Hemithoracic Irradiation with Proton Therapy in Malignant Pleural Mesothelioma

Sponsor: University College London
Funder: Asthma + Lung UK
Mesothelioma UK (participant travel expenses)
References: IRAS: 322732
EDGE: 148232
Clinicaltrials.gov: NCT05655078

Target accrual: 148 patients (1:1 randomisation)
Number of sites: 18-20 UK sites, including 2 PBT centres (UCLH, London & the Christie, Manchester)
Recruitment period: 3 years (April 2024-March 2027)

Overall aim:

- To determine if delivering proton beam therapy (PBT) to the involved hemithorax can improve progression-free survival and overall survival
- To determine if hemithoracic radiotherapy with PBT affects the quality of life of patients with MPM over 2 years
- To determine the relative cost-effectiveness of hemithoracic radiotherapy with PBT in MPM compared with current standard of care therapy over 2 years

Co-primary endpoints:

i. Progression-free survival (PFS) defined as the time from randomisation to the date of progression, using mesothelioma-modified RECIST v1.1, or date of death from any cause
ii. Overall survival (OS) defined as the time from randomisation to the date of death from any cause

Secondary endpoints: Time to first subsequent therapy, local-failure-free survival, distant-metastases-free survival, safety and toxicity, health related Quality of Life (QoL), health and social care resource use and costs, incremental cost-effectiveness

Exploratory biological endpoints: Archival tissue FFPE from biopsies, longitudinal blood and pleural effusion samples, and FFPE tissue from progression rebiopsy (if clinically indicated) are collected to identify if there are any blood based or imaging biomarkers that can predict which patients will benefit most from PBT for MPM.

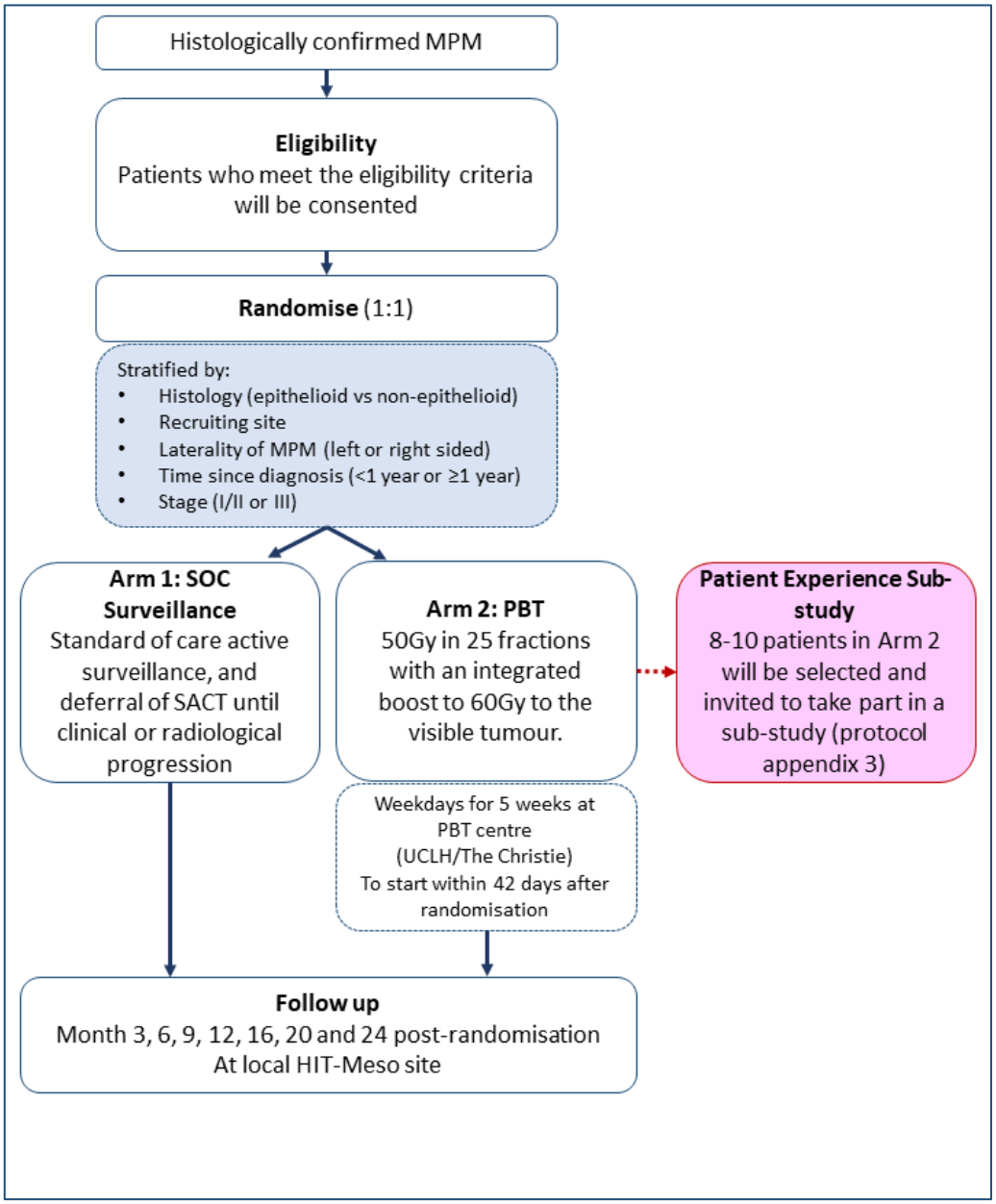
Qualitative sub-study: Investigating patient expectations prior to PBT, experiences of receiving PBT, and how/if expectations of the trial were met.
8-10 consenting patients on arm 2 (PBT) will be invited to complete an online questionnaire pre-treatment and have a semi-structured interview 3 months post-treatment with research staff from the University of Sheffield

Treatment arms:

Arm 1 (control)
Active surveillance and deferral of systemic anti-cancer therapy (SACT) until clinical or radiological progression.

Arm 2 (interventional)
Proton Beam Therapy 50Gy in 25 fractions with an integrated boost to 60Gy to the visible tumour if organs at risk constraints are not exceeded.
Follow up at local referring centre.

Schema



Inclusion criteria:

- Patients ≥18 years of age, with histologically (Biopsy) confirmed MPM
- N0 or N1 and M0 disease
- Patient and responsible clinician opt for active surveillance, and deferral of SACT until clinical or radiological progression
- Written informed consent
- WHO Performance Status 0-1
- Disease confined to one hemithorax based on CT assessment
- Adequate pulmonary function:
  ≥ 40% predicted post-FEV1;
  ≥ 40% predicted DLCO/TLCO
- Agreement to travel to the PBT site for PBT treatment if randomised to arm 2
- Agreement to be followed up at a local HIT-Meso site

Exclusion criteria:

- Presence of metastatic or contralateral disease
- Prior thoracic radiotherapy, chemotherapy, immunotherapy for MPM
- Prior radical surgery for MPM (Extrapleural pneumonectomy or extended pleurectomy decortication or pleurectomy decortication)
- Initial systemic therapy or surgery is required and the patient and responsible clinician do not opt for active surveillance
- Involvement of contralateral or supraclavicular lymph nodes
- T4 disease with clear invasion of the myocardium
- N2 and/or M1 disease
- Presence of new effusion that is not amenable to drainage
- WHO Performance Status ≥ 2
- Women who are pregnant or breast feeding
- History of other malignancy; Exception: (a) Subjects who have been successfully treated and are disease-free for 3 years, (b) a history of treated non-melanoma skin cancer, (c) successfully treated in situ carcinoma, (d) CLL in stable remission, or (e) indolent prostate cancer requiring no or only anti-hormonal therapy.

Schedule of assessments

Arm 1 (SOC, active surveillance):

Assessments	Screening[a]	Baseline visit	Follow up - Months post date of randomisation All visits ± 2 weeks							Progression[e]
		Post-randomisation [d]	3 (12 ±2 weeks)	6	9	12	16	20	24	
Medical history	x									
Concomitant mediations	x		x	x	x	x	x	x	x	x
Informed Consent	x									
Physical examination	x									
Vital signs	x									
Pulmonary function test	x[c]									
WHO Performance status	x									
FBC/biochem U&Es	x[b]		x			x			x	x
Bone & Liver profile	x[b]		x			x			x	x
Pregnancy test (urine/serum)	x									
Research bloods *3x Streck, 1x Tempus*		x	x	x	x	x	x	x	x	x
Pleural effusion fluid collection (if clinically indicated)	x		x	x	x	x	x	x	x	x
Archival FFPE Tissue Collection (biopsies)		x								x
PET scan of the chest and abdomen	x[c]									

Continues on next page

Assessments	Screening[a]	Baseline visit	Follow up - Months post date of randomisation All visits ± 2 weeks							Progression[e]
		Post-randomisation [d]	3 (12 ±2 weeks)	6	9	12	16	20	24	
CT scan of chest and abdomen with venous phase contrast, modified RECIST v1.1 reporting	x[b]		x	x	x	x	x	x	x	x
EORTC QLQ-C30 Questionnaire		x	x			x			x	x
EQ-5D-5L		x	x	x	x	x	x	x	x	x
Resource use collection (modified CSRI and iVICQ questionnaires)		x	x	x	x	x	x	x	x	x

a) All screening assessments to be performed within 14 days prior to randomisation, unless specifically indicated otherwise
b) Performed within 28 days prior to randomisation
c) Performed within 42 days prior to randomisation
d) Post-randomisation assessments must be performed within 14 days after randomisation
e) Patients continue the trial follow up schedule up to 24 months post randomisation following progression

Arm 2 (PBT):

Assessments	Screening[a]	Baseline visit	Proton Beam Therapy (PBT)[e]					Follow up - Months post randomisation All visits ±2 weeks							Progression [g]
		Post-randomisation [d]	Week 1	Week 2	Week 3	Week 4	Week 5	3[f]	6	9	12	16	20	24	
Medical history	x														
Concomitant mediations	x							x	x	x	x	x	x	x	x
Consent	x														
Physical exam	x														
Vital signs	x														
Pulmonary function test	x														
WHO Performance status	x[b]														
FBC/biochem U&Es	x[b]		x	x	x	x	x	x			x			x	x
Bone & Liver profile	x[b]		x	x	x	x	x	x			x			x	x
Pregnancy test (urine/serum)	x		x												
Research bloods *3x Streck, 1x Tempus*		x		x			x	x	x	x	x	x	x	x	x
Pleural effusion fluid collection (if clinically indicated)		x						x	x	x	x	x	x	x	x
Archival FFPE Tissue Collection		x													x

Continues on next page

Assessments	Screening[a]	Baseline visit	Proton Beam Therapy (PBT)[e]					Follow up - Months post randomisation All visits ±2 weeks							Progression [g]
		Post-randomisation [d]	Week 1	Week 2	Week 3	Week 4	Week 5	3[f]	6	9	12	16	20	24	
PET scan of the chest and abdomen	x[c]														
CT scan of the chest and abdomen with contrast, modified RECIST v1.1 reporting	x[b]							x	x	x	x	x	x	x	x
CT scan of the chest and abdomen with contrast for PBT planning purposes (reactive)		x			x										
MRI of the chest and abdomen for PBT planning		x													
EORTC QLQ-C30 Questionnaire		x						x			x			x	x
EQ-5D-5L		x		x			x	x	x	x	x	x	x	x	x
Resource use collection (modified CSRI and iVICQ questionnaires)		x						x	x	x	x	x	x	x	x
Qualitative bespoke Questionnaire[h]		x													
Qualitative interview[h, i]									x						

a) All screening assessments to be performed within 14 days prior to randomisation, unless specifically indicated otherwise
b) Performed within 28 days prior to randomisation
c) Performed within 42 days prior to randomisation
d) Post-randomisation assessments must be performed within 14 days post-randomisation
e) PBT to start within 42 days post-randomisation
f) 3 month follow up visit should be conducted 12 ± 2 weeks post-randomisation, and will incorporate follow up for side effects 2 weeks post-treatment.
g) Patients continue the trial follow up schedule up to 24 months post randomisation following progression
h) Selected 8-10 patients only (see appendix 3)
i) Interview conducted 3 months after completion of PBT