<td>Log(MRD)</td>
<td>33.0</td>
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<td>Response post ASCT^</td>
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<td>International Staging System (1-3)</td>
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<td>Cytogenetics*</td>
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<td>Log(β2 microglobulin)</td>
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<td>Platelets*</td>
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<td>Haemoglobin**</td>
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<td>Age (continuous)</td>
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<td>.75</td>
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<td>Gender</td>
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Rawstron *et al*, Blood 2015
Myeloma XI/XI+ (n=2998).

- Induction n=1466
- Day 100 n=899
- Maintenance n=399
- Unassigned n=234
Myeloma XI – transplant ineligible schema

Induction 1
- CTD
- CRD

Max. response
- PD
- SD
- MR
- PR
- VGPR
- CR

Induction 2
- CVD
- No CVD

Maintenance
- Lenalidomide
- Observation

N=297/1852
- Median age 74.0 yrs (56-87)
- 62.8% male
- IgG 60.5%
- ISS III 34.2%
PFS according to MRD (qualitative)

Log-Rank
$\chi^2_1 = 15.5200$
$P < 0.0001$
HR: 0.44 95% CI [0.29, 0.67]
Impact of therapy.
Phase II study of Bortezomib, Adriamycin and Dexamethasone (PAD) therapy for previously untreated patients with multiple myeloma: Impact of minimal residual disease (MRD) in patients with deferred ASCT (PADIMAC).

MRD samples = 196
Myeloma X Study Schema

Relapse following prior ASCT

Bortezomib, Doxorubicin & Dexamethasone (PAD)

PBSC Mobilization

Melphalan 200mg/m² iv ASCT

Cyclophosphamide 400mg/m² PO/week x12

Follow-up: TTP PFS OS

PD
Or
CD34⁺ cells <2x10⁶/kg

Off study

297 pts
184 pts randomised
Day 100 MRD 90 pts
Myeloma X: TTP according to MRD

Log-Rank
\(X^2_1 = 17.5474\)
P < 0.0001
HR: 0.39 95% CI (0.24, 0.61)

- MRD+
- MRD−
The Future

• Regulatory endpoint
• MRD directed academic studies
• Routine care