

A Phase I study of the anti-kappa monoclonal antibody, MDX-1097, in previously treated multiple myeloma patients

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Background

MDX-1097 is a chimeric monoclonal antibody that binds specifically to malignant plasma cells present in the bone marrow of patients with kappa restricted multiple myeloma. The antigen, kappa myeloma antigen (KMA), has also been demonstrated on kappa myeloma cell lines and consists of membrane associated kappa light chain that is not associated with immunoglobulin heavy chain. Previously, *in vitro* studies have demonstrated that MDX-1097 induces antibody dependent cellular cytotoxicity (ADCC) in kappa myeloma cell lines in the presence of human donor effector cells. The antibody was also shown to mediate antibody dependent cellular phagocytosis (ADCP) in the presence of macrophages derived from normal human donors. In addition, a human tissue cross-reactivity study demonstrated that MDX-1097 was highly specific for human free kappa light chain and a non human primate study showed a favorable toxicology profile. Based on these promising preclinical data a Phase I study to determine the safety and efficacy of MDX-1097 was conducted in previously treated kappa myeloma patients with stable measurable disease.

Purpose

The primary purpose of the study was to determine the safety, tolerability and maximum tolerated dose (MTD) of MDX-1097 when administered as a single dose treatment to previously treated multiple myeloma patients with stable measurable disease.

Secondary objectives were:

- Determination of the biologically relevant dose (BRD) of MDX-1097 where the BRD was defined as the dose of MDX-1097 that could safely be administered and was associated with measurable levels of MDX-1097 for 7 days in the serum following the administration of a single dose
- Measurement of serum free kappa light chain (κFLC) and free lambda light chain (λFLC)
- Characterization of the pharmacokinetic profile of single dose MDX-1097
- Measurement of immunogenicity of MDX-1097
- Evaluation of changes in the serum M protein in response to MDX-1097

Patient demographic data

	Dose of MDX-1097			
	0.3 mg/kg (N=3)	1.0 mg/kg (N=3)	3.0 mg/kg (N=3)	10 mg/kg (N=3)
Age (years)	75 (10.4)	57 (10.2)	60 (6.3)	64 (3.2)
BMI (kg/m²)	22.0 (3.49)	28.2 (4.00)	25.4 (1.28)	26.7 (3.48)

Arithmetic mean (SD) data are presented
N = Number of patients studied

- Seven patients were white males and five patients were white females
- Patient age ranged from 47 to 83 years
- Patients who had received at least one prior line of standard therapy, had achieved at least a minimal response (> 25% reduction in M protein) and had stable measurable disease for at least 3 months prior to study enrolment were eligible for the study.

Patient previous and concomitant medications

All patients had received between 4 and 13 previous antineoplastic medications related to multiple myeloma and these included chemotherapy, immunotherapy and steroid drugs.

During the study 9 of the 12 patients (75%) had ongoing low dose maintenance medication for multiple myeloma.

- 8 patients (67%) were receiving thalidomide or lenalidomide
- 7 patients (58%) were receiving dexamethasone or prednisolone
- 1 patient was receiving cyclophosphamide

Methods

Four dose levels of MDX-1097 (0.3, 1.0, 3.0 and 10 mg/kg) were administered.

A total of 12 patients (4 cohorts of 3 patients) completed the study and as there were no dose limiting toxicities (DLTs) only 3 patients were required per cohort.

MDX-1097 was administered as a single intravenous infusion over a duration of 90 minutes and within each cohort only one patient was treated per week.

Pharmacodynamics and efficacy were evaluated by analysis of serum M protein, serum κFLC and λFLC, total immunoglobulins, β2-microglobulin, C-reactive protein, exploratory biomarkers and anti-MDX-1097 antibodies.

Safety evaluations included:

- Eastern Cooperative Oncology Group (ECOG) performance
- Vital signs
- 12-lead electrocardiogram (ECG)
- Clinical Laboratory Evaluations including clinical chemistry, hematology, urinalysis and adverse events (AEs)
 - * AEs were graded using the Cancer Therapy Evaluation Program (CTEP) Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0

Study completion was day 45 post-infusion and patients were followed up on days 75, 105 and 135 post-infusion.

Safety

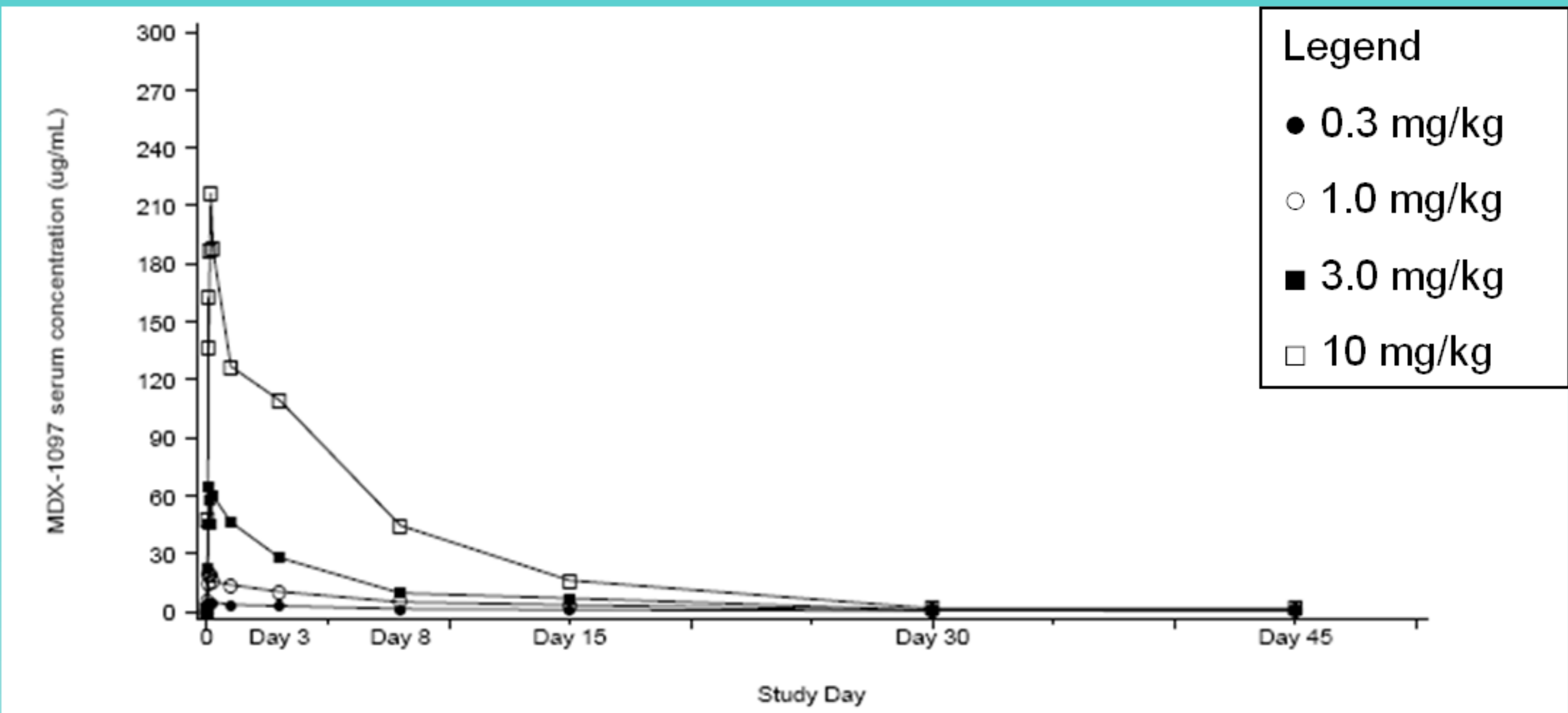
MDX-1097 was well tolerated when administered to male and female patients and no DLTs or SAEs were observed.

No significant QT interval prolongation was seen on ECGs.

Only two patients at the highest dose level experienced drug-related adverse events of Grade 1 or 2 in severity

- One patient had a mild infusion reaction (flushing, dyspnoea and nausea) which resolved after interruption of the infusion and administration of promethazine and paracetamol/acetaminophen.
 - A second patient experienced drug related AEs of nausea, pain in extremity and eructation on Day 1 post infusion.
- No patients developed antibodies to MDX-1097 (HACA).

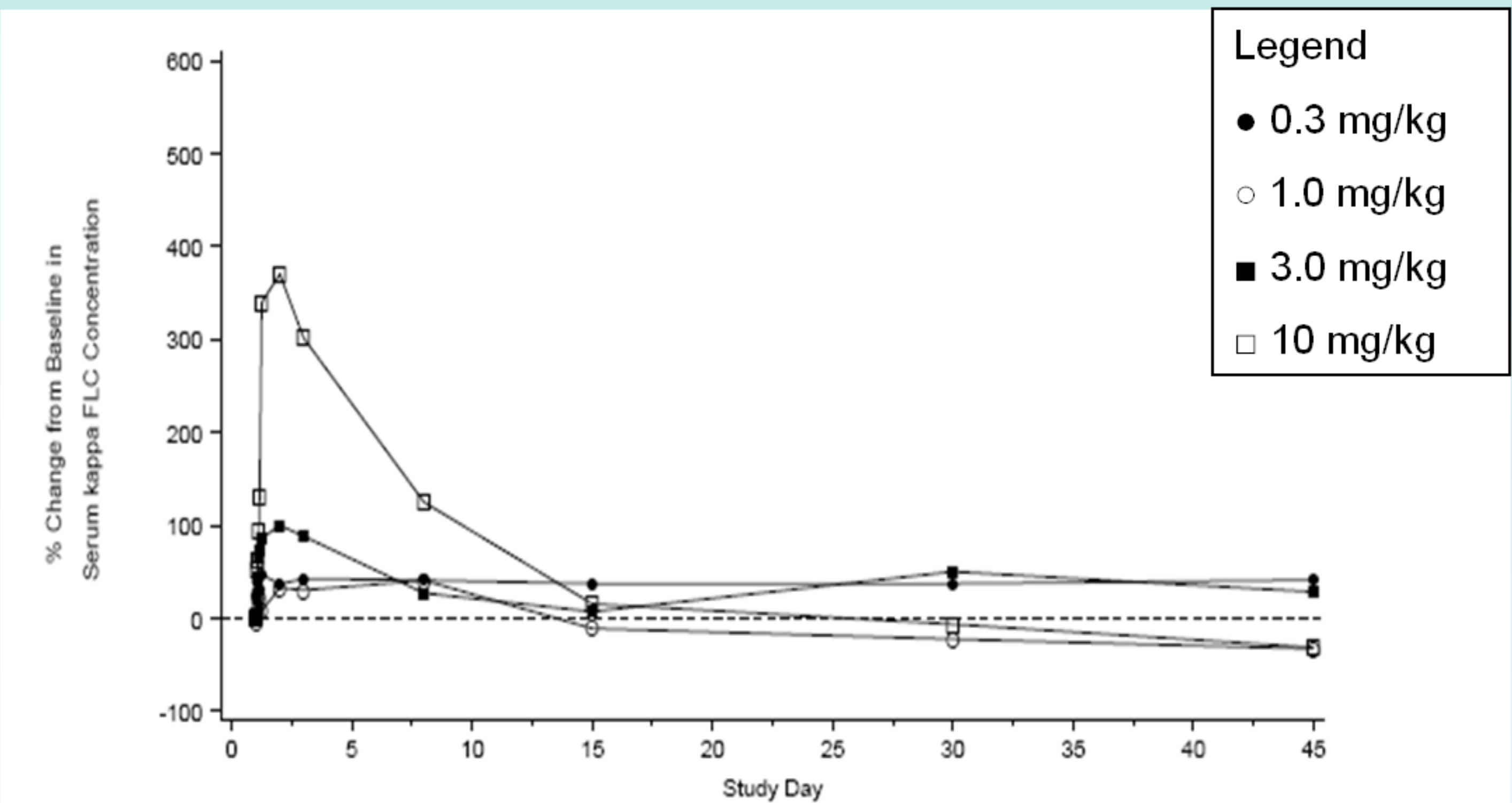
Pharmacokinetics



All patients had detectable plasma levels of MDX-1097 from 1 hour after infusion until at least Day 14, at each dose level from 0.3mg/kg to 10mg/kg. With increasing dose there was a sub-proportional increase in peak level of MDX-1097.

- No antigen sink was observed as MDX-1097 clearance increased with increasing dose
- The volume of distribution across all doses was confined to the blood and extracellular fluid spaces and was independent of dose
- The terminal elimination half life (t^{1/2}) decreased from a mean value of 10 days at 0.3 mg/kg to 5 days at 10 mg/kg

Pharmacodynamics



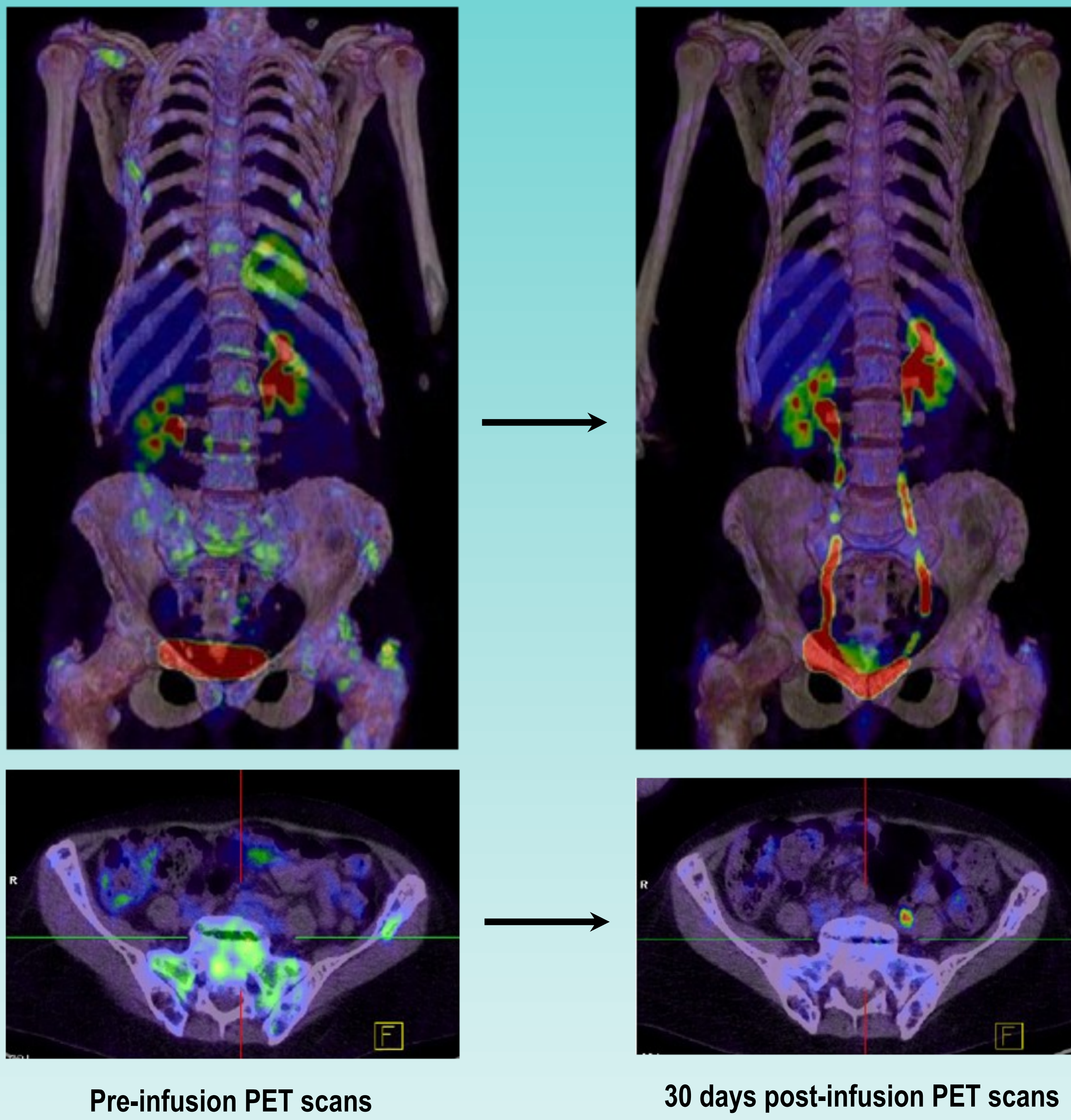
All patients showed an increase in serum κFLC following MDX-1097 infusion beginning within 24 hours of the infusion and lasting for at least 15 days.

Two notable exceptions were:

- serum κFLC in one patient (3.0 mg/kg cohort) showed a return to baseline at day 15 with a subsequent increase on days 30 and 45. However, by day 105 κFLC levels returned to baseline
- A second patient (10 mg/kg cohort) had a dramatic increase (692% above baseline) 6 hours post infusion. On days 45,105 and 135 his serum κFLC levels were between 55% and 61% below baseline which is indicative of a partial response

Efficacy

- Based on changes in serum M protein levels no patients were classified as responders
- However, one patient recruited to the trial based on her PET scan findings indicating extensive skeletal disease, showed a favorable and almost complete metabolic response 30 days post MDX-1097 infusion. The patient also showed symptomatic improvement including resolution of bone pain



Conclusions

- Single i.v. doses of MDX-1097 were safe and well tolerated in the range 0.3-10 mg/kg
- No DLT was observed at 10 mg/kg so the MTD was not reached
- Clearance of MDX-1097 increased with increasing dose and was dose dependent whereas the volume of distribution was dose independent. Therefore the t^{1/2} decreased with increasing dose from 10 days at 0.3 mg/kg to 5 days at 10 mg/kg
- Transient increases in serum κFLC were observed post infusion and this was attributed to MDX-1097 binding to light chain and hence reducing renal clearance
- There was no evidence of an effect on λFLC
- No responders were observed based on changes in serum M protein
- A Phase II study of repeated dosing of MDX-1097 in myeloma patients will use the 10mg/kg dose weekly for 8 weeks to determine potential efficacy and safety of this monoclonal antibody against kappa-restricted myeloma

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Dr Simon Harrison of the Peter MacCallum Cancer Centre, VIC, Australia referred the patient and provided the PET scans for this study.