INTRAPERITONEAL ADMINISTRATION OF RADIO-LABELLED MONOCLONAL ANTIBODY PEMTUMOMAB (YTTRIUM-90-HMFG1) IN GASTRIC CANCER

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ABSTRACT

Aim: To evaluate the feasibility of treatment method (intraperitoneal administration of radiolabelled monoclonal antibody) for patients with gastric cancer.

Method: A total of 15 eligible patients, with histologically proven adenocarcinoma of the stomach or gastro-oesophageal junction, who had undergone resection to remove the primary tumour mass, were enrolled in the study. Eight patients were treated with the study drug and 7 of patients were enrolled into the standard care control arm.

Materials and Results: Mean blood radioactivity peaked between 36 and 48 hours, with a mean peak value of approximately 15% ID. Data previously reported on intraperitoneal Y-HMFG1 treatment of patients with ovarian cancer show peak values of 25 - 35% ID seen at 48 hour post-injection. The present results require confirmation in a large population of gastric cancer patients, but suggest that the transfer of radioactivity into the blood pool is decreased compared with the ovarian cancer patients.

Conclusions: A HAMA response was detected in all patients after treatment, and there is some suggestion that is follows a bi-phasic pattern. If as hypothesised, a HAMA response provides a boost to the immune system, leading to a potential longer term benefit, then the HAMA response seen in this study following pemtumomab treatment is encouraging.

Key words: gastric cancer, intraperitoneal infusion, radiolabelled monoclonal antibody.

INTRODUCTION

Gastric cancer is a leading cause of cancer death, with five-year survival rates in the USA currently below 15%. The primary mode of treatment is surgery, and recently post-operative chemoradiation has been proposed as a regimen to prolong survival [1].

Pemtumomab is a HMFG1 murine monoclonal antibody radiolabelled with Yttrium-90 (Y-HMFG1). The antibody targets the MUC1 protein, which is expressed by a high proportion of gastric carcinomas. High levels of MUC1 expression have been correlated with progression and poor prognosis [2].

After surgery for gastric cancer, relapse and disease progression frequently occur within the peritoneal cavity. It is proposed that intraperitoneal administration of pemtumomab could prevent progression of the disease or improve survival in patients with minimal disease after resection. Previous experience with this treatment suggests that it is more readily tolerated than chemotherapy, and in an earlier phase-II study, adjuvant use of intraperitoneal pemtumomab in ovarian cancer patients (who also often show intraperitoneal disease on relapse) improved survival in comparison with conventional treatment [3].

STUDY DESCRIPTION

The aim the 15 TARGET-1 (Targeted Antibody Radioimmunotherapy Gastric Evaluation Trial) study is to determine the safety, tolerability and preliminary efficacy of a single dose of intraperitoneally administered pemtumomab (25 mg antibody labeled with up to 1110 MBq Yttrium-90) in the treatment of gastric

cancer. This is a randomized, pilot phase-II trial comparing best supportive care (standard care) with study medication, conducted at centers in Poland and UK.

METHODS

A total of 15 eligible patients, with histologically proven adenocarcinoma of the stomach or gastro-oesophageal junction, who had undergone resection to remove the primary tumour mass, were enrolled in the study. Eight patients were treated with the study drug and 7 were enrolled into the standard care control arm. Ethics approval was sought and obtained at all centers prior to enrolling patients. All patients provided a written informed consent prior to entrolment. Patient demographics are shown in *Table 1*.

Table 1. Patient's characteristic in the study.

Patient #	Sex	Age at entry	Stage of disease	Randomisation
T4	M	80	T4N2	Standard Care
T5	M	63	T3N2	Standard Care
T7	M	55	T3N1	Standard Care
T9	M	61	T3N0	Study drug
T10	F	61	T2N0M1	Study drug
T11	M	71	T3N0	Standard Care
T12	M	50	T3N3	Standard Care
T13	M	55	T3N2	Study drug
T14	M	63	T2N1	Study drug
T16	F	48	T3N0	Standard Care
T17	M	74	T3N2	Study drug
T19	F	62	T3N1	Standard Care
T20	M	74	T3N0	Study drug
T21	M	69	T3N2	Study drug

The patients under treatment underwent a second-look laparoscopy to assess their disease status and place the treatment catheter. An individualised dose (666 MBq/m2 body surface area, up to 1110 MBq maximum) of pemtumomab was administered intraperitoneally in a saline infusion (approx. 1L). Blood and urine samples were collected from the patients over the first few days post-treatment and analysed for levels of radioactivity. Patients were then followed up on a weekly basis for 8 weeks, at week 12 and at 3 monthly intervals thereafter for up to 1 year.

RESULTS

Preliminary data were collected when the last enrolled patient completed the three month follow-up, and are reported here. The study will complete a 12-month follow-up for all patients during 2003, and full data will be reported then.

Pharmacokinetic data

Samples were collected for 5/8 of the patients treated over the first 4 days post-treatment. Blood radioactivity values from individual patients with means (and SDs) are indicated in *Figure 1.*

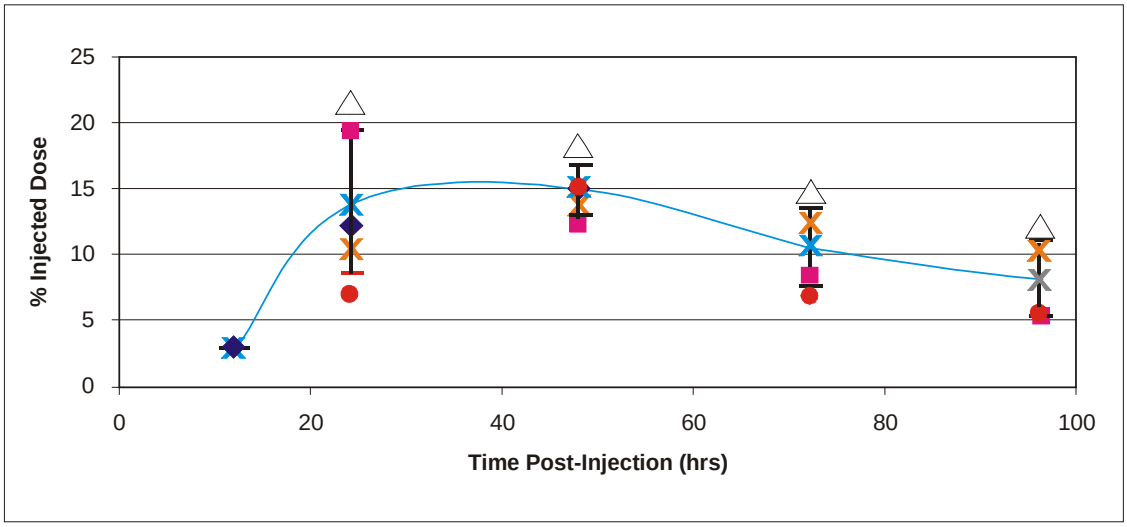

Fig. 1. Blood Radioactivity vs Time Profile: Mean (+/-SD) & Individual Values for 5 patients.

Approximately 5% of the injected was excreted in the urine over the first 24 hours, with a further 2% ID on day 2.

Mean blood radioactivity peaked between 36 and 48 hours, with a mean peak value of approximately 15% ID. Data previously reported on intraperitoneal Y-HMFG1 treatment of patients with ovarian cancer [4] show peak values of 25-35% ID seen at 48 hour post-injection. The present results require confirmation in a large population of gastric cancer patients, but suggest that the transfer of radioactivity into the blood pool is decreased compared with the ovarian cancer patients. This finding could reflect either (a) greater impairment of lymphatic drainage associated with the initial surgery or (b) residual disease at second-look and treatment (The ovarian patients were free of macroscopic disease at treatment).

BLOOD PARAMETERS

It is known that the treatment with ^{90}Y radiolabelled antibodies can have an effect on haematological parameters. Individual data points and mean values for platelet and white blood cell levels (n=8) following treatment are shown in *Figures 2 and 3*.

The White Blood Cell nadir occurred at 7-8 weeks post-treatment at NCI grade 1-2; recovery was spontaneous and no intervention was required. An additional, earlier dip was seen at weeks 3-4 after-treatment.

The pattern of haematological toxicity appears similar to that seen previously in ovarian cancer patients [4].

HUMAN ANTI MOUSE ANTIBODY (HAMA) RESPONSE

Treatment of patients with murine monoclonal antibodies often generates an immunological response in patients, known as the HAMA response.

Rashes, arthralgia and myalgia have been associated with such treatment (Maraveyas 1994). In this study, the prescription of analgesics and antihistamines at one week post-treatment was intended

to control these effects. To date, there have been three incidences of rash (one serious), and one event of myalgia reported in the patients treated.

The assay of the patients' blood for HAMA titres (Boehringer-Mannheim assay, which detects human antibodies against all mouse IgG subclasses-IgG1, IgG2a, IgG2b, IgG3) shows that all the treated patients seem to develop a HAMA response after week 1, suggesting that gastric cancer is not immunosuppressive. Individual patient results are shown in *Figure 4*.

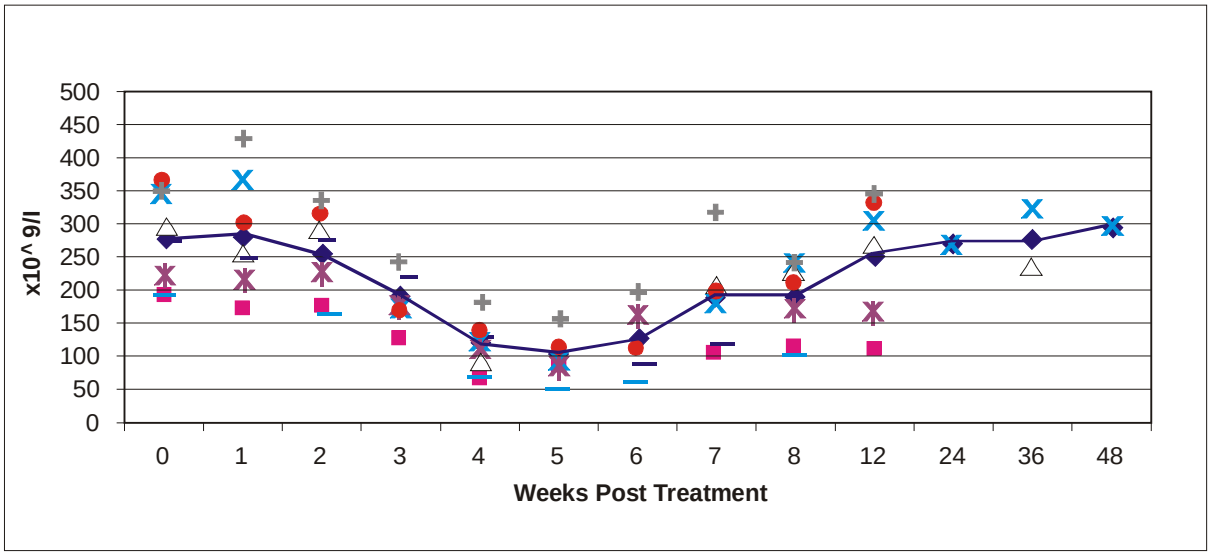

Fig. 2. Platelet Count Following Pemtumomab Treatment.

The platelet nadir occurred at week 5, was typically grade 0-2 (NCI), and recovery was spontaneous with no intervention required.

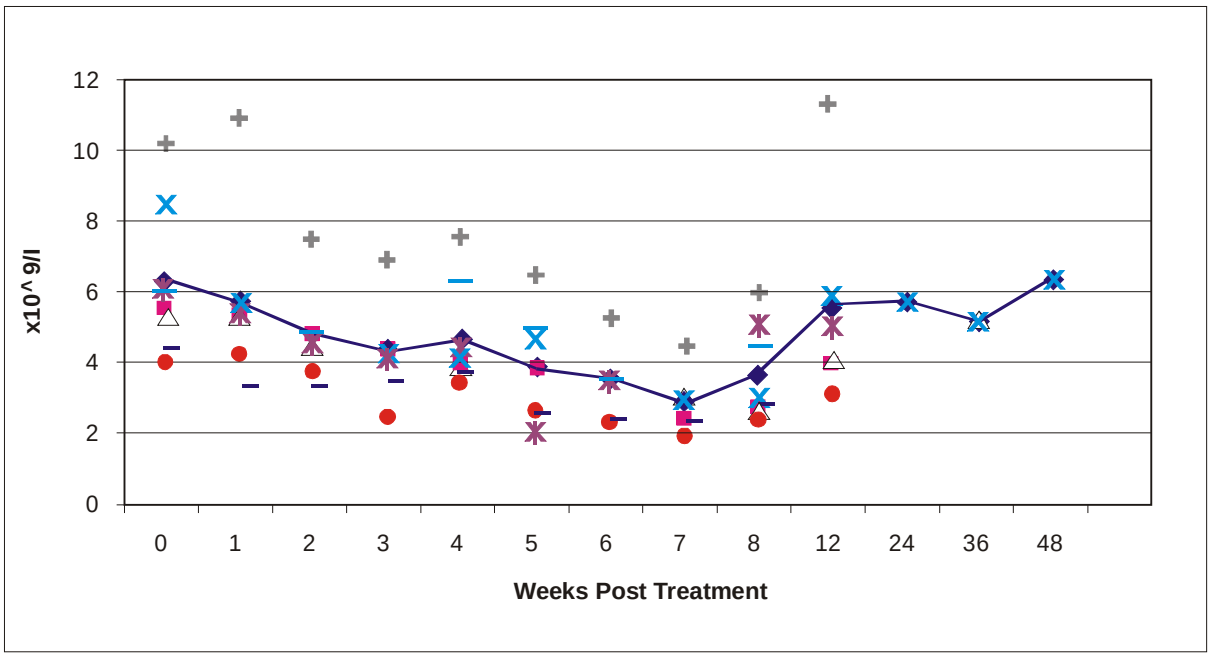

Fig. 3. White Blood Cell Count Following Pemtumomab Treatment.

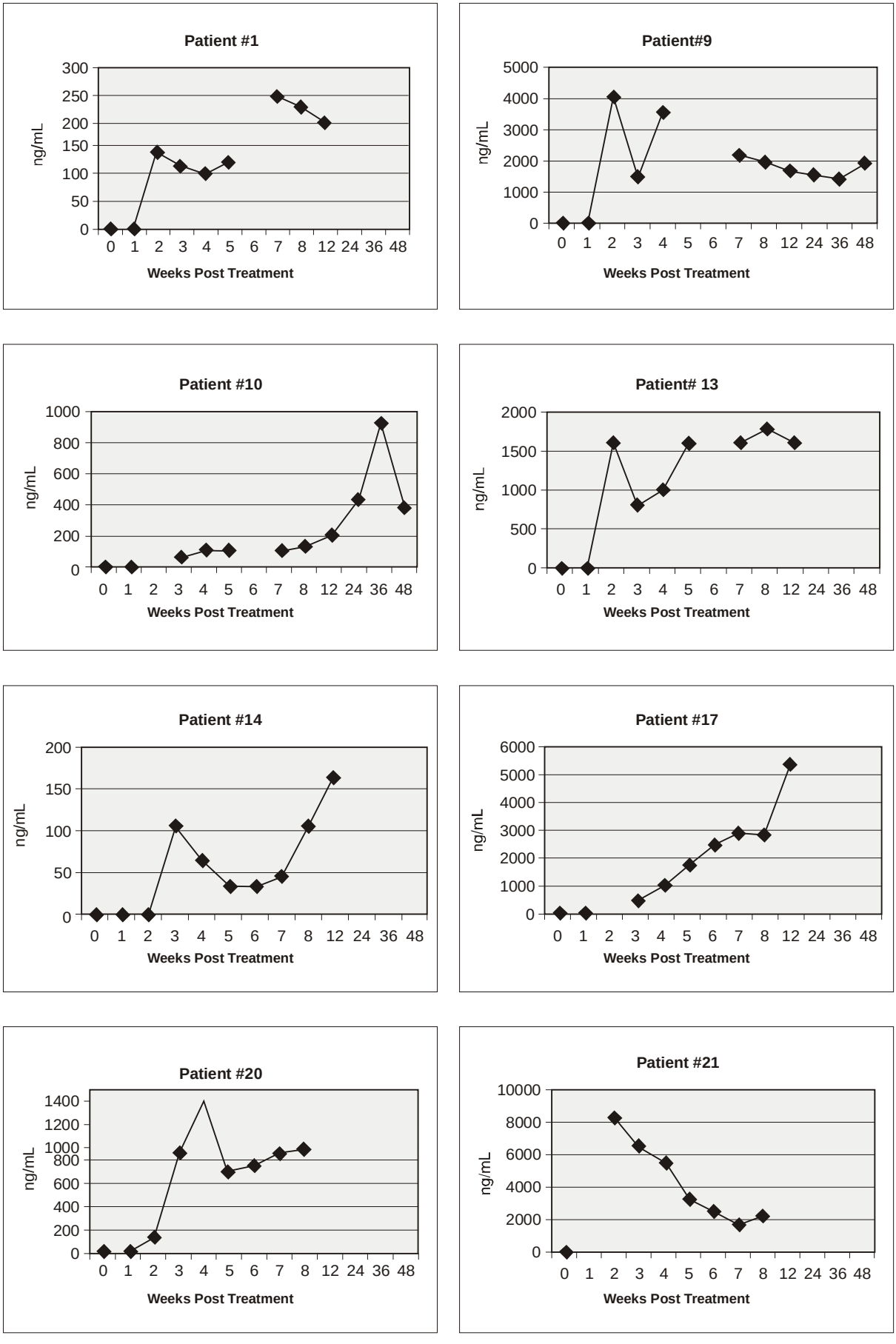

Fig. 4. Individual HAMA Titres Following Pemtumomab Treatment.

The limited data currently available suggest a bi-phasic HAMA response, although further evaluation is required. It may be that the initial HAMA response at later timepoints.

It has been hypothesised that, in addition to any immediate effects mediated by the targeted delivery of radioisotopes, murine monoclonal antibodies may induce a potential longer term benefit via a boost to the immune system provided by the HAMA response [5,6]. If this hypothesis is correct, then the HAMA response in seen these gastric cancer patients following pemtumomab treatment is encouraging.

ADVERSE EVENT PROFILE

There have been a total of 63 adverse events (of all causalities) recorded to date, of which 43 were in the Study Drug group (10 Serious) and 20 in the Standard Care group (6 Serious). Of these, the most common adverse event recorded was abdominal pain, followed by nausea and diarrhoea. Such events were expected during this study as they have also been reported following treatment of the ovarian cancer patients in earlier studies.

Table. 2. Reported Adverse Events with incidence > 1.

Adverse Event Description	Study Drug		Standard Care	
	Serious	Non-serious	Serious	Non-serious
Abdominal	1	3		1
Nausea		2	1	2
Diarrhoea		4		
Abdominal discomfort		1		2
Intestinal obstruction	2		1	
Rash	1	2		
Vomiting		1	1	1
Abdominal pain upper	1	1		
Dizziness		2		
Influenza like illness		2		
Pneumonia		1	1	
Thrombocytopenia	1	1		

The therapeutic study medication consisted of 25 mg of HMFG1 antibody labeled with ^{90}Yttrium to deliver a dose of 666 MBq/m^2 (18 mCi/m^2) of a body surface, but not greater than 1110 MBq (30 mCi) in total. A kit containing the study medication was delivered to the hospital. The kit contained two bottles: one with HMFG1 antibody, and the other with HMFG1-CITC-DTPA immunoconjugate.

The kit was ready for radiolabeling procedure. All components were mixed in proper proportions, time and temperature. After stating the purity of the medication, using chromatography, the syringe was filled with physiological salt up to 10 cm^3. The medication was ready to apply through the catheter to the abdomen. The time of application was one minute.

All solutions were sterile and the labeling, purification and dispensing processes were performed in an environment accurate for preparing radioactive materials, such as the nuclear medicine department and the department of medical physics.

All processes were performed in the nuclear medicine department in the hospital. The radiopharmacist was properly protected from radiation, wearing a lead apron, a single use lab coat, lead glasses, single use rubber gloves, a lead collar for the thyroid gland and a dosimeter attached to the lead apron. The syringe with the medication was protected with a special plexi shield. Because of the radioactive nature and a short half-life, ^{90}Yttrium was delivered to the hospital right before the treatment. Until the end of the treatment the patient was placed in a separated room. Measurements of doses were performed using a Portable Dose Ratemeter type PDR2 made by NE Technology Limited. The dosimeter was calibrated to measure the irradiation of ^{90}Y. The measurements were carried out within 24, 48, 72 and 96 hours after the application of the medication, 10 cm from the patient's skin above the catheter. After the first 24 hours after the application, the dose rate was 22,4 μSv/h, after 48 hours it was 5,3 μSv/h. After 72 hours, the dose rate was 3,76 μSv/h. On the last day of measurements the dose rate was 2,34 μSv/h.

The accumulated radioactive and medical wastes were also measured. After the measurements the wastes were transported to the storage and kept there until the loss of their radioactivity.

The dose rate of wastes was 1 μSv/h. The greater part of ^{90}Y was excreted from the organism. Radioimmuinoisotope was bound with cancer cells. After four days from the application the radioactivity decreased to the level that allowed the patient to leave the hospital.

CONCLUSION

The interim analysis of the data from the TARGET-1 study suggests that in gastric cancer patients treatment with intraperitoneal is generally well tolerated.

The platelet nadir occurred at week 5, was typically grade 0-2 (NCI), and recovery was spontaneous with no intervention required, a pattern similar to the previously reported for ovarian cancer patients.

A HAMA response was detected in all patients after treatment, and there is some suggestion that is follows a bi-phasic pattern. If, as hypothesised, a HAMA response provides a boost to the immune system, leading to a potential longer term benefit, then the HAMA response seen in this study following pemtumomab treatment is encouraging.

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