

One year follow-up for the Phase I MTD study of Ultratrace Iobenguane I 131 in patients with malignant pheochromocytoma/paraganglioma (pheo)

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Abstract #C6

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BACKGROUND

Neuroendocrine Tumors (NETs): NETs are rare tumors of the nervous and endocrine systems. They are typically slow-growing and difficult to diagnose. Functional NETs secrete excess hormone, leading to a variety of clinical syndromes.

Pheochromocytomas are NETs that arise from sympathetic nervous system cells (chromaffin cells) in the adrenal gland and often produce catecholamines, resulting in hypertension in many patients. Extra-adrenal pheochromocytomas are called paragangliomas. Approximately 10–15% of patients with pheochromocytoma / paraganglioma (pheo) develop malignant disease. The five-year survival rate for malignancy is 50%. No treatments have been approved in the United States for these rare tumors.

Iobenguane I 131 Therapy and Ultratrace Technology: Iobenguane I 131, a substrate for the norepinephrine transporter, has been shown to be effective in the treatment of neuroendocrine cancers such as Pheo. Non-radioactive iobenguane has been shown to inhibit uptake of radiolabeled iobenguane by tumors and has potential to cause cardiovascular AEs. Ultratrace iobenguane I 131 (Ultratrace) is devoid of cold iobenguane thereby enhancing tumor accumulation of radiolabeled iobenguane and limiting iobenguane dose dependent adverse experiences.

Study Objectives: This phase I, dose-escalation study was designed to identify the maximum tolerated dose (MTD) of Ultratrace iobenguane I 131 and to evaluate the safety and efficacy of this targeted radiotherapeutic pharmaceutical in patients with malignant pheo.

METHODS

Study Overview: Patients were recruited from three sites (Duke University Medical Center, New York Presbyterian Hospital, Rhode Island Hospital). Dose escalation began at 6 mCi/kg and proceeded according to the 3+3 trial design with dose increases at 1 mCi/kg increments. Patients were dosed by weight up to 75 kg (e.g., 6 mCi/kg dose cannot exceed 450 mCi). Long term follow-up is ongoing.

Dose-limiting Toxicities (DLTs) are defined as: Febrile neutropenia (temperature ≥ 38.5 C and ANC $< 1000/\mu\text{L}$), Grade 3 thrombocytopenia with active bleeding, Grade 4 hematologic toxicity > 1 week duration, and/or Grade 3-4 non-hematologic toxicity.

Efficacy Assessments: Objective tumor response per Response Criteria in Solid Tumors (RECIST) and tumor marker response were evaluated at 3, 6, 9, and 12 months. In addition, reduction in antihypertensive medication, for those patients on antihypertensive medication at baseline, was evaluated.

Table 1. Baseline Study Population and Dosing

	6.0 mCi/kg (n = 3)	7.0 mCi/kg (n = 6)	8.0 mCi/kg (n = 6)	9.0 mCi/kg (n = 6)	Total (N=21)
Age in years					
Mean (SD)	52 (18.2)	54 (17.3)	48 (6.1)	48 (13.3)	50 (13.0)
Range	36–72	30–72	39–55	34–65	30–72
Gender					
Male (%)	0 (0)	5 (83)	4 (67)	4 (67)	13 (62)
Female (%)	3 (100)	1 (17)	2 (33)	2 (33)	8 (38)
Weight in kg					
Mean (SD)	62.3 (7.4)	68.9 (16.4)	97.6 (25.1)	91.3 (10.6)	82.6 (21.6)
Range	56–70	42–84	60–126	78–103	42–126
Race					
Black (%)	1 (33.3)	0	1 (16.7)	1 (16.7)	3 (14.3)
White (%)	2 (66.7)	5 (83.3)	4 (66.7)	3 (83.3)	16 (76.2)
Other (%)	0	1 (16.7)	1 (16.7)	0	2 (9.5)
Dose (mCi)					
Mean (SD)	375 (45.1)	463 (84.2)	572 (50.2)	661 (24.2)	538 (115.3)
Range	333-423	325-536	473-609	633-696	325-696

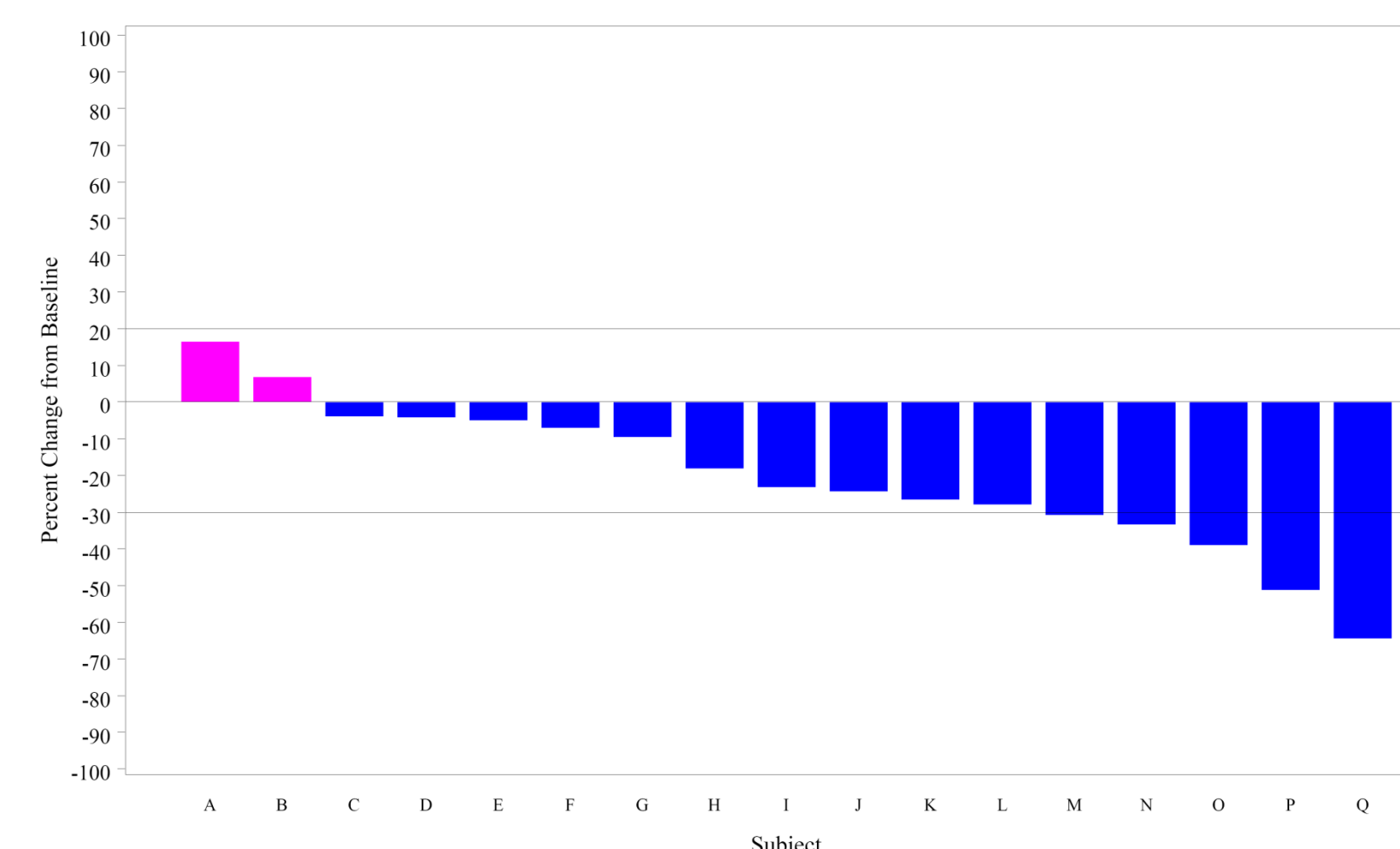
RESULTS

Safety: Twenty-one patients were treated: 3 at 6 mCi/kg (0/3 DLTs), 6 at 7 mCi/kg (1/6 DLTs), 6 at 8 mCi/kg (1/6 DLTs), and 6 at 9 mCi/kg (2/6 DLTs). The DLTs were neutropenia (2), febrile neutropenia (1), and thrombocytopenia (1). Two patients died within the 12 month efficacy follow-up (hepatic failure, pulmonary embolism).

Figure 1. Posterior Bone Scans at 0, 12 and 18 Months



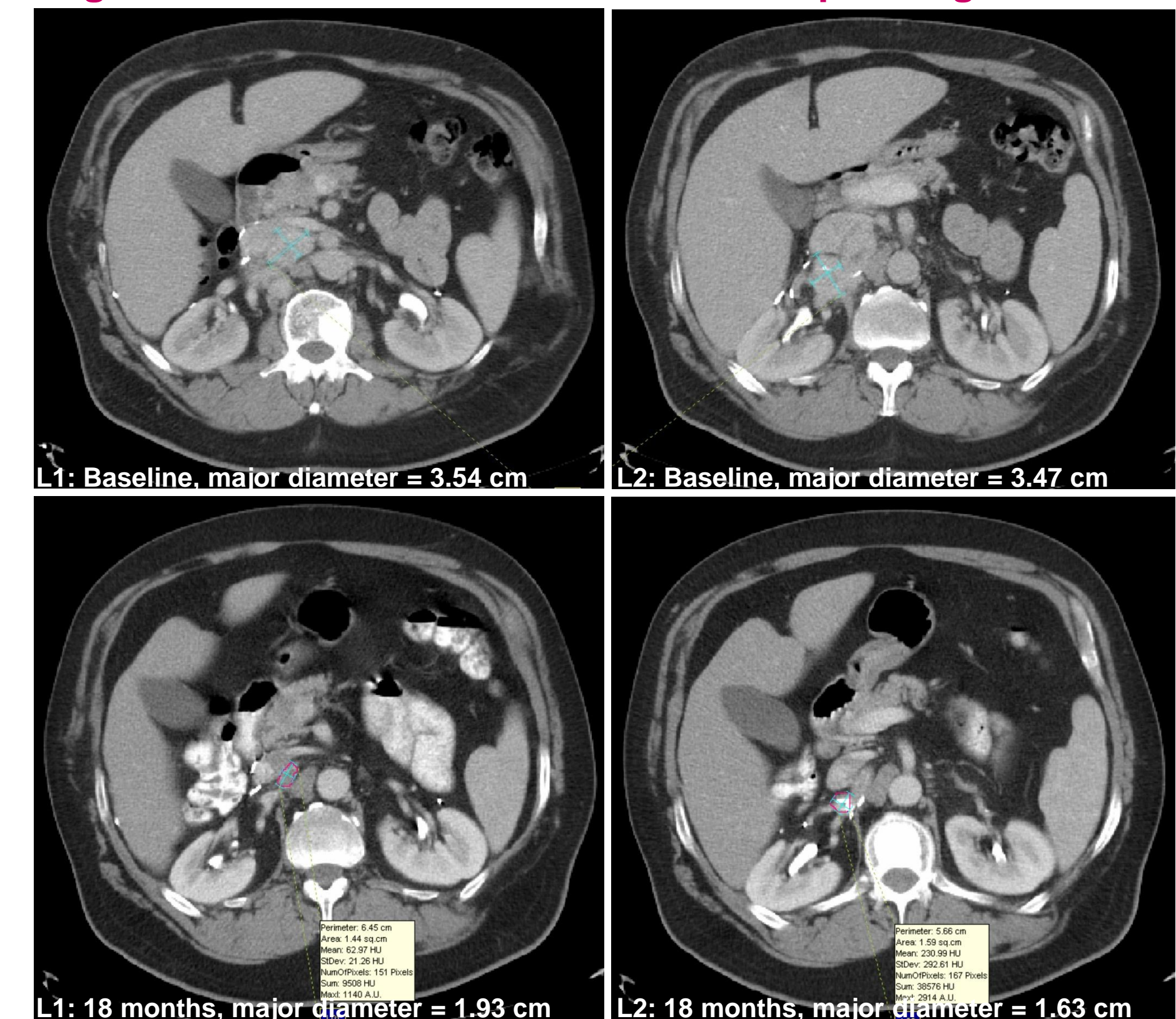
Figure 2. Best Decrease in Target Tumor Size



RESULTS, cont.

Efficacy: Best response per RECIST was partial response (PR) for 3 patients (14%), stable disease for 14 (67%), progressive disease for 2 (10%), and not evaluable for 2 (10%). All 3 PRs were documented at 3 months and continued through 12 months. Mean serum chromogranin A and vanillylmandelic acid levels were decreased from baseline at 3, 6 and 9 months. Furthermore, 5 of 15 (33%) patients taking antihypertensives at time of therapy reduced or discontinued use following treatment.

Figure 3. CT Scans for 2 lesions in a Responding Patient



SUMMARY AND CONCLUSIONS

- The MTD in this dose escalation study was 8 mCi/kg.
- Related adverse events were primarily hematologic, as expected.
- A single dose of Ultratrace iobenguane I 131 demonstrated clinical benefit and stabilized or reduced tumor dimensions and tumor marker levels.
- Objective tumor response was sustained through 12 Months.