Frailty-Adjusted Therapy in Transplant Non-Eligible Patients with Newly Diagnosed Multiple Myeloma

David A Cairns1, Charlotte Pawlyn2,3, Kara-Louise Royle1, Phillip Best1, Bryony Dawkins1, Rowena Henderson1, Jenny Bird3, Stella Bowcock4, Kevin Boyd5,6, Mark Drayson7, Matthew Jenner8, John Jones9, Martin Kaiser2,3, Bhuvan Kishore10, David Meads11, Rebecca Mottram1, Neil Rabin11, Roger Owen12, Graham Johnson11, Gordon Cook14

Background

Outcomes for transplant non-eligible (TNE) myeloma patients have improved with the use of combination therapy including proteasome inhibitors (PI) and immunomodulatory (IMiD) agents.

Progression-free survival and overall survival in MRC-IX and NCRI-XI TNE pathways

It remains a challenge to deliver therapy to older TNE patients with a greater rate of modifications, resulting in fewer cycles of treatment being delivered and a greater percentage of patients ceasing treatment due to toxicity.

Dose modifications, number of cycles of induction and reason for ceasing induction treatment in NCRI-XI CRD group (n=928)

International Myeloma Working Group (IMWG) Frailty Score: TNE myeloma patients are heterogeneous and are not well defined on the basis of age, but rather by the interplay of age, physical function, cognitive function and comorbidity better defined as ‘frailty’.

IMWG frailty score defined by: age, the Katz Activity of Daily Living (ADL), the Lawton Instrumental Activity of Daily Living (IADL), and the Charlson Comorbidity Index (CCI).

Trial Design and Schema

A national, phase III, multi-centre, (double blind) randomised controlled trial

Bone marrow and blood sample consent and registration at the time of diagnostic bone marrow procedure, where possible*

Following confirmation of myeloma diagnosis: Full informed consent and trial registration

Eligibility confirmation, frailty indexing (age, Charlson index, ADL and IADL), and (for consenting participants) QL and Healthcare resource use questionnaires

Randomisation 1 (R1) (n = 740)

Standard IRD

Frailty score-adjusted IRD

Response assessed after each cycle in line with IMWG Uniform Response Criteria. Frailty score repeated after cycle 2, 4, 6 and 12th. QoL & HFE questionnaires after cycles 2, 4, 6 and 12th (for consenting participants)

Or months from R1 if off trial prior to progression

Randomisation 2 (R2) (n = 478)

R + placebo vs R + I maintenance (1:1 randomisation)

R + I maintenance

Response assessed after each cycle in line with IMWG Uniform Response Criteria. Frailty score repeated after maintenance cycles 6 and 12th. QoL & HFE questionnaires after maintenance cycles 8 and 12th (for consenting participants)

Or months from R2 if off trial prior to progression

Primary objectives:

- Early treatment cessation (within 60 days of R1)
- Progression-free survival (PPS, from R2)

Secondary objectives:

- PFS for R1, overall survival, overall response rate, treatment compliance, toxicity and safety including second primary malignancies, Quality of Life, cost effectiveness.

Sample size:

- Interim statistical summaries will be presented to the Data Monitoring and Ethics Committee at approximately yearly intervals. Two formal interim analyses will be undertaken for early efficacy.
- The trial will start with 50% of required participants have reached 60 post-R1. The second when 50% of required PPS events have been observed (151 events) following R2.
- No other formal analysis of the study is planned before the primary endpoints have been attained.

Monitoring and Statistical Analysis:

Interim statistical summaries will be presented to the Data Monitoring and Ethics Committee at approximately yearly intervals. Two formal interim analyses will be undertaken for early efficacy. The trial will start with 50% of required participants have reached 60 post-R1. The second when 50% of required PPS events have been observed (151 events) following R2. No other formal analysis of the study is planned before the primary endpoints have been attained.

Status:

The trial is due to open at >70 centres in the UK in January 2020.