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MESOTHELIOMA UK

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	MESO-PRIME	MiST
Trial title	Pembrolizumab and Hypofractionated Stereotactic Radiotherapy in patients with Malignant Pleural Mesothelioma	A stratified multi-arm phase IIa clinical trial to enable accelerated evaluation of targeted therapies for relapsed malignant mesothelioma
Type	CTIMP	Second line and beyond
Treatment/study focus	Malignant Pleural Mesothelioma (MPM)	Molecular Pre-screening, Drug Treatment, Genomic Profiling
Phase	Phase I	Phase IIa
Sponsor	Royal Marsden NHS Foundation Trust	University of Leicester
Drug companies involved	Funding provided by MSD	Clovis Oncology, Inc. I Eli Lilly and Company I GSK I Merck Sharp & Dohme Corp. (MSD) I BerGenBio ASA I Roche Pharma AG
Principal investigator	Chief Investigator: Dr Fiona McDonald (Royal Marsden) Dr Fiona McDonald = Royal Marsden PI Dr Nicola Steele = Beatson PI	Principal Investigator: Professor Anne Thomas Scientific Lead: Professor Dean Fennell
Contact	mesoprime.trial@rmh.nhs.uk	MiST Management Team: MiSTmailbox@leicester.ac.uk
Description	This is a non-randomised open-label phase 1 trial of pembrolizumab given in combination with SBRT to part of a pleural-based lesion in patients with unresectable MPM. This study will recruit up to 18 patients whose MPM has progressed beyond first-line of palliative chemotherapy, with a platinum-based doublet, and now requires further palliative systemic treatment, or have declined first-line palliative chemotherapy, however must have been considered suitable for a platinum doublet chemotherapy	Stage 1 - molecular pre-screening: The MiST Master protocol describes the identification of patients, biomarker testing and analysis. 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 - Treatment: 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) will be detailed separately in each of the separate treatment protocols. Stage 3 - Molecular Profiling : In order 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 For MiST 5: For Dostarlimab, 1 cycle of treatment constitutes 21 days of treatment for cycles 1 – 4, and 42 days from cycle 5 onwards. For Niraparib, 1 cycle constitutes 21 days of treatment. Both will take a total of 24 weeks. If patients are benefitting after 8 cycles of study treatment have been received they may be able to continue receiving treatment either in combination or as a monotherapy.
Randomised? Y/N	No	No
Treatment Schedule	Part A – Initial safety cohort Patients will receive an initial dose of pembrolizumab in week 1 dosed at 200 mg. They will then receive SBRT dosed at 30 Gy in 3 fractions (#) alternate days in week 3. Treatment with pembrolizumab will be continued dosed at 200 mg given every 3 weeks. Part B – Expansion cohort. An additional 12 patients will be recruited for this cohort. Patients will receive an initial dose of pembrolizumab at 200 mg in week 1. This will be followed in by SBRT dosed at 30 Gy in 3 fractions (#) alternate days in week 3. Treatment with pembrolizumab will be continued dosed at 200 mg given every 3 weeks.	A course of treatment will be defined as follows: (For MiST1 & MiST2: 1 cycle of treatment constitutes 28 days of treatment therefore all 6 cycles/a course will take a total of 24 weeks). If patients are benefitting after all 6 cycles of study treatment have been received may be able to continue receiving treatment. (For MiST3 & MiST4: 1 cycle of treatment constitutes 21 days of therapy therefore all 8 cycles/a course will take a total of 24 weeks). If patients are benefitting after all 8 cycles of study treatment have been received may be able to continue receiving treatment either in combination or as a monotherapy.
Treatment route	Intravenous Pembrolizumab and External Beam Stereotactic Body Radiotherapy (SBRT)	Oral tablet and IV depending on treatment arm – please see below.
Drugs used	Pembrolizumab	MiST4 Atezolizumab & Bevacizumab. *Recruiting* No specific biomarker requirement: Atezolizumab 1200 milligrams via intravenous infusion; Bevacizumab 15 milligrams per kilogram via IV infusion both on Days 1 every 21-days. Add: MiST5 Dostarlimab & Niraparib. Recruiting No specific biomarker requirement – platinum sensitivity (response or stable disease, but not progression as their best response to first line or re-challenge platinum doublet therapy): Dostarlimab 500mg IV infusion on Day 1 of each 21 day cycle for 4 cycles, followed by 1000mg on Day 1 of each 42 day cycle from cycle 5 onwards. Niraparib orally once daily for each 21 day cycle, with starting dose of 300mg or 200mg MiST1 Rucaparib. *Fully recruited.*: BRCA1/BAP1 negative mesothelioma; 600mg twice daily (BID) every 28 days. MiST2 Abemaciclib. *Fully recruited.*: p16INK4A negative mesothelioma; 200mg orally twice daily every 28 days. MiST3 Pembrolizumab & Bemcentinib. *Fully Recruited*: No specific biomarker requirement: Pembrolizumab 200mg IV infusion on Day 1 only: Bemcentinib loading dose of 400mg on days 1-3, on day 4 onwards 200mg daily every 21-days.
Entry criteria	1. Patients should be ≥18 years old on the day of signing the informed consent. 2. Patients must have a histological or cytological diagnosis of MPM. 3. Patients should have non-radically treatable MPM (i.e. not being considered for extrapleural pneumonectomy or pleurectomy and decortication). 4. Patients must have measurable disease as assessed by mRECIST. 5. Patients must have had disease progression or be intolerant of standard first-line palliative chemotherapy for MPM. Patients who have declined first-line palliative chemotherapy must have been suitable for platinum-doublet combination chemotherapy. 6. Patient should have an ECOG performance status 0-1 7. Patients should be able to tolerate a course of SBRT as assessed by the investigator. 8. Patients should have pleural-based disease, away from critical structures, suitable for treatment to part of lesion with SBRT. 9. Patients must have adequate organ function including MRC dyspnoea score <3 and adequate baseline lung function tests, with an FEV1 >0.8L or >30% of predicted and a TLCO >30% 10. Demonstrate adequate organ function as detailed in Table 2 (based on bloods within 10 days of C1D1). 11. Have provided tissue from an archival tissue sample or newly obtained tissue sample. 12. Female patient of childbearing potential should have a negative serum pregnancy within 72 hours prior to receiving the first dose of study medication (C1D1). 13. Female patients of childbearing potential should be willing to use highly effective methods of contraception for the course of the study through 120 days after the last dose of study medication. 14. Male patients should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy. 15. Be willing to provide informed consent for the trial.	1. Histologically confirmed MM with an available biopsy for research purposes 2. Male or female patients aged ≥18 years. 3. Expected survival of ≥12 weeks or greater 4. ECOG PS 0-1 5. CT scan chest, abdomen (and pelvis if applicable) confirming disease progression. 6. Patients must have 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)
Exclusion criteria	1. Patients who have taken any investigational medicinal product or have used an investigational device within 4 weeks of the first dose of pembrolizumab. Patients are allowed to participate in additional observational studies. 2. Patients who have received prior chemotherapy, targeted small molecule therapy or radiotherapy within 4 weeks prior to the first dose of pembrolizumab. 3. Patients with a diagnosis of immunodeficiency or be receiving systemic steroid therapy (>7.5 mg of prednisone / >1 mg of dexamethasone or their equivalent dose) or any other form of immunosuppressive therapy within 7 days prior to the first dose. 4. Patients with evidence of active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents or an autoimmune disease that is currently quiescent off any treatment, but deemed at risk of a significant flare if treated on this protocol. 5. Patients who have received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways). 6. Patients with evidence of active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided the brain metastases are stable and there is no evidence of new or enlarging brain metastases. 7. Patients who have had previous radiotherapy to the thorax or other neighbouring region that would preclude the safe administration of SBRT for MPM. 8. Patients with evidence of interstitial lung disease, or history of pneumonitis (including non-infectious pneumonitis) that required steroids, or current pneumonitis (including non-infectious pneumonitis). 9. Patients with evidence of additional malignancy that is progressing or requires active treatment. 10. Patients with a history or current evidence of any condition, therapy, or laboratory abnormality that might confound trial results, interfere with the patient's participation or is not in the best interest of the patient. 11. Patients with psychiatric or substance abuse disorders that would interfere with patients participation. 12. Patients who are pregnant / breastfeeding or expecting to conceive within the duration of the trial, starting with the screening visit through 120 days after the last dose. 13. Patients with a history of HIV, HIV 1/2 antibodies, Hepatitis B or Hepatitis C. 14. Patients with any active infection requiring systemic treatment 15. Patients who have received a live vaccine within 30 days prior to the first dose of trial treatment. 16. Patients with known hypersensitivity to the active substance pembrolizumab or to any of the excipients listed in the IB.	1. Patients with a diagnosis of a second malignancy except prostate or cervical cancer in remission, patients with 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. Patients with severe hepatic insufficiency or severe renal impairment. 5. Patients 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.
Performance status criteria	Patient should have an ECOG performance status 0-1	0-1
Participants required	18	200 – pre-screening, 26 in to each treatment arm
No. of participants to date	3	MiST Master : 146 patients recruited, MiST 1: Complete, MiST 2: Complete, MiST 3: 17 patients recruited, MiST 4: Complete, MiST 5: 0 patients recruited
Centres opening & recruiting	Beatson West of Scotland Cancer Centre - Open to recruitment Royal Marsden NHS Foundation Trust - Open to recruitment	Currently open and recruiting: Northern Centre for Cancer Care, Newcastle Southampton General Hospital The Christie in Manchester University Hospitals of Leicester NHS Trust In setup: Wythenshawe
Where can patients get more information?	https://clinicaltrials.gov/ct2/show/NCT04166734?term=NCT04166734&draw=2&rank=1 or mesoprime.trial@rmh.nhs.uk	https://clinicaltrials.gov/ct2/show/NCT03654833
Where can healthcare professionals get more information?	https://clinicaltrials.gov/ct2/show/NCT04166734?term=NCT04166734&draw=2&rank=1 or mesoprime.trial@rmh.nhs.uk	MiSTmailbox@le.ac.uk

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	BEAT-Meso Limited slots available on request	SYSTEMS-2	ASSESS-MESO
Trial title	ETOP 13-8 Bevacizumab and atezolizumab in malignant pleural mesothelioma. A multicentre randomised phase III trial comparing atezolizumab plus bevacizumab and standard chemotherapy versus bevacizumab and standard chemotherapy as first-line treatment for advanced malignant pleural mesothelioma	SYSTEMS-2: A Randomised Phase II trial of standard versus dose escalated radiotherapy in the treatment of pain in malignant pleural mesothelioma	A prospective observational cohort study collecting data on demographics, symptoms and biomarkers in people with mesothelioma that will provide a resource for future trials
Type	First line	Radiotherapy	Non-interventional, observational
Treatment/study focus	Drug treatment / all histological subtypes of malignant pleural mesothelioma	Radiotherapy for pain control	To collect information about mesothelioma and the people who develop it, their symptoms, and how things change over time, whilst also screening participants for clinical trial participation.
Phase	Phase III	Phase II	N/A
Sponsor	European Thoracic Oncology Platform (ETOP)	Sponsor: Beatson Cancer Charity and June Hancock Mesothelioma Research Fund Academic Institution: University of Glasgow	North Bristol NHS Trust
Drug companies involved	F. Hoffman-La Roche Ltd.	None	None
Principal investigator	Prof. Sanjay Popat (Trial Co-Chair)	Professor Anthony Chalmers	Dr Anna Bibby
Contact	Maria.Piga@rmh.nhs.uk (Lead Clinical Research Nurse)	Dr Miranda Ashton (Clinical Oncology Registrar) Miranda.ashton@ggc.scot.nhs.uk	Anna.bibby@bristol.ac.uk (PI) Jenny Symonds (Study coordinator)
Description	This is a randomised, open-label, multicentre phase III trial. Patients will be randomly assigned (1:1) to one of two treatment arms: 1) control arm: standard chemotherapy (carboplatin and pemetrexed) and bevacizumab, or 2) treatment arm: standard chemotherapy (carboplatin and pemetrexed) and bevacizumab plus atezolizumab. The efficacy (whether the treatment works), safety and tolerability (side effects of treatment) of atezolizumab plus bevacizumab in combination with standard chemotherapy versus bevacizumab in combination with standard chemotherapy will be investigated in the first-line treatment of advanced malignant pleural mesothelioma	A randomised, multicentre trial of radiotherapy dose escalation for pain control in malignant pleural mesothelioma. Patients will be randomised to receive either standard dose radiotherapy (20Gy in 5 treatments) over 1 week, or a higher dose (36Gy in 6 treatments) over 2 weeks. The aim of the trial is to assess whether the higher dose of radiotherapy is more effective for pain 5 weeks after the start of treatment. Methods of radiotherapy delivery which limit the dose received by normal tissues will be used to minimise side effects.	We want to learn more about mesothelioma, specifically whether there are any patient characteristics, factors relating to the tumour, or blood tests that will allow us to predict which patients might respond better to chemotherapy or other treatments, or to live longer. We also want to know about people's symptoms and how these may change over time. ASSESS-meso is a 'real-life' study that will collect information from patients at their routine clinic appointments. This information includes symptom scores, imaging such as x-rays, ultrasounds and CT scans, and blood tests and collection of pleural fluid (if present). We will also screen participants to see if there are any clinical trials they may be eligible for. If you are not having regular appointments in hospital, there is an option to undergo telephone study assessments.
Randomised? Y/N	Yes	Yes	No
Treatment Schedule	Treatment arm 1 (control): • 4-6 cycles of: standard chemotherapy (carboplatin + pemetrexed) plus bevacizumab followed by maintenance bevacizumab Treatment arm 2 (experimental): • 4-6 cycles of standard chemotherapy (carboplatin + pemetrexed) plus bevacizumab plus atezolizumab followed by maintenance bevacizumab plus atezolizumab ** Drugs will be given every 3 weeks until progression, refusal or unacceptable toxicity*	• Visit 1: Screening visit (up to 1 month before radiotherapy) • Visit 2: Baseline visit (up to 1 week before radiotherapy) • Visit 3: Final day of radiotherapy • Visit 4: Week 5 after the start of radiotherapy • Visit 5: Week 9 after the start of radiotherapy • Visit 6: Week 26 after the start of the radiotherapy	Study assessment visits will be co-ordinated with routine clinic appointments
Treatment route	Intravenous	External beam radiotherapy	All participants will continue to receive treatment as usual whilst participating in this study.
Drugs used	Treatment arm 1 (control): carboplatin, pemetrexed, and bevacizumab Treatment arm 2 (experimental): carboplatin, pemetrexed, bevacizumab, and atezolizumab	No drugs used (radiotherapy trial) Treatment arm: 36Gy in 6 fractions delivered over 2 weeks Control arm: 20Gy in 5 fractions delivered over 1 week	All participants will continue to receive treatment as usual whilst participating in this study.
Entry criteria	1. Histologically confirmed advanced malignant pleural mesothelioma (all histological subtypes are eligible) 2. Not amenable for radical surgery based on local standards 3. Evaluable disease or measurable disease as assessed according to the modified response evaluation criteria for solid tumours for mesothelioma (mRECIST) v1.1 4. Availability of tumour tissue for translational research 5. Age ≥18 years 6. Performance Status 0-1 7. Life expectancy ≥3 months 8. Adequate haematological, renal and liver function 9. Completed baseline quality of life (QoL) questionnaire 10. Women of childbearing potential and sexually active men must agree to use highly effective contraception 11. Able to understand and give written informed consent and comply with trial procedures	1. Malignant pleural mesothelioma (histological or MDT diagnosis) 2. Predicted life expectancy >12 weeks 3. CT scan within 8 weeks of starting radiotherapy 4. Worst pain score ≥ 4/10 after analgesia optimisation 5. Radiotherapy plan compatible with treatment arm (36Gy/6 fractions or 30Gy in 5 fractions) prior to randomisation	Any patient with mesothelioma, whose diagnosis has been confirmed at multidisciplinary team meeting, and who is willing (and able) to attend study follow up assessments.
Exclusion criteria	1. Prior treatment for malignant pleural mesothelioma 2. Treatment with systemic immune-stimulatory agents within 4 weeks or five half-lives of the drug prior to randomisation and during protocol treatment. 3. Treatment with systemic immunosuppressive medications within 2 weeks prior to randomisation and during protocol treatment. 4. Previous allogeneic tissue/solid organ transplant 5. Live vaccines within 4 weeks prior to first dose of protocol treatment 6. Inadequately controlled hypertension 7. Prior history of hypertensive crisis or hypertensive encephalopathy 8. Significant vascular disease within 6 months prior to randomisation 9. History of haemoptysis	1. Anticancer therapy 4 weeks prior to study entry or 6 weeks after radiotherapy 2. Patients who have previously received palliative radiotherapy and where there is concern that the proposed treatment volume would overlap with the previously irradiated area. This does not include patients who have received superficial photon or electron therapy to drain sites 3. Coexisting lung tumours at the time of study entry	1. Age <18 years old 2. Unable to give written informed consent 3. Declines ongoing hospital follow up
Performance status criteria	0-1	0-2	All
Participants required	320 randomised patients in total	112	700
No. of participants	44	81	208
Centres opening & recruiting	Limited slots available on request in UK: Addenbrooke's | Royal Marsden Hospital - Chelsea, Sutton | Royal Cornwall Hospital (Truro) | Guy's and St Thomas' Hospital | Kent Oncology Centre (Maidstone) | Plymouth Hospitals NHS Trust | Clatterbridge Cancer Centre | Weston Park Hospital (Sheffield) | Wythenshawe Hospital. 45 centres in 8 European countries (Belgium, France, Italy, Portugal, Slovenia, Spain, Switzerland, United Kingdom)	Aberdeen | Beatson, Glasgow | Belfast City Hospital | The Christie Hospital | Churchill Hospital. Oxford | Forth Valley Royal Hospital, Larbert | Guy's and St Thomas', London | Kent and Canterbury Hospital | Leeds | Maidstone | New Cross Hospital, Wolverhampton | Royal Shrewsbury Hospital | Southend University Hospital, Essex | The Royal Marsden | University Hospital Southampton | Western General, Edinburgh | Weston Park Hospital, Sheffield	**Sites currently open:** Bath | Hywel Dda | Leicester | Manchester | NHS Greater Glasgow and Clyde | North Bristol | Northumbria Healthcare NHS Foundation | Oxford | Papworth | Pennine Acute Hospitals NHS Trust (North Manchester) | Plymouth | Sherwood Forest Hospitals Foundation Trust | Taunton | University Hospitals of Derby and Burton NHS Foundation Trust | Wales - Velindre Cancer Centre **Sites in set up:** Norfolk & Norwich | Northern General Hospital | Sheffield | South Tyneside **Other interested sites:** Mid & South Essex NHS Foundation Trust | University Hospitals Morecambe Bay NHS Trust
Where can patients get more information?	https://clinicaltrials.gov/ct2/show/study/NCT03762018	Their local clinical oncologist miranda.ashton@ggc.scot.nhs.uk www.systems-2.co.uk	anna.bibby@bristol.ac.uk (PI)
Where can healthcare professionals get more information?	Maria.Piga@rmh.nhs.uk (Lead Clinical Research Nurse)	laura.alexander@glasgow.ac.uk miranda.ashton@ggc.scot.nhs.uk www.systems-2.co.uk	anna.bibby@bristol.ac.uk