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Personalising treatment for myeloma patients based on initial response to NHS treatment and their overall fitness level

Submission date
07/08/2025

Recruitment status
Recruiting

Registration date
01/06/2026

Overall study status
Ongoing

Last Edited
14/07/2026

Condition category
Cancer

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
iFIT is a trial for newly diagnosed transplant-ineligible patients with the bone marrow cancer myeloma. These patients are generally older and have a lower level of fitness than others.

Who can participate?
Patients can take part if their doctor would otherwise recommend the standard NHS treatment daratumumab, lenalidomide and dexamethasone (DRd).

What does the study involve?
After six months of DRd, the subsequent treatment a patient receives in iFIT is based on two factors: the patient's fitness level and treatment response. The trial compares different treatment strategies to determine whether outcomes can be improved for specific patient groups.

What are the possible benefits and risks of participating?
Benefits:
This research study will look at participants' individual results following a period of standard of care induction treatment to determine further treatment. This is a form of personalised treatment. This may or may not be a better approach to treating myeloma compared to the usual approach to treatment in the NHS. Some of the further treatment combinations are not available in the NHS, and participants could receive the new immunotherapy treatments earlier than would be the case in their usual care. The goal of this research study is to gain a greater understanding of these new treatment options and how they compare to each other. By taking part participants will be helping to answer important questions which may improve treatment for people with myeloma now and in the future.
Risks:
There are potential risks associated with the research study as well as potential side effects from the trial treatments. A small number of patients may develop additional types of cancer, and this risk may be increased with lenalidomide treatment. The new immunotherapy treatments teclistamab and talquetamab are associated with cytokine release syndrome (CRS)

and immune effector cell-associated neurotoxicity syndrome (ICANS) which usually occur after the first few doses. Hospital doctors will help to prevent these serious side effects with additional medications, and participants are asked to remain close or stay in hospital for monitoring when starting these treatments. Participants will also be advised not to drive a car or operate machinery whilst starting these treatments or if they have any neurological side effects. Some medications, and complementary health supplements such as St John's Wort, should not be used during this study as they may interact with the study medications.

Where is the study run from?
The study will be run by the Clinical Trials Research Unit (CTRU) at the University of Leeds. The study will be conducted in multiple hospitals throughout the UK.

When is the study starting and how long is it expected to run for?
June 2026 to May 2037

Who is funding the study?
This research study is funded by Cancer Research UK and Blood Cancer UK, and Johnson & Johnson Innovative Medicine. Johnson & Johnson Innovative Medicine will also provide some of the treatments used in this research (daratumumab, teclistamab and talquetamab).

Who is the main contact?
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Additional identifiers

Integrated Research Application System (IRAS)
1010810

Central Portfolio Management System (CPMS)
70417

Study information

Scientific Title
Immunotherapy approaches adapted for fitness in newly diagnosed transplant ineligible patients with Myeloma

Acronym
iFIT (UK-MRA Myeloma XVIII)

Study objectives
Primary objectives:
There are several primary objectives for this trial, specific to each randomisation pathway. The overarching aim is to explore the optimum treatment strategy for each participant based on response to six cycles of DRd induction therapy and International Myeloma Working Group (IMWG) frailty subgroup. The primary objectives are:
• iFIT1 (MRD positive and FIT/UNFIT): To determine the impact on progression-free survival when switching from daratumumab, lenalidomide and dexamethasone (DRd) maintenance therapy to progression to either daratumumab with teclistamab (Dara-Tec) for a fixed duration or daratumumab with talquetamab (Dara-Tal) for a fixed duration for participants who are MRD positive and FIT/UNFIT by IMWG frailty after six cycles of DRd induction therapy.
• iFIT2 (MRD positive and FRAIL): To determine the impact on event-free survival when switching from DRd maintenance therapy to progression to daratumumab and lenalidomide (DR)

maintenance therapy to progression for participants who are MRD positive and FRAIL by IMWG frailty after six cycles of DRd induction therapy.
• iFIT3 (MRD negative): To determine the impact on progression-free survival and participant-reported overall health and quality of life, when switching from DR maintenance therapy to progression to DR maintenance therapy for 18 cycles only for participants who are MRD negative after six cycles of DRd induction therapy.

Secondary objectives:
To assess the impact on the secondary endpoints of:
• iFIT1: switching from DRd maintenance therapy to progression to either Dara-Tec for a fixed duration or Dara-Tal for a fixed duration.
• iFIT2: switching from DRd maintenance therapy to progression to DR maintenance therapy to progression.
• iFIT3: switching from DR maintenance therapy to progression to DR maintenance therapy for 18 cycles only.

The exploratory and translational objectives are:
• To perform an investigation into bone disease and therapy: observe and understand current UK bone therapy practice and investigate how it impacts on various bone and clinical myeloma outcomes, in order to generate hypotheses to inform future research in this area, and
• To collect patient samples at key timepoints to enable the delivery of key translational endpoints.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 08/10/2025, South Central - Oxford C Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 207 104 8089; oxfordc.rec@hra.nhs.uk), ref: 25/SC/0279

Primary study design
Interventional

Study design
Multi-centre, open-label, phase III platform trial with three randomised-controlled parallel-group components of transplant non-eligible patients with newly diagnosed multiple myeloma

Study type(s)
Efficacy, Safety

Health condition(s) or problem(s) studied
Multiple myeloma; plasma cell leukemia (PCL)

Interventions
All participants receive six cycles of standard of care induction treatment with DRd. Each treatment cycle is 28 days.

At the end of the six cycles, participants will undergo an MRD response assessment and an assessment for frailty according to the IMWG Frailty Index to be categorised as FIT, UNFIT or FRAIL.

Participants who are MRD positive and FIT/UNFIT are assigned to the iFIT1 pathway and are randomised 1:1:1 to continuing DRd treatment until progressive disease vs receiving daratumumab with teclistamab for a fixed duration vs receiving daratumumab with talquetamab for a fixed duration.

Participants who are MRD positive and FRAIL are assigned to the iFIT2 pathway and are randomised 1:1 to continuing DRd treatment until progressive disease vs continuing DR treatment until progressive disease.

Participants who are MRD negative are assigned to the iFIT3 pathway and are randomised 1:1 to continuing DR treatment until progressive disease vs continuing DR treatment for 18 cycles.

Participants randomised to a treatment for a fixed duration will be actively monitored until progressive disease.

Randomisation will be completed using a computer generated minimisation program that incorporates a random element to ensure that all arms are well balanced for specific participant characteristics, details of which will be required at randomisation.

Daratumumab is given as an injection under the skin.
Lenalidomide is taken by mouth (orally) as capsules.
Dexamethasone is taken by mouth as either liquid, soluble or hard tablets. It may also be given as an injection into the vein.
Teclistamab is given as an injection under the skin.
Talquetamab is given as an injection under the skin.

Lenalidomide and dexamethasone dosing can be adjusted for frailty and renal function.

The duration of trial treatment for individual participants will vary, as treatment will continue for a fixed duration, until disease progression or intolerable toxicity. For participants not receiving treatment for a fixed duration, it is expected that a participant will receive trial treatment for an average of 62 months: they will receive six cycles of DRd induction, followed by a median of 56 cycles of treatment thereafter. All treatment cycles last for 28 days.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Daratumumab, lenalidomide, dexamethasone, DARZALEX [daratumumab], TECVAYLI [teclistamab], TALVEY [talquetamab]

Primary outcome(s)
Measured using eCRFs and patient records, unless otherwise indicated. If disease response is required, this is measured in accordance with the IMWG Uniform Response Criteria for Multiple Myeloma.

iFIT1: Progression-free survival, measured as the time from iFIT1 randomisation to progression or death from any cause. Participants alive and progression-free at the time of analysis will be censored at their last known date to be alive and progression-free.

iFIT2: Event-free survival, measured as the time from iFIT2 randomisation to the first of the following events: grade 4 haematological adverse events (AEs) (anaemia, neutropenia, thrombocytopenia), grade 3 and 4 non-haematological AEs (including secondary primary malignancies; SPMs), discontinuation of trial treatment, progression or death. Events will be graded according to NCI-CTCAE V5. Participants event-free at the time of analysis will be censored at their last date known to be alive and event-free.

iFIT3: iFIT3 has co-primary endpoints. Progression-free survival, measured as the time from iFIT3 randomisation to progression or death from any cause. Participants alive and progression-free at the time of analysis will be censored at their last known date to be alive and progression-free. Participant-reported overall health and quality of life, measured using the EORTC QLQ-C30 global health status (GHS)/QoL scale score at 30 months after iFIT3 randomisation.

Key secondary outcome(s)

Measured using eCRFs and patient records, unless otherwise indicated. If disease response is required, this is measured in accordance with the IMWG Uniform Response Criteria for Multiple Myeloma.

1. Progression-free survival (iFIT2 only), measured from iFIT2 randomisation to progression or death from any cause. Participants alive and progression-free at the time of analysis will be censored at their last known date to be alive and progression-free.
2. Time to progression, measured from iFIT1/iFIT2/iFIT3 randomisation to first documented evidence of disease progression. Participants who died without progression will be censored at their date of death. Participants alive and progression-free at the time of analysis will be censored at their last known date to be alive and progression-free.
3. Time to second PFS event, measured from iFIT1/iFIT2/iFIT3 randomisation to the second documented evidence of PD or death from any cause. Participants alive and for whom a second progression has not been observed at the time of analysis will be censored at their last known date to be alive and second progression-free.
4. Overall survival, measured from iFIT1/iFIT2/iFIT3 randomisation to death from any cause. Participants alive at the time of analysis will be censored at their last known date to be alive.
5. Event-free survival (iFIT1 only), measured from iFIT1 randomisation to the first of the following events: grade 4 haematological AEs (anaemia, neutropenia, thrombocytopenia), grade 3 and 4 non-haematological AEs (including SPMs), discontinuation of trial treatment, progression, or death. Participants event-free at the time of analysis will be censored at their last date known to be alive and event-free.
6. Survival after progression, measured from first documented evidence of disease progression to death from any cause. Participants alive at the time of analysis will be censored at their last known date to be alive. This endpoint is only defined for those who experience progression.
7. Time to next treatment, measured from registration to the date of commencement of next treatment. Participants who do not receive next line treatment will be censored at the date of the last assessment or follow-up visit where they are known to have received no new therapy.
8. Overall response rate, the disease response category (sCR, CR, VGPR, PR, MR, SD, or PD) measured at the end of standard of care induction DRd treatment, and further timepoints up to approximately 30 months post-iFIT1/iFIT2/iFIT3 randomisation, dependent on treatment pathway.
9. Attainment of ≥VGPR, the binary disease response category (≥VGPR: sCR, CR, VGPR vs. <VGPR: PR, MR, SD, PD) measured at the same timepoints as overall response rate.

10. Attainment of MRD negativity, the binary MRD status category (negative vs. positive) measured using flow cytometry at the same timepoints as overall response rate. MRD negativity is defined as at least a serological VGPR and MRD negative bone marrow aspirate at the 10^-5 threshold.
11. Maximum response, at any point after iFIT1/iFIT2/iFIT3 randomisation.
12. Time to improved response, measured from iFIT1/iFIT2/iFIT3 randomisation to first recorded improved response, where the baseline response is that recorded at the start of randomised treatment (iFIT1/iFIT2/iFIT3 cycle 1, day 1). Participants whose disease progresses or who die before an improved response is recorded will be censored at the time of progression or death, respectively. Participants alive with no improved response recorded at the time of analysis will be censored at their last known date to be alive.
13. Treatment compliance, including whether all cycles of treatment were completed, the number of cycles completed, the total dose of each trial medication received, the number and causes of dose omissions, dose delays, and dose reductions.
14. Toxicity and safety based on the adverse events reported as graded by NCI-CTCAE v5. Pregnancies will also be reported.
15. Incidence of secondary primary malignancies reported during standard of care induction DRd treatment and following iFIT1/iFIT2/iFIT3 randomisation.
16. Incidence, rate, and type of infections, measured using the proportion of participants experiencing an infection of any type or grade as graded by NCI-CTCAE v5 during standard of care induction DRd treatment and following iFIT1/iFIT2/iFIT3 randomisation.
17. Quality of life, measured using the EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-IL413 questionnaires at the start of DRd induction, end of DRd induction, and further timepoints up to 30 months post-randomisation. This will also be measured using the EORTC QLQ-IL414 questionnaire at the start and end of standard of care induction DRd and in iFIT1 only, and the Scale of Subjective Total Taste Acuity questionnaire at the end of standard of care induction DRd and in iFIT1 only.
18. Objective measures of function, measured using the 4 metre walk test and mini-cog assessments at the start of, after 3 cycles, and at the end of standard of care induction DRd.
19. Cost-utility, measured using costs, QALYs and net health benefit (QALYs below £20,000).

Exploratory endpoints include the following and are to be defined in the statistical analysis plan:
1. Bone therapy planned and prescribed
2. Dental assessment received during the trial
3. Bone disease (including skeletal-related events; SREs) experienced during the trial
4. Infection interactions and infection risk (iFIT1 only)

Translational endpoints are yet to be defined by the translational research teams.

Completion date
31/05/2037

Eligibility

Key inclusion criteria
Inclusion criteria for registration:
1. Newly diagnosed as having symptomatic MM, plasma cell leukaemia or non-secretory MM according to IMWG diagnostic criteria 2014,
2. Considered not suitable to receive autologous stem cell transplant as part of their first line therapy by the treating clinician,
3. Planned for treatment with Daratumumab, Lenalidomide and dexamethasone (DRd) as first

line therapy as standard of care,
4. Aged 18 years or greater,
5. Able to provide full informed consent, and
6. Prepared to comply with pregnancy prevention plan.

Inclusion criteria for randomisation into all iFIT1/iFIT2/iFIT3 pathways:
• Completed 6 cycles of DRd induction therapy after registering within the iFIT study,
• Able to provide full informed consent, and
• Prepared to comply with pregnancy prevention plan.

Inclusion criteria specific to randomisation pathways:
• Dexamethasone may have been stopped due to toxicity and the participant will remain eligible (iFIT1 and iFIT3),
• Planned to continue on at least daratumumab (monthly) and lenalidomide (at any dose level) (iFIT1 and iFIT3),
• Planned to continue on all three DRd medications (dose reductions are allowed) (iFIT2),
• Achieved a partial response (PR) biochemically (irrespective of MRD status) or achieved a ≥VGPR and are MRD positive, as confirmed by HMDS (central laboratory) (iFIT1 and iFIT2),
• Achieved a ≥VGPR and are MRD negative, as confirmed by HMDS (central laboratory) (iFIT3),
• Categorised as FIT or UNFIT according to the IMWG frailty index (iFIT1),
• Categorised as FRAIL according to the IMWG frailty index (iFIT2), and
• Meet the blood criteria specified in the protocol within 14 days before randomisation (haematological and biochemical) (iFIT1).

Full inclusion criteria are listed in the protocol.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
0

Key exclusion criteria
Exclusion criteria for registration:
1. Smouldering myeloma (SMM), primary amyloidosis, solitary plasmacytoma of bone or extramedullary plasmacytoma (without additional evidence of myeloma),
2. Pregnant, breastfeeding, plans to become pregnant, or plans to father a child whilst enrolled in the study or within 3 months after the last dose,
3. Previous treatment for myeloma, except as specified in the protocol,
4. Active systemic viral, fungal or bacterial infection requiring systemic therapy. Criteria for

specific chronic infections clarified in the protocol, or
5. Participation in any other interventional study for myeloma that involves an IMP during treatment and active monitoring.

Exclusion criteria for randomisation into all iFIT1/iFIT2/iFIT3 pathways:
• Received systemic anti-myeloma therapy other than DRd prior to randomisation. Steroids given (by any route) for reasons other than myeloma disease control are allowed,
• Received a stem cell transplant,
• Participation in any other interventional study for myeloma that involves an IMP during treatment and active monitoring, and
• Pregnant, breast feeding, plans to become pregnant, or plans to father a child whilst enrolled in the study or within a specified period after the last dose.

Exclusion criteria specific to randomisation pathways:
• Stable disease (SD) or progressive disease (PD) as per IMWG response criteria (iFIT1 and iFIT2),
• Partial response (PR), stable disease (SD) or progressive disease (PD) as per IMWG response criteria (iFIT3), and
• Further exclusion criteria related to safety of interventions (iFIT1).

Full exclusion criteria are listed in the protocol.

Date of first enrolment
26/06/2026

Date of final enrolment
30/06/2030

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
-
-
-
England
-

Sponsor information

Organisation
University of Leeds

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK

Funder Name
Blood Cancer UK

Alternative Name(s)
Blood Cancer UK Research

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Funder Name
Johnson & Johnson Innovative Medicine

Results and Publications

Individual participant data (IPD) sharing plan
De-identified individual participant data datasets generated and/or analysed during the current study will be available upon request from the Clinical Trials Research Unit, University of Leeds (contact CTRU-DataAccess@leeds.ac.uk in the first instance). Data will be made available at the end of the trial, i.e. usually when all primary and secondary endpoints have been met and all key analyses are complete. Data will remain available from then on for as long as CTRU retains the data.

CTRU makes data available by a 'controlled access' approach. Data will only be released for legitimate secondary research purposes, where the Chief Investigators, Sponsor and CTRU agree

that the proposed use has scientific value and will be carried out to a high standard (in terms of scientific rigour and information governance and security), and that there are resources available to satisfy the request. Data will only be released in line with participants' consent, all applicable laws relating to data protection and confidentiality, and any contractual obligations to which the CTRU is subject. No individual participant data will be released before an appropriate agreement is in place setting out the conditions of release. The agreement will govern data retention, usually stipulating that data recipients must delete their copy of the released data at the end of the planned project.

The CTRU encourages a collaborative approach to data sharing, and believe it is best practice for researchers who generated datasets to be involved in subsequent uses of those datasets. Recipients of trial data for secondary research will also receive data dictionaries, copies of key trial documents and any other information required to understand and reuse the released datasets.

The conditions of release for aggregate data may differ from those applying to individual participant data. Requests for aggregate data should also be sent to the above email address to discuss and agree suitable requirements for release.

IPD sharing plan summary

Available on request