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MESOTHELIOMA UK

September 2020
Last Updated: 2nd September 2020

	BEAT-Meso	ATOMIC-meso	MiST 3	BAY2287411	DENIM
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	Randomized, Double-Blind, Phase 2/3 Study in Subjects with Malignant Pleural Mesothelioma to Assess ADI-PEG 20 with Pemetrexed and Cisplatin (ATOMIC-Meso Phase 2/3 Study)	A stratified multi-arm phase IIa clinical trial to enable accelerated evaluation of targeted therapies for relapsed malignant mesothelioma	An Open-label, First-in-human, Multi-center Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Anti-tumor Activity of a Thorium-227 Labeled Antibody-chelator Conjugate, BAY2287411 Injection, in Patients With Solid Tumors Known to Express Mesothelin	DENdritic Cell Immunotherapy for Mesothelioma (DENIM): A Randomized, Open-Label Phase II/III Study With Dendritic Cells Loaded With Allogeneic Tumour Cell Lysate (PheraLys) in Subjects With Mesothelioma as Maintenance Treatment (MesoPher) After Chemotherapy
Type	First line	First line	Second line and beyond	Second Line	Maintenance
Treatment/study focus	Drug treatment / all histological subtypes of malignant pleural mesothelioma	Non-epithelioid MPM	Molecular Pre-screening, Drug Treatment, Genomic Profiling	Drug treatment	Drug (MesoPher)
Phase	Phase III	Phase II/III	Phase IIa	Phase I	Phase II/III
Sponsor	European Thoracic Oncology Platform (ETOP)	Polaris Pharma	University of Leicester	Bayer	Amphera BV
Drug companies involved	F. Hoffman-La Roche Ltd.	Polaris Pharma	Clovis Oncology, Inc. | Eli Lilly and Company | Merck Sharp & Dohme Corp. (MSD) | BerGenBio ASA | Roche Pharma AG	Bayer	TMC Pharma
Principal investigator	Prof. Sanjay Popat (Trial Co-Chair)	Peter Szlosarek	Principal Investigator: Professor Anne Thomas Scientific Lead: Professor Dean Fennell		UK: Professor Dean Fennell
Contact	Maria.Piga@rmh.nhs.uk (Lead Clinical Research Nurse)	kriedel@polarispharma.com	MiST Management Team: MiSTmailbox@leicester.ac.uk	clinical-trials-contact@bayer.com	Contact Mesothelioma UK for advice
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	This is a phase 2/3, randomised, double-blind trial. Weekly ADI-PEG 20 at 36 mg/m2 (or placebo) will be combined with pemetrexed 500 mg/m2 and cisplatin 75 mg/m2 both given every 3 weeks as first-line chemotherapy to non-epithelioid (biphasic and sarcomatoid) MPM. Eligible subjects will be randomised in a 1:1 ratio to ADIPemCis or PlaceboPemCis. The randomisation will be stratified by histology (biphasic or sarcomatoid). Subjects may receive a maximum of 6, 3-week cycles of ADIPemCis or PlaceboPemCis for a total of 18 weeks of treatment. Those subjects completing ADIPemCis or PlaceboPemCis treatment may continue on ADI-PEG 20 or Placebo monotherapy if they have SD or better. Subjects who do not tolerate cisplatin may be switched to carboplatin.	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	The purpose of this study is to evaluate, in patients with tumors known to express the protein mesothelin, the following properties of BAY2287411 injection: • safety (to identify, assess, minimize, and appropriately manage the risks associated to the study drug) • tolerability (the degree to which side effects can be tolerated by your body) • maximum tolerated dose • pharmacokinetics (the effect of your body on the study drug) • anti-tumor activity • recommended dose for further clinical development	This study is to evaluate the overall survival (OS) rate (determined from the time of randomization in the study) of subjects who receive dendritic cell immunotherapy with MesoPher plus best supportive care (BSC) compared to BSC alone.
Randomised? Y/N	Yes	Yes	No	No	Yes
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	Standard Pem/CIS + Weekly ADI-PEG20 or placebo	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.	Drug: BAY2287411 Dose Escalation part: A single dose will be administered intravenously on Day 1 of each cycle lasting 6 weeks (42 days). Drug: BAY2287411 Dose Expansion part:The selection of the dose level(s) /regimen(s) to be evaluated will be based on the overall benefit / risk and PK profile observed in the dose escalation	The treatment with Mesopher will start within 9 to 13 weeks after the last dose of chemotherapy. Subjects will receive 3 bi-weekly injections with MesoPher in addition to BSC. In case of stable disease or partial/complete response, an additional 2 injections will be given at weeks 18 and 30. Subjects will be administered with a maximum of 5 doses of MesoPher.
Treatment route	Intravenous	Standard Pem/CIS + Weekly ADI-PEG20 or placebo	Oral tablet and IV depending on treatment arm – please see below.	IV	IV
Drugs used	Treatment arm 1 (control): carboplatin, pemetrexed, and bevacizumab Treatment arm 2 (experimental): carboplatin, pemetrexed, bevacizumab, and atezolizumab	Standard Pem/CIS + Weekly ADI-PEG20 or placebo	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 ***Recruiting soon*** No specific biomarker requirement: Pembrolizumab 200mg IV infusion on Day 1 only: Bemcentinib loading dose of 400mg on days 1-3, on day 4 on-wards 200mg daily every 21-days. MiST4 Atezolizumab & Bevacizumab. ***Recruiting*** PDL1 expression positive mesothelioma: Atezolizumab 1200 milligrams via intravenous infusion; Bevacizumab 15 milligrams per kilogram via IV infusion both on Days 1 every 21-days.	Thorium 227	MesoPher
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	1. Histologically proven advanced MPM of biphasic or sarcomatoid histology. 2. Naïve to prior chemotherapy or immunotherapy (i.e. this is a first-line systemic therapy study). 3. Measurable disease as assessed by modified RECIST or RECIST 1.1 4. ECOG performance status of 0 - 1 5. Predicted life expectancy of at least 12 weeks.	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)	1. Signed informed consent 2. Male or female subjects ≥ 18 years of age 3. ECOG PS (Eastern Cooperative Oncology Group Performance Status) of 0 or 1 4. Patients with advanced malignant epithelioid mesothelioma or advanced recurrent serous ovarian cancer, who have exhausted available therapeutic options; in addition, in the dose expansion part of the study, patients with metastatic pancreatic adenocarcinoma, who have exhausted available therapeutic options 5. Availability of fresh or archival tumor tissue samples 6. Adequate bone marrow, liver and renal function, as assessed by pre-defined laboratory requirements (within 28 days before start of study drug treatment) 7. A negative serum pregnancy test in women of childbearing potential (WOCBP) rformed within 7 days before the start of study drug administration. Women and men of reproductive potential must agree to use highly effective methods of contraception, when sexually active	1. Male or female patients aged ≥18 years. 2. Subjects will only be included with a histologically confirmed diagnosis of pleural malignant mesothelioma, who are non-progressive after 4 to 6 cycles with first line chemotherapy with antifolate/platinum.
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. Radiotherapy (except for palliative reasons) the previous two weeks before. 2. Ongoing toxic manifestations of previous treatments. 3. Symptomatic brain or spinal cord metastases. 4. Major thoracic or abdominal surgery from which the patient has not yet recovered. 5. Serious infection requiring treatment with intravenous antibiotics at the time of study entrance or 7 days prior. 6. Known to be serologically positive for human immunodeficiency virus (HIV).	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.	1. Impaired cardiac function, clinically significant cardiac disease or cardiac arrhythmias 2. Pericarditis (any CTCAE grade) or pericardial effusion (CTCAE Grade ≥ 2) 3. Left Ventricular Ejection Fraction (LVEF) < 50% (as measured at screening by echocardiogram). 4. History of anaphylactic reactions to monoclonal antibody therapy 5. History of Myelodysplastic syndrome (MDS)/treatment-related acute myeloid leukemia (t-AML) or with features suggestive of MDS/AML 6. Infections of CTCAE (Common Terminology Criteria for Adverse Events) version 5.0 Grade 2 not responding to therapy or active clinically serious infections of CTCAE Grade >2; known human immunodeficiency virus (HIV) infection; active hepatitis B virus (HBV) or hepatitis C virus (HCV)infection requiring treatment. Patients with chronic HBV or HCV infection are eligible at the investigator's discretion provided that the disease is stable and sufficiently controlled under treatment 7. Known brain, spinal or meningeal metastases	
Performance status criteria	0-1	0-1	0-1	0-1	
Participants required	320 randomised patients in total	386	120 – pre-screening, 26 in to each treatment arm	228	230
No. of participants to date	44	149	MiST Master : 97 patients recruited, MiST 1: Complete, MiST 2: Complete, MiST 4: 6 patiens recruited	Not available	Not available
Centres opening & recruiting	Currently recruiting 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) Being activated: Wythenshawe Hospital. 45 centres in 8 European countries (Belgium, France, Italy, Portugal, Slovenia, Spain, Switzerland, United Kingdom)	Addenbrookes, Cambridge | Barts Cancer Centre, QMU, London | Beatson, Glasgow | Broomfield, Chelmsford | Derriford, Plymouth | Edinburgh | Leicester | Manchester University Hospital | Oxford | Scunthorpe | Southampton | South Manchester | St James', Leeds | Northumbria | Velindre, Cardiff Also USA, Italy and Australia	Northern Centre for Cancer Care, Newcastle University Hospitals of Leicester NHS Trust	Royal Marsden NHS Trust, UK. Also sites in US and Europe	Leicester Also: Belgium, France, Italy, Netherlands,
Where can patients get more information?	https://clinicaltrials.gov/ct2/show/study/NCT03762018	p.w.szlosarek@qmul.ac.uk or https://clinicaltrials.gov/ct2/show/NCT02709512	https://clinicaltrials.gov/ct2/show/NCT03654833	https://clinicaltrials.gov/ct2/show/NCT03507452	https://clinicaltrials.gov/ct2/show/study/NCT03610360
Where can healthcare professionals get more information?	Maria.Piga@rmh.nhs.uk (Lead Clinical Research Nurse)	p.w.szlosarek@qmul.ac.u	MiSTmailbox@le.ac.uk	https://clinicaltrials.gov/ct2/show/NCT03507452	https://clinicaltrials.gov/ct2/show/study/NCT03610360

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	INFINITE	SYSTEMS-2	MARS 2	ASSESS-MESO	NEMO
Trial title	Efficacy & Safety of rAd-IFN Administered With Celecoxib & Gemcitabine in Patients With Malignant Pleural Mesothelioma (INFINITE)	SYSTEMS-2: A Randomised Phase II trial of standard versus dose escalated radiotherapy in the treatment of pain in malignant pleural mesothelioma	Mesothelioma and Radical Surgery 2: a multicentre randomised trial comparing (extended) pleurectomy decortication versus no (extended) pleurectomy decortication for patients with 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	Nintedanib as maintenance treatment of malignant pleural mesothelioma (NEMO): a double-blind randomized phase II study of the EORTC Lung Cancer Group
Type	Second or third line	Radiotherapy	Surgery vs No surgery. All patients receive standard of care chemotherapy	Non-interventional, observational	Maintenance treatment
Treatment/study focus	Drug	Radiotherapy for pain control	Surgery, progression-free survival, serious adverse health events, quality of life and resource use for at least two years, until the end of the study (Sept 2022).	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 participa-	Drug (nintedanib maintenance treatment compared to placebo)
Phase	Phase III	Phase II	Phase III	N/A	Phase 2
Sponsor	Trizell Ltd	Sponsor: Beatson Cancer Charity and June Hancock Mesothelioma Research Fund Academic Institution: University of Glasgow	Sponsor: Royal Brompton and Harefield NHS Foundation Trust Co-ordination and Management: Clinical Trials and Evaluation Unit, University of Bristol Funding: NIHR – HTA Programme (15/188/31)	North Bristol NHS Trust	EORTC
Drug companies involved	Trizell Ltd	None	None	None	Boehringer Ingelheim
Principal investigator	Dr Nicola Steele (Chief Investigator UK)	Professor Anthony Chalmers	Professor Eric Lim, Consultant Thoracic Surgeon, Royal Brompton and Harefield NHS Foundation Trust	Dr Anna Bibby	Dr Sanjay Popat
Contact	Recruiting sites, as listed on http://clinicaltrials.gov/ct2/show/NCT03710876	Dr Miranda Ashton (Clinical Oncology Registrar) Miranda.ashton@ggc.scot.nhs.uk	MARS 2 study team (mars2-trial@bristol.ac.uk)	Anna.bibby@bristol.ac.uk (PI) Jenny Symonds (Study coordinator)	Joanna Krzystyniak (Clinical Operations Manager, EORTC) 08112@eortc.org
Description	This study will evaluate intrapleural administration of Adenovirus-Delivered Interferon Alpha-2b (rAd-IFN) in combination with Celecoxib and Gemcitabine in patients with histologically confirmed Malignant Pleural Mesothelioma (MPM) who have failed a minimum of 1 treatment regimen and a maximum of 2 treatment regimens, 1 of which must have been an anti-folate and platinum combination regimen. Eligible patients will be randomized 1:1 to either: 1. Treatment group: rAd-IFN + Celecoxib followed by Gemcitabine 2. Control group: Celecoxib followed by Gemcitabine Patients randomized to the treatment group will receive rAd-IFN administered into the pleural space via an Intrapleural catheter (IPC) or similar intrapleural device on study Day 1. The primary objective of this study is to compare the overall survival (OS) associated with rAd IFN, when administered with celecoxib and gemcitabine, versus that associated with celecoxib and gemcitabine alone for the treatment of patients with MPM	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.	To compare the effectiveness and cost-effectiveness of (extended) pleurectomy versus no (extended) pleurectomy decortication for treatment of pleural mesothelioma. To test the hypothesis that (extended) pleurectomy decortication and chemotherapy is superior to chemotherapy alone with respect to overall survival.	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.	The primary objective of phase II part of this study is to evaluate activity in terms of progression-free survival of nintedanib versus placebo as switch maintenance after first line chemotherapy treatment for patients with unresectable Malignant Pleural Mesothelioma (MPM).
Randomised? Y/N	Yes	Yes	Yes	No	Yes and double-blinded
Treatment Schedule	Control arm: 14 days celecoxib followed by gemcitabine. 21-day gemcitabine cycles then continue until progression/early termination Treatment arm: rAd-IFN at day 1, 14 days of celecoxib, followed by gemcitabine. 21-day gemcitabine cycles then continue until progression/early termination	• 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	2 cycles chemotherapy followed by surgery/ no surgery, followed by up to 4 cycles of chemotherapy. Follow-up at 6 weeks, 6 months, 12 months, 18 months, 24 months (at routine visit/ phone call/ postal), after 24 months follow up every 6 months by postal questionnaire.	Study assessment visits will be co-ordinated with routine clinic appointments	Nintedanib 200 mg twice daily (one cycle will consist of 28 days);
Treatment route	rAd-IFN (some patients): intrapleural Celecoxib: oral Gemcitabine: IV	External beam radiotherapy	All patients will receive standard of care chemotherapy with either surgery or no surgery.	All participants will continue to receive treatment as usual whilst participating in this study.	Oral
Drugs used	rAd-IFN (treatment arm only); celecoxib & gemcitabine	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 patients will receive the usual standard of care chemotherapy (eg Platinum / Pemetrexed). After 2 cycles, participants will be re-assessed by CT to screen for progressive disease. Patients with no evidence of disease progression beyond the limits of surgical resection will be randomised to either: a) (Extended) pleurectomy decortication OR b) No surgery All patients will then receive the remaining 4 cycles of chemotherapy.	All participants will continue to receive treatment as usual whilst participating in this study.	Nintedanib/matched Placebo
Entry criteria	1. Aged 18 years or older at the time of consent; 2. Able to give informed consent; 3. Has a confirmed histological diagnosis of MPM with histological type epithelioid or biphasic (predominantly [>50%] epithelioid). Histological diagnosis of MPM will be confirmed centrally using specimens or slides from tumor specimens obtained at the time of initial presentation or a subsequent procedure. Central confirmation of diagnosis with immunohistochemistry will be performed, and independent central confirmation will be required for study entry; 4. Measurable disease, per modified Response Evaluation Criteria in Solid Tumor [RECIST] for pleural mesothelioma; 5. Has failed a minimum of 1 treatment regimen and a maximum of 2 treatment regimens, which may have been chemotherapeutic and/or immunotherapeutic treatment regimens for MPM which included at least 1 anti-folate and platinum combination regimen. Patients who have undergone primary surgical resection and/or radiation therapy to the pulmonary site are eligible to participate. For clarity, surgical resection and/or radiation therapy to the pulmonary site are not exclusionary and are not considered a line of therapy; 6. Has a pleural space accessible for pleural catheter insertion. Patients with a previously inserted pleural catheter may be enrolled, and the pre-existing catheter can be used for vector administration as long as it is functional and has no evidence of local infection; 7. Life expectancy >12 weeks in the judgement of the Investigator; 8. Eastern Cooperative Oncology Group (ECOG) status of 1 or 0; 9. Protocol defined contraception requirements 10. Adequate laboratory values at screening	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	1. 16 years of age or over 2. Tissue (cytology or histology) confirmed epithelioid, Sarcomatoid or biphasic mesothelioma 3. Disease confined to one hemi-thorax based on CT assessment 4. Disease deemed surgically resectable 5. Fit for surgery 6. Capacity to provide written informed consent to participate in the trial	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.	1. Histological diagnosis of unresectable Malignant Pleural Mesothelioma (MPM); 2. Response or Stable disease according to modified RECIST criteria after first line platinum-pemetrexed chemotherapy for 4-6 cycles; 3. Last platinum chemotherapy dose administered within 60 days 4. Age >18 years; 5. ECOG performance status (PS) 0-2; 6. Life expectancy of at least 12 weeks in the opinion of the investigator; 7. Other protocol defined inclusion criteria
Exclusion criteria	1. Is "treatment-naïve" (i.e., has not received at least 1 anti-folate and platinum combination regimen); 2. Has previously received 3 or more lines of systemic chemotherapeutic or immunotherapeutic treatment; 3. Has previously received treatment with gemcitabine; 4. Has stage IV extrathoracic metastatic disease; 5. Inadequate pulmonary function of clinical significance as per Investigator review; 6. Clinically significant pericardial effusion (i.e., as judged by the Investigator and/or requiring drainage) detected by computed tomography (CT) scan at Screening; 7. Other protocol defined exclusion criteria	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. Severe shortness of breath (this is defined as an Eastern Cooperative Oncology Group (ECOG) status ≥ 2, or if lung function test are performed: pre-operative forced expiratory volume after one second (FEV1) or transfer factor of the lung for carbon monoxide (TLco) less than 20%); 2. Serious concomitant disorder that would compromise participant safety during surgery (e.g. evidence of end organ failure) 3. Severe heart failure (this is defined as NYHA III or IV or if an echocardiogram is performed an ejection fraction less than 30%) 4. End stage kidney failure requiring dialysis 5. Liver failure (e.g. encephalopathy and/or coagulation abnormalities) 6. Prisoner 7. Patient lacks capacity to consent	1. Age <18 years old 2. Unable to give written informed consent 3. Declines ongoing hospital follow up	1. Prior systemic anticancer therapy for MPM, other than first line platinum-based doublet chemotherapy; 2. Previous extra-pleural pneumonectomy 3. Previous Vascular Endothelial Growth Factor (VEGF) inhibitors 4. Patients that, in the opinion of the investigator, have reduced performance status by 2 ECOG levels (e.g. PS 0 to 2 or PS 1 to 3) from beginning to completion of 1st line chemotherapy; 5. Radiotherapy (with the exception of palliative radiotherapy) during study or within 3 weeks of start of study drug; 6. Active brain metastases (e.g. stable for < 4 weeks) 7. Leptomeningeal metastases 8. Centrally located tumours with radiographic evidence of local invasion of major blood vessels 9. Clinically active cancer other than mesothelioma within 5 years prior to start of study treatment; 10. Other protocol defined exclusion criteria
Performance status criteria	0-1	0-2	0-1	All	0-2
Participants required	300	112	n=328	700	116
No. of participants	11	89	319	113	30
Centres opening & recruiting	Global. US Sites are open. 10 additional countries including UK. Beatson West of Scotland Cancer Centre Churchill Road Hospital, Oxford Derriford Hospital, Plymouth Guys and St. Thomas The Royal Marsden Wythenshawe Hospital, Manchester	Aberdeen | Beatson, Glasgow | Belfast City Hospital | The Christie Hospital | Churchill Hospital. Oxford | Forth Valley Royal Hospital, Larbert | Guy's and St Thomas', London | 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	Medical: Barking | Beatson, Glasgow | Birmingham | Clatterbridge | Colchester | Derby | Maidstone | Manchester | North Bristol Trust | Norwich | Oxford | Papworth | Peterborough | Plymouth | Royal Gwent | Royal Marsden | Sheffield | South Tees (James Cook) | South Tyneside | Wolverhampton Royal Marsden subsites: Sutton, Fulham Road and Kingston Leeds no longer recruiting Surgical and Medical: Guy's and St. Thomas' | Leicester | Sheffield | St. Bartholemews Surgical: Glasgow Golden Jubilee	Study was suspended due to COVID but sites are beginning to reopen now. Churchill Hospital, Oxford Hywel Dda Health Board, West Wales Manchester University Foundation Trust Musgrove Park Hospital Royal United Hospital Bath Southmead Hospital, Bristol University Hospitals Leicester University Hospitals Plymouth NHS Trust Further sites planned across the UK, TBC later this year.	Activated sites: East & North Hertfordshire NHS Trust Maidstone Hospital Mount Vernon Hospital Musgrove Park Hospital (Taunton & Somerset NFT) Royal Marsden Hospital - Chelsea, Kingston & Sutton South Tyneside District Hospital Weston Park Hospital (Sheffield Teaching Hospitals NFT) Wythenshawe Hospital (MFT)
Where can patients get more information?	http://clinicaltrials.gov/ct2/show/NCT03710876 www.myinfinitestudy.com	Their local clinical oncologist miranda.ashton@ggc.scot.nhs.uk www.systems-2.co.uk	mars2-trial@bristol.ac.uk https://clinicaltrials.gov/ct2/show/NCT02040272	anna.bibby@bristol.ac.uk (PI)	Patients should contact their doctor to get further information. Patients interested in participation within this catchment area should discuss this with their physician who may contact the trial team.
Where can healthcare professionals get more information?	http://clinicaltrials.gov/ct2/show/NCT03710876 www.myinfinitestudy.com	laura.alexander@glasgow.ac.uk miranda.ashton@ggc.scot.nhs.uk www.systems-2.co.uk	mars2-trial@bristol.ac.uk https://clinicaltrials.gov/ct2/show/NCT02040272	anna.bibby@bristol.ac.uk	https://clinicaltrials.gov/ct2/show/NCT02863055 08112@eortc.org http://www.eortc.org/research_field/clinical-detail/08112/