MESOTHELIOMA UK
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Supporting People With This Asbestos Cancer

April 2017 Issue

	VIM	SYSTEMS-2	MARS 2	PROMISE-meso	ATOMIC-meso	LUME-MESO	Real-Time Symptom Assessment	CheckMate 743	CONFIRM
Trial title	A randomised phase II trial of oral vinorelbine as second line therapy for patients with malignant pleural mesothelioma	SYSTEMS-2	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 Ver-sus Placebo in Combination With Peme-trexed / Cisplatin Followed by Continuing Placebo Monotherapy 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	Checkpoint blockade for inhibition of relapsed mesothelioma
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
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	Drug	Symptom Management and Quality of Life	Drug/ patients quality of life	Drug
Phase	Phase II	Phase II	Phase II (Pilot study)	Phase III	Phase II/III	Phase II/III		Phase III	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	Academic institution: Bristol Myers Squibb	Academic institution: University of Southampton
Drug companies involved	Pierre Fabre	None	None	Merck Sharp & Dohme Corp	Polaris Pharma	Boehringer Ingelheim		N/A	Bristol Myers Squibb (BMS)
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	Information not provided	Prof Roma Maguire	Professor Dean Fennell	Prof Dean Fennell
Contact	Georgina Gardner, Trial Manager Gardnerg@Cardiff.ac.uk 029 20687950	Dr Miranda Ashton (Clinical Research Fellow) Miranda.ashton@glasgow.ac.uk	MARS 2 study team (phn-tr.mars2@nhs.net)	Mark Finlayson (Project Manager ETOP) mark.finlayson@etop-eu.org		Boehringer Ingelheim Call Center 1-800-243-0127 clintriage.rdg@boehringer-ingelheim.com	Dr Anne Arber (a.arber@surrey.ac.uk) or Dr Naomi Klepacz (n.klepacz@surrey.ac.uk)	Bukola Hassan and Gemma Thorp	Emma Kirkpatrick - confirmtrial@soton.ac.uk - 023 8120 3785
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 phase II trial of standard versus dose escalated radiotherapy for the treatment of pain in malignant pleural mesothelioma Compares the standard dose with a higher dose of radiotherapy 36 Gy delivered over 2 weeks • Aim is to provide better pain control in a higher proportion of patients whilst minimising side effects. risks of serious 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		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.	Research Hypothesis: In patients with untreated unresectable pleural mesothelioma, the administration of nivolumab in combination with ipilimumab as first line treatment compared to pemetrexed plus cisplatin or carboplatin regimen will lead to increased overall survival (OS) and progression free (PFS).	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.
Radomised? Y/N	Yes	Yes	Yes	Yes	Yes	Yes	No	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	Information not provided	Study visits will be combined with patient's normal hospital appointments	Depending on the study arm; either every 2 weeks or every 3 weeks	Fortnightly
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	Information not provided		IV	IV
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	Pemetrexed, Cisplatin and Nintedanib		Information above, in Study Design	Treatment arm: Nivolumab Control arm: palcebo
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 measurable 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 pleu-ral 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. • Naïve 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.	Inclusion criteria: •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	Pleural Male and female subjects (18 years of age). Histologically proved diagnosis of malignant pleural Mesothelioma (MPM), thoracoscopy is highly recommended. Must have advanced unresectable disease that is not amenable to therapy with curative intent (surgery with or without chemotherapy). Subjects that refuse potentially curative salvage surgery for recurrent disease are ineligible. Available (archival and/or fresh) pathological samples for centralized PD-L1 IHC testing during the screening period. Subjects cannot randomize until the tumor tissue for PD-L1 testing has been received at the Central Lab, however, the result of the testing is not required prior to randomization. Subjects can initiate therapy before the result of PD-L1 testing. Prior palliative radiotherapy is acceptable, but at least 14 days must have passed since the administration of the radiotherapy and all signs of early toxicity must have remitted. ECOG Performance Status of 0-1 (Appendix 1). Measurable disease, defined as at least 1 lesion measured in two positions at three separate levels on transverse cuts of CT scan that is suitable for repeated assessment using modified Response Evaluation Criteria in Solid Tumors [m-RECIST] for pleural mesothelioma. Adequate hematological, renal and hepatic functions.	Both pleural and peritoneal
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 • Phase II patients with sarcomatoid subtype MPM or Phase III 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. Brain metastasis, except if surgically resected or treated with stereotaxic radiotherapy with no evolution within the 3 months before inclusion, and asymptomatic patient. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to randomization. Prior treatment with systemic anti-cancer therapy for MPM, Prior intraoperative intracavitary chemotherapy for Pleural Mesothelioma. Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways. History of chronic inflammatory or autoimmune disease. Other active malignancy requiring concurrent intervention. Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.	• 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
Performance status criteria	0-1	0-2	0-1	0-1	0-1	0-1	N/A [although the patient must be expected to live for the 3-month study period, and 1-month follow-up]	ECOG Performance Status of 0-1	ECOG PS 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	600 treated globally to include 36 within the UK	336
No. of participants to date	32	6	n=57 patients	0 (activation not before April 2017)	plee@polarispharma.com		0	53 treated globally and 0 in the UK	0 (due to open in next month)
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	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	Open in US, Taiwan; due to open UK 14.3.2017 (15 sites); Europe (France, Italy, Belgium, Germany, Austria); Australia (Perth + 4 other sites)	120 study locations internationally. UK site information not provided.	Queen Elizabeth University Hospital, Glasgow Hairmyres Hospital, Lanarkshire Queen Alexandra's Hospital, Portsmouth Ashford & St Peter's Hospitals, Surrey Recruitment will open May 2017	No centres yet opened in the UK as all approvals only just received last week. However 6 UK sites have been chosen for the study. - Wythenshawe Hospital - Leicester Royal Infirmary - St Bart's Hospital - Edinburgh Cancer centre - Royal Cornwall Hospital - Southampton General Hospital	Leicester Royal Infirmary due to open before end March 2017
Where can patients get more information?	http://www.cardiff.ac.uk /centre-for-trials-research	• Their local clinical oncologist • Miranda.ashton@glasgow.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		Boehringer Ingelheim Call Center 1-800-243-0127 clintriage.rdg@boehringer-ingelheim.com	ASyMSmeso@Surrey.ac.uk	Clinicaltrial.gov	Contact local clinicians for further information
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	Boehringer Ingelheim Call Center 1-800-243-0127 clintriage.rdg@boehringer-ingelheim.com	ASyMSmeso@Surrey.ac.uk or Dr Naomi Klepacz on n.klepacz@surrey.ac.uk	Clinicaltrial.gov	Email trial team confirmtrial@soton.ac.uk
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	http://trials.boehringer-ingelheim.com		Clinicaltrial.gov	N/A