

Mesothelioma Stratified Therapy (MiST): A multi-drug phase II trial in malignant mesothelioma

Submission date 18/09/2018	Recruitment status No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
Registration date 01/10/2018	Overall study status Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
Last Edited 30/08/2022	Condition category Cancer	<input type="checkbox"/> Individual participant data

Plain English summary of protocol

<https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-targeted-drugs-for-mesothelioma-mist>

Study website

www.mesothelioma-research-leicester.com/mist/

Contact information

Type(s)

Scientific

Contact name

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Additional identifiers

EudraCT/CTIS number

2017-003353-41

IRAS number

ClinicalTrials.gov number
NCT03654833

Secondary identifying numbers
0627

Study information

Scientific Title

Mesothelioma Stratified Therapy (MiST): A stratified multi-arm phase II clinical trial to enable accelerated evaluation of targeted therapies for relapsed malignant mesothelioma.

Acronym

MiST

Study objectives

1. Following standard platinum treatment, does the proposed IMP intervention exhibit a significant disease control rate response in biomarker selected malignant mesothelioma?
2. What are the genomic characteristics of exceptional responders or chemo-refractory tumours in the MiST trial?

Ethics approval required

Old ethics approval format

Ethics approval(s)

East Midlands - Leicester South Research Ethics Committee, 05/07/2018, 18/EM/0118

Study design

Interventional non-randomised study

Primary study design

Interventional

Secondary study design

Non randomised study

Study setting(s)

Hospital

Study type(s)

Treatment

Participant information sheet

Not available in web format, please contact: MiSTmailbox@leicester.ac.uk to request a participant information sheet.

Health condition(s) or problem(s) studied

Mesothelioma

Interventions

Current intervention as of 30/08/2022:

Stage 1 of this study is a molecular pre-screening. Patients with relapsed mesothelioma will be offered to consent for molecular panel testing of their diagnostic tumour block for predictive biomarkers.

Stage 2 is the treatment stage. The MiST treatment protocol will be specific to the treatment allocated to the patient, based on the results of their biomarker testing in stage 1. Specific agent(s) are as follows:

1. MiST1: Rucaparib for patients with BRCA1/BAP1 negative mesothelioma (600 mg twice daily (BID) every 28 days) for 6 cycles. Closed to recruitment.

2. MiST2: Abemaciclib for patients with p16INK4A negative mesothelioma (200 mg orally twice daily (BID) every 28 days) for 6 cycles. Closed to recruitment.

3. MiST3: Pembrolizumab & bemcentinib. There is no specific biomarker requirement.

Bemcentinib will be administered orally once daily every 21 days for 8 cycles. On the first 3 days of administration, the dose will be a loading dose of 400 mg (days 1, 2 and 3); from day 4 onwards, patients will receive a daily dose of 200 mg. Pembrolizumab will be given at a fixed dose of 200 mg via intravenous infusion (IV) on day 1 of each 21 day cycle for 8 cycles. - closed to recruitment.

4. MiST4: Atezolizumab & bevacizumab for patients with PDL1 expression positive mesothelioma. Atezolizumab will be given at a dose of 1200 mg via intravenous infusion (IV) and bevacizumab will be given at a dose of 15 mg/kg via intravenous infusion (IV). Both drugs will be given on day 1 every 21 days for 8 cycles. Closed to recruitment.

5. MiST 5: Dostarlimab and niraparib in Patients with platinum-sensitive relapsed mesothelioma. Niraparib will be administered once daily depending on patient's weight and platelet count. A cycle consists of 21 days and there will be up to 35 cycles in total:

5.1. ≥ 77 kg and $\geq 150,000$ μ L 300 mg (3 X 100 mg capsules)

5.2. < 77 kg or $< 150,000$ μ L 200 mg (2 X 100 mg capsules)

Dostarlimab will be given at a fixed dose of 500 mg via IV infusion on Day 1 of each 21-day cycle for 4 cycles. Followed by 1000 mg via IV infusion on Day 1 of each 42-day cycle for up to 24 months.

Stage 3 involves molecular profiling, to understand the genomic basis of drug response in the MiST trial. Archival tumour tissue from all patients enrolled will be interrogated using molecular inversion probe-based microarray analysis of the somatic copy number aberrations. Optional re-biopsy of patients who progress on treatment, followed confirmed radiological response, will be offered, to investigate genomic interrogation of tumours at the time of acquired resistance. For arms 3, 4 & 5, immune checkpoint, transcriptomic and gut microbiome correlative studies are planned.

Previous intervention:

Stage 1 of this study is a molecular pre-screening. Patients with relapsed mesothelioma will be offered to consent for molecular panel testing of their diagnostic tumour block for predictive biomarkers. The results of this assessment will be used to classify patients into one of several possible molecularly defined treatment arms. Patients will therefore be offered a specific study treatment determined by their molecular profile. Patients, who exhibit positive testing in more than one biomarker, will potentially be eligible to subsequently be treated on a different treatment protocol upon disease progression or treatment failure.

Stage 2 is the treatment stage. The MiST treatment protocol will be specific to the treatment allocated to the patient, based on the results of their biomarker testing in stage 1. Specific agent (s) are as follows:

1. MiST1: Rucaparib for patients with BRCA1/BAP1 negative mesothelioma (600 mg twice daily (BID) every 28 days) for 6 cycles
2. MiST2: Abemaciclib for patients with p16INK4A negative mesothelioma (200 mg orally twice daily (BID) every 28 days) for 6 cycles.
3. MiST3: Pembrolizumab & Bemcentinib. There is no specific biomarker requirement. Bemcentinib will be administered orally once daily every 21 days for 8 cycles. On the first 3 days of administration, the dose will be a loading dose of 400 mg (days 1, 2 and 3); from day 4 onwards, patients will receive a daily dose of 200 mg. Pembrolizumab will be given at a fixed dose of 200 mg via intravenous infusion (IV) on day 1 of each 21 day cycle for 8 cycles.
4. MiST4 Atezolizumab & Bevacizumab for patients with PDL1 expression positive mesothelioma. Atezolizumab will be given at a dose of 1200mg via intravenous infusion (IV) and Bevacizumab will be given at a dose of 15 mg/kg via intravenous infusion (IV). Both drugs will be given on day 1 every 21 days for 8 cycles.

Stage 3 involves molecular profiling, to understand the genomic basis of drug response in the MiST trial. Archival tumour tissue from all patients enrolled will be interrogated using molecular inversion probe-based microarray analysis of the somatic copy number aberrations. Optional re-biopsy of patients who progress on treatment, followed confirmed radiological response, will be offered, to investigate genomic interrogation of tumours at the time of acquired resistance. For arms 3 and 4, immune checkpoint, transcriptomic and gut microbiome correlative studies are planned.

Intervention Type

Drug

Phase

Phase II

Drug/device/biological/vaccine name(s)

Rucaparib, abemaciclib, pembrolizumab, bemcentinib, atezolizumab, bevacizumab, dostarlimab, niraparib

Primary outcome measure

Disease control rate (DCR) after 12 weeks, assessed using modified RECIST 1.1 criteria with CT scan evidence. Scans will be undertaken every 6 weeks and analysis will be timed from study entry using the baseline CT scan results until completion of the treatment cycles, confirmed disease progression or death (whichever occurs first)

Secondary outcome measures

1. Disease control rate (DCR) after 24 weeks, assessed using modified RECIST 1.1 criteria with CT scan evidence. Scans will be undertaken every 6 weeks and analysis will be timed from study entry using the baseline CT scan results until completion of the treatment cycles, confirmed disease progression or death (whichever occurs first)
2. Objective response rate (ORR), assessed using modified RECIST 1.1. criteria with CT scan evidence for 12 months (up to 6 months during treatment and 6 months of follow-up)
3. Safety, assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) criteria for up to 6 months during treatment and 6 months of follow-up
4. Adverse events, recorded in relation to each cycle of treatment and graded according to CTCAE criteria. The incidence of each adverse event (all grades and grade 3/4) will be reported

as a per-patient-cycle rate and as a per-patient rate. Investigators expect patients to participate in the study for a maximum of 6 months of treatment and 6 months of follow-up; however we cannot guarantee that some patients may participate over 12 months

5. Toxicity, assessed according to CTCAE criteria for up to 6 months during treatment and 6 months of follow-up

Overall study start date

01/04/2017

Completion date

01/10/2023

Eligibility

Key inclusion criteria

Pre-screening:

1. Histologically confirmed MM with an available biopsy for research purposes
 2. Aged 18 years or older
 3. Expected survival of ≥ 12 weeks or greater
 4. Eastern Cooperative Oncology Group (ECOG) performance status 0-1
 5. CT scan of chest and abdomen (and pelvis if applicable) confirming disease progression
 6. Received at least one prior line of therapy to include a platinum doublet first-line chemotherapy (within or outside of another clinical trial)
 7. Willing to consent for molecular screening of archived tumour block (PIS1 & CF1)
- Each individual MiST drug protocol contains the eligibility criteria specific to the treatment allocated to the patient and these are yet to be finalised.

Participant type(s)

Patient

Age group

Adult

Lower age limit

18 Years

Sex

Both

Target number of participants

200

Key exclusion criteria

Pre-screening:

1. Diagnosis of a second malignancy except prostate or cervical cancer in remission, or a diagnosis of basal cell carcinoma of the skin or superficial bladder cancer
2. Uncontrolled CNS disease (asymptomatic brain metastases are allowed if previously treated with radiotherapy > 28 days prior to starting the investigational agent)
3. New York Heart Association Class II or greater congestive heart failure
4. Severe hepatic insufficiency or severe renal impairment

5. Requiring long term oxygen therapy.

6. Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial

Date of first enrolment

01/01/2019

Date of final enrolment

31/01/2023

Locations

Countries of recruitment

England

United Kingdom

Study participating centre

University Hospitals of Leicester NHS Trust

Leicester Royal Infirmary

Infirmary Square

Leicester

United Kingdom

LE1 5WW

Study participating centre

The Christie NHS Foundation Trust

550 Wilmslow Road

Withington

Manchester

United Kingdom

M20 4BX

Study participating centre

The Newcastle upon Tyne Hospitals NHS Foundation Trust

Freeman Hospital

Freeman Road

High Heaton

Newcastle upon Tyne

United Kingdom

NE7 7DN

Study participating centre**Wythenshawe Hospital**

Southmoor Road
Wythenshawe
Manchester
United Kingdom
M23 9LT

Study participating centre**Southampton**

Southampton General Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD

Sponsor information

Organisation

University of Leicester

Sponsor details

Research Governance Office
Academic Departments
Leicester General Hospital
Leicester
England
United Kingdom
LE5 4PW

Sponsor type

University/education

Website

www.le.ac.uk

ROR

<https://ror.org/04h699437>

Funder(s)

Funder type

Not defined

Funder Name

British Lung Foundation

Alternative Name(s)

BLF

Funding Body Type

Private sector organisation

Funding Body Subtype

Trusts, charities, foundations (both public and private)

Location

United Kingdom

Results and Publications

Publication and dissemination plan

The results of the trial will be published in a high-impact peer reviewed scientific journal around six months after each individual trial treatment protocol has completed.

Intention to publish date

01/06/2020

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are/will be available for sharing via controlled access by authorised University of Leicester staff (as delegated by the trial sponsor) and anonymised IPD within the clinical trial dataset will be available for sharing via open access after the trial is published.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	MiST1	01/06/2021	28/06/2022	Yes	No
Results article	MiST2	01/03/2022	28/06/2022	Yes	No
HRA research summary			28/06/2023	No	No