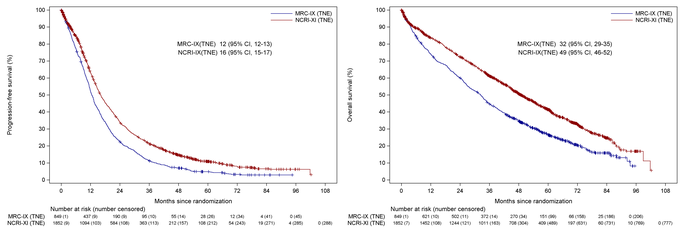
Frailty-Adjusted Therapy in Transplant Non-Eligible Patients with Newly Diagnosed Multiple Myeloma

David A Cairns[1], Charlotte Pawlyn[2,3], Kara-Louise Royle[1], Phillip Best[1], Bryony Dawkins[4], Rowena Henderson[1], Jenny Bird[5], Stella Bowcock[6], Kevin Boyd[2,3], Mark Drayson[7], Matthew Jenner[8], John Jones[9], Martin Kaiser[2,3], Bhuvan Kishore[10], David Meads[4], Rebecca Mottram[1], Neil Rabin[11], Roger Owen[12], Graham Jackson[13], Gordon Cook[1,14]

Background

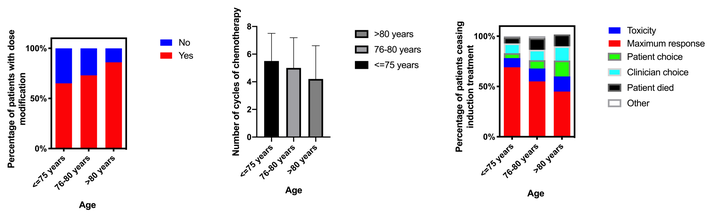
Background:

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

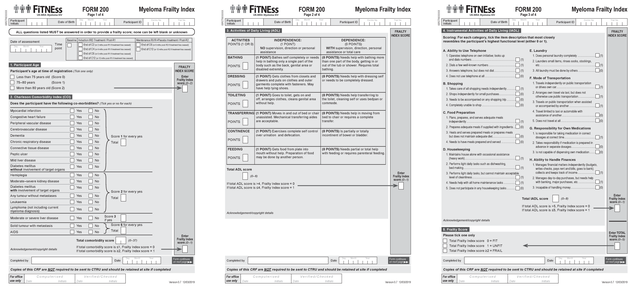
It remains a challenge to deliver therapy to older TNE patients with a greater rate of modifications, resulting in fewer cycles of treatment being delivered and a greater percentage of patients ceasing treatment due to toxicity.



Dose modifications, number of cycles of induction and reason for ceasing induction treatment in NCRI-XI CRDa 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*

*NB: If considering patient for inclusion in the trial, please obtain consent to send diagnostic bone marrow and a peripheral blood sample to trial central laboratories at the time of the procedure

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) QoL and Healthcare resource use questionnaires

Randomisation 1 (R1) (n = 740)
Standard (reactive) *vs* Frailty score-adjusted (adaptive) (1:1 randomisation)

Standard IRD
28-day cycle

	STANDARD DOSE	Days
I	4mg	1, 8, 15
R	25mg	1-21
D	40mg if age ≤75yrs 20mg if age >75 yrs	1, 8, 15, 22

Frailty score-adjusted IRD
28-day cycle

	FIT	UNFIT	FRAIL	Days
I	4mg	4mg	4mg	1, 8, 15
R	25mg	15mg	10mg	1-21
D	40mg	20mg	10mg	1, 8, 15, 22

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

*Or months from R1 if off trial prior to progression

In the absence of disease progression or intolerance, treat for 12 cycles, then assess end of induction response

≥ Minimal response

Stable Disease or Disease Progression

Treat off-trial
Annual follow-up

Randomisation 2 (R2) (n = 478)
R + placebo *vs* R + I maintenance (1:1 randomisation)

R + placebo maintenance
28-day cycle
R – 10 mg† D1 – 21
Placebo – 4 mg† D1, 8, 15
† or final doses administered at the end of induction treatment if lower

R + I maintenance
28-day cycle
R – 10 mg† D1 – 21
I – 4 mg† D1, 8, 15
† or final doses administered at the end of induction treatment if lower

Response assessed after each cycle in line with IMWG Uniform Response Criteria
Frailty Score repeated after maintenance cycles 6 and 12*
QoL & HE questionnaires after maintenance cycles 6 and 12* (for consenting participants)

*Or months from R2 if off trial prior to progression

Continue until disease progression or intolerance

Post-progression annual follow-up for survival

Trial Details

Hypothesis:

- By defining patient subgroups using the IMWG frailty score, we can personalise therapy to improve treatment tolerability and short-term outcome.
- By using a maintenance doublet with IMiD and PI and, we can improve long-term outcome.

Participants:

Newly diagnosed TNE patients according to the 2014 IMWG diagnostic criteria. FiTNEss is an all-comers study. Exclusions include patients with grade≥2 peripheral neuropathy, current systemic infection, recent surgery or other cancer are excluded.

Randomisation:

Minimisation with a random element.

Stratification factors	
R1	**R2**
• Centre	• Centre
• IMWG frailty category (Fit, Unfit, Frail)	• Allocated induction group (standard, frailty-adjusted)
• Beta-2 microglobulin (<3.5, 3.5–<5.5, ≥5.5 mg/L)	• Response to induction (<VGPR, >VGPR)
• Haemaglobin (<100, ≥100 g/L)	
• Serum creatinine (<175, ≥175 μmol/L)	
• Corrected serum calcium (<2.75, ≥2.75 mmol/L)	
• Platelets (<150, ≥150 x10⁹/L)	

Primary objectives:

- Early treatment cessation (within 60 days of R1)
- Progression-free survival (PFS, 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:

R1		R2		
Proportion of patients ceasing treatment*		**Median PFS (months)**		
Standard	0.20	R	21	Hazard ratio 0.72
Frailty-adjusted	0.09	I+R	29	
		Number of events#	302	
N_{R1}	324	N_{R2}	478	
N_{TOTAL} = 740†				
Significance level = 5%, power = 80%				

*Amongst intermediate-fitness and frail participants. #In 3 years of recruitment and 2 years of follow-up.
†Total sample size assumes 65% of patients are progression-free at 12 months to pass through R2

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 first when 50% of required participants have reached 60 days post-R1. The second when 50% of required PFS 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.

Affiliations: 1. Clinical Trials Research Unit, University of Leeds, Leeds; 2. The Institute of Cancer Research, London; 3. The Royal Marsden Hospital, London; 4. Academic Unit of Health Economics, University of Leeds, Leeds; 5. University Hospitals Bristol NHS Foundation Trust, Bristol; 6. King's College Hospital Foundation Trust, Orpington; 7. Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham; 8. Southampton University Hospitals NHS Trust, Southampton; 9. King's College Hospital NHS Foundation Trust; 10. Birmingham Heartlands Hospital, Birmingham; 11. University College London Hospital, London; 12. Haematological Malignancy Diagnostic Service (HMDS), St James's University Hospital, Leeds; 13. Department of Haematology, Newcastle University, Newcastle; 14. Leeds Institute of Medical Research at St James's, Leeds.

Sponsor: University of Leeds

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Contact: d.a.cairns@leeds.ac.uk; g.cook@leeds.ac.uk; ctru_myelomaxiv@leeds.ac.uk

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