

CHR# H7015-96457-15
Principal Investigator: Paul A. Fitzgerald, M.D.
Co-Principal Investigator: Katherine Matthay, M.D.

**UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
COMPREHENSIVE CANCER CENTER**

**A PHASE II STUDY OF ¹³¹I-LABELED MIBG
(METAiodobenzylguanidine) IN PATIENTS WITH UNRESECTABLE
MALIGNANT PHEOCHROMOCYTOMA & RELATED TUMORS
CHR# H7015-06457-15
CC# 03991**

Principal Investigator
Paul A. Fitzgerald, M.D.
Clinical Professor of Medicine
Department of Medicine
Division of Endocrinology
University of California, San Francisco
350 Parnassus Avenue, Suite 710
San Francisco, CA 94117
Phone: 415-665-1136
Fax: 415-665-8500
paulf@itsa.ucsf.edu

Co-Principal Investigator
Katherine K. Matthay, M.D.
Professor of Pediatrics
Department of Pediatrics
Chief, Division of Pediatric Hematology-Oncology
Box 0106, 505 Parnassus Avenue, Moffitt 647
University of California, San Francisco
San Francisco, CA 94143-0106
Phone: 415-476-3831
Fax: 415-502-4372
matthayk@peds.ucsf.edu

Robert Goldsby, M.D.
Assistant Professor of Clinical Pediatrics
Department of Pediatrics
Box 0106, 505 Parnassus Avenue, Moffitt M653
University of California, San Francisco
San Francisco, CA 94143-0106
Phone: 415-476-3831
Fax: 415-502-4372
goldsbyr@peds.ucsf.edu

CHR# H7015-96457-15

Principal Investigator: Paul A. Fitzgerald, M.D.

Co-Principal Investigator: Katherine Matthay, M.D.

Randall A. Hawkins, M.D., Ph.D.
Professor of Radiology
Chief, Division of Nuclear Medicine
Box 0628, 513 Parnassus Avenue, Long-333
University of California, San Francisco
San Francisco, CA 94143-0628
Phone: 415-353-1886
Fax: 415-353-8571
randy.hawkins@radiology.ucsf.edu

David C. Price, M.D.
Professor of Radiology
Department of Radiology
Division of Nuclear Medicine
Box 0252, 505 Parnassus Avenue, Long-340
University of California, San Francisco
San Francisco, CA 94143-0252
Phone: 415-353-1665
Fax: 415-353-8571
david.price@radiology.ucsf.edu

Thierry M. Jahan, M.D.
Assistant Clinical Professor of Medicine
Department of Medicine
Division of Hematology-Oncology
Box 1705, Cancer Center, 7th Floor
University of California, San Francisco
San Francisco, CA 94143-1705
Phone: 415-885-3792
Fax: 415-353-7150
thierry.jahan@ucsfmedctr.org

Charles A. Linker, M.D.
Clinical Professor of Medicine
Department of Medicine
Division of Hematology-Oncology
Box 0324, 1600 Divisadero A-502
University of California, San Francisco
San Francisco, CA 94143-0324
Phone: 353-2737
Fax: 353-2467
linkerc@medicine.ucsf.edu

CHR# H7015-96457-15

Principal Investigator: Paul A. Fitzgerald, M.D.

Co-Principal Investigator: Katherine Matthay, M.D.

Lloyd Damon, M.D.
Professor of Medicine
Department of Medicine
Division of Hematology-Oncology
Box 0324, A-523
University of California, San Francisco
San Francisco, CA 94143-0324
Phone: 415-353-2749
damonl@medicine.ucsf.edu

John P. Huberty, Ph.D.
Nuclear Medicine Pharmacology
Department of Radiology
Division of Nuclear Medicine
Box 0628, 505 Parnassus Avenue, Long-340
University of California, San Francisco
San Francisco, CA 94143-0628
Phone: 415-353-1549
Fax: 415-353-8571
hubertj@itsa.ucsf.edu

Janet J. Veatch, R.N., C.N.S.
Department of Nursing
Box 0106, 505 Parnassus Avenue
University of California, San Francisco
San Francisco, CA 94143-0106
Janet@VeatchSolutions.com

QUALIFICATIONS OF INVESTIGATORS

Dr. Paul Fitzgerald is an experienced board-certified adult endocrinologist with extensive experience treating pheochromocytoma. He also has a broad internal medicine background.

Dr. Katherine Matthay is an experienced board-certified pediatric hematologist-oncologist. She has extensive experience with neuroblastoma, dealing with the side effects of chemotherapy and radiation therapy and in bone marrow transplantation. She has a broad background in clinical research and has concluded the preliminary studies in ¹³¹I-MIBG in neuroblastoma.

Dr. Robert Goldsby is an experienced board-certified pediatric hematologist-oncologist. He has extensive experience treating children with malignancies. He has experience treating children with neuroblastoma, pheochromocytoma, and paraganglioma. Dr. Goldsby also has expertise in clinical research and clinical trial management.

Dr. Randall Hawkins and Dr. David Price are specialists in nuclear medicine with previous experience in administration of targeted radionuclides. They have personally directed the synthesis and administration of ¹³¹I-MIBG for the scans and treatment in patients with neuroblastoma and pheochromocytoma. John Huberty is an extremely experienced radiopharmacist who will prepare and tag the ¹³¹I-MIBG.

Dr. Charles Linker and Dr. Lloyd Damon are experienced hematologists who have done bone marrow transplantations and will harvest marrow and transplant it if required.

Dr. Thierry Jahan is an experienced board-certified adult hematologist-oncologist. He has extensive experience treating patients with neuroendocrine tumors.

Janet Veatch is a registered nurse and a certified nurse specialist in pediatric oncology with extensive experience in treating patients with ¹³¹I-MIBG. She has been the coordinator for the scheduling and treatment of pediatric and adult patients with malignant pheochromocytoma and paraganglioma.

TABLE OF CONTENTS

<u>SECTION</u>	<u>PAGE</u>
1.0 INTRODUCTION.....	6
2.0 OBJECTIVES.....	12
3.0 ON-STUDY GUIDELINES.....	12
4.0 ELIGIBILITY CRITERIA.....	13
5.0 REGISTRATION & DATA SUBMISSION.....	15
6.0 REQUIRED DATA.....	17
7.0 TREATMENT PLAN.....	19
8.0 MANAGEMENT OF TOXICITY.....	21
9.0 DRUG FORMULATION AND PREPARATION.....	22
10.0 ANCILLARY THERAPY.....	22
11.0 CRITERIA FOR RESPONSE, PROGRESSION, RELAPSE...	23
12.0 STATISTICAL CONSIDERATIONS.....	23
13.0 DATA SAFETY MONITORING PLAN.....	25
14.0 REVIEW AND OVERSIGHT REQUIREMENTS.....	25
15.0 EXPEDITED ADVERSE EVENT REPORTING (AER).....	27
16.0 STOPPING RULES.....	29
17.0 REFERENCES.....	30

APPENDIX A: Stem Cell Harvest and Transplant Protocol

APPENDIX B: Consent Form

CHR# H7015-96457-15
Principal Investigator: Paul A. Fitzgerald, M.D.
Co-Principal Investigator: Katherine Matthay, M.D.

**UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
COMPREHENSIVE CANCER CENTER**

**A PHASE II STUDY OF ¹³¹I-LABELED MIBG
(METAIODOBENZYLGUANIDINE) IN PATIENTS WITH UNRESECTABLE
MALIGNANT PHEOCHROMOCYTOMA & RELATED TUMORS
CHR# H7015-06457-15
CC# 03991**

INVESTIGATORS

Paul A. Fitzgerald, M.D., Robert Goldsby, M.D., Randall Hawkins, M.D., Ph.D.,
John Huberty, M.S. David Price, M.D. Janet Veatch, R.N., C.N.S., Thierry Jahan, M.D.,
Charles A. Linker, M.D. Lloyd Damon, M.D, Katherine Matthay, M.D.

1.0 INTRODUCTION

1.1 Malignant Pheochromocytoma

Malignant pheochromocytoma is a rare disease with an incidence of about 3/10,000,000 persons per year. Common sites of metastatic disease include lung, lymph nodes, and bone. Although the effects of excessive catecholamine can be reduced by adrenergic blockade (phenoxybenzamine or propranolol) or blocking of catecholamine synthesis (metyrosine), these drugs do not halt tumor growth. Five-year survival has been 44%.

For malignant pheochromocytoma, radiation therapy has been palliative but not curative. Chemotherapy trials have previously failed to produce cures or significant remissions^{50,51,52}. A more recent study reported the combined use of a chemotherapy regimen (CVD:cyclophosphamide, vincristine and dacarbazine) in 14 patients with malignant pheochromocytoma: A complete or partial response was provided in 57% of patients (median duration, 21 months); however, disease progression occurred in 9 of the 14 patients and there were 6 deaths with short-term follow-up⁵³.

For malignant paraganglioma, a remission was reported in one patient utilizing combination chemotherapy (CAP:cyclophosphamide, doxorubicin, cisplatin) with an 11 month follow-up. Treatments for malignant paraganglioma have been otherwise ineffective⁵⁴. Any potential therapeutic innovation requires careful investigation. Tumor targeted systemic radiotherapy for pheochromocytoma with ¹³¹I- metaiodobenzylguanidine (MIBG) is promising in this regard.

1.2 History of the Use of ¹³¹I-MIBG for Treatment of Malignancy

Metaiodobenzylguanidine is a guanethidine derivative structurally resembling norepinephrine. Originally synthesized by Short and Darby as a potential antihypertensive agent²⁸, MIBG was investigated by Wieland and his colleagues at the University of Michigan as a potential radiolabeled adrenergic neuron imaging agent. In this regard MIBG was found to be ineffective as an antihypertensive drug, but had marked affinity for, and concentration in, the adrenal medulla.^{31,37,38} From pharmacologic studies MIBG has been found to participate in both uptake pathways by adrenal medullary neural cells where it is subsequently stored in neurosecretory granules.^{14,31,33}

MIBG can be labeled with radioactive isotopes of iodine, suitable for diagnostic imaging applications, or to characterize of adrenal masses incidentally discovered during CT.^{12,26,27,29} In the meantime, MIBG has been shown to concentrate in several neoplasms of neuroectodermal origin, including neuroblastoma, where a unique value in staging this tumor is recognized.^{7,11,16,20} Although having been categorized as an Orphan Drug by the United States Food and Drug Administration, MIBG has not been developed commercially, for economic reasons.

Because of the effectiveness of ¹³¹I for the treatment of hyperthyroidism and thyroid cancer, ¹³¹I-MIBG has undergone limited clinical trials for the treatment of malignant pheochromocytoma where some early success and limited toxicity has been reported³⁰. The experience of 116 patients treated with ¹³¹I-MIBG throughout the world has been published^{9,10,15,18,30,34,35,36} and summarized by Loh et al.⁶³ Five patients with malignant pheochromocytoma were treated at the University of Michigan with ¹³¹I-MIBG at ten month intervals.³⁰ Total doses were: (1) 484 mCi in 4 treatments over 15 months; (2) 373 mCi in 3 treatments over 8 months; (3) 410 mCi in 3 treatments over 17 months; (4) 270 mCi in 2 treatments over 3 months; (5) 293 mCi in 2 treatments over 3 months. Patients (1) and (2) had predominantly soft tissue metastases and had significant responses with disappearance of symptoms and a reduction in volume and function of tumors to less than 50% of pretreatment values. The remissions lasted over 1 year to the date of publication. There was no significant toxicity reported. Tumor absorbed doses were stated to range between 1,300 and 12,000 cGy, but detailed methods of dose estimation are not clear.

Charbonnel et al.⁴⁵ in France have reported successful treatments with ¹³¹I-MIBG in 7 patients with metastatic pheochromocytomas (3 with soft tissue metastasis, 3 with soft tissue and bone metastasis, and 1 with bone metastasis). There was a decrease in catecholamine of greater than 50% in all 7 patients and a decrease in tumor mass of greater than 50% in all 7 patients. Treatment was with 100-200 mCi every 3-6 months. Toxicity included moderate pancytopenia in one patient with diffuse osseous metastasis after the second ¹³¹I-MIBG dose which resolved

within 3 months but which recurred after the third treatment (cumulative dose 394 mCi:) requiring blood and platelet transfusion. A mild increase in blood pressure was noted in 3 patients 2-3 days after treatment that resolved over several days.

Troncone et al.⁴⁹ in Italy reported treatment with ¹³¹I-MIBG of advanced pheochromocytoma. One patient with residual tumor received 300 mCi in 3 courses at 3 month intervals and had complete regression of tumor, normalization of catecholamine levels and had no evidence of disease 20 months after start of therapy. Another patient with metastases had an 18 month remission after 670 mCi ¹³¹I-MIBG over 9 courses at 3 month intervals, but refused further treatment and died 6 months later. Another patient died after 15 month stabilization of the disease after 340 mCi ¹³¹I-MIBG over 3 courses. No change was noted in the fourth patient with massive abdominal recurrence who received only 150 mCi ¹³¹I-MIBG and died 2 months later. There were no adverse reactions reported.

Troncone et al.⁴⁹ also reported ¹³¹I-MIBG treatment for 4 patients with medullary thyroid carcinomas (MTC). One patient with MTC had a complete response to a dose of 360 mCi over two treatments with a 20 month follow-up. Another 2 patients (receiving 430 mCi over 2 courses and 891 mCi over 6 courses) have had partial responses with a follow-up of 23 and 24 months respectively.

Brendel et al.⁴⁴ in France reported 2 patients with malignant pheochromocytoma treated with ¹³¹I-MIBG. One patient with bone and lung metastases received 2,030 mCi ¹³¹I-MIBG over 10 courses at 3 month intervals; had remission in pain and asthenia, regression of >50% in skull and lung tumors and a decrease in VMA of 35%. The second patient received 950 mCi ¹³¹I-MIBG over 5 courses at 3 month intervals. She had normalization of VMA levels and a reduction by >50% in the volume of metastatic lymph nodes. Side effects included transient leukopenia. One patient had unstable hypertension and nausea 48-72 hours after each treatment.

Limone et al.⁴⁸ and Konings⁴⁶ each reported 1 patient with clinical improvement following ¹³¹I-MIBG treatment. The later authors suggest that treatment results could be improved if ¹³¹I-MIBG were given to patients with low metastatic tumor burden.

Mukerjee et al.⁶⁶ in Britain reported ¹³¹I-MIBG treatment of 15 patients with metastatic pheochromocytoma or paraganglioma patients were treated repeatedly to a cumulative dose of 592 mCi (21.0 GBq); range 200 – 1592 mCi (7.4 – 58.9 Gbq). No patients had complete remissions, but 82% had stable disease. The overall 5-year survival was 85%. Hormonal control was attained in 50%.

Higher doses of ¹³¹I-MIBG may need to be used which would suppress bone marrow. However, current techniques of peripheral blood stem cell collection, storage and transplantation can mitigate these side effects (i.e., marrow rescue). Pheochromocytoma is less likely to involve bone marrow than is neuroblastoma,

making marrow suppression less likely; autologous transplantation of marrow is less likely to contain malignant cells than marrow from patients with neuroblastoma.

Facts concerning patients with neuroblastoma treated with ^{131}I -MIBG (prior to the current UCSF study, see below) are sketchy. Single doses administered by others have ranged from 27-200 mCi, with a maximum cumulative dose in one patient of 1,200 mCi. Concerning efficacy, most workers observe that ^{131}I -MIBG therapy can ameliorate pain, and in a minority of patients reduce tumor bulk. Response rates have ranged from 10-50%, but definition of response has been poorly defined and qualitative, ranging from pain relief or decreased catecholamines to actual disappearance of lesions by scans. Toxicity even at substantial doses has been minimal and included brief nausea and vomiting, mild reversible myelosuppression, and transient hepatic dysfunction.^{9,10,15,18,34,36}

1.2 Report of UCSF Phase I Study of ^{131}I -MIBG Treatment of Patients with Malignant Neuroblastoma:

In 1986, Dr. Katherine Matthay established at UCSF a Phase I ^{131}I -MIBG therapy protocol for treating children with malignant neuroblastoma.

The necessary radiation safety and quality control procedures for preparation of large quantities of high specific activity ^{131}I -MIBG was established and nurses were trained in the Pediatric Clinical Research Center and 11L in the proper care of the patients and radiation precautions.

By May 1997, 31 patients have received courses of ^{131}I -MIBG at UCSF for malignant neuroblastoma. Patients received the following doses of ^{131}I -MIBG in Phase I dose escalation: 3 mCi/kg (2); 6 mCi/kg (3); 9 mCi/kg (6); 12 mCi/kg (7); 15 mCi/kg (7); ≤ 18 mCi/kg (6). The only significant toxicity was hematological, with grade 4 thrombocytopenia in 85% of first courses and grade 4 neutropenia in 50% of first courses. No patients receiving doses of 12 mCi/kg or less required bone marrow or stem cell infusion after the first course. However, 4 of 6 patients at the 15 mCi/kg level required bone marrow infusion, and 4 of 6 patients at the 18 mCi level required re-infusion after one course of ^{131}I -MIBG. All patients engrafted neutrophils promptly.

There was no significant (grade 3 or 4) non-hematological toxicity from the ^{131}I -MIBG up through the 18 mCi/kg dose level. Nausea and vomiting (grade 1 or 2) were common on the first and second day after treatment. Several patients had mild xerostomia. Two patients developed mild asymptomatic hypothyroidism at 1.5 and 8 months post-treatment, requiring thyroid replacement, but one of these patients had also received IL-2, known to cause hypothyroidism. One adult patient who was already amenorrheic pre-treatment was diagnosed with ovarian failure after 3 courses of ^{131}I -MIBG. No cardiac, renal, hepatic, or adrenal

dysfunction has been detected on standard testing. However, one child with an 8 year prior history of chemotherapy including VP16 and alkylating agents, developed secondary ANLL after her second ¹³¹I-MIBG treatment for neuroblastoma. In 1997, following the review of the above dose escalation data, the above UCSF protocol entered phase II. The phase one experience (summarized above) has been published: Matthay KK, DeSantes K, Hasegawa B, Huberty J, Hattner RS, Ablin A, Reynolds CP, Seeger RC, Weinberg VK, Price D: Phase I dose escalation of ¹³¹I-metaiodobenzylguanidine with autologous bone marrow support in refractory neuroblastoma. *Journal of Clinical Oncology* 16:229-236, 1998.⁶⁴

UCSF is now actively involved in a large multi-center phase II study involving the use of ¹³¹I-MIBG for pediatric malignant neuroblastoma.

1.3 Report of the UCSF Experience with ¹³¹I-MIBG Treatment of Patients with Malignant Pheochromocytoma and Related Tumors:

In 1991, Dr. Paul Fitzgerald et al. established at UCSF a Phase I-II protocol for ¹³¹I-MIBG therapy for malignant pheochromocytoma and related tumors. In 1997, on the basis of Dr. Matthay's Phase I data summarized above, this protocol was revised and entered Phase II, being approved by UCSF's Committee on Human Research.

A paper describing the UCSF experience with our the first 12 patients receiving ¹³¹I-MIBG therapy for malignant pheochromocytoma has been published: Rose B, Matthay KK, Price D, Huberty J, Klencke B, Norton JA, Fitzgerald PA: High-dose ¹³¹I-Metaiodobenzylguanidine therapy for 12 patients with malignant pheochromocytoma. *Cancer* 2003;98:239-48.⁶⁷ Three patients experienced complete remissions. The median dose ¹³¹I-MIBG was 800 mCi. Hematologic toxicity was significant but usually transient and tolerable. One patient required PBSC infusion. The over-all response rate was: 3/12 CR; 5/12 PR; 4/12 PD.

To-date, a total of 32 patients have been treated at UCSF with ¹³¹I-MIBG for malignant pheochromocytoma and related tumors: 8 children and 24 adults. Two girls, treated with 3 courses of ¹³¹I-MIBG, developed primary amenorrhea. One man developed partial hypogonadism after 3 courses of ¹³¹I-MIBG. One girl developed myelofibrosis and monosomy 7 five years after her first of 3 courses of ¹³¹I-MIBG; she died suddenly after chemotherapy and allogenic stem cell transplantation at another institution. The overall *sustained* response rate (CR, PR, SD) to ¹³¹I-MIBG has been 67% of the 30 patients with follow-up (4 CRs, 15 PRs, 1 SD). Additional patients have had subjective responses without significant tumor shrinkage or have had a reduction in the tumors' growth velocity. Following their treatment with high-dose ¹³¹I-MIBG, 7 of the 8 children remain alive; 17 of the 24 adults remain alive. One adult death was not tumor-related.

1.5 Rationale

Malignant pheochromocytoma has been resistant to external beam radiation therapy as well as conventional chemotherapy. There are no standard chemotherapeutic regimens for the treatment of patients with malignant pheochromocytoma. The most commonly used regimen of cyclophosphamide, vincristine, and dacarbazine (CVD) typically produces severe gastrointestinal, hematologic, neurologic, and other toxicities. The CVD regimen must be repeated every 21 days in order to produce occasional partial remissions for patients with malignant pheochromocytoma.

¹³¹I-MIBG therapy is now widely recognized as an effective treatment for patients with malignant pheochromocytoma. While lower-dose ¹³¹I-MIBG therapy (<300 mCi) has been used extensively for treating patients with malignant pheochromocytoma, complete remissions and sustained partial remissions have been rare at these doses, particularly among patients with bone metastases.

In order for ¹³¹I-MIBG therapy to achieve a remission for patients with malignant pheochromocytoma, sufficient doses of ¹³¹I-MIBG must enter tumor cells. In the past, high-dose ¹³¹I-MIBG therapy has not been possible, due to the dangers of myelosuppression and the logistical difficulties and unreliability of bone marrow harvest and transplant. The development of peripheral blood stem cell leukaphoresis and cryopreservation has made it possible to treat other malignancies more aggressively and more successfully. Similarly, it is now possible to treat patients with malignant pheochromocytoma more aggressively with ¹³¹I-MIBG, since peripheral blood stem cells may be collected in advance such that they may be reinfused in the event of prolonged myelosuppression following high-dose ¹³¹I-MIBG therapy.

The feasibility and short-term safety of using high-dose ¹³¹I-MIBG therapy has been demonstrated in a Phase I clinical trial at U.C.S.F. for the treatment of patients with malignant neuroblastoma, a neuroendocrine tumor closely related to pheochromocytoma (see Section 1.3). This UCSF protocol differs from others throughout the world in that it uses higher doses of ¹³¹I-MIBG, approximately three times the doses used at most other centers.

Our experience to-date suggests a role for high-dose ¹³¹I-MIBG therapy for patients with malignant pheochromocytoma. Compared to available chemotherapy and radiation therapy, high-dose ¹³¹I-MIBG appears to constitute a relatively inexpensive, non-toxic, and widely available drug, offering new hope for these unfortunately stricken patients. UCSF is currently the only center in the United States available for cell-specific radiotherapy for pheochromocytoma and related tumors with ¹³¹I-MIBG.

1.6 Inclusion of Women and Minorities

Patients who meet the eligibility criteria will be included in this study without regard to gender, race, or ethnicity, which are not expected to influence response or toxicity to the treatment. However, gender, race, and ethnicity will be analyzed as important co-variants in reporting the results.

2.0 OBJECTIVES

2.1 Primary Objective: To assess the efficacy of high-dose ^{131}I -MIBG in the treatment of patients with malignant pheochromocytoma and related tumors, with the basis of this initial examination being the percentage of patients in CR or PR, and the percentage of patients without PD for 3 years after the initial administration on ^{131}I -MIBG therapy.

2.2 Secondary Objectives

- 2.2.1 To describe the response rate of malignant pheochromocytoma patients treated with high-dose ^{131}I -MIBG.
- 2.2.2 To describe the toxicity of high-dose ^{131}I -MIBG in patients with malignant pheochromocytoma.
- 2.2.3 To describe the overall survival and failure-free survival of malignant pheochromocytoma patients treated with high-dose ^{131}I -MIBG.
- 2.2.4 To determine the utility of using the serum level of Chromogranin A as a tumor marker for patients with malignant pheochromocytoma.

3.0 ON-STUDY GUIDELINES

The following guidelines are to assist referring physicians in selecting patients for whom high-dose ^{131}I -MIBG is safe and appropriate. Physicians should recognize that the following factors will disallow participation in the study:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Patients with an estimated life expectancy <12 weeks.
- ^{131}I -MIBG is potentially teratogenic. Therefore, women must agree to use an appropriate method of birth control for at least 2 months preceding high-dose ^{131}I -MIBG and for at least 6 months thereafter. Appropriate methods of birth control include oral contraceptives, abstinence, or double barrier method (diaphragm plus condom). Men must agree to use an appropriate method of birth control for at least 6 months after high-dose ^{131}I -MIBG. Appropriate methods of birth control include abstinence or double barrier method (diaphragm plus condom).

4.0 ELIGIBILITY CRITERIA

4.1 Histologic Documentation: Histologic documentation of malignant pheochromocytoma or related tumors (paraganglioma, neuroblastoma, medullary thyroid carcinoma, carcinoid tumors), not amenable to curative surgery. Any site of origin of malignant pheochromocytoma, including but not limited to: adrenal, neck, thorax, abdominal, or pelvis is allowed.

4.2 Prior Treatment:

- No cytotoxic chemotherapy for at least 3 weeks prior to high-dose ^{131}I -MIBG or concurrent with high-dose ^{131}I -MIBG.
- > 2 weeks since major surgery.
- > 4 weeks since completion of prior radiation therapy, as long as measurable disease lies outside the radiation port.
- No treatment with an investigational agent concurrent or within 30 days of high-dose ^{131}I -MIBG.
- Patients who have received previous chemotherapy or radiation therapy must have evidence of persistent disease on ^{123}I -MIBG scan and elevated tumor markers or measurable CT lesions before receiving high-dose ^{131}I -MIBG.

4.3 Metastases Excluding Eligibility: No patients with a known significant MIBG-avid parenchymal brain metastasis; leptomeningeal metastases do not exclude eligibility. Hepatic metastases exclude eligibility if they functionally impair liver function (AST or total bilirubin ≥ 2.5 times the ULN).

4.4 Measurable Disease

Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as > 10 mm as measured with CT scanning.

Lesions < 10 mm diameter or bone lesions in the presence of demonstrable uptake of ^{123}I -MIBG on diagnostic scanning, plus elevated levels of tumor markers that are specific for malignant pheochromocytoma: plasma catecholamines or metanephrines, urine catecholamines or metanephrines, serum chromogranin A.

Lesions whose size is considered non-measurable include the following:

- Bone lesions (see above)
- Leptomeningeal disease
- Ascites
- Pleural/pericardial effusion
- Chylothorax
- Lesions within the chest or abdomen that are not confirmed to be pheochromocytoma by biopsy or ^{123}I -MIBG scanning.

4.5 ^{131}I -MIBG or ^{123}I -MIBG Avidity: All patients must have ^{123}I -MIBG or ^{131}I -MIBG whole-body scanning prior to therapy. Metastases must be avid for the isotope such that their measured gamma radiation measures \geq twice that of background radiation.

4.6 Age: ≥ 4 years of age.

4.7 Life Expectancy: greater than 12 weeks.

4.8 Karnofsky Performance Status: 60% or higher.

4.9 Anticoagulation: Heparin, LMW heparin, coumadin, and other anticoagulants may be used only when platelet counts are $\geq 100,000/\mu\text{L}$. Platelet counts will be monitored twice weekly after ^{131}I -MIBG therapy. (Section 6.2.3)

4.10 Pregnancy & Nursing: Non-pregnant and non-nursing because the effects of high-dose ^{131}I -MIBG on the fetus/infant are unknown.

4.11 Second Malignancies:

- Patients with a “currently active” second malignancy, other than non-melanoma skin cancers, are not eligible.
- Patients are not considered to have a “currently active” second malignancy if they have been cancer-free for ≥ 5 years.

4.12 Intercurrent Illness: No patients with uncontrolled intercurrent illness including but not limited to: ongoing active infections, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements

4.13 Required Initial Laboratory Data (Minimum Levels):

- Neutrophil count $\geq 1,000/\mu\text{L}$
- Platelet count $\geq 80,000/\mu\text{L}$
- AST (SGOT) $\leq 2.5 \times \text{ULN}$
- Total bilirubin $\leq 2.5 \times \text{ULN}$
- Creatinine $\leq 2 \times \text{ULN}$

5.0 REGISTRATION & DATA SUBMISSION

5.1 Registration

5.1.1 Registration Requirements

- **Informed Consent:** The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts.
- **Protocol Approval:** Current approval for this protocol is required from the UCSF Committee on Human Research (CHR) and from the UCSF Comprehensive Cancer Center Protocol Committee.

5.1.2 Registration Procedures: Patients must be registered at UCSF with either Dr. Katherine Matthay, M.D. (patients \leq age 18 years) or Dr. Paul Fitzgerald, M.D. (patients \geq age 19 years). The following information is required:

- Confirmation of eligibility criteria (Section 4.0)
- Name of treating UCSF physician
- Patient's full name, address, phone number, date of birth
- Patient's Social Security #, and UCSF medical record #
- Patient's race and gender
- Patient's weight in kg and height in cm
- Patient's disease diagnosis
- Patient's Karnofsky performance status
- Patient's type of insurance/method of payment
- Referring physician's name, address, phone number, fax number, and e-mail address
- Signed and dated consent form

5.2 Data Submission: All subject data will be sent to Paul Fitzgerald, M.D. 350 Parnassus Avenue, Suite 710, San Francisco, California, 94117. fax: 415-665-8500; e-mail: paulf@itsa.ucsf.edu.

Required data & submission schedule:

Data	Submission Schedule
• Registration information	-Initial & yearly update
• Copies of baseline pathology, CT & MIBG scan reports	-At registration
• Lab data (baseline)	-At registration
• Lab data (1 st yr post ¹³¹ I-MIBG)	-First 2 mos (2x/wk send stat) then q 3 mos – send in 1 wk
• CT & MIBG scan f/u reports (1 st yr post ¹³¹ I-MIBG)	-Every 3 mos – send in 1 wk
• Adverse Events (AE) Form (detailing toxicities, esp Gr 4 & 5)	-Within 1 week of AE
• Long-Term f/u Form	-Every 6 months beginning 18 months after ¹²³ I-MIBG for up to 10 years, at relapse, progression, or death
• Notification of Death Form	-At time of death

5.2.1 Common Toxicity Criteria: This study will utilize the Common Terminology Criteria for Adverse Events version 3.0 for toxicity and adverse event reporting. A copy of the CTCAE version 3.0 can be accessed: <http://ctep.cancer.gov/forms/CTCAEv3.pdf>

5.2.2 Blood & Urine Sample Processing: All assays of blood and urine are to be performed in a licensed clinical laboratory (i.e., UCSF or the referring institution).

6.0 REQUIRED DATA

6.1 Pre- ¹³¹I-MIBG Evaluation: Physical assessment and laboratory data to be performed ≤ 2 weeks before ¹³¹I-MIBG therapy. Volumetric scanning studies to be performed ≤ 4 weeks before ¹³¹I-MIBG therapy.

6.1.1 Assessment of Disease Status

- History & Physical Examination
- Karnofsky Performance Status Assessment
- ¹²³I-MIBG or ¹³¹I-MIBG whole-body scan
- CT scan or MRI scan with tumor volumetric measurements
- For patients with pheochromocytoma: Serum chromogranin A and 24-hour urine collection for fractionated catecholamines, metanephrines, and creatinine
- For patients with carcinoid tumor: serum serotonin and 24-hour urine for 5-HIAA
- For patients with medullary thyroid carcinoma: serum calcitonin

6.1.2 Organ Baseline Function Evaluation

- CBC with differential and platelet count.
- Serum TSH and free T₄.
- Serum creatinine.
- Serum cortisol and ACTH.
- Serum bilirubin, AST, ALT.
- Pulmonary function testing: if there are pulmonary metastases that have significant ($\geq 2x$ background) uptake of MIBG on diagnostic scanning.
- Echocardiogram: if the heart has significant ($\geq 2x$ background) uptake of MIBG on diagnostic scanning.

6.2 Post- ¹³¹I-MIBG Evaluation: All patients will require life-long follow-up for organ toxicity and for tumor surveillance until death.

6.2.1 Duration & Frequency of Physician Visits:

- Weekly for 8 weeks after ¹³¹I-MIBG.
- Monthly for months 2 to 12 after ¹³¹I-MIBG, then quarterly for life.

6.2.2 Karnofsky Performance Status: Reports will be sent to UCSF quarterly for 5 years and then yearly.

6.2.3 Hematologic Monitoring: CBC with absolute differential and platelet count will be obtained following ¹³¹I-MIBG as follows:

- Twice weekly “stat” for 6 weeks after ¹³¹I-MIBG.
- Monthly for months 2 to 4 after ¹³¹I-MIBG, then quarterly for 5 years, and then yearly.

6.2.4 Metabolic Monitoring: Serum BUN, Cr, Alk Phos, AST, bilirubin, sodium, potassium, calcium, albumin, glucose as follows:

- Weekly for 6 weeks after ¹³¹I-MIBG.
- Monthly for months 2 to 4 after ¹³¹I-MIBG, then quarterly for 5 years, and then yearly.

6.2.5 Thyroid Function Assessment: Serum TSH and free T₄

- Monthly for months 2 to 4 after ¹³¹I-MIBG, then quarterly for 5 years, and then yearly.

6.2.6 Cardiac & Pulmonary Assessment:

- Echocardiogram 3 months after ¹³¹I-MIBG, if cardiac isotope uptake is seen on post-therapy scan.
- Pulmonary function testing 3 months after ¹³¹I-MIBG, if lung isotope uptake is seen on the post-therapy scan.

6.2.7 Tumor Marker Assessment:

- Serum chromogranin A: monthly for 4 months after ¹³¹I-MIBG, then quarterly for 5 years, then yearly for life.
- 24-hour urine determinations for fractionated catecholamines, fractionated metanephrines, and creatinine: quarterly for first year, then every 6 months for 5 years, then yearly for life.

6.2.8 ¹²³I-MIBG Scanning with Volumetric Measurements: Every 3 months for first year after ¹³¹I-MIBG, then every 6 months for 5 years after ¹³¹I-MIBG, then yearly for 5 years.

6.2.9 CT or MRI Scanning: Every 3 months for first year after ¹³¹I-MIBG, then every 6 months for 5 years after ¹³¹I-MIBG, then yearly for 5 years.

7.0 TREATMENT PLAN

7.1 Dose of ¹³¹I-MIBG: 18 mCi/kg body weight or the maximum that can be prepared by the UCSF Nuclear Medicine Department (current maximum of approximately 1200 mCi). Patients who do not have cryopreserved stem cells must receive reduced doses of ≤ 12 mCi/kg *and* ≤ 500 mCi ¹³¹I-MIBG in order to reduce the risk of prolonged myelosuppression. Examples:

- A 30 kg child's calculated dose at 18 mCi/kg would be 540 mCi.
- A 70 kg adult's calculated dose at 18 mCi/kg would be 1260 mCi; however, UCSF Nuclear Medicine is capable of synthesizing only about **1200** mCi. This adult would receive **1200** mCi (**17.1** mCi/kg).
- A 30 kg child's calculated dose without stem cells would be 360 mCi (12 mCi/kg).
- A 70 kg adult's calculated dose without stem cells would be 500 mCi (7.1 mCi/kg).

7.2 Administration of ¹³¹I-MIBG: The ¹³¹I-MIBG will be infused intravenously over a minimum of 2 hrs behind 2.5 cm thick lead shields.

- An automatic device will measure blood pressure and pulse every 15 minutes during the infusion of ¹³¹I-MIBG.
- Hydration will be maintained with an intravenous infusion of 0.9 NS at 150 cc/hr that will be continued for at least 48 hours after ¹³¹I-MIBG.
- A Foley catheter will be used for continuous bladder drainage for 72 hours to prevent unnecessary bladder and pelvic irradiation. Urine will drain into a lead-shielded container, the contents of which will be pumped into a constant-draining toilet.
- Radiation safety precautions will be observed. Patients will be monitored daily by UCSF Environmental Health & Safety (Radiation Safety).

7.3 Thyroid Protection: A small amount of ¹³¹I naturally dissociates from MIBG in the body after ¹³¹I-MIBG administration. The thyroid, potentially causing hypothyroidism, may actively absorb free circulating ¹³¹I. To prevent post-treatment hypothyroidism, patients who are not already hypothyroid will be given the following regimen:

- Potassium iodide will be given orally beginning 12 hours prior to therapy and for 6 weeks after ¹³¹I-MIBG (6 mg/kg loading dose, then 0.88 mg/kg p.o. q 4 h x 7 d (the 2 AM dose will be omitted), then 1 mg/kg orally q.d.).
- Potassium perchlorate will be given orally beginning 12 hours prior to therapy and for five days after ¹³¹I-MIBG (8 mg/kg loading dose, then 2 mg/kg orally at meals and bedtime).

7.4 Prevention & Treatment of Radiation-Induced Nausea:

- Granisetron (Kytril) 2 mg daily will be given orally daily for at least 5 days, beginning 2 hours prior to ¹³¹I-MIBG administration.
- Lorazepam (Ativan) 1 mg will be administered orally 1 hour prior to ¹³¹I-MIBG administration and then as needed for nausea. In the event of vomiting, the lorazepam may be given intravenously. Maximum daily dose: 10 mg.
- Phenothiazine anti-emetics will not be given since they inhibit the uptake of ¹³¹I-MIBG into tumor cells.

7.5 Prevention of Deep Vein Thrombosis (DVT): Patients are confined to bed for three days after ¹³¹I-MIBG due to the requirement for bladder catheterization to a fixed lead-shielded container. This puts them at risk DVT.

- Enoxaparin (Lovenox) will be administered sc to all adult patients (\geq 21 years of age) in a dose of 40 mg daily for three days beginning in the morning prior to ¹³¹I-MIBG administration.
- Patients will be advised to ambulate within their lead-shielded room once their bladder catheter is removed.

7.6 Radiation Safety: UCSF Environmental Health and Safety will monitor radiation safety. Therapies with ¹³¹I-MIBG are to be performed only in lead-shielded rooms (currently available on the PCRS and on 11L).

Additionally, a portable lead shield will be placed between the patient and the door to the room. Additional safety precautions will include the following:

- Room preparation by Radiation Safety Office including covering of the floor with absorbent paper, covering the mattress and pillow with rubber covers, and covering fixtures with cellophane wrap.
- Plastic lined trash cans and linen hampers are to be placed in the room.
- Posting: The door is to be posted with a “Caution Radioactive Material” sign.
- Food service: Disposable utensils must be used. Radiation Safety Officer should bag dishes and waste in the designated trash can for pick-up.
- Radiation monitoring: A radiation dosimeter will be placed outside the room and must be worn by all personnel or guests visiting the patient after the administration of ¹³¹I-MIBG. A log book will be placed outside the room and all visitors must register their name, date, and time in room, and dosimeter reading before and after visiting the patient.
- Visiting restrictions: No pregnant persons or persons < 18 years of age are allowed to visit the patient. Visitors must stop at the nurse’s desk for instructions. Visitation inside the room is severely restricted for the first 72 hours following ¹³¹I-MIBG. Visitors must stay behind the portable lead shield unless given permission to touch the patient. Visitors must wear disposable shoe covers and disposable gloves (if touching patient).

- Nursing care: No pregnant staff shall be assigned to care for patients after they have received ^{131}I -MIBG. Reduce exposure as much as possible by staying behind portable lead shield, by using automatic blood pressure monitors, and by limiting time in the room. Standard precautions listed above must be followed.
- Emergencies: In case of medical emergencies such as cardiac or respiratory arrest, seizures, or trauma, follow normal protocols for treatment of the patient. If time allows, use precautions noted above. Use Geiger counter to monitor personnel and equipment when leaving area. Call Radiation Safety Officer.
- All persons involved with direct care of a patient receiving ^{131}I -MIBG must receive radiation safety instructions prior to their involvement.

8.0 MANAGEMENT OF TOXICITY

8.1 Hematologic Toxicity:

- 8.1.1 Bone marrow biopsy:** Bone marrow biopsy will be required prior to stem cell harvest if patients have significant pheochromocytoma metastases to bone as determined by ^{123}I -MIBG diagnostic scanning and CT or MRI scanning. Significant metastases are defined as ≥ 4 areas of bone metastasis exceeding 1 cm in diameter.
- 8.1.2 Peripheral Blood Stem Cell Harvest:** Patients will require a pre-treatment stem cell harvest if they are to receive >12 mCi/kg **or** >500 mCi ^{131}I -MIBG. The Stem Cell Harvest and Transplant Protocol is detailed in Appendix A.
- 8.1.3 Platelet transfusions:** Patients whose platelet count drops to $<10,000/\mu\text{L}$ or who develop significant bleeding with platelet counts $<40,000/\mu\text{L}$, are to be transfused platelets.
- 8.1.4 Filgrastim (GCSF):** Patients whose absolute neutrophil count (ANC) falls below $500/\mu\text{L}$ may receive filgrastim at a dose of $5\mu\text{g}/\text{kg}$ sc daily until ANC rises above $5,000/\mu\text{L}$.
- 8.1.5 Erythropoietin (EPO):** Use of epoetin or darbepoetin is permitted at the discretion of the treating physician for persistent anemia.
- 8.1.6 Blood transfusions:** Patients who develop a significant anemia (e.g., $\text{HCT} \leq 25\%$) may receive transfusions of packed RBCs

8.1.7 Stem Cell Infusion: For prolonged (e.g., over 2 weeks) significant cytopenia (e.g., ANC < 200/ μ L, or platelet count < 20,000/ μ L, or Hct < 25%) stem cells may be infused. (Appendix A)

8.2 Non-Hematologic Toxicity: Gastrointestinal toxicity (radiation sickness) will be managed as described in Section 7.4. Other toxicity is not expected, but any unexpected toxicity will be managed according to standard medical practice.

9.0 DRUG FORMULATION AND PREPARATION

9.1 ^{131}I Metaiodobenzylguanadine (^{123}I -MIBG) Formulation: ^{131}I will be obtained by UCSF Nuclear Medicine from commercial sources as a fission product. It will be prepared on-site at UCSF in a protected hot-cell designed for this purpose. ^{131}I will be attached to MIBG by a high-temperature Cu-catalyzed exchange reaction, incubating approximately 1 Ci ^{131}I with ^{127}I -MIBG. Alternatively, a no-carrier-added methodology may be used.

9.2 ^{131}I -MIBG Preparation: ^{131}I -MIBG will be prepared in doses as described in Section 7.1. The isotope will be delivered to the patient's room by the nuclear pharmacist in a special lead-shielded container.

10.0 ANCILLARY THERAPY

10.1 Patients should receive full supportive care, including transfusions of blood, and blood products, antiemetics, etc., when appropriate.

10.2 Palliative radiation therapy may not be administered within 1 month before or 2 months following ^{131}I -MIBG. Any lesion treated with radiation therapy will not be considered evaluable for this study.

10.3 Hematopoietic Growth Factors: These may be used at the discretion of the treating physician as described in Section 8.1.

11.0 CRITERIA FOR RESPONSE, PROGRESS, AND RELAPSE

For the purposes of this study, patients should be reevaluated every 3 months. In addition to a baseline scan, confirmatory scans should also be obtained following initial documentation of objective response.

11.1 Complete Response (CR): Disappearance of all lesions visible on CT scan and disappearance of all abnormal tumoral ¹²³I-MIBG uptake on diagnostic scanning. A tumor marker CR is considered to be the complete normalization of initially elevated urinary catecholamine and metanephrine excretion, and the normalization of serum chromogranin A levels.

11.2 Partial Response (PR): At least a 30% confirmed decrease in the sum of the longest diameter of target lesions. A tumor marker PR is considered to be a decrease of $\geq 50\%$ in initially elevated urinary catecholamine and metanephrine excretion, or $\geq 50\%$ decrease in serum chromogranin A.

11.3 Progressive Disease (PD): At least 20% increase in the sum of the longest diameter of target lesions noted on CT scan, or $> 20\%$ increase in initially-elevated tumor markers: urinary catecholamine and metanephrine excretion, or serum chromogranin A levels.

11.4 Stable Disease (SD): Neither sufficient shrinkage or change in tumor markers to qualify for PR, nor sufficient increase to qualify for PD.

12.0 STATISTICAL CONSIDERATIONS

12.1 Background and Primary Endpoint

The primary endpoint and basis for sample size determination will be to determine the percentage of patients who remain in CR or PR, and the percentage of patients without PD after administration of ¹³¹I-MIBG.

12.2 Sample Size Determination

For the purposes of this study, a patient will be considered to have been successfully treated if that patient remains without PD for 3 years after initial administration of ¹³¹I-MIBG. Such patients will be considered to have a “successful treatment.” Otherwise, the patient will be considered to have a “failed treatment.”

Fifty (50) patients will be enrolled in the study. If 33 or less of these patients are successful in their treatment, it will be concluded that the treatment regimen is not worthy of additional investigation.

The characteristics of this design are as follows:

- The probability of erroneously concluding that the treatment regimen is worthy of further investigation (i.e., $p \geq 0.75$) when the success rate is truly 55% or less (i.e., $p \leq 0.55$) is 0.043.
- The probability of erroneously concluding that the treatment regimen is NOT worthy of further investigation (i.e., $p \leq 0.55$) when in reality the success rate was 75% or greater (i.e., $p \geq 0.75$) is 0.10.

12.3 Analytical Methods

- Kaplan-Meier's product limit estimator will be used to describe the distribution of survival and failure-free survival among the full patient group treated with ^{131}I -MIBG. Kaplan-Meier curves will be used to estimate survival and failure-free survival rate for the full patient group. An exact binomial confidence interval will be generated for these proportions.
- To determine whether the dose of ^{131}I -MIBG affects the likelihood of PD, the cumulative doses and mCi/kg values for responders and non-responders will each be compared with a Cox Proportional Hazard Model.
- To determine whether children (< 21 years) or adults fare better as a group, Kaplan-Meier curves will be determined for each group, and the curves will be compared with a Log Rank Test.

12.4 Accrual Period

Since metastatic pheochromocytomas are rare malignancies, an accrual period of 5 years will be allowed to accrue a total of 50 patients

13.0 DATA SAFETY MONITORING PLAN

13.1 Oversight And Monitoring Plan:

The U.C.S.F. Comprehensive Cancer Center (UCSFCCC) Data Monitoring Committee (DMC) is responsible for monitoring data quality and patient safety for all UCSFCCC clinical studies. A summary of DMC activities follows:

- Review of all clinical trials conducted at the UCSFCCC for progress and safety.
- Review of all adverse events requiring expedited reporting as defined in the protocol.
- Review of reports generated by the UCSFCCC data quality control review process.
- Submit recommendations for corrective action to the Clinical Research Steering Committee (CRSC).
- Notify the Principal Investigator of the DMC recommendation to the CRSC.

13.2 Monitoring And Reporting Guidelines

Data related to this trial will be discussed at regularly scheduled study group or site committee meetings where the result of each patient's treatment is discussed and the discussion is documented in the minutes. The discussion will include for each treatment arm/dose level, the number of patients, significant toxicities as described in the protocol, dose adjustments, and responses observed. Twice yearly, summaries will be submitted to the Data Monitoring Committee for review.

14.0 REVIEW AND OVERSIGHT REQUIREMENTS

14.1 Adverse Event (AE) – Reported By Phone Within 24 Hours:

Adverse events requiring expedited reporting by phone within 24 hours (as described in the protocol) will also be reported by phone to the Clinical Research Support Services (CRSS) administrator within one working day. Confirmation that all appropriate parties (including the U.C.S.F. Committee on Human Research) were notified will be done at this time. Hardcopies or electronic versions of the National Cancer Institute (NCI) ADEERS form (#3500) and/or any other documentation available at that time will also be reviewed by the Data Monitoring Committee (DMC) Committee Chair who will determine if immediate action is required. Within ten working days all subsequent SAE documentation that is available will be submitted to the DMC Committee Chair who will determine if further action is required. All information will be tracked in the U.C.S.F. Comprehensive Cancer Center (UCSFCCC) database.

14.2.1 Adverse Event (AE) – Reported within 10 Days:

Adverse events requiring expedited AE reports in writing within 10 working days (as described in the protocol) will be sent to the Clinical Research Support Services (CRSS) office. Hardcopies or electronic versions of the National Cancer Institute (NCI) ADEERS form (#3500) or other required forms will be submitted for review by the Data Monitoring Committee (DMC) Committee Chair to determine if further action is required. This information will be tracked in the U.C.S.F. Comprehensive Cancer Center (UCSFCCC) database.

14.3 Study Progress – Quarterly Review:

Principal Investigators are required to submit quarterly study progress reports to the study site committee summarizing all new patient accruals and treatments performed during that period, along with adverse reactions. These quarterly reports are reviewed at quarterly meetings. Failure to submit such reports will result in trial suspension. Semiannual meetings will also review the data on patient responses, progressive disease, and deaths to determine if the trial should be continued based upon efficacy, safety and the likelihood of timely completion. (Stopping Rules, Section 16.0)

An overall assessment of accrual, toxicities as described in the protocol, and responses will enable the committee members to assess whether significant benefits or risks are occurring that would warrant study closure. This information is provided by study site committee meeting minutes, internal data quality audits, and annual DMC audits; all of these are required of all research studies at U.C.S.F. Comprehensive Cancer Center (UCSFCCC).

The DMC recommendations for modifications to the trial or corrective actions are forwarded to the Protocol Review Committee and the Clinical Research Steering Committee. The Principal Investigator is notified of this recommendation in order that he/she may alert all investigators at the UCSFCCC about the potential action. At this time the Principal Investigator may submit to the Clinical Research Steering Committee additional information that could affect the Committee's decision. The Clinical Affairs Committee will notify the Principal Investigator if they concur with the Data Monitoring Committee recommendations, including suspension or closure. The DMC Chair will notify all investigators involved with the study at UCSFCCC and external sites, and the CHR.

14.4 Review of Adverse Event (AE) Rates:

Once a month, adverse event rates will be monitored utilizing the U.C.S.F. Comprehensive Cancer Center (UCSFCCC) Clinical Trials database. If any study has had two or more of the same AE reported in a month or more than six of the same AE in six months, the Data Monitoring Committee (DMC) Chair will review the summary serious adverse events (SAEs), discuss events with the Principal Investigator, and conduct a more detailed review with the Principal Investigator or the external DSMB if warranted. The Committee Chair will determine if further action is required.

If this occurs on a multiple-institutional clinical trial coordinated by the UCSFCCC , the Safety Coordinator will insure that all participating sites are notified of the resulting action.

15.0 EXPEDITED REPORTING OF ADVERSE EVENTS (AEs)

Depending on the nature, severity, and attribution of the event, an adverse reaction (ADR) report will be phoned in, submitted in writing, or both according to the Tables below. Such AEs must be reported by phone to the U.C.S.F. Comprehensive Cancer Center (UCSFCCC) Data Monitoring Committee within one working day of the event. Such adverse events must also be reported to the U.C.S.F. Institutional Review Board (IRB)/Committee on Human Research (CHR).

<p>Telephone reports to: UCSFCCC Data Monitoring Committee Administrator 415-502-5487 within one working day of the event</p>
<p>Written reports to: UCSFCCC Data Monitoring Committee Administrator – FAX 415-476-5106 or deliver to Box 0947 U.C.S.F. CHR – 415-476-1814; Fax 415-502-1347</p>

EXPEDITED REPORTING TABLE

TABLE A-I-2			
Summary Of Reporting Requirements For Adverse Events On Trials Supported By Grant Or Contract Where NCI Is the IND Sponsor			
<i>EXPEDITED REPORTING FOR PHASE 2 AND PHASE 3 STUDIES</i>			
Unexpected Event		Expected Event	
GRADES 2 - 3 Attribution of Possible, Probable, or Definite	GRADES 4 and 5 Regardless of Attribution	GRADES 1 - 3	GRADES 4 and 5, Regardless of Attribution
<p>Expedited report within 10 working days to IDB.</p> <p>(Grade 1 - Adverse Event Expedited Reporting NOT required.)</p>	<p>Report by phone to IDB within 24 hrs. Expedited report to follow within 10 working days.</p> <p>This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution.</p> <p>Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.</p>	<p>Adverse Event Expedited Reporting NOT required.</p>	<p>Report by phone to IDB within 24 hrs. Expedited report to follow within 10 working days.</p> <p>This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution.</p> <p>Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.</p> <p>Grade 4 Myelosuppression or other Grade 4 events that do not require expedited reporting will be specified in the protocol.</p>

IDB = Investigational Drug Branch

For Hospitalization Only – Any medical event equivalent to the CTC Grade 3,4,5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of requirements for phase of study, expected or unexpected and attribution.

Expedited reporting will not be necessary for Grade 4 myelosuppression following high-dose ¹³¹I-MIBG therapy, since myelosuppression is an expected consequence of this therapy.

16.0 STOPPING RULES

- 16.1** Interim Analyses: The principal investigator will submit quarterly study progress reports (Section 14.3) to the site committee and semiannual summaries (Section 13.3) to the site committee and the U.C.S.F. Data Monitoring Committee (DMS). Expedited adverse event reports will be reviewed by the DMC as determined by the DMC Committee Chair. Additionally, the site committee will review the accumulated data semiannually to determine whether the study should be stopped. The DMC will conduct an audit of patient charts and perform a comprehensive review of the protocol and data summaries at least yearly.
- 16.2** Efficacy Stopping Rules: The study will be stopped if the accumulated data reveal that $\leq 20\%$ of enrolled patients are without progressive disease (PD) after 3 years from the date of their first ¹³¹I-MIBG treatment.
- 16.3** Safety Stopping Rules: The study will be stopped for cumulative treatment-related mortality exceeding 20%. The study will be also be stopped if the cumulative rate of treatment-related (expected or unexpected) non-hematologic Grade 4 or 5 toxicity exceeds 40%.

17.0 REFERENCES

1. August CS, Serota FT, Koch PA, Burkey E, Schlesinger H, Elkins WL, Evans AE, and D'Angio GJ: Treatment of advanced neuroblastoma with supralethal chemotherapy, radiation, and allogeneic or autologous marrow reconstitution. *J Clin Oncol* 2:609, 1984.
2. D'Angio GJ, August C, Elkins W, Evans AE, Seeger R, Lenarsky C, Feig S, Wells J, Ramsay N, Kim T, Woods W, Krivit W, Strandjord S, Coccia P and Novak L: Metastatic neuroblastoma managed by supralethal and bone marrow reconstitution (BMRC). Results of a four-institution Children's Cancer Study Group Pilot Study. *In: Advances in Neuroblastoma Research*, 1985, pages 557-563.
3. Engelstad BL, Matthay KK, Huberty JP and Hattner RS: Programmatic considerations for ¹³¹I-MIBG therapy of advanced neuroblastoma. Submitted for presentation at the Society of Nuclear Medicine, Toronto, June, 1987.
4. Engelstad BL, Huberty JP, Matthay KK and Hattner RS: Efficacy and safety of ¹³¹I-MIBG therapy for advanced neuroblastoma. Submitted for presentation at the Society of Nuclear Medicine, Toronto, June, 1987.
5. Fernbach DJ, Williams TE and Donaldson MH: Neuroblastoma. *In: Clinical Pediatric Oncology*, Edited by Sutton WW, St. Louis, 1977, pp. 506-537.
6. Fojo AT, Ueda K, Slamon DJ, Poplack DG, Gottesman MM and Pastan I: Expression of a multidrug-resistance gene in human tumors and tissues. *Proc Nat'l Academy of Science USA* 84:265-269, 1987.
7. Geatti O, Shapiro B, Sisson JC, Hutchinson RJ, Mallette S, Eyre P, Beierwaites WH: ¹³¹I-metaiodobenzylguanidine (¹³¹I-MIBG) scintigraphy for the location of neuroblastoma: Preliminary experience in 10 cases. *J Nucl Med* 26:736-742, 1985.
8. Hann H-W L, Evans AE, and Siegel SE: Prognostic importance of serum ferritin in patients with Stage III and IV neuroblastoma: The Children's Cancer Study Group Experience. *Cancer Research* 45:2843, 1985.
9. Happ J, Griese J, Maui FD, Baum RP, Manegold KH, Gerein V, Schwabe D, Klinger D, Szepesi S, Kornhuber B and Hor G: *In: Nuclear Medicine in Clinical Oncology*, Edited by C. Winkler, Springer-Verlag Pub.. Co., Berlin and Heidelberg, 1986, pages 331-336.
10. Hartmann O: Personal communication, Villejuif, France, 1987.

11. Hattner RS, Huberty JP, Engelstad BL, Gooding CA and Ablin AR: Localization of m-iodo (131-I) benzylguanidine in neuroblastoma. *Am J Roentgenol* 143:373-374, 1984.
12. Hattner RS, Huberty, Engelstad BL, Roizen MP and Tyrrell JB: Scintigraphic detection of pheochromocytomas using m-iodo (I-131) benzylguanidine. *Noninvasive Med Imaging* 1:105-109, 1984.
13. Huberty J, Matthay K, Engelstad B, Hattner R, Yano Y, Budinger T, and Ablin A: Considerations in the development of an 131-I-MIBG therapy program for advanced neuroblastoma. *Clin Nuc Med* 11:14, 1986.
14. Jacques Jr S, Tober MC, Sisson JC, Baker JA, and Wieland DM: Comparison of the sodium dependency of uptake of metaiodobenzylguanidine and norepinephrine into cultured bovine adrenomedullary cells. *Mol Pharm* 26:439-546, 1984.
15. Hutchinson R, Beierwaites W, Sisson J, Shapiro B, Evans AE, Ablin A, Holbrook CT, Malette S, Rabbani R, Dmuchowski C: Regressions of neuroblastoma from I-131-metaiodobenzylguanidine (MIBG) treatment after failure with standard treatment. In: *Proceedings of the American Society of Clinical Oncology*, 1987, In Press.
16. Kimmig B, Brandeis EW, Eisenhut M, Bubeck B, Hermann HM, zum Winkel K: Scintigraphy of a neuroblastoma with I-131 metaiodobenzylguanidine. *J Nucl Med* 25:773-775, 1984.
17. Ladisch S and Wu Z-L: Circulating gangliosides as tumor markers. In: *Advances in Neuroblastoma Research*, 1985, pages 277-284.
18. Matthay KK, Engelstad BL, Huberty JP, Ablin AR, Hattner RS: Efficacy and safety of 131-I Metaiodobenzylguanidine (MIBG) therapy for patients with refractory neuroblastoma. In: *Advances in Neuroblastoma Research*, 1987.
19. Moss TJ, Seeger RC, Kindler-Rohrborn A, Marangos PJ, Rajewsky MF and Reynolds CP. Immunohistologic detection and phenotyping of neuroblastoma cells in bone marrow using cytoplasmic neuron specific enolase and cell surface antigens. In: *Advances in Neuroblastoma Research*, Edited by Evans AE, New York, 1985, pages 367-378.
20. Munker T: 131-I-metaiodobenzylguanidine scintigraphy of neuroblastoma. *Semin Nuci Med* 15:154-160, 1985.
21. Pama AM, Marangos PJ and Goodwin FK: A more sensitive radioimmunoassay for neuron specific enolase suitable for cerebrospinal fluid determinations. *J Neurochemo* 36:1093-1097, 1981.

22. Philip T, Biron P, Philip I, Favrot M, Bernard JL, Zucker JM, Lutz B, Plouvier E, Rebattu P, Carton M, Chauvot P, Dutou L, Souillet G, Phillippe N, Bordigoni P, Lacroze M, Clapisson G, Olive D, Treleaven J, Kemshead JT, Brunat-Mentigny M: Autologous bone marrow transplantation for very bad prognosis neuroblastoma. In: Advances in Neuroblastoma Research, Edited by Evans AE, New York, 1985, pages 569-586.
23. Roninson IB, Chin JE, Choi K, Gros P, Housman DE, Fojo A, Shen D-W, Gottesman MM and Pastan I: Isolation of human mdr DNA sequences amplified in multidrug-resistant KB carcinoma cells. Proc Natl Acad Sci USA 83:4538-4542, 1986.
24. Seeger RC, Reynolds CP, Vo DD, Ugelstad JR and Wells J: Depletion of neuroblastoma cells from bone marrow with monoclonal antibodies and magnetic immunobeads. In: Advances in Neuroblastoma Research, Edited by Evans AE, New York, 1985, pages 443-458..
25. Seeger RC, Brodeur GM, Sather H, Dalton A, Siegel SE, Wong KY and Hammond D: Multiple copies of the N-myc oncogene in neuroblastomas are associated with rapid tumor progression`. N Eng J Med 313:1111-1116, 1985.
26. Shapiro B, Copp JE, Sisson JC, Eyre PL, Wallis J and Beierwaites WH: Iodine-131 metaiodobenzylguanidine for the locating of suspected pheochromocytoma. Experience in 400 cases. J Nucl Med 26:576-585, 1985.
27. Shapiro B, Sisson JC, Kalff V, Glowniak JV, Satterlee W, Glazer G, Francis I, Bowers R, Thompson N, Orringer M, Gross M and Beierwaites WH: The location of middle mediastinal pheochromocytomas. J Thoracic Cardiovasc Surg 87:814-820, 1984.
28. Short JH and Darby TD: Sympathetic nervous system blocking agents. III Derivatives of benzylguanidine. J Med Chem 10:833-840, 1967.
29. Sisson JC, Frager MS, Valk TW, Gross MD, Swanson DP, Wieland DM, Tobes MC, Beierwaites WH, and Thompson NW: Scintigraphic localization of pheochromocytoma. N Engl J Med 305:12-17, 1981.
30. Sisson JC, Shapiro B, Beierwaites WH, Glowniak J, Nakajo M, Mangner TJ, Carey JE, Swanson DP, Copp JE, Satterlee WG and Wieland DM: Radiopharmaceutical treatment of malignant pheochromocytoma. J Nucl Med 24:197-206, 1984.
31. Sisson JC and Wieland CM: Radiolabeled metaiodobenzylguanidine: Pharmacology and Clinical Studies. Amer J Physiol Imag 1:96-103, 1986.
32. Siamon DJ, Boone TC, Seeger RC, Keith DE, Chazin V, Lee HC and Sonza LM: Identification and characterization of the protein encoded by the human N-myc oncogene. Science 232:768-772, 1986.

33. Tobes MC, Jaques Jr S, Wieland DM and Sisson JC: Effect of uptake-one inhibitors on the uptake of norepinephrine and metaiodobenzylguanidine. *J Nucl Med* 26:907-987, 1985.
34. Treuner J, Klingebiel T, Feine U, Buck J, Bruchelt G, Dopfer R, Girgert R, Muller-Schauenburg W, Meinke J, Kaiser W and Niethammer D: Clinical experiences in the treatment of neuroblastoma with ¹³¹I-metaiodobenzylguanidine. *Ped Hematol and Oncol* 3:205-216, 1986.
35. Valk TW, Frager MS, Gross MD, Sisson JC, Wieland DM, Swason DP, Manger TJ and Beierwaites WH: Spectrum of pheochromocytoma in multiple endocrine neoplasia. *Ann Intern Med* 94:762-767, 1981.
36. Voute T: Personal communication, Amsterdam, Netherlands, 1987.
37. Wieland DM, Brown LE, Tobes MC, Rogers WL, Marsh DD, Mangner TJ, Swanson DP and Beierwaites WH: Imaging the primate adrenal medulla with I-123 and I-131 metaiodobenzylguanidine. *Concise Communication. J Nucl Med* 22:358-364, 1981.
38. Wieland D, Wu J-L, Brown LE, Manger TJ, Swanson DP and Beierwaites WH: Radiolabeled adrenergic neuron-labeling agents: Adrenomedullary imaging with ¹³¹I iodobenzylguanidine. *J Nucl Med* 21:349-353, 1980.
39. Zeltzer PM, Marangos PJ, Sather H, Evans A, Siegel S, Wong KY, Dalton A, Seeger R and Hammond D: Prognostic importance of serum neuron specific enolase in local and widespread neuroblastoma. *In: Advances in Neuroblastoma Research*, Edited by AE Evans, New York, 1985, pages 319-329.
40. Zeltzer PM, Marangos PJ, Parma AM, Sather H, Dalton A, Hammond D, Siegel SE and Seeger RC: Raised neuron-specific enolase in serum of children with metastatic neuroblastoma. *Lancet* ii:361-363, 1983.
41. Siddiqui MZ, Von Eyben FE, Spanos G: High voltage irradiation and combination chemotherapy for malignant pheochromocytoma. *Cancer* 62:686-690, 1988.
42. Shapiro B, Fig LM: Management of pheochromocytoma. *Endo and Metab Clin of N Amer* 18:443, 1989.
43. Keiser HR, et al.: Treatment of malignant pheochromocytoma with combination chemotherapy. *Hypertension* 7 (Suppl I): 1-18, 1985.

44. Brendel A, Jeandot R, Guyot M, Lambert B, Drouillard J: Radionuclide therapy of pheochromocytomas and neuroblastomas using Iodine-131-metaiodobenzylguanidine (MIBG). *Clin Nuc Med* 14 (1):19-21, 1989.
45. Charbonnel B, Chatal JF, Brendel AS, Laineche B, Lumbroso J, Marchandise X, Maruex R, Schlumberger and Wemeau JL: Le traitement des pheochromocytomas malins par la 131-I-metaiodobenzylguanidine. *Annales d'Endocrinologie (Paris)* 49:344-347, 1988.
46. Konings JE, Bruning PF, Abeling NGGM, van Gennip AH, Hoefnagel CA: Diagnosis and treatment of malignant pheochromocytoma with 131-I-metaiodobenzylguanidine: A case report. *Radiother and Oncol* 17:103-108, 1990.
47. Koral KF, Wang X, Sisson JC, Botti J, Meyer L, Mallett S, Glazer GM, Adler RS: Calculating radiation absorbed dose for pheochromocytoma tumors in 131-I MIBG therapy. *Int J Rad Oncol Bio Phys* 17:211-218, 1989.
48. Limone P, Pogliano G, Castellano G, Argiro G, Isaia GC, Favero A, Coftino F, Rizz G, Molinatti GM: 131-I-meta-iodobenzylguanidine for the diagnosis and treatment of pheochromocytoma. *Panminerva Medica* 30:169-172, 1988.
49. Troncome L, Rufin V, Montemaggi, Danza FM, Lasorella A, Mastrangelo R: The diagnostic and therapeutic utility of radioiodinated metaiodobenzylguanidine (MIBG). 5 years experience. *Europ J Nuc Med* 16(4-6):325-335, 1990.
50. Drasin H: Treatment of malignant pheochromocytoma. *West J Med* 128:106-11, 1978.
51. Bukowski RM, Vidt DG: Chemotherapy trials in malignant pheochromocytoma: report of two patients and review of the literature. *J Surg Oncol* 27:89-92, 1984.
52. Lewi HJ, Reid R, Mucci B, et al.: Malignant pheochromocytoma. *Br J Urol* 57:394-398, 1985.
53. Averbuch SD, Steakley CS, Young RC, et al.: Malignant pheochromocytoma: effective treatment with a combination of cyclophosphamide, vincristine, and dacarbazine. *Ann Internal Med* 109:267-273, 1988.
54. Koshihara K, Komita I, Watanabe M, et al.: Remarkable regression of malignant paraganglioma in the retroperitoneum and neck after chemotherapy: Report of a case and a review of the literature. *Jpn J Med* 28:772-776, 1989.
55. Fischer M: Therapy of pheochromocytoma with ¹³¹I- metaiodobenzylguanidine. *Journal of Nuclear Biol. Medicine* 35:292-294, 1991.

56. Khafagi FA, Shapiro B, Fischer M, Sisson JC, Hutchinson R, Bierwalts WH: Phaeochromocytoma and functioning paraganglioma in childhood and adolescents: Role of iodine-131 metaiodobenzylguanidine. *European Journal of Nuclear Medicine* 18:191-198, 1991
57. Krempf M, Lumbroso J, Mornex R, Brendel AJ, Wemeau JL, Delisle MJ, Aubert B, Carpentier T, Fleury-Goion MC, Gibold C, Guiot M, Lahneche B, Marchandise X, Schlumberger M, Charbonnel B, Chatal JF: Use of m-[¹³¹I] iodobenzylguanidine in the treatment of malignant pheochromocytoma. *Journal of Clinical Endocrinology and Metabolism* 72:455-461, 1991
58. Schwartz C, Gubuld C, Vuillemin B, Delisle MJ: Results of ¹³¹I-metaiodobenzylguanidine therapy administered to three patients with malignant pheochromocytoma. *Journal of Nuclear Biol. Medicine* 35:305-307, 1991.
59. Troncone L, Rufini V, Daidone MS, DeSantis M, Luzi S: ¹³¹I – metaiodobenzylguanidine treatment of malignant pheochromocytoma: experience of the Rome Group. *Journal of Nuclear Biol. Medicine* 35:295-299, 1999
60. Krempf M, Lumbroso J, Mornex R, Brendel AJ, Wemeau JL, Delisle MJ, Aubert B, Carpentier T, Fleury-Goion MC, Gibold C, Guiot M, Lahneche B, Marchandise X, Schlumberger M, Charbonnel B, Chatal JF: Treatment of malignant pheochromocytoma with ¹³¹I- metaiodobenzylguanidine: a French multi-center study. *Journal of Nuclear Biological Medicine* 35:284-287, 1991
61. Bomanji J, Britton KE, Ur E, Hawkins L, Grossman AB, Besser GM: Treatment of malignant phaeochromocytoma, paraganglioma and carcinoid tumors with ¹³¹I – metaiodobenzylguanidine. *Nuclear medicine communications* 14:856-861, 1993
62. Schlumberger M, Gicquel C, Lumbroso J, Tenenbaum F, Comoy E, Bosq J, Fonseca E, Jhillani PP, Aubert B, Travheli JP, Gardet T, Parmentier C. Malignant pheochromocytoma: clinical, biological, histologic and therapeutic data in a series of 20 patients with distant metastasis. *Journal of Endocrinological Investigation* 15:631-642, 1992.
63. Loh KC, Fitzgerald PA, Matthay KK, Yeo PPB, Price DC: The treatment of malignant pheochromocytoma with Iodine-131 metaiodobenzylguanidine (¹³¹I-MIBG): a comprehensive review of 116 reported patients. *Journal of Endocrinological Investigation* 20:648-658, 1997.
64. Matthay KK, DeSantes K, Hasegawa B, Huberty J, Hattner RS, Ablin A, Reynolds CP, Seeger RC, Weinberg VK, Price D: Phase I dose escalation of ¹³¹I-metaiodobenzylguanidine with autologous bone marrow support in refractory neuroblastoma. *Journal of Clinical Oncology* 16:229-236, 1998.

65. Rose B, Matthay K, Price D, Klencke B, Huberty J, Damon L, Veatch J, Fitzgerald PA: High-dose ^{131}I –labeled metaiodobenzylguanidine (MIBG) for the treatment of metastatic pheochromocytoma and paraganglioma. Programs and abstracts 82nd Annual Meeting of the The Endocrine Society, Toronto, Ontario Canada. Abstract 2041, Page 494. June 21-24, 2000.
66. Mukherjee JJ, Kaltsas GA, Islam N, Plowman PN, Foley R, Hikmat J, Britton KE, Jenkins PJ, Chew SL, Monson JP, Besser, GM, Grossman AB: Treatment of metastatic carcinoid tumors, phaeochromocytoma, paraganglioma and medullary carcinoma of the thyroid with ^{131}I – meta-iodobenzylguanidine (^{131}I -mIBG). *Clinical Endocrinology* 55:47-60, 2001.
67. Rose B, Matthay KK, Price D, Huberty J, Klencke B, Norton JA, Fitzgerald PA: High-dose ^{131}I -Metaiodobenzylguanidine therapy for 12 patients with malignant pheochromocytoma. *Cancer* 98 (2): 1-10, 2003.
68. Safford SD, Coleman RE, Gockerman JP, Moore J, Feldman JM, Leight GS Jr, Tyler DS, Olson JA Jr: Iodine-131 metaiodobenzylguanidine is an effective treatment for malignant pheochromocytoma and paraganglioma. *Surgery* 2003 Dec;134(6):956-62; discussion 962-3. PMID: 14668728 This paper describes Duke University's experience treating 33 patients with ^{131}I -MIBG for malignant pheochromocytoma or paraganglioma. The majority of patients experienced symptomatic relief and improved survival. The mean dose of ^{131}I -MIBG was 388 mCi and patients who received high-dose (>500 mCi) ^{131}I -MIBG had the best response.