MESOTHELIOMA UK

Supporting People With This Asbestos Cancer

June 2017 Issue

	VIM	SYSTEMS-2	MARS 2	PROMISE-meso	ATOMIC-meso	LUME-MESO	ASyMS-meso	CheckMate 743	CONFIRM	MesoTRAP
Trial title	A randomised phase II trial of oral vinorelbine as second line therapy for patients with 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 pilot study to determine if it is feasible to recruit into a randomised trial comparing (ex-tended) pleurectomy decortication versus no pleurectomy decortication in the multimo-dality management of patients with malignant pleural mesothelioma	PembROlizuMab Immunotherapy versus Standard chemotherapy for advanced prE-treated malignant pleural mesothelioma	Ph 2/3 Study in Patients With malignant pleural mesothelioma (MPM) w/Low ASS 1 Expression to Assess ADI-PEG 20 With Pemetrexed and Cisplatin (ATOMIC)	Double Blind, Randomised, Multicentre, Phase II/III Study of Nintedanib in Combination With Pemetrexed / Cisplatin Followed by Continuing Nintedanib Monotherapy Versus Placebo in Combination With Pemetrexed / Cisplatin Followed by Continuing Placebo Monother-apy for the Treatment of Patients With Unresectable Malignant Pleural Mesothelioma	Real-Time Symptom Assessment using the Advanced Symptom Management System (ASyMS) for Patients with Malignant Pleural Mesothelioma (MPM): a Feasibility Study	A Phase III, Randomized, Open Label Trial of Nivolumab in combination with Ipilimumab versus Pemetrexed with Cisplatin or Carboplatin as First Line Therapy in unresectable Pleural Mesothelioma	CONFIRM: Checkpoint blockade for inhibition of relapsed mesothelioma	A pilot clinical trial and feasibility study comparing video-assisted thoracoscopic partial pleurectomy/decortication (VAT-PD) with indwell-ing pleural catheter (IPC) in patients with trapped lung.
Type	Second Line	Radiotherapy	Surgery vs No surgery. All patients receive standard of care chemotherapy	International, multi-centre, randomised, phase III, pre-treated patients (2nd+ line)	First line	First Line	Test of a medical device	First Line	Third line	Surgery versus insertion of indwelling pleural catheter
Treatment/study focus	Drug treatment	Radiotherapy for pain control	Surgery, patient experience and quality of life	Trial to demonstrate superiority of pembrolizumab versus standard chemotherapy	Non-epithelioid MPM	This is a Phase II/III confirmatory study designed to evaluate the safety and efficacy of nintedanib (BIBF 1120) in combination + (pemetrexed / cisplatin) followed by nintedanib (BIBF 1120) versus placebo + pemetrexed / cisplatin followed by placebo for the treatment of patients with unresectable malignant pleural mesothelioma	Symptom Management and Quality of Life	Drug	Drug	Symptom management for patients with trapped lung
Phase	Phase II	Phase II	Phase II (Pilot study)	Phase III	Phase II/III	Phase III	N/A	Phase III	Phase III	Feasibility, pre-Phase III
Sponsor	Academic Institution: University of Leicester	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: Papworth Hospital NHS Foundation Trust Funding: Cancer Research UK (Grant number: CRUK/12/030)	ETOP	Polaris Pharma	Boehringer Ingelheim	Academic institution: University of Strathclyde	Bristol-Myers Squibb	Academic institution: University of Southampton	Papworth Hospital NHS Foundation Trust
Drug companies involved	Pierre Fabre	None	None	Merck Sharp & Dohme Corp	Polaris Pharma	Boehringer Ingelheim	None	Bristol-Myers Squibb	Bristol Myers Squibb (BMS)	N/A
Principal investigator	Professor Dean Fennell	Professor Anthony Chalmers	Mr Eric Lim, Consultant Thoracic Surgeon, Royal Brompton and Harefield NHS Foundation Trust	Trial Chairs: Sanjay Popat (UK), Alessandra Curioni-Fontecedro (Switzerland) Trial Co-Chair: Solange Peters (Switzerland)	Peter Szlosarek	Dr Sanjay Popat (Royal Marsden Hospital)	Prof Roma Maguire	Prof Dean Fennell	Prof Dean Fennell	Dr Robert Rintoul
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Description	Patients will be randomised (1:2) to receive either active symptom control (ASC) or ASC with vinorelbine. Patients will continue vinorelbine treatment until evidence of disease progression (or unacceptable toxicity to the drug or patient withdrawal). If vinorelbine activity is demonstrated.	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.	The objective of the trial is to determine if it is feasible to recruit patients with malignant pleural mesothelioma with disease amenable to surgical resection into a trial of (extended) pleurectomy decortication (lung sparing surgery) versus no surgery. All patients will receive standard of care. The pilot component will also assess if there is any evidence of harm associated with (extended) pleurectomy decortication.	Randomised phase III multicentre clinical trial to demonstrate superiority of pembrolizumab versus standard, institutional-choice chemotherapy (gemcitabine or vinorelbine) in patients progressing after previous platinum-based chemotherapy. Patients randomised to chemotherapy will be allowed to cross over to receive pembrolizumab at progression.	plee@polarispharma.com	Double Blind, Randomised, Multicentre, Phase II/III Study of Nintedanib in Combination With Pemetrexed / Cisplatin Followed by Continuing Nintedanib Monotherapy Versus Placebo in Combination With Pemetrexed / Cisplatin Followed by Continuing Placebo Monotherapy for the Treatment of Patients With Unresectable Malignant Pleural Mesothelioma	ASyMS-meso is a 'real-time' symptom monitoring system for people with Mesothelioma. Patients using ASyMS-meso will complete a symptom questionnaire once daily and at any time they feel unwell. This information will be sent via the mobile phone to a computer server which will determine whether any of the reported symptoms are a cause for concern and will trigger an alert at the patient's hospital if they require attention. Patients will receive self-care advice and additional information through the mobile phone. This study is being conducted in two parts. In part one we will work with patients, carers and clinical staff to develop the symptom questionnaire and self-care advice to be provided through ASyMS-meso. In part two, patients will use ASyMS-meso for a period of 3-months and will be asked to provide us with feedback regarding their experience of using the system.	The PD-1 inhibitor nivolumab (Opdivo) is approved in the EU for the treatment of patients with advanced melanoma, locally advanced or metastatic non-small cell lung cancer, and advanced renal cell carcinoma. It is also in development for a range of other cancers. The combination of nivolumab and ipilimumab has also been approved for the treatment of previously untreated metastatic melanoma. Nivolumab in combination with ipilimumab is being tested in this study to determine whether it can improve outcomes in patients with unresectable pleural mesothelioma undergoing treatment for the first time. Following a screening period, suitable patients will be randomly assigned to one of two treatment arms. Patients will receive either: Arm A: nivolumab in combination with ipilimumab Arm B: pemetrexed plus cisplatin or carboplatin chemotherapy Approximately 600 patients will be treated in this study. Approximately 36 of these patients will be from the UK.	A double blind, placebo controlled randomised phase III trial comparing nivolumab (anti PD-1 antibody) monotherapy 240mg Q2W versus placebo until disease progression, for a maximum of 12 months. The treatment allocation ratio will be 2:1 in favour of nivolumab.	The overarching aim of our research programme is to determine the best treatment for managing trapped lung in patients with malignant pleural mesothelioma (MPM) and pleural effusion Prior to undertaking a full Phase III randomised controlled trial of VAT-PD versus IPC to determine the best method of controlling/palliating dyspnoea and chest pain, there are some uncertainties that need to be addressed to inform the best design of a study. These are: 1) How prevalent is trapped lung in MPM? 2) Will patients accept randomisation to IPC or VAT-PD? iii) What is the standard deviation of Visual Analogue Scale scores for dyspnoea and chest pain in each treatment group? (This will be used to estimate parameters that will be included in the sample size estimates for a phase III trial) We will also investigate the feasibility of undertaking a cost-effectiveness analysis from the perspective of the NHS.
Radomised? Y/N	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Treatment Schedule	3 weekly cycles until progression	• 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	Patients will be reviewed at their routine clinical follow up visits (6 weeks, 3, 6, 9, 12, 18 and 24 months and annually thereafter for 5 years).	Frequency of visits: 3-weekly. Pembrolizumab administered up to a maximum of 2 years.	Standard Pem/CIS + Weekly ADI-PEG20 or placebo	Variable	Study visits will be combined with patient's normal hospital appointments	This is dependent on treatment arm.	Fortnightly	Follow-up visits at 6 weeks, 3, 6 and 12 months post-randomisation are planned to coincide with clinical care visits.
Treatment route	Oral	External beam radiotherapy	All patients will receive standard of care chemotherapy	Pembrolizumab: IV Standard chemotherapy: oral/IV (institutional-choice)	Standard Pem/CIS + Weekly ADI-PEG20 or placebo	Oral nintedanib with IV Cisplatin/Pemtrexed	All patients will continue to receive usual care while using the medical device.	IV	IV	N/A
Drugs used	Treatment arm: Vinorelbine + active symptom control Control arm: Active symptom control	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.	Treatment Arm: pembrolizumab Control Arm: (institutional-choice): gemcitabine (IV) or vinorelbine (IV/oral)	Standard Pem/CIS + Weekly ADI-PEG20 or placebo	• Placebo Comparator: Placebo + pemetrexed/cisplatin • Experimental: Nintedanib 200mg + pemetrexed/cisplastin • Experimental arm	None	Control arm: pemetrexed plus cisplatin or carboplatin chemotherapy Treatment arm: nivolumab in combination with ipilimumab	Treatment arm: Nivolumab Control arm: placebo	N/A
Entry criteria	• Histological diagnosis of malignant pleural mesothelioma • Prior treatment with first-line standard platinum doublet based chemotherapy. Patients who will have received re-challenge with 1st line platinum based therapy , and/or maintenance therapy in the front line setting are allowed. • Expected survival ≥ 3 months • ECOG performance status 0-1 • Adequate haematological and liver function • Willing to consent to provide diagnostic tissue for translational research • Disease which is measur-able using modified RECIST. • Radiological evidence of disease progression	• Malignant pleural mesothelioma (histological or MDT diagnosis) • Predicted life expectancy >12 weeks • CT scan within 8 weeks of starting radiotherapy • Worst pain score ≥ 4/10 after analgesia optimisation • Radiotherapy plan compatible with treatment arm (36Gy/6 fractions or 30Gy in 5 fractions) prior to randomisation	• Histological confirmation of pleural mesothelioma • Disease confined to one hemi-thorax.	(selection) •Histologically confirmed malignant pleural mesothelioma (all subtypes) • Progressing after or on previous platinum based chemotherapy • Availability of tumour tissue for translational research • Older than 18 years • ECOG performance status 0-1 • Life expectancy of at least 3 months • Measurable or evaluable disease according to RECIST 1.1 criteria • Adequate haematological, renal, and liver function	• Histologically proven advanced MPM of biphasic or sarcomatoid histology. • Naive to prior chemotherapy or immunotherapy (i.e. this is a first-line systemic therapy study). • MPM tumor sample for determination of ASS1 status. ASS1-deficiency is not required for study entry at study start, but tumor sample for ASS1 status is required. • Measurable disease as assessed by modified RECIST or RECIST 1.1 • ECOG performance status of 0 - 1 • Predicted life expectancy of at least 12 weeks.	• Age – 18 years and older • Histologically confirmed malignant pleural mesothelioma (MPM) (Epithelioid or biphasic subtype for Phase II patients; epithelioid subtype only for Phase III patients) • Life expectancy of at least 3 months in the opinion of the investigator • Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 • Measurable disease according to modified RECIST (Response Evaluation Criteria In Solid Tumours) criteria	Malignant Pleural Mesothelioma	• Males and Females at least 18 years of age • Histologically confirmed pleural malignant mesothelioma not eligible for curative surgery • ECOG Performance status of 0 or 1 • Available tumour sample for testing • Acceptable blood work Other protocol defined inclusion criteria may apply	Both	1. Confirmed MPM 2. Trapped lung, defined as a "clinically significant trapped lung requiring intervention in the opinion of the clinical team" 3. Pleural effusion present (following re-accumulation) 4. Considered by the clinical team to be suitable and fit enough to undergo VAT-PD 5. Considered by the clinical team to be equally suitable for treatment with VAT-PD or IPC, and therefore eligible for treatment allocation by randomisation. 6. Patient willing to receive either VAT-PD or IPC and attend the respective designated centre for their treatment 7. Community services or patient/carer able to drain IPC at least twice weekly 8. Expected survival of at least 4 months, as assessed by managing clinician 9. Age ≥ 18 years 10. Able to provide informed consent
Exclusion criteria	• Uncontrolled CNS disease • 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. • Any live vaccine within 30 days of consent • Severe hepatic insufficiency • Patients on long term oxygen therapy	• Anticancer therapy 4 weeks prior to study entry or 6 weeks after radiotherapy • 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 • Coexisting lung tumours at the time of study entry	• Unable to give informed consent • Patients unwilling to be randomised • Extent of disease not deemed to be surgically resectable • ECOG status 2 or more • Patients with predicted pre-operative FEV1 or TLco less than 20% • Patients with severe heart failure (EF less than 30%) • Patients with end stage kidney failure requiring dialysis • Patients with liver failure • Patients who are participating in another interventional clinical trial in mesothelioma.	(selection) • Prior therapy with an anti-PD-1, anti-PD-L1/L2, anti-CD137, or anti-CTLA-4 antibody • Prior therapy with gemcitabine or vinorelbine • Known active central nervous system metastases and/or carcinomatous meningitis. • Active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs).	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).	• Previous systemic chemotherapy for MPM • Prior treatment with nintedanib or any other prior line of therapy • Patients with biphasic or sarcomatoid subtype MPM • Patients with symptomatic neuropathy • Radiotherapy (except extremities) within 3 months prior to baseline imaging • Active brain metastases (e.g. stable for < 4 weeks) • Radiographic evidence of cavitary or necrotic tumours or local invasion of major blood vessels by MPM • Significant cardiovascular diseases • Inadequate hematologic, renal, or hepatic function	Patients with brain metastases or for which the participation is deemed inappropriate by their clinician	• Primitive peritoneal, pericardial and tunica vaginalis testis mesotheliomas • Prior chemotherapy for pleural mesothelioma • Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2 or anti-CTLA-4 antibody • History of other malignancy unless the subject has been disease-free for at least 3 years • Active, untreated central nervous system (CNS) metastasis Other protocol defined exclusion criteria may apply	• Patients with untreated, symptomatic CNS metastases • Patients with carcinomatous meningitis • Patients with active, known or suspected autoimmune disease • Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of the first dose of study drug administration • Other active malignancy requiring concurrent intervention • Patients with previous malignancies (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, endometrial, cervical/dysplasia, melanoma or breast) unless a complete remission was achieved at least 2 years prior to study entry AND no additional therapy is required during the study period • Any serious or uncontrolled medical disorder or active infection that, in the opinion of the investigator, may increase the risk associated with study participation, study drug administration, or would impair the ability of the patient to receive protocol therapy. • All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue not resolved to Grade 1 (NCI CTCAE version 4.03) or baseline before administration of study drug • Patients who have not recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study treatment • Known alcohol or drug abuse • Patients who have received prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti- CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting Tcell co-stimulation or checkpoint pathways) or who have previously taken part in a randomised Bristol Myers Squibb clinical trial for nivolumab or ipilimumab including study CA209-743 (CheckMate 172) • Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). • Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection. • History of severe hypersensitivity reactions to other monoclonal antibodies	1. Lung re-expands fully following pleural fluid drainage i.e. no entrapment 2. Previous attempt at pleurodesis on ipsilateral side 3. Evidence of active pleural infection 4. IPC in situ for more than 28 days 5. Current participation in an RCT or receiving a CTIMP 6. Females: pregnant or lactating
Performance status criteria	0-1	0-2	0-1	0-1	0-1	0 or 1	N/A [although the patient must be expected to live for the 3-month study period, and 1-month follow-up]	0-1	0-1	0 - 1
Participants required	200	112	n=50 patients in the Pilot phase (n=327 in full-study)	142	386	537	45 patients are needed to test the ASyMS-meso system	36 in UK	336	38
No. of participants to date	45	14	n=57 patients	0 (activation not before April 2017)	plee@polarispharma.com	Confidential information not in public domain	0	1 (in UK)	2	0
Centres opening & recruiting	Leicester Royal Infirmary Velindre Cancer Centre, Cardiff Churchill Hospital, Oxford Aberdeen Royal Infirmary Weston Park Hospital, Sheffield	Beatson West of Scotland Cancer Centre, Glasgow Forth Valley Royal Hospital, Larbert University Hospital Southampton Weston Park Hospital, Sheffield The Royal Marsden	Leicester, Sheffield, Burton, South Tyneside, Papworth, Cardiff, Colchester, South Tees, Clatterbridge, Derby, Leeds, Wythenshawe, Wolverhampton, Royal Gwent, Royal Marsden, Peterborough	Planned: Royal Marsden Hospital, London Kent Oncology Centre, Maidstone Clatterbridge Cancer Centre, Liverpool Guy's and St Thomas' Hospital, London St Bartholomew's Hospital, London Castle Hill Hospital, Hull Weston Park Hospital, Sheffield Plymouth Hospitals NHS Trust + 5 sites in Switzerland "+ 3 sites in Spain	Open in US, Taiwan; due to open UK in June (15 sites); Europe (France, Italy, Belgium, Germany, Austria); Australia (Perth + 4 other sites)	Leicester Royal Infirmary (recruiting) North Tees & Hartlepool NHS Foundation Trust (not yet recruiting) Royal Marsden Hospital (Recruiting) Beatson Hospital West of Scotland Cancer Centre (Recruiting) Wythenshawe Hospital, Manchester (Recruiting) Guys Hospital, London (Recruiting)	Queen Elizabeth University Hospital, Glasgow Hairmyres Hospital, Lanarkshire Queen Alexandra's Hospital, Portsmouth Ashford & St Peter's Hospitals, Surrey	Royal Cornwall Hospital, Truro Leicester Royal Infirmary Barts Cancer Institute, Queen Mary University of London Edinburgh Cancer Centre, Western General Hospital	Leicester Royal Infirmary Aberdeen Royal Infirmary	Recruitment has not yet started, but the following sites are in set up: Barts; Blackpool; Bristol; Cambridge; Golden Jubilee Glasgow; Greater Glasgow; Lancashire; Leeds; Leicester; Mid Essex; North Midlands; Oxford; Papworth; Peterborough; Sheffield and Wythenshawe/UHSM;
Where can patients get more information?	http://www.cardiff.ac.uk /centre-for-trials-research	• Their local clinical oncologist • Miranda.ashton @glagsow.ac.uk • www.systems-2.co.uk	By discussing the MARS 2 study with the clinician who manages their mesothelioma and the MARS 2 website: http://mars2.org.uk/ Also, by contacting Mesothelioma UK at mesothelioma.uk@uhl-tr.nhs.uk and www.mesothelioma.uk.com	www.etop-eu.org		www.clinicaltrials.gov ClinicalTrials.gov Identifier: NCT01907100	ASyMSmeso@Surrey.ac.uk	Patients/carers should contact their doctor to get further information.	http://www.cancerresearchuk.org/about-cancer/ find-a-clinical-trial/a-trial-looking-at-nivolumab-for-mesothelioma-confirm	Please email papworth.mesotraptrial@nhs.net or telephone 01480 830541 and ask for Dr Rintoul or Kate Slaven
Where can healthcare professionals get more information?	NIHR Website and Clinicaltrial.gov websites	• Laura.alexander @glasgow.ac.uk • Miranda.ashton @glasgow.ac.uk • www.systems-2.co.uk	Contacting the MARS 2 study team by email: phn-tr.mars2@nhs.net and the MARS 2 website: http://mars2.org.uk/	www.etop-eu.org	p.w.szlosarek@qmul.ac.uk	Clinical Operations Department, Boehringer Ingelheim	ASyMSmeso@Surrey.ac.uk or Dr Naomi Klepacz on n.klepacz@surrey.ac.uk	medical.information@bms.com	Email trial team confirmtrial@soton.ac.uk	Please email papworth.mesotraptrial@nhs.net or telephone 01480 830541 and ask for Dr Rintoul or Carol Freeman
Trial/Study website	http://www.cardiff.ac.uk /centre-for-trials-research	www.systems-2.co.uk	http://mars2.org.uk/	www.etop-eu.org	TBC	www.clinicaltrials.gov ClinicalTrials.gov Identifier: NCT01907100		https://clinicaltrials.gov/ct2/show/record/ NCT02899299?term=CA209-743&rank=1	N/A	This is currently in set up