Immune responses following intrapleural administration of oncolytic HSV SEPREHVIR® in patients with malignant pleural mesothelioma

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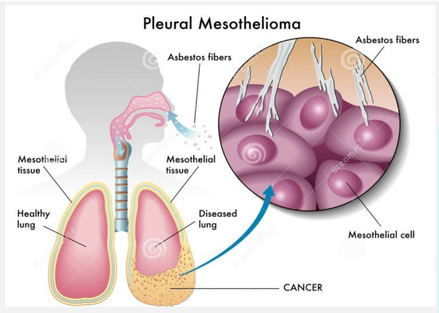
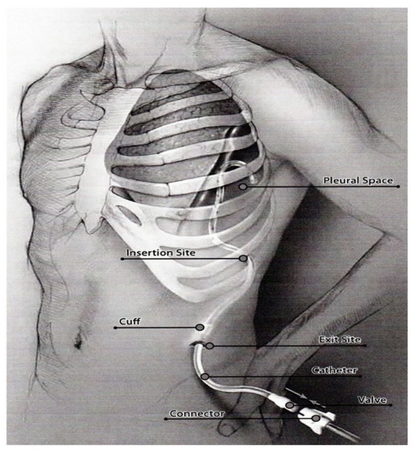
Oncolytic herpes virus therapy for mesothelioma – a phase 1/2a study of intrapleural Seprehvir (NCT01721018)

Malignant pleural mesothelioma (MPM) is an aggressive, asbestos-related tumour of the pleural and peritoneal cavities and remains a major challenge with limited therapeutic options. The disease has a dismal prognosis, a high symptom burden (pain, breathlessness) and is fatal with the median overall survival following treatment of ~1 year.

MPM incidence is increasing steadily with peak mortality expected to occur between 2020 and 2050 and current treatment options of surgery, radiotherapy, chemotherapy and palliative care have limited evidence of effectiveness in MPM. Thus, new therapeutic options are required.

Seprehvir (HSV1716) is a mutant oncolytic herpes simplex virus type 1 deleted in the RL1 gene which encodes the protein ICP34.5, a specific determinant of virulence. Seprehvir is a multi-functional oncolytic immunotherapeutic with highly selective cancer cell killing capable of initiating an anti-tumour immune response.





Study Design

The trial is currently recruiting at Weston Park Hospital, Sheffield and Queen Elizabeth University Hospital, Glasgow. It is a Phase 1/2a 3+3 dose escalating (1, 2 & 4 doses at weekly intervals) study delivering Seprehvir via existing intra-pleural catheter.

Primary objectives:

- Determine the safety and tolerability of Seprehvir given intrapleurally in patients with inoperable malignant pleural mesothelioma.

Secondary objective:

- Obtain evidence of Seprehvir replication and patient's immune responses through analysis of pleural fluid and plasma samples.

Exploratory objective:

- Assess tumour response by CT on days 29 and 57 using modified RECIST criteria.

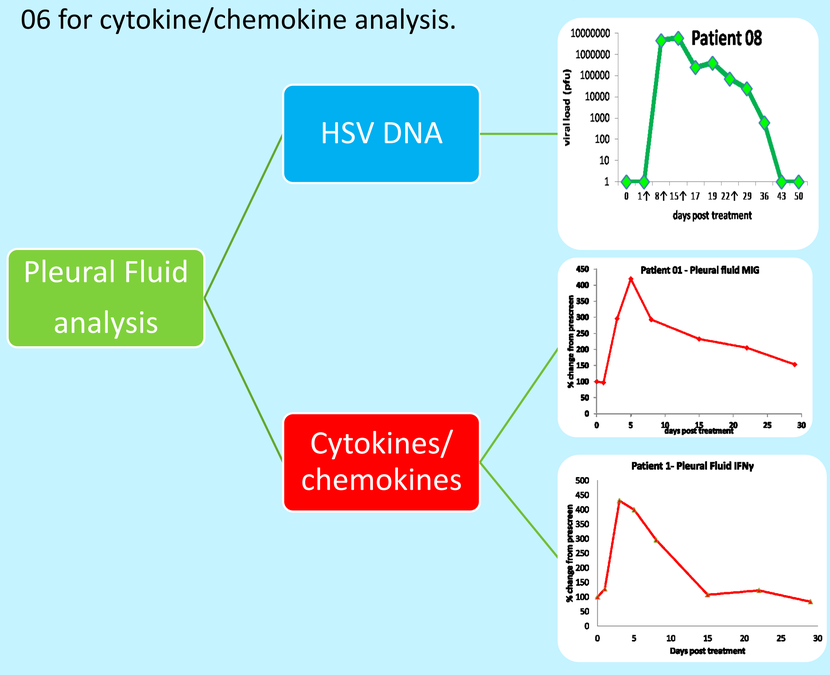
	No. of doses	Number of patients	Status
Part A	1 dose of $1x10^7$ i.u.	Patients 1-3	Completed
Part B: Group 1	2 doses of $1x10^7$ i.u.	Patients 4-6	Completed
Part B: Group 2	4 doses of $1x10^7$ i.u.	Patients 7-9	Completed
Group 2 extension	4 doses of $1x10^7$ i.u.	3 patients	1/3

Analysis

- Pleural fluid and plasma samples are collected on treatment days and days 3, 5, 8, 15, 22 and 29 after the last virus dose.

Evidence of Seprehvir replication and patient's immune responses through analysis of pleural fluid and plasma samples.

a) Pleural fluids were analysed for HSV DNA by PCR (see Summary Table below) and for cytokine/chemokine levels by ELISA. Cytokines/chemokines status in pleural fluids before treatment is given in Table (i) and individual patient responses are presented in Table (ii). Cytokines/chemokines that showed little or no responses are shown in Table (iii). There were insufficient pleural fluids from Patient 06 for cytokine/chemokine analysis.



(i)

High (ng/ml)	Low (pg/ml)	absent
IL-6, IL-8, IL-27, MIG, VEGF	IL-2, IL-10, IL-12, IL-21, IP10	IFNγ, IFNα, IL-1α, IL-4, TNFα, GM-CSF

(ii)

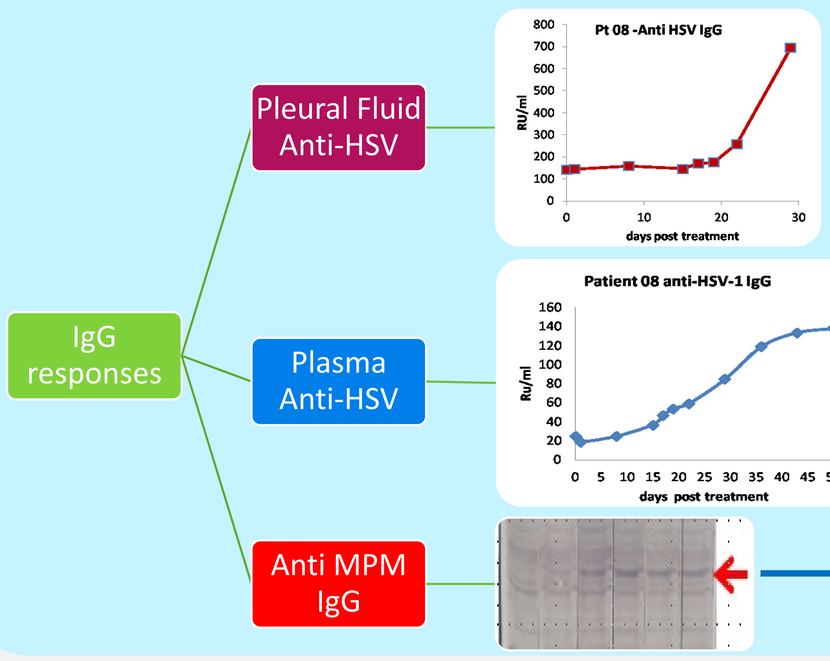
	IFNγ	IP10	MIG	VEGF	TNFα	IL2	IL6	IL8	IL10	IL12
Pt 01	++	+++	+++	↓	++	↓	+	+	+	-
Pt 02	-	↓	-	+++	+/↓	↓	↓	+/↓	+	↓
Pt 03	++	+++	+++	+++	+	↓	+	+	-/↓	++
Pt 04	+++++	+++	++++	↓	+++	↓	+	↓	+	-
Pt 05	-	-	-	++	↓	↓	↓	-	-/↓	-
Pt 07	+++++	++++	+++	-	+	++	+	+++	++	+++
Pt 08	+++++	+++	+++	↓	+	++	+++	+++	+++	+
Pt 09	++	+++	+++	+++	nd	++	+	++	+	+

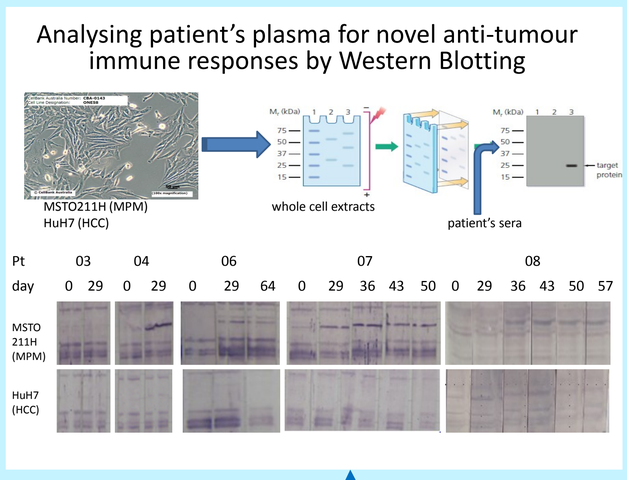
(iii)

	IFNα	IL1α	IL4	IL21	IL27	GM-CSF
Pt 01	-	-	-	-	↓	-
Pt 02	-	+	-	+	↓	-
Pt 03	-	-	-	↓	↓	-
Pt 04	-	-	-	-	-	-
Pt 05	-	-	-	+	+	-
Pt 07	-	-	-	↓	++	-
Pt 08	+	-	+	+	-	-
Pt 09	nd	nd	nd	+	-	-

= cytokine/chemokine associated with aTh1 response - = unchanged, + = weak to +++++ = strong response, ↓ = decrease, nd = not done

b) Pleural fluids and plasma samples were analysed for anti-HSV IgG by ELISA and plasma samples for anti-tumour IgG responses with results summarised in Table (iv)





Whole cell extracts from a MPM (MSTO211H) and a HCC (HuH7) were probed with patient 's plasma to detect novel IgG responses

(iv)

Pt no	No doses	status	Plasma Anti-HSV-1 IgG response	Pleural Fluid Anti-HSV-1 IgG response	Novel anti-tumour IgG response
01	1	Seropositive	++	+++	-
02		Seropositive	-	++	++
903		Seropositive	-	↓	-
04	2	Seropositive	+++	++	+++
05		Seropositive	+++	+++	-
06		Seropositive	+++	ND (no samples)	++
07	4	Seropositive	+++	++	+++
08		Seronegative	+++	+++	++
09		Seropositive	+++	++++	+

Pt no./ Gender	HSV DNA in pleural fluids	Pleural fluid Th1 response	CT result	Status/months post treatment
01/F	-	+++	Progressive disease	Died/20
02/M	+++++	-	Stable disease	Died/13
903/M	-	++	Stable disease	Died/17
04/M	-	+++++	Stable disease	Died/18
05/M	+	-	Stable disease	Died/4
06/M	+++	no samples	Progressive disease	Alive/20
07/F	+++	+++	Progressive disease	Died/10
08/M	++++	+++++	Stable disease/ partial response	Alive/16
09/F	+	++	Stable disease	Alive/15

Summary Table and Trial Results

- **Well tolerated with few virus-related adverse events**
- **Potential signals of efficacy**
  - 9 patients evaluated, 1 PR, 5 SD, 3 PD
- **Evidence of viral replication/persistence in pleural fluid**
- **Evidence of Th1 cytokine response post Seprehvir administration**
- **Th1 response potentially indicative of extended survival (green shading in Summary Table)**
  - Median survival for 6 patients with Th1 response = 16.5 mths vs 9.5 mths historical median survival for all MPM patients (Beckett et al (2015) Lung Cancer 88, 344).
- **Evidence of a novel patient immune response**