Carfilzomib, Cyclophosphamide and Dexamethasone (KCd) Versus Bortezomib, Cyclophosphamide and Dexamethasone (VCd) For Treatment of First Relapse or Primary Refractory Multiple Myeloma (MM): First Final Analysis of the Phase 2 MUK five Study

Kwee L Yong, Samantha Hinsley, Holger Auner, Debbie Sherratt, Ruth M de Tute, Sarah Brown, Louise Flanagan, Catherine Williams, Jamie Cavenagh, Martin F Kaiser, Neil Rabin, Karthik Ramasamy, Mamta Garg, Stephen Hawkins, Ceri Bygrave, Gareth Morgan, Faith Davies and Roger G Owen

on behalf of the MUK five investigators and Myeloma UK Early Phase Clinical Trial Network
MUK five: Background

• Three proteasome inhibitors are licensed for the treatment of multiple myeloma: bortezomib, carfilzomib and ixazomib

• Head-to-head comparisons of carfilzomib with bortezomib have used differing dosing schedules in different patient groups
  • ENDEAVOR in Relapsed disease: Carfilzomib 20/56mg/m2 + Dex vs Bortezomib + Dex (Doublet, extended therapy)
  • CLARION in ND NTE MM: Carfilzomib 20/36mg/m2 + Melphalan + Prednisolone (MP) vs Bortezomib + MP (Triplet, nine cycles)

• We designed MUK five to assess anti-myeloma activity of carfilzomib versus bortezomib in triplet regimen with Cyclo + Dex at second line only
**MUK five: Design**

**Randomisation** 2:1 (n=300)

**KCd (n=201)** 6 cycles of 28 days (24 weeks)
- Carfilzomib IV 20 mg/m²* 36 mg/m² Days 1, 2, 8, 9, 15, 16
- Cyclophosphamide Oral 500 mg Days 1, 8, 15
- Dexamethasone Oral 40 mg Days 1, 8, 15, 22

*Stratified by:*
- Previous Bortezomib
- β2 microglobulin
- Previous ASCT
- Time from diagnosis

**VCd (n=99)** 8 cycles of 21 days (24 weeks)
- Velcade (bortezomib) SC 1.3 mg/m² Days 1, 4, 8, 11
- Cyclophosphamide Oral 500 mg Days 1, 8, 15
- Dexamethasone Oral 40 mg Days 1, 8, 15

**Primary endpoint (KCd vs. VCd)**
- ≥VGPR at 24 weeks
- Non-inferiority (NI) comparison KCd vs. VCd
- NI margin of 5% (i.e. allowing KCd to be up to 5% worse)
- Designed assuming ≥VGPR = 35% VCd, 45% KCd

*Carfilzomib maintenance (n=69)*
- for up to 18 months
- 6 cycles of 28 days:
  - 36 mg/m² days 1, 2, 15, 16
- then 12 cycles of 28 days:
  - 36 mg/m² days 1, 2

*No maintenance therapy (n=72)*

**Randomisation 1:1 (n=141)**
- Participants with ≥ stable disease
**MUK five: Inclusion/exclusion criteria**

**Key inclusion criteria**
- MM patients at first relapse, or refractory to 1 prior line of therapy
- ECOG 0-2
- Hb ≥ 80g/L, neutrophils ≥1.0x10^9/L, platelets ≥75x10^9/L
- GFR ≥20ml/min
- LVEF ≥40%

**Key exclusion criteria**
- Significant co-morbidity or cardiovascular disease (NYHA Class III/IV heart failure, myocardial infarction within 6 months))
- Uncontrolled hypertension
- Previous carfilzomib therapy
- Previous refractory to bortezomib (<PR or progression within 6 months of last dose)
- Significant neuropathy (G≥3 or G2 with pain) within 14 days
Two Co-Primary Endpoints
• ≥VGPR rate at 24 weeks (non-inferiority activity of KCd)
• PFS (superiority of maintenance treatment with Carfilzomib post-KCd vs no maintenance post-KCd)

Secondary Endpoints
• Key: Rate of ≥G3 neuropathy or ≥G2 neuropathy with pain during the initial treatment period
• Safety, toxicity, overall response, overall survival, time to next treatment
• MRD at end of treatment and after 6 and 12 months of maintenance
• Correlation of treatment outcomes with genetic subgroups
### Patient and disease characteristics

#### Previous bortezomib

<table>
<thead>
<tr>
<th></th>
<th>KCd (n=201) n (%)</th>
<th>VCD (n=99) n (%)</th>
<th>Total (n=300) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous bortezomib</td>
<td>44 (21.9)</td>
<td>21 (21.2)</td>
<td>65 (21.7)</td>
</tr>
</tbody>
</table>

#### Previous ASCT

<table>
<thead>
<tr>
<th></th>
<th>KCd (n=201) n (%)</th>
<th>VCD (n=99) n (%)</th>
<th>Total (n=300) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous ASCT</td>
<td>133 (66.2)</td>
<td>67 (67.7)</td>
<td>200 (66.7)</td>
</tr>
</tbody>
</table>

#### β2 microglobulin

<table>
<thead>
<tr>
<th></th>
<th>KCd (n=201) n (%)</th>
<th>VCD (n=99) n (%)</th>
<th>Total (n=300) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3.5 mg/L</td>
<td>120 (59.7)</td>
<td>57 (57.6)</td>
<td>177 (59.0)</td>
</tr>
<tr>
<td>3.5 to ≤5.5 mg/L</td>
<td>53 (26.4)</td>
<td>27 (27.3)</td>
<td>80 (26.7)</td>
</tr>
<tr>
<td>&gt;5.5 mg/L</td>
<td>28 (13.9)</td>
<td>15 (15.2)</td>
<td>43 (14.3)</td>
</tr>
</tbody>
</table>
### Patient and disease characteristics

<table>
<thead>
<tr>
<th></th>
<th>KCd (n=200)*</th>
<th>VCd (n=99)</th>
<th>Total (n=299)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age: Median (years)</strong></td>
<td>67</td>
<td>69</td>
<td>68</td>
</tr>
<tr>
<td>≥75 years</td>
<td>37 (18.4%)</td>
<td>21 (21.2%)</td>
<td>58 (19.3%)</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>115 (57.5%)</td>
<td>64 (64.6%)</td>
<td>179 (59.9%)</td>
</tr>
<tr>
<td><strong>ECOG PS 0-1</strong></td>
<td>187 (93.5%)</td>
<td>94 (94.9%)</td>
<td>281 (94.0%)</td>
</tr>
<tr>
<td><strong>Median time since diagnosis (months)</strong></td>
<td>32.5</td>
<td>36.1</td>
<td>33.7</td>
</tr>
<tr>
<td><strong>Median time from last tmt (months)</strong></td>
<td>20.1</td>
<td>20.5</td>
<td>20.2</td>
</tr>
<tr>
<td><strong>ISS II / III</strong></td>
<td>100 (50.0%)</td>
<td>45 (45.5%)</td>
<td>145 (48.5%)</td>
</tr>
<tr>
<td><strong>Creatinine clearance &lt;30mL/min</strong></td>
<td>2 (1.0%)</td>
<td>2 (2.0%)</td>
<td>4 (1.3%)</td>
</tr>
<tr>
<td><strong>Received previous autograft</strong></td>
<td>133 (66.2%)</td>
<td>67 (67.7%)</td>
<td>200 (66.7%)</td>
</tr>
<tr>
<td><strong>High risk disease</strong></td>
<td>44/87 (50.6%)</td>
<td>26/50 (52.0%)</td>
<td>70/137 (51.1%)</td>
</tr>
</tbody>
</table>

*No baseline data received for one participant found to be ineligible after randomisation

**At least one of del(17p), gain(1q), t(4;14), t(14;16), t(14;20). Available in 46% of patients.
MUK five: Treatment received

Planned number of cycles

Proportion of patients (%)

Number of cycles started

- KCd
- VCd
## Treatment discontinuation reasons

<table>
<thead>
<tr>
<th>Reasons for not receiving planned number of cycles</th>
<th>KCd (n=201) (%)</th>
<th>VCd (n=99) (%)</th>
<th>Total (n=300) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinician decision</td>
<td>6 (3.0)</td>
<td>11 (11.1)</td>
<td>17 (5.7)</td>
</tr>
<tr>
<td>Unacceptable toxicity</td>
<td>11 (5.5)</td>
<td>18 (18.2)</td>
<td>29 (9.7)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>12 (6.0)</td>
<td>5 (5.1)</td>
<td>17 (5.7)</td>
</tr>
<tr>
<td>Withdrew consent</td>
<td>5 (2.5)</td>
<td>9 (9.1)</td>
<td>14 (4.7)</td>
</tr>
<tr>
<td>Patient died</td>
<td>4 (2.0)</td>
<td>1 (1.0)</td>
<td>5 (1.7)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (1.5)</td>
<td>1 (1.0)</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>41 (20.4)</strong></td>
<td><strong>45 (45.4)</strong></td>
<td><strong>86 (28.7)</strong></td>
</tr>
</tbody>
</table>
MUUK **Five:** Response at 24 weeks

**PRIMARY ENDPOINT MET**

- **CR/VGPR Difference:** 8.3, 90% CI: (-1.6, 18.2)
  - Odds Ratio (OR): 1.48, 90% CI: (0.95, 2.31)
  - NON-INFERIOR

- **Overall response rate**
  - Odds Ratio: 2.72, 90% CI: (1.62, 4.55)
  - SUPERIOR (p=0.0014)

- **MRD Negativity**
  - Odds Ratio: 1.40, 90% CI: (0.61, 3.24)
  - (Total N=134 KCd; 48 VCd)
MUKLfive: Response at 24 weeks by genetic risk

<table>
<thead>
<tr>
<th>Genetic Risk</th>
<th>High risk</th>
<th>Standard Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCd</td>
<td>35.7</td>
<td>30.3</td>
</tr>
<tr>
<td>VCD</td>
<td>17.2</td>
<td>37.5</td>
</tr>
</tbody>
</table>
MUK five: Neuropathy

Treatment emergent neuropathy

Key secondary endpoint:
≥G3 neuropathy or ≥G2 neuropathy with pain

Difference: -18.3%
95% CI: (-26.4, -10.1)
p<0.0001
### MUK five: Safety and toxicity: SAEs

<table>
<thead>
<tr>
<th></th>
<th>KCd (n=196)</th>
<th>VCd (n=96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of SAEs</td>
<td>142</td>
<td>74</td>
</tr>
<tr>
<td>Number of patients with an SAE</td>
<td>88 (44.9%)</td>
<td>45 (46.9%)</td>
</tr>
<tr>
<td>Proportion of SAEs categorized as:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td>0.7%</td>
<td>8.1%</td>
</tr>
<tr>
<td>Cardiac</td>
<td>4.2%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Renal and urinary</td>
<td>3.5%</td>
<td>5.4%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>7.7%</td>
<td>5.4%</td>
</tr>
<tr>
<td>Infections</td>
<td>51.4%</td>
<td>47.3%</td>
</tr>
</tbody>
</table>
### Safety and toxicity: ARs of interest

<table>
<thead>
<tr>
<th>AR Type</th>
<th>Proportion</th>
<th>KCd (n=196)</th>
<th>VCd (n=96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac (all grades)</td>
<td>17 (8.7%)</td>
<td>8 (8.3%)</td>
<td></td>
</tr>
<tr>
<td>Cardiac (≥ Grade 3)</td>
<td>6 (3.7%)*</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Grade ≥3 neutropenia</td>
<td>11.3%</td>
<td>21.9%</td>
<td></td>
</tr>
<tr>
<td>Grade ≥3 thrombocytopenia</td>
<td>11.8%</td>
<td>36.5%</td>
<td></td>
</tr>
<tr>
<td>Grade ≥3 anaemia</td>
<td>16.8%</td>
<td>10.4%</td>
<td></td>
</tr>
<tr>
<td>Grade ≥3 infections</td>
<td>12.8%</td>
<td>16.7%</td>
<td></td>
</tr>
<tr>
<td>Grade ≥2 hypertension</td>
<td>4.1%</td>
<td>2.1%</td>
<td></td>
</tr>
</tbody>
</table>

*Dilated cardiomyopathy, acute coronary syndrome, arrhythmia, myocardial infarction, hypertension, other*
MUK five: Summary and Conclusions

- **MUK five** is the third head-to-head study comparing carfilzomib and bortezomib, and the second study in the relapsed setting.
- Carfilzomib meets the primary endpoint of non-inferiority in $\geq$VGPR rate.
- Overall response rate ($\geq PR$) was higher in patients receiving carfilzomib.
  - This was the case for both high and standard risk patients.
- 81.6% of patients completed KCd treatment compared to 53.5% for VCd.
- Adverse events were consistent with known toxicity profile of each drug.
  - More neurotoxicity with bortezomib but more cardiac AE’s with carfilzomib.
- Additional follow up is needed for evaluation of extended K treatment and PFS readout.
Acknowledgements

Myeloma UK Early Phase Clinical Trial Network
Holger Auner
Catherine Williams
Jamie Cavenagh
Neil Rabin
Karthik Ramasamy
Mamta Garg
Stephen Hawkins
Ceri Bygrave
Gareth Morgan
Faith Davies

Institute of Cancer Research
Martin F Kaiser

Leeds CTRU
Samantha Hinsley
Debbie Sherratt
Sarah Brown
Louise Flanagan
Paul McGarry
Saqib Saghir
Sue Bourne
Emma Ingleston
Katie Robinson
Alan Wan
Wendy Burton
Diane Hartley
Matthew Newby
Lucy Bailey
Suja George
Rachel Naylor
Walter Gregory
Alex Szubert
Jenny Fell

Leeds HMDS
Ruth M de Tute
Roger G Owen

Trial Steering Committee
Chris Twelves
Simon Rule
Tomasz Burzykowski
Michael Brown

Data Monitoring and Ethics Committee
Alan Anthoney
Graham Jackson
James Wason

Recruiting centres
Royal Marsden Hospital
Royal Devon & Exeter
Addenbrookes Hospital
Christie
Leicester Royal Infirmary
New Cross Hospital
Nottingham City Hospital
St James
UCLH
Manchester Royal Infirmary
Countess of Chester Hospital
Grantham Hospital
Lincoln County Hospital
Pilgrim Hospital, Boston
Royal Hallamshire Hospital
Birmingham Heartlands
Royal Bournemouth General Hospital
Southampton General Hospital

Royal Cornwall Hospital
Torbay District General Hospital
St Bartholomew's Hospital
Royal Sussex County Hospital
Oxford
Kings College Hospital
Queens Hospital Burton
George Eliot Hospital
Bristol Haematology and Oncology Centre
Ninewells Hospital
University Hospital of Wales, Cardiff
Beatson West of Scotland Cancer Centre
Princess Royal University Hospital
Ayr Hospital
University Hospital of North Tees
University Hospital Coventry
Imperial College London

MUK five participants

Myeloma UK Early Phase Clinical Trial Network
Leeds CTRU
Leeds HMDS

National Institute for Health Research

Myeloma UK Early Phase Clinical Trial Network
Leeds CTRU
Leeds HMDS

National Institute for Health Research

Myeloma UK Early Phase Clinical Trial Network
Leeds CTRU
Leeds HMDS

National Institute for Health Research

Myeloma UK Early Phase Clinical Trial Network
Leeds CTRU
Leeds HMDS

National Institute for Health Research

Myeloma UK Early Phase Clinical Trial Network
Leeds CTRU
Leeds HMDS

National Institute for Health Research

Myeloma UK Early Phase Clinical Trial Network
Leeds CTRU
Leeds HMDS

National Institute for Health Research

Myeloma UK Early Phase Clinical Trial Network
Leeds CTRU
Leeds HMDS

National Institute for Health Research

Myeloma UK Early Phase Clinical Trial Network
Leeds CTRU
Leeds HMDS

National Institute for Health Research

Myeloma UK Early Phase Clinical Trial Network
Leeds CTRU
Leeds HMDS

National Institute for Health Research

Myeloma UK Early Phase Clinical Trial Network
Leeds CTRU
Leeds HMDS

National Institute for Health Research

Myeloma UK Early Phase Clinical Trial Network
Leeds CTRU
Leeds HMDS

National Institute for Health Research

Myeloma UK Early Phase Clinical Trial Network
Leeds CTRU
Leeds HMDS

National Institute for Health Research

Myeloma UK Early Phase Clinical Trial Network
Leeds CTRU
Leeds HMDS

National Institute for Health Research

Myeloma UK Early Phase Clinical Trial Network
Leeds CTRU
Leeds HMDS

National Institute for Health Research

Myeloma UK Early Phase Clinical Trial Network
Leeds CTRU
Leeds HMDS

National Institute for Health Research

Myeloma UK Early Phase Clinical Trial Network
Leeds CTRU
Leeds HMDS

National Institute for Health Research

Myeloma UK Early Phase Clinical Trial Network
Leeds CTRU
Leeds HMDS

National Institute for Health Research

Myeloma UK Early Phase Clinical Trial Network
Leeds CTRU
Leeds HMDS

National Institute for Health Research

Myeloma UK Early Phase Clinical Trial Network
Leeds CTRU
Leeds HMDS

National Institute for Health Research

Myeloma UK Early Phase Clinical Trial Network
Leeds CTRU
Leeds HMDS

National Institute for Health Research

Myeloma UK Early Phase Clinical Trial Network
Leeds CTRU
Leeds HMDS

National Institute for Health Research

Myeloma UK Early Phase Clinical Trial Network
Leeds CTRU
Leeds HMDS

National Institute for Health Research

Myeloma UK Early Phase Clinical Trial Network
Leeds CTRU
Leeds HMDS

National Institute for Health Research

Myeloma UK Early Phase Clinical Trial Network
Leeds CTRU
Leeds HMDS

National Institute for Health Research

Myeloma UK Early Phase Clinical Trial Network
Leeds CTRU
Leeds HMDS

National Institute for Health Research

Myeloma UK Early Phase Clinical Trial Network
Leeds CTRU
Leeds HMDS

National Institute for Health Research

Myeloma UK Early Phase Clinical Trial Network
Leeds CTRU
Leeds HMDS

National Institute for Health Research

Myeloma UK Early Phase Clinical Trial Network
Leeds CTRU
Leeds HMDS

National Institute for Health Research